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The generation and reactivity of *N*-substituted, stabilised α,β:γ,δ-unsaturated azomethine ylides

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Abstract—The generation of *N*-substituted, stabilised azomethine ylides in the presence of *N*-phenylmaleimide gave the bicyclo[3.3.0] octane-3-carboxylate cycloadducts. In the absence of a dipolarophile, these azomethine ylides gave novel piperazine-6-carboxylates.

1. Introduction

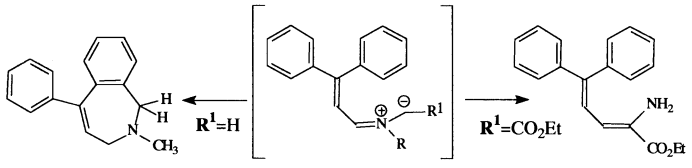
The 1,3-dipolar cycloaddition of azomethine ylides represents perhaps the most important example of the variety of reaction pathways available to these dipoles.[1] There are, however, many other synthetically useful reactions of these dipoles, including the 1,5-electrocyclic ring closure of appropriately substituted dipolar systems.[2] Recently, we[3] and others[4] published the first examples of the 1,7-electrocyclisation of azomethine ylides with α,β:γ,δ-unsaturation.[5] During these studies we have found significant differences between the reactivity of α,β:γ,δ-unsaturated, *N*-substituted, non-stabilised **1** and α,β:γ,δ-unsaturated, *N*-unsubstituted stabilised azomethine ylides **2**. The former dipoles react via a 1,7-electrocyclisation, followed by a [1,5]-hydrogen shift to give dihydrobenzazepines **4**,[3] whilst the latter give didehydroamino acid derivatives **5** as the stable products of a novel rearrangement (Scheme 1).[6]

As a continuation of these studies we have now examined the reactivity of some α,β:γ,δ-unsaturated, *N*-substituted stabilised azomethine ylides **3**. We wish to report here the generation of these 1,3-dipoles and their subsequent reactions in the presence and absence of dipolarophiles.

2. Results and discussion

The condensation of various aldehydes with *N*-alkyl or *N*-aryl α-amino esters leads to *N*-substituted azomethine ylides.[7] These ylides may be formed directly from the amino-carbinol intermediate via loss of water and can be trapped by added dipolarophiles since there are no other reactive reagents (e.g. base, Lewis acids) present.

Upon refluxing a solution of β-phenylcinnamaldehyde **6a** and sarcosine ethyl ester **7b** in the presence of *N*-phenylmaleimide **8**, a mixture of three isomers of the cycloadducts,



1 R = CH_3, R^1 = H
2 R = H, R^1 = CO_2Et
3 R = CH_3, R^1 = CO_2R^2

4 **5**

Scheme 1.

Keywords: azomethine ylides; piperazines; cycloadducts.

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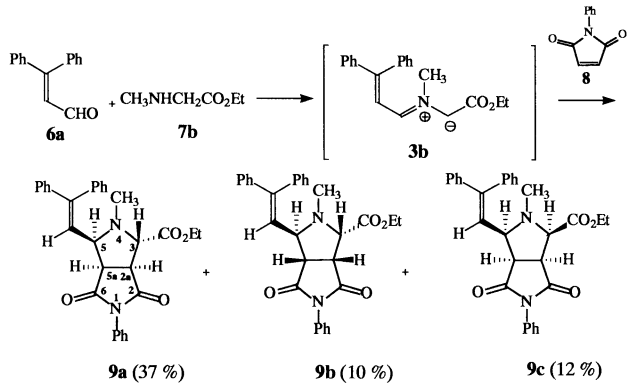
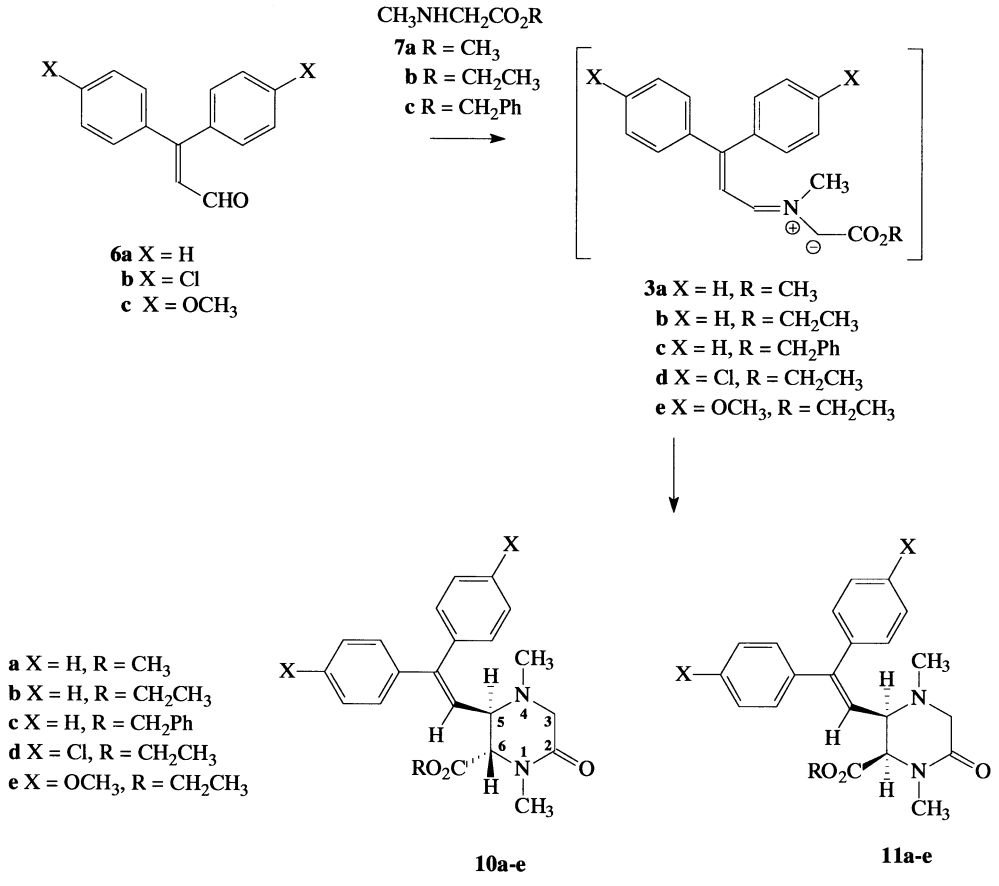


Scheme 2.

