Iodine-Catalysed Bohlmann–Rahtz Cyclodehydration Reactions

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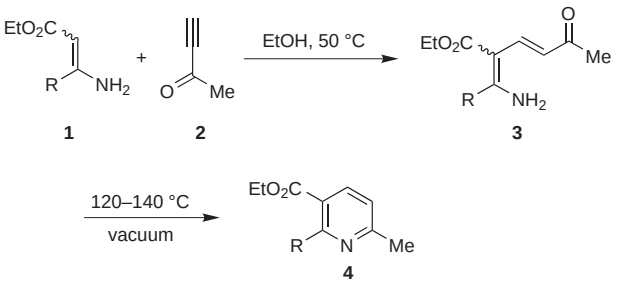
Abstract: The cyclodehydration of Bohlmann–Rahtz aminodienones is catalysed by iodine in ethanol at room temperature to give 2,3,6-trisubstituted pyridines in excellent yield, with total regiocontrol and without the need for chromatographic purification.

Key words: pyridines, enamines, heterocycles, Bohlmann–Rahtz

Bohlmann and Rahtz first described the two-step synthesis of 2,3,6-trisubstituted pyridines by the reaction of enamino esters **1** and ethynyl ketones, such as butynone **2**, in 1957.[1] This totally regioselective process proceeds by Michael addition and enamine C-alkylation to give an aminodienone intermediate **3** that is isolated and cyclodehydrated by heating, typically at 120–140 °C under vacuum, to give pyridine **4** in 80–90% overall yield (Scheme 1). We have established that both the Michael addition and cyclocondensation reaction can be effected in a single preparative step by the use of acetic acid or Amberlyst 15® ion exchange resin,[2] microwave irradiation in a sealed tube[3] or the action of a Lewis acid catalyst.[4] The two step procedure can be incorporated into a one-pot three-component reaction of a β-ketoester, ethynyl ketone and ammonium acetate through the use of protic solvents[5] or an acid catalyst[6] and can be combined in a tandem oxidation–heteroannulation reaction in the presence of manganese dioxide to give rapid access to pyridine targets from common building blocks.[7] These mild methods have been shown to tolerate a wide range of substituents[8] and have been applied by us and others in the solution-phase synthesis of pyrido[2,3-*d*]pyrimidines,[9] uracil derivatives,[10] combinatorial pyridine libraries,[11] heterocyclic amino acids[12] and the central domain of thiopeptide natural products, including the promothiocins,[13] amythiamicins[14] and sulfomycins.[15]

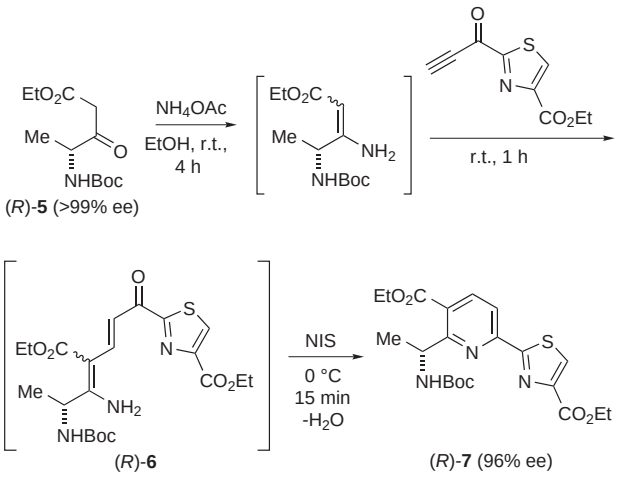
During a previous study to extend the scope of the Bohlmann–Rahtz pyridine synthesis, it was observed that the treatment of aminodienones **3** with *N*-iodosuccinimide (NIS) facilitated a remarkably facile low temperature cyclodehydration to give 2,3,6-trisubstituted pyridines **4** with total regiocontrol.[16] Recently, we have utilised this mild procedure in the synthesis of the γ-lactam hydrolysate of cyclothiazomycin from heptadienone **6** (Scheme 2),[12a] which was generated in situ from the corresponding β-ketoester **5**. Cyclodehydration with NIS proceeded in only 15 minutes at 0 °C and proved to be the



