AN EFFICIENT SYNTHESIS OF 3-ALKYL-5-ARYL-2(1H)-PYRAZINONES

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Abstract - The preparation of several 3-alkyl-5-aryl-2(1H)-pyrazinones is described. The regiochemical outcome of the condensation reaction between amino acid amides and phenylglyoxal is discussed and an alternative, more efficient route is reported, involving ring-closure of α-oxo-N-(2-oxoethyl)carboxamides.

During the course of a medicinal chemistry project we required significant quantities of a number of 3-alkyl-5-aryl-2(1H)-pyrazinones (1). In this paper we wish to describe a new route to this class of compounds, involving ring-closure of diketo amides (7) with ammonium acetate (Scheme 2), and to indicate its advantages over the previous synthesis of 2(1H)-pyrazinones with this substitution pattern.

Of the known routes to 2(1H)-pyrazinones, only the condensation of amino acid amides with glyoxals appeared readily applicable to the required disposition of substituents. It has been reported, both for alkyl-3,5- and arylglyoxals, that this process gives mainly 3,5-disubstituted 2(1H)-pyrazinones, together with lesser amounts of the 3,6-disubstituted isomers, which in some instances have proved difficult to separate. We applied this method to the synthesis of several 3-alkyl-5-phenyl-2(1H)-pyrazinones as summarised in Scheme 1. Reaction of amino acid amides (2a-d) with phenylglyoxal under basic conditions in aqueous methanol at -40°C gave modest yields of 3,5-disubstituted compounds 3a-d. In the
Scheme 1

\[
\begin{align*}
\text{R} & \quad \text{NH}_2 + \text{O} & \quad \text{O} \\
\text{2} & \quad \text{N} & \quad \text{OH} \\
\text{Ph} & \quad \text{Ph} \\
\text{NaOH} / \text{H}_2\text{O} / \text{MeOH} / \text{-40°C} \quad \xrightarrow{} \quad \text{N} & \quad \text{NH} \\
\text{3} & \quad \text{N} & \quad \text{NH} \\
\text{Ph} & \quad \text{Ph} \\
\end{align*}
\]

<table>
<thead>
<tr>
<th>2, 3, 4</th>
<th>( R )</th>
<th>Yield 3 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>( \text{CH}_2=\text{CHCH}_2 )</td>
<td>36\text{a}</td>
</tr>
<tr>
<td>b</td>
<td>( \text{CH}_3\text{C}_2\text{H}_3 )</td>
<td>30\text{a}</td>
</tr>
<tr>
<td>c</td>
<td>( \text{CH}_3\text{SCH}_2\text{CH}_2 )</td>
<td>41\text{a}</td>
</tr>
<tr>
<td>d</td>
<td>( \text{(CH}_3\text{)}_2\text{CHCH}_2 )</td>
<td>36\text{b}</td>
</tr>
</tbody>
</table>

\( \text{a} \) Yield after recrystallisation of crude product.
\( \text{b} \) Yield after chromatographic separation from 4d (see Experimental).

Scheme 2

\[
\begin{align*}
\text{R} & \quad \text{COONa} + \text{C} & \quad \text{NH}_2\text{HCl} \quad \xrightarrow{\text{DCCI}} \quad \text{NH}_2\text{C} & \quad \text{NH} \\
\text{5} & \quad \text{A} & \quad \text{NH}_2\text{HCOOCH}_2\text{CH}_2 \quad \text{CH}_2\text{C} & \quad \text{Ar} \\
\text{6} & \quad \text{A} & \quad \text{NH}_2\text{HCOOCH}_2\text{CH}_2 \quad \text{CH}_2\text{C} & \quad \text{Ar} \\
\text{7} & \quad \text{R} & \quad \text{Ar} \\
\text{8} & \quad \text{R} & \quad \text{Ar} \\
\end{align*}
\]

<table>
<thead>
<tr>
<th>5</th>
<th>( R )</th>
<th>6</th>
<th>( \text{Ar} )</th>
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<tbody>
<tr>
<td>a</td>
<td>( \text{CH}_3\text{C}_2\text{H}_2 )</td>
<td>a</td>
<td>( \text{Ph} )</td>
</tr>
<tr>
<td>b</td>
<td>( \text{(CH}_3\text{)}_2\text{CHCH}_2 )</td>
<td>b</td>
<td>( \text{N} )</td>
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</table>

