ChemComm

Cite this: *Chem. Commun.*, 2011, **47**, 7965–7967

www.rsc.org/chemcomm

COMMUNICATION

Imidazolium ylides from a conjugate addition–proton transfer route and their cycloaddition reactions†

Raymond C. F. Jones,*[a] James N. Iley,[b] Maria Sanchis-Amat,[a] Xiaohui Zhang,[b] Vickie McKee,[a] Simon J. Coles[c] and Thomas Gelbrich[c]

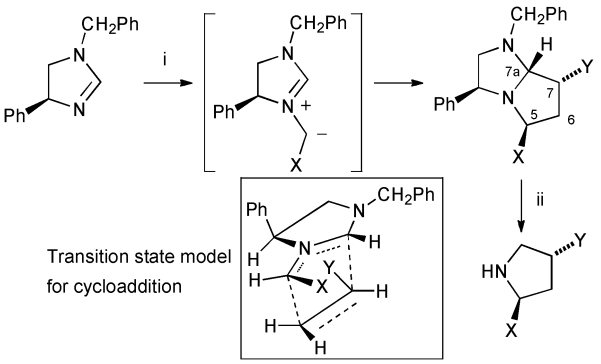
Received 18th April 2011, Accepted 27th May 2011
DOI: 10.1039/c1cc12255j

4,5-Dihydroimidazolium ylides formed by conjugate addition–proton transfer from dihydroimidazoles and doubly-activated electron-deficient alkenes afford 2 : 1 cycloadducts in a one-pot process wherein the alkene also acts as a dipolarophile.

Uncovering new methods for stereocontrolled construction of pyrrolidine rings continues, fuelled by the biologically active molecules containing this substructure.[1] Dipolar cycloaddition of azomethine ylides is a key method,[2] and we have developed 4,5-dihydroimidazolium ylides for stereoselective pyrrolidine synthesis *via* pyrrolo[1,2-*a*]imidazoles.[3] Three of five bonds in the new pyrrolidine ring are formed *via* an ylide formation-cycloaddition cascade. We have reported the ylide formation from 4,5-dihydroimidazoles by (i) N-alkylation-deprotonation (*e.g.* Scheme 1),[3] or (ii) a catalytic cycle of metal carbenoid insertion onto the imine N-atom.[4] The diastereoselection is rationalised by an *anti* dipole conformation and *endo* approach of dipole to dipolarophile (Scheme 1) to establish the stereochemistry at C-5 and C-7 of the cycloadducts.

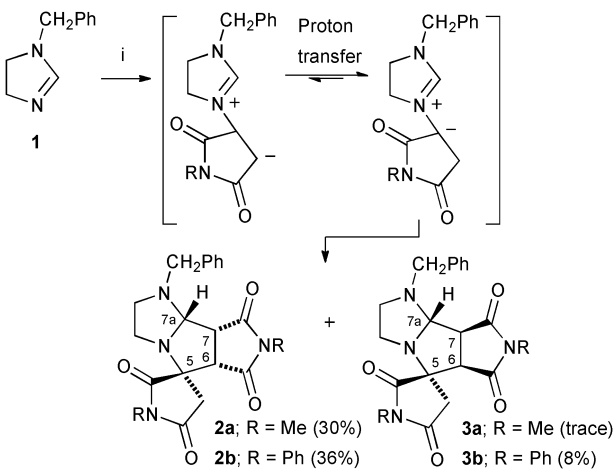
Protocol (i) involves stoichiometric base and approach (ii) metal complexes as catalysts. Whilst developing protocol (ii), we made the serendipitous discovery of a novel route to the dihydroimidazolium ylides involving no added reagent beyond the dihydroimidazole and a doubly activated dipolarophile, that provides unexpected 2 : 1 adducts between dihydroimidazole and dipolarophile. This approach avoids (often lachrymatory) active halide alkylating agents of method (i) and reactive diazo compounds of method (ii). We report here on this third approach to dihydroimidazolium ylides, which provides derivatives related to spiro-oxindole alkaloids[5] and complex α,α-disubstituted proline natural products.[6]

