A facile one-pot synthesis of 2-pyrazolyl-4-aryl-thiazoles in a three-component reaction

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A one-pot multi-component reaction of phenacylbromide, thiosemicarbazide and acetyl acetone or ethyl acetoacetate is described for the preparation of the title compounds. The key features of this methodology are its operational simplicity, mild reaction conditions, and good yields.

Keywords: thiazoles, pyrazoles, phenacyl bromides, thiosemicarbazide, β-ketoesters, β-diketones, multicomponent reactions

Multi component reactions (MCRs) are a promising field of chemistry because the synthesis of complicated molecules can be achieved rapidly and efficiently without the isolation of intermediates. As a result, laboratory effort is reduced, minimising the environmental loading, and so is acceptable from a Green Chemistry point of view. In recent years, the development of new MCRs has been a popular area of research in current organic chemistry.[1,2]

Thiazoles are most generally synthesised by Hantzsch's thiazole synthesis from α-halogenoketones and thioureas or thioamides.[3,4] Later, King *et al*.[5,6] and others[7,8] synthesised aminothiazoles by a modification of the method. The method still remains cumbersome and time-consuming.

Many pyrazole derivatives possess anti-inflammatory activity.[9-11] In continuation of our earlier work[12,13] on the synthesis of heterocyclic systems, we report here the facile one-pot multi-component reaction forming 4-aryl-2-pyrazolylthiazoles in a single step from the readily available starting materials phenacyl bromides, thiosemicarbazide and acetyl acetone or ethyl acetoacetate.

Results and discussion

We report here the Hantzsch thiazole synthesis and concomitant formation of pyrazolothiazoles in a single-step reaction. The procedure involves refluxing an equimolar mixture of phenacyl bromides, thiosemicarbazide, and acetyl acetone or ethyl acetoacetate in dry ethanol for 4–6 hours. The progress of the reaction was monitored by TLC. After completion of the reaction, the mixtures were cooled to room temperature. The solids that separated out were filtered off and dried to obtain the corresponding title compounds. The solid product was recrystallised from a suitable solvent and fully characterised by IR, ^{1}H NMR and mass spectrometry and elemental analysis.

In the literature,[14,15] it has been reported that the synthesis of the title compounds requires a multi step process. The first step involves in the preparation of *N*-acetyl thiosemicarbazide. This on reaction with various phenacylbromides gives the corresponding 2-*N*-acetylhydrazino-4-phenylthiazoles. These are deacetylated to yield the corresponding 2-hydrazino-4-phenylthiazoles, which on reaction with acetylacetone or ethyl acetoacetate lead to the formation of the polycyclic ring system. Though the above methodologies are quite useful, they have some limitations, such as the requirement of the isolation of intermediates and longer reaction times, and the overall yields are lower.

It is thus evident that there remains scope for the development of clean and efficient methodologies involving single step reactions for the preparation of the title compounds. We have developed a one-pot synthesis of these compounds in good yields when compared to alternative available methods. The condensation of phenacyl bromides with thiosemiarbazide in acetylacetone or ethyl acetoacetate indeed gave a thiazolyl pyrazole rather than a thiazolo-triazepine (**7**, **8**) structure. This is based on our earlier observations[16] and also from others in the literature.[17] In order to distinguish between a 5- and 7-membered ring structure an alternative synthesis was employed. Refluxing ethanolic solution of an equimolar amounts of 3,5-dimethyl-1-carbamylpyrazole[18] and 5-hydroxy-3-methylpyrazole-1-thiocarboxamide[19] with **1** gave **4** and **6** respectively. The products obtained by both the methods were identical from mixed melting-point measurements, co-TLC and IR spectra. According to a recent observation by Peet *et al.*,[20] synthetic design of seven membered ring system should require a careful consideration of the competitive five or six membered ring closures which are usually favoured from acyclic precursors.

The IR spectrum of **4a** showed prominent peaks at 1216 (C–S) and 1619 cm^{-1} (C=N), consistent with the assigned structure. The ^{1}H NMR ($CDCl_3$) spectrum of **4a** showed signals at δ 2.30 (s, 3H, C3–CH_3), 2.77 (s,3 H, C5–CH_3),3.85 (s, 3H, OCH_3), 6.0 (s, 1H, pyrazole proton), 7.06 (s, 1H, thiazole proton). In the ^{13}C NMR spectrum **4a** showed signals at δ 13.5 and 13.78 (CH_3 of pyrazole) and 55.3 (OCH_3). Further support for the presence of the pyrazole ring was provided by the signals at *ca* 151, 109 and 142 ppm, in excellent agreement with the values reported for C-3, C-4 and C-5 respectively of pyrazoles.[21] The newly synthesised compounds were characterised by their analytical and spectral data.

