1,3-Dipolar Cycloaddition of Benzonitrilium *N*-Phenylimide to Didehydropeptides†

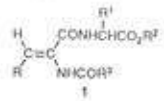
J. Chem. Research (S), 1993, 182–183†

Magda A. Abdallah,* Hassan A. Albar* and Ahmad S. Shawali**

**Department of Chemistry, Faculty of Science, University of Cairo, Giza, Egypt*
**Department of Chemistry, Faculty of Science, King Abdulaziz University, Jeddah 21413, Saudi Arabia*

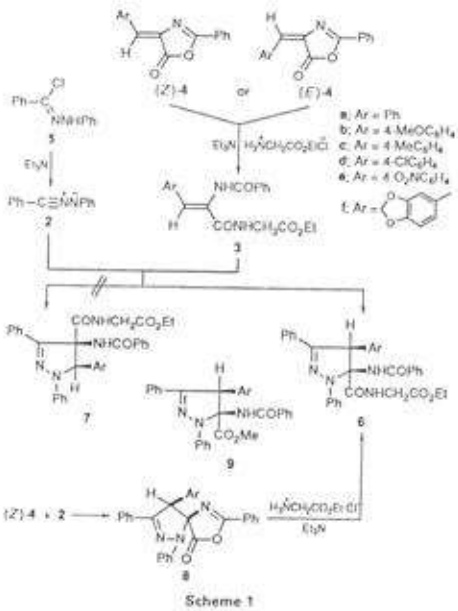
N-Benzoyl-α,β-didehydrophenylalanylglycine ethyl esters **3a–f** add benzonitrilium *N*-phenylimide **2** regioselectively to yield the pyrazolylaminocarboxylic acid peptides **6a–f**.

α,β-Didehydropeptides (DDP, **1**) have attracted much interest during the past 20 years owing to their antitumor activity,[1] CNS inhibiting properties[2] and their use as intermediates in the synthesis of chiral peptides[3,4] and imidazole derivatives.[5,6] The 1,3-dipolarophilic reactivity of such a class of peptides has not yet been explored, however. Our interest in peptides having *N*-terminal heterocyclic amino-acid residues led us to study the cycloaddition of benzonitrilium *N*-phenylimide **2** to a series of *N*-benzoyl-α,β-didehydrophenylalanylglycine ethyl esters **3a–f** and to determine the regiochemistry of the reaction products (Scheme 1).



1

The didehydropeptides **3a–f** were prepared by ring-cleavage of the corresponding (*Z*)-oxazolone derivatives (*Z*)-**4a–f** with ethyl glycinate hydrochloride in dimethylformamide in the presence of triethylamine. The physical properties of the known DDP (*Z*)-**3a,d** were identical with those reported in the literature.[7,8] The structures of the other new DDP (*Z*)-**3b,c,e,f** were established by their elemental analyses, IR and ^{1}H NMR spectral data. Their IR spectra exhibit two amide NH bands near 3250 and 3060 cm^{-1}, an ester carbonyl band near 1755 cm^{-1} and two amide carbonyl bands near 1680 and 1660 cm^{-1}. Their ^{1}H NMR spectra revealed characteristic signals near δ 1.25 (3H, t), 4.0 (2H, q) and 4.15 (2H, d) in addition to two NH proton signals in the region δ 7.8–8.7.



