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One-pot synthesis of 5*H*-1,3,4-thiadiazolo[3,2-*a*]pyrimidin-5-one derivatives

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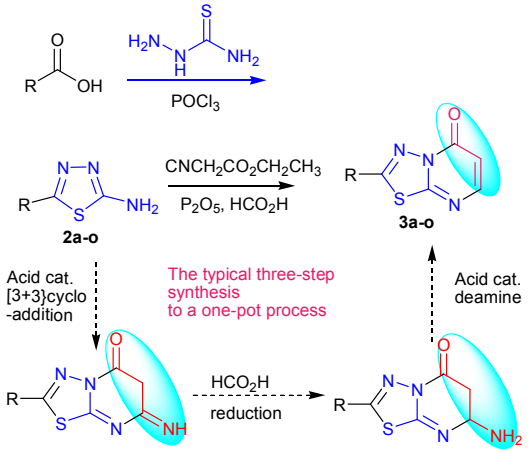
A novel and efficient one-pot method has been developed for the synthesis of 2-substituted-5*H*-1,3,4-thiadiazolo[3,2-*a*]pyrimidin-5-one derivative by the combination of [3+3] cycloaddition, reduction, deamine reactions. The fused heterocyclic compounds 2-substituted-5*H*-1,3,4-thiadiazolo [3,2-*a*]pyrimidin-5-ones was synthesized by the catalytic diversity-oriented. As an extension of the synthetic methodology, some 4*H*-Pyrido[1,2-*a*]pyrimidin-4-one 4a-c was synthesized. The π-π accumulation structure of supramolecular self-assembly was discussed in the crystal.

Thiadiazolopyrimidines, analogous structure compounds display an important role in pharmacological chemistry. The nucleus and a number of its substituted products exhibit interesting biological and pharmacological properties.[1-10] Because of their importance; the synthesis of these compounds has attracted considerable attention. In recent years, many papers concerning the synthesis of 2,7-disubstituted-1,3,4-thiadiazolo[3,2-*a*]pyrimidin-5-one derivatives have been reported.[11-15] However, little attention has been paid to the synthesis of 2-substituted-1,3,4-thiadiazolo[3,2-*a*]pyrimidin-5-ones, which are unsubstituted on the 7-position. And up to now, there are few reports on the synthesis of them in literature. The structure of 1,3,4-thiadiazolo[3,2-*a*]pyrimidin-5-one was alike with mother structure of importance quinolone antimicrobial agents. The study on methodology of synthesis or the structure of them and their derivatives analogous compounds in biological and pharmacological fields was importance.

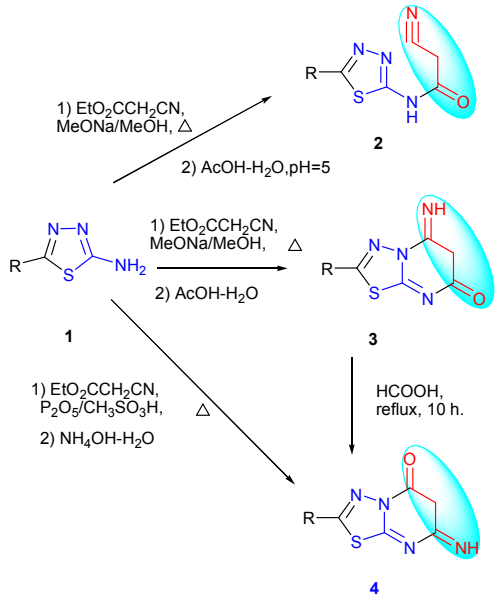
The two-steps synthesis method of 2-amino-7-substituted-1,3,4-thiadiazolo[3,2-*a*]pyrimidin-5-one derivatives have been reported, which was prepared from 2-amino-thiadiazole derivatives and *β*-keto esters, but yield was low.[13-14] Cascade, tandem, one-pot, multicomponent domino reactions, atom economy, catalyst-free, ring opening, supramolecular self-assembly and diversity-oriented synthesis (DOS) are increasingly applied to the construction of natural and designed molecules.[16] A novel and efficient one-pot method has been developed for the synthesis of 2-substituted-5*H*-1,3,4-thiadiazolo[3,2-*a*]pyrimidin-5-one derivative. Some novel fused-ring systems 2-substituted-5*H*-1,3,4-thiadiazolo[3,2-*a*]pyrimidin-5-one derivatives **3a-o** were synthesized by the one-pot reaction of the corresponding 2-amino-5-substituted-1,3,4-thiadiazoles **2a-o** and ethyl cyanoacetate under present of catalytic agent (**Scheme 1**).



