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Application of Phase Transfer Catalysis (PTC) without Solvent in Organic Synthesis. IV [1]

Selective *O*-Alkylation of Hydroxy-phenothiazine and Hydroxy-diphenylamine Derivatives

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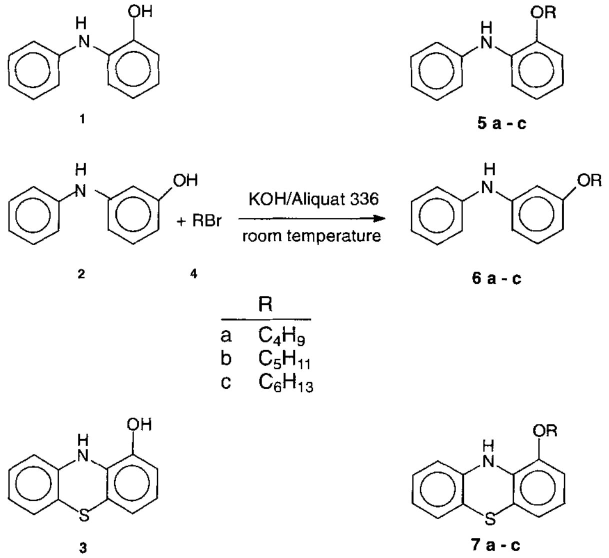
Abstract. The exclusive *O*-alkylation reaction of hydroxy-phenothiazine **3** and hydroxy-diphenylamine derivatives **1** and **2** by PTC without solvent is described.

The reactions in absence of solvent, so called "dry media" reactions, exhibit not only an enhanced reactivity, in very mild experimental conditions, but also give rise to a very interesting selectivity due to the heterogeneous media [2].

Phenothiazine derivatives are of interest because of their well-known pharmacodynamic properties. For that reason we tried to obtain new *O*-alkylated hydroxy-phenothiazines and *O*-alkylated hydroxy-diphenylamines, that are phenothiazine precursors, by direct alkylation of these compounds. It is worth remarking that, to our knowledge, these derivatives were very rarely obtained by direct alkylation until now [3–9].

First attempts to carry out the direct *O*-alkylation of the above mentioned compounds by liquid-liquid PTC failed. We succeed in achieving our goal using a PTC method without solvent according to the following scheme :



Our experimental results are shown in the table.

The mass spectra of compounds **5a–c**, **6a**–**c** and **7a–c** show

Table 1 *O*-Alkylated Phenothiazine and Diphenylamine Derivatives Prepared by PTC without Solvent

Comp.	Reaction time (h)	Yield (%)	*b.p.* (lit. *b.p.*) °C/mm Hg	IR ν_{NH} (cm^{-1})	Mass spectra *m/z*
5a	15	78	180–183/1 (183–85/1 [7])	3215	214 (M$^+$), 185 (M$^+$–56), 184 (M$^+$–57)
5b	13	78	170–172/0.5	3210	255 (M$^+$), 185 (M$^+$–70), 184 (M$^+$–71)
5c	14	80	184–186/0.5	3250	269 (M$^+$), 185 (M$^+$–84), 184 (M$^+$-85)
6a	19	77	164–166/0.2 (160–164/0.2 [7])	3230	214 (M$^+$), 185 (M$^+$–56), 184 (M$^+$–57)
6b	20	75	173–175/0.2	3210	255 (M$^+$), 185 (M$^+$–70), 184 (M$^+$–71)
6c	20	70	190–193/0.2	3215	269 (M$^+$), 185 (M$^+$–84), 184 (M$^+$–85)
7a [a])	7	80	–	3210	271 (M$^+$), 215 (M$^+$–56), 214 (M$^+$–57)
7b [a])	9	78	–	3220	285 (M$^+$), 215 (M$^+$–70), 214 (M$^+$–71)
7c [a])	10	80	–	3225	299 (M$^+$), 215 (M$^+$–84), 214 (M$^+$–85)

[a]) Isolated as oil that undergoes decomposition during vacuum distillation.

that these derivatives undergo fragmentation that are characteristic of ethers (see table):

a) O–C alkyl bond cleavage [*e.g.* for **5a** *m/z* 148 (M^{+}– 57)]

b) McLafferty rearrangement [*e.g.* for **5a** *m/z* 185 (M^{+} – 56)]

The reaction was monitored by TLC until the substrate disappeared. The yields correspond to pure compounds obtained after work-up of the raw reaction products.

The alkylation reaction is selective, only *O*-alkylation reaction took place because the pure compounds (TLC only one spot) exhibit ν_{N-H} vibration in IR spectra (see Table).

The PTC method without solvent allows us to obtain *O*-alkylated products with good yields and under very mild conditions.

Due to the fact that the results of other authors [10–12] in *O*-alkylation of organic substrates are also excellent, it seems that this procedure is one of the best method for carrying out this synthesis.

Experimental

TLC analyses were run on plates covered with silica gel, eluted with toluene-acetone (4:1,v/v). The elemental analyses of new compounds were within ± 0.4% of the theoretical values. IR spectra were recorded in nujol with an Unicam SP 200 G spectrophotometer. Mass spectra were recorded on a double focusing Varian Matt 311 instrument with an electron impact source of 70 eV and 300 μ A.

O-Alkylation of the Hydroxy-derivatives 1–3 (General Procedure)

The corresponding hydroxy-derivative (0.3 mmol), solid potassium hydroxide powder (2 mmol) and Aliquat 336 (0.5 g, 0.124 mmol) were well mixed with magnetically stirring and subsequently the alkylating agent (0.3 mmol) was added. The reaction mixture was stirred at room temperature for the appropriate time (see Table) and after that it was diluted with toluene, the mixture was well washed with water, the organic layer separated and toluene evaporated *in vacuo*. Alkoxy-diphenylamine derivatives were purified by vacuum distillation (see Table). Phenothiazine derivatives were purified by column chromatography (silica gel, toluene : acetone = 4:1 v/v as eluent) and isolated as oils.

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