1,3-Dipolar Cycloadditions of 4,5-Dihydroimidazolium Ylides: New Protocols for the Synthesis of Pyrrolidines and Pyrrolo[1,2-*a*]pyrazines

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1,3-Dipolar cycloadditions of 4,5-dihydroimidazolium ylides formed from 1-benzyl-4,5-dihydroimidazole proceed *via* a convenient one-step, one-pot protocol to give hexahydropyrrolo[1,2-*a*]imidazole esters, reduction of which leads to either hexahydropyrrolo[1,2-*a*]pyrazines or *N*-substituted pyrrolidines depending on the nature of the ester.

We recently revealed a novel route to *N*-substituted pyrrolidines **3** by the 1,3-dipolar cycloaddition of imidazolium ylides **1** to dipolarophiles followed by aminal reduction of the hexahydropyrrolo[1,2-*a*]imidazole cycloadducts **2**.[1,2] The reported protocols involved a two-step process of quaternisation of 1-benzyl-4,5-dihydroimidazole **4a** followed by generation of ylide **1** and *in situ* cycloaddition.[1] We report now a revised single step protocol that renders the cycloadditions much more convenient; we also record a revision of the reduction findings that demonstrates the formation of hexahydropyrrolo[1,2-*a*]-pyrazines, and an alternative sequence that does terminate in *N*-substituted pyrrolidines.

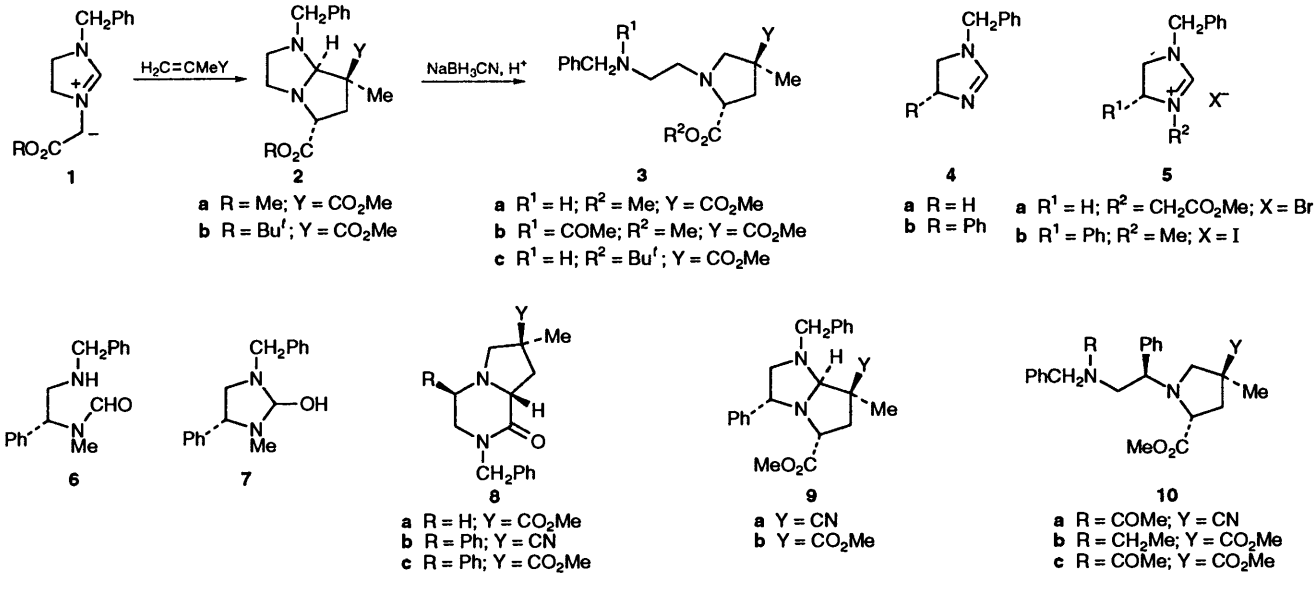
Initially 1-benzyl-4,5-dihydroimidazole **4a** had been quaternised by an α-halo ester such as methyl bromoacetate, in diethyl ether or tetrahydrofuran (THF) (20 °C, 2 h), with isolation of the salt **5a** by filtration or evaporation of volatile materials before ylide generation using 1,8-diazabicyclo-[5.4.0]undec-7-ene (DBU) in THF at reflux.[1] Avoiding the isolation by performing the alkylation in THF (20 °C, 2 h) before direct addition of dipolarophile and base improved the yield of a test reaction using methyl methacrylate as dipolarophile to afford adduct **2a**,†,‡ from a maximum of 37% to a maximum of 60%. Nevertheless an observed variability in yield led us to examine the quaternisation further. TLC revealed only approximately half of the dihydroimidazole **4a** had reacted after 2 h, and a further 23 h did not see the reaction reach completion; continuing with the cycloaddition after this time led to adduct **2a** in only 38% yield. Our earlier observation of the hygroscopic nature of the isolated dihydroimidazolium salts suggested the destruction of the quaternary salts by adventitious moisture, a problem exacerbated by longer reaction times or extra manipulations. In accord with this idea, when the 4-phenyl-4,5-dihydroimidazole **4b**§ was treated with iodomethane (THF, 20 °C) until complete disappearance of starting material (by TLC; 48 h), spectral data for the isolated product were not consistent with the expected quaternary salt **5b**. Instead they indicated the *N*-formyl diamine **6** (no dihydromidazole C-2 signal in the ^{1}H NMR; ν_{max} 1650 cm^{-1}) which would be formed by ring opening of a pseudo-base adduct **7** of the salt.

