A convenient synthesis of some novel pyrazole derivatives

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A range of some novel pyrazole derivatives has been prepared in moderate to good yield by the reaction of 3-aryl-1-phenyl-1H-pyrazole-4-carbaldehydes 1a,b as a starting material with some reagents such as acylglycine, benzamidine hydrochloride, malononitrile and ethyl azidoacetate giving the oxazolone derivatives 2a,b and 3a,b, dihydroimidazolone derivatives 6a,b, pyridine derivatives (8a,b and 9a,b) and pyrrolopyrazole derivatives 11a,b, respectively. Structures of all the synthesized products have been confirmed by physical and spectroscopic data.

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Pyrazole and its synthetic analogues have been found to exhibit industrial, agricultural and biological applications. As a part of our continuing interest in synthesis and reactivity of five-membered heterocyclic compounds, recently, we have shown a new synthetic route for the synthesis of some novel pyrazole derivatives from 3-aryl-1-phenyl-1H-pyrazole-4-carbaldehydes 1a,b, which is obtained according to the literature procedure. Reaction of 1a,b with benzoylglycine or acetylglycine in acetic anhydride and in the presence of sodium acetate resulted in the production of 4-(3-aryl-1-phenyl-1H-pyrazol-4-ylmethylene)-2-phenyl(or methyl) oxazol-5(4H)-ones 2a,b and 3a,b respectively in moderate to good yield. The alkaline hydrolysis of compounds 2a,b and 3a,b were carried out using different alkaline media. It was found that hydrolysis using aqueous 2% ethanolic sodium hydroxide solution afforded 2-benzoylaminio(or 2-acetylamino)-3-(3-aryl-1-phenyl-1H-pyrazol-4-yl)acrylic acids (4a,b and 4c,d, respectively) in an excellent yield. While, on carrying out hydrolysis using sodium acetate in boiling methanol, methyl 2-benzoylamino (or 2-acetylamino)-3-(3-aryl-1-phenyl-1H-pyrazol-4-yl) acrylates (5a,b and 5c,d, respectively) were obtained in good yield.

We turned our attention to investigate the reaction of 1a,b with a mixture of benzamidine hydrochloride and ethyl chloroacetate in the presence of sodium bicarbonate in boiling n-propanol to afford 2-phenyl-5-(3-aryl-1-phenyl-1H-pyrazol-4-ylmethylene)-3H-4,5-dihydroimidazol-4-ones 6a,b. In order to obtain some cyanopyridine derivatives attached to the pyrazole ring, 1a,b were treated with malononitrile in boiling ethanol and in the presence of piperidine to give 2-(3-aryl-1-phenyl-1H-pyrazol-4-ylmethylene)malononitriles 7a,b, which could be cyclized with acetonitrile and ammonium acetate to give the desired 3-amino-4-(3-aryl-1-phenyl-1H-pyrazol-4-yl)-6-methylpyridine-2-carbonitriles 8a,b. But on carrying out the reaction of 1a,b with malononitrile and acetonitrile, respectively, in the presence of ammonium acetate, 2-amino-5-(3-aryl-1-phenyl-1H-pyrazol-4-yl)-4-phenyl-substituted oxazolones 9a,b were obtained, which on treatment with formamide in boiling ethanol yielded 6-(3-aryl-1-phenyl-1H-pyrazol-4-yl)-5-phenylpyrrolidin-4-ylamines 10a,b. Reaction of 1a,b with ethyl azidoacetate in ethanolic sodium hydroxide solution, followed by thermal cyclization afforded ethyl 3-aryl-1-phenyl-1H,6H-pyrrolo[2,3-c]pyrazole-5-carboxylates 11a,b. Finally, by applying Aldol condensation on compounds 1a,b with cyclohexanone in aqueous sodium hydroxide and dimethyl sulphoxide, 2,6-bis (3-aryl-1-phenyl-1H-pyrazol-4-ylmethylene)cyclohexanones 12a,b were obtained as yellow crystals in good yields (Scheme I, Table I).

