AN UNEXPECTED FORMATION OF DIETHYL *TRANS*-2,3-PIPERAZINEDICARBOXYLATES

Alan R. Katritzky,* Zuoquan Wang and Hengyuan Lang

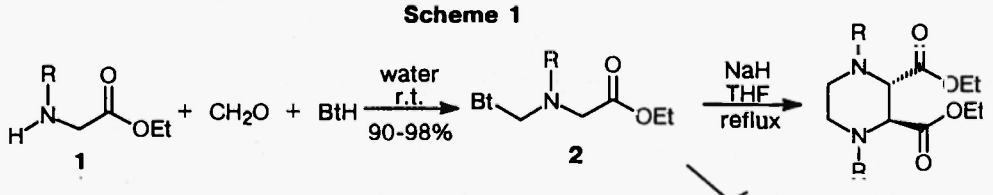
Center for Heterocyclic Compounds, Department of Chemistry
University of Florida, Gainesville, FL 32611-7200

Peter J. Steel
Department of Chemistry, University of Canterbury, Christchurch, New Zealand

Abstract: Heating *N*-(benzotriazol-1-yl)glycine ethyl esters 2, obtained by Mannich condensation of glycine ethyl esters 1, formaldehyde and benzotriazole, in THF in the presence of excess of NaH unexpectedly gave diethyl *trans*-2,3-piperazinedicarboxylates 3.

Work in our group has demonstrated the versatility of benzotriazole as a synthetic auxiliary in organic synthesis (1-4). The benzotriazole anion is a good leaving group and can be used in place of a halogen or other substituents in many transformations. In particular, we found that the benzotriazole group in Mannich adducts ($R^1R^2NCHRBt$), readily prepared from condensation of a secondary amine, an aldehyde and benzotriazole, can be easily displaced by carbanions from RMgBr and RLi or reduced by $NaBH_4$ under mild conditions to give tertiary amines (5-7). These convenient intermolecular substitutions prompted us to investigate the possibility of intramolecular substitution utilizing benzotriazole as a leaving group to synthesize cyclic compounds.

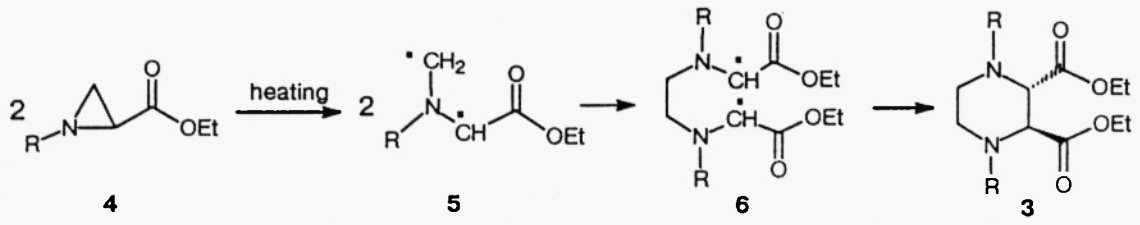
Scheme 1



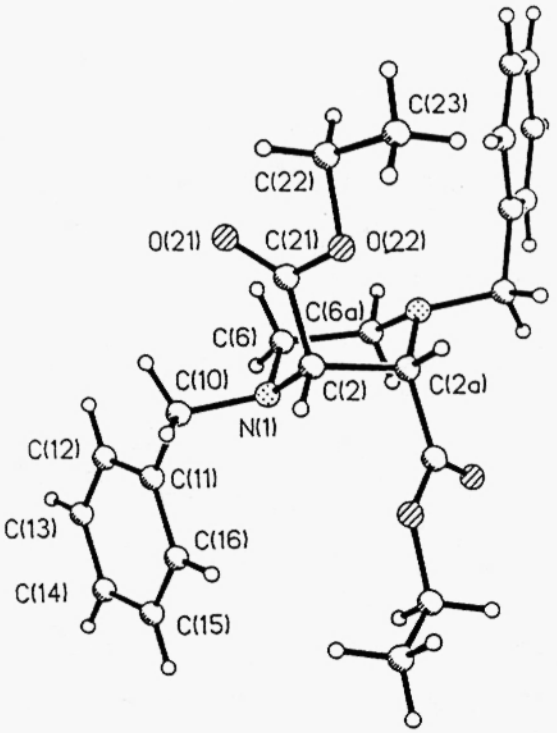
		R	Yield (3) %
1,2,3,4	a	$PhCH_2$	80
	b	4-Me-$C_6H_4CH_2$	56
	c	2-Cl-$C_6H_4CH_2$	58
	d	Me	20

Reaction of *N*-alkylglycine ethyl esters 1a-d, formaldehyde and benzotriazole in water at room temperature readily gave benzotriazole adducts 2a-d in excellent yields according to the general procedure for the preparation of aminoalkylbenzotriazoles developed in this laboratory (8). We anticipated that α-

deprotonation of compounds 2 with a strong base and subsequent intramolecular displacement of benzotriazole would afford the aziridine derivatives 4. However, treatment of benzotriazole adduct 1a with NaH in refluxing THF for 2-5.5 h unexpectedly generated the six-membered ring compound, diethyl 1,4-diphenyl-*trans*-2,3-dibenzylpiperazinedicarboxylate 3a in 80% yield instead of the three-membered aziridine 4a. Compounds 3b-d were similarly obtained in 26-58% yields. The reactions were monitored by TLC, and no aziridines 4 were detected either by TLC or from the NMR spectra.



