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.
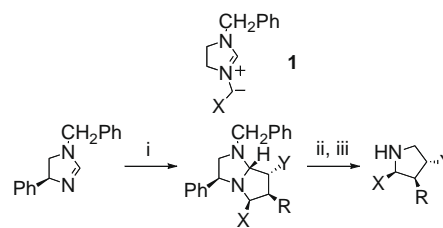
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Finding new methods of synthesis for saturated nitrogen heterocycles such as pyrrolidines remains an ongoing challenge for synthetic chemists due to the pharmacological potential of these systems.[1] We have reported a method for the diastereoselective 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.

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.

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]

Scheme 1. Dihydroimidazolium ylides in pyrrolidine synthesis. Reagents: (i), XCH$_2$Br, RCH=CHY, DBU; (ii), NaBH$_3$CN, H$^+$; (iii), Pd(OH)$_2$, H$_2$.
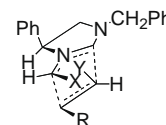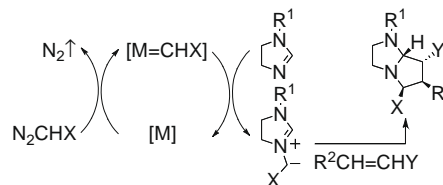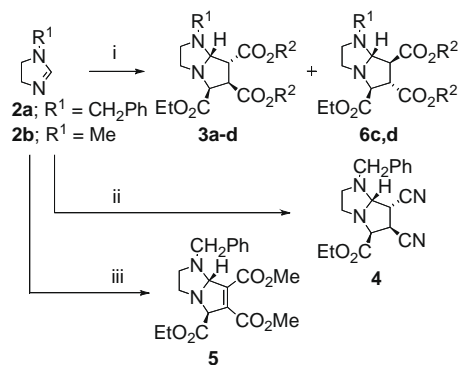

Figure 1. Transition state model, dihydroimidazolium ylide cycloaddition.

Scheme 2. Proposed catalytic cycle for ylide generation and cycloaddition.

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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.

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)$_2$).

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 performed 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

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

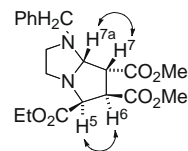| Dihydroimidazole	Cycloadduct	R^1	R^2	Yield (%)
2a	**3a**	CH_2Ph	Me	48
2a	**3b**	CH_2Ph	Et	30
2b	**3c, 6c**	Me	Me	40, 21
2b	**3d, 6d**	Me	Et	68, 23

Figure 2. NOE 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).

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 (see Table 1).[9]

The relative stereochemistry of the cycloadducts **3a–d** was determined by NOE difference studies using ^1H 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).

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 attempts to scope this protocol, it would appear that double activation of the dipolarophile is preferred. For
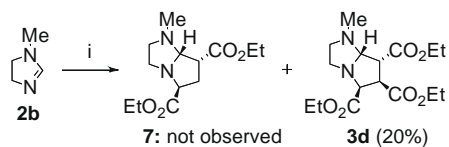
Scheme 4. Preference for doubly activated dipolarophiles. Reagents: EtO_2CCHN_2, CH_2=CHCO$_2$Et, Cu(acac)$_2$ (10 mol %), CH_2Cl_2 reflux.
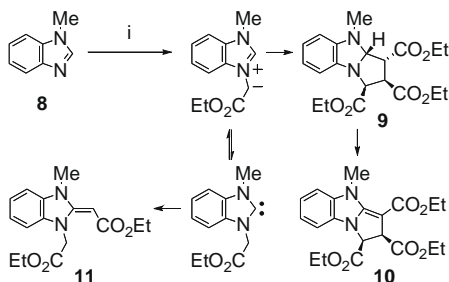
Scheme 5. Cycloaddition using *N*-methylbenzimidazole **8**. Reagents: (i), EtO_2CCHN_2, $EtO_2CCH=CHCO_2Et$, Cu(OTf)$_2$, Yb(OTf)$_3$ (each 10 mol %), CH_2Cl_2 reflux.
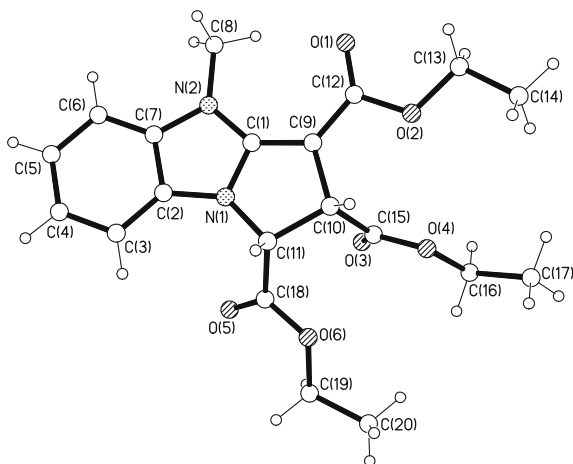
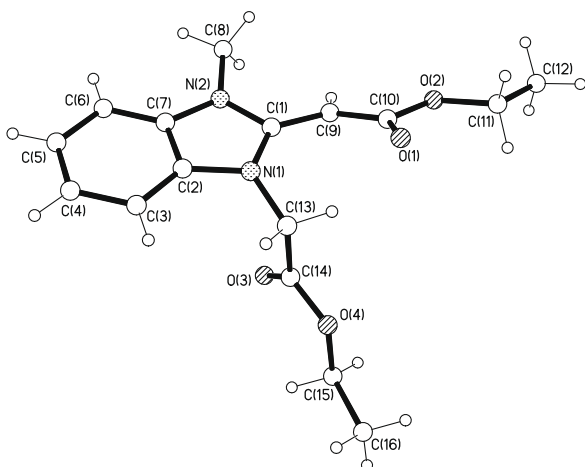**Figure 3.** X-ray crystal structure of cycloadduct **10**.