Scheme 1 The synthesis of 2-substituted-5*H*-1,3,4-thiadiazolo[3,2-*a*]pyrimidin-5-one derivatives for combination of [3+3] cycloaddition, eduction, eamine

When a solution of 2-amino-5-substituted-1,3,4-thiadiazole, ethyl cyanoacetate and CH_3ONa in dry methanol was refluxed, the 2-cyano-*N*-(5-substituted-1,3,4-thiadiazol-2-yl)acetamide **2** was given.[17] Previously, the solution of 2-amino-5-substituted-1,3,4-thiadiazole, ethyl cyanoacetate and CH_3ONa in dry methanol was refluxed, the reaction gave other structure compound, 5,6-dihydro-5-imino-2-substituted-1,3,4-thiadiazolo[3,2-*a*]pyrimidin-7-one[18] **3**. The same type reaction gave difference form results. The ring conversion reaction of 5,6-dihydro-5-imino-2-substituted-1,3,4-thiadiazolo[3,2-*a*]pyrimidin-7-one in formic acid at 100 °C for 10 h was carried to 6,7-dihydro-7-imino-2-substituted-1,3,4-thiadiazolo[3,2-*a*]pyrimidin-5-one **4**.[19] The reaction of 2-amino-5-substituted-1,3,4-thiadiazole, ethyl cyanoacetate and methanesulfonic acid-phosphorus pentoxide gave 6,7-dihydro-7-imino-2-substituted-1,3,4-

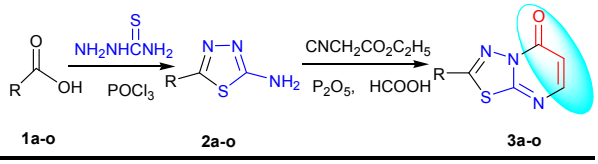
thiadiazolo[3,2-*a*]pyrimidin-5-one **4**.[16] In same starting materials, reagents, solvents and catalytic agent, the reaction gives different products to the intermediate 2-cyano-*N*-(5-substituted-1,3,4-thiadiazol-2-yl)acetamide **2** or 5,6-dihydro-5-imino-2-substituted-1,3,4-thiadiazolo[3,2-*a*]pyrimidin-7-one **3**. With same starting materials, reagents and solvents, the reaction also gives equally type products under different catalytic agent. 6,7-Dihydro-7-imino-2-substituted-1,3,4-thiadiazolo[3,2-*a*]pyrimidin-5-one **4** could be synthesized by 2-3 steps or one step from 2-amino-5-substituted-1,3,4-thiadiazole. The diversity synthesis is shown in **Scheme 2**.



Scheme 2 The synthesis of 6,7-dihydro-7-imino-2-substituted-1,3,4-thiadiazolo[3,2-a]pyrimidin-5-one

In order to obtain new 6,7-dihydro-7-imino-2-substituted-1,3,4-thiadiazolo[3,2-*a*]pyrimidin-5-one derivatives, the reaction of 2-amino-5-substituted-1,3,4-thiadiazoles **2a-o** and ethyl cyanoacetate under the presence of phosphorus pentoxide and formic acid was utilized. The phosphorus pentoxide or formic acid was utilized respectively to the reaction catalytic of 2-amino-5-substituted-1,3,4-thiadiazoles **2a-o** and ethyl cyanoacetate, but phosphorus pentoxide and formic acid has not been utilized together to the reaction. Here, we obtained the synthesis of a new series of 2-substituted-5*H*-1,3,4-thiadiazolo[3,2-*a*]pyrimidin-5-one derivatives **3a-o**. The synthesis pathway is shown in **Table 1**.