Experimental Section

All melting points were taken on Gallen Kamp apparatus and are uncorrected. Microanalysis were performed by Microanlysis unit, Faculty of Science, Cairo University. IR spectra (KBr) were recorded on a Pye Unicam SP 200G and SP 1200 spectrophotometer; 1H NMR spectra on a JEOL-100MHz and Varian T-90MHz with CDC13 or DMSO-d6 as solvents using TMS as internal reference (chemical shifts in δ, ppm); and mass spectra on an MSZ mass spectrometer fitted with a direct inlet system at 70eV.

4-(3-Aryl-1-phenyl-1H-pyrazol-4-ylmethylene)-2-phenyl­oxazol-5(4H)-ones 2a,b. A mixture of 1a,b (0.01 mole), benzoylglycine (1.79 g, 0.01 mole) and sodium acetate (0.83 g, 0.01 mole) in acetic anhydride (5 mL) was heated under reflux for 3 hr. The reaction mixture was cooled and hydrolysed in ice-water and the solid product that formed was filtered, washed.
with water till pH 7, then dried and recrystallized from carbon tetrachloride; IR: (1740-1760), (1635-1645), (1605-1610) and (1210-1230) cm\(^{-1}\) due to C=O, C=C, C=N and C-O, respectively; \(^1\)H NMR of 2b (DMSO-\(d_6\)): \(\delta\) 2.35 (s, 3H, CH\(_3\)), 7.20 (s, 1H, CH=C), 7.30-8.10 (m, 14H, ArH) and 8.40 (s, 1H, CH-pyrazole); MS (El) of 2a: m/z 391 (M\(^+\), 65%), 258 (11%), 105 (94%), 77 (100%).
4-(3-Aryl-1-phenyl-1H-pyrazol-4-ylmethylene)-2-methylazoxazol-5(4H)-ones 3a,b. The procedure is the same as described for synthesis of compounds 2a,b in which acetylglycine was used instead of benzoylglycine. The reaction mixture was heated under reflux for 5 hr and the product that obtained was recrystallized from ethanol: IR: (1745-1760), (1620-1640), (1600-1610) and (1210-1240) cm\(^{-1}\) due to C=O, C=C, C=N and C-O, respectively; MS (EI) of 3a: m/z 329 (M\(^{+}\), 100%), 406 (22%), 378 (12%), 258 (16%), 105 (13%), 77 (76%).

Methyl 2-benzylamino(or 2-acetylamino)-3-(3-aryl-1-phenyl-1H-pyrazol-4-yl)acrylates 5a-d. A suspension of 2a,b and 3a,b (0.01 mole) in methanol (30 mL) and sodium acetate (0.82 g, 0.01 mole) was heated under reflux for 30 hr. The reaction mixture was concentrated, cooled and the solid thus obtained was collected by filtration, dried and recrystallized from ethanol;

