Reaction of α,α-dibromoketones with 4-amino-5-mercapto-3-methyl-s-triazole: synthesis of some 7*H*-7-alkoxy-6-aryl-3-methyl-*s*-triazolo [3,4-*b*][1,3,4]thiadiazines

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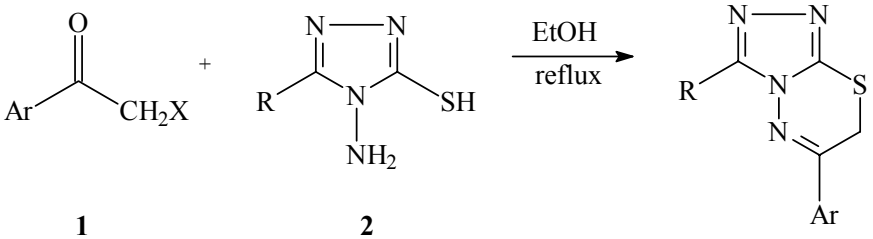
Abstract

The reaction of α,α-dibromoacetophenones with 4-amino-5-mercapto-3-methyl-*s*-triazole in different alcohols (MeOH, EtOH, n-PrOH, iso-PrOH) as solvent furnishes some 7*H*-7-alkoxy-6-aryl-3-methyl-*s*-triazolo[3,4-*b*][1,3,4]thiadiazines under reflux conditions.

Keywords: α,α-Dibromoacetophenones, 4-amino-5-mercapto-3-methyl-s-triazole, 7*H*-7-alkoxy-6-aryl-3-methyl-s-triazolo[3,4-*b*][1,3,4]thiadiazines

Introduction

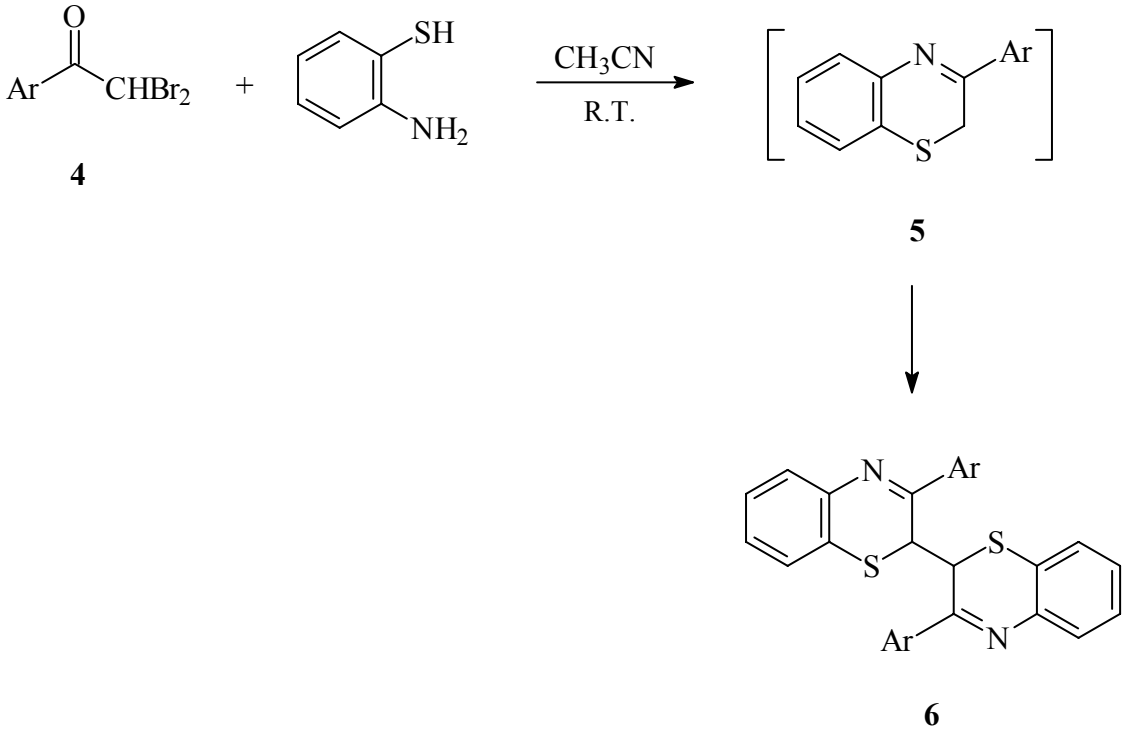
The synthetic utility of α-halocarbonyl compounds is well known for more than a century. They have been widely used as versatile intermediates[1-6] for the synthesis of variety of heterocycles. In one of such reports, it is mentioned that α-halocarbonyl compounds **1** when treated with 4-amino-5-mercapto-s-triazoles **2** in anhydrous ethanol under reflux results in the formation of triazolothiadiazines[7] **3** (Equation 1).



