Phase-Transfer Catalysis in the *N*-Alkylation of 1,4-Dihydropyridines[1,2]

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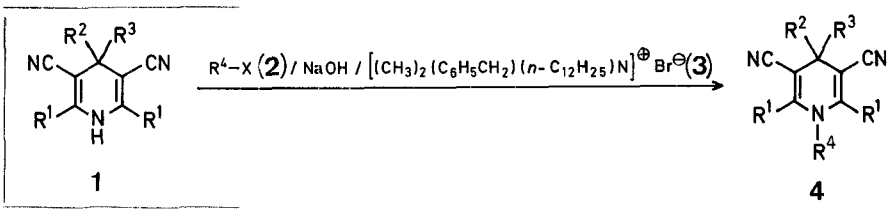
Recent reports on the applications of phase-transfer catalysis[3,4] to the *N*-alkylation of organic substrates have been limited to diphenylhydrazine[5], indole[6], and acetanilide[7].

The use of effective methods for the *N*-alkylation of dihydropyridine derivatives is especially actual because the lower basicity of their heterocyclic nitrogen atoms[8] renders them less reactive towards the usual alkylating agents. The known preparative procedures have therefore been based on the reaction of alkylating agents with dihydropyridine anions generated *in situ* by means of sodium hydride[9–12] or organometallic reagents[10] in aprotic polar solvents such as dimethyl sulfoxide, diemthylformamide, or hexamethylphosphoric triamide. In this paper we wish to report that the use of phase-transfer catalysis enabled us to transform different 3,5-dicyano-1,4-dihydropyridines (**1**) to the corresponding *N*-alkylated products (**4**) by means of alkylating agents (**2**) and catalysts (**3**) in a two-phase system consisting of an aqueous solution and an organic layer.



The results are summarised in the Table. The yields of **4** appear to be satisfactory from the preparative point of view. Thus, the phase-transfer catalysis seems to be advantageous especially for larger scale *N*-alkylations of **1**.

According to our experiments, the formation of **4** does not occur in the absence of quarternary salts **3** in the two-phase system used and only the starting compounds **1** can be isolated unchanged from the organic layer. However, the use of more reactive potassium hydroxide in (one-phase) dimethyl sulfoxide solution leads in some cases to another effective *N*-alkylating procedure from **1** to **4**. In 1973 a similar observation[13] on the *N*-alkylation of indole was published.

N-Alkylation of Substituted 3,5-Dicyano-1,4-dihydropyridines (1); General Procedure Using Phase-Transfer Catalysis:

A mixture of the dihydropyridine derivative (**1**, 0.02 mol), the alkylating agents (**2**, 0.03 mol), catalyst (**3**, 0.002 to 0.01 mol), 50% aqueous sodium hydroxide solution (5 ml) and an appropriate organic solvent (50–70 ml) was heated at 40 to 45° with stirring for 6 h. The organic layer was then separated, washed with saturated aqueous sodium chloride solution, and dried over anhydrous magnesium sulfate. After evaporating off the solvent in vacuo, the residue was recrystallised from an appropriate solvent (active charcoal).

N-Ethylation of 3,5-Dicyano-2,4,4,6-tetramethyl-1,4-dihydropyridine (1a):

Ethyl iodide (0.05 mol) was added in dry nitrogen atmosphere during 20 minutes at 20–30° to a stirred mixture of 3,5-dicyano-2,4,4,6-tetramethyl-1,4-dihydropyridine (**1a**; 0.025 mol), pulverised potassium hydroxide (0.1 mol), and dimethyl sulfoxide (50 ml). After 2 hours the solvent was removed in vacuo and the residue was diluted with water. The crude solid product (yield: 5.0 g, 93%) was recrystalised twice from ethanol (active charcoal) to give **4b**; yield: 3.97 g (74%); m.p. 151–152°; Lit.[10] m.p. 152–153°.

N-Benzylation of 3,5-Dicyano-2,4,4,6-tetramethyl-1,4-dihydropyridine (1a):

The reaction of benzyl bromide (0.05 mol) with 3,5-dicyano-2,4,4,6-tetramethyl-1,4-dihydropyridine (**1a**; 0.025 mol) and potassium hydroxide (0.1 mol) in dimethylformamide (50 ml) was accomplished analogously as cited above at 35–40° for 5 h (after the addition of the alkylating agent during 30 minutes). The reaction mixture gave **4c**; yield: 4.6 g (66%); m.p. 131–132°; Lit.[10] m.p. 133–134°.

Table. *N*-Alkylation of 3,5-Dicyano-1,4-dihydropyridines (**1**) Catalyzed by Benzyldimethyldodecylammonium Bromide (**3**)

Substrate	R^1	R^2	R^3	Alkylating agent **2** R^4—X	Solvent	Product	Yield (%)[a]	m.p. (solvent)	Lit. m.p.
1a	CH_3	CH_3	CH_3	H_3C—J	toluene[b]	**4a**	86	167–168° (C_2H_5OH/H_2O)	169–170°[10]
1a	CH_3	CH_3	CH_3	C_2H_5—J	CH_2Cl_2	**4b**	80	152–153° (C_2H_5OH/H_2O)	152–153°[10]
1a	CH_3	CH_3	CH_3	$C_6H_5CH_2$—Br	C_6H_6	**4c**	86	131–132° (C_2H_5OH/H_2O)	133–134°[10]
1b	CH_3	C_6H_5	H	C_2H_5—J	C_6H_6	**4d**	60	170–171° (C_2H_5OH)	171–172°[11]
1c	4-H_3CO—C_6H_4	CH_3	CH_3	H_3C—J	toluene	**4e**	52	193–194° (C_2H_5OH/H_2O)	–[c]
1d	CH_3	C_2H_5	CH_3	C_2H_5—J	C_6H_6	**4f**	81	121–122° (pet. ether)	–[d]
1e	C_6H_5	C_6H_5	H	H_3C—J	CH_2Cl_2	**4g**	75	226–227° (C_2H_5OH)	222–224°[14]

[a] Yield of isolated products.

[b] Catalysed by ethyltridodecylammonium iodide.

[c] New compound: $C_{24}H_{23}N_3O_2$ (385.5) calc. C 74.78 H 6.01 N 10.90; found 74.80 6.26 10.88

[d] New compound: $C_{14}H_{19}N_3$ (229.3) calc. C 73.32 H 8.35 N 18.33; found 73.30 8.40 18.25

The crude reaction mixtures were analysed by T.L.C. on silica gel with the use of U.V. detection[10].

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