SHORT PAPER

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Synthesis of heterocyclic oxyalkynylamines†

A. Matijoška*, G. K. Kupetis, O. Eicher-Lorka and L. Rastenyté

Institute of Chemistry, Goštauto Str. 9, LT-2600 Vilnius, Lithuania

The synthesis and characterisation of butynoxy- and butyndioxyalkylated piperidine and morpholine derivatives having one or two phenyl groups are reported.

Keywords: alkynes, amines, phase transfer, morpholines, piperidines

2-Benzhydryloxyethyl(dimethyl)amine hydrochloride (benadryl, dimedrol) has been used as an antiallergenic antiseptic preparation in pharmacology for quite some time,[1] and various benzhydrylpiperazine derivatives (the structures of which include unsaturated bonds as well as piperidine and morpholine rings) act as calcium antagonists.[2] A number of phenylpiperidines have been synthesised and their antidepressive activity analysed.[3]

In the course of this analysis, the possibility of using phase transfer catalysis (PTC) during the synthesis of oxyalkynes was investigated.[4,5] An analysis of the chemical properties of the oxyalkynes during their aminomethylation reactions was also carried out. In addition, a number of acetylenic analogues of benadryl were synthesised.[5] As a continuation of the project, using PTC and applying triethylbenzylammonium chloride (TEBACl), we synthesised 1-[3-(2-propynyloxy) propoxymethyl]benzene and 3-(benzhydryloxypropoxy)-1-propyne (**1, 2)** (Scheme 1). The reaction was performed at a temperature of 70 °C for ~15 hours and 50.5–61.5 % of the respective oxyalkynes were separated.

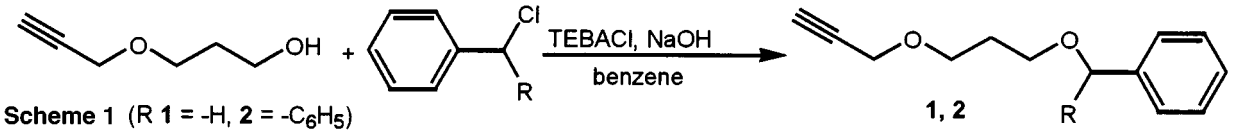
In addition the mentioned oxyalkynes, we used the previously[4,5] synthesised 1-[2-(propynyloxy)ethoxymethyl] benzene, 3-(2-benzhydryloxyethoxy)-1-propyne, 1-[3-(2-propynyloxy)propyl]benzene, 1-[(*E*)-3-(2-propynyloxy)-1-propenyl]benzene, and 1-[3-(2-propynyloxy)-1-propynyl] benzene in aminomethylation reactions with heterocyclic amines, and various butynoxy- and butyndioxyalkynylamines were obtained. We performed aminomethylation reactions of oxyalkynes with piperidine and morpholine according to previously published methods,[4] with the exception that benzene was used as solvent instead of dioxane. Reactions were performed for 10–12 hours at a temperature of 50–60 °C. During the reaction, 41.5–62.0 % of the respective heterocyclic oxyalkynamines **3–11** were obtained (Scheme 2).

Because the boiling temperatures of all the oxyalkynylamines were very high and they decomposed during fractionation, they were separated by repeatedly applying dilute HCl and NaOH aqueous solutions, by extraction of the products with benzene, the solvent was distilled and the product was further dried in a vacuum. The amine ^{1}H NMR spectra in deuterated acetone were also carried out. Hydrohalides of some of the amines were also obtained.

Experimental

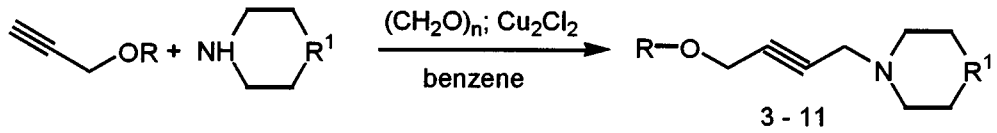
Synthesis of oxyalkynes **(1, 2):** 1 g of TEBACl, 4 g (0.1 mol) of NaOH, 14 g (0.12 mol) of 3-(2-propynyl-oxy)-1-propanol were added to 100 ml of benzene while stirring; 13 g (0.1 mol) of benzyl chloride or 20.3 g (0.1 mol) of diphenylchloromethane was added drop by drop during an hour at 60 °C; the mixture of the reaction was stirred for another 15 hours at a temperature of 70 °C. After the reaction completed, the mixture was cooled to ~20 °C and washed with water, the benzene solution was dried with $MgSO_4$, the solvent was distilled off, the product was re-distilled in vacuum. Obtained: 10.3 g (50.5%) of **1**, b.p. 140–144 °C (7 mm), n_D^{20} 1.5081, δ_H (CD_3COCD_3) 1.96 (2H, q), 3.05 (1H, t), 3.66 (2H, t), 3.72 (2H, t), 4.25 (2H, d), 4.6 (2H, s), 7.45 (5H, m). (Found: C, 76.14; H, 8.12. $C_{13}H_{16}O_2$ requires: C, 76.44; H, 7.89%); and 17.2 g (61.5%) of **2**, b.p. 205–207 °C (7 mm), n_D^{20} 1.5545, δ_H (CD_3COCD_3) 2.01 (2H, q 3.05 (1H, t), 3.66 (2H, t), 3.74 (2H, t), 4.25 (2H, d), 5.55 (2H, s), 7.48 (10H, m). (Found: C, 81.17; H, 7.35. $C_{19}H_{20}O_2$ requires: C, 81.39; H, 7.19%).

