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Pyrrolo[1,2,3-*de*]quinoxalines: unexpected products from 1,3-dipolar cycloaddition of dihydroimidazolium ylides

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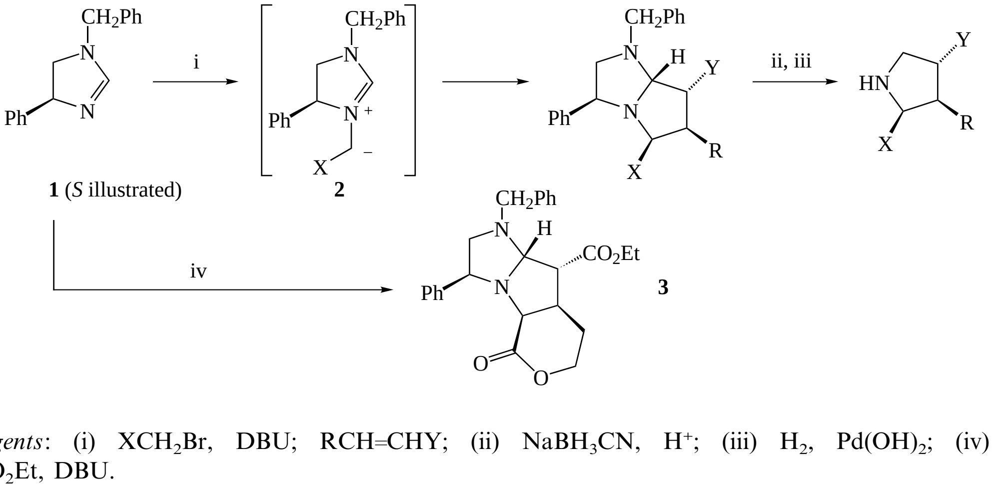
Abstract—4,5-Dihydroimidazoles undergo an *N*-alkylation and 1,3-dipolar cycloaddition cascade with unsaturated α-bromoketones, with subsequent eliminative ring-opening, recyclisation and tautomerisation to form unexpected hexahydropyrrolo[1,2,3-*de*]quinoxalines. © 2001 Elsevier Science Ltd. All rights reserved.

1. Introduction

We have recently reported on the 1,3-dipolar cycloaddition reactions of 4,5-dihydroimidazolium ylides **2**,[1] formed in situ from dihydroimidazoles **1** and an alkylating agent, and the application of the adducts in a synthesis of optically active pyrrolidines (Scheme 1).[2] As part of this programme, we have demonstrated an intramolecular cycloaddition using an α-haloester dipolarophile to give adducts **3**.[3] We wished to extend this latter process to α-haloketone dipolarophiles, and report herein that this sequence led to the unexpected isolation of hexahydropyrrolo[1,2,3-*de*]quinoxalines. This ring system has been reported rather infrequently,[4] including in the pharmaceutical patent literature.[5] Indeed, some derivatives have affinity for the NMDA–glycine binding site.[4g,h] Syntheses have invariably involved annulation of a preformed bicycle (quinoxaline or indole), rendering the approach herein as novel, and furthermore, these previous reports do not include the hexahydro oxidation level with a pyrrole sub-unit, that is afforded by the current work.



Scheme 1. *Reagents*: (i) XCH_2Br, DBU; RCH=CHY; (ii) $NaBH_3CN$, H^+; (iii) H_2, $Pd(OH)_2$; (iv) *E*-$BrCH_2CO_2(CH)_2CH{=}CHCO_2Et$, DBU.

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2. Results and discussion

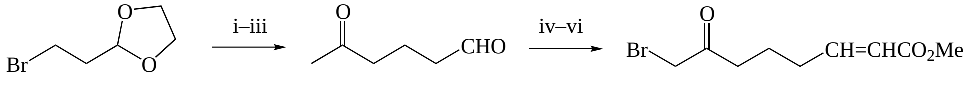
A suitable dipolarophile **4**, methyl 8-bromo-7-oxooct-2-enoate, was prepared (Scheme 2) from commercial 2-(2-bromoethyl)-1,3-dioxolane by reaction with ethyl acetoacetate (NaH, THF, reflux 18 h; 45%), hydrolysis–decarboxylation (5% aq. NaOH, reflux 16 h; 89%) and acid-mediated acetal cleavage (1 M hydrochloric acid, 50°C, 5 h; 79%) to afford 5-oxohexanal. Chain extension by Wittig reaction (Ph_3PCHCO_2Me, DCM, 20°C, 18 h; 90%; 8:1 *E*:*Z*) and bromination of the separated methyl ketones (LDA, THF, Me_3SiCl, −78°C; then $NaHCO_3$, THF, *N*-bromosuccinimide, −78°C→80°C; 45%) gave *E*- and *Z*-dipolarophiles **4a** (45%) and **4b**.

