NEW FUNCTIONALIZED PYRAZOLES FROM ISOXAZOLOPYRIDAZINONES

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Abstract—Treatment of 3-methylisoxazolo[3,4-d]pyridazin-7(6H)-ones (1a–d) with dilute NaOH affords in good yields new pyrazole derivatives which can be regarded as building blocks for condensed heterocycles with potential biological activity.

Previous papers from our laboratory have dealt with the conversion of 3-(2-substituted ethenyl)isoxazolopyridazinones into 5H-1,2-diazepinones which under acidic conditions undergo ring transformation into pyrazoles. We wish to call further attention here to the synthesis of new pyrazoles containing o-functional groups, promising intermediates to formation of condensed heterocycles with potential biological activity, by alkaline hydrolysis of 3-methylisoxazolo[3,4-d]pyridazin-7(6H)-ones.

Conversion of compounds 1a–d into pyrazoles was effectively performed in basic medium but the nature of the obtained products is strictly correlated to the substituents at position 4 and 6 of the pyridazine ring.

SCHEME 1
Thus, treatment of compounds 1a-b (R\(^1\)=Ph, R\(^2\)=H or Me) with dilute sodium hydroxide afforded regiospecifically the 4-cyanopyrazoles 4 and 5, respectively, whereas the isoxazolopyridazinone 1c, with R\(^1\)=R\(^2\)=Ph, gave as the sole product and in good yield (82%) the amino-ketone 2. Finally, compound 1d (R\(^1\)=Me, R\(^2\)=Ph) afforded mainly the pyrazole 3 (65%), with minor amounts of derivatives 7 and 8. Assigned structures for the new pyrazoles (2-6,8) were supported by their chemical and spectroscopic properties (see Table and Experimental) and elemental analysis data. In particular, for compounds 2, 4, and 5, \(^1\)H- and \(^13\)C-nmr analysis of the crude reaction mixtures showed no traces of the alternative products.

Table 1. \(^1\)H- and \(^13\)C-nmr data (CDCl\(_3\))

<table>
<thead>
<tr>
<th>Compound</th>
<th>(^1)H-nmr (6: ppm)</th>
<th>(^13)C-nmr (6: ppm)</th>
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</thead>
<tbody>
<tr>
<td>2</td>
<td>1.39(s,6H,COCH(_3)), 6.10(exch. br s,2H,(\mathrm{NH}_2)), 7.30-7.80 (m,10H,ArH(_2))</td>
<td>22.9(q,COCH(_3)), 105.0(s,6H,CH(_3)), 203.0, 128.0, 188.1, 128.4, 128.6, 129.0 (d, C=CH(_2)), 133.4 (s, C-(\mathrm{CH}_3)), 3-Ph(_2)), 179.0 (s, C=(\mathrm{COCH}_3)), 180.0 (s, C=(\mathrm{COCH}_3))</td>
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<tr>
<td>3</td>
<td>2.42 (s,3H,COCH(_3)/(\mathrm{CH}_2)), 2.49 (s,3H,(\mathrm{CH}_2))/COCH(_3)), 8.09 (exch. br s,2H,(\mathrm{NH}_2)), 7.65-7.80 (m,5H,ArH(_2))</td>
<td>15.6(q,3-CH(_2)), 39.0(q,COCH(_3)), 104.9(s,6H,CH(_3)), 128.6 (d, C=CH(_2)), 128.76 (d, C=CH(_2)), 128.6 (d, C=CH(_2)), 138.9 (s, C-(\mathrm{CH}_3)), 148.8 (s, C=(\mathrm{COCH}_3)), 150.0 (s, C=(\mathrm{COCH}_3)), 183.0 (s, C=(\mathrm{COCH}_3))</td>
</tr>
<tr>
<td>4</td>
<td>2.40 (s,3H,CH(_2)), 7.32-7.80 (m,5H,ArH(_2)), 7.73-8.00 (m,2H,ArH(_2)), 11.03 (exch. br s,1H,(\mathrm{NH}_2))</td>
<td>10.8(q,5-CH(_2)), 39.6(s,6H,CH(_3)), 116.5 (s, CH(_3)), 125.6 (d, C=CH(_2)), 129.0 (d, C-(\mathrm{CH}_3)), 138.9 (d, C=CH(_2)), 138.9 (d, C=CH(_2)), 150.0 (s, C=(\mathrm{COCH}_3)), 151.7 (s, C=(\mathrm{COCH}_3))</td>
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<tr>
<td>5</td>
<td>2.59 (s,3H,CH(_2)), 3.80 (s,3H,(\mathrm{NH}_2)), 7.21-7.30 (m,5H,ArH(_2)), 7.80-8.00 (m,5H,ArH(_2))</td>
<td>10.5(q,5-CH(_2)), 38.6(q,5-CH(_2)), 82.5 (s, CH(_3)), 129.0 (d, C=CH(_2)), 129.8 (d, C=CH(_2)), 129.9 (d, C=CH(_2)), 138.6 (s, C=(\mathrm{COCH}_3)), 145.6 (s, C=(\mathrm{COCH}_3)), 145.6 (s, C=(\mathrm{COCH}_3)), 115.3 (s, C=(\mathrm{COCH}_3))</td>
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<tr>
<td>6</td>
<td>2.60(s,3H,CH(_2)), 3.68 (s,3H,(\mathrm{NH}_2)), 5.38 (exch. br s,2H,(\mathrm{NH}_2)), 7.30-7.70 (m,5H,ArH(_2))</td>
<td>10.8(q,5-CH(_2)), 36.0(q,5-CH(_2)), 111.6 (s, CH(_3)), 128.8 (d, C=CH(_2)), 128.8 (d, C=CH(_2)), 129.8 (d, C=CH(_2)), 143.5 (s, C=(\mathrm{COCH}_3)), 143.5 (s, C=(\mathrm{COCH}_3)), 143.5 (s, C=(\mathrm{COCH}_3)), 146.8 (s, C=(\mathrm{COCH}_3)), 146.8 (s, C=(\mathrm{COCH}_3)), 146.8 (s, C=(\mathrm{COCH}_3))</td>
</tr>
<tr>
<td>7</td>
<td>2.61(s,3H,(\mathrm{NH}_2)), 3.76 (exch. br s,2H,(\mathrm{NH}_2)), 7.46 (s,5H,ArH(_2))</td>
<td>12.8(q,5-CH(_2)), 14.0(q,5-CH(_2)), 113.6 (s, CH(_3)), 125.4 (d, C=CH(_2)), 129.8 (d, C=CH(_2)), 129.8 (d, C=CH(_2)), 138.9 (s, C=(\mathrm{COCH}_3)), 148.75 (s, C=(\mathrm{COCH}_3)), 147.6 (s, C=(\mathrm{COCH}_3)), 166.6 (s, CO)</td>
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</table>
A probable pathway for the ring closure to pyrazoles may be depicted as a process in which the unstable ion \((A^-)\) decarboxylates with ring opening, as reported for 3-unsubstituted isoxazoles in alkaline medium, giving rise to a reactive cis-cyanoenolate ion \((B^-)\). This intermediate eventually gives the pyrazoles by intramolecular nucleophilic attack of the 1-NH group on the carbonyl carbon (route a) and/or on the cyano group (route b).

