# Synthesis of a novel heterocyclic ring system: imidazo[3,2-*d*][1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazine

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Synthesis of the novel compounds 3-substituted-6-arylimidazo[3,2-*d*][1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazines was achieved by the reaction of 6-amino-3-substituted-7H-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazines with 4-substituted-phenacyl bromides in refluxing ethanol.

**Keywords:** triazolothiadiazines, imidazotriazolothiadiazines, phenacyl bromide, 4-bromophenacyl bromide, 4-nitrophenacyl bromide

1,2,4-Triazoles and the n-bridged heterocycles derived from them are associated with diverse pharmacological activities.[1,2] Triazolothiadiazine derivatives are of wide interest due to their diverse biological activities and clinical applications.[3-6] Procedures for synthesis of some triazolothiadiazines have been published.[7-11] We have recently reported the synthesis of substituted 7H-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazines.[12] Armed with this experience, a ready availability of the starting material, and prompted by the various biological properties of fused [1,3,4]thiadiazines, a project aimed at the synthesis of tricyclic compounds derived from triazolo [3,4-*b*][1,3,4]thiadiazines was undertaken. In this paper, we report the synthesis of the novel heterocyclic ring system imidazo[3,2-*d*][1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazine.

6-Amino-3-substituted-7H-[1,2,4]triazolo[3,4-*b*][1,3,4] thiadiazines **2** were synthesised by the reaction of 4-amino-5-substituted-1,2,4-triazole-3-thiones **1** with chloroacetonitrile.[7,12] Reaction of compound **2** (R = Me) with further chloroacetonitrile in refluxing ethanol led to the production of either 6-aminoacetonitrile-3-methyl-7H-[1,2,4]triazolo[3,4-*b*] [1,3,4]thiadiazine **3** or N-acetonitrile-6-imino-3-methyl-7H-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazine **4** (Scheme 1). Assignment of the structure of the product was made by its spectral data. The $^1$H NMR spectrum of the product was devoid of the signal for the $NH_2$ group of the precursor at δ7.03[12] and instead, showed an upfield signal at δ5.76 for the NH (amino) proton, which was exchanged with $D_2O$, and a singlet at δ4.65 (2H, N–$CH_2$) appeared. The IR spectrum of the product showed an NH stretching frequency at 3200 cm$^{-1}$ and a CN stretching frequency at 2200 cm$^{-1}$, which confirmed the structure of the product (compound **3**).

Subsequently, a number of compounds with the novel 3-substituted-6-aryl imidazo[3,2-*d*][1,2,4]triazolo[3,4-*b*][1,3,4] thiadiazine ring system were prepared *via* the route described in Scheme 2.

6-Amino-7H-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazine **2** (R = H) was treated with phenacyl bromide **5** (X = H) in ethanol to afford 6-phenylimidazo[3,2-*d*][1,2,4]triazolo [3,4-*b*][1,3,4]thiadiazine **6** (R = H, X = H) in good yield. The structure assigned to compound **6a** was substantiated from its elemental analysis and spectral data (Table 1). Its IR spectrum lacked the N-H stretching frequency of its precursor **2** (R = H, X = H). The $^1$H NMR spectrum of compound **6a** was devoid of the signal at δ7.10 for $NH_2$ group and showed an additional set of aromatic protons at δ7.50–8.10, indicating the construction of an imidazole ring around positions 5 and 6 of the triazolothiadiazine.

In summary, we have described a convenient one-step synthesis of 6-aryl-3-substituted-imidazo[3,2-*d*][1,2,4]triazolo [3,4-*b*][1,3,4]thiadiazine **6** *via* heterocyclisation of 6-amino-3-substituted-7H-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazines **2** with 4-substituted- phenacyl bromides **5**. The generality is shown by synthesis of the other analogues **6b–i** (see Table 1).

## Experimental

Melting points were recorded on an electrothermal type 9100 melting point apparatus.

IR spectra were obtained on a 4300 Shimadzu spectrometer as KBr disk.

