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Naser Foroughifar [a b], Akbar Mobinikhaledi [b] & Sattar Ebrahimi [b]

[a] Faculty of Chemistry, Islamic Azad University, North Tehran Branch, Tehran, Iran

[b] Department of Chemistry, Faculty of Sciences, Arak University, Arak, Iran

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EFFICIENT AND CONVENIENT PROTOCOL FOR THE SYNTHESIS OF NOVEL 1,2,4-TRIAZOLO[3,4-b][1,3,4]THIADIAZINES

Naser Foroughifar,[1,2] Akbar Mobinikhaledi,[2] and Sattar Ebrahimi[2]

[1]*Faculty of Chemistry, Islamic Azad University, North Tehran Branch, Tehran, Iran*

[2]*Department of Chemistry, Faculty of Sciences, Arak University, Arak, Iran*

The novel triazolothiadiazine analogs 5a–p were obtained via a multistep synthetic sequence beginning with 5-substituted 4-amino-1,2,4-triazole-3-thiols 1. Compound 1, in reaction with various aromatic aldehydes 2 in acetic acid, afforded Schiff bases 3a–p. Cyclization of 3a–p with ethyl chloroacetate 4 in the presence of sodium hydride at room temperature gave triazolothiadiazines 5a–p in good yields.

Keywords: Schiff-base; 1,2,4-triazole; triazolothiadiazine

INTRODUCTION

Heterocyclic compounds are rich sources of diverse physical, chemical, and biological properties.[1] They are commonly used as templates to design biologically active agents[2,3] in medicinal chemistry. Moreover, in the past 20 years, the drug-discovery process has undergone extraordinary changes, and high-throughput biological screening of potential drug candidates has led to an ever-increasing demand for novel drug-like compounds. In the past few decades, the chemistry of 1,2,4-triazoles and their fused heterocyclic derivatives have received considerable attention as a result of their synthetic and effective biological importance. 1,2,4-Triazole moieties have been incorporated into a wide variety of therapeutically interesting drug candidates including anti-inflammatories, central nervous system stimulants, sedatives, anti-anxiety compounds, and antimicrobial agents.[4–6] In addition, some s-triazolo[3,4-b]-[1,3,4]thiadiazines are reported to have antidepressant,[7] fungicidal, anticancer,[8] and antiviral[9] activities.

The triazole fused six-membered ring system also has diverse applications in the field of medicine. The commonly known systems are triazoles fused with pyridines,[10] pyridazines,[11] pyrazines,[12] imidazoles,[13] pyrimidines, and triazines.[14] A literature survey reveals that there are not many examples of triazoles fused with

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Address correspondence to Naser Foroughifar, Faculty of Chemistry, Islamic Azad University, North Tehran Branch, Tehran, Iran. E-mail: n_foroughifar@yahoo.com

thiadiazines. Those incorporating the N-C-S linkage as in the skeleton of 1,2,4-triazolo[3,4-b][1,3,4]thiadiazine exhibit a broad spectrum of biological activity.

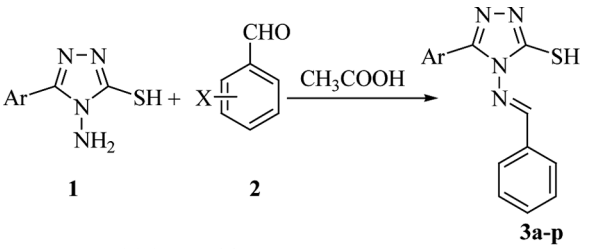
Various methods are available for the construction of 1,2,4-triazolo[3,4-b]-[1,3,4]thiadiazine. Recently, Vainilavicius et al. used ethyl chlroacetate and 5-substituted 4-amino-1,2,4-triazole-3-thione for the synthesis of triazolo thiadiazine.[15] Some other routes have been also reported for the synthesis of triazolothiadiazines, include the reactions of 5-substituted-4-amino-1,2,4-triazole-3-thione with (a) phenacyl bromides,[16,17] (b) substituted α-bromo-2-propen-1-one,[18] and (c) oxalyl chloride.[19] However, these methodologies suffer from one or more disadvantages such as poor yield, lack of availability and difficult preparation of the starting materials, and harsh reaction conditions.