Attempts to synthesize pyrazolopyrimidines and pyridines starting from compounds 2 and 3 are now in progress and will be shortly reported.

**EXPERIMENTAL**

Melting points were determined on a Büchi 510 melting point apparatus and are uncorrected. IR spectra were measured for nujol mulls with a Perkin-Elmer 337 spectrometer. \(^1\)H-nmr spectra were recorded with either a Varian EM-360 or a Perkin-Elmer R32 spectrometers and \(^13\)C-nmr spectra with a Varian FT-80A instrument; chemical shifts are reported in ppm from internal tetramethylsilane. Extracts were dried over sodium sulfate and solvents were removed under reduced pressure. Silica-gel plates (Merck F254) were used for analytical and preparative t.l.c.. Compounds 1a-d were prepared as reported in Ref. 7 and 8.

All the new compounds gave satisfactory (± 0.3%) microanalytical data (C, H, and N).
General Procedure for Hydrolysis of Compounds 1a-d

A mixture of 1a-d (2 mmoles), 2-4N NaOH (25 ml), and EtOH (10 ml) was refluxed for 2-6 h. After dilution with H$_2$O the reaction mixture was filtered or exhaustively extracted with chloroform.

4-Acetyl-5-amino-1,3-diphenylpyrazole (2): (y 82%); white crystals, mp 154°C (from cyclohexane); ir 3380 and 3280 (NH$_2$), 1620 cm$^{-1}$ (CO).

4-Acetyl-5-amino-3-methyl-1-phenylpyrazole (3): (y 65%); yellow oil which was purified by preparative layer chromatography (CHCl$_3$); ir 3400 and 3310 (NH$_2$), 1630 cm$^{-1}$ (CO); [picrate, mp 163°C (from ethanol)].

4-Cyano-5(3)-methyl-3(5)-phenylpyrazole (4): (y 70%); pale yellow crystals, mp 155°C (from benzene); ir 3400 and 3310 (NH$_2$), 1630 cm$^{-1}$ (CO).

4-Cyano-3(5)-methyl-1-phenylpyrazole (5): hydrolysis of 1b gives compound 5 as the main product (yield 72%) which was separated by preparative t.l.c. with CHCl$_3$-CH$_2$OH (10:1 v/v) as eluent; white crystals, mp 107°C (from cyclohexane); ir 2220 cm$^{-1}$ (CN). Treatment of compound 5 with H$_2$SO$_4$ (80%) for 42 h at 105°C afforded 1,5-dimethyl-3-phenylpyrazole-4-carboxylic acid, mp 197°C (from H$_2$O) [lit. $^9$ mp 197-198°C (from EtOH/H$_2$O)].

1,5-Dimethyl-3-phenylpyrazole-4-carboxamide (6): i) compound 6 is obtained (yield 9%) as by-product from the hydrolysis of 1b; ii) treatment of compound 5 with H$_2$SO$_4$ (96%) at 65°C for 2.5 h afforded the amide 6 (yield 67%); white crystals, mp 181°C (from H$_2$O); ir 3380 and 3270 (NH$_2$), 1640 cm$^{-1}$ (CO).

3,5-Dimethyl-1-phenylpyrazole-4-carboxamide (8): compound 8 was obtained as by-product from the hydrolysis of 1d (yield 10%); white crystals, mp 188°C (from cyclohexane); ir 3380 and 3190 (NH$_2$), 1640 cm$^{-1}$ (CO).

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REFERENCES AND NOTES

* Dedicated to Prof. C. Musante on the tenth anniversary of his death.


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