9a–c, was obtained in a 4:1:1 ratio (Scheme 2). The stereochemistry of these products was elucidated by HH-COSY and NOESY experiments. In this trapping experiment, the dominant conformer of the conjugated azomethine ylide **3b** is the *anti*, leading to the adducts **9a** (*anti-endo*) and **9b** (*anti-exo*). Similarly, with other *N*-substituted stabilised azomethine ylides the exclusive involvement of one of the *anti* conformers was observed when the electron withdrawing group was an ester[8] and the replacement of the ester with a nitrile group reduced the stereoselectivity of the reaction.[9]

Refluxing a solution of β-phenylcinnamaldehyde **6a** and various sarcosine esters **7** in the absence of any dipolarophile led to the formation, in all cases, of only two products. After careful chromatographic separation these two compounds were identified as the two stereoisomers of 2-oxopiperazine-6-carboxylates, *trans* **10a–c** and *cis* **11a–c** (Scheme 3, Table 1). The isomeric ratio and stereochemistry of these products were also determined by ^{1}H



Scheme 3.

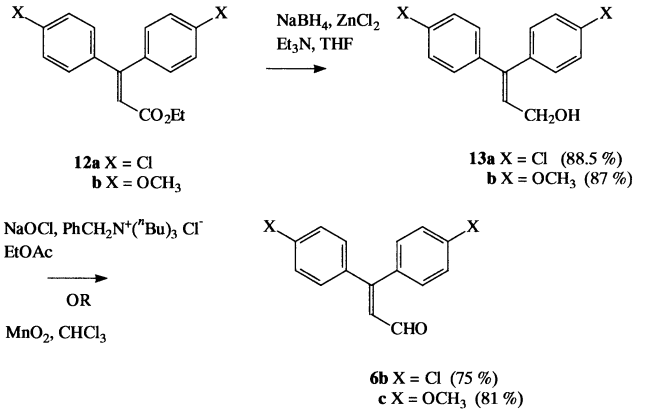
Table 1. Yields and conditions for the formation of piperazines **10**,**11**

Entry	R	X	Time (h)	Yield (%)[a]	**10/11** ratio[b]
a	CH_3	H	10	62	2:1
b	CH_2CH_3	H	13	68	2:1
c	CH_2Ph	H	14	62	6:1
d	CH_2CH_3	Cl	1	72	1:1
e	CH_2CH_3	OCH_3	1	77	3:1

[a] Combined yield of the two isomers before separation.
[b] Determined by ^{1}H NMR spectroscopy of the crude mixtures.

NMR spectroscopy (nOe and NOESY), the *cis* isomers **11** giving a 5–6% nOe between the hydrogens at positions 5 and 6.

This reaction was then repeated with 4′,4′-substituted β-phenylcinnamaldehydes **6b**,**c** and sarcosine ethyl ester **7b**. These substituted β-phenylcinnamaldehydes **6b**,**c** were prepared by the reduction of the corresponding esters **12**,[10] to the alcohols **13**, followed by oxidation to the aldehydes **6b**,**c** (Scheme 4). Oxidation of the chloro derivative **13a** was



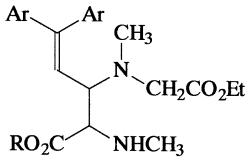
Scheme 4.

accomplished with aq. sodium hypochlorite but these conditions proved unsuccessful for the methoxy derivative **13b**, which was eventually oxidised with activated MnO_2 in chloroform. These aldehydes were then reacted with sarcosine ethyl ester **7b** to give the corresponding substituted piperazines **10d**,**e** and **11d**,**e**. The use of other carbonyl compounds, such as aromatic aldehydes, cinnamaldehyde etc. in place of β-phenylcinnamaldehyde **6a** resulted in the formation of complex mixtures of products.

The piperazine-6-carboxylates **10**,**11**, which are novel products from the reactions of azomethine ylides, are presumably formed from an intermediate secondary amine **14**, itself formed from the nucleophilic attack of the active methylene of the sarcosine ester **7** on the azomethine ylide **3**.

In order to account for the 1,7-electrocyclisation of only the non-stabilised, substituted dipoles **1**, we have performed energy calculations on these dipoles **1**–**3** and the products of their electrocyclisations **15** (Scheme 5) using semi-empirical (MOPAC PM3)[11] methods with Insight II (Release 2000)/MOPAC software (MSI/Biosym, CA, USA) on a Silicon Graphics Octane workstation (Table 2).

As expected, the azomethine ylide **1** is the least stable, due to the absence of an ester group and thus lack of resonance stabilisation of the anion. Presumably the stabilisation of the dipoles **2** and **3** results in a greater half-life in solution, and so a greater probability of their reaction with their precursors. In addition, however, the non-stabilised, substituted dipole **1** can cyclise to the intermediate **15a** (which again is less stable than its analogs **15b**,**c**) and this process is some 52 kJ mol^{-1} more exothermic than the cyclisation of the other dipoles **2**,**3** to their respective intermediates **15b**,**c**. It is presumably this greater exothermicity, in addition to the decreased stability of this dipole, which accounts for the 1,7-electrocyclisation of this dipole **1**, whilst the other dipoles **2**,**3** do not cyclise but react with their precursors.