Table 1 Diversity-synthesis oriented of compounds **2a-o** to **3a-o**

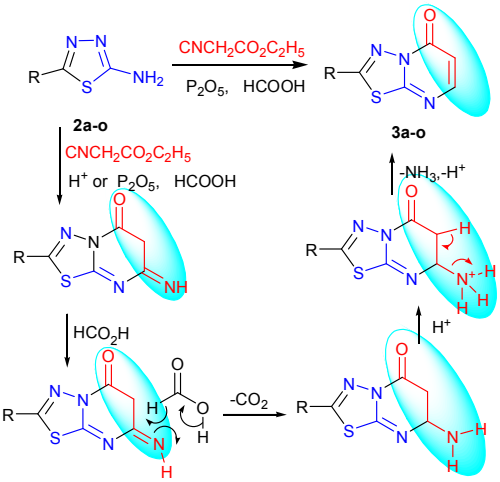


1a-o **2a-o** **3a-o**

Entry	Substrate	R	Yield(%)[a]
1	**3a**	2-ethoxyphenyl	90
2	**3b**	4-methylphenyl	75
3	**3c**	3-methoxyphenyl	78.5
4	**3d**	4-methoxyphenyl	93
5	**3e**	phenyl	30
6	**3f**	4-chlorophenyl	48
7	**3g**	4-bromophenyl	45
8	**3h**	furan-2-yl	52.5
9	**3i**	2-chlorophenyl	69.5
10	**3j**	3-methylphenyl	82
11	**3k**	2-bromophenyl	56
12	**3l**	2-fluorophenyl	62
13	**3m**	benzyl	67
14	**3n**	2-methoxyphenyl	85
15	**3o**	2-methylphenyl	76

[a] Isolated yield

The tandem reaction of diversity-oriented synthesis was carried out by method of typical three-step synthesis to a one-pot process under the presence phosphorus pentoxide-formic acid. How, the target product was given by formic acid which was thinked for the reductant of Eschweiler-Clarke and Leuckart-Wallach reaction conditions.[20-21] The synthesis of a new series of 2-substituted-5*H*-1,3,4-thiadiazolo[3,2-*a*]pyrimidin-5-one derivatives **3a-o** was combination of [3+3] cycloaddition, reduction, deamine reactions and 30~93% yield, which is the tandem reaction. The reaction was combination of many type and step reactions in one-pot reaction, 7-imino was given by Tsuji modes,[16] was eliminated by tandem reaction of reduction and deamine when methanesulfonic acid-phosphorus pentoxide was changed to formic acid-phosphorus pentoxide as the catalytic agent. Compounds **2a-o** were synthesized by the method reported in the literature.[18,22-32] The mechanism of synthesis is shown in **Scheme 3**.



Scheme 3 The reaction mechanism of transformation of **2a-o** to **3a-o**

Seeing that above, the synthesis of target product was explored by 2-amino-5-(4-methylphenyl)-1,3,4-thiadiazole, ethyl cyanoacetate, phosphorus pentoxide and concentrated H_2SO_4. The reaction was carried out at 100-105 ^oC for 12 h, monitored by TLC, which didn't give relevant target product. Then, the synthesis of the targe product was probed by the addition of 2-amino-5-(2-ethoxyphenyl)-1,3,4-thiadiazole, ethyl cyanoacetate, phosphorus pentoxide and glacial acetic acid, and so it didn't give the target product. When we only choose phosphorus pentoxide-formic acid as condensation reagent at

the same conditions, the target product (**3d**) was obtained in yield of 93%. Phosphorus pentoxide-formic acid was an efficient condensation regent for the synthesis of 2-substituted-5*H*-1,3,4-thiadiazolo[3,2-*a*]pyrimidin-5-one derivatives **3a-o**. The synthesis reaction didn't give target product by 2-amino-5-substituted-1,3,4-thiadiazole, ethyl cyanoacetate, phosphorus pentoxide and glacial acetic acid (or concentrated H_2SO_4 or methanesulfonic acid), but target product was given by formic acid which is the reducing reagent as Leuckart-Wallach, Eschweiler-Clarke reaction conditions. The tandem reaction of 2-amino-5-substituted-1,3,4-thiadiazole, ethyl cyanoacetate and methanesulfonic acid-phosphorus pentoxide gave 6,7-dihydro-7-imino-2-substituted-1,3,4-thiadiazolo[3,2-*a*]pyrimidin-5-one.[16] Then the imino group of 7-position was reductive converted to amino by formic acid.[20,33] After elimination of ammonia, the target product was given under acid alike Fischer indole synthesis.[34] Described herein is our approach, which reduces the typical three-step synthesis to a one-pot process. The mechanism of reaction is shown in **Scheme 3**. The molecular structure of the product **3d** and **3i** was established by the X-ray diffraction (**Fig 1**, **Fig 2**). **The supramolecular structure of compound 40a is shown in Figure 3.**