1 **2** **3**

Equation 1

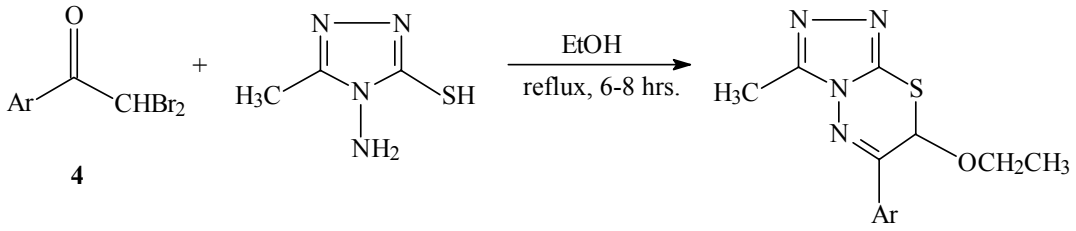
There has been considerable recent interest in the use of α,α-dihaloketones as synthetic equivalents[8-11] to their corresponding α-haloketones because of their non-lachrymatory nature and reactions involving mild experimental conditions. In a recent report from our laboratory,[12] it has been shown that the reaction of α,α-dibromoacetophenones **4** with *o*-aminothiophenol offers a mild and convenient method for the synthesis of 2,2'-bi-2*H*-3,3'-diaryl-1,4-benzothiazines **6** (Equation 2). Although this reaction affords the dimers **6** rather than the expected 3-aryl-benzothiazines **5**, a reasonable route for the formation of the products **6** involves oxidative dimerization of primary product **5**.



Equation 2

On the basis of these observations, it was anticipated that the reaction between α,α-dibromoacetophenone and **2** might afford **3** or its dimer. To determine the fate of this proposal, particularly with the aim of developing a new convenient method for the synthesis of **3**, we became interested in investigating the reaction of **4** with **2**. We started our investigation with α,α-dibromoacetophenone (**4a**) which was refluxed with 4-amino-5-mercapto-3-methyl-s-triazole (**2,** R=CH_3) in ethanol as solvent. The reaction gave a brown solid product, Mpt 199-200 ºC. The ^{1}H NMR spectrum of this product showed a three proton triplet at δ 1.2, a three proton singlet at δ 2.6, a one proton multiplet at δ 3.6, another multiplet for one proton at δ 4.0, a one proton singlet at δ 5.7 and a multiplet of five protons in aromatic region. IR spectrum of the product did not show any peak in functional group region (i.e. CO, NH_2). This data was not in accordance with the expected structure **3**. Further analysis of the spectral data (^{1}H, ^{13}C NMR, mass and elemental