The main fragmentation in the mass spectrum of **4f** involves fission of the thiazole moiety resulting in an abundant ion at *m/z* 134,which undergoes cleavage via several pathways. In a competing process, the pyrazole ring also suffers cleavage, and methyl cyanide is lost from the molecular ion. The molecular ion undergoes rearrangement yielding a prominent ion at *m/z* 107. This process involves the loss of C_8H_6NS from the molecular ion in one or several steps. The appearance of the same ion in the mass spectrum of **4d** (where the phenyl ring carries a chlorine atom) shows that the aryl ring does not participate in the formation of this ion. An obvious pathway involves ring expansion of the pyrazole moiety, and the ion may thus be formulated as 2,4-dimethylpyrimidinium. From the mass spectral fragmentation it is evident that the product **4** has a pyrazole structure rather than a triazepine structure.

The IR spectrum **6a** showed prominent peaks at 1216 (C–S) and 1616 cm^{-1} (C=N) and 3400 cm^{-1} (OH). In the NMR spectra a singlet at δ 2.1 is due to CH_3 of pyrazole, and one at δ 3.83 (s) to OCH_3 group. The pyrazole and thiazole protons show as singlets at δ 6.05 and 7.6 respectively. The PMR spectra of **6** in neutral or basic solvent ($CDCl_3$ or DMSO-d_6) displayed signals at 6.06 and 12.4 integrating for one proton each, assignable to 4H and OH respectively, besides the other signals.[24] This observation showed that **6** exists in the enol form in $CDCl_3$ or DMSO-d_6. It may be inferred that in basic or neutral solvent due to strong hydrogen bonding the enol form exists. The ^{13}C NMR spectrum of **6a** in $CDCl_3$ showed signals at δ 19.1 (CH_3 of pyrazole) and 55.4 (methoxy group).

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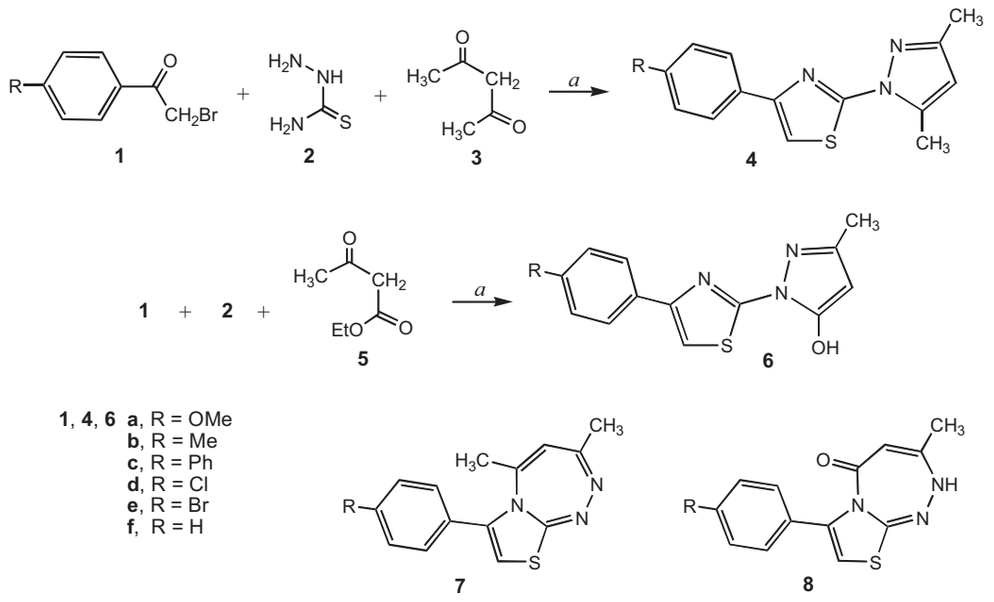

Scheme 1 Synthesis of pyrazolythiazoles. Conditions: *a*, dry EtOH/HCl, reflux.

