# One-Pot Synthesis of Pyridines or Pyrimidines by Tandem Oxidation-Heteroannulation of Propargylic Alcohols

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*Received 5 June 2003*

**Abstract:** Pyridines and pyrimidines are prepared in a single step from propargylic alcohols by in situ oxidation with *o*-iodoxybenzoic acid or manganese dioxide and reaction with enamines or amidines, respectively, under either thermal or microwave-assisted conditions in a new one-pot tandem oxidation-heteroannulation procedure. The reaction of a β-ketoester, propargylic alcohol and ammonium acetate, with in situ oxidation, constitutes a highly facile three-component reaction for the synthesis of pyridines that accomplishes four distinct synthetic operations in one-pot, good yield and with total regiocontrol.

**Key words:** heterocycles, pyridines, pyrimidines

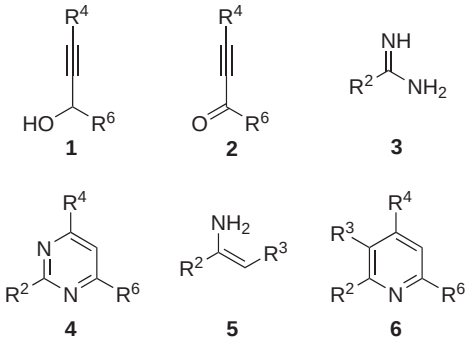
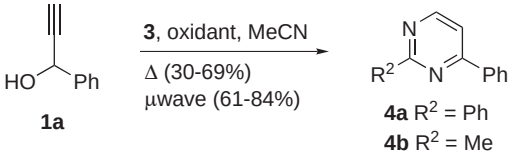



**Figure 1**

Facile one-pot transformations involving alcohol oxidation followed by in situ trapping of the resulting aldehyde have attracted considerable attention in recent years. Taylor has reported a number of tandem manganese dioxide mediated processes,[1] particularly in situ oxidation–Wittig methodology that avoids the need to isolate aldehyde intermediates that may be toxic, volatile or highly reactive. Similar procedures using a range of different oxidants, including *o*-iodoxybenzoic acid (IBX),[2] the Dess–Martin periodinane[3] and barium manganate,[4] have been shown to be successful in a number of tandem processes for rapid access to different synthetic targets. Following on from our work on the development of new heteroannulation procedures[5] and multiple-component reactions,[6] we set out to establish a whole new type of tandem process that was appropriate for the rapid synthesis of pyridines **6** and pyrimidines **4**, thus preparing different heteroaromatic building blocks[7] from a single propargylic alcohol subset **1** by in situ oxidation to alkynone **2** and subsequent heteroannulation with a *bis*-nucleophile such as amidine **3** or enamine **5** in a single preparative step (Figure 1).

In order to examine if the tandem oxidation–heteroannulation of propargylic alcohols was viable as a new one-pot method for the synthesis of nitrogen-containing heterocycles, the oxidation of 1-phenyl-2-propyn-1-ol (**1a**) was investigated under microwave-assisted conditions that were successful in preliminary studies for the heteroannulation of alkynones **2** and amidines **3**.[8] However, irradiating a mixture of 1-phenyl-2-propyn-1-ol (**1a**) and manganese dioxide in wet acetonitrile at 100 °C, 120 °C or 140 °C in a self-tunable CEM Discover microwave synthesizer failed to generate more than a trace (typically less than 5%) of the oxidized product 1-phenyl-2-propynone (**2a**) even after 1 hour irradiation time, making the prospect of establishing an efficient one-pot microwave-assisted process unlikely.

In spite of this set back, we decided to try a simple tandem oxidation–heteroannulation reaction under either conductive or microwave heating regardless, in order to establish if difficulties encountered in propargylic alcohol oxidation were reflected in the overall efficiency of the process. Two different oxidants, manganese dioxide and IBX, were investigated for the one-pot oxidation–heteroannulation of 1-phenyl-2-propyn-1-ol (**1a**) with benzamidine or acetamidine, **3a** or **3b** respectively (Scheme 1). Surprisingly, when the reaction was carried out in the presence of amidine **3a** or **3b**, pyrimidines **4a**,**b** were generated in up to 84% yield, the reaction under microwave-assisted conditions with manganese dioxide, irradiating at 120 °C over 40 minutes, proving to be the most efficient (Table 1).[9]




