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Advances in 1,2,4-Triazepines Chemistry

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ABSTRACT

This review reported the literature survey of 1,2,4-triazepines. The investigated heterocycles are monocyclic and fused 1,2,4-triazepines. The different sections cover: theoretical calculations of conformations and tautomerism; synthesis and reactions of monocyclic and fused heterocycles incorporated 1,2,4-triazepines. The biological evaluation of the target compounds and the related compounds are described, as well as, the synthetic applications. The reaction mechanisms are discussed. The bibliography includes mainly 152 references.

Keywords:
1,2,4-Triazepines
Tautomerism
Synthesis
Reactions
Biological and Synthetic Importance.

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1. Introduction and Scope

The triazepines consist of a group of four triazacycloheptatrienes. The four possible isomers **1-4** are numbered as indicated (Fig. 1).

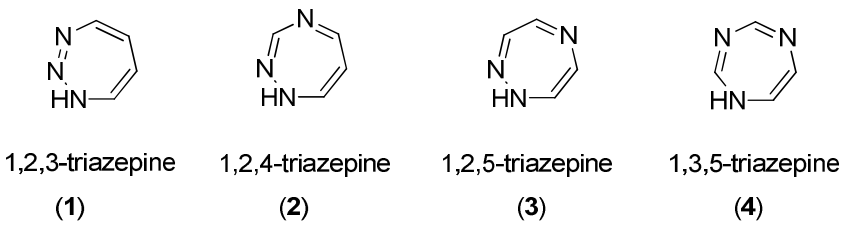


Figure 1. Structures of triazepines **1-4**.

Heterocycles that contains nitrogen are indispensable structural units for medicinal chemists. It has been demonstrated that heterocycles attached to seven membred rings showed important biological activities [1-3]. In previous studies, triazepines have attracted a great deal of attention as starting materials in the synthesis of fused heterocyclic systems of prospective pharmacological activities [4-9].

Triazepines are very interesting both from the pharmacological and chemical point of view [10-13]. Yamamoto et al. [14] patented triazepine derivatives as inhibitors associated cytokine production.

Compounds containing triazepine skeletons possess attracted significantly interest due to their fascinating biological properties [15, 16]. Alternatively, condensed heterocyclic 1,2,4-triazepines were found to have salidiuretic and renal vasodilator, antioxidant as well as analgesic and immunomodulating activities [17-19]. Additionally, the fusion of pyrimidine along with triazepine moiety shows improved pharmacological consequences as antiviral, antifungal [20], and antidiabetic [21] and also acts as inhibitors [22] in cancer chemotherapy.

Similarly, fused triazepine derivatives having a bridgehead nitrogen atom within the molecule display interesting biological properties [23-26]. Different conventional techniques for the synthesis of fused triazepines are exemplified in the literature [27, 28] applying cycloaddition [15] and photochemical methods, but pyrimido[3',2':4,5]thieno[3,2:4,5]pyrimido[1,6-b][1,2,4]triazepines include the least investigated group one of many fused triazepines.

It was additionally reported [27] within the synthesis of 7-alkyl-5-aryl-1,2,4-triazepine-3-thiones utilizing hydrazinediium dithiocyanate and α,β-unsaturated ketones as starting materials. Viallefont and his co-workers reported on the methods used to prepare several derivatives of 1,2,4-triazepines disubstituted by oxo, thioxo, methoxy or methylthio groups [29]. Moreover, triazepines might serve as black toning agents for laminated photographs or as starting materials for the synthesis of thiazolo[3,2-b][1,2,4]triazepines, which are supposed to have immunomodulating activities [30-32].

A few methods for the preparation of 1,2,4-triazepine nucleus have been reported: these include synthetic strategies based on a nucleophile electrophile coupling [33] and methodologies relying on the thermal cycloaddition of 1-azirines to sym-tetrazines [34]. Our goal in this study is to report the chemistry of 1,2,4-triazepines including their synthesis, reactions and their applications as active biological agents.

2. Tautomerism

UV–vis Absorption spectra of the tautomeric system 3,5-dithio-2,7-dimethyl[1,2,4]triazepine in acetonitrile, were measured at room temperature different water volume percentages. The evaluation of the acquired measures to the measured allowed absorption transitions, applying ZINDO/S package, revealed the coexistence of all the tautomeric forms in aprotic polar solution with a high dominance of the dithione form. The measurements and ZINDO/S calculations indicated that: (i) in non-protic polar solvents, the most stable tautomeric forms seem to be the dithione form followed by the isomers **7** and **8**; (ii) when the solvent cage contains water, hydrogen bonding interactions shift the tautomeric equilibrium in the disadvantage of the dithione isomer. The supermolecule solute–water seems to be of 1: *n*-type; (iii) standing at ambient laboratory conditions in the dark favours the dithione tautomeric form, while indirect sunlight favours rather the monothiol and dithiol ones (Fig. 2) [35].

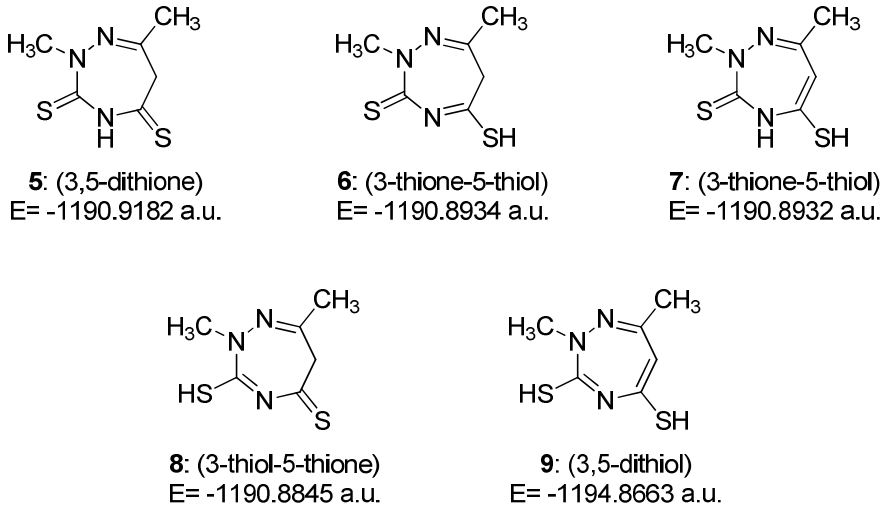


Figure 2. Tautomeric forms of 3,5-dithio-2,7-dimethyl-[1,2,4]-triazepine.

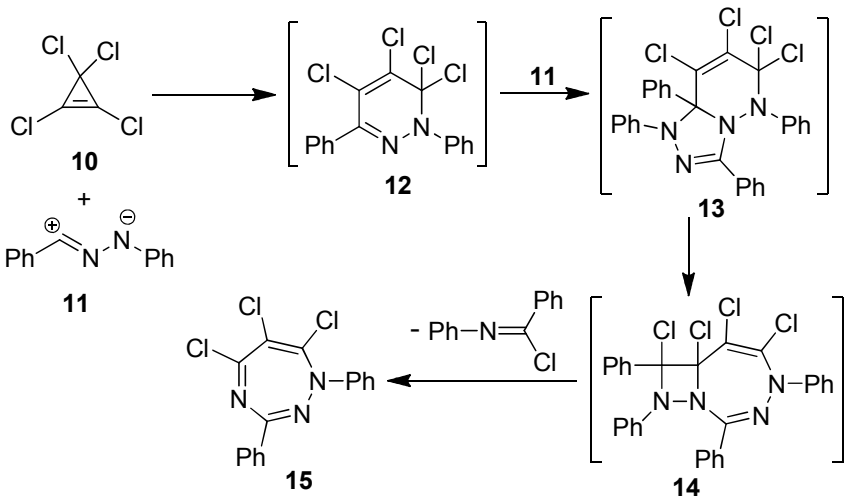
The most stable tautomer corresponds systematically to the oxo-thione structure, followed by the corresponding oxo-mercapto or thione-mercapto forms. The oxo-hydroxy and the thione-hydroxy forms were slightly less stable, while the hydroxy-mercapto tautomers are the least stable ones. The relative stabilities should change, however, in aqueous solution because the corresponding prototropic tautomerisms are accompanied by significant changes in the dipole moment of the system [36].

3. Synthesis

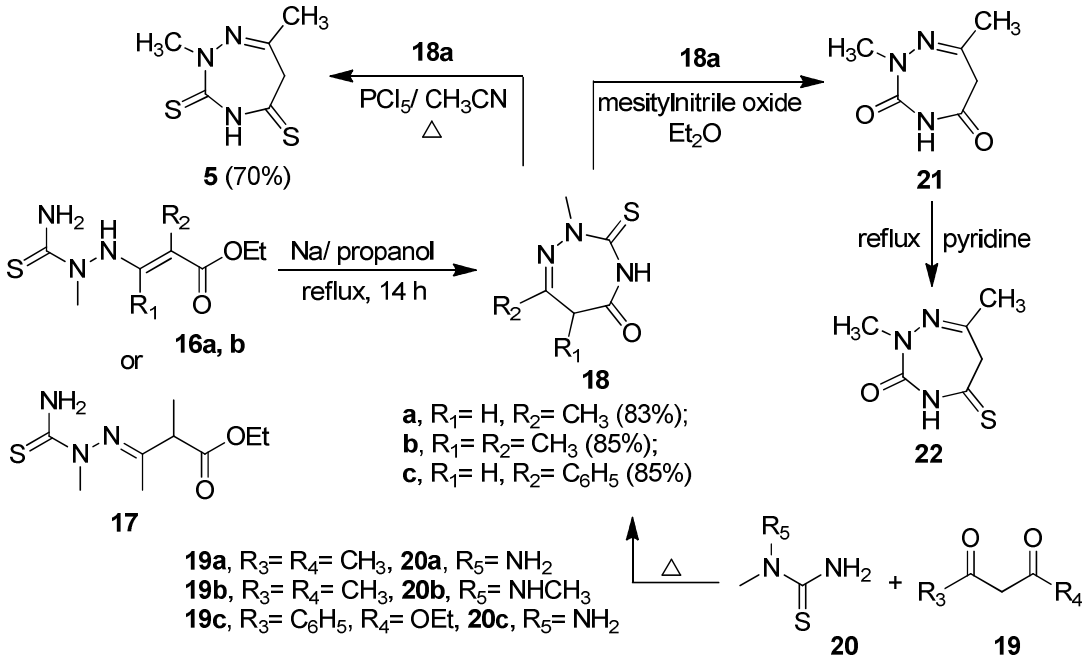
3.1. Synthesis of mono cyclic 1,2,4-triazepines

3.1.1. Synthesis of 1,2,4-triazepines

The reaction of tetrachloro-cyclopropene (**10**), [which functions as both a reactant and reaction solvent], with diphenyl nitrilimine (**11**), [generated *in situ* [37], from triethyl amine and N-phenyl benzenecarbohydrazonoyl chloride] at room temperature 1,2,4-triazepine **15** in 93% yield (Scheme 1) [33].



Scheme 1. Synthesis of 5,6,7-trichloro-1,3-diphenyl-1H-1,2,4-triazepine.

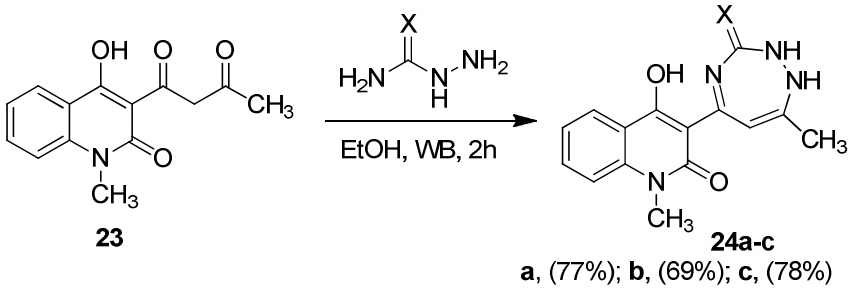


Scheme 2. Synthesis of 1,2,4-triazepine-3,5-dithione, 1,2,4-triazepine-3,5-dione and 5-thioxo-1,2,4-triazepin-3(4H)-one.

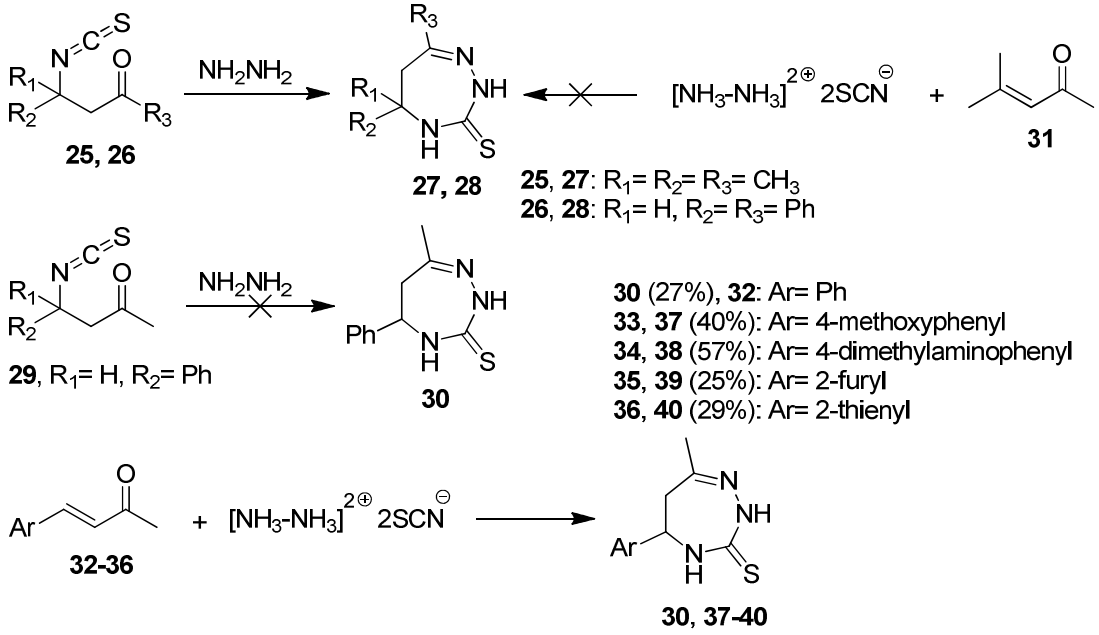
The preparation of 1,2,4-triazepine **18a** has been reported for the first time by Loss et al. [38] and refined by Hasnaoui et al. [5, 6, 29, 39]. 1,2,4-Triazepin-5(6H)-ones **18a-c** were prepared from the reaction of acrylate **16a**, **b** or **17**, respectively, in boiling propanol containing sodium. Also, heating of 1,3-dicarbonyl compounds **19** with cabothioamides **20** gave **18a-c** [40]. Dithione derivative **5** was obtained in 70% yield from heating of **18a** with phosphorus pentasulfide in acetonitrile [41], or

heating **18a** with tetraphosphorus decasulfide in acetonitrile [42]. The condensation of **18a** (**3S5O**) with mesitylnitrile oxide in dry diethyl ether yielded the corresponding 1,2,4-triazepin-3,5-dione **21** (**3O5O**). Treatment of the latter with phosphorus pentasulfide in refluxing dry pyridine afforded 1,2,4-triazepine (**3O5S**) **22** [5, 8] (Scheme 2).

The bifunctional amonia derivatives such as semicarbazide, thiosemicarbazide or aminoguanidine reacted with 1,2-dihydroquinolin-3-yl-butane-1,3-dione **23** in refluxing ethanol to furnish triazepinone, triazepinthione and iminotriazepine **24a-c**, respectively (Scheme 3) [43].



Scheme 3. Synthesis of triazepine derivatives.

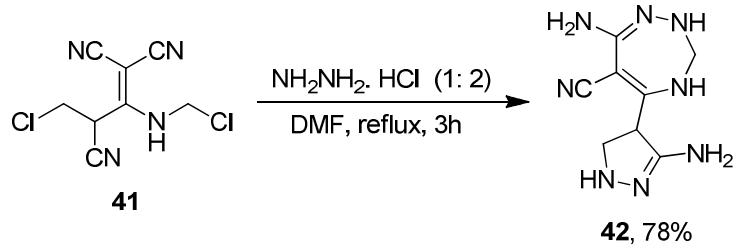


Scheme 4. Synthesis of triazepinethiones.

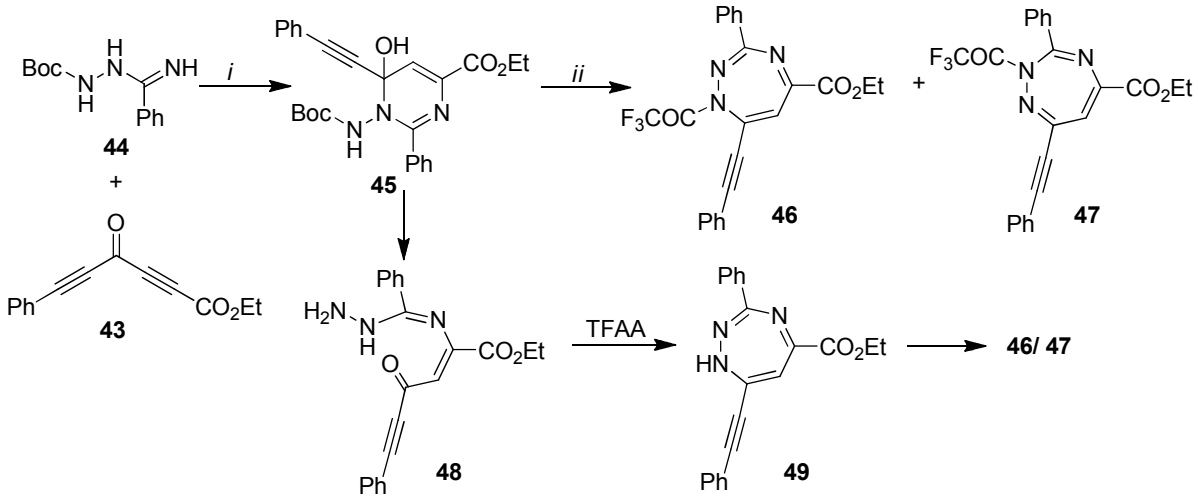
The cyclization of isothiocyanatopentan-2-one (**25**) to triazepinethione (**27**) with hydrazine hydrate was carried out under alkaline conditions or in refluxing benzene. The preparation of the 5,7-diphenyl analogue **28** from **26** was succeeded in

acidic medium, but, isothiocyanate **29** did not gave triazepine-thione **30** by the above methods. Compound **30** was synthesized from the reaction of benzylidene acetone (**32**) with hydrazinediium dithiocyanate in boiling dimethyl formamide. By the same procedure the α,β-unsaturated 3-arylketones **33-36** were cyclized with hydrazinediium dithiocyanate to give the alkyl-aryl substituted triazepinethiones **37-40**. However, compound **27** was not formed from mesityloxide (**31**) by the previous method (Scheme 4) [27].

Treatment of **41** with hydrazine hydrate in 1:2 mole ratio in refluxing DMF afforded the corresponding pyrazol-4-yl-1,2,4-triazepine **42** (Scheme 5) [44].



Scheme 5. Synthesis of 1,2,4-triazepine-6-carbonitrile.

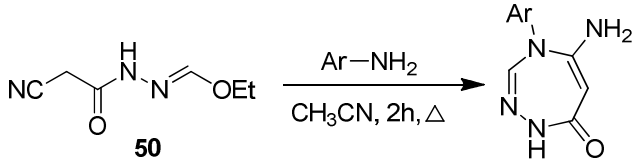


Scheme 6. Synthesis of 1,2,4-triazepine-5-carboxylates. (*i*) 1 mmol of **43**, 1.1 mmol of **44**, solvent. (*ii*) 1 mmol of **45**, DCM (5 mL), TFAA (5 mL), reflux, 3 h.

It was confirmed that the preparation of **46** and **47** could be carried out directly from **45** through a one-pot procedure. Therefore by coupling of **43**, **44** and following addition of trifluoroacetic acid (TFAA), trifluoro-acetyltriazepine was isolated in 82% yield as a 4:1 mixture of regioisomers **46** and **47**. The mechanism of conversion of **45** to **46** or **47** most likely involves ring opening and deprotection of **45** to the

corresponding ketone **48** which undergoes ring closure to the triazepine ring system **49** before acylation to **46** and **47** (Scheme 6) [45].

Heating of ethyl N'-(2-cyanoacetyl)formohydrazonate (**50**) with primary amines i.e. p-anisidine or p-fluoroaniline in acetonitrile gave N-substituted-1,2,4-triazepinones **51a**, **b** (Scheme 7) [46].

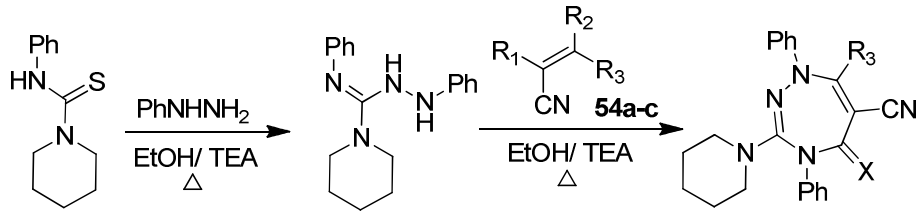


50 **51**

a, Ar= 4-OCH_3-C_6H_4 (81%)
b, Ar= 4-F-C_6H_4 (88%)

Scheme 7. Synthesis of 5-amino-4-substituted-1H-1,2,4-triazepin-7(4H)-ones.

Condensation of N-phenylpiperidine-1-carbothioamide (**52**) with phenyl hydrazine in boiling ethanol containing triethylamine (TEA) gave Schiff base **53**, which upon heating with arylidines **54a-c** in ethanol catalyzed by TEA gave 3-(piperidin-1-yl)-4,5-dihydro-1H-1,2,4-triazepines **55a-c**, respectively (Scheme 8) [47].



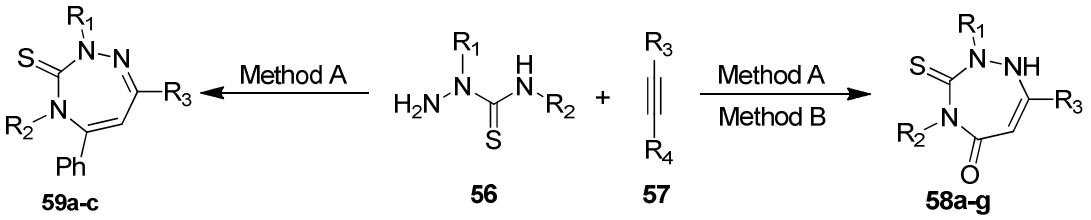
52 **53** **55a-c**

54a, R_1= COOEt, R_2= R_3= SCH_3
54b, R_1= CN, R_2= H, R_3= C_6H_5
54c, R_1= COOEt, R_2= H, R_3= C_6H_5

55a, X= O, R_3= SCH_3
55b, X= NH, R_3= C_6H_5
55c, X= O, R_3= C_6H_5

Scheme 8. Synthesis of 3-(piperidin-1-yl)-4,5-dihydro-1H-1,2,4-triazepines.

1,2,4-Triazepine-3-thiones **58** and **59** were obtained from the respective reactions of N-substituted-hydrazino carbothioamides **56** with dimethyl acetylenedicarboxylate and dibenzoyl acetylene **57** under prolonged reflux in acetic acid and/or DMF. However, the reaction of the starting materials in DMF under microwave irradiation afforded the same products in higher yields within a few minutes (Scheme 9) [48].



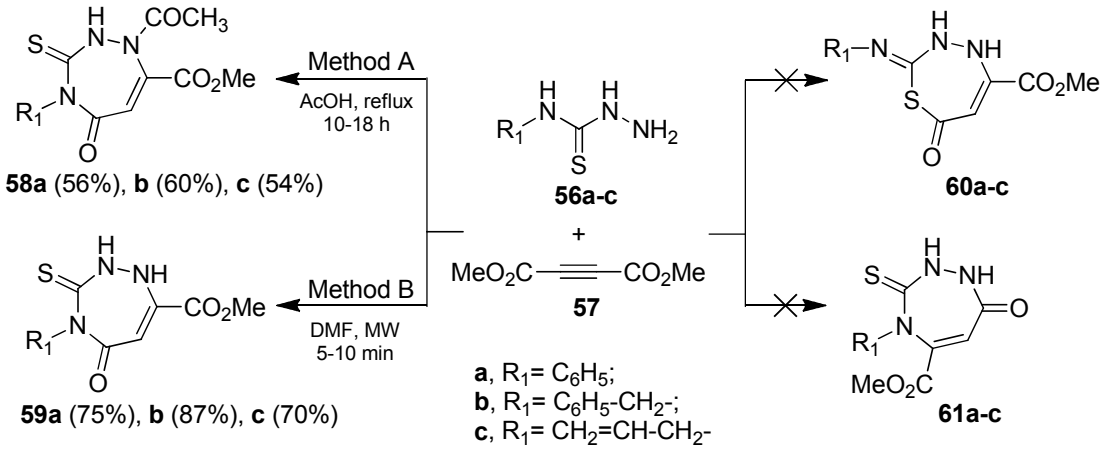
a, R_1= H, R_2= CH_2-CH=CH_2, R_3= R_4= COPh (92%)
b, R_1= H, R_2= CH_2Ph, R_3= R_4= COPh (82%)
c, R_1= H, R_2= Ph, R_3= R_4= COPh (98%)

a, R_1= H, R_2= CH_2-CH=CH_2, R_3= R_4= CO_2Me (A, 70%; B, 54%)
b, R_1= H, R_2= CH_2Ph, R_3= R_4= CO_2Me (A, 87%; B, 60%)
c, R_1= R_2= Ph, R_3= R_4= CO_2Me (A, 84%)
d, R_1= Ph, R_2= CH_2Ph, R_3= R_4= CO_2Me (A, 92%)
e, R_1= 4-Cl-C_6H_4, R_2= Ph, R_3= R_4= CO_2Me (A, 76%)
f, R_1= 4-CH_3-C_6H_4, R_2= CH_2Ph, R_3= R_4= CO_2Me (A, 96%)
g, R_1= H, R_2= Ph, R_3= R_4= CO_2Me (A, 75%; B, 56%)

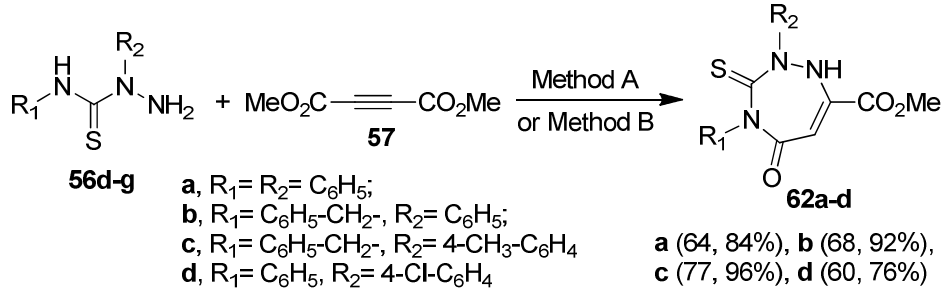
Method A: N,N-dimethyl-formamide, T= 100 °C , microwave irradiation
Method B: acetic acid, Time= 18h, Heating

Scheme 9. Synthesis of 1,2,4-triazepin-5(2H)-ones and 1,2,4-triazepine-3(4H)-thiones.

