Synthesis of 1-Aryl-1,2,3-triazole-4,5-dimethanol-4,5-bis(isopropylcarbamates) as Potential Antineoplastic Agents

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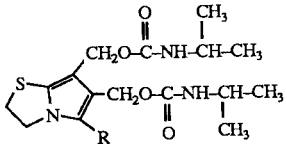
Received August 21, 1989

Dedicated to Professor Ernest Campaigne on the occasion of his 75th birthday

Starting with aryl azides, 1-aryl-1,2,3-triazole-4,5-dimethanol-4,5-bis(isopropylcarbamates), a new class of potential antineoplastic agents, were synthesized. *In vitro* antileukemic and antitumor activities of the compounds synthesized were also evaluated.

J. Heterocyclic Chem., **27**, 687 (1990).

Recently, we have synthesizesd and found that 5-aryl-2,3-dihydropyrrolo[2,1-*b*]thiazole-6,7-dimethanol-6,7-bis-(isopropylcarbamates) **1** exhibited *in vitro* antileukemic

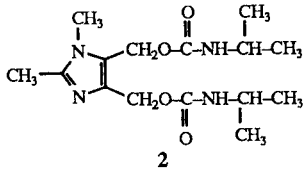


Formula 1

1 **1a** R = 4-ClC$_6$H$_4$

activity against HL-60 human leukemia and antitumor activity against HT-29 human colon carcinoma cells. The 5-*p*-Chloro derivative **1a** was found to be the most active compound [1]. However, the compounds suffer from solubility properties.

Anderson *et al.* [2] extensively studied bis(carbamate) derivatives with significant *in vivo* and *in vitro* antineoplastic activities. They recently reported that some water soluble bis(carbamate) derivatives of 4,5-bis(hydroxymethyl)imidazoles such as **2** were very active against various human tumor cell lines both *in vitro* and *in vivo*.

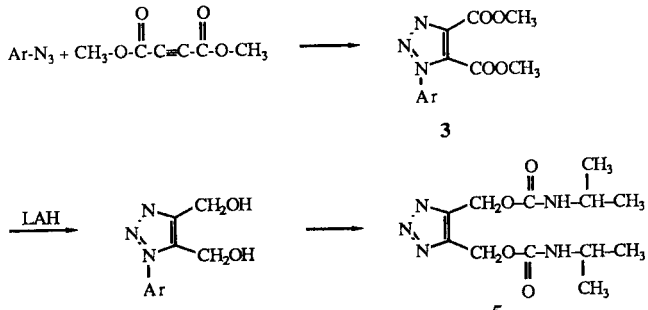


Formula 2

2

In this work, we present the synthesis of five new bis(carbamate) derivatives. Dimethyl 1-aryl-1,2,3-triazole-4,5-dicarboxylates **3** were synthesized by a modified method originally described by Michael *et al.* [3] almost one hundred years ago. Aryl azides and dimethyl acetylenedicarboxylate were refluxed in carbon tetrachloride solution. Pure dimethyl esters **3** were obtained in almost theoretical yields. Lithium aluminum hydride reduction of these esters **3** gave the corresponding-4,5-dimethanol **4** in moderate to low yields. This is in accordance with the instability of 1,2,3-triazole ring system which is sensitive towards some reducing agents. Although the 1,2,3-triazole ring system resists hydrogenation with different reagents such as amalgamated sodium in methanol or tin or zinc in acid solutions as well as catalytic hydrogenation in the presence of nickel at 240-270°, sodium in ethanol is reported to decompose this ring system to give mixtures of amines [4]. The 4,5-dimethanols **4** were reacted with isopropyl isocyanate in methylene chloride. It was found that the addition of a large excess of isopropyl isocyanate periodically during 3-5 days to the refluxing mixture would give high yields of the desired carbamates **5**.

Scheme 1



3,4,5 Ar

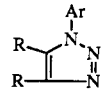
a C_6H_5
b 4-ClC_6H_4
c 4-BrC_6H_4
d 3,4-$Cl_2C_6H_3$
e 4-$CH_3OC_6H_4$

EXPERIMENTAL

Melting points (uncorrected) were taken with a Fisher-Johns apparatus. NMR spectra were determined for deuteriochloroform or hexadeuterio dimethyl sulfoxide solutions containing 1% trimethylsilane with a Varian Anaspect EM360 NMR Spectrometer.

