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Received February 14, 1991

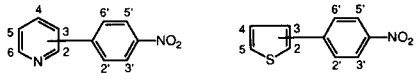
Competitive free radical 4-nitrophenylation of pyridine and thiophene shows a relative reactivity of thiophene:pyridine of 1.3:1 as based on product isolation. A three-center reaction is proposed to account for the predominance of alpha substitution in each system. Column chromatography and ^{1}H nmr are used for separation and identification of products.

J. Heterocyclic Chem., **28**, 1153 (1991).

A number of studies have been reported in the literature on free radical arylation of either pyridine by itself or thiophene by itself. However, we have found no case where arylation of a mixture of pyridine and thiophene has been conducted in an effort to ascertain relative susceptibilities of the two ring systems to free radical substitution. We now report use of the 4-nitrophenyl group as a free radical probe for investigating competitive reactivities of these rings.

Selection of the 4-nitrophenyl radical in our study is particularly pertinent for three main reasons. First, it is known that pyridine and thiophene separately undergo free radical 4-nitrophenylation to yield isolable, crystalline products [2-5]. Second, these colored products are easily detected visually during adsorption chromatography, of value in identification and separation of isomers. Third, the AB system of protons in each 4-nitrophenyl substituent permits facile identification and quantitation by means of ^{1}H nmr of components (especially isomers) present in product mixtures [6,7].

The reaction method we used is that described by Haworth *et al.* [3] for 4-nitrophenylation of pyridine alone, except that we used an excess quantity of a 1:1 molar mixture of pyridine (0.631 mole) and thiophene with an aqueous solution of 4-nitrophenyldiazonium chloride at 40°. On processing the reaction mixture nitrophenylpyridines **1** (13% yield) were isolated from an acidic aqueous solution, while nitrophenylthiophenes **2** (17% yield) were isolated from an organic layer. On this basis it appears that the reactivity of thiophene to 4-nitrophenylation is 1.3 times as great as that of pyridine. Camaggi *et al.* reported that thiophene is 3.6 times as reactive as benzene in 4-nitrophenylation in a competitive reaction [4]. Thus, these crude data indicated an overall relative order of reactivity of thiophene:pyridine:benzene of 3.6:2.8:1. It should be noted, however, that the reactivity ratio which we found for pyridine may be low because some of this solvent-reactant serves to neutralize the excess acid (0.078 mole) used in the diazotization and to convert the diazonium chloride into its hydroxide (0.103 mole) before evolution of nitrogen gas will occur [8]. It is not clear if protonation of some of the pyridine will alter its susceptibility toward free radical substitution [9]. For comparison, one has various reports of relative reactivities of pyridine:benzene of 1.0-1.5:1 in phenylation under non-diazonium conditions [10a].



1

a, 2-isomer
b, 3-isomer
c, 4-isomer

2

a, 2-isomer
b, 3-isomer

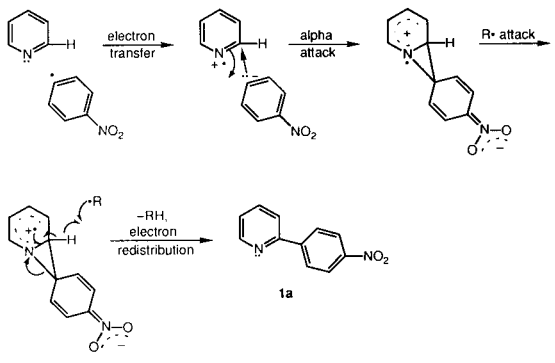
Column chromatgraphy of **1** with silica gel/chloroform gave partial separation into isomeric products in relative yields of 54% for the 2-isomer **1a**, R_f 0.73 (silica gel/ethyl acetate), 30% for the 3-isomer **1b**, R_f 0.44, and 16% for the 4-isomer **1c**, R_f0, *i.e.* an isomeric ratio of **1a:1b:1c** of 1.8:1.0:0.53. This is the same order of positional reactivity as the values of 2.7-2.9:1.0:0.50 found by Haworth *et al.* for 4-nitrophenylation of pyridine alone [3]. Our isomeric ratio agrees much better with data of 46-58%, 28-43%, and 11-21% for isomeric composition of the mixed 2-, 3-, and 4-phenylpyridines which result from various free radical phenylations of pyridine [10b].

Consistent with observations by Gomberg and Bachmann and also by Gokel and coworkers [2,5,11], our nitrophenylthiophene product contains only the 2-isomer **2a**, mp 137-139°. This is slightly different from the results of Camaggi *et al.* [4] who found a ratio of **2a:2b** of 24:1 [14]. While thiophene is, thus, only slightly more reactive than pyridine (if at all), it seems clear that 4-nitrophenylation in the *alpha* position of the ring occurs 2-3 times as frequently in thiophene as it does in pyridine under conditions of competition.