Scheme 1 Original two-step Bohlmann–Rahtz reaction

best Bohlmann–Rahtz (B–R) cyclodehydration method for the stereoselective synthesis of the cyclothiazomycin pyridine domain **7**. Although treatment with NIS is highly effective for this transformation, the products from these reactions, as with the original thermal procedure, still require purification by column chromatography. In this study, we set out to understand the surprising facility of reaction and in so doing have uncovered new catalytic conditions for B–R cyclodehydration that are experimentally simple and require no purification on silica, constituting a facile new method for the synthesis of trisubstituted pyridines.

It was proposed[16] that the Lewis acidity of NIS was responsible for the remarkably facile cyclodehydration of B–R aminodienone intermediates, that traditionally require temperatures well in excess of 120 °C to react. Although it was evident that traces of HI had not catalysed the process, it could not be ruled out that traces of iodine were mediating the reaction. To test this hypothesis,



Scheme 2 Stereoselective synthesis of cyclothiazomycin domain **7**

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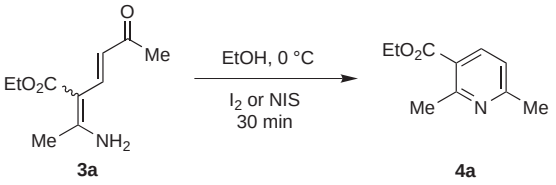
aminoheptadienone **3a**, the least efficient substrate in NIS cyclodehydration reactions,[16] was prepared according to literature procedures[1,8] and reacted with a stoichiometric amount of either iodine or NIS in ethanol at 0 °C for 30 minutes (Scheme 3). Under these conditions both reactions gave efficient conversion to pyridine **4a**, but the iodine cyclodehydration was superior, generating the product in quantitative yield after only a simple work up (Table 1). These transformations were then repeated in the presence of an excess of sodium thiosulfate (2 equiv), added prior to the cyclodehydrating agent, to establish if iodine generated from NIS was responsible for the reaction's facility. As expected, the iodine-mediated reaction now failed, giving only a 9% yield of the product and predominantly returning unreacted starting material **3a** (91% recovery). In contrast, the cyclodehydration mediated by NIS was chiefly unaffected by the presence of sodium thiosulfate and gave pyridine **4a** in 80% yield, supporting the hypothesis that it was the Lewis acidity of NIS that was responsible for the reactivity. If this is the case, the low-temperature activity of this catalyst compares very favourably to the action of a range of other Lewis acids.[4]



Scheme 3 Cyclodehydration of B–R intermediate **3a**

Table 1 Comparing Stoichiometric I_2 and NIS

Entry	Reagent	Yield (%)	Yield (%)[a]
1	I_2	>98	9[b]
2	NIS	88[c]	80[c]

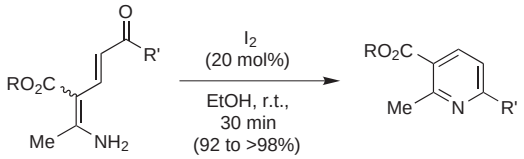
[a] Reaction was run in the presence of $Na_2S_2O_3$.
[b] Starting material **3a** was recovered (91%).
[c] Purification on silica was required.

These iodine-mediated cyclodehydration reactions employed a stoichiometric quantity of reagent. Following the success of our intial studies, an alternative heptadienone **3b** derived from *tert*-butyl 3-aminocrotonate was reacted with iodine (0.1–100 mol%) in ethanol at room temperature in an effort to establish if a process could be developed that was catalytic in reagent. Essentially quantitative conversions to pyridine **4b** were observed under catalytic conditions even at very low iodine concentrations (0.5 mol%, Table 2). Only when 0.1 mol% of iodine was used did the reaction fail to give complete conversion to the product, returning instead predominantly unreacted starting material.