Synthesis of heterocyclic oxyalkynamines **(3–11):** 1.5 g (0.05 mol) of paraformaldehyde, 0.5 g of Cu_2Cl_2, 0.05 mol of corresponding



Scheme 1 (R **1** = -H, **2** = -C_6H_5)

Scheme 1



Scheme 2 (R **3** = $CH_2CH_2CH_2C_6H_5$, **4, 5** = $CH_2CH{=}CHC_6H_5$, **6, 7** = $CH_2C{\equiv}CC_6H_5$, **8** = $CH_2CH_2OCH_2C_6H_5$, **9** = $CH_2CH_2OCH(C_6H_5)_2$, **10** = $CH_2CH_2CH_2OCH_2C_6H_5$, **11** = $CH_2CH_2CH_2OCH(C_6H_5)_2$; R^1 **3, 4, 6, 9, 10** = CH_2, **5, 7, 8, 11** = O)

Scheme 2

* To receive any correspondence.

† This is a Short Paper, there is therefore no corresponding material in *J Chem. Research (M).*

Table 1 Data of oxyalkynylamines **3–11**

Cpd no.	Yield, %	Mp/°C HCl	Found / requires % C	H	N	Formula	NMR ^{1}H data (δ, p pm)
3	55.5	–	79.36 79.65	9.43 9.28	4.97 4.61	$C_{18}H_{25}NO$	1.57 (6H,m), 1.97 (2H, q), 2.56 (4H, m), 2.81 (2H, t), 3.37 (2H, t), 3.63(2H, t), 4.28 (2H, t), 7.37 (5H, m)
4	55.7	77–79	79.86 80.25	9.05 8.60	4.86 5.19	$C_{18}H_{23}NO$	1.59 (6H, m), 2.59 (4H, t), 3.41 (3H, m), 3.41 (2H, t), 4.36 (2H, d), 6,28÷6.91 (2H, m), 7.5 (5H, m)
5	60.0	110–111	74.89 75.24	8.21 7.80	4.86 5.16	$C_{17}H_{21}NO_2$	2.65 (4H, t), 3.45 (2H, t), 3.79 (4H, t), 4.36 (2H, t),4.38 (2H, d), 6,24÷6.91 (2H, m), 7.47 (5H, m)
6	56.0	92–94	80.39 80.86	8.35 7.91	4.83 5.23	$C_{18}H_{21}NO$	1.68 (6H, m), 2.62 (4H, t), 3.42 (2H, t), 4.46 (2H, t), 4.6 (2H,s), 7.52 (5H, m)
7	53.5	124–125	75.57 75.81	7.37 7.11	4.95 5.20	$C_{17}H_{19}NO_2$	2.64 (2H, m), 3.47 (2H, t), 3.74 (4H, t), 4.48 (2H, t), 4.61 (2H, s), 7.53 (5H, m)
8	45.8	80–82	66.29 66.36	8.03 7.59	4.05 4.38	$C_{17}H_{23}NO_3$	2.63 (4H, t), 3.41 (2H, t), 3.79 (4H, t), 3.81 (4H,t), 4.35 (2H, t), 4.68 (2H, s), 7.46 (5H, m)
9	62.0	_	79.01 79.32	8.26 8.04	3.61 3.85	$C_{24}H_{29}NO_2$	1.59 (6H, m), 2.59 (4H, t), 3.41 (2H, t), 3.80 (4H,m), 4.36(2H,t), 5.63 (1H,s), 7.46 (10H,m)
10	41.5	_	75.53 75.71	9.27 9.02	4.35 4.64	$C_{19}H_{27}NO_2$	1.61 (6H, m), 2.01 (2H, q, 3.60 (4H, t), 3.40 (2H, t), 3.68 (2H, t), 3.75 (2H, t), 4.28 (2H, t), 4.65 (2H, s), 7.48 (5H, s)
11	62.0	_	75.95 75.73	7.70 7.61	3.69 3.85	$C_{24}H_{29}NO_3$	2.02 (2H, q), 2.56 (4H, t), 3.40 (2H, t), 3.67 (4H, t), 3.77 (4H, t), 4.28 (2H, t), 5.55 (1H, s), 7.49 (10H, m)

oxyalkyne and 0.06 mol of corresponding amine was added drop by drop during an hour at a temperature of ~20 °C to 150 ml of benzene while stirring. Then, during the synthesis of **4–7** the temperature of the reaction mixture was gradually increased to 50 °C and then stirred for ~10 hours; the remaining amines are stirred for ~12 hours at a temperature of 60 °C. After the reaction completed the mixture was cooled to 20 °C and washed with saturated NH_4Cl aqueous solution and with water. 0.06 mol of diluted HCl (~10%) was poured into the benzene solution, then 20 ml of water was added; 10% of NaOH was then added to the aqueous solution (separated and washed with 50 ml of benzene) until pH ≈ 8 and then extracted with 150 ml of benzene. The benzene solution is washed with water until pH ≈ 7 and dried with $MgSO_4$; after the solvent was distilled the product was further dried in vacuum. If after the ^{1}H NMR spectrum was recorded in deuterated acetone it appeared that the product was not pure, then it was cleaned again using HCl and NaOH solutions, and only then the element analysis of the product was carried out. Hydrochlorides of some amines were synthesised by treating their solutions in ethyl alcohol with conc. HCl and by recrystallising the oily mass from the mixture of absolute ethyl alcohol and absolute ethyl ether. Information about the obtained compounds is provided in Table **1**.

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