A New Modification of the Bohlmann-Rahtz Pyridine Synthesis

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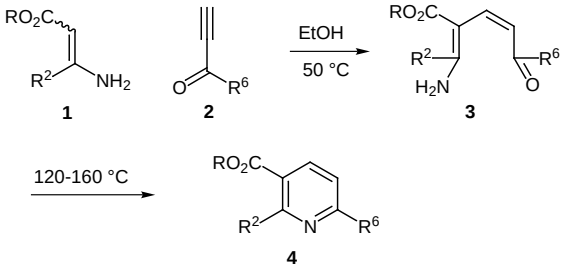
Abstract: A range of highly functionalised pyridines is prepared from enamino esters and alkynones in a single synthetic step by the use of acetic acid or amberlyst 15 ion exchange resin at 50 °C.

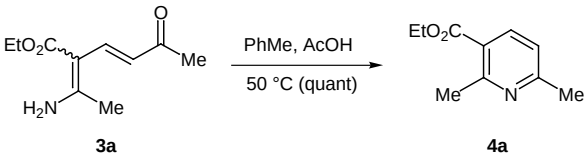
Key words: pyridines, cyclisations, heterocycles, Michael additions

The synthesis of trisubstituted pyridines from β-aminocrotonates and ethynyl ketones was first reported by Bohlmann and Rahtz in 1957.[1] This reaction is a two step process, the initial conjugate addition of enamine **1** to alkynone **2** at 50 °C in ethanol generates an aminopentadienone intermediate **3** that is isolated and subsequently cyclodehydrated to give pyridine **4**. The conditions required to affect this cyclisation are quite harsh, typically requiring temperatures of 120-160 °C under reduced pressure (Scheme 1). Since its discovery, only a few examples of this transformation have been reported including, most notably, a synthesis of the modified oxazole-thiazole-pyridine core of the promothiocin antibiotics.[2-4] Thus, in spite of great interest in the synthesis and biological properties of pyridine derivatives, the use and application of this transformation remains largely unexplored.



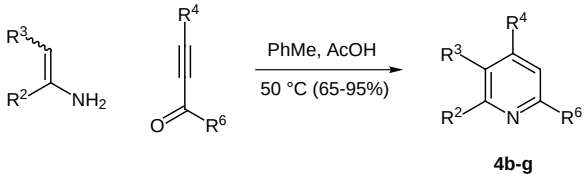
Scheme 1

In order to improve the utility of the Bohlmann-Rahtz pyridine synthesis, and to facilitate the transfer of this technology to the solid phase, we decided to investigate a new and simple method to affect the conjugate addition and cyclodehydration in a single preparative step. It was proposed that the presence of an acid would promote cyclodehydration of **3** at a lower temperature and obviating the need to isolate the conjugate addition product. In order to test this hypothesis, aminoheptadienone **3a** was prepared, according to the standard Bohlmann-Rahtz protocol,[1] and stirred at 50 °C in toluene-acetic acid (5:1) for 6 hours to generate pyridine **4a** in excellent yield and without any need for further purification (Scheme 2).



Scheme 2

The successful cyclodehydration of dienone **3a** under acidic conditions established the validity of this approach. The problem remained to affect the conversion of enamine **1** to pyridine **4** in a single synthetic step and facilitate the initial conjugate addition in the presence of an acid. To this end, a range of enamino esters was prepared by standard procedures[5] and reacted with a number of alkynones[6] at 50 °C in toluene-acetic acid (5:1)[7] to provide highly functionalised pyridines **4b-g** in good to excellent yield (Scheme 3, Table 1).[8] It was apparent that 4-substituted butynones were good substrates for this reaction, a finding that has not been reported previously for the Bohlmann-Rahtz pyridine synthesis. Only reactions involving 4-phenylbut-3-yn-2-one (R^4 = Ph, R^6 = Me), β-aminocrotonitrile (R^2 = Me, R^3 = CN) or *tert*-butyl aminocrotonate (R^2 = Me, R^3 = $CO_2{}^tBu$) failed to generate the desired products and these difficulties were attributed to the acid catalysed decomposition of the material. Thus the new modified reaction conditions for Bohlmann-Rahtz pyridine synthesis allow conjugate addition and subsequent cyclodehydration to be conducted in a single step without any need for isolation of intermediates and at a much lower reaction temperature.