When **4a** was heated with 1-benzyl-4,5-dihydroimidazole **5a** in THF at reflux, with dropwise addition of DBU over 4 h,[1] the expected cycloadduct **6** was not observed but instead 1-benzyl-6-methoxy-carbonyl-2,3,7,8,9,10-hexahydro-1*H*-pyrrolo[1,2,3-*de*]quinoxaline **7a** was isolated (31%).[6] The formation of this unexpected heterocycle can be rationalised as shown in Scheme 3, via initial dipole formation and cycloaddition, with eliminative ring-opening of the primary adduct **6** and closure of the liberated secondary amine onto the ketone carbonyl group.[7] Formation of an enamine such as **8** (regiochemistry unknown) followed by a prototropic shift leads to the aromatic pyrrole substructure and formation of **7a**. As would be expected based on this proposal, the pyrroloquinazoline **7a** was also isolated (20%) when the diastereomeric *Z*-dipolarophile **4b** was used in the reaction.

Further examples of this dipolar cycloaddition ring-opening recyclisation cascade were observed. Use of the ethyl ester **4c** (prepared in similar fashion to **4a**,**b**) led to the 6-ethoxycarbonyl tricycle **7b** (30%), and the *tert*-butyl ester **4d** afforded the corresponding pyrroloquinazoline **7c** (33%). Changing the dihydroimidazole to 1-benzyl-2-phenyl-4,5-dihydroimidazole **5b**[8] likewise gave the 5-phenyl-6-alkoxycarbonyl heterocycles **7d**–**f** (33, 31 and 34%, respectively) with the three α-haloketone dipolarophile variants **4a**,**c**,**d**. (*R*)-1-Benzyl-4-phenyl-4,5-dihydroimidazole **5c**[2] similarly led to isolation of the products **7g**,**h**, respectively (each 30%), when the methyl and ethyl ester dipolarophiles **4a**,**c** were utilised.

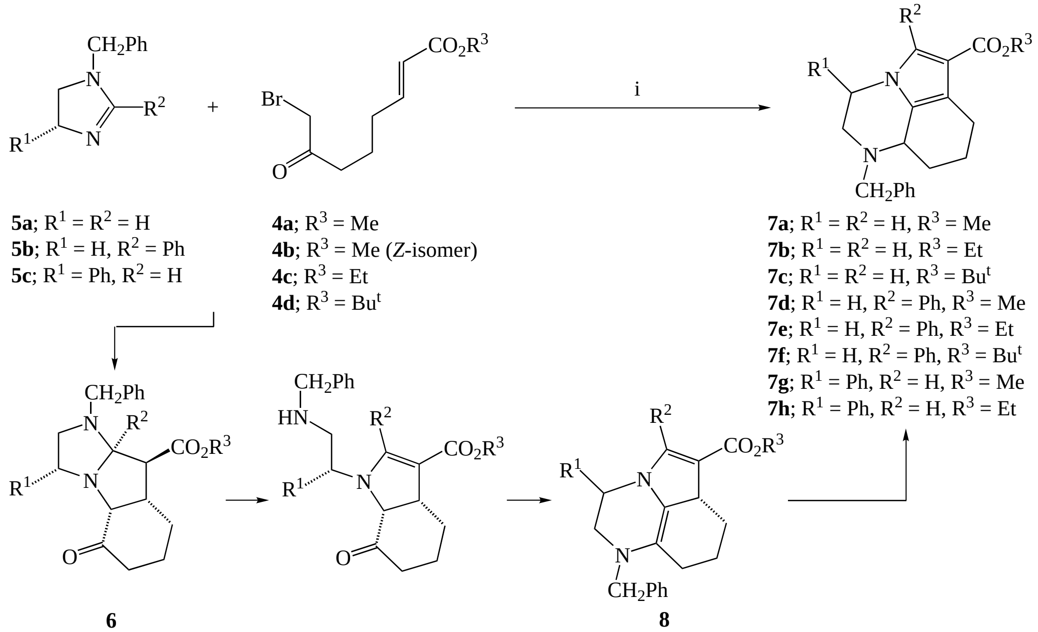
Interestingly, when the procedure was applied to dihydroimidazole **5c** and the *tert*-butyl ester dipolarophile **4d**, the primary cycloadduct **6a** (R^1 = Ph, R^2 = H, R^3 = Bu^t) was isolated (31%) rather than the rearrangement product. This supports the suggested sequence for pyrroloquinazoline formation (Scheme 3). We speculate that this particular substituent combination disfavours the elimination step, possibly on steric grounds.