<table>
<thead>
<tr>
<th>Compd</th>
<th>m.p. °C</th>
<th>Yield (%)</th>
<th>Mol. formula.</th>
<th>% N Calcd (Found)</th>
<th>Compd</th>
<th>m.p. °C</th>
<th>Yield (%)</th>
<th>Mol. formula.</th>
<th>% N Calcd (Found)</th>
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<td>2a</td>
<td>196-98</td>
<td>55</td>
<td>C(_2)H(_7)N(_2)O(_2) (391.43)</td>
<td>10.73 (10.60)</td>
<td>6b</td>
<td>370-71</td>
<td>52</td>
<td>C(_2)H(_7)N(_2)O (404.48)</td>
<td>13.85 (13.60)</td>
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<tr>
<td>2b</td>
<td>200-01</td>
<td>60</td>
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<td>10.36 (10.00)</td>
<td>7a</td>
<td>190-91</td>
<td>83</td>
<td>C(_2)H(_7)N(_2) (296.33)</td>
<td>18.91 (18.60)</td>
</tr>
<tr>
<td>3a</td>
<td>135</td>
<td>50</td>
<td>C(_2)H(_7)N(_2)O(_2) (329.35)</td>
<td>12.75 (13.00)</td>
<td>7b</td>
<td>178-79</td>
<td>85</td>
<td>C(_2)H(_7)N(_2) (310.36)</td>
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<tr>
<td>3b</td>
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<td>55</td>
<td>C(_2)H(_7)N(_2)O(_2) (343.39)</td>
<td>12.23 (12.50)</td>
<td>8a</td>
<td>232-33</td>
<td>50</td>
<td>C(_2)H(_7)N(_2) (351.41)</td>
<td>19.93 (20.10)</td>
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<td>4a</td>
<td>198-200</td>
<td>90</td>
<td>C(_2)H(_7)N(_2)O(_2) (409.44)</td>
<td>10.26 (10.00)</td>
<td>8b</td>
<td>145-46</td>
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<td>9.92 (9.60)</td>
<td>9a</td>
<td>180-81</td>
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<td>C(_2)H(_7)N(_2) (413.49)</td>
<td>16.94 (16.60)</td>
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<td>140-42</td>
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<td>C(_2)H(_7)N(_2)O(_2) (347.37)</td>
<td>12.09 (11.80)</td>
<td>9b</td>
<td>195-96</td>
<td>95</td>
<td>C(_2)H(_7)N(_2) (427.51)</td>
<td>16.38 (16.20)</td>
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<td>100-02</td>
<td>75</td>
<td>C(_2)H(_7)N(_2)O(_2) (361.40)</td>
<td>11.62 (11.10)</td>
<td>10a</td>
<td>235-36</td>
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<td>C(_2)H(_7)N(_2) (440.51)</td>
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<td>C(_2)H(_7)N(_2)O(_2) (423.47)</td>
<td>9.92 (9.60)</td>
<td>10b</td>
<td>160-61</td>
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<tr>
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<td>11.62 (12.00)</td>
<td>11b</td>
<td>198-99</td>
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<td>12.17 (12.50)</td>
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<tr>
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<td>11.19 (11.00)</td>
<td>12a</td>
<td>260-62</td>
<td>85</td>
<td>C(_2)H(_7)N(_2) (558.69)</td>
<td>10.03 (9.90)</td>
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<tr>
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<td>50</td>
<td>C(_2)H(_7)N(_2)O(_2) (390.44)</td>
<td>14.35 (14.50)</td>
<td>12b</td>
<td>240-41</td>
<td>90</td>
<td>C(_2)H(_7)N(_2) (586.74)</td>
<td>9.55 (9.80)</td>
</tr>
</tbody>
</table>

\( ^{1}H\) NMR (DMSO-\(d_6\)) of 4b: \( \delta \) 2.35 (s, 3H, CH\(_3\)), 7.20 (s, 1H, CH=C), 7.40-8.10 (m, 14 H, ArH), 8.60 (s, 1H, CH-pyrazole), 9.50 (s, 1H, NH) and 9.90 (s, 1H, COOH); MS (EI) of 4b: \( m/z \) 423 (M\(^{+}\), 100%), 406 (22%), 378 (12%), 258 (16%), 105 (13%), 77 (76%).

