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Stereoisomeric Styryl-substituted Pyrrolidines, 3,7-Diazobicyclo[3.3.0]octanes and 2-Styrylpyrroles from Cinnamaldehyde Iminium-*N*-methanide 1,3-Dipoles†

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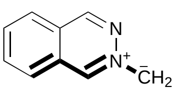
The reaction of cinnamaldehyde *N*-aryliminium methanide 1,3-dipoles with dimethyl maleate, dimethyl fumarate and some *N*-arylmaleimides gives equal mixtures of stereoisomeric substituted pyrrolidines and a route to 2-styrylpyrroles with dimethyl acetylenedicarboxylate.

Azomethine methanide (ylide) 1,3-dipoles have proved to be important synthons for the pyrrole system.[1–3] Routes to these dipoles include thermal ring-opening of aziridines,[1–4] reactions of α-amino esters with carbonyl compounds,[5–6] reactions of amines with aldehydes[7] and desilylation of trimethylsilylmethyliminium salts.[8,9] We have recently examined[10] the stereochemistry of the cycloadducts of the phthalazinium-2-methanide 1,3-dipole **1**. This contains a more rigid structural component than the analogous cinnamaldehyde iminium–methanide dipole **3** and we wished to compare the behaviour of **1** with this more flexible structure **3**.



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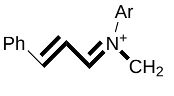

3 (*EZ*)

In the generation of 1,3-dipoles from iminium salts the possible *EZ* stereochemistry of the trimethylsilylmethyl iminium triflate salts has not been commented on, since these salts were generally not isolated in earlier studies. In the present work with cinnamaldehyde imines the salts **2** were readily isolated by stirring cinnamaldehyde *N*-arylimines with trimethylsilylmethyl trifluoromethanesulfonate in diethyl ether and varying mixtures of the *EZ* and *EE* forms were obtained (Scheme 1; Table 1, entries 1–5). The ratios were readily established by the ^{1}H NMR spectra which showed the styryl α-CH (a doublet of doublets) more upfield when in the shielding region of the *N*-aryl ring in the *EZ* form (Scheme 1). When the salts **2** were desilylated in the presence of the dipolarophiles dimethyl acetylenedicarboxylate (DMAD), *N*-(*p*-substituted phenyl)maleimides, dimethyl fumarate and dimethyl maleate, the respective products **4**, stereoisomer pairs **6**,**7**, **12**,**13**, **14**,**15** (all 1:1 ratio) and **10**,**11** (1:1 ratio) were obtained in high yields (Table 1). Interestingly the ratio of *EZ* and *EE* isomers in the dipole precursor **2** did not influence the stereoisomer ratio of the cycloadducts, suggesting that the same dipole **3** (*EE* or *EZ*) enters the cycloaddition from either precursor. The 2,5-dihydropyrrole derivatives **4** and the pyrrolidine derivatives **8–11** could be readily oxidised to 2-styrylpyrroles **5** with PbO_2 in CH_2Cl_2. The product series **6**, **7**, **12–15** are new 6-styryl-substituted 3,7-diazabicyclo[3.3.0]octane-2,4-diones. In all cases the isomeric pairs were readily separated by column chromatography.

All the compounds gave the expected microanalyses and IR and ^{1}H and ^{13}C NMR spectra with the required splitting patterns (Scheme 1 and Experimental section). The stereoisomers were distinguished by the NOE effects of the pyrrolidine 2- and 3-H atoms when these were *cis* and the absence of this NOE effect when these H atoms were *trans* (5-H and 6-H in products **6**, **7**, **12–15**). In the *exo* cycloadducts **7**, **13** and **15** the 6-CH was also significantly more shielded when *cis* to the imido π-electrons, a feature we have also noted[10] for the C-10a bridgehead hydrogen in cycloadducts from the dipole **1**. Varying and unequal *endo:exo* ratios were formed[10] in the cycloadditions of the dipole **1**. The consistent 1:1 ratio of stereoisomers observed herein with the dipole **3** probably reflects the lower steric

