Condensation of 2-Benzoyl-1-cyano-1,2dihydroisoguinoline with Electrophilic Alkenes Under Phase-transfer Catalytic (PTC) Conditions*

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Condensation of Reissert compound 1 with electrophilic alkenes 2 carried out in the presence of 50% aqueous sodium hydroxide and benzyltriethylammonium chloride (TEBAC) as a catalyst, affords 1-(2-substituted-ethyl)isoquinolines 3 and/or 4.

Alkylation^{1,2} of 2-benzoyl-1-cyano-1,2-dihydroisoquinoline² (isoquinoline Reissert compound) $\mathbf{1}$ and its condensation^{2,3} with aldehydes or ketones can be conveniently and efficiently carried out in the presence of concentrated aqueous alkali-metal hydroxides and a quaternary ammonium salt as a catalyst (phase-transfer catalysis, PTC⁴⁻⁷). On the other hand, application of PTC for synthetically useful reactions of nitrile 1 with electrophilic alkenes has not been described, but these processes were conducted with



Scheme 1

Reaction of 1 with electrophilic alkenes 2 Table 1



PhLi in ethereal solvents^{8–11} or with Bu^tOK in DMSO,¹² to give the products in good to low yield (Scheme 1).

Now we report that a simple stirring of nitrile 1, slight excess of electrophilic alkene 2, benzyltriethylammonium chloride (TEBAC) as a catalyst (5 mol%), and 50% aqueous sodium hydroxide, in benzene or acetonitrile, at 20-30 °C, resulted in the formation of products 4 or their mixtures with 3 (Scheme 2, Tables 1 and 2).

Analysis of the crude reaction products by ¹H NMR spectroscopy reveals that the use of acrylates 2a-c resulted

Entry	2, 3, 4		Desetien	Product, yield (%)		
	R	Z	time/h	3 (mp °C)	4 (mp °C)	
1 ^a 2 ^a 3 ^a 4 5 6 ^c 7 8	a, H b, H c, H d, Me e, Me f, H g, Me h, H	$\begin{array}{c} CO_2Me\\ CO_2Pr^i\\ CO_2Bu^t\\ CO_2Me\\ CO_2Bu^n\\ CN\\ CN\\ SO_2Ph \end{array}$	2.0 3.5 2.0 2.0 6.0 2.0 1.0 2.0	a , 42 (132–134) b , 73 (71–72) c , 44 (64–66) — — —	a ^b , — b , oil c , oil d , 56 (88–90) e , 47 (oil) f , 65 (89–91) g , 53 (62–64) h , 25 (136–137)	

^aRatio of **3**:4 determined by ¹H NMR spectra in crude reaction mixtures: **3a**: **4a** \approx 3.3:1; **3b**: **4b** \approx 5.0:1; **3c**: **4c** \approx 3.8:1. ^bAnalytical sample was not isolated. ^cIn MeCN, other reactions in benzene.

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in the formation of mixtures of 3a-c and 4a-c in which the former prevail. Pure products 3a-c were easily isolated by crystallization, while separation of analytical samples of 4b, c required the use of column chromatography. Particularly

^{*}This is a Short Paper as defined in the Instructions for Authors, Section 5.0 [see J. Chem. Research (S), 1998, Issue 1]; there is therefore no corresponding material in J. Chem. Research (M).