<table>
<thead>
<tr>
<th>7</th>
<th>( R )</th>
<th>( \text{Ar} )</th>
<th>Yield 3 (%)</th>
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</thead>
<tbody>
<tr>
<td>a</td>
<td>( \text{CH}_3\text{C}_2\text{H}_2 )</td>
<td>( \text{Ph} )</td>
<td>70</td>
</tr>
<tr>
<td>b</td>
<td>( \text{(CH}_3\text{)}_2\text{CHCH}_2 )</td>
<td>( \text{Ph} )</td>
<td>67</td>
</tr>
<tr>
<td>c</td>
<td>( \text{CH}_3\text{C}_2\text{H}_2 )</td>
<td>( \text{Ph} )</td>
<td>53</td>
</tr>
</tbody>
</table>

\( \text{a} \) Overall yield from 5 and 6.
\( \text{b} \) DCCI = \( \text{N},\text{N}' \)-Dicyclohexylcarbodiimide.
\( \text{HOBt} \) = 1-Hydroxybenzotriazole.
preparation of 3a-c, examination of the 1H- and 13C-nmr spectra of the crude products indicated the presence of less than 10% of the unwanted regioisomers (4a-c), which could be removed during recrystallisation.

For our medicinal chemical studies it was important to establish unambiguously that the major products corresponded to the 3,5-disubstitution pattern. By analogy with earlier work, the regiochemistry of 3a-d was assigned initially on the basis of the values of the carbon to proton coupling constants observed for the C2 carbon atom in the 13C-nmr spectrum. Two coupling constants were apparent with values typically in the ranges 2-3 Hz and 5-6 Hz, these being assigned respectively to coupling with the adjacent CH2 protons of the 3-alkyl substituent and the meta H5 proton. This interpretation is in agreement with data reported previously for 3,5-dimethyl-2(1H)-pyrazinone. As mentioned below in relation to 4d, the magnitude of the meta-coupling between C2 and H5 contrasts with a typical value of less than 2 Hz for the analogous para-coupling of C2 to H3 in 3,6-disubstituted-2(1H)-pyrazinones. An X-ray crystal structure determination on 3a confirmed unequivocally the assigned regiochemistry.

In the case of preparation of 3d, the crude product contained ca 25% of the unwanted isomer (4d), which could only be removed by a tedious chromatographic separation. In accord with previous data for 3,6-dimethyl-2(1H)-pyrazinone, the 13C-nmr spectrum of the 3,6-disubstituted isomer (4d) the signal due to C2 showed essentially no para-coupling to the H5 proton.

Since we required large amounts of pyrazinone (3d) for our medicinal chemistry programme, we developed an efficient regiospecific synthesis of 3,5-disubstituted 2(1H)-pyrazinones as outlined in Scheme 2. Carboxdiimide mediated coupling of sodium 4-methyl-2-oxopentanoate (5b) with 2-aminoacetophenone hydrochloride (6a) in dichloromethane in the presence of 5-hydroxybenzotriazole gave cleanly the intermediate diketo amide (7b). As both 5b and 6a have low solubility in dichloromethane it was important to powder both reagents in order to obtain complete conversion. Without purification 7b was treated with ammonium acetate in refluxing ethanol to give 3d in 67% overall yield from starting 5b and 6a. Pyrazinone (3a) was obtained similarly, and the method was also extended to preparation of 5-heterocaryl-2(1H)-pyrazinones, as illustrated by the synthesis of 3e from 3-(aminoacetyl)pyridine.
In view of the ready availability of aminoacetyl heterocycles\textsuperscript{11} from the corresponding acetyl compounds by Neber rearrangement of the derived oxime tosylates, this procedure is of potentially general applicability for the synthesis of 5-heteroaryl-2(1H)-pyrazinones.

As a method of ring synthesis, this process is related to a previous\textsuperscript{12,13} formation of pyrazinones. Involving acylation of \( \alpha \)-amino ketones with \( \alpha \)-bromoacetyl bromides followed by cyclisation with ammonia and \textit{in situ} oxidation. Compared with this earlier synthesis, the ring-closure described here has the advantage of much higher yields due to formation of the pyrazine ring directly at the required oxidation level. In addition, coupling of the starting keto acids and amino ketones as salts avoids the self-condensation of free amino ketones, which proved problematic in the earlier work.

**EXPERIMENTAL**

All operations were carried out at ambient temperatures unless otherwise stated. All evaporations were done at below 50°C using a Buchi rotary evaporator. Flash chromatography was performed on silica gel (Merck Kieselgel: Art. 9385). Melting points were taken on a Buchi apparatus using glass capillary tubes and are uncorrected. \( ^1\)H- and \( ^{13}\)C-nmr spectra were recorded on Bruker WM200, WM250 or WM400 instruments and are reported as \( \delta \) values ppm relative to Me\(_4\)Si as an internal standard. Electron impact mass spectra were recorded on a VG 12-12 Quadrupole or a VG 70-250 SE spectrometer.