In Scheme 1 we suggest a three-center reaction to account for predominantly alpha substitution into pyridine. First of all, the 4-nitrophenyl radical is highly electrophilic [10c,15]. This radical attacks the heterocycle at the heteroatom, the location of a high concentration of available electrons. For simplicity Scheme 1 indicates a transfer of a non-bonding electron from pyridine to the radical, though one could invoke alternative transfer of a

π electron from the heteroatomic site as well [16]. The resultant 4-nitrophenyl carbanion then attacks the *alpha* position of the heterocyclic cation radical, probably without moving out of the solvent cage [19]. The resultant polarized radical intermediate or transition state proceeds to 2-isomer **1a** by loss of a hydrogen atom at the *alpha* position through attack by an available free radical (R•) from the reaction mixture. Electron redistribution occurs during the final step. The reaction pathway for formation of **2a** would be analogous. However, it is clearly established that thiophene has a lower first ionization potential (8.86 eV) than does pyridine (9.3 ± 0.03 eV) and a lower electrochemical half-wave oxidation potential (1.70 V versus 1.82 V) to form a cation radical [20,21]. Therefore, one might well expect to obtain a greater preference for alpha substitution in thiophene than in pyridine when they react separately and a still larger difference when the two heterocycles compete as in our reaction. For substitution by free radicals in non-alpha positions of pyridine and thiophene the less facile mechanism proposed for aromatic hydrocarbons as substrates seems adequate [9].

Scheme 1



R• is any available free radical in the reaction mixture.

The large differences in R_f values of the isomeric nitrophenylpyridines in the system silica gel/ethyl acetate are of interest. One expects three main structural factors to be involved in adsorption of the molecules to the hydrogen-bonding silica gel, listed in decreasing order to importance: (a) basicity of the pyridine nitrogen atom, as modified by steric hindrance and electronic effect of the 4-nitrophenyl substituent, (b) hydrogen-bonding to the nitro group, and (c) coplanarity or lack of it in the molecule [22,23]. The high R_f value (0.73) for the 2-isomer is ascribed to a low basicity of the pyridine nitrogen and more significantly, to steric hindrance to anchoring of this nitrogen to the surface. The very low R_f value (0) for the 4-isomer may result from coplanarity in the molecule with anchoring at both ends. The 3-isomer should be the most basic, not subject to steric hindrance at the pyridine nitrogen, and probably non-coplanar in solution. Hence, it shows an intermediate R_f value (0.44). These results are somewhat different from those reported for the phenylpyridines with the same tlc system, *i.e.* R_f 0.63 for the 2-isomer (steric hindrance), 0.36 for the 4-isomer (most basic), and 0.27 for the 3-isomer [23].

In the ^{1}H nmr spectra of mixtures of the isomers of **1** it is easy to identify certain patterns for each one. The 4-isomer shows only four signals due to its symmetry. The 3-isomer has a doublet for H-2 which is further downfield by 0.15 ppm than the nearest signal in the others. The 2-isomer shows the combined electron-attracting effects of the nitro group and the pyridine nitrogen atom on the protons in the 4-nitrophenyl group such that the resultant doublets fall close together ($\Delta\delta$ = 0.14 ppm), centered at 8.26 ppm. In the other isomers the doublets are separated by 0.55-0.6 ppm.

EXPERIMENTAL [24]

Competitive 4-Nitrophenylation of Pyridine and Thiophene.

A solution of 4-nitrobenzenediazonium chloride was prepared from 14.2 g (0.103 mole) of 4-nitroaniline, 15 ml (0.181 mole) of concentrated hydrochloric acid, 7.1 g (0.103 mole) of sodium nitrite, and 35 ml of water at 5° following a standard procedure [25]. This solution was added dropwise to a mechanically stirred mixture of 51 ml (0.631 mole) of pyridine and 50 ml (0.631 mole) of thiophene, maintained at 40° over a period of 1.5 hours [3]. The black, tarry mixture was kept at 40° for another hour, allowed to stand at room temperature for 3 days and acidified with 10% aqueous hydrochloric acid. Aqueous and organic (*i.e.* nonaqueous) layers were separated and the former was extracted first with ether and then with chloroform. The organic layer was combined with the organic extracts and this mixture was extracted further with hydrochloric acid. Acidic solutions and extracts were examined for the presence of nitrophenylpyridine (see next paragraph) and the organic mixture was examined for the presence of nitrophenylthiophenes (*vide infra*).

