Free Radical 4-Nitrophenylation of Thieno[2,3-*b*]pyridine. Part 1: General Experimental Procedure and Prediction of Isomeric Ratios of Products

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Thieno[2,3-*b*]pyridine (**1**) was warmed at 45 ± 7° with diazotized 4-nitroaniline (**2**) (molar ratio **1**:**2** = 3.6:1) in buffered (sodium acetate-acetic acid) aqueous solution until gas evolution ceased. The reaction mixture was separated into these fractions: (a) water-soluble (discarded), (b) acetone-soluble (tars), (c) ether-soluble, and (d) ether- and chloroform-soluble, but acetone-insoluble (rust-colored solids, *Y*, 12% yield as 4-nitrophenyl-**1** isomers, **3**). Fractional evaporative distillations of (b) and (c) gave recovered **1** (69%) and yellow-red sublimates (*Z*, 20% yield as **3**). *Y* and *Z* were handled separately for isolation and identification of isomers [2]. Three general methods for predicting the isomeric ratios of **3** which one should obtain are presented, *viz*. (1) an amalgamation of reported free-radical phenylation results for quinoline and benzo[*b*]thiophene, (2) calculations of Frontier Radical Densities for positions 2-6 only, and (3) Molecular Orbital calculations for electron densities and superdelocalizabilities for free-radical attack at positions 1-7, as modified by a proposed rearrangement of the attacking group from the heteroatomic N and S positions to adjacent alpha positions.

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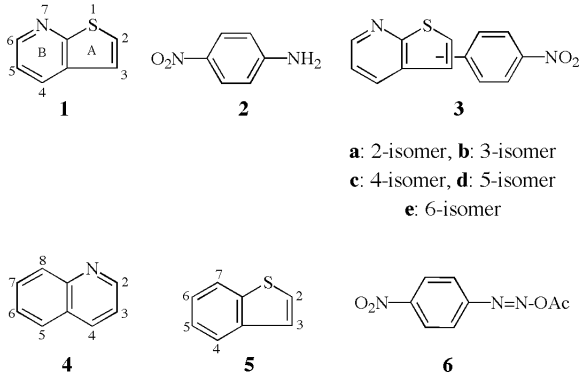
Over a period of years Klemm and coworkers have investigated orientation rules for electrophilic and nucleophilic substitution into thieno[2,3-*b*]pyridine (**1**). In general it was found that electrophilic substitution occurs in the thiophene ring, predominantly at the 3-position. Contrariwise, nucleophilic substitution (as exemplified by reaction with alkyllithiums) occurs in the pyridine ring at the 6-position by a process of addition-elimination. However, lithiation also takes place at the 2-position in the thiophene ring [3]. These results and others led to the interpretation that **1** exhibits a substitution pattern which one would expect for an amalgamation of the patterns for quinoline (**4**) and benzo[*b*]thiophene (**5**) [3,4]. We now report the results of our studies on 4-nitrophenylation of **1** to see if this concept of amalgamation of substitution patterns extends to free radical reactions also.

Predictions on Free radical Substitution into **1**.

Apparently neither quinoline nor benzo[*b*]thiophene has been subjected to free radical 4-nitrophenylation. However, phenylations of both compounds have been described and 2,4-dinitrophenylation of **5** has also been investigated. The most definitive results on the isomeric ratio of phenyl-quinolines formed from reaction of **4** were reported by Vernin, Dou and Metzger who thermally decomposed benzoyl peroxide in excess quinoline at 110° and analyzed the product mixture by gas chromatography plus comparison of effluent fractions with *bona fide* isomerically pure reference samples [5,6]. The isomeric ratio found was 8 (32%) > 5 (22%) > 4 (18%) > 2 (11%) > 3 (6%) ≅ 6 ≅ 7 [5], *i.e*. 35% substitution into the pyridine ring. Treatment of an equimolar mixture of **5** and benzene (both in excess) with *N*-nitrosoacetanilide at 40º for 50 hours plus product analysis as before gave isomeric ratios for phenylbenzo[*b*]thiophenes of 4 (28%) > 3 (21%) = 2 > 7 (18%) > 5 plus 6 (12%) [7], *i.e.* 42% substitution into the thiophene ring or a ratio of 1.2:1 for free-radical substitution into rings A/B expected in **1**. Addition of 2,4-dinitrobenzenediazonium bisulfate to an equimolar amount of **5** in glacial acetic acid, plus stirring at 0° for 52 hours produced crystalline mono- (26%) and bis- (14%) 2,4-dinitrophenyl-**5** derivatives, suggested to result from 2- and 2,3-substitution, respectively, but without experimental verification. In addition, 48% of unreacted **5** was recovered [8]. In **1**, positions corresponding to 7 and 8 in **4** and 7 in **5** are not available for substitution. From analogy with the other preceding data, one would expect free-radical 4-nitrophenylation of **1** to occur in the order 3,4>>2,5,6.