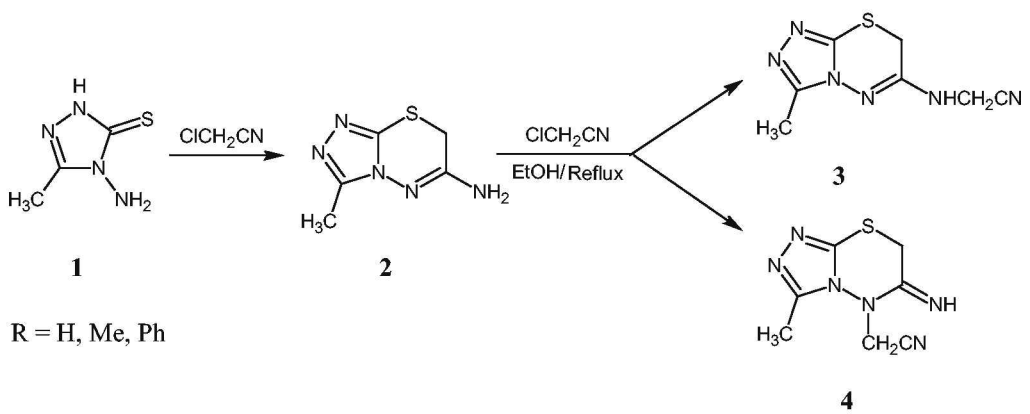
$^1$H NMR spectra were recorded on a Bruker BRX 500 AVANCE spectrometer.

Mass spectra were obtained using a Varian CH-7 instrument at 70 eV.

Elemental analysis results were obtained using a Thermo Finnigan Flash EA microanalyser.

*Preparation of 6-aminoacetonitrile-3-methyl-7H-[1,2,4]triazolo[3,4-b] [1,3,4]thiadiazine* **3**

A mixture of 6-amino-3-methyl-7H-[1,2,4]triazolo[3,4-b][1,3,4] thiadiazine **2** (R = Me) (10 mmol) and chloroacetonitrile (10 mmol)




**Scheme 1**

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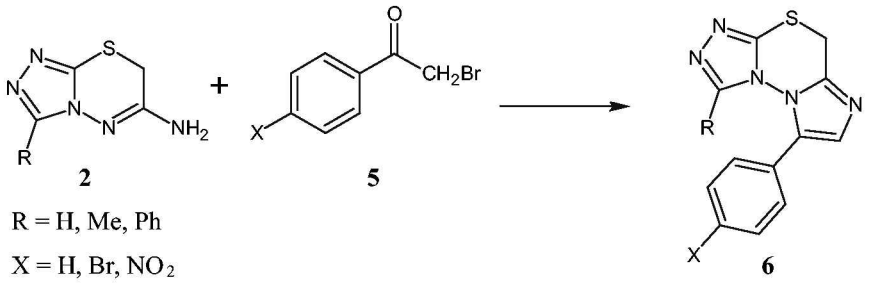


**Scheme 2**

in absolute ethanol (10 ml) was heated under reflux for 3 hours. After cooling, the precipitate was collected and recrystallised from ethanol. M.p. 240–241 °C. IR ($cm^{-1}$): 3200 (NH), 2200 (CN). $^1H$ NMR δ (DMSO-$d_6$), 2.40 (s, 3H, Me), 3.90 (s, 2H, S–$CH_2$), 4.65 (s, 2H, N–$CH_2$), 5.76 (s, 1H, NH). *m/z:* 208 (M), Anal. Calcd for $C_7H_8N_6S$: C, 40.37; H, 3.87; N, 40.36; S, 15.40. Found: C, 40.18; H, 3.74; N, 40.18; S, 15.25%.

*General procedure for the preparation of imidazotriazolothiadiazines* **6a–i**

A mixture of the triazolothiadiazine **2** (10 mmol) and 4-substituted-phenacyl bromides **5** (10 mmol) in absolute ethanol (15 ml) was heated under reflux for 5–10 hours. After cooling, the precipitate was collected and recrystallised from ethanol/water (data in Table 1).

