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PII: S0040-4039(09)00572-3
DOI: 10.1016/j.tetlet.2009.03.064
Reference: TETL 35726

To appear in: *Tetrahedron Letters*

Received Date: 13 January 2009
Revised Date: 2 March 2009
Accepted Date: 9 March 2009

Please cite this article as: Jones, R.C.F., Iley, J.N., Sanchis-Amat, M., Zhang, X., Elsegood, M.R.J., A catalytic dipolar cycloaddition route to pyrroloimidazoles, *Tetrahedron Letters* (2009), doi: 10.1016/j.tetlet.2009.03.064

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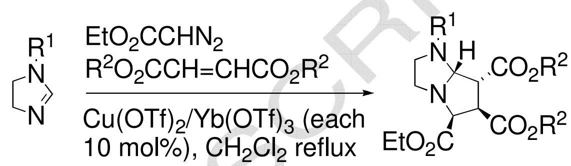
Raymond C. F. Jones,* James N. Iley, Maria Sanchis-Amat, Xiaohui Zhang and Mark R. J. Elsegood

A catalytic method involving carbenoid insertion onto dihydroimidazoles is reported for the generation of dihydroimidazolium ylides, and their subsequent diastereoselective cycloaddition to form pyrrolo[1,2-*a*]imidazoles



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A catalytic dipolar cycloaddition route to pyrroloimidazoles

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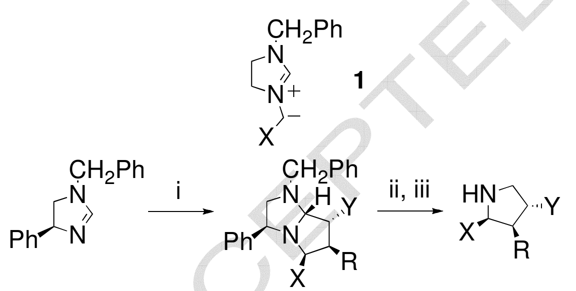
Abstract—A catalytic method involving carbenoid insertion onto dihydroimidazoles is reported for the generation of dihydroimidazolium ylides, and their subsequent diastereoselective cycloaddition to form pyrrolo[1,2-*a*]imidazoles

Finding new methods of synthesis for saturated nitrogen heterocycles such as pyrrolidines remains an ongoing challenge for synthetic chemists due to the pharmacological potential of these systems.[1] We have reported a method for the diastereoselective synthesis of pyrrolidines using 4,5-dihydroimidazolium ylides **1**, formed by *in situ* alkylation-deprotonation of a dihydroimidazole, in a 1,3-dipolar cycloaddition to form pyrrolo[1,2-*a*]imidazoles.[2] We have also applied this cycloaddition, followed by removal of the templating atoms, to optically active ylides to prepare optically active pyrrolidines in a diastereoselective fashion.[3] This is exemplified in Scheme 1, and forms three bonds of the new pyrrolidine in one pot.



Scheme 1. Dihydroimidazolium ylides in pyrrolidine synthesis. Reagents: i, XCH_2Br, RCH=CHY, DBU; ii, $NaBH_3CN$, H^+; iii, $Pd(OH)_2$, H_2

The diastereoselection follows our simple model of *endo* approach of dipole to dipolarophile and an *anti* conformation of the dipole,[2,4] with the cyclic dipole providing a conformational restraint on the chiral auxiliary that allows simple prediction of the facial selectivity of the cycloaddition (Fig. 1). This successful protocol nevertheless uses stoichiometric base (DBU) and a reactive (often lachrymatory) halide.

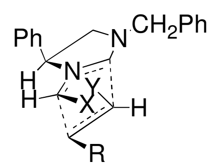
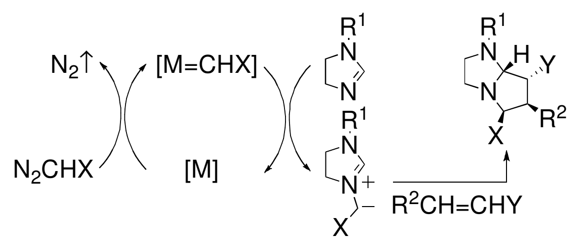