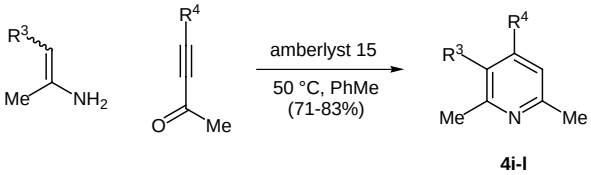


Scheme 3

Table 1 Synthesis of Functionalised Pyridines **4a-j**

R^2	R^3	R^4	R^6	Product	Yield/%
Me	EtO_2C	Me_3Si	Me	**4b**	79
Me	EtO_2C	Et	Me	**4c**	85
Me	EtO_2C	Ph	CO_2Et	**4d**	95
Ph	EtO_2C	Et	Me	**4e**	65
Ph	EtO_2C	H	Me	**4f**	73
2-furyl	EtO_2C	Me_3Si	Me	**4g**	80
Me	NC	Et	Me	**4h**	0
Me	EtO_2C	Ph	Me	**4i**	0
Me	$^tBuO_2C$	Me_3Si	Me	**4j**	0

Although the objective had been reached, it remained to explore milder conditions for conjugate addition/cyclodehydration that would be compatible with acid sensitive substrates. Thus, in separate experiments, enamine **1** and a range of alkynones[6] were stirred in toluene at 50 °C in the presence of amberlyst 15 ion exchange resin for 26 hours (Scheme 4).[9] Although reactions involving β-aminocrotonitrile were unsuccessful, in all other experiments pyridines **4i-l** were formed in good yield (Table 2).[10] It was interesting to note that, in the case of 4-(trimethylsilyl)but-3-yn-2-one, desilylation occurred in the presence of an acidic resin to give pyridine **4j**, a phenomenon that was not observed for reactions with this alkynone using acetic acid as the catalyst.



Scheme 4

Table 2 Synthesis of Functionalised Pyridines **4i-l**

R^3	R^4	Product	Yield/%
EtO_2C	Ph	**4i**	71
$^tBuO_2C$	Me_3Si	**4j**	83†
$^tBuO_2C$	Et	**4k**	80
$^tBuO_2C$	Ph	**4l**	76

† Product is the desilylated pyridine (R^4 = H) 4j

The new modified conditions for Bohlmann-Rahtz pyridine synthesis using either acetic acid or an acidic ion exchange resin were successful in both reducing the temperature of this transformation and, more importantly, affecting the synthesis in a single preparative step. Work is now underway to transfer this technology to the solid phase and apply this improved procedure to the synthesis of a number of heterocyclic natural products.

