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THE INTRAMOLECULAR NITRILE IMINE CYCLOADDITION ROUTE TO PYRAZOLO[1,5-a][1,4]BENZODIAZEPINES

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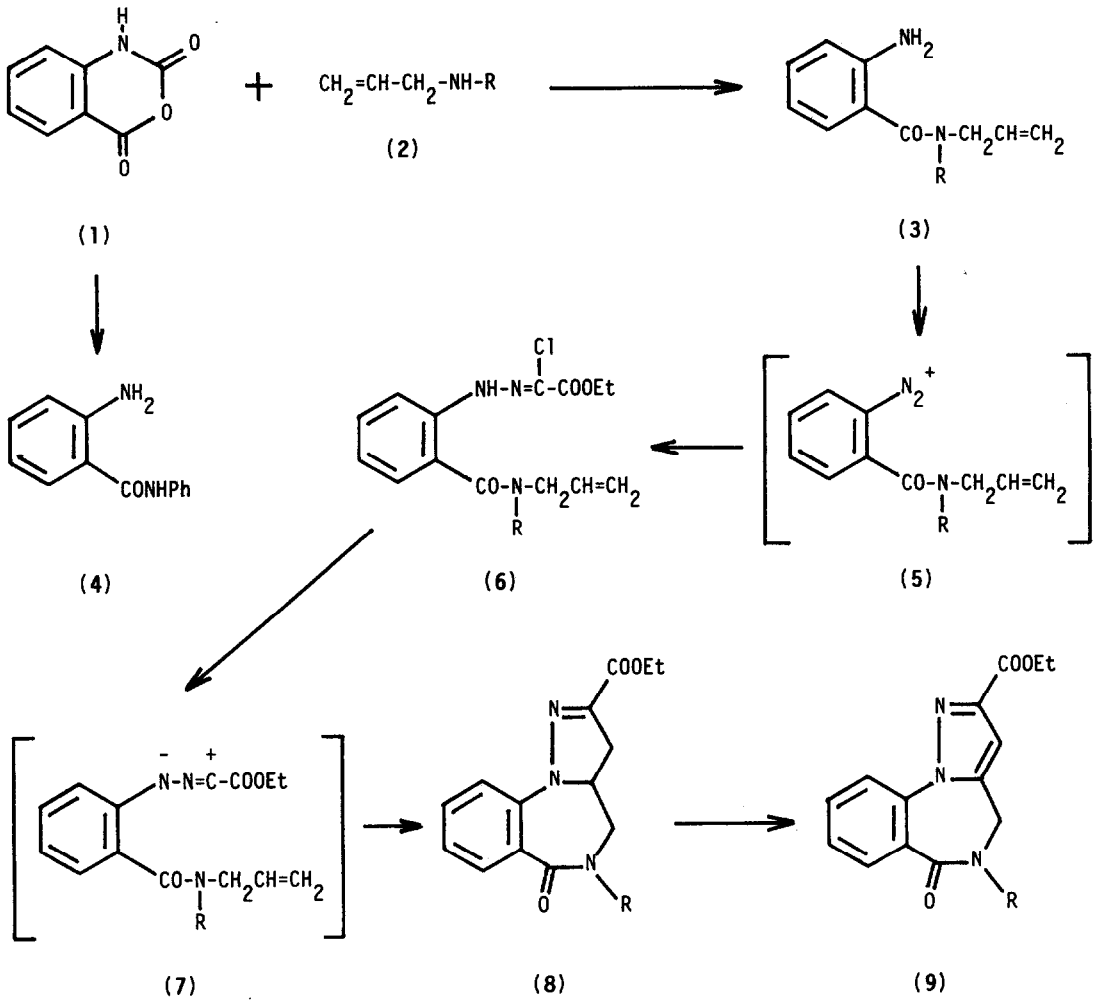
Abstract. A synthetic route to the title ring system is described, which starts from isatoic anhydride and allylamines, and involves as the key step an intramolecular nitrile imine cycloaddition.