Table 1

1,4,5-Trisubstituted-1,2,3-Triazoles



Compound	R	Aryl	Formula	C% Calcd./Found		H% Calcd./Found		N% Calcd./Found	
3a	$-COOCH_3$	C_6H_5	$C_{12}H_{11}N_3O_4$	55.17	54.91	4.24	4.60	16.09	15.69
3b	$-COOCH_3$	$4-ClC_6H_4$	$C_{12}H_{10}ClN_3O_4$	48.74	48.50	3.40	3.41	14.21	14.29
3c	$-COOCH_3$	$4-BrC_6H_4$	$C_{12}H_{10}BrN_3O_4$	42.37	42.31	2.96	2.94	12.35	12.29
3d	$-COOCH_3$	$3,4-Cl_2C_6H_3$	$C_{12}H_9Cl_2N_3O_4$	43.65	43.58	2.74	2.70	12.72	12.74
3e	$-COOCH_3$	$4-CH_3OC_6H_4$	$C_{13}H_{13}N_3O_4$	53.61	53.57	4.50	4.48	14.43	14.29
4a	$-CH_2OH$	C_6H_5	$C_{10}H_{11}N_3O_4$	58.53	58.40	5.40	5.31	20.48	20.31
4b	$-CH_2OH$	$4-ClC_6H_4$	$C_{10}H_{10}ClN_3O_2$	50.11	49.75	4.20	4.11	17.53	17.40
4c	$-CH_2OH$	$4-BrC_6H_4$	$C_{10}H_{10}BrN_3O_2$	42.27	42.19	3.54	3.51	14.79	14.75
4d	$-CH_2OH$	$3,4-Cl_2C_6H_3$	$C_{10}H_9Cl_2N_3O_2$	43.81	43.75	3.30	3.26	15.33	15.28
4e	$-CH_2OH$	$4-CH_3OC_6H_4$	$C_{11}H_{13}N_3O_3$	56.16	56.14	5.57	5.59	17.86	17.83
5a	$-CH_2OCONHCH(CH_3)_2$	C_6H_5	$C_{18}H_{25}N_5O_4$	57.58	57.19	6.71	7.03	18.66	18.25
5b	$-CH_2OCONHCH(CH_3)_2$	$4-ClC_6H_4$	$C_{18}H_{24}ClN_5O_4$	52.74	52.33	5.90	5.61	17.08	16.83
5c	$-CH_2OCONHCH(CH_3)_2$	$4-BrC_6H_4$	$C_{18}H_{24}BrN_5O_4$	47.58	47.90	5.32	5.69	15.41	15.79
5d	$-CH_2OCONHCH(CH_3)_2$	$3,4-Cl_2C_6H_3$	$C_{18}H_{23}Cl_2N_5O_4$	48.65	48.82	5.21	5.30	15.76	16.01
5e	$-CH_2OCONHCH(CH_3)_2$	$4-CH_3OC_6H_4$	$C_{19}H_{27}N_5O_4$	56.28	55.95	6.71	6.40	17.27	17.68

Compound	mp (°C)	yield (%)	^{1}H NMR, ppm
3a [1]	127-128	95	4.11 (s, CH_3), 4.14 (s, CH_3), 7.87 (s, aromatics)
3b	135	98	4.20 (s, CH_3), 4.24 (s, CH_3), 7.90 (s, aromatics)
3c	127	93	4.25 (s, CH_3), 4.28 (s, CH_3), 7.81-8.32 (q, aromatics)
3d	136-139	97	4.11 (s, CH_3), 4.16 (s, CH_3), 7.68-8.20 (m, aromatics)
3e	92-94	89.5	4.03 (s, CH_3), 4.08 (s, CH_3), 4.25 (s, OCH_3), 7.31-7.90 (m, aromatics)
4a	151-153	26	4.81 (s, CH_2), 4.09 (s, CH_2), 5.61-5.72 (br, 2OH), 8.01 (m, aromatics)
4b	174-176	11	4.80 (s, CH_2), 4.86 (s, CH_2), 5.49-5.73 (br, 2OH), 7.70-8.82 (m aromatics)
4c	182-184	10	4.76 (s, CH_2), 4.81 (s, CH_2), 5.50-5.72 (br, 2OH), 7.76-8.29 (q, aromatics)
4d	160	15	4.86 (s, CH_2), 4.93 (s, CH_2), 5.51 (br, OH), 5.72 (br, OH), 8.02-8.61 (m, aromatics)
4e	90-92	8	4.25 (s, OCH_3), 4.83 (s, CH_2), 4.91 (s, CH_2), 5.50 (br, OH), 5.70 (br, OH), 7.56-8.40 (q, aromatics)
5a [2]	167-169	97	1.15 (s, $2CH_3$), 1.32 (s, $2CH_3$), 3.97 (m, 2CH), 5.28 (br, 2NH), 5.50 (s, CH_2), 5.68 (s, CH_2), 7.91 (s, aromatics)
5b	150-152	98	0.98 (d, $2CH_3$), 1.18 (d, $2CH_3$), 3.61 (m, 2CH), 5.4 (s, $2CH_2$), 7.31 (br, 2NH), 8.01 (s, aromatics)
5c	163-164	74	1.01 (d, $2CH_3$), 1.19 (d, $2CH_3$), 3.51 (m, 2CH), 5.42 (s, $2CH_2$), 7.28 (br, 2NH), 8.1 (m, aromatics)
5d	152-154	81	0.91 (d, $2CH_3$), 1.10 (d, $2CH_3$), 3.65 (m, 2CH), 5.51 (d, $2CH_2$), 7.41 (m, 2NH), 8.18-8.48 (m, aromatics)
5e	105-107	40	1.02 (d, CH_3), 1.10 (d, CH_3), 3.68 (m, 2CH), 4.18 (s, OCH_3), 5.41 (s, CH_2), 5.70 (br, 2NH), 7.40-8.10 (q, aromatics)

