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A new one-pot three-component condensation reaction for the synthesis of 2,3,4,6-tetrasubstituted pyridines

Mark C. Bagley,*[a] James W. Dale[a] and Justin Bower[b]

[a] *Department of Chemistry, Cardiff University, PO Box 912, Cardiff, UK CF10 3TB. E-mail: bagleymc@cf.ac.uk; Fax: 44 29 20874030; Tel: +44 29 20874029*

[b] *RiboTargets Ltd, Granta Park, Abington, Cambridge, UK CB1 6GB*

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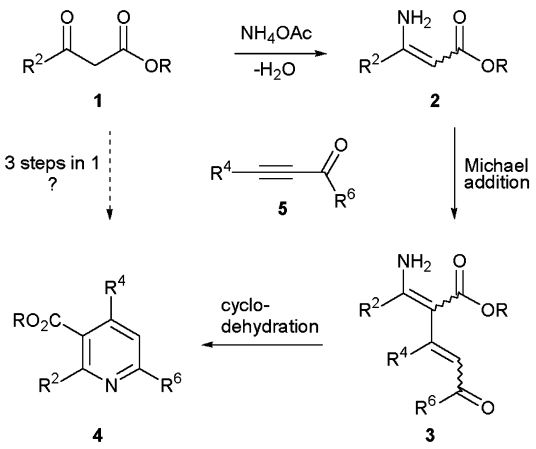
The one-pot three-component condensation of a β-ketoester, ammonia and an alkynone in the presence of a Brønsted or Lewis acid or Amberlyst 15 ion exchange resin provided 2,3,6-trisubstituted or 2,3,4,6-tetrasubstituted pyridines directly in good yield and with total regiocontrol.

The synthesis, reactions and biological properties of pyridine-containing derivatives constitutes a significant part of modern heterocyclic chemistry. This heterocyclic motif may be found in a large number of pharmaceutical agents,[1] as a pharmacophore of considerable historical importance, and so new and facile methods for their synthesis are of great current interest. Bohlmann and Rahtz first reported the preparation of a trisubstituted pyridine **4** (R^4 = H) from enamine **2** and alkynone **5** by Michael addition and subsequent cyclodehydration back in 1957.[2] This two-step method requires harsh cyclodehydration conditions (up to 200 °C) and isolation of the aminodienone intermediate **3**. The poor availability of enamine substrates has also restricted the applicability of this reaction; typically enamine **2** is prepared from β-ketoester **1** by reaction with ammonium acetate under acidic conditions (benzene–acetic acid) with azeotropic removal of water according to the procedure of Baraldi *et al*. (Scheme 1).[3] This long-winded and somewhat laborious three-step process, nevertheless, displays great potential for the synthesis of pyridine-containing heterocycles of biological interest and has been put to a few notable uses since its discovery.[4–7]

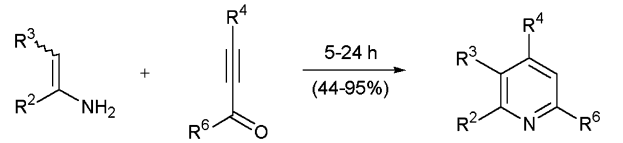
In order to increase the scope and application of the Bohlmann–Rahtz reaction, we have reported new facile procedures using zinc(II) bromide, acetic acid or Amberlyst 15 ion exchange resin as catalysts to affect Michael addition–cyclodehydration in a single synthetic step and at a lower reaction temperature (Scheme 2).[8,9] However, in order to overcome problems of poor substrate availability, to improve the facility of the whole process and as part of our interest in the discovery of new multiple-component condensation reactions in heterocyclic chemistry,[10] it was proposed that the three-component condensation of a β-keto ester **1**, alkynone **5** and ammonia would provide a much more efficient approach towards poly-substituted pyridine **4** (see Scheme 1). This new tandem addition–elimination–Michael addition–cyclodehydration process would be related to the Hantzsch dihydropyridine synthesis[11] but with the advantage of total control of regiochemistry and access to the target heterocycle in the correct oxidation state.