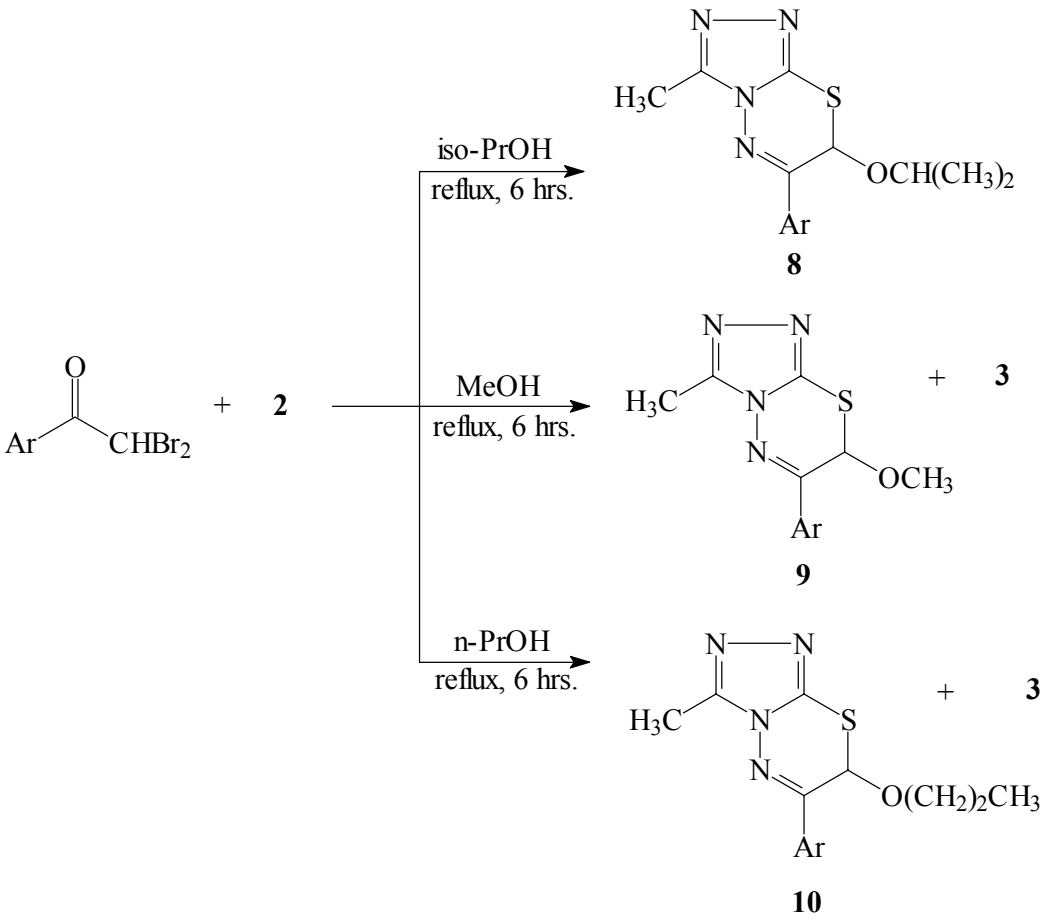
analysis) of the product obtained from this reaction established its structure as 7*H*-7-ethoxy-3-methyl-6-phenyl-s-triazolo[3,4-*b*][1,3,4]thiadiazine (**7a**). In view of the fact that such a product is not known in literature, it was considered worthwhile to assess the generality of this reaction for the synthesis of variously substituted thiadiazines by employing various α,α-dibromoacetophenones (**4b-f**). The reaction occurred in similar conditions to afford (**7b-f**) in good yields (Scheme 1).[13]



