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ORGANIC SYNTHESES WITHOUT SOLVENT : PREPARATION OF ALKOXYPHTHALIMIDES AND OF ALKOXYLAMINES

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Abstract Alkoxyphthalimides are prepared by alkylation of N-hydroxyphthalimide under solid-liquid phase transfer catalysis without solvent. When conversion of alkoxyphthalimides into alkoxylamines is nearly complete, neat hydrazine hydrate is added at room temperature.

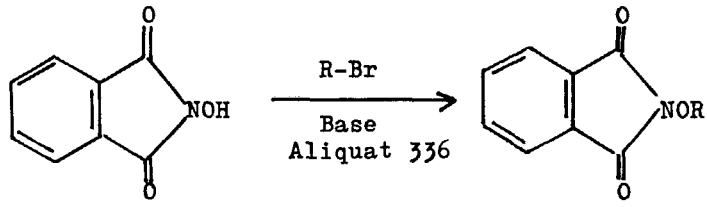
Alkoxylamines 3 are useful intermediates for the preparation of numerous compounds of biological interest [1] and of heterocycles [2-3]. The synthesis of alkoxylamines by alkylation of N-hydroxycarbamates and acid deprotection has been proposed [4] but most of the time 3 is obtained by alkylation of N-hydroxyphthalimide 1 followed by acid or basic hydrolysis of the resulting N-alkoxyphthalimides 2 [5].

The anionic activation of N-hydroxyphthalimide generally requires trialkylamines [5-6] in dipolar aprotic solvents. Liquid-liquid phase transfer catalysis (PTC) has also been proposed but the method seems to be limited to reactive alkylating agents, and, even then, large excesses of alkyl halides are necessary[7]. N-alko-

xyphthalimides 2 have also been obtained by the condensation of 1 and an alcohol in the presence of diethyl azidocarboxylate and triphenylphosphine [8]. In most cases the deprotection step is achieved by refluxing compounds 2 in an ethanolic solution of hydrazine hydrate.

A simple preparation of compounds 2 and 3 is reported herein : Alkoxyphthalimides 2 were formed by solid liquid PTC without added organic solvent. This method has been previously used to achieve alkylations by S_N2 [9] or Michael reactions [10]. The most significant results obtained by alkylation of N-hydroxyphthalimide under solid-liquid PTC conditions are listed in Table I.

Solid potassium carbonate or potassium tert-butoxide were used as bases. Solid potassium hydroxide was also tested but led to the competitive formation of alkylanthranilates. We have verified that no reaction occured in the absence of Aliquat 336 (mostly trioctylmethylammonium chloride).

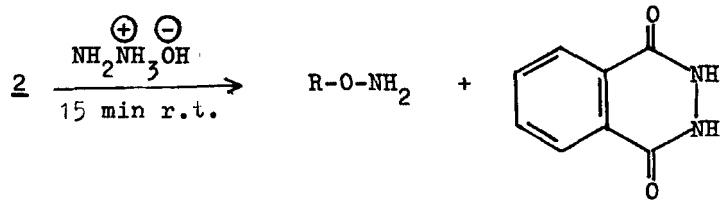


1 2

TABLE I Alkylation of N-hydroxyphthalimides.

2	R	Reaction Conditions	Yield (%)
a	CH_2CCH	20°C, 2h	93
b	$CH_2COOC_2H_5$	20°C, 2h	77
c	$CH_2CHCHCOOCH_3$	20°C, 2h	86
d	$(CH_2)_3COOCH_3$	60°C, 3h	71
e	$n\text{-}C_4H_9$	60°C, 3h	86
f	$n\text{-}C_8H_{17}$	60°C, 3h	65
g	$n\text{-}C_{18}H_{37}$	60°C, 3h	73

In order to avoid any eventual side reaction in the preparation of functionnalized oximes [11], the following mild deprotection process was tried: the alkoxyphthalimides 2 were reacted in the presence of any solvent with a slight excess (5 %) of hydrazine hydrate. The results are gathered in Table II.



3

TABLE II Conversion of alkoxyphthalimides into alkoxylamines

3	Yield (%)	3	Yield (%)
a	95	e	86
b	91	f	81
c	89	g	94
d	93		

Compared to previously known preparations, the proposed synthesis of compounds 2 and 3 offers the following advantages :

- The use of dipolar aprotic solvent is avoided in the alkylation step ;
- The introduction of long chain alkyl groups can be realized with alkylbromides whereas alkyl iodides where previously necessary [12] ;
- The conversion of 2 into 3 is realized under mild conditions and the yield remains good with long chain alkyl substituted alkoxylamines ;
- The whole procedure is rapid and easy to carry out.

EXPERIMENTAL

Melting points were not corrected. The ^{1}H-N.M.R. spectra were recorded on a Varian EM 390 spectrometer. All products gave satisfactory microanalyses.

Alkoxyphthalimides 2a-g ; General Procedure :
A mixture of N-hydroxyphthalimide (1.63 g, 10 mmol), base (see Table I ; 10 mmol) and Aliquat 336 (0.12 g, 0.3 mmol) is vigorously shaken for 15 min at room temperature. The alkylating agent (10 mmol) is added and shaking is restarted at the requisite temperature for 2 h. The mixture is eventually cooled to room temperature, water (10 ml) is added, the solid is filtered and washed with water until washings are no longer red coloured. The solid is dried under vacuum, unreacted long chain alkyl halides ($n\text{-}C_8H_{17}Br$ and $n\text{-}C_{18}H_{37}Br$) are eliminated by trituration of the solid residue in n-hexane. After drying alkoxyphthalimides 2 are recrystallized in ethyl acetate. Physical data of alkoxyphthalimides 2a-g are gathered in Table III.