Heating achiral substrate 1-benzyl-4,5-dihydroimidazole **1** with N-methylmaleimide (CH_2Cl_2 reflux, 24 h) afforded



Scheme 1 Reagents: i, $BrCH_2X$, $CH_2{=}CHY$, THF reflux, then DBU; ii, $NaBH_3CN$, H^+; then $Pd(OH)_2$, H_2.

unexpected 2 : 1 adduct **2a** (30%) (Scheme 2); the relative stereochemistry was secured by X-ray crystallographic analysis (Fig. 1).† Formation of such 2 : 1 adducts is rationalised by conjugate addition of the dihydroimidazole to the electron-deficient alkene moiety of the maleimide, followed by proton transfer in the zwitterionic intermediate to give the more stable 1,3-dipole (Scheme 2).[7] The imidazolium ylide then undergoes dipolar cycloaddition to a second molecule of maleimide, which thus acts as both Michael acceptor and dipolarophile. The relative stereochemistry of **2a** is consistent with our model for the transition



Scheme 2 Reagent: i, N–R maleimide, CH_2Cl_2 reflux, 24 h.

[a] *Department of Chemistry, Loughborough University, Loughborough, Leics, LE11 3TU, UK. E-mail: r.cf.jones@lboro.ac.uk; Fax: +44 1509 223925; Tel: +44 1509 222557*
[b] *Department of Chemistry & Analytical Sciences, The Open University, Walton Hall, Milton Keynes, MK7 6AA, UK*
[c] *EPSRC National Crystallography Service, School of Chemistry, University of Southampton, Highfield, Southampton, SO17 1BJ, UK*

† Electronic supplementary information (ESI) available: Typical experimental procedure, data for key compounds, X-ray crystallographic data tables. CCDC 823959–823961. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c1cc12255j

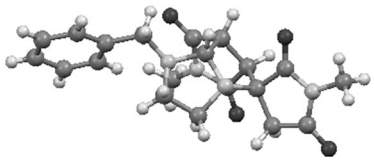


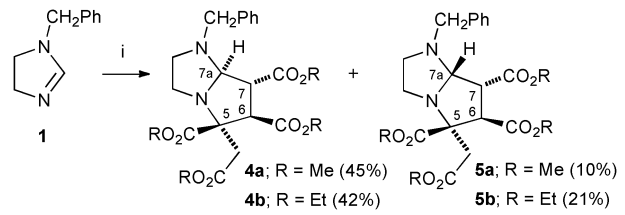
Fig. 1 X-Ray crystal structure of 2 : 1 cycloadduct **2a**.

state (Scheme 1):[3] the *anti* dipole refers to the non-activating dipole substituent, and the *endo* approach to C-7 of the cycloadduct pyrrolo[1,2-*a*]imidazole core. Using N-phenylmaleimide in this reaction led to corresponding 2 : 1 adduct **2b** (36%).

In both examples, a minor product was found: a trace of **3a** isolated alongside adduct **2a**, and **3b** (8%) isolated with **2b**. These minor products, relative stereochemistry determined by NOE studies, correspond to *exo* approach of dipole to dipolarophile. Adduct **2b** showed significant enhancement of C-7(H) and C-6(H) signals on irradiation of C-7a(H) and C-7(H), respectively (pyrrolo[1,2-*a*]imidazole numbering of the cycloadduct core), indicating all three protons to be *cis*. In contrast, isomer **3b** showed only small enhancement of C-7a(H) on irradiation of C-7(H) but a large enhancement of the *cis*-proton at C-6(H), suggesting an *anti* arrangement of C-7(H) and C-7a(H); irradiation of C-5(CH_2) showed enhancement of C-6(H), confirming them to be on the same face of the molecule. Coupling constants ^3J(7,7a) were also characteristic: in **2a,b** J = 7.6 Hz, where models show a dihedral angle close to 0°, whereas in **3a,b** with a dihedral angle nearer to 90°, J = *ca.* 2 Hz.

Replacing the maleimide by a fumarate ester, the corresponding 2 : 1 adducts were obtained in a slower reaction (CH_2Cl_2 reflux, 48 h). Thus dimethyl fumarate led to major **4a** (45%) and minor **5a** (10%) 2 : 1 adducts (Scheme 3). Minor adduct **5a**, stereostructure secured by X-ray crystal structure (Fig. 2),† proved to be the diastereisomer predicted by our transition state model, whereas major product **4a** was determined (comparison NOE studies) to be the C-7a epimer.