Methyl 2-benzylamino(or 2-acetylamino)-3-(3-aryl-1-phenyl-1H-pyrazol-4-yl)acrylic acids 4a-d. A solution of 2a,b or 3a,b (0.01 mole) in ethanolic sodium hydroxide (10%, 50 mL) was heated under reflux for 3 hr. It was concentrated, diluted with water (100 mL), acidified with 2% hydrochloric acid. The solid that resulted was filtered, dried and recrystallized from ethanol; IR (1735-1740), (1710-1730), (1630-1640), (1600-1605) and (3210-3225) cm\(^{-1}\) due to COO, C=O, C=C, C=N and NH, respectively; \( ^{1}H\) NMR (CDCl\(_3\)) of 5a: \( \delta \) 3.85 (s, 3H, OCH\(_3\)), 7.10 (s, 1H, CH=C), 7.30-8.20 (m, 15H, ArH), 8.45 (s, 1H, CH-pyrazole) and 9.60 (s, 1H, NH); \( ^{1}H\) NMR (CDCl\(_3\)) of 5b: \( \delta \) 2.35 (s, 1H, CH\(_3\)), 3.85 (s, 3H, OCH\(_3\)), 7.20 (s, 1H, CH=C), 7.30-8.10 (m, 14H, ArH), 8.30 (s, 1H, CH-pyrazole) and...
9.60 (s, 1H, NH); MS (El) of 5a: m/z 423 (M⁺, 12%), 392 (14%), 303 (16%), 105 (100%), 77 (44%); MS (El) of 5b: m/z 437 (M⁺, 10%), 406 (15%), 317 (22%), 246 (14%), 105 (100%), 77 (48%).

2-Phenyl-5-(3-aryl-1-phenyl-1H-pyrazol-4-ylmethylene)-3H-4,5-dihydroimidazol-4-ones 6a,b. A mixture of 1a,b (0.01 mole), benzamide hydrochloride dihydrate (3.48 g, 0.02 mole) and ethyl chloroacetate (2.26 mL, 0.02 mole) in n-propanol (20 mL) was heated under reflux with stirring for 1 hr. The product that formed was collected by filtration, dried and recrystallized from n-butanol; IR: (1700-1710), (1625-1635), (3480-3490) and (2240-2250) cm⁻¹ due to NH, C=N, C=C and C=N, respectively; MS (EI) of 6a: m/z 296 (M⁺, 100%), 277 (44%), 377 (16%), 286 (16%), 285 (71%), 105 (18%), 77 (100%); MS (EI) of 6b: m/z 311 (M⁺, 100%), 376 (26%), 296 (M⁺, 15%), 285 (71%), 270 (21%), 105 (15%), 77 (60%).

3-Amino-4-(3-aryl-1-phenyl-1H,6H-pyrrolo[2,3-c]pyrazole-S-carboxylates 11a,b. Ethyl azidoacetate (10.3 g, 0.08 mole) was added to a mixture of 1a,b (0.02 mole) and sodium ethoxide (1.84 Na in 20 mL abs. EtOH) dropwise with stirring at a rate which maintained the temperature below 0°C. Stirring was continued at room temperature until TLC indicated that all the aldehyde has been consumed. The reaction mixture was poured onto ice-cold water and the solid separated was taken in toluene (30 mL) and heated under reflux for 1 hr. The resulting product was collected by filtration and recrystallized from ethanol; IR: (3260-3270), (1670-1680), (1635-1640) and (1595-1600) cm⁻¹ due to NH, C=O, C=C and C=N, respectively; MS (EI) of 11a: m/z 331 (M⁺, 11%), 316 (64%), 286 (16%), 285 (71%), 105 (18%), 77 (100%).

2.6-Bis(3-aryl-1-phenyl-1H-pyrazol-4-ylmethylene)cyclohexanones 12a,b. A mixture of 1a,b (0.01 mole), cyclohexanone (1.9 mL, 0.02 mole) in aqueous dimethylsulfoxide (50%, 10 mL) and aqueous sodium hydroxide (20%, 10 mL) was heated with stirring at 100°C for 5 hr. The reaction mixture was cooled and neutralized with dilute hydrochloric acid, then the resulting product was collected by filtration, washed with water and recrystallized from ethanol; IR: (1705-1715) cm⁻¹ due to C=O; MS (El) of 2a: m/z 558 (M⁺, 15%), 531 (36%), 530 (23%), 232 (20%), 77 (100%).

References