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1-(N-ARYLTHIOCARBAMOYL)AMIDINO-3,5-DIMETHYL PYRAZOLES–PREPARATION AND USE IN HETEROCYCLE SYNTHESIS

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Abstract On reaction with α-haloketones or hydrazine, 1-(N-arylthiocarbamoyl)amidino-3,5-dimethylpyrazoles (**1**) afford 2,4-diaminothiazoles and 3,5-diamino-1,2,4-triazoles in good yield. A convenient route to **1** is also reported.

The amidino carbon of the carboxamidine group in 1-amidinopyrazole is susceptible to nucleophilic attack by aliphatic amines. In this addition-elimination reaction, the pyrazole ring serves as a good leaving group and the reaction leads to the formation of guanidines from amines[1]. This route to simple and protected guanidines has received much current attention and several new 1-amidinoazole–based guanylation methods have been reported recently[2–6]. We have also observed that 1-(N-arylthiocarbamoyl)amidino-3,5-dimethylpyrazole[7] reacts with alkylamines to provide N-alkyl- and N, N-dialkyl-N′-(arylthiocarbamoyl)guanidines in good yield. The ease with which the pyrazole group is eliminated during the reaction of **1** with amines prompted us to study the use of **1** in heterocyclisation reactions. Accordingly, the synthesis, of 2,4-diaminothiazoles

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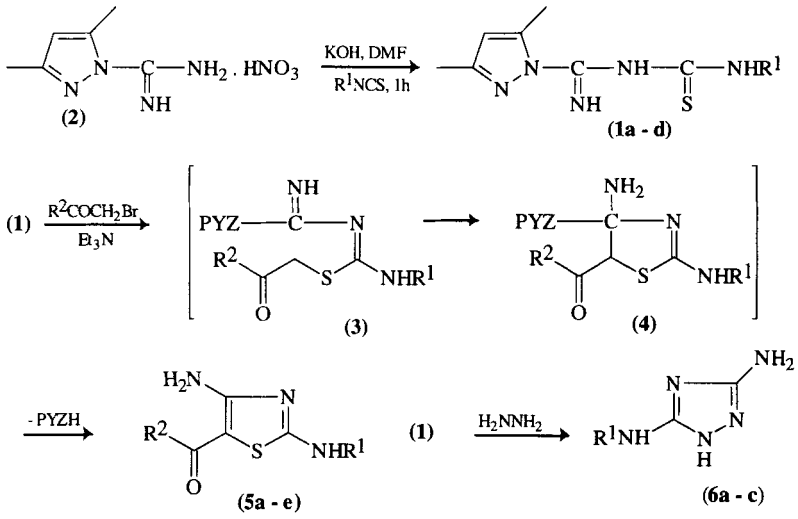
and 3,5-diamino-1,2,4-triazoles from **1** as a common precursor along with a convenient modification for the preparation of **1** are now reported.



PYZ = 3, 5 - dimethylpyrazol-1-yl

	1a	**1b**	**1c**	**1d**	
R^1	4-ClC_6H_4	C_6H_5	4-$MeOC_6H_4$	4-MeC_6H_4	
	5a	**5b**	**5c**	**5d**	**5e**
R^1	4-ClC_6H_4	C_6H_5	4-MeC_6H_4	C_6H_5	4-ClC_6H_4
R^2	C_6H_5	4-ClC_6H_4	4-ClC_6H_4	4-MeC_6H_4	Me
	6a	**6b**	**6c**		
R^1	4-ClC_6H_4	C_6H_5	4$MeOC_6H_4$		

Only a few examples of 1-(N-arylthiocarbamoyl)amidinopyrazoles are known and these have been obtained from 1-amidino-3,5-dimethylpyrazole (**2**), obtained by the basification of an aqueous solution of its nitrate salt, and aryl isothiocyanates

in refluxing benzene in an overall yield (based on the nitrate salt) of ≈64%[8,9]. The release of the free base from the nitrate salt entails considerable loss due to the rapid hydrolysis of the free amidine (**2**) to 3,5-dimethylpyrazole and urea.