The structures of the pyrrolo[1,2,3-*de*]quinazolines **7** were supported by standard spectral data. In addition, X-ray crystal structure determinations were performed on products **7b**, **7d** and **7g**, which confirmed their structures.[9] The latter is illustrated in Fig. 1 and shows that the phenyl 3-substituent and the bridgehead proton at C-9a are located on the same face of the molecule,



4a: *E*; **4b**: *Z*

Scheme 2. *Reagents*: (i) NaH, $CH_3COCH_2CO_2Et$, THF reflux; (ii) 5% aq. NaOH, reflux; (iii) 1 M aq. HCl, 50°C; (iv) Ph_3PCHCO_2Me, DCM, 20°C; (v) LDA, THF, −78°C, Me_3SiCl; (vi) $NaHCO_3$, THF, NBS, −78→80°C.



5a; R^1 = R^2 = H
5b; R^1 = H, R^2 = Ph
5c; R^1 = Ph, R^2 = H

4a; R^3 = Me
4b; R^3 = Me (*Z*-isomer)
4c; R^3 = Et
4d; R^3 = Bu^t

7a; R^1 = R^2 = H, R^3 = Me
7b; R^1 = R^2 = H, R^3 = Et
7c; R^1 = R^2 = H, R^3 = Bu^t
7d; R^1 = H, R^2 = Ph, R^3 = Me
7e; R^1 = H, R^2 = Ph, R^3 = Et
7f; R^1 = H, R^2 = Ph, R^3 = Bu^t
7g; R^1 = Ph, R^2 = H, R^3 = Me
7h; R^1 = Ph, R^2 = H, R^3 = Et

6

8

Scheme 3. *Reagents*: (i) DBU, THF reflux.

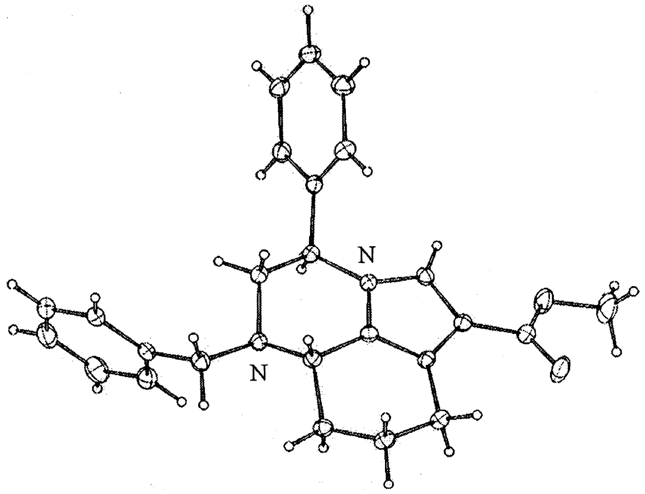


Figure 1. Crystal structure of pyrroloquinoxaline **7a**.

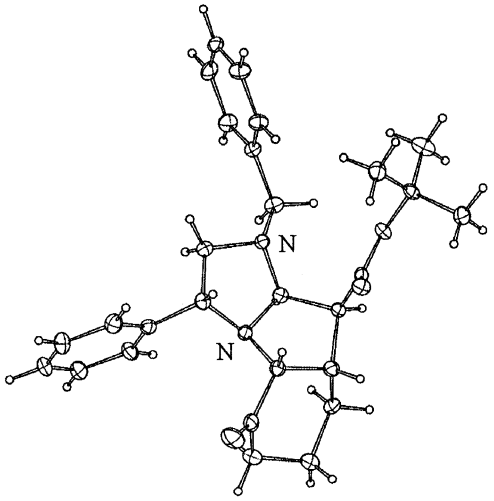


Figure 2. Crystal structure of cycloadduct **6a**.

presumably arising from thermodynamic control of the prototropic shift (Scheme 3). In addition, an X-ray crystal structure was obtained for the primary cycloadduct **6a**[9] and showed (Fig. 2) that the cycloaddition had indeed proceeded in the *endo*-mode that we have consistently observed in earlier reports on dihydroimidazolium ylides;[1–3] NOE studies further support this stereochemical assignment.

