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A facile synthesis of some novel triazolo[3,4-b]thiadiazines and triazolo[4,3-*b*]tetrazines

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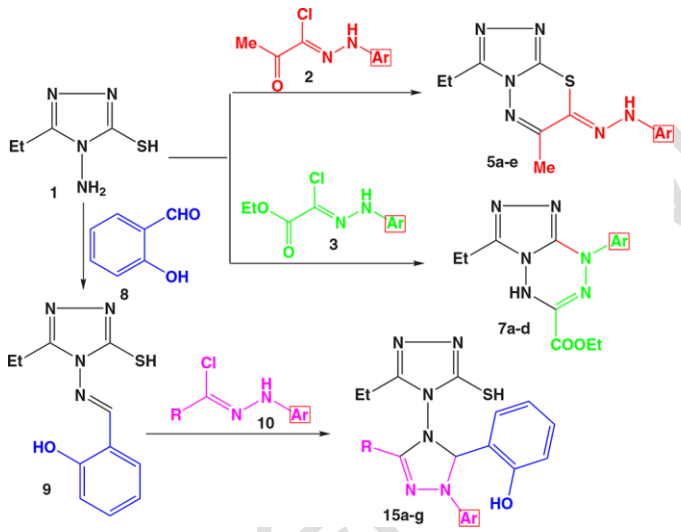
ABSTRACT

4-Amino-5-ethyl-4*H*-1,2,4-triazole-3-thiol was used as a key intermediate for the synthesis of triazolo[3,4-*b*][1,3,4]thiadiazines, triazolo[4,3-*b*][1,2,4,5]tetrazines and Schiff's base *via* reactions with various hydrazonoyl halides and salicyaldehyde, respectively. Moreover triazolyl-N-N`-triazole derivatives were prepared from reaction of Schiff's base with various hydrazonoyl halides. The structures of all the newly synthesized heterocyclic compounds were established by considering elemental analysis and spectral data.

GRAPHICAL ABSTRACT



KEYWORDS: 1,2,4-aminomercaptotriazole, hydrazonoyl halides, triazolo[3,4-b]thiadiazine, triazolo[4,3-b]tetrazine

Introduction

A considerable number of heterocyclic compounds containing 1,2,4-triazole residue and their fused heterocyclic derivatives manifests diverse pharmacological properties such as antimicrobial, antifungal, anticancer, anticonvulsant, antiviral, anti-HIV, and antimycobacterial

activities.[1–10] A large number of ring systems containing 1,2,4-triazoles have been incorporated into a wide variety of therapeutically interesting drug candidates such as Fluconazole, Itraconazole and Voriconazole. Also FDA approved drugs like Triazolam, Alprazalam, Etizolam, Furacylin, Ribavirin, Hexaconazole, Triadimefon, Mycobutanil, Rizatriptan, Propiconazole, and Fluotrimazole.[11] 1,2,4-Triazoles coupled to another heterocyclic ring exhibited wide spread applications as antibacterial, antiviral, antihypertensive, antidepressant, anti-inflammatory, anticonvulsant and antitumorial agents, pesticides, herbicides, lubricants, dyes and analytical reagents.[12,13] Among these, the most common systems are triazoles combined to thiadiazines or tetrazines, incorporated into a wide variety of therapeutically important compounds possessing a broad spectrum of biological activities such as antiviral, antifungal, antihelmintic, antitumor, antibacterial, anti-inflammatory, antitubercular, analgesic, antiviral, diuretics, CNS-stimulant, PDE4 inhibitors and hypoglycemic agents.[14–20] The recent literature survey revealed that 1,2,4-triazolo[3,4-b][1, 3, 4]thiadiazine derivatives have promising biological activities such as anti-HIV,[21] CNS stimulant,[22] antifungal,[23] and anti-inflammatory.[24] Studies have also confirmed that triazolothiadiazine derivatives possess anti-Candidal activity.[25–29]

In the last two decades we have been involved in a program directed to synthesize functionally substituted heterocyclic compounds that can be used as biodegradable agrochemicals from cheap laboratory available starting materials.[30–42] Within the frame of this program, some new functionally substituted triazolo-thiadiazine or triazolo-tetrazine compounds were required for biological activity screening. 4-Amino-5-ethyl-4*H*-1,2,4-triazol-3-thiol (**1**) (Scheme 1) seemed a suitable starting material to achieve our goal via its (or its Schiff base) reaction with different hydrazonoyl chlorides to synthesize our target compounds.

