

The Free-Radical Phenylation of Isoquinolinium Cation

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Abstract

Free-radical phenylation of isoquinolinium cation has been effected by photolysis of phenylthallium(III) di(trifluoroacetate) in a trifluoroacetic acid solution of isoquinoline. Analysis (g.l.c. and h.p.l.c.) of the isomeric phenylisoquinoline mixture showed that the dominant product (81.1%) was 1-phenylisoquinoline, in accordance with two published theoretical predictions.

This work was undertaken to establish the relative reactivities of the seven available positions in isoquinolinium cation to radical substitution. Two theoretical predictions have been made, both by Zahradník and Párkányi;¹ one uses free valences, and the other uses superdelocalizabilities. With a Coulomb integral $\delta_N = 2$, the reactivity order based on free valences was

$$1 \gg 3 > 8 > 5 > 4 > 6 > 7$$

while the superdelocalizability order was

$$1 \gg 8 > 3 > 5 > 4 > 6 > 7$$

It is worth noting that these two authors also calculated the reactivity order for the free base, and came close to the order we established experimentally.²

We now report an experimental reactivity order obtained by radical phenylation. Photolysis of phenylthallium(III) di(trifluoroacetate) in a trifluoroacetic acid solution of isoquinoline was reasonably successful, the yields of phenylisoquinolinium cations in two runs being 25 and 33%. Our combined g.l.c. and h.p.l.c. analysis of the mixture of isomeric phenylisoquinolines showed that the 1-position is by far the most reactive, the 1-phenyl isomer being 81.1% of the mixture. No effective distinction was made between the low reactivities at the other six available ring positions (see Table 1).

Our analytical method did not resolve either the mixture of the 5- and 8-phenyl isomers, or that of the 6- and 7-phenyl isomers. Combined yields of these isomer pairs are given in Table 1, and we have no evidence that both members of either pair are actually present. We have commented elsewhere² on the difficulties of separating these isomers.

¹ Zahradník, R., and Párkányi, C., *Collect. Czech. Chem. Commun.*, 1965, **30**, 355.

² Dyll, L. K., and Pullin, C., *Aust. J. Chem.*, 1979, **32**, 345.

The two theoretical predictions of Zahradník and Párkányi are both correct insofar as the 1-position is by far the most reactive towards radical phenylation. The rest of the phenylisoquinoline product (18.9%) is divided rather evenly between the six available isomers, and provides no basis for discriminating between the two theoretical predictions. These predictions refer to relative ease of formation of radical adduct at the nuclear positions of isoquinoline. Thus, small differences in yields of isomeric phenylisoquinolines are not useful in a situation where the relative extents of radical adduct partition between phenylisoquinoline, dimer and phenyldihydroisoquinoline³ are unknown.

Table 1. Isomer distribution in free-radical phenylation of isoquinolinium cation

The percentage isomer ratios quoted for each run are the averages of triplicate analyses. Errors quoted are average errors

	1-Ph	3-Ph	4-Ph	(5+8)-Ph	(6+7)-Ph
Run 1	79.4±1.2	2.4±0.3	1.9±0.1	8.9±0.2	7.4±0.3
Run 2	82.8±0.8	2.6±0.1	2.3±0.1	6.5±0.5	5.9±0.2
Average of runs 1 and 2	81.1±1.7	2.5±0.1	2.1±0.2	7.7±1.2	6.7±0.8

The free-radical benzylation of isoquinolinium cation has been reported by Bass and Nababsing,⁴ using radicals derived from pyrolysis both of dibenzylmercury(II) at 190–195° and of lead(IV) tetra(phenylacetate) at about 95°. The former reagent gave a benzyloisoquinoline fraction with the 1-, 3- and 4-isomers in 98:1:1 ratio, while the other reaction system gave a similar isomer distribution but a very low yield of product. Thus, the phenylation and benzylation studies both concur on the high reactivity of the 1-position. More detailed comparison is not possible because Bass and Nababsing had no samples of 5-, 6-, 7- or 8-benzyloisoquinoline with which to check their g.l.c. analysis.

