RSC Advances

ROYAL SOCIETY OF CHEMISTRY

www.rsc.org/advances

Cite this: DOI: 10.1039/c0xx00000x

www.rsc.org/xxxxxx

ARTICLE TYPE

A simple copper-catalysed tandem cyclisation of ynamides leading to triazolo-1,2,4-benzothiadiazine-1,1-dioxides in PEG-400 medium

Alla Siva Reddy, M. Nagarjuna Reddy and K. C. Kumara Swamy*

Received (in XXX, XXX) XthXXXXXXXXX 20XX, Accepted Xth XXXXXXXXX 20XX
DOI: 10.1039/b000000x

An efficient one-pot approach for the synthesis of fused triazolo 1,2,4-benzothiadiazine-1,1-dioxide derivatives from functionalised ynamides and sodium azide in the presence of CuI using PEG-400 as the medium is described. The cyclisation process involves the intermolecular C-N bond formation and subsequent cycloaddition between ynamide and azide. Thus three new C-N bonds are formed in a single step. It is also demonstrated that the triazole ring in triazolo-1,2,4-benzothiadiazine-1,1-dioxide can be readily decyclised in the presence of glacial acetic acid with the elimination of molecular nitrogen.

Introduction

Alkynes have been extensively used in many organic transformations to synthesize important molecules and natural products.[1] Heteroatom substituted alkynes, especially ynamides (N-substituted alkynes) have drawn prominent attention from a synthetic perspective due to their high reactivity.[2] These precursors are utilized in both electrophilic and nucleophilic reactions.[3] They also act as surrogates of allenes. Over the last few years, a rapid expansion in the cycloaddition reactions of ynamides has taken place.[4] However, there is still enormous scope to explore reactions of functionalised ynamides in cycloaddition and cyclisation reactions.

Benzosultams display a significant role in drug discovery because of their diverse medicinal uses.[5, 6] Recently, much interest has been directed towards sultams such as 1,2,4-benzothiadiazine-1,1-dioxides and triazolothiadiazepine 1,1-dioxides because of their wide range of biological activities.[7, 8] Recently, Majumdar's group reported the synthesis of triazolothiadiazepine 1,1-dioxides by basic alumina supported azide-alkyne cycloaddition whereas Sun's group reported the synthesis of triazoloquinazolinones[9a] via copper catalysed tandem click and intramolecular C-H amidation.[9b] It should be noted that 1,2,3-triazole moiety is also important in synthetic, medicinal as well as materials chemistry.[10, 12] In this context, we envisioned that compounds having both 1,2,3-triazole and sultam moieties will have utility in medicinal chemistry. Representative examples are shown in Figure 1.[13] To the best of our knowledge, formation of benzosultam fused triazoles directly from ynamide is not reported. In continuation to our studies on [Cu]-catalysed synthesis of fused triazoles,[14] we report herein a simple route for benzosultam fused triazoles from ynamides using PEG-400 as a solvent in this work.

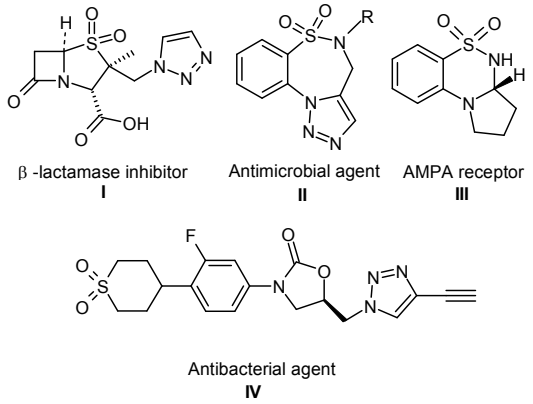


Figure 1. Examples of pharmaceutically useful sultams and triazoles.

Results and Discussion

The precursors used in the present study are N-alkynyl 2-halo-benzenesulfonamides. These were prepared using 2-halo-benzenesulfonamides **1a-i** and the corresponding bromo-alkynes **2a-g** following a literature method.[15] However, all these compounds **3a-p** (Figure 2) are new. These substrates readily undergo hydrolysis at room temperature but can be stored at low temperature. Details of their synthesis are given in the supporting information.

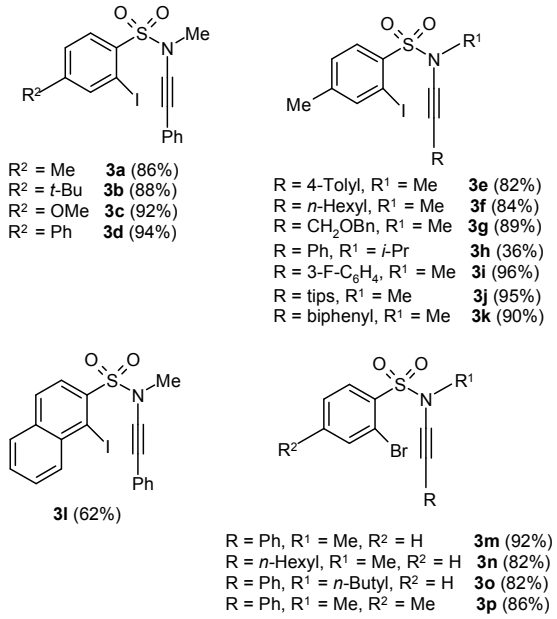
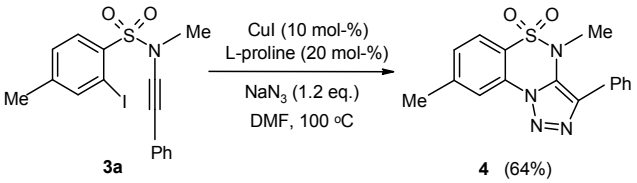


Figure 2. Ynamides used in the present study.

Initially, we performed the reaction between N-alkynyl 2-iodo-benzenesulfonamide **3a** and sodium azide in the presence of CuI (10 mol-%) and L-proline (20 mol-%) in DMF solvent at 100 °C for 12 h. To our delight, we got the desired benzosultam fused 1,2,3-triazole product **4** in 64% isolated yield. This reaction proceeds *via* intermolecular C-N bond formation followed by cycloaddition between alkyne and azide. Our next step was directed towards screening various reaction parameters to improve the yield of the product and the details are given in Table 1.



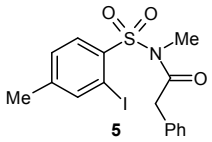
Scheme 1. One-pot [Cu]-catalysed reaction of ynamide **3a** with sodium azide to afford compound **4**.

Table 1: Optimization of the catalytic system for the synthesis of triazolo 1,2,4-benzothiadiazine 1,1-dioxide **4** (cf Scheme 1)[a]

Entry	CuX (mol-%)	NaN_3 (eq.)	Solvent	Temp. (°C)	Yield (%)[b]
1	CuI (10)	1.2	DMF	100	64
2	CuI (10)	1.2	$(EtO)_2CO$	100	0
3	CuI (10)	1.2	H_2O	100	20[c]
4	CuI (10)	1.2	PEG-400	100	65
5	CuI (5)	1.2	PEG-400	100	65
6	CuI (2)	1.2	PEG-400	100	58
7	**CuI (5)**	**2.0**	**PEG-400**	**100**	**78**
8	CuCl (5)	2.0	PEG-400	100	65
9	$CuSO_4.5H_2O$(5)	2.0	PEG-400	100	62
10	$CuCl_2.2H_2O$(5)	2.0	PEG-400	100	48
11	CuBr (5)	2.0	PEG-400	100	68
12	CuI (5)	2.0	PEG-400	100	56[d]
13	CuI (5)	2.0	PEG-400	80	72[e]
14	CuI (5)	2.0	PEG-400	60	38
15	CuI (5)	2.0	PEG-400	r.t.	52

[a]Ynamide (0.24 mmol), CuI (x mol-%), NaN_3, solvent (1 mL) in the absence of L-proline for entries **1-15**. [b]Yield of the isolated product. [c]Hydrolysed product **5** was isolated (36%). [d]Reaction was performed in an open air. [e]CuI (30 mol-%), $TMSN_3$ (2.5 eq.), DIPEA (3 eq.), DMF (1 mL) were used.