We speculate that kinetic product **5a** epimerizes to the thermodynamic isomer **4a** either under the reaction conditions or during silica gel chromatography, presumably *via* aminal-aminoiminium ion equilibrium (Scheme 4), as we have reported in other dihydroimidazolium ylide cycloadditions.[3] The latter possibility is consistent with the observation that an isolated sample of minor product **5a** is converted into the same mixture of products **4a**/**5a** by the trace of acid present in untreated $CDCl_3$ during NMR examination. In support of our mechanistic proposal, when dimethyl maleate was used instead of fumarate under the same conditions, a mixture of the same two products was observed, **4a** (38%) and **5a** (2%). Interconversion of maleate to the more stable fumarate can be mediated by initial reversible conjugate addition of the dihydroimidazole to the electron-deficient maleate alkene.[8]



Scheme 3 Reagent: i, (*E*)- or (*Z*)-$RO_2CH{=}CHCO_2R$, CH_2Cl_2 reflux, 48 h.

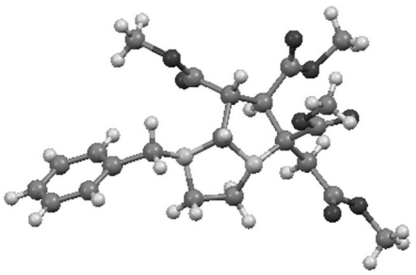
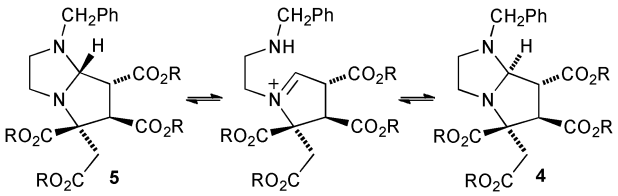
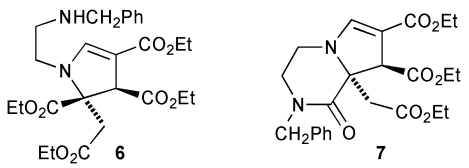


Fig. 2 X-Ray crystal structure of minor 2 : 1 cycloadduct **5a**.



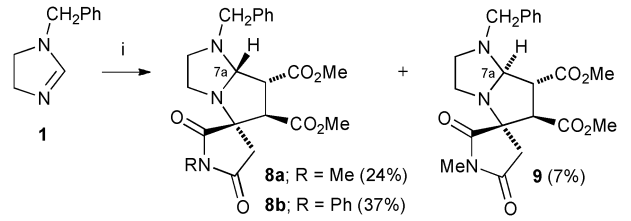
Scheme 4 Epimerisation at C-7a.

The dipolarophile-derived portion of the isolated adducts clearly shows the C-6 and C-7 ester groups to be *trans*, *i.e.* the alkene has fumarate geometry when it acts as dipolarophile, suggesting the conjugate addition is rate-determining. Using diethyl fumarate led to the corresponding 2 : 1 adducts **4b** (42%) and **5b** (21%). Allowing this latter reaction to proceed for an extended period (CH_2Cl_2 reflux, 10 days), the major 2 : 1 adduct **4b** (20%) was isolated along with secondary products that provided further support for the proposed mechanism. Thus the formation of enamino ester **6** (3%) and pyrrolo[1,2-*a*]pyrazine **7** (6%) is rationalised by proton loss from the aminoiminium ion involved in **4b**/**5b** equilibration (Scheme 4) and lactam formation from **6**. Kinetic product **5b** was not observed after these extended reaction times.



