

Isotope Effects in the *p*-Tolylolation of Pyridine

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(Received October 11, 1980)

Synopsis. *p*-Toluoyl peroxide, *p*-iodotoluene, and di-*p*-tolyl sulfone, sulfoxide, and sulfide were photolyzed in an equimolar pyridine-pyridine-*d*₅ mixture to give rise to isomeric *p*-tolylpyridines (α , β , and γ) and their deuterated compounds. Isotopic distribution ratios (Y_H/Y_D) in the isomeric products were determined to be slightly larger than unity.

Vidal and coworkers¹⁾ reported that in the phenylation of 4-methylpyridine with benzoyl peroxide (BPO), the deuterium isotope effect (K_H/K_D) at 2-position of the substrate was somewhat large, 3.7, though that at 3-position was 1.0. In order to check the generality of this tendency, isotope effects in arylation of pyridine with various aryl radical sources were determined. We have found previously²⁾ that *p*-toluoyl peroxide and *p*-iodotoluene, as well as di-*p*-tolyl sulfone, sulfoxide, and sulfide, are photolyzed in pyridine to afford isomeric *p*-tolylpyridines (α , β , and γ , respectively). Here, the isotope effects at the three nuclear positions of pyridine in the free-radical *p*-tolylation with these radical precursors were determined from the isotope distribution ratios (Y_H/Y_D) in the reaction products. The results are summarized in Table 1.

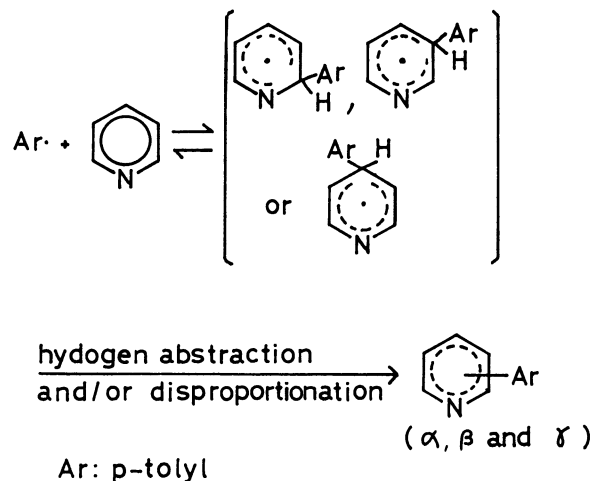
TABLE 1. ISOTOPIC DISTRIBUTION RATIOS (Y_H/Y_D)^{a)} IN ISOMERIC *p*-TOLYLPYRIDINES PRODUCED IN THE REACTION

Run No.	Compound ^{b)}	<i>p</i> -Tolylpyridines		
		α	β	γ
0.015 mol dm ⁻³ Solution				
1	ArSO ₂ Ar	1.06	1.15	1.09
2	ArSOAr	1.08	1.20	1.05
3	ArSAr	1.05	1.35	1.12
4	(ArCO ₂) ₂	1.26	1.27	1.10
5	ArI	1.06	1.19	1.17
0.15 mol dm ⁻³ Solution				
1'	ArSO ₂ Ar	1.09	1.14	1.08
2'	ArSOAr	1.05	1.18	1.07
3'	ArSAr	1.14	1.45	1.11
4'	(ArCO ₂) ₂	1.30	1.30	1.13
5'	ArI	1.06	1.12	1.12

a) Experimental error is ± 0.05 . b) Ar is *p*-tolyl.

As shown in Table 1, only small isotope effects (<1.5) were observed for *p*-tolylation of all positions of pyridine; no case was found in which 2-arylation showed a larger isotope effect than 3-arylation. The difference with the result by Vidal *et al.*¹⁾ appears to depend on the radical sources.

Eliel and coworkers³⁾ reported that, in the phenylation of benzene-*d*₆ with the phenyl radical generated from BPO, the isotope effects ($K_H/K_D=1.0-6.6$) vary with the concentrations of BPO used in the reaction. As Table shows, however, the values of Y_H/Y_D in the present reactions were independent of the concentrations of the radical sources used under our conditions.



On the basis of the mechanism³⁻⁵⁾ proposed for homolytic arylations of aromatic compounds, it seems reasonable to consider that the product isotope effect is observed in either of the following cases: (1) reversal of the addition of *p*-tolyl radicals on pyridine, or (2), disproportionation and combination between *p*-tolyl-dihydropyridyl radicals takes place in competition with the production of the *p*-tolylpyridines. In order to check the reversibility of addition of *p*-tolyl radicals to pyridine, the peroxide and the iodide were allowed to react with a small excess of an equimolar pyridine-pyridine-*d*₅ mixture, and isotopic compositions of the recovered pyridine were compared with those of the starting one. The data in Table 2 reveal that the recovered pyridine was completely unchanged in its isotopic composition within the experimental errors. This finding implies that the values of Y_H/Y_D larger slightly than unity are due to disproportionation and combination between the dihydropyridyl radicals; the disproportionation and combination compete with the hydrogen abstraction from the radical to yield the *p*-tolylpyridines.