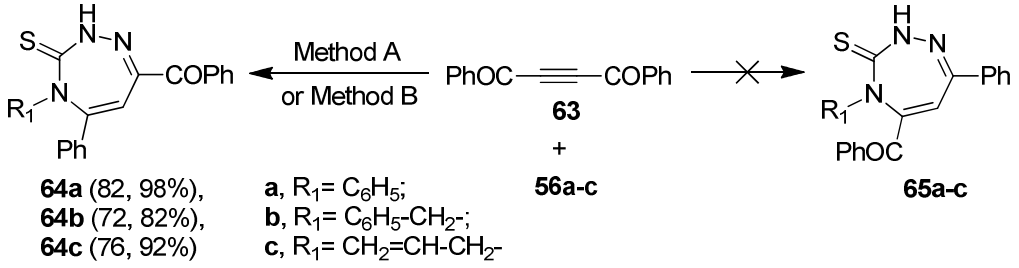
The synthesis of 1,2,4-triazepines **58a-c** was accomplished by refluxing equimolar amounts of N-aryl-hydrazino carbothioamides **56a-c** with dimethyl acetylene-dicarboxylate (**57**) in acetic acid (Method A). Unfortunately, on applying the same procedure using microwave irradiation in a small amount of DMF, the triazepines **58a-c** were not obtained. Instead, the reaction afforded, within a few minutes, the triazepines **59a-c** in 70-87% yields (Method B) (Scheme 10). Treatment of thiosemicarbazides **56d-g** with **57** in refluxing DMF or methanol (Method **A**) produced the corresponding 2-aryl-triazepine-4-substituted-2-thiones **62a-d** in good yields. However, the reaction of **56d-g** with **57** under microwave irradiation in a small amount of DMF produced **62a-d** (Method B) in better yields and in a shorter time than the conventional method (Method **A**) (Scheme 11). The reaction of **56a-c** with dibenzoyl acetylene (**63**) in acetic acid was failed, while in DMF afforded, after 24-48 hours of reflux, the triazepines **64a-c** (Method **A**). Compounds **64a-c**, could also be obtained from the reaction of **56a-c** with **63** under microwave irradiation in a small amount of DMF (Method B) for 10-20 minutes (Scheme 12) [48].



Scheme 10. Synthesis of 4-substituted-1,2,4-triazepine-3-thiones.

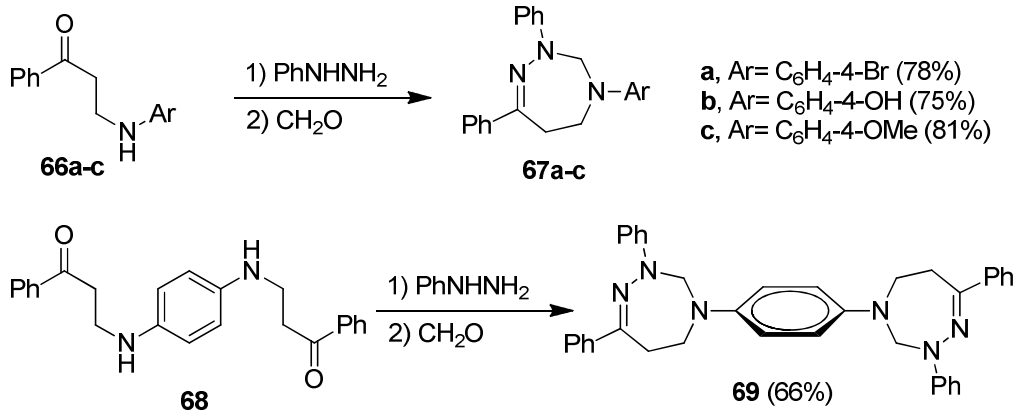


Scheme 11. Synthesis of 2,4-disubstituted-1,2,4-triazepine-3-thiones. Method **A**: MeOH or DMF, reflux 15-36 h; Method **B**: DMF, MW 10-20 min.



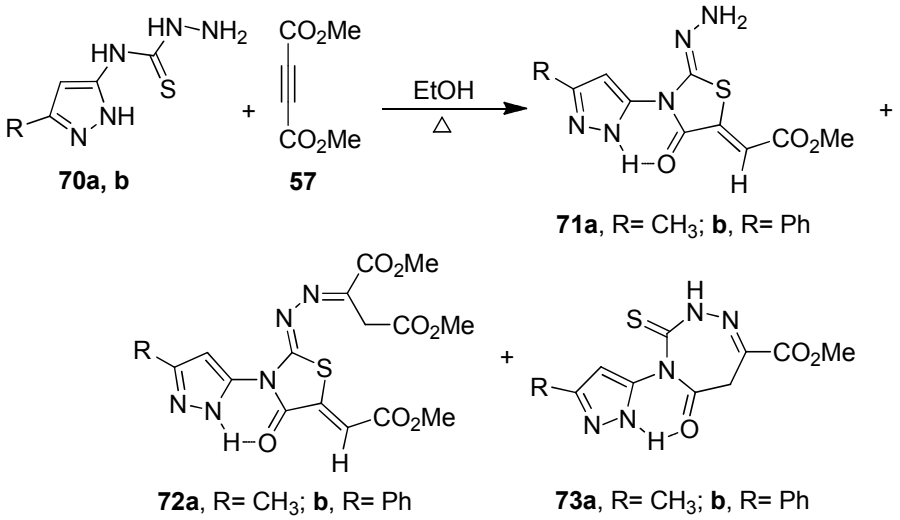
Scheme 12. Synthesis of 7-benzoyl-5-phenyl-2H-3-substituted-1,2,4-triazepine-3-thiones. Method A: DMF, reflux 24-48 h; Method B: DMF, MW 10-20 min.

A convenient route to the 2H-1,2,4-triazepine ring system starting with the ketonic *sec*-amine bases of the type **66**, which were treated with phenyl hydrazine and subsequently with formaldehyde under mild conditions to give 3,4,5,6-tetrahydro-4-aryl-2,7-diphenyl-2H-1,2,4-triazepines **67a-c**. A similar reaction takes place by treatment of diphenyl hydrazone of the bis-(*sec*-amine base) **68** with formaldehyde to yield 4,4'-[p-phenylenebis(3,4,5,6-tetrahydro-2,7-diphenyl-2H-1,2,4-triazepine)] (**69**) (Scheme 13) [49].



Scheme 13. Synthesis of N-aryl-1,2,4-triazepines **67a-c** and bis-1,2,4-triazepine **69**.

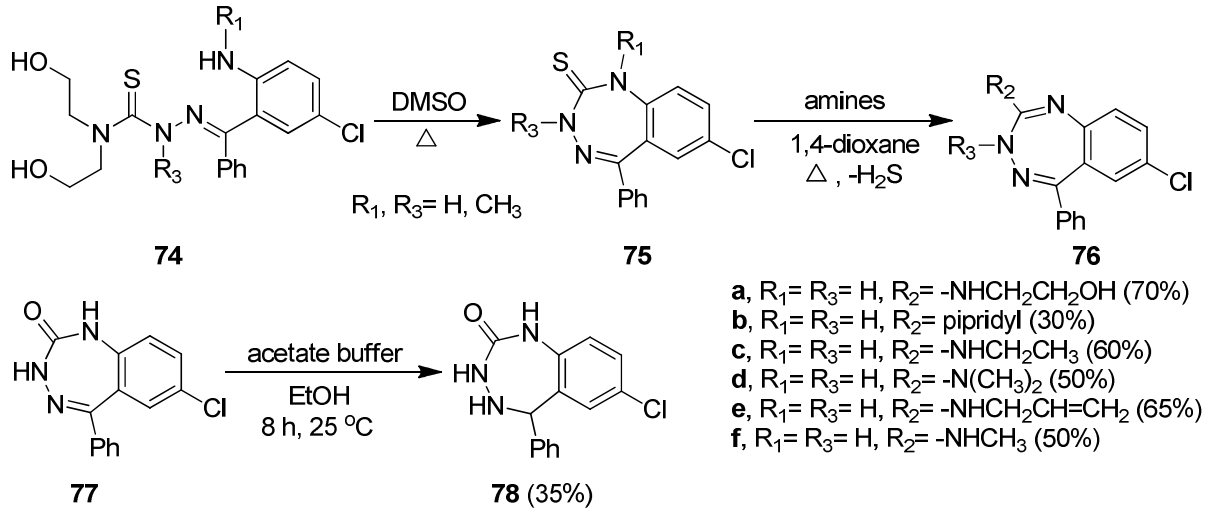
Cyclization of **70a**, **b** by intermolecular nucleophilic attack on the C≡C triple bond of **57** in ethanol at reflux for 3 h followed by heterocyclization gave the pyrazolylthiazolones **71a**, **b**, (3-substituted-1H-pyrazol-5-yl)thiazolidin-2-ylidene) hydrazinecarboxylates **72a**, **b** and pyrazolyl triazepinethiones **73a**, **b** with elimination of MeOH (Scheme 14) [50].



Scheme 14. Synthesis of 1,2,4-triazepine-7-carboxylate.

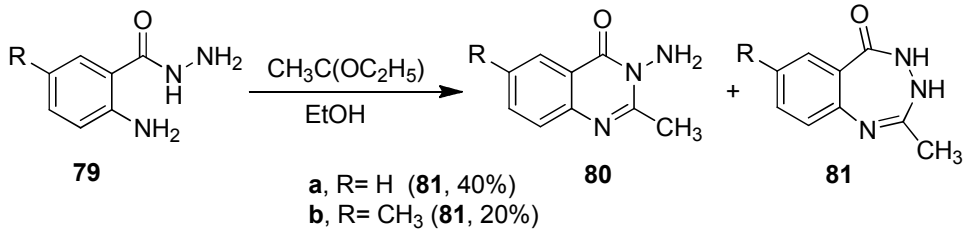
3.1.2. Synthesis of benzo and naphtho[1,2,4]triazepines

Cyclization of **74** in boiling dimethyl sulfoxide (DMSO) afforded benzo[e][1,2,4] triazepin-2(3H)-thiones **75**. Compounds **75** reacted in boiling 1,4-dioxane with various amines to give benzo[e][1,2,4]triazepines **76** [51, 52]. Reduction of **77** was carried out in ethanol at room temperature using acetate buffer to give 4,5-dihydro-1H-benzo[e][1,2,4]triazepin-2(3H)-one **78** (Scheme 15) [53].



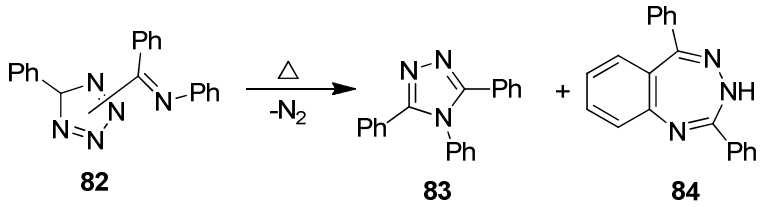
Scheme 15. Reduction of benzo[e][1,2,4]triazepin-2(3H)-one (thione) derivatives.

The reaction of 2-amino-5-substituted-benzohydrazides **79** with ethyl orthoacetate in ethanol, gave a mixture of two products, pyrimidines **80** and benzo[e][1,2,4]triazepin-5(4H)-ones **81** (Scheme 16) [54].



Scheme 16. Synthesis of benzo[e][1,2,4]triazepin-5(4H)-ones.

In 1960, the convenient method for the synthesis of 3,4,5-trisubstituted 1,2,4-triazoles from the reaction of 5-aryltetrazoles with imidoyl chlorides in boiling pyridine was proposed by Huisgen et al [55], for a long time it was assumed. By examination of this process, it was found that the reaction of 5-aryltetrazoles with N-arylbenzimidoyl chlorides in a dicholoromethane- water two phase system in the presence of tetrabutyl ammonium bromide resulted in the formation not only of 2-imidoyltetrazoles but also of isomeric 1-imidoyltetrazoles **82** and both 1-imidoyl- and 2-imidoyl-tetrazoles as E, Z-isomers. The reaction also, upon heating to 85-120 ^{o}C in the absence of solvent or in toluene, m-xylene or dioxane, 3H-1,2,4-benzotriazepines **84** were formed instead of 1,2,4-triazoles **83** (Scheme 17) [56, 57].



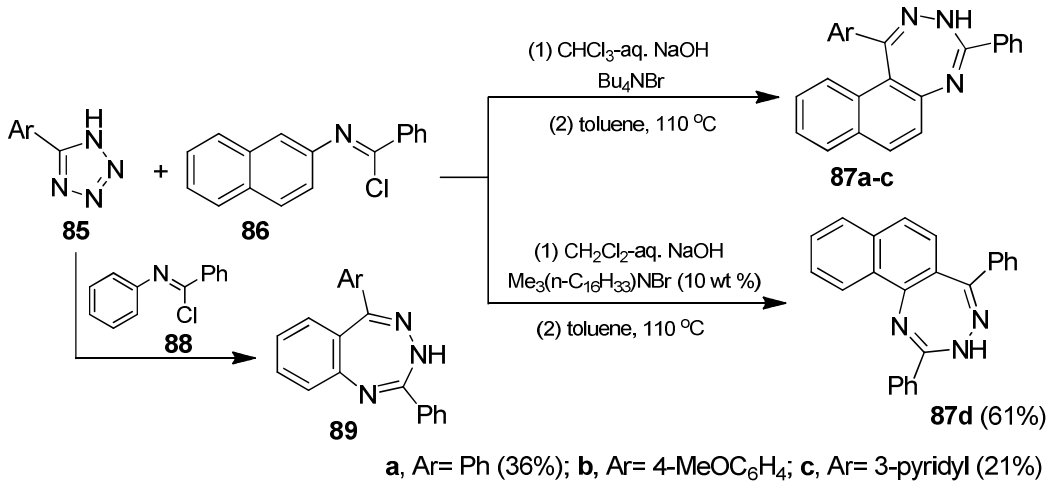
82 83 84

Solvent	Yield (%)	
	Triazole 83	Triazepine 84
--	--	33
Toluene	--	65
Dioxane	--	63
Pyridine	21	31
Benzonitrile	--	71
DMF	17	25

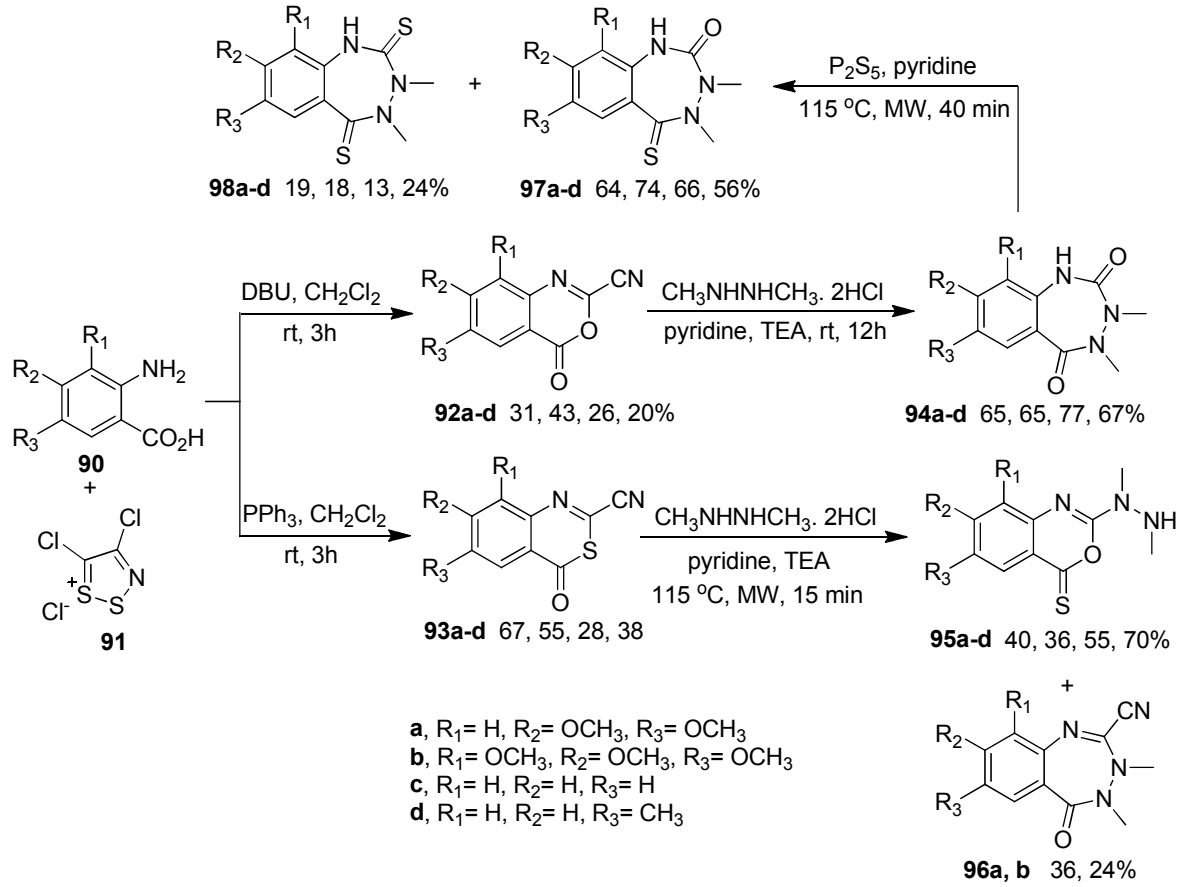
Scheme 17. Synthesis of 2,5-diphenyl-3H-benzo[e][1,2,4]triazepine.

Imidoylation of 5-phenyl- and 5-(3-pyridyl)tetrazoles **85** was performed under conditions of phase-transfer catalysis using tetrabutylammonium bromide or cetyl-(trimethyl)ammonium bromide. N-Imidoyltetrazoles thus obtained were heated in toluene at 110°C with **86** to give triazepines **87c** and **87d** [58] in 21 and 61% yield, respectively [59]. In addition, 5-(aryl)tetrazoles reacted with N-phenylbenzimidoyl chloride **88** to give 5-aryl-2-phenyl-3H-benzo[e][1,2,4]triazepines **89** (Scheme 18) [57].

The reaction of anthranilic acids **90** with Appel's salt **91** in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) or triphenylphosphine in methylene chloride and at room temperature, allowed the synthesis of benzo(thia)(xa)zine-2-carbonitriles **92a-d** and **93a-d**, respectively. Treatment of **92a-d** with 1,2-dimethylhydrazine dihydrochloride gave 1,3,4-benzotriazepine-2,5-diones **94a-d**. Condensation of 1,2-dimethylhydrazine with **93a**, **b** afforded two different products (**95a**, **b** and **96a**, **b**), whilst starting from compounds **93c**, **93d** gave only one product identified as the N-substituted benzoxazine-4-thiones **95c**, **d**. The 5-thioxobenzo[1,3,4]triazepin-2-ones **97a-d** were obtained as the major products, with a small amount of the corresponding dithiones **98** from the reaction of **94a-d** with phosphorus pentasulfide in pyridine (Scheme 19) [60].

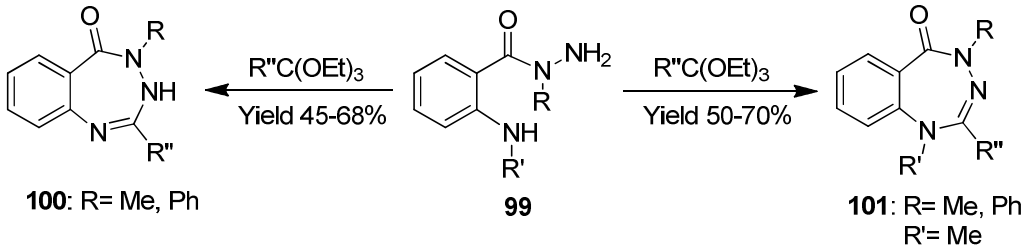


Scheme 18. Synthesis of naphtho[1,2,4]triazepines.

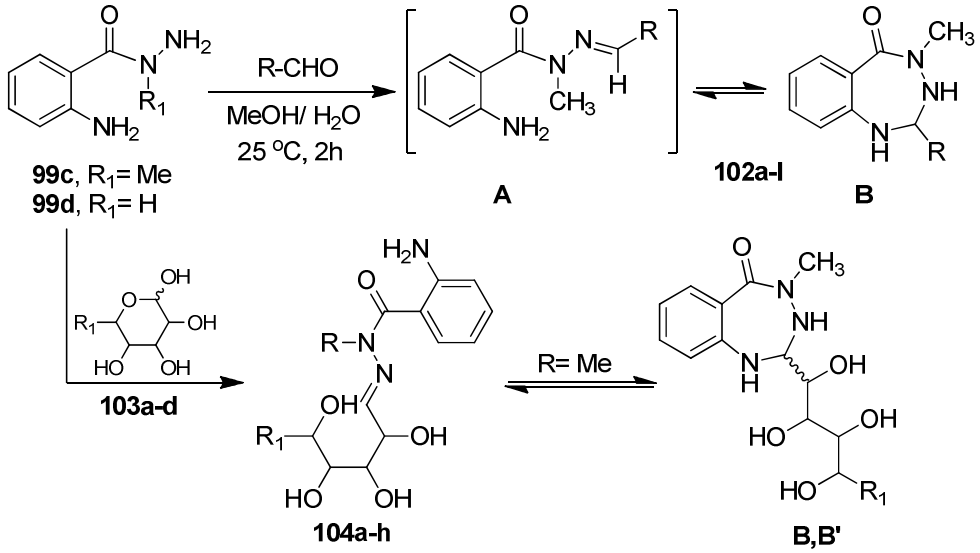


Scheme 19. Synthesis of benzo[e][1,2,4]triazepines.

Cyclization of substituted o-aminohydrazides **99** with ethyl orthoformates [61, 62], resulted in the synthesis of benzotriazepine derivatives **100** and **101** (Scheme 20) [63].



Scheme 20. Possible reactions between o-aminohydrazides and orthoformates.



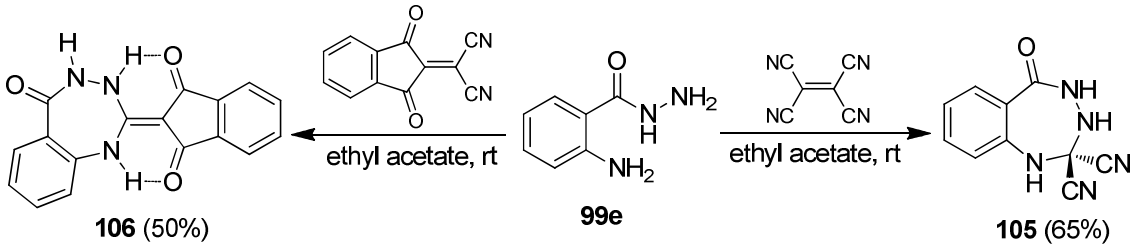
102a, R= CH_2Ph (70%); **b**, R= CH_2CH_2Ph (75%); **c**, R= Me (55%); **d**, R= Et (50%); **e**, R= Pr (60%); **f**, R= Bu (50%); **g**, R= i-Pr (60%); **h**, R= i-Bu (60%); **i**, R= 4-NO_2-C_6H_4 (90%); **j**, R= 3-NO_2-C_6H_4 (70%); **k**, R= Ph (60%); **l**, R= 4-MeO-C_6H_4 (70%)

Scheme 21. Synthesis of benzo-1,2,4-thiadiazepines. **104a-d** R = H, **e–h** R = Me; **99d** R = H; **103a**,**b** R_1 = H, **a** D-riboze, **b** L-arabinose; **c**,**d** R_1 = CH_2OH, **c** D-glucose, **d** D-mannose, **a**,**b**,**e**,**f** R_1 = H, **a**,**e** D-ribose, **b**,**f** L-arabinose; **c**,**d**,**g**,**h** R_1 = CH_2OH, **c**,**g** D-glucose, **d**,**h** D-mannose.

