INTRAMOLECULAR NITRILE IMINE CYCLOADDITIONS TO THE ACETYLENIC BOND IN THE SYNTHESIS OF PYRAZOLO[1,5-*a*][4,1]-BENZOXAZEPINES AND PYRAZOLO[1,5-*a*][5,1]BENZOXAZOCINES

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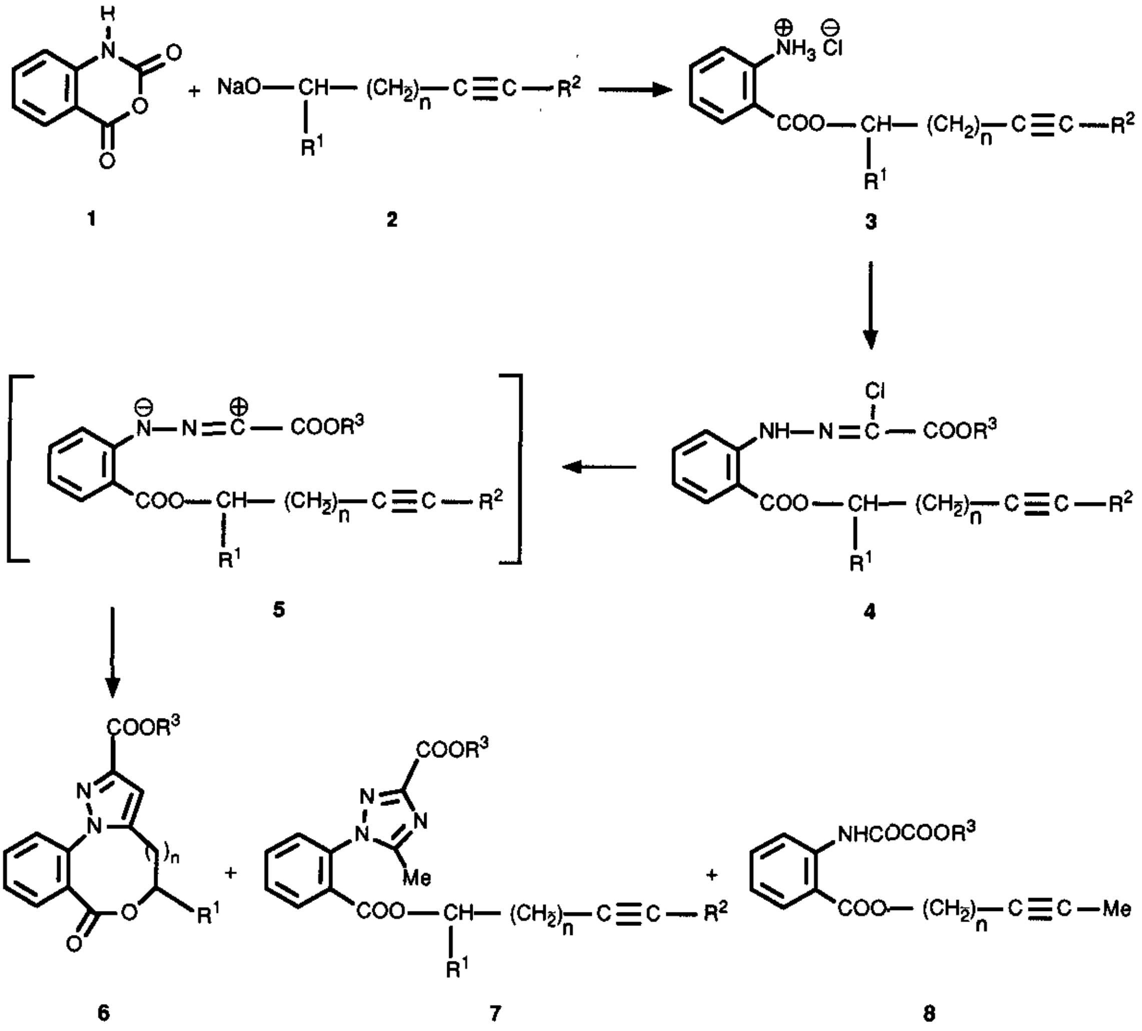
Abstract - The intramolecular nitrile imine cycloaddition methodology has been applied to the construction of the title heterocyclic systems. The efficiency of this synthetic approach is rather variable, being markedly dependent on the kind of substitution at the acetylenic bond.