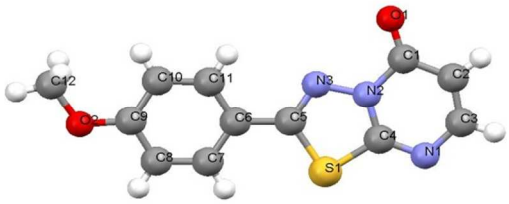


Figure 1 A Mercury (1.4, CCDC, 2005) view of the molecular structure of **3d**[35]

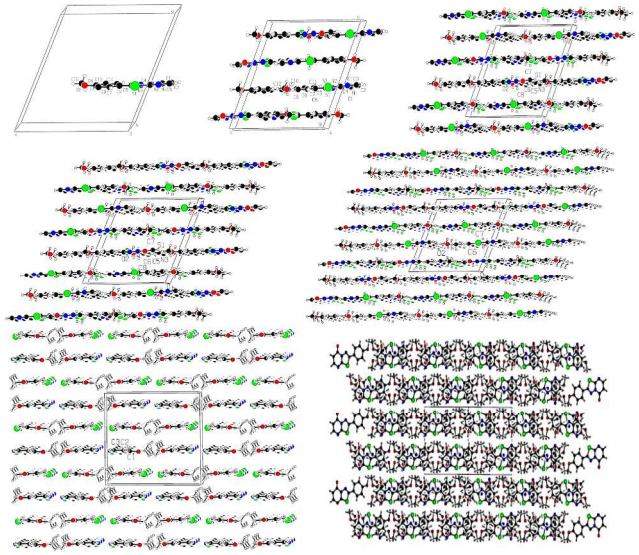


Figure 2. The π-π accumulation structure of 3d supramolecular self-assembly.

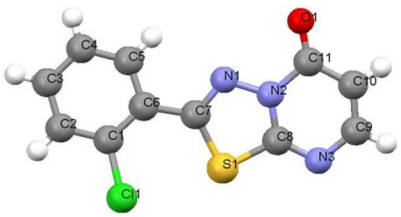


Figure 3 A Mercury (1.4, CCDC, 2005) view of the molecular structure of **3i**[36]

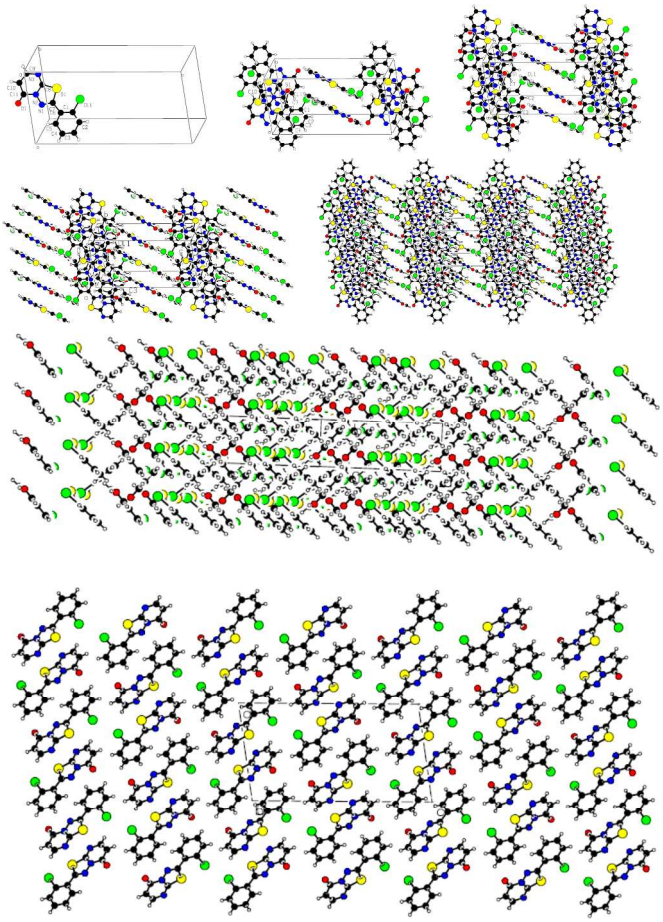
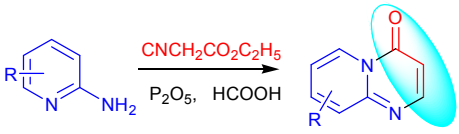


Figure 4. The π-π accumulation structure of 3i supramolecular self-assembly.