Alkoxylamines 3a-g ; General Procedure :
A mixture of Alkoxyphthalimides 2a-g (20 mmol) and hydrazine monohydrate (1 ml, 20.5 mmol) is stirred at room temperature for 15 min. Diethyl ether (50 ml) is added and shaking is restarted for 15 min. The solid which separates is filtered and washed with ether (3 x 30 ml). Anhydrous hydrogen chloride is bubbled into the combined ether solutions. The alkoxylamine hydrochlorides are filtered, washed with ether and recrystallized in isopropanol. Physical data of alkoxylamines 3a-g are gathered in Table IV.

TABLE III Physical data of alkoxyphthalimides 2a-g.

2	Melting point (°C)	^{1}H-N.M.R. ($CDCl_3$ unless otherwise stated, TMS) (δ ppm)
a	147-150, Litt.[13] : 150	2.62 (t, 1H, J=2Hz, CH) ; 4.86 (d, 2H, J=2Hz, CH_2) ; 7.78 (s, 4H arom.).
b	96-98, Litt.[5] : 97	1.28 (t, 3H, J=7Hz, CH_3) ; 4.25 (q, 2H, J=7Hz, CH_2CH_3) ; 4.88 (s, (2H, CH_2ON) ; 7.83 (s, 4H arom.).
c	156-157	[a] 3.74 (s, 3H, CH_3) ; 4.97 (dxd, J=5Hz, J=1Hz) ; 6.28 (dxt, 1H, J=16Hz, J=1Hz, $=C<^{CH_2}_{H}$) ; 6.96 (dxt, 1H, J=16Hz, J=5Hz, $=C<^{COOCH_3}_{H}$) ; 7.93 (s, 4H arom.).
d	83	2.18 (q, 2H, J=7Hz, $CH_2CH_2CH_2$) ; 2.47 (t, 2H, J=7Hz, $CH_2C=O$) ; 3.68 (s, 3H, CH_3) ; 4.18 (t, 2H, CH_2ON) ; 7.88 (s, 4H arom.).
e	30, Litt.[6] : 29	0.98 (t, 3H, J=7Hz, CH_3) ; 1.3-1.9 (m, 4H, $CH_2-(CH_2)_2-CH_3$) ; 4.15 (t, 2H, J=7Hz, CH_2ON).
f	56-58	0.92 (t, 3H, J=7Hz, CH_3) ; 1.2-1.9 (m, 12H, $CH_2-(CH_2)_6-CH_3$) ; 4.18 (t, 2H, CH_2ON) ; 7.84 (s, 4H arom)
g	84-87	0.94 (t, 3H, J=7Hz, CH_3) ; 1.2-1.9 (m, 32H, $CH_2-(CH_2)_{16}-CH_3$) ; 4.15 (t, 2H, CH_2ON) ; 7.88 (s, 4H arom)

[a] Solvent DMSO-d_6.

TABLE IV Physical data of alkoxylamines 3a-g.

3	Melting point (°C)	^{1}H-N.M.R. (DMSO-D_6) (δ ppm)
a	163-166, Litt.[14] : 162	2.58 (t, 1H, J=2Hz, CH) ; 4.82 (d, 2H, J=2Hz, CH_2) ; 6.5 (s, 3H, NH_3).
b	224-227, Litt. [5] : 230	1.25 (t, 3H, J=7Hz, CH_3) ; 4.18 (q, 2H, J=7Hz, CH_2CH_3) ; 4.83 (s, 2H, $CH_2C=O$) ; 7.12 (s, 3H, NH_3).
c	194-196	3.78 (s, 3H, CH_3) ; 4.95 (d, 2H, J=3.5Hz, CH_2) ; 6.22 (d, 1H, J=12Hz, $=C<^{CH_2}_{H}$) ; 6.97 (dxt, 1H, J=12Hz, J=3.5Hz, $=C<^{COOCH_3}_{H}$) ; 7.65 (s, 3H, NH_3).
d	158-160	2.08 (p, 2H, J=7Hz, $CH_2CH_2CH_2$) ; 2.47 (t, 2H, J=7Hz, $CH_2C=O$) ; 3.68 (s, 3H, CH_3O) ; 4.18 (t, 2H, J=7Hz, CH_2ON) ; 6.6 (s, 3H, NH_3).
e	153-155, Litt. [5] : 153	0.95 (t, 3H, J=7Hz, CH_3) ; 1.28-1.38 (m, 4H, $(CH_2)_2$) ; 4.07 (t, 2H, J=7Hz, CH_2ON) ; 7.28 (s, 3H, NH_3).
f	148-150 Litt.[12] : 152	0.97 (t, 3H, J=7Hz, CH_3) ; 1.2-1.9 (m, 12H, CH_2-$(CH_2)_6$-CH_3) ; 4.12 (t, 2H, CH_2ON) ; 7.15 (s, 3H, NH_3).
g	142-144	0.92 (t, 3H, J=7Hz, CH_3) ; 1.2-1.9 (m, 32H, CH_2-$(CH_2)_{16}$-CH_3) ; 4.14 (t, 2H, CH_2ON) ; 6.6 (s, 3H, NH_3).

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