This information led us to a new abbreviated and convenient protocol for the cycloadditions in which the quaternary salt is consumed as it is formed. Thus, alkylating agent and dipolarophile are added together and in one portion to the dihydroimidazole **4** heated at reflux in THF, followed immediately by dropwise addition of DBU over 4 h, and a further 2 h at reflux. By this one-step, one-pot protocol the test

† All new compounds gave spectral data (IR UV, NMR, MS) in accord with the assigned structure, and satisfactory combustion analysis or accurate mass measurement.

‡ The relative stereochemistry of all cycloadducts was secured by ^{1}H NMR NOE experiments.

§ Preparation of the 4-phenyl-4,5-dihydroimidazoles and their cycloadditions will be reported fully elsewhere.



reaction gave reproducible 60–65% yields of cycloadduct **2a**; it is applicable to all such cycloadditions reexamined.

Reduction of the cycloadducts **2** ($NaBH_3CN$, HCl–EtOH) was originally reported to afford *N*-substituted pyrrolidines **3**,[1] but in practice the amino esters **3** underwent ready cyclization to the hexahydropyrrolo[1,2-*a*]pyrazines **8**, *e.g.* **3a** to **8a**. This latter was first observed as 'impurity' during prompt column chromatography after reduction of cycloadduct **2a** from our test reaction (see above) and, moreover, was the sole material present (by ^1H NMR; 84% isolated) on allowing **3a** to stand for several days. Attempted trapping of the *N*-(2-benzylaminoethyl)pyrrolidine **3a** by acetylation (Ac_2O, AcOH) proved inefficient but aminal reduction with *in situ* acylation was effective ($NaBH_3CN$, AcOH–Ac_2O) in producing **3b** (53%). In the case of the 3-phenyl cycloadduct **9a** (methacrylonitrile as dipolarophile), the pyrrolopyrazine **8b** was the only isolated product (42%) from reduction in the absence of acylating agent ($NaBH_3CN$, HCl–EtOH). Compound **8b** was also formed (42%) along with *N*-acetyl derivative **10a** (48%) even in the presence of acetic anhydride [$NaBH_3CN$, AcOH, Ac_2O (2 mol. equiv.)]. Increasing the proportion of acylating agent, however, led to increased pyrrolidine and less bicycle, for example using the methyl methacrylate cycloadduct **9b**, although *N*-ethyl material **10b** now appeared, possibly from *in situ* borane generation and acetamide reduction. For example, with 140 mol equiv. Ac_2O, acetamide **10c** (44%), bicyclic pyrazine **8c** (5%) and *N*-ethyl compound **10b** (7%) were isolated.

Our objective of *N*-substituted pyrrolidine formation was cleanly secured by the simple expedient of using a more bulky ester. Thus, 1-benzyl-4,5-dihydroimidazole **4a**, *tert*-butyl bromoacetate, methyl methacrylate and DBU gave cycloadduct **2b** in 71% yield and reduction ($NaBH_3CN$, HCl–EtOH) afforded pyrrolidine **3c** (60%) which was stable towards cyclization over extended periods. This tactic was successful also in the cyclization-sensitive phenyl-substituted series.

We have therefore demonstrated (*a*) a major simplification of the experimental protocol, and (*b*) a selective approach to either *N*-substituted pyrrolidines[3] or hexahydropyrrolo[1,2-*a*]pyrazines.

