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Intramolecular Nitrile Imide Cycloadditions leading to Benzo[*c*]pyrazolo[1,5-*e*][1,5]-oxazonine and -oxazecine Skeletons†

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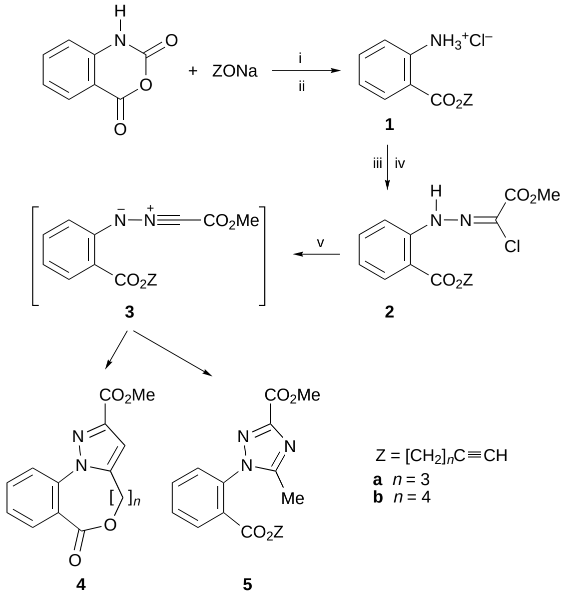
A synthetic route to the new title compounds **4**, which involves an intramolecular nitrile imide cycloaddition to an acetylenic moiety as the key step, is described.

Intramolecular 1,3-dipolar cycloadditions represent a valuable tool in the synthesis of a large variety of heterocyclic systems containing a five-membered heterocycle fused or bridged to another hetero- or carbo-cyclic ring.[1] However, despite copious literature on this methodology, examples which involve the formation of a medium-sized ring are still rare.[2–5] A fruitful approach to the hitherto unreported benzo[*c*]pyrazolo[1,5-*e*][1,5]oxazonine and benzo[*c*]pyrazolo[1,5-*e*][1,5]oxazecine skeletons is here reported, based on the intramolecular cycloaddition of appropriately chosen nitrile imides.

The hydrazonoyl chlorides **2**, which we have devised as the precursors for the *in situ* generation of the nitrile imides **3**, were obtained starting from isatoic anhydride and the appropriate alkynols (see Scheme 1). Treatment of **2** with silver carbonate in refluxing acetonitrile gave the desired cycloadducts **4** in good yields (see Experimental section). It needs to be added that, under the experimental conditions described above, the nitrile imides **3** underwent, as a side-reaction, a 1,3-dipolar cycloaddition onto the solvent to give the triazole derivatives **5**.

In order to prevent the formation of such by-products, the hydrazonoyl chloride **2a** was treated with silver carbonate in dioxane at 80 °C. The choice of this solvent was determined on the basis of the highly satisfactory results reported in some of our previous works.[6] However, in this case, the latter conditions led to a lower yield of the cycloadduct **4a**, since large amounts of tarry material were formed.

In spite of the well known factors working against the formation of nine- and ten-membered rings,[7] the cycloadditive approach to compounds **4** has been proven to be successful and the observed yields of cyclization are valuable on a preparative scale.



Scheme 1 *Reagents and conditions:* i, pyridine, heat; ii, HCl–Et$_2$O; iii, HCl–NaNO$_2$; iv, MeCOCHClCO$_2$Me; v, Ag$_2$CO$_3$–MeCN, reflux

Experimental

Analytical and spectroscopic instruments were as described in a previous paper.[8] *J* Values are given in Hz.

Preparation of Alkynyl Anthranilate Hydrochlorides **1**. *General Procedure.*—A solution of the appropriate alkynol (12.0 mmol) in anhydrous toluene (13 ml) was treated with sodium hydride (0.39 g, 16.4 mmol) and then refluxed for 1 h. Isotoic anhydride (1.96 g, 12.0 mmol) in hot pyridine (7 ml) was added and the solution was refluxed for 4 h. The mixture was poured onto crushed ice (50 ml) and extracted with diethyl ether (50 ml). The organic layer was washed with water, dried over sodium sulfate and evaporated. The oily residue was dissolved in anhydrous diethyl ether (70 ml) and a solution of hydrogen chloride in diethyl ether (4 M; 12.0 ml) was added under stirring. The white precipitate was filtered out and dried to give **1**.

