Free-radical 4-Nitrophenylation of Thieno[2,3-*b*]pyridine. Part 3: Consideration of Mechanistic and Selectivity Factors Involved in the Substitution Process

LeRoy H. Klemm* and Scott M. Reed

Department of Chemistry, University of Oregon, Eugene, Oregon, 97403-1253
Received May 21, 2001

A 1:1 geometrically oriented encounter complex between thieno[2,3-*b*]pyridine (**1**) and 4-nitrophenyldiazoacetate (**2**) is proposed to account for the dominant formation (*ca*. 64%) of the 2-isomer in the mixture of 4-nitrophenyl-**1** isomers obtained previously. A mechanism involving one-electron transfer from **1** to **2** plus fragmentation of $2^{\bullet-}$ into 4-nitrophenyl free radical, N_2, and acetate ion is invoked. Formation of other isomers is discussed.

It is noted that there is a close correlation between orientational rules plus mechanisms of reaction for numerous free-radical substitutions (S_R) with S_N reactions of alkyllithiums on furan, thiophene, *N*-alkylpyrroles, pyridine, and their condensed aromatic molecules, including **1**, as substrates. Also isomeric selectivities for S_E, S_N, and S_R substitutions into **1** were shown to be qualitatively consistent with one another. While S_E reactions occur largely at position 3 and then at 2, S_N and S_R reactions occur either at 2 or 6. Selectivity for positions 4 or 5 is small or zero.

J. Heterocyclic Chem., **38**, 1433 (2001).

I. Introduction.

In previous papers in this series [1,2] we described an experimental procedure for the free-radical 4-nitrophenylation of thieno[2,3-*b*] pyridine (**1**) by means of the hypothetical intermediate 4-nitrophenyldiazoacetate (**2**) under buffered conditions to yield a mixture of crystalline monosubstituted 4-nitrophenyl derivatives **3** in 32% yield. Isolated from this mixture were samples of isomerically pure **3a** (the 2-isomer) and **3e** (the 6-isomer) plus an analytically pure sample containing **3a, 3b**, and **3c** (2-,3-, and 4-isomers). Surprisingly, no **3d** (5-isomer) was isolated or specifically identified in the mixture. Semi-quantitatively, relative isomeric yields fit the pattern 2- (64%) >> 6- (14%) ≥ 3- (12%) > 4- (6%) ≥ 5- (≤ 4%). In this paper we summarize three mechanisms which have been proposed in the literature for free-radical arylation of benzene and thiophene systems. We have then adapted and extended these proposals to a rationalization of the predominance of the 2-isomer in our product mixture. We make the

Chart 1

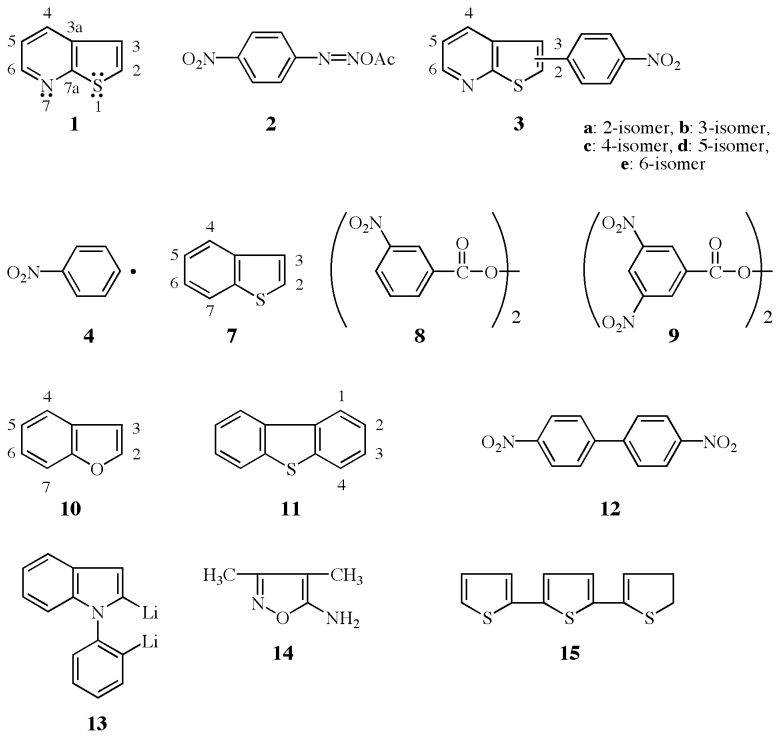
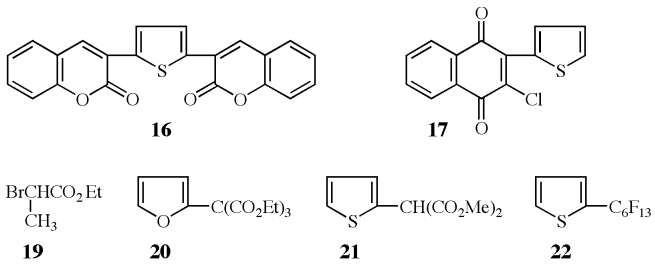


Chart 1 (continued)



assumption that all of the five possible mono(4-nitrophenyl) derivatives of **1** are stable to our reaction processing and are not lost in that operation.