Figure 1. Transition state model, dihydroimidazolium ylide cycloaddition

We wanted to generate a 'cleaner' catalytic procedure for ylide generation, and conceived the cycle shown in Scheme 2 wherein the ylide is formed by insertion of a metal carbenoid formed from a diazo compound, onto the imine nitrogen atom lone pair of a dihydroimidazole.[5] The ylide undergoes cycloaddition and the metal complex is liberated for further carbenoid formation. We report here the realisation of this approach to pyrroloimidazoles and thence potentially, as previously reported, to pyrrolidines.[3]



Keywords: dihydroimidazole; carbenoid; dihydroimidazolium ylide; dipolar cycloaddition; pyrroloimidazole
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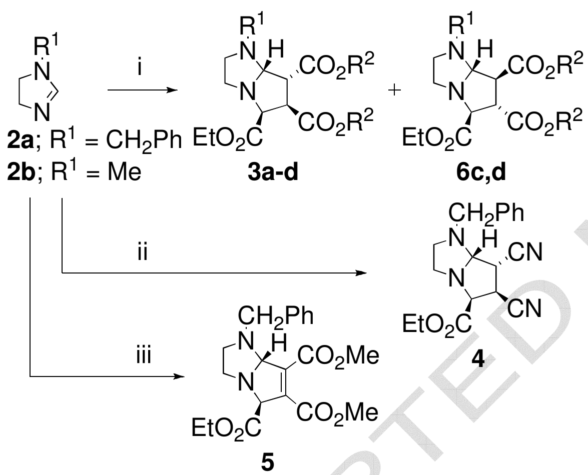
Scheme 2. Proposed catalytic cycle for ylide generation and cycloaddition

The starting materials were dihydroimidazoles **2a,b**. The former was prepared as reported previously from *N*-benzyldiaminoethane,[2] and *N*-methyl analogue **2b** was prepared from commercial *N*-methyldiaminoethane and dimethylformamide diethyl acetal (THF, reflux, 65%).[6]

Initial experiments using dihydroimidazole **2a** with ethyl diazoacetate and copper(II) acetylacetonate $Cu(acac)_2$ (10 mol%) in the presence of dimethyl or diethyl fumarate (CH_2Cl_2 reflux), indeed produced low yields of the desired cycloadducts **3a,b** (R^2 = Me, 33%; R^2 = Et, 25%) (Scheme 3). Dimethyl maleate as dipolarophile also produces cycloadduct **3a** (17%), presumably via maleate–fumarate equilibration prior to cycloaddition and mediated by the basic dihydroimidazole. Further examples were completed using other dipolarophiles to give cycloadducts **4** from fumaronitrile (23%) with copper(II) trifluoromethanesulfonate (copper triflate, $Cu(OTf)_2$) catalyst and **5** using dimethylacetylene dicarboxylate (12% using $Cu(acac)_2$; 14% using $Cu(OTf)_2$).



Scheme 3. Catalytic dipolar cycloadditions. Reagents: i, EtO_2CCHN_2, $R^2O_2CCH{=}CHCO_2R^2$, $Cu(acac)_2$ or $Cu(OTf)_2$, $Yb(OTf)_3$ (each 10 mol%, see text), CH_2Cl_2 reflux; ii, EtO_2CCHN_2, NCCH=CHCN, $Cu(OTf)_2$ (10 mol%), CH_2Cl_2 reflux; iii, EtO_2CCHN_2, $MeO_2CC{\equiv}CCO_2Me$, $Cu(acac)_2$ or $Cu(OTf)_2$ (10 mol%) (see text), CH_2Cl_2 reflux.

During these studies, and related to the maleate–fumarate interconversion above, a new competing mode of ylide generation via conjugate addition–proton transfer was serendipitously uncovered and extensively investigated. These results will be fully reported separately.[7] Further investigations were undertaken to suppress this alternative pathway. Use of Rh(II) catalysis (e.g. $Rh_2(OAc)_4$) offered no advantage (cycloaddition of the diazo ester to the dipolarophile predominated), and neither did slow generation of the diazo compound by the base-mediated decomposition of ethyl glyoxylate tosylhydrazone.[8]

