SYNTHESIS OF [1,2,3]TRIAZOLO[1,5-*a*][4,1]BENZOXAZEPINES *via* INTRAMOLECULAR AZIDE CYCLOADDITION

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Abstract - Starting from isatoic anhydride and propargyl alcohols, we developed a synthetic approach to the title compounds, where the key step is an intramolecular cycloaddition of the azido group onto the acetylenic bond.

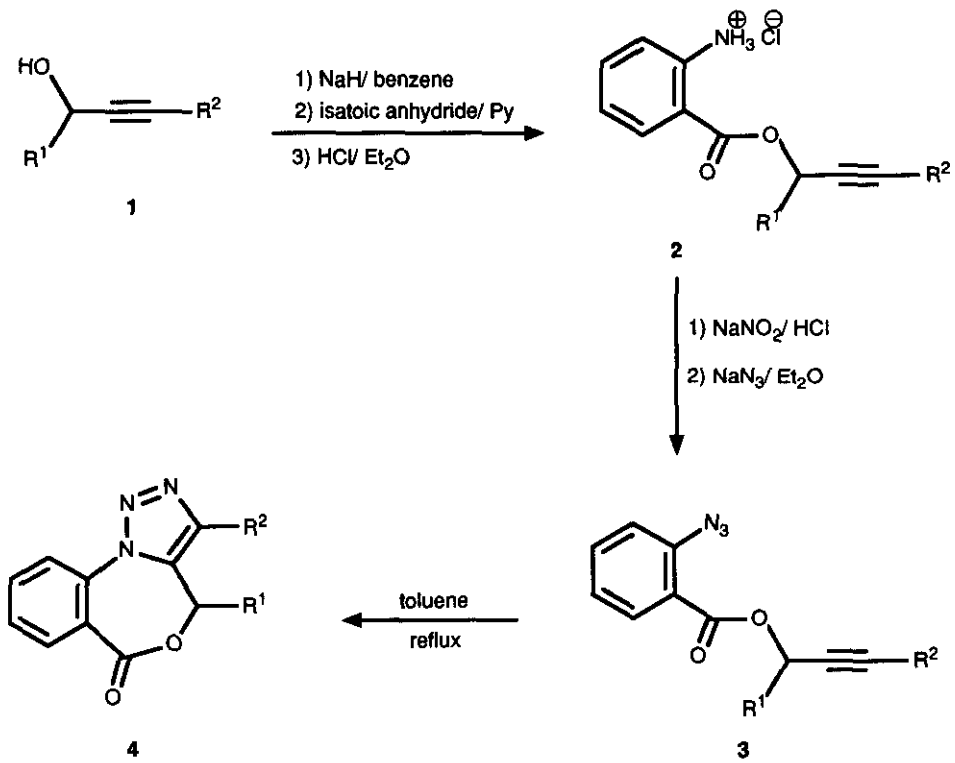
In the last decade, intramolecular 1,3-dipolar cycloadditions have attracted an increasing attention due to their versatile potential in heterocyclic syntheses.[1-3] On pursuing our research line in this field,[4-7] we report here the synthesis of [1,2,3]triazolo[1,5-*a*][4,1]benzoxazepines (**4**) by intramolecular cycloaddition of the properly *ortho*-substituted aryl azides (**3**). Compounds (**4**) could be of pharmacological interest in view of the known anxiolytic activity of some [1,3,4]triazolo[1,2-*a*][1,4]benzodiazepines such as triazolam, alprazolam and estazolam.[8]

The reaction of isatoic anhydride with the sodium salts of propargyl alcohols (**1**) gave the corresponding alkynyl antranilates, which were characterised as hydrochlorides (**2**) (Table 1).

Diazotisation of the latter and subsequent treatment with sodium azide furnished the appropriate azido derivatives (**3**) (Table 2). The intramolecular cycloaddition step leading to the tricyclic products (**4**) was accomplished upon refluxing (**3**) in toluene. Reaction times and yields are given in Table 3, along with the characteristic data of the products.

It must be noted that compounds (**4**) are formed in a yield ranging from modest to excellent as a function of the substituents R^1 and R^2. Steric encumbrance by the latter reasonably hinders the intramolecular approach of the reactive π systems in parallel planes, as required for 1,3-dipolar cycloadditions.[9] Whenever the intramolecular cycloaddition pathway is made impervious, the concurrent thermolysis of the azido group

can occur to generate a transient nitrene which evolves to disappointing side-products.



1 2 3 4

	a	b	c	d	e
R^1	H	Me	Ph	H	H
R^2	H	H	H	Me	Ph

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. ^{1}H Nmr spectra were obtained on a Bruker 300 MHz apparatus; chemical shifts are given as ppm from tetramethylsilane.

Compound (**1a-d**) were commercially available. Compounds (**1e**) was prepared according to the literature.[10]

Alkynyl Antranilates Hydrochlorides (2a-e); General Procedure. A solution of alcohol (**1**) (0.20 mol) in dry benzene (100 ml) was treated with 80% NaH (7.50g, 0.25 mol) and refluxed for 1 h. Isatoic anhydride (32.6g, 0.20 mol) in pyridine (100 ml) was added and the solution was refluxed for 4 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 oily residue was dissolved in anhydrous ether and a 4M solution of HCl in anhydrous ether (75 ml) was added dropwise under stirring. The precipitate was collected by filtration and washed with anhydrous ether to afford pure hydrochloride (**2**) (Table 1).