*Pent-*4*-yn-*1*-yl anthranilate hydrochloride* (**1a**) (1.06 g, 37%) had mp 167 °C; ν_{max}/cm^{-1} (Nujol) 3230, 2110, 1730; δ_H (CDCl$_3$) 1.92–2.08 (3 H, m), 2.38 (2 H, dt, *J* 6.5, 2.4), 4.46 (2 H, t, *J* 6.5), 7.43–8.02 (4 H, m), 8.45 (3 H, br s); *m*/*z* 239 (M$^+$) (Found: C, 60.02; H, 5.92; Cl, 14.62; N, 5.77. $C_{12}H_{14}ClNO_2$ requires C, 60.13; H, 5.89; Cl, 14.79; N, 5.84%).

*Hex-*5*-yn-*1*-yl anthranilate hydrochloride* (**1b**) (0.91 g, 30%) had mp 137 °C; ν_{max}/cm^{-1} (Nujol) 3240, 2110, 1730; δ_H (CDCl$_3$) 1.58–1.91 (4 H, m), 1.95 (1 H, t, *J* 2.5), 2.39 (2 H, dt, *J* 6.5, 2.5), 4.36 (2 H, t, *J* 6.5), 7.39–8.06 (4 H, m), 8.50 (3 H, br s); *m*/*z* 253 (M$^+$) (Found: C, 61.48; H, 6.30; Cl, 14.08; N, 5.60. $C_{13}H_{16}ClNO_2$ requires C, 61.54; H, 6.36; Cl, 13.97; N, 5.52%).

Preparation of Hydrazonoyl Chlorides **2**. *General Procedure.*—A solution of **1** (3.5 mmol) in water (12 ml) and methanol (1.5 ml) was treated with hydrochloric acid (12 M; 1.5 ml) and then cooled to 0 °C. Sodium nitrite (0.33 g, 4.7 mmol) in water (2.5 ml) was added dropwise to the reaction mixture whilst it was cooled and stirred. After 30 min, the cold mixture was adjusted to pH 5 with sodium acetate and then methyl 2-chloroacetoacetate (0.53 g, 3.5 mmol) in methanol (3 ml) was added under stirring. The mixture was stirred at room temperature for 15 h and then extracted with diethyl ether (60 ml). The organic layer was washed with sodium hydrogencarbonate, dried (Na$_2$SO$_4$) and evaporated. Recrystallization from diisopropyl ether gave the pure hydrazonoyl chlorides **2**.

*Pent-*4*-yn-*1*-yl* 2-[2-(1*-chloro-*2*-methoxy-*2*-oxoethylidene*)*hydrazino*]*benzoate* (**2a**) (0.85 g, 75%) had mp 90 °C; ν_{max}/cm^{-1} (Nujol) 3280, 3210, 2100, 1730, 1680; δ_H (CDCl$_3$) 1.93–2.53 (5 H, m), 3.95 (3 H, s), 4.46 (2 H, t, *J* 6.3), 7.00–7.85 (4 H, m), 11.80 (1 H, br s); *m*/*z* 322 (M$^+$) (Found: C, 55.71; H, 4.66; Cl, 11.07; N, 8.75. $C_{15}H_{15}ClN_2O_4$ requires C, 55.82; H, 4.68; Cl, 10.98; N, 8.68%).

*Hex-*5*-yn-*1*-yl* 2-[2-(1*-chloro-*2*-methoxy-*2*-oxoethylidene*)*hydrazino*]*benzoate* (**2b**) (1.13 g, 96%) had mp 60 °C; ν_{max}/cm^{-1} (Nujol) 3280, 3200, 2105, 1730, 1680; δ_H (CDCl$_3$) 1.50–1.93 (4 H, m), 1.95 (1 H, t, *J* 2.4), 2.27 (2 H, dt, *J* 6.2, 2.4), 3.90 (3 H, s), 4.35 (2 H, t, *J* 6.2), 6.97–7.95 (4 H, m), 11.80 (1 H, br s); *m*/*z* 336 (M$^+$) (Found: C, 57.20; H, 5.13; Cl, 10.61; N, 8.44. $C_{16}H_{17}ClN_2O_4$ requires C, 57.06; H, 5.09; Cl, 10.53; N, 8.32%).