RESULTS AND DISCUSSION

In continuation of our effort to develop the synthesis of new fused heterocyclic derivatives,[20,21] we report herein a simple and efficient method for the synthesis of substituted triazolo[3,4-b][1,3,4]thiadiazines **5a–p** for the first time. Our synthetic approaches are depicted in Figures 1 and 2. The required 4-amino-5-aryl substituted-3-mercapto-1,2,4-triazoles **1** were prepared in good yields through a multistep reaction using the method of Reid and Heindel.[22] The synthesis of 4-(substituted-benzylideneamino)-5-aryl-4H-1,2,4-triazole-3-thiols **3a–p** were accomplished in a single step by reacting 4-amino-5-aryl substituted-3-mercapto-1,2,4-triazoles with various aromatic aldehydes in refluxing acetic acid initially (Figure 1). The reaction conditions between Schiff base **3a** and ethyl chloroacetate **4** in dried tetrahydrofuran (THF) was examined (Figure 2). Reaction of compound **3a** (1.0 equiv) with 1.0 equiv of compound **4** and 2.0 equiv of NaH in THF at room temperature gave the desired product **5a** in 30% yield (Table 1, entry 1).

Optimization of the reaction conditions was carried out. Different ratios of starting materials were compared, and the ratio 1:1.4 (**3a/4**) was favored (Table 1, entry 4). With the optimized condition in hand, the scope of the reaction was investigated, and the typical results are summarized in Table 2.

Compounds **3a–p** were used as key intermediates for the synthesis of novel triazolothiadiazine derivatives. Sodium hydride was added to a solution of compounds **3a–p** in dry THF. Salt formation was allowed to proceed, and the resulting salt was



Ar= 4-pyridyl, 3-pyridy

X= H, 4-Me, 4-OMe, 3-Br, 2-Cl, 4-Cl, 2-NO_2, 4-NO_2

Figure 1. Synthesis of 4-(substituted-benzylideneamino)-5-aryl-4H-1,2,4-triazole-3-thiols **3a–p**.

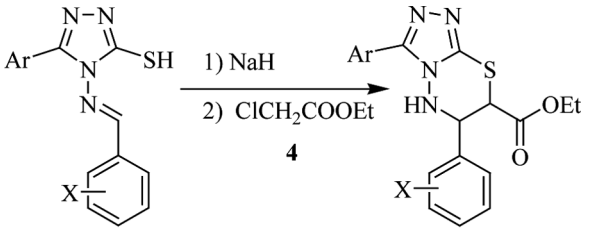


Figure 2. Synthesis of **5a–p**.

Table 1. Optimization of conditions for the synthesis of triazolothia-diazine **5a**

Entry	Base	**3a**/**4**	Yields (%)[a]
1	NaH	1:1	30
2	NaH	1:1.2	52
3	NaH	1:1.3	40
4	NaH	1:1.4	74
5	NaH	1:1.5	74

[a]Isolated yields.

Table 2. Synthesis of compounds **3a–p** and **5a–p**

			Yields (%)[a]	
Entry	Ar	X	3	5
a	4-Pyridyl	H	70	74
b	3-Pyridyl	H	60	70
c	4-Pyridyl	4-Me	71	68
d	3-Pyridyl	4-Me	65	70
e	4-Pyridyl	4-OMe	68	75
f	3-Pyridyl	4-OMe	65	75
g	4-Pyridyl	3-Br	58	65
h	3-Pyridyl	3-Br	64	70
i	4-Pyridyl	2-Cl	60	65
j	3-Pyridyl	2-Cl	50	60
k	4-Pyridyl	4-Cl	75	70
l	3-Pyridyl	4-Cl	75	75
m	4-Pyridyl	2-NO_2	85	78
n	3-Pyridyl	2-NO_2	80	81
o	4-Pyridyl	4-NO_2	85	81
P	3-Pyridyl	4-NO_2	83	80