Table 2	Proton	NMR	data	of	products	3 and 4	1
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Product	δ_{H} (CDCl ₃), J/Hz
3a	3.69 (s, 3 H, CH ₃), 4.06, 4.10 (part AB of ABX, J _{AB} ≈17.2, 2 H, CH ₂), 5.58 (part X of ABX, J _{AX} ≈9.0, J _{BX} ≈5.0, 1 H, CH),
3b	7.45–7.82 (m, / H, ArH), 8.12–8.26 (m, 4 H, ArH) 1.10 and 1.12 [two d, $J \approx 6.3$, 6 H together, C(CH ₃) ₂], 4.05 (d, $J \approx 7.1$, 2 H, CH ₂), 4.99 (sep, $J \approx 6.3$, 1 H, CH), 5.50 (t, $J \approx 7.1$, 1 H, CH) – 7.1 1 H, CH) – 7.1 (H, CH) – 7.1
3c	$(1, 3 \approx 7.1, 14, -7.8)$ (m, 7.44–7.80 (m, 7.11, Arr), 8.10–8.28 (m, 4.11, Arr) 1.31 [s, 9 H, C(CH ₃) ₃], 4.00, 4.05 (part AB of ABX, $J_{AB}\approx$ 16.7, 2 H, CH ₂), 5.44 (part X of ABX, $J_{AX}\approx$ 7.7, $J_{BX}\approx$ 6.6, 1 H, CH), 7.44–7.84 (m, 7 H, ArH), 8.10–8.28 (m, 4 H, ArH)
4a ^ª 4b	2.96–3.04 (m, 2 H, CH ₂), 3.61–3.69 (m, 2 H, CH ₂), 3.69 (s, 3 H, CH ₃), ArH overlapped with those of 3a 1.19 [d, $J \approx 6.3$, 6 H, C(CH ₃) ₂], 2.89–2.97 (m, 2 H, CH ₂), 3.58–3.66 (m, 2 H, CH ₂), 5.02 (sep, $J \approx 6.3$, 1 H, CH), 7.48–7.81 (m, 4 H, ArH) 8.17 (dm, $I \approx 7.8$ 1 H, ArH) 8.39 (d, $I \approx 5.7$ 1 H, ArH)
4c	1.41 [s, 9 H, C(CH ₃) ₃], 2.83–2.91 (m, 2 H, CH ₂), 3.54–3.62 (m, 2 H, CH ₂), 7.46–7.80 (m, 4 H, ArH), 8.16 (dm, $J \approx 8.0$, 1 H, ArH). 8.40 (d. $J \approx 5.7$, 1 H, ArH)
4d	1.29 (d, J ≈ 6.8, CH ₃), 3.24–3.39 (m, 2 H, CH ₂), 3.36 (s, 3 H, CH ₃ O), 3.70–3.84 (m, 1 H, CH), 7.51 (d, J ≈ 5.5, 1 H, ArH), 7.55–7.83 (m, 3 H, ArH), 8.17 (dm, J ≈ 8.0, 1 H, ArH), 8.42 (d, J ≈ 5.7, 1 H, ArH)
4e	0.85 (t, $J \approx 7.0$, 3 H, CH ₃), 1.15–1.60 and 1.30 (m and d, $J \approx 6.0$, 7 H, CH ₂ CH ₂ and CH ₃ CH), 3.20–3.40 (m, 2 H, CH ₂ CH), 3.65–3.85 (m, 1 H, CH), 4.03 (t, $J \approx 6.6$, 2 H, CH ₂ O), 7.47 (d, $J \approx 5.4$, 1 H, ArH), 7.51–7.79 (m, 3 H, ArH), 8.16 (dm, $J \approx 8.4$, 1 H, ArH) 8.42 (d, $J \approx 5.8$ ArH)
4f	3.03–3.13 (m, 2 H, CH ₂), 3.63–3.71 (m, 2 H, CH ₂), 7.50–7.90 (m, 4 H, ArH), 8.09 (dm, $J \approx 8.0$, 1 H, ArH), 8.45 (d $J \approx 6.1$ H ArH)
4g	(a) $(2, 3, 4)$ (b) $(3, 4)$ (c) $(3, 4)$ (
4h	3.80 [br s, 4 H, (CH ₂) ₂], 7.49–7.85 (m, 7 H, ArH), 7.95–8.01 (m, 2 H, ArH), 8.10 (dm, $J \approx 7.9$, 1 H, ArH), 8.31 (d, $J \approx 5.7$, 1 H, ArH)

^aTaken from the spectrum of a mixture of **3a** and **4a**.

significant are the results of reaction of 1 with acrylonitrile **2f**. According to the literature^{8,12} this process affords a benzopyrrocoline derivative, under PTC conditions in benzene a complex mixture of products, while in acetonitrile 1-(2-substituted-ethyl)isoquinoline **4f**, is formed, in good yield.

The mechanistic pathway leading to the formation of **3** comprises a series of anionic reactions visualized in Scheme $2.^2$ A driving force is the regeneration of an aromatic system in the last step. The products **4** are possibly formed either *via* cleavage of **3** or directly from alkylated Reissert compounds; both processes are promoted by base.

In conclusion, the presented work demonstrates the usefulness of PTC for carbanionic reactions of Reissert compound **1** with electrophilic alkenes **2**.