Intramolecular 1,3-dipolar cycloadditions are attracting several chemists owing to their versatile potential in the synthesis of multi-ring heterocycles,[1,2] as well as of complex carbocyclic compounds.[2-4] Our previous contributions in this field deal with the preparation of condensed pyrazoles by intramolecular cycloadditions of nitrile imines to the acetylenic bond.[5-8] In continuing this line of research, we report here the application of the same methodology to the synthesis of pyrazolo[1,5-*a*][4,1]benzoxazepines (**6**) (n=0) and pyrazolo[1,5-*a*][5,1]benzoxazocines (**6**) (n=1) (see Scheme).

RESULTS

On starting from isatoic anhydride and a series of appropriate alkynols, we prepared the alkynyl anthranilates (**3**) which were then submitted to diazotation and coupling with alkyl 2-chloroacetoacetate to give the hydrazonyl chlorides (**4**). The latter compounds we had devised as precursors of the desired nitrile imines (**5**) were found slow to react with triethylamine and similar bases. Hence, we treated **4** with silver carbonate in acetonitrile, thus obtaining the results summarised in Table 1. The product structures were unequivocally shown by the spectral data (see Table 2).

Scheme



entry	a	b	c	d	e	f	g	h
n	0	0	0	0	0	1	1	1
R^1	H	Me	Ph	H	H	H	Me	H
R^2	H	H	H	Me	Ph	H	H	Me
R^3	Et	Me	Me	Et	Et	Me	Me	Me

One can note that the intramolecular cycloaddition pathway is really operative, although to a variable extent, whenever $R^2 = H$. This means that a group other than hydrogen at the outer position of the dipolarophilic site hinders the intramolecular approach of the reactive π systems in parallel planes, as required for concerted cycloadditions. Steric factors are probably responsible for this behaviour.

The formation of the side - products, compound (**7e**) is clearly the consequence of the nitrile imine cycloaddition onto the solvent, while the oxalamides (**8d,h**) arise from a degradative process of the nitrile imine moiety, which possibly involves a transient diazirine.[9]

Table 1. Reaction of Hydrazonyl Chlorides (**4**) with Silver Carbonate.

Compd	Time (h)	Product[a, b]	Yield (%)	Eluent[c]
4a	96	**6a**	43	Et_2O / LP 9 : 1
4b	240	**6b**	36	LP / MeCOOEt 7 : 3
4c	72	**6c**	27	Et_2O / LP 9 : 1
4d	24	**8d**	10	Et_2O / LP 6 : 1
4e	24	**7e**	15	Et_2O / LP 3 : 1
4f	290	**6f**	21	MeCOOEt / Et_2O 9 : 1
4g	170	**6g**	47	MeCOOEt / Et_2O 9 : 1
4h	96	**8h**	7	$CHCl_3$ / MeCOOEt 9 : 1

[a] After column chromatography on silica gel.

[b] Some amount of uncharacterisable resinous material was usually formed.

[c] LP = light petroleum, bp 40 - 60°C

Table 2. Characterisation of Compounds (**6**, **7**, and **8**).

