# Base and copper(I) catalyzed Mannich, alkyne hydroamination cascades for the direct synthesis of 2-methylenepyrrolidines†

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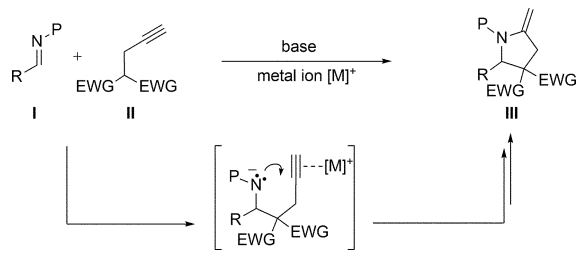
*Received (in Cambridge, UK) 20th March 2009, Accepted 11th May 2009*
*First published as an Advance Article on the web 1st June 2009*
**DOI: 10.1039/b905629g**

**An efficient, simple-to-perform, one-pot reaction cascade to 2-methylenepyrrolidines from *p*-toluenesulfonyl protected imines and propargylated malonates under a combination of base and copper(I) catalysis is reported.**

The desire for practically simple and synthetically efficient organic transformations has led to the development of many innovative strategies, concepts and methodologies. One attractive approach is to employ reaction cascades. These multi-step reaction sequences significantly improve the overall yield and resource efficiency compared to one-reaction, one-pot approaches.[1] A myriad of elegant cascade sequences catalyzed either by single chemical entities[2] or by multiple, mutually compatible catalysts have facilitated some elegant transformations of relatively simple starting materials to more complex molecular architectures. One area in particular within the cascade field that has witnessed significant interest over the past decade is that of additions to alkyne functionality,[3] more specifically, cascade reactions involving alkyne functionality, wherein 'soft' transition metal ions are employed to provide the necessary activation to trigger the process.[4] To this end our group recently reported a one-pot, multi-step reaction cascade to cyclopentenes from α,β-unsaturated ketones and propargylated carbon acids using a combination of pyrrolidine and copper ion catalysts.[5]




**Scheme 1** Concept of the Mannich, alkyne hydroamination cascade for the direct synthesis of 2-methylenepyrrolidines.

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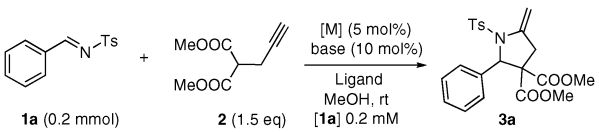
† Electronic supplementary information (ESI) available: Experimental procedures and spectral data for compounds **3–5**. See DOI: 10.1039/b905629g

As a new development of this research herein we report our studies leading to a two component Mannich, alkyne hydroamination cascade[6] for the direct synthesis of 2-methylenepyrrolidines. The outline design of the cascade is shown in Scheme 1. Initially, under base catalysis it was envisaged that a propargylated carbon acid should undergo addition (a Mannich reaction) to a suitably protected and activated imine resulting in the formation of a protected β-amino ester product. This adduct would then be poised to react with the pendent alkyne group when suitably activated by a 'soft' alkynophilic metal ion complex. Protodemetallation should then afford the product and release the catalysts back into the cycle. In part, this proposed cascade is supported by the work of Balme[7c] and co-workers who have described domino aza Michael, metal-catalyzed cycloisomerization reactions leading to 3-methylenepyrrolidines.[7]

Ours would bring together new components at different stages and thus result in the production of isomeric 2-methylenepyrrolidines through initial carbon–carbon bond