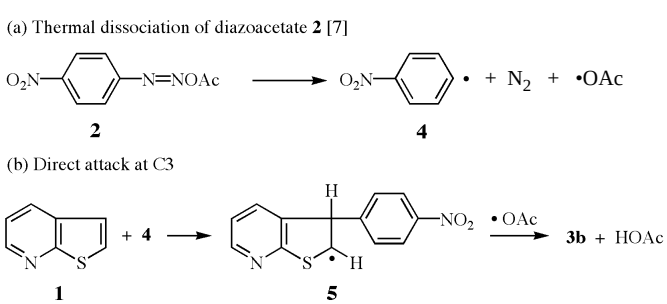
II. Mechanistic Considerations.

In our procedure cold, aqueous 4-nitrophenyldiazonium chloride was added slowly to a mixture of excess **1** and anhydrous sodium acetate (2 moles per mole of hydrochloric acid used to generate the diazonium compound) at such a rate as to control the rate of evolution of nitrogen gas and maintain the temperature at 45 ± 7°. In this modified Gomberg-Bachmann-Hey reaction [3-6] diazo compound **2** is assumed to undergo thermal dissociation to yield the 4-nitrophenyl free radical (**4**) [7] which attacks a CH carbon atom, *e.g.* C3 of **1**, directly to give a resonance-stabilized free radical **5** [8], from which an adventitious free radical (usually acetoxy, as shown) abstracts a hydrogen atom to give **3b** (See Scheme 1). Based on Hückel MO or CNDO π-electron density calculations, one would expect nearly equal yields (18-23%) of all five isomers [9-11]. This prediction is clearly inconsistent with our high yield of the 2-isomer.

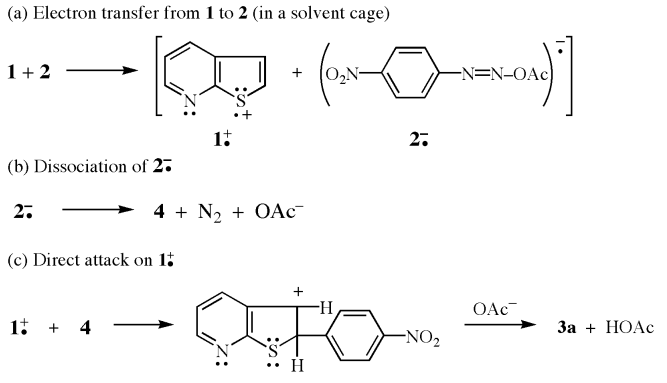
Scheme 2 is modeled after a mechanism proposed by Japanese workers who reacted thiophene with bis(heptafluorobutanoyl) peroxide (**6**) at 40° in Freon-113 to give a 98% yield of isomerically pure 2-heptafluoropropylthiophene and a 99% yield of heptafluorobutanoic acid (Scheme 3) [12,13]. These authors proposed that the first step in the reaction involves an electron transfer from thiophene (or one of its monosubstituted derivatives) to the strongly electron-attracting diacyl peroxide **6** in a solvent cage. They pointed out that this free-radical 2-substitution into thiophene follows the orientation rule for S_E reactions, but failed to note that the same orientation rule applies to lithiation with alkyllithium (S_N reaction on hydrogen, *vide infra*) [14]. A more definitive case is their heptafluoropropylation of benzo[*b*]thiophene (**7**) where lithiation occurs at C2 and S_E reactions give predominantly 3-substitution [15]. Thus, **7** gave a 54% yield of 2-heptafluoropropyl derivative and a 20% yield of its 7- (or possibly 4-) isomer. They did not isolate any 3-isomer [16].

It should be noted that use of an acyl peroxide on **1** would seem inappropriate in our study, since (a) pyridine plus **6** yield pyridine *N*-oxide plus pyridinium heptafluorobutanoate salt instead of fluoroalkylpyridines [12], (b) analogous salts are formed from reaction of pyridine with 3-nitrobenzoyl peroxide (**8**) and of quinoline with 3,5-dinitrobenzoyl peroxide (**9**) [17], and (c) compound **1** is known to give the *N*-oxide with hydrogen peroxide in acetic acid [18] or with 3-chloroperoxybenzoic acid in chloroform [19]. Also benzoyl peroxide gives a complex mixture of products with thiophene [20], although with **7** it did yield a mixture of monophenyl derivatives in a ratio of 21:21:28:0:12:18 for isomers 2-7, respectively [21]. The failure to obtain any 5-isomer is noteworthy. The same isomeric ratio was obtained from reaction of **7** with *N*-nitrosoacetanilide, except that a yield of 12% was assigned to a mixture of the 5- and 6-isomers, unseparated [22]. Although intermediate **2** is expected to be less elec-