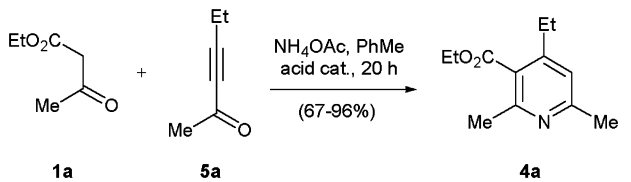
Scheme 1 The three-step heteroannulation procedure for the synthesis of 2,3,4,6-tetrasubstituted pyridine **4**.

In order to test the validity of this proposal for a one-step synthesis of poly-substituted pyridines, ethyl acetoacetate **1a** was reacted with either one or two equivalents of hex-3-yn-2-one **5a** and ammonium acetate in toluene, heated at reflux in the presence of either acetic acid or zinc(II) bromide (Scheme 3), catalysts employed to good effect in our previously reported modified Bohlmann–Rahtz reactions.[8,9] In all cases, pyridine **4a** was formed directly as the only reaction product, isolated in good to excellent yield in a single preparative step (Scheme 3). The reaction† proceeded with total regiocontrol, established by comparing spectroscopic data of the product with an authentic sample of **4a**.[8] The optimum reaction conditions used the Lewis acid catalyst (0.2 equivalents) and an excess of hex-3-yn-2-one **5a** to generate pyridine **4a** in 96% yield after chromatographic purification on silica (Table 1).

In order to investigate the scope of this reaction and establish its tolerance of different substrates, a range of different β-ketoesters **1a–d** and alkynones **5a–d** were heated at reflux in toluene under acidic conditions in the presence of an excess of ammonium acetate (Scheme 4). In all of the cases that were



Scheme 2 The one-step Bohlmann–Rahtz reaction using acetic acid, Amberlyst 15 ion exchange resin or zinc(II) bromide catalysis.



Scheme 3 Three-component condensation of ethyl acetoacetate **1a**, hex-3-yn-2-one **5a** and ammonia under acidic conditions.

Table 1 Reaction conditions

Entry	**5a** equivalents	Acid catalyst	Yield[a] of **4a** (%)
1	1	AcOH	68
2	2	AcOH	78
3	1	$ZnBr_2$	67
4	2	$ZnBr_2$	96

[a] Isolated yield after purification on silica.

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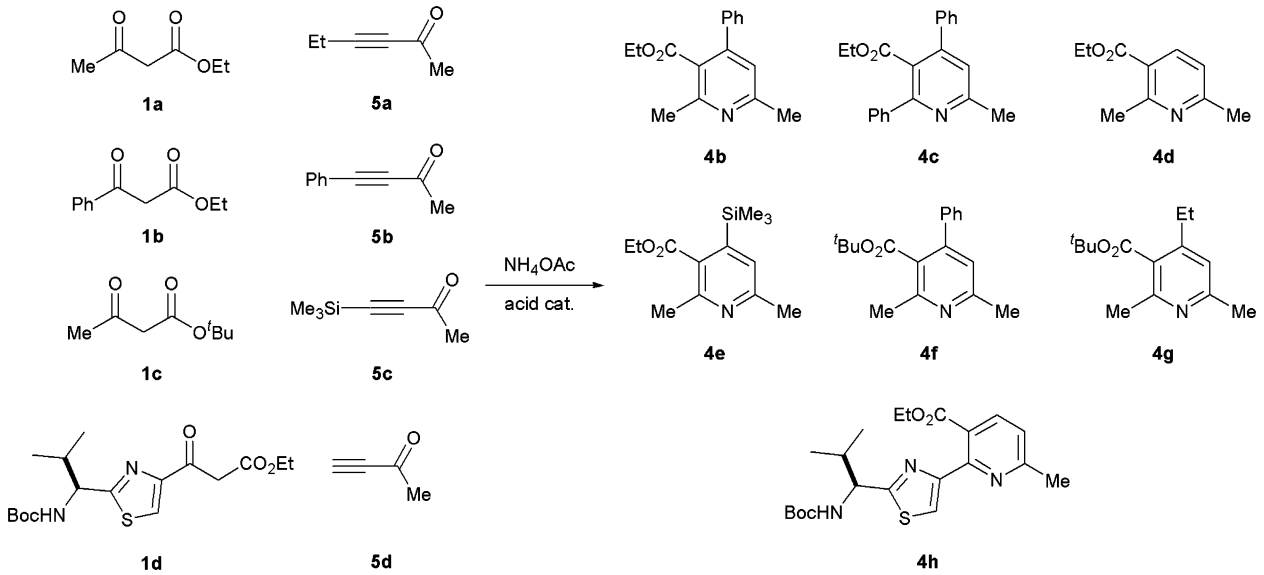

Scheme 4 Three-component heteroannulation of β-ketoester **1**, alkynone **5** and ammonia under acidic conditions.