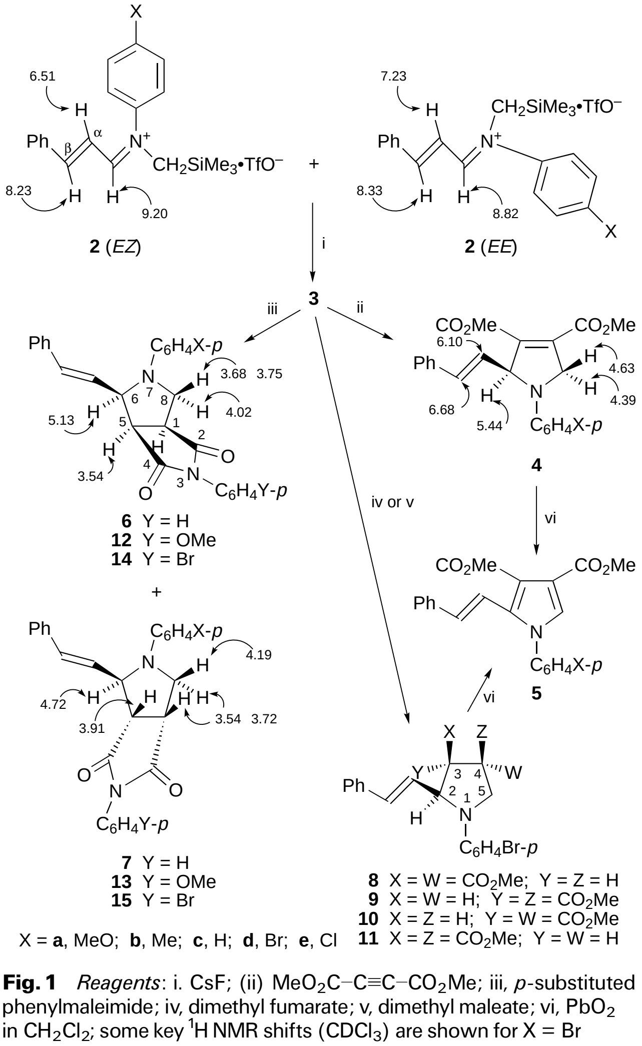

Fig. 1 *Reagents*: i. CsF; (ii) $MeO_2C-C\equiv C-CO_2Me$; iii, *p*-substituted phenylmaleimide; iv, dimethyl fumarate; v, dimethyl maleate; vi, PbO_2 in CH_2Cl_2; some key ^{1}H NMR shifts ($CDCl_3$) are shown for X = Br

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Table 1 Substrates and cycloadducts

Entry	Compd.	Mp[a] (T °/C)	Yield (%)	δ_H	Compd.	Mp[a] (T °/C)	Yield (%)	δ_H
1	**2a**	158–159[b]	95(4:1)[d]	–	**4a**[h]	143–145	88	5.38[g]
2	**2b**	163–164[b]	93(1.5:1)	–	**4b**	104–106	63	5.41[g]
3	**2c**	135–137[b]	92(1:3)	–	**4c**	99–100	60	5.45[g]
4	**2d**	156–158[b]	90(1.2:1)	–	**4d**[h]	164–166	80	5.44[g]
5	**2e**	146–148[b]	90(1:1)	–	**4e**	154–155	80	5.40[g]
6	**6d**	99–100	40	5.13[e,f]	**7d**	174–175	40	4.72[e]
7	**6c**	198–200[c]	40	5.19[e,f]	**7c**	173–174[c]	40	4.75[e]
8	**12d**	120–122	30	5.10[e,f]	**13d**	190–192	30	4.71[e]
9	**14d**	178–180	46	5.09[e,f]	**15d**	152–154	46	4.70[e]
10	**8**	84–85	35	4.58[f,g]	**9**[h]	88–89	35	4.66[g]
11	**10**	124–126	20	4.59[g]	**11**	130–132	20	4.62[f,g]

[a] From EtOH unless stated otherwise. [b] Washed with Et_2O. [c] From MeOH. [d] Parentheses contain *EZ:EE* ratio. [e] δ_H for H-6. [f] NOE enhancement from adjacent *cis* H. [g] δ_H for H-2. [h] Oxidation gave compounds **5a** and **5d**.

strain and greater flexibility in the cycloaddition transition state.