Klemm and Dorsey studied competitive free radical 4-nitrophenylation of pyridine and thiophene under conditions somewhat more acidic than those used in the present study [9]. They found that thiophene is more reactive than pyridine (in a ratio of 1.3:1) and, in agreement with reports from other workers [10], that substitution alpha to the heteroatom predominates in both rings. Klemm

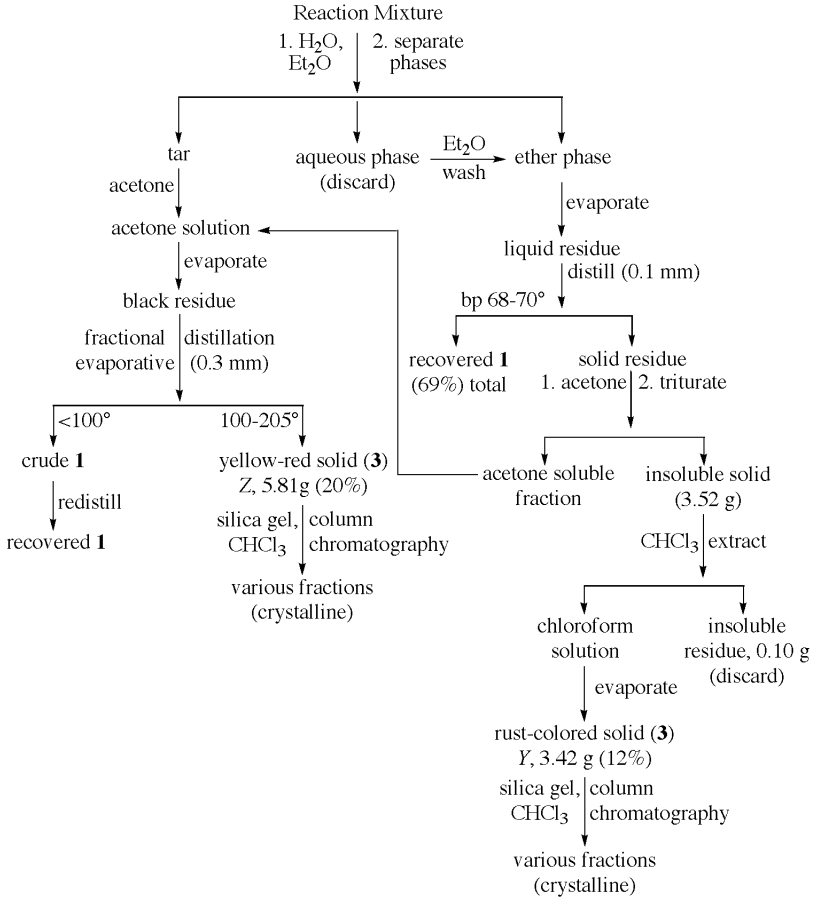


1 **2** **3**

a: 2-isomer, **b**: 3-isomer
c: 4-isomer, **d**: 5-isomer
e: 6-isomer

4 **5** **6**

Scheme 1
Workup of reaction mixture



and Dorsey proposed that attack by an electron-seeking free radical (such as 4-nitrophenyl) will occur preferentially at the heteroatom (S or N), where electrons are readily available, but that a rearrangement of the free radical will occur to an alpha position *via* a three-center reaction mechanism [9,11]. Since the sulfur atom of thiophene should furnish an electron more readily than the nitrogen atom of pyridine one can rationalize the greater reactivity of thiophene. Extending the Klemm-Dorsey concept to compound **1** leads to the prediction that 2-(4-nitrophenyl)-**1** (**3a**) should be the isomer obtained in highest yield.

