Heterocycles by Cycloaddition. Part 8.[1] Preparation of [1]Benzopyrano[4,3-*b*]-pyrroles by Intramolecular Cycloaddition–Extrusion of Mesoionic Oxazolium-5-olates

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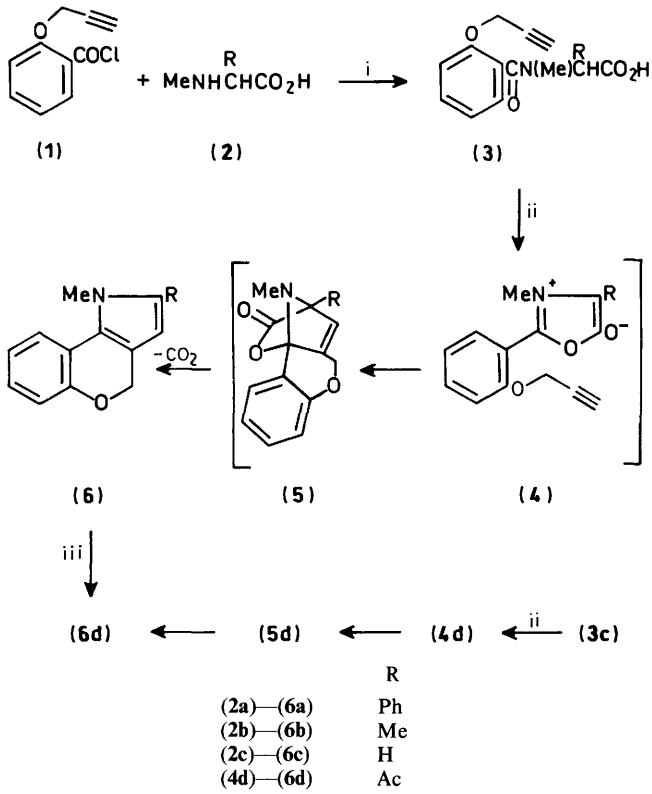
The *in situ* intramolecular cycloaddition–extrusion of the 2-[2-(prop-2-ynyloxy)phenyl]oxazolium-5-olates (**4**), prepared by cyclisation of the *N*-acylamino acids (**3**), gave the [1]benzopyrano[4,3-*b*]-pyrroles (**6a—c**) in good yields. Also the 2-acetylated product (**6d**) was formed from the α-unsubstituted acid (**3c**). These intramolecular cycloadditions occurred preferentially even in the presence of an added dipolarophile.

Mesoionic compounds, which may be regarded as resonance-stabilised cyclic 1,3-dipoles, have been widely used as building blocks for variety of heterocycles.[2] Only a few intramolecular cycloadditions of mesoionic compounds have been reported,[3–5] although there are many reports concerning intramolecular cycloadditions.[6] Most such reactions with mesoionic compounds involve systems bearing a side-chain with a double bond. In these cases, the cycloadducts are generally isolated. Intramolecular cycloadditions with a triple bond have been reported with a mesoionic dithioliumolate[5a] and mesoionic thiazoliumolate[5b] which afforded products arising from cycloaddition–extrusion. We report here intramolecular cycloaddition–extrusion of mesoionic oxazolium-5-olates bearing a substitutent with a triple bond [*i.e.* 2-(prop-2-ynloxy)phenyl] on the 2-position of the ring. Padwa and his co-workers have reported the intramolecular cycloadditions of mesoionic oxazolium-5-olates which have a double bond-containing side-chain at the 2- or 3-position of the ring.[3] The 2-substituted oxazoliumolates gave condensed pyrroles in very low yields by cycloaddition–extrusion and dehydrogenation, whereas the 3-substituted oxazoliumolates gave intramolecular cycloadducts.

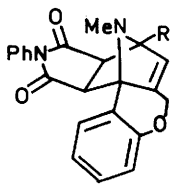
The *N*-substituted *N*-acylamino acid precursors (**3**) were prepared by treatment of the methylaminoacetic acids (**2**) with 2-(prop-2-ynyloxy)benzoyl chloride (**1**)[7] under Schotten–Baumann conditions. As illustrated by the 2-phenyl derivative (**3a**) in the Experimental section, the acylamino acids (**3**) showed temperature-dependent n.m.r. signals: both the *N*-methyl and methine groups of compound (**3a**), for example, showed three peaks at room temperature, which coalesced and sharpened to single signals at higher temperatures. This is probably due to the restricted rotation around the Aryl–CO group, caused by the presence of the bulky *ortho*-substituent, in addition to the commonly observed restricted rotation around the amide C–N bond.