4 **7**

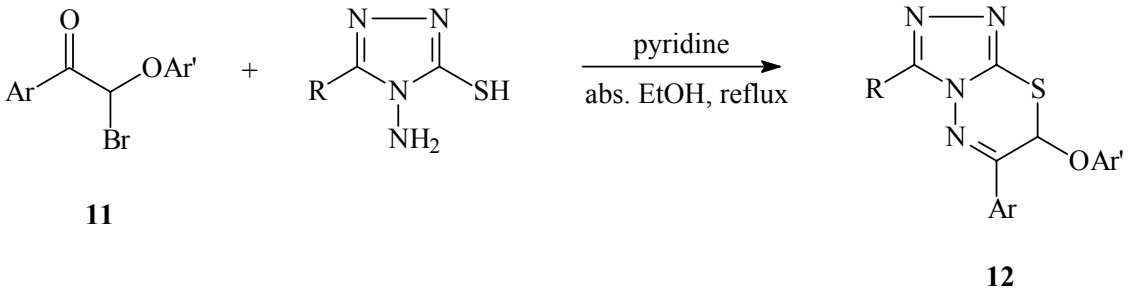
Scheme 1

Based on these encouraging results, it was expected that replacing ethanol by other alcohols might lead to the formation of corresponding 7-alkoxy derivatives. To test the feasibility of this proposal, we carried out a series of experiments on substrate **4a** with MeOH, n-PrOH, and *i*-PrOH. The reaction, however, did not follow similar trends in all these cases. In typical experiments, one equivalent of **4a** was refluxed with **2** in MeOH/n-PrOH/iso-PrOH followed by basification with ammonium hydroxide. In case of iso-PrOH as solvent we got the expected product 7*H*-3-methyl-6-phenyl-7-iso-propoxy-*s*-triazolo[3,4-*b*][1,3,4]thiadiazine **8a**, whereas, using MeOH and n-PrOH as solvents, in addition to alkoxy derivatives **9a** and **10a**, formation of **3a** was observed. All the products were characterized on the basis of their spectral data (^{1}H, ^{13}C NMR, IR, mass and elemental analysis) (Scheme 2) and the results of these reactions are summarized in Table 1.



Scheme 2

It is worthwhile to mention here that some antimicrobial triazolothiadiazines **12** with aryloxy substituents at 7th position have been reported in literature by the condensation of α-bromo-α-aryloxyacetophenones **11** with 3-substituted-4-amino-5-mercapto-s-triazoles in absolute ethanol in the presence of pyridine[14] (Equation 3).



Equation 3

In order to compare the results of present study, we attempted the preparation of 7-phenoxy triazolothiadiazines **12** by using α,α-dibromoacetophenones in the presence of phenols. However, the reaction did not give the expected products **12**, rather it led to the formation of **3**. This observation clearly reflects that the scope of our method is limited towards the synthesis of 7-alkoxy triazolothiadizines i.e. 7-aryloxy derivatives can not be prepared by this method.

In conclusion, the present study offers an application of α,α-dibromoacetophenones in a mild and efficient synthesis of some 7*H*-7-alkoxy-6-aryl-3-methyl-*s*-triazolo[3,4-*b*][1,3,4]thiadiazines (**7a-f, 8a, 9a, 10a-c**).

Table 1. The reaction of α,α-dibromoacetophenones with 4-amino-5-mercapto-3- methyl-s-triazole in alcohols

Substrate	Ar	Alcohol	Product(s)	Mp (ºC)	Yield (%)[a]
4a	C_6H_5	EtOH	**7a**	199-200	67
4b	4-MeC_6H_4	EtOH	**7b**	155-58	61
4c	4-ClC_6H_4	EtOH	**7c**	195-97	73
4d	4-BrC_6H_4	EtOH	**7d**	203-05	77
4e	4-FC_6H_4	EtOH	**7e**	208-10	65
4f	4-$NO_2C_6H_4$	EtOH	**7f**	204-05	81
4a	C_6H_5	iso-PrOH	**8a**	197-200	70
4a	C_6H_5	MeOH	**9a**	176-78	25
			3a	174-75 (183)[7]	26
4a	C_6H_5	n-PrOH	**10a**	162-63	32
			3a	174-75 (183)[7]	31
4b	4-MeC_6H_4	n-PrOH	**10b**	122-26	34
			3b	187-89 (197)[7]	31
4c	4-ClC_6H_4	n-PrOH	**10c**	144-46	38
			3c	210-12 (215)[7]	41

[a] The yields of the isolated pure products **7, 8, 9,** and **10** w.r.t. **4**

Experimental Section

General Procedures. Melting points were taken in open capillaries and are uncorrected. ^{1}H NMR spectra were recorded on a Bruker 300 MHz instrument using TMS as an internal standard. IR spectra were recorded on a Buck Scientific IR M-500 spectrophotometer. The α,α-dibromoacetophenones[8] and 4-amino-5-mercapto-3-methyl-s-triazole[7] were synthesized according to literature procedure.

Synthesis of 7*H*-7-alkoxy-6-aryl-3-methyl-*s*-triazolo[3,4-*b*][1,3,4]thiadiazines (7a-f, 8a, 9a, 10a-c) from α,α-Dibromoacetophenones and 4-Amino-5-mercapto-3-methyl-*s*-triazole. General procedure

A solution of appropriate α,α-dibromoacetophenone (**4a-f,** 2 mmol) in different alcohols (MeOH, EtOH, n-PrOH, iso-PrOH) was refluxed with **2** (R= CH_3, 2 mmol) for 6-8 hrs. The reaction mixture was cooled and neutralized with ammonium hydroxide. In case of EtOH and iso-PrOH as solvent, solid thus separated was filtered, washed with water and recrystallized to get pure **7a-f**, and **8a** respectively**.** A gummy mass was obtained in case of MeOH, which was purified by column chromatography to get two products **9a** and **3a**. A white solid containing mixture of two products (**10a-c, 3a-c**) in case of n-PrOH was purified by column chromatography on silica gel using pet ether-ethyl acetate as eluent.