Holland and Skancke [12] calculated Frontier Radical Densities (FRD) for positions 2-6 of **1** by means of CNDO Molecular Orbital theory. If one assumes that the isomeric yield for each position decreases linearly with its FRD value, then one predicts the quantitative substitution pattern of 3 (32%) > 2 (26%) > 6 (20%) > 4 (15%) > 5 (6%), as shown in Table 1 [13].

Additionally, Holland and Skancke used Pariser-Parr-Pople (PPP) and CNDO MO calculations for predicting free-radical attack on **1** at positions 1-7, as based on the π-and/or σ-electron densities, q_r, where *r* is the position on **1**. Earlier, Klemm and coworkers [14] had employed Hückel MO reactivity calculations for predicting free-radical attack at these 7 positions, as based on either π-electron density or superdelocalizability, $S_r^{radical}$. To obtain quantitative predictions for the isomeric ratios to be found, we assume here that only direct substitutions occur at positions 3,4, and 5, while those at positions 2 and 6 are additive as based on direct attacks there plus rearrangements from attacks at positions 1 and 7, respectively. These quantitative data are shown in the last three columns of Table 1.

Observation of Table 1 shows four separate distributions of yields, which should be experimentally distinguishable from one another, *viz.* (1) FRD which predicts the order of isomeric yields **3b** > **3a** > **3e** > **3c** > **3d**, (2) Hückel, essentially identical for either $q_r(\pi)$ or $S_r^{radical}$, where one has **3a** > **3e** >> **3b** > **3c** = **3d**, (3) PPP or CNDO for $q_r(\pi)$, where **3a** >> **3e** >> **3b** = **3c** = **3d**, and (4) CNDO for $q_r(\sigma)$, or $q_r(\sigma + \pi)$, where **3a = 3e** > **3b** = **3c** = **3d**. These orders all differ from the prediction of **3b**, **3c** >> **3a**, **3d**, **3e** for amalgamation of the results from phenylation of quinoline and benzo[*b*]thiophene conducted under reaction conditions considerably

Table 1

Predicted Distribution of Isomeric Mono(4-nitrophenyl) Derivatives of Thieno[2,3-*b*]pyridine (**1**) from Free-radical Substitution

Position *r* in **1**	Product formed	Isomeric Distribution (%) as Based on the method of calculation [a] FRD [b]	Hückel [c]	$q_r(\pi)$ [d]	$q_r(\sigma + \pi)$ [e]
2	**3a**	26	32-34	37-38	31-32
3	**3b**	32	16-17	12	13
4	**3c**	15	12-13	12-13	13
5	**3d**	6	11-14	12-13	13
6	**3e**	20	25-26	25	29-30

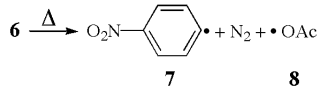
[a] See text for process of calculation. [b] Frontier Radical Density from CNDO (Complete Neglect of Differential Overlap) calculations. See references [12,13]. [c] From Hückel MO calculation for either $q_r(\pi)$ or S_r^{radical}. See reference [14]. [d] From data presented by Holland and Skancke for either CNDO or PPP (Pariser-Parr-Pople) methods. See reference [12]. [e] From CNDO data presented by Holland and Skancke for either $q_r(\sigma)$ alone or $q_r(\sigma + \pi)$. See reference [12].

different from those used in the present study. As indicated later [2], distributions (2) and (3), *i.e.* calculations of $q_r(\pi)$ plus rearrangements from positions 1 and 7, lie closest to experimental observations.