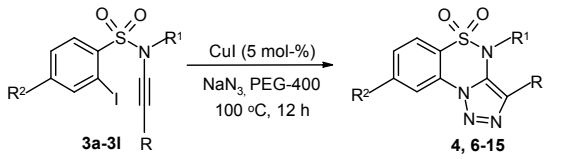
The absence of ligand (L-proline) did not affect the yield of the product (entry 1). Diethyl carbonate was ineffective and did not furnish the desired product (entry 2). Water as a solvent led to only 20% of **4** along with 36% of the hydrolyzed product **5** (entry 3).[16] Thus, hydrolysis was a major problem in water medium. Surprisingly, in PEG-400 as a solvent compound **4** was isolated in 65% yield (entry 4). Although all the solvents checked had oxygen donors, PEG-400 has a combination of ether and residual hydroxyl groups which may promote the reaction better.[17] This might be responsible for the improved yield of the product. Later, we found that 5 mol-% of CuI furnished similar yield (entry 5). Further decreasing catalyst loading to 2 mol-% CuI, decreased the yield of the product (entry 6). The yield was increased to 78% by using 2 equiv of NaN_3 instead of 1.2 equiv of NaN_3 (entry 7). No reaction was observed in the absence of CuI. Utilization of other copper salts did not improve yield of the desired product. Decrease in the yield of the product was observed when the reaction was performed in open air (entry 12). Lowering the reaction temperature also decreased the yield of the product. The reaction proceeds at room temperature but the yield was only 52% even after longer reaction times (48 h) (entry 15). It is interesting to note that Yao's conditions[8a] did give decent yields (ca 70%) but in view of the use of simple NaN_3, the environmentally friendly solvent PEG-400, and lesser load of CuI, in this work we have chosen conditions shown in entry 7 as the best.

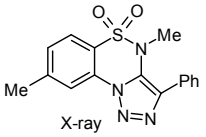
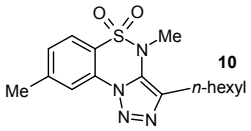
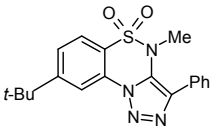
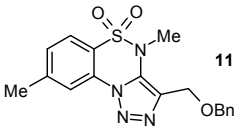
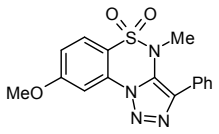
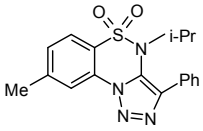
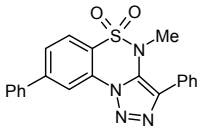
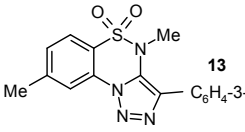
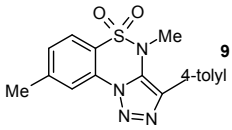
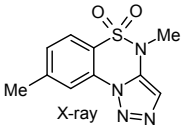
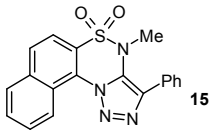


With the optimized conditions (entry 7) in hand, we examined the scope of this [Cu]-catalysed one-pot reaction by employing various N-alkynyl 2-iodo-benzenesulfonamides **3a-l** with sodium azide. Gratifyingly, the triazolo 1,2,4-benzothiadiazine 1,1-dioxide derivatives (**4**, **6-15**) were isolated in good to excellent yields (Table 2). The structure of compound **4** was confirmed by X-ray crystallography (Figure 3). There was no significant effect on yields of the products by changing the substituent on the benzene ring of 2-iodo-benzenesulfonamides. While changing the substituent on the nitrogen of sulfonamide, we encountered a difficulty in the preparation of ynamide **3h**, however we did not find any difficulty in the course of cyclisation process. The triisopropylsilyl substituted ynamide **3j** afforded the desired product **14** in 80% yield with the removal of triisopropylsilyl group and the structure was confirmed by X-ray crystallography (Figure 4). On the other hand the bulkier 1-bromo-2-biphenyl ethyne gave the corresponding ynamide **3k** in excellent yield, but unfortunately the cyclisation reaction was not observed. This may be due to the steric effect caused by the biphenyl moiety. Both alkyl and aryl alkynyl ynamides were readily subjected to this one-pot protocol to obtain benzosultam

fused triazoles. Overall the reaction involves the formation of three new C-N bonds.

Table 2: Synthesis of triazolo 1,2,4-benzothiadiazine 1,1-dioxides from N-alkynyl 2-iodo-benzene sulfonamides.



Product		Yield (%)	Product		Yield (%)
	**4**	78		**10**	72
	**6**	84		**11**	48
	**7**	70		**12**	64
	**8**	78		**13**	62
	**9**	78		**14**	80
				**15**	72

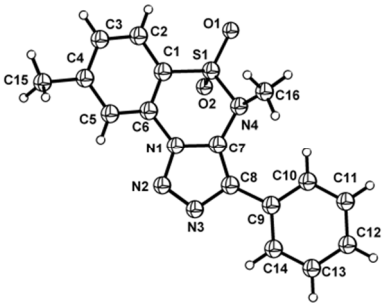


Figure 3. ORTEP diagram for compound **4.** Selected bond lengths [Å] with esds in parentheses: C(6)-N(1) 1.411(2), C(7)-N(1) 1.367(2), C(8)-N(3) 1.377(2), S(1)-O(1) 1.4229(13), S(1)-O(2) 1.4201(15), S(1)-N(4) 1.6487(15).

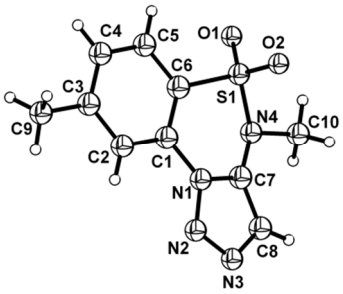
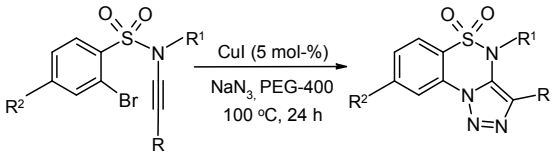


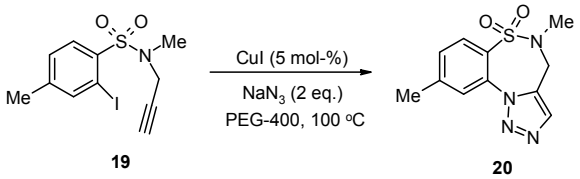
Figure 4. ORTEP diagram for compound **14.** Selected bond lengths [Å] with esds in parentheses: C(1)-N(1) 1.403(2), C(7)-N(1) 1.348(3), C(8)-N(3) 1.357(3), S(1)-O(1) 1.4188(18), S(1)-O(2) 1.4233(19), S(1)-N(4) 1.6491(18).

In a manner similar to above, N-alkynyl-2-bromo-benzenesulfonamides **3m-p** were subjected to the tandem reaction following optimized conditions. This procedure afforded the desired cyclised products **16-18** and **4** in lower yields and required longer reaction time (Scheme 2). This shows that aryl bromides are less reactive than aryl iodides, which is in accordance with the literature reports.[14b]



Scheme 2. One-pot synthesis of fused triazoles **16-18** and **4** from ynamides **3m-p**.