[a]Isolated yields.

reacted with ethyl chloroacetate at room temperature to give the triazolothiadiazines **5a–p** as shown in Figure 2. The isolated compounds were obtained as *cis*-diastereomers. The stereochemistry of the products was determined by the coupling constant between two vicinal methine protons. In the ^{1}H NMR spectra of compounds **5a–p,** the coupling constant ($^3J_{\text{N-CH, CH-S}} \approx 4.3$–$7.0$ Hz) is a typical for the *cis* configuration. The purity of compounds was checked on thin-layer chromatography (TLC) in the solvent system ethanol/n-hexane (1:2).

The ^{1}H NMR spectra of the Schiff bases **3a–p** showed a broad signal at the region $\delta = 9.41$–9.82 ppm attributed to the resonance of the CH=N proton, which was not present in the spectra of compounds **5a–p**. The appearance of the infrared (IR) absorptions and ^{1}H NMR signals due to the NH group of synthesized compounds **5a–p** clearly confirmed the formation of triazolothiadiazines.

CONCLUSION

In conclusion, a novel and efficient methodology was reported for the synthesis of triazolothiadiazines by reaction of Schiff bases and ethyl chloroacetate. In addition to the efficiency and simplicity provided, this protocol describes good yields of cyclization and simple purification for these products.

EXPERIMENTAL

General Procedures

All products were characterized using IR, ^{1}H NMR, and ^{13}C NMR spectra as well as the elemental analysis data. All yields refer to isolated products. IR spectra were prepared on a Galaxy series Fourier transform (FT)–IR 5000 spectrophotometer using KBr discs. NMR spectra were recorded on a Brucker spectrophotometer (300 MHZ) in dimethylsulfoxide (DMSO-d_6) using tetramethylsilane (TMS) as an internal standard. Elemental analyses were performed on a Vario EL III elemental analyzer.

General Procedure for the Synthesis of Schiff Bases 3a–p

Aromatic aldehydes **2** (5.0 mmol) was added to a solution of aminotriazoles **1** (5.0 mmol) in glacial acetic acid (25 ml), and the mixture was refluxed for 3 h. After cooling, the mixture was poured into ice-water (50 ml). The resulting precipitate was filtered and recrystallized from an appropriate solvent to give the desired compounds **3a–p**.

Selected Characterization Data

3-(4-Methylbenzylideneamino)-5-(pyridin-3-yl)-4H-1,2,4-triazole-3-thiol (3d). IR (KBr) ν_{max}: 3119 (CH=N) 3064 (aromatic CH stretch.), 2712 (SH stretch.), 1602 (C=N), 1508, 1419 (C=C ring stretch.) cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 14.37 (s, 1H, SH), 9.71 (s, 1H, CH=N), 9.03 (s, 1H, $H_{arom.}$), 8.72 (s, 1H, $H_{arom.}$), 8.25 (d, 1H, $J = 7.6$ Hz, $H_{arom.}$), 7.78 (d, 2H, $J = 5.6$ Hz, $H_{arom.}$), 7.58 (br,

1H, $H_{arom.}$), 7.38 (d, 2H, $J = 6.0$ Hz, $H_{arom.}$), 2.38 (s, 3H, CH_3);^{13}C NMR (75 MHz, DMSO d_6) δ (ppm): 21.8, 122.5, 124.2, 129.2, 129.6, 130.3, 136.3, 143.9, 147.1, 149.1, 151.7, 162.9, 167.0. Calcd. for $C_{15}H_{13}N_5S$ 61.00: H, 4.44; N, 23.71; S, 10.86%. Found: C, 59.85; H, 4.36; N, 23.53; S, 10.69%.

