Pergamon

Tetrahedron Letters 43 (2002) 8331–8334

TETRAHEDRON LETTERS

A new one-step synthesis of pyridines under microwave-assisted conditions

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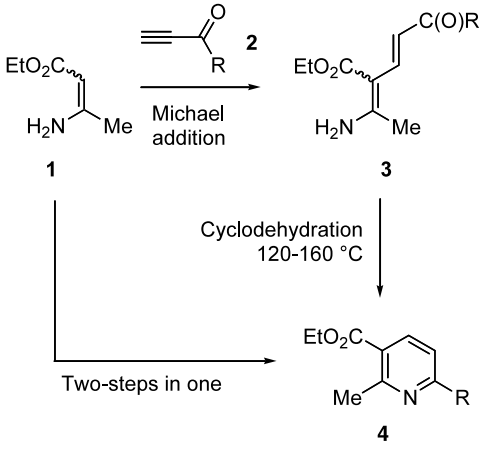
Received 22 July 2002; accepted 13 September 2002

Abstract—Tri- or tetrasubstituted pyridines are prepared by microwave irradiation of ethyl β-aminocrotonate and various alkynones in a single synthetic step and with total control of regiochemistry. This new one-pot Bohlmann–Rahtz procedure conducted at 170°C in a self-tunable microwave synthesiser gives superior yields to similar experiments conducted using conductive-heating techniques in a sealed tube and can be carried out in the presence of a Brønsted or Lewis acid catalyst. © 2002 Published by Elsevier Science Ltd.

In recent years, the use of microwave dielectric heating in synthetic chemistry has emerged as a valuable alternative to conventional conductive heating methods.[1] With no direct contact between the chemical reactants and the energy source, microwave-assisted chemistry has been heralded as being more efficient, in terms of the energy used, capable of providing faster heating rates and able to improve reaction rates and efficiencies. With many possible benefits and as a result of improvements in instrumentation, with the advent of dedicated ovens for synthesis that focus microwaves in a monomodal cavity, the development of new reproducible microwave-assisted procedures has been a popular area of chemistry of late.[2]

The Bohlmann–Rahtz synthesis of trisubstituted pyridines **4**, from ethyl β-aminocrotonate **1** and an ethynyl ketone **2**, was first reported in 1957[3] and has since found application in the preparation of the modified oxazole–thiazole–pyridine core of the promothiocin antibiotics,[4–6] the synthesis of novel heterocyclic substituted α-amino acids[7] and the transformation of 1,6-diaminopyrimidin-4-one and uracil derivatives to pyrido[2,3-*d*]pyrimidines.[8,9] This high-yielding reaction proceeds via dienone intermediate **3**, formed by Michael addition of enamine **1** and alkynone **2**, that is isolated and heated to high temperatures to effect cyclodehydration to pyridine **4** in a two-step procedure (Scheme 1). We have developed a number of methods to effect this transformation in a single synthetic step, and at a lower reaction temperature, using either a Brønsted or Lewis acid catalyst,[10,11] and applied this new methodology to the synthesis of heterocycles containing the tetrasubstituted pyridine motif.[12] We now wish to report a new and extremely simple method to facilitate this transformation in only 20 min using microwave irradiation, which proceeds in good yield and with total control of regiochemistry.

A solution of ethyl β-aminocrotonate **1** and an excess of phenylpropynone **2a** (R = Ph) (Scheme 2) was stirred in toluene or DMSO, solvents that have been shown to promote Michael addition in traditional Bohlmann–Rahtz reactions in previous studies within the group,[12] at 170°C by irradiating initially at 150 or 160 W using a self-tunable microwave synthesiser (Table 1). The reaction conducted in toluene was found to be sluggish



Scheme 1. The two-step Bohlmann–Rahtz pyridine synthesis.

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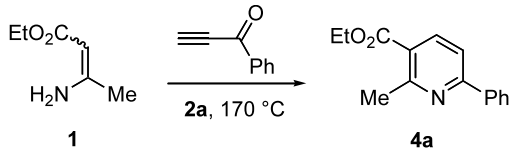
PII: S0040-4039(02)01975-5



1 4a

Scheme 2. One-step Bohlmann–Rahtz synthesis of pyridine **4a**.