Compd	mp (°C)	Microanalyses (%) C calcd found	H calcd found	N calcd found	ms m/z M^+	Ir (Nujol)[a] ν (cm^{-1})	^1H Nmr ($CDCl_3$) δ, J (Hz)
6a	152	61.8 61.6	4.4 4.3	10.3 10.5	272	1685 1680	1.40 (3H, t, J=7.5), 4.43 (2H, q, J= 7.5), 5.15 (2H, s), 7.00 (1H, s), 7.3 - 8.1 (4H, m)
6b[b]	147	61.8 61.9	4.4 4.3	10.3 10.2	272	1730	1.88 (3H, d, J=6.5), 3.95 (3H, s), 5.30 (1H, q, J=6.5), 6.97 (1H, s), 7.5 - 8.1 (4H, m)
6c[b]	161	68.3 68.2	4.2 4.2	8.4 8.7	334	1750 1730	3.90 (3H, s), 6.23 (1H, s), 6.36 (1H, s), 7.4 - 8.2 (9H, m)
8d	161	62.3 62.1	5.2 5.1	4.8 4.7	289	3315 1730	1.40 (3H, t, J=7.5), 1.85 (3H, t, J=3), 4.40 (2H, q, J=7.5), 4.91 (2H, m), 6.7 - 8.1 (3H, m), 8.76 (1H, dd, J=8.5 and 2), 12.50 (1H, br s)
7e[b]	179	66.8 66.5	5.1 5.0	11.1 11.1	389	1730 1720	1.30 (3H, t, J=7.5), 2.35 (3H, s), 4.33 (2H, q, J=7.5), 4.90 (1H, s), 7.1 - 8.2 (9H, m)
6f	159	61.8 61.7	4.4 4.5	10.3 10.5	272	1750 1730	3.0 - 3.6 (2H, m), 3.90 (3H, s), 4.50 (2H, m), 6.72 (1H, s), 7.5 - 7.7 (4H, m)
6g[b]	191	62.9 62.8	4.9 4.8	9.8 9.7	286	1730 1725	1.50 (3H, d, J=7), 3.0 - 3.2 (2H, m), 3.90 (3H, s), 4.81 (1H, m), 6.70 (1H, s), 7.5 - 7.7 (4H, m)
8h	153	62.3 62.0	5.2 5.1	4.8 4.9	289	1735 1710 1685	1.75 (3H, t, J=2.5), 2.5 - 2.8 (2H, m), 3.94 (3H, s), 4.42 (2H, t, J=7), 7.05 - 8.15 (3H, m), 8.72 (1H, dd, J=8.2 and 1.5), 12.40 (1H, br s)

[a] The Ir absorption for the acetylenic bond was not observable.

[b] Uv λ_{max} (EtOH) nm (ε); **6b**: 210 (5260), 264 (2470); **6c**: 208 (5250), 240 (3050); **7e**: 203 (10000), 240 (5580); **6g**: 212 (5250), 265 (5220).

EXPERIMENTAL

Melting points were taken on a Büchi apparatus and are not corrected. Ir spectra were recorded on a FT IR Perkin Elmer 1725 X spectrophotometer. Mass spectra were determined with a VG - 70EQ apparatus. ^{1}H Nmr spectra were obtained on a Bruker 300 MHz apparatus; chemical shifts are given as ppm from tetramethylsilane.

Alcohols (**2**) were commercially available with the exception of **2e** which was prepared according to the literature.[10] The preparation of compounds (**3a-e**) has been already reported.[11]

Alkynyl Antranilates Hydrochlorides (3f-h); General Procedure. A solution of alcohol (**2**) (0.10 mol) in dry benzene (60 ml) was treated with 80% NaH (3.0 g, 0.10 mol) and refluxed for 1 h. Isatoic anhydride (16.3 g, 0.10 mol) in pyridine (60 ml) was added and the solution was refluxed for 3 h. The resulting mixture was poured into water and extracted with ether. The organic layer was washed with water, dried (Na_2SO_4), and evaporated. The residue was dissolved in anhydrous ether and a 4M solution of HCl in anhydrous ether (35 ml) was added dropwise under stirring. The precipitate was collected by filtration and washed with anhydrous ether to afford pure hydrochloride (**3**) (Table 3).

Table 3. Preparation and Characterisation of Alkynyl Antranilates Hydrochlorides (**3**)

Compd	Yield (%)	mp (°C)	Microanalyses (%) C calcd found	H calcd found	N calcd found	Cl calcd found	Ir (Nujol) ν (cm^{-1})	^{1}H Nmr[a] δ, J (Hz)
3f	92	161	58.5 58.3	5.4 5.3	6.2 6.0	15.7 15.8	3250 1730	2.10 (1H, t, J=2.5), 2.62 (2H, m), 4.31 (2H, t, J=7), 7.3 - 8.2 (4H, m)
3g	80	159	60.1 60.0	5.9 6.0	5.8 5.5	14.8 14.6	3300 1730	1.38 (3H, d, J=6.5), 2.03 (1H, t, J=2.5), 2.4 -2.6 (2H, m), 5.15 (1H, q, J=6.5), 6.6 -7.9 (4H, m)
3h	90	142	60.1 59.8	5.9 5.6	5.8 5.8	14.8 14.7	3300 1700	1.82 (3H, s), 2.80 (2H, t, J=6.5), 4.63 (2H, t, J=6.5), 7.5 - 8.3 (4H, m)

[a] Solvent: D_2O for **3f,h**, $(CD_3)_2CO$ / D_2O for **3g**.