Results and Discussion

4-Amino-5-ethyl-4*H*-1,2,4-triazol-3-thiol (**1**)[43] (Scheme 1) was allowed to react with the hydrazonoyl chlorides **2** and **3**[44] in refluxing dioxane containing triethylamine as catalyst. The reflux was continued for 4-8h (monitored by TLC) to afford the 7-(2-arylhydrazono)-7*H*-[1,2,4]triazolo [3,4-b][1,3,4]thiadiazines **5a-e** and the 8-aryl-5,8-dihydro-[1,2,4]triazolo[4,3-b][1,2,4,5]tetrazine-6-carboxylates **7a-d** respectively (Scheme 1). The structures of these products were established on the basis of elemental analyses as well as spectral data. The ^{1}H NMR spectra of **5a-e** showed characteristic singlet signal near δ = 10.14ppm, assignable for NH of hydrazone tautomer[45] beside the signals assigned for aliphatic and aromatic protons. IR spectra in each case revealed one band at υ = 3290-3432cm $^{-1}$ assigned to NH group and revealed the absence of the absorption band corresponding to CO group.

The reactions between **1** and **2** /or **3** presumably take place *via* HCl elimination to afford the S-alkylated intermediates **4**. Intermediates **4** (with R = CH_3) are cyclized by elimination of H_2O to afford the triazolo[3,4-b]thiadiazines **5a-e**; while the intermediates **4** (with R = OC_2H_5) apparently undergoes Smiles rearrangement[46] to afford the arylhydrazinyl-2-thioxoacetate intermediates **6** which cyclize via loss of H_2S to afford the triazolo[4,3-b]tetrazines **7a-d**.

On the other hand compound **1** was condensed with salicylaldehyde **8**in refluxing acetic acid for 2hours to afford the Schiff's base **9** (Scheme 2). This Schiff's base **9** was allowed to react with the appropriate hydrazonoyl halides **10**in refluxing dioxane containing catalytic amount of triethylamine for 4-8h (monitored by TLC) to afford 1:1 cycloadducts. We assumed that the reaction will proceed *via* the S-alkylation with elimination of HCl which would lead to the thiohydrazonate intermediates **12** which after Smiles rearrangement and cyclization would have led to the triazolo[4,3-b]tetrazine derivatives **13**. However, based on the presence of the SH signal in the ^{1}H-NMR spectra of all the obtained products at 12.51ppm this assumption was ruled out.

It is apparent that the hydrazonoyl chlorides **10** underwent *in situ* elimination of HCl in presence of triethylamine to afford the nitrile imines **11** which undergo 1,3-cycloaddition reaction to the C = N function in **9**. Two theoretically possible structures **14** or **15** could in principle be obtained. However based on the fact that nitrile-imine cycloaddition take place always regioselective; structure **14** was ruled out and the triazolyl-triazole structures **15a-g** were assigned to these products. Analytical and spectral data are in complete agreement with these structures. Thus the ^{1}H NMR of **15a** showed four singlet signals at 2.27, 5.80, 8.82 and 10.66ppm assignable for CH_3, triazole-H5, OH and SH protons, in addition to the expected signals of ethyl group and aryl protons. The mass spectra of products **15a-g** showed in each case a molecular ion peak at the correct molecular weight (see experimental section).

Synthesis of [1,2,4]triazolo[3,4-b][1,3,4]thiadiazines 5a-e and [1,2,4]triazolo[4,3-b][1,2,4,5]tetrazines 7a-d: General method

A mixture of aminomercaptotriazole **1** (0.144g, 1 mmol) and the appropriate hydrazonoyl halides **2**(**3**) (1 mmol of each) in dioxane (20mL) containing triethylamine (0.1g, 1 mmol) was refluxed for 4-8h (monitored by TLC). The formed precipitate was isolated by filtration, washed with methanol, dried and recrystallized from the proper solvent to give the respective triazolothiadiazines **5a-e** and triazolotetrazines **7a-d.**

3-Ethyl-6-methyl-7-(2-phenylhydrazono)-7H-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazine (5a)

Yellow solid; 82% yield; mp = 265-276 °C (dioxane); IR (KBr): *v* 1598 (C = N), 2994, 3045 (CH), 3430 (NH) cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 1.28 (t, J = 7.5Hz, 3H, CH_2CH_3), 2.45 (s, 3H, CH_3), 2.83 (q, J = 7.5Hz, 2H, CH_2CH_3), 6.97-7.33 (m, 5H, Ar-H), 10.14 (brs, 1H, NH); MS

m/z (%): 286 (M^+, 44), 140 (17), 92 (52),77 (100), 65 (60). Anal. Calcd. for $C_{13}H_{14}N_6S$ (286.36): C, 54.53; H, 4.93; N, 29.35. Found C, 54.38; H, 4.77; N, 29.18%.

Conclusions

This paper describes a facile and efficient synthesis of triazolo[3,4-b]thiadiazines, triazolo[4,3-b]tetrazines and triazolyl-N-N`-triazoles from reaction of 1,2,4-triazole derivative **1** or its Schiff's base **9** with different hydrazonoyl chlorides **2**, **3** and **10**. The structures of the final products were elucidated by elemental analyses and FTIR, MS, and ^{1}H NMR spectra.

