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

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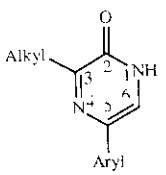
Abstract - The preparation of several 3-alkyl-5-aryl-2(1H)-pyrazinones is described. The regiochemical outcome of the condensation reaction between amino acid amides and phenylglyoxal is discussed and an alternative, more efficient route is reported, involving ring-closure of α-oxo-N-(2-oxoethyl)carboxamides.

During the course of a medicinal chemistry project[1] 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.

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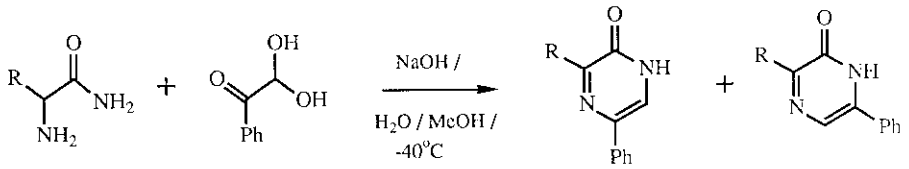
Of the known routes[2] to 2(1H)-pyrazinones, only the condensation of amino acid amides with glyoxals appeared readily applicable to the required disposition of substituents.[3,4] It has been reported, both for alkyl-[3-5] and arylglyoxals,[3,6] that this process gives mainly 3,5-disubstituted 2(1H)-pyrazinones, 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[4] in aqueous methanol at -40°C gave modest yields of 3,5-disubstituted compounds **3a-d**. In the

**Scheme 1**

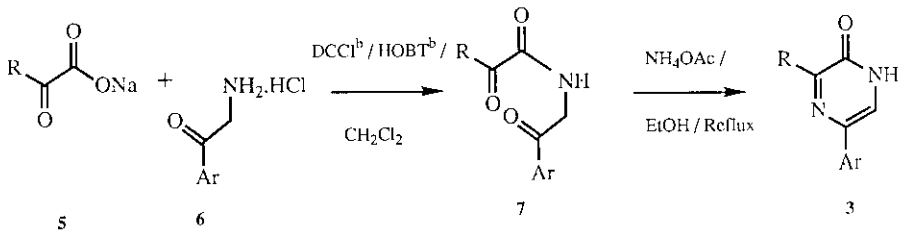



2 3 4

| 2, 3, 4 | R | Yield 3 ( % ) |
|---|---|---|
| a | $CH_2$=$CHCH_2$ | 36[a] |
| b | $CH_3CH_2CH_2$ | 30[a] |
| c | $CH_3SCH_2CH_2$ | 41[a] |
| d | $(CH_3)_2CHCH_2$ | 36[b] |

[a] Yield after recrystallisation of crude product.
[b] Yield after chromatographic separation from **4d** (see Experimental).

**Scheme 2**




5 6 7 3

| 5 | R |
|---|---|
| a | $CH_3CH_2CH_2$ |
| b | $(CH_3)_2CHCH_2$ |

| 6 | Ar |
|---|---|
| a | Ph |
| b |  |

| 7 | 3 | R | Ar | Yield 3 ( % ) [a] |
|---|---|---|---|---|
| a | b | $CH_3CH_2CH_2$ | Ph | 70 |
| b | d | $(CH_3)_2CHCH_2$ | Ph | 67 |
| c | e | $CH_3CH_2CH_2$ |  | 53 |

[a] Overall yield from **5** and **6**.
[b] DCCI = *N,N'*-Dicyclohexylcarbodiimide.
HOBT = 1-Hydroxybenzotriazole.

preparation of 3a-c, examination of the $^{1}H$- and $^{13}C$-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[1] it was important to establish unambiguously that the major products corresponded to the 3,5-disubstitution pattern. By analogy with earlier work,[7,8] the regiochemistry of 3a-d was assigned initially on the basis of the values of the carbon to proton coupling constants observed for the $C_2$ carbon atom in the $^{13}C$-nmr spectrum. Two coupling contants were apparent with values typically in the ranges 2-3 Hz and 5-6 Hz, these being assigned respectively to coupling with the adjacent $CH_2$ protons of the 3-alkyl substituent and the meta $H_6$ proton. This interpretation is in agreement with data reported previously[7] for 3,5-dimethyl-2(1H)-pyrazinone. As mentioned below in relation to 4d, the magnitude of the meta-coupling between $C_2$ and $H_6$ contrasts with a typical value of less than 2 Hz for the analogous para-coupling of $C_2$ to $H_5$ in 3,6-disubstituted-2(1H)-pyrazinones.[7] An X-ray crystal structure determination[9] 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,[7] in the $^{13}C$-nmr spectrum of the 3,6-disubstituted isomer (4d) the signal due to $C_2$ showed essentially no para-coupling to the $H_5$ proton.