Treatment of Hydrazonoyl Chlorides **2** *with Silver Carbonate in Acetonitrile. General Procedure.*—A solution of **2** (2.5 mmol) in dry acetonitrile (200 ml) was treated with silver carbonate (2.76 g, 10

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†This is a **Short Paper** as defined in the Instructions for Authors, Section 5.0 [see *J. Chem. Research (S)*, 1998, Issue 1]; there is therefore no corresponding material in *J. Chem. Research (M)*.

mmol) and the mixture was refluxed in the dark for 7 h (entry **a**) or 3 h (entry **b**). The undissolved material was filtered off, the solvent was evaporated and then the residue was chromatographed on a silica gel column with dichloromethane–ethyl acetate (3:1). The intramolecular cycloadduct **4** was eluted first, followed by the triazole derivative **5**.

Methyl 8-*oxo*-5,6-*dihydro*-4H,8H-*benzo*[c]*pyrazolo*[1,5-e][1,5]*oxazonine*-2-*carboxylate* (**4a**) (0.29 g, 41%) had mp 148 °C (from hexane–benzene); ν_{max}/cm^{-1} (Nujol) 1730, 1720; δ_H ($CDCl_3$) 2.30–2.55 (4 H, m), 3.94 (3 H, s), 4.95 (2 H, br t), 6.69 (1 H, s), 7.38–7.86 (4 H, m); *m*/*z* 286 (M^+) (Found: C, 63.03; H, 4.98; N, 9.75. $C_{15}H_{14}N_2O_4$ requires C, 62.93; H, 4.93; N, 9.79%).

Methyl 5-*methyl*-1-{3-[(*pent*-4-*yn*-1-*yloxy*)*carbonyl*]*phenyl*}-1H-1,2,4-*triazole*-3-*carboxylate* (**5a**) (0.12 g, 15%) had mp 171 °C (from diisopropyl ether); ν_{max}/cm^{-1} (Nujol) 1730, 1710; δ_H ($CDCl_3$) 1.70–1.85 (2 H, m), 1.92 (1 H, t, *J* 2.4), 2.18 (2 H, dt, *J* 6.5, 2.4), 2.32 (3 H, s), 3.94 (3 H, s), 4.18 (2 H, t, *J* 6.5), 7.32–8.21 (4 H, m), 11.80 (1 H, br s); *m*/*z* 327 (M^+) (Found: C, 62.45; H, 5.20; N, 13.00. $C_{17}H_{17}N_3O_4$ requires C, 62.38; H, 5.23; N, 12.84%).

Methyl 9-*oxo*-4,5,6,7-*tetrahydro*-9H-*benzo*[c]*pyrazolo*[1,5-e][1,5]-*oxazecine*-2-*carboxylate* (**4b**) (0.45 g, 60%) had mp 110 °C (from hexane–benzene); ν_{max}/cm^{-1} (Nujol) 1740, 1720; δ_H ($CDCl_3$) 1.70–3.00 (6 H, m), 3.92 (3 H, s), 4.74–4.98 (2 H, m), 6.74 (1 H, s), 7.40–8.30 (4 H, m); *m*/*z* 300 (M^+) (Found: C, 63.88; H, 5.37; N, 9.35. $C_{16}H_{16}N_2O_4$ requires C, 63.99; H, 5.37; N, 9.33%).

Methyl 1-{3-[(*hex*-5-*yn*-1-*yloxy*)*carbonyl*]*phenyl*}-5-*methyl*-1H-1,2,4-*triazole*-3-*carboxylate* (**5b**) (0.13 g, 15%) had mp 146 °C (from diisopropyl ether); ν_{max}/cm^{-1} (Nujol) 1730, 1710; δ_H ($CDCl_3$) 1.55–1.90 (4 H, m), 1.95 (1 H, t, *J* 2.5), 2.15 (2 H, dt, *J* 6.2, 2.5), 2.31 (3 H, s), 3.92 (3 H, s), 4.11 (2 H, t, *J* 6.0), 7.20–8.20 (4 H, m); *m*/*z* 341 (M^+) (Found: C, 63.26; H, 5.58; N, 12.27. $C_{18}H_{19}N_2O_4$ requires C, 63.33; H, 5.61; N, 12.31%).

Treatment of Hydrazonoyl Chloride **2a** *with Silver Carbonate in* 1,4-*Dioxane*.—A solution of **2a** (0.64 g, 2 mmol) in dry 1,4-dioxane (160 ml) was treated with silver carbonate (2.76 g, 10 mmol), and the mixture was warmed to 80 °C in the dark for 24 h. The undissolved material was filtered off, the solvent was evaporated, and then the residue was chromatographed on a silica gel column with diethyl ether affording the cycloadduct **4a** (86 mg, 15%).

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