Acknowledgement

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References and Notes

(1) Bohlmann, F.; Rahtz, D. *Chem. Ber.* **1957**, *90*, 2265.
(2) Moody, C. J.; Bagley, M. C. *Synlett* **1998**, 361.
(3) Moody, C. J.; Bagley, M. C. *Chem. Commun.* **1998**, 2049.
(4) Bagley, M. C.; Bashford, K. E.; Hesketh, C. L.; Moody, C. J. *J. Am. Chem. Soc.* **2000**, *122*, 3301.
(5) Prepared by reaction of corresponding β-ketoester with ammonium acetate in toluene-acetic acid or in benzene in the presence of amberlyst 15 ion exchange resin. For a similar procedure, see: Baraldi, P. G.; Simoni, D.; Manfredini, S. *Synthesis* **1983**, 902.
(6) 4-Phenylbut-3-yn-2-one, 4-(trimethylsilyl)but-3-yn-2-one and hex-3-yn-2-one were commercially available. Ethyl 2-oxo-4-phenylbut-3-ynoate (R^3 = Ph, R^4 = CO_2Et) was prepared by the addition of lithium phenylacetylide to the corresponding Weinreb amide, see: Chiu, C. C.; Jordan, F. *J. Org. Chem.* **1994**, *59*, 5763.
(7) *Typical experimental procedure:* A solution of the enamine (0.79 mmol) and alkynone (1.0 mmol) in toluene-glacial acetic acid (5:1) (3.5 mL) was stirred at 50 °C for between 5 and 24 h. The mixture was partitioned between toluene (20 mL) and saturated aqueous sodium hydrogen carbonate solution (20 mL), the aqueous layer was extracted with toluene (2 × 15 mL) and the combined organic layers were washed sequentially with saturated aqueous sodium hydrogen carbonate solution (15 mL) and brine (15 mL), dried ($MgSO_4$), evaporated in vacuo, and the residue purified by flash chromatography on silica to give the product.
(8) Ethyl 2,6-dimethyl-4-(trimethylsilyl)pyridine-3-carboxylate **4b** (Found MH^+, 252.1420. $C_{13}H_{22}NO_2Si$ requires 252.1420); ν_{max} (film) 2956, 2903, 1724, 1573, 1529, 1104, 1085, 1016 cm^{-1}; δ_H (400 MHz; $CDCl_3$) 7.12 (1H, s, CH), 4.35 (2H, q, *J* 7.2, C*H*$_2$Me), 2.54 (3H, s, Me), 2.51 (3H, s, Me), 1.37 (3H, t, *J* 7.2, CH$_2$*Me*), 0.26 (9H, s, $SiMe_3$); δ_C (100 MHz, $CDCl_3$) 171.1 (C), 158.5 (C), 154.9 (C), 149.4 (C), 131.5 (C), 126.6 (CH), 62.1 (CH_2), 25.3 (Me), 24.1 (Me), 14.9 (Me); Ethyl 2,6-dimethyl-4-ethylpyridine-3-carboxylate **4c** (Found MH^+, 208.1339. $C_{12}H_{16}NO_2$ requires 208.1337); ν_{max} (film) 2975, 2937, 1726, 1595, 1561, 1190, 1089 cm^{-1}; δ_H (400 MHz; $CDCl_3$) 6.85 (1H, s, CH), 4.32 (2H, q, *J* 7.1, OC*H*$_2$Me), 2.50 (2H, q, *J* 7.6, C*H*$_2$Me), 2.44 (3H, s, Me), 2.42 (3H, s, Me), 1.30 (3H, t, *J* 7.1, OCH$_2$*Me*), 1.12 (3H, t, *J* 7.6, CH$_2$*Me*); δ_C (100 MHz, $CDCl_3$) 169.5 (C), 158.9 (C), 154.7 (C), 151.5 (C), 126.7 (C), 120.7 (CH), 61.6 (CH_2), 26.6 (CH_2), 24.7 (Me), 23.2 (Me), 15.0 (Me), 14.5 (Me); Diethyl 2-methyl-4-phenylpyridine-3,6-dicarboxylate **4d** (Found MH^+, 314.1388. $C_{18}H_{20}NO_4$ requires 314.1392); ν_{max} (film) 2982, 2932, 1730, 1582, 1552, 1148, 1081, 1024 cm^{-1}; δ_H (400 MHz; $CDCl_3$) 7.93 (1H, s, Py*H*), 7.36 (5H, m), 4.43 (2H, q, *J* 7.1, OC*H*$_2$Me), 4.08 (2H, q, *J* 7.1, OC*H*$_2$Me), 2.65 (3H, s, Me), 1.37 (3H, t, *J* 7.1, OCH$_2$*Me*), 0.95 (3H, t, *J* 7.1, OCH$_2$*Me*); δ_C (100 MHz, $CDCl_3$) 168.6 (C), 165.2 (C), 156.6 (C), 149.4 (C), 148.3 (C), 138.0 (C), 131.7 (C), 129.4 (CH), 129.1 (CH), 128.4 (CH), 123.7 (CH), 62.6 (CH_2), 62.2 (CH_2), 23.5 (Me), 14.7 (Me), 14.1 (Me); ethyl 4-Ethyl-6-methyl-2-phenylpyridine-3-carboxylate **4e** (Found MH^+, 270.1495. $C_{17}H_{20}NO_2$ requires 270.1494); ν_{max} (film) 2976, 2937, 1723, 1590, 1555, 1145, 1086, 1015, 918, 870, 768 cm^{-1}; δ_H (400 MHz; $CDCl_3$) 7.36 (5H, m), 6.97 (1H, s, CH), 4.01 (2H, q, *J* 7.2, OCH_2), 2.62 (2H,