**Table 1** Proof of principle, catalyst identification and reaction optimization studies




**1a** (0.2 mmol) **2** (1.5 eq) **3a**

| Entry | Base | Metal/ligand | Time/h | Yield[a] (%) |
|---|---|---|---|---|
| 1 | BEMP | — | 48 | 0 |
| 2 | BEMP | $Au(PPh_3)Cl$, AgOTf | 16 | 27 |
| 3 | BEMP | AgOTf | 18 | 24 |
| 4 | BEMP | $CuOTf/PPh_3$ | 16 | 69 |
| 5 | BEMP | $Cu(OTf)_2/PPh_3$ | 16 | 68 |
| 6 | BEMP | $Cu(OTf)_2$ | 24 | 0 |
| 7 | BEMP | CuOTf | 24 | 0 |
| 8 | BEMP | CuI | 24 | 0 |
| 9 | BEMP | $Yb(OTf)_3$ | 24 | 0 |
| 10 | BEMP | $RuCl_2(PPh_3)_3$ | 24 | 0 |
| 11 | BEMP | $(PPh_3)_2NiCl_2$ | 24 | 0 |
| 12 | BEMP | $Zn(OTf)_2$ | 24 | 0 |
| 13 | BEMP | $PdCl_2(PPh_3)_2$ | 24 | 0 |
| 14 | PS-BEMP | $Cu(OTf)_2/PPh_3$(20 mol%) | 24 | 65 |
| 15 | DBU | $Cu(OTf)_2/PPh_3$ (20 mol%) | 31 | 34 |
| 16 | DABCO | $Cu(OTf)_2/PPh_3$ (20 mol%) | 36 | Trace |
| 17 | $Et_3N$ | $Cu(OTf)_2/PPh_3$ (20 mol%) | 24 | Trace |
| 18 | NaOAc | $Cu(OTf)_2/PPh_3$ (20 mol%) | 27 | 0 |
| 19 | NaOMe | $Cu(OTf)_2/PPh_3$ (20 mol%) | 27 | 49 |
| 20 | KO$^t$Bu | $Cu(OTf)_2/PPh_3$ (20 mol%) | 16 | 73 |
| 21 | KO$^t$Bu | $CuOTf\cdot\frac{1}{2}C_6H_6/PPh_3$ (15 mol%) | 16 | 74 |
| 22[b] | KO$^t$Bu | $CuOTf\cdot\frac{1}{2}C_6H_6/PPh_3$ (15 mol%) | 16 | 94 |

[a] Isolated yield after flash column chromatography. [b] [**1a**] 0.4 mM.

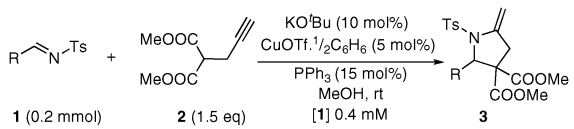
formation followed by hydroamination. Having direct experience of Mannich reactions using malonate pro-nucleophiles[8] we were confident of the reactivity match between the malonate functionality and the imine, however finding a catalyst combination that would allow this and the concomitant hydroamination remained the challenge.

Preliminary catalyst screening studies were performed using *p*-toluenesulfonyl imine **1a** and malonate **2** in methanol at room temperature. A range of base and metal ion catalyst combinations were screened for overall performance (reaction efficiency and rate) and the results are presented in Table 1. Various combinations of strong bases (organic or inorganic) and copper complexes were soon identified as effective for the process and additional screening revealed potassium *tert*-butoxide (10 mol%) and Cu(I)OTf benzene complex (5 mol%) in the presence of triphenylphosphine (15 mol%) in methanol at room temperature to be optimal for the cascade. With optimal conditions identified the scope of the reaction with respect to the imine substrate was then probed. The results are presented in Table 2.

A range of electron rich and electron poor aromatic and heteroaromatic toluenesulfonyl imines were good components in the cascade and yielded the desired 2-methylenepyrrolidine products in high yields in between 10 and 48 hours. A representative aliphatic imine (derived from butyraldehyde) also underwent the reaction albeit in lower yield (entry 17).[9] Interestingly, analogous *N*-Boc, *N*-phenyl, *N*-*p*-methoxyphenyl and *N*-*tert*-butyl sulfoxide imines did not afford the 2-methylenepyrrolidine cascade products under the same reaction conditions, and either unreacted starting materials or the Mannich addition product was isolated from the reaction mixture.

The proposed course of the reaction cascade (Scheme 2) begins with a rapid and reversible formation of the Mannich

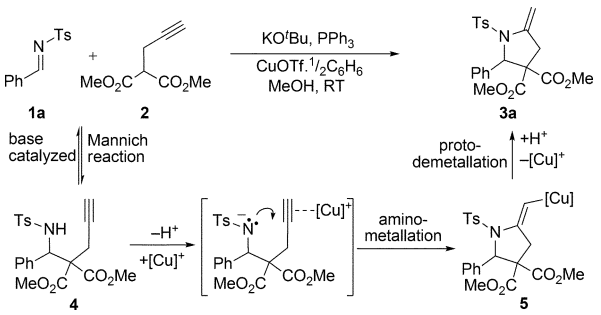
**Table 2** Scope of the Mannich, alkyne hydroamination cascade