Experimental

Melting points were determined in open capillaries with a Cintex melting point apparatus Mumbai, India. CHN analysis was done on a Carlo Erba EA 1108 automatic elemental analyser. The purity of the compounds was checked by TLC plates (E.Merck, Mumbai, India), IR spectra (KBr) were recorded on a BrukerWM-4(X) spectrometer (577 model). ^{1}H NMR spectra were recorded on a Bruker WM-300 spectometer using TMS as internal standard. Mass spectra (EI-MS) were determined on Perkin Elmer (SCIEX API-2000,ESI) at 12.5eV and at 70eV on MS12 mass spectrometer fitted with a direct inlet system; source temperature was kept at about 165°C. Phenacyl bromides were procured from Aldrich, Mumbai, India. Acetyl acetone, ethyl acetoacetate and thiosemicarbazide were procured from Loba chemicals, Mumbai, India.

Synthesis of pyrazolylthiazoles **4** *from phenacyl bromides: general procedure*

The phenacyl bromide (1 mmol), thiosemicarbazide (0.091 g, 1 mmol) and acetylacetone (0.090 g, 1 mmol) were refluxed for 4–6 hours in dry ethanol containing a few drops of conc. HCl. The mixture was cooled to room temperature and the solid which separated was filtered off, dried and recrystallised.

2-(3,5-Dimethylpyrazol-1-yl)-4-(4-methoxyphenyl)thiazole (**4a**): Yield 95%, m.p. 122–124°C (from ethyl acetate/hexane). IR: ν_{max} 1247 (C-S), 1607 cm^{-1} (C=N). NMR ($CDCl_3$) δ_H 2.30 (s, 3H, CH_3), 2.77 (s, 3H, CH_3), 3.86 (s, 3H, OCH_3), 6.0 (s, 1H pyrazole), 7.06 (s, 1H, thiazole), 6.94–6.97 (d, 2H, ArH), and 7.81–7.84 (d, 2H, ArH); δ_C 13.5, 13.8, 55.3, 106.5, 109.4, 114.0, 127.2, 127.3, 141.6, 151.3, 152.0, 159.5, 161.7. EI-MS 285 (M^+). Anal. calcd. for $C_{15}H_{15}N_3OS$: C, 63.13: H, 5.3; N, 14.72. Found: C, 63.00; H, 5.41; N, 14.64%.

2-(3,5-Dimethylpyrazol-1-yl)-4-(4-tolyl)thiazole (**4b**): Yield 90%, m.p. 96–98°C (from ethyl acetate/hexane). IR: ν_{max} 1214 (C–S),1616 cm^{-1} (C=N). NMR ($CDCl_3$): δ_H 2.09 (s,3H, pyrazole CH_3), 2.17 (s, 3H, CH_3), 2.36 (s, 3H, CH_3), 6.64 (s, 1H, pyrazole), 7.54 (s, 1H, thiazole) and 7.23–7.26 (m, H, ArH), 7.54–7.57 (m, 2H, ArH); δ_C 13.5, 13.8, 21.2, 107.6, 109.4, 124.7, 126.9, 129.3, 137.9, 139.0, 141.0, 151.4, 152.0. EI-MS 269 (M^+). Anal. Calcd.for $C_{15}H_{15}N_3S$: C, 66.88; H, 5.61; N, 15.60. Found: C, 66.81; H, 5.68; N, 15.54%.

4-Biphenyl-4-yl-2-(3,5-dimethylpyrazol-1-yl)thiazole (**4c**): Yield 88% m.p. 146–148°C (from ethyl acetate/hexane). IR: ν_{max} 1216 (C-S), 1619 cm^{-1} (C=N). NMR ($CDCl_3$): δ_H 2.25 (s, 3H, CH_3 of pyrazole), 2.8 (s, 3H, CH_3), 6.05 (s, 1H pyrazole), 8.0 (s, 1H, thiazole), and 7.3–7.7 (m, 9H, ArH). EI-MS 331 (M^+). Anal. Calcd. for $C_{20}H_{17}N_3S$: C, 72.48; H, 5.17; N, 12.68. Found: C, 72.41; H, 5.12; N,12.62%.

4-(4-Chlorophenyl)-2-(3,5-dimethylpyrazol-1-yl)thiazole (**4d**): Yield 88%, m.p. 151–152°C (lit.[14] m.p. 151–152°C) (from ethanol). MS (70eV), *m/z* (%) 289 (100), 288 (8), 274 (6), 248 (5), 247 (6), 167 (24), 107 (15).