q, *J* 7.6, CH_2), 2.53 (3H, s, Me), 1.19 (3H, t, *J* 7.6, Me), 0.89 (3H, t, *J* 7.2, Me), δ_C (100 MHz, $CDCl_3$) 169.5 (C), 159.4 (C), 156.8 (C), 140.8 (C), 128.8 (CH), 128.7 (CH), 128.7 (CH), 126.5 (C), 121.8 (CH), 61.7 (CH_2), 26.6 (CH_2), 25.0 (Me), 15.1 (Me), 14.0 (Me); Ethyl 6-methyl-2-phenylpyridine-3-carboxylate **4f** (Found MH^+, 242.1181. Calculated for $C_{15}H_{16}NO_2$ (MH^+) 242.1181); ν_{max} (film) 2981, 2926, 1718, 1589, 1137, 1052, 838, 766 cm^{-1}; δ_H (400 MHz; $CDCl_3$) 7.93 (1H, d, *J* 8.0, CH), 7.37 (5H, m), 7.10 (1H d, *J* 8.0, CH), 4.03 (2H, q, *J* 7.2, CH_2), 2.56 (3H, s, Me), 0.94 (3H, t, *J* 7.2, CH_2*Me*), δ_C (100 MHz, $CDCl_3$) 168.6 (C), 161.2 (C), 159.1 (C), 141.0 (C), 138.7 (CH), 129.2 (CH), 128.9 (CH), 128.5 (CH), 124.8 (C), 121.6 (CH), 61.7 (CH_2), 27.8 (Me), 14.0 (Me); Ethyl 2-(2-furyl)-6-methyl-4-(trimethylsilyl)pyridine-3-carboxylate **4g** (Found MH^+, 304.1370. $C_{16}H_{22}NO_3Si$ requires 304.1369); ν_{max} (film) 2962, 2898, 1727, 1570, 1520, 1165, 1087, 1015, 836, 757 cm^{-1}; δ_H (400 MHz; $CDCl_3$) 7.49 (1H, s, CH), 7.17 (1H, s, CH), 6.93 (1H, d, *J* 2, CH), 6.43 (1H, d, *J* 2, CH), 4.26 (2H, q, *J* 7.2, CH_2), 2.54 (3H, s, Me), 1.21 (3H, t, *J* 7.2, Me), 0.26 (9H, s, $SiMe_3$); δ_C (100 MHz, $CDCl_3$) 169.2 (C), 156.9 (C), 147.9 (C), 142.3 (CH), 125.9 (CH), 110.8 (CH), 109.5 (CH), 60.5 (CH_2), 23.6 (Me), 13.0 (Me), 0.0 (Me).

