SYNTHESIS OF TETRAZOLO[1,5-*a*][1,4]BENZODIAZEPIN-6-ONES *VIA* INTRAMOLECULAR AZIDE CYCLOADDITIONS ONTO THE CYANO GROUP

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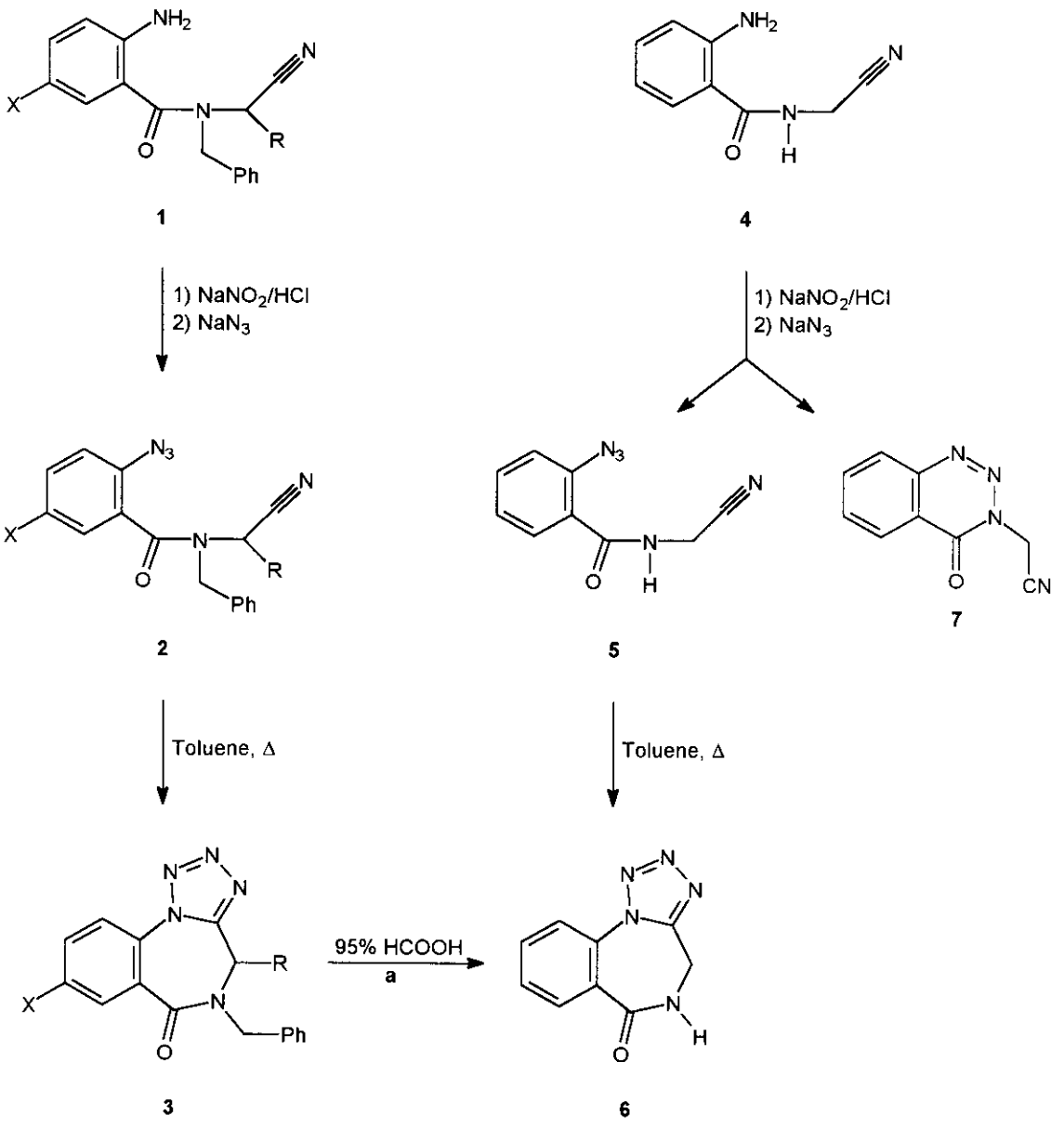
Abstract - Intramolecular azide cycloadditions onto the cyano group are described as a synthetic tool for a number of tetrazolo[1,5-*a*][1,4]benzodiazepin-6-ones (**3**).