General Experimental Procedure

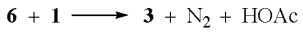
The experimental procedure was a variation on the Gomberg-Bachmann-Hey diazoacetate method for synthesis of a biaryl [15-17]. As used by Hey and coworkers [16], an acidic aqueous solution of an aromatic diazonium chloride was mixed with the aromatic reactant (*e.g.* benzene or a monosubstituted benzene, used in excess) and then the mixture was slowly basified by dropwise addition of an aqueous solution of sodium acetate at a reaction temperature of 5-25°. In our procedure a cold, aqueous solution of 4-nitrobenzenediazonium chloride in excess hydrochloric acid was added slowly to a stirred mixture (originally at room temperature) of excess thieno[2,3-*b*]pyridine (**1**) (a liquid) and anhydrous sodium acetate (2 moles per mole of acid used) [18]. The rate of addition of the diazonium solution was controlled so that the reaction mixture remained near 45°, while nitrogen gas was evolved at a convenient rate. In contrast to the Hey method the concentration of water was kept low during the 4-nitrophenylation of **1**, so as to limit a possible side reaction of phenol formation, and the reaction mixture remained basic or buffered (expected final pH 4-5) throughout the process. Thus, at no time should reactant **1** (pK_a 2.75 [19]) have existed in a protonated form during the free-radical arylation. In an effort to avoid the formation of bis-(4-nitrophenyl)-**1** products, compound **1** was used in 260% molar excess over that of 4-nitroaniline (**2**), the source of the diazonium chloride. That this goal was achieved was established by a mass spectrum on a crude, mixed reaction product which indicated that less than 2 mole % of the mixture could be disubstituted.

It is generally proposed that the active arylating agent in the Hey procedure is an aryldiazoacetate, *i.e.* 4-nitrophenyldiazoacetate (**6**) in our reaction, [15,16,20,21] and that this intermediate undergoes thermal dissociation according to equation 1. As indicated by the isolated products, the overall free-radical substitution is then represented by Equation 2, whereby the acetoxy entity **8** serves to abstract a hydrogen atom from **1** and the 4-nitrophenyl group replaces a hydrogen on the ring. The yield of **3** was 35% as based on the amount of **2** used and 32% as based on that of **1** used. No side products were isolated.



7 **8**

Equation 1



Equation 2

Processing of the reaction mixture is described in the Experimental section and outlined in Scheme 1.

EXPERIMENTAL

4-Nitrophenylation of Thieno[2,3-*b*]pyridine (**1**).

A solution of 4-nitrobenzenediazonium chloride was prepared from 14.2 g (0.103 mole) of 4-nitroaniline (**2**), 20 ml (0.24 mole) of concentrated hydrochloric acid, 7.1 g (0.103 mole) of sodium nitrite, and 20 ml of water at 0° following a standard procedure [22]. This cold solution was added slowly (over 35 minutes) to a mechanically stirred mixture of 50 g (0.37 mole) of distilled thieno[2,3-*b*]pyridine (**1**) and 39.6 g (0.48 mole) of anhydrous sodium acetate at such a rate that the reaction temperature spontaneously remained at 38-51°. Thereafter, external heat was applied to maintain a temperature of 40° for 2 hours. These conditions caused controlled evolution of nitrogen gas. The mixture

(volume 210 ml) was then allowed to stand for two days at room temperature and poured into 1.2 L of water and 300 ml of ether. The two liquid layers and the black, gooey tar which formed were separated. The tar, which clung tenaciously to the glassware, was dissolved in acetone (*vide infra*). The aqueous layer was extracted with more ether and then discarded. Combined ether layers were evaporated at water aspirator pressure and then distilled to recover unreacted thienopyridine, bp 68-70° (0.1 mm), yield (after combination with small purified amounts from processing of acetone solutions) 34.5 g (0.256 mole, 69%). The black residue from this distillation was triturated with acetone to leave 3.52 g of rust-colored solid, of which 3.42 g (designated *Y*) was soluble in chloroform (0.10 g discarded). The solvent was removed from the combined acetone solutions at water aspirator pressure and the residue which remained was evaporatively distilled at 0.3 mm to give impure **1** at temperatures below 100° and a yellow-red sublimate (designated *Z*, 5.81 g, mp 170-185°) at 100-205°; total yield of solids 9.23 g, indicated by a mass spectrum [23] to be almost exclusively **3**, (35% yield, based on **2** used; or 32%, based on non-recovered **1**).

Thin-layer chromatography (silica gel F_{254}/chloroform or chloroform-ethylacetate-1:1) on *Y* and *Z* indicated that four (or more) components were present in each portion. The total amounts of *Y* and *Z* were fractionated by column chromatography (silica gel/chloroform) with an average 93% recovery by weight of crystalline solids. Liquid and tarry fractions were discarded. Identical fractions, as based on appearance, R_f values, and mp, were combined and either recrystallized to analytical purity or separated further by thick-layer chromatography. Structural identification and properties of three analytically pure products are presented in a following paper [2].