**Scheme 1** Tandem oxidation–heteroannulation of 1-phenyl-2-propyn-1-ol (**1a**) in the synthesis of pyrimidines **4a**,**b**

A one-pot synthesis of pyrimidines from amidines and propargylic alcohols by a coupling–isomerization–cyclocondensation sequence has been reported by Müller[10] but our new route is quicker, simpler and proceeds under

Synlett 2003, No. 10, Print: 05 08 2003.
Art Id.1437-2096,E;2003,0,10,1443,1446,ftx,en;D12803ST.pdf.

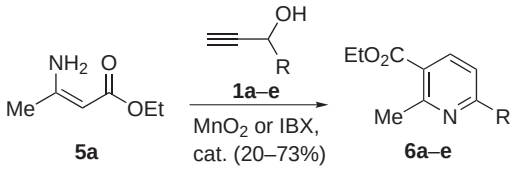
**Table 1** Effect of Substrate, Oxidant and Heating Method

| Entry | Product | Oxidant | Yield[a] (%) | Yield (%)[b] |
|---|---|---|---|---|
| 1 | **4a** | IBX | 30 | 80 |
| 2 | **4a** | $MnO_2$ | 69 | 84 |
| 3 | **4b** | IBX | 54 | 61 |
| 4 | **4b** | $MnO_2$ | 56 | 65 |

[a] Isolated yield after heating at reflux and purification on silica.
[b] Isolated yield after microwave irradiation at 120 °C for 40 min and purification on silica.

much more facile conditions, representing the first example of a tandem oxidation–heteroannulation reaction using propargylic alcohols to access these heterocyclic targets.

In order to extend these findings and establish a new one-pot method for the synthesis of pyridine heterocycles, propargylic alcohol **1a** (R = Ph) was reacted with ethyl β-aminocrotonate (**5a**) in the presence of IBX or manganese dioxide (Scheme 2). Pyridine formation from 1-phenyl-prop-2-yn-1-one (**2a**) traditionally requires very high temperatures[11] and so these tandem processes were conducted in the presence of either a Brønsted or Lewis acid as a catalyst to facilitate cyclodehydration to the target heterocycle.[5a] A range of conditions were investigated (Table 2) and although in situ oxidation with $MnO_2$ and IBX gave comparable yields, the IBX mediated process was found to be superior for the synthesis of pyridine **6a**. Optimum conditions involved heating enamine **5a** and a one-fold excess of both the propargylic alcohol **1a** and IBX in DMSO–acetic acid (5:1) at 65 °C overnight to give pyridine **6a** in 70% isolated yield after purification on silica.[12]




**Scheme 2** Tandem oxidation–heteroannulation of propargylic alcohols **1a**–**e** in the synthesis of pyridines **6a**–**e**

With successful conditions established for the tandem process, a range of propargylic alcohols **1a-e** was submitted to in situ oxidation–heteroannulation with ethyl β-aminocrotonate (**5a**) mediated by IBX in DMSO–acetic acid (5:1) at 65 °C.[12] It was found that the efficiency of the reaction was highly dependent upon the nature of the propargylic alcohol, pyridines **6a-e** generated in between 20% and 73% yield (Table 3). Although the efficiency of the transformation was quite variable, in most instances it nonetheless compared quite favourably with traditional methods involving three separate preparative steps.[5a] It was postulated that the moderate yield of the one-pot process was a consequence of the oxidative degradation of

**Table 2** Optimizing the Synthesis of Pyridine **6a** by Tandem Oxidation–Heteroannulation of 1-Phenyl-2-propyn-1-ol (**1a**)

| Oxidant | **5a**:**1a**: Oxidant | Conditions | Yield (%)[a] |
|---|---|---|---|
| IBX | 1:1:1 | DMSO–HOAc (5:1), 65 °C | 54 |
| **IBX** | **1:2:2** | **DMSO–HOAc (5:1), 65 °C** | **70** |
| IBX | 1:2:2 | DMSO–HOAc (5:1), 55 °C | 69 |
| IBX | 1:2:4 | DMSO–HOAc (5:1), 65 °C | 24 |
| $MnO_2$ | 1:2:10 | PhMe–HOAc (5:1), 50 °C | 45 |
| $MnO_2$ | 1:2:10 | $CHCl_3$–HOAc (5:1), reflux | 23 |
| $MnO_2$ | 1:2:10 | PhMe, $ZnBr_2$ (20 mol%), reflux | 64 |