On interacting 2-mercaptobenzoylhydrazine with carbonyl compounds derivatives of benzo-1,2,4-thiadiazepine are formed [64-67]. The formation of cyclic reaction products assumes the intramolecular nucleophilic addition of NH_2 or SH groups of the aromatic ring to the C=N bond of the hydrazone fragment. Compounds **102a** and **102b** were obtained in 70 and 75% yield after briefly maintaining hydrazides **99c** and the appropriate aldehyde in aqueous alcoholic solution at 25 °C [68]. Continued research for the synthesis of benzo-1,2,4-thiadiazepines **102c-l** was reported using the same previous reaction conditions and reactants [69]. 2-Aminobenzoylhydrazones and N-(2-aminobenzoyl)-N-methylhydrazones **104a-h** are the products of condensation of aldoses, D-ribose **103a**, L-arabinose **103b**, D-glucose

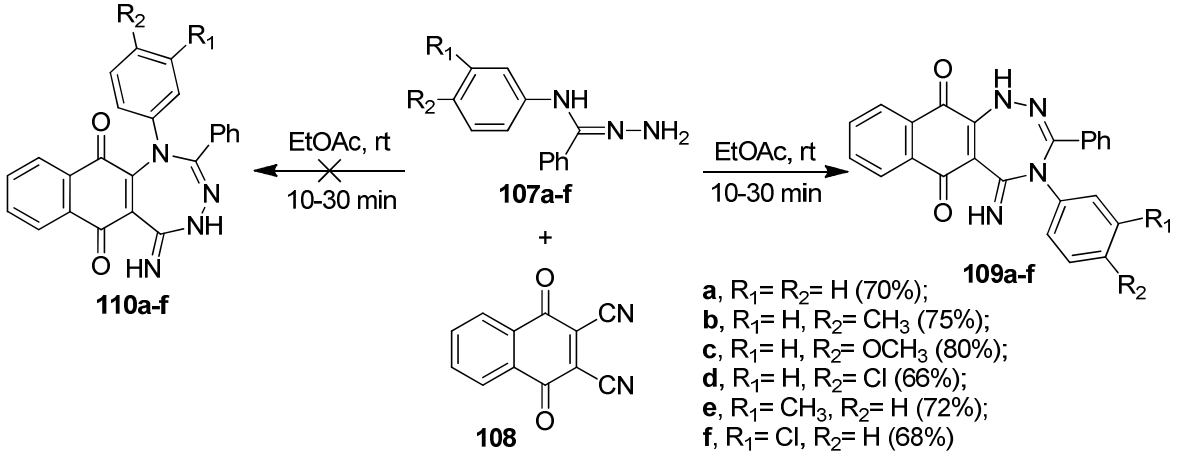
103c, and D-mannose **103d** with N-(2-aminobenzoyl)-N-methylhydrazine **99c** and 2-aminobenzoylhydrazine **99d**. Compounds **104a-h** are complex tautomeric mixtures capable of cyclization to give a seven-membered 1,3,4-triazepine form **B** (Scheme 21) [69].

2-Aminobenzohydrazide (**1**) reacted with tetracyanoethylene to give benzo[e] [1,2,4]triazepine-2,2(3H)-dicarbonitrile **105**. The product benzo[e][1,2,4]triazepin-2(5H)-ylidene)-1H-indene-1,3(2H)-dione **106** was obtained on treatment of **99e** with 2-dicyanomethylene-indan-1,3-dione at room temperature (Scheme 22) [70].



Scheme 22. Synthesis of 1,2,4-benzotriazepine derivatives.

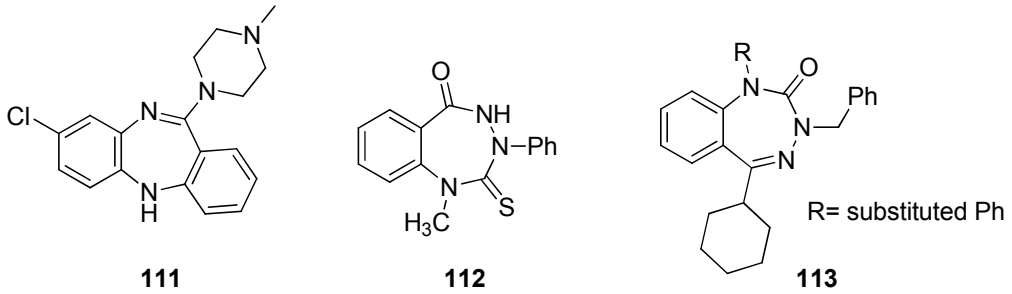
It was reported that the reaction between amidrazones **107a-f** with 1,4-dioxo-1,4-dihydronaphthalene-2,3-dicarbonitrile (**108**) in dry ethyl acetate under N_2 atmosphere in a few minutes yielded, after chromatographic purification and recrystallization, compounds **109a-f** (66-80%) (Scheme 23) [71].



Scheme 23. Synthesis of 4,5-dihydro-1H-naphtho[2,3-f][1,2,4]triazepine-6,11-dione.

Various benzene-fused triazepine and triazepinone derivatives were synthesized and shown that a variety of biological activities [72-74]. 2-Thioxobenzotriazepinone **112** was subjected to a ptosis test using clozapine (**111**) as

a reference drug to evaluate its antipsychotic activity. It was found that **112** has the same antipsychotic activity as the reference drug clozapine, but with lesser side effects [75]. On the other hand, 1,2,4-benzotriazepines **113** were found to be suitable as a nonpeptide parathyroid hormone-1 receptor (PTH1R) antagonist [76]. Recent 3D QSAR studies of various 1,2,4-benzotriazepines exhibited a cholecystokinin (CCK_2) receptor antagonist (Scheme 24) [77-79].



111 **112** **113**

Scheme 24. Structures of clozapine, 2-thioxobenzotriazepinone and benzotriazepine.

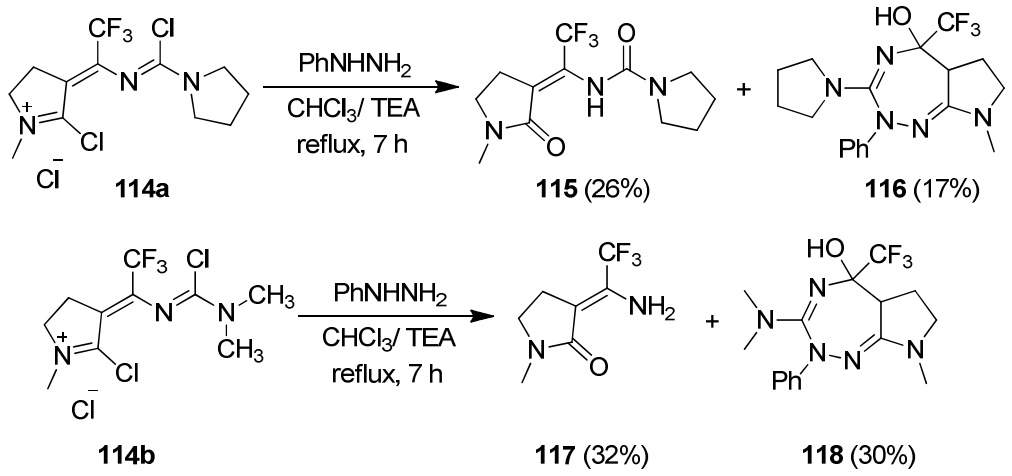
3.2. Synthesis of fused heterocyclic 1,2,4-triazepines

3.2.1. Synthesis of pyrrolo[1,2,4]triazepines

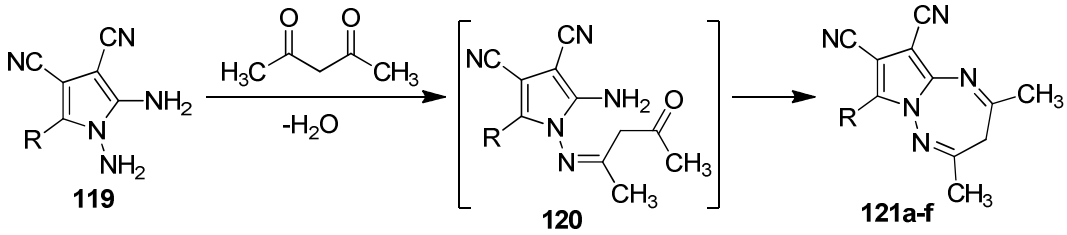
The condensation of **114a** or **114b** with phenyl hydrazine in refluxing chloroform containing triethylamine gave a mixture of two products in each reaction, 2,5,5a,6,7,8-hexahydropyrrolo[3,2-f][1,2,4]triazepin-5-ol derivatives **116** and **118** in low yields (Scheme 25) [80].

Pyrrolo[1,2-b][1,2,4]triazepines **121a-f** were synthesized by boiling pyrroles **119** in acetylacetone containing a catalytic amount of p-toluenesulfonic acid for 2-4 h (Scheme 26) [81].

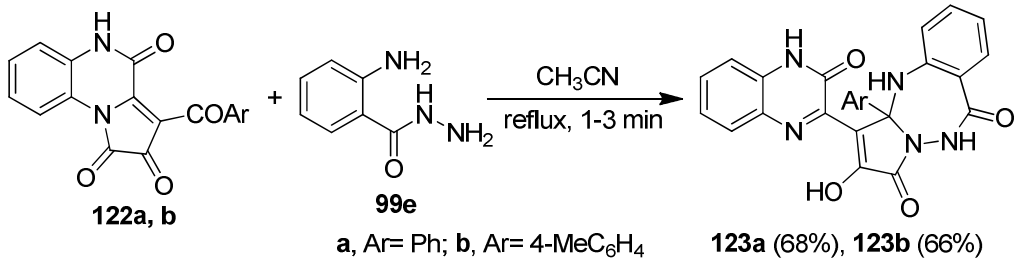
Interaction of 3-aroylpyrrolo[1,2-a]quinoxalines **122a**, **b** with benzoic acid hydrazide **99e** at a ratio of 1:1 by boiling in absolute acetonitrile for 1-3 min led to the formation of benzo[e]pyrrolo[1,2-b][1,2,4]triazepines **123a**, **b** (Scheme 27) [82, 83].



Scheme 25. Synthesis of 2,5,5a,6,7,8-hexahydropyrrolo[3,2-f][1,2,4]triazepin-5-ol derivatives.



Scheme 26. Synthesis of pyrrolo[1,2-b][1,2,4]triazepines. **a**, R= Me (88%); **b**, R= Pr (50%); **c**, R= C_5H_{11} (55%); **d**, R= Ph (52%); **e**, R= 4-MeO-C_6H_4 (77%); **f**, R= 2-furyl (22%)

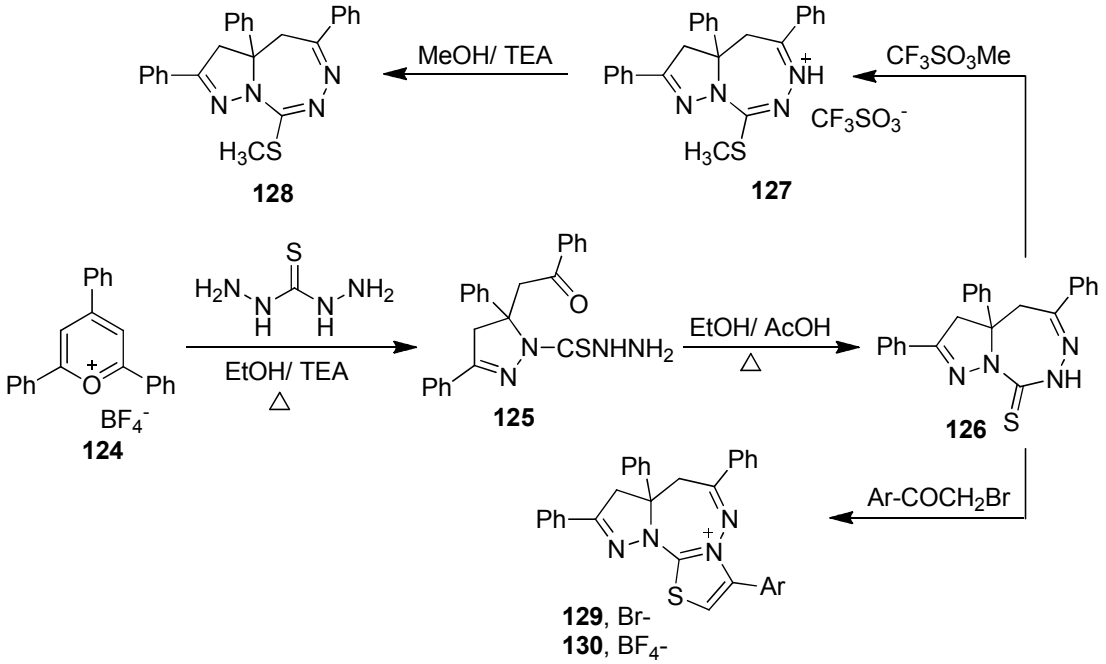


Scheme 27. Synthesis of benzo[e]pyrrolo[1,2-b][1,2,4]triazepine-3,6(5H)-diones.

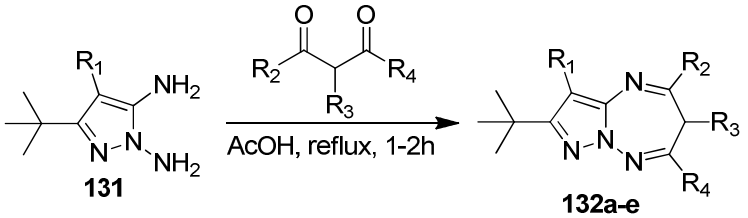
3.2.2. Synthesis of pyrazolo[1,2,4]triazepines

The reaction of 2,4,6-triphenylpyrylium salt (**124**) with thiocarbohydrazide in ethanol, in the presence of triethylamine gave 2-pyrazolines **125** (85%) which undergo cyclization in boiling ethanol, in the presence of acetic acid to yield pyrazolo[2,3-d]-1,2,4-triazepine **126** (89%). Compound **126** undergoes *S*-methylation on reaction with methyl trifluoromethanesulfonate, in boiling dry dichloromethane,

to give pyrazolo[2,3-d]-1,2,4-triazepin-7-ium trifluoromethanesulfonate **127** as crystalline solid in 86% yield. When compound **127** was treated with triethylamine or potassium hydroxide in methanolic solution at reflux temperature for 2 h, the methylthio derivative **128** was obtained (50%). Reaction of **126** with phenacyl bromides gave pyrazolo[2,3-d]-1,2,4-triazepin-4-iums **129** and **130** in high yields (76-87%) (Scheme 28) [84].



Scheme 28. Synthesis of pyrazolo[1,2,4]triazepines.



a, R_1= R_3= H, R_2= R_4= Me (39%);
b, R_1= R_3= H, R_2= Me, R_4= OEt (44%)
c, R_1= H, R_2= R_3= Me, R_4= OEt (55%);
d, R_1= H, R_2= n-propyl, R_3= H, R_4= OEt (42%);
e, R_1= Cl, R_2= Me, R_3= H, R_4= OEt (81%)

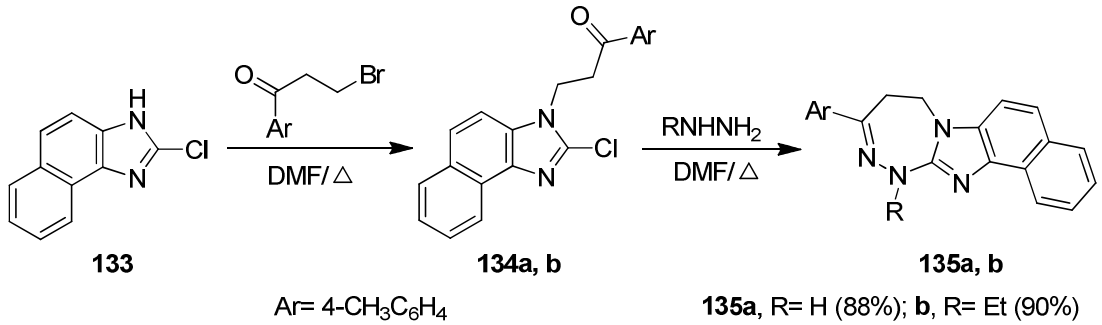
Scheme 29. Synthesis of pyrazolo[1,5-b][1,2,4]triazepines.

Reaction of **131** with acetylacetone in refluxing acetic acid provided the first example of the pyrazolo[1,5-b]1,2,4-triazepine system **132a**. β-Ketoesters also reacted with the diaminopyrazoles **131** in refluxing acetic acid to give pyrazolo[1,5-b]1,2,4-triazepin-2-ones **132b-e**. Compounds **132b-d** were prepared in 42-55% yield

using the appropriate ketoesters, though ethyl benzoylacetate and ethyl pivaloylacetate failed to react, presumably for electronic and steric reasons respectively. When the chloropyrazole **131** was employed, the yield of **132e** was almost doubled relative to its unsubstituted analogues (Scheme 29) [85].

3.2.3. Synthesis of imidazo[1,2,4]triazepines

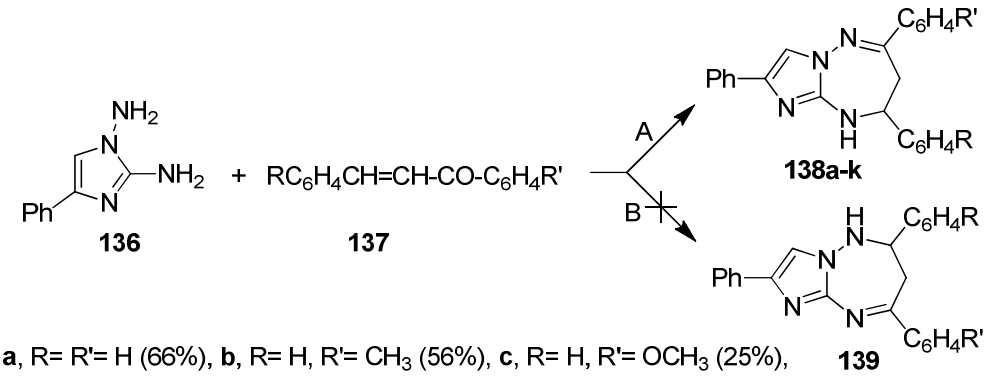
2-Chloro-3-substituted-3H-naphtho[1,2-d]imidazoles **134a**, **b** were prepared from the reaction of **133** with 3-bromo-1-(p-tolyl)propan-1-one in boiling dimethyl formamide. Compounds **134a**, **b** reacted with hydrazine hydrate and ethylhydrazine in boiling dimethyl formamide to give naphtho[1',2':4,5]imidazo[2,1-c][1,2,4] triazepines **135a**, **b** in excellent yields (Scheme 30) [86].



Scheme 30. Synthesis of naphtho[1',2':4,5]imidazo[2,1-c][1,2,4]triazepines.

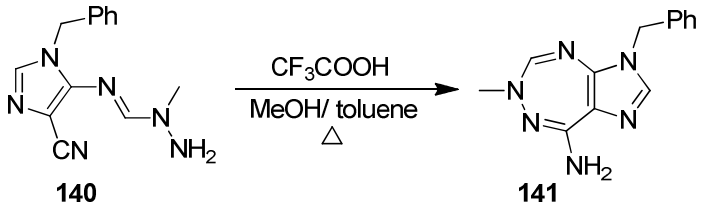
The conditions for the synthesis of 2,4-diaryl-1H-2,3-dihydro-l,5-benzodiazepines was reported [87] on the basis of o-phenylenediamine and chalcones; the reaction was catalyzed by tertiary alkylamines in alcohol. The reaction of 1,2-diamino-4-phenylimidazole (**136**) with chalcones **137** afforded imidazo[l,2-b]-1,2,4-triazepines **138a-k** using the same previous conditions; the yields of the desired products averaged 15-20% lower than in the case of the reaction of chalcones with o-phenylenediamine, probably because of the decreased reactivity of starting diamine **136** (Scheme 31) [88].

Afshar et al [89], have reported the cycloaddition reaction of N''-(1-benzyl-4-cyano-1H-imidazol-5-yl)-N-methylformimidohydrazide (**140**) in trifluoroacetic acid in refluxing methanol and toluene gave 3,6-dihydroimidazo[4,5-e][1,2,4]triazepin-8-amine **141** (Scheme 32).

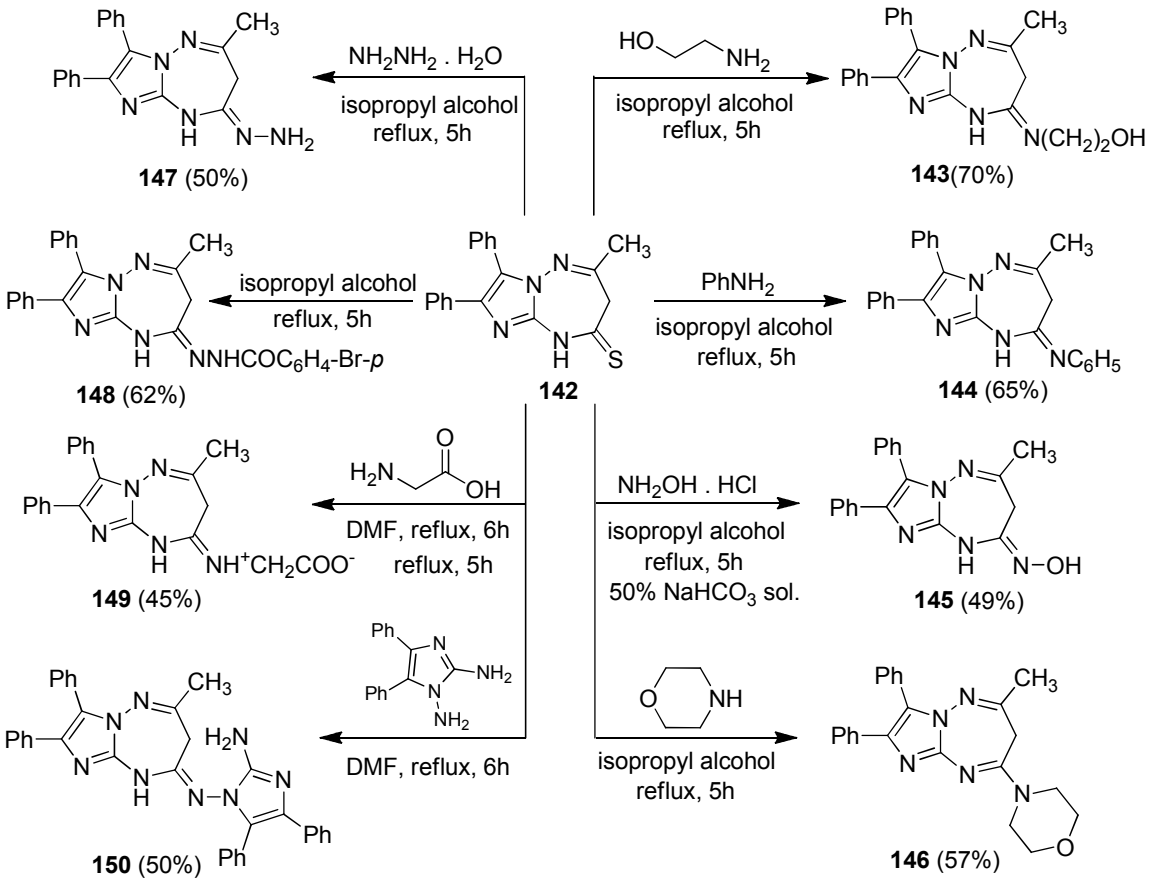


a, R= R'= H (66%), **b**, R= H, R'= CH_3 (56%), **c**, R= H, R'= OCH_3 (25%), **d**, R= H, R'= Cl (53%), **e**, R= H, R'= Br (64%), **f**, R= H, R'= NO_2 (62%), **g**, R= H, R'= 2-thienyl (48%), **h**, R= H, R'= styryl (54%), **i**, R= 2-OH, R'= H (73%), **j**, R= 4-OCH_3, R'= H (28%), **k**, R= 4-Cl, R'= H (50%)

Scheme 31. Synthesis of imidazo[1,2,4]triazepines.



Scheme 32. Synthesis of imidazo[4,5-e][1,2,4]triazepin-8-amine.



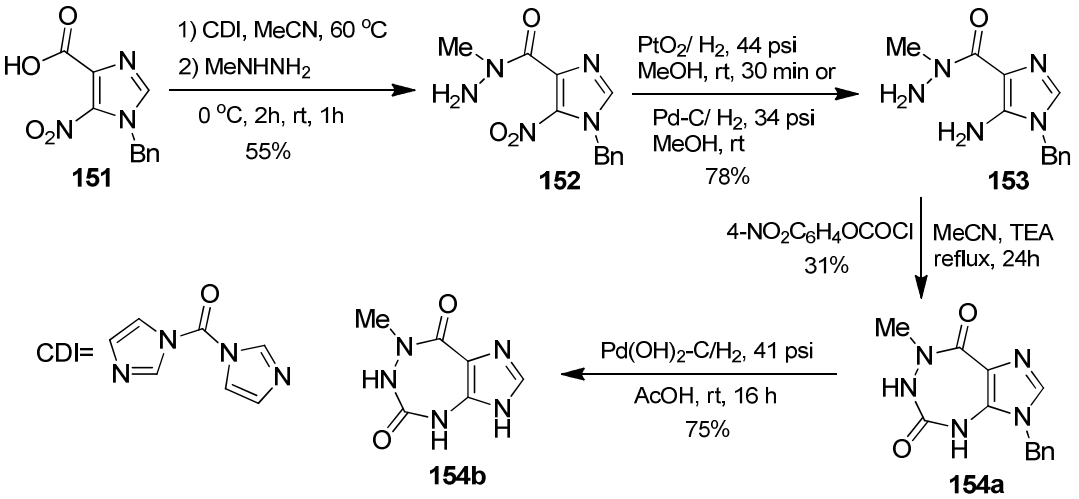
Scheme 33. Synthesis of imidazo[1,2,4]triazepines.

A series of 4-imino-substituted 2-methyl-7,8-diphenyl-5H-imidazo[l,2-b]-l,2,4-triazepines **143-150** were synthesized by replacing the *S* atom in 2-methyl-7,8-diphenyl-5H-imidazo[l,2-b]-l,2,4-triazepine-4-thione **142** [90] by the action of nitrogen-containing nucleophiles. The reaction of thione **142** with monoethanolamine, aniline, hydroxyiamine, morpholine, hydrazine hydrate, or p-bromobenzoic acid hydrazide was proceeded in refluxing alcohols, while the substitution with aminoacetic acid and 1,2-diamino-4,5-diphenylimidazole was observed when it was carried out in refluxing DMF (Scheme 33) [91].

