Chemistry of Heterocyclic Compounds, Vol. 31, No. 1, 1995

SYNTHESIS OF N-SUBSTITUTED 4-AMINOMETHYL-1,3-DIOXANES

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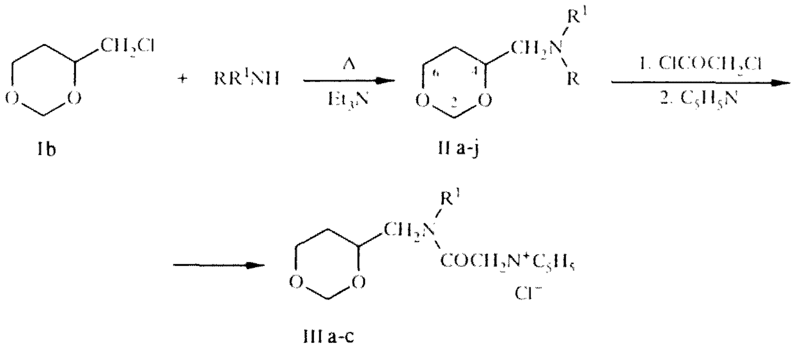
4-(R-Amino)methyl-1,3-dioxanes were synthesized from 4-chloromethyl-1,3-dioxanes. Some of these products were converted into water-soluble pyridinium chlorides by consecutive treatment with chloroacetyl chloride and pyridine.

4-Aminomethyl-1,3-dioxanes have attracted attention as promising intermediates in the synthesis of pyrrolidines, nucleosides, and other compounds with pharmacological activity. Attempts have been made to synthesize these compounds from 4-halomethyl-1,3-dioxanes (I). However, this conversion was achieved only in the synthesis of 4-(ethylamino)-1,3-dioxane from 4-bromoethyl-1,3-dioxane (Ia) in 18% yield [1]. There have been no reports of the preparation of amines from 4-chloromethyl-1,3-dioxane (Ib), which is a more available precursor [2]. The low reactivity of dioxanes Ia and Ib in substitution reactions is probably related to their β-haloether structure [3]. Nevertheless, Zlotskii et al. [4, 5] have obtained primary, secondary, and tertiary amines from the closest homolog of Ib, namely, 4-chloromethyl-1,3-dioxolane with suitable yields. This result led us to undertake a careful re-examination of the reaction of dioxane Ib with amines.

The reaction of chloride Ib with benzylamine in DMF in the presence of triethylamine proceeds with low selectivity. The yield of 4-benzylaminomethyl-1,3-dioxane (IIb) was 30% when the reaction was carried out in absolute ethanol with a two-fold excess of starting Ib. However, difficulties were encountered in separating this product from the starting amine. The reaction of dioxane Ib with amines in triethylamine proved a more suitable method for the synthesis of aminodioxanes. The yields of the desired reaction products IIa-IIj ranged from 30 to 69% depending on the basicity of the starting amine (see Table 1).



IIa–i R = H a $R^1 = C_6H_5$, b $R^1 = CH_2C_6H_5$, c $R^1 = C_6H_4CH_3$-*o*, d $R^1 = C_6H_4CH_3$-*p*, e $R^1 = C_6H_4CH_3$-*m*, f $R^1 = C_6H_4OCH_3$-*p*, g $R^1 = C_6H_3(CH_3)_2$-*o,o*, h $R^1 = C_6H_4Cl$-*o*, i R^1 = 2-pyrimidyl; IIj R + $R^1 = (CH_2)_6$; IIIa–c a $R^1 = C_6H_5$, b $R^1 = CH_2C_6H_5$, c $R^1 = C_6H_4CH_3$-*o*

The structures of the amines synthesizes were indicated by PMR spectroscopy (Table 1). Some of the amines obtained were converted into water-soluble pyridinium chlorides IIIa-IIIc by consecutive treatment with chloroacetyl chloride and pyridine in order to confirm their structures.

Bashkir State University, 450074 Ufa. Institute of Fine Organic Synthesis, 450029 Ufa. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 1, pp. 21-23, January, 1995. Original article submitted November 11, 1994.

