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A facile synthesis of annelated pyridines from β-formyl enamides under microwave irradiation

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Abstract

The condensation of β-formyl enamides with cyanomethylenes under microwave irradiation is catalysed by basic alumina to afford fused pyridines in excellent yields.

Keywords: β-formyl enamide; cyanomethylene; microwave; Knoevenagel.

The widespread occurrence and biological activity of pyridines in natural products and pharmaceuticals make them important targets for synthetic chemists.[1] The development of new strategies that allow pyridine functionalisation is therefore of great interest[2] including heteroannulation with *o*-amino aldehydes which has been a topic of extensive studies.[3] Recently, research efforts in our laboratory explored the use of β-formyl enamides as organic synthons.[4] The enormous growth in the use of microwave irradiation[5] prompted us to plan the synthesis of a pyridine hybrid of a steroid using a β-formyl enamide, as a challenging prospect. In continuation of our interests,[6] we describe herein a facile microwave mediated synthesis of annelated pyridines from β-formyl enamides.

In a typical reaction, β-formylenamide (**1a**) and cyanomethylene (**5a**, R^3=CN) were intimately mixed with basic alumina and irradiated in a domestic microwave oven for 8 min to afford[7] β-acetoxy-6′-amino-5′-cyanopyrido(17,16-*b*)androst-5,16-diene (**7a**) and *N*-acetyl-6′-imino-5′-cyanopyrido(17,16-*b*)androst-5-ene (**6a**) in 88% and 10% yields, respectively (Scheme 1). The aromatic protons of **7a** appeared as a singlet at δ 7.43, whereas compound **6a** exhibited an electron deficient enamine proton singlet at δ 7.72. Similarly, alicyclic (**2** and **3**) and aromatic β-formyl enamides (**4a**–**b**) reacted with **5a**–**b** to yield **8a**–**b**, **9a**–**b** and **10a**–**d** respectively in 81–86% yields (Table 1). The 2-iminopyridines (**6**) were isolated as minor products in each case. On the other hand, microwave irradiation of **1a** with **5a** without basic alumina or in silica gel led to condensation product **A**.

The formation of **7a** is envisaged to occur via a mechanism which involves Knoevenagel condensation[8] of **1a** with **5a** into intermediate **A** followed by basic alumina catalysed intramolecular cyclisation into **6a** under microwave irradiation. The formation of **7a** from **6a** may be accounted for by an intramolecular

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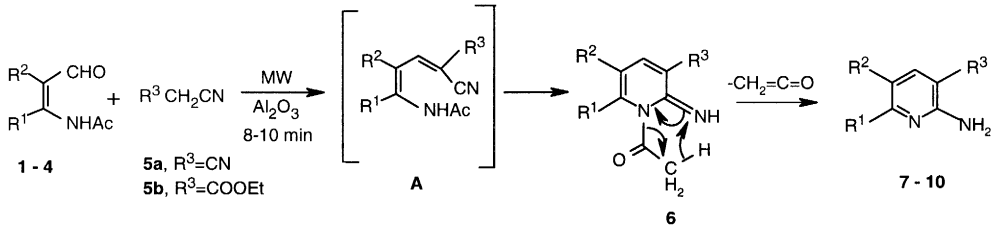
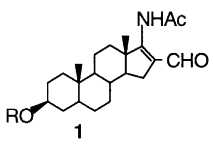
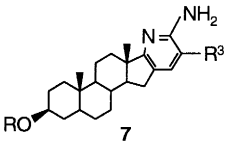
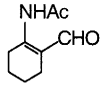
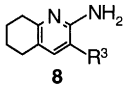
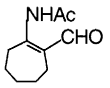
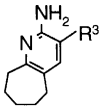
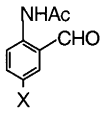
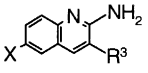


Scheme 1.

Table 1

Microwave mediated reaction[a] of β-formylenamide **1** with cyanomethylenes **5**

Entry	β-Formylenamide[b]		Cyano-methylene	Time/ min	Product		Yield[c] %
1	 1	**1a**, R = Ac	**5a**	8	 7	**7a**	88
2		**1b**, R = Bz	**5a**	9.5		**7b**	85
3		**1a**	**5b**	10		**7c**	83
4		**1b**	**5b**	10		**7d**	81
5	 2	**2**	**5a**	9	 8	**8a**	86
6		**2**	**5b**	9		**8b**	85
7	 3	**3**	**5a**	8	 9	**9a**	86
8		**3**	**5b**	8.5		**9b**	82
9	 4	**4a**, X = H	**5a**	8	 10	**10a**	84
10		**4a**	**5b**	8.5		**10b**	83
11		**4b**, X = Cl	**5a**	10		**10c**	81
12		**4b**	**5b**	10		**10d**	82

[a]All the reactions were carried in basic alumina without solvent. [b] Equimolar equivalents of formyl enamide and cyanomethylene were employed. [c]Isolated yields.

hydride shift from the *N*-acetyl group to the imino group followed by loss of ketene involving a six-membered transition state. The isolation of diketene as a side product rendered support to ketene elimination from **6a** to **7a**.

In summary, we have described a simple, facile method for the high yield synthesis of pyridine hybrids via a one-pot reaction. The β-formylenamides are easily accessible[4] from conjugated oximes or enamides. Furthermore, the reaction is advantageous for being carried out rapidly in dry media under microwave irradiation, thus avoiding harsh reaction conditions.

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7. All compounds gave satisfactory spectroscopical and elemental analysis. Spectral data of representative compounds: **6a**, R_f=0.3 (40% EtOAc/hexane); mp 153–154°C; IR (KBr): ν_{max} 3200, 2900, 2240, 1720, 1700, 1600, 1560, 1500, 1425, 1375, 1250, 1050 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 8.00 (s, 1H, =NH), 7.72 (s, 1H), 5.43 (bs, 1H), 4.65 (m, 1H), 2.71 (m, 1H), 2.55 (m, 1H), 2.33 (s, 3H), 2.12 (m, 1H), 2.02 (s, 3H), 2.20–0.92 (m, 14H), 1.10 (s, 3H), 0.95 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 177.5, 170.8, 168.5, 140.6, 137.9, 122.1, 96.5 (2C), 74.0, 56.1, 50.8, 46.6, 38.5, 37.3 (2C), 33.5, 32.0, 31.6, 31.1, 30.1, 28.1, 24.6, 23.2, 21.7, 20.8, 19.7, 17.5. MS: *m/z* 387 ($M^+ - CH_3COOH$), 344, 331. **7a**, R_f=0.4 (20% EtOAc/hexane); mp 249–50°C; IR (KBr): ν_{max} 3392, 3222, 2945, 2860, 2224, 1733, 1705, 1657, 1612, 1553, 1462, 1424, 1380, 1249, 1020 cm^{-1}.^1H NMR (300 MHz, $CDCl_3$): δ 7.43 (s, 1H), 5.41 (bs, 1H), 5.20 (bs, 2H, -NH_2), 4.59 (m, 1H), 2.61 (m, 1H), 2.35 (m, 2H), 2.02 (s, 3H), 1.93–1.16 (m, 14H), 1.09 (s, 3H), 0.95 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 178.0, 170.5, 159.6, 140.5, 137.1, 126.3, 125.9, 122.2, 96.5 (2C), 74.0, 55.9, 50.8, 46.5, 38.5, 37.2, 33.5, 31.6, 31.1, 29.7, 28.1, 21.7, 20.9, 19.7, 17.3. MS: *m/z* 345 ($M^+ - CH_3COOH$), 331, 303.
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