We have modified the reaction condition so that **1** may now be prepared directly from the commercially available nitrate salt of **2** and aryl isothiocyanates in 80–88% yield.

The reaction of **1a-d** with α-haloketones was investigated first. The initially formed S-alkyl intermediate (**3**) was expected to generate a carbanion which would attack the amidino carbon in an intramolecular nucleophilic reaction. The resulting cyclic intermediate (**4**) could expel 3,5-dimethylpyrazole. It was found that the reaction in presence of triethylamine afforded 5-acyl-4-amino-2-arylaminothiazoles (**5a-e**) (68–82%). This route to diaminothiazoles complements our earlier synthesis[10] of such compounds from 1-(N-arylthiocarbamoyl)guanidines (also termed as 1-amidino-3-arylthioureas) and α haloketones.

To explore the use of **1** as a heterocycle precursor, the reaction of **1a-c** with hydrazine was studied. The reaction led to 3-amino-5-arylamino-1,2,4-triazoles (**6a-c**) in 68–75% yield.

In summary, we show that 1-(N-arylthiocarbamoyl)amidino-3,5-dimethylpyrazole is an useful starting material for heterocyclic synthesis. In addition to the already known oxidative cyclization of **1** to 1,2,4-thiadiazole derivatives[9,11], diamino thiazoles and 1,2,4-triazoles may also be obtained from **1** as reported here. In this respect, **1** serves as a versatile synthetic equivalent of the unstable N-aryl-N′-cyanothiourea[12] and its S-alkyl derivative[11].

EXPERIMENTAL SECTION

Melting points are uncorrected. All new compounds gave satisfactory C, H and N

analyses (CDRI, Lucknow, India). Spectra were recorded on Varian 390 or Bruker WM–400 NMR and JEOL D-300 mass spectrometers.

Preparation of 1-(N-arylthiocarbamoyl)amidino-3,5-dimethylpyrazole (1a-d)

To dimethylformamide (10 mL) cooled in ice, powdered potassium hydroxide (0.01 mol) was added followed by 1-amidino-3,5-dimethylpyrazole nitrate (0.01 mol). The mixture was stirred to obtain a clear solution (10 min) to which aryl isothiocyanate (0.01 mol) was added with stirring. The ice-bath was replaced by a warm water bath at 50–60°C and the stirring was continued for another 1h. The mixture was poured into ice-water (250 mL), stored to coagulate the precipitate which was collected, washed with little petroleum ether and crystallized from ethanol-water (1: 1). The compounds prepared are:

Compound (1a): m. p. 136–137°C (85%). ^{1}H NMR (90 MHz, $CDCl_3$) δ: 1.90 (s, 3H); 2.20 (s, 3H); 5.95 (s, 1H); 7.20–7.89 (m,, 4H); 8.30 (b, 2H); 10.8 (b, 1H)

Compound (1b): m. p. 105–6°C (82%). The Lit[8]. m. p. 106°C. ^{1}H NMR (90 MHz, $CDCl_3$) δ: 1.90 (s, 3H); 2.20 (s, 3H); 5.85 (s, 1H); 7.00–7.65 (m, 5H); 8.35 (b, 2H); 10.7 (b, 1H)

Compound (1c): m. p. 136–7°C (84%). ^{1}H NMR (90 MHz, $CDCl_3$) δ: 1.90 (s, 3H); 2.20 (s, 3H); 3.83 (s, 3H); 5.82 (s, 1H); 6.85 (m, 2H); 7.15 (d,, 2H); 8.30 (b, 2H); 10.6 (b, 1H)

Compound (1d): m. p. 127–8°C (81%) ^{1}H NMR (90 MHz, $CDCl_3$) δ: 1.90 (s, 3H); 2.20 (s, 3H); 2.28 (s, 3H); 5.85 (s, 1H); 7.0-7.45 (m, 4H); 8.25 (6,2H); 10.6 (b, 1H)