The rate difference between maleimide and fumarate reactions, attributed to the latter being less effective conjugate addition acceptors, was exploited in formation of 1 : 1 : 1 adducts where the Michael acceptor and dipolarophile were not the same compound. When N-methylmaleimide was added slowly over 72 h to a mixture of dihydroimidazole **1** and dimethyl fumarate (CH_2Cl_2 20 °C), 1 : 1 : 1 adduct **8a** was isolated (24%) (Scheme 5), stereochemistry as predicted by the transition state model and secured by an X-ray crystal structure (Fig. 3)† and NOE studies, along with C-7a epimer **9** (7%) and traces of the 2 : 1 adducts **2a**/**3a** derived from the maleimide. N-Phenylmaleimide likewise afforded 1 : 1 : 1 adduct **8b** (37%) and the 2 : 1 adducts **2b**/**3b** (6%, 0.5%, respectively). These results suggest the maleimides react preferentially as acceptors and that the 1,3-dipole formed is trapped by the fumarate present in excess.

The dihydroimidazolium ylide formation and reaction was extended to chiral dihydroimidazoles: (*R*)-1-benzyl-4-phenyl-4,5-dihydroimidazole **10**[3] and N-methylmaleimide



Scheme 5 Reagent: i, (*E*)-$MeO_2CH{=}CHCO_2Me$, N–R maleimide added slowly, CH_2Cl_2 20 °C, 72 h.

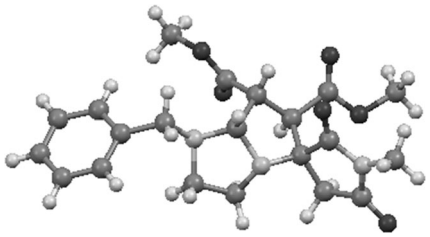
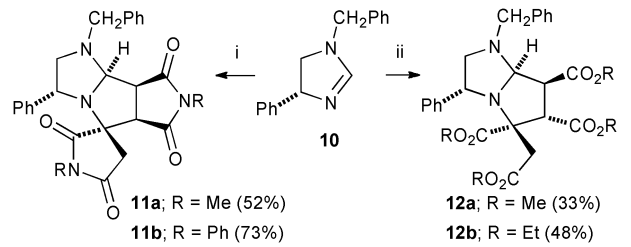


Fig. 3 X-Ray crystal structure of 1 : 1 : 1 cycloadduct **8a**, stereochemistry inverted from refined coordinates to correlate with Scheme 5. There are two enantiomorphous molecules in the asymmetric unit and the space group is centrosymmetric.

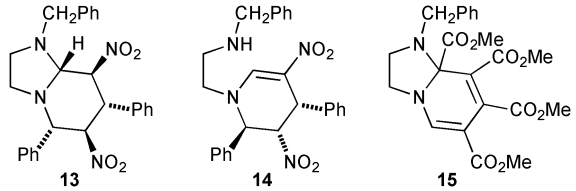
(CH_2Cl_2 reflux, 72 h) afforded 2 : 1 adduct **11a** as the only identifiable product (52%) (Scheme 6). This stereochemistry, supported by spectroscopic data, is as predicted by the transition state model. The chiral centre in **10** confers optical activity on the adduct; cycloaddition occurs on the face of the formed dipole opposite to the phenyl group as expected from our earlier reports.[3] N-Phenylmaleimide provided 2 : 1 adduct **11b** (73%), structure assigned by NMR methods in comparison to **11a**. Methyl or ethyl fumarate esters as acceptors and dipolarophiles led to the 2 : 1 adducts **12a,b** (33, 48%, respectively) in a much slower reaction.

We have established that the acceptor/dipolarophile alkene must carry two electron-withdrawing groups by attempting reactions of **1** with mono-activated alkenes such as propenoate esters and 2-phenylnitroethene, when no pyrrolidine formation was observed.‡ These experiments did nevertheless provide support for our proposed mechanistic sequence. In the case of 2-phenylnitroethene (CH_2Cl_2 20 °C, 24h) the initial conjugate adduct did not undergo proton transfer (which would now be unfavourable) and behaved as a 1,4-dipole to afford six-membered adducts **13** in low yield (3%) along with the ring-opened derivative **14** (36%) of a diastereomeric cycloadduct. This cycloaddition is rationalised as a two-step process: a second conjugate addition and closure of the generated



Scheme 6 Reagents: i, N–R maleimide, CH_2Cl_2 reflux, 72 h; ii, (*E*)-$RO_2CH{=}CHCO_2R$, CH_2Cl_2 reflux, 17 days.