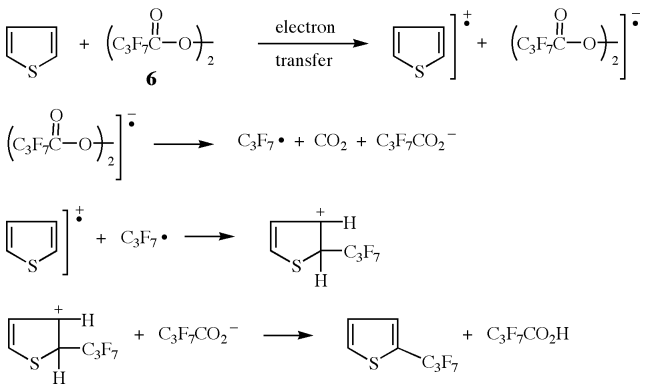
Scheme 1: The Hey Thermal Route to **3b** [6]



Scheme 2: The Electron Transfer Route to **3a**



Scheme 3: Mechanism for Perfluoroalkylation of Thiophene [12]



tron-attracting than **6**, Porter has suggested that thiophene might even transfer an electron to a phenyldiazonium cation, with formation of nitrogen gas and a phenyl free radical [20]. Whatever the reaction mechanism might be, the diazonium intermediates from 2-nitro-, 4-nitro-, and 2,4-dinitroanilines all give preferential substitution into the alpha position of thiophene [23-26].

Comparison of reactivity in thiophene and benzene toward free-radical substitution yields the order α-thiophene > benzene > β-thiophene as based on partial rate factors [20]. In a study of arylation by diazotized anilines in an aprotic mixture, it was found that (a) the relative reactivity of thiophene (as compared to benzene) follows the order of reagents nitroaniline > aniline > methoxyaniline and (b) the α/β isomeric selectivity decreases in the same order [20]. For use of 4-nitroaniline an isomeric selectivity of 24:1 was reported. This compares favorably with other data from the literature [25]. Extending these relationships to 4-nitrophenylation of **1**, we expect that the reaction should be kinetically controlled and could well result in markedly different yields of the five possible isomers **3a-3e** (as observed).

To ascertain what effect the loss of an electron from **1** would have on charge distribution in the molecule we conducted AM1 calculations as presented in Table 1. For the neutral molecule one obtains a total electronic charge separation corresponding to a drift of 0.15 unit from the thiophene ring onto the pyridine ring [27]. The +1 charge on $\mathbf{1}^{+\bullet}$ is also shared unevenly, with +0.54 ascribed to the thiophene ring and +0.45 to the pyridine ring. Significantly the Δq_r calculations show that the two heteroatoms N and S contribute almost equally to the change in electronic charge distribution on going from **1** to $\mathbf{1}^{+\bullet}$. However, these figures apply to a stationary (equilibrium) state, and not to a kinetic situation (transition state) where the larger and more polarizable sulfur atom should be the better electron-donor.

Table 1
AM1 Calculations [a] of the Electronic Charge Distribution in **1** and $\mathbf{1}^{+\bullet}$

Position	Electronic Charge, q_r [b]		
r	For **1** [c]	For $\mathbf{1}^{+\bullet}$ [d]	Δq_r [e]
1 (S)	+ 0.55	+ 0.83	+ 0.28
2 (CH)	- 0.24	- 0.19	+ 0.05
3 (CH)	+ 0.02	+ 0.11	+ 0.09
3a (C)	- 0.12	- 0.06	+ 0.06
4 (CH)	+ 0.09	+ 0.19	+ 0.10
5 (CH)	- 0.05	+ 0.07	+ 0.12
6 (CH)	+ 0.10	+ 0.25	+ 0.15
7 (N)	- 0.10	+ 0.15	+ 0.25
7a (C)	- 0.26	- 0.36	- 0.10

[a] M. J. S. Dewar, E. G. Zoebisch, E. F. Healey and J. J. P. Stewart, *J. Am. Chem. Soc.*, **107**, 3902 (1985); [b] The charge q_r for each position 2-6, except 3a, is the sum of calculated values for C and H; [c] $\sum q_r$ for the thiophene ring, including half of the q_r values for C-3a and C-7a, equals +0.14. Analogously, for the pyridine ring $\sum q_r$ = -0.15. [d] $\sum q_r$ = +0.54 for the thiophene ring and + 0.45 for the pyridine ring. [e] For the transformation $\mathbf{1} \rightarrow \mathbf{1}^{+\bullet} + e^-$.