When benzene solutions of the acylamino acids (**3a**) and (**3c**) and acetic anhydride were warmed, the expected intramolecular cycloaddition–extrusion products (**6a**) and (**6c**) were isolated in yields of *ca.* 60%. When high dilution conditions were maintained during the cycloaddition *via* the slow addition of a solution of the acylamino acids (**3a—c**) to a refluxing benzene solution of acetic anhydride, the benzopyranopyrroles (**6a—c**) were isolated in yields above 85%. For the α-unsubstituted acid (**3c**), the 2-acetylated product (**6d**) was isolated (0.4%) in addition to the 2-unsubstituted product (**6c**) (85%) under the conditions described above. The yield of compound (**6d**) was raised to 5% when compound (**3c**) was heated in neat acetic anhydride. However, the acetyl derivative (**6d**) was not formed when the benzopyranopyrrole (**6c**) was heated with acetic anhydride. These results suggest that a fraction of oxazoliumolate (**4c**) is acetylated at the 4-position before intramolecular cycloaddition occurs, and that the acetyl derivative (**4d**) is reactive enough to undergo the cycloaddition. The structure of the acetylated product (**6d**) was determined by comparison with an authentic sample prepared by treatment of the pyrrole (**6c**) with acetyl chloride in the presence of tin(IV) chloride.



Scheme. *Reagents:* i, OH^-; ii, AcCl; iii, AcCl–$SnCl_4$

Even when the acylamino acids (**3a**) and (**3b**) were heated with acetic anhydride in the presence of *N*-phenylmaleimide, the same intramolecular cycloadducts (**6a**) and (**6b**) were formed in high yields, rather than the expected consecutive intermolecular cycloaddition–extrusion and intramolecular cycloaddition products (**7**). In contrast to the above results, Padwa, *et al.*[3a] have reported that intermolecular cycloadduct (**8**) was isolated as the sole product after the related 2-alkenyl substituted oxazoliumolate (**9**) had been formed in the presence of an excess



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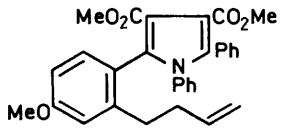

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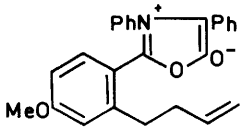

(9)

of acetylenedicarboxylate. Other examples of intermolecular in preference to intramolecular dipolar cycloadditions have been reported.[8]

In summary, the results presented above show that the intramolecular cycloaddition–extrusion of the 2-alkynyl substituted oxazoliumolates (**4**) proceeds readily to afford the desired tricyclic heterocycles (**6**) in high yields. This ring system has been prepared by intramolecular cycloadditions of azomethine ylides which contain a triple bond.[7,9] However, the practical yields are only moderate, and other products are also formed. Therefore, the reaction described here may present an attractive alternative preparative route to the condensed heterocycles (**6**) and related ring systems.

Experimental

M.p.s were determined on a Yanagimoto hot-stage apparatus. I.r. (KBr) spectra were recorded on a Hitachi 345 spectrophotometer. Unless otherwise stated, ^1H and ^{13}C n.m.r. spectra were measured with a JEOL FX90Q spectrometer (90 and 22.5 MHz, respectively) with 8K sampling points for solutions in $CDCl_3$ at 30 and 55 °C, respectively (Me_4Si as internal standard). Mass spectra were measured with a JEOL 01 SG spectrometer. T.l.c. separations were performed on Merck Kieselgel 60 PF_{254}. The yields are based on isolated products with sufficient purity.

N-*Methyl*-N-[2-(*prop*-2-*ynyloxy*)*benzoyl*]*glycines* (**3**).—A stirred solution of 2-(2-prop-2-ynyloxy)benzoyl chloride (**1**) (9.8 mmol) in benzene (10 ml) was added to a solution of amino acid (**2**) (10.0 mmol) in aqueous sodium hydroxide. After 30 min, the aqueous layer was acidified with hydrochloric acid and extracted with dichloromethane. The extract was dried ($CaCl_2$), concentrated, and the residue was recrystallised.

