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A One Pot Synthesis of Various Pyrrolidines *via* a Tandem Michael Addition-Transition Metal-Catalysed Cyclisation Reaction.

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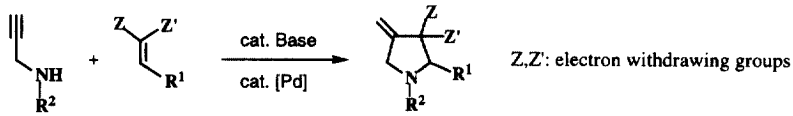
Abstract: A variety of substituted 3-methylene pyrrolidines may be obtained by reaction of propargyl amines with Michael acceptors in a single step catalysed by copper(I).

Keywords: propargyl amines, Michael addition, copper-catalysed cyclisation, 3-methylene pyrrolidines.

Five-membered nitrogen containing heterocycles are common subunits in many naturally occuring compounds displaying diverse and potent biological activities.[1] Numerous strategies for the synthesis of this functional moeity have been developed including intramolecular cyclisations involving radical,[2] anionic[3] or transition metal-catalysed[4] processes. However, the most effective strategy for the construction of these heterocycles is a one step synthesis involving two variable components.[5]

As part of our ongoing interest in new synthetic routes for heterocyclic synthesis,[6] we have recently described a new method for the preparation of a variety of highly functionalized 3-methylene tetrahydrofurans.[7] A palladium-mediated carbocyclisation is employed: intermolecular conjugate addition of a propargyl alcohol to a Michael acceptor is followed by attack of the resulting enolate upon the triple bond activated by coordination to palladium. An extension of this process to the synthesis of 3-methylene-pyrrolidines from propargylamines and a variety of Michael acceptors (Scheme 1) is now reported. The results are collated in Table 1.



Scheme 1

Initially the commercially available *N*-methylpropargylamine **1a** was employed as the nucleophilic substrate. Exposure of **1a** to diethyl benzylidenemalonate **2a** under the same reaction conditions used in the 3-methylene tetrahydrofuran synthesis[7] (10 mol% *n*BuLi, 5 mol% $Pd(OAc)_2(PPh_3)$, THF, 20°C) resulted in an efficient cyclisation, affording the pyrrolidine **3a** in 79% yield. Reaction of **1a** with ethyl *trans* α-cyanocinnamate **2b** also led to the formation of the target pyrrolidine **3b**. The overall yield of 85% was obtained

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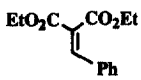
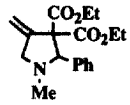
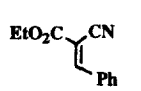
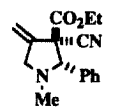
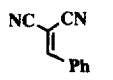
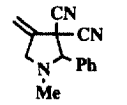
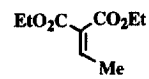
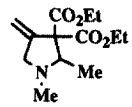
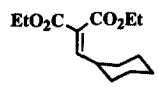
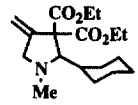
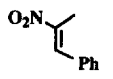
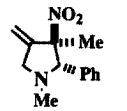
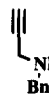
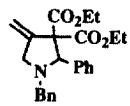
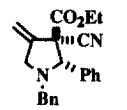
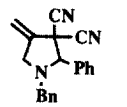
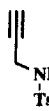
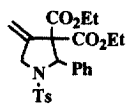
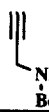
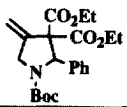
Table 1 : One pot synthesis of 3-methylene pyrrolidines[a]

entry	propargyl amine	Michael acceptor	product[b]		yield % (time)[c]	
					$Pd(OAc)_2PPh_3$	CuI
1	 1a	 2a		3a	79 (3h)	89 (2h)
2		 2b		3b (85/15)	75 (6h)	78 (6h)
3		 2c		3c	- (7h)[d]	- (7h)[d]
4		 2d		3d	16 (6h)	19 (6h)
5		 2e		3e	-[e]	48 (7h)
6[f]		 2f		3f (100/0)	-[e]	64 (8h)
7	 1b	2a		3g	- (24h)[d]	73 (5h)
8		2b		3h (90/10)	-[e]	79 (6h)
9		2c		3i	-[e]	73 (5h)
10[g]	 1c	2a		3j	- (48h)[d]	84 (48h)
11	 1d	2a		3k	- (48h)[d]	- (48h)[d]

[a] Unless otherwise stated all reactions were performed on a 1 mmol scale in THF at 20°C using the following molar ratios 1:2: *n*-BuLi: CuI = 1.5 : 1 : 0.1 : 0.03. [b] Major diastereomer shown. [c] Isolated yields. [d] No product detected (GC) within the time alloted. [e] Not attempted. [f] Reaction performed with ratios 1:2: *n*-BuLi: CuI = 1.5 : 1 : 0.5 : 0.2. [g] Reaction performed with ratios 1:2: *n*-BuLi: CuI = 1 : 1.5 : 0.1 : 0.03.