TABLE 2. ISOTOPIC COMPOSITIONS OF STARTING^{a)} AND RECOVERED PYRIDINE-PYRIDINE-*d*₅ MIXTURE

Run No. ^{b)}	Compound ^{c)}	Pyridine, (% in mol)	Pyridine- <i>d</i> ₅ , (% in mol)
1	(ArCO ₂) ₂	48.72(48.72)	51.28(51.28)
2	ArI	48.88(48.93)	51.02(51.07)

a) The figures in parentheses indicate those for starting materials. b) In run 1, refluxed for 6 h at boiling point of pyridine. c) Ar is *p*-tolyl.

Table 1 indicates that the values of Y_H/Y_D change with the radical sources to some extent and that in most runs, the values of Y_H/Y_D of β -(*p*-tolyl)pyridines are somewhat larger than those of α - and γ -compounds. The reason for these tendencies is not clear at present.

Experimental

Materials. Commercial available di-*p*-tolyl sulfone and sulfoxide and *p*-iodotoluene were purified by recrystallization and employed for the reaction. *p*-Toluoyl peroxide and authentic *p*-tolylpyridines (α , β , and γ) were prepared and purified by the method²⁾ reported previously. Di-*p*-tolyl sulfide was prepared by the literature method⁶⁾ from reduction of the corresponding sulfoxide with trichlorosilane and recrystallized from ethanol (mp 58.5 °C). Pyridine-pyridine- d_5 (isotope purity 99%) were purchased from E. Merck, Darmstadt, and used for the reaction without further purification.

General Procedure for Photolysis of Radical Sources in Pyridine-Pyridine- d_5 Mixture. The procedure for the sulfone is described here as a typical run. An equimolar pyridine-pyridine- d_5 mixture was prepared and its isotopic content was determined by GC-MS analysis. In the case of 0.15 mol dm⁻³ solution, 0.3 mmol (74.1 mg) of the sulfone was dissolved in 2 ml of the pyridine mixture. Each solution was placed in a Pyrex cylinder, degassed five times, sealed, and irradiated for 200 h at room temperature with a 400 W medium-pressure mercury arc lamp. After evaporating the excess pyridine under a reduced pressure, the residue was subjected to preparative GLC to collect a mixture of isomeric *p*-tolylpyridines produced. The preparative GLC was done on a 3 mm $\times$ 2 m stainless steel column packed with 3% OV-17 on Chromosorb GAW (DMCS), using a JEOL Chromatograph JGC-650. Three isomeric *p*-tolylpyridines were then fractionated from the mixture on a preparative HPLC with THF-hexane (1 : 9 in volume) as a solvent. The instrument used was a Waters Model 6000 A High-Pressure Liquid Chromatograph equipped with a 4 mm $\times$ 30 cm column packed with μ -porasil. Each isomeric *p*-tolylpyridine thus separated was identified by comparison of its retention time with that of authentic specimen, and its deuterium content was determined by GC-MS analysis at 70 eV using a Shimadzu-LKB 9000 Gas Chromatograph-Mass Spectrometer equipped with a 3 mm $\times$ 2 m glass column packed with 0.5% OV-17 on Chromosorb GAW (DMCS). The values of Y_H/Y_D of isomeric *p*-tolylpyridines

were calculated from its parent peak ratios (I_{169}/I_{173}). The parent peak ratios were determined by repeated scans of a range of $m/e=160$ to $m/e=185$. It was ascertained that the parent peak ratios did not change when ionization potentials were changed from 20 to 70 eV.

Isotopic Compositions of Starting and Recovered Pyridine-Pyridine- d_5 Mixture. *p*-Toluoyl peroxide (1.35 g, 5 mmol) was added to an equimolar pyridine-pyridine- d_5 (1 g, 12.5 mmol) mixture. The mixture was refluxed at the boiling point of pyridine until evolution of CO₂ gas ceased. The unchanged pyridine was recovered by distillation and subjected to GC-MS analysis by using a small glass vessel in place of the OV-17 column. Its isotopic composition was calculated from the parent peak ratios (I_{78}/I_{84}) by the technique mentioned above. *p*-Iodotoluene (2.18 g, 10 mmol) was dissolved in 1 g (12.5 mmol) of the equimolar pyridine-pyridine- d_5 mixture. The solution was placed in a small Pyrex cylinder, degassed, and irradiated for 200 h at room temperature with a 400 W medium-pressure mercury arc lamp. After irradiation, the unchanged pyridine was recovered by distillation and analyzed on the GC-MS. Its isotopic composition was calculated in the way described above. After irradiation for 200 h, GLC analysis indicated that 50% of the initially charged iodide remained unchanged.

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