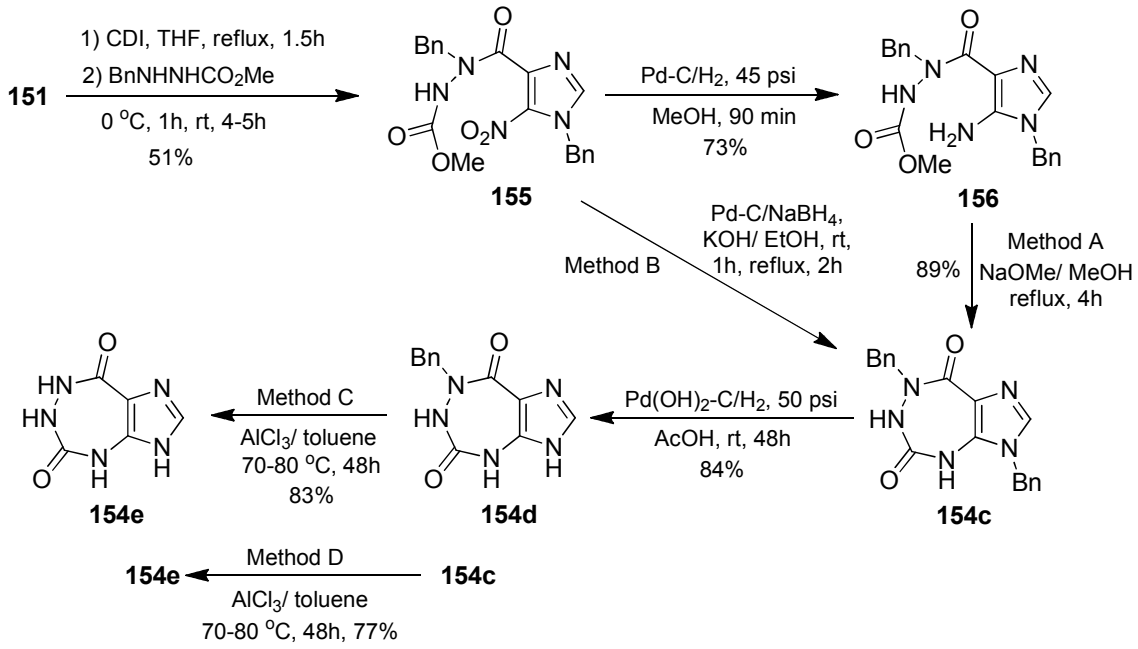
Compound **153** was prepared from **151** by the reaction with 1,1'-carbonyl-diimidazole (CDI)/methyl hydrazine (to give **152**), followed by hydrogenation over platinum oxide. Ring-closure of **153** to **154a** was effected by reaction with p-nitrophenyl chloroformate, in the presence of triethyl amine. Compound **154a** was debenzylated by reaction with palladium hydroxide/ hydrogen in glacial acetic acid to give **154b** (Scheme 34) [92]. Compound **155** could be obtained by reaction of **151** with CDI and methyl N^2-benzyl carbazate. Sequential reaction of **155** involving reduction over palladium (to give **156**), cyclization with sodium methoxide/ methanol (to give **154c**) and debenzylation by hydrogenation over palladium hydroxide gave the monodebenzylated product **154d**. reduction and ring- closure of **155** to form **154c** was also accomplished in a one-pot reaction, employing palladium on carbon/ sodium hydroxide/ potassium hydroxide in ethanol. Further debenzylation of **154d** to **154e** by catalytic hydrogenation at elevated temperatures or by treatment with sodium naphthalide or boron tribromide/ xylene was not successful. Debenzylation was achieved by heating **154d** with aluminum chloride in toluene. With the latter reagent, **154e** could also be obtained directly from **154c** (Scheme 35) [92].

1,5-Diamino-4-cyanoimidazole (**157**) reacted with β-diketones in alcohol containing perchloric acid or sodium methylate to give imidazo[1,5-b][1,2,4] triazepines **158a-c**. Heating of **157** with ethyl 3-oxobutanoate in sodium methylate in methanol gave sodium 9-cyano-4-methyl-3H-imidazo[1,5-b][1,2,4]triazepin-2-olate (**159**). On the other hand, the reaction of **157** with 1-phenylbutane-1,3-dione gave a

mixture of two products, imidazo[1,5-b][1,2,4]triazepines **160** and **161** (Scheme 36) [93].



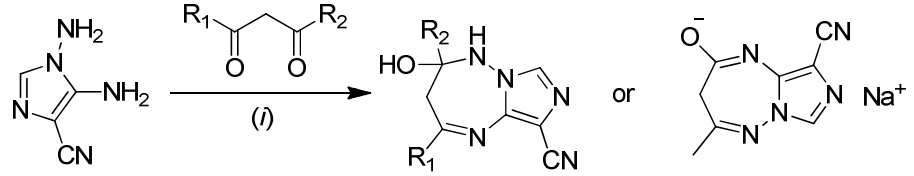
Scheme 34. Synthesis of imidazo[4,5-e][1,2,4]triazepine-5,8(3H,4H)-dione.



Scheme 35. Synthesis of 6,7-dihydroimidazo[4,5-e][1,2,4]triazepine-5,8(3H,4H)-dione.

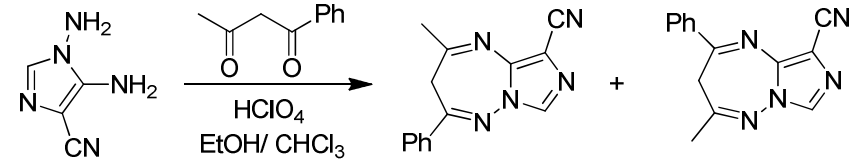
Accordingly, imidazo[1,2-b]-l,2,4-triazepine **162** exists predominantly in the hydrazone form. A compound with such a structure has the possibility of reacting with nucleophiles at the amino group and N_5 with annelation to the triazepine unit of the bicycle **162**. When the hydrazine **162** was boiled in formic acid (2 h) or in

triethoxymethane, 2-methyl-9,10-diphenylimidazo[1,2-b]-l,2,4-triazolo-[4,3-d]-l,2,4-triazepine **163** was formed, while when equimolar amounts of **162** and cyanogen bromide were boiled in methanol (**163**), its 6-amino derivative **3** was formed. 4H-2,6-Dimethyl-(**165**) and 4H-2-methyl-6-(β-carboxyethyl)-9,10-diphenylimidazo-[1,2-b]1,2,4-triazino[4,3-d]triazepin-7-ones (**166**) were produced by reaction of the hydrazine **162** with pyruvic or α-ketoglutaric acid (mole ratio 1:1.5) in boiling isopropanol (5 h) (Scheme 37) [94].



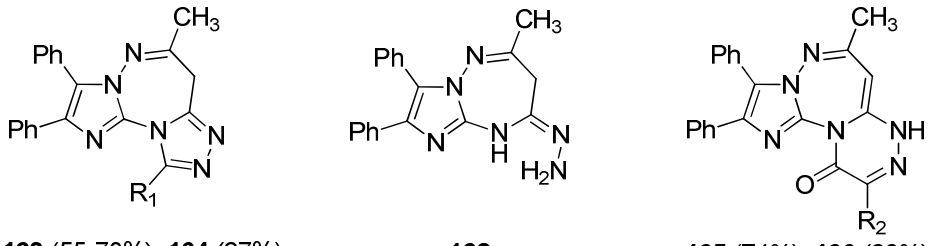
157 **158a-c** **159** (42%)

158a, R_1= CH_3, R_2= CF_3 (63%); **b**, R_1= CH_3, R_2= OEt (61%); **c**, R_1= CH_3, R_2= CH_3 (77%)



157 **160** **161**

Scheme 36. Synthesis of 3H-imidazo[1,5-b][1,2,4]triazepines. Reagents and conditions: (*i*) **158a**, perchloric acid in ethanol, 504 h; **158b**, sodium methylate in ethanol, rt, 10 d, then reflux, 2 h; **158c**, perchloric acid in methanol, 48 h; **3**, sodium methylate in methanol, 6 h, heating.



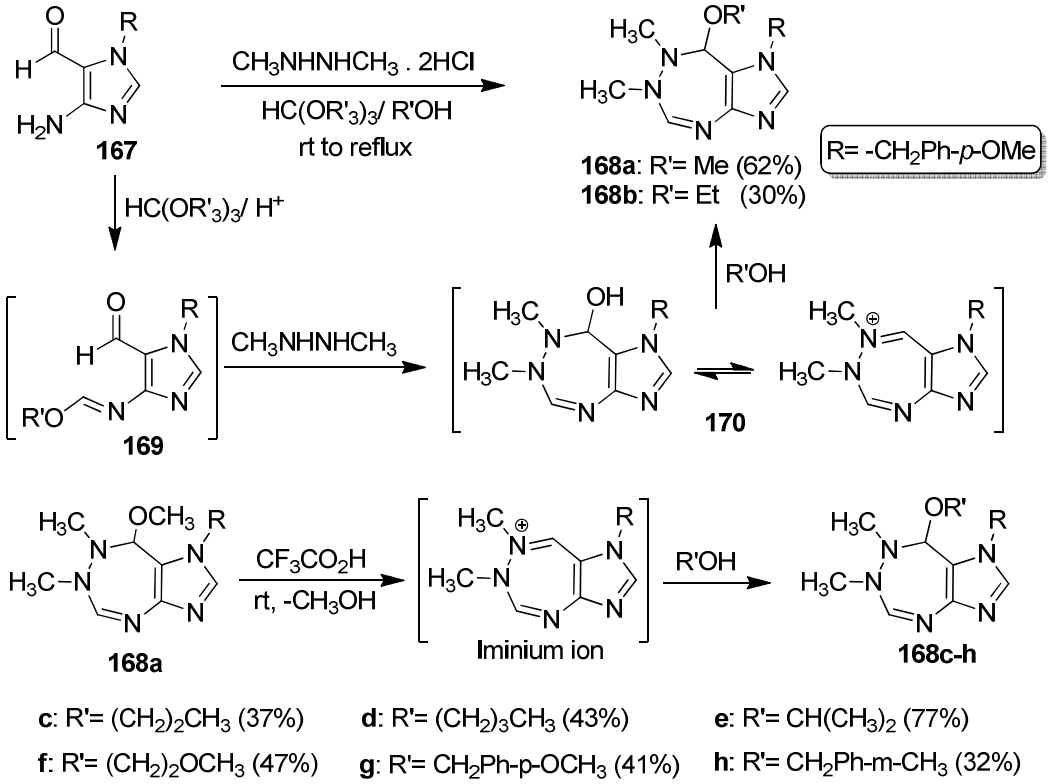
163 (55-70%), **164** (67%) **162** **165** (74%), **166** (68%)

R_1= H, NH_2; R_2= Me, $(CH_2)_2COOH$

Scheme 37. Structures of imidazo[1,2,4]triazepines.

A series of analogues **168a-h** containing the imidazo[4,5-e][1,2,4]triazepine ring system has been synthesized from the reaction of **167** with dimethylhydrazinium hydrochloride in refluxing alcohol. Compounds **168a-h** were evaluated in vitro against a mammalian adenosine deaminase for inhibitory activity. Compounds **168a**

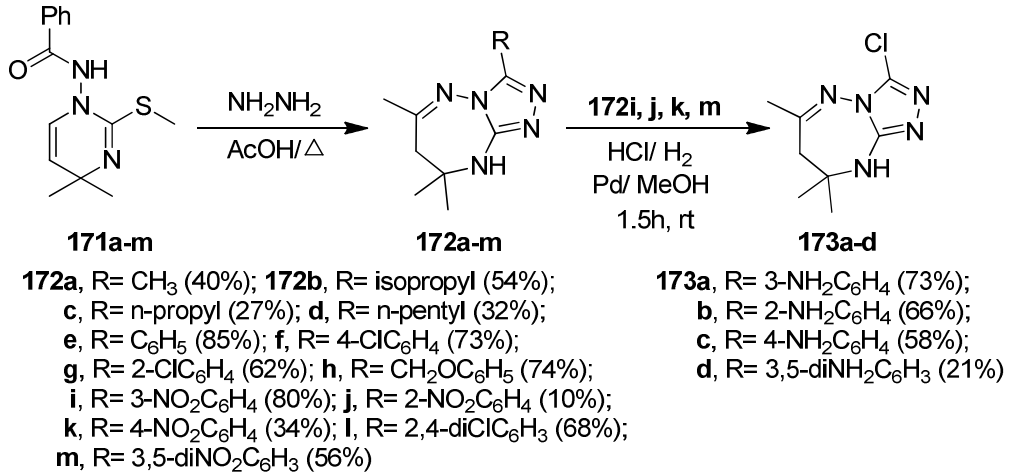
and **168b** [95] were synthesized in five steps starting from 4-nitroimidazole, others were derived from **168a** through simple exchange reactions with the appropriate alcohols. The observed kinetics profiles and K_i values suggest that the target compounds are competitive inhibitors that bind 6-9 orders of magnitude less tightly to the enzyme. Compounds **168c** and **168d** were the most active in the series with K_i's ranging from 12 to 15 μM (Scheme 38) [96].



Scheme 38. Synthesis of imidazo[4,5-e][1,2,4]triazepines.

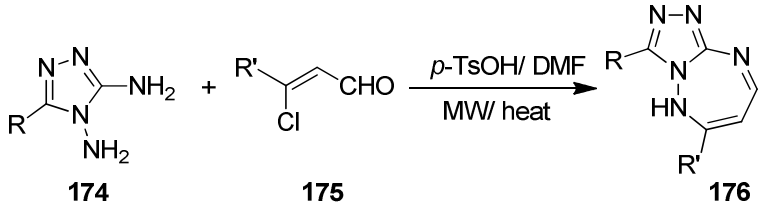
3.2.4. Synthesis of triazolo[1,2,4]triazepines

Cyclization reaction of N-(4,4-dimethyl-2-(methylthio)pyrimidin-1(4H)-yl)aryl or alkyl –amide derivatives **171a-m** with hydrazine hydrate in acetic acid under reflux gave the corresponding 3-substituted-6,8,8-trimethyl-8,9-dihydro-7H-[1,2,4]triazolo-[4,3-b][1,2,4]triazepines **172a-m**. Consequently, reduction of nitro derivatives **172i**, **172j**, **172k**, and **172m** in methanol containing hydrochloric acid under hydrogen / palladium catalyst led to the amino derivatives **173a-d**, respectively (Scheme 39) [97].



Scheme 39. Synthesis of 3-substituted-6,8,8-trimethyl-8,9-dihydro-7H-[1,2,4] triazolo[4,3-b][1,2,4]triazepines.

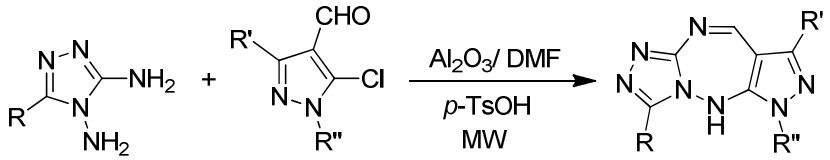
Condensation of 5-aryl-3,4-diamino-1,2,4-triazoles (**174**) with β-chloro-cinnamaldehydes **175** in N,N-dimethylformamide and p-TsOH, followed by cyclization gave 3,6-diaryl-5H-[1,2,4]triazolo[4,3-b][1,2,4]triazepines **176a-j** (Scheme 40) [98].



Cpd. No.	R	R'	Yield (%)	
			Microwave (MW)	Oil-bath heating at 80 °C
a	C_6H_5	(4-F)C_6H_4	70 [a]	69 [a]
b	2-ClC_6H_4	(4-Br)C_6H_4	76 [b]	75 [b]
c	4-ClC_6H_4	(4-F)C_6H_4	71 [a]	70 [a]
d	$CH_2C_6H_5$	(4-Cl)C_6H_4	80 [a]	85 [a]
e	(4-NO_2)C_6H_4	(4-Cl)C_6H_4	78 [b]	70 [b]
f	C_6H_5	(4-Br)C_6H_4	82 [a]	85 [a]
g	2-ClC_6H_4	(4-NO_2)C_6H_4	70 [a]	62 [a]
h	$CH_2C_6H_5$	(4-NO_2)C_6H_4	63 [a]	61 [a]
i	(4-NO_2)C_6H_4	(4-Br)C_6H_4	68 [a]	65 [a]
j	C_6H_5	(4-NO_2)C_6H_4	92 [a]	60 [a]

Scheme 40. Synthesis of triazolo[4,3-b][1,2,4]triazepines. [a] Products were purified by crystallization from ethyl acetate. [b] Products were purified by passing through column of alumina and elution with ethyl acetate: pet. ether.

One-pot reaction of 5-aryl-3,4-diamino-1,2,4-triazoles (**174**) and (1-substituted-3-alkyl/aryl-5-chloropyrazol-4-yl)formaldehydes (**177**) in the presence of N,N-dimethylformamide as an energy transfer medium, p-TsOH as catalyst and basic alumina as solid support under microwave irradiation gave 1-substitued-8-aryl-3-alkyl/aryl-4H-pyrazolo[4,5-f][1,2,4]triazolo[4,3-b][1,2,4]triazepines **178a-j** (Scheme 41). Compounds **178a-c**, **178e**, **178h** and **178j** showed moderate activity against *Penicillium* species and *Rhizopus* species, while low activity was observed against *A. niger* and *A. flavus*. Compounds **178d**, **178f**, **178g** and **178i** showed excellent activity against *A. niger* and *Penicillium* species at 500 μg as well as 1000 μg concentrations whereas, these compounds showed good to moderate activity against *A. flavus* and *Rhizopus* species [15].



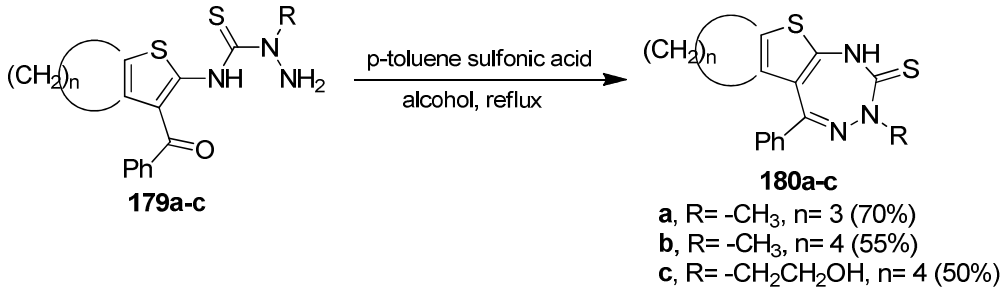
174 **177** **178**

Compound	R	R'	R''	Time (min)	Yield (%)
a	C_6H_5	CH_3	H	11	62
b	4-ClC_6H_4	CH_3	H	4	72
c	C_6H_5	C_6H_5	C_6H_5	20	68
d	$CH_2C_6H_5$	4-BrC_6H_4	C_6H_5	23	74
e	4-ClC_6H_4	4-BrC_6H_4	C_6H_5	17	64
f	(4-NO_2)C_6H_4	4-BrC_6H_4	C_6H_5	14	68
g	C_6H_5	4-BrC_6H_4	C_6H_5	25	71
h	C_6H_5	(4-NO_2)C_6H_4	C_6H_5	8	73
i	$CH_2C_6H_5$	(4-NO_2)C_6H_4	C_6H_5	13	72
j	(4-NO_2)C_6H_4	(4-NO_2)C_6H_4	C_6H_5	22	76

Scheme 41. Synthesis of pyrazolo[4,3-f][1,2,4]triazolo[4,3-b][1,2,4]triazepines.

3.2.5. Synthesis of thieno[1,2,4]triazepines

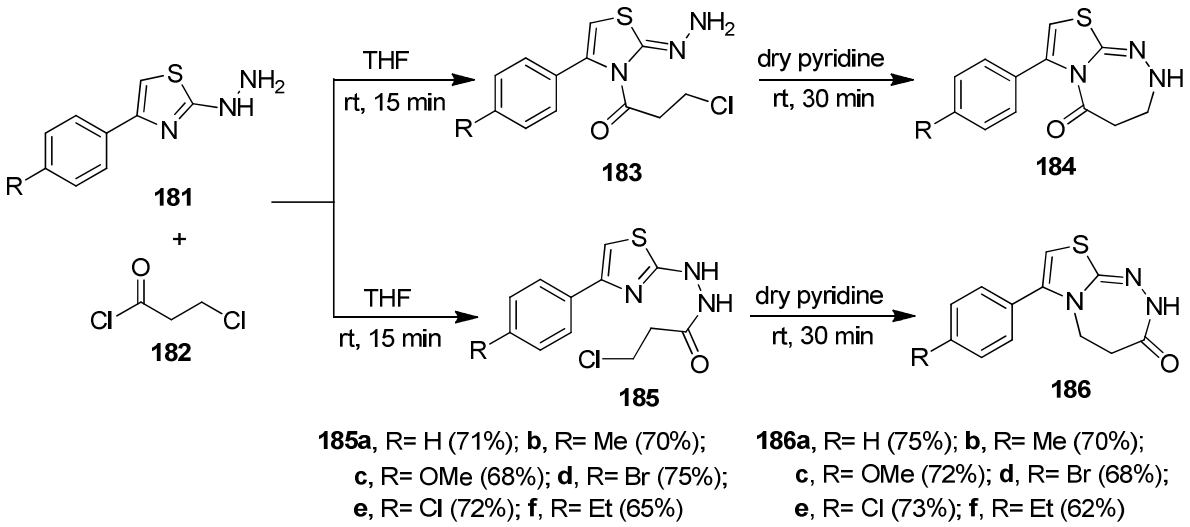
Cyclocondensation of hydrazinecarbothioamides **179a-c** in refluxing n-propanol [compounds **179a** and **179c**] or n-butanol [compound **179b**] gave 3-substituted-5-phenyl-3,6,7,8-tetrahydrocyclo(penta/hexa)[4,5]thieno[2,3-e][1,2,4]triazepine-2(1H)-thiones **180a-c**, respectively (Scheme 42) [99].



Scheme 42. Synthesis of cyclo(penta/ hexa)[4,5]thieno[2,3-e][1,2,4]triazepine-2(1H)-thiones.

3.2.6. Synthesis of thiazolo[1,2,4]triazepines

It was reported that the most direct route to thiazolo[2,3-c]-1,2,4-triazepine **186** and its derivatives would be from the reaction of **181** [100] with **182** via the intermediate **185**. The reaction of **181** with β-chloro-propionyl chloride (**182**) may give either of the two heterocycles **184** [101] and **186** (Scheme 43) [102].

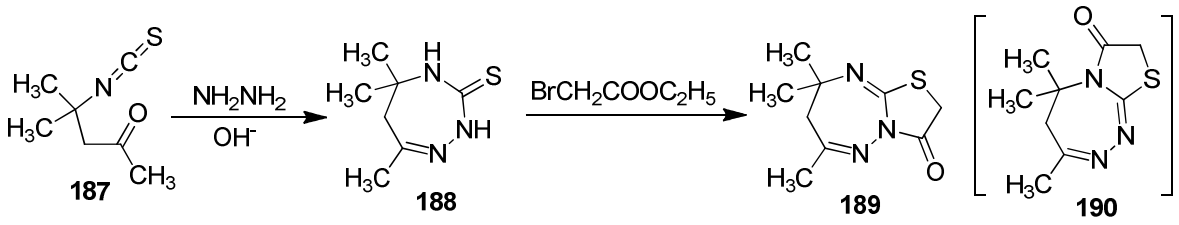


Scheme 43. Synthesis of thiazolo[2,3-c]-1,2,4-triazepines.

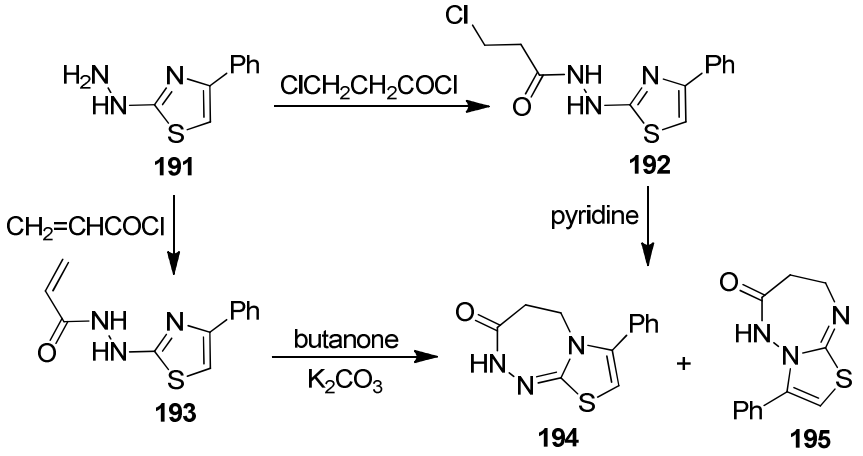
Condensation of triazepine **188** with ethyl bromoacetate led to a thiazolo[3,2-b][1,2,4]triazepine **189** and/or the isomeric thiazolo[2,3-c][1,2,4]triazepine **190** (Scheme 44) [103].

On the other hand, Mahajan et al, [102] have reported on the preparation of a thiazolo[2,3-c][1,2,4]triazepine **194** by reacting 2-hydrazino-4-phenylthiazole **191** with 3-chloropropionyl chloride followed by ring closure in pyridine. Later Mahajan et al. and others [104, 105] repeated this reaction using acetylacetone, dibenzoyl-

methane and ethyl acetoacetate, respectively, instead of 3-chloropropionyl chloride, and reported on the isolation of analogous **194**. In contrast with the above results, Peet et al. [106, 107] concluded that compound **194** cannot be prepared by the above method. The same authors prepared the thiazolotriazepine ring system by cyclization of the unsaturated precursor **193** yielding an isomeric mixture of **194** and **195**. Although it is difficult to explain the formation of isomer **195** from the precursor **193**, Peet et al. suggested a partial Dimroth type rearrangement (Scheme 45).