5-Phenyl-3-(2-propenyl)-2(1H)-pyrazinone (3a). 12.5 M Sodium hydroxide solution (4.8 ml, 60.0 mmol) was added to a stirred solution of phenylglyoxal monohydrate (9.1 g, 60.0 mmol) and allylglycinamide\textsuperscript{14} (6.8 g, 60.0 mmol) in methanol (150 ml) at -40°C under Ar. The solution was kept at -40°C for 2 h, warmed to ambient temperature over 0.5 h and left to stand for 1 h. Water (600 ml) was added and the mixture was extracted with ether (2 x 300 ml). The aqueous phase was cooled to 0°C and acidified to pH 5 with conc. hydrochloric acid. The precipitated solid was collected and recrystallised from methanol to give 3a (4.6 g, 36%), as pale yellow needles, mp 168-169°C; \( ^1\)H nmr (CDCl\(_3\)): 3.7 (d, \( J = 6.7 \) Hz, 2H), 5.2-5.35 (complex m, 2H), 6.15-6.4 (complex m, 1H), 7.3-7.5 (complex m, 3H), 7.6 (s, 1H), 7.8-7.9 (m, 2H); \( ^{13}\)C nmr (CDCl\(_3\)): 37.3 (CH\(_2\)), 117.0 (CH\(_2\)-C), 122.1 (pyrazine C\(_\delta\), \( J_{CH} = 181.2 \) Hz), 124.6 (phenyl C\(_{ortho}\)), 127.3 (phenyl C\(_{para}\)), 128.7 (phenyl C\(_{meta}\)), 130.9
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(pyrazine C6, \( \Delta_{CH} = 3.9 \) Hz), 134.1 (CH-C), 166.1 (phenyl CH2), 156.9 (pyrazine C2, \( \Delta_{CH} = 2.6 \), 5.2 Hz), 156.7 (pyrazine C3, \( \Delta_{CH} = 7.3 \) Hz); as m/z: 212 (M+H)+, 183, 158; Anal. Calcd for C13H12N2O: C, 73.58; H, 5.66; N, 13.21. Found: C, 73.84; H, 5.92; N, 13.16.

Compounds (3b,c) were obtained by a similar procedure:

5-Phenyl-3-propyl-2(1H)-pyrazinone (3h) (from phenylglyoxal monohydrate and norvalinamide): yield 30%; mp 187-188°C (from methanol); \(^1\)H nmr ((CD3)2SO): 1.0 (d, \( J = 6.7 \) Hz, 3H), 1.6-1.9 (m, 2H), 2.7 (t, \( J = 6.7 \) Hz, 2H), 7.2-7.5 (complex m, 3H), 7.5-7.9 (complex m, 3H); \(^{13}\)C nmr ((CD3)2SO): pyrazine C\(_2\) 154.7 (JCH = 2.2, 5.8 Hz); Anal. Calcd for C13H14N2O: C, 72.90; H, 6.54; N, 13.08. Found: C, 73.07; H, 6.61; N, 13.10.

3-(2-Hydroxyethyl)-5-phenyl-2(1H)-pyrazinone (3c) (from phenylglyoxal monohydrate and methioninamide): yield 41%; mp 174-176°C (from methanol); \(^1\)H nmr ((CD3)2SO): 2.1 (s, 3H), 2.8-3.1 (complex m, 4H), 7.25-7.55 (complex m, 3H), 7.8-7.9 (complex m, 3H); \(^{13}\)C nmr ((CD3)2SO): pyrazine C\(_2\) 154.9 (JCH = 2.0, 6.1 Hz); Anal. Calcd for C13H14N2O2S: C, 63.41; H, 5.69; N, 11.38; S, 12.96. Found: C, 63.44; H, 5.74; N, 11.44; S, 12.96.

