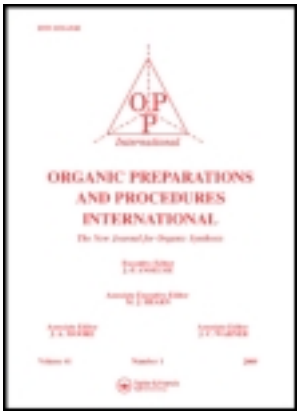


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# Synthesis of Some Novel 3-(4-Pyridinyl)-6-aryl-1,2,4-triazolo[3,4-b]-1,3,4-thiadiazoles

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It is well known that the thiadiazole nucleus possesses interesting biological properties such as antimicrobial,[1–3] antiinflammatory,[4–6] antituberculosis,[7] antihypertensive,[8,9] and anticancer[10] activities. Furthermore, the triazole nucleus[11–13] and the pyridine[14] unit have attracted special attention from chemists due to their attractive biological activities. Incorporating a pyridine ring into active compounds sometimes improves their biological or physiological activities.[15] Several heterocycles containing a thiadiazole or triazole moiety have been reported;[1–14] however, the synthesis of heterocyclic systems containing a thiadiazole nucleus fused to a pyridine-substituted triazole ring has rarely been reported.[16–18] A combination of these three rings may have a variety of structural and biological activities. As a continuation of our studies on the synthesis of thiadiazoles,[18] we now report the synthesis of some novel 3-(4-pyridinyl)-6-aryl-1,2,4-triazolo[3,4-b]-1,3,4-thiadiazoles in good yields and purity by a method that recommends itself for its simplicity and convenience.

Treatment of 4-pyridinecarboxylic acid hydrazide **(1)** with base and carbon disulfide in ethanol gave potassium 4-pyridinyldithiocarbazate **(2)** in good yield. The carbazate was then cyclized to triazole **3** by reaction with hydrazine hydrate under reflux. A variety of aromatic carboxylic acids were subsequently treated with **3** (4:1 molar ratio) in the presence of phosphorus oxychloride to produce the title compounds **4a-j** as shown in Scheme 1.

The conversion of **3** to **4** proceeded without complication under simple reflux for 8–10 h, and the products were readily isolated by pouring the reaction mixture onto crushed ice, neutralization with bicarbonate and collection of the resulting solid (40–63% yields). One recrystallization from ethanol-water was sufficient to obtain the analytical samples; with aliphatic carboxylic acids only low yields (10–15%) were obtained. The elemental analyses and spectrometric data for the compounds were consistent with the expected structures. Notably, signals near 1600 $cm^{-1}$ in the infrared spectra and $\delta$ 8.8 in the $^1$H-NMR spectra indicated the presence of the pyridine moiety in all of the compounds prepared. Our method suggests itself as a useful one for the further investigation of this uncommon combination of heterocyclic units.

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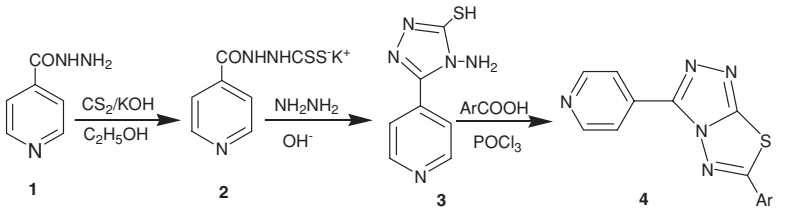


Ar: a) $C_6H_5$, b) 2-$MeC_6H_4$, c) 3-$MeC_6H_4$, d) 4-$ClC_6H_4$, e) 2-$ClC_6H_4$, f) 4-$BrC_6H_4$, g) 4-$CH_3OC_6H_4$, h) 4-$NO_2C_6H_4$, i) 3-$NO_2C_6H_4$, j) 4-Cl-3-$NO_2C_6H_3$

**Scheme 1**



## Experimental Section

All chemicals used were obtained from Merck or Fluka Company. Melting points were determined on an electrothermal digital melting point apparatus. The IR spectra were acquired on a Unicom Galaxy series FT-IR 5000 spectrometer as KBr discs. $^1$H-NMR spectra were recorded on a Brucker spectrophotometer (300 MHz) in DMSO-$d_6$ using TMS as an internal standard. Microanalyses were performed on an elemental analyzer (Elemental, Vario EL III) at Arak University. Reactions were monitored by thin layer chromatography using silica gel $F_{254}$ aluminum sheets (Merck). Reactions involving evolution of $H_2S$ or use of $POCl_3$ must be carried out with due safety precautions in the hood.

### *Preparation of Potassium 4-Pyridinyldithiocarbazate (2)*

4-Pyridinecarboxylic acid hydrazide (0.007 mol, 1 g) was treated with a solution of potassium hydroxide (0.01 mol, 0.6 g) in ethanol (20 mL) at 0–5°C with stirring. Carbon disulfide (0.11 mol) was added slowly and the reaction mixture stirred overnight at room temperature. The solution was concentrated on rotary evaporator to give a precipitate. The yellow solid product was collected, washed with diethyl ether and air dried to yield 1.32 g (75%) product. It was used directly for the next step without purification. FT-IR: 3348, 3362 (NH), 3041 (CH aromatic), 1610 (C = O) $cm^{-1}$.