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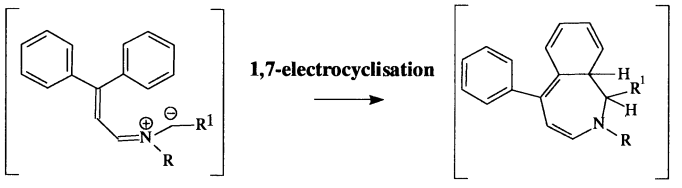
3. Experimental

3.1. General

Mps were determined on a Gallenkamp apparatus and are uncorrected. Elemental analyses were performed on a Perkin–Elmer 240C or Carlo Erba 1106 Elemental Analyser. IR spectra were recorded on a NICOLET FT-IR instrument or Perkin–Elmer 1600 series FTIR using sodium chloride plates. ^{1}H NMR spectra were recorded on Bruker 250, 300 or JEOL 270 MHz spectrometers. Coupling constants are given in Hz and all chemical shifts are relative to an internal standard of tetramethylsilane. ^{13}C NMR spectra were obtained on a Jeol GFX 270 FT NMR (68 MHz) or Bruker 250 MHz (63 MHz) spectrometer. Low resolution electron impact mass spectra were obtained on a Trio 2000 VG. High resolution spectra were obtained on Bruker APEX II FTMS. Column chromatography was



1 R = CH_3, R^1 = H
2 R = H, R^1 = CO_2Et
3 R = CH_3, R^1 = CO_2R^2

15a R = CH_3, R^1 = H
b R = H, R^1 = CO_2Et
c R = CH_3, R^1 = CO_2R^2

Scheme 5.

Table 2. Heats of formation for dipoles **1**–**3** and intermediates **15a**–**c**

Dipole	ΔH_f (kJ mol^{-1})	Intermediate	ΔH_f (kJ mol^{-1})	$\Delta\Delta H_f$ (kJ mol^{-1})
1	413.8	**15a**	248.9	−164.9
2	17.4	**15b**	−80.9	−98.3
3	34.9	**15c**	−77.9	−112.8

performed using Merck Kieselgel 60 70–230 mesh, TLC on aluminium sheets coated with Kieselgel 60 F_{254}.

3.2. Materials

Ethyl 3,3-bis(4′-chlorophenyl)prop-2-enoate **12a** and ethyl 3,3-bis(4′-methoxyphenyl)prop-2-enoate **12b** were prepared by the method of Collomb, Chantegrel, and Deshayas.[10]

3.2.1. 3,3-Bis(4′-chlorophenyl)prop-2-enol 13a. A mixture of ethyl 3,3-bis(4′-chlorophenyl)prop-2-enoate **12a** (3.21 g, 10.0 mmol), sodium borohydride (1.52 g, 40.0 mmol), zinc chloride (2.73 g, 20.0 mmol), and triethylamine (2.78 mL, 20.0 mmol) was refluxed, with stirring, under nitrogen in THF (30 mL) for 2.5 h. The reaction mixture was cooled in ice-water, and 10% aq. hydrochloric acid (30 mL) and diethyl ether (50 mL) were added, with stirring. The organic layer was separated, washed consecutively with sat. aq. sodium hydrogen carbonate solution (20 mL), water (20 mL), sat. aq. sodium chloride solution (20 mL), and dried over magnesium sulphate. The solvent was evaporated under reduced pressure and the residue was purified by column chromatography on silica, eluting with hexane/ethyl acetate (70:30) to give *3,3-bis(4′-chlorophenyl)prop-2-enol* **13a** as a white solid (2.47 g, 88.5%), mp 66–68°C; IR 3302 (OH), 1591 (C═C), 1491 (C═C) cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ=1.95 (1H, s, OH), 4.17 (2H, d, J=6.6 Hz, CH_2), 6.20 (1H, t, J=6.6 Hz, ═CH), 7.04–7.15 (4H, m, H-2′,6′), 7.21–7.35 (4H, m, H-3′,5′); ^{13}C NMR (68 MHz, $CDCl_3$) δ=60.3 (CH_2), 128.3 (═CH), 128.4 (2×CH), 128.6 (2×CH), 128.8 (2×CH), 131.0 (2×CH), 133.7 (q), 133.8 (q), 136.9 (q), 139.8 (q), 141.9 (q); MS (EI): *m/z* 282 (M^+,4%), 280 (M^+, 21), 278 (M^+, 31), 262 (14), 260 (18), 245 (44), 243 (100), 237 (77), 235 (95), 141 (22), 139 (68), 127 (18), 125 (53), 103 (49), and 77 (35); Anal. Calcd for $C_{15}H_{12}Cl_2O$: C, 64.5; H, 4.3%. Found: C, 64.3; H, 4.4%.

3.2.2. 3,3-Bis(4′-methoxyphenyl)prop-2-enol 13b. Ethyl 3,3-bis(4′-methoxyphenyl)prop-2-enoate **12b** (2.14 g, 6.86 mmol) and sodium borohydride (1.04 g, 27.4 mmol) were reacted using the method above to give, after column chromatography on silica eluting with hexane/ethyl acetate (70:30), *3,3-bis(4′-methoxyphenyl)prop-2-enol* **13b** as a colourless oil (1.61 g, 87%); IR (neat) 3458 (OH), 1607 (C═C), 1511 (C═C) cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ=2.40 (1H, s, OH), 3.75 (3H, s, OCH_3), 3.78 (3H, s, OCH_3), 4.17 (2H, d, J=6.6 Hz, CH_2), 6.07 (1H, t, J=6.6 Hz, ═CH), 6.75–6.87 (4H, m, H-3′,5′), 7.02–7.17 (4H, m, H-2′,6′); ^{13}C NMR (68 MHz, $CDCl_3$) δ=55.1 (2×OCH_3), 60.5 (CH_2), 113.4 (4×CH), 125.5 (═CH), 128.7 (2×CH), 130.8 (2×CH), 131.5 (q), 134.8 (q), 143.0 (q), 158.8 (q), 159.0 (q); MS (EI): *m/z* 270 (M^+, 53%), 252 (32), 242 (48), 227 (100), 135 (84), and 77 (36); HRMS (ESI): Found: M^+, 253.1220, Calcd for $C_{17}H_{17}O_2$: $(M-OH)^+$=253.1223.