Experimental

Mps were measured on an Electrothermal apparatus. IR spectra were measured with a Perkin Elmer 983G spectrophotometer. NMR spectra were measured on JEOL GX FT270 and GXFT400 spectrometers using $CDCl_3$ as solvent. Cinnamaldehyde *N*-arylimines separated on cooling after a dry EtOH solution of the aldehyde and the *p*-substituted aniline (1:1 mol) was heated under reflux for 1 h. The salts **2** were obtained in 90–95% yields when equimolar quantities of the imine and trimethylsilylmethyl triflate were stirred in dry Et_2O at ambient temperature for 12 h.

Cycloadditions (*Typical Examples*).—3,7-*Diphenyl*-6-exo-[(E)-*styryl*]-3,7-*diazabicyclo*[3.3.0]*octane*-2,4-*dione* **7c** *and the* endo *isomer* **6c** (*Table* 1, *entry* **7**). A solution of the triflate salt **2c** (0.50 g, 1.38 mmol) in dry CH_2Cl_2 (20 cm^3) was treated with *N*-phenylmaleimide (0.48 g, 2.76 mmol) followed by an excess of CsF. The mixture was stirred under anhydrous conditions at ambient temperatures for 24 h and then filtered. The filtrate (together with the CH_2Cl_2 filter-cake washings) was evaporated under reduced pressure to 4 cm^3, placed on a column of silica gel (230–400 mesh) and eluted slowly with CH_2Cl_2. First eluted was the endo *isomer* **6c** (40%) mp 198–200 °C (from MeOH) (Found: C, 79.0; H, 5.5; N, 7.0. $C_{27}H_{22}NO_2$ requires C, 79.2; H, 5.6; N, 7.1%) ν_{max}/cm^{-1} (mull) 1709 br (amido C=O; $\delta_H(CDCl_3)$ 3.54 (d, *J* 7.3 Hz, H-5), 3.64–3.79 (m, 2 H, H-1, H-8_{endo}), 4.08 (d, *J* 9.5 Hz, H-8_{exo}), 5.19 (d, *J* 6.6 Hz, 1 H, H-6), 6.08–6.16 (dd, 1 H, styryl, Hα), 6.62 (d, *J* 15.4 Hz, 1 H, styryl, Hβ), 6.74–6.8 (m, 3 H, Ar), 7.21–7.49 (m, 12 H, Ar); δ_C ($CDCl_3$) (off-res) 43.6 (d, C-1), 49.6 (t, C-8), 51.5 (d, C-5), 63.3 (d, C-6), 145.1, 115.1, 128.5, 118.7 (N-7-Ph, C-1′, C-2′, C-3′, C-4′ resp.), 135.9, 126.6, 129.3, 125.7 (styryl phenyl, C-1′, C-2′, C-3′, C-4′ resp.), 131.5, 126.5, 128.7, 128.2 (N-3-Ph, C-1′, C-3′, C-4′ resp.), 128.9 (d, styryl C-α), 133.2 (d, styryl C-β), 176.8, 177.9 (s, C=O).

Next eluted was the exo *isomer* **7c** (40%), 173–174 °C (from MeOH) (Found: C, 79.1; H, 5.4; N, 6.9. $C_{27}H_{22}NO_2$ requires C, 79.2; H, 5.6; N, 7.1%); ν_{max}/cm^{-1} (mull) 1712 br (amido C=O); δ_H ($CDCl_3$) 3.68–3.76 (m, 2 H, H-8_{endo}, H-1), 3.85–3.92 (m, 1 H, H-5), 4.23–4.26 (m, 1 H, H-8_{exo}), 4.75 (m, 1 H, H-6), 6.17–6.26 (dd, *J* 16.1, 5.9 Hz, 1 H, styryl, H-α), 6.56 (d, 1 H, styryl, Hβ), 6.78–6.86 (m, 3 H, Ar), 7.03–7.07 (2 H, m, Ar), 7.22–7.30 (10 H, m, Ar); δ_C ($CDCl_3$) (off-res). 44.9 (d, C-1), 49.9 (d, C-5) 50.9 (t, C-8), 62.3 (d, C-6), 146.4, 115.3, 128.6, 119.1 (N-7-Ph, C-1′, C-2′, C-3′, C-4′ resp.), 135.9, 126.6, 129.2, 126.8 (styryl phenyl C-1′, C-2′, C-3′, C-4′ resp.), 131.6, 124.9, 129.2, 128.1 (N-3-Ph, -1′, C-2′, C-3′, C-4′ resp.), 128.7 (d, styryl C-α) 133.1 (d, styryl, C-β), 174.8, 177.3 (s, C=O).

