Lipophilic Heterocycles. Convenient Synthesis of Long-Chain Alkyl Heteroaryl Ethers using Potassium Hydroxide in Dimethyl Sulfoxide

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Ethers of aliphatic alcohols with heterocyclic hydroxy compounds can be prepared by the Williamson synthesis[1]. Either an aromatic halide and an alkoxide or a phenoxide and an alkyl halide can be used as starting materials[2]. In the latter case, alkylation of a heterocyclic N-atom may occur as a side reaction. On the other hand, preparation of the anion of long-chain alcohols is difficult. In these cases, the use of powdered sodium or sodium-potassium alloy is required[1].

We present here a simple method for the preparation of ethers of aromatic and heterocyclic hydroxy compounds with long-chain saturated alcohols using the system potassium hydroxide in dimethyl sulfoxide.

As compared with the usually polar methyl and ethyl ethers of heterocyclic hydroxy compounds, the C_{10}—C_{16} ethers are more lipophilic and can probably pass cell membranes more easily. Physiological properties different from those of the methyl and ethyl ethers have also been found for a phenyl ether[3].

Potassium hydroxide in dimethyl sulfoxide has been shown to be a useful reagent for *O*-methylation of hydroxypyridines and hydroxyquinolines[4]. We have used this system to effect the nucleophilic substitution of a Cl-atom on aromatic and heterocyclic systems, as shown in the following schemes.

The reaction is carried out at room temperature or at a maximum temperature of 50 °C using freshly powdered potassium hydroxide in commercial dimethyl sulfoxide[4]. The use of sodium hydroxide in dimethyl sulfoxide affords less satisfactory results[5].