In Scheme 4 we propose a geometric adaptation of Scheme 2 which could account for the predominance of the 2-isomer of **1** from a kinetically controlled reaction. In this proposal the molecules **1** and **2** approach one another in a particular orientation with the plane of **1** perpendicular to the benzene ring of **2** and the polarizable *n*-electron pair of the sulfur atom directed toward the π-electron deficient benzene ring to form an encounter complex [28], as depicted in Figure 1. In Figure 1, structures **1** and **2** are obtained from an AM1 program [29], wherein **2** is placed

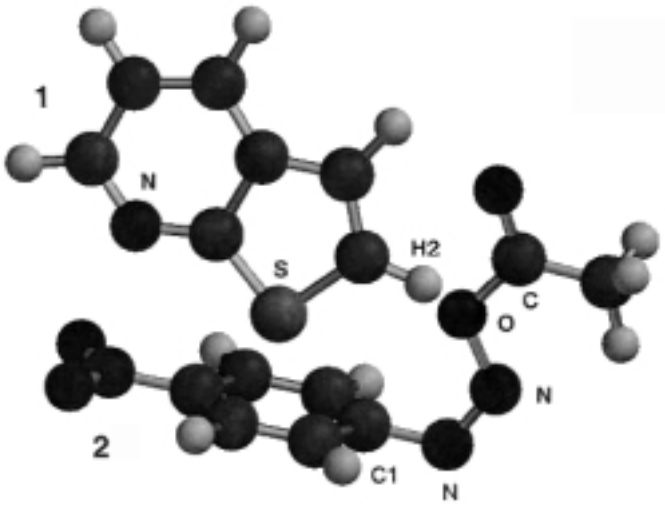
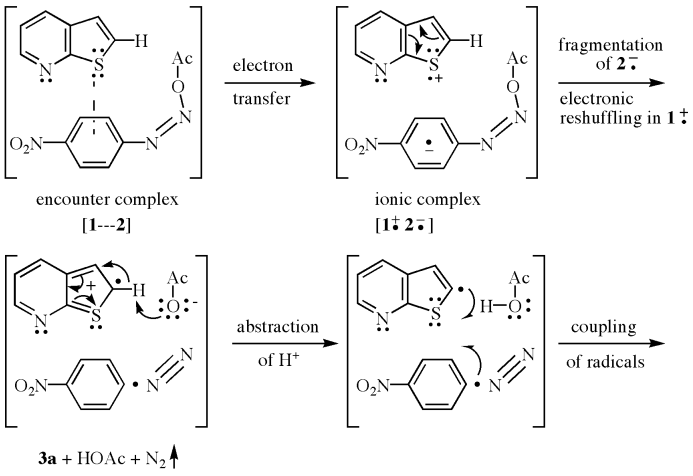


Figure 1. Proposed geometry of the encounter complex between thieno[2,3-*b*]pyridine (**1**) and 4-nitrophenyldiazoacetate (**2**), as based on AM1 molecular modeling. Compound **1** and the N=N–O–C portion of **2** are in the plane of the paper, while the 4-nitrophenyl portion of **2** is perpendicular to the plane of the paper. See Scheme 4.

in its conformation of minimal energy, *i.e*. with a twist of 90° along the C1-N bond so as to bring the plane of the N-O-C triad also perpendicular to the plane of the benzene ring. In this conformation the non-bonding electron pair on the oxygen atom of the triad can be directed toward the relatively acidic H2 atom of the tilted molecule **1**. We have docked the two molecules together to show the plausibility of the geometric relationship in this encounter complex. We suggest that concurrent with the docking of these reactants an electron jumps from the sulfur atom to the benzene ring with the resultant fragmentation of $2^{-\bullet}$ into free radical **4**, nitrogen gas, and the acetate ion. The acetate ion then abstracts a proton from C2 of $\mathbf{1}^{+\bullet}$ in a process which may be rate-controlling, an S_N reaction on hydrogen [30,31]. The free radicals 2-thieno[2,3-*b*]-pyridyl and **4** then couple to form **3a**. An analogous mechanism can be written for the predominant formation of the 2-isomer from thiophene and **2** [25,32]. Conceivably, this concept can be extended to Scheme 3, where a much less stringent geometric relationship would be required between the thiophene molecule and one heptafluoropropyl group of **6** in the encounter complex. For heptafluoropropylation of benzo[*b*]thiophene analogous encounter complexes can be invoked for C2 and (albeit less clearly) for C7 substitution [16].

Scheme 4: An Internal Encounter Complex Route to **3a** in a Solvent Cage



The intermediate yield of **3e**, the 6-isomer from **1**, can be explained if a limited quantity of the encounter complex has the thienopyridine molecule turned end for end with the heteroatomic nitrogen serving as the electron donor to **2** and H6 directed toward the N-O-C oxygen. In contrast, the lower yields of **3b** and **3c** probably result from Hey thermal processes with direct attack of **4** on C3 and C4, respectively, outside of a solvent cage (see Scheme 1). Discussion of a failure to detect any **3d** is presented later. Evidence for the presence of **4** in the reaction mixture was obtained by the isolation of its dimer, 4,4'-dinitrobiphenyl (**12**) by countercurrent chromatography [33].

The ratio of substitution of **4** into the thiophene and the pyridine rings of **1** is 3.8:1, a larger ratio than that of 1.3:1 found in competitive 4-nitrophenylation of a mixture of thiophene and pyridine [25]. This difference is easily explained by Scheme 4 where the preferred orientation of **1** as shown, facilitates substitution at C2 and precludes it at C6. In the competitive experiment substitutions into pyridine and thiophene occur independently.

III. Mechanistic Similarities Between Alkyllithium and Free-Radical Substitution into Heterocyclic Compounds.

a. Alkyllithium reactions.