Intramolecular 1,3-dipolar cycloadditions have gained increasing popularity in the last two decades, owing to their versatility in the construction of ring-fused or ring-bridged heterocycles.[1-4] Among them, intramolecular azide cycloadditions have been exploited on a variety of dipolarophiles giving rise to interesting structures in which an annulated 1,2,3-triazole or tetrazole ring constitutes the main feature of the whole system.[1-5] On pursuing our research line in this field,[6] we report here the synthesis of a number of tetrazolo[1,5-*a*][1,4]benzodiazepin-6-ones (**3**) by intramolecular azide cycloaddition onto the cyano group. It needs to be underlined that (i) the synthetic entries to the tetrazolo[1,5-*a*][1,4]benzodiazepine skeleton are still rare,[7,8] and (ii) compounds (**3**) could show interesting pharmacological properties, in the light of the known sedative effect of 8-chloro-6-phenyl-4*H*-tetrazolo[1,5-*a*][1,4]benzodiazepine.[9]

The intermediate 2-aminocarbonylanilines (**1**) were accessible according to literature procedures.[10] Diazotisation of the latter and subsequent treatment with sodium azide gave the properly *ortho*-substituted aryl azides (**2**), which were not obtained in the analytically pure state due to the presence of small amounts of cycloadducts (**3**). The intramolecular cycloadditions were performed by refluxing crude **2** in dry toluene. Reaction times, eluants in chromatography and yields are given in Table 1, while analytical and spectroscopic data of both reactants and products are collected in Tables 2 and 3.

The parent 4,5,7-unsubstituted term (**6**) was also devised as a valuable target. Hence, we synthesised 2-amino-*N*-cyanomethylbenzamide (**4**) by reacting isatoic anhydride with 2-aminoacetonitrile in dry dimethylformamide, and submitted it to diazotisation and subsequent treatment with sodium azide.

Scheme



entry	a	b	c	d	e	f	g
X	H	Cl	H	H	H	H	H
R	H	H	Me	Ph	4-Me-C_6H_4	4-MeO-C_6H_4	4-Cl-C_6H_4

Table 1 Thermal reaction of azides (**2a-g**) and (**5**).

Compd	Time[a] (h)	Products and yields (%)			Eluant
		3	**4**	**6**	
2a	33	75	–	–	AcOEt - LP[b] (2:1)
2b	77	95	–	–	–
2c	64	30	–	–	Et_2O
2d	15	57	–	–	Et_2O - LP[b] (2:1)
2e	16	56	–	–	Et_2O
2f	15	47	–	–	Et_2O
2g	16	65	–	–	–
5	480	–	5	6	CH_2Cl_2 - AcOEt (10:1)

[a]0.02 M in refluxing toluene. [b]LP= light petroleum, bp 45-60°C.

The formation yield of pure **5** was low because of the concurrent formation of 3-cyanomethyl-benzotriazin-4-one (**7**). Refluxing **5** in dry toluene really gave **6**, but the intramolecular cycloaddition was troublesome since a very long reaction time was required and extensive decomposition of the starting material took place (see Table 1). In addition, concurrent thermolysis of **5** occurred, with loss of molecular nitrogen, generating the corresponding nitrene intermediate which subsequently evolved to **4**. This disappointing outcome was circumvented by preparing **6** in 37% yield upon benzyl group cleavage of **3a** with 95% formic acid.[11]

Intramolecular cycloaddition yields were usually satisfactory, despite the poor dipolarophilic character of nitriles towards azides,[12] with the exception of **5**. The peculiar role played by the benzyl moiety remains to be underlined; perhaps its flexibility could facilitate the intramolecular approach of the addends in parallel planes, as required for 1,3-dipolar cycloadditions.[13]

Table 2. Characterisation of new compounds.[a]