Table. Alkyl Aryl/Heteroaryl Ethers prepared

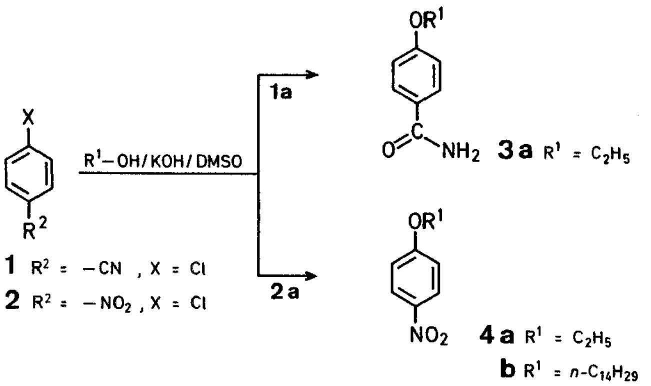
Product	Reaction Time [h] and Temperature [°C]	Yield [%]	m.p. or b.p. [°C]	Molecular formula[a] or Lit. Data [°C]	I.R. (KBr)[b] ν [cm^{-1}]	^{1}H-N.M.R. (DMSO-d_6/TMS$_{int}$)[c] δ [ppm]
3a	2,50°	53	141° (ethanol)	141°[9]		
4a	3,50°	71	57–58° (ethanol)	57–58°[10]		
4b	2,50°	47	55–56° (ethanol)	59.5–60.5°[3]	2920, 2860, 1610, 1595	(in $CDCl_3$): 0.9 (m, 3H); 1.25 (m, 24H); 4.03 (t, 2H, J = 8 Hz); 6.9 (m, 2H); 8.0 (m, 2H)
7a	6,50°	81	235–236° (ethanol)	235–237°[11]	3420, 3330, 3230, 2980, 2220, 1640, 1580	1.34 (t, 3H, J = 8 Hz); 2.10 (s, 3H); 4.37 (q, 2H, J = 8 Hz); 7.75 (s, 2H)
7b	5,50°	27	138° (ethanol)	$C_{22}H_{34}N_4O$ (370.5)	3440, 3340, 3240, 2920, 2860, 2220, 1640, 1580	0.8 (m, 3H); 1.2 (m, 22H); 2.42 (s, 3H); 4.33 (t, 3H); 7.80 (s, 2H)
8a	0.1,50°	43	215° (dec, acetone/H_2O)	200–210°[7]	3380, 3340, 3225, 2240, 1685, 1660	1.35 (t, 3H, J = 8 Hz); 4.42 (q, 2H, J = 8 Hz); 8.45 (s, 2H)
8b	3,20°	32	171–173° (ethanol)	$C_{18}H_{23}N_5O$ (324.4)	3410, 3340, 3240, 2925, 2860, 2230, 1655, 1585	0.8 (m, 3H); 1.23 (m, 16H); 4.31 (t, 2H, J = 8 Hz); 8.45 (s, 2H)
8c	0.1,20°	39	263° (dec, acetone/H_2O)	$C_9H_8N_4O_2$ (204.2)	3430, 3320, 3280, 3220, 2230, 1740, 1675, 1630, 1585	1.34 (t, 3H, J = 8 Hz); 4.40 (q, 2H, J = 8 Hz); 7.69 (s, 2H); 9.60 (s, 1H)
10a	1,50°	65	221–222° (methanol)	221–222°[12]	3340, 3150, 2240, 1675, 1610	3.83 (s, 3H); 7.73 (s, 2H) 8.40 (s, 1H)
10b	1,50°	61	183–184° (ethanol)	$C_7H_8N_4O$ (164.2)	3280, 3240, 2215, 1665, 1590	1.30 (t, 3H, J = 8 Hz); 4.27 (q, 2H, J = 8 Hz); 7.66 (s, 2h); 8.40 (s, 1H)
10c	48,20°	52	146–147° (methanol)	$C_9H_{12}N_4O$ (192.2)	3380, 3165, 2230, 1665, 1595	0.90 (t, 3H, J = 8 Hz); 1.5 (m, 4H); 4.21 (t, 2H, J = 8 Hz); 7.68 (s, 2H); 8.36 (s, 1H)
10d	50, 20°	48	112–113° (methanol)	$C_{11}H_{16}N_4O$ (220.3)	3370, 3180, 2960, 2930, 2860, 2240, 1670, 1600	0.9 (m, 3H); 1.35 (m, 8H); 4.25 (t, 2H, J = 8 Hz); 7.77 (s, 2H); 8.49 (s, 1H)
10e	50,20°	46	125–127° (methanol)	$C_{15}H_{24}N_4O$ (276.4)	3390, 3190, 2930, 2860, 2230, 1650, 1595	(in $CDCl_3$): 1.34 (m, 20H); 4.35 (t, 2H, J = 8 Hz); 5.72 (s, 2H); 8.39 (s, 1H)
10f	48,50°	34	121–122° (ethanol)	$C_{21}H_{36}N_4O$ (360.5)	3420, 3120, 2920, 2860, 2225, 1665, 1590, 1555	1.25 (m, 31H); 4.28 (t, 2H, J = 8 Hz); 7.80 (s, 2H); 8.52 (s, 1H)
10g	50,20°	8	174° (methanol)	$C_{11}H_{14}N_4O$ (218.3)	3380, 3180, 2940, 2860, 2230, 1655, 1595	1.4 (m, 10H); 4.85 (m, 1H); 7.62 (s, 2H); 8.33 (s, 1H)
10h	45,20°	6	160–162° (methanol)	$C_8H_{10}N_4O$ (178.2)	3475, 3140, 2290, 2235, 1680, 1600	1.25 (d, 6H, J = 7 Hz); 5.15 (q, 1H, J = 7 Hz); 7.70 (s, 2H); 8.43 (s, 1H)
10i	1,50°	15	225° (dec, DMF/H_2O)	$C_5H_4N_4O.H_2O$ (154.1)	3470, 3290, 3140, 2210, 1720, 1670, 1650, 1610	7.37 (s, 2H); 8.97 (s, 1H)
12a	2,50°	62	b.p. 266°	b.p. 266°[13]		1.29 (t, 3H, J = 8 Hz); 4.43 (q, 2H, J = 8 Hz); 6.90 (d, 1H, J = 9 Hz); 7.8 (m, 5H)
12b	2.8,50°	86	31–32° (methanol)	$C_{23}H_{35}NO$ (341.6)	2930, 2860, 1625, 1610	(in CCl_4): 0.9 (m, 3H); 1.24 (m, 24H); 4.41 (t, 2H, J = 8 Hz); 6.77 (d, 1H, J = 9 Hz); 7.45 (m, 5H)

[a] The microanalyses (performed on a Carlo Erba Analyzer 1106) were in satisfactory agreement with the calculated values: C, ±0.36; H, ±0.20; N, ±0.34.

[b] The I.R. spectra were recorded on a Perkin Elmer 298 spectrophotometer.

[c] The ^{1}H-N.M.R. spectra were measured on a Varian EM 360 A spectrometer.