### *3-(4-Pyridinyl)-4-amino-5-mercapto-1,2,4-triazole (3)*

In an efficient hood, a suspension of potassium 4-pyridinyldithiocarbazate (0.02 mol, 0.5 g) in water (4 mL) and 85% hydrazine hydrate (0.08 mol, 0.25 mL) was refluxed for 3 h. The color of the reaction mixture changed to green with the evolution of the hydrogen sulfide gas. The homogeneous reaction mixture was cooled to room temperature and diluted with water (30 mL) and acidified to pH 7 with conc. hydrochloric acid. The white precipitate was collected, washed with cold water (15–20 mL) and recrystallized from EtOH/$H_2O$ (1:1) to yield 3.10 g (80%) of **3**, mp. 250–251°C [*lit.*[19] mp. 259–261°C]. FT-IR: 3491, 3528 ($NH_2$), 2754 (SH) $cm^{-1}$. $^1$H-NMR (DMSO-$d_6$): $\delta$ 5.86 (s, 2H, $NH_2$), 8.02 (m, 2H, $H_2$), 8.75 (t, J = 4.5 Hz, 2H, $H_1$), 14.19 (s, 1H, SH) ppm.

**Table 1**
Yields, mps, $^1$H NMR and Element Analysis for Compounds **4a-j**.

| Cmpd[a] | Yield | m.p. | $^1$H NMR[b] | Combustion Analysis (Found) | | | |
|---|---|---|---|---|---|---|---|
| | (%) | (°C) | ($\delta$) | C | H | N | S |
| **4a** | 53 | 246–247 | 7.68–8.84 (m, 9H, aromatic) | 60.19 (60.25) | 3.25 (3.50) | 25.08 (25.15) | 11.48 (11.39) |
| **4b** | 54 | 183–185 | 2.67 (s, 3H, $CH_3$), 7.48v8.83 (m, 8H, aromatic) | 61.41 (61.31) | 3.79 (3.85) | 23.88 (23.66) | 10.93 (10.71) |
| **4c** | 58 | 228–229 | 2.45 (s, 3H, $CH_3$), 7.53–8.86 (m, 8H, aromatic) | 61.41 (61.65) | 3.79 (3.70) | 23.88 (23.65) | 10.93 (11.03) |
| **4d** | 60 | 295–296 | 7.72–8.85 (m, 8H, aromatic) | 53.58 (53.81) | 2.57 (2.51) | 22.32 (22.53) | 10.22 (10.14) |
| **4e** | 55 | 200–202 | 7.60–8.82 (m, 8H, aromatic) | 53.58 (53.41) | 2.57 (2.71) | 22.32 (22.54) | 10.22 (10.11) |
| **4f** | 62 | 278–279 | 7.76–8.86 (m, 8H, aromatic) | 46.94 (46.66) | 2.56 (2.63) | 19.55 (19.49) | 8.95 (8.98) |
| **4g** | 63 | 252–253 | 3.85 (s, 3H, $CH_3$), 7.11–8.82 (m, 8H, aromatic) | 58.23 (58.01) | 3.59 (3.64) | 22.64 (22.74) | 10.37 (10.29) |
| **4h** | 45 | 360–361 | 7.74–8.77 (m, 8H, aromatic) | 51.84 (51.69) | 2.49 (2.54) | 25.92 (25.70) | 9.89 (9.98) |
| **4i** | 40 | 285–286 | 7.74–8.87 (m, 8H, aromatic) | 51.84 (52.05) | 2.49 (2.70) | 25.92 (25.74) | 9.89 (9.81) |
| **4j** | 45 | 291–292 | 7.73–8.76 (m, 7H, aromatic) | 46.86 (46.59) | 1.97 (2.02) | 23.43 (23.51) | 8.94 (9.07) |

[a]All compounds are white crystals except for **4f** which is yellow. [b]In DMSO-$d_6$

### *General Preparation of 3-(4-Pyridinyl)-6-aryl-1,2,4-triazolo[3,4-b]-1,3,4-thiadiazole (4)*

In an efficient hood, a mixture of 3-(4-pyridinyl)-4-amino-5-mercapto-1,2,4-triazole (0.25 mol, 0.048 g), the corresponding carboxylic acid (1 mmol) in $POCl_3$ (5 mL) was refluxed for 8–10 h. The reaction mixture was poured slowly into crushed ice with stirring and neutralized with solid potassium bicarbonate. The mixture was allowed to stand overnight and the precipitate was collected and washed with cold water (10 mL). The crude product was crystallized from ethanol-water. Physical and spectral data of compounds **4a-j** are shown in Table 1.

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