N-*Methyl*-2-*phenyl*-N-[2-(*prop*-2-*ynyloxy*)*benzoyl*]*glycine* (**3a**). Colourless prisms (50%), m.p. 133—134 °C (from ethanol–benzene) (Found: C, 70.3; H, 5.1; N, 4.3%; M^+, 323. $C_{19}H_{17}NO_4$ requires C, 70.6; H, 5.3; N, 4.3%; *M*, 323); $\nu_{max.}$ 3 305 (≡CH), 2 130 (C≡C), 1 738 (CO_2), and 1 630 cm^{-1} (CON); δ_H(30 °C) 2.47 and 2.54 (0.2 and 0.8 H, respectively, t, *J* 2.2 Hz, ≡CH), 2.64, 2.85, and 2.94 (2.0, 0.4, and 0.6 H, respectively, s, NMe), 4.65 and 4.78 (0.4 and 1.6 H, respectively, d, *J* 2.2 Hz, OCH_2), 5.41, 5.46, and 6.59 (0.2, 0.2, and 0.6 H, s, NCH), 6.96—7.37 (9 H, m, ArH), and 9.55 (1 H, s, CO_2H); δ_H[$(CD_3)_2SO$, 170 °C] 2.70 (3 H, s, NMe), 3.08 (1 H, t, *J* 2.4 Hz, ≡CH), 4.75, (2 H, d, *J* 2.4 Hz, OCH_2), 6.0 (1 H, br s, NCH), and 6.96—7.40 (9 H, m, ArH); δ_C(55 °C) 30.3 (q, NMe), 33.6 (q, NMe), 56.5 (t, OCH_2), 60.6 (d, NCH), 76.0 (d, ≡CH), 78.2 (s, *C*≡CH), 113.0—153.3 (nine peaks, Ar), 170.7 (s, CON), and 172.9 p.p.m. (s, CO_2).

N-*Methyl*-N-[2-(*prop*-2-*ynyloxy*)*benzoyl*]*alanine* (**3b**). Colourless prisms (58%), m.p. 110.5—111.5 °C (from ethanol) (Found: C, 64.5; H, 5.7; N, 5.4%; M^+, 261. $C_{14}H_{15}NO_4$ requires C, 64.4; H, 5.8; N, 5.4%; *M*, 261); $\nu_{max.}$ 3 270 (≡CH), 2 128 (C≡C), 1 718 (CO_2), and 1 597 cm^{-1} (CON); δ_H[$(CD_3)_2SO$, 170 °C] 1.38 (3 H, d, *J* 7.2 Hz, CMe), 2.81 (3 H, s, NMe), 3.16 (1 H, t, *J* 2.4 Hz, ≡CH), 4.6 (1 H, br s, NCH), 4.75 (2 H, d, *J* 2.4 Hz, OCH_2), and 6.92—7.46 (4 H, m, ArH); δ_C 14.0 (q, Me), 15.5 (q, Me), 28.7 (q, NMe), 32.6 (q, NMe), 52.3 (d, NCH), 56.1 (t, OCH_2), 56.5 (d, OCH_2), 75.9 (d, ≡CH), 78.2 (s, *C*≡CH), 112.9—153.3 (nine peaks, Ar), 169.9 (s, CON), 170.2 (s, CON), 173.3 (s, CO_2), and 174.5 p.p.m. (s, CO_2).

N-*Methyl*-N-[2-(*prop*-2-*ynyloxy*)*benzoyl*]*glycine* (**3c**). Colourless prisms (87%), m.p. 87—89 °C (from benzene) (Found: C, 63.0; H, 5.3; N, 5.6%; M^+, 247. $C_{13}H_{13}NO_4$ requires C, 63.15; H, 5.3; N, 5.7%; *M*, 247); $\nu_{max.}$ 3 258 (≡CH), 2 130 (C≡C), 1 743 (CO_2), 1 591 (CON), and 668 cm^{-1} (≡CH); δ_H[$(CD_3)_2SO$, 170 °C] 2.89 (3 H, s, NMe), 3.20 (1 H, t, *J* 2.4 Hz, ≡CH), 4.0 (2 H, br s, NCH_2), 4.77 (2 H, d, *J* 2.4 Hz, OCH_2), and 7.0—7.5 (4 H, m, ArH); δ_C 34.0 (q, NMe), 37.3 (q, NMe), 48.8 (t, NCH_2), 52.2 (t, NCH_2), 56.1 (t, OCH_2), 56.4 (t, OCH_2), 76.0 (d, ≡CH), 76.1 (d, ≡CH), 78.2 (s, *C*≡CH), 113.2—153.3 (nine peaks, Ar), 170.1 (s, CON), 170.3 (s, CON), 170.8 (s, CO_2), and 171.3 p.p.m. (s, CO_2).