(9) *Typical experimental procedure:* A suspension of amberlyst 15 ion exchange resin (100 mg) in a solution of the enamine (0.89 mmol) and alkynone (1.2 mmol) in toluene (3.5 mL) was stirred at 50 °C overnight. The mixture was filtered, the solid residue washed with chloroform (5 mL), and the filtrate evaporated in vacuo and purified by flash chromatography on silica to give the product.

(10) Ethyl 2,6-dimethyl-4-phenylpyridine-3-carboxylate **4i** (Found MH^+, 256.1334. $C_{16}H_{18}NO_2$ requires 256.1337); ν_{max} (film) 2926, 1724, 1588, 1552, 1083, 1024; δ_H (400 MHz; $CDCl_3$) 7.30 (5H, m, PhH), 6.94 (1H, s, CH), 4.01 (2H, q, *J* 7.1, CH_2), 2.54 (3H, s, Me), 2.50 (3H, s, Me), 0.90 (3H, t, *J* 7.1, CH_2*Me*); δ_C (100 MHz, $CDCl_3$) 169.5 (C), 159.1 (C), 155.5 (C), 148.9 (C), 139.2 (C), 128.9 (CH), 128.8 (CH), 128.2 (CH), 126.1 (C), 121.6 (CH), 61.7 (CH_2), 24.9 (Me), 23.2 (Me), 14.0 (Me); *tert*-Butyl 2,6-dimethylpyridine-3-carboxylate **4j** (Found MH^+, 208.1337. $C_{12}H_{18}NO_2$ requires 208.1337); ν_{max} (film) 2977, 2930, 2856, 1720, 1592, 1568, 1127, 1083 cm^{-1}; δ_H (400 MHz; $CDCl_3$) 7.95 (1H, d, *J* 8.0, 4-PyH), 6.97 (1H, d, *J* 8.0, 5-PyH), 2.71 (3H, s, Me), 2.51 (3H, s, Me), 1.53 (9H, s, CMe_3); δ_C (100 MHz, $CDCl_3$) 166.6 (C), 161.0 (C), 159.1 (C), 139.1 (CH), 124.9 (C), 120.8 (CH), 82.1 (C), 28.6 (Me), 25.2 (Me), 25.0 (Me); *tert*-Butyl 2,6-dimethyl-4-ethylpyridine-3-carboxylate **4k** (Found MH^+, 236.1651. $C_{14}H_{22}NO_2$ requires 236.1650); ν_{max} (film) 2974, 2932, 1721, 1594, 1562, 1162, 1092 cm^{-1}; δ_H (400 MHz; $CDCl_3$) 6.83 (1H, s, PyH), 2.54 (2H, q, *J* 7.6, CH_2), 2.45 (3H, s, Me), 2.44 (3H, s, Me), 1.53 (9H, s, CMe_3); δ_C (100 MHz, $CDCl_3$) 171.2 (C), 160.7 (C), 156.5 (C), 152.6 (C), 130.4 (C), 123.1 (CH), 85.0 (C), 30.8 (Me), 28.8 (CH_2), 27.1 (Me), 25.4 (Me), 17.4 (Me); *tert*-Butyl 2,6-dimethyl-4-phenylpyridine-3-carboxylate **4l** (Found MH^+, 284.1647. $C_{18}H_{22}NO_3$ requires 284.1650); ν_{max} (film) 2976, 2928, 2855, 1722, 1588, 1551, 1138, 1089, 1031 cm^{-1}; δ_H (400 MHz; $CDCl_3$) 7.32 (5H, m, PhH), 6.91 (1H, s, PyH), 2.53 (3H, s, Me), 2.50 (3H, s, Me), 1.22 (9H, s, CMe_3); δ_C (100 MHz, $CDCl_3$) 168.9 (C), 159.1 (C), 155.7 (C), 148.9 (C), 139.7 (C), 129.2 (CH), 129.1 (CH), 129.0 (CH), 128.0 (CH), 122.0 (C), 82.4 (C), 28.1 (Me), 25.3 (Me), 23.6 (Me).

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