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A new mild method for the one-pot synthesis of pyridines

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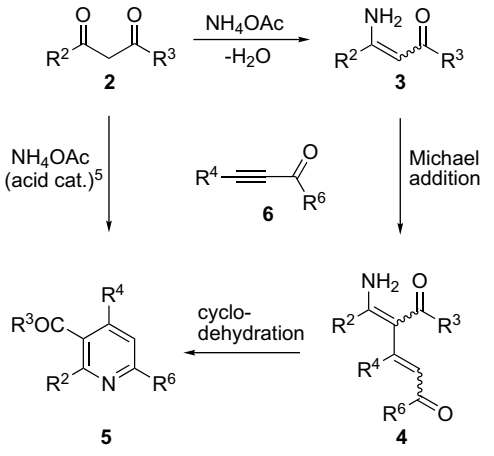
Abstract—Polysubstituted pyridines are prepared in good yield and with total regiocontrol by the one-pot reaction of an alkynone, 1,3-dicarbonyl compound and ammonium acetate in alcoholic solvents. This new three-component heteroannulation reaction proceeds under mild conditions in the absence of an additional acid catalyst and has been used in the synthesis of dimethyl sulfomycinamate, the acidic methanolysis degradation product of the sulfomycin family of thiopeptide antibiotics.

In our recent synthesis of dimethyl sulfomycinamate **1**,[1] the acidic methanolysis degradation product of the thiopeptide antibiotic sulfomycin I,[2] we described a Bohlmann–Rahtz[3] strategy (Scheme 1) for the preparation of the oxazole–thiazole–pyridine central domain (Scheme 2). This heteroannulation of an enamine **3**, often derived from a 1,3-dicarbonyl compound **2** by reaction with ammonium acetate, and alkynone **6** proceeds by Michael addition, typically at 50 °C, to give an aminodienone intermediate **4** that is cyclodehydrated at high temperature or under acidic conditions to tetrasubstituted pyridine **5**.[4] Our 13 step total synthesis of dimethyl sulfomycinamate **1**, which proceeded in 8% overall yield, used 1-(oxazol-4-yl)enamine **3a**, obtained from the corresponding β-ketoamide **2a**, and methyl 4-(trimethylsilyl)-2-oxobut-3-ynoate **6a** in a multistep heteroannulation reaction to give pyridine **5a** in 93% yield as a single regioisomer (Scheme 2). Curiously, this reaction occurred at room temperature in alcoholic solvent and did not give any trace of the Bohlmann–Rahtz intermediate **4a**; conditions, which appeared remarkably facile for spontaneous cyclodehydration to the pyridine.



Scheme 1. Bohlmann–Rahtz and three-component pyridine **5** synthesis.

We recently reported a one-pot method for the synthesis of pyridines from a β-ketoester, ammonia and an alkynone using a Brønsted or Lewis acid catalyst (Scheme 1)[5] and wanted to apply this methodology to the synthesis of dimethyl sulfomycinamate **1** in order to shorten the number of steps to this target. However, in all of the three-component reactions that we investigated acid-catalyzed degradation of the highly sensitive 2-(2-propenyl)oxazole unit prevented the isolation of the oxazole–pyridine product **5a**. In view of the facility of the Bohlmann–Rahtz pyridine synthesis in alcoholic solvent,[6,7] and the surprising ease with which the heteroannulation of enamine **3a** and alkynone **6a** gave the required pyridine **5a**, we set out to explore a new multistep three-component condensation process for the synthesis of pyridine heterocycles that would be compatible with these precursors and that avoided the use of an acid catalyst (Scheme 1).