3.2.3. 3,3-Bis(4′-chlorophenyl)prop-2-enal 6b. A mixture of 3,3-bis(4′-chlorophenyl)prop-2-enol **13a** (2.70 g, 9.09 mmol), ethyl acetate (50 mL), benzyltri-*n*-butylammonium chloride (0.1 g) and sodium hypochlorite solution (ca. 14% available chlorine, 30 mL) was stirred for 0.5 h. The organic layer was separated and the aq. phase was extracted with diethyl ether (3×20 mL). The combined organic phases were washed with sat. aq. sodium hydrogen carbonate (20 mL) and dried over magnesium sulphate. The solvent was evaporated under reduced pressure to give a liquid, which was purified by column chromatography on silica, eluting with hexane/ethyl acetate (90:10) to give *3,3-bis(4′-chlorophenyl)prop-2-enal* **6b** as a yellow oil (2.02 g, 75%);[6] IR (neat) 1667 (C═O), 1586 (C═C), 1490 (C═C) cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ=6.55 (1H, d, J=7.9 Hz, ═CH), 7.22–7.46 (8H, m, ArH), 9.49 (1H, d, J=7.9 Hz, CHO); ^{13}C NMR (68 MHz, $CDCl_3$) δ=127.6 (═CH), 128.7 (2×CH), 128.9 (2×CH), 129.7 (2×CH), 131.8 (2×CH), 134.5 (q), 135.8 (q), 136.7 (q), 137.6 (q), 159.0 (q), 192.3 (C═O); MS (EI): *m/z* 280 (M^+, 8%), 278 (M^+, 44), 276 (M^+, 67), 243 (49), 241 (94), 214 (23), 212 (61), 178 (77), 176 (79), 136 (100), 88 (82), and 75 (88); HRMS (EI): Found: M^+, 276.0110, Calcd for $C_{15}H_{10}Cl_2O$: M^+=276.0109.

3.2.4. 3,3-Bis(4′-methoxyphenyl)prop-2-enal 6c. To a stirred suspension of activated manganese dioxide (3.41 g, 39.22 mmol) in chloroform (30 mL) was added 3,3-bis(4′-methoxyphenyl)prop-2-enol **13b** (2.65 g, 9.81 mmol). The mixture was stirred for 48 h at room temperature then filtered. The filtrate was then evaporated under reduced pressure, and the residue was purified by column chromatography on silica, eluting with hexane/ethyl acetate (70:30) to give *3,3-bis(4′-methoxyphenyl)prop-2-enal* **6c** as a light yellow oil (2.13 g, 81%); IR (neat) 1657 (C═O), 1605 (C═C), 1511 (C═C) cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ=3.81 (3H, s, OCH_3), 3.85 (3H, s, OCH_3), 6.48 (1H, d, J=8.1 Hz, ═CH), 6.81–6.97 (4H, m, H-3′,5′), 7.20–7.32 (4H, m, H-2′,6′), 9.49 (1H, d, J=8.1 Hz, CHO); ^{13}C NMR (68 MHz, $CDCl_3$) δ=55.1 (2×OCH_3), 113.5 (2×CH), 113.8 (2×CH), 125.2 (═CH), 128.9 (q), 130.3 (2×CH), 132.1 (q), 132.2 (2×CH), 160.6 (q), 161.5 (q), 161.7 (q), 193.2 (C═O); MS (EI): *m/z* 268 (M^+, 92%), 267 (76), 237 (58), 135 (84), and 132 (100); HRMS (ESI): Found: MH^+, 269.1173, Calcd for $C_{17}H_{17}O_3$: MH^+=269.1172.

3.3. 1,3-Dipolar cycloaddition between *N*-phenylmaleimide 8 and the azomethine ylide 3b derived from β-phenylcinnamaldehyde 6a and sarcosine ethyl ester 7b

Sarcosine ethyl ester **7b** (64 mg, 0.42 mmol), β-phenylcinnamaldehyde **6a** (86 mg, 0.42 mmol) and *N*-phenylmaleimide **8** (71 mg, 0.42 mmol) were dissolved in toluene (5 mL), and the mixture was refluxed for 24 h. After 12 h, further sarcosine ethyl ester **7b** (64 mg, 0.42 mmol) was added to the reaction mixture. When the reaction was complete, the solvent was removed in vacuo. The ^1H NMR spectrum of the crude residue gave the isomer ratio as 4:1:1. The three isomers were separated by column chromatography on silica, eluting with hexane/ether (50:50).

3.3.1. Ethyl 1,4-diaza-4-methyl-2,6-dioxo-1-phenyl-5-(2′,2′-diphenylethenyl)bicyclo[3.3.0]octane-3-carboxylate 9a (*anti-endo* isomer). Colourless oil (0.074 g, 37%); IR (nujol) 1778 (C═O), 1716 (C═O), 1596 (C═C), 1496 (C═C) cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ=1.16 (3H, t,

J=7.0 Hz, CH_3), 2.37 (3H, s, NCH_3), 3.41 (1H, m, H-2a and H-5a), 3.94 (1H, m, H-5), 4.11 (2H, m, OCH_2), 4.19 (1H, s, H-3), 5.74 (1H, d, J=9.9 Hz, =CH), 7.25–7.48 (15H, m, ArH); ^{13}C NMR (68 MHz, $CDCl_3$) δ=14.7 (CH_3), 35.8 (CH_3), 48.5 (CH_2), 49.6 (CH), 61.3 (CH), 63.6 (CH), 68.1 (CH), 125.3 (=CH), 126.3 (CH), 126.9 (2×CH), 128.0 (2×CH), 128.2 (CH), 128.6 (2×CH), 128.8 (2×CH), 129.1 (CH), 129.6 (2×CH), 129.8 (2×CH), 140.1 (q), 142.1 (q), 170.5 (q), 175.4 (2×q), 176.9 (q); MS (EI): m/z 480 (M^+, 50%), 465 (28), 407 (100), 307 (12), 260 (20), 234 (68), 202 (28), 191 (88), 178 (50), 167 (57), 115 (25), 84 (45); HRMS (EI): Found: M^+, 480.2050, Calcd for $C_{30}H_{28}N_2O_4$: M^+=480.2049.