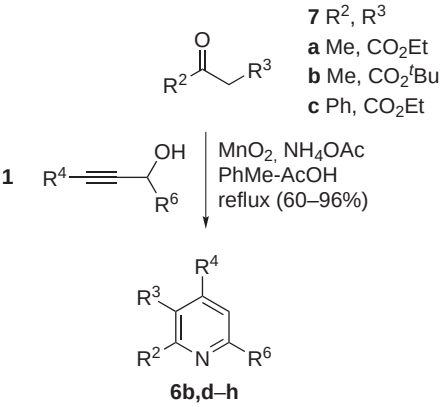
[a] Isolated yield after purification on silica.

**Table 3** One-Pot Synthesis of Pyridines **6** Mediated by IBX[12]

| Entry | Alcohol **1** | Pyridine **6** | R | Yield (%)[a] |
|---|---|---|---|---|
| 1 | **1a** | **6a** | Ph | 70 |
| 2 | **1b** | **6b** | Me | 45 |
| 3 | **1c** | **6c** | Et | 20 |
| 4 | **1d** | **6d** | 4′-$C_6H_4Cl$ | 73 |
| 5 | **1e** | **6e** | 4′-$C_6H_4OMe$ | 53 |

[a] Isolated yield after purification on silica.

ethyl β-aminocrotonate (**5a**) under the reaction conditions. Thus, generating enamine **5** in situ by the condensation of a β-ketoester precursor and ammonia should reduce enamine degradation and furthermore establish a new and highly facile 3-component cyclocondensation route to these targets that affects four transformations in a single preparative step. When a range of propargylic alcohols **1**, β-ketoesters **7** and ammonium acetate was heated at reflux in toluene–acetic acid (5:1) in the presence of manganese dioxide (Scheme 3), pyridines **6b**,**d**–**h** were formed directly in up to 96% yield (Table 4) and with total regiocontrol.




**Scheme 3** New three-component synthesis of pyridines **6** from propargylic alcohols **1** and β-keto esters **7**

**Table 4** Variation in Yield Using Different Propargylic Alcohols **1** and β-Ketoesters **7**

| **1** | **7** | **6** | $R^2$ | $R^3$ | $R^4$ | $R^6$ | Yield (%)[a] |
|---|---|---|---|---|---|---|---|
| **1b** | **7a** | **6b** | Me | $CO_2Et$ | H | Me | 66 |
| **1d** | **7a** | **6d** | Me | $CO_2Et$ | H | 4′-$C_6H_4Cl$ | 96 |
| **1e** | **7a** | **6e** | Me | $CO_2Et$ | H | 4′-$C_6H_4OMe$ | 85 |
| **1f** | **7b** | **6f** | Me | $CO_2$-*t*-Bu | Et | Me | 60 |
| **1a** | **7b** | **6g** | Me | $CO_2$-*t*-Bu | H | Ph | 73 |
| **1d** | **7c** | **6h** | Ph | $CO_2Et$ | H | 4′-$C_6H_4Cl$ | 63 |

[a] Isolated yield after purification on silica.

This highly facile one-pot process[13] presumably proceeds by in situ oxidation of propargylic alcohol **1** and simultaneous enamine formation, followed by Michael addition, double bond isomerization under the acidic reaction conditions and subsequent cyclodehydration (Scheme 4), although the involvement of an alternative mechanistic pathway that proceeds via Michael addition of the β-ketoester **7** and alkynone **2** prior to condensation with ammonia cannot be discounted.

In conclusion, the in situ oxidation–heteroannulation of propargylic alcohols with either IBX or manganese dioxide provides a new one-pot tandem route to nitrogen-containing heteroaromatic building blocks, affecting up to four separate synthetic transformations in a single preparative step. Many of these heteroannulation reactions proceed in good yield and, for the synthesis of pyridines, with total regiocontrol from either enamine or β-ketoester precursors.

## Acknowledgment

We thank Pfizer Ltd and the BBSRC for their generous support, and the EPSRC Mass Spectrometry Service, Swansea for high-resolution spectra.