Experimental

General

G.l.c. analyses were done on a Hewlett–Packard 5721 gas chromatograph with a flame ionization detector. All the analyses used a 1.7 m column (4 mm i.d.) packed with 3% poly(diethylene glycol) adipate on Chromosorb W, operated at 205° and 30 cm³ min⁻¹ flow rate of nitrogen. H.p.l.c. analyses used a Waters ALC-202 instrument fitted with a 6000A solvent delivery system, a 30-cm μ Porasil column (3.9 mm i.d., 2400 theoretical plates), and a u.v. detector set at 254 nm. The eluting solvent was 10% v/v propan-2-ol in hexane, with a flow rate of 2 cm³ min⁻¹.

Materials

Isoquinoline was redistilled, b.p. 55°/0.2 mm, and water was removed with Linde 4A molecular sieves. The purified solvent had m.p. 24.2° (lit. 24°), and g.l.c. detected no impurities above 0.01% level.

Pure samples of all seven phenylisoquinolines were available from previous work.²

Phenylthallium(III) di(trifluoroacetate) was made by the method of McKillop *et al.*,⁵ and had m.p. 189–191° (lit. 184–189°).

³ DeTar, D. F., and Long, R. A., *J. Am. Chem. Soc.*, 1958, **80**, 4742.

⁴ Bass, K. C., and Nababsing, P., *J. Chem. Soc. C*, 1969, 388.

⁵ McKillop, A., Fowler, J. S., Zelesco, M. J., Hunt, J. D., Taylor, E. C., and McGillivray, G., *Tetrahedron Lett.*, 1969, 2423.

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Isoquinoline (25.8 g, 200 mmol) and phenylthallium(III) di(trifluoroacetate) (2.03 g, 4.00 mmol) were dissolved in trifluoroacetic acid (100 cm³) in a Hanovia II photochemical reactor. Nitrogen was bubbled through, and after 15 min the medium-pressure mercury lamp (254–366 nm output) was switched on. Photolysis under N₂ was continued for 45 h at 30°, and the mixture slowly turned brown.

As much trifluoroacetic acid as possible was removed by distillation (water bath/20 mm). The cooled residue was then basified (conc. NH₃), and the isoquinolines were extracted into ether (6 × 100 cm³).

The extracted material was distilled under reduced pressure to remove as much isoquinoline as possible. Three distillation cuts were taken, and each was analysed by g.l.c. to check for codistillation of phenylisoquinolines. There was no codistillation (detection limit 0.02 mg) in the first two cuts (about 20 cm³ total), but the third (about 5 cm³) contained phenylisoquinolines (c. 10 mg). This head fraction could not be analysed by h.p.l.c. (the very high proportion of isoquinoline having a deleterious effect on the resolution), but the g.l.c. trace was indistinguishable from that of the phenylisoquinolines (195–259 mg) in the distillation residue. It is assumed, therefore, that the small loss of product during distillation does not distort the isomer ratio.

The distillation residue (1.1 and 1.3 g in the two runs) was taken up in chloroform and chromatographed over a 10-cm silica column to remove high polymers (c. 5% of its weight). After exhaustive elution with chloroform, the eluted material was subjected to g.l.c. and h.p.l.c. analysis. The yields of phenylisoquinolines were 25 and 33% in the two runs.

Analyses

The gas-liquid chromatogram consisted of four peaks: isoquinoline, 1-phenylisoquinoline (with a trailing edge from the 4-, 5- and 8-phenyl isomers), 3-phenylisoquinoline, and a composite peak of 6- and 7-phenylisoquinoline. Whereas we resolved the 8-phenyl compound from its isomers in our previous work,² we found in the present study that it was not resolved in trial mixtures containing high proportions of 1-phenylisoquinoline.

The trailing edge was resolved graphically to obtain a composite peak area for the 4-, 5- and 8-phenyl isomers, and the yields of phenylisoquinolines were calculated by reference to acridine internal standard. Further analysis on the mixture by h.p.l.c. gave separate peaks for the 1-, 3- and 4-phenyl isomers. Thus, proportions of 1-, 3-, 4-, (5+8)- and (6+7)-phenylisoquinolines were obtained (see Table 1). 3-Phenylisoquinoline was estimated directly by both g.l.c. and h.p.l.c.; we have quoted the h.p.l.c. result. The g.l.c. analyses gave comparable results of lower precision for this isomer.

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