Preparation of highly substituted pyrrolidines *via* an organometallic dipole†

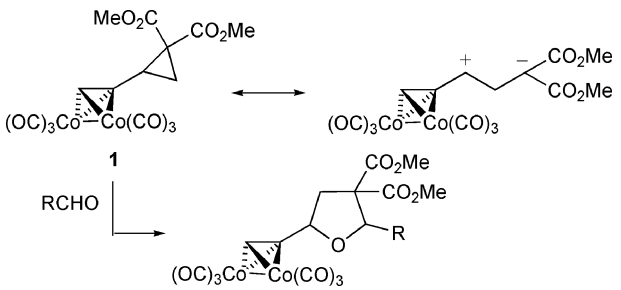
Steven D. R. Christie,* Ryan J. Davoile and Raymond C. F. Jones*

Received 13th April 2006, Accepted 1st June 2006
First published as an Advance Article on the web 14th June 2006
DOI: 10.1039/b605329g

Highly substituted pyrrolidines are prepared by formal cycloaddition of imines to a metal-stabilised 'Nicholas' dipole derived from an alkyne–cyclopropane dicobalt complex.

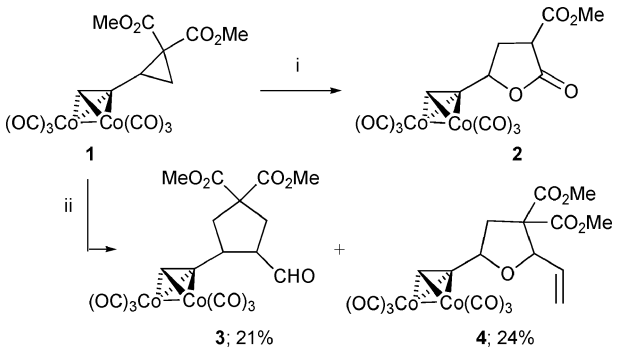
The use of transition metal-promoted reactions of small rings has been reported as the key step in a number of useful transformations. Of particular relevance to this paper are vinyl cyclopropanes, which have seen use as substrates for palladium-mediated transformations in a number of different reactions. Tsuji and coworkers' original use of vinyl cyclopropanes in the preparation of cyclopentane units[1] has been followed by other reactions with, for example, isocyanates.[2] In related chemistry, Ma and Jiao have recently reported the use of allenic cyclopropanes in reaction with imines to produce pyrrolidines.[3]

We recently reported the use of an organometallic dipole in a formal cycloaddition to produce tetrahydrofurans.[4] The metal–alkyne cyclopropane **1** is unique in that it provides access to a Nicholas carbocation[5] through the novel cleavage of a carbon–carbon sigma bond. The formal anionic terminus of the dipole is stabilised by a malonate unit. We found that reaction of this species under Lewis acid conditions with a series of aldehydes produced tetrahydrofuran products wherein the dicobalt alkyne unit remained intact, Scheme 1. We now report an extension of this methodology to the synthesis of other heterocyclic systems.[6]



Scheme 1

The propensity of cyclopropane **1** towards carbon–heteroatom cycloaddition was highlighted by the outcome of studies designed to produce carbocycles. We initially anticipated that an electron-deficient alkene could act as a Michael acceptor for the malonate, with the resultant enolate cyclising on to the Nicholas carbocation, Scheme 2. Thus, reaction with dimethyl maleate or methyl propenoate was attempted in various solvents with a variety of Lewis acids, including $BF_3{\cdot}OEt_2$, $TiCl_4$, $SnCl_4$, $AlCl_3$ and $ZnBr_2$, but none of these produced the desired carbocyclic product, and only $BF_3{\cdot}OEt_2$ and $AlCl_3$ produced small amounts of the lactone by-product **2** that we had noted previously, presumably from intramolecular cyclisation. The other Lewis acids succeeded only in decomposing the starting material. Initial studies with propenal, in an attempt to find a more reactive substrate, showed that while we could indeed gain access to the carbocycle **3**, this was produced in almost equal amounts with the corresponding tetrahydrofuran **4** (Scheme 2). Interestingly, the carbocycle showed a 2 : 1 ratio of diastereoisomers, while the tetrahydrofuran was produced as a 1 : 1 mixture. Prompted by this tendency towards carbon–heteroatom addition, we turned our attention to the reaction with imines.