N-*Methyl*-2-*phenyl*-1H,4H-[1]*benzopyrano*[4,3-b]*pyrrole* (**6a**).—A solution of the *N*-acylamino acid (**3a**) (500 mg, 1.55 mmol) in benzene (100 ml) was slowly added over a period of 3.5 h from the top of a reflux condenser to a refluxing solution of acetic anhydride (10 ml) in benzene (100 ml) under argon. The solution was refluxed for another 1.5 h, concentrated, and the residue was triturated with methanol to give colourless prisms of the title pyrrole (**6a**) (388 mg, 96%), m.p. 132.5—133.5 °C (from benzene–ethanol) (Found: C, 82.8; H, 5.65; N, 5.3%; M^+, 261. $C_{18}H_{15}NO$ requires C, 82.7; H, 5.8; N, 5.4%; *M*, 261); $\nu_{max.}$ 2 885, 1 496, 1 281, and 753 cm^{-1}; δ_H 3.70 (3 H, s, NMe), 5.15 (2 H, s, OCH_2), 6.03 (1 H, s, =CH), and 6.78—7.45 (9 H, m, ArH); δ_C 34.8 (q, NMe), 65.9 (t, OCH_2), 104.4 (d, =CH), and 116.5—153.5 p.p.m. (thirteen peaks, Ar).

N-*Methyl*-2-*methyl*-1H,4H-[1]*benzopyrano*[4,3-b]*pyrrole* (**6b**).—This was prepared in 92% yield by a similar addition of a solution of the alanine (**3b**) (500 mg, 1.91 mmol) in benzene (500 ml). During the addition, a portion of the solvent was distilled off continuously to avoid the increase of the volume of the reaction mixture. M.p. 86—87 °C (from ethanol) (Found: C, 78.4; H, 6.5; N, 7.1%; M^+, 199. $C_{13}H_{13}NO$ requires C, 78.4; H, 6.6; N, 7.0%; *M*, 199); $\nu_{max.}$ 2 846, 1 504, and 766 cm^{-1}; δ_H 2.11 (3 H, s, Me), 3.51 (3 H, s, NMe), 5.07 (2 H, s, OCH_2), 5.63 (1 H, s, =CH), and 6.72—7.34 (4 H, m, ArH); δ_C 12.1 (q, Me), 32.2 (q, NMe), 65.9 (t, OCH_2), 102.3 (d, =CH), and 115.3—152.8 p.p.m. (nine peaks, Ar).

N-*Methyl*-1H,4H-[1]*benzopyrano*[4,3-b]*pyrrole* (**6c**) *and the* 2-*Acetyl Derivative* (**6d**).—The acyl glycine (**3c**) (500 mg) was treated similarly to give the benzopyranopyrrole (**6c**), colourless prisms (318 mg, 85%), m.p. 62—63 °C (Found: C, 77.8; H, 6.0; N, 7.45%; M^+, 185. $C_{12}H_{11}NO$ requires C, 77.8; H, 6.0; N, 7.6%; *M*, 185); $\nu_{max.}$ 2 930, 1 502, 1 219, and 737 cm^{-1}; δ_H 3.75 (3 H, s, NMe), 5.16 (2 H, s, OCH_2), 5.88 (1 H, d, *J* 2.7 Hz, 3-H), 6.51 (1 H, d, *J* 2.7 Hz, 2-H), and 6.77—7.40 (4 H, m, ArH); δ_C 36.4 (q, NMe), 66.2 (t, OCH_2), 103.1 (d, 3-C), and 116.6—153.2 p.p.m. (nine peaks, Ar). The mother liquor of recrystallisation was separated on t.l.c. (silica–CH_2Cl_2) to give the 2-acetylpyrrole (**6d**) (2 mg, 0.4%), identical (m.p., mixed m.p., i.r., and n.m.r.) with the specimen prepared by the method described below.

2-*Acetyl*-N-*methyl*-1H,4H-[1]*benzopyrano*[4,3-b]*pyrrole* (**6d**).—A solution of compound (**6c**) (270 mg, 1.46 mmol) and acetyl chloride (230 mg, 2.93 mmol) in dry ether (5 ml) was allowed to cool over 5.5 h, in the presence of tin(IV) chloride (0.3 ml, 2.6 mmol). The mixture was poured into water and extracted with dichloromethane. The extract was separated by t.l.c. (silica–CH_2Cl_2) to give colourless prisms of the pyrrole (**6d**) (48 mg, 14.5%), m.p. and mixed m.p. 165.5—166.5 °C (from ethanol) (Found: C, 73.8; H, 5.8; N, 6.1%; M^+, 227. $C_{14}H_{13}NO_2$ requires C, 74.0; H, 5.8; N, 6.2%; *M*, 227); $\nu_{max.}$ 1 632 (CO) and 763 cm^{-1}; δ_H 2.45 (3 H, s, Me), 4.19 (3 H, s, NMe), 5.10 (2 H, d, *J* 1.5 Hz, OCH_2), 6.77 (1 H, s, =CH), and 6.91—7.63 (4 H, m, ArH); δ_C 27.6 (q, Me), 35.8 (q, NMe), 65.3 (t, OCH_2), 114.6—155.2 (ten peaks, Ar), and 188.2 p.p.m. (s, CO).

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