4-(4-Methoxybenzylideneamino)-5-(pyridin-4-yl)-4H-1,2,4-triazole-3-thiol (3e). IR (KBr) ν_{max}: 3124 (CH=N) 3070 (aromatic CH stretch.), 2720 (SH stretch.), 1603 (C=N), 1514, 1433 (C=C ring stretch.), 1257 (Ph-O stretch.), 1165 (C-O stretch.) cm^{-1}; ^{1}H NMR (300 MHz, DMSO d_6) δ (ppm): 14.48 (s, 1H, SH), 9.53 (s, 1H, CH=N), 8.74 (d, 2H, $J = 6.0$ Hz, $H_{arom.}$), 7.87 (br, 4H, $H_{arom.}$), 7.12 (d, 2H, $J = 7.1$ Hz, $H_{arom.}$), 3.85 (s, 3H, OCH_3);^{13}C NMR (75 MHz, DMSO d_6) δ (ppm): 56.1, 115.3, 122.1, 124.7, 131.4, 133.3, 146.8, 150.8, 163.4, 164.4, 167.4. Calcd. for $C_{15}H_{13}N_5OS$: C, 57.86; H, 4.21; N, 22.49; S, 10.30%. Found: C, 57.72; H, 4.13; N, 22.24; S, 10.14%.

General Procedure for the Synthesis of Compounds 5a–p

Sodium hydride (2.0 mmol) was added to a solution of compounds **3a–p** (1.0 mmol) in dry THF (20 mL) at room temperature. Salt formation was allowed to proceed at ambient temperature for 10 min. Ethyl chloroacetate (1.4 mmol) was then added, and the solution was stirred for 8 h. The solvent was removed under vacuum and extracted with ethyl acetate; the organic layer was washed with water (3×10 mL), dried (Na_2SO_4), and evaporated under vacuum. The residue was crystallized, from ethyl acetate and petroleum ether to give triazolothiadiazines **5a–p**.

Selected Characterization Data

Ethyl-6-phenyl-3-(4-pyridyl)-6,7-dihydro-5H-[1,2,4]triazolo[3,4-b][1,3,4]-thiadiazine-7-carboxylate (5a). IR (KBr) ν_{max}: 3248 (NH stretch.), 2978 (aliphatic CH stretch.) 1714 (C=O), 1602 (C=N), 1514, 1481 (C=C ring stretch.), 1190 (C-O) cm^{-1}; ^{1}H NMR (300 MHz, DMSO d_6) δ (ppm): 8.72 (d, 2H, $J = 5.0$ Hz, $H_{arom.}$), 8.03 (s, 2H, $H_{arom.}$), 7.55 [s, 1H, NH, (D_2O exchange)], 7.33–7.40 (m, 5H, H_{arom}), 4.99 (d, 1H, $J = 4.3$ Hz, CH), 4.90 (d, 1H, $J = 4.6$ Hz, CH), 4.10 (q, 2H, $J = 5.9$ Hz, OCH_2), 1.09 (t, 3H, $J = 6.3$ Hz, CH_3,); ^{13}C NMR (75 MHz, DMSO d_6) δ (ppm): 14.1, 43.6, 59.2, 62.5, 121.3, 127.7, 128.8, 129.2, 133.7, 136.6, 143.7, 150.1, 150.7, 169.3. Calcd. for $C_{18}H_{17}N_5O_2S$: C, 58.84; H, 4.66; N, 19.06; S, 8.73%. Found: C, 58.61; H, 4.57; N, 18.91; S, 8.56%.