Table 1. Reaction under microwave-assisted conditions

Entry	Solvent	Time (min)	Yield%[a]
1	Toluene	90	76
2	Dimethyl sulfoxide	20	87
3	Toluene–$ZnBr_2$ (15 mol%)	10	80
4	Toluene–acetic acid (5:1)	10	98
5	Neat	20	84

[a] Isolated yield after purification by column chromatography on silica.

at best, providing pyridine **4a** in 76% yield after 90 min following purification by column chromatography on silica (entry 1). The use of a more polar solvent, DMSO that can couple more efficiently with the microwave radiation, resulted in a more rapid reaction, Michael addition and spontaneous cyclodehydration complete after 20 min, to give pyridine **4a** in 87% yield (entry 2).[13] Reactions conducted in toluene were accelerated dramatically by the presence of zinc(II) bromide (15 mol%) as a Lewis acid catalyst providing the product in 80% yield after 10 min at 170°C (entry 3). However, the optimum conditions for this transformation employed acetic acid as a Brønsted acid catalyst. After stirring for 10 min in a solution of toluene–acetic acid (5:1) at 170°C (160 W), pyridine **4a** was isolated in 98% yield following purification on silica; the highest ever yield reported for a Bohlmann–Rahtz reaction to date (entry 4). Finally, in a bid to explore solventless reaction conditions, a mixture of enamine **1** and alkynone **2a** was irradiated at 170°C (150 W) for 20 min to give the product in 84% yield (entry 5). Although this final experiment was not as efficient, the use of solventless reaction conditions does have some intrinsic ecological and chemical value.[2c]

All of the microwave-assisted experiments facilitated both Michael addition and cyclodehydration in a single synthetic step and had generated the target pyridine **4a** as a single regioisomer. Although the use of microwave irradiation had been successful, it was decided to investigate if traditional conductive heating methods could facilitate a similar one-pot transformation. The reaction of ethyl β-aminocrotonate **1** and phenylpropynone **2a** (Scheme 2) was repeated in a range of different solvents in a sealed tube using an oil bath as an external heat source (Table 2) and the results were compared with the microwave-assisted reactions (Table 1). In almost all of the experiments, the microwave-assisted conditions gave the product in a higher yield, of particular relevance for the reaction conducted in toluene in the

Table 2. Reaction in a sealed tube using conventional heating techniques

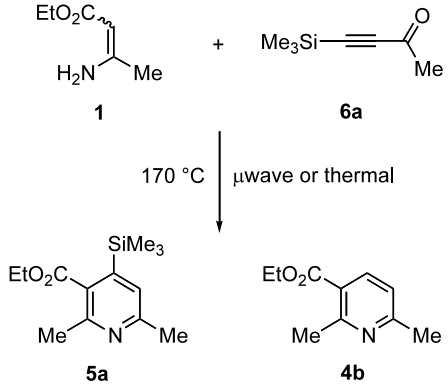
Entry	Solvent	Time (min)	Yield%[a]
1	Toluene	90	54
2	Dimethyl sulfoxide	20	80
3	Toluene–$ZnBr_2$ (15 mol%)	10	33
4	Toluene–acetic acid (5:1)	10	95
5	Neat	20	93

[a] Isolated yield after purification by column chromatography on silica.

presence of 15 mol% of zinc(II) bromide (entry 3), although in many instances comparable yields were obtained (entries 2, 4 and 5). Only the solventless reaction (entry 5) gave superior results in a Carius tube, making the microwave irradiation procedure the method of choice for a rapid one-pot entry to trisubstituted pyridines.

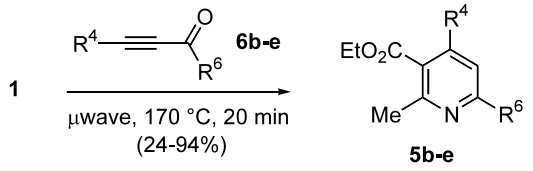
With successful experimental procedures established for the one-pot synthesis of pyridines, the heteroannulation of ethyl β-aminocrotonate **1** and 4-(trimethylsilyl)but-3-yn-2-one **6a** was investigated under microwave-assisted conditions and using conventional heating techniques (Scheme 3). This alkynone has been shown to undergo spontaneous desilylation under traditional Bohlmann–Rahtz conditions,[12] giving trisubstituted pyridine **4b** in preference to tetrasubstituted pyridine **5a**, and so these experiments would explore the scope of our new one-pot reactions.

When a mixture of ethyl β-aminocrotonate **1** and (trimethylsilyl)butynone **6a** was irradiated at 170°C in a



1 6a 5a 4b

Scheme 3. One-pot heteroannulation of enamine **1** and butynone **6a**.