enolate onto the dihydroimidazolium function. Using dimethyl ethynedicarboxylate (CH_2Cl_2 20 °C, 72 h), where no proton shift in the conjugate adduct is possible, six-membered adduct **15** was observed in low yield (5%). The unexpected structure of **15** was supported by, for example, methine proton signals at δ_H 7.8 and δ_C 147 showing an sp^2 methine carbon atom, and implying that the initial 1,4-cycloadduct has ring-opened and the pendant amino function reclosed onto the alternative pyridinium ion C-2 position.[9]



We have demonstrated a novel conjugate addition-proton transfer protocol for formation of dihydroimidazolium ylides, and their 2 : 1 or 1 : 1 : 1 adducts with suitable dipolarophiles. The cycloadducts are of value as building blocks towards heterocyclic molecules of biological potential. Although some yields are moderate, the cascade rapidly generates complexity, with three new bonds and two new rings, so has good utility.

We acknowledge studentship support from Loughborough University (M. S-A.) and The Open University (X. Z.), and the EPSRC Mass Spectrometry Service Centre (Swansea) for high resolution MS data, and thank STFC for access to station 16.2SMX of the SRS at Daresbury.

Notes and references

‡ We have to date been unable to isolate 1 : 1 : 1 adducts from reactions of dihydroimidazole **1** with a doubly activated alkene as Michael acceptor and a mono-activated alkene as dipolarophile.

1 For example: F. Bellina and R. Rossi, *Tetrahedron*, 2006, **62**, 7213; I. Coldham and R. Hufton, *Chem. Rev.*, 2005, **105**, 2765; D. O'Hagan, *Nat. Prod. Rep.*, 2000, **17**, 435.
2 For example: G. Pandey, P. Banerjee and S. R. Gadre, *Chem. Rev.*, 2006, **106**, 4484; 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, p. 169.
3 Leading references: (*a*) R. C. F. Jones, K. J. Howard, J. S. Snaith, A. J. Blake, W.-S. Li and P. J. Steel, *Org. Biomol. Chem.*, 2011, **9**, 297; (*b*) R. C. F. Jones, S. Rafiq, M. R. J. Elsegood, V. McKee and M. J. Slater, *Chem.–Asian J.*, 2010, **5**, 461; (*c*) P. M. J. Lory, R. C. F. Jones, J. N. Iley, S. J. Coles and M. B. Hursthouse, *Org. Biomol. Chem.*, 2006, **4**, 3155; (*d*) R. C. F. Jones, K. J. Howard, J. R. Nichols and J. S. Snaith, *J. Chem. Soc., Perkin Trans. 1*, 1998, 2061.
4 R. C. F. Jones, J. N. Iley, M. Sanchis-Amat, X. Zhang and M. R. J. Elsegood, *Tetrahedron Lett.*, 2009, **50**, 3577.
5 For recent references: P. Prasanna, K. Balamurugan, S. Perumal, P. Yogeeswari and D. Sriram, *Eur. J. Med. Chem.*, 2010, **45**, 5653; M.-N. Cheng, H. Wang and L.-Z. Gong, *Org. Lett.*, 2011, **13**, 2418.
6 For example: C. L. Bagwell, M. G. Moloney and M. Yaqoob, *Bioorg. Med. Chem. Lett.*, 2010, **20**, 2090; C. J. Hayes, A. E. Sherlock, M. P. Green, Claire Wilson, A. J. Blake, M. D. Selby and J. C. Prodger, *J. Org. Chem.*, 2008, **73**, 2041.
7 *Cf.* L. Zirngibl, *Tetrahedron Lett.*, 1971, **12**, 4189; L. Zirngibl, T. Wagner-Jauregg and E. Pretsch, *Tetrahedron*, 1971, **27**, 2203.
8 For example: V. Majce, M. Kocevar and S. Polanc, *Tetrahedron Lett.*, 2011, **52**, 3287.
9 *Cf.* P. J. Abbott, R. M. Acheson, M. Y. Kornilov and J. K. Stubbs, *J. Chem. Soc., Perkin Trans. 1*, 1975, 2322.