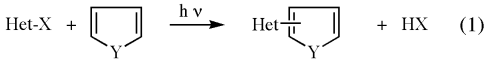
As indicated previously for thiophene, benzo[*b*]thiophene (**7**) and **1** lithiation by means of an alkyllithium reagent occurs predominantly at C2, *i.e*. the alpha position to the heteroatomic sulfur. In pyridine, quinoline, and **1** an alkyllithium adds to the aromatic C-N bond to give, on further work-up (hydrolysis and dehydrogenation), alpha alkylation to the heteroatomic nitrogen. Both processes are designated as S_N reactions, the former as nucleophilic attack on H2 and the latter as nucleophilic attack on the CH-carbon alpha to the heteroatomic nitrogen [14,34-36]. In this section we show a correlation between these two S_N reactions and ring substitution by a free radical that could be generated by electron transfer from a nitrogen, oxygen, or sulfur heteroatom present in a heterocyclic ring, as exemplified in Scheme 4 and the discussion in Section II. For simplicity, we consider only thiophene, furan, *N*-alkylpyrroles [37], pyridine, and their condensed aromatic molecules as substrates. Disubstitution is included both for the alkyllithium reactions [35,38] and for free-radical substitution. However, those cases where substitution by the poorly selective phenyl free radical led to more than two isomers in significant yields (such as with the substrates **7** [21,22], quinoline [39] and dibenzothiophene (**11**) [40]) are excluded from this comparison [41].

For the five-membered rings α-lithiation occurs at C2 and dilithiation occurs at both alpha positions, C2 and C5 [34,36]. However, in one experiment 2,5-dilithio-1-methylpyrrole gradually changed to the 2,4-isomer on extended refluxing of a hexane solution [36]. Benzo[*b*]thiophene (**7**) lithiates at C2 (55%) and dilithiates at C2 and C7 (12%) [38], *i.e*. it gives both α and *ortho* lithiation. Benzo[*b*]furan also undergoes α-lithiation and probably *ortho* lithiation. *N*-Methylindole lithiates at C2 (78%), while *N*-phenylindole gives first α-lithiation in the pyrrole ring and then *ortho* lithiation in the phenyl ring to form **13** [42]. Dibenzofuran, dibenzothiophene, and *N*-alkylcarbazole all lithiate in the *ortho* position, at C4. As indicated before, **1** shows properties of both **7** and quinoline in that it lithiates at C2 and/or alkylates at C6 [9].

b. Free-radical Substitutions.

In this subsection we call attention to the fact that the orientation rules for formation of the major one (or two) isomers on free-radical substitution into the preceding heterocyclic systems are identical to those for lithiation or alkylation by an RLi reagent [43]. The data to illustrate this relationship have already been presented for thiophene, pyridine, quinoline, **1**, and **7**. Examples from the furan and pyrrole systems plus other results on the thiophene system are presented here. Treatment of various substituted anilines with 3-methylbutyl nitrite in excess thiophene gives mixtures of 2- and 3-arylthiophenes in isomeric ratios varying from 83:17 to 92:8 [44]. Similarly, reaction of aminoisoxazole **14** with tertiary butyl nitrite and ultraviolet light gave high yields (90 and 83%) of 2-substituted thiophene and furan, respectively [45]. In contrast to results with **7** (*vide supra*), compound **10** plus *N*-nitrosoacetanilide or benzoyl peroxide gives a high yield (76%) of 2-phenylbenzo[*b*]furan and small yields. (0:18:0:0:7) for isomers 3-7, respectively [21,22]. The enhanced ability of a hetero-oxygen (as compared to a hetero-sulfur) atom to direct an attacking group to the α-position has been noted by many authors. On reacting with highly fluorinated alkanoyl peroxides, thiophene and furan show closely similar results, *i.e.*, comparable yields of 2-isomers as the only isolated compounds [12,13b,46].

A simple synthesis of biheteroarenes is accomplished by photochemical reaction, as illustrated in equation 1, where X is a halogen atom (usually I), and Y is O, S, or NMe. It is



(1)

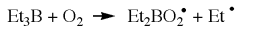
proposed that the C-X bond is broken homolytically [47] and the Het free radical substitutes into the five-membered ring. For Het-X equals 2- or 3-iodopyridine one obtains only α-substitution into furan or *N*-methylpyrrole, but both α- and β-substitution (4 or 7:1) into thiophene. Total yields vary from 28-72% [48,49]. For 2-, 3-, or 4-iodoquinoline the procedure works well for both furan and *N*-methylpyrrole (76-93% yield, α-isomers only) with a low-pressure lamp. But reactions were sluggish with thiophene (4-13% yield) unless a high pressure lamp was used (35, 80, and 48% yields, from the three iodoquinolines, respectively). From 3-iodoquinoline, the ratio of α/β substitution into thiophene was 71:9 [50]. Similarly, from 5-iodopyrimidine exclusive α-substitution occurs with furan (62%) and *N*-methylpyrrole (46%) but not with thiophene (64%, α/β 29:3) [51]. In another synthesis 2,5-diiodothiophene in thiophene produced α,α'-terthienyl (**15**) (91%) [52]. An α-thienyl derivative of cytidine [53] and an α-furyl one of uracil [54] are reported. Additionally 3-bromocoumarin and 2,3-dichloro-1,4-naphthoquinone react with thiophene to yield products **16** (48%) and **17** (57%), respectively [55,56]. In both of these cases evidence was presented to support the formation of an initial charge-transfer complex between the reactants.