Experimental

Typical procedures: 1-*Benzyl*-5,7-*bis*(*methoxycarbonyl*)-7-*methylhexahydropyrrolo*[1,2-a]*imidazole* **2a**.—Methyl bromoacetate (0.96 g, 0.59 cm^3, 6.25 mmol) was added to a solution of 1-benzyl-4,5-dihydroimidazole **4a** (1.0 g, 6.25 mmol) in dry THF (30 cm^3), stirred at reflux under nitrogen. Methyl methacrylate (1.88 g, 2.00 cm^3, 18.75 mmol) was then added in one portion followed by the dropwise addition, over 4 h, of DBU (0.95 g, 0.93 cm^3, 6.25 mmol). Stirring at reflux was continued for 2 h. The solvent was then evaporated under reduced pressure and the residue was partitioned between chloroform (3 × 30 cm^3) and water (30 cm^3). The organic phase was dried (Na_2SO_4), evaporated under reduced pressure and the residue was purified by column chromatography on silica gel, eluting with ethyl acetate–hexane (2:1 v/v) to yield the *title compound* as a pale-yellow oil (1.33 g, 64%) (Found: M^+ 332.1742. $C_{18}H_{24}N_2O_4$ requires, *M*, 332.1736); ν_{max}(film)/cm^{-1} 2949, 2842, 2802, 1730, 1453, 1202, 1159, 1137 and 701; δ_H(400 MHz; $CDCl_3$) 1.42 (s, 3 H, CMe), 2.10 (dd, 1 H, *J* 10.1, 13.2, C*H*HCMe), 2.57 (m, 1 H, NC*H*HCH$_2$N), 2.77 (m, 2 H, CH*H*CMe and NCH$_2$C*H*HN), 3.00 (m, 1 H, NCH*H*CH$_2$N), 3.22 (m, 2 H, NCH$_2$CH*H*N and PhC*H*H), 3.72 and 3.74 (each s, 3 H, OMe), 4.04 (m, 3 H, 7a-H, PhCH*H* and C*H*CO$_2$Me) and 7.27 (m, 5 H, ArH); δ_C(100 MHz; $CDCl_3$) 23.1 (C*Me*), 42.6 (CH*C*H$_2$), 51.7 and 51.96 (OMe), 5.27 (*C*Me), 53.1 and 54.7 (NCH$_2$CH$_2$N), 58.6 (PhCH$_2$), 67.7 (*C*HCO$_2$Me), 95.1 (C-7a), 126.9, 128.2 and 128.5 (ArCH), 138.7 (ArC) and 174.3 and 174.9 (*C*O$_2$Me); *m*/*z* 332 (M^+, 2%), 301 (6), 273 (8), 232 (100), 141 (89), 114 (13) and 91 (58).

2-*Benzyl*-7-*methoxycarbonyl*-7-*methyloctahydropyrrolo*[1,2-a]*pyrazin*-1-*one* **8a**.—A solution of 1-benzyl-5,7-bis(methoxycarbonyl)-7-methylhexahydropyrrolo[1,2-*a*]imidazole **2a** (0.56 g, 1.7 mmol) in ethanol (20 cm^3) was made acidic to methyl green indicator by the dropwise addition of hydrochloric acid (2 mol dm^{-3}). Sodium cyanoborohydride (118 mg, 1.87 mmol) was added portionwise while maintaining the acidity, and the resulting mixture was stirred at 20 °C for 3 h. The mixture was basified to pH 8 by the portionwise addition of solid potassium bicarbonate and partitioned between chloroform (2 × 50 cm^3) and water (50 cm^3). The organic phase was dried (Na_2SO_4) and evaporated under reduced pressure. The residue was purified by column chromatography, eluting with ethyl acetate–triethylamine (99.5:0.5 v/v) and on standing this yielded the *title compound* as a colourless oil (0.43 g, 84%) (Found: M^+ 302.1642. $C_{17}H_{22}N_2O_3$ requires, *M*, 302.1630); ν_{max}(film)/cm^{-1} 2950, 1730, 1647, 1493, 1434, 1224, 1194 and 732; δ_H (400 MHz; $CDCl_3$) 1.37 (s, 3 H, CMe), 1.87 (dd, 1 H, *J* 8.4, 13.3, CHC*H*H), 2.74 (d, 1 H, *J* 9.0, NC*H*HCMe), 2.87 (m, 2 H, CHCH*H* and NC*H*HCH$_2$N), 2.95 (m, 1 H, NCH*H*CH$_2$N), 3.10 (m, 2 H, NCH$_2$C*H*HN and NCH*H*CMe), 3.44 (m, 2 H, NCH$_2$CH*H*N and C*H*CH$_2$), 3.70 (s, 3 H, OMe), 4.45 (d, 1 H, *J* 14.6, PhC*H*H), 4.70 (d, 1 H, *J* 14.6, PhCH*H*) and 7.27 (m, 5 H, ArH); δ_C(100 MHz; $CDCl_3$) 24.7 (C*Me*), 39.5 (CH*C*H$_2$), 44.3 and 46.7 (NCH$_2$CH$_2$N), 47.9 (*C*Me), 49.6 (PhCH$_2$), 52.2 (OCH$_3$), 62.5 (NCH$_2$CMe), 63.6 (*C*HCH$_2$), 127.5, 128.1 and 128.6 (ArCH), 136.8 (ArC), 170.4 (CO$_2$Me) and 177.0 (CON).

