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Novel One-Step Synthesis of Thiazolo[3,2-*b*]1,2,4-triazoles

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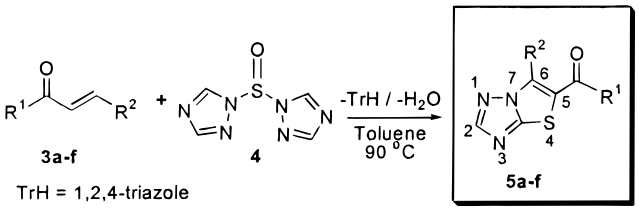
ABSTRACT



Reactions of chalcones 3a–f with bis(1*H*-1,2,4-triazolyl) sulfoxide 4 formed the thiazolo[3,2-*b*]1,2,4-triazoles 5a–f, which resemble closely some previously prepared COX-2 inhibitors. The structure of 5a was confirmed by X-ray analysis.

A recent survey[1] claims that side effects of nonsteroidal antiinflammatory drugs, such as aspirin, cause as many deaths each year as AIDS. The development of COX-2 inhibitor drugs, known to lack these harmful side effects while providing pain relief, has broadened the range of therapeutic options. Thiazolotriazoles possess a broad spectrum of biological activities: for example **1** and **2** (R^3 = Ar) are potent and selective COX-2 inhibitors;[2] **2** (R^3 = H) also exhibits pronounced antiinflammatory and analgesic activity[3] (Figure 1).

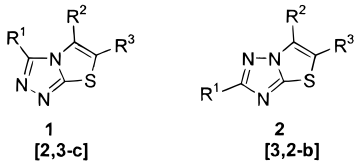


Figure 1.

Available methods for the preparation of the heterocyclic core of **2**[2,4] involve multistep procedures, and some are specific to a given substituent pattern. The most straightforward approach to **2**, from the corresponding triazole-2-thiones and aryl α-bromobenzyl derivatives, provides only the aromatic substituents R^2 and R^3.[2] Other methods cyclize triazole-2-thiones with epoxyphosphonates[4b] or utilize 2-formamidothiazoles[4d] or other procedures.[4a,c]

We now report a one-step preparation of thiazolo[3,2-

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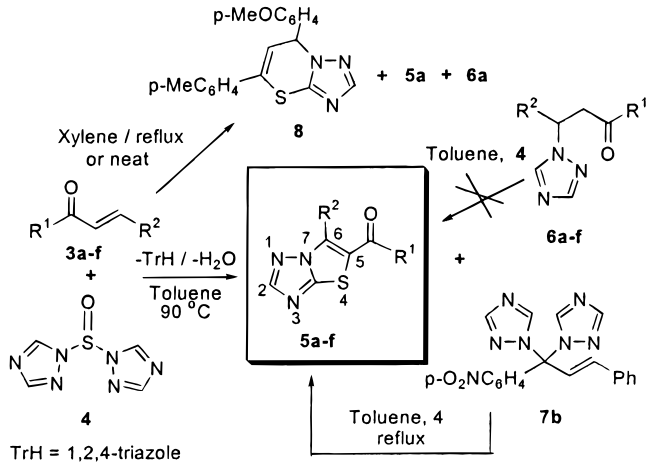
b]1,2,4-triazoles of the general formula **2**, where R^1 = H (Scheme 1). In the context of ongoing research on the 1,1-

Scheme 1



bis(1,2,4-triazolyl) derivative **4**,[5] we investigated the behavior of **4** toward chalcones **3**. When **3a**−**f** were heated in the presence of 1.3 equiv of **4**, compounds **5a**−**f** were isolated by column chromatography in 11−30% yields. The highest yields of **5a**−**f** were achieved when toluene was employed, while THF afforded no desired product.

Along with compounds **5a**−**f**, the corresponding Michael adducts **6a**−**f**[6] were isolated in 8−51% yield and, in one case, a small amount of the corresponding 1,1-bis(1,2,4-triazolyl) derivative **7b**.[5] When it was heated in xylene or reacted neat, a mixture of **3a** and **4** gave a detectable amount of the side product **8** (Scheme 1). The experimental results are summarized in Table 1.[7]

Table 1. Synthesis of Thiazolo[3,2-*b*]-1,2,4-triazoles **5a**−**f**

entry	R^1	R^2	mp (°C)	yield (%)
5a	*p*-MeC_6H_4	*p*-$MeOC_6H_4$	140−141	22
5b	*p*-$NO_2C_6H_4$	C_6H_5	151−152	13
5c	*p*-MeC_6H_4	*p*-ClC_6H_4	162−163	20
5d	C_6H_5	C_6H_5	148−149	30
5e	*p*-MeC_6H_4	C_4H_3S	oil	18
5f	*p*-ClC_6H_4	C_6H_5	154−155	12
6a	*p*-MeC_6H_4	*p*-$MeOC_6H_4$	134−135	31
6b	*p*-$NO_2C_6H_4$	C_6H_5	110−111	25
6c	*p*-MeC_6H_4	*p*-ClC_6H_4	82−83	19
6d	C_6H_5	C_6H_5	oil	12
6e	*p*-MeC_6H_4	C_4H_3S	103−105	32
6f	*p*-ClC_6H_4CO	C_6H_5	89−90	51

While the mechanism of the conversion **3** → **5** is not clear, **7** is a possible intermediate. In fact, while **7b** afforded product **5b** under the reaction conditions, similar treatment of **6b** gave no **5b** (Scheme 1).