Ethyl-6-(4-methylphenyl-3-(4-pyridyl)-6,7-dihydro-5H-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazine-7-carboxylate (5c). IR (KBr) ν_{max}: 3244 (NH stretch.), 3067 (aromatic CH stretch.), 2976 (aliphatic CH stretch.) 1726 (C=O), 1601 (C=N), 1530, 1475 (C=C ring stretch.), 1185 (C-O) cm^{-1}; ^{1}H NMR (300 MHz, DMSO d_6) δ (ppm): 8.73 (d, 2H, $J = 4.1$ Hz, $H_{arom.}$), 8.03 (d, 2H, $J = 4.0$ Hz, $H_{arom.}$), 7.45 [s, 1H, NH, (D_2O exchange)], 7.28 (d, 2H, $J = 7.6$ Hz, $H_{arom.}$), 7.15 (d, 2H, $J = 7.4$ Hz, $H_{arom.}$), 4.91 (d, 1H, $J = 7.1$ Hz, CH), 4.86 (d, 1H, $J = 6.8$ Hz, CH), 4.10 (q, 2H, $J = 6.9$ Hz, OCH_2), 2.26 (s, 3H, CH_3), 1.09 (t, 3H, $J = 7.0$ Hz, CH_3); ^{13}C NMR (75 MHz, DMSO d_6) δ (ppm): 14.2, 21.1, 43.6, 59.0, 62.5, 121.3, 127.6, 129.7,

133.5, 138.2, 143.7, 150.1, 150.6, 169.2. Calcd. for $C_{19}H_{19}N_5O_2S$: C, 59.82; H, 5.02; N, 18.36; S, 8.41. Found: C, 59.61; H, 4.94; N, 18.18; S, 8.14%.

Ethyl-6-(4-methylphenyl-3-(3-pyridyl)-6,7-dihydro-5H-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazine-7-carboxylate (5d). IR (KBr) ν_{max}: 3243 (NH stretch.), 3070 (aromatic CH stretch.), 2974 aliphatic CH stretch.), 1716 (C=O), 1600 (C=N), 1530, 1481 (C=C ring stretch.), 1184 (C-O) cm^{-1}; ^1H NMR (300 MHz, DMSO d_6) δ (ppm): 9.15 (s, 1H, H_{arom}), 8.67 (s, 1H, H_{arom}), 8.35 (d, 1H, $J = 6.4$ Hz, $H_{arom.}$), 7.55 (br, 1H, $H_{arom.}$), 7.40 [br, 1H, NH, (D_2O exchange)], 7.26 (d, 2H, $J = 6.5$ Hz, $H_{arom.}$), 7.16 (d, 2H, $J = 6.3$ Hz, $H_{arom.}$), 4.90 (d, 1H, $J = 6.8$ Hz, CH), 4.85 (d, 1H, $J = 6.4$ Hz, CH), 4.10 (q, 2H, $J = 7.1$ Hz, OCH_2), 2.25 (s, 3H, CH_3) 1.10 (t, 3H, $J = 6.8$ Hz, CH_3); ^{13}C NMR (75 MHz, DMSO d_6) δ (ppm): 14.2, 21.1, 43.8, 59.2, 62.4, 123.0, 124.2, 127.6, 129.7, 133.5, 135.2, 138.3, 142.9, 148.4, 150.3, 151.0, 169.2. Calcd. for $C_{19}H_{19}N_5O_2S$: C, 59.82; H, 5.02; N, 18.36; S, 8.41. Found: C, 59.71; H, 4.95; N, 18.22; S, 8.20%.

Ethyl-6-(4-methoxyphenyl-3-(4-pyridyl)-6,7-dihydro-5H-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazine-7-carboxylate (5e). IR (KBr) ν_{max}: 3246 (NH stretch.) 3067 (aromatic CH stretch.), 2978 aliphatic CH stretch.), 1720 (C=O), 1597 (C=N), 1531, 1475 (C=C ring stretch.), 1190 (C-O) cm^{-1}; ^1H NMR (300 MHz, DMSO d_6) δ (ppm): 8.72 (d, 2H, $J = 4.0$ Hz, $H_{arom.}$), 8.02 (d, 2H, $J = 3.9$ Hz, $H_{arom.}$), 7.45 [s, 1H, NH, (D_2O exchange)], 7.34 (d, 2H, $J = 7.8$ Hz, $H_{arom.}$), 6.91 (d, 2H, $J = 7.4$ Hz, $H_{arom.}$), 4.91 (d, 1H, $J = 6.5$ Hz, CH), 4.84 (d, 1H, $J = 6.6$ Hz, CH), 4.10 (q, 2H, $J = 6.0$ Hz, OCH_2), 3.79 (s, 3H, OCH_3), 1.09 (t, 3H, $J = 5.9$ Hz, CH_3); ^{13}C NMR (75 MHz, DMSO d_6) δ (ppm): 14.2, 43.7, 55.6, 58.8, 62.4, 114.5, 121.3, 128.3, 129.0, 133.8, 143.7, 150.1, 150.7, 159.6, 169.2. Calcd. for $C_{19}H_{19}N_5O_3S$: C, 57.42; H, 4.82; N, 17.62; S, 8.07%. Found: C, 57.21; H, 4.76; N, 17.46; S, 7.94%.

