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Novel formation of 6-acyl-5-(2-pyrrolyl)-3*H*-pyrrolizines by base-catalysed condensation of pyrrole-2-aldehyde with methyl ketones

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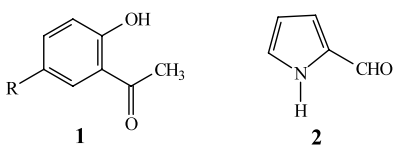
Abstract—Pyrrole-2-aldehyde undergoes condensation with methyl ketones in aqueous ethanolic alkali in a 2:1 mole ratio yielding 6-acyl-5-(2-pyrrolyl)-3*H*-pyrrolizines as novel products in moderate yield. © 2002 Published by Elsevier Science Ltd.

Our two recent important findings in the area of base-catalysed 1:2 condensations of *o*-hydroxyacetophenones **1** and aromatic aldehydes were: (i) novel formation of *trans*-2,3-dimethoxy-3-(*p*-formylphenylamino)-4′-nitroflavanones from **1** and *p*-nitrobenzaldehyde in aqueous methanol[1] and (ii) successful synthesis of *E*-3-benzylideneflavanones and some of their heterocyclic analogues from **1** and aromatic aldehydes in a reaction medium which favours precipitation of the final product.[2] Being encouraged by these findings we undertook a similar study involving **1** and pyrrole-2-aldehyde (**2**). The present communication reports a novel result obtained in this study.



1 **2**

a: R = H; **b**: R = Cl; **c**: R = Me

When each of the *o*-hydroxyacetophenones **1a–c** was allowed to undergo condensation with 2 molar equivalents of **2** in aqueous ethanolic KOH (20%) (4 days, rt), two products, one orange and the other red, were obtained after careful acidification of the reaction mixture followed by the usual work up and chromatographic separation. The orange compound was the usual 1:1 condensation product[3] **3**, while the analytical and spectral data of the red compound definitely indicated that it was formed by condensation of two molecules of **2** with one molecule of **1** in some unusual fashion. Detailed NMR spectroscopic analysis including COSY, homodecoupling and HETCOR (one bond as well as long range) studies established the structures of these compounds as the pyrrolizine derivatives **4a–c**.[4] The presence of a phenolic OH group in each of **4a–c** indicated that the same group of **1a–c** possibly played no role in the reaction process, and this was substantiated by isolation of **4d** starting from acetophenone, and compounds **5** and **6** starting from acetone in place of **1**.[5] It is interesting to note that even by starting from **1a** and **2** in a 1:1 mole ratio, **4a** could be obtained, which is contrary to a previous report.[6] Again, in the reaction of the same two starting materials taken in a 1:4 mole ratio, the yield of **4a** was found to increase significantly but this compound was not the exclusive product. Similar was the result with **1b**, **1c** and acetophenone. All the results are presented in Table 1.

The 3*H*-pyrrolizine derivatives **4** are formed by combination of 1 molecule of **1** with 2 molecules of **2**. However, the reaction possibly does not proceed fully through the intermediacy of the 1:1 condensation product **3** since by subjecting the 1:1 mixtures from each of **3a–d** and **2** to the reaction conditions **4** was obtained in only poor yield (ca. 10%). So the mechanistic path delineated in Scheme 1 may be suggested for

Keywords: pyrrole-2-aldehyde; methyl ketones; base-catalysed condensation; 6-acyl-5-(2-pyrrolyl)-3*H*-pyrrolizines.

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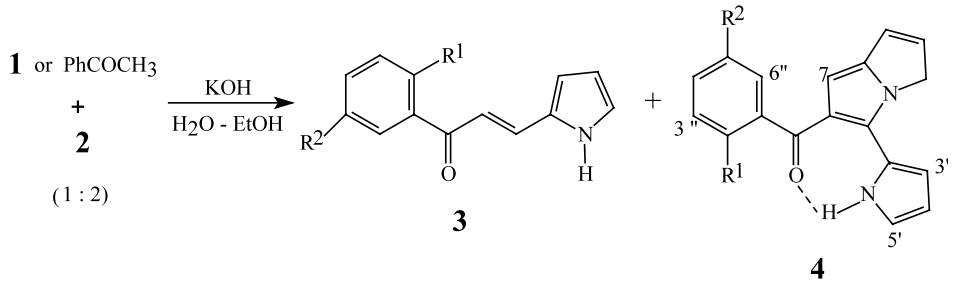