Scheme 1

Reaction of the oxazolones (*E*)-**4a–f** with ethyl glycinate hydrochloride under the same conditions as mentioned above also afforded the corresponding (*Z*)-**3a–f**. The formation of the latter seems to be due to the known conversion of the labile (*E*)-**4** to the more stable (*Z*)-**4** in the presence of amines.[11]

Benzonitrilium *N*-phenylimide **2**, generated *in situ* by the action of triethylamine on *N*-phenylbenzohydrazonoyl chloride **5** in chloroform at reflux, reacted with **3a–f** to give the corresponding cycloadducts (Scheme 1). The reactions proved to be regioselective as only one regioisomer was obtained in each case as evidenced by ^{1}H NMR spectral analysis of the crude reaction products. The regiochemistry of the isolated cycloadducts was evidenced by the alternative synthesis of **6a** from the previously reported spiropyrazole **8a**.[12,13] Thus treatment of **8a** with ethyl glycinate hydrochloride in dimethylformamide in the presence of triethylamine at room temperature afforded a product identical in all respects (m.p., mixed m.p. and IR) with that obtained from **3a** and **2**. This finding indicates that the products isolated from the reactions of **2** with (*Z*)-**3a–f** have the structure **6** and not **7**. This regiochemical assignment is further substantiated by comparison of the chemical shift of the 4,5-dihydro-1*H*-pyrazole ring proton of the cycloadducts **6a–f** with those of the related 4,5-dihydro-1*H*-pyrazole derivatives **9**. In their ^{1}H NMR spectra, each of the peptides **6a–f** exhibited a singlet signal in the region δ 5.1–5.4. The similarity between such values with those reported for **9** (δ 5.4–5.7)[12] seems to be in support of structure **6** assigned to the peptides prepared. The other ^{1}H NMR and IR spectral data of **6a–f** are also compatible with their assigned structure.

Experimental

M.p.s were recorded on a Gallenkamp apparatus. ^{1}H NMR spectra were recorded on a Varian EM-390 spectrometer for solutions in $CDCl_3$ with Me_4Si as internal standard; 'b' indicates a broad signal. IR spectra were obtained on a Pye–Unicam SP3 spectrophotometer using samples in KBr. Microanalyses were performed with a Perkin-Elmer 240-B elemental analyser at King Abdulaziz University. All solvents and reagents were purchased from Aldrich. The hydrazonyl chloride **5**[14] and the oxazolones (*Z*)-**4** and (*E*)-**4**[15] were prepared according to literature methods.

Reactions of Ethyl Glycinate Hydrochloride with **4a–f** *and* **8a**; *General Procedure*.—To a stirred solution of the appropriate oxazolone (*Z*)-**4** or (*E*)-**4** (5 mmol) in dimethylformamide (20 ml) was added a suspension of ethyl glycinate hydrochloride (0.8 g, 6 mmol) and triethylamine (5 mmol) in DMF (10 ml). After 4 h at room temperature, the mixture was poured into cold water with stirring. The solid that precipitated was collected and crystallized from methanol to give the corresponding **3**. Repetition of the same procedure using **8a** in place of **4** afforded a product (m.p. 162 °C) identical in all respects (m.p., mixed m.p. and IR) with **6a** obtained below.

*To receive any correspondence.
†This is a Short Paper as defined in the Instructions for Authors [*J. Chem. Research (S)*, 1993, Issue 1, p. viii]; there is therefore no corresponding material in *J. Chem. Research (M)*.