Scheme 2 Reagents: (i) XCH=CHCO$_2$Me (X = H, CO$_2$Me), Lewis acid; (ii) H$_2$C=CHCHO, $BF_3{\cdot}OEt_2$, CH_2Cl_2, 0 °C.

We envisaged that reaction with imines would provide a short and regiocontrolled access to pyrrolidines. Pyrrolidines remain a ubiquitous building unit in organic chemistry, with application in the pharmaceutical industry and are seen in numerous natural products. Cycloadditions to generate pyrrolidines are well known, but based almost exclusively on a CNC (azomethine ylide) plus CC strategy,[7] whereas our approach offers an *alternative CCC plus CN disconnection.*[8] A further intriguing aspect of this chemistry is the use of a nitrogen nucleophile to quench the formal propargylic carbocation. While the use of oxygen nucleophiles in the Nicholas reaction is well documented,[9] the analogous nitrogen-based chemistry has not been examined to the same extent.[10] This work will thus both expand the scope of our new cycloaddition and increase the utility of nitrogen in the Nicholas reaction. Imines do not to date appear to have been reported as substrates in either the Pd-mediated vinyl cyclopropane reactions, or cycloadditions with donor–acceptor cyclopropanes.[11]

Alkynyl cyclopropane complex **1** was readily prepared in four steps from 1,4-dibromobut-2-ene and diethyl malonate as we have described previously.[4] The required imines were prepared

Chemistry Department, Loughborough University, Loughborough, Leics, LE11 3TU, UK. E-mail: S.D.Christie@lboro.ac.uk, R.C.F.Jones@lboro.ac.uk; Fax: +44 1509 223926; Tel: +44 1509 222587 (S. D. R. Christie); Tel: +44 1509 222557 (R. C. F. Jones)

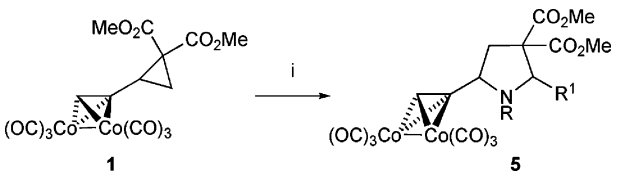
† Electronic supplementary information (ESI) available: Experimental details for compounds **5a–e**, **6**. See DOI: 10.1039/b605329g

Table 1 Reaction of imines $R^1CH{=}NR$ with alkynylcyclopropane dicobalt complex **1**

Product	R^1	R	T/°C	Yield[a] (%)	*trans*:*cis*
5a	CO_2Et	4-$MeOC_6H_4$	0	91	1:1
			25	75	1:1
			40	91	1:1
5b	CO_2Et	2,4-$(MeO)_2C_6H_3$	0	85	2:1
			25	73	2:1
			40	80	2:1
5c	CO_2Et	4-MeC_6H_4	0	79	1:1
			25	81	1:1
			40	85	1:1
5d	CO_2Et	2-NCC_6H_4	0	65	1:2
			25	72	1:3
			40	69	1:3
5e	2-$O_2NC_6H_4$	C_6H_5	25	23	2:1
			40	30	2:1

[a] Reaction time 10 h.

by standard condensation chemistry, treating the amine with the aldehyde in diethyl ether at 25 °C over molecular sieves for 18 h. The imines were then used directly in the cycloaddition with dicobalt complex **1** to produce pyrrolidines **5** (Scheme 3). Optimisation studies revealed $BF_3{\cdot}OEt_2$ as the Lewis acid of choice from those investigated, and that at least two equivalents of Lewis acid were required to produce pyrrolidines **5a–e** in good yield (Table 1) and to minimise the formation of the lactone **2**, just as we had observed earlier in the tetrahydrofuran synthesis.



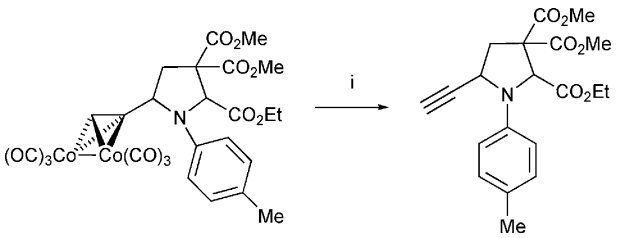
1 **5**

Scheme 3 Reagents: (i) $R^1CH{=}NR$, $BF_3{\cdot}OEt_2$, CH_2Cl_2.