a: R^1 = OH, R^2=H; **b**: R^1=OH, R^2=Cl

c: R^1=OH, R^2=Me; **d**: R^1=R^2 = H

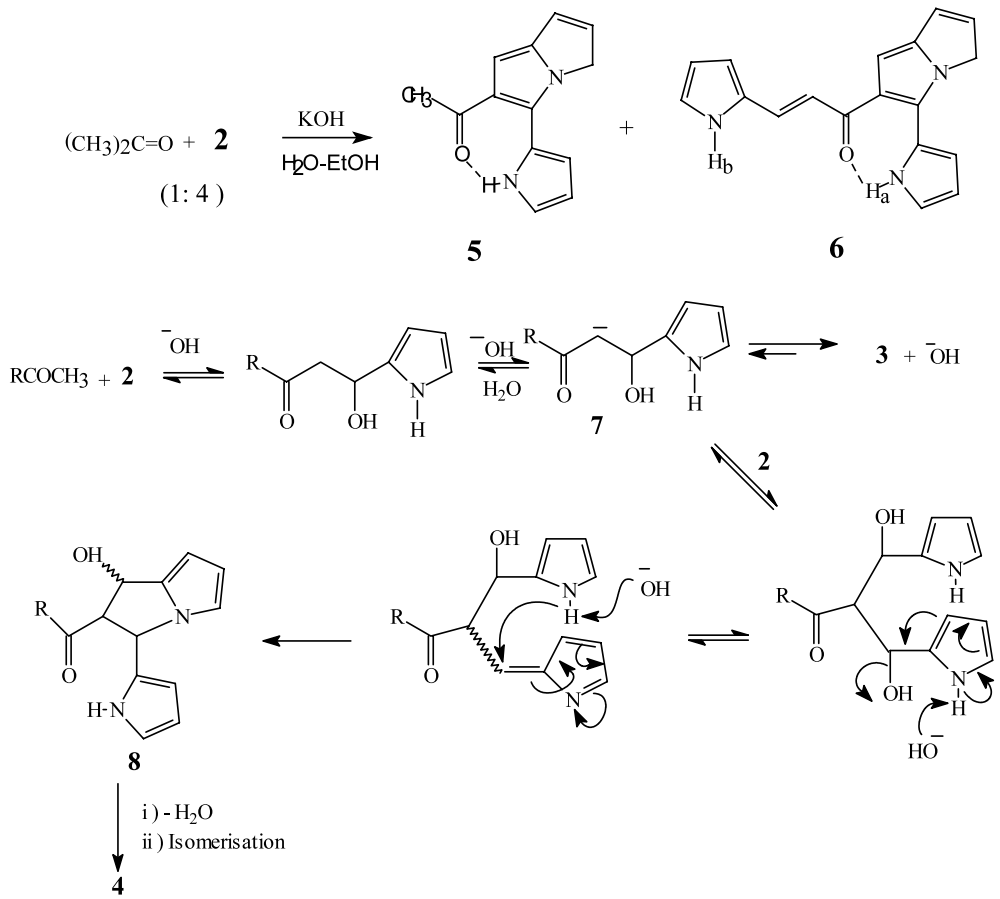
Table 1. Condensation of methyl ketones with pyrrole-2-aldehyde (**2**)

Ketone	Ketone:**2** (mole ratio)	Product(s) (yield[a], %)
1a	1:2	**3a** (34)+**4a** (31)
1a	1:1	**3a** (46)+**4a** (8)
1a	1:4	**3a** (13)+**4a** (41)
1b	1:2	**3b** (27)+**4b** (24)
1b	1:4	**3b** (9)+**4b** (44)
1c	1:2	**3c** (32)+**4c** (26)
1c	1:4	**3c** (11)+**4c** (46)
Acetophenone	1:2	**3d** (29)+**4d** (29)
Acetophenone	1:4	**3d** (14)+**4d** (39)
Acetone	1:4	**5** (17)+**6** (32)

[a] Based on the amount of ketone.

the process. Isomerisation of pyrrolizines similar to that required for the conversion of the initial dehydration product of **8** to **4** is not without precedent.[7] It may be pointed out here that the structures of **3a–d** suggest that $^-$OH would preferentially effect deprotonation of the N–H of these compounds rather than attack at their β-position leading to **7**, thus making the conversion **3**→**4** a less favourable process.