Keywords: Pyridines; Multicomponent reactions; Heterocycles; Sulfomycin; Bohlmann–Rahtz.
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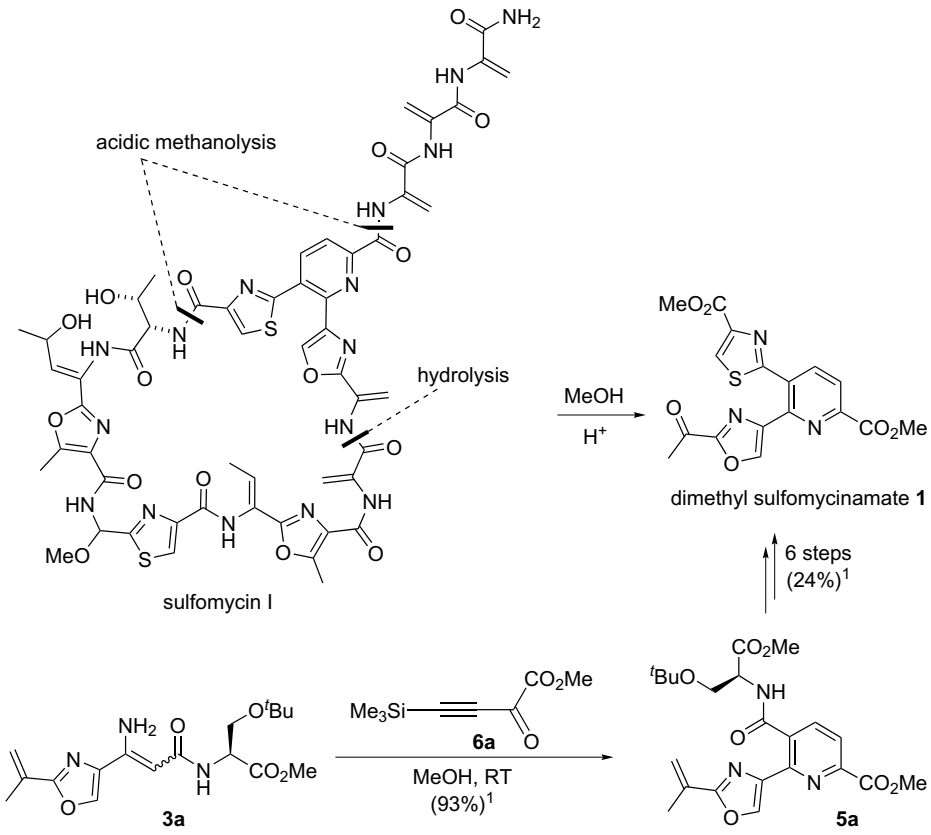
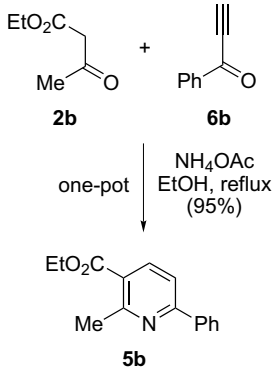


Scheme 2. Degradation of sulfomycin I and synthesis of dimethyl sulfomycinamate **1** via a Bohlmann–Rahtz heteroannulation strategy.

In order to examine if a one-step three-component heteroannulation reaction was possible under mild conditions without an acid catalyst, a mixture of ethyl acetoacetate **2b**, 1-phenylprop-2-yn-1-one **6b**, and ammonium acetate was stirred in ethanol for up to 3 days (Scheme 3). Reactions conducted at room temperature or at reflux with up to 4 equiv of ammonium acetate did not go to completion, giving mixtures of pyridine **5b**, aminodienone **4b** and/or enamine **3b** (Table 1). However, when the reaction was carried out at reflux with a large excess of ammonium acetate, pyridine **5b** was isolated as the only product in excellent yield, cyclodehydration occurring spontaneously under the reaction conditions without the use of an acid catalyst. Optimally, heating an excess of ethyl acetoacetate **2b** (1.7 equiv) and ammonium acetate (10 equiv with respect to **2b**) with **6b** for 24 h gave pyridine **5b** as a single regioisomer in 95% yield after purification on silica (Table 1, entry 5).[8]



Scheme 3. One-pot synthesis of pyridine **5b** under mild conditions.