3.3.2. Ethyl 1,4-diaza-4-methyl-2,6-dioxo-1-phenyl-5-(2′,2′-diphenylethenyl)bicyclo[3.3.0]octane-3-carboxylate 9b (*anti-exo* isomer). White crystalline solid (0.020 g, 10%), mp 128°C; IR (nujol) 1712 (C=O), 1496 (C=C) cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ=1.33 (3H, t, J=7.0 Hz, CH_3), 2.30 (3H, s, NCH_3), 3.15 (1H, d, J=7.9 Hz, H-3), 3.19 (1H, d, J=9.9 Hz, H-5), 3.25 (1H, t, J=7.9 Hz, H-2a), 3.51 (1H, d, J=7.9 Hz, H-5a), 4.28 (2H, m, OCH_2), 6.11 (1H, d, J=9.9 Hz, =CH), 7.18–7.48 (15H, m, ArH); ^{13}C NMR (68 MHz, $CDCl_3$) δ=14.1 (CH_3), 38.8 (CH_3), 46.4 (CH_2), 48.0 (CH), 61.4 (CH), 66.7 (CH), 69.8 (CH), 125.0 (=CH), 126.5 (2×CH), 127.4 (2×CH), 127.5 (CH), 127.7 (CH), 128.2 (2×CH), 128.5 (2×CH), 128.6 (CH), 129.0 (2×CH), 129.4 (2×CH), 139.8 (q), 141.2 (q), 146.6 (q), 169.0 (q), 169.1 (q), 174.0 (q); MS (EI): m/z 480 (M^+, 27%), 407 (100), 260 (25), 234 (45), 215 (12), 191 (30), 115 (16), 84 (13); HRMS (EI): Found: M^+, 480.2050, Calcd for $C_{30}H_{28}N_2O_4$: M^+=480.2049.

3.3.3. Ethyl 1,4-diaza-4-methyl-2,6-dioxo-1-phenyl-5-(2′,2′-diphenylethenyl)bicyclo[3.3.0]octane-3-carboxylate 9c (*syn-endo* isomer). Pale yellow oil (0.025 g, 12%); IR (nujol) 1712 (C=O), 1596 (C=C), 1496 (C=C) cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ=1.15 (3H, t, J=7.0 Hz, CH_3), 2.25 (3H, s, NMe), 3.44 (1H, dd, J=9.2 and 4.5 Hz, H-5a), 3.82 (1H, t, J=9.0 Hz), 4.12 (2H, m), 4.18 (1H, d, J=9.0, H-3), 4.25 (1H, dd, J=10.2 and 4.5 Hz, H-5), 5.99 (1H, d, J=10.2 Hz, =CH), 7.22–7.48 (15H, m, ArH); ^{13}C NMR (68 MHz, $CDCl_3$) δ=14.1 (CH_3), 35.9 (NCH_3), 47.1 (OCH_2), 50.9 (CH), 61.2 (CH), 63.6 (CH), 67.2 (CH), 125.1 (=CH), 126.5 (2×CH), 127.5 (2×CH), 127.6 (2×CH), 128.0 (CH), 128.3 (CH), 128.6 (CH), 129.1 (2×CH), 130.0 (2×CH), 132.5 (q), 138.5 (q), 142.9 (q), 164.5 (C=O), 175.5 (2×C=O); MS (EI): m/z 480 (M^+, 25%), 407 (100), 260 (40), 234 (69), 215 (25), 191 (65), 167 (23), 115 (28), 91 (38), 84 (52); HRMS (EI): Found: M^+, 480.2049, Calcd for $C_{30}H_{28}N_2O_4$: M^+=480.2049.

3.4. Reaction of β-phenylcinnamaldehyde 6a with sarcosine esters 7a–c in the presence of triethylamine—general procedure

The *N*-substituted glycine ester **7a–c** (2 mmol), β-phenylcinnamaldehyde **6a** (210 mg, 1 mmol) and triethylamine (0.14 mL, 100 mg, 2 mmol) were dissolved in toluene (10 mL), and the solution was refluxed for 10–14 h under an argon atmosphere. When the reaction was complete, the precipitate was filtered off and the solvent was removed evaporated under reduced pressure. The ^{1}H NMR spectrum of the residue gave the isomer ratio. The isomers were separated by column chromatography on silica, eluting with hexane /ether (50:50).

3.4.1. Methyl *trans*-1,4-dimethyl-2-oxo-5-(2′,2′-diphenylethenyl)piperazine-6-carboxylate 10a. White powder (0.124 g, 34%), mp 135–137°C; IR (KBr) 1748 (C=O), 1655 (C=O), 1489 (C=C), 1212 (C–O) cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ=2.12 (3H, s, NCH_3), 2.98 (3H, s, NCH_3), 3.35 (2H, s, CH_2), 3.70 (3H, s, OCH_3), 3.86 (1H, d, J=3.1 Hz, H-6), 3.90–3.94 (1H, m, H-5), 6.20 (1H, d, J=10.2 Hz, =CH), 7.17–7.21 (2H, m, ArH), 7.22–7.43 (5H, m, ArH), 7.34–7.47 (3H, m, ArH); ^{13}C NMR (63 MHz, $CDCl_3$) δ=34.4 (NCH_3), 41.9 (NCH_3), 52.7 (OCH_3), 54.5 (CH_2), 58.8 (CH), 66.7 (CH), 120.2 (=CH), 127.4 (2×CH), 127.8 (CH), 128.2 (CH), 128.4 (2×CH), 128.5 (2×CH), 129.6 (2×CH), 138.8 (q), 141.3 (q), 148.7 (q), 167.5 (C=O), 170.2 (C=O); Anal. Calcd for $C_{22}H_{24}N_2O_3$: C 72.5; H 6.6; N 7.7%. Found: C, 73.0; H, 6.6; N, 7.5.