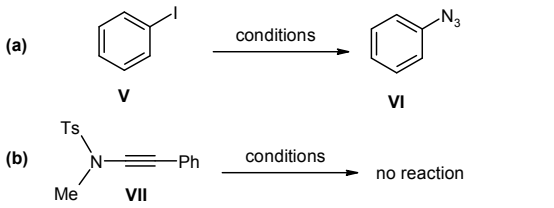
In continuation to above reactions, we made an attempt to synthesize seven membered benzosultam fused triazole. Following optimized reaction conditions, we employed the reaction between N-propargyl 2-iodo-benzenesulfonamide **19** and sodium azide (Scheme 3). Here, we were able to isolate the expected product **20** in 30% yield. There were also other byproducts that were not isolated. Thus it appears that for these systems, conditions available in the literature[8a] were better.



Scheme 3. Synthesis of triazolothiadiazepine 1,1-dioxide **20**.

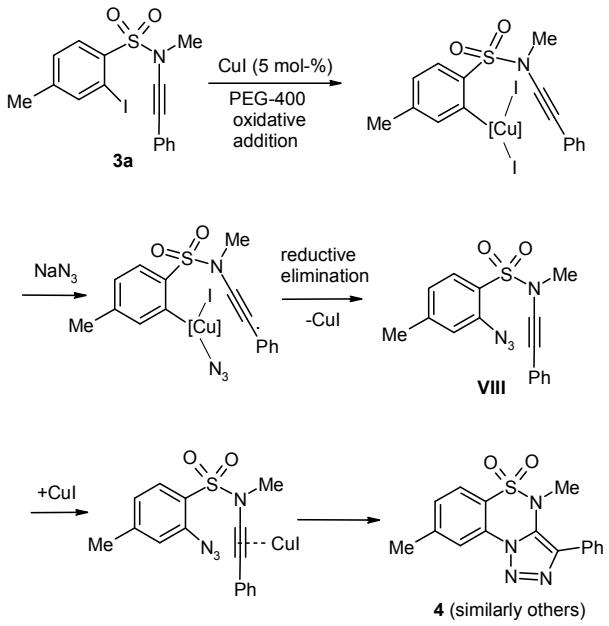
To understand the reaction pathway, we performed the reaction between phenyl iodide and ynamide with NaN_3 in the presence of [Cu]-catalyst. We observed the formation of phenyl azide **VI** from phenyl iodide, but there was no reaction with ynamide **VII** (Scheme **4a-b**). Thus the azide is formed first. The other possibility involving cycloaddition between alkyne and sodium azide followed by intramolecular C-N bond formation

catalysed by [Cu] [8a, 18] is not observed here. Thus, the plausible catalytic cycle for the synthesis of triazolo 1,2,4-benzothiadiazine 1,1-dioxide derivative is shown in Scheme **5**. The intermediate **VIII** is not isolated. Later, the [3+2] cycloaddition between alkyne and azide affords the benzosultam fused triazole.



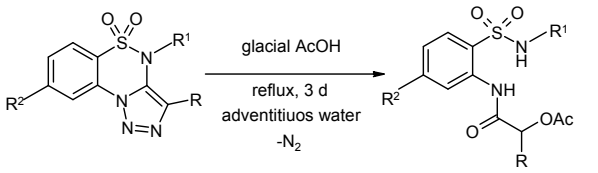
conditions: CuI (5 mol-%), NaN_3 (2 equiv), PEG-400 (1 mL), 100 °C.

Scheme 4. Control experiments.



Scheme 5. Plausible pathway for the formation of benzothiadiazines.

Later, we made an attempt to utilize the 1,2,3-triazoles synthesized so far. We found that in the presence of glacial acetic acid 1,2,3-triazoles tend to undergo nitrogen elimination.[19] We employed benzosultam fused triazoles under this condition. However, we isolated sulfonamides **21-24** in good yields (Scheme 6). These were formed by the cleavage of sulfonamide N-C bond along with nitrogen elimination from triazole moiety. The products may have considerable interest for chemists as they contain two functional groups amide and sulfonamide in a single molecule. The structure of compound **21** was confirmed by X-ray crystallography. This type of cleavage followed by acetic acid/water addition was not reported earlier in the literature.



R = Ph, R¹ = Me, R² = Me **4** — **21** (80%); X-ray
R = Ph, R¹ = Me, R² = *t*-Bu **6** — **22** (86%)
R = Ph, R¹ = Me, R² = Ph **8** — **23** (78%)
R = H, R¹ = Me, R² = Me **14** — **24** (90%)

Scheme 6. Utilization of the benzosultam fused triazoles.

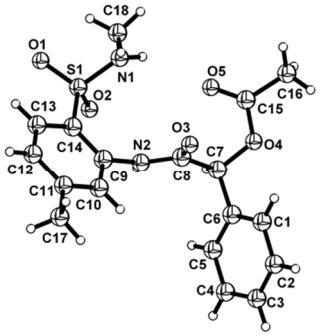


Figure 5. ORTEP diagram for compound **21.** Selected bond lengths [Å] with esds in parentheses: C(8)-O(3) 1.224(5), C(7)-O(4) 1.435(5), C(7)-C(8) 1.528(6), S(1)-O(1) 1.420(4), S(1)-O(2) 1.430(4), S(1)-N(1) 1.615(5).

Conclusions

In conclusion, we have described a sequential one-pot reaction to synthesize triazolo 1,2,4-benzothiadiazine 1,1-dioxide derivatives from functionalised ynamides and sodium azide using CuI as the catalyst under PEG-400. The reaction involves intermolecular C-N bond formation followed by cycloaddition between alkyne and azide. The main attractive feature of this methodology is using low catalyst loadings of air stable CuI and PEG-400, an eco-friendly solvent system.

Experimental Section

The general experimental conditions and synthesis of the precursors are described in the supplementary information.

*Synthesis of triazolo 1,2,4-benzothiadiazine 1,1-dioxide derivatives (compounds **4-18**)- Representative procedure for compound **4**:*

To an oven dried Schlenk tube was added 2-iodo-4,N-dimethyl-N-phenylethynyl-benzenesulfonamide **3a** (0.24 mmol), CuI (10 mol-%), NaN_3 (0.48 mmol) and PEG-400 (1 mL). The contents were sealed under nitrogen atmosphere and heated at 100 °C (oil bath temperature) overnight. After completion of the reaction as monitored by TLC, the crude reaction mixture was cooled to rt. The mixture was diluted with ethyl acetate (20 mL) and washed with water. The aqueous layer was extracted twice with ethyl acetate (20 mL). The combined organic layer was washed with brine solution, dried over sodium sulfate and concentrated in vacuum. The crude residue was then purified by using silica gel column chromatography using hexane-ethyl acetate (9:1) as the eluent to afford triazolo-1,2,4-benzothiadiazine 1,1-dioxide **4**. Compounds **5-17** were prepared following same procedure and same molar quantities.

4,8-dimethyl-3-phenyl-4H-benzo[e][1,2,3]triazolo[5,1-c][1,2,4]thiadiazine 5,5-dioxide (4). White solid; Yield 0.062 g (78%); Mp 196 °C; IR υ_{max} (KBr): 2992, 1605, 1468, 1353, 1178, 1123, 992, 849, 679 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 2.60 (s, 3H, Ar-CH_3), 3.15 (s, 3H, NCH_3), 7.44-7.47 (m, 2H, Ar-*H*), 7.53 (t, *J* = 7.2 Hz, 2H, Ar-*H*), 7.88 (d, *J* = 8.0 Hz, 1H, Ar-*H*), 8.03 (d, *J* = 7.2 Hz, 2H, Ar-*H*), 8.20 (s, 1H, Ar-*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.0 (Ar-*C*H_3), 38.1 (N*C*H_3), 118.9, 121.2, 124.7, 126.4, 128.6, 129.1, 129.7, 131.6, 133.1, 138.0, 146.3; HRMS (ESI): Calcd. for $C_{16}H_{15}N_4O_2S$ $[M^+$+H]: *m/z* 327.0915. Found: 327.0913. This compound was crystallized from ethyl acetate/hexane (2:1) mixture at room temperature. X-ray structure was determined for this compound.

N-((2-iodo-4-methylphenyl)sulfonyl)-N-methyl-2-phenylacetamide (5). This compound was isolated when water was used as solvent (Table 1, entry 3) along with the triazole **4** (20%). White solid; Yield 0.038 g (36%); Mp 106 °C; IR υ_{max} (KBr): 2942, 2909, 1704, 1578, 1457, 1336, 1161, 1073, 865, 766, 673 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 2.37 (s, 3H, Ar-CH_3), 3.39 (s, 3H, NCH_3), 3.96 (s, 2H, CH_2), 7.16 (d, *J* = 7.2 Hz, 1H, Ar-*H*), 7.27-7.34 (m, 4H, Ar-*H)*, 7.88 (s, 1H, Ar-*H*), 8.17 (d, *J* = 8.0 Hz, 1H, Ar-*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.9 (Ar-*C*H_3), 34.0 (N*C*H_3), 43.3 (*C*H_2), 91.4 (*C*I), 127.3, 128.7, 129.3, 129.4, 132.8, 138.6, 143.1, 145.7, 171.3; HRMS (ESI): Calcd. for $C_{16}H_{17}INO_3S$ $[M^+$+H]: *m/z* 429.9974. Found: 429.9969.

8-(tert-butyl)-4-methyl-3-phenyl-4H-benzo[e][1,2,3]triazolo[5,1-c][1,2,4]thiadiazine 5,5-dioxide (6). White solid; Yield 0.075 g (84%); Mp 152 °C; IR υ_{max} (KBr): 2970, 1600, 1458, 1364, 1189, 1129, 992, 833, 658, 641 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.45 (s, 9H, C(CH_3)$_3$), 3.16 (s, 3H, NCH_3), 7.44 (t, *J* = 7.6 Hz, 1H, Ar-*H*), 7.53 (t, *J* = 7.6 Hz, 2H, Ar-*H*), 7.68 (d, *J* = 8.4 Hz, 1H, Ar-*H*), 7.92 (d, *J* = 8.4 Hz, 1H, Ar-*H*), 8.04 (d, *J* = 8.4 Hz, 2H, Ar-*H*), 8.39 (s, 1H, Ar-*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ 31.0 (C(*C*H_3)$_3$), 36.0 (*C*(CH$_3$)$_3$), 38.1 (N*C*H_3), 115.7, 121.1, 124.6, 126.2, 126.5, 128.6, 129.1, 131.6, 133.1, 138.0, 159.5; HRMS (ESI): Calcd. for $C_{19}H_{20}N_4O_2SNa$ $[M^+$+Na]: *m/z* 391.1205. Found: 391.1224.

8-methoxy-4-methyl-3-phenyl-4H-benzo[e][1,2,3]triazolo[5,1-c][1,2,4]thiadiazine 5,5-dioxide (7). White solid; Yield 0.056 g (70%); Mp 192 °C; IR υ_{max} (KBr): 3003, 2937, 2844, 1605, 1595, 1458, 1353, 1178, 981, 844, 773 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 3.15 (s, 3H, NCH_3), 4.01 (s, 3H, Ar-OCH_3), 7.14 (dd, *J* = 8.8 and 2.4 Hz, 1H, Ar-*H*), 7.44 (t, *J* = 7.2 Hz, 1H, Ar-*H*), 7.53 (t, *J* = 7.2 Hz, 2H, Ar-*H*), 7.83 (d, *J* = 2.4 Hz, 1H, Ar-*H*), 7.90 (d, *J* = 8.8 Hz, 1H, Ar-*H*), 8.03 (d, *J* = 7.2 Hz, 2H, Ar-*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ 38.1 (N*C*H_3), 56.4 (Ar-O*C*H_3), 102.9, 115.8, 115.9, 126.5, 126.7, 128.6, 129.1, 133.4, 138.2, 164.4; HRMS (ESI): Calcd. for $C_{16}H_{15}N_4O_3S$ $[M^+$+H]: *m/z* 343.0865. Found: 343.0864.

4-methyl-3,8-diphenyl-4H-benzo[e][1,2,3]triazolo[5,1-c][1,2,4]thiadiazine 5,5-dioxide (8). White solid; Yield 0.073 g (78%); Mp 180 °C; IR υ_{max} (KBr): 3058, 1605, 1468, 1392, 1370, 1178, 992, 827, 762 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 3.21 (s, 3H, NCH_3), 7.43-7.49 (m, 1H, Ar-*H*), 7.51-7.58 (m, 5H, Ar-*H*), 7.72 (d, *J* = 7.2 Hz, 2H, Ar-*H*), 7.86 (dd, *J* = 8.4 and 1.2 Hz, 1H, Ar-*H*), 8.04-8.07 (m, 3H, Ar-*H*), 8.59 (s, 1H, Ar-*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ 37.5 (N*C*H_3), 116.3, 121.7, 125.9, 126.8, 126.9, 127.9, 128.5, 128.8, 131.5, 132.5, 137.5, 147.5; HRMS (ESI): Calcd. for $C_{21}H_{17}N_4O_2S$ $[M^+$+H]: *m/z* 389.1072. Found: 389.1071.

4,8-dimethyl-3-(*p*-tolyl)-4H-benzo[e][1,2,3]triazolo[5,1-c][1,2,4]thiadiazine 5,5-dioxide (9). White solid; Yield 0.064 g (78%); Mp 190 °C; IR υ_{max} (KBr):2926, 1595, 1463, 1353, 1178, 1123, 986, 849, 822, 619 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 2.43 (s, 3H, Ar-CH_3), 2.59 (s, 3H, Ar-CH_3), 3.14 (s, 3H, NCH_3), 7.33 (d, *J* = 8.0 Hz, 2H, Ar-*H*), 7.45 (d, *J* = 8.0 Hz, 1H, Ar-*H*), 7.87 (d, *J* = 8.0 Hz, 1H, Ar-*H*), 7.91 (d, *J* = 8.0 Hz, 2H, Ar-*H*), 8.19 (s, 1H, Ar-*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.4 (Ar-*C*H$_3$), 22.0 (Ar-*C*H$_3$), 38.0 (N*C*H$_3$), 118.9, 121.2, 124.7, 125.7, 126.4, 129.6, 129.8, 131.6, 132.7, 138.2, 139.1, 146.3; HRMS (ESI): Calcd. for $C_{17}H_{17}N_4O_2S$ $[M^+$+H]: *m/z* 341.1072. Found: 341.1068.

3-hexyl-4,8-dimethyl-4H-benzo[e][1,2,3]triazolo[5,1-c][1,2,4]thiadiazine 5,5-dioxide (10). gummy liquid; Yield 0.058 g (72%); IR υ_{max}(neat): 2926, 2860, 1605, 1468, 1364, 1184, 1123, 838, 679 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 0.90 (t, *J* = 6.8 Hz, 3H), 1.32-1.43 (m, 6H, 3 CH_2), 1.76-1.84 (m, 2H, CH_2), 2.56 (s, 3H, Ar-CH_3), 2.80 (t, *J* = 8.0 Hz, 2H, CH_2), 3.26 (s, 3H, NCH_3), 7.41 (d, *J* = 8.0 Hz, 1H, Ar-*H*), 7.83 (d, *J* = 8.0 Hz, 1H, Ar-*H*), 8.12 (s, 1H, Ar-*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.1, 22.0 (Ar-*C*H_3), 22.6, 24.7, 28.8, 28.9, 31.5, 37.8 (N*C*H_3), 118.7, 121.6, 124.4, 129.3, 131.7, 133.6, 139.1, 146.1; HRMS (ESI): Calcd. for $C_{16}H_{23}N_4O_2S$ $[M^+$+H]: *m/z* 335.1541. Found: 335.1544.

3-((benzyloxy)methyl)-4,8-dimethyl-4H-benzo[e][1,2,3]triazolo[5,1-c][1,2,4]thiadiazine 5,5-dioxide (11). White solid; Yield 0.043 g (48%); Mp 106 °C; IR υ_{max} (KBr): 3063, 2860, 1605, 1479, 1359, 1310, 1173, 1068, 877, 745 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 2.44 (s, 3H, Ar-CH_3), 3.38 (s, 3H, NCH_3), 4.47 (s, 2H, OCH_2), 4.58 (s, 2H, OCH_2), 6.54 (s, 1H, Ar-*H*), 7.30-7.32 (m, 1H, Ar-*H*), 7.34-7.38 (m, 4H, Ar-*H*), 7.43 (s, 1H, Ar-*H*), 7.84 (d, *J* = 8.0 Hz, 1H, Ar-*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.9 (Ar-*C*H$_3$), 34.0 (N*C*H$_3$), 68.4 (O*C*H$_2$), 71.7 (O*C*H$_2$), 113.4, 122.1, 124.6, 127.9, 128.1, 128.2, 128.6, 133.1, 137.7, 142.8; HRMS (ESI): Calcd. for $C_{18}H_{19}N_4O_3S$ $[M^+$+H]: *m/z* 371.1178. Found: 371.1178.

4-isopropyl-8-methyl-3-phenyl-4H-benzo[e][1,2,3]triazolo[5,1-c][1,2,4]thiadiazine 5,5-dioxide (12). White solid; Yield 0.054 g (64%); Mp 154 °C; IR υ_{max} (KBr): 2981, 1605, 1468, 1370, 1348, 1184, 1118, 986, 778, 674 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 0.98 (d, *J* = 6.8 Hz, 6H, (CH(CH_3)$_2$), 2.59 (s, 3H, Ar-CH_3), 4.19 (m, 1H, NC*H*), 7.44 (d, *J* = 7.2 Hz, 2H, Ar-*H*), 7.50 (t, *J* = 7.2 Hz, 2H, Ar-*H*), 7.86 (d, *J* = 8.0 Hz, 1H, Ar-*H*), 8.02 (d, *J* = 7.2 Hz, 2H, Ar-*H*), 8.16 (s, 1H, Ar-*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.9 (CH(*C*H$_3$)$_2$), 22.0 (Ar-*C*H$_3$), 59.1 (N*C*H), 119.0, 124.2, 124.3, 127.3, 128.9, 129.1$_9$, 129.2$_1$, 129.6, 130.8, 131.8, 141.2, 146.0; HRMS (ESI): Calcd. for $C_{18}H_{19}N_4O_2S$ $[M^+$+H]: *m/z* 355.1228. Found: 355.1229.

3-(3-fluorophenyl)-4,8-dimethyl-4H-benzo[e][1,2,3]triazolo[5,1-c][1,2,4]thiadiazine 5,5-dioxide (13). White solid; Yield 0.052 g (62%); Mp 206 °C; IR υ_{max} (KBr): 3079, 1600, 1463, 1364, 1178, 1123, 893, 789, 734, 674 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 2.60 (s, 3H, Ar-CH_3), 3.16 (s, 3H, NCH_3), 7.14 (dt, *J* = 8.4 and 2.4 Hz, 1H, Ar-*H*), 7.47-7.53 (m, 2H, Ar-*H*), 7.75-7.78 (m, 1H, Ar-*H*), 7.82 (d, *J* = 8.4 Hz, 1H, Ar-*H*), 7.89 (d, *J* = 8.0 Hz, 1H, Ar-*H*), 8.19 (s, 1H, Ar-*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.0 (Ar-*C*H$_3$), 113.4 (d, *J* = 20 Hz), 116.0 (d, *J* = 20 Hz), 118.9, 121.2, 122.0, 124.9, 129.8, 130.6, 130.7, 130.8, 131.5, 133.5, 137.0, 146.4, 164.3 (d, *J* = 240 Hz); HRMS (ESI): Calcd. for $C_{16}H_{15}N_4O_2S$ $[M^+$+H]: *m/z* 345.0821. Found: 345.0821.

4,8-dimethyl-4H-benzo[e][1,2,3]triazolo[5,1-c][1,2,4]thiadiazine 5,5-dioxide (14). White solid; Yield 0.048 g (80%); Mp 172 °C; IR υ_{max} (KBr): 3134, 1595, 1496, 1452, 1326, 1244, 1085, 975, 811, 685 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 2.58 (s, 3H, Ar-CH_3), 3.47 (s, 3H, NCH_3), 7.43-7.45 (m, 2H, Ar-*H* + triazole-C*H*), 7.90 (d, *J* = 8.0 Hz, 1H, Ar-*H*), 8.17 (s, 1H, Ar-

H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.0 (Ar-*C*H_3), 31.5 (N*C*H_3), 118.3, 119.5, 121.3, 123.4, 129.2, 131.5, 137.9, 146.4; HRMS (ESI): Calcd. for $C_{16}H_{15}N_4O_2S$ [M^++H]: *m/z* 251.0602. Found: 251.0601. This compound was crystallized from ethyl acetate/hexane (2:1) mixture at room temperature. X-ray structure was determined for this compound.

4-methyl-3-phenyl-4H-naphtho[1,2-e][1,2,3]triazolo[5,1-c][1,2,4]thiadiazine 5,5-dioxide (15). White solid; Yield 0.064 g (72%); Mp 184 ^oC; IR υ_{max} (KBr): 2921, 2855, 1595, 1447, 1353, 1178, 1118, 811, 690, 559 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.18 (s, 3H, NC*H*$_3$), 7.47 (d, *J* = 7.6 Hz, 1H, Ar-*H*), 7.56 (t, *J* = 7.6 Hz, 2H, Ar-*H*), 7.77-7.86 (m, 2H, Ar-*H*), 7.99-8.05 (m, 2H, Ar-*H*), 8.12 (d, *J* = 8.4 Hz, 1H, Ar-*H*), 9.66 (d, *J* = 8.4 Hz, 1H, Ar-*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ 37.9 (N*C*H_3), 119.3, 122.2, 124.0, 126.5, 127.4, 128.5, 128.6, 129.0, 129.1, 129.2, 129.6, 129.7, 130.3, 133.6, 136.7, 137.9; HRMS (ESI): Calcd. for $C_{19}H_{15}N_4O_2S$ [M^++H]: *m/z* 363.0915. Found: 363.0914.

4-methyl-3-phenyl-4H-benzo[e][1,2,3]triazolo[5,1-c][1,2,4]thiadiazine 5,5-dioxide (16). White solid; Yield 0.042 g (56%); Mp 190 ^oC; IR υ_{max} (KBr): 2997, 2931, 1589, 1485, 1370, 1255, 1184, 986, 822, 778, 641 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.18 (s, 3H, NC*H*$_3$), 7.45 (t, *J* = 7.6 Hz, 1H, Ar-*H*), 7.53 (t, *J* = 7.6 Hz, 2H, Ar-*H*), 7.68 (t, *J* = 8.0 Hz, 1H, Ar-*H*), 7.89 (t, *J* = 8.0 Hz, 1H, Ar-*H*), 8.01-8.04 (m, 3H, Ar-*H*), 8.39 (d, *J* = 8.0 Hz, 1H, Ar-*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ 38.1 (N*C*H_3), 118.7, 124.0, 124.8, 126.5, 128.5, 128.9, 129.1, 129.2, 131.7, 132.9, 134.7, 138.0; HRMS (ESI): Calcd. for $C_{16}H_{15}N_4O_2S$ [M^++H]: *m/z* 313.0759. Found: 313.0757.

3-hexyl-4-methyl-4H-benzo[e][1,2,3]triazolo[5,1-c][1,2,4]thiadiazine 5,5-dioxide (17). gummy liquid; Yield 0.040 g (52%); IR υ_{max}(neat): 2937, 2860, 1605, 1490, 1364, 1189, 1047, 849, 767 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.90 (t, *J* = 6.8 Hz, 3H, C*H*$_3$), 1.33-1.43 (m, 6H, 3 C*H*$_2$), 1.79-1.83 (m, 2H, C*H*$_2$), 2.81 (t, *J* = 7.8 Hz, 2H, C*H*$_2$), 3.29 (s, 3H, NC*H*$_3$), 7.63 (t, *J* = 7.6 Hz, 1H, Ar-*H*), 7.84 (t, *J* = 7.6 Hz, 1H, Ar-*H*), 7.97 (d, *J* = 7.2 Hz, 1H, Ar-*H*), 8.31 (d, *J* = 8.4 Hz, 1H, Ar-*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.1, 22.6, 24.7, 28.8, 28.9, 31.5, 37.8 (N*C*H_3), 118.6, 124.3, 124.5, 128.5, 131.8, 133.5, 134.5, 139.0; HRMS (ESI): Calcd. for $C_{15}H_{21}N_4O_2S$ [M^++H]: *m/z* 321.1385. Found: 321.1384.

4-butyl-3-phenyl-4H-benzo[e][1,2,3]triazolo[5,1-c][1,2,4]thiadiazine 5,5-dioxide (18). White solid; Yield 0.052 g (60%); Mp 92 ^oC; IR υ_{max} (KBr): 2953, 2860, 1595, 1474, 1359, 1249, 1189, 1118, 981, 773, 636 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.60 (t, *J* = 7.4 Hz, 3H, C*H*$_3$), 0.90-1.16 (m, 4H, 2 C*H*$_2$), 3.66 (t, *J* = 8.0 Hz, 2H, C*H*$_2$), 7.43-7.54 (m, 3H, Ar-*H*), 7.66 (t, *J* = 7.6 Hz, 1H, Ar-*H*), 8.39 (d, *J* = 8.4 Hz, 1H, Ar-*H*), 7.87 (t, *J* = 8.0 Hz, 1H, Ar-*H*), 7.97-8.01 (m, 3H, Ar-*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.2, 19.4, 29.1, 51.3, 118.7, 123.9, 126.1, 126.9, 128.7, 128.9, 129.0, 129.2, 131.6, 131.7, 134.5, 138.2; HRMS (ESI): Calcd. for $C_{16}H_{15}N_4O_2S$ [M^++H]: *m/z* 355.1228. Found: 355.1228.

General Procedure for the synthesis of esters ***21-24***

To an oven dried Schlenk vessel was added triazolo-1,2,4-benzothiadiazine 1,1-dioxide (**4**, **6**, **8** or **14**; 0.3 mmol) and glacial acetic acid (2 mL). Then the vessel was stoppered and heated under reflux for 3 d. After completion of reaction (tlc), the reaction mixture was quenched with saturated sodium bicarbonate solution (30 mL) and extracted twice with ethyl acetate (20 mL). The combined organic layers were washed with brine solution, dried over sodium sulfate and concentrated *in vacuo*. The crude product was purified by using silica gel column chromatography using hexane-ethyl acetate (4:1) as the eluent.

2-((5-methyl-2-(N-methylsulfamoyl)phenyl)amino)-2-oxo-1-phenylethyl acetate (21). White solid; Yield 0.090 g (80%); Mp 130 ^oC; IR υ_{max} (KBr): 3315, 2980, 1737, 1682, 1518, 1414, 1332, 1244, 1173, 1068, 756, 663 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.32 (s, 3H, COC*H*$_3$), 2.39 (s, 3H, Ar-C*H*$_3$), 2.51 (d, *J* = 5.2 Hz, 3H, NHC*H*$_3$), 4.67 (qrt, *J* = 5.2 Hz, 1H, SO_2N*H*), 5.99 (s, 1H, Ar-C*H*), 7.07 (d, *J* = 8.0 Hz, 1H, Ar-*H*), 7.44 (d, *J* = 6.8 Hz, 3H, Ar-*H*), 7.57 (d, *J* = 6.4 Hz, 2H, Ar-*H*), 7.76 (d, *J* = 8.0 Hz, 1H, Ar-*H*), 7.94 (s, 1H, Ar-*H*), 9.63 (s, 1H, CON*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.2 (*C*OC*H*$_3$), 21.7 (Ar-*C*H$_3$), 29.1 (N*C*H$_3$), 76.7, 124.6, 124.8, 125.6, 127.4, 129.0, 129.4, 129.7, 134.3, 134.4, 145.2, 167.1, 171.4; HRMS (ESI): Calcd. for $C_{18}H_{20}N_2O_5SNa$ [M^++Na]: *m/z* 399.0991. Found: 399.1036. This compound was crystallized from methanol at 4 ^oC. X-ray structure was determined for this compound.

2-((5-(tert-butyl)-2-(N-methylsulfamoyl)phenyl)amino)-2-oxo-1-phenylethyl acetate (22). gummy liquid; Yield 0.106 g (86%); IR υ_{max}(neat): 3310, 2964, 1759, 1704, 1567, 1529, 1403, 1326, 1222, 1167, 1052, 838 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.32 (s, 9H, C(C*H*$_3$)$_3$), 2.32 (s, 3H, COC*H*$_3$), 2.53 (d, *J* = 5.6 Hz, 3H, NHC*H*$_3$), 4.64 (qrt, *J* = 5.6 Hz, 1H, SO_2N*H*), 6.02 (s, 1H, Ar-C*H*), 7.27 (s, 1H, Ar-*H*), 7.44 (d, *J* = 7.6 Hz, 3H, Ar-*H*), 7.58 (d, *J* = 7.6 Hz, 2H, Ar-*H*), 7.78 (d, *J* = 8.4 Hz, 1H, Ar-*H*), 8.22 (s, 1H, Ar-*H*), 9.74 (s, 1H, CON*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.2 (*C*OC*H*$_3$), 29.2 (N*C*H$_3$), 30.9 (C(*C*H$_3$)$_3$), 35.4 (*C*(CH$_3$)$_3$), 77.1, 121.4, 121.8, 124.3, 127.4, 129.0, 129.4, 129.5, 134.4, 134.6, 158.2, 167.1, 171.3; HRMS (ESI): Calcd. for $C_{21}H_{26}N_2O_5SNa$ [M^++Na]: *m/z* 441.1460. Found: 441.1465.

2-((4-(N-methylsulfamoyl)-[1,1'-biphenyl]-3-yl)amino)-2-oxo-1-phenylethyl acetate (23). gummy liquid; Yield 0.102 g (78%); IR υ_{max}(neat): 3315, 2921, 1759, 1699, 1567, 1414, 1321, 1222, 1162, 1074, 701 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.33 (s, 3H, COC*H*$_3$), 2.56 (d, *J* = 5.2 Hz, 3H, NHC*H*$_3$), 4.87-4.88 (m, 1H, SO_2N*H*), 6.05 (s, 1H, Ar-C*H*), 7.37-7.48 (m, 7H, Ar-*H*), 7.58-7.61 (m, 4H, Ar-*H*), 7.93 (d, *J* = 8.0 Hz, 1H, Ar-*H*), 8.42 (s, 1H, Ar-*H*), 9.83 (s, 1H, CON*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.2 (*C*OC*H*$_3$), 29.2 (N*C*H$_3$), 76.8, 122.8, 123.1, 125.9, 127.4, 128.7, 128.9$_8$, 129.0$_3$, 129.4, 130.2, 134.4, 134.9, 138.7, 147.0, 167.3, 171.4; HRMS (ESI): Calcd. for $C_{23}H_{22}N_2O_5SNa$ [M^++Na]: *m/z* 461.1147. Found: 461.1150.

2-((5-methyl-2-(N-methylsulfamoyl)phenyl)amino)-2-oxoethyl acetate (24). White solid; Yield 0.082 g (90%); Mp 110 ^oC; IR υ_{max} (KBr): 3271, 1753, 1688, 1589, 1419, 1321, 1244, 1140, 827, 767 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.29 (s, 3H, Ar-C*H*$_3$), 2.43 (s, 3H, COC*H*$_3$), 2.56 (d, *J* = 5.2 Hz, 3H, NHC*H*$_3$), 4.69 (s, 2H, COC*H*$_2$O), 4.82-4.83 (m, 1H, SO_2N*H*), 7.07 (d, *J* = 8.0 Hz, 1H, Ar-*H*), 7.75 (d, *J* = 8.0 Hz, 1H, Ar-*H*), 8.13 (s, 1H, Ar-*H*), 9.66 (s, 1H, CON*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.9 (*C*OC*H*$_3$), 21.8 (Ar-*C*H$_3$), 29.1 (N*C*H$_3$), 63.4, 77.1, 123.9, 124.0, 125.4, 129.7, 134.3, 145.3, 165.9, 171.5; HRMS (ESI): Calcd. for $C_{12}H_{16}N_2O_5SNa$ [M^++Na]: *m/z* 323.0678. Found: 323.0677.

Single crystal X-ray data were collected on a Bruker AXS-SMART or OXFORD diffractometer using Mo-K_α (λ = 0.71073 Å) radiation. The structures were solved by direct methods and refined by full-matrix least squares method using standard procedures.[20] Absorption corrections were done using SADABS program, where applicable. In general, all non-hydrogen atoms were refined anisotropically; hydrogen atoms were fixed by geometry or located by a Difference Fourier map and refined isotropically.

Crystal data

4,8-dimethyl-3-phenyl-4H-benzo[e][1,2,3]triazolo[5,1-c][1,2,4]thiadiazine 5,5-dioxide (4): $C_{16}H_{14}N_4O_2S$, M = 326.37, triclinic, Space group *P-1*, a = 7.1492(7), b = 7.7691(8), c = 14.105(2) Å, α = 97.012(10), β = 102.997(10), γ = 98.628(8)°, V = 744.79(15) Å^3, Z = 2, μ = 0.233 mm^{-1}, data/restraints/parameters: 3024 / 0 / 210, R indices ($I > 2\sigma(I)$): R1 = 0.0405, *wR*2 (all data) = 0.1171. CCDC No. 992617.

4,8-dimethyl-4H-benzo[e][1,2,3]triazolo[5,1-c][1,2,4]thiadiazine 5,5-dioxide (14): $C_{10}H_{10}N_4O_2S$, M = 250.28, Monoclinic, Space group *P2(1)/c*, a = 8.0936(11), b = 21.469(3), c = 6.2322(8) Å, β = 95.001(11)°, V = 1078.8(2) Å^3, Z = 4, μ = 0.295 mm^{-1}, data/restraints/parameters: 2203/ 0/ 156, R indices ($I > 2\sigma(I)$): R1 = 0.0442, *wR*2 (all data) = 0.1167. CCDC No. 992618.

2-((5-methyl-2-(N-methylsulfamoyl)phenyl)amino)-2-oxo-1-phenylethyl acetate (21): $C_{18}H_{20}N_2O_5S$, M = 376.43, Monoclinic, Space group *P2(1)/c*, a = 10.3978(17), b = 19.4530(4), c = 9.6211(19) Å, β = 97.179(16)°, V = 1930.7(6) Å^3, Z = 4, μ = 1.754 mm^{-1}, data/restraints/parameters: 3614/ 0/ 238, R indices ($I > 2\sigma(I)$): R1 = 0.0622, *wR*2 (all data) = 0.2664. CCDC No. 992619.

Acknowledgments

We thank Department of Science and Technology (DST, New Delhi) for financial support and Single Crystal X-ray diffractometer facility, and the University Grants Commission (UGC, New Delhi) for equipment under UPE and CAS programs. ASR and MNR thank Council of Scientific and Industrial Research (CSIR, New Delhi) for fellowship. KCK thanks DST for the J. C. Bose fellowship.

Notes and references

[a]*School of Chemistry, University of Hyderabad, Hyderabad 500 046, A. P., India. Fax: (+91)-40-23012460; Tel: (+91)-40-23134856; E-mail: kckssc@yahoo.com; kckssc@uohyd.ac.in*

† Electronic Supplementary Information (ESI) available: [details on the synthesis of precursors **3a-o**,^{1}H and ^{13}C NMR spectra and CIF files]. See DOI: 10.1039/b000000x/