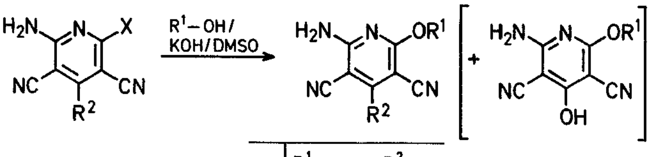
For the preparation of simple ethers, the above method is not better than the standard procedure using alkoxide in the corresponding alcohol. Thus, for example, the yield of ethyl ether **10b** is 61% by our method and 69% by the alkoxide/alcohol method. With secondary alcohols, the yields obtained by our method are not satisfactory (e.g., **10g, h**). On the other hand, our method gives satisfactory yields of ethers derived from higher primary alcohols (see Table).



1 $R^2 = -CN$, X = Cl
2 $R^2 = -NO_2$, X = Cl

3a $R^1 = C_2H_5$

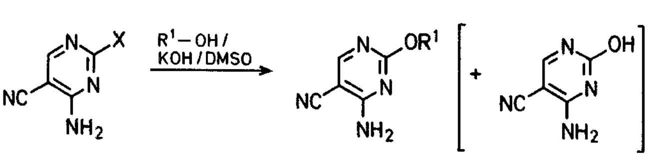
4a $R^1 = C_2H_5$
b $R^1 = n\text{-}C_{14}H_{29}$



5 $R^2 = CH_3$, X = Cl
6 $R^2 = CN$, X = Cl

	R^1	R^2
7a	C_2H_5	CH_3
7b	$n\text{-}C_{14}H_{29}$	CH_3
8a	C_2H_5	CN
8b	$n\text{-}C_{10}H_{21}$	CN

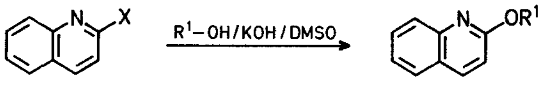
8c $R^1 = C_2H_5$



9 X = Cl
[**9′** X = Br]

10	R^1	10	R^1
a	CH_3	**e**	$n\text{-}C_{10}H_{21}$
b	C_2H_5	**f**	$n\text{-}C_{16}H_{33}$
c	$n\text{-}C_4H_9$	**g**	$c\text{-}C_6H_{11}$
d	$n\text{-}C_6H_{13}$	**h**	$i\text{-}C_3H_7$

10i



11 X = Cl

12a $R^1 = C_2H_5$
b $R^2 = n\text{-}C_{14}H_{29}$

Under the conditions employed, nitrile groups in the substrate molecule are in general not affected. However, in the case of the tricyano-substituted ether **8b** we could isolate a by-product **8c** in which the 4-cyano group had been replaced by a hydroxy group. On the other hand, the by-products observed in other cases generally are base-soluble phenols generated via hydrolysis of the reactive Cl-substitutent in the substrate. This hydrolysis could be shown to be the main reaction when the bromo derivative **9′** was subjected to the reaction with ethanol under our conditions, the hydroxy compound **10i** being obtained in 52% yield and the ethoxy compound **10b** in only 24% yield.

The reaction of 4-chlorobenzonitrile (**1**) with ethanol/potassium hydroxide in dimethyl sulfoxide affords 4-ethoxybenzamide (**3a**) instead of the expected nitrile. 4-Nitrophenyl tetradecyl ether (**4b**) which is obtained from 4-nitrochlorobenzene (**2**) in nearly 50% yield has previously been prepared from silver 4-nitrophenoxide and 1-iodotetradecane[3]; the amine obtained by reduction of **4b** is bacteriostatic (analogous amines with a chain shorter than C_{12} are less effective).

Alkyl Aryl/Heteroaryl Ethers (3, 4, 7, 8, 10, 12); General Procedure: To a stirred mixture of freshly powdered potassium hydroxide (1.68 g, 30 mmol) and dimethyl sulfoxide (30–50 ml) under nitrogen, the alcohol R^1–OH (30 mmol) is added and stirring is continued for 15 min. Then, the C-chloro compound (**1, 2, 5, 6, 9, 11**; 15 mmol) is added slowly, with cooling in an ice bath if necessary. The mixture is stirred for the time and at the temperature given in the Table. Completion of the reaction is checked by T.L.C. The cooled mixture is poured into ice water (70–100 ml) and this mixture stirred vigorously for 15 min. The precipitate is isolated by suction and washed free of alkali with water. Oily products are extracted with ether (2 × 40 ml), the extract is dried with magnesium sulfate, the solvent is evaporated, and the remaining product purified by distillation. Solid products are recrystallized from the solvents given in the Table. For the isolation of phenolic by-products, the mother liquor of the precipitation is acidified to pH 2–3 with dilute hydrochloric acid, and the precipitate isolated and recrystallized.

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