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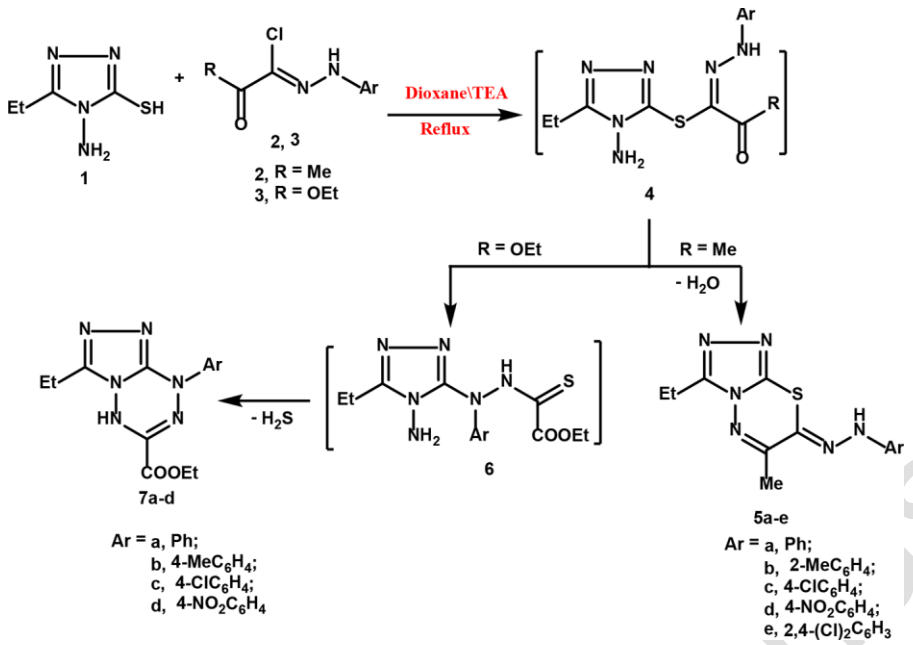
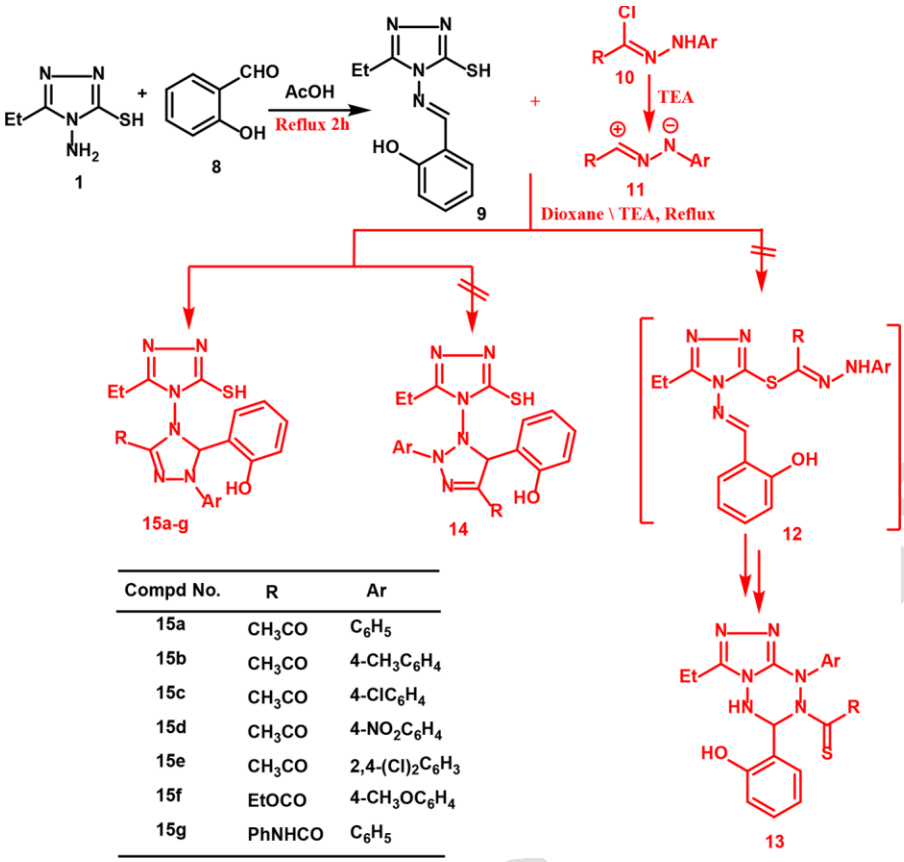
Scheme 1. Synthesis of triazolo[3,4-b]thiadiazines **5a-e** and triazolo[4,3-b]tetrazines **7a-d**.



Scheme 2. Synthesis of the 4.4`-bi-triazoles **15a-g**.



Compd No.	R	Ar
15a	CH_3CO	C_6H_5
15b	CH_3CO	$4\text{-}CH_3C_6H_4$
15c	CH_3CO	$4\text{-}ClC_6H_4$
15d	CH_3CO	$4\text{-}NO_2C_6H_4$
15e	CH_3CO	$2,4\text{-}(Cl)_2C_6H_3$
15f	EtOCO	$4\text{-}CH_3OC_6H_4$
15g	PhNHCO	C_6H_5