A third general method for forming free radicals as intermediates uses a one-electron oxidation or reduction process to obtain (oftentimes) synthetically useful substituted five-membered heterocycles. A typical, proposed reaction mechanism is shown in Scheme 5 for the synthesis of **18** in 56% yield and its 2-furyl analog (60%). Also ethyl 2-bromopropionate (**19**), used instead of ethyl iodoacetate, gave analogous products with thiophene (47%) and *N*-methylpyrrole (without added ferric ion) (39%) [57]. Using hydrogen peroxide and ferrous ion, without triethylboron, as the redox mixture gave even higher yields of **18** and its 2-furyl and 2-(*N*-methylpyrrole) analogs. Other substituents were introduced as well [58]. With manganese (III) acetate in buffered solution one can obtain compound **20** (92%) or its thiophene analog (55%) [59]. Other workers used cerium (IV) salts in alcohol solution with dimethyl malonate to give **21** (85%), as well as its 2-substituted analogs in the furan (75%), benzo[*b*]furan (48%) and benzo[*b*]thiophene (41%) series [60]. While no β or *ortho* substitution was reported in any of these various redox combinations the cerium (IV) agent did yield some non-aromatized 2,5-addition products with thiophene and furan [60]. Ruthenium (III) plus benzyl bromide gave various isomeric mixtures due to a low selectivity by the benzyl free radical [61]. However, ruthenium (II) plus perfluorohexanesulfonyl chloride gave a good yield (77%) of 2-perfluorohexylthiophene (**22**) and a low yield (30%) of its furan analog [62].

In summary of Section III one sees that, except for the poor selectivities of the relatively non-polar phenyl and benzyl free radicals, orientation for free-radical and alkyllithium substitutions into the furan, thiophene, pyridine, *N*-alkylpyrrole and their condensed systems follow the same rules.

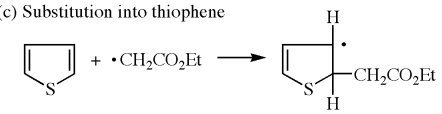
Scheme 5: Reaction Mechanism for Use of O_2 plus Fe (III) in a Route to α-Substituted Five-membered Heterocycles [57]

(a) Oxidation of Et_3B with O_2

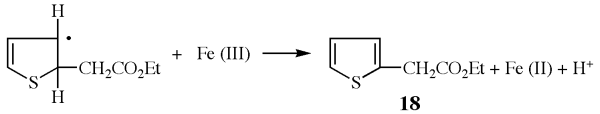


(b) Generation of attacking free radical

(c) Substitution into thiophene



(d) Oxidation by Fe (III)



18

IV. A Correlaton of Isomeric Selectivities in Electrophilic, Nucleophilic and Free-Radical Substitutions into Thieno[2,3-*b*]pyridine (**1**).

Over a period of years Klemm and coworkers have conducted a series of electrophilic (S_E) and nucleophilic (S_N) substitutions into **1**. With the present results on free-radical (S_R) substitution we are now able to compare experimental selectivities for each of the five possible positions of substitution 2-6 in **1**. We take a cue from the theoretical reactivity index superdelocalizability (S_r) [63] to develop a qualitative relationship between the observed isomeric distribution of products from S_E, S_N, and S_R reactions at each position *r* on **1**. According to Fukui, the developer of S_r, one expects the relationship shown in equation 2, *i.e.* the reactivity of position *r* toward free-radical substitution by

$$S_r^{(R)} = \frac{S_r^{(E)} + S_r^{(N)}}{2} \qquad (2)$$

an electrically neutral agent is the average of the reactivities of position *r* toward attack by an electrophilic agent (probably a positive ion) and a nucleophilic agent (probably a negative ion). Since experimentally each of these reactivities should be measured by the isomeric yield of product for position *r*, Y_r, one can write equation 3 for the expected relationship amongst yields of products. Ideally,

$$Y_r^{(R)} = \frac{Y_r^{(E)} + Y_r^{(N)}}{2} \qquad (3)$$

one would need complete quantitative data on the relative yields of all five possible isomers from representative S_E, S_N, and S_R reactions. While these data are now available for 4-nitrophenylation of **1**, only yields of isolated isomers are generally available for S_E (nitration and halogenation) and S_N (reaction with alkyllithium plus conversion of intermediates to isolable compounds) processes. Nonetheless, a qualitative test of equation 3 is possible at this time, as shown in Table 2 [64,65]. There isomeric yields are listed only as L (largest), M (intermediate in size), S (small), 0 (zero), or – (unknown, but presumably less than M). From this table one sees that direct substitutions into positions 2, 3, or 6 can be arranged by selection of the type of reaction. Little, if any, substitution occurs at positions 4 or 5 with any of the reactions on **1** which we have investigated [66]. At this time it is not clear why these positions should be so unreactive. However, in general, selectivity for the 4-nitrophenyl free-radical is clearly intermediate between those for S_E and S_N studies on **1**, as predicted by equation 3.

