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Heterocyclic [4⁺ + 2] Cycloadditions: The Reactivity of Pyridinium Salts with Electron-rich Olefins

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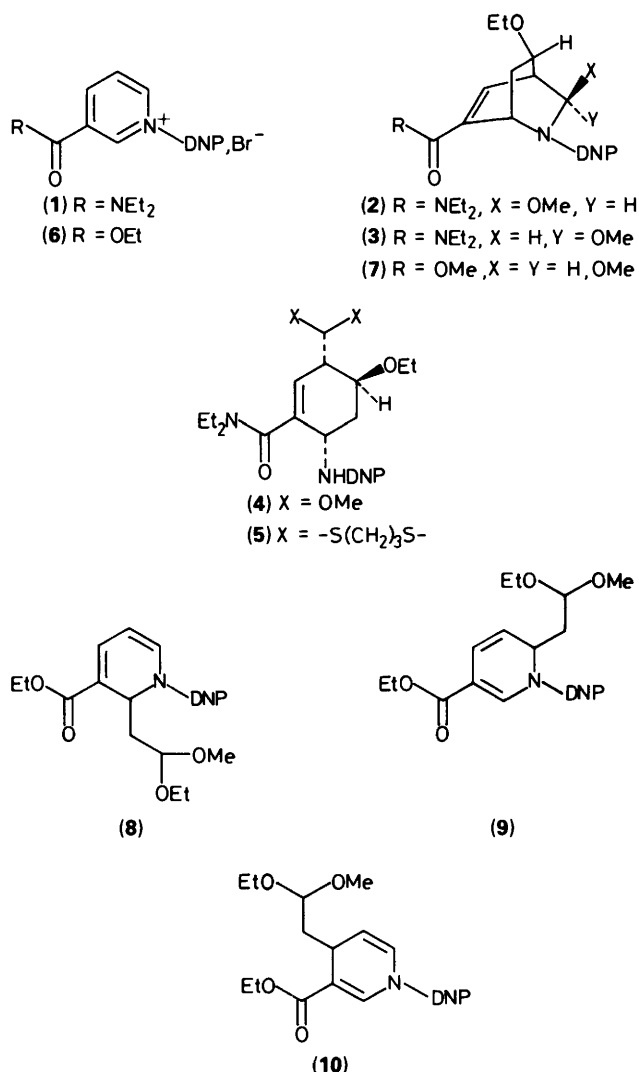
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The *N*-(2,4-dinitrophenyl) salts of *N,N*-diethylnicotinamide and ethyl nicotinate undergo [4⁺ + 2] cycloaddition with enol ethers at room temperature, providing the first examples of Bradsher cyclization by monocyclic quaternary aza-aromatics; other derivatives and salts of pyridine are inert under these conditions.

The [4⁺ + 2] cycloaddition¹ of quaternary aza-aromatic salts, first observed by Bradsher and Solomons,² is formally related to the classical Diels–Alder reaction. As a consequence in part of the resident positive charge on the 4π-component, [4⁺ + 2] cyclizations with easily polarizable, unsymmetrical dienophiles are often highly or totally regio- and stereospecific.³ Recent reports⁴ from these and other laboratories have illustrated the synthetic utility of Bradsher-type cyclizations, but, to date, only fused polycyclic aromatics have been explored. In continuation of our interest in the scope and preparative applications of this methodology, we describe herein a preliminary account of the reactivity of pyridinium salts towards [4⁺ + 2] cycloaddition with electron-rich olefins.

Treatment of a methanolic solution of salt (1), prepared from *N,N*-diethylnicotinamide and 1-bromo-2,4-dinitrobenzene (DNP-Br), with excess ethyl vinyl ether at ambient temperature for 12 h in the presence of powdered CaCO₃ provided two cycloadducts (1:1.3, 85%) after chromatographic purification [SiO₂:ethyl acetate–hexane (1:1), *R_f* ~ 0.20 and 0.35]. Extensive NMR analysis (COSY, NOE) established their structures as (2) and (3), respectively, the result of *exo*-addition across C(2)–C(5) and trapping of the resultant immonium ion by solvent. The assignments were confirmed by nearly quantitative conversion of (2) and (3) to the same ring-opened acetal (4) using Dowex 50X8-400(H) resin in anhydrous methanol.^{4a} Dithiane (5) could be obtained directly from (1) and ethyl vinyl ether by cycloaddition in CH₂Cl₂ containing an equimolar amount of 1,3-propanedithiol. Analogous results were achieved with 2,3-dihydrofuran and (*Z*)-1-methoxypropene as dienophiles whereas styrene and phenyl vinyl sulphide were largely unreactive even under forcing conditions.

Cyclization, as above, between the DNP salt of ethyl nicotinate (6), m.p. 179–180 °C (dec.), and ethyl vinyl ether furnished adduct (7) (14%) as a mixture of C(6) epimers, accompanied by (8), (9), and (10) (13%, 21%, 13%, respectively). The latter addition products are in accord with the two step mechanism for the Bradsher cyclization proposed by Gupta and Franck^{4a} involving initial nucleophilic addition to the heterocyclic ring, except, in this case, interception of the intermediate oxocarbenium ion by solvent is competitive with ring closure. In contrast, the *N*-



methiodide and *N*-(2-methoxycarbonylvinyl) salts* of *N,N*-diethylnicotinamide, ethyl nicotinate and pyridine proved inert to ethyl vinyl ether and other electron-rich dienophiles.

