AN INVESTIGATION OF THE INFLUENCE OF HALOARENES AND HETARYLACETONITRILES ON THE COMPETITION BETWEEN POSSIBLE ARYNE ARYLATION AND TANDEM ADDITION-REARRANGEMENT PATHWAYS

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Abstract - Attempts to extend the LDA-mediated 1-aminoisoquinoline arynic synthesis to 1,2-dibromo-3,4,5,6-tetramethylbenzene (**1a**) and the hetarylacetonitriles 2-(**2a**) and 3-pyridylacetonitrile (**2b**), 2- (**2c**) and 3-thiophene acetonitrile (**2d**), and 2-benzimidizoylacetonitrile (**2e**) failed; only rearranged 2-hetarylmethyl-3,4,5,6-tetramethyl-benzonitriles (**3aa-ae**) were obtained. Additionally, the reaction of 1-chloro-2,5-dimethylbenzene (**1b**), 2-bromo-4-methylanisole (**1c**), bromobenzene (**1d**), 2-bromoanisole (**1e**), and 1-bromo-2,5-dimethoxybenzene (**1f**) with **2a-e** gave rearranged nitriles (**3**) by the tandem addition-rearrangement aryne pathway and/or aryne arylated nitriles (**4**) by the aryne arylation pathway. By evaluating product **3**:**4** ratios from these reactions, an assessment of the influence of the nature of the haloarenes and hetarylacetonitriles on the competing tandem addition-rearrangement and aryne arylation pathways was made, which showed that the preference of the haloarenes for the rearrangement pathway to be **1a** ~ **1b** > **1c** > **1d** > **1e** > **1f** and that for the hetarylacetonitriles to be **2c** ~ **2d** > **2b** > **2a** > **2e**. An explanation in terms of the influence of the haloarene substituents on the ring-closure step of the rearrangement pathway and the heterocyclic ring of the hetarylacetonitrile on the proton abstraction step of the alternate aryne arylation pathway is presented.

INTRODUCTION

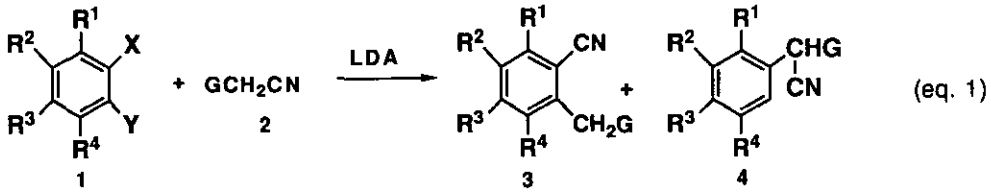
The impetus for studying the base-initiated aryne reactions of hetarylacetonitriles with haloarenes was prompted by several recent findings in our laboratory.[1-4] For example, we[1] showed that 1-chloro-2,5-dimethylbenzene (**1b**) reacts with 2-pyridylacetonitrile (**2a**)

and LDA to give predominantly 1-amino-3,8-di-(2-pyridylmethyl)-7-methylisoquinoline, and only trace amounts of the expected rearranged product, 3,6-dimethyl-2-(2-pyridylmethyl)benzonitrile. We suggested that the expected product was probably formed initially by the tandem-addition rearrangement aryne pathway.[5] However, the 6-methyl group, whose acidity is enhanced by the introduction of the 1-cyano group, underwent successive metalation and addition to another molecule of **2a** to yield an ortho imino-nitrile intermediate which cyclized to the observed 1