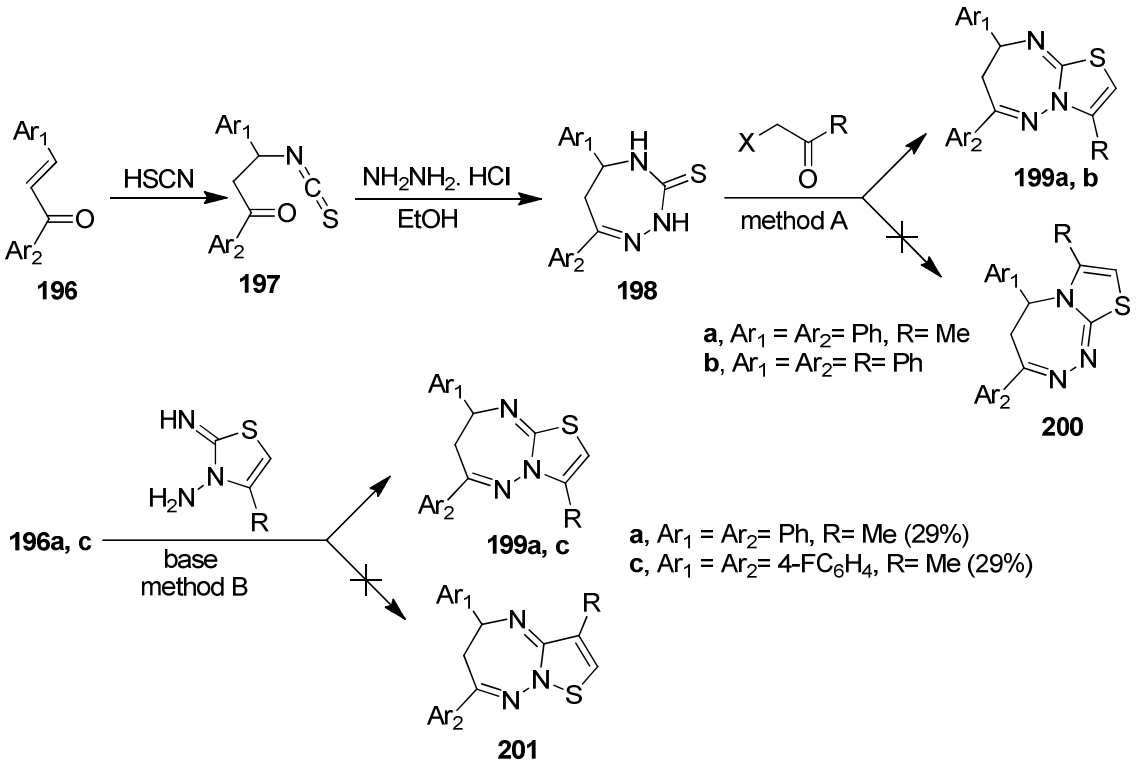


Scheme 44. Synthesis of thiazolo[1,2,4]triazepines.



Scheme 45. Synthesis of thiazolo[1,2,4]triazepines.

The thiones **198** (32%) were obtained by the addition of thiocyanic acid to the chalcones **196** followed by reaction of the intermediate **197** with hydrazine hydrochloride. The reaction of the thiones **198** with 2-haloketones (method A) afforded in each case a single product **199** (**199a**, 68%; **199b**, 30%) and its isomer **200** was not obtained. Next, an attempt was made to prepare isomers **199** and **200** by other routes, i.e. starting with the appropriate thiazole derivatives. Addition and condensation of chalcones **196** with 3-amino-2-imino-4-R-thiazolines can led to **199**, while the inversely oriented **201** was not obtained (Scheme 46) [11].



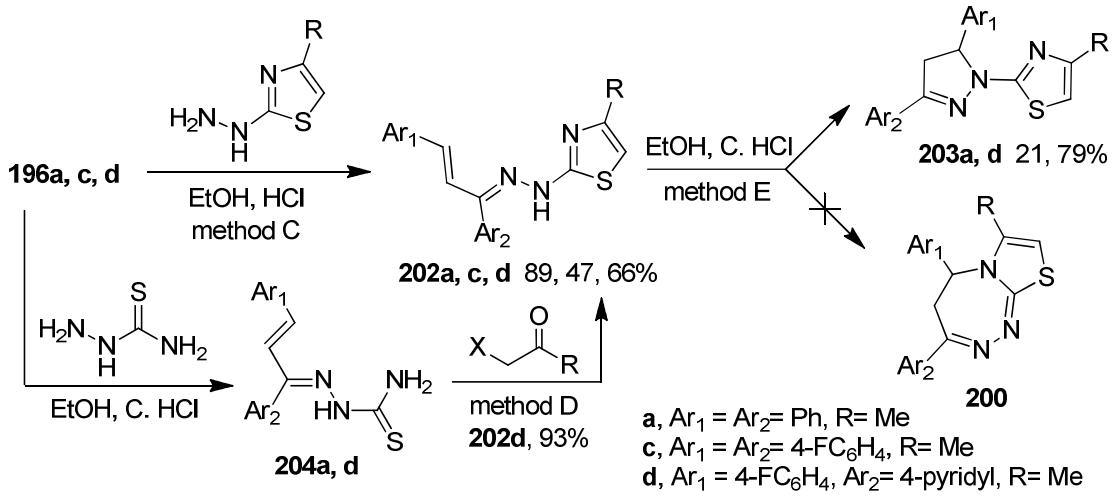
Scheme 46. Synthesis of thiazolo[1,2,4]triazepines.

For the preparation of isomer **200** the ring closure of the hydrazone **202** was considered, similarly to the cyclization of **193** by Peet [106]. This hydrazone could be prepared on one hand directly by condensation of **196** with the 2-hydrazino-4-R-thiazoles (method C). On the other hand, under acidic conditions the reaction of chalcones **196** with thiosemicarbazide afforded the thiosemicarbazones **204**, which could also be transformed into the hydrazones **202** using 2-haloketones (method D). Attempts to cyclize **202** under basic conditions similar to those applied by Peet [106, 107] were failed. Upon heating **202** in HC1 (method E) a product **203** was obtained (Scheme 47) [11].

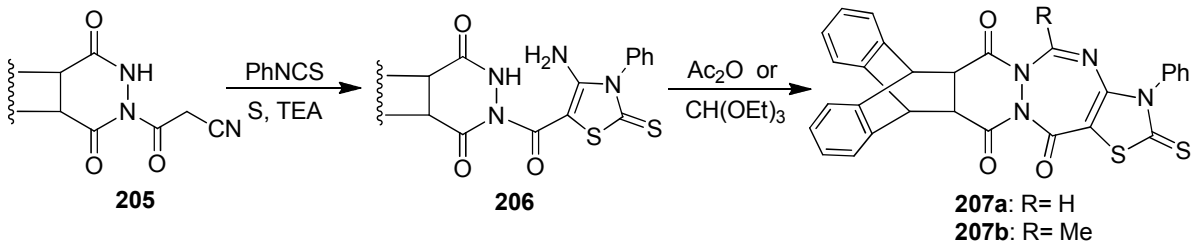
Khalil et al [108], reported the reaction of **205** with elemental sulfur and phenyl isothiocyanate in warming dimethylformamide containing a catalytic amount of triethylamine to yield the thiazole derivative **206**. Cyclization of **206** by refluxing with either triethylorthoformate or acetic anhydride gave 1,2,4-triazepine derivatives **207a**, **b** (Scheme 48).

Cyclocondensation of isothiocyanates **208** and **211** with hydrazine hydrate in a water containing sodium hydroxide gave the corresponding triazepine derivatives

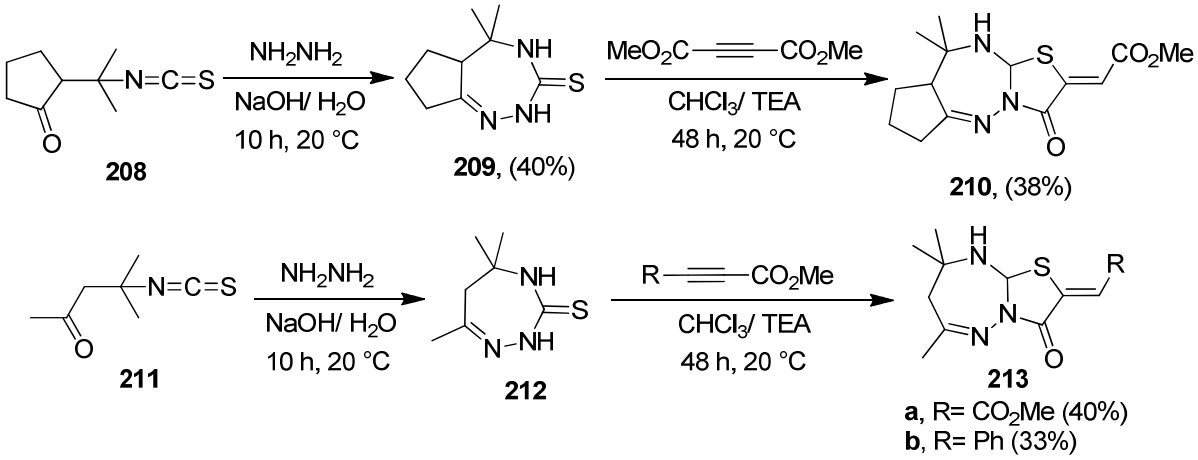
209 and **212**. Addition of acetylene derivatives to triazepines **209** and **212** in chloroform catalyzed by triethyl amine gave tetrahydrothiazolo[3,2-b][1,2,4] triazepines **210** and **213a**, **b** (Scheme 49) [109].



Scheme 47. Synthesis of thiazolo[1,2,4]triazepines.



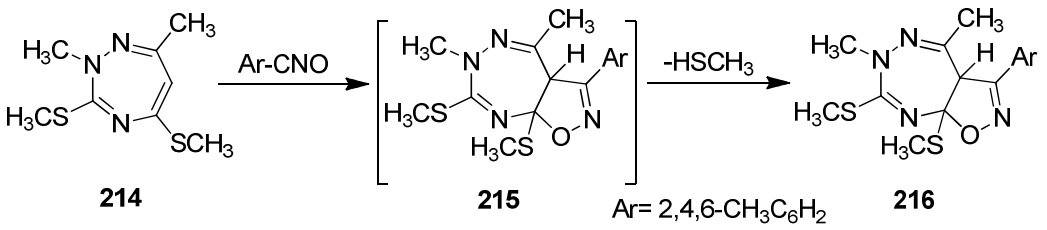
Scheme 48. Synthesis of thiazolo[1,2,4]triazepines.



Scheme 49. Synthesis of tetrahydrothiazolo[3,2-b][1,2,4]triazepines.

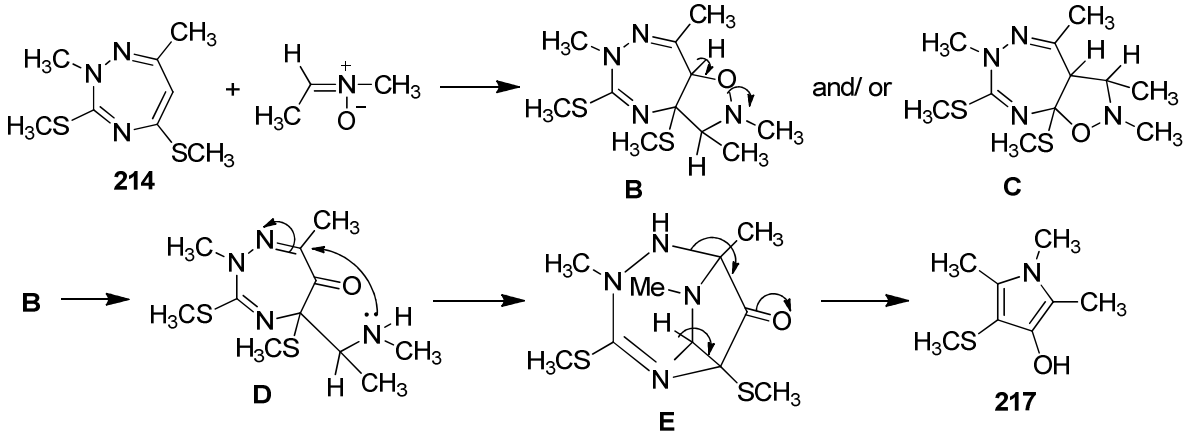
3.2.7. Synthesis of isoxazolo[1,2,4]triazepine

Cycloaddition [1,3-dipolar] of 2,7-dimethyl-3,5-bis(methylthio)-2H-1,2,4-triazepine (**214**) and mesitonitrile gave isoxazolo[5,4-e][1,2,4]triazepine **216** in a quantitative yield (Scheme 50) [110].



Scheme 50. Synthesis of isoxazolo[5,4-e][1,2,4]triazepine.

1,3-Dipolar cycloaddition of **214** with C,N-dimethylnitrone (N-ethylidene-methanamine oxide) in boiling benzene gave cycle isoxazolidine. 1,2,5-Trimethyl-4-(methylthio)-1H-pyrrol-3-ol (**217**) was obtained from the previous reaction in 40% yield (Scheme 51) [110].

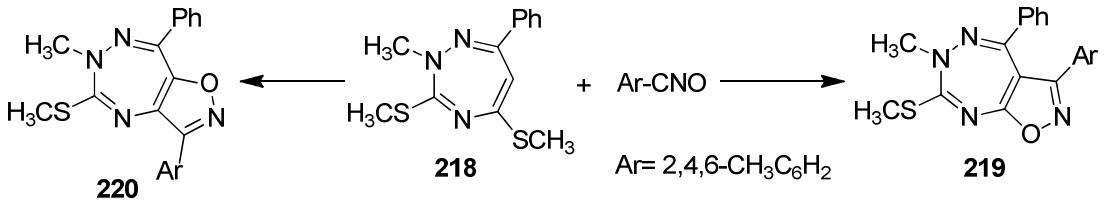


Scheme 51. Mechanism of formation of isoxazolo[1,2,4]triazepine and pyrrol-3-ol.

The condensation reaction of mesitonitrile oxide with 2-methyl-3,5-bis(methylthio)-7-phenyl-1,2,4-triazepine **218** is peri and regioselective. The 1,3-dipolar cycloaddition occurs in a unique way on the C=C double bond of the 1,2,4-triazepine **218** and led to the title compound, $C_{22}H_{22}N_4OS$. The isoxazole ring is planar while the triazepine ring adopts a boat conformation (Scheme 52) [111].

The immunosuppressive activities of an isoxazolo[5,4-e]triazepine (**221**) were reported [63, 112]. In general, these compounds exhibited differential immuno-suppressive actions. The inhibition of the pro-inflammatory cytokine-TNF-α and a

lack of inhibition of the anti-inflammatory cytokines, such as IL-6 and IL-10, indicate that **221** selectively affects the cytokine network. In addition, it was demonstrated that the compound ameliorated clinical symptoms of experimental autoimmune encephalomyelitis in Lewis rats, suggesting that **221** may also suppress the autoimmune disorders. Of note, **221** was also active when given *per os* and its toxicity was very low. Compound **222** represents, in turn, an example of the isoxazole derivative, with an activity quite opposite as compared with **221**. The unpublished results indicate that **222** strongly up-regulated lipopolysaccharide (LPS)-induced production of TNF-α by cultures of human mononuclear peripheral blood cells. That finding does not mean that **222** is a pro-inflammatory compound since pretreatment of LPS-injected mice with **222** significantly reduced serum TNF-α level. **222** was also active when administered *per os* and was more stimulatory than the reference drug levamisole in the investigated models. It was suggested that **222** may even replace levamisole in some therapeutic interventions. Such a property opens a possibility of clinical application of **222** [113] (Fig. 3).



Scheme 52. Synthesis of isoxazolo[4,5-e][1,2,4]triazepines.

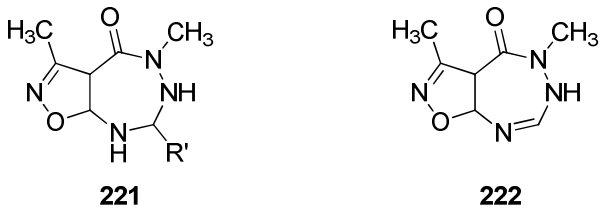
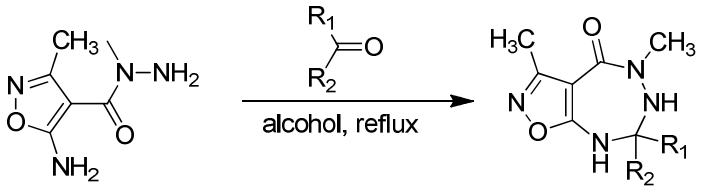


Figure 3. Structures of isoxazolo[5,4-e][1,2,4]triazepin-4(5H)-ones.

7-Substituted 3-methylisoxazolo[5,4-e][l,2,4]triazepin-4-ones **224a-j** were prepared from 5-amino-3-methylisoxazole-4-carboxylic acid methyl hydrazide (**223**) and carbonyl compounds in refluxing methanol / water containing hydrochloric acid [compound **224a**] or isopropyl alcohol [compounds **224b-h**] or in ethanol

[compounds **224i** and **224j**]. These compounds exhibited immunosuppressive properties in the murine humoral immune response in vivo and the proliferative response of mouse splenocytes to mitogens. The X-ray structure of a representative compound was reported (Scheme 53) [114].



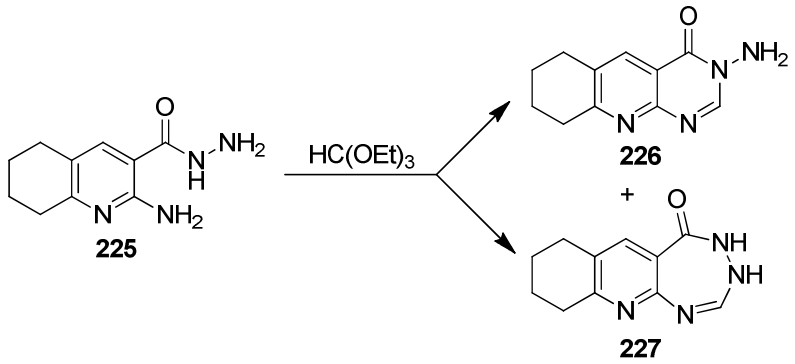
223 **224a-j**

a, R_1= R_2= H (82%); **b**, R_1, R_2= -$(CH_2)_9$- (59%);
c, R_1, R_2= -$(CH_2)_5$- (76%); **d**, R_1= H, R_2= 4-ClC_6H_4 (68%);
e, R_1= H, R_2= 2-ClC_6H_4 (31%); **f**, R_1= H, R_2= C_6H_5 (45%);
g, R_1= H, R_2= 4-OHC_6H_4 (42.6%); **h**, R_1= H, R_2= 3-ClC_6H_4 (37%);
i, R_1= H, R_2= C_6H_5 (59.6%); **j**, R_1= R_2= CH_3 (78%)

Scheme 53. Synthesis of 7-substituted 3-methylisoxazolo[5,4-e][l,2,4]triazepin-4-ones.

3.2.8. Synthesis of pyrido[1,2,4[triazepines

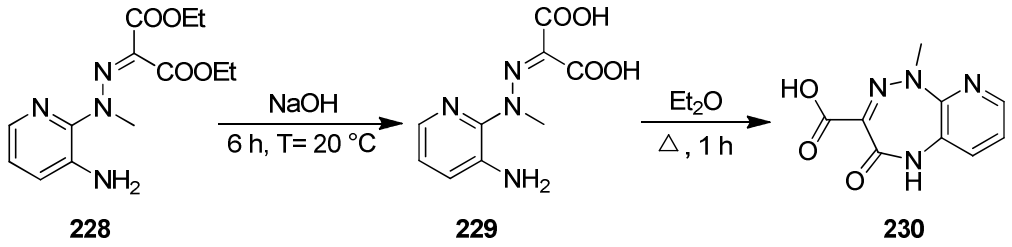
The reaction of **225** with triethyl orthoformate gave a mixture of two products, 3-amino-6,7,8,9-tetrahydropyrimido[4,5-b]quinolin-4(3H)-one (**226**) and 7,8,9,10-tetrahydro-3H-[1,2,4]triazepino[5,6-b]quinolin-5(4H)-one (**227**) (25%) (Scheme 54) [54].



225 **226** + **227**

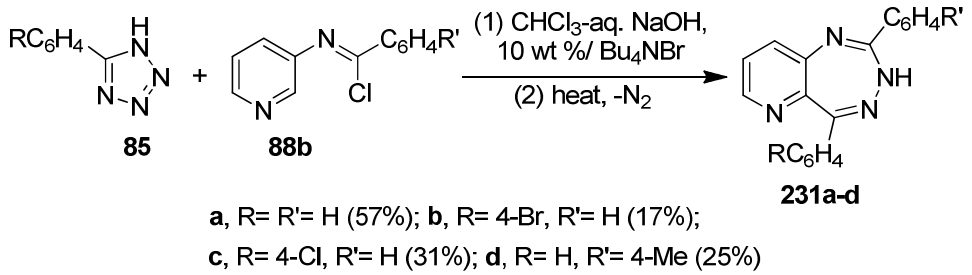
Scheme 54. Synthesis of [1,2,4]triazepino[5,6-b]quinolin-5(4H)-one.

Savelli et al [115], have reported the hydrolysis of diester **228** in sodium hydroxide solution to form the dicarboxylic acid derivative **229**, which cyclized in diethyl ether after heating to give pyrido[2,3-c][1,2,5]triazepine-3-carboxylic acid **230** in 45% yield (Scheme 55).



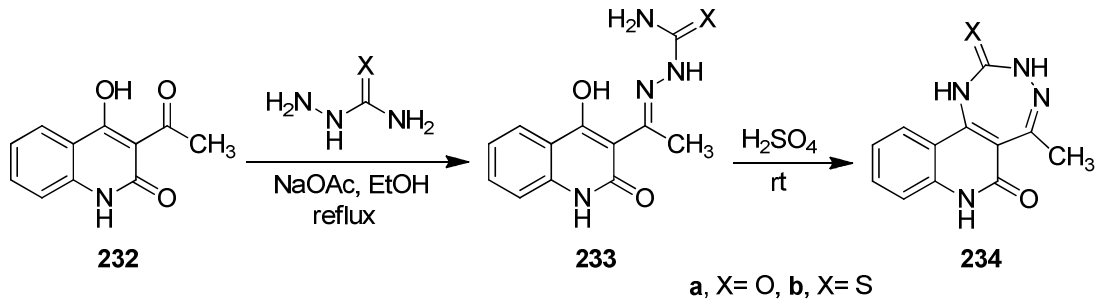
Scheme 55. Synthesis of pyrido[2,3-c][1,2,5]triazepine-3-carboxylic acid.

Thermolysis of N-imidoyltetrazoles obtained under conditions of the phase-transfer catalysis from 5-aryltetrazoles **85** and N-(m-pyridyl)benzimidoyl chloride **88b** gave rise to 2,5-aryl-3H-pyrido[3,2-e][1,2,4]triazepines **231a-d** (Scheme 56) [116].

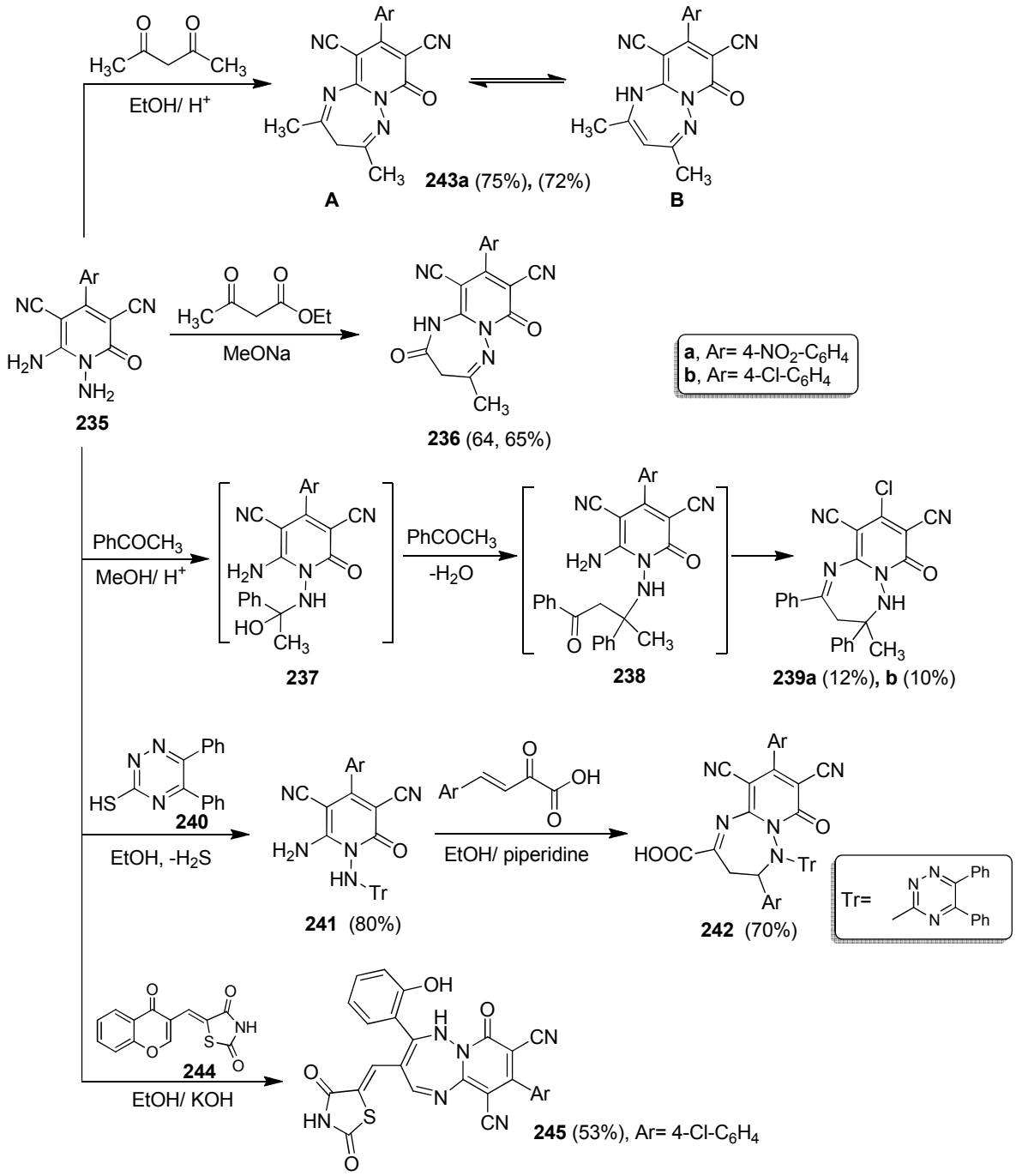


Scheme 56. Synthesis of 2,5-aryl-3H-pyrido[3,2-e][1,2,4]triazepines.