Preceding aqueous acidic solutions were basified to *p* 8 by means of 10% aqueous sodium hydroxide solution to give a brown precipitate, which was extracted into chloroform. Components of the concentrated, dried (sodium sulfate) solution were partially separated by means of chromatography (118 g of silica gel) into three crystalline fractions: (1) red-brown, R_f (silica gel/ethyl acetate) 0.73, 0.79, mp 125-132°; (2) yellow-orange, R_f's 0.73 and 0.44, 0.95 g, mp 112-130°; and (3) yellow, R_f's 0.73, 0.44, and 0, 0.98 g, mp 102-127°. Other fractions were liquids and were discarded as basic byproducts. The ^{1}H nmr spectra showed that fraction 1 was only the 2-isomer **1a**, fraction 2 contained both **1a** and the 3-isomer **1b**, while fraction 3 consisted of **1a**, **1b**, and the 4-isomer **1c**-overall composition 54% **1a**, 30% **1b**, and 16% **1c** for the three fractions, combined yield 2.72 g (13%).

Recrystallization of fraction 1 from 95% ethanol gave tan needles of isomerically pure 2-(4-nitrophenyl)pyridine (**1a**), mp 134-136°, lit. 130-131° [3]; ir: 1516 and 1357 (nitro group), 1317, 859, 786, 739 [26]; ^{1}H nmr: δ 8.758 (d, $J_{5,6}$ = 4.2 Hz, 1 H, H-6), 8.255 (AB system, $J_{2',3'} = J_{5',6'}$ = 8.7 Hz, $\Delta\delta$ = 42.6 Hz, 4 H, H-2', H-3', H-5', H-6'), 7.8-7.9 (m, 2 H, H-3 and H-4), 7.3-7.4 (m, 1 H, H-5); ms: m/e 200 (M^+, 100), 170 (M^+-NO,28), 154 (M^+-NO_2, 87),

142 (170^+ - CO, 28), 127 (154^+-HCN, 53), 115 (142^+ - HCN, 8).

The ^{1}H nmr spectrum of 3-(4-nitrophenyl)pyridine (**1b**) was obtained by difference from fraction 2: δ 8.912 (d, $J_{2,4}$ = 1.5 Hz, 1 H, H-2), 8.714 (d, 1 H, H-6), 8.369 (d, $J_{2',3'} = J_{5',6'}$ = 8.7 Hz, 2 H, H-3' and H-5'), 7.947 (dt, $J_{4,5}$ = 8.0 Hz, $J_{2,4} = J_{4,6}$ = 1.5 Hz, 1 H, H-4), 7.772 (d, 2 H, H-2' and H-6'), 7.463 (dd, $J_{5,6}$ = 5.0 Hz, 1 H, H-5).

The ^{1}H nmr spectrum of 4-(4-nitrophenylpyridine (**1c**) was obtained by difference from fraction 3: δ 8.759 (d, $J_{2,3} = J_{5,6}$ = 5.7 Hz, 2 H, H-2 and H-6), 8.355 (d, $J_{2',3'} = J_{5',6'}$ = 8.7 Hz, 2 H, H-3' and H-5'), 7.809 (d, 2 H, H-2' and H-6'), 7.547 (d, 2 H, H-3 and H-5).

Combined nonaqueous layers (*vide supra*) were dried (sodium sulfate) and evaporated to leave a tarry residue which was evaporatively distilled up to 112° (0.3 mm) to give 3.59 g (17%) of crude nitrophenylthiophene, mp 120-139°. Recrystallization from 95% ethanol yielded greenish yellow flakes of 2-(4-nitrophenyl)thiophene (**2a**), mp 137-139°, lit. 137-138° [2]; ir: 1593, 1508 and 1338 (nitro group), 1319, 849, 750, 729 cm^{-1}; ^{1}H nmr: δ 8.197 (d, $J_{2',3'} = J_{5',6'}$ = 8.7 Hz, 2 H, H-3' and H-5'), 7.702 (d, 2 H, H-2' and H-6'), 7.441 (d, $J_{3,4}$ = 3.6 Hz, 1H, H-3), 7.408 (d, $J_{4,5}$ = 5.1 Hz, 1 H, H-5), 7.118 (dd, 1 H, H-4) [27].

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[7] One might note that these attributes of the 4-nitrophenyl probe do not apply to the simpler phenyl probe. Two of the phenylpyridnes are liquids. Additionally, at least in a solvent of dimethyl sulfoxide (which we did not use in our work), it is claimed that 4-nitrobenzene-diazonium salt reacts in a homolytic process while benzenediazonium salt gives "essentially a heterolytic reaction." [B. Gloor, B. L. Kaul and H. Zollinger, *Helv. Chim. Acta*, **55**, 1596 (1972).]

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