3.4.2. Methyl *cis*-1,4-dimethyl-2-oxo-5-(2′,2′-diphenylethenyl)piperazine-6-carboxylate 11a. Colourless oil (0.055 g, 15%); IR (neat) 1744 (C=O), 1652 (C=O), 1486 (C=C), 1203 (C–O) cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ=2.26 (3H, s, NCH_3), 2.83 (3H, s, NCH_3), 2.84 (1H, d, J=16.8 Hz, H-3a), 3.39 (1H, d, J=10.0 and 4.0 Hz, H-5), 3.60 (1H, d, J=17.1 Hz, H-3b), 3.82 (1H, d, J=4.0 Hz, H-6), 3.84 (3H, s, OCH_3), 5.98 (1H, d, J=10.0 Hz, =CH), 7.16–7.22 (2H, m, ArH), 7.23–7.35 (5H, m, ArH), 7.35–7.46 (3H, m, ArH); ^{13}C NMR (63 MHz, $CDCl_3$) δ=33.6 (NCH_3), 42.7 (NCH_3), 58.4 (CH_2), 61.1 (CH), 65.6 (CH), 123.9 (=CH), 127.2 (2×CH), 127.7 (CH), 128.0 (CH), 128.3 (2×CH), 128.7 (2×CH), 129.3 (2×CH), 139.1 (q), 141.1 (q), 146.2 (q), 167.6 (C=O), 169.6 (C=O); Anal. Calcd for $C_{22}H_{24}N_2O_3$: C, 72.5; H, 6.6; N, 7.7%. Found: C, 72.6; H, 6.6; N, 7.5.

3.4.3. Ethyl *trans*-1,4-dimethyl-2-oxo-5-(2′,2′-diphenylethenyl)piperazine-6-carboxylate 10b. White powder (0.140 g, 37%), mp 143°C; IR (KBr) 1742 (C=O), 1654 (C=O), 1488 (C=C), 1206 (C–O) cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ=1.18 (3H, t, J=7.2 Hz, CH_3), 2.11 (3H, s, NCH_3), 2.98 (3H, s, NCH_3), 3.35 (2H, s, CH_2), 3.86–3.92 (2H, m, H-5 and H-6), 4.04–4.25 (2H, m, OCH_2), 6.21 (1H, d, J=10.6 Hz, =CH), 7.15–7.22 (2H, m, ArH), 7.22–7.35 (5H, m, ArH), 7.35–7.45 (3H, m, ArH); ^{13}C NMR (63 MHz, $CDCl_3$) δ=14.0 (CH_3), 34.3 (NCH_3), 41.8 (NCH_3), 54.5 (CH_2), 58.9 (CH), 61.5 (CH_2), 66.7 (CH), 120.5 (=CH), 127.4 (2×CH), 127.8 (CH), 128.2 (CH), 128.4 (2 × CH), 128.5 (2×CH), 129.6 (2×CH), 138.9 (q), 141.3 (q), 148.7 (q), 167.5 (C=O), 169.7 (C=O); MS (CI): m/z 379 (MH^+, 61%), 308 (10), 234 (100), 192 (13), 158 (47); Anal. Calcd for $C_{23}H_{26}N_2O_3$: C, 73.0; H, 6.9; N, 7.4%. Found: C, 73.0; H, 7.0; N, 7.5.

3.4.4. Ethyl *cis*-1,4-dimethyl-2-oxo-5-(2′,2′-diphenylethenyl)piperazine-6-carboxylate 11b. Colourless oil (0.068 g, 18%); IR (neat) 1741 (C=O), 1655 (C=O), 1490 (C=C), 1209 (C–O) cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ=1.28 (3H, t, J=7.0 Hz, CH_3), 2.26 (3H, s, NCH_3), 2.83 (1H, d, J=16.9 Hz, H-3a), 2.84 (3H, s,

NCH_3), 3.39 (1H, dd, J=10.0 and 4.0 Hz, H-5), 3.60 (1H, d, J=17.0 Hz, H-3b), 3.81 (1H, d, J=4.0 Hz, H-6), 4.23–4.37 (2H, m, OCH_2), 6.00 (1H, d, J=10.0 Hz, =CH), 7.15–7.35 (4H, m, ArH), 7.35–7.48 (6H, m, ArH); ^{13}C NMR (63 MHz, $CDCl_3$) δ=14.2 (CH_3), 33.5 (NCH_3), 42.6 (NCH_3), 58.3 (CH_2), 61.0 (CH), 61.7 (CH_2), 66.0 (CH), 124.1 (=CH), 127.3 (2×CH), 127.7 (CH), 128.0 (CH), 128.3 (2×CH), 128.7 (2×CH), 129.3 (2×CH), 139.1 (q), 141.2 (q), 146.2 (q), 167.7 (C=O), 170.0 (C=O); Anal. Calcd for $C_{23}H_{26}N_2O_3$: C, 73.0; H, 6.9; N, 7.4%. Found: C, 73.2; H, 6.8; N, 7.4.