Since we required large amounts of pyrazinone (3d) for our medicinal chemistry programme,[1] we developed an efficient regiospecific synthesis of 3,5-disubstituted 2(1H)-pyrazinones as outlined in Scheme 2. Carbodiimide mediated coupling of sodium 4-methyl-2-oxopentanoate (5b) with 2-aminoacetophenone hydrochloride (6a) in dichloromethane in the presence of N-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-heteroaryl-2(1H)-pyrazinones, as illustrated by the synthesis of 3e from 3-(aminoacetyl)pyridine

dihydrochloride.[10] In view of the ready availability of aminoacetyl heterocycles[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[12,13] formation of pyrazinones, involving acylation of α-amino ketones with α-bromoacetyl bromides followed by cyclisation with ammonia and 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 $Me_4Si$ as an internal standard. Electron impact mass spectra were recorded on a VG 12-12 Quadrapole 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[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, $J$ = 6.7Hz, 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 ($\underline{C}H_2$=C), 122.1 (pyrazine $C_6$, $\underline{J}_{CH}$ = 181.2 Hz), 124.6 (phenyl $C_{ortho}$), 127.3 (phenyl $C_{para}$), 128.7 (phenyl $C_{meta}$), 130.9

(pyrazine $C_5$, $J_{CH}$ = 3.9 Hz), 134.1 (CH=C), 136.1 (phenyl $C_{ipso}$), 154.9 (pyrazine $C_2$, $J_{CH}$ = 2.6, 5.2 Hz), 156.7 (pyrazine $C_3$, $J_{CH}$ = 7.3 Hz); ms m/z: 212 $(M+H)^+$, 183, 158; Anal. Calcd for $C_{13}H_{12}N_2O$: 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 (3b)** (from phenylglyoxal monohydrate and norvalinamide): yield 30%; mp 187-188°C (from methanol); $^1H$ nmr ($(CD_3)_2SO$): 1.0 (t, J = 6.7Hz, 3H), 1.6-1.9 (m, 2H), 2.7 (t, J = 6.7Hz, 2H), 7.2-7.5 (complex m, 3H), 7.8-7.9 (complex m, 3H); $^{13}C$ nmr ($(CD_3)_2SO$): pyrazine $C_2$ 154.7 ($J_{CH}$ = 2.2, 5.8 Hz); Anal. Calcd for $C_{13}H_{14}N_2O$: C, 72.90; H, 6.54; N, 13.08. Found: C, 73.07; H, 6.61; N, 13.10.

**3-(2-Methylthioethyl)-5-phenyl-2(1H)-pyrazinone (3c)** (from phenylglyoxal monohydrate and methioninamide): yield 41%; mp 174-176°C (from methanol); $^1H$ nmr ($(CD_3)_2SO$): 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 ($(CD_3)_2SO$): pyrazine $C_2$ 154.9 ($J_{CH}$ = 2.0, 6.1 Hz); Anal. Calcd for $C_{13}H_{14}N_2OS$: C, 63.41; H, 5.69; N, 11.38; S, 13.01. 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; $^1H$ nmr ($CDCl_3$): 1.0 (d, 6H), 2.1-2.3 (m, 1H), 2.8 (d, 2H), 4.75 (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; $^1H$ nmr

($CDCl_3$): 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); $^{13}C$ nmr ($CDCl_3$): pyrazine $C_2$ 157.4 ($J_{CH}$ = 2.5, 5.7 Hz); ms m/z 228 $(M+H)^+$, 186, 77; Anal. Calcd for $C_{14}H_{16}N_2O$: C, 73.68; H, 7.02; N, 12.28. Found: C, 73.33; H, 7.18; N, 12.22.

Compounds (**3b,e**) 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,[10] 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 ($(CD_3)_2SO$): 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, 4.0Hz, 1H), 9.1 (d, J = 2.0Hz, 1H); Anal. Calcd for $C_{12}H_{13}N_3O$: 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 ($CDCl_3$): 1.0 (d, J = 6.7Hz, 6H), 2.2-2.4 (m, 1H), 2.75 (d, J = 6.7Hz, 2H), 7.4-7.6 (complex m, 3H), 7.7 (s, 1H), 7.8-7.9 (m, 2H); $^{13}C$ nmr ($CDCl_3$): aromatic carbon signals at 121.7 (pyrazine $C_5$, $J_{CH}$ = 185.2 Hz), 126.5 (phenyl $C_{ortho}$), 129.0 (phenyl $C_{meta}$), 130.0 (phenyl $C_{para}$), 130.9 (pyrazine $C_6$, $J_{CH}$ not determined), 136.5 (phenyl $C_{ipso}$), 157.9 (pyrazine $C_3$, $J_{CH}$ not determined) 158.1 (pyrazine $C_2$, $J_{CH}$ = 2.9 Hz); Anal. Calcd for $C_{14}H_{16}N_2O$: 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%).

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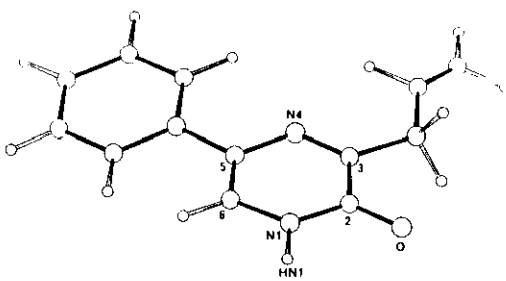



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