3a (70% yield), m.p. 128 °C (lit. m.p.[10] 114–115 °C); δ ($CDCl_3$) 1.25 (3H, t), 4.10 (2H, q), 4.25 (2H, d), 7.0–7.6 (11H, m), 7.9 (1H, b) and 8.5 (1H, s) (Found: C, 68.15; H, 5.7; N, 7.8. $C_{17}H_{15}NO_3$ requires C, 68.16; H, 5.72; N, 7.95%). **3b** (78% yield), m.p. 160 °C; δ ($CDCl_3$) 1.20 (3H, t), 3.7 (3H, s), 4.10 (2H, q), 4.20 (2H, d), 6.7–7.6 (10H, m), 7.8 (1H, b) and 8.6 (1H, s) (Found: C, 65.7; H, 5.7; N, 7.2). $C_{18}H_{17}NO_4$ requires C, 65.95; H, 5.80; N, 7.30. **3c** (75% yield), m.p. 170 °C; δ ($CDCl_3$) 1.20 (3H, t), 2.13 (3H, s), 4.10 (2H, q), 4.15 (2H, d), 6.7–7.9 (10H, m), 7.8 (1H, b) and 8.5 (1H, s) (Found: C, 68.5; H, 5.9; N, 7.6. $C_{18}H_{17}NO_3$ requires C, 68.84; H, 6.05; N, 7.64%). **3d** (88% yield), m.p. 202 °C (lit. m.p.[10] 200–202 °C); δ ($CDCl_3$) 1.25 (3H, t), 4.15 (2H, q), 4.3 (2H, d), 7.1–7.8 (10H, m), 8.05 (1H, b) and 9.5 (1H, s) (Found: C, 62.2; H, 4.9; N, 7.2. $C_{17}H_{14}ClNO_3$ requires C, 62.09; H, 4.95; N, 7.24%). **3e** (68% yield), m.p. 208 °C; δ ($CDCl_3$) 1.30 (3H, t), 4.10 (2H, q), 4.25 (2H, d), 7.3–7.9 (10H, m), 8.2 (1H, b), 9.5 (1H, s) (Found: C, 59.2; H, 4.7; N, 10.5. $C_{17}H_{14}N_2O_5$ requires C, 60.45; H, 4.81; N, 10.57%). **3f** (85% yield), m.p. 205 °C; δ ($CDCl_3$) 1.25 (3H, t), 4.10 (2H, q), 4.20 (2H, d), 5.85 (2H, s), 6.5–7.6 (9H, m), 7.9 (1H, b) and 9.3 (1H, s) (Found: C, 63.6; H, 5.1; N, 7.1. $C_{18}H_{17}NO_4$ requires C, 63.63; H, 5.05; N, 7.07%).

Reactions of **2** *with* **3a–f**. *General Procedure*.—To a hot solution of the appropriate **3** (5 mmol) in chloroform (30 ml) and triethylamine (5 mmol) was added *N*-phenylbenzohydrazonoyl chloride **5** (1.15 g, 5 mmol). The mixture was refluxed for 24 h, then the solvent was distilled under reduced pressure and the crude oil left was triturated with methanol. The solid formed was collected and crystallized from methanol to give **6**.

6a (70% yield), m.p. 160 °C, ν_{max}/cm^{-1} (KBr) 3339, 3061 (NH), 1745, 1695 and 1675 (CO); δ ($CDCl_3$) 1.25 (3H, t), 4.0 (2H, q), 4.22 (2H, d), 5.3 (1H, s) and 6.8–8.2 (22H, m) (Found: C, 72.1; H, 5.55; N, 10.35. $C_{34}H_{30}N_4O_4$ requires C, 72.51; H, 5.53; N, 10.25%). **6b** (55% yield), m.p. 198 °C, ν_{max}/cm^{-1} (KBr) 3400, 3320 (NH), 1750, 1740 and 1690 (CO); δ ($CDCl_3$) 1.30 (3H, t), 3.6 (3H, s), 4.0 (2H, q), 4.2 (2H, d), 5.22 (1H, s) and 6.5–8.0 (21H, m) (Found: C, 70.3; H, 5.6; N, 9.7. $C_{35}H_{32}N_4O_5$ requires C, 70.82; H, 5.59; N, 9.72%). **6c** (60% yield), m.p. 192 °C, ν_{max}/cm^{-1} (KBr) 3290, 3220 (NH), 1740, 1700 and 1670 (CO); δ ($CDCl_3$) 1.32 (3H, t), 2.13 (3H, s), 4.05 (2H, q), 4.22 (2H, d), 5.10 (1H, s) and 6.8–8.2 (21H, m) (Found: C, 73.7; H, 6.1; N, 10.0. $C_{35}H_{32}N_4O_3$ requires C, 72.84; H, 5.75; N, 9.98%). **6d** (60% yield), m.p. 190 °C, ν_{max}/cm^{-1} 3330, 3210 (NH), 1740, 1705 and 1680 (CO); δ ($CDCl_3$) 1.30 (3H, t), 4.0 (2H, q), 4.24 (2H, d), 5.40 (1H, s) and 6.8–7.9 (21H, m) (Found: C, 68.3; H, 5.0; N, 9.5. $C_{34}H_{29}ClN_4O_4$ requires C, 68.21; H, 5.03; N, 9.67%). **6e** (50% yield), m.p. 120 °C, ν_{max}/cm^{-1} 3280, 3200 (NH), 1750, 1700 and 1670 (CO) (Found: C, 67.0; H, 4.9; N, 11.8. $C_{34}H_{29}N_5O_6$ requires C, 66.99; H, 4.94; N, 11.84%). **6f** (70% yield), m.p. 215 °C, ν_{max}/cm^{-1} 3390, 3250 (NH), 1750, 1740 and 1680 (CO); δ ($CDCl_3$) 1.30 (3H, t), 4.0 (2H, q), 4.3 (2H, d), 5.3 (1H, s), 5.8 (2H, s) and 6.5–7.9 (20H, m) (Found: C, 69.8; H, 5.15; N, 9.5. $C_{40}H_{34}N_4O_4$ requires C, 69.14; H, 5.12; N, 9.48%).