Table 2

Relative Distribution of Isomeric Products from S_E, S_N, and S_R Substitution into **1**

Substitution Mechanism	Relative Isomeric Yield for Position *r* [a] position *r* on **1**				
	2	3	4	5	6
S_E	M	L	-	-	-
S_R [b]	L	M	S	0 [c]	M
S_N	L [d]	-	-	-	M-L [e]

[a] Symbolism used: L, largest; M, intermediate; S, small; -, none isolated, relative yield is apparently either S or 0; 0, none found in reaction mixture; [b] From the present study; [c] Based on a countercurrent chromatographic analysis of our sample; See reference [33]; [d] For lithiation by RLi; [e] For alkylation by RLi (see text).

REFERENCES AND NOTES

[1] L. H. Klemm and K. Miller, *J. Heterocyclic Chem.*, **38**, 185 (2001).

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

[3] W. E. Bachmann and R. A. Hoffman, in Organic Reactions, Vol. **2**, R. Adams, ed-in-chief, John Wiley, New York, 1944, p 228.

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

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

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

[7] Alternatively, Rüchardt and coworkers [*Tetrahedron Lett.*, 2431, 3623 (1964)] propose that free radical **4** would arise by thermolysis of an intermediate ArN=N-O-N=NAr formed from **2**, especially at high pH (*e.g.* 12). It is doubtful that this situation applies in our experiment. However, if it does, then the ArN=N-O radical would serve the same function as we assign to the AcO radical in extracting a hydrogen atom from **5** (Scheme 1). For simplicity we retain the Hey concept.

[8] For simplicity the unpaired electron is shown as localized on one atom, and only the proposed mechanism for substitution at C3 is presented.

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

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

[11] It is assumed that the isomeric yield is directly proportional to the π-electron density on each of the carbon atoms 2-6.

[12] H. Sawada, M. Yoshida, H. Hagii, K. Aoshima and M. Kobayashi, *Bull. Chem. Soc. Jpn.*, **59**, 215 (1986) and references therein.

[13a] M. Yoshida, S. Sasage, N. Kamigata, H. Sawada and M. Nakayama, *Bull. Chem. Soc. Jpn.*, **62,** 2416 (1989); [b] H. Sawada and M. Nakayama, *J. Fluorine Chem.*, **51**, 117 (1991).

[14] S. Gronowitz, in Advances in Heterocyclic Chemistry, Vol. **1**, A. R. Katritzky, ed, Academic Press, New York, 1963, pp 43-75.

[15] B. Iddon and R. M. Scrowston, in Advances in Heterocyclic Chemistry, Vol. **11**, A. R. Katritzky and A. J. Boulton, eds, Academic Press, New York, 1970, pp 244-245, 370.

[16] M. Yoshida, T. Yoshida, N. Kamigata and M. Kobayashi, *Bull. Chem. Soc. Jpn.*, **61**, 3549 (1988).

[17] D. H. Hey, K. S. Y. Liang and M. J. Perkins, *J. Chem. Soc.* (*C*), 2679 (1967).

[18] L. H. Klemm, I. T. Barnish and R. Zell, *J. Heterocyclic Chem.*, **7**, 81 (1970).

[19] L. H. Klemm, J. J. Lu, D. S. Greene and W. Boisvert, *J. Heterocyclic Chem.*, **24**, 1467 (1987).

[20] A. E. A. Porter, in Thiophene and Its Derivatives, Part 1, S.

Gronowitz, ed, John Wiley, New York, 1985, pp 657-666; C. M. Camaggi, R. Leardini, M. Tiecco and A. Tundo, *J. Chem. Soc., B*, 1683 (1970).

[21] M. Tiecco and A. Tundo, *Int. J. Sulfur Chem.*, **8**, 295 (1973).

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

[23] P. A. S. Smith and J. H. Boyer, *J. Am. Chem. Soc.*, **73,** 2626 (1951).

[24] S. H. Korzeniowski, L. Blum and G. W. Gokel, *Tetrahedron Lett.*, 1871 (1977).

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

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

[27] This compares with a π-electronic drift of 0.31 unit as based on Hückel MO calculations [L. H. Klemm, *Heterocycles*, **15**, 1285 (1981)].

[28] For a discussion of encounter complexes see M. B. Smith and J. March, March's Advanced Organic Chemistry, 5th Ed., John Wiley, New York, 2001, p 680; L. M. Stock, *Prog. Phys. Org. Chem.*, **12**, 21 (1976).

[29] See footnote *a*, Table 1.

[30] This mechanism is closely related to the single-electron transfer initiation of S_N2 reactions, but extended over a multiatomic cyclic system; A. Pross, in Nucleophilicity, J. M. Harris and S. P. McManus, eds, Am. Chem. Soc., Washington, D.C., 1987, Chap. 23; A. Pross, in Advances in Physical Organic Chemistry, Vol. **21**, V. Gold and D. Bethell, eds, Academic Press, New York, 1985, pp 145-157; A. Pross, *Acct. Chem. Res.*, **18**, 212 (1985).