Hydrazonyl Chlorides (4a-h); General Procedure. A solution of **3** (9.3 mmol) in 1M HCl (25 ml) was cooled at 0°C and treated with a solution of $NaNO_2$ (970 mg, 14.1 mmol) in water (5.0 ml). A solution of alkyl 2-chloroacetoacetate (9.3 mmol) was added dropwise under stirring and ice- cooling. The mixture was adjusted to pH 5 with AcONa, stirred at room temperature for 15 h and extracted with ether (50 ml). The organic layer was washed with aqueous $NaHCO_3$ and dried (Na_2SO_4). The solvent was removed under reduced pressure. The residue was recrystallised to give pure **4** (Table 4).

Table 4. Preparation and Characterisation of Hydrazonyl Chlorides (**4**)

Compd	Yield (%)	mp (°C)	Microanalyses (%) C calcd found	H calcd found	N calcd found	Cl calcd found	Ir (Nujol) ν (cm^{-1})	^1H Nmr ($CDCl_3$) δ, J (Hz)
4a	66	118[a]	54.5 54.3	4.2 4.1	9.0 8.8	11.5 11.6	3265 1715 1675	1.45 (3H, t, J=7), 2.54 (1H, t, J=3), 4.42 (2H, q, J=7), 4.95 (2H, d, J=3), 6.2 - 8.0 (4H, m), 11.60 (1H, br s)
4b	71	103[a]	54.5 54.5	4.2 4.0	9.0 8.7	11.5 11.6	3280 1730 1700	1.65 (3H, d, J=7), 2.52 (1H, d, J=2.5), 3.92 (3H, s), 5.69 (1H, dq, J=7 and 2.5), 7.0 - 8.0 (4H, m), 11.60 (1H, br s)
4c	55	115[a]	61.5 61.7	4.1 4.0	7.6 7.6	9.5 9.7	3290 1730 1690	2.75 (1H, t, J=3), 3.95 (3H, s), 6.68 (1H, d, J=3), 6.8 - 8.1 (9H, m), 11.60 (1H, br s)
4d	81	101[a]	55.8 55.9	4.7 4.9	8.7 8.4	11.0 10.8	3250 1730 1690	1.50 (3H, t, J=7), 1.95 (3H, t, J=2.5), 4.45 (2H, q, J=7), 4.95 (2H, q, J=2.5), 6.8 - 8.0 (4H, m), 11.60 (1H, br s)
4e	70	133[b]	61.2 61.0	4.6 4.4	7.5 7.4	9.5 9.5	3250 1730 1695	1.40 (3H, t, J=7), 4.40 (2H, q, J=7), 5.15 (2H, s), 6.8 -8.1 (9H, m), 11.60 (1H, br s)
4f	85	121[a]	54.5 54.5	4.2 4.3	9.0 8.9	11.5 11.3	3295 1740 1680	2.02 (1H, d, J=3), 2.60 (2H, m), 3.90 (1H, s), 4.42 (2H, t, J=6.5), 6.9 -7.9 (4H, m), 11.70 (1H, br s)
4g	92	96[a]	55.8 55.6	4.7 4.7	8.7 8.5	11.0 11.2	3295 1730 1685	1.30 (3H, d, J=7), 2.00 (2H, m), 2.60 (2H, m), 3.90 (3H, s), 5.2 -5.4 (1H, m), 7.0 - 8.0 (4H,m), 11.70 (1H, br s)
4h	90	122[a]	55.8 55.9	4.7 4.8	8.7 8.5	11.0 11.2	3260 1730 1690	1.82 (3H, s), 2.60 (2H, t, J=6.5), 3.90 (3H, s), 4.41 (2H, t, J=6.5), 7.0 - 8.0 (4H, m), 11.70 (1H, br s)

[a] From diisopropyl ether.

[b] From diisopropyl ether / ethyl acetate.

Reaction of Hydrazonyl Chlorides (4) with Silver Carbonate. A solution of 4 (3 mmol) in acetonitrile (100 ml) was treated with silver carbonate (1.65 g, 6 mmol) and stirred at room temperature in the dark for the time indicated in Table 1. The undissolved material was filtered off, the solvent was removed under reduced pressure and the residue was chromatographed on a silica gel column to give the product reported in Table 1. Characteristic data of the products are collected in Table 2.

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Received, 28th February, 1994