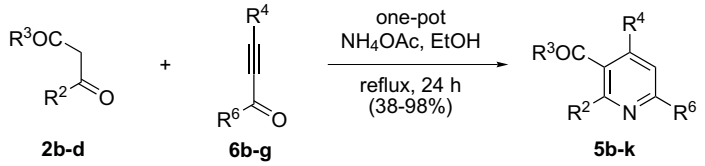
In order to investigate the scope of this reaction, a range of different 1,3-dicarbonyl compounds **2b–e** and alky-

Table 1. Optimizing the one-pot synthesis of ethyl 2-methyl-6-phenylpyridine-3-carboxylate **5b**

Entry	Ratio of **6b/2b**	NH_4OAc equivalents[a]	Temperature	Time (h)	Product (Yield[b] %)
1	0.6	5	Room temperature	72	**4b** (70) and **5b** (23)
2	1.0	2	Reflux	24	**3b** and **5b** (1:1)
3	1.0	4	Reflux	24	**3b** and **5b** (1.4:1)
4	1.0	10	Reflux	24	**5b** (89)
5	0.6	10	Reflux	24	**5b** (95)
6	1.7	10	Reflux	24	**5b** (91)

[a] Equivalents of NH_4OAc with respect to β-ketoester **2b**.
[b] Isolated yield after purification on silica.

Table 2. Examining the scope of a one-pot three-component reaction for the synthesis of pyridines **5b–k**



2b-d **6b-g** **5b-k**

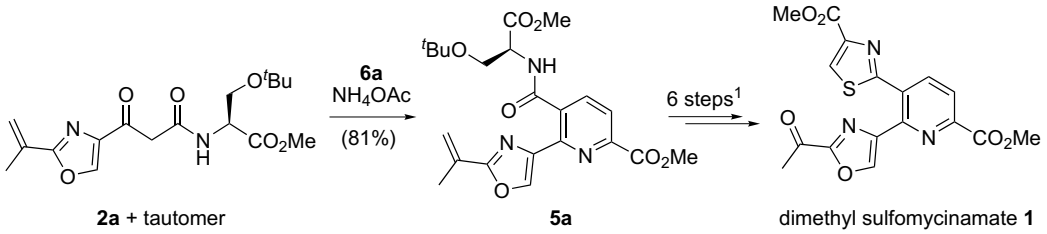
Entry	1,3-Dicarbonyl compound **2**	Alkynone **6**	R^2	R^3	R^4	R^6	NH_4OAc equivalents[a]	Product	Yield[b] (%)
1	**2b**	**6b**	Me	OEt	H	Ph	10	**5b**	95[c]
2	**2b**	**6c**	Me	OEt	H	4′-C_6H_4Cl	10	**5c**	84[c]
3	**2b**	**6d**	Me	OEt	H	4′-C_6H_4OMe	10	**5d**	90[c]
4	**2b**	**6e**	Me	OEt	Et	Me	10	**5e**	38
5	**2b**	**6f**	Me	OEt	TMS	Me	1	**5f**	90[d]
6	**2b**	**6f**	Me	OEt	TMS	Me	10	**5f**	90[d]
7	**2b**	**6g**	Me	OEt	Ph	Me	1	**5g**	51
8	**2c**	**6b**	Me	O^{t}Bu	H	Ph	10	**5h**	89
9	**2c**	**6e**	Me	O^{t}Bu	Et	Me	1	**5i**	71
10	**2c**	**6e**	Me	O^{t}Bu	Et	Me	10	**5i**	63
11	**2c**	**6f**	Me	O^{t}Bu	TMS	Me	1	**5j**	98[d]
12	**2d**	**6b**	Me	NH_2	H	Ph	1	**5k**	98

[a] Equivalents of NH_4OAc with respect to 1,3-dicarbonyl compound **2**.
[b] Isolated yield of pyridine **5** after purification on silica.
[c] An excess (1.7 equiv) of the β-ketoester **2** was employed.
[d] Only protodesilylated pyridine ($R^4 = H$) was produced.

