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Synthetic Approach Toward Heterocyclic Hybrids of [1,2,4]Triazolo[3,4-b][1,3,4]thiadiazines

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Abstract The synthesis of novel heterocyclic [1,2,4]triazolo[3,4b][1,3,4]thiadiazine hybrids by a bimolecular reaction of 2-(4-amino-5mercapto-4*H*-[1,2,4]triazol-3-yl)phenol with an aromatic or heterocyclic α -bromoacetyl derivatives is described. This synthetic procedure starts from an unprotected phenol.

Key words triazolothiadiazines, triazolylphenol, bromomethyl ketones, polycycles, heterocycles, cyclization

The structural combination of heterocycles with various types and numbers of heteroatoms has been intensively used in molecular engineering to generate a significant diversity of fused heterocycles, usually bearing nitrogen ring junctions. These so-called 'heterocyclic hybrids' are designed for specific biological or technological applications. In this context, the [1,2,4]triazolo[3,4-b][1,3,4]thiadiazine fused system, which combines nitrogen and sulfur atoms in a unique scaffold, has proved to be useful in biological and agricultural areas, such systems being employed as antimicrobial, antibacterial, antifungal, herbicidal, or anthelmintic agents.¹ In pharmaceutical applications, these structures have been reported to present a broad spectrum of properties, including antitubercular, diuretic, and hypoglycemic activities.² In the other hand, coumarins and pyran-2-ones form a class of oxygen-containing heterocyclic compounds that play key roles in biological and physiological systems. Synthetic coumarin derivatives constitute one of the most widely used groups of anti-HIV, antiviral, antiinflammatory, and antioxidant agents.³ In the past few years, our group has devoted considerable efforts to exploring the valuable anticancer activities of coumarins and pyran-2-ones.⁴

Syntheses of 3,6-disubstituted [1,2,4]triazolo[3,4b][1,3,4]thiadiazine derivatives by condensing 3-(alkyl or aryl)-4-amino-5-mercapto-1,2,4-triazoles with α -halocarbonyl compounds has been reported.⁵ In the present work, we describe a synthetic protocol for constructing the heterocyclic [1,2,4]triazolo[3,4-b][1,3,4]thiadiazine hybrids **3a-e** bearing aryl, dehydroacetic acid (DHA), or coumarin moieties. The main reaction is a bimolecular condensation of 2-(4-amino-5-mercapto-4*H*-[1,2,4]triazol-3-yl)phenol (**1**) with aromatic or heterocyclic α -bromoacetyl derivatives **2a-e** (Scheme 1).





The key starting compound (4-amino-5-mercapto-4*H*-1,2,4-triazol-3-yl)phenol (**1**) was prepared from 2-hydroxybenzohydrazide (**5**), obtained by the reaction of methyl 2hydroxybenzoate (**4**) with hydrazine hydrate in methanol

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(Scheme 2). Compound **5** was then treated with an equimolar mixture of potassium hydroxide and carbon disulfide to afford potassium 2-(2-hydroxybenzoyl)hydrazinecarbadithionate (**6**), which gave phenol **1** upon treatment with an excess of hydrazine (see Supporting Information).⁶



Scheme 2 Synthesis of (4-amino-5-sulfonyl-4H-1,2,4-triazol-3-yl)phenol 1.

In parallel, 3-(bromoacetyl)coumarins **2a** and **2b** were prepared from the corresponding salicylaldehydes **7a** and **7b** by Knoevenagel condensation with ethyl acetoacetate followed by α -bromination of the resulting 3-acetylcoumarins **8a** and **8b**, respectively (Scheme 3; see Supplementary Information).⁷ A similar strategy was used to prepare the 3-(bromoacetyl)-4-hydroxy-6-methyl-2*H*-pyran-2-one **2c** and 3-bromoacetophenones **2d** and **2e** by brominating the corresponding ketones (see Supplementary Information).⁷

With the functionalized triazole **1** and the α -bromoacetyl synthons **2a–e** in hand, we went on to develop the synthesis of a novel series of the aryl-, pyran-2-one-, or coumarin-substituted [1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazine hybrids **3a–e** (Scheme 1), which incorporate three important heterocyclic pharmacophores. We propose a mechanistic pathway based on sequential (consecutive or simultaneous) thianucleophilic substitution of the α -bromoacetyl moiety and imine formation (Scheme 4). Experimentally, moderate-to-good yields (50–72%) were obtained, and the pure products **2a–e** were isolated by filtration.⁸ This process is general and efficient without byproduct formation; the purity of the resulting compounds **2a–e** was verified by HPLC.