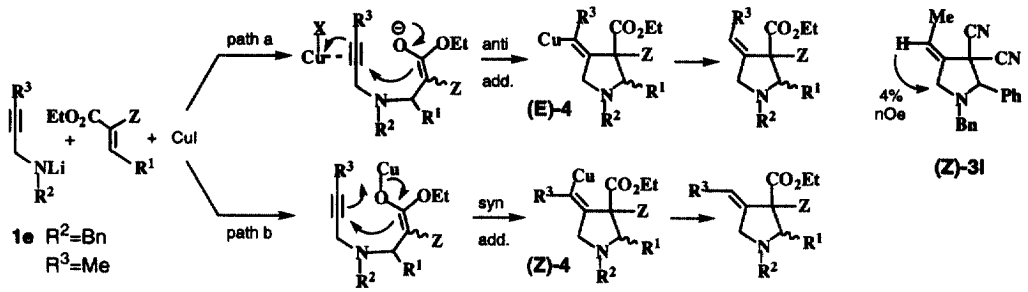
as a 85:15 mixture of two diastereomers as revealed by GC and NMR analysis. In marked contrast with the results obtained for the reaction of propargyl alcohol with benzylidenemalononitrile **2c**, the reaction with **1a** did not proceed cleanly. A separation of reaction products failed to recover any of the desired cyclisation product. Only modest yields of cycloadduct **3d** were obtained when diethylethylidenemalonate **2d** was used. In this case, the propargyl lithium amide is thought to act as a base rather than as a nucleophile.

Attempts to realise this reaction using propargyl amine proved to be unsuccessful. The primary amine catalysing a retro-Knovenagel reaction,[8] indicated the importance of an amine protecting group in the cyclisation reaction. The nature of this protecting group is also important as shown by results for addition of the three propargyl amines **1b-1d.** Even after prolonged reaction time at elevated temperatures no reaction was observed in each case and the starting materials were recovered. The reasons for the failure of these latter three addition reactions remain obscure. Whilst steric and electronic differences in each protecting group may adversely affect the reaction (particularly in the case of **1d**) the precise reasons for this failure are probably more complex.

We have already demonstrated[9] that cyclisation of ε-acetylenic enolates can be promoted by copper(I) species and this may be envisaged as an alternative catalyst. Indeed this tandem reaction with both *N*-benzyl propargylamine **1b** and tosylamine **1c** with benzylidene malonate **2a** using CuI (3%), *n*Buli (10%) in THF at room temperature, afforded the corresponding pyrrolidines in good yield. However, the Boc-protected **1d** failed to undergo cycloaddition under the same reaction conditions. Encouraged by this successful copper-mediated tandem reaction, a study of various Michael acceptors using this new procedure was compared with the results obtained with the palladium catalyst. The results of these reactions are also collected in table 1. The yields obtained for reactions involving *N*-methylpropargylamine **1a** were improved by substituting $Pd(OAc)_2(PPh_3)$ for CuI (entries 1-2,4). Surprisingly, the reaction of the benzylamine **1b** with benzylidene malononitrile **2c** resulted in a clean and efficient conversion into **3i** (73%, entry 9), while the less bulky *N*-methyl amine failed to give any cyclic product even under drastic conditions (entry 3). It is well known[10] that Michael addition of lithium alkoxides and amides to nitroolefins does not undergo a clean reaction. However, reaction of **1a** with nitroalkene **2f** in presence of *n*BuLi (50%) and CuI (20%) produced 3-methylenepyrrolidine **3f** as a single isomer in 64 % yield.

At the present time, the precise role of copper iodide is not clear. A mechanism for the formation of the nitrogen heterocycle, involving the conjugate addition of the nitrogen anion, followed by copper-promoted cycloisomerisation, may be proposed. This thesis is supported by our recent results, in which this kind of enolate attacks a triple bond activated by a copper(I) species.[9] In the present case, although we have no evidence on the nature of the active catalyst, we may suggest the formation of a copper(I) amide[11] species (CuX in path a, scheme 2) by reaction of the propargyl lithium amide with cuprous iodide. The propargylamine present in the reaction medium may then act as a proton transfer species protonating the (E)-vinylcopper intermediate, thus regenerating the active catalyst and affording the expected methylene derivative.

Another explanation for the surprising difference between the two catalysts may be envisioned. Indeed, it has been reported that copper iodide catalyses the Michael addition of lithium amides to enoates.[12] In this case, the copper enolate[13] produced in this putative copper catalysed conjugate addition of the nitrogen-based anion may then add to the triple bond in a *syn* fashion leading to the (Z)-vinylcopper species **4** (scheme 2, path b).



Scheme 2

These two proposed mechanisms would give opposite configurations of the double bond if a substituted propargylamine ($R^3 \neq H$) was employed. The reaction of **1e** with diester **2a** was undertaken but none of the desired product was obtained, even under drastic conditions. Reaction of **1e** with the malononitrile derivative **2c**, however, yielded the (Z)-isomer **3l** (nOe studies,[14] scheme 2) exclusively. It should be noted that additional quantities of base (20%) and catalyst (10%) are required in this reaction. The generation of the (Z)-isomer as the only reaction product unambiguously establishes that the diastereoselective control of this reaction arises from anti-addition of the enolate and copper catalyst to the acetylenic moiety, i.e. path a in scheme 2.

In conclusion, we have developed a new and efficient approach to highly substituted nitrogen heterocycles. The application of this chemistry to the synthesis of pyrrolidine-containing natural products is currently under way.

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14. While irradiation of the vinylic hydrogen resonance caused enhancement for the adjacent methyl protons and methylene protons α to the double bond, irradiation of the signal for vinylic methyl group resulted in significant enhancement of only the adjacent vinylic proton.