In general, yields were good to excellent when an electron-withdrawing group was present on the imine carbon and an electron-donating group was present on the nitrogen atom, for example, in the preparation of **5a–c**, where the imine was a glyoxal derivative of aromatic amines carrying electron-donating substituents. This would be consistent with ring-opening of the vinyl cyclopropane to give the formal Nicholas cation/malonate anion dipole; attack of the malonate nucleophile onto the imine carbon atom is followed by cyclisation of the amide anion onto the Nicholas carbocation.[12]

Placing an *ortho*-substituted aryl group on either position gave an increase in the 2,5-diastereoselectivity in the new pyrrolidine ring. For pyrrolidine **5d**, the *ortho*-nitrile group gave a maximum of a 3 : 1 ratio in favour of the *cis* isomer. In contrast, having an *ortho*-nitro group in the aryl group of the imine carbon substituent gave a 2 : 1 ratio in favour of the *trans* isomer of pyrrolidine **5e**, but in a reduced yield. It is unclear at this point whether this is due to steric interactions. The diastereoselectivities were measured directly when the isomers were separable, otherwise they were measured from ^1H NMR spectroscopy. In all cases the identifications of the *cis* and *trans* isomers were consistent with previous work.[4] Variation in reaction temperature had no predictable effect on yield or diastereoselectivity.

In order to access the metal-free heterocycle, we have looked briefly at the removal of the cobalt unit. As illustrated in Scheme 4, reaction of one of the cycloaddition products **5c** with ceric ammonium nitrate (Et_3N, acetone) cleanly oxidises the metal in acceptable yield to afford the free alkynyl pyrrolidine **6** (60%; 1 : 1 *trans* : *cis*). This procedure could also be used in the work-up of the cycloaddition reaction to allow access to the metal-free pyrrolidine products in a two-step, one pot procedure.



5c **6**

Scheme 4 Reagents: (i) $(NH_4)_2Ce(NO_3)_6$, Et_3N, Me_2CO.

We have thus demonstrated a novel formal cycloaddition to produce functionalised pyrrolidines *via* a CCC/CN strategy. Work is continuing with the alkynyl cyclopropane complex **1** to further explore its utility in ring-forming reactions. We acknowledge the support of the EPSRC (studentship to R. J. D.).

Notes and references

1 J. Tsuji, I. Shimizu and Y. Ohashi, *Tetrahedron Lett.*, 1985, **26**, 3825–3828.
2 K. Yamamoto, T. Ishida and J. Tsuji, *Chem. Lett.*, 1987, 1157–1158.
3 S. M. Ma and N. Jiao, *Angew. Chem., Int. Ed.*, 2002, **41**, 4737–4740.
4 S. D. R. Christie, R. J. Davoile, M. R. J. Elsegood, R. Fryatt, R. C. F. Jones and G. J. Pritchard, *Chem. Commun.*, 2004, 2474–2475.
5 K. M. Nicholas and R. Pettit, *Tetrahedron Lett.*, 1971, **12**, 3474–3477.
6 For related studies with nitrone dipolarophiles ('homo[3 + 2]dipolar cycloaddition'), see: T. P. Lebold, C. A. Carson and M. A. Kerr, *Synlett*, 2006, 364–368, and references. therein.
7 See for example: L. M. Harwood and R. J. Vickers, in *Synthetic Applications of 1,3-Dipolar Cycloaddition Chemistry Toward Heterocycles and Natural Products*, ed. A. Padwa and W. H. Pearson, Wiley-Interscience, Hoboken, 2003, pp. 169–252.
8 For the transformation of homo[3 + 2]dipolar cycloadducts (ref. 6) into pyrrolidines, see: I. S. Young, J. L. Williams and M. A. Kerr, *Org. Lett.*, 2005, **7**, 953–955.
9 See for example: S. D. R. Christie, R. J. Davoile and R. C. F. Jones, *Tetrahedron Lett.*, 2002, **43**, 7167–7170, and references therein.
10 For recent reviews of the Nicholas reaction, see: B. J. Teobald, *Tetrahedron*, 2002, **58**, 4133–4170; J. R. Green, *Curr. Org. Chem.*, 2001, **5**, 809–826.
11 For recent reviews of the chemistry of donor–acceptor cyclopropanes, see: M. Yu and B. L. Pagenkopf, *Tetrahedron*, 2005, **61**, 321–347; H.-U. Reissig and R. Zimmer, *Chem. Rev.*, 2003, **103**, 1151–1196.
12 For an alternative mechanistic speculation in the case of homo[3 + 2]dipolar cycloaddition, see ref. 6.