Huisgen *et al.* (9) reported that heating methyl 1-phenylaziridine-2-carboxylate 4 (R = Ph) at 200 °C for 6 h gave dimethyl 1,4-diphenyl--*trans*-2,3-piperazinedicarboxylate 3 (R = Ph) in 50% yield. Although in Huisgen's paper (9) no mechanistic details were given, the present formation of 3 from 1 may also involve intermediates 4. Under the reaction conditions, spontaneous ring-opening could give diradicals 5, which subsequently couple to the six-membered piperazine derivatives 3. However, a frontier MO calculation sugests that reactions 5 → 3 are less favorable than the formation of isomeric 2,5-diethoxycarbonyl substituted derivatives.



The structures for compounds 3a-d were established by ^{1}H NMR, ^{13}C NMR and mass spectroscopy or elemental analyses. NMR spectra clearly showed that only the *trans*-isomer was formed in the reactions. ^{1}H NMR indicates two doublets coupling to each other at 2,32-2,51 ppm and 2.46-3.29 ppm which is from the protons at C5 and C6, and one singlet at 3.07- 3.88 ppm from C2 and C3. ^{13}C NMR indicates two ring carbon signals at 52.4-59.2 ppm (C5 and C6) and 62.5-68.6 ppm (C2 and C3). APT technique was also used for the assignment of the signals.

For further confirmation, a single crystal X-ray structure determination was carried out for compound 3a. Figure 1 shows a perspective view and atom labeling of the structure. In the solid state this compound crystallizes in the space group C2/c with half a molecule in the asymmetric unit, the other half being related by a crystallographic two-fold rotation axis that passes through the centers of the two carbon-carbon bonds of the piperazine ring. The six-membered piperazine ring exists in a chair conformation with the ethoxycarbonyl substituents in axial orientations. The benzyl substituents are in equatorial positions that are torsionally oriented such that the phenyl rings are rotated away from the adjacent ethoxycarbonyl substituent.

Experimental

Melting points were determined on a Kofler hot stage apparatus without correction. ^{1}H nmr and ^{13}C nmr spectra were recorded on a Varian VXR 300 MHz spectrometer in deuterochloroform using tetramethylsilane as an internal reference for ^{1}H and deuterochloroform for ^{13}C spectra. High resolution mass spectra measurements were recorded on an AEI MS-30 mass spectrometer. THF were distilled from sodium/benzophenone ketyl under nitrogen immediately before use.

Compounds 1a and 1d were purchased from Aldrich. 1b.c were prepared by adaption of the general procedure for the preparation of α-alkylamino esters (10).

Ethyl *N*-(4-methylbenzyl)aminoacetate 1b. Obtained as a light yellow oil. Yield 80%. (MS found: M^+ = 207; $C_{12}H_{17}NO_2$ requires M = 207); ^{1}H NMR δ 1.27 (t, 3 H, *J* = 7.1 Hz), 1.91 (s, 1 H), 2.33 (s, 3 H), 3.39 (s, 2 H), 3.76 (s, 2 H), 4.18 (q, 2 H, *J* = 7.1 Hz), 7.13 (d, 2 H, *J* = 8.1 Hz), 7.22 (d, 2 H, *J* = 8.1 Hz); ^{13}C NMR δ 14.0, 20.8, 49.9, 52.8, 60.4, 128.0, 128.9, 136.3, 136.4, 172.2.

Ethyl *N*-(2-chlorobenzyl)aminoacetate 1c. Obtained as a light yellow oil. Yield 65%. (Found: C, 58.10; H, 6.22; N, 6.53. $C_{11}H_{14}ClNO_2$ requires C, 58.03; H, 6.20; N, 6.15); ^{1}H NMR δ 1.29 (t, 3 H, *J* = 7.1 Hz), 2.07 (br s, 1 H), 3.44 (s, 2 H), 3.93 (s, 2 H), 4.20 (q, 2 H, *J* = 7.1 Hz), 7.18-7.30 (m, 2 H), 7.36-7.45 (m, 2 H); ^{13}C NMR δ 13.9, 49.9, 50.3, 60.4, 126.5, 128.1, 129.2, 129.8, 133.6, 136.8, 171.9.