We eventually alighted on a successful protocol: the dihydroimidazoles **2a** or **2b** were treated with the diazo ester ethyl diazoacetate and sub-stoichiometric copper triflate, in the presence of a fumarate dipolarophile and ytterbium triflate (CH_2Cl_2 reflux; 10 mol% of each of $Cu(OTf)_2$ and $Yb(OTf)_3$). The reactions were perfomed by simultaneous addition of separate solutions of ethyl diazoacetate and dimethyl fumarate or diethyl fumarate in CH_2Cl_2 dropwise over 2 h using syringe pumps, to a solution of the dihydroimidazole **2** in CH_2Cl_2 at reflux, containing the Cu(II) and Yb(III) catalysts and 4 Å molecular sieves to scavenge water. After 20 h at reflux, complete consumption of the dihydroimidazole **2** was observed and after work-up, the 1:1:1 cycloadducts **3a-d** were isolated as principal products (Scheme 3) in yields of 48, 30, 40 and 68%, respectively.[9]

Table 1. Cycloadducts **3** and **6** from the $Cu(OTf)_2/Yb(OTf)_3$ protocol

Dihydroimidazole	Cycloadduct	R^1	R^2	Yield %
2a	**3a**	CH_2Ph	Me	48
2a	**3b**	CH_2Ph	Et	30
2b	**3c, 6c**	Me	Me	40, 21
2b	**3d, 6d**	Me	Et	68, 23

The relative stereochemistry of the cycloadducts **3a-d** was determined by n.O.e difference studies using ^{1}H NMR spectroscopy. For example, for cycloadduct **3a** the following enhancements were observed (Fig. 2): irradiation of bridgehead proton C-7a(H) at δ 4.56 gave significant enhancement of C-7(H) and irradiation of C-6(H) at δ 3.89 showed enhancement at C-5(H), demonstrating the *cis*-relationships between the protons at C-7 and C-7a, and C-5 and C-6. There is minimal interaction between C-6(H) and C-7(H), indicative of a *trans*-relationship. No interaction is observed between C-7a(H) or C-7(H) and C-5(H). This relative stereochemistry is consistent with the transition state model that we have previously proposed (Fig. 1), having an anti-dipole conformation and an *endo* mode of approach of dipolarophile to dipole (with reference to the activating group located at C-7 in the cycloadduct). In the cases of the *N*-methyl compounds **3c** and **3d** some *exo* adduct was also found, affording **6c** and **6d** (21% and 23% yield, respectively).

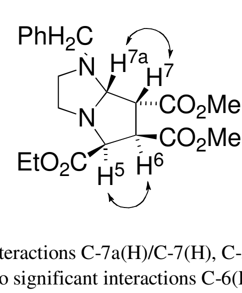
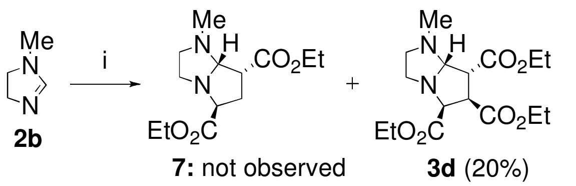


Figure 2. n.O.e. interactions C-7a(H)/C-7(H), C-5(H)/C-6(H) for cycloadduct **3a**. No significant interactions C-6(H)/C-7(H), C-5(H)/C-7/7a(H)

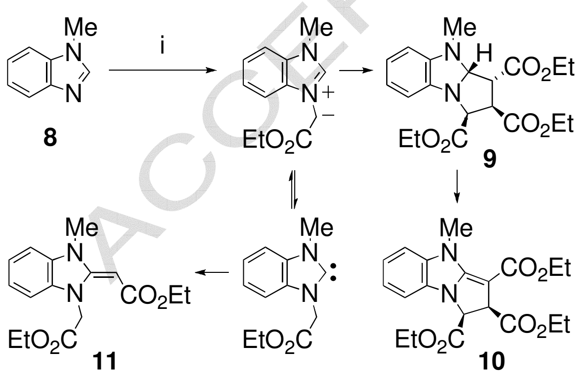
Ytterbium(III) triflate has been reported to accelerate 1,3-dipolar cycloadditions of carbonyl ylides with imines more effectively than other lanthanide triflates.[10] It has been proposed to complex the imine to lower its LUMO, which accelerates the Sustmann type-II dipolar cycloaddition.[11] We tentatively propose that in the present cases, $Yb(OTf)_3$ can complex the imine function of the dipole; it is also possible that $Yb(OTf)_3$ can additionally complex to a dipolarophile carbonyl group to enhance the dipolar cycloaddition, but we have no experimental evidence for these postulates.