nones **6b–g** were heated in ethanol at reflux in the presence of one or 10 equiv of ammonium acetate. In most experiments (Table 2), pyridine **5b–k** was generated in moderate to excellent yield (entries 1–12, 38–98% yield) as the only regioisomeric product. When 4-(trimethylsilyl)but-3-yn-2-one **6f** was used, only protodesilylated pyridines **5f** and **5j** were obtained. Unfortunately, reactions carried out using a mixture of ethyl benzoylacetate **2e** ($R^2 = Ph$), ammonium acetate and 1-arylprop-2-ynones **6b–d** did not give the desired pyridines and instead produced the corresponding enamine, ethyl 3-amino-3-phenylpropenoate, and a number of side products with degradation of the alkynone. In spite of this limitation, the reaction was successful for a wide variety of substrates (entries 1–12), and constitutes a mild method for the synthesis of polysubstituted pyridines **5b–k**.

Having established a one-pot three-component condensation method that operates under mild conditions, this methodology was applied to the synthesis of pyridine **5a**, the acid-sensitive intermediate in our total synthesis of dimethyl sulfomycinamate **1**. Although the three-component reaction had failed for ethyl benzoylacetate **2e**, the reaction of β-ketoamide **2a** (in equilibrium with its enol tautomer) prepared by our established route[1] with methyl 4-(trimethylsilyl)-2-oxobut-3-ynoate **6a** in the presence of 10 equiv of ammonium acetate was successful and gave pyridine **5a** in 81% yield (Scheme 4).[9] Employing this new multistep process, the total synthesis of dimethyl sulfomycinamate **1** is now complete in only 12 preparative steps and proceeds in 9% overall yield.

In conclusion, we have developed a novel one-pot three-component condensation for the synthesis of pyridines that combines a 1,3-dicarbonyl compound, ammonia and an alkynone without the use of an additional acid catalyst. The resulting polysubstituted pyridines are isolated in modest to excellent yield and as single regioisomers. The advantages that this methodology offers, in particular for the synthesis of acid-sensitive targets, have been highlighted by its application in the total synthesis of dimethyl sulfomycinamate **1** and now will be extended to prepare components of other thiopeptide antibiotics.



2a + tautomer **5a** dimethyl sulfomycinamate **1**

Scheme 4. Synthesis of pyridines **5a** under mild conditions by a one-pot three-component condensation reaction.[9]

Acknowledgements

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8. In a typical procedure, a solution of ethyl acetoacetate **2b** (0.13 g, 1.0 mmol), 1-phenylprop-2-yn-1-one **6b** (80 mg, 0.6 mmol) and ammonium acetate (0.77 g, 10.0 mmol) in ethanol (10 mL) was stirred at reflux for 24 h, allowed to cool and evaporated in vacuo. The residue was partitioned between saturated aqueous sodium hydrogencarbonate solution (30 mL) and ethyl acetate (30 mL) and the aqueous layer was further extracted with ethyl acetate (20 mL). The combined organic extracts were washed sequentially with saturated aqueous sodium hydrogencarbonate solution (20 mL) and brine (20 mL), dried (Na_2SO_4) and evaporated in vacuo. Purification by column chromatography on silica, eluting with dichloromethane–light petroleum (1:1) gave pyridine **5b** (0.14 g, 95%), as a pale yellow solid whose characterization data agreed with literature reports (Ref. 4).
9. A solution of β-ketoamide **2a** (35 mg, 0.1 mmol), methyl 4-(trimethylsilyl)-2-oxobut-3-ynoate **6a** (49 mg, 0.25 mmol) and ammonium acetate (77 mg, 1.0 mmol) in methanol (10 mL) was stirred at reflux for 5 h, allowed to cool and evaporated in vacuo. The residue was partitioned between saturated aqueous sodium hydrogencarbonate solution (5 mL) and ethyl acetate (8 mL) and the aqueous layer was further extracted with ethyl acetate (5 mL). The combined organic extracts were washed sequentially with saturated aqueous sodium hydrogencarbonate solution (5 mL) and brine (5 mL), dried (Na_2SO_4) and evaporated in vacuo. Purification by column chromatography on silica, eluting with ethyl acetate–light petroleum (2:1) gave pyridine **5a** (36 mg, 81%), as a pale yellow oil whose characterization data agreed with the literature (Ref. 1).