A catalytic dipolar cycloaddition route to pyrroloimidazoles

How to cite:


For guidance on citations see FAQs.

© 2009 Elsevier Ltd.

Version: [not recorded]

Link(s) to article on publisher’s website:
http://dx.doi.org/doi:10.1016/j.tetlet.2009.03.064

Copyright and Moral Rights for the articles on this site are retained by the individual authors and/or other copyright owners. For more information on Open Research Online’s data policy on reuse of materials please consult the policies page.

oro.open.ac.uk
A catalytic dipolar cycloaddition route to pyrroloimidazoles

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

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

This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.
Graphical Abstract

To create your abstract, type over the instructions in the template box below. Fonts or abstract dimensions should not be changed or altered.

A catalytic dipolar cycloaddition route to pyrroloimidazoles
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.
A catalytic dipolar cycloaddition route to pyrroloimidazoles

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

a Chemistry Department, Loughborough University, Loughborough, Leicestershire LE11 3TU, UK

b Chemistry & Analytical Sciences Department, The Open University, Walton Hall, Milton Keynes MK7 6AA, UK

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 © 2009 Elsevier Science. All rights reserved

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, 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.

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

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

Keywords: dihydroimidazole; carbenoid; dihydroimidazolium ylide; dipolar cycloaddition; pyrroloimidazole

* Corresponding author. Tel.: +44 1509 222557; fax: +44 1509 223925; e-mail: r.c.f.jones@lboro.ac.uk
We eventually alighted on a successful protocol: the decomposition of ethyl glyoxylate tosylhydrazone. The starting materials were dihydroimidazoles 2a,b. The former was prepared as reported previously from N-benzylthiobenziminothiolan, and N-methyl analogue 2b was prepared from commercial N-methylthiobenziminothiolan and dimethylformamide diethyl acetal (THF, reflux, 65%).

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 diisocyanoacetyl diethyl acetylate (12% using Cu(acac)_2; 14% using Cu(OTf)_2).

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

<table>
<thead>
<tr>
<th>Dihydroimidazole</th>
<th>Cycloadduct</th>
<th>R^1</th>
<th>R^2</th>
<th>Yield %</th>
</tr>
</thead>
<tbody>
<tr>
<td>2a</td>
<td>3a</td>
<td>CH_3Ph</td>
<td>Me</td>
<td>48</td>
</tr>
<tr>
<td>2a</td>
<td>3b</td>
<td>CH_3Ph</td>
<td>Et</td>
<td>30</td>
</tr>
<tr>
<td>2b</td>
<td>3c, 6c</td>
<td>Me</td>
<td>Me</td>
<td>40, 21</td>
</tr>
<tr>
<td>2b</td>
<td>3d, 6d</td>
<td>Me</td>
<td>Et</td>
<td>68, 23</td>
</tr>
</tbody>
</table>

The relative stereochemistry of the cycloadducts 3a-d was determined by n.O.e 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).

![Figure 2](image-url)
Tetrahedron Letters

Ytterbium(III) triflate has been reported to accelerate 1,3-dipolar cycloadditions of carbonyl ylides with imines more effectively than other lanthanide triflates. It has been proposed to complex the imine to lower its LUMO, which accelerates the Sustmann type-II dipolar cycloaddition. 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 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$_2$CCHN$_2$, CH$_2$=CHCO$_2$Et, Cu(acac)$_2$ (10 mol%), CH$_2$Cl$_2$, 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). 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$_2$CCHN$_2$, EtO$_2$CCH=CHCO$_2$Et, Cu(OTf)$_2$, Yb(OTf)$_3$ (each 10 mol%), CH$_2$Cl$_2$, 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 carbeneid. The structure of 11 was also confirmed by X-ray crystal structure analysis (Fig. 4).

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.

References

12. Crystal data for 10 (m.p. 130-132 °C): C$_{24}$H$_{28}$N$_{2}$O$_{6}$, M = 388.41, monochinic, a = 12.557(4), 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-K$_\lambda$ radiation, χ = 0.71073 Å, Z = 4, D$_0$= 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 < 28.19°, 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$.^2$ > 2σ(F$^2$)). Crystal data for 11 (m.p. 101-105 °C): C$_{40}$H$_{32}$N$_{2}$O$_{6}$, M = 504.34, monochinic, a = 10.7411(10), b = 8.772(9), c = 17.121(17) Å, β = 100.231(13), U = 1587(3) Å$^3$, T = 150(2) K, space group P2$_1$/n, silicon 111 monochromated synchrotron radiation, χ = 0.8462 Å, Z = 4, D$_0$= 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. wR$_2$ = 0.2554 (all data, 203 parameters); R$_1$ = 0.0940 (1433 data with F$.^2$ > 2σ(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).