Thus, we report a novel result from a very simple condensation reaction. Potential biological activities of the substituted 3*H*-pyrrolizines formed and the existence of ample scope for extension of the reaction to other substrates are two important aspects which require mentioning here.



Scheme 1.

Acknowledgements

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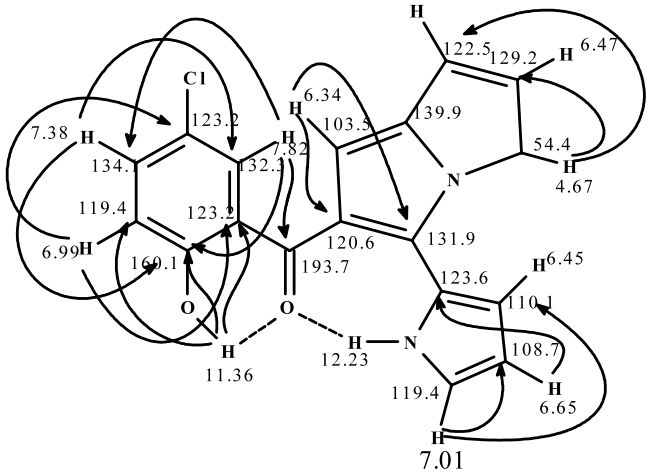
3. Compounds **3a**–**c** gave satisfactory analytical and spectral data, **3a**, mp 136–137°C; **3b**, mp 165–167°C; **3c**, mp 148–149°C.
4. Selected data for **4**: **4a**, mp 147–148°C. Anal. found C, 74.11; H, 4.89; N, 9.47%; calcd for $C_{18}H_{14}N_2O_2$ C, 74.47; H, 4.86; N, 9.65%. IR (ν, $CHCl_3$, cm^{-1}): 3400–3100 (O-H and N-H), 1612 (C=O). ^1H NMR (300 MHz, $CDCl_3$): δ 4.70(2H, br.s, H_2-3), 6.36 (1H, s, H-7), 6.44 (1H, m, H-3′), 6.47 (1H, dt, $J=6.1$ and 1.8 Hz, H-2), 6.65 (1H, m, H-4′), 6.68 (1H, dt, $J=6.1$ and 2.1 Hz, H-1), 6.89 (1H, br.t, $J=7.5$ Hz, H-5″), 7.01 (1H, m, H-5′), 7.04 (1H, br d, $J=8.1$ Hz, H-3″), 7.44 (1H, dt, $J=8.4$ and 1.9 Hz, H-4″), 7.85 (1H, dd, $J=8.1$ and 1.9 Hz, H-6″), 11.50 (1H, s, exchangeable with D_2O, O-H) and 12.26 (1H, br s, exchangeable with D_2O, N-H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 54.3 (C-3), 103.9 (C-7), 108.3 (C-4′), 109.9 (C-3′), 117.9 (C-5″), 118.3 (C-3″), 119.1 (C-5′), 121.0 (C-6), 122.3 (C-1″), 122.5 (C-1), 123.8 (C-2′), 128.9 (C-2), 131.3 (C-5), 133.3 (C-6″), 134.5 (C-4″), 139.4 (C-7a), 161.8 (C-2″) and 195.3 (C=O). EIMS: (rel. intensity): m/z 290 (100, M^+), 170 (66.8), 169 (68.4), 121 (23.2) and 65 (19.8). **4b**, mp 182–183°C. **4c**, mp 163–164°C. ^1H–^1H COSY and HETCOR [one bond and long range (optimised for $J\approx7$ Hz)] done on **4b** showed the following correlations:
^1H–^1H COSY: δ 4.67 (br.s) with 6.70, 6.47, 6.34; 6.34 (s) with 4.67; 6.45 (m) with 7.01, 6.65; 6.47 (dt) with 6.70, 4.67; 6.65 (m) with 7.01, 6.45; 6.70 (dt) with 6.47, 4.67; 6.99 (d) with 7.38; 7.01 (m) with 6.65, 6.45; 7.38 (dd) with 7.82, 6.99 and 7.82 (d) with 7.38.

HETCOR



5. Compounds **3d** (mp 133–134°C), **4d** (mp 120–121°C), **5** (mp 76–77°C) and **6** (mp 173–175°C) gave satisfactory analytical and spectroscopic data. For **5** and **6** homodecoupling, ^1H–^1H COSY and HETCOR (one bond) studies were also done.
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