From preliminary atempts to scope this protocol, it would appear that double activation of the dipolarophile is preferred. For example, a reaction using dihydroimidazole **2b**, ethyl diazoacetate and ethyl propenoate did not produce the expected cycloadduct **7** (Scheme 4) but instead afforded the fumarate adduct **3d** (20%), presumably via dimerization of the carbene formed from the diazoacetate.



Scheme 4: Preference for doubly activated dipolarophiles. Reagents: EtO_2CCHN_2, $CH_2{=}CHCO_2Et$, $Cu(acac)_2$ (10 mol%), CH_2Cl_2 reflux

A further instance of the catalytic generation of an imidazolium ylide was found when commercial *N*-methylbenzimidazole **8** was treated using the copper triflate/ytterbium triflate protocol in the presence of diethyl fumarate to afford fused tricycle **10** (47%) (Scheme 5). The structure of adduct **10** was deduced using NMR spectroscopy and confirmed by an X-ray crystal structure determination (Fig. 3).[12,13] It appears that the presumed primary cycloadduct **9** undergoes spontaneous dehydrogenation to leave the oxidised isolated product **10**.



Scheme 5. Cycloaddition using *N*-methylbenzimidazole **8**.Reagents: i, EtO_2CCHN_2, $EtO_2CCH{=}CHCO_2Et$, $Cu(OTf)_2$, $Yb(OTf)_3$ (each 10 mol%), CH_2Cl_2 reflux.

An additional by-product was isolated in this reaction, the 2-ethoxycarbonylmethylenebenzimidazole **11** (20%); we suggest its pathway of formation (Scheme 5) is via *N*-heterocyclic carbene formation by proton transfer within the first-formed dipole, followed by combination with the diazo ester-derived carbenoid. The structure of **11** was also confirmed by X-ray crystal structure analysis (Fig. 4).[12,13]

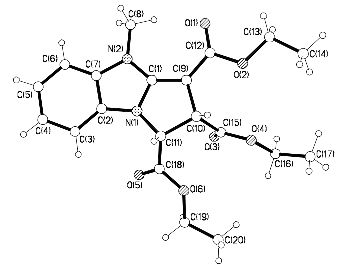


Figure 3. X-ray crystal structure of cycloadduct **10**.

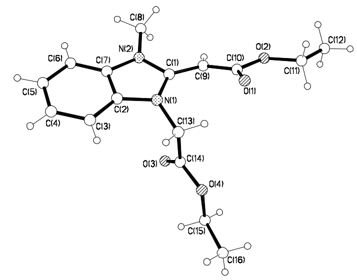


Figure 4. X-ray crystal structure of carbene combination product **11**.

We have thus demonstrated that catalytic generation of 4,5-dihydroimidazolium ylides is possible as an alternative to alkylation-deprotonation, and that the ylides react as expected to form pyrrolo[1,2-*a*]imidazoles. Optimisation of the detailed experimental protocol awaits further investigation.

Acknowledgements

We thank Loughborough University for a studentship (M. S. A.), The Open University for a studentship (X. Z.), the EPSRC National Crystallography Service at the University of Southampton for the diffraction data for compound **10**, the STFC for beam time at Daresbury Laboratory SRS Station 16.2 SMX, Drs. J. E. Warren and T. J. Prior for scientific support at the SRS, and, and the EPSRC Mass Spectrometry Service Centre (Swansea) for high resolution MS data.