Uncyclized products **233a** and **233b** were formed from condensation reaction of 4-hydroxy-3-acyl quinoline-2-one **232** with semicarbazide and thiosemicarbazide in refluxing sodium ethoxide. Treatment of compounds **233a** and **233b** with sulfuric acid at room temperature gave [1,2,4]triazepino[6,5-c]quinolinones **234a** and **234b** (Scheme 57). The antioxidant power of these compounds were screened against six methods. Compound **234a** (12.3 mg EDTA/g) showed comparable activity with the standard BHA (13.2 mg EDTA/g) and slightly less than that of BHT (16.1 mg EDTA/g), while, compound **234b** exhibited moderate to exceptional activity [117].



Scheme 57. Synthesis of triazepino[6,5-c]quinolinones **234a** and **234b**.

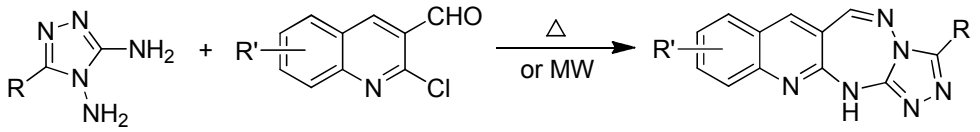


Scheme 58. Synthesis of pyrido[1,2-b][1,2,4]triazepines.

Compounds **235a** and **235b** [118] were reacted with ethyl acetoacetate in methanolic sodium methoxide solution to give the corresponding pyrido[1,2-b][1,2,4]triazepine-8,10-dicarbonitriles **236a** and **236b** via EtOH and H_2O elimination. In addition, the corresponding pyrido-[1,2-b][1,2,4]triazepine-8,10-dicarbonitrile **239a** was isolated as by-product from the reaction of pyridine derivative **235a** with acetophenone in methanol. The reaction of **235** with pentane-

2,4-dione under the same experimental conditions gave **243a** and **243b** which may be in two tautomers (**A** and **B**) is the suitable structure for the isolated product [119]. 2-Oxo-1-(5,6-diphenyl-1,2,4-triazin-3-ylamino)-1,2-dihydropyridine-3,5-dicarbonitrile (**241**) was obtained from refluxing of compound **235** with 5,6-diphenyl-1,2,4-triazin-3-thiole (**240**) [120] in boiling ethanol. Treatment of **241** with α,β-unsaturated oxo acid in boiling ethanol with a few drops of piperidine led to the direct formation of pyrido[1,2-b][1,2,4]triazepine-2-carboxylic acid **242** [121]. Thus, condensation of **3** with 5-((4-oxo-4H-chromen-3-yl)methylene)thiazolidine-2,4-dione (**244**) under basic conditions [122] gave pyrido[1,2-b][1,2,4]triazepine **245** (Scheme 58) [123].

[1,2,4]Triazolo[4',3':2,3][1,2,4]triazepino[5,6-b]quinoline derivatives **247**, were synthesized from the reaction of 5-aryl-3,4-diamino-1,2,4-triazoles **174** with 2-chloro-3-formylquinolines **246** in ionic liquid as solvent under microwave heating as well as using oil-bath heating at 80 ^{o}C (Scheme 59). Compounds **247a**, **247b**, **247c** and **247d** showed excellent activity against *Aspergillus niger* 1000 μg concentration and *Pencillium notatum* species at 500 μg as well as 1000 μg concentrations whereas, these compounds show good to moderate activity against *Aspergillus flavus* and *Rhizopus* species at both the concentrations [16].

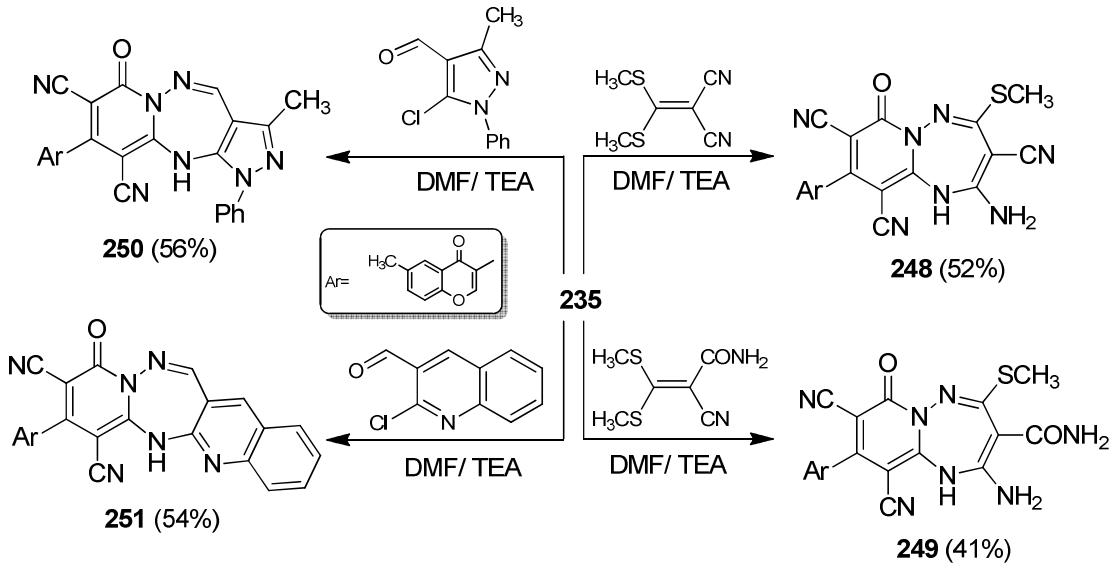


174 **246** **247**

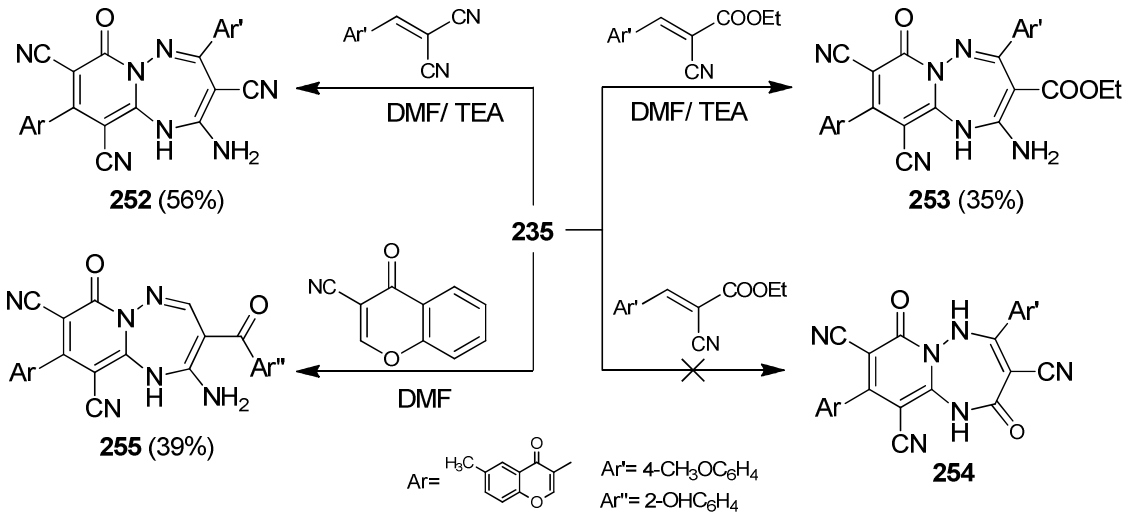
Compound	R	R'	Microwave (MW) Yield (%)	Oil-bath heating at 8 ^{o}C Yield (%)
a	C_6H_5	H	70	58
b	$(NO_2)C_6H_4$	H	78	66
c	2-ClC_6H_4	3-CH_3	68	65
d	(4-NO_2)C_6H_4	3-CH_3	72	62
e	2-ClC_6H_4	4-OCH_3	80	70
f	$CH_2C_6H_5$	4-CH_3	70	62
g	C_6H_5	4-CH_3	78	65
h	4-ClC_6H_4	4-OCH_3	85	70
i	(4-NO_2)C_6H_4	4-OCH_3	80	76
j	(4-NO_2)C_6H_4	4-CH_3	74	60

Scheme 59. Synthesis of triazolo[4',3':2,3][1,2,4]triazepino[5,6-b]quinolines.

Treatment of **235** [122] with 2-cyano-3,3-bis(methylthio)acrylonitrile, 2-cyano-3,3-bis(methylthio)prop-2-enamide, 5-chloro-3-methyl-1-phenylpyrazole-4-carbox-aldehyde [124] and 2-chloro-3-formylquinoline [125] in DMF containing few drops in triethylamine afforded pyrido[1,2-b][1,2,4]triazepines **248-251**, respectively (Scheme 60) [126].



Scheme 60. Synthesis of pyrido[1,2-b][1,2,4]triazepines.



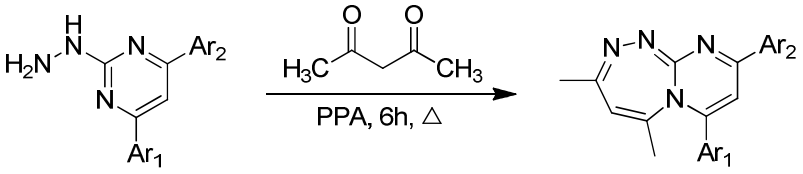
Scheme 61. Synthesis of pyrido[1,2-b][1,2,4]triazepines.

Treatment of **235** with p-methoxybenzylidene-malononitrile in DMF containing two drops of triethylamine gave pyrido[1,2-b][1,2,4]triazepine **252**. Also, condensation of **235** with ethyl 2-cyano-3-(4-methoxyphenyl)prop-2-enoate under the same reaction conditions yielded pyrido[1,2-b][1,2,4]triazepine **253** and not the

other possible product **254**. Similarly, treatment of **235** with chromone-3-carbonitrile gave pyridotriazepine derivative **255** (Scheme 61) [126].

3.2.9. Synthesis of pyrimido[1,2,4]triazepines

Heating of 4,6-diaryl-2-hydrazinylpyrimidines **256a-c** with acetyl acetone in poly phosphoric acid gave 7,9-diaryl-3,5-dimethylpyrimido[2,1-c][1,2,4]triazepines **257a-c**, respectively (Scheme 62) [127].

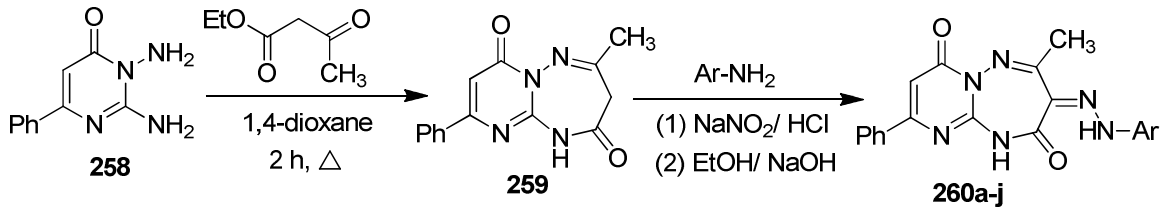


256 **257a-c**

a, Ar_1= Ph, Ar_2= 2,4-diOCH_3-C_6H_3 (64%)
b, Ar_1= Ph, Ar_2= 2,4-diOEt-C_6H_3 (63%)
c, Ar_1= 3-$CH_3OC_6H_4$, Ar_2= 2,4-diOEt-C_6H_3 (73%)

Scheme 62. Synthesis of 7,9-diaryl-3,5-dimethylpyrimido[2,1-c][1,2,4]triazepines.

Cyclocondensation of 2,3-diamino-6-phenyl-pyrimidin-4(3H)-one (**258**) with ethyl 3-oxobutanoate in 1,4-dioxane under reflux, gave 2-methyl-7-phenyl-pyrimido[1,2-b][1,2,4]triazepine-4,9(3H,5H)-dione (**259**) in 19% yield. A series of 3-arylazo-2-methyl-7-phenylpyrimido[1,2-b][1,2,4]triazepine-4,9-diones **260a-j** were prepared from diazotization of **259** with different aromatic amines in ethanol containing sodium hydroxide solution (Scheme 63). The acid dissociation constants were determined for the series prepared and were correlated by a Hammett-type equation using enhanced substituent constants [128].

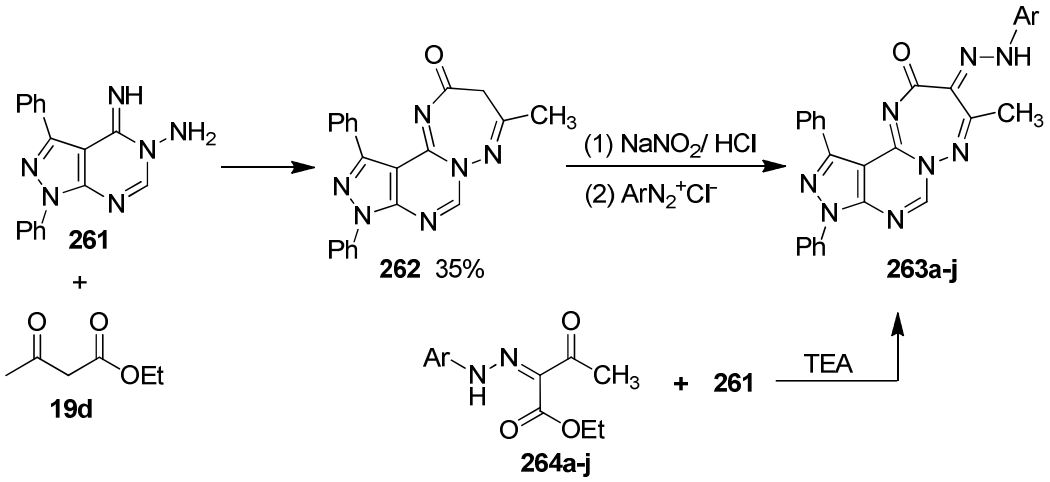


258 **259** **260a-j**

a, Ar= 4-$CH_3C_6H_4$ (75%); **b**, Ar= 4-ClC_6H_4 (83%); **c**, Ar= 4-$COCH_3C_6H_4$ (82%);
d, Ar= 4-$OCH_3C_6H_4$ (72%); **e**, Ar= 4-$NO_2C_6H_4$ (80%); **f**, Ar= C_6H_5 (79%);
g, Ar= 3-ClC_6H_4 (78%); **h**, Ar= 3-$CH_3C_6H_4$ (80%); **i**, Ar= 3-$NO_2C_6H_4$ (78%);
j, Ar= 4-$COOEtC_6H_4$ (80%)

Scheme 63. Synthesis of 3-arylazo-2-methyl-7-phenylpyrimido[1,2-b][1,2,4] triazepine-4,9-diones.

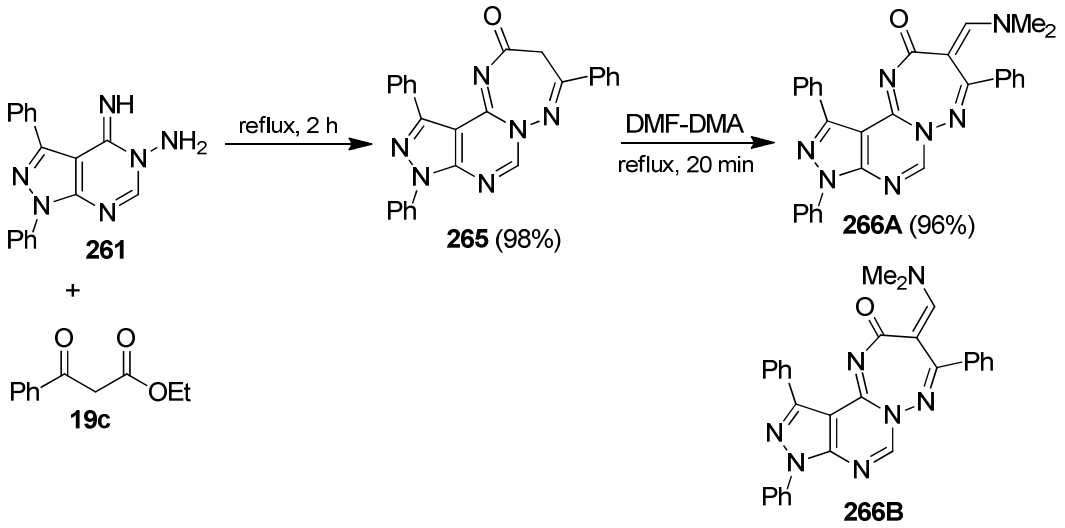
Condensation of ethyl acetoacetate (**19d**) with 5-amino-1,3-diphenyl-4,5-dihydro-4-imino-1H-pyrazolo[3,4-d]pyrimidine (**261**) [129] gave pyrazolo[3',4':4,5]pyrimido[1,6-b][1,2,4]triazepin-5(6H)-one **262**. In aqueous ethanol in the presence of sodium hydroxide, compound **262** reacted with diazotized anilines to afford the respective arylazo derivatives **263a-j**. Treatment of **261** with each of the compounds **264a**, **264d**, and **264h** [130] in dioxan in presence of triethylamine gave the products **263a**, **263d**, and **263h** (Scheme 64). The acid dissociation constants for **263a-j** were determined and were correlated by the Hammett equation, the compounds exist predominantly in the hydrazone tautomeric form [131].



a, Ar= 4-$OCH_3C_6H_4$ (62%); **b**, Ar= 4-$CH_3C_6H_4$ (70%); **c**, Ar= 3-$CH_3C_6H_4$ (50%);
d, Ar= C_6H_5 (68%); **e**, Ar= 4-ClC_6H_4 (71%); **f**, Ar= 3-ClC_6H_4 (57); **g**, Ar= 3-$NO_2C_6H_4$ (51%);
h, Ar= 4-$NO_2C_6H_4$ (68%); **i**, Ar= 4-$COCH_3C_6H_4$ (56%); **j**, Ar= 4-$EtOCOC_6H_4$ (42%)

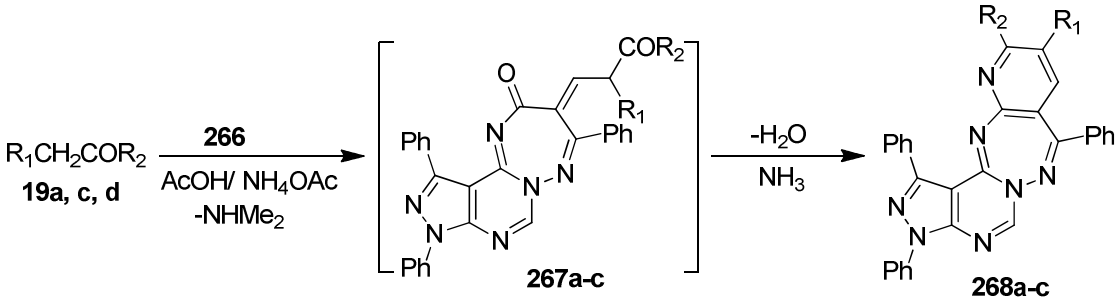
Scheme 64. Synthesis of arylazo derivatives.

Pyrazolo[3,4-d]pyrimidine derivative **261** [132] with ethyl benzoylacetate **19c** under heating to afford pyrimido[1,6-b][1,2,4]triazepinone **265**. Condensation of **265** with dimethylformamide-dimethylacetal (DMF-DMA) gave enaminone **266**, which exhibited antitumor and antimicrobial activities against human breast cell line MCF-7, liver carcinoma cell line HEPG2-1, HELA cells, *E. coli* and *S. aureus* (Scheme 65) [133].



Scheme 65. Synthesis of pyrimido[1,6-b][1,2,4]triazepin-2-ones.

Reactions of enaminone **266** with active methylene compounds, namely, acetylacetone (**19a**), ethyl benzoylacetate (**19c**) and ethyl acetoacetate (**19d**) in glacial acetic acid in the presence of ammonium acetate gave pyrimido[1,2,4]triazepines **268a-c**, *via* the non-isolable intermediates **267a-c** (Scheme 66) [133].

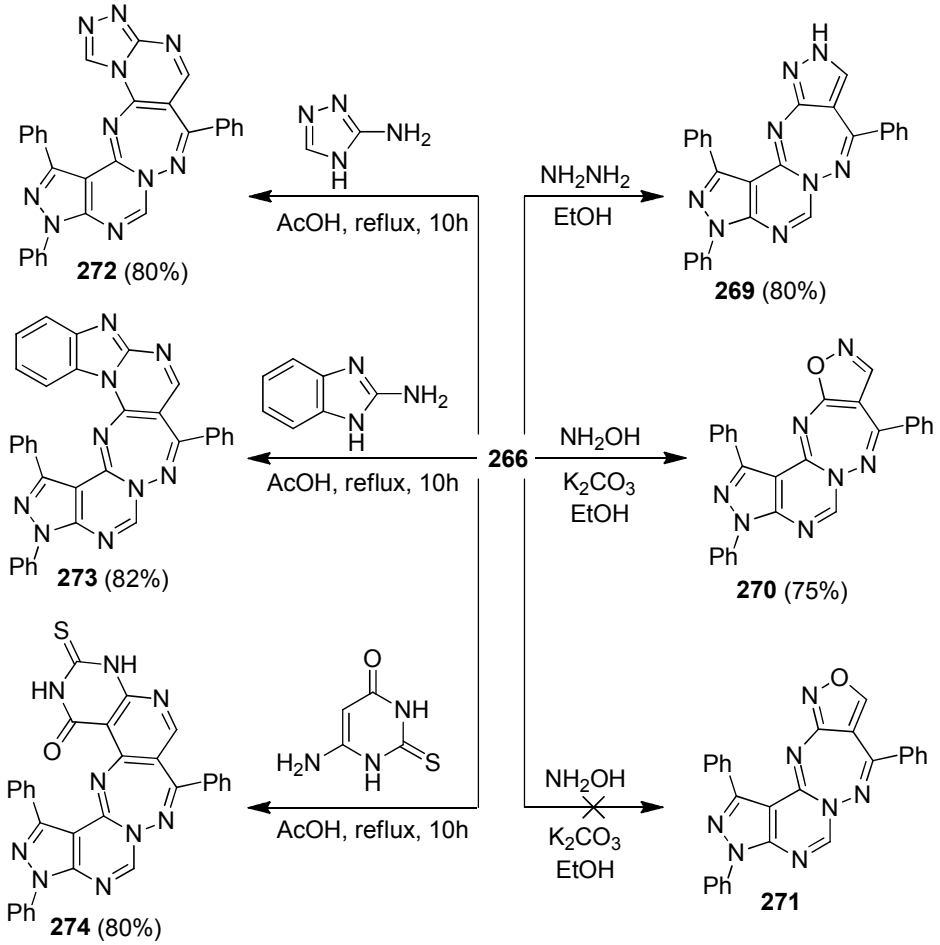


268a, R_1= CH_3CO, R_2= CH_3 (79%)
268b, R_1= COOEt, R_2= Ph (86%)
268c, R_1= COOEt, R_2= CH_3 (83%)

Scheme 66. Reaction of enaminone with active methylene compounds.

Reaction of the enaminone **266** with bisnucleophiles i.e. hydrazine hydrate, hydroxyl amine in absolute ethanol, 4H-1,2,4-triazol-3-amine, 1H-benzo[d] imidazol-2-amine and 6-amino-2-thioxo-2,3-dihydropyrimidin-4(1H)-one in refluxing acetic acid resulted in the formation of pyrimido[1,2,4]triazepines **269-274**,

respectively (Scheme 67). Compound **270** exhibited antimicrobial activity against *E. coli* and *S. aureus* [133].

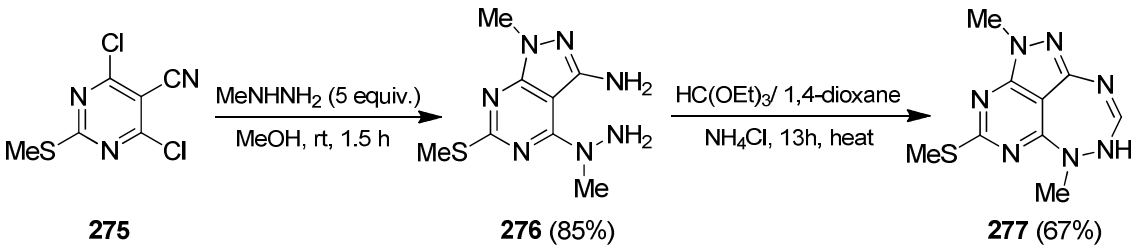


Scheme 67. Reaction of enaminone with bisnucleophiles.

Performing the reaction of **275** with five equivalents of methylhydrazine at room temperature gave pyrazolo[3,4-d]pyrimidine **276** in 85% yield already after 1.5 h. Indeed, when **276** reacted with an excess of triethyl orthoformate in the presence of ammonium chloride as an acidic catalyst, pyrazolo[3,4,5-ef]pyrimido[5,4-f][1,2,4]triazepine **277** was formed (Scheme 68) [127, 134].