Table 2 Room Temperature Cyclodehydration of **3b** Varying Quantity of I_2

Entry	I_2 (mol%)	Yield (%)
1	100	>98
2	50	>98
3	20	>98
4	10	>98
5	1.0	>98
6	0.5	>98
7	0.1	18[a,b]

[a] From ^{1}H NMR analysis of the crude reaction mixture.
[b] A mixture of **3b**:**4b** (5.3:1) was obtained.



3 R, R'
a Et, Me;
b *t*-Bu, Me;
c Et, Ph;
d Et, 4-$MeOC_6H_4$;
e Et, 4-ClC_6H_4;
f *t*-Bu, Ph;
g *t*-Bu, 4-$MeOC_6H_4$;
h *t*-Bu, 4-ClC_6H_4.

4 R, R'
a Et, Me;
b *t*-Bu, Me;
c Et, Ph;
d Et, 4-$MeOC_6H_4$;
e Et, 4-ClC_6H_4;
f *t*-Bu, Ph;
g *t*-Bu, 4-$MeOC_6H_4$;
h *t*-Bu, 4-ClC_6H_4.

Scheme 4 Catalytic cyclodehydration of B–R intermediates **3a**–**h**

With conditions established for catalytic cyclodehydration, a range of aminodienones **3a**–**h** were generated from the corresponding β-aminocrotonates by literature methods[1,8,16] and reacted with catalytic iodine (20 mol%) in ethanol at room temperature for 30 minutes (Scheme 4).[17] After a simple aqueous work up with sodium thiosulfate solution, the 2,3,6-trisubstituted pyridines **4a**–**h**[18] were obtained in excellent yield (Table 3). Only in the case of the I_2-catalysed cyclodehydration of **3d** (entry 4) was any further purification required and this was attributed to the poor solubility of the substrate in ethanol.

In conclusion, the iodine-mediated catalytic cyclodehydration of B–R aminodienone intermediates is rapid at ambient temperature and has a number of advantages over equivalent methods using NIS[16] or other Lewis acids.[4] The procedure is simple to perform, giving 2,3,6-trisubstituted pyridines in excellent yield, without the need for column chromatography and with total regiocontrol.

Acknowledgment

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Table 3 Catalytic Cyclodehydration of **3a**–**h**

Entry	**3**	R	R′	**4**	Yield (%)[a]
1	**a**	Et	Me	**a**	>98
2	**b**	*t*-Bu	Me	**b**	>98
3	**c**	Et	Ph	**c**	>98
4	**d**	Et	4-$MeOC_6H_4$	**d**	92[b]
5	**e**	Et	4-ClC_6H_4	**e**	>98
6	**f**	*t*-Bu	Ph	**f**	97
7	**g**	*t*-Bu	4-$MeOC_6H_4$	**g**	>98
8	**h**	*t*-Bu	4-ClC_6H_4	**h**	92

[a] Isolated yield of pure **4** after an aqueous work up.
[b] Not isolated yield of pyridine **4d** but from analysis of ^1H NMR spectrum which showed that dienone **3d** (8%) was also present.

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(17) **General Procedure for the Catalytic Cyclodehydration of Aminodienones 3 Using I_2.**
A solution of aminodienone **3** (0.2 mmol, 1 equiv) and iodine (0.04 mmol, 20 mol%) in EtOH (4 mL) was stirred at r.t. for 30 min and an aq solution of $Na_2S_2O_3$ (10% w/v, 10 mL) was added. The mixture was extracted with CH_2Cl_2 (3×20 mL) and the organic extracts were combined, dried (Na_2SO_4) and evaporated in vacuo to give pyridine **4**.
(18) Pyridines **4a**–**h** exhibited physical and spectroscopic properties that were in agreement with literature data (see refs. 1, 8, 11a, and 15b for detailed information).