Compd (Formula)	mp[b] (°C)	IR (nujol) ν (cm^{-1})	Microanalyses C Found (Calcd)	H Found (Calcd)	N Found (Calcd)	MS *m/z* M^+
2a ($C_{16}H_{13}N_5O$)	oil	2240, 2130, 1650	–	–	–	[c]
2b ($C_{16}H_{12}N_5OCl$)	oil	2236, 2120, 1655	–	–	–	[c]
2c ($C_{17}H_{15}N_5O$)	oil	2434, 2130, 1650	–	–	–	[c]
2d ($C_{22}H_{17}N_5O$)	oil	2228, 2130, 1651	–	–	–	[c]
2e ($C_{23}H_{19}N_5O$)	oil	2228, 2130, 1651	–	–	–	[c]
2f ($C_{23}H_{19}N_5O_2$)	oil	2245, 2130, 1650	–	–	–	[c]
2g ($C_{22}H_{16}N_5OCl$)	oil	2245, 2130, 1650	–	–	–	[c]
4 ($C_9H_9N_3O$)	95	3420, 3280, 1650	61.75 (61.69)	5.23 (5.18)	23.92 (24.00)	175
5 ($C_9H_7N_5O$)	93	3380, 2140, 1655	53.77 (53.71)	3.56 (3.51)	34.91 (34.82)	[c]
7 ($C_9H_6N_4O$)	109	1690	58.12 (58.05)	3.21 (3.25)	30.02 (30.11)	186
3a ($C_{16}H_{13}N_5O$)	105	1652	65.90 (65.95)	4.46 (4.50)	23.96 (24.05)	291
3b ($C_{16}H_{12}N_5OCl$)	167	1650	59.11 (59.06)	3.75 (3.72)	21.50 (21.54)	325
3c ($C_{17}H_{15}N_5O$)	70	1640	66.91 (66.86)	5.01 (4.95)	23.04 (22.95)	305
3d ($C_{22}H_{17}N_5O$)	110	1649	71.88 (71.91)	4.70 (4.67)	19.13 (19.07)	367
3e ($C_{23}H_{19}N_5O$)	180	1630	72.45 (72.41)	4.95 (5.02)	18.46 (18.37)	381
3f ($C_{23}H_{19}N_5O_2$)	137	1640	69.52 (69.49)	4.79 (4.82)	17.70 (17.63)	397
3g ($C_{22}H_{16}N_5OCl$)	159	1637	65.88 (65.82)	3.99 (4.02)	17.53 (17.46)	401
6 ($C_9H_7N_5O$)	219	3360, 1660	53.67 (53.71)	3.55 (3.51)	34.90 (34.82)	201

[a]NMR data are given in Table 3. [b]From diisopropyl ether. [c]Details on mass spectra for compounds **2a-g** and **5** are given in the Experimental section.

Table 3. ^{1}H-NMR data of new compounds.

Compd	^{1}H-NMR ($CDCl_3$) δ, J (Hz)
2a	4.32 (2H, s), 4.49 (2H, s), 7.20-7.50 (9H, m)
2b	4.30 (2H, s), 4.46 (2H, s), 7.10-7.50 (8H, m)
2c	1.44 (3H, d, J=7.3), 4.47 (1H, AB, J=15.2), 4.54 (1H, AB, J=15.2), 5.48 (1H, q, J=7.3), 7.20-7.50 (9H, m)
2d	4.18 (1H, AB, J=15.4), 4.38 (1H, AB, J=15.4), 5.25 (1H, s), 7.00-7.50 (14H, m)
2e	2.45 (3H, s), 4.15 (1H, AB, J=15.4), 4.35 (1H, AB, J=15.4), 5.28 (1H, s), 7.00-7.50 (13H, m)
2f	3.80 (3H, s), 4.20 (1H, AB, J=15.4), 4.35 (1H, AB, J=15.4), 5.30 (1H, s), 6.70-7.40 (13H, m)
2g	4.20 (1H, AB, J=15.6), 4.42 (1H, AB, J=15.6), 5.24 (1H, s), 6.80-7.50 (13H, m)
4	4.25 (2H, d, J=7.0), 6.30 (2H, br s), 6.50-7.50 (4H, m), 8.80 (1H, br t, J=7.0)
5	4.40 (2H, d, J=6.7), 7.25-8.20 (4H, m), 8.10 (1H, br t, J=6.7)
7	5.30 (2H, s), 7.85-8.40 (4H, m)
3a	4.58 (2H, s), 4.85 (2H, s), 7.25-7.40 (5H, m), 7.60-7.80 (2H, m), 7.92 (1H, dd, J=8.2, 1.2), 8.22 (1H, dd, J=8.4, 2.6)
3b	4.59 (2H, s), 4.84 (2H, s), 7.28-7.37 (5H, m), 7.71 (1H, dd, J=9.3, 3.4), 7.90 (1H, d, J=9.3), 8.21 (1H, d, J=3.4)
3c	1.21 (3H, d, J=6.9), 4.53 (1H, AB, J=14.8), 5.05 (1H, AB, J=14.8), 5.30 (1H, q, J=6.9), 7.08-7.15 (5H, m), 7.22 (1H, dt, J=8.0, 2.2), 7.28 (1H, dt, J=7.60, 1.2), 7.97 (1H, dd, J=8.0, 2.2), 8.24 (1H, dd, J=7.8, 1.2)
3d	4.94 (1H, AB, J=14.4), 5.19 (1H, AB, J=14.4), 6.44 (1H, s), 7.00-7.50 (12H, m), 7.70 (1H, dd, J=8.1, 0.8), 7.96 (1H, dd, J=8.1, 1.3)
3e	2.12 (3H, s), 4.90 (1H, AB, J=13.9), 5.18 (1H, AB, J=13.9), 6.38 (1H, s), 6.60-7.50 (11H, m), 7.70 (1H, dd, J=8.3, 0.8), 8.00 (1H, dd, J=8.2, 1.4)
3f	3.62 (3H, s), 4.92 (1H, AB, J=15.0), 5.13 (1H, AB, J=15.0), 6.38 (1H, s), 6.50-7.50 (11H, m), 7.72 (1H, dd, J=8.4, 0.8), 7.96 (1H, dd, J=8.4, 1.4)
3g	5.00 (2H, s), 6.39 (1H, s), 6.60-7.55 (11H, m), 7.72 (1H, dd, J=8.4, 0.6), 7.96 (1H, dd, J=7.8, 1.2)
6	4.70 (2H, d, J=7.2), 6.85 (1H, br t, J=7.2), 7.65-8.22 (4H, m)