REFERENCES AND NOTES

[1] Undergraduate research student, 1993.

[2] See Part II: L. H. Klemm, T. J. R. Weakley, and R. D. Gilbertson, *J. Heterocyclic Chem.*, **38**, 189 (2001).

[3] L. H. Klemm, *Heterocycles*, **15**, 1285 (1981).

[4] L. H. Klemm, in Trends in Heterocyclic Chemistry, Vol. **5**, Research Trends, Trivandrum, India, 1997, pp 37-55.

[5] G. Vernin, H. J. M. Dou and J. Metzger, *Bull. Soc. Chim. Fr.*, 2612 (1971).

[6] Less definitive studies using benzoyl peroxide were described by H. J. M. Dou and B. M. Lynch [*C. R. Hebd. Seances Acad. Sci.*, **262C**, 1537 (1966); *Bull. Soc. Chim. Fr.*, 3815 (1966)], D. H. Hey and E. W. Walker [*J. Chem. Soc.*, 2213 (1948)], and K. H. Pausacker [*Aust. J. Chem.*, **11**, 200 (1958)].

[7] P. Spagnolo, M. Tiecco, A. Tundo and G. Martelli, *J. Chem. Soc., Perkin 1*, 556 (1972).

[8] M. Bartle, S. T. Gore, R. M. Mackie and J. M. Tedder, *J. Chem. Soc., Perkin 1*, 1636 (1976).

[9] L. H. Klemm and J. Dorsey, *J. Heterocyclic Chem.*, **28**, 1153 (1991).

[10] See references given in [9].

[11] Bartle *et al*. proposed a similar three-center reaction involving initial attack of an ArN_2 cation on the sulfur atom in thiophene as "a new type of aromatic [alpha] substitution which has no exact parallel" [8]. Loss of a proton and of nitrogen gas then follow.

[12] A. Holland and P. N. Skancke, *Acta Chem. Scand.*, **26**, 2601 (1972).

[13] FRD values for the corresponding positions are 0.27, 0.22, 0.17, 0.13, and 0.05. Note that no involvement of heteroatoms N and S is assumed in this case.

[14] L. H. Klemm, C. E. Klopfenstein, R. Zell, D. R, McCoy and R. A. Klemm, *J. Org. Chem.*, **34**, 347 (1969).

[15] W. E. Bachmann and R. A. Hoffman, in Organic Reactions, Vol. **2**, R. Adams, ed-in-chief, John Wiley, New York, 1944, pp 224-261.

[16] J. Elks, J. W. Haworth and D. H. Hey, *J. Chem. Soc.*, 1284 (1940).

[17] A. W. Johnson, *J. Chem. Soc.*, 895 (1946).

[18] Compare the procedures of S. H. Korzeniowski, L. Blum and G. W. Gokel [*Tetrahedron Lett.*, 1871 (1977)] and of J. R. Beadle, S. H. Korzeniowski, D. E. Rosenberg, B. C. Garcia-Slanga and G. W. Gokel [*J. Org. Chem.*, **49**, 1594 (1984)]. In an earlier experiment in our laboratory we reacted dry 4-nitrobenzenediazonium tetrafluoroborate [E. B. Starkey, *Org. Syn.*, Coll. Vol. **2**, 225 (1943)] with a 2-molar amount of anhydrous potassium acetate and excess **1** (diluted with 7 volume % of acetonitrile) in the manner described in the second of these references. However, the procedure was abandoned when it was found that the products from the reaction showed extraneous nmr signals, perhaps due to the presence of fluorine therein.

[19] L. H. Klemm and R. D. Jacquot, *J. Electroanal. Chem. Interfacial Electrochem.*, **45**, 181 (1973).

[20] D. H. Hey and W. A. Waters, *Chem. Rev.*, **21**, 169 (1937).

[21] W. A. Pryor, Free Radicals, McGraw-Hill, New York, 1966, pp 253-254.

[22] L. F. Fieser and K. L. Williamson, Organic Experiments, 4th Ed, D. C. Heath, Lexington, MA, 1979, pp 228-229.

[23] Conducted by Dr. G. O'Bannon of this laboratory on a VG 12-250 instrument.