Preparation of 5-acyl-4-amino-2-arylaminothiazoles (5a-c)

To a solution of 1-(N-arylthiocarbamoyl)amidino-3,5-dimethylpyrazole (**1a-d**) (1 mmol) in dimethylformamide (3 mL) containing triethylamine (1.1 mmol), α-haloketone (1 mmol) was added and the mixture was stirred at 50–70°C for 60

min, diluted with ice-water (150 mL) and the product obtained was collected, dried and examined by TLC (Eastman Chromatogram plastic backed silica plates) using chloroform. Purification was either by column chromatography on silica, which confirmed the formation of only a single thiazole derivative, or by crystallization from benzene-methanol. The thiazoles obtained are:

Compound (5a): m. p. 200–1°C (80%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.26–7.74 (m, 9H); 8.2 (b, 2H); 8.9 (b, 1H). EIMS; m/z (%): 331 (10); 329 (39, M^+); 328 (19); 153 (10); 149 (10); 105 (68); 77 (100); 51 (65).

Compound (5b): m. p. 196°C (82%). ^{1}H NMR (DMSO-d_6, 90 MHz) δ: 7.2–7.8 (m, 9H); 10.7 (s, 1H)

Compound (5c): m. p. 195°C (78%). ^{1}H NMR (DMSO-d_6, 90 MHz) δ: 2.20 (s, 3H); 7.3–7.9 (m, 8H); 10.8 (s, 1H)

Compound (5d): m. p. 207–208°C (68%). ^{1}H NMR (DMSO-d_6, 90 MHz) δ: 2.31 (s, 3H); 6.8–7.6 (m, 9H); 10.9 (b, 1H)

Compound (5e): m. p. 234–5°C (73%). ^{1}H NMR (DMSO-d_6, 90 MHz) δ: 1.85 (s, 3H); 7.2–7.6 (m, 4H); 10.4 (s, 1H).

Preparation of 3-amino-5-arylamino-1,2,4-triazoles (6a-c)

To a solution of **1a-c** (1 mmol) in acetonitrile (10 mL), hydrazine hydrate (10 mmol) was added and the mixture was kept at 50–60°C with stirring for 2h. The solvent was removed under reduced pressure and the residue was triturated with petroleum ether-diethyl ether (1:1, 1 mL×4) to obtain a solid product which was crystallized from ethanol. The triazole derivatives thus prepared are:

Compound (6a): m. p. 230-231°R (59%) ^{1}H NMR ($CDCl_3$ + DMSO-d_6, 90 MHz) δ: 7.28 (d, 2H); 7.86 (b, 2H); EIMS m/z (%): 211 (46); 210 (19); 209 (M^+, 100); 178 (9); 67 (9); 155 (11); 154 (15); 153 (29); 138 (19); 127 (18); 126 (10); 111 (37); 44 (58).

Compound (6b): m. p. 155°C (60%). Lit.[11] m. p. 159–162°C. EIMS m/z (%); 176 (14); 175 (M^+, 100); 174 (18); 144 (8); 133 (11); 131 (10); 119 (17); 118 (16); 104 (19); 92 (8); 91 (13); 77 (67); 44 (57).

Compound (6c): m. p. 195–6°C (56%). ^1H NMR ($CDCl_3$+DMSO-d_6, 300 MHz) δ: 3.76 (s, 3H); 4.88 (b, 1H); 6.80 (dd, 2H); 7.20 (b, 1H); 7.35 (dd, 2H); 7.45 (s, 1H). EIMS m/z (%): 206 (17); 205 (M^+, 100); 204 (11); 190 (8); 179 (6); 174 (8); 163 (9); 149 (32); 148 (9); 134 (12); 122 914); 121 910); 107 (19); 99 (23); 95 (12); 81 (18); 44 (38).

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