Benzotriazole adducts 2a-d were prepared as a mixture of benzotriazolyl 1-isomer and 2-isomer in a ratio of 4:1 to 8:1 according to the literature (8). Benzotriazole (1.19 g, 10 mmol) and the appropriate *N*-alkylglycine ethyl esters 1 (10 mmol) were stirred in water (10 ml) for 5 min at 20 °C. Formaldehyde (0.81g, 37% aq. solution, 10 mmol) was added to the reaction mixture and the stirring was continued for 2 h at room temperature. In the case of 2a, a white solid was formed and filtered. In the other cases, the reaction mixture was extracted with diethyl ether (50 ml), dried with $MgSO_4$. Evaporation of the solvent gave the expected product.

Ethyl (*N*-benzotriazolylmethyl-*N*-benzyl)aminoacetate 2a. Yield 90%; White crystals, mp 77-79 °C (Found: C, 66.79; H, 6.15; N, 17.28. $C_{18}H_{20}N_4O_2$ requires C, 66.63; H, 6.22; N, 17.28), (1-isomer/2-isomer =

6:1); ^{1}H NMR δ 1.23 (t, 3 H, *J* = 7.2 Hz), 3.50 (s, Bt^1) and 3.62 (s, Bt^2) (total 2 H), 3.95 (s, Bt^1) and 3.98 (s, Bt^2) (total 2 H), 4.13 (q, 2 H, *J* = 7.2 Hz), 5.66 (s, Bt^1) and 5.68 (s, Bt^2) (total 2 H), 7.27-7.50 (m), 7.89-7.94 (m) and 8.07 (d, 1 H, *J* = 8.2 Hz) (total 9 H); ^{13}C NMR δ 13.9, 52.3, 52.9 (Bt^2), 56.0 (Bt^2), 56.2, 60.4 (Bt^2), 60.5, 65.4, 73.3 (Bt^2), 109.8, 118.1 (Bt^2), 119.6, 123.7, 126.2 (Bt^2), 127.2, 127.5, 128.3, 128.7, 129.0, 133.4, 137.1, 144.1 (Bt^2), 145.7, 170.5.

Ethyl *N*-[benzotriazolylmethyl-*N*-(4-methyl)benzyl)]aminoacetate 2b. Obtained as a light yellow oil, yield 100%; (1-isomer/2-isomer = 4:1); ^{1}H NMR δ 1.24 (t, 3 H, *J* = 7.1 Hz), 2.35 (s, 3 H), 3.51 (s, Bt^1) and 3.62 (s, Bt^2) (total 2 H), 3.92 (s, Bt^1) and 3.95 (s, Bt^2) (total 2 H), 4.14 (q, 2 H, *J* = 7.1 Hz), 5.67 (s, Bt^1) and 5.69 (s, Bt^2) (total 2 H), 7.13-7.60 (m), 7.91-7.94 (m) and 8.08 (d, 1 H, *J* = 8.3 Hz) (total 8 H); ^{13}C NMR δ 13.9, 20.9, 52.1, 55.8, 60.5, 65.3, 73.5 (Bt^2), 109.8, 118.1 (Bt^2), 119.5, 123.7, 126.1 (Bt^2), 127.1, 128.7, 128.9, 129.0, 133.4, 134.0, 137.0, 144.1 (Bt^2), 145.7, 170.4.

Ethyl *N*-[benzotriazolylmethyl-*N*-(2-chloro)benzyl)]aminoacetate 2c. Obtained as a light yellow oil, yield 100%; (1-isomer/2-isomer = 4:1); ^{1}H NMR δ 1.13 (t, 3 H, *J* = 7.1 Hz), 3.54 (s, Bt^1) and 3.64 (s, Bt^2) (total 2 H), 3.94 -4.20 (m, 4 H), 5.71 (s, 2 H), 7.19-7.46 (m), 7.89-7.94 (m) and 8.06 (d, 1 H, *J* = 8.4 Hz) (total 8 H); ^{13}C NMR δ 14.0, 52.5, 53.3 (Bt^2), 53.7, 60.7, 65.9, 73.8 (Bt^2), 109.8, 118.2 (Bt^2), 119.7, 123.9, 126.3 (Bt^2), 126.8, 127.4, 128.8, 129.6, 130.7, 133.4, 134.4, 134.9, 144.3 (Bt^2), 145.8, 170.6.