5b-e

Scheme 4. One-pot heteroannulation of enamine **1** and alkynones **6b–e**.

Table 3. Comparison of microwave-assisted conditions and conventional heating techniques for heteroannulation of enamine **1** and butynone **6a**

Entry	Solvent	Time (min)	Carius tube product	Carius tube yield%[a]	Microwave product	Microwave yield%[a]
1	DMSO	20	**4b**	21	**4b**	62
2[b]	DMSO	20	**4b**	8	**4b**	69
3	Toluene–$ZnBr_2$ (15 mol%)	10	**5a**	27	**5a**	60
4	Neat	20	None	0	**5a**	10
5	Toluene–acetic acid (5:1)	10	**4b**, **5a** (1:2.8)	29	**4b**, **5a** (1:2.8)	25

[a] Isolated yield after purification by column chromatography on silica.
[b] A one-fold excess of enamine **1** was used.

range of different solvents (Table 3) pyridine **5a** or **4b** was formed, depending upon the solvent and catalyst employed. These transformations proved to be less efficient than the reactions of phenylpropynone **2a** (Table 1) and the experiment conducted under solventless conditions (entry 4, Table 3) gave only a very meagre yield of pyridine **5a**. However, in comparison with experiments conducted using conventional heating techniques, which were extremely inefficient with alkynone **6a**, the microwave-assisted reactions were a success—the optimum experimental conditions[13] involving irradiation of reagents in DMSO for 20 min to give trisubstituted pyridine **4b** in 69% yield, desilylation occurring spontaneously throughout the course of the reaction.

In order to test the microwave-assisted reaction that had performed the best overall with the two alkynones, **2a** and **6a**,[13] ethyl β-aminocrotonate **1** was reacted with four other alkynyl ketones, **6b–e** by irradiating a solution of the reagents in DMSO at 170°C for 20 min (Scheme 4). In all of the experiments, a single regioisomeric pyridine was formed (Table 4). Although the efficiency of the reaction of enamine **1** and phenylbutynone **6b** was low (entry 1), this alkynone has been noted to be problematic in similar heteroannulation reactions.[10] The other microwave-assisted reactions gave pyridine products **5c–e** in good yields after purification by column chromatography (entries 2–4), illustrating that the one-pot microwave-assisted Bohlmann–Rahtz reaction represents a simple and highly-expedient route to tri- and tetrasubstituted pyridines.

In conclusion, we have explored two new methods for the synthesis of pyridines using either microwave irradiation or conductive heating techniques in a sealed tube to facilitate the rapid Michael addition–cyclodehydration of an enamine and alkynone in a single preparative step and with total control of regiochemistry.

Acknowledgements

We are grateful to CEM (Microwave Technology) Ltd for assistance, Dr. Justin Bower of RiboTargets Ltd for valuable discussions and the EPSRC Mass Spectrometry Service, Swansea, for high resolution mass spectra.

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Table 4. Microwave-assisted synthesis of pyridines **5b–e**

Entry	Alkynone	R^4	R^6	Product	Yield%[a]
1	**6b**	Ph	Me	**5b**	24
2	**6c**	Et	Me	**5c**	94
3	**6d**	H	4′-C_6H_4Cl	**5d**	75
4	**6e**	H	4′-C_6H_4OMe	**5e**	66

[a] Isolated yield after purification by column chromatography on silica.

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13. In a typical procedure, a solution of ethyl β-aminocrotonate **1** (0.26 g, 2.0 mmol) and 1-phenylprop-2-yn-1-one **2a** (0.13 g, 1.0 mmol) in DMSO (3.0 ml) in a sealed pressure-rated reaction tube (10 ml) was irradiated at 170°C (initial power 150 W) for 20 min in a self tuning single mode CEM Discover™ Focused Synthesiser. The mixture was cooled rapidly to room temperature, by passing compressed air through the microwave cavity for 5 min, poured into water (15 ml) and extracted with ethyl acetate (8 ml). The aqueous layer was further extracted with ethyl acetate (8 ml) and the organic extracts were combined, washed successively with saturated aqueous sodium hydrogen carbonate solution (10 ml) and brine (10 ml), dried (Na_2SO_4) and evaporated in vacuo. Purification by flash chromatography on silica, eluting with dichloromethane-light petroleum (1:1), gave *ethyl 2-methyl-6-phenylpyridine-3-carboxylate* **4a** as a pale yellow solid (0.21 g, 87%); spectroscopic properties agreed with literature data according to Ref. 12.