Phase Transfer Catalysis under Ultrasound. Alkylation of Isoquinoline Reissert Compound

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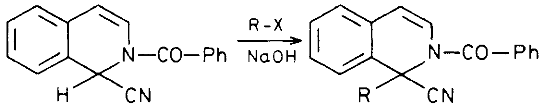
Comparative experiments showed that ultrasonic irradiation improved the yields and reduced the reaction times in the phase-transfer catalysed alkylation of the Reissert compound 2-benzoyl-1,2-dihydroisoquinoline-1-carbonitrile.

The synthetic applications of ultrasonic (u.s.) radiation have attracted increasing interest recently,[1,2] particularly in heterogeneous systems, and the applications of phase-transfer catalysis (p.t.c.) are also still being developed. Most reports on p.t.c. reactions do not emphasize the need for rapid stirring,[3,4] but, sometimes it has proved difficult to obtain reproducible results using 50% aqueous NaOH[5—7] owing to its viscosity. Some authors have recommended minimum stirring speeds for liquid–liquid and solid–liquid reactions.[4] We have attempted to overcome these problems by a combination of u.s. and p.t.c. techniques, as part of our current systematic investigation into the effects of u.s. radiation on p.t.c. reactions. Previous u.s. experiments by Tomoi and Ford[8] on three-phase systems did not give positive results.

We now report the effects of u.s. radiation on the alkylation [reaction (1)] of the isoquinoline Reissert compound 2-benzoyl-1,2-dihydroisoquinoline-1-carbonitrile, a well known procedure for the preparation of 1-substituted iso-



(1)

Table 1. Alkylation of 2-benzoyl-1,2-dihydroisoquine-1-carbonitrile.

				% Yield[b]			
Expt.	R	X	Method[a]	U.s.[c]	P.t.c.[d]	P.t.c.–u.s.[e]	M.p. (t °C)
i	$PhCH_2$	Cl	A	—	50	60[f]	126[h]
ii	o-$ClC_6H_4CH_2$	Cl	A	—	80	88	167
iii	p-$ClC_6H_4CH_2$	Cl	A	—	26	50	139—140
iv	p-$NO_2C_6H_4CH_2$	Br	B		40	50	194—195
v	p-$NO_2C_6H_4CH_2$	Cl	B		46	76	
vi	$2,4$-$(NO_2)_2C_6H_3$	Cl	B		64	66	164—165[i,j]
vii	EtO_2CCH_2	Br	A		45	24[g]	133—134[j]

[a] Method A (ref. 11): typically a suspension of the Reissert compound (5.7 mmol), the halide RX (8.2 mmol), and triethylbenzylammonium chloride (13 mg) in 50% aqueous NaOH (2.5 ml) was mechanically stirred and sonicated at room temperature for 20—25 min; the temperature rose to 25—30 °C. The suspension was filtered, and the solid washed with water and crystallized, normally from methanol. Method B (ref. 12): typically, a mixture of the Reissert compound (5.7 mmol), the halide RX (6 mmol), hexadecyltrimethylammonium bromide (33 mg), toluene (20 ml), and 50% aqueous NaOH (3.3 ml) was mechanically stirred and sonicated for 20—25 min at room temperature; the temperature rose to 25—30 °C. The mixture was acidified to pH 6 (5% H_2SO_4) and the product extracted into toluene. The dried extract was concentrated and the residue recrystallized, normally from n-butanol. [b] Yield of pure, isolated product; all new compounds gave satisfactory microanalytical and spectroscopic data. [c] U.s. alone; methods A and B without catalyst. After sonication for 25 min, the Reissert compound was recovered (i, 80%; ii, 90; iii, 92%). [d] P.t.c. alone; reaction for 2 h. [e] P.t.c.–u.s. combined; reaction for 20 min unless indicated otherwise. [f] Reaction for 25 min. [g] Reaction for 45 min. [h] Lit.[11] m.p. 129 °C. [i] Lit.[14] m.p. 164—165 °C. [j] From absolute ethanol.

quinolines[9,10] to which p.t.c. techniques have been applied with great success. The results are in Table 1.† The reactions were performed in the manner reported,[11,12] and studied: (a) with u.s./without catalyst; (b) with p.t.c./without u.s.; and (c) with u.s./with p.t.c. Experiments performed with u.s. alone showed that the process was a real phase transfer one, and interfacial effects seemed to be of minor importance. As no alkylated products were isolated in the initial examples, only experiments i—iii were studied. Comparison of p.t.c./u.s. and p.t.c. columns in Table 1 shows how u.s. irradiation improved yields in all examples except for experiment vi, in which ester hydrolysis could compete with alkylation of the Reissert anion;[13] the reaction time was reduced from 2 h to *ca.* 25 min.

From the examples studied, chlorides produced the best yields (see experiment iv), and bromides produced lower yields or led to only traces of alkylation (as did 1-bromomethylnaphthalene or *o*-nitrobenzyl bromide). As is usual in many p.t.c. reactions, methyl iodide did not react at all.

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† U.s. irradiations were carried out by immersion of the reaction flask in a Branson 220 Ultrasound Laboratory Cleaner (150 W; 50—60 Hz).

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