Table 1. Alkynyl Antranilates Hydrochlorides (**2**)

Compd	Yield (%)	mp (°C)	Microanalyses (%) C calcd found	H calcd found	N calcd found	Cl calcd found	^{1}H Nmr[a] δ, J (Hz)
2a	92	169	56.7 56.6	4.7 4.6	6.6 6.4	16.8 16.9	2.90 (1H ,t ,J=3), 5.11 (2H, d, J=3), 7.65-8.25 (4H, m)
2b	71	161	58.5 58.5	5.3 5.4	6.2 6.0	15.7 15.6	1.70 (3H, d, J=6), 2.98 (1H, d, J=2.5), 5.71 (1H, m), 7.50-8.50 (4H,m)
2c	51	160	66.8 66.9	4.9 5.0	4.9 4.8	12.3 12.1	2.70 (1H, d, J=2.5), 6.65 (1H, d, J=2.5), 7.10-8.10 (9H, m)
2d	91	162	58.5 58.4	5.3 5.1	6.2 6.3	15.7 15.9	1.85 (3H, t, J=2.5), 4.95 (2H, q, J=2.5), 7.45-8.85 (4H, m)
2e	88	168	66.8 66.7	4.9 4.7	4.9 5.0	12.3 12.4	5.15 (2H, s), 7.30-8.30 (9H, m)

[a]Solvent: CD_3COOD for **2a**, D_2O for **2b-e**.

Alkynyl 2-Azidobenzoates (3a-e); General Procedure. Sodium nitrite (1.52g, 22 mmol) was added portionwise to a solution of **2** (11 mmol) in 1N aqueous HCl (55 ml) under stirring and cooling at 0°C. After addition of ether (100 ml), NaN_3 (3.58g, 55 mmol) was added portionwise under vigorous stirring and ice-cooling. After 30 min, the organic layer was separated, washed with 5% aqueous $NaHCO_3$, and dried (Na_2SO_4). The solvent was removed under reduced pressure and the residue was recrystallised from a mixture of diisopropyl ether and pentane to give pure (**3**) (Table 2).

Table 2. Alkynyl 2-Azidobenzoates (**3**)

Compd	Yield (%)	mp (°C)	Microanalyses (%) C calcd found	H calcd found	N calcd found	Ir (Nujol) ν (cm^{-1})	^{1}H Nmr ($CDCl_3$) δ, J (Hz)
3a	86	65	59.7 59.8	3.5 3.6	20.9 21.0	2100 1725	2.51 (1H, t, J=3), 4.90 (2H, d, J=3), 7.10-7.90 (4H, m)
3b[a]	27	44	61.4 61.5	4.2 4.3	19.5 19.6	2110 1730	1.60 (3H, d, J=6), 2.52 (1H, d, J=2.5), 5.65 (1H, m), 7.20-7.90 (4H, m)
3c[a]	40	61	69.3 69.1	4.0 4.1	15.2 15.3	2110 1730	2.71 (1H, d, J=2.5), 6.68 (1H, d, J=2.5), 7.10-7.90 (9H, m)
3d	77	46	61.4 61.2	4.2 4.1	19.5 19.3	2110 1730	1.85 (3H, t, J=2.5), 4.90 (2H, q, J=2.5), 7.10-7.90 (4H, m)
3e	82	67	69.3 69.3	4.0 3.9	15.2 15.2	2120 1735	5.15 (2H, s), 7.10-8.00 (9H, m)

[a]This compound decomposed in part during the chromatographic separation.

[1,2,3]Triazolo[1,5-*a*][4,1]benzoxazepines (4a-e); General Procedure. A solution of **3** (4 mmol) in toluene (150 ml) was refluxed for the time indicated in Table 3, then the solvent was removed under reduced pressure. In the case of **3a,b**, the residue was recrystallised from diisopropyl ether to give pure **4a,b**. In the case of **3c-e**, the residue was chromatographed on a silica gel column with CH_2Cl_2-AcOEt 9:1 as eluant to give (**4c-e**) (Table 3).

Table 3. [1,2,3]Triazolo[1,5-*a*][4,1]benzoxazepines (4)

Compd	Time (h)	Yield (%)	mp[a] (°C)	Microanalyses (%) C calcd found	H calcd found	N calcd found	Ir (Nujol) ν (cm^{-1})	^{1}H Nmr ($CDCl_3$) δ, J (Hz)
4a	12	82	194	59.7 59.8	3.5 3.6	20.9 21.0	1710	5.25 (2H, s), 7.90 (1H, s), 7.65-8.15 (4H, m)
4b	16	75	190	61.4 61.2	4.2 4.2	19 5 19.6	1710	1.90 (3H, d, J=6), 5.35 (1H, q, J=6), 7.82 (1H, s), 7.60-8.10 (4H, m)
4c	22	32	141	69.3 69.5	4.0 4.1	15.2 15.1	1725	6.25 (1H, s), 7.32 (1H, s), 7.40-8.20 (9H, m)
4d	24	50	155	61.4 61.5	4.2 4.1	19.5 19.5	1720	2.50 (3H, s), 5.22 (2H, s), 7.55-8.05 (4H, m)
4e	24	31	165	69.3 69.2	4.0 4.0	15.2 15.4	1730	5.40 (2H, s), 7.40-8.20 (9H, m)

[a]Recrystallised from diisopropyl ether.

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