**Table 1** Physical and spectral data for 3-substituted-6-arylimidazo[3,2-*d*][1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazine **6a–i**

| Entry | R | X | Reaction time/h | Yield/% | M.p./°C | C% Calcd (Found) | H% Calcd (Found) | N% Calcd (Found) | S% Calcd (Found) | Spectral data |
|---|---|---|---|---|---|---|---|---|---|---|
| **6a** | H | H | 10 | 70 | 260–261 | 56.47 (56.72) | 3.52 (3.66) | 27.45 (27.70) | 12.54 (12.29) | $^1H$ NMR: δ (DMSO-$d_6$), 3.90 (s, 2H, S–$CH_2$), 7.50–8.10 (m, 6H, imidazole and $C_6H_5$), 9.02 (s, 1H, triazole), *m/z*: 255 (M) |
| **6b** | H | Br | 8 | 74 | 282–283 | 43.24 (43.34) | 2.40 (2.53) | 21.02 (20.83) | 9.60 (9.37) | $^1H$ NMR: δ (DMSO-$d_6$), 4.02 (s, 2H, S–$CH_2$), 7.59–8.26 (m, 5H,imidazole and Ar), 9.04 (s, 1H, triazole), *m/z*: 333 (M), 335 (M + 2) |
| **6c** | H | $NO_2$ | 7 | 82 | 285–286 | 48.00 (48.35) | 2.67 (2.81) | 28.00 (28.21) | 10.67 (10.45) | $^1H$ NMR: δ (DMSO-$d_6$), 3.92 (s, 2H, S–$CH_2$), 7.60–8.41 (m, 5H, imidazole and Ar), 9.01 (s, 1H, triazole), *m/z*: 300 (M) |
| **6d** | Me | H | 8 | 76 | 239–240 | 57.99 (58.23) | 4.08 (4.20) | 26.02 (26.38) | 11.89 (12.17) | $^1H$ NMR: δ (DMSO-$d_6$), 2.50 (s, 3H, Me), 3.95 (s, 2H, S–$CH_2$), 7.52–8.15(m, 6H, imidazole and $C_6H_5$), *m/z*: 269 (M) |
| **6e** | Me | Br | 6 | 75 | 277–278 | 44.95 (44.77) | 2.88 (2.67) | 20.17 (20.35) | 9.22 (9.02) | $^1H$ NMR: δ (DMSO-$d_6$), 2.51 (s, 3H, Me), 3.92 (s, 2H, S–$CH_2$), 7.53–8.21 (m, 5H, imidazole and Ar), 347 (M), 349 (M + 2), |
| **6f** | Me | $NO_2$ | 5 | 88 | 270–271 | 49.68 (49.46) | 3.18 (3.05) | 26.75 (26.92) | 10.19 (10.38) | $^1H$ NMR: δ (DMSO-$d_6$), 2.53 (s, 3H, Me), 4.01 (s, 2H, S–$CH_2$), 7.63–8.36 (m, 5H, imidazole and Ar), *m/z*: 314 (M) |
| **6g** | Ph | H | 6 | 80 | 180–181 | 65.25 (65.52) | 3.92 (4.12) | 21.14 (21.41) | 9.66 (9.83) | $^1H$ NMR: δ (DMSO-$d_6$), 4.01 (s, 2H, S–$CH_2$), 7.51–8.10 (m, 11H, imidazole and $C_6H_5$), *m/z*: 331 (M) |
| **6h** | Ph | Br | 6 | 78 | 260–261 | 52.81 (52.83) | 2.93 (2.81) | 17.11 (17.29) | 7.82 (7.65) | $^1H$ NMR: δ (DMSO-$d_6$), 4.03 (s, 2H, S–$CH_2$), 7.61–8.22 (m, 10H, imidazole, $C_6H_5$ and Ar) *m/z*: 409 (M), 411 (M + 2) |
| **6i** | Ph | $NO_2$ | 5 | 85 | 270–271 | 57.44 (57.18) | 3.19 (3.04) | 22.34 (22.51) | 8.51 (8.39) | $^1H$ NMR: δ (DMSO-$d_6$), 4.06 (s, 2H,S–$CH_2$), 7.63–8.38 (m, 10H, imidazole, $C_6H_5$ and Ar), *m/z*: 376 (M) |

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