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(9) **Typical Procedure for the One-Pot Synthesis of Pyrimidines 4.** A mixture of 1-phenyl-2-propyn-1-ol (**1a**) (0.13 g, 1.0 mmol), benzamidine hydrochloride salt (**2a**·HCl) (0.19 g, 1.2 mmol), $Na_2CO_3$ (0.25 g, 2.4 mmol) and activated $MnO_2$ (0.87 g, 10 mmol) in acetonitrile (5 mL) was irradiated for 40 min in a self-tunable CEM microwave synthesizer at 120 °C (initial power 90 W) and then allowed to cool. The solution was filtered through Celite® and evaporated in vacuo. Purification by flash chromatography on silica gave pure 2,4-diphenylpyrimidine (**3a**)[8] as a pale yellow solid (0.19 g, 84%).

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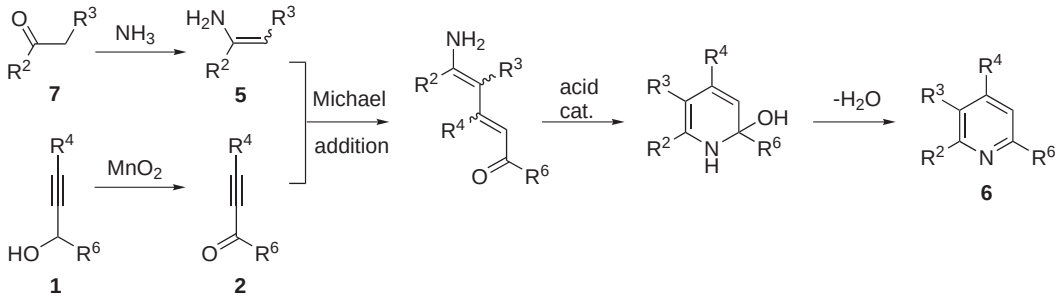
(12) **Typical Procedure for the One-Pot Synthesis of Pyridines 6 from Enamines 5.** A solution of IBX (0.56 g, 2.0 mmol) in DMSO–HOAc (5:1) (18 mL) was stirred at 65 °C until homogeneous. A solution of 1-phenyl-2-propyn-1-ol (**1a**) (0.26 g, 2.0 mmol) and ethyl β-aminocrotonate (**5a**) (0.13 g, 1.0 mmol) in DMSO (1 mL) was added and the resulting solution was stirred at 65 °C overnight. Water (10 mL) was added and the mixture was stirred for 10 min, allowed to cool, diluted with water (40 mL) and extracted with EtOAc (2 × 30 mL). The organic extracts were




**Scheme 4** Proposed mechanistic course of the one-pot three-component synthesis of pyridines **6** from propargylic alcohols **1** and β-ketoesters **7**

combined, washed sequentially with sat. aq $NaHCO_3$ solution (20 mL) and brine (20 mL), dried ($Na_2SO_4$) and evaporated in vacuo. Purification by flash chromatography on silica gave pure ethyl 2-methyl-6-phenylpyridine-3-carboxylate (**6a**)[5a] as a pale yellow solid (169 mg, 70%).

(13) **Typical Procedure for the One-Pot Synthesis of Pyridines 6 from β-Ketoesters 7.** A solution of ethyl acetoacetate (**7a**) (39 mg, 0.3 mmol), 1-(4-chlorophenyl)prop-2-yn-1-ol (**1d**)[5a] (100 mg, 0.6 mmol), ammonium acetate (0.46 g, 6.0 mmol)) and activated $MnO_2$ (0.52 g, 6.0 mmol) in toluene–glacial acetic acid (5:1) (5 mL) was heated at reflux overnight. The mixture was allowed to cool, filtered through Celite®, partitioned between sat. aq $NaHCO_3$ solution (30 mL) and EtOAc (30 mL) and the aqueous layer was further extracted with EtOAc (20 mL). The combined organic layers were washed sequentially with sat. aq $NaHCO_3$ solution (20 mL) and brine (20 mL), dried ($Na_2SO_4$) and evaporated in vacuo. Purification by flash chromatography on silica gave pure pyridine **6d**[5a] as a pale yellow solid (80 mg, 96%).