0009-3122/95/3101-0017$12.50 ©1995 Plenum Publishing Corporation

TABLE 1. Physicochemical Indices of 4-(R-aminomethyl)-1,3-dioxanes

Compound	Bp, °C (3-5 mm Hg)*	n_D^{20}	R_f*2	PMR spectrum, δ, pp	Yield, %
IIa	160...162	1,5752	0,48	1,0...1,1 (2H, m, 5-H), 3,0...4,0 (6H, m, CH_2N, NH, 4-H, 6-H), 4,1...4,9 (2H, d.d., 2-H), 6,1...7,2 (5H, m, H_{Ph})	50
IIb	127...130	1,5351	0,46	1,2 (2H, m, 5-H), 1,5 (1H, s, NH), 3,0...4,5 (7H, m, CH_2Ph, CH_2N, 4-H, 6-H), 4,7...5,0 (2H, d.d., 2-H), 6,5...7,0 (5H, m, H_{Ph})	60
IIc	160...162	1,5499	0,64	1,1...1,2 (2H, m, 5-H), 2,0 (3H, s, CH_3), 3,0 (2H, m, CH_2N), 3,5...4,0 (4H, m, NH, 4-H, 6-H), 4,4...5,0 (2H, d.d, 2-H), 6,2...7,0 (4H, m, H_{Ar})	63
IId	165...167	1,5537	0,45	1,2...1,5 (2H, m, 5-H), 2,2 (3H, s, CH_3), 3,2...4,2 (6H, m, CH_2N, NH, 4-H, 6-H), 4,6...5,2 (2H, d.d, 2-H), 6,5...7,5 (4H, d.d, H_{Ar})	69
IIe	163...165	1,5655	0,63	1,2...1,3 (2H, m, 5-H), 2,2 (3H, s, CH_3), 3,0...4,2 (6H, m, CH_2N, NH, 4-H, 6-H), 4,6...5,2 (2H, d.d, 2-H), 6,3...7,0 (4H, m, H_{Ar})	67
IIf	180...183	1,5575	0,54	1,2...1,3 (2H, m, 5-H), 3,0...4,5 (8H, m, CH_2N, NH, 4-H, 6-H, CH_3), 4,9...5,1 (2H, d.d, 2-H), 6,5...7,5 (4H, d.d, H_{Ar})	58
IIg	139...142	1,5381	0,49	1,1...1,2 (2H, m, 5-H), 2,0 (6H, s, CH_3), 2,9...4,0 (6H, m, CH_2N, NH, 4-H, 6-H), 4,2...5,0 (2H, d.d, 2-H), 6,2...7,0 (3H, m, H_{Ar})	70
IIh	157...160	1,5641	0,43	1,2...1,4 (2H, m, 5-H), 3,2...4,3 (6H, m, CH_2N, NH, 4-H, 6-H), 4,7...5,2 (2H, d.d, 2-H), 6,6...7,4 (4H, m, H_{Ar})	35
IIi	193...198	1,4769	0,29	1,6 (2H, m, 5-H), 3,5...4,4 (5H, m, CH_2N, 4-H, 6-H), 5,5 (1H, s, NH), 4,8...5,2 (2H, d.d, 2-H), 6,4...6,5 (1H, t, 5′-H_{Het}), 8,0...8,2 (2H, d, 4′-H_{Het}, 6′-H_{Het})	38
IIj	121...122	1,4871	0,70	1,5...1,8 (10H, m, 5-H), 2,5...2,9 (6H, m, CH_2N), 3,4...4,2 (3H, m, 4-H, 6-H), 4,6...5,1 (2H, d.d, 2-H)	62
IIIa	12	—	—	1,2...1,3 (2H, m, 5-H) 3,4...4,5 (7H, m, CH_2N, $COCH_2$, 4-H, 6-H), 4,6...5,0 (2H, d.d., 2-H), 7,0...7,5 (5H, m, H_{Ph}), 7,8...9,2 (5H, m, H_{Py})	61
IIIb	10	—	—	1,1...1,2 (2H, m, 5-H), 3,1...4,0 (7H, m, CH_2N, CH_2Ph, 4-H, 6-H), 4,2 (2H, s, $COCH_2$), 4,7...5,0 (2H, d.d., 2-H), 7,0...7,5 (5H, m, H_{Ph}), 7,7...9,0 (5H, m, H_{Ph})	60
IIIc	15	—	—	1,3...1,4 (2H, m, 5-H), 2,2 (3H, s, CH_3), 3,5...4,5 (7H, m, CH_2N, $COCH_2$, 4-H, 6-H), 4,6...5,2 (2H, d.d, 2-H), 7,0...7,4 (4H, m, H_{Ar}), 7,8...9,1 (5H, m, H_{Py})	45

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*The solidification temperatures are given for IIIa-IIIc

*2Thin-layer chromatography with eluents: $CHCl_3$ for IIa-IIc, IIg, IIh, and IIj, 9:1 CCl_4−EtOH for IId, 9:1 CH_3Ph−EtOH for IIe, and 1:9 MeOH−$CHCl_3$ for IIf and IIi.

EXPERIMENTAL

The PMR spectra were taken on a Tesla BS-487 spectrometer at 80 MHz in $CDCl_3$ or DMSO (for IIIa-IIIc) with HMDS as the internal standard. The gas−liquid chromatographic analyses were carried out on an LKhM-8MD chromatography with a flame ionization detector on a 3500 × 3-mm stainless steel column packed with 15% SE-30 on Chromaton N-AW-HMDS. The nitrogen carrier gas flow rate was 20 ml/min. The thin-layer chromatography was carried out on Silufol plates.

A sample of 4-chloromethyl-1,3-dioxane (Ib) was prepared according to Farberov and Ustavshchikov [2].

4-(R-Aminomethyl)-1,3-dioxanes IIa-IIj. A mixture of 25 mmoles starting amine and 25 mmoles dioxane Ib in 75 mmoles triethylamine was maintained in a sealed glass ampule at 125-130°C for 25-30 h. Upon cooling, the ampule contents were diluted with dry acetone. The precipitate was filtered off and the filtrate was evaporated. The reaction product was isolated from the residue either by distillation at reduced pressure (IIb, IIg, IIh, and IIj) or chromatography on silica gel.

Pyridinium Chlorides IIIa-IIIc. A sample of 53 mmoles chloroacetyl chloride was added to cooled suspension of 50 mmoles amine and 100 mmoles potassium carbonate in 30 ml dry ether. The reaction mixture was stirred with heating for 30 min and filtered. A sample of 50 ml pyridine was added to the filtrate, stirred for 6 h, and let stand for an additional 24 h. Ether was removed and the low-melting products were cooled with ice and washed with dry ether.

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