As an extension of the synthetic methodology, some 4*H*-Pyrido[1,2-*a*]pyrimidin-4-one **4a-e** was synthesized. The synthesis pathway is shown in **Table 2**.

Table 2 Diversity-synthesis oriented of compounds **4a-c**.



4a-c

Entry	Substrate	R	Yield(%)[a]
1	**4a**	H	20
2	**4b**	7- methyl	37.5
3	**4c**	7-chloro	33
4	**4e**	2-chloro	42.5

[a] Isolated yield

Conclusions

In conclusion, a novel and efficient one-pot method has been developed for the synthesis of 2-substituted-5*H*-1,3,4-thiadiazolo[3,2-*a*]pyrimidin-5-one derivative by the tandem

reaction of [3+3] cycloaddition, reduction, deamine reactions under the present of formic acid-phosphorus pentoxide as the catalytic agent. The fused heterocyclic compounds 2-substituted-5*H*-1,3,4-thiadiazolo[3,2-*a*]pyrimidin-5-ones was synthesized by the catalytic diversity-oriented.

Notes and references

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† Footnotes should appear here. These might include comments relevant to but not central to the matter under discussion, limited experimental and spectral data, and crystallographic data.

Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/c000000x/

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35. **3d**, $C_{12}H_9N_3O_2S$, crystal size 0.35×0.32×0.29 mm^3, space group C2/c(monoclinic), a=14.1942(13), b=13.4679(13), c=12.8940 (12) Å, β=112.384(7)º, V=2279(4) Å^3, Z=8, ρ_{calcd}=1.511 g cm^{-3}, $\mu_{(MoKa)}$=0.281mm^{-1}. Data were measured on a Bruker SMART APEX diffractometer (MoKa radiation, λ=0.71073 Å) at 296 K, and the structure was solved by direct methods. Of 5973 reflections collected, 2116 were unique reflections (R_{int} =0.0336); data/restraints/parameters 2116/0/165; final R indices [I>2σ(I)]: R_1 =0.0422, wR2 =0.0982; R indices (all data): R_1 =0.0677, wR_2 =0.1099. CCDC 779780 contains the supplementary crystallographic data for **3d**. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre at www.ccdc.cam.ac.uk/data_request/cif.
36. **3i**, $C_{11}H_6ClN_3OS$, crystal size 0.38×0.35×0.31 mm^3, space group P2(1)/n (monoclinic), a=10.838(4), b=4.9244(19), c=20.011(7) Å, β=98.505(6)º, V=1056(7) Å^3, Z=4, ρ_{calcd}=1.658 g cm^{-3}, $\mu_{(MoKa)}$=0.542mm^{-1}. Data were measured on a Bruker SMART APEX diffractometer (MoKa radiation, λ=0.71073 Å) at 296 K, and the structure was solved by direct methods. Of 5348 reflections collected, 2061 were unique reflections (R_{int} =0.0237); data/restraints/parameters 2061/0/154; final R indices [I>2σ(I)]: R_1 =0.0330, wR2 =0.0846; R indices (all data): R_1 =0.0397, wR_2 =0.0902. CCDC 779674 contains the supplementary crystallographic data for **3d**. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre at www.ccdc.cam.ac.uk/data_request/cif.

One-pot synthesis of 5*H*-1,3,4-thiadiazolo [3,2-*a*]pyrimidin-5-one derivatives

H.-R. Dong, Z.-L. Gao, R.-S. Li, Y.-M. Hu, H.-S. Dong,* Z.-X. Xie *

Abstract

A novel and efficient one-pot method has been developed for the synthesis of 2-substituted-5*H*-1,3,4-thiadiazolo[3,2-*a*]pyrimidin-5-one derivative by the tandem reaction of [3+3] cycloaddition, reduction, deamine.