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9. Typical procedure: Preparation of cycloadduct **3a**. Ethyl diazoacetate (1.07 g, 9.37 mmol) in CH_2Cl_2 (10 mL) and dimethyl fumarate (1.61 g, 9.37 mmol) in CH_2Cl_2 (10 mL) were added simultaneously and dropwise over 2 h at 37 °C to 1-benzyl-4,5-dihydroimidazole **2a** (1 g, 6.25 mmol), $Cu(OTf)_2$ (0.22 g, 0.62 mmol), $Yb(OTf)_3$ (0.39 g, 0.62 mmol) and 4 Å molecular sieves in anhydrous CH_2Cl_2 (20 mL) under nitrogen. The solution was stirred at reflux for 20 h, diluted with CH_2Cl_2 (10 mL), washed with water (2 x 10 mL), dried over $MgSO_4$ and concentrated under reduced pressure to give an oil, which was purified by column chromatography on silica gel [light petroleum (b.p. 40-60 °C):ethyl acetate, 1:1 v/v with 2% of triethylamine] to give **3a** as a pale yellow oil (0.59 g, 1.25 mmol, 48%) as a single diastereoisomer. *m/z* (ES) calcd. for $C_{20}H_{26}N_2O_6$: MH^+ 391.1869; Found: 391.1864. ν_{max} (KBr, cm^{-1}) 2952, 1737, 1435, 1202, 1027 and 701. δ_H (400 MHz, $CDCl_3$) 1.25-1.32 (m, 3H, CH_2CH_3), 2.47-2.53, 2.78-2.85 (2 x m, each 1H, NCH_2CH_2N), 2.97-3.02, 3.25-3.30 (2 x m, each 1H, NCH_2CH_2N), 3.35 (d, 1H, *J* 7.7 Hz, NC*H*HPh), 3.68, 3.69 (2 x s, each 3H, CH_3), 3.73-3.76 (m, 1H, H-7), 3.89 (m, 1H, H-6), 4.00 (d, 1H, *J* 18 Hz, H-5), 4.05 (d, 1H, *J* 7.7 Hz, NCH*H*Ph), 4.14-4.23 (m, 2H, CH_2CH_3), 4.56 (d, 1H, *J* 6.8 Hz, H-7a) and 7.26-7.31 (m, 5H, Ph). δ_C (100 MHz, $CDCl_3$) 14.2 (CH_2CH_3), 47.6 (CH-6), 51.0 (CH-7), 52.0, 52.4 (OCH_3), 53.0 (CH_2Ph), 53.2, 56.6 (CH_2N), 61.2 (CH_2CH_3), 68.5 (CH-5), 86.2 (CH-7a), 127.1, 128.2, 128.7 (Ar-CH), 138.8 (Ar-C), 171.1, 171.2 and 171.6 (C=O).
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11. Sustmann R. *Tetrahedron Lett.* **1971**, *12*, 2717-2720.
12. *Crystal data* for **10** (m.p. 130-132 °C): $C_{20}H_{24}N_2O_6$, M = 388.41, monoclinic, a = 12.2557(6), b = 10.7641(3), c = 14.1749(7) Å, β = 95.573(2), U = 1861.14(14) Å^3, T = 120(2) K, space group $P2_1/n$, monochromated Mo-Kα radiation, λ = 0.71073 Å, Z = 4, D_c = 1.386 g cm^{-3}, $F(000)$ = 824, colourless, dimensions 0.17 × 0.11 × 0.02 mm^3, μ = 0.103 mm^{-1}, 2.99 < 2θ < 27.62°, 21475 reflections measured, 4262 unique, R_{int} = 0.0758 . The structure was solved by direct methods and refined by full-matrix least-squares on F^2. $wR2$ = 0.1159 (all data, 258 parameters); $R1$ = 0.0529 [3061 data with $F^2 > 2\sigma(F^2)$]. *Crystal data* for **11** (m.p. 101-105 °C): $C_{16}H_{20}N_2O_4$, M = 304.34, monoclinic, a = 10.741(11), b = 8.772(9), c = 17.121(17) Å, β = 100.321(13), U = 1587(3) Å^3, T = 150(2) K, space group $P2_1/n$, silicon 111 monochromated synchrotron radiation, λ = 0.8462 Å, Z = 4, D_c = 1.274 g cm^{-3}, $F(000)$ = 648, colourless, dimensions 0.21 × 0.13 × 0.03 mm^3, μ = 0.092 mm^{-1}, 3.72 < 2θ < 28.19°, 8147 reflections measured, 2267 unique reflections, R_{int} = 0.1398. The structure was solved and refined as above. $wR2$ = 0.2554 (all data, 203 parameters); $R1$ = 0.0940 [1433 data with $F^2 > 2\sigma(F^2)$].
13. Crystallographic data (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos. 721010 (**10**) and 721172 (**11**). Copies of these data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, (fax: +44-(0)1223-336033 or e-mail: deposit@ccdc.cam.ac.uk).