Table 2 Examining the scope of the three-component heteroannulation reaction

Entry	β-Ketoester **1**	Alkynone **5**	Equivalents of **5**	Acid catalyst	Conditions	Product	Yield[a] (%)
1	**1a**	**5a**	2	$ZnBr_2$	Toluene/reflux	**4a**	96
2	**1a**	**5b**	2	AcOH	Toluene/reflux	**4b**	80
3	**1b**	**5b**	2	AcOH	Toluene/reflux	**4c**	70
4	**1b**	**5b**	2	$ZnBr_2$	Toluene/reflux	**4c**	88
5	**1a**	**5c**	2	$ZnBr_2$	Toluene/reflux	**4d**,**4e** (44:56)	55
6	**1a**	**5c**	2	AcOH	Toluene/reflux	**4d**	75
7	**1c**	**5a**	3	$ZnBr_2$	Toluene/reflux	**4f**	49
8	**1c**	**5b**	2	Amberlyst 15	Toluene/reflux	**4f**	53
9	**1c**	**5b**	3	Amberlyst 15	Toluene/reflux	**4f**	60
10	**1c**	**5a**	3	Amberlyst 15	Toluene/reflux	**4g**	55
11	**1d**	**5d**	3	AcOH	Toluene/reflux	**4h**	68[b]
12	**1d**	**5d**	3	AcOH	Benzene/reflux	**4h**	71[b]

[a] Yield of pure isolated product. [b] Formed in 78% *ee* (entry 11) or 98% *ee* (entry 12) by HPLC analysis [Chiralpak AD column, hexane-IPA (92:8)].

investigated (Table 2), pyridine **4** was isolated in good to excellent yield (entries 1–4, 70–96% yield) as the only regioisomeric reaction product. When 4-(trimethylsilyl)but-3-yn-2-one **5c** was reacted with ethyl acetoacetate **1a** in the presence of zinc(II) bromide, partial desilylation occurred to give a mixture of pyridine **4d** and **4e** (entry 5). However, by employing acetic acid as the catalyst, only a single pyridine **4d** was produced in 75% yield (entry 6). The use of *tert*-butyl acetoacetate **1c** (entries 7–10), caused a reduction in the efficiency of the process but pyridine **4f** was still isolated in moderate yield under zinc(II) bromide or Amberlyst 15 ion exchange resin catalysed conditions. In the synthesis of pyridine **4h** a high degree of racemisation accompanied the reaction in toluene, but by switching to benzene these problems were avoided.[12]

In conclusion, this new three-component condensation greatly simplifies and shortens the laborious traditional procedure and proceeds with total control of regiochemistry and so should offer considerable advantages over existing methodology.

Notes and references

† *General experimental procedure for the three-component cyclocondensation reaction catalysed by acetic acid*: a solution of ethyl acetoacetate (0.28 ml, 2.2 mmol), hex-3-yn-2-one (0.50 ml, 4.5 mmol) and ammonium acetate (1.7 g, 23 mmol) in toluene–glacial acetic acid (5:1) (12 ml) was heated at reflux for 20 h. The mixture was partitioned between aqueous saturated sodium hydrogen carbonate solution (25 ml) and ethyl acetate (25 ml) and the aqueous layer was further extracted with ethyl acetate (2 × 20 ml). The combined organic layers were washed with brine (10 ml), dried ($MgSO_4$) and evaporated *in vacuo*. Purification by flash chromatography on silica, eluting with light petroleum–ethyl acetate (3:1), gave pure *pyridine* **4a** as a pale yellow oil (0.36 g, 78%), with spectroscopic data that were identical with an authentic sample.

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