1-(p-*Bromophenyl*)-3,4-*bis*(*methoxycarbonyl*)-2-[(E)-*styryl*]-2,5-*dihydropyrrole* **4d** *and -pyrrole* **5d** (*Table* 1, *entry* 4).–A solution of the triflate salt **2d** (0.50 g, 1.13 mmol) in dry CH_2Cl_2 (20 cm^3) was treated with dimethyl acetylenedicarboxylate (0.28 ml, 2.6 mmol) followed by an excess of CsF. The mixture was stirred under anhydrous conditions at ambient temperatures for 24 h and then filtered. The filtrate (together with the CH_2Cl_2 filter-cake washings) was evaporated under reduced pressure to 4 cm^3, placed on a flash column of silica gel (230–400 mesh ASTM) and eluted with gradient mixtures of petroleum spirit (bp 40–60 °C)–CH_2Cl_2 (1:0 to 1:1) to give the dihydropyrrole **4d** (80%), mp 164–166 °C (from EtOH) (Found C, 59.5; H, 4.7; N, 3.1. $C_{22}H_{20}BrNO_4$ requires C, 59.7; H, 4.5; N, 3.1.1%); ν_{max}/cm^{-1} (mull) 1725, 1730 (ester C=O); δ_H ($CDCl_3$) 3.81 (s, 3 H, CO_2Me), 3.85 (s, 3 H, CO_2Me), 4.39 (dd, 1 H, H-5 *trans* relative to styryl), 4.63 (dd, 1 H, H-5 *cis*), 5.44 (m, 1 H, H-2), 6.10 (dd, 1 H, styryl, H-α), 6.49–6.53 (m, 2 H, N-ArBr), 6.68 (d, *J* 16.1 Hz, 1 H, styryl, H-β), 7.27–7.32 (m, 7 H, Ar); δ_C ($CDCl_3$) (off-res) 52.6 (q, OMe), 55.9 (t, C-5), 69.3 (d, C-2), 144.6, 113.9, 132.0, 109.5 (N-1-*p*-BrC_6H_4,C-1′, C-2′, C-3′, C-4′ resp.), 139.9, 126.8, 128.2, 126.2 (styryl phenyl, C-1′, C-2′, C-3′, C-4′ resp.), 132.4 (s, C-4), 135.9 (s, C-3), 128.1 (d, styryl C-α), 135.9 (d, styryl, C-β), 162.9, 163.5 (s, C=O).

Oxidation of **4d** (0.45 mmol) with PbO_2 (4.5 mmol) in CH_2Cl_2 (20 cm^3) for 48 h at ambient temperate gave the pyrrole **5d** (50%), mp 94–95 °C (from EtOH) (isolated by elution from a flash column of silica gel 230–400 mesh ASTM with petroleum spirit (bp 40–60 °C–CH_2Cl_2 (20:1 v/v) (Found: C, 59.7; H, 4.0; N, 3.2. C_{22} $H_{18}BrNO_4$ requires C, 60.0; H, 4.1; N, 3.2%); ν_{max}/cm^{-1} (mull), 1724, 1710 (ester C=O); δ_H ($CDCl_3$) 3.85 (s, 3 H, OMe), 3.93 (s, 3 H, OMe), 6.79 (dd, 2 H, N-1-*p*-BrC_6H_4, H-2′), 7.23–7.35 (m, 9 H, aromatic protons, styryl, Hα, Hβ), 7.64 (m, 1 H, H-5); δ_C ($CDCl_3$) (off-res.), 51.7, 52.4 (q, OMe), 137.5, 115.3, 132.9, 116.3 (N-1-*p*-BrC_6H_4, C-1′, C-2′, C-3′, C-4′ resp.), 136.5, 127.8, 128.7, 126.5 (styryl phenyl, C-1′, C-2′, C-3′, C-4′ resp.), 122.6 (s,C-4), 127.9 (s, C-3), 128.0 (d, styryl, C-α), 128.5 (d, styryl, C-β), 132.7 (C-2), 133.5 (d, -5), 163.8, 166.3 (s, C=O).

The 1-(*p*-methoxyphenyl) pyrrole **5a**, mp 104–106 °C (from EtOH), was similarly obtained.

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