**1** (0.2 mmol) **2** (1.5 eq) **3**

| Entry | R | Time/ h | 3 | Yield[a] (%) |
|---|---|---|---|---|
| 1 | Ph | 14 | **a** | 94 |
| 2 | *p*-$CH_3$Ph | 34 | **b** | 85 |
| 3 | *m*-$CH_3$Ph | 34 | **c** | 86 |
| 4 | *o*-$CH_3$Ph | 34 | **d** | 81 |
| 5 | *p*-$CH_3$OPh | 48 | **e** | 75 |
| 6 | *o*-$CH_3$OPh | 48 | **f** | 69 |
| 7 | *o*-FPh | 14 | **g** | 79 |
| 8 | *p*-CNPh | 14 | **h** | 91 |
| 9 | *p*-ClPh | 14 | **i** | 96 |
| 10 | *m*-ClPh | 14 | **j** | 89 |
| 11 | *o*-ClPh | 14 | **k** | 87 |
| 12 | *p*-$NO_2$Ph | 10 | **l** | 92 |
| 13 | *p*-BrPh | 14 | **m** | 85 |
| 14 | *o*-BrPh | 14 | **n** | 81 |
| 15 | 2-Furyl | 14 | **o** | 88 |
| 16 | 3-Pyridyl | 18 | **p** | 82 |
| 17 | *n*-Propyl | 24 | **q** | 32 |

[a] Isolated yield after flash column chromatography.

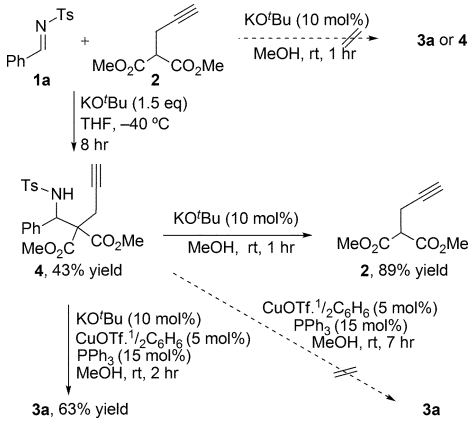



**Scheme 2** Proposed mechanistic pathway.

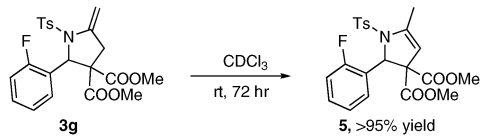
adduct under (alkoxide) base catalysis. This adduct with its acidic sulfonamide N–H and the tethered terminal alkyne group cyclizes under base and copper(I) catalysis to give a vinyl copper species which then undergoes protodemetallation in the methanolic solvent to give the observed 2-methylenepyrrolidine product.

Support for this proposed pathway comes from a number of experiments performed to probe the mechanism (Scheme 3). In the reaction of **1a** and **2**, omission of any added copper complex from the optimized reaction conditions resulted in the formation of neither Mannich product **4** nor 2-methylenepyrrolidine **3a**, and the propargyl malonate **2** was returned unreacted. However, in THF at –40 °C for 8 hours with 1.5 eq. of KO$^t$Bu the Mannich product **4** was the major reaction product. Subsequent treatment of **4** with KO$^t$Bu in methanol at room temperature resulted in degradation to the propargyl malonate **2**, presumably *via* retro-Mannich reaction. Treatment of **4** with Cu(I)OTf benzene complex and triphenylphosphine in the absence of any base resulted in no reaction. However, subjection of **4** to the standard cascade led to the production of the 2-methylenepyrrolidine product **3a**. This result supports the intermediacy of **4** in the reaction sequence and the need for both base and copper catalysts in the second stage of the cascade. The suggested *anti* addition of nitrogen and copper to the alkyne is in agreement with the results of Urabe and co-workers who isolated a single *Z*-stereoisomer in their CuI catalyzed intramolecular hydroamination study of a non-terminal alkyne.[10]

The 2-methylenepyrrolidines are the kinetic products in the reaction. This was readily demonstrated when **3g** was




**Scheme 3** Probing the mechanism.




**Scheme 4** Product isomerization studies.

dissolved in deuterochloroform and the sample left for 3 days. Essentially complete conversion to the *endo*-isomer **5** was observed (Scheme 4).

In summary, a mutually compatible combination of potassium *tert*-butoxide and CuOTf/$PPh_3$ catalysts have been identified that promote a two stage cascade to 2-methylene-pyrrolidine products from *N*-*p*-toluenesulfonyl protected imines and propargylated malonates. Initiated through a base catalyzed Mannich reaction, the β-amino ester product is poised to undergo aminocupration with the copper(I) activated alkyne. Subsequent protodemetallation afforded the 2-methylenepyrrolidine products in good yields for a wide range of aryl and heteroaryl *N*-*p*-toluenesulfonyl imines. Further work to uncover and develop new catalysis cascades is under investigation and the results will be reported in due course.

We thank the Universities UK, the University of Manchester, and AstraZeneca (studentship to TY) for support. We are grateful for the financial support of the National Natural Science Foundation of China (NSFC No. 20772051).

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