We have thus demonstrated formation of the rare hexahydropyrrolo[1,2,3-*de*]quinoxaline ring system as a secondary product of intramolecular dihydroimidazolium ylide cycloaddition. Exploitation of both the primary and secondary processes is under investigation.

Acknowledgements

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References

1. Jones, R. C. F.; Howard, K. J.; Nichols, J. R.; Snaith, J. S. *J. Chem. Soc., Perkin Trans. 1* **1998**, 2061–2072.
2. (a) Jones, R. C. F.; Howard, K. J.; Snaith, J. S. *Tetrahedron Lett.* **1996**, *37*, 1707–1710; (b) Jones, R. C. F.; Howard, K. J.; Snaith, J. S. *Tetrahedron Lett.* **1996**, *37*, 1711–1714.
3. Jones, R. C. F.; Howard, K. J.; Snaith, J. S. *Tetrahedron Lett.* **1997**, *38*, 1647–1650.
4. See, for example: (a) Richardson, A. *J. Org. Chem.* **1965**, *30*, 2589–2593; (b) Suschitzky, H.; Wakefield, B. J.; Whittaker, R. A. *J. Chem. Soc., Perkin Trans. 1* **1975**, 401–403; (c) Grinev, A. N.; Trofimkin, Y. I.; Lomanova, E. V.; Adreeva, N. I.; Mashkovskii, M. D. *Khim.-Farm. Zh.* **1978**, *12*, 80–84; (d) Bogatskii, A. V.; Ivanova, R. Yu; Andronati, S. A.; Zhilina, Z. I. *Khim. Geterotsikl. Soedin.* **1979**, *15*, 839–841; (e) Grinev, A. N.; Lomanova, E. V. *Khim. Geterotsikl. Soedin.* **1983**, *19*, 1690; (f) Sudoh, Y.; Onitsuka, K.; Imafuku, K.; Matsumura, H. *Bull. Chem. Soc. Jpn.* **1983**, *56*, 3358–3363; (g) Walser, A.; Flynn, T.; Mason, C.; Crowley, H.; Mareska, C.; Jaremko, B.; O'Donnell, M. *J. Med. Chem.* **1991**, *34*, 1209–1221; (h) Kubicki, M.; Kindoop, T. W.; Capparelli, M. V.; Codding, P. W. *Can. J. Chem.* **1994**, *72*, 2028–2036; (i) Nagata, R.; Tanno, N.; Kodo, T.; Ae, N.; Yamaguchi, H.; Nishimura, T.; Antoku, F.; Tatsuno, T.; Kato, T.; Tanaka, Y.; Nakamura, M. *J. Med. Chem.* **1994**, *37*, 3956–3968; (j) Mickelson, J. W.; Jacobsen, E. J.; Carter, D. B.; Im, H. K.; Im, W. B.; Schreuer, P. J. K. D.; Sethy, V. H.; Tang, A. H.; McGee, J. E.; Petke, J. D. *J. Med. Chem.* **1996**, *39*, 4654–4666.
5. (a) US Patent 3,813,392; *Chem. Abstr.* **1974**, *81*, 49700; (b) US Patent 3,891,643; *Chem. Abstr.* **1975**, *83*, 147502; (c) US Patent 3,892,746; *Chem. Abstr.* **1975**, *83*, 147503; (d) US Patent 4,087,527; *Chem. Abstr.* **1978**, *89*, 109587; (e) US Patent 4,075,206; *Chem. Abstr.* **1978**, *88*, 190901.
6. All new compounds had spectra in accord with the assigned structures, and gave satisfactory combustion analyses or high resolution mass spectra. Data for **7a**: mp 120–123°C. Found: MH^+ 311.1763. $C_{19}H_{22}N_2O_2$ requires MH 311.1759; ν_{max} (Nujol)/cm^{-1} 2944, 2881, 1735, 1697, 1524, 1463, 1390, 1248, 1172, 1098, 1051, 916, 732; δ_H ($CDCl_3$; 300 MHz) 1.45 (1H, dtd, *J* 2.5, 11.6, 13.5 Hz, 9-C*H*H), 1.76 (1H, dddt, *J* 2.1, 6.0, 11.6, 13.7 Hz, 8-C*H*H), 2.12 (1H, m, 8-CH*H*), 2.29 (1H, m, 9-CH*H*), 2.49 (1H, ddd, *J* 7.5, 10.0, 12.5 Hz, 2-C*H*H), 2.66 (1H, dddd, *J* 2.1, 5.8, 11.2, 16.8 Hz, 7-C*H*H), 2.86 (1H, dd, *J* 6.4, 16.8 Hz, 7-CH*H*), 3.02 (1H, ddd, *J* 2.3, 3.9, 12.5 Hz, 2-CH*H*), 3.13 (1H, d, *J* 13.2 Hz, PhC*H*H), 3.28 (1H, br. d, *J* 10.6 Hz, 9a-CH), 3.76 (3H, s, OCH_3), 3.85 (2H, m, 3-CH_2), 4.25 (1H, d, *J* 13.2 Hz, PhCH*H*), 7.12 (1H, s, 5-CH), 7.23-7.37 (5H, m, Ar-H); δ_C ($CDCl_3$; 75 MHz) 22.4, 22.5 and 27.9 (C-7, 8, 9), 44.9 and 49.7 (C-2, 3), 50.6 (OCH_3), 57.3 (PhCH_2), 59.7 (C-9a), 113.8 (C-6a), 117.0 (C-6), 124.3 (C-5), 127.2, 128.4, and 129.0 (Ar-CH), 130.2 (C-9b), 138.4 (Ar-C), 165.9 (CO); *m*/*z* 311 (MH^+, 10%), 283 (10), 282 (41), 191 (39), 161 (6), 91 (100), 49 (21), 43 (17).
7. c.f. Refs. 1 and 3 for related ring-opening–lactam formation.
8. Prepared from (2-benzylamino)ethylamine and ethyl benzimidate hydrochloride: Howard, K. J. Ph.D. Thesis, University of Nottingham, 1995.