3-(2-Methylpropyl)-5-phenyl-2(1H)-pyrazinone (3d). A solution of 1,3-dicyclohexylcarbodiimide (157.0 g, 0.76 mol) in dichloromethane (200 ml) was added dropwise over 2 h to an efficiently stirred mixture of powdered sodium 4-methyl-2-oxopentanoate (115.5 g, 0.76 mol), 2-aminoacetophenone hydrochloride (130.4 g, 0.76 mol), and 1-hydroxybenzotriazole hydrate (103.0 g, 0.76 mol) in dichloromethane (1 l). The mixture was stirred overnight and the insoluble dicyclohexylurea was removed by filtration. The filtrate was concentrated to a volume of 500 ml. After further filtration, the filtrate was washed with saturated sodium hydrogen carbonate solution (500 ml), water (500 ml) and saturated sodium chloride solution (500 ml). The organic phase was dried (MgSO\(_4\)) and evaporated to give the intermediate 4-methyl-2-oxo-N-(2-oxo-2-phenylethyl)pentanamide (7b) (183.6 g), as a foam which was used without purification; \(^1\)H nmr (CDCl3): 1.0 (d, 6H), 2.1-2.3 (m, 1H), 2.8 (d, 2H), 7.4-7.7 (complex m, 3H), 7.8-7.9 (br s, 1H), 7.95-8.05 (m, 2H). The crude product was dissolved in ethanol (1.2 l) and heated under reflux with ammonium acetate (183.6 g, 2.38 mol) for 3.5 h. After standing overnight the resulting precipitate was filtered off to give 3d (115.8 g, 67%), as pale yellow needles, mp 205-207°C; \(^1\)H nmr
(CDCl₃): 1.1 (d, J = 6.7Hz, 6H), 2.3–2.5 (m, 1H), 2.8 (d, J = 6.7Hz, 2H), 7.3–7.5 (complex m, 3H), 7.8–7.9 (m, 2H); 13C nmr (CDCl₃): pyrazine C₂ 157.4 (JCH = 2.5, 5.7 Hz); m/z 228 (M+H)+, 186, 77. Anal. Calcd for C₁₄H₁₂N₂O: C, 73.68; H, 7.02; N, 12.28. Found: C, 73.33; H, 7.18; N, 12.22.

Compounds (3b,c) were obtained using a similar procedure: 3b (from sodium 2-oxopentanoate and 2-aminoacetophenone hydrochloride, via 7a): yield 70%;

3-Propyl-5-(pyridin-3-yl)-2(1H)pyrazinone (3e) (from sodium 2-oxopentanoate and 3-(aminoacetyl)pyridine dihydrochloride, with addition of 1 equiv. of triethylamine in the initial acylation step to form 7c): yield 53%; mp 193–195 °C (from ethanol); 1H nmr ((CDCl₃)SO): 1.0 (t, J = 6.7Hz, 3H), 1.6–1.8 (m, 2H), 2.7 (t, J = 6.7Hz, 3H), 7.4 (dd, J = 4.0, 8.0Hz, 1H), 8.0 (s, 1H), 8.2 (dt, 1H), 8.45 (dd, J = 2.0, 6.0Hz, 1H), 9.1 (d, J = 2.0Hz, 1H); Anal. Calcd for C₁₂H₁₃N₃O: C, 66.98; H, 6.05; N, 19.53. Found: C, 66.60; H, 6.21; N, 19.39.

3-(2-Methylpropyl)-6-phenyl-2(1H)-pyrazinone (4d). Phenylglyoxal monohydrate (15.2 g, 0.1 mol) was condensed with leucinamide (13.0 g, 0.1 mol) using the procedure described for the preparation of 3a. The crude product was purified by flash chromatography, eluting with ethyl acetate/hexane on a gradient from 1:1 v/v to 9:1 v/v, to give initially 4d (2.3 g, 10%), as pale yellow needles, mp 166–167°C (from methanol); 1H nmr (CDCl₃): 1.0 (d, J = 6.7Hz, 6H), 2.2–2.4 (m, 1H), 2.75 (t, J = 6.7Hz, 2H), 7.4–7.6 (complex m, 3H), 7.7 (s, 1H), 7.8–7.9 (m, 2H); 13C nmr (CDCl₃): aromatic carbon signals at 121.7 (pyrazine C₅, JCH = 185.2 Hz), 126.5 (phenyl Cortho), 129.0 (phenyl Cmeta), 130.0 (phenyl Cpara), 130.9 (pyrazine C₆, JCH not determined), 136.5 (phenyl Cipso), 157.9 (pyrazine C₃, JCH not determined) 158.1 (pyrazine C₂, JCH = 2.9 Hz); Anal. Calcd for C₁₄H₁₄N₂O: C, 73.68; H, 7.02; N, 12.28. Found: C, 74.01; H, 7.28; N 12.14. Further elution of the chromatography column gave 3d (8.1 g, 36%).

ACKNOWLEDGEMENTS

We thank B. Wright for assistance with interpretation of 13C nmr data, and M. McPartlin (The Polytechnic of North London) for performing the X-ray analysis.
REFERENCES AND NOTES


9. Suitable crystals were obtained from mechnol with monoclinic space group symmetry of P21/n and cell constants of a = 19.211 (4) Å, b = 5.437 (1) Å, c = 6.2 65 (2) Å, calculated density = 1.09 g cm⁻³, determined using 1752 reflections (I/σ (I) > 3.0) on a Philips PW1100 automatic four circle diffractometer equipped with MoKα radiation. The atomic coordinates are available from the Director of the Cambridge Crystallographic Centre.


14. Obtained from allylglycine by esterification (conc. sulphuric acid/ethanol/reflux/24 h), followed by reaction with ammonia (ethanol/20°C/14 days).

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