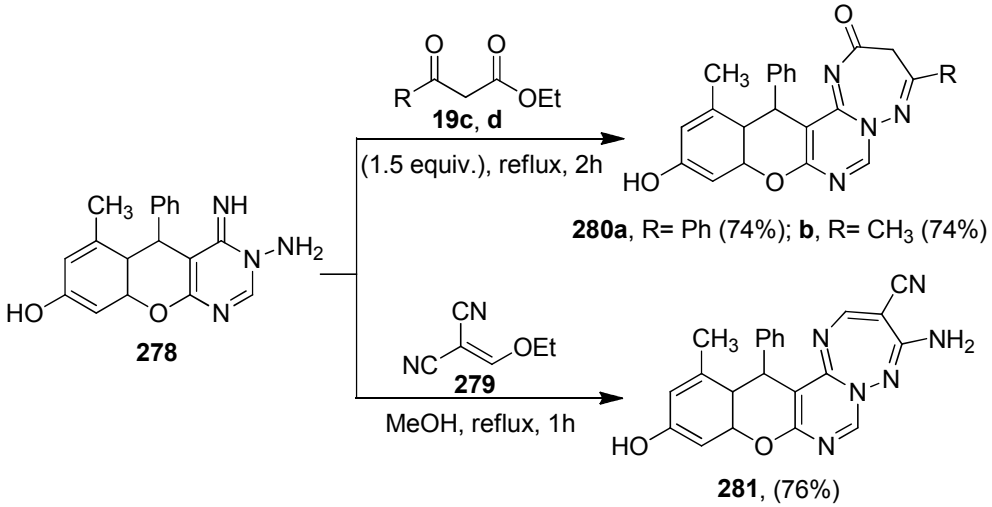
The reaction of chromeno[2,3-d]pyrimidin-8-ol **278** with active methylene reagents such as ethyl benzoylacetate (**19c**) and ethyl acetoacetate (**19d**) gave the triazepinones **280a**, **b**, respectively. Also, the reaction of **287** with 2-(ethoxymethylene) malononitrile (**279**) in methanol furnished the expected triazepine derivative **281**. The reaction proceeded through the addition to the olefinic double

bond followed by loss of ethanol to (Scheme 69). Compound **280b** is a more active cytotoxic agent against human hepatocellular carcinoma cell line HepG2 [135].



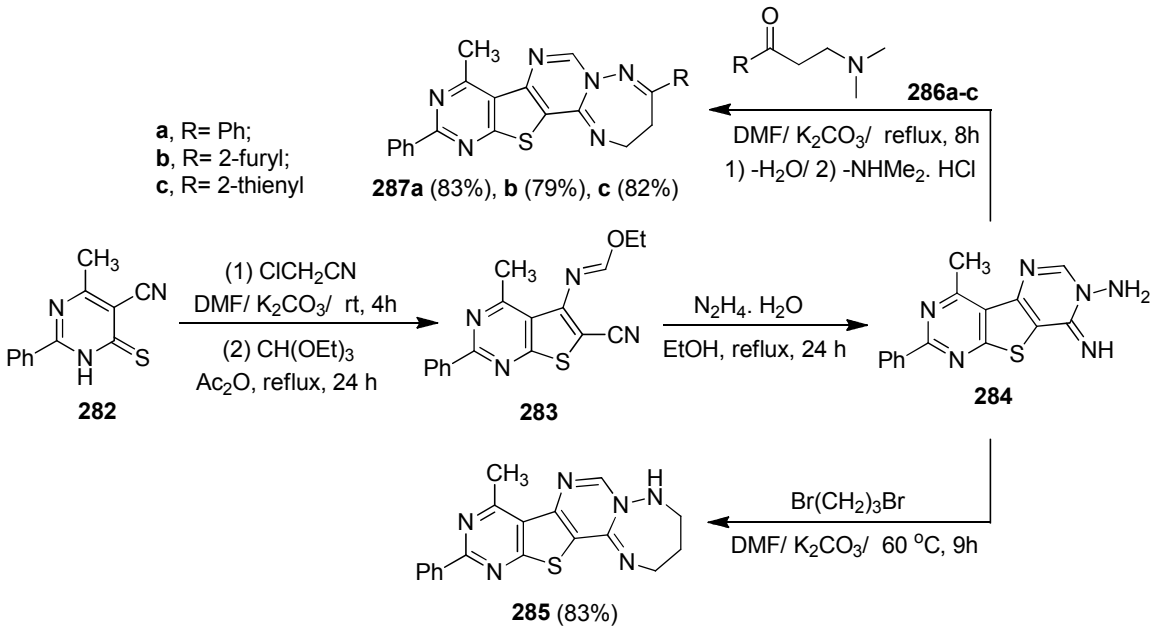
275 **276** (85%) **277** (67%)

Scheme 68. Synthesis of pyrazolo[3,4,5-ef]pyrimido[5,4-f][1,2,4]triazepine.

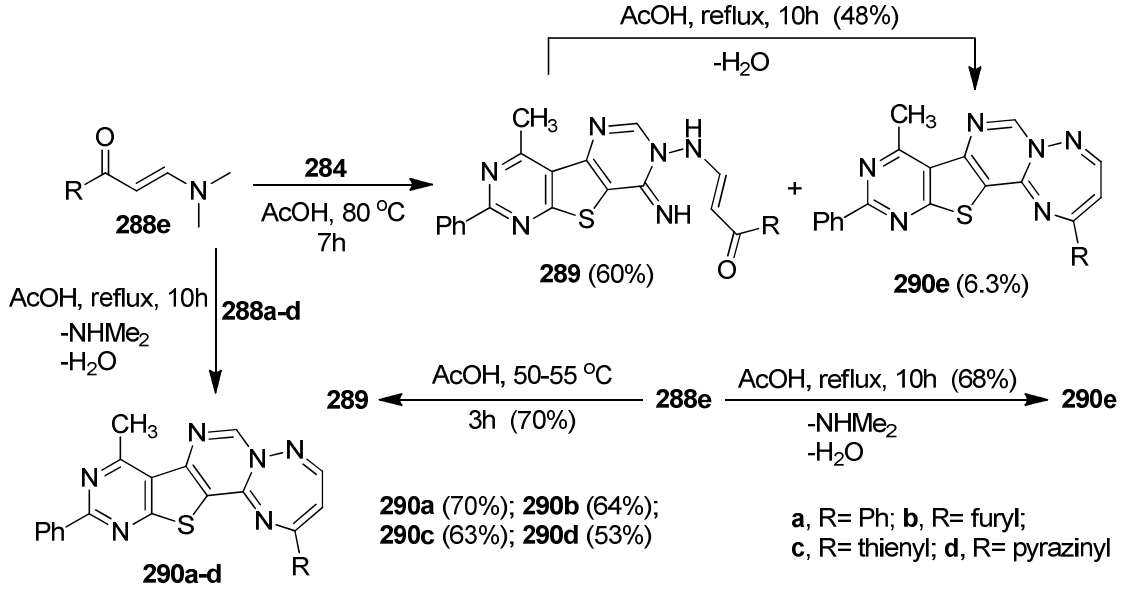


Scheme 69. Synthesis of chromeno[2',3':4,5]pyrimido[1,6-b][1,2,4]triazepines.

Cyclization of thioxopyrimidine **282** with chloroacetonitrile in DMF in the presence of excess anhydrous potassium carbonate followed by its reaction with triethyl orthoformate to give the thieno[2,3-d]pyrimidine **283** in the second step. Next, hydrazinolysis of **283** in ethanol yielded the key intermediate **284** for the preparation of triazepines. Cyclocondensation of **284** with 1,3-dibromopropane in DMF in the presence of excess anhydrous potassium carbonate at 60 ^{o}C gave the pyrimido[1,6-b][1,2,4]triazepine **285**. Treatment of **284** with Mannich bases [136, 137] **286a-c** in DMF in the presence of excess anhydrous potassium carbonate afforded the corresponding pyrimido[1,6-b][1,2,4]triazepines **287a-c** (Scheme 70) [138].



Scheme 70. Synthesis of pyrimido[1,6-b][1,2,4]triazepines.



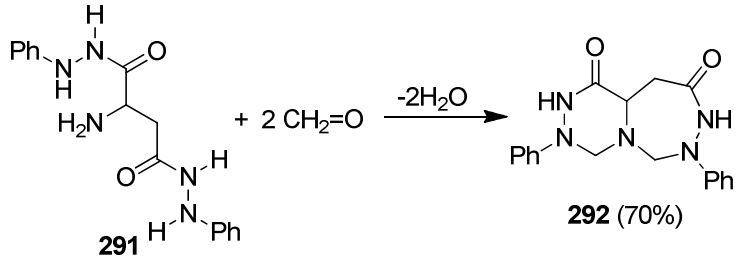
Scheme 71. Synthesis of pyrimido[1,6-b][1,2,4]triazepines.

In addition, the reaction of **284** with enaminone **288e** was studied in glacial acetic acid, at different temperatures such as 50 -55 °C, 80 °C, and reflux, respectively. The reaction at 50-55 °C for 3h only afforded the open-chain product **289** in 70% yield, while at 80 °C for 7h incomplete cyclocondensation yielded a mixture of two products **289** (60% yield) and **290e** (6.3% yield) which were separated. Also, for the reaction time (10 h) and increasing the reaction temperature (reflux), the yield for compound **290e** increased greatly from 6.3% to 68%.

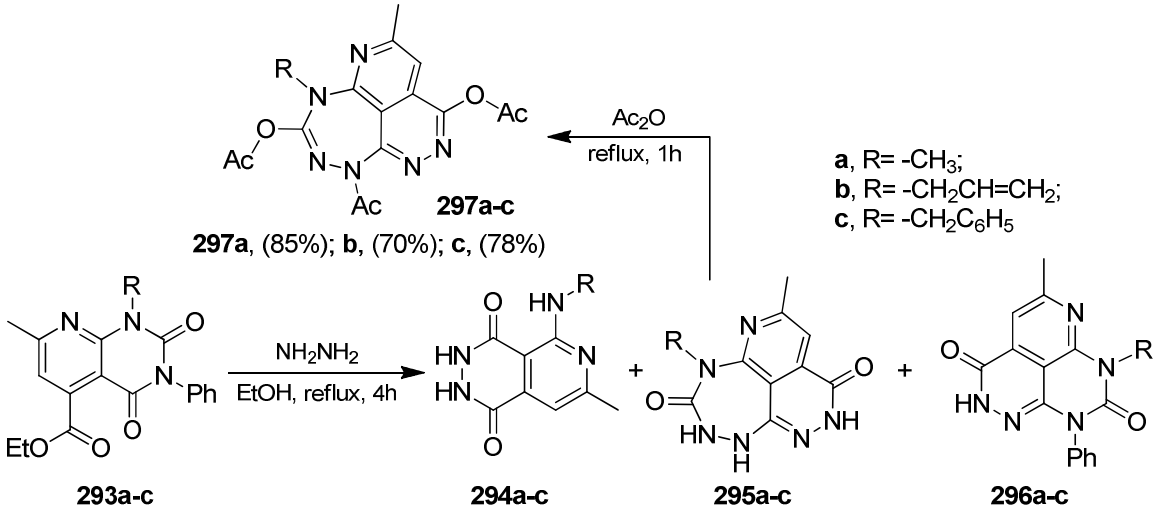
Moreover, treatment of **284** with enaminones **288a-d** in glacial acetic acid under reflux afforded the corresponding pyrimido[1,6-b][1,2,4]triazepines **290a-d**, respectively (Scheme 71) [138].

3.2.10. Synthesis of triazino[1,2,4]triazepines

L-aspartic acid 1,4-bis(2-phenylhydrazide) (**291**) reacted with two molecules of formaldehyde to give an interesting triazine ring fused with a seven-membered heterocycle, namely perhydro-4,6-dioxo-2,8-diphenyl[1,2,4]triazino[4,5-d][1,2,4] triazepine (**292**) (Scheme 72) [13].



Scheme 72. Synthesis of triazino[4,5-d][1,2,4]triazepine-1,9(2H,6H)-dione.



Scheme 73. Synthesis of pyrido[2,3,4-ef]pyridazino[3,4-e]-1,2,4-triazepines.

3.2.11. Synthesis of pyrido[2,3,4-ef]pyridazino[3,4-e]-1,2,4-triazepines

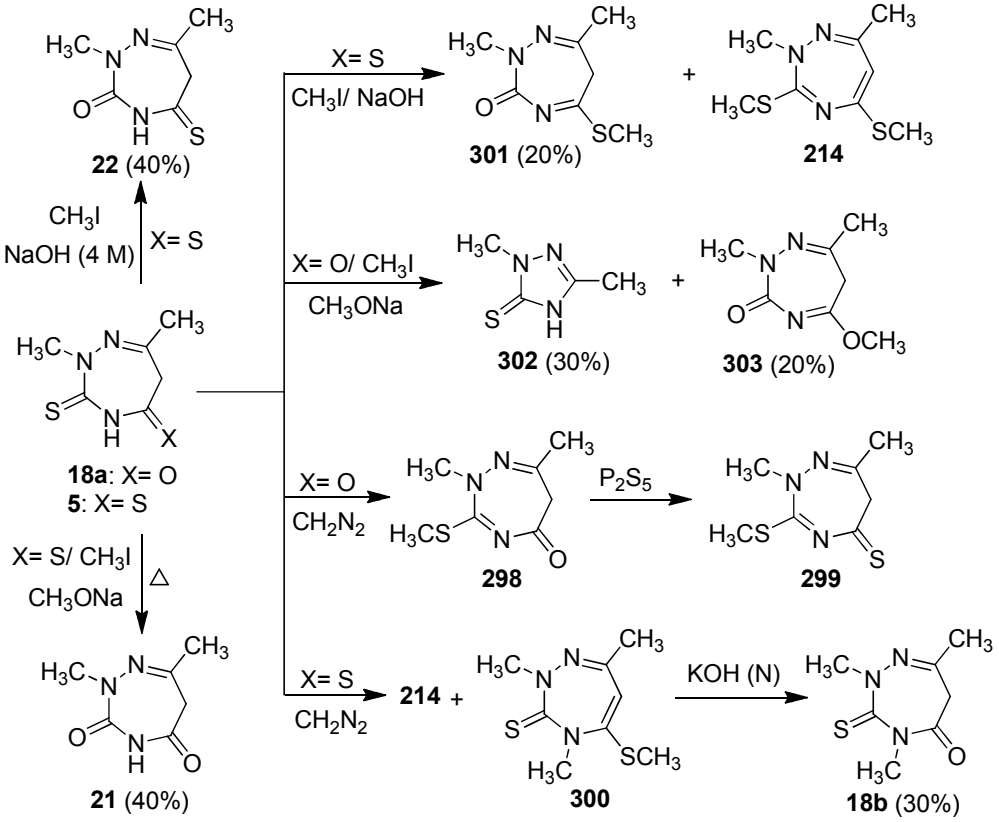
It was reported that three analogous ethyl 2,4-dioxo-1,2,3,4-tetrahydropyrido[2,3-d]pyrimidine-5-carboxylates **293a-c** reacted with hydrazine hydrate to give derivatives of pyrido[3,4-d]pyridazine **294a-c**, pyrido[2,3,4-ef]pyridazino[3,4-e]-1,2,4-triazepine **295a-c** and pentazaphenalenes **296a-c**. The latter compounds were

formed in low yields. Acetylation of compounds **295a-c** in acetic anhydride after heating led to the acetyl derivatives **297a-c** (Scheme 73) [139].

4. Reactions

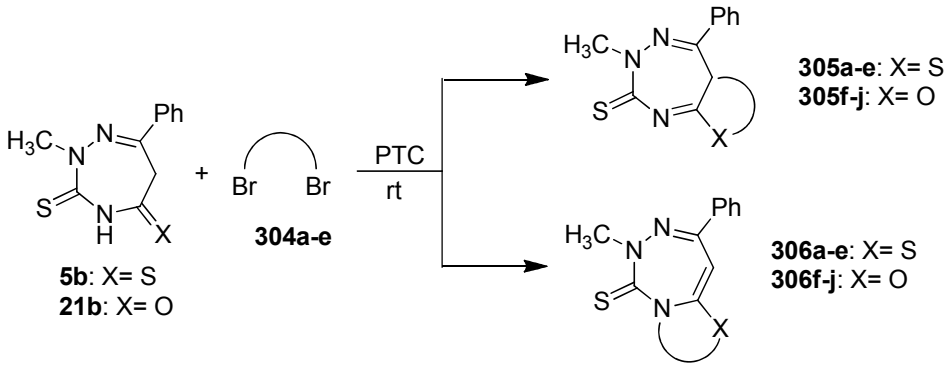
4.1. Alkylation

Alkylation of 1,2,4-triazepin-5(6H)-one **18a** with diazomethane and methyl iodide in a basic medium afforded triazepines **298** and **303**. Treatment of **298** with phosphorous pentasulfide gave methyl mercaptan derivative **299**. Similarly, 1,2,4-triazepine-3,5(4H,6H)-dithione **5** was alkylated with diazomethane to give a mixture of triazepines **214** and **300**. Treatment of **214** with potassium hydroxide gave triazepine **18b**. The reaction of **5** with methyl iodide in sodium hydroxide gave a mixture of methyl mercaptan derivatives **214** and **301**. The same previous reaction upon using sodium hydroxide in high concentration (4 M) gave **22**. On the other side, heating of **5** with methyl iodide in sodium methoxide medium gave triazepindione **21** (Scheme 74) [29].



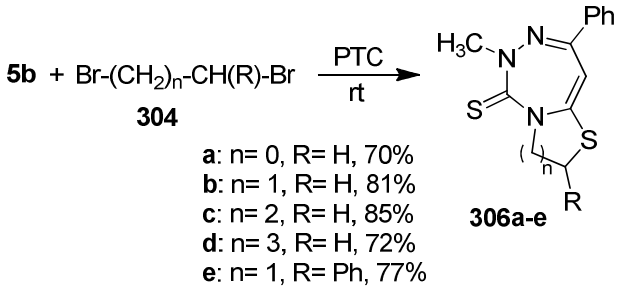
Scheme 74. Alkylation of triazepin-5(6H)-one and triazepine-3,5(4H,6H)-dithione

At room temperature, 1,2,4-triazepines **5b** and **21b** [39] reacted with equimolar quantities of dibromoalkanes **304a-e** using the liquid-liquid phase transfer catalysis conditions (P.T.C) technique to give **305a-j** and **306a-j**. Since in such triazepines the thioxo and the oxo groups, the N-4 nitrogen and the C-6 carbon could be reactive towards alkylating agents [29, 140], the formation of two regioisomers is expected (Scheme 75) [141].



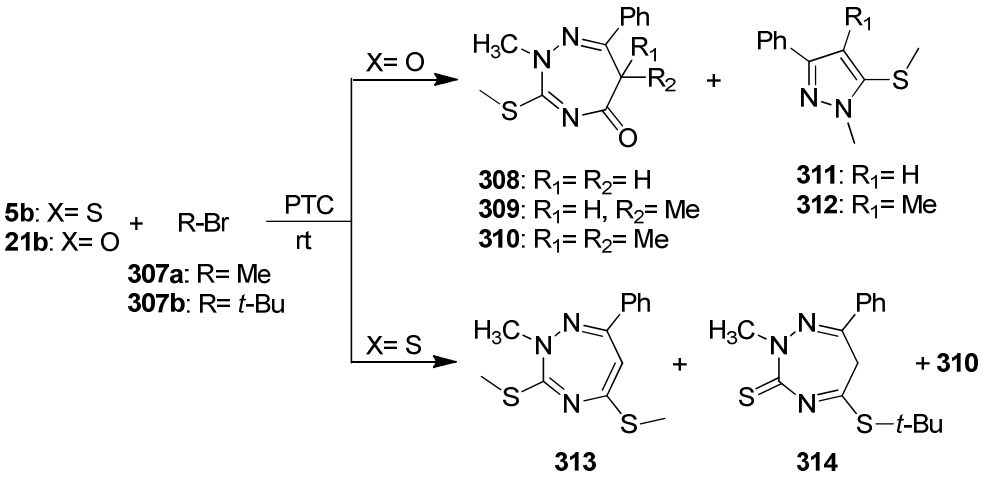
Scheme 75. Synthesis of two regioisomers of thiazolo[1,2,4]triazepines.

The condensation of **5b** with all the alkyldibromides **304a-e** was achieved readily to afford good yields of the unique regioisomers **306a-e** (Scheme 76) [141].



Scheme 76. Synthesis of thiazolo[3,2-d][1,2,4]triazepine-5(6H)-thiones.

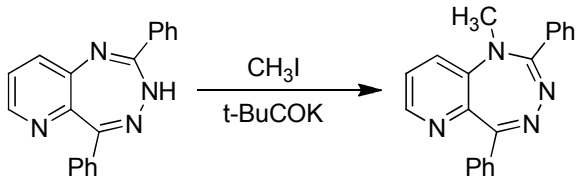
To account for this reactivity, it seemed reasonable to investigate the chemical behaviour of the triazepines **5b** and **21b** towards monoalkyl bromides **307a**, **b** in the same P.T.C conditions. Thus, either with alkyl bromides or alkyl dibromides the oxo group of the triazepine **21b** is inactive while the thioxo group at C-3 position is very reactive. It must be noticed that after attacking this reactive center, the triazepine **21b** could readily rearrange to pyrazoles; due to the C-6 reactivity. On the other hand, **21b** was inactive towards either the dibromides **304c-e** or the alkyl bromide **307b** regardless of the quantity used (Scheme 77) [141].



X	S	S	S	S	O	O	O
R-Br (equiv.)	**307a** (1)	**307a** (2)	**307a** (3)	**307b**	**307a** (1)	**307a** (2)	**307a** (3)
Product (Yield %)	**313** (35)	**313** (90)	**313** (85), **310** (10)	**314** (25)	**308** (26), **311** (45)	**308** (30), **309** (10), **311** (32), **312** (12)	**308** (18), **310** (35), **311** (20), **312** (10)

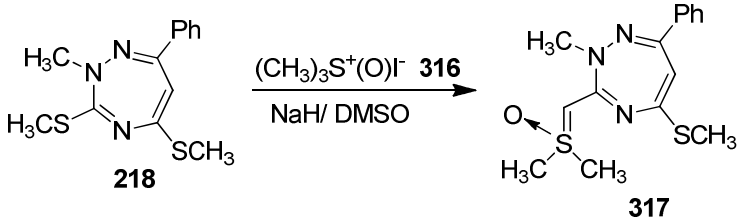
Scheme 77. Alkylation of triazepines with akylbromides.

Treatment of **231a** with methyl iodide in the presence of potassium tert-butylate afforded the corresponding N-methyl derivative **315** (Scheme 78) [116].



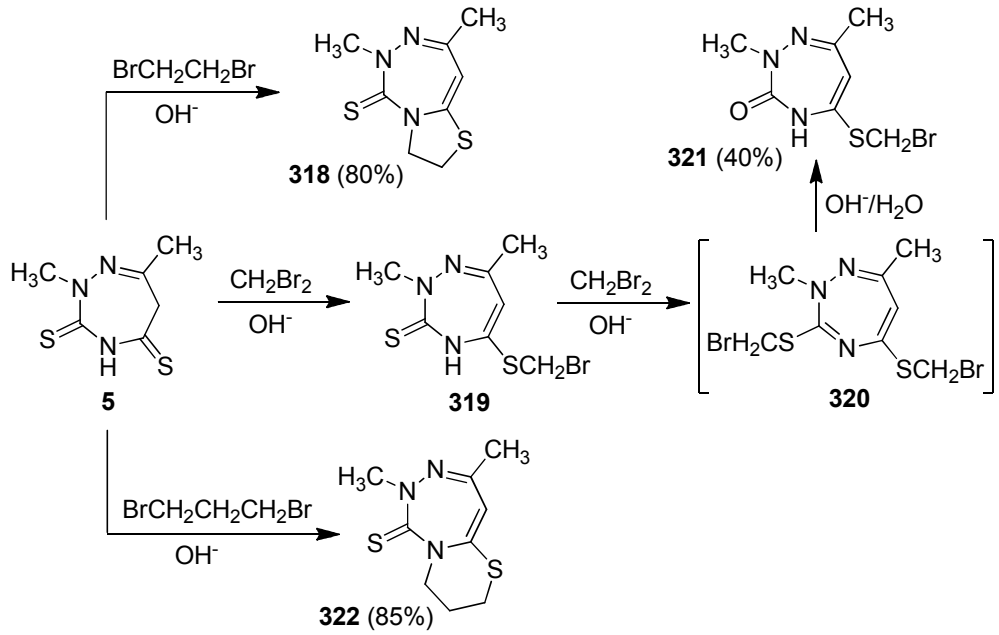
Scheme 78. Alkylation of 1-methyl-2,5-diphenyl-1H-pyrido[3,2-e][1,2,4]triazepine.

Under an inert atmosphere, trimethyloxosulfonium iodide (**316**) reacted with 1,2,4-triazepine **218** [141] in anhydrous DMSO and sodium hydride (80%) at room temperature then cooled to 10 °C to give **317** (85% yield) (Scheme 79) [142].



Scheme 79. Synthesis of *S*-alkyl triazepine derivative.

The chemo- and regioselective alkylation reactions of 3,5-dithioxo-[1,2,4]triazepine **5** in a basic medium with α,ω-dibromoalkanes **304a-c** [in benzene using triethylammoniumbenzylchloride as a catalyst] have been investigated experimentally and theoretically. These reactions afforded several products **318**, **321** and **322** depending on the length of the α,ω-dibromoalkane. Thus, dibromomethane **304a**, led to alkylation on the sulfur atom at position 5 with 40% yield. In the presence of a large excess of **304a**, triazepine **5** is subsequently alkylated at position 3. In contrast, the use of 1,2-dibromoethane **304b**, and 1,3-dibromopropane **304c**, led to the formation of a new five- and six-membered fused heterocycles via an intermolecular alkylation on the thioxo sulfur atom at position 5, followed by an intramolecular alkylation at the nitrogen atom of triazepine **5** with 80% yield (Scheme 80) [143].

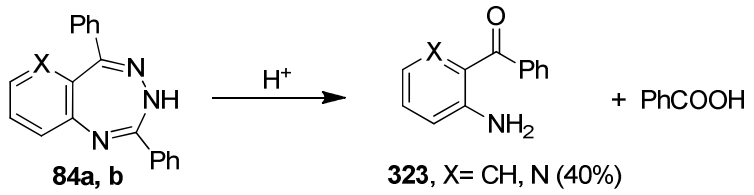


Scheme 80. Alkylation of 2,7-dimethyl-2H-1,2,4-triazepine-3,5(4H,6H)-dithione.