Ethyl (*N*-benzotriazolylmethyl-*N*-methyl)aminoacetate 2d. Obtained as a colorless oil, yield 98% (Found: C, 58.24; H, 6.64; N, 22.28. $C_{12}H_{16}N_4O_2$ requires C, 58.03; H, 6.64; N, 22.57), (1-isomer/2-isomer = 8:1); ^{1}H NMR δ 1.28 (t, 3 H, *J* = 7.1 Hz), 2.55 (s, Bt^1) and 2.59 (s, Bt^2) (total 3 H), 3.50 (s, Bt^1) and 3.60 (s, Bt^2) (total 2 H), 4.20 (q, 2 H, *J* = 7.1 Hz), 5.62 (s, Bt^1) and 5.68 (s, Bt^2) (total 2 H), 7.40 (t, 1 H, *J* = 7.2 Hz), 7.52 (t, 1 H, *J* = 7.2 Hz), 7.69 (d, 1 H, *J* = 8.3 Hz), 8.07 (d, 1 H, *J* = 8.3 Hz); ^{13}C NMR δ 13.9, 40.1 (Bt^2), 40.4, 55.1, 55.3 (Bt^2), 60.7, 67.9, 70.9 (Bt^2), 76.2 (Bt^2), 109.7, 118.1 (Bt^2), 119.6, 123.8, 126.3 (Bt^2), 127.4, 133.5, 144.1 (Bt^2), 145.6, 170.2.

General Procedure for the Preparation of Compounds 3a-d: Benzotriazole adduct 2a-d (10 mmol) was dissolved in THF (30 ml) under nitrogen. Sodium hydride (95%, 0.54 g, 20 mmol) was added and the mixture was refluxed for the appropriate time (for 2a,d, 2h; for 2b.c. 5.5 h). After adding water (20 ml) and extraction with diethyl ether (3 x 100 ml), evaporation of the solvent gave the products. In the case of 3a, pure compound was obtained. The other cases required purification by flash column chromatography.

Diethyl 1,4-dibenzyl-*trans*-2,3-piperazinedicarboxylate 3a. Yield 80%. White crystals, m.p. 98-99 °C (HRMS found: M+1 = 411.2262; $C_{24}H_{30}N_2O_4$ requires M+1 411.2283); ^{1}H NMR δ 1.21 (t, 6 H, *J* = 7.2 Hz), 2.53 (d, 2 H, *J* = 7.1 Hz), 3.29 (d, 2 H, *J* = 7.1 Hz), 3.89 (s, 2 H), 3.93 (s, 4 H), 4.10-4.25 (m, 4 H), 7.20-7.35 (m, 10 H); ^{13}C NMR δ 14.1, 46.4, 59.2, 60.1, 62.5, 126.8, 128.0, 128.5, 138.8, 170.7.

Diethyl 1,4-bis(4-methylbenzyl)-*trans*-2,3-piperazinedicarboxylate 3b. Yield 56%. White crystals, m.p. 65-67 °C (Found: C, 60.55; H, 5.93; N, 5.94. $C_{26}H_{34}N_2O_4$ requires C, 60.13; H, 5.89; N, 5.84); ^{1}H NMR δ 1.23 (t, 6 H, *J* = 7.1 Hz), 2.32 (s, 6 H), 2.52 (d, 2 H, *J* = 7.2 Hz), 3.26 (d, 2 H, *J* = 7.2 Hz), 3.87-3.88 (m, 6 H), 4.10-4.28 (m, 4 H), 7.07-7.21 (m, 8 H); ^{13}C NMR δ 14.2, 21.0, 46.5, 59.1, 60.2, 62.7, 128.6, 128.8, 135.8, 136.4, 170.9.

Diethyl 1,4-bis(2-chlorobenzyl)-*trans*-2,3-piperazinedicarboxylate 3c. Yield 58%. White crystals, m.p. 94-96 °C (Found: C, 71.00; H, 7.76; N, 6.28. $C_{24}H_{28}N_2O_4Cl_2$ requires C, 71.21; H, 7.81; N, 6.39); ^{1}H NMR

δ 1.24 (t, 6 H, *J* = 7.2 Hz), 2.56 (d, 2 H, *J* = 6.9 Hz), 3.38 (d, 2 H, *J* = 6.9 Hz), 4.01-4.31 (m, 10 H), 7.19-7.45 (m, 8 H); ^{13}C NMR δ 14.2, 46.2, 56.8, 60.4, 63.2, 126.4, 128.1, 129.4, 130.3, 134.4, 136.6, 170.9.

Diethyl 1,4-dimethyl-*trans*-2,3-piperazinedicarboxylate 3d. Obtained as a colorless oil; yield 20%. (HR MS found: M^+ = 258.1558; $C_{12}H_{22}N_2O_4$ requires M = 258.1580); ^{1}H NMR δ 1.30 (t, 6 H, *J* = 7.1 Hz), 2.32 (s, 6 H), 2.46 (d, 2 H, *J* = 8.3), 2.90 (d, 2 H, *J* = 8.3 Hz), 3.07 (s, 2 H), 4.12-4.32 (m, 4 H); ^{13}C NMR δ 13.9, 43.2, 52.4, 60.9, 68.6, 169.9.

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