Received, 11th January 1993; Accepted, 20th January 1993
Paper E/5/00177F

References

1 E. Eschenberg, W. Opitz and S. Raddatz, *Ger. Pat.* (DOS), 2659114, 1978; 2745584, 1979 (*Chem. Abstr.*, 1979, **90**, 55277; 1979, **91**, 74980).
2 E. Eschenberg, H. Jacobi and W. Opitz, *Ger. Pat.* (DOS), 2904512, 1980 (*Chem. Abstr.*, 1981, **94**, 47753).
3 E. Eschenberg, W. Opitz and S. Raddatz, *U.S. Pat.*, 4310517, 1982 (*Chem. Abstr.*, 1982, **97**, 72781).
4 I. Lupsa and C. Bilegan, *Rev. Chim. (Bucharest)*, 1974, **25**, 95 (*Chem. Abstr.*, 1974, **81**, 49610).
5 I. Ojima, T. Kogura, N. Yoda, T. Suzuki, M. Yatabe and T. Tanaka, *J. Org. Chem.*, 1982, **47**, 1329.
6 J. C. Poulin and H. B. Kagan, *J. Chem. Soc., Chem. Commun.*, 1982, 1261.
7 A. M. Islam, A. M. Khalil and I. I. Abdelgawad, *Aust. J. Chem.*, 1973, **26**, 827.
8 A. M. Islam, A. M. Khalil and M. S. Elhousemi, *Aust. J. Chem.*, 1973, **26**, 1701.
9 P. Kumar and A. K. Mukerji, *Indian J. Chem.*, 1983, **24B**, 416.
10 S. S. Parmar, P. C. Joshi, B. Ali and S. J. Brumleve, *J. Pharm. Sci.*, 1973, **62**, 1986.
11 Y. S. Rao and R. Filler, *Synthesis*, 1980, 836; 1975, 749.
12 A. S. Shawali, A. A. Fahmi, H. M. Hassaneen, M. A. Abdallah and H. A. Abdelhamid, *J. Chem. Res.*, 1992, (*S*) 360; (*M*) 2936.
13 E. C. Argyropoulou, N. G. Argyropoulos and E. Thessalonikos, *J. Chem. Res.*, 1990, (*S*) 202; (*M*) 1557.
14 P. Wolkoff, *Can. J. Chem.*, 1975, **53**, 1333.
15 C. Cativiela, M. D. de Villegas and J. Mylendez, *Tetrahedron*, 1986, **42**, 583; I. Arenal, M. Bernabe and E. F. Alvarez, *An. Quim., Ser. C*, 1981, **77**, 56.