[1] The ^{1}H nmr spectra of all compounds **3** were taken in deuteriochloroform. [2] The ^{1}H nmr spectro of all compounds **4** and **5** were taken in DMSO-d_6.

Aryl azides used in this work were synthesized according to the literature [5].

Dimethyl-1-(4-chlorophenyl)-1,2,3-triazole dicarboxylate (**3b**).

A mixture of 3.99 g (0.026 mole) of 4-chlorophenylazide, 3.7 g (0.026 mole) of dimethyl acetylene dicarboxylate and 5 ml of carbon tetrachloride was refluxed overnight. After cooling the precipitate formed was dissolved in chloroform, charcoaled and evaporated to half volume. Precipitation was induced by the addition of petroleum ether and small white needles were collected. Yield and physical properties are reported in Table 1. All other dimethyl-1-aryl-1,2,3-triazole dicarboxylates were prepared following the same procedure (see Table 1).

1-Phenyl-1,2,3-triazole-4,5-dimethanol (**4a**).

To an ice-salt cold suspension of 1.71 g (0.045 mole) of lithium aluminum hydride in 50 ml of dry diethyl ether was slowly added 3.92 g (0.015 mole) of dimethyl-1-phenyl-1,2,3-triazole-4,5-dicarboxylate while stirring. Stirring was continued overnight at room temperature. Water was carefully added, and the precipitate formed was filtered and washed with hot chloroform. The organic layer was evaporated to dryness. The solid was recrystallized from hot water as beige needles. Yield and physical properties are reported in Table 1. All other compounds **4** were synthesized similarly (see Table 1).

1-(4-Bromophenyl)-1,2,3-triazole-4,5-dimethanol-4,5-bis(isopropylcarbamate) (**5c**).

A mixture of 1-(4-bromophenyl)-1,2,3-triazole dimethanol 0.44 g (0.0015 mole), 4-dimethylaminopyridine 0.25 g (0.002 mole) and isopropyl isocyanate 0.29 g (0.004 mole) was stirred and refluxed in 60 ml of methylene chloride with periodic addition of 0.29 g of isopropyl isocyanate every 8 hours during 4 days. The methylene chloride was evaporated. The product was dissolved in methanol and precipitation induced by the addition of cold water to give white needles. Yield and physical properties are reported in Table 1. All other compounds **5** were synthesized similarly (see Table 1).

Biological Studies.

The cytotoxic activity of the dicarbamates was tested on HL-60, a human myeloid cell line and YAC-1, a mouse lymphoma cell line. The inhibition of growth of HL-60 and YAC-1 was assessed by incubation of these cells with various concentrations of the compounds for 7 days in RPMI-1640 containing 10% heat inactivated fetal calf serum. The cells were then counted with a coulter counter. The percent cytotoxicity was calculated using the following equation:

$$\% \text{ Cytoxicity} = \left[1 - \frac{\text{No. of live cells in test culture}}{\text{No. of live cells in control culture}} \right] \times 100$$

The compounds were dissolved in DMSO such that the maximum concentration of DMSO was 0.25%. Control cultures contained the same concentration of DMSO as the test cultures. The results indicate (Table 2) that compound **5d** killed 75% of the cells when used at 10×10^{-6} M final concentration and its cytotoxicity diminished when used at 5 and 2.5×10^{-6} M. The rest of the compounds had little or no activity. Compound **1a** was used as a control which showed much higher activity.

Table 2

Compound	Concentration	% Cytotoxicity [1] HL-60	YAC-1
5a	$10x10^{-6}M$ (10 μM)	0	0
5b	$10x10^{-6}M$	0	25
5c	$10x10^{-6}M$	20	47
	$5x10^{-6}M$	14	0
	$2.5x10^{-6}M$	4	0
5d	$10x10^{-6}M$	74	75
	$5x10^{-6}M$	53	34
	$2.5x10^{-6}M$	16	11
5e	$10x10^{-6}M$	0	0
1a (control)	$10x10^{-6}M$	94	100
	$5x10^{-6}M$	96	99
	$2.5x10^{-6}M$	95	99

[1] Duplicate cultures with a cell density of 10^5/ml were incubated in growth medium with and without compounds. The perecnt cytotoxicity was calculated from determination of the number of cells in test relative to control.

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