7*H*-3-Methyl-7-ethoxy-6-phenyl-s-triazolo[3,4-*b*][1,3,4]thiadiazine (7a). IR ($\nu_{max.}$ KBr): 1070, 1464, 1590 cm.$^{-1}$ ^{1}H NMR ($CDCl_3$, 300 MHz): 1.23 (t, 3H, -$OCH_2\mathbf{CH_3}$), 2.60 (s, 3H, -CH_3), 3.6 (m, 1H, -$O\mathbf{CH_2}CH_3$), 4.0 (m, 1H, -$O\mathbf{CH_2}CH_3$), 5.78 (s, 1H, -CH), 7.5-7.8 (m, 5H, Ar-H). ^{13}C NMR ($CDCl_3$, 300 MHz): 10.33 (-CH_3), 14.47 (-$OCH_2\mathbf{CH_3}$), 64.02 (-OCH_2-), 73.20 (C_7), 127.20-137.12 (C_6 and aromatic carbons), 150.25 (C_3 of triazole), 151.05 (C_5 of triazole). Anal cald for $C_{13}H_{14}N_4OS$: C, 56.93; H, 5.11; N, 20.43. Found: C, 56.47; H, 4.94; N, 20.12. Mass, m/z (%): 275 (100 %, M).

7*H*-3-Methyl-7-ethoxy-6-(4-methylphenyl)-*s*-triazolo[3,4-*b*][1,3,4]thiadiazine (7b). IR ($\nu_{max.}$ KBr): 1077, 1463,1613 cm.$^{-1}$ ^{1}H NMR ($CDCl_3$, 300 MHz): 1.23 (t, 3H, -$OCH_2\mathbf{CH_3}$), 2.4(s, 3H, -CH_3), 2.60 (s, 3H, -CH_3), 3.6 (m, 1H, -$O\mathbf{CH_2}CH_3$), 4.0 (m, 1H, -$O\mathbf{CH_2}CH_3$), 5.76 (s, 1H, -CH), 7.3 (d, 2H, J=7.8, Ar-H), 7.7 (d, 2H, J=7.8, Ar-H). Anal. Calc. for $C_{14}H_{16}N_4OS$: C, 58.33; H, 5.55; N, 19.44. Found: C, 58.45; H, 5.43; N, 19.19

7*H*-3-Methyl-7-ethoxy-6-(4-chlorophenyl)-*s*-triazolo[3,4-*b*][1,3,4]thiadiazine (7c). IR ($\nu_{max.}$ KBr): 1081, 1467, 1591 cm.$^{-1}$ ^{1}H NMR ($CDCl_3$, 300 MHz): 1.24 (t, 3H, -$OCH_2\mathbf{CH_3}$), 2.60 (s, 3H, -CH_3), 3.6 (m, 1H, -$O\mathbf{CH_2}CH_3$), 4.0 (m, 1H, -$O\mathbf{CH_2}CH_3$), 5.75 (s, 1H, -CH), 7.5(d, 2H, J=8.4, Ar-H), 7.8 (d, 2H, J=8.4, Ar-H). Anal. Calc. for $C_{13}H_{13}N_4OSCl$: C, 50.65; H, 4.22; N, 18.18. Found: C, 50.15; H, 4.05; N, 17.88