1-*Benzyl*-5-tert-*butoxycarbonyl*-7-*methoxycarbonyl*-7-*methylhexahydropyrrolo*[1,2-a]*imidazole* **2b** *and* 1-[(2-*Benzylamino*)*ethyl*]-2-tert-*butoxycarbonyl*-4-*methoxycarbonyl*-4-*methylpyrrolidine* **3c**.—The cycloadduct **2b** was prepared using the method described above for the preparation of **2a** but using *tert*-butyl bromoacetate (1.22 g, 0.92 cm^3, 6.25 mmol). Purification by column chromatography, eluting with hexane–ethyl acetete (3:1) yielded the *title compound* **2b** as a colourless oil (1.67 g, 71%). Pyrrolidine **3c** was prepared from **2b** (0.5 g, 1.34 mmol) using the method described above for the preparation of bicycle **8a**, but using sodium cyanoborohydride (92.6 mg, 1.47 mmol). Purification by column chromatography, eluting with ethyl acetate–triethylamine (95:5 v/v) yielded the *title compound* **3c** as a pale yellow oil (0.30 g, 60%) (Found: C, 66.7; H, 8.9; N, 7.45%; M^+ 376.2363. $C_{21}H_{32}N_2O_4$ requires: C, 67.0; H, 8.6; N, 7.4%; *M*, 376.2362); ν_{max}(film)/cm^{-1} 2975, 2817, 1732, 1453, 1366, 1151 and 1114; δ_H(250 MHz; $CDCl_3$) 1.38 (s, 3 H, CMe), 1.45 (s, 9 H, CMe$_3$), 1.75 (dd, 1 H, *J* 6.8, 13.3, CHC*H*H), 2.71 (m, 5 H, NCH$_2$CH$_2$N and CHCH*H*), 2.88 (dd, 2 H, *J* 9.3, 11.0, NC*H*$_2$CMe), 3.25 (dd, 1 H, *J* 6.8, 9.2, C*H*CH$_2$), 3.67 (s, 3 H, OMe), 3.79 (2 × d, 2 H, *J* 13.0, PhC*H*$_2$) and 7.29 (m, 5 H, ArH); δ_C(68 MHz, $CDCl_3$) 24.2 (C*Me*), 27.9 (C*Me*$_3$), 40.3 (*C*H$_2$CMe), 47.2 (NCH$_2$CH$_2$N), 47.6 (CH$_2$*C*Me), 52.0 (OMe), 53.5 (NCH$_2$*C*H$_2$N), 53.7 (PhCH$_2$), 62.4 (NCH$_2$CMe), 66.0 (*C*HCH$_2$), 80.6 (*C*Me$_3$), 126.6, 128.0 and 128.1 (ArCH), 140.3 (ArC), 172.9 and 176.9 (CO); *m*/*z* 376 (M^+, 1%), 275 (20), 200 (100), 156 (22) and 91 (78).

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References

1 R. C. F. Jones, J. R. Nichols and M. T. Cox, *Tetrahedron Lett.*, 1990, **31**, 2333.
2 For other examples of amidines as a source of azomethine ylides, see: R. Smith and T. Livinghouse, *Tetrahedron*, 1985, **41**, 3559; O. Tsuge, S. Kanemasa and K. Matsuda, *J. Org. Chem.*, 1986, **51**, 1997.
3 For a recent related approach to pyrrolidines using cyclic azomethine ylides, see: L. M. Harwood and I. A. Lilley, *Tetrahedron Lett.*, 1993, **34**, 537, and references therein; R. M. Williams, W. Zhai, D. J. Aldous and S. C. Aldous, *J. Org. Chem.*, 1992, **57**, 6527.

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