The simultaneous formation of two new rings, often accompanied by a high degree of regio- and stereo-selectivity, makes the intramolecular 1,3-dipolar cycloadditions an efficient tool for the construction of fused-ring heterocycles.[1] Our previous contributions in this area deal with intramolecular cycloadditions of nitrile imines, in which however the length of the chain between the reaction centres was such to determine the formation of structures containing a pyrazole unit annulated with a five- or six-membered ring.[2] We now wish to describe the application of the same synthetic strategy to the preparation of pyrazolo[1,5-a][1,4]benzodiazepines. Up to now, very little is reported about this ring system,[3,4] despite its potential interest in pharmacology in the light of the known biological activity of several hetero-annulated 1,4-benzodiazepines.

RESULTS AND DISCUSSION

The Scheme illustrates the reaction sequence we followed to reach the desired target. It is to be stressed that the given sequence starts from a trivial compound such as isatoic anhydride, which was reacted with a series of commercially available allylamines (2). This reaction was carried out in anhydrous dimethylformamide and gave the suitably ortho-substituted anilines (3) in good yields with the exception of (3d), probably because of steric factors. The latter compound was obtained more satisfactorily in an alternative way, i.e. by preparation of (4) and its treatment with allyl bromide in the presence of a

SCHEME



mixture of sodium hydroxide, potassium carbonate, and tetrabutylammonium hydrogen sulphate.

Diazotisation of anilines (3) and subsequent coupling of the corresponding diazonium salts (5) with ethyl 2-chloroacetoacetate provided the ortho-substituted arylhydrazonyl chlorides (6). An excess of the reagent was advisable to prevent the formation of 1,2,3-benzotriazin-4-ones[5] upon intramolecular capture of the diazonium group by the amidic nitrogen (particularly in the case of R=H).

According to the well-known procedure for the in situ generation of nitrile imines,[6] we submitted the hydrazonyl chlorides (6) to reaction with triethylamine. However, no change was practically observed in boiling benzene in the presence of a stoichiometric amount of triethylamine. Good results were obtained under more severe conditions, namely in boiling xylene in the presence of a large excess of base. Under these conditions, compounds (**6b-d**) reacted cleanly within 1h to give the tricyclic products (**8b-d**) in 75-80% isolation yields. In the case of (**6a**), the reaction was markedly slower and led to a product mixture, from which (**8a**) was isolated in modest yield (17%). Treatment of (**8a-d**) with DDQ in boiling toluene caused oxidation of the pyrazolinic nucleus, thus furnishing the final products (**9a-d**) in 80-86% yields.

It is worthy of noting that the intramolecular cycloaddition of the nitrile imines (7), which constitutes the key step of the above synthetic sequence, proceeds in highly efficient manner, with the exception of (**7a**). As a possible explanation of this behaviour difference, one may think that the intramolecular approach of the reacting centres could be facilitated by some steric congestion due to the R substituent. Otherwise, it may be that the deprotonation of the amidic NH group in (**6a**) could be operative to some extent, thus interfering with the formation of the nitrile imine (**7a**).

EXPERIMENTAL

Melting points were determined on a Büchi apparatus and are uncorrected. Infrared spectra were run on a Perkin-Elmer 298 spectrophotometer. NMR spectra were usually recorded on a Varian EM-390 instrument; a Varian XL-200 instrument was used in the case of (**8a-d**). Chemical shifts are given in ppm from internal tetramethylsilane.

Compounds (1) and (**2a-d**) were commercial materials. Compounds (**3a**) and (**4**) were available according to the literature.[7]

All new compounds gave satisfactory elemental analyses (C $\pm$ 0.3, H $\pm$ 0.25, N $\pm$ 0.25)

and correct molecular peaks in the mass spectra.

Preparation of 2-Amino-N-methyl-N-(2-propenyl)benzamide (**3b**). A solution of (1) (1.65 g)and (**2b**) (1.42 g) in anhydrous DMF (10 ml) was heated under stirring at 100°C for 1h. The mixture was poured into water (100 ml), adjusted to pH 9 with 30% sodium hydroxide, and extracted with chloroform. The organic solution was dried (Na_2SO_4) and evaporated under reduced pressure. The residue was taken up with di-isopropyl ether and cooled at 0°C. Filtration gave (**3b**) (1.2 g, 63%); m.p. 54-55°C (from hexane-ethanol); ν(Nujol) 3470, 3360, and 1640 cm^{-1}; $\delta_H(CDCl_3)$: 3.03 (3H,s), 4.02 (2H,d,J 6Hz), 4.27 (2H,br s), 5.0-5.2 (2H,m), 5.5-6.0 (1H,m), 6.5-6.7 (2H,m), 7.0-7.2 (2H,m).