Scheme 4 Proposed mechanism for the formation of substituted [1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazines **3a**–e

All the new structures **3a-e** were characterized by means of 1D- and 2D-NMR spectroscopy (see Supplementary Information). As a representative example, the ¹H NMR spectrum of the hybrid of coumarin with triazolo[3,4*b*][1.3.4]thiadiazine **3b** showed four characteristic singlets. including those of the labile protons 7-OH and 2"-OH at δ = 11.33 and 10.23 ppm, respectively.⁹ The vinylic C=CH group of the pyran-2-one ring was observed at δ = 8.77 ppm, followed by the methylene group CH_2 of the thiadiazine at δ = 5.00 ppm. With help of HSQC spectroscopy, all the protonated carbons could be assigned, particularly the peaks at δ = 43.9 ppm, assigned to the C-7' methylene carbon, and at δ = 149.9 ppm, assigned to the C-4 vinylic carbon. In **3b**, the ten different quaternary carbons were assigned by examination of HMBC connectivities (Figure 1). Aromatic carbons C-2" $(\delta = 156.5 \text{ ppm})$ and C-7 $(\delta = 165.4 \text{ ppm})$ were localized by means of HMBC correlations with protons 2"-OH and 7-OH, respectively. Among the functional carbons, three different imine C=N groups could be distinguished through the cross-correlations observed between H-6" and C-3' (δ = 164.9 ppm) and between H-7' and C-8'a (δ = 163.3 ppm). In addition, the hybrid junction C-3 (δ = 117.9)–C6' (δ = 189.9) was identified by considering the connectivity between H-4 and C-3 and H-7', and between H-4 and C-6', respectively. The carbonyl carbon of the pyran-2-one was assigned to the resonance at δ = 159.6 ppm; this was confirmed by HMBC



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correlations with H-4 and H-8 of the coumarin ring. Thus, by in-depth analyses of the HMBC NMR spectra, all structures of compounds **3a–e** were confirmed.



In conclusion, a simple synthesis of heterocyclic and aromatic hybrids of [1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazines is disclosed. The reported approach provides such advantages as short reaction times, good yields, and simple workup. The resulting highly functionalized hybrids contain up to three types of oxygen-, nitrogen-, and sulfur-based heterocycles.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0036-1591991.

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- (8) [1,2,4]Triazolo[3,4-b][1,3,4]thiadiazines 3a-e; General Procedure

Equimolar amounts of the appropriate α -bromoacetyl derivative **2a–e** (1.0 mmol) and triazolylphenol **1** (0.2 g; 1.0 mmol) were dissolved in absolute EtOH (10 mL) containing a catalytic amount of AcOH (1 mL), and the mixture was heated for 2 h, then cooled to r.t. The resulting solid was collected by filtration and washed with EtOH and Et₂O to give the pure product.

(9) **7-Hydroxy-3-[3-(2-hydroxyphenyl)-7H-[1,2,4]triazolo[3,4b][1,3,4]thiadiazin-6-yl]-2H-chromen-2-one (3b)** $C_{19}H_{12}N_4O_4S$. Green solid; yield: 0.23 g (60%); mp 239–241 °C. ¹H NMR (400 MHz, DMSO- d_6): $\delta = 5.00$ (s, 2 H, H-7'), 6.80 (d, J = 2.2 Hz, 1 H, H-8), 6.89 (dd, J = 8.6, 2.2 Hz, 1 H, H-6), 6.93–7.01 (m, 1 H, H-5"), 7.06 (dd, J = 8.3, 0.7 Hz, 1 H, H-3"), 7.41–7.46 (m, 1 H, H-4"), 7.71 (dd, J = 7.8, 1.7 Hz, 1 H, H-6"), 7.85 (d, J = 8.6 Hz, 1 H, H-5), 8.77 (s, 1 H, H-4), 10.23 (s, 1 H, 2"-OH), 11.33 (s, 1 H, 7-OH). ¹³C NMR (100 MHz, DMSO- d_6): $\delta = 44.0$ (C-7'), 102.4 (C-8), 110.0 (C-1"), 111.4 (C-4a), 115.1 (C-6), 117.7 (C-3"), 117.9 (C-3), 120.1 (C-5"), 129.3 (C-6"), 133.6 and 133.7 (C-4" and C-5), 149.9 (C-4), 156.5 (C-2"), 158.0 (C-8a), 159.6 (C-2), 163.3 (C-8'a), 164.9 (C-3', C=N), 165.4 (C-7), 189.9 (C-6', C=N). HRMS-ESI⁺: m/z [M + H]⁺ calcd for $C_{19}H_{13}N_4O_4S$: 393.0658; found: 393.0677.