9. Crystal data for compounds **7b**, **7d**, **7g** and **6a** are deposited with the Cambridge Crystallographic Database. *Crystal data* for **7g**: $C_{25}H_{26}N_2O_2$, $M=386.48$, monoclinic, $a=10.559(2)$, $b=9.6567(19)$, $c=11.052(2)$ Å, $\beta=112.47(3)$, $U=1041.5(4)$ Å^3, $T=150(2)$ K, space group $P2_1$, monochromated Mo Kα radiation, $\lambda=0.71073$ Å, $Z=2$, $D_c=1.232$ Mg m^{-3}, $F(000)=412$, colourless block, dimensions 0.25×0.25×0.10 mm, μ(Mo Kα)$=0.078$ mm^{-1}, $1.99<2\theta<27.48°$, 12212 reflections measured, 4640 unique reflections. The structure was solved by direct methods and refined by full-matrix least-squares on F^2. The final cycle (for 264 parameters) converged with $wR2=0.0897$ (for all data) and $R1=0.0373$ [$F^2>2\sigma(F^2)$]. *Crystal data* for **6a**: $M=446.57$, monoclinic, $a=5.8566(4)$, $b=22.8548(18)$, $c=9.1424(7)$ Å, $\beta=92.913(6)°$, $U=1222.14(16)$ Å^3, $T=150(2)$ K, space group $P2_1$, monochromated Mo Kα radiation, $\lambda=0.71073$ Å, $Z=2$, $D_c=1.214$ Mg m^{-3}, $F(000)=480$, colourless blocks, dimensions 0.20×0.20×0.10 mm, μ(Mo Kα)$=0.079$ mm^{-1}, $3.48<2\theta<24.71°$, 6900 reflections measured, 3346 unique reflections. The structure was solved by direct methods and refined by full-matrix least-squares on F^2. The final cycle (for 299 parameters) converged with $wR2=0.1075$ (for all data) and $R1=0.0500$ [$F^2>2\sigma(F^2)$].