The structures of **5a** and **8** were determined by single-crystal X-ray diffraction. Figure 2 shows a perspective view

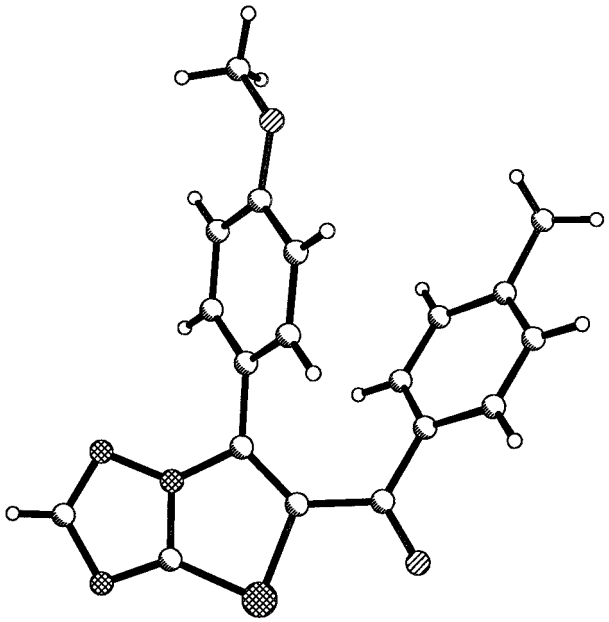


Figure 2. Perspective view of the crystal structure of **5a**.

of the structure of **5a**.[8] The thiazolo[3,2-*b*]1,2,4-triazole ring system is planar (maximum deviation 0.027 Å) and has a geometry similar to that reported in two previous crystal structures of compounds with this ring system,[2,3] except for a slight lengthening of the bond containing the two aryl substituents (1.375 Å). This is presumably a result of the polarization of this bond due to the very different electron demands of the two substituents. The planes of the two aryl rings are inclined to the plane of the thiazolotriazole system at angles of 47.6 and 43.7°.

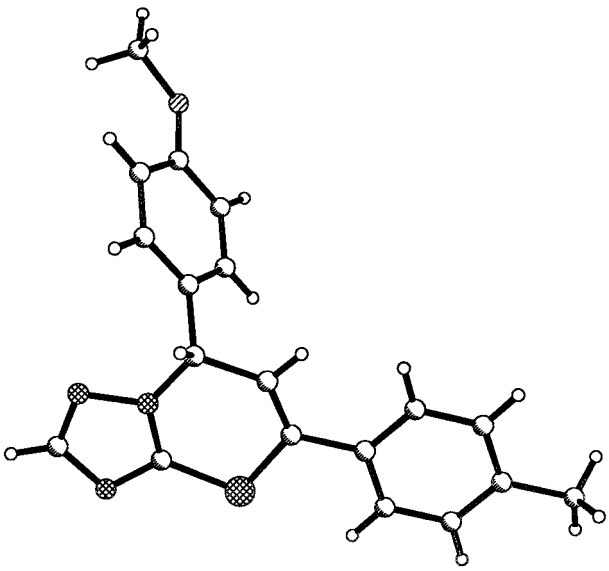


Figure 3. Perspective view of the crystal structure of **8**.

The structure of **8**[9] is shown in Figure 3. This is only the second crystal structure determination of this heterocyclic ring system.[10] Once again, the fused bicyclic ring system is planar (maximum deviation 0.054 Å). The 4-methylphenyl ring is approximately coplanar with the attached ring (2.1°), while the 4-methoxyphenyl ring is nearly orthogonal to it (71.2°).

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Supporting Information Available: Full characterization details, proton and carbon spectra, and elemental analysis or HRMS data for compounds **5a**−**f**, **6a**−**f,** and **8**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(7) **General Procedure for the Preparation of Thiazolo[3,2-*b*]-1,2,4-triazoles 5a−f.** 1-(Trimethylsilyl)-1*H*-1,2,4-triazole[5] (11 mmol) was weighed in a round-bottomed flask under argon, and thionyl chloride (6 mmol) was then added neat via syringe dropwise at room temperature. A yellow solid precipitated after the addition of the first drops. The mixture was stirred at room temperature under argon for 15 min, and the resulting solid was dried under vacuum. Dry toluene (10 mL) was then added, followed by addition of the corresponding chalcone (5 mmol); the resulting mixture was heated at 90 °C overnight. The reaction mixture was then cooled to room temperature and concentrated in vacuo to afford a crude oil. Purification was achieved by column chromatography on silica gel (with 1:1 hexanes/ethyl acetate as eluent).

(8) Crystal data for **5a**: $C_{19}H_{15}N_3O_2S$, mol wt 349.4, monoclinic, *C*2/*c*, $a = 23.266(6)$ Å, $b = 7.385(2)$ Å, $c = 20.466(5)$ Å, $\beta = 109.320(3)°$, $V = 3318.3(1)$ Å^3, $Z = 8$, $T = -105$ °C, μ(Mo Kα) = 0.21 mm^{-1}, $D_{calcd} = 1.399$ g cm^{-3}, $2\theta_{max} = 53°$ (CCD area detector), $R_w(F^2) = 0.096$ (all 3385 data), $R = 0.036$ (2852 data with $I > 2\sigma(I)$).

(9) Crystal data for **8**: $C_{19}H_{17}N_3OS$, mol wt 335.4, triclinic, $P\bar{1}$, $a = 6.333(3)$ Å, $b = 6.356(3)$ Å, $c = 21.935(9)$ Å, $\alpha = 92.391(5)°$, $\beta = 97.937(5)°$, $\gamma = 105.777(6)°$, $V = 838.6(1)$ Å^3, $Z = 2$, $T = -110$ °C, μ(Mo Kα) = 0.20 mm^{-1}, $D_{calcd} = 1.328$ g cm^{-3}, $2\theta_{max} = 45°$ (CCD area detector), $R_w(F^2) = 0.189$ (all 2093 data), $R = 0.067$ (1536 data with $I > 2\sigma(I)$).

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