Ethyl-6-(4-chlorophenyl-3-(3-pyridyl)-6,7-dihydro-5H-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazine-7-carboxylate (5l). IR (KBr): ν_{max}: 3230 (NH stretch.), 3084 (aromatic CH stretch.), 2980 aliphatic CH stretch.), 1730 (C=O), 1606 (C=N), 1516, 1450 (C=C ring stretch.), 1195 (C-O) cm^{-1}; ^1H NMR (300 MHz, DMSO d_6) δ (ppm): 9.16 (s, 1H, H_{arom}), 8.67 (s, 1H, H_{arom}), 8.36 (d, 1H, $J = 7.4$ Hz, $H_{arom.}$), 7.58 [s, 1H, NH, (D_2O exchange)], 7.56 (s, 1H, H_{arom}), 7.43 (s, 4H, $H_{arom.}$), 4.99 (d, 1H, $J = 6.8$ Hz, CH), 4.92 (d, 1H, $J = 6.4$ Hz, CH), 4.10 (q, 2H, $J = 6.9$ Hz, OCH_2), 1.11 (t, 3H, $J = 6.9$ Hz, CH_3); ^{13}C NMR (75 MHz, DMSO d_6) δ (ppm): 14.2, 43.6, 58.8, 62.4, 123.0, 124.2, 129.2, 129.7, 133.6, 135.2, 135.7, 142.8, 148.4, 150.3, 151.0, 169.1. Calcd. for $C_{18}H_{16}ClN_5O_2S$: C, 53.80; H, 4.01, N, 17.43; S, 7.98%. Found: C, 53.55; H, 3.92; N, 17.29; S, 7.81%.

Ethyl-6-(2-nitrophenyl-3-(4-pyridyl)-6,7-dihydro-5H-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazine-7-carboxylate (5m). IR (KBr) ν_{max}: 3235 (NH stretch.), 3070 (aromatic CH stretch.), 2982 (aliphatic CH stretch.), 1732 (C=O), 1604 (C=N), 1531, 1359 (NO_2), 1186 (C-O) cm^{-1}; ^1H NMR (300 MHz, DMSO d_6) δ (ppm): 8.69 (d, 2H, H_{arom}, $J = 5.4$ Hz), 7.94 [s, 1H, NH, (D_2O exchange)], 7.89 (d, 2H, $J = 5.0$ Hz, H_{arom}), 7.74–7.66 (m, 4H, $H_{arom.}$), 5.50 (d, 1H, $J = 6.8$ Hz, CH), 5.05 (d, 1H, $J = 6.6$ Hz, CH), 4.11 (q, 2H, $J = 6.7$ Hz, OCH_2), 1.11 (t, 3H, $J = 6.6$ Hz, CH_3); ^{13}C NMR (75 MHz, DMSO d_6) δ (ppm): 14.1, 43.5, 55.1, 62.8, 121.0, 125.6, 128.4 129.0, 130.6, 133.4, 134.0, 144.5, 149.1, 150.1, 150.6, 168.8. Calcd. for

$C_{18}H_{16}N_6O_4S$: C, 52.42; H, 3.91; N, 20.38; S, 7.77%. Found: C, 52.21; H, 3.79; N, 20.20; S, 7.58%.

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