3.4.5. Benzyl *trans*-1,4-dimethyl-2-oxo-5-(2′,2′-diphenylethenyl)piperazine-6-carboxylate 10c. Colourless oil (0.207 g, 47%); IR (neat) 1744 (C=O), 1659 (C=O), 1501 (C=C), 1226 (C–O) cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ=2.06 (3H, s, NCH_3), 2.99 (3H, s, NCH_3), 3.36 (2H, s, N–CH_2), 3.92–3.97 (2H, m, H-5 and H-6), 5.05 (1H, d, J=12.4 Hz, Ph–CHa), 5.20 (1H, d, J=12.4 Hz, Ph–CHb), 6.22 (1H, d, J=11.0 Hz, =CH), 7.12–7.34 (15H, m, Ar-H); ^{13}C NMR (63 MHz, $CDCl_3$) δ=34.5 (NCH_3), 41.8 (NCH_3), 54.2 (CH_2-3), 58.6 (CH), 66.7 (CH), 67.1 ($PhCH_2$), 119.8 (=CH), 127.4 (2×CH), 127.7 (CH), 127.8 (q+CH), 128.2 (CH), 128.3 (2×CH), 128.4 (2×CH), 128.5 (4×CH), 129.5 (2×CH), 138.8 (q), 141.1 (q), 148.8 (q), 167.5 (C=O), 169.5 (C=O); Anal. Calcd for $C_{28}H_{28}N_2O_3$: C, 76.3; H, 6.4; N, 6.4%. Found: C, 76.2; H, 6.6; N, 6.4.

3.4.6. Benzyl *cis*-1,4-dimethyl-2-oxo-5-(2′,2′-diphenylethenyl)piperazine-6-carboxylate 11c. Colourless oil (0.028 g, 6.5%); IR (neat) 1745 (C=O), 1655 (C=O), 1500 (C=C), 1222 (C—O) cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ=2.24 (3H, s, NCH_3), 2.82 (3H, s, NCH_3), 2.83 (1H, d, J=17.0 Hz, H-3a), 3.35–3.41 (1H, m, H-5), 3.60 (1H, d, J=17.0 Hz, H-3b), 3.85 (1H, d, J=3.8 Hz, H-6), 5.08 (1H, d, J=12.0 Hz, Ph–CHa), 5.33 (1H, d, J=12.0 Hz, Ph–CHb), 5.93 (1H, d, J=10.0 Hz, =CH), 7.07–7.35 (15H, m, ArH); ^{13}C NMR (63 MHz, $CDCl_3$) δ=33.6 (NCH_3), 42.5 (NCH_3), 58.5 (CH_2), 61.2 (CH), 65.7 (CH), 67.5 (Ph–CH_2), 123.9 (=CH), 126.3 (CH), 127.2 (3×CH), 127.9 (CH), 128.1 (q), 128.4 (2×CH), 128.5 (2×CH), 128.6 (2×CH), 128.7 (2×CH), 129.3 (2×CH), 139.0 (q), 140.9 (q), 146.3 (q), 167.6 (C=O), 169.1 (C=O); Anal. Calcd for $C_{28}H_{28}N_2O_3$: C, 76.3; H, 6.4; N, 6.4%. Found: C, 76.3; H, 6.6; N, 6.5.

3.5. The reaction of 3,3-bis(4′-chlorophenyl)propenal 6b with sarcosine ethyl ester 7b

A mixture of 3,3-bis(4′-chlorophenyl)propenal **6b** (0.38 g, 1.37 mmol), sarcosine ethyl ester hydrochloride **7c** (0.42 g, 2.74 mmol) and dry triethylamine (0.38 mL, 2.74 mmol) in anhydrous toluene (25 mL) was refluxed for 1 h under nitrogen. After cooling to room temperature, the triethylamine hydrochloride was removed by filtration and the filtrate was then evaporated under reduced pressure. The residue was purified by column chromatography on silica, eluting with diethyl ether to give a brown oil (0.44 g, 72%) containing *trans*- **10d** and *cis*-ethyl 5-[2′,2′-bis(4″-chlorophenyl)ethenyl]-1,4-dimethyl-2-oxopiperazine-6-carboxylate **11d** (isomeric ratio 1:1, determined by ^{1}H NMR spectroscopy). The oil was further purified by column chromatography on silica eluting with hexane/ether (50:50).

3.5.1. Ethyl *trans*-5-[2′,2′-bis(4″-chlorophenyl)ethenyl]-1,4-dimethyl-2-oxopiperazine-6-carboxylate 10d. White solid (0.19 g, 31%), mp 132–134°C (from ethanol); IR (KBr) 1733 (C=O), 1670 (C=O), 1250 (C–O) cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ=1.21 (3H, t, J=6.9 Hz, CH_3), 2.11 (3H, s, NCH_3), 2.98 (3H, s, NCH_3), 3.30 (1H, d, J=17.2 Hz, H-3a), 3.38 (1H, d, J=17.2, H-3b), 3.81–3.86 (2H, m, H-5 and H-6), 4.07–4.28 (2H, m, OCH_2), 6.19 (1H, d, J=9.9 Hz, =CH), 7.10–7.18 (4H, m, H-2′,6′), 7.25–7.43 (4H, m, H-3′,5′); ^{13}C NMR (68 MHz, $CDCl_3$) δ=14.0 (CH_3), 34.4 (NCH_3), 41.8 (NCH_3), 54.3 (CH_2-3), 58.8 (CH), 61.7 (OCH_2), 66.5 (CH), 121.6 (=CH), 128.6 (4×CH), 128.9 (2×CH), 130.9 (2×CH), 134.1 (q), 134.4 (q), 136.8 (q), 139.3 (q), 146.4 (q), 167.3 (C=O), 169.5 (C=O); MS (ESI): m/z 451 (MH^+, 8%), 449 (MH^+, 60), 447 (MH^+, 100); Anal. Calcd for $C_{23}H_{24}Cl_2N_2O_3$: C, 61.75; H, 5.4; N, 6.3%. Found: C, 61.4; H, 5.3; N, 6.0%; HRMS (ESI): Found: MH^+, 447.1237. Calc. for $C_{23}H_{25}Cl_2N_2O_3$: MH^+=447.1237.