Preparation of 2-Amino-N,N-di-(2-propenyl)benzamide (**3c**). Following the procedure described in the preceding preparation, compounds (1) and (**2c**) were reacted to afford (**3c**) in 47% yield; m.p. 56-57°C (from hexane-benzene); ν(Nujol) 3450, 3340, and 1620 cm^{-1}; $\delta_H(CDCl_3)$: 4.05 (4H,d,J 6Hz), 4.2 (2H,br s), 5.0-5.2 (4H,m), 5.6-6.0 (2H,m), 6.5-6.7 (2H,m), 7.0-7.2 (2H,m).

Preparation of 2-Amino-N-phenyl-N-(2-propenyl)benzamide (**3d**). A suspension of sodium hydroxide (3.4 g), potassium carbonate (3.4 g), and tetrabutylammonium hydrogen sulphate (0.56 g) in benzene (30 ml) was heated at 70°C. A solution of allyl bromide (3.42 g) in benzene (10 ml) was then added dropwise under stirring and the resulting mixture was stirred at 70°C for 2h. After addition of a further amount of benzene, the mixture was treated with water, and the organic layer was separated, dried (Na_2SO_4), and evaporated under reduced pressure. The residue was passed through a short silica gel column with diethyl ether-light petroleum (2:1) as eluant to give (**3d**) (2.17 g, 51%); m.p. 67-68°C (from benzene-hexane); ν(Nujol) 3450, 3390, and 1615 cm^{-1}; $\delta_H(CDCl_3)$: 4.50 (2H,d,J 6Hz), 4.6 (2H,br s), 5.0-5.2 (2H,m), 5.7-6.1 (1H,m), 6.1-6.3 (1H,m), 6.5-7.3 (8H,m).

General Procedure for the Preparation of Arylhydrazonyl Chlorides (**6a-d**). Aniline (**3**) (10 mmol) was dissolved in a 1.2 N solution of HCl in 60% aqueous acetic acid (22 ml), ethyl 2-chloroacetoacetate (30 mmol) was added, and the resulting mixture was cooled at -5°C. A solution of sodium nitrite (14 mmol) in water (10 ml) was added dropwise under vigorous stirring and ice-cooling. The reaction mixture was adjusted to pH 4 with sodium acetate, stirred at room temperature for 2 h, and extracted with dichloromethane. The organic solution was dried (Na_2SO_4) and evaporated under reduced pressure. The residue was

Table. Preparation and Characterisation of Compounds (6), (8), and (9)