4-(4-Bromophenyl)-2-(3,5-dimethylpyrazol-1-yl)thiazole (**4e**): Yield 85%, m.p.151–152°C, (lit.[14] m.p. 149–150°C).

2-(3,5-Dimethylpyrazol-1-yl)-4-phenylthiazole (**4f**): Yield 92%, m.p. 100–102°C (lit.[14] 102–104°C) (from ethanol). MS (70eV): *m/z* (%) 255 (M^+,100), 214 (M–CH_3–CN, 5), 213 (M–CH_3–CN–H, 7), 134 (40), 107 (10), 102 (19) and 89 (12).

Synthesis of pyrazolols **6** *from phenacyl bromides: general procedure*

The phenacyl bromide (1 mmol), thiosemicarbazide (0.091 g, 1 mmol) and ethyl acetoacetate (0.13 g, 1 mmol) were refluxed for 4–6 hours in dry ethanol containing a catalytic amount of conc. HCl. The mixture was cooled to room temperature and the solid that separated was filtered off, dried and recrystallised.

2-[4-(4-Methoxyphenyl)thiazol-2-yl]-5-methyl-2H-pyrazol-3-ol (**6a**): Yield 96%, m.p. 206–208°C (from ethyl acetate/hexane). IR: ν_{max} 1215 (C–S), 1616 (C=N), 3400 cm^{-1} (OH). NMR ($CDCl_3$), δ_H 2.1 (s, 3H, CH_3) 3.83 (s, 3H, OMe), 6.5 (s, 1H, pyrazole), 7.6 (s, 1H, thiazole) and 12.4 (OH, D_2O exchangeable). EI-MS 287 (M^+). Anal. calcd. for $C_{14}H_{13}N_3O_2S$: C, 58.52; H, 4.56; N, 14.62. Found: C, 58.60; H, 4.50; N,14.54%.

5-Methyl-2-[4-(4-tolyl)thiazol-2-yl]-2H-pyrazol-3-ol (**6b**): Yield 94%, m.p. 214–216°C (from ethyl acetate/hexane). IR: ν_{max} 1215 (C–S),1620 (C=N), 3409 cm^{-1} (OH). NMR ($CDCl_3$) δ_H 2.3 (s, 3H, CH_3 of pyrazole), 2.78 (s, 3H, Me) 6.0 (s, 1H, pyrazole),7.3 (s, 1H, thiazole) and 7.2–7.8 (m, 4H, ArH), 15.75 (OH, 1H, D_2O, exchangeable); δ_C 19.0, 21.3, 24.8, 99.6, 124.6, 125.4, 130.5, 140.4, 140.6, 159.1, 169.5. EI-MS: *m/z* 271 (M^+). Anal. Calcd. for $C_{14}H_{13}N_3OS$: C, 61.97; H, 4.83; N, 15.49. Found: C, 61.91; H, 4.80; N, 15.42%.

2-[4-(Biphenyl-4-yl)thiazol-2-yl]-5-methyl-2H-pyrazole-3-ol (**6c**): Yield 92%,m.p. 200–202°C (from ethyl acetate/hexane). IR: ν_{max} 1216 (C–S), 1565 (C=N), 3432 cm^{-1} (OH). NMR ($CDCl_3$): δ_H 2.0 (s, 3H, CH_3), 6.9 (s, 1H, pyrazole) 7.8 (s, 1H, thiazole) and 7.3–7.7 (m, 9H, ArH), 15.85 (OH, 1H, D_2O, exchangeable). EI-MS: *m/z* 333 (M^+). Anal. Calcd. for $C_{19}H_{15}N_3OS$: C, 68.45; H, 4.53; N, 12.60. Found: C, 68.40; H, 4.50; N, 12.54%.

2-[4-(4-Chlorophenyl)thiazol-2-yl]-5-methylpyrazol-3-ol (**6d**): Yield 87%, m.p. 192–194°C (lit.[19] m.p. 191°C).

2-[4-(4-Bromophenyl)thiazol-2-yl]-5-methylpyrazol-3-ol (**6e**): Yield 85%, m.p. 206–208°C (lit.[19] m.p. 208°C).

5-Methyl-2-(4-phenylthiazol-2-yl)pyrazol-3-ol (**6f**): Yield, 90%, m.p. 192–194°C (lit.[19,22,23] m.p. 193°C).

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