EXPERIMENTAL

Melting points were determined with a Büchi apparatus and are uncorrected. IR spectra were recorded on a FT IR Perkin Elmer 1725 X spectrophotometer. MS spectra were determined with a VG-70EQ apparatus. ^{1}H-NMR spectra were taken with a Bruker AC 300 instrument in $CDCl_3$ solutions; chemical shifts are given as ppm from Me_4Si and *J* values are given in Hz.

***N*-Cyanomethyl-2-aminobenzamide (4).** A solution of isatoic anhydride (8.00 g, 49.0 mmol) and 2-aminoacetonitrile hydrochloride (6.81 g, 74.0 mmol) in dry dimethylformamide (60 mL) was heated to 80°C. Triethylamine (7.58 g, 75.0 mmol) was slowly added (1 h) and the mixture was heated to 80°C for further 2.5 h. The crude was poured in water (600 mL), basified with 10% aqueous NaOH (35 mL) and extracted with dichloromethane (3×100 mL). The organic layer was dried (Na_2SO_4) and evaporated at reduced pressure. The residue was washed with cold hexane (50 mL), filtered off, and the solid material was recrystallised from diisopropyl ether giving pure **4** with 70% yield (Tables 2 and 3).

***N*-Cyanomethyl-2-azidobenzamides (2a-g) and (5); General Procedure.** Sodium nitrite (2.00 g, 28.9 mmol) was added portionwise to a solution of **1** or **4** (19.3 mmol) in 2N aqueous HCl (34 mL) under stirring and cooling at 0°C. After addition of cold ether (75 mL), NaN_3 (6.5 g, 0.10 mol) was added portionwise under vigorous stirring and ice-cooling. After 1 h, the organic layer was separated, washed firstly with 5% aqueous $NaHCO_3$ (50 mL), then with water (75 mL), and dried (Na_2SO_4). The solvent was evaporated under reduced pressure affording **2a-g** in the crude state: **2a**, 70%; MS *m/z* (rel. intensity) 291 (12%), 263 (5%); **2b**, 86%; MS *m/z* (rel. intensity) 325 (15%), 297 (8%); **2c**, 30%; MS *m/z* (rel. intensity) 305 (10%), 277 (5%); **2d**, 70%; MS *m/z* (rel. intensity) 367 (20%), 339 (16%); **2e**, 44%; MS *m/z* (rel. intensity) 381 (15%), 353 (10%); **2f**, 56%; MS *m/z* (rel. intensity) 397 (25%), 369 (4%); **2g**, 72%; MS *m/z* (rel. intensity) 401 (18%), 373 (6%). In the case of **4** the residue was chromatographed on a silica gel column with CH_2Cl_2-AcOEt 10:1 as eluant. *N*-Cyanomethyl-2-azidobenzamide (**5**) was eluted first, followed by the 3-cyanomethylbenzotriazin-4-one (**7**). Subsequent recrystallisation from diisopropyl ether gave **5** (20%); MS *m/z* (rel. intensity) 201 (7%), 173 (3%); and **7** (26%) in the pure state (Tables 2 and 3).

Tetrazolo[1,5-*a*][1,4]benzodiazepin-6-ones (3a-g) and (6); General Procedure. A solution of **2** or **5** (2.5 mmol) in dry toluene (125 mL) was refluxed for the time indicated in Table 1. The solvent was evaporated and the residue was recrystallised from diisopropyl ether in the case of **2b** and **2g** or chromatographed on a silica gel column (see Table 1) to give **3** or **6** in the analytically pure state (Tables 2 and 3).

4*H*-Tetrazolo[1,5-*a*][1,4]benzodiazepin-6-one (6). A solution of **3a** (1.0 mmol) in 95% formic acid (1.0 mL) was stirred at rt for 2 h, and then at 80°C for 5 h. The mixture was taken up with dichloromethane (15 mL) and washed firstly with 5% aqueous $NaHCO_3$ (5 mL), then with water (10 mL). The organic layer was dried (Na_2SO_4) and evaporated, and the residue was recrystallised from diisopropyl ether giving pure **6** with 37% yield.

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