[31] The pertinence of propinquity and geometric relationships of bond-forming atoms has been pointed out; F. M. Menger, in Nucleophilicity, J. M. Harris and S. P. McManus, eds, Am. Chem. Soc. Washington, D.C., 1987, Chap. 14.

[32] We prefer the concept of an encounter complex to that of the 3-center reaction proposed in reference [25], but the former suggestion cannot be excluded at this time. For examples of electron transfer plus molecule-induced homolysis see M. J. Perkins, Radical Chemistry, Ellis Horwood, New York, 1994, pp 30-32.

[33] Y. Ito, H. Ziffer, and C. LaFleur, preliminary unpublished data on our sample from a separate laboratory.

[34] H. Gilman and J. W. Morton, in Organic Reactions, Vol. **8**, R. Adams, ed-in-chief, John Wiley, New York, 1954, Chap. 6.

[35] H. W. Gschwend and H. R. Rodriguez, in Organic Reactions, Vol. **26**, W. G. Dauben, ed-in-chief, John Wiley, New York, 1979, Chap. 1.

[36] J. M. Mallan and R. L. Bebb, *Chem. Rev.*, **69**, 693 (1969).

[37] *N*-Substitution on pyrrole is necessary in order to avoid replacement of the hydrogen in the NH-group by lithium.

[38] D. J. Chadwick and C. Wilbe, *J. Chem. Soc., Perkin 1*, 887 (1977).

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

[40] E. B. McCall, A. J. Neale and T. J. Rawlings, *J. Chem. Soc.*, 5288 (1962).

[41] It seems likely that these reactions do not involve *n*-π encounter complexes.

[42] D. A. Shirley and P. A. Roussel, *J. Am. Chem. Soc.*, **75**, 375 (1953).

[43] The examples given here are not meant to cover all of the available literature, but rather are ones encountered on surveying for reactions of thiophene and its condensed systems.

[44] G. Vernin, J. Metzger and C. Parkanyi, *J. Org. Chem.*, **40**, 3183 (1975).

[45] M. Julliard, C. Siv, G. Vernin and J. Metzger, *Helv. Chim. Acta.*, **61**, 2941 (1978).

[46] M. Yoshida, Y. Morinaga, M. Ueda, N. Kamigata and M. Iyoda, *Chem. Lett.*, **227** (1992).

[47] R. K. Sharma and N. Kharasch, *Angew. Chem. Int. Ed. Eng.*, **7**, 36 (1968).

[48] H.-S. Ryang and H. Sakurai, *J. Chem. Soc., Chem. Commun.*, 594 (1972).

[49] K. Seki, K. Ohkura and M. Terashima, *Heterocycles*, **22**, 2347 (1984).

[50] K. Ohkura, K. Seki, M. Terashima and Y. Kanaoka, *Heterocycles*, **30**, 957 (1990).

[51] D. W. Allen, D. J. Buckland, B. G. Hutley, A. C. Oades and J. B. Turner, *J. Chem. Soc., Perkin 1*, 621 (1977).

[52] M. D'Auria, *Gazz. Chim. Ital.*, **119**, 419 (1989).

[53] M. E. Hassan, *Nucleosides Nucleotides*, **10**, 1277 (1991).

[54] R. D. Youssefyeh and L. Lictenberg, *J. Chem. Soc., Perkin 1*, 2655 (1974).

[55] J. Meng, M. Shen, D. Fu, Z. Gao, R. Wang, H. Wang and T. Matsuura, *Synthesis*, 719 (1990).

[56] K. Maruyama and H. Tamiaki, *Bull. Chem. Soc. Jpn.*, **60**, 1847 (1987).

[57] E. Baciocchi and E. Muraglia, *Tetrahedron Lett.*, **34**, 5015 (1993).

[58] E. Baciocchi, E. Muraglia and G. Sleiter, *J. Org. Chem.*, **57**, 6817 (1992).

[59] I.-S. Cho and J. M. Muchowski, *Synthesis*, 567 (1991).

[60] L. M. Weinstock, E. Corley, N. L. Abramson, A. O. King and S. Karady, *Heterocycles*, **27**, 2627 (1988).

[61] R. Jaquhari and P. H. Dixneuf, *Inorg. Chim. Acta.*, **145**, 179 (1988).

[62] N. Kamigata, T. Ohtsuka, T. Fukushima, M. Yoshida and T. Shimizu, *J. Chem. Soc., Perkin 1*, 1339 (1994).

[63] A. Streitwieser, Molecular Orbital Theory for Organic Chemists, John Wiley, New York, 1961, pp 329-334; K. Fukui, Theory of Orientation and Stereoselection, Springer Verlag, New York, 1975, pp 34-36.

[64] See the reference in footnote [27].

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

[66] One might note that selectivity toward positions 4, 5, or 6 occurs with S_E and S_N (non-lithiation) reactions on **1**-*N*-oxide. See references [64,65].