While providing the first examples of Bradsher cyclization by a monocyclic quaternary aza-aromatic,† these data also reveal the finely balanced reactivity of pyridinium salts towards [4⁺ + 2] cycloaddition. The application of this methodology to other heterocyclic systems will help to define its limitations and synthetic potential.

Experimental

DNP-salt (1).—*N,N*-Diethylnicotinamide (2.55 g, 14.3 mmol) and 2,4-dinitrobromobenzene (3.89 g, 15.7 mmol) were heated in refluxing acetonitrile (20 ml) for 5 h under an argon atmosphere. After cooling, the mixture was reduced to approximately one-quarter volume on a rotary evaporator, then diluted with diethyl ether (20 ml) and allowed to stand for several hours. The yellow precipitate was collected by filtration, washed with a minimum volume of Et₂O–CH₂Cl₂ (1:1), and dried *in vacuo* to give (1) (4.02 g, 66%), m.p. 203–205 °C (Found: C, 45.30; H, 3.95; N, 13.40. C₁₆H₁₇BrN₄O₅ requires C, 45.19; H, 4.03; N, 13.17%); δ_H(90 MHz; [2H₆]DMSO) 1.20 (6 H, t, *J* 7 Hz), 3.38 (4 H, q, *J* 7 Hz), 8.34 (1 H, dd, *J* 6 and 8 Hz), 8.57–8.84 (3 H, m), 9.02 (1 H, br s), 9.53 (1 H, d, *J* 6 Hz), and 9.58 (1 H, s).

Cycloadducts (2) and (3).—To a stirring 0 °C solution of DNP-salt (1) (137 mg, 0.322 mmol) in anhydrous MeOH (5 ml) containing powdered CaCO₃ (200 mg, 2.60 mmol) was added dropwise ethyl vinyl ether (220 mg, 3.05 mmol). After stirring at room temperature for 12 h, the solvent was removed on a rotary evaporator and the residue was dissolved in CH₂Cl₂, filtered to remove the CaCO₃, and the filtrate concentrated. Flash column chromatography on silica gel using EtOAc–hexane (1:1) containing 1% Et₃N afforded (2) (54 mg, 37%), m.p. 137–141 °C (from Et₂O–hexane) (Found: C, 56.50; H, 6.45; N, 12.85.

* *N*-(2-methoxycarbonylvinyl) salts were prepared according to M. E. Jung and K. R. Buszek, *J. Am. Chem. Soc.*, 1988, **110**, 3965.

† The first example of an inverse electron demand Diels–Alder reaction with an uncharged pyridine derivative was reported recently: A. E. Frissen, A. T. M. Marcelis, G. Geurtsen, D. A. de Bie, and H. C. van der Plas, *Recl. Trav. Chim. Pays-Bas*, 1987, **106**, 547.

C₂₁H₂₈N₄O₇ requires C, 56.24; H, 6.29; N, 12.49%); δ_H(200 MHz, CDCl₃) 1.15 (6 H, t, *J* 6.9 Hz), 1.21 (3 H, t, *J* 6.9 Hz), 1.76 (1 H, ddd, *J* 1.5, 2.3, and 13.8 Hz), 2.71 (1 H, ddd, *J* 3.0, 7.8, and 13.8 Hz), 3.24 (3 H, s), 3.40–3.58 (6 H, complex m), 3.62–3.68 (1 H, m), 4.12 (1 H, ddd, *J* 2.3, 2.6, and 7.8 Hz), 4.50 (1 H, d, *J* 2.4 Hz), 4.90 (1 H, dd, *J* 1.5 and 3.0 Hz), 6.48 (1 H, d, *J* 6.2 Hz) 7.18 (1 H, d, *J* 9.5 Hz), 8.26 (1 H, dd, *J* 2.6 and 9.5 Hz), and 8.63 (1 H, d, *J* 2.6 Hz).

(3) (70 mg, 48%), m.p. 147–149 °C (from Et₂O–hexane) (Found: C, 56.10; H, 6.25; N, 12.20. C₂₁H₂₈N₄O₇ requires C, 56.24; H, 6.29; N, 12.49%); δ_H(200 MHz, CDCl₃) 1.14 (6 H, t, *J* 6.9 Hz), 1.18 (3 H, t, *J* 6.9 Hz), 1.72 (1 H, ddd, *J* 1.5, 2.3, and 13.8 Hz), 2.37 (1 H, ddd, *J* 3.0, 7.8, and 13.8 Hz), 2.99 (3 H, s), 3.34 (4 H, q, *J* 6.9 Hz), 3.46 (2 H, q, *J* 6.9 Hz), 3.58–3.63 (1 H, m), 3.94 (1 H, ddd, *J* 2.3, 2.6, and 7.8 Hz), 4.55 (1 H, d, *J* 1.3 Hz), 4.93 (1 H, dd, *J* 1.5 and 3.0 Hz), 6.26 (1 H, d, *J* 6.2 Hz), 8.08 (1 H, d, *J* 9.5 Hz), 8.25 (1 H, dd, *J* 2.6 and 9.5 Hz), and 8.54 (1 H, d, *J* 2.6 Hz).

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