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

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 dimerisation of the carbene formed from the diazoacetate.

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**.

An additional by-product was isolated in this reaction, the 2-ethoxycarbonylmethylenebenzimidazole **11** (20%); we suggest that 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]

We have thus demonstrated that catalytic generation of 4,5-dihydroimidazolium ylides is possible as an alternative to alkyl-

ation-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

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9. *Typical procedure: Preparation of cycloadduct* **3a**. Ethyl diazoacetate (1.07 g, 9.37 mmol) in CH₂Cl₂ (10 mL) and dimethyl fumarate (1.61 g, 9.37 mmol) in CH₂Cl₂ (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 CH₂Cl₂ (20 mL) under nitrogen. The solution was stirred at reflux for 20 h, diluted with CH₂Cl₂ (10 mL), washed with water (2 × 10 mL), dried over MgSO₄ and concentrated under reduced pressure to give an oil, which was purified by column chromatography on silica gel [light petroleum (bp 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 C₂₀H₂₆N₂O₆: MH⁺ 391.1869; found: 391.1864. ν_{max} (KBr, cm⁻¹) 2952, 1737, 1435, 1202, 1027 and 701. δ_H (400 MHz, CDCl₃) 1.25–1.32 (m, 3H, CH₂C*H*₃), 2.47–2.53, 2.78–2.85 (2 × m, each 1H, NC*H*₂CH₂N), 2.97–3.02, 3.25–3.30 (2 × m, each 1H, NCH₂C*H*₂N), 3.35 (d, 1H, *J* 7.7 Hz, NC*H*HPh), 3.68, 3.69 (2 × s, each 3H, CH₃), 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, C*H*₂CH₃), 4.56 (d, 1H, *J* 6.8 Hz, H-7a) and 7.26–7.31 (m, 5H, Ph). δ_C (100 MHz, CDCl₃) 14.2 (CH₂*C*H₃), 47.6 (CH-6), 51.0 (CH-7), 52.0, 52.4 (OCH₃), 53.0 (*C*H₂Ph), 53.2, 56.6 (CH₂N), 61.2 (*C*H₂CH₃), 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** (mp 130–132 °C): C₂₀H₂₄N₂O₆, *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) Å³, *T* = 120(2) K, space group *P*2₁/*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 mm³, 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. wR_2 = 0.1159 (all data, 258 parameters); R_1 = 0.0529 [3061 data with $F^2 > 2\sigma$ (F^2)]. *Crystal data* for **11** (mp 101–105 °C): C₁₆H₂₀N₂O₄, *M* = 304.34, monoclinic, *a* = 10.741(11), *b* = 8.772(9), *c* = 17.121(17) Å, β = 100.321(13), *U* = 1587(3) Å³, *T* = 150(2) K, space group *P*2₁/*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 mm³, 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. wR_2 = 0.2554 (all data, 203 parameters); R_1 = 0.0940 [1433 data with $F^2 > 2\sigma$ (F^2)].
13. Crystallographic data (excluding structure factors) for the structures in this Letter 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).