Compd.	Yield (%)	M.p.[a] (°C)	ν[Nujol] (cm⁻¹)	δ_H[b,c]
(6a)	54	114 (hexane-EtOH)	3310 1725 1625	1.40 (3H,t,J 7), 4.0-4.2 (2H,m), 4.40 (2H,q,J 7), 5.1-5.3 (2H,m), 5.7-6.1 (1H,m), 6.3 (1H,br s), 6.8-7.8 (4H,m), 12.1 (1H,br s)
(6b)	65	51 (i-Pr_2O)	3260 1720 1620	1.40 (3H,t,J 7), 3.07 (3H,s), 4.05 (2H,d,J 6), 4.40 (2H,q,J 7), 5.1-5.3 (2H,m), 5.6-6.0 (1H,m), 6.8-7.7 (4H,m), 10.0 (1H,br s)
(6c)	63	d	3250 1725 1625	1.43 (3H,t,J 7), 4.05 (4H,d,J 5), 4.40 (2H,q,J 7), 5.1-5.3 (4H,m), 5.6-6.0 (2H,m), 6.8-7.7 (4H,m), 9.9 (1H,br s)
(6d)	68	45 (i-Pr_2O)	3250 1725 1630	1.43 (3H,t,J 7), 4.43 (2H,q,J 7), 4.57 (2H,d,J 5), 5.1-5.3 (2H,m), 5.8-6.2 (1H,m), 6.4-7.6 (9H,m), 10.5 (1H,br s)
(8a)	17	205 (benzene)	3360 1710 1645	1.38 (3H,t,J 7), 2.95 (1H,dd,J 18.5 and 10.5), 3.3-3.6 (3H,m), 4.32 (2H,q,J 7), 4.3-4.5 (1H,m), 7.0-7.4 (2H,m), 7.5 (1H,br s), 7.7-8.2 (2H,m)
(8b)	80	128 (benzene)	1710 1610	1.35 (3H,t,J 7), 2.98 (1H,dd, J 18 and 11), 3.19 (3H,s), 3.3-3.5 (2H,m), 3.73 (1H,dd,J 15 and 7), 4.32 (2H,q,J 7), 4.2-4.4 (1H,m), 6.9-8.0 (4H,m)
(8c)	75	121 (benzene)	1720 1620	1.13 (3H,t,J 7), 2.23 (1H,dd,J 18 and 12), 2.50 (1H,d,J 15), 2.73 (1H,dd,J 18 and 12), 2.87 (1H, dd,J 15 and 9), 3.3-3.6 (1H,m), 3.98 (2H,d,J 5), 4.20 (2H,q,J 7), 4.7-5.0 (2H,m), 5.3-5.8 (1H,m), 6.7-8.5 (4H,m)
(8d)	78	192 (benzene)	1685 1620	1.35 (3H,t,J 7), 2.92 (1H,dd,J 18 and 11), 3.41 (1H,dd,J 18 and 12), 3.83 (1H,dd,J 15 and 1.5), 4.06 (1H,dd,J 15 and 7), 4.33 (2H,q,J 7), 4.5-4.7 (1H,m), 7.0-8.1 (9H,m)
(9a)	82	250 (benzene)	3280 1715 1680	*1.33 (3H,t,J 7), 4.2-4.4 (4H,m), 6.90 (1H,s), 7.3-8.0 (4H,m),* 8.83 (1H,t,J 6)
(9b)	86	144 (benzene)	1710 1640	*1.45 (3H,t,J 7), 3.27 (3H,s), 4.40 (2H,s), 4.47* (2H,q,J 7), 6.87 (1H,s), 7.3-8.0 (4H,m)
(9c)	83	137 (benzene)	1710 1650	*1.45 (3H,t,J 7), 4.27 (2H,d,J 6), 4.33 (2H,s),* 4.47 (2H,q,J 7), 5.2-5.3 (2H,m), 5.6-6.0 (1H,m), 6.80 (1H,s), 7.3-8.1 (4H,m)
(9d)	80	173 (benzene)	1710 1650	1.47 (3H,t,J 7), 4.47 (2H,q,J 7), 4.77 (2H,s), 6.87 (1H,s), 7.2-8.1 (9H,m)

[a] Recrystallisation solvent in parentheses. [b] In $CDCl_3$ with the exception of (8c) (C_6D_6) and (9a) (CD_3SOCD_3). [c] J in Hz. [d] Undistillable viscous oil.

chromatographed on a silica gel column with diethyl ether-light petroleum (3:1) as eluant to give the arylhydrazone (**6**). Yields and characterisation data are collected in the Table.

General Procedure for the Reaction of Arylhydrazonyl Chlorides (**6a-d**) with Triethylamine. A solution of (**6**) (4 mmol) in xylene (250 ml) was treated with triethylamine (0.3 mol) and refluxed for 45 min. The mixture was washed with water and the organic solution was dried (Na_2SO_4) and evaporated under reduced pressure. The residue was taken up with hexane and filtered to afford the tricyclic product (**8**). When starting from (**6a**), the reaction time was 12 h and the cyclisation product (**8a**) was isolated by chromatography on a silica gel column with ethyl acetate as eluant. Yields and characterisation data are collected in the Table.

General Procedure for the Oxidation of (**8a-d**). A solution of (**8**) (2.5 mmol) in toluene (40 ml) was treated with DDQ (5 mmol) and refluxed for 6 h. The hot mixture was filtered to remove the undissolved material and the filtrate was evaporated under reduced pressure. The residue was chromatographed on a silica gel column with ethyl acetate as eluant to afford (**9**). Yields and characterisation data are given in the Table.

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