Experimental

Melting points are uncorrected. Proton NMR spectra were measured on a Varian Gemini 200 spectrometer in CDCl₃. Column chromatography was performed on Merck silica gel 60, eluent: hexane–AcOEt (gradient). Reissert compound **1** was prepared by a described procedure.¹³ All reactions were carried out under argon.

General Procedure for the Reaction of 1 with 2.—Nitrile 1 (1.30 g, 5 mmol), benzene (7 cm³), TEBAC (0.057 g, 0.25 mmol) and alkene **2a–e,g,h** (6 mmol) were stirred, then 50% aqueous NaOH (*ca.* 5 cm³) was added dropwise at 20-30 °C. The mixture was stirred for the time indicated in Table 1, diluted with water, the phases were separated, the water phase was extracted with benzene, the organic phases were washed with water and worked-up according to procedure A or B. Procedure A. In the case of reactions 1-4 (Table 1) the organic phases were dried (MgSO₄), the solvent was evaporated and the products were isolated by crystallization (3a-c, 4d) or by column chromatography (**4b**,c). 1-(2-*Benzoyl-2-methoxycarbonyl-ethyl)isoquinoline* (**3a**). (Found: C, 74.88; H, 5.30; N, 4.39. $C_{20}H_{17}NO_3$ requires C, 75.22; H, 5.36; N, 4.38%). 1-(2-*Benzoyl-2*isopropoxycarbonylethyl)isoquinoline (3b). (Found: C, 76.18; H, 5.97; 3.95. C₂₂H₂₁NO₃ requires C, 76.06; H, 6.09; N, 4.03%). 1-(2-Benzoyl-2-tert-butoxycarbonylethyl)isoquinoline (3c). (Found: C, 76.54; H, 6.38; N, 3.80. $C_{23}H_{23}NO_3$ requires C, 76.43; H, 6.41; N, 3.87%). 1-(2-Iso-propoxycarbonylethyl)isoquinoline (4b). (Found: C, 74.24; H, 6.75; N, 5.54. C₁₅H₁₇NO₂ requires C, 74.05; H, 7.04; N, 5.75%). 1-(2-*tert-Butoxycarbonyl)isoquinoline* (**4c**). (Found: C, 74.76; H, 7.35; N, 5.42. C₁₆H₁₉NO₂ requires C, 74.71; H, 7.39; N, 5.45%). 1-(2-Methoxycarbonylpropyl)isoquinoline (4d). (Found: C, 73.01; H, 6.59; N, 5.96. C₁₄H₁₅NO₂ requires C, 73.34; H, 6.59; N, 6.10%). Procedure B: in the case of reactions 5, 7 and 8 (Table 1) the organic phases were extracted with 5% HCl, the combined extracts were made more alkaline with Na2CO3, reextracted

with benzene, the organic phases were washed with brine, dried (MgSO₄), the solvent was evaporated, and the residue was purified by column chromatography (4e) or by crystallization (4g,h). 1-(2-*Butoxycarbonylpropyl)isoquinoline* (4e). (Found: C, 75.28; H, 7.85; N, 5.20. C₁₇H₂₁NO₂ requires C, 75.25; H, 7.79; N, 5.16%). 1-(2-*Cyanopropyl)isoquinoline* (4g). (Found: C, 79.78; H, 6.12; N, 14.22. C₁₃H₁₂N₂ requires C, 79.60; H, 6.12; N, 14.28%). 1-(2-*Phenylsulfonylethyl)isoquinoline* (4h). (Found: C, 68.16; H, 5.07; N, 4.55. C₁₇H₁₅NO₂S requires C, 68.66; H, 5.08; N, 4.71%). 1-(2-*Cyanoethyl)isoquinoline* (4f).—Nitrile 1 (1.30 g, 5 mmol),

1-(2-*Cyanoethyl)isoquinoline* (**4f**).—Nitrile **1** (1.30 g, 5 mmol), acetonitrile (8 cm³), TEBAC (0.057 g, 0.25 mmol), and 50% aqueous NaOH (*ca.* 5 cm³) were stirred, then nitrile **2f** (0.32 g, 6 mmol) was added at 20–30 °C, and the mixture was stirred for 2 h (during stirring *ca.* 10 cm³ of acetonitrile in three portions was added). The mixture was worked-up according to procedure **B**, and the residue was crystallized (EtOH) to give **4f**, 0.59 g, 65% (Found: C, 78.79; H, 5.37; N, 15.39. C₁₂H₁₀N₂ requires C, 79.09; H, 5.53; N, 15.37%).

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