4.2. Hydrolysis

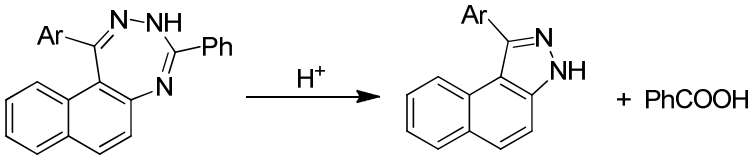
Acid hydrolysis of the pyrido(benzo)[3,2-e][1,2,4]triazepines **84a**, **b** led to the corresponding amino ketones **323** and benzoic acid (Scheme 81) [59, 116].

Hydrolysis of naphthotriazepines **87a-c**, gave **324a-c**, that means that their structures synthesized previously from 5-aryltetrazoles and N-(2-naphthyl) benzimidoyl chlorides corresponds to this isomer (Scheme 82) [59].



84a, b **323**, X= CH, N (40%)

Scheme 81. Hydrolysis of 2,5-diphenyl-3H-pyrido(benzo)[3,2-e][1,2,4]triazepines.

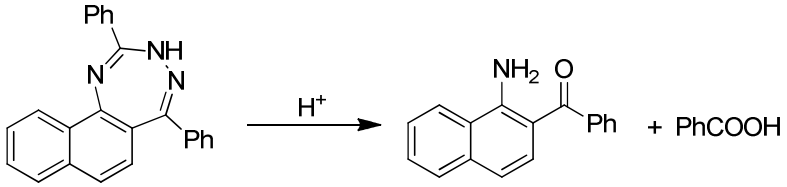


87a-c **324a-c**

a, Ar= Ph (86%); **b**, Ar= 4-MeOC$_6$H$_4$ (85%); **c**, Ar= 3-pyridyl (92%)

Scheme 82. Hydrolysis of 1-aryl-4-phenyl-3H-naphtho[2,1-e][1,2,4]triazepines.

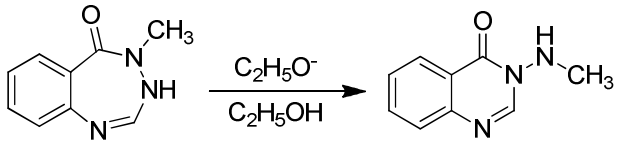
The acid hydrolysis of triazepine **87d** afforded in a good yield the corresponding amino ketone **325** and benzoic acid (Scheme 83) [59].



87d **325** (88%)

Scheme 83. Hydrolysis of 2,5-diphenyl-3H-naphtho[1,2-e][1,2,4]triazepine.

Alcoholysis of 4-methyl-3H-benzo[e][1,2,4]triazepin-5(4H)-one (**100a**) in ethoxide gave 3-(methylamino)quinazolin-4(3H)-one (**326**) (Scheme 84) [54].



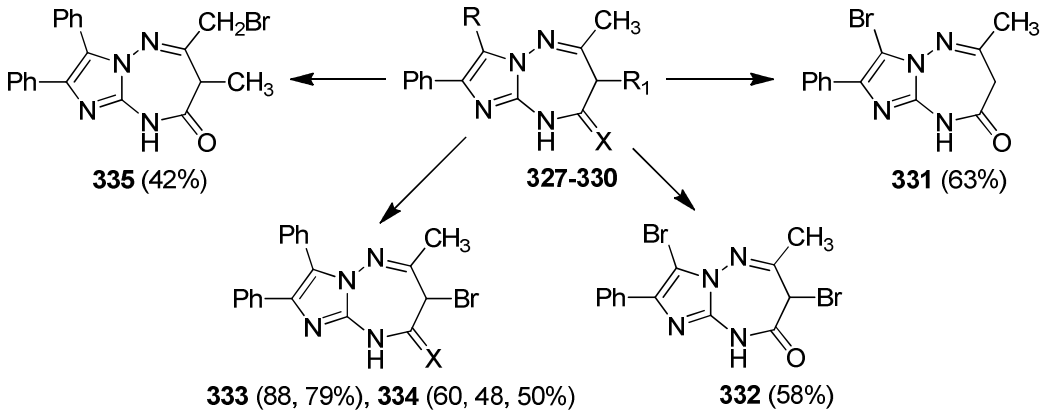
100a **326**

Scheme 84. Hydrolysis of 4-methyl-3H-benzo[e][1,2,4]triazepin-5(4H)-one.

4.3. Halogenation

The reaction of imidazo[1,2-b]-1,2,4-triazepine-4-one(thione) derivatives **327-330** with bromine and N-bromosuccinimide (NBS) was reported. The direction of the bromination of monophenyl-substituted compound **327** was found to depend on the

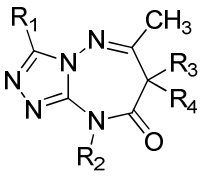
nature of the brominating agent, the solvent, the ratio of the reagents, and temperature. Only 8-bromoimidazotriazepine **331** was isolated when equimolar amounts of **327** and NBS were heated in carbon tetrachloride to 60°C. Reaction of **327** with bromine in acetic acid at room temperature led to predominant formation of 3,8-dibromo derivative **332**, while bromination in DMF at heating gave only 8-bromoimidazotriazepine **331**. Reaction of thione **329** with bromine in acetic acid at 20-25°C or with NBS in boiling CCl_4 gave **334**. The bromination of the bicyclic **330**, in which the reactive positions 3 and 8 are blocked by methyl and phenyl substituents, occurs quite differently. When compound **330** was boiled with NBS in CCl_4, 5H-2-bromomethyl-3-methyl-7,8-diphenylimidazo[1,2-b]-1,2,4-triazepin-4-one (**335**) was obtained (Scheme 85) [144].



327, R= R_1= H; **328**, **329**, R= Ph, R_1= H; **330**, R= Ph, R_1= Me; **327**, **328**, **330**, **333**, X= O; **329**, **334**, X= S

Scheme 85. Bromination of imidazo[1,2-b][1,2,4]triazepines. Compound **331** was crystallized from methanol, **332** from 2-propanol, **333** and **334** from acetic acid, and **335** from 2-methylpropan-1-ol.

Halogenation of **336** led to the mono and di-chlorinated and brominated triazolo[4,3-b][1,2,4]triazepinones **348-351**. On the other hand, halogenation of **337** led to mono and dichloro and bromo compounds **342**, **343**, **350**, **352**, **353** and **355**. Also, halogenation of **338** afforded monohalogenated compounds **344**, **345** and dihalogenated compounds **356** and **357**. Halogenation of **339**, gave monohalogenated products **346**, **347**, **353** and **354** (Scheme 86) [145].

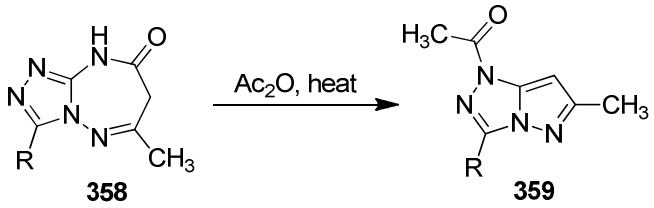


Cpd.	R_1	R_2	R_3	R_4	Cpd.	R_1	R_2	R_3	R_4
336	H	H	H	H	**347**	H	CH_3	CH_3	Br
337	H	CH_3	H	H	**348**	H	H	Cl	Cl
338	H	H	CH_3	H	**349**	H	H	Br	Br
339	H	CH_3	CH_3	H	**350**	H	CH_3	Cl	Cl
340	H	H	H	Cl	**351**	H	CH_3	Br	Br
341	H	H	H	Br	**352**	Br	CH_3	H	H
342	H	CH_3	H	Cl	**353**	Cl	CH_3	CH_3	H
343	H	CH_3	H	Br	**354**	Br	CH_3	CH_3	H
344	H	H	CH_3	Cl	**355**	Br	CH_3	H	Br
345	H	H	CH_3	Br	**356**	Cl	H	CH_3	Cl
346	H	CH_3	CH_3	Cl	**357**	Br	H	CH_3	Br

Scheme 86. Halogenation of triazolo[4,3-b][1,2,4]triazepinones.

4.4. Ring contraction

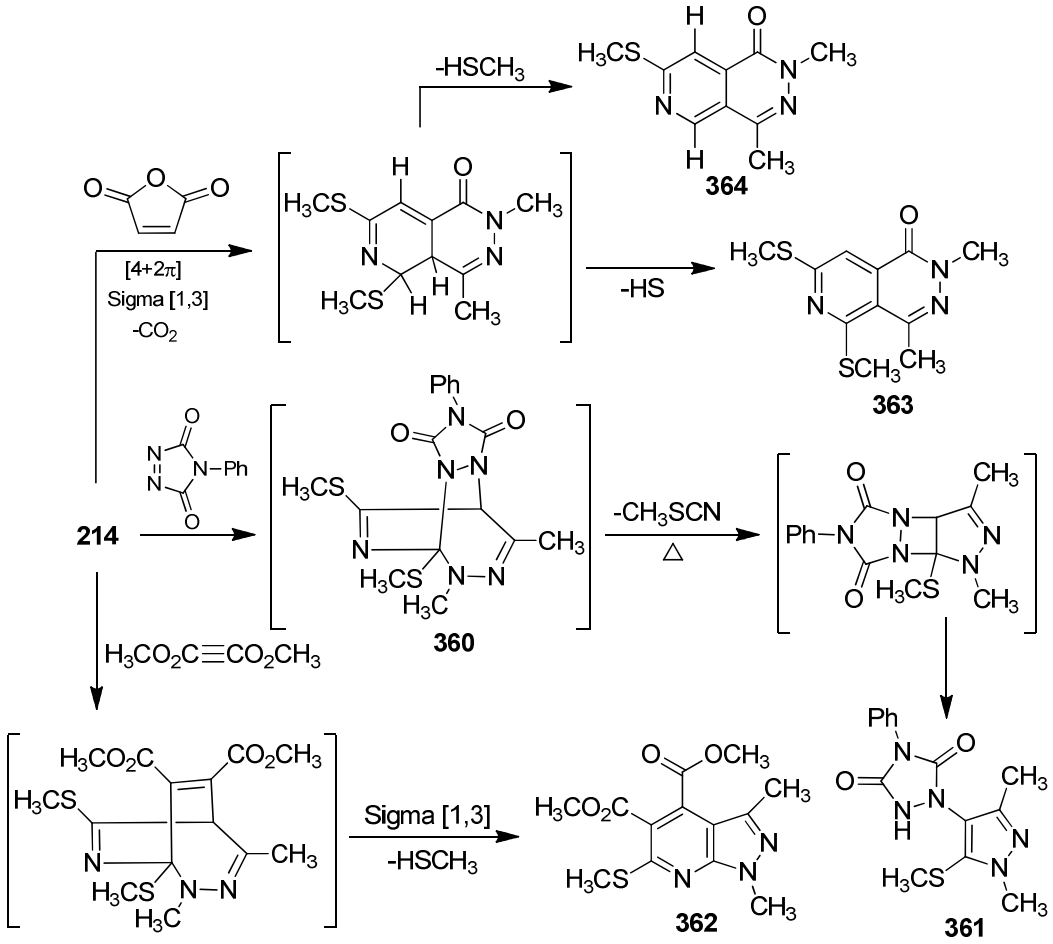
Claramunt and co-workers [146] have reported that analogous triazolo[4,3-b]1,2,4-triazepin-2-ones **358** can undergo an unusual ring contraction on heating in acetic anhydride to give 1-acylated pyrazolo[5,1-c]1,2,4-triazoles **359**, by formal loss of HCNO (Scheme 87).



358 **359**

Scheme 87. Ring contraction of triazolotriazepinones to pyrazolotriazoles.

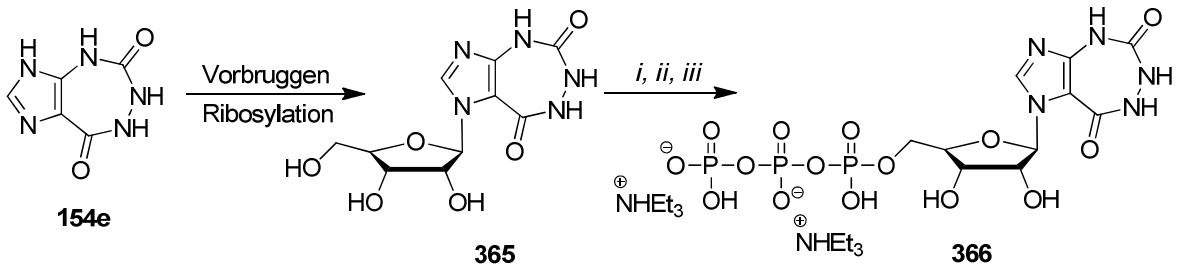
[4+2]π Cycloaddition reaction of 1,2,4-triazepine **214** with 4-phenyl-3H-1,2,4-triazole-3,5(4H)-dione gave 1,2,4-triazolidine-3,5-dione **361** (60%). Also, cycloaddition of **214** to 1,2-bis(methyl-peroxy)ethyne followed by sigmatropic rearrangement afforded pyrazolo[3,4-b]pyridine **362** (60%). In addition, [4+2]π cycloaddition of maleic anhydride to **214** followed by 1,3 sigmatropic rearrangement gave pyrido[3,4-d]pyridazin-1(2H)-ones **363** (20%) and **364** (40%) (Scheme 88) [5].



Scheme 88. Synthesis of 1,2,4-triazolidine-3,5-dione and pyrazolo[3,4-b]pyridine.

4.5. Reactions with carbohydrates

The ring-expanded nucleoside-5'-triphosphate, **366** containing the 5:7-fused heterocyclic systems, imidazo[4,5-e][1,2,4]triazepine, was synthesized from the corresponding nucleoside **365** [147], employing the procedure of Ludwig [148]. The procedure is a one-pot process consisting of sequential operations involving (a) reaction with phosphorus oxychloride/trimethyl phosphate to form the 5'-monophosphate derivative, (b) treatment with bis(tri-n-butylammonium) pyrophosphate to yield the 5'-triphosphate, (c) purification by DEAE-cellulose chromatography on a DEAE-Sephadex A-25 column, using triethylammonium bicarbonate (TEAB) buffer to prepare the bis(triethylammonium) salt of the triphosphate, and (d) conversion of the latter, if necessary, into the corresponding sodium salt by treatment with sodium iodide in acetone (Scheme 89) [149].



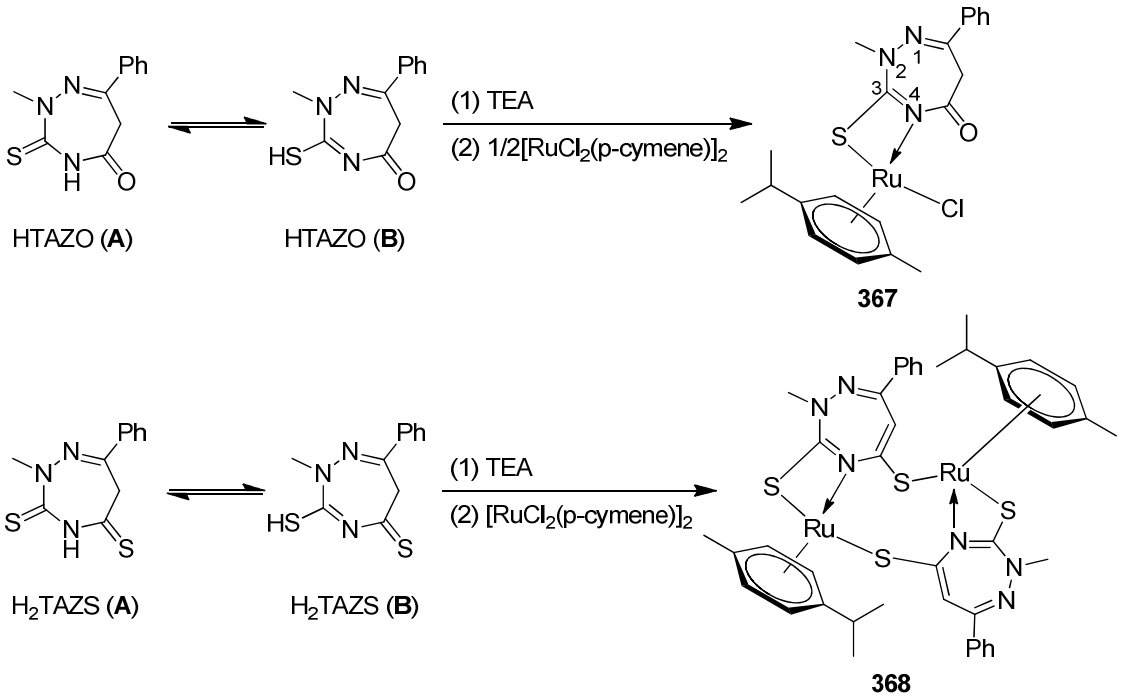
Scheme 89. Synthesis of ribofuranosylimidazo[4,5-e][1,2,4]triazepine-5'-triphosphate Bis(triethylammonium)salt. (i) trimethyl phosphate/ $POCl_3$. (ii) bis(tri-n-butylammonium) pyrophosphate/ DMF/ tri-n-butylamine (iii) triethylammonium hydrogen carbonate (TEAB) buffer

4.6. Coordination chemistry

In spite of the frequent use of heterocyclic compounds as ligands, mainly with transition metals, complexes containing 1,2,4-triazepines are not known. This type of chelate which presents different coordination sites, could provide efficient catalysts with great conformational rigidity. Two unprecedented 1,2,4-triazepine-ruthenium(II) complexes were prepared by reacting $[Ru(p\text{-cymene})Cl_2]_2$ with 2-methyl-5-oxo-7-phenyl-3-thioxo-3,4,5,6-tetrahydro-2H-1,2,4-triazepine (HTAZO) and 2-methyl-7-phenyl-3,5-dithioxo-3,4,5,6-tetrahydro-2H-1,2,4-triazepine (H_2TAZS) [39, 141] (4 equiv.), respectively, in the presence of an excess of triethylamine under 2-propanol reflux conditions. When HTAZO reacts with $[Ru(p\text{-cymene})Cl_2]_2$, only one chlorine atom is removed leading to formation of the mononuclear complex [RuCl(p-cymene)TAZO] (**367**). However, with H_2TAZS, the two chlorine atoms are displaced from the complex precursor to afford readily a good yield of binuclear $[Ru(p\text{-cymene})TAZS]_2$ (**368**) (Scheme 90) [150].

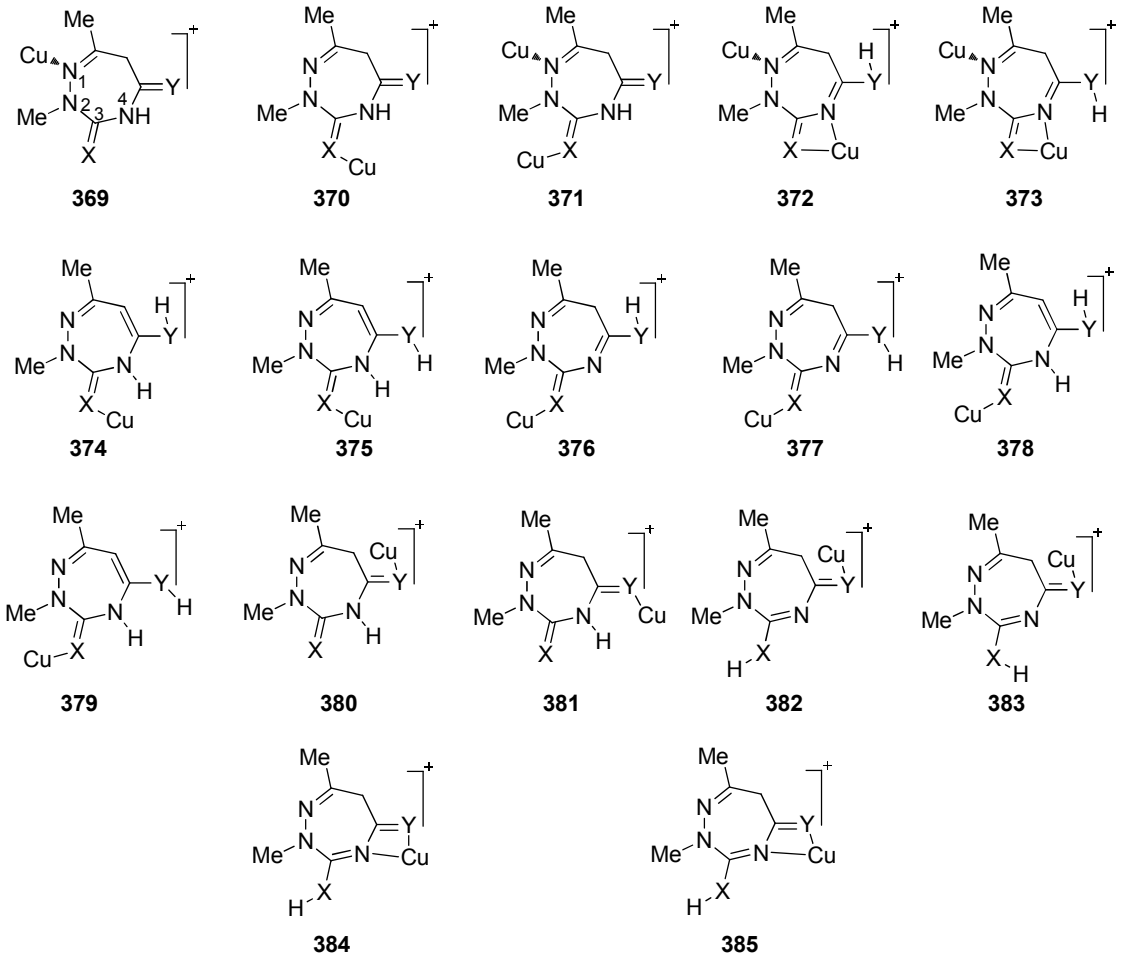
Fdil et al [151] reported aerobic epoxidation of a range of natural terpenic olefines using the triazepinic complexes [RuCl(TAZO)(p-cymene)] $\mathbf{C_1}$ and $[Ru(TAZS)(p\text{-cymene})]_2$ $\mathbf{C_2}$, which were prepared from $[RuCl_2(p\text{-cymene})]_2$ and the corresponding 1,2,4-triazepines (HTAZO and H_2TAZS). While, good similar stereoselectivity was observed for the two complexes, $\mathbf{C_1}$ was shown to be more effective and chemioselective.

On the other hand, complexes between triazepine thioxo derivatives and molecular iodine have a 1:1 stoichiometry in dilute solution. The 3-oxo-5-thioxo-2,7-dimethyl-[1,2,4]-triazepine seems to be an oxygen base towards I_2. The good correlation between calculated and experimental free energies indicates that the structural effects are similar in the gas phase and in solution [49].



Scheme 90. Preparation of 1,2,4-triazepine-ruthenium(II) complexes.

For 2,7-dimethyl-3,5-dioxo-[1,2,4]-triazepine-Cu^+ and 2,7-dimethyl-3,5-dithio-[1,2,4]-triazepine-Cu^+, the initial adduct in which Cu^+ interacts with the heteroatom attached to position 3 is expected to evolve toward a more stable four-membered ring structure in which the metal ion bridges between the heteroatom at position 3 and the amino group at position 4 of the corresponding enolic tautomer. Although these minima cannot be formed by direct attachment of the metal cation to the base, the required tautomerization process involved activation barriers which lie in energy below the entrance channel, so the overall process is always exothermic. Among all the compounds considered, 3,5-dithiotriazepine is the one that binds Cu^+ in the gas phase more strongly. A good correlation between calculated Cu^+ binding energies and the experimental proton affinities exists (Scheme 91) [152].



Scheme 91. Schematic representation of different tautomers of triazepine-Cu^{+} and thiotriazepine-Cu^{+} complexes in all possible conformers.

5. Conclusion

This review reported the synthesis of monocyclic 1,2,4-triazepines, benzo, naphtho[1,2,4]triazepines and heterocycles fused with five and six membered ring systems. There are many sections on the synthesis of 1,2,4-triazepine heterocycles from different starting materials: for example, starting from acyclic compounds such as 1,3-diketones, bis-acetylenic ketones, thiosemicarbazides and benzohydrazides and from other heterocycles such as azoles (monocyclic and fused), 1,2-dihydropyridine-3,5-dicarbonitrile, N-(m-pyridyl)benzimidoyl chloride, and 2-hydrazinylpyrimidine. Besides, reactions of these heterocycles with different electrophiles i.e., alkylation and halogenations. The titled compounds undergo hydrolysis in acid and alcohol medium. The ring-expanded nucleoside-5'-

triphosphate and ring contraction were discussed. The coordination chemistry of 1,2,4-triazepines was described.

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Biographical Sketch

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Mohamed A. Abozeid was born in Egypt (1987). In 2008, he received B.Sc in chemistry(excellent with honor). In 2012, he finished his M.Sc. in organic chemistry under the supervision of professors Abdel-Rahman. H. Abdel-Rahman, Ezzat. M. Kandeel and El-Sayed. I. El-Desoky at Mansoura University, Egypt. Subsequently, he got the Japanese Government Scholarship (MEXT) to study Ph.D in 2012. Now, he is doing his PhD under the supervision of prof. Hiroaki Sasai at Osaka University, Japan. He is a member of The American Chemical Society (ACS), Chemical Society of Japan (CSJ) and Pharmaceutical Society of Japan (PSJ). His scientific interests are focused in the synthesis of medicinally active heterocyclic compounds, organometallic chemistry and asymmetric catalysis.

Ibrahim Abdel-Motaleb Mousa was born in 1975 in Mansoura, Egypt and received his B.Sc. 1997 and M.Sc. 2002 from faculty of science, South Valley University, Qena, Egypt. He obtained his Ph.D. in organic chemistry 2006 from the same university under the supervision of professor A.M. Hussien and professor A.A. Harb. He has been a lecturer at the South Valley University. His interest is the synthesis of organic compounds with its biological activity using sulfa drug compounds.

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GRAPHICAL ABSTRACT

Advances in 1,2,4-Triazepines Chemistry

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This review reported the chemistry of 1,2,4-triazepines. Heterocyclic 1,2,4-triazepines are mono and fused cycles.