3.5.2. Ethyl *cis*-5-[2′,2′-bis(4″-chlorophenyl)ethenyl]-1,4-dimethyl-2-oxopiperazine-6-carboxylate 11d. Light yellow oil (0.15 g, 25%); IR (neat) 1740 (C=O), 1682 (C=O), 1258 (C–O) cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ=1.27 (3H, t, J=6.9 Hz, CH_3), 2.24 (3H, s, NCH_3), 2.85 (3H, s, NCH_3), 2.86 (1H, d, J=17.2 Hz, H-3a), 3.37 (1H, dd, J=10.6, 4.0 Hz, H-5), 3.59 (1H, d, J=17.2 Hz, H-3b), 3.78 (1H, d, J=4.0 Hz, H-6), 4.24–4.31 (2H, m, OCH_2), 5.99 (1H, d, J=10.6 Hz, =CH), 7.09–7.16 (4H, m, ArH), 7.24–7.29 (2H, m, ArH), 7.40–7.43 (2H, m, ArH); ^{13}C NMR (68 MHz, $CDCl_3$) δ 14.3 (CH_3), 33.6 (NCH_3), 42.6 (NCH_3), 58.1 (CH_2-3), 60.8 (CH), 61.8 (OCH_2), 65.5 (CH), 125.3 (=CH), 128.4 (2×CH), 128.6 (2×CH), 129.2 (2×CH), 130.7 (2×CH), 134.1 (q), 134.2 (q), 137.0 (q), 139.3 (q), 143.9 (q), 167.5 (C=O), 168.9 (C=O); m/z (ESI) 451 (MH^+, 8%), 449 (MH^+, 59), 447 (MH^+, 100); HRMS (ESI): Found: MH^+, 447.1236. Calc for $C_{23}H_{25}Cl_2N_2O_3$: MH^+=447.1237.

3.6. The reaction of 3,3-bis(4′-methoxyphenyl)propenal 6c with sarcosine ethyl ester 7b

The reaction of 3,3-bis(4′-methoxyphenyl)propenal **6c** (0.51 g, 1.90 g mmol) and sarcosine ethyl ester hydrochloride **7b** (0.59 g, 3.84 mmol) as described earlier, gave a mixture which was purified by column chromatography on silica eluting with ethyl acetate to give a brown oil (0.64 g, 77%) containing *trans*-**10e** and *cis*-ethyl 5-[2′,2′-bis(4″-methoxylphenyl)ethenyl]-1,4-dimethyl-2-oxopiperazine-6-carboxylate **11e** (isomeric ratio 3:1, determined by ^{1}H NMR spectroscopy). This brown oil was separated by column chromatography on silica, eluting with hexane/diethyl ether (20:80).

3.6.1. Ethyl *trans*-5-[2′,2′-bis(4″-methoxyphenyl)ethenyl]-1,4-dimethyl-2-oxopiperazine-6-carboxylate 10e. White solid (0.38 g, 46%), mp 143–145°C (from ethanol); IR (KBr) 1735 (C=O), 1666 (C=O), 1606 (C=C), 1510 (C=C), 1247 (C–O) cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ=1.21 (3H, t, J=7.3 Hz, CH_3), 2.10 (3H, s, NCH_3), 2.98

(3H, s, NCH_3), 3.33 (2H, s, CH_2), 3.80 (3H, s, OCH_3), 3.85 (3H, s, OCH_3), 3.89–3.94 (2H, m, H-5 and H-6), 4.09–4.23 (2H, m, OCH_2), 6.05 (1H, d, J=9.9 Hz, =CH), 6.80–6.95 (4H, m, H-3′,5′), 7.06–7.18 (4H, m, H-2′,6′); ^{13}C NMR (68 MHz, $CDCl_3$) δ=13.9 (CH_3), 34.1 (NCH_3), 41.6 (NCH_3), 54.3 (OCH_3), 55.0 (OCH_3), 55.1 (CH_2-3), 58.7 (CH), 61.4 (OCH_2), 66.6 (CH), 113.5 (2×CH), 113.6 (2×CH), 118.0 (=CH), 128.6 (2×CH), 130.7 (2×CH), 131.2 (q), 134.1 (q), 147.6 (q), 158.9 (q), 159.5 (q), 167.4 (C=O), 169.7 (C=O); Anal. Calcd for $C_{25}H_{30}N_2O_5$: C, 68.5; H, 6.9; N, 6.4%. Found: C, 68.8; H, 6.9; N, 6.2.

3.6.2. Ethyl *cis*-5-[2′,2′-bis(4″-methoxyphenyl)ethenyl]-1,4-dimethyl-2-oxopiperazine-6-carboxylate 11e. Light yellow oil (0.11 g, 13%); IR (neat) 1741 (C=O), 1665 (C=O), 1606 (C=C), 1511 (C=C), 1245 (C–O) cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ=1.27 (3H, t, J=7.3 Hz, CH_3), 2.24 (3H, s, NCH_3), 2.84 (3H, s, NCH_3), 2.85 (1H, d, J=17.2 Hz, H-3a), 3.41 (1H, dd, J=9.9, 4.0 Hz, H-5), 3.59 (1H, d, J=17.2 Hz, H-3b), 3.80 (3H, s, OCH_3), 3.81 (1H, d, J=4.0 Hz, H-6), 3.86 (3H, s, OCH_3), 4.22–4.34 (2H, m, OCH_2), 5.86 (1H, d, J=9.9 Hz, =CH), 6.79–6.96 (4H, m, H-3′,5′), 7.06–7.26 (4H, m, H-2′,6′); ^{13}C NMR (68 MHz, $CDCl_3$) δ=14.2 (CH_3), 33.5 (NCH_3), 42.6 (NCH_3), 55.2 (OCH_3), 55.3 (OCH_3), 58.2 (CH_2-3), 61.0 (CH), 61.6 (OCH_2), 65.6 (CH), 113.6 (2×CH), 114.0 (2×CH), 121.9 (=CH), 128.4 (2×CH), 130.5 (2×CH), 131.4 (q), 134.2 (q), 145.3 (q), 159.0 (q), 159.4 (q), 167.7 (C=O), 169.2 (C=O); MS (ESI): m/z 440 (28%), 439 (MH^+, 100); HRMS (ESI): Found: MH^+, 439.2225. Calc for $C_{25}H_{31}N_2O_5$: MH^+=439.2227.

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