7*H*-3-Methyl-7-ethoxy-6-(4-bromophenyl)-*s*-triazolo[3,4-*b*][1,3,4]thiadiazine (7d). IR ($\nu_{max.}$ KBr): 1074, 1467, 1585 cm.$^{-1}$ ^{1}H NMR ($CDCl_3$, 300 MHz): 1.24 (t, 3H, -$OCH_2\mathbf{CH_3}$), 2.60 (s, 3H, -CH_3), 3.6 (m, 1H, -$O\mathbf{CH_2}CH_3$), 4.0 (m, 1H, -$O\mathbf{CH_2}CH_3$), 5.75 (s, 1H, -CH), 7.6 (d, 2H, J=8.4, Ar-H), 7.7 (d, 2H, J=8.4, Ar-H). Anal. Calc. for $C_{13}H_{13}N_4OSBr$: C, 44.19; H, 3.68; N, 15.86. Found: C, 44.95; H, 3.44; N, 15.52. Mass, m/z (%): 353 (90%, M), 355 (100%, M+2)

7*H*-3-Methyl-7-ethoxy-6-(4-fluorophenyl)-*s*-triazolo[3,4-*b*][1,3,4]thiadiazine (7e). IR ($\nu_{max.}$ KBr): 1072, 1464, 1600 cm.$^{-1}$ ^{1}H NMR ($CDCl_3$, 300 MHz): 1.24 (t, 3H, -$OCH_2\mathbf{CH_3}$), 2.60 (s, 3H, -CH_3), 3.6 (m, 1H, -$O\mathbf{CH_2}CH_3$), 4.0 (m, 1H, -$O\mathbf{CH_2}CH_3$), 5.77 (s, 1H, -CH), 7.2 (d, 2H, J=8.1, Ar-H), 7.8 (d, 2H, J=8.1, Ar-H). Anal. Calc. for $C_{13}H_{13}N_4OSF$: C, 53.42; H, 4.45; N, 19.18. Found: C, 53.01; H, 4.23; N, 18.98.

7*H*-3-Methyl-7-ethoxy-6-(4-nitrophenyl)-*s*-triazolo[3,4-*b*][1,3,4]thiadiazine (7f). IR ($\nu_{max.}$ KBr): 1073, 1348, 1462, 1520, 1598 cm.$^{-1}$ ^{1}H NMR ($CDCl_3$, 300 MHz): 1.18 (t, 3H, -

$OCH_2\mathbf{CH_3}$), 2.60 (s, 3H, $-CH_3$), 3.6 (m, 1H, $-O\mathbf{CH_2}CH_3$), 3.9 (m, 1H, $-O\mathbf{CH_2}CH_3$), 5.70 (s, 1H, -CH), 7.9(d, 2H, J=8.7, Ar-H), 8.2 (d, 2H, J=8.7, Ar-H). Anal. Calc. for $C_{13}H_{13}N_5O_3S$: C, 48.90; H, 4.07; N, 21.94. Found: C, 49.26; H, 3.88; N, 21.34.

7*H*-3-Methyl-6-phenyl-7-isopropoxy-*s*-triazolo[3,4-*b*][1,3,4]thiadiazine (8a). IR ($\nu_{max.}$ KBr): 1064, 1462, 1619 $cm.^{-1}$ ^1H NMR ($CDCl_3$, 300 MHz): 1.15 (d, 3H, $-OCH(\mathbf{CH_3})_2$), 1.32 (d, 3H, $-OCH(\mathbf{CH_3})_2$), 2.64 (s, 3H, $-CH_3$), 4.27 (m, 1H, $-O\mathbf{CH}-$), 5.84 (s, 1H, -CH), 7.5-7.9 (m, 5H, Ar-H). ^{13}C NMR ($CDCl_3$, 300 MHz): 10.29 ($-CH_3$), 20.60 ($-OCH(\mathbf{CH_3})_2$), 23.64 ($-OCH(\mathbf{CH_3})_2$), 70.03 (-OCH-), 70.98 (C_7), 127.22-137.30 (C_6 and aromatic carbons), 150.63 (C_3 of triazole), 151.01 (C_5 of triazole). Anal. Calc. for $C_{14}H_{16}N_4OS$: C, 58.33; H, 5.55; N, 19.44. Found: C, 58.88; H, 5.21; N, 18.71.