1. (a) N. E. Schore, *Chem. Rev*. 1988, **88**, 1081-1119; (b) R. Chinchilla, C. Najera, *Chem. Rev*. 2014, **114**, 1783-1826; (c) B. Godoi, R. F. Schumacher, G. Zeni, *Chem. Rev*. 2011, **111**, 2937-2980.
2. (a) K. A. Dekorver, H. Li, A. G. Lohse, R. Hayashi, Z. Lu, Y. Zhang, R. P. Hsung, *Chem. Rev*. 2010, **110**, 5064-5106; (b) G. Evano, A. Coste, K. Jouvin, *Angew. Chem. Int. Ed*. 2010, **49**, 2840-2859.
3. (a) Y. Zhang, *Tetrahedron Lett.* 2005, **46**, 6483-6486; (b) Y. Zhang, *Tetrahedron* 2006, **62**, 3917-3927; (c) J. Oppenheimer, W. L. Johnson, M. R. Tracey, R. P. Hsung, P. Y. Yao, R. Liu, K. Zhao, *Org. Lett*. 2007, **9**, 2361-2364.
4. (a) X. N. Wang, H. S. Yeom, L. C. Fang, S. He, Z. X. Ma, B. L. Kedrowski, R. P. Hsung, *Acc. Chem. Res*. 2014, **47**, 560-578; (b) B. C. Boren, S. Narayan, L. K. Rasmussen, L. Zhang, H. Zhao, Z. Lin, G. Jia, V. V. Fokin, *J. Am. Chem. Soc.* 2008, **130**, 8923-8930; (c) X. Zhang, R. P. Hsung, H. Li, *Chem. Commun*. 2007, 2420-2422; (d) X. Zhang, R. P. Hsung, L. You, *Org. Biomol. Chem*. 2006, **4**, 2679-2682; (e) S. Oppilliart, G. Mousseau, L. Zhang, G. Jia, P. Thuery, B. Rousseau, J. C. Cintrat, *Tetrahedron* 2007, **63**, 8094-8098.
5. (a) K. C. Majumdar, S. Mondal, *Chem. Rev*. 2011, **111**, 7749–7773; (b) M. V. Pham, B. Ye, N. Cramer, *Angew. Chem. Int. Ed*. 2012, **51**, 10610 –10614; (c) A. Mustafa, *Chem. Rev*. 1954, **54**, 195-223.
6. (a) W. R. Buckheit, V. Fliaka-Boltz,; W. D. Decker, J. L. Roberson, C. A. Pyle, E. L. White, B. J. Bowden, J. B. McMahon, M. R. Boyd, J. P. Bader, D. G. Nickell, H. Barth, T. K. Antonucci, *Antiviral Res*. 1994, **25**, 43-56; (b) M. E. Arranz, J. A. Diaz, S. T. Ingate, M. Witvrouw, C. Pannecouque, J. Balzarini, E. D. Clercq, S. Vega, *Bioorg. Med. Chem*. 1999, **7**, 2811-2822. (c) M. Nagarjuna Reddy, K. C. Kumara Swamy, *Synthesis*, 2014, **46**, 1091-1099.
7. (a) P. Francotte, E. Goffin, P. Fraikin, P. Lestage, J. C. Van Heugen, F. Gillotin, L. Danober, J. Y. Thomas, P. Chiap, D. H. Caignard, B. Pirotte, P. De Tullio, *J. Med. Chem*. 2010, **53**, 1700-1711; (b) X. Chen, C. Zhu, F. Guo, X. Qiu, Y. Yang, S. Zhang, M. He, S. Parveen, C. Jing, Y. Li, B. Ma, *J. Med. Chem*. 2010, **53**, 8330-8344; (c) P. Francotte, P. De Tullio, E. Goffin, G. Dintilhac, E. Graindorge, P. Fraikin, P. Lestage, L. Danober, J. Y. Thomas, D. H. Caignard, B. Pirotte, *J. Med. Chem*. 2007, **50**, 3153-3157.
8. (a) B. Deepak Kumar, Y. C. Tu, V. Kavala, C. W. Kuo, C. F. Yao. *Adv. Synth. Catal*. 2011, **353**, 41-48; (b) J. G. Topliss, L. M. Konzelman, E. P. Shapiro, N. Sperber, F. E. Roth, *J. Med. Chem.* 1964, **7**, 269-273; (c) A. Zhou, D. Rayabarapu, P. R. Hanson, *Org. Lett*. 2009, **11**, 531-534; (d) T. B. Samarakoon, J. K. Loh, A. Rolfe, L. S. Le, S. Y. Yoon, G. H. Lushington, P. R. Hanson, *Org. Lett*. 2011, **13**, 5148-5151.
9. (a) K. C. Majumdar, S. Ganai, B. Sinha, *Tetrahedron*. 2012, **68**, 7806-7811. (b) M. Selvaraju, C. M. Sun, *Adv. Synth. Catal*. 2014, **356**, 1329-1336.
10. (a) F. Amblard, J. H. Cho, R. F. Schinazi, *Chem. Rev*. 2009, **109**, 4207-4220; (b) *Chem. Soc. Rev.* 2010, **39**, 1221-1408; c) E. A. Shafran, V. A. Bakulev, Yu. A. Rozin, Yu. M. Shafran, *Chem. Hetero. Comp*. 2008, **44**, 1040-1069.
11. (a) A.W. Thomas, *Bioorg. Med. Chem. Lett*. 2002, **12**, 1881-1984; (b) D. K. Mohapatra, P. K. Maity, M. Shabab, M. I. Khan, *Bioorg. Med. Chem. Lett***.** 2009, **19**, 5241-5245.
12. (a) A. Lauria, C. Patella, G. Dattolo, A. M. Almerico, *J. Med. Chem*. 2008, **51**, 2037 – 2046; (b) A. Martinez, H. Gutierrez-de-Teran, J. Brea, E. Ravina, M. I. Loza, M. I. Cadavid, F. Sanz, B. Vidal, V. Segarra, E. Sotelo, *Bioorg. Med. Chem*. 2008, **16**, 2103 – 2113; (c) R. Li, D. J. Jansen, A. Datta, *Org. Biomol. Chem*. 2009, **7**, 1921-1930.
13. (a) P. Thirumurugan, D. Matosiuk, K. Jozwiak, *Chem. Rev*. 2013, **113**, 4905-4979; (b) M. Meldal, C. W. Tornqe, *Chem. Rev*. 2008, **108**, 2952-3015; (c) M. Kidwai, P. Sapra, P. Misra, R. K. Sexena, M. Singh, *Bioorg. Med. Chem*. 2001, **9**, 217-220; (d) B. S. Holla, B. Kalluraya, K. R. Sridhar, E. Drake, L. M. Thomas, K. K. Bhandary, M. J. Levine, *Eur. J. Med. Chem*. 1994, **29**, 301-308.
14. (a) M. Nagarjuna Reddy, K. C. Kumara Swamy, *Eur. J. Org. Chem.* 2012, 2013–2022; (b) M. Nagarjuna Reddy, K. C. Kumara Swamy, *Org. Biomol. Chem.* 2013, **11**, 7350-7360; (c) M. Chakravarty, N. N. Bhuvan Kumar, K. V. Sajna, K. C. Kumara Swamy, *Eur. J. Org. Chem*. 2008, 4500–4510.
15. (a) Y. Zhang, R. P. Hsung, M. R. Tracey, K. C. M. Kurtz, E. L. Vera, *Org. Lett*. 2004, **6**, 1151-1154; (b) R. B. Dateer, B. S. Shaibu, R. S. Liu, *Angew. Chem. Int. Ed*. 2012, **51**, 113 –117.
16. Compound **5** and analogous derivatives (**A-D**) could be obtained by simple hydrolysis of **3a-d** and **3h**, respectively, in chloroform (see supplementary information for details).
17. (a) G. A. Burley, D. L. Davies, G. A. Griffith, M. Lee, K. Singh, *J. Org. Chem.* 2010, **75,** 980-983; (b) J. Mao, J. Guo, F. Fang, S. J. Ji , *Tetrahedron* 2008, **64**, 3905-3911; (c) W. Han, C. Liu, Z. L. Jin, *Org. Lett*. 2007, **9**, 4005-4007.
18. (a) Q. Cai, J. Yan, K. Ding, *Org. Lett*. 2012, **14**, 3332-3335; (b) J. Yan, F. Zhou, D. Qin, T. Cai, K. Ding, Q. Cai, *Org. Lett*. 2012, **14**, 1262-1265.
19. (a) Y. Y. Hu, J. Hu, X. C. Wang, L. N. Guo, X. Z. Shu, Y. N. Niu, Y. M. Liang, *Tetrahedron* 2010, **66**, 80-86; (b) Y. Xie, G. Gong, Y. Liu, S. Deng, A. Rinderspacher, L. Branden, D. W. Landry, *Tetrahedron Lett.* 2008, **49**, 2320-2323.
20. (a) G. M. Sheldrick, *SADABS, Siemens Area Detector Absorption Correction*, University of Gottingen, Germany, 1996; (b) G. M. Sheldrick, *SHELX-97- A program for crystal structure solution and refinement,* University of Gottingen, 1997; (c) G. M. Sheldrick, *SHELXTL NT Crystal Structure Analysis Package*, Bruker AXS, Analytical X-ray System, WI, USA, 1999, version 5.10.

Tandem cyclisation of ynamides to triazolo-1,2,4-benzothiadiazine-1,1-dioxides by using copper-catalysis is reported.