***7H*-7-Methoxy-3-methyl-6-phenyl-*s*-triazolo[3,4-*b*][1,3,4]thiadiazine (9a).** IR ($\nu_{max.}$ KBr): 1070, 1462, 1600 $cm.^{-1}$ ^1H NMR ($CDCl_3$, 300 MHz): 2.66 (s, 3H, $-CH_3$), 3.54 (s, 3H, $-OCH_3$), 5.69 (s, 1H, -CH), 7.5-7.9 (m, 5H, Ar-H). ^{13}C NMR ($CDCl_3$, 300 MHz): 10.29 ($-CH_3$), 64.02 ($-OCH_3$), 74.90 (C_7), 127.23-136.90 (C_6 and aromatic carbons), 150.35 (C_3 of triazole), 151.03 (C_5 of triazole). Anal. Calc. for $C_{12}H_{12}N_4OS$: C, 55.38; H, 4.62; N, 21.54. Found: C, 55.65; H, 4.75; N, 21.49.

7*H*-3-Methyl-6-phenyl-7-propoxy-*s*-triazolo[3,4-*b*][1,3,4]thiadiazine (10a). IR ($\nu_{max.}$ KBr): 1072, 1462, 1590 $cm.^{-1}$ ^1H NMR ($CDCl_3$, 300 MHz): 0.81 (t, 3H, $-OCH_2CH_2\mathbf{CH_3}$), 1.59 (m, 2H, $-OCH_2\mathbf{CH_2}-$), 2.59 (s, 3H, $-CH_3$), 3.40 (m, 1H, $-O\mathbf{CH_2}-$), 3.80 (m, 1H, $-O\mathbf{CH_2}-$), 5.66 (s, 1H, -CH), 7.4-7.8 (m, 5H, Ar-H). Anal. Calc. for $C_{14}H_{16}N_4OS$: C, 58.33; H, 5.55; N, 19.44. Found: C, 58.60; H, 5.23; N, 18.98.

7*H*-3-Methyl-6-(4-methylphenyl)-7-propoxy-*s*-triazolo[3,4-*b*][1,3,4]thiadiazine (10b). IR ($\nu_{max.}$ KBr): 1070, 1463, 1604 $cm.^{-1}$ ^1H NMR ($CDCl_3$, 300 MHz): 0.88 (t, 3H, $-OCH_2CH_2\mathbf{CH_3}$), 1.59 (m, 2H, $-OCH_2\mathbf{CH_2}-$), 2.45 (s, 3H, $-CH_3$), 2.66 (s, 3H, $-CH_3$) 3.47 (m, 1H, $-O\mathbf{CH_2}-$), 3.92 (m, 1H, $-O\mathbf{CH_2}-$), 5.74 (s, 1H, -CH), 7.33 (d, 2H, J=8.4, Ar-H), 7.76(d, 2H, J=8.4, Ar-H). Anal cald for $C_{15}H_{18}N_4OS$: C, 59.60; H, 5.96; N, 18.54. Found: C, 60.08; H, 5.67; N, 18.02.

7*H*-3-Methyl-6-(4-chlorophenyl)-7-propoxy-*s*-triazolo[3,4-*b*][1,3,4]thiadiazine (10c). IR ($\nu_{max.}$ KBr): 1067, 1465, 1591 $cm.^{-1}$ ^1H NMR ($CDCl_3$, 300 MHz): 0.88 (t, 3H, $-OCH_2CH_2\mathbf{CH_3}$), 1.59 (m, 2H, $-OCH_2\mathbf{CH_2}-$), 2.66 (s, 3H, $-CH_3$) 3.47 (m, 1H, $-O\mathbf{CH_2}-$), 3.93 (m, 1H, $-O\mathbf{CH_2}-$), 5.73 (s, 1H, -CH), 7.52 (d, 2H, J=8.4, Ar-H), 7.80(d, 2H, J=8.4, Ar-H). ^{13}C NMR ($CDCl_3$, 300 MHz): 10.30 ($-CH_3$), 10.42 ($-OCH_2CH_2\mathbf{CH_3}$), 22.12 ($-OCH_2\mathbf{CH_2}-$), 70.11 ($-OCH_2-$), 73.25 (C_7), 128.50-138.14 (C_6 and aromatic carbons), 149.25 (C_3 of triazole), 150.95 (C_5 of triazole). Anal. Calc. for $C_{14}H_{15}N_4OSCl$: C, 52.17; H, 4.65; N, 17.39. Found: C, 52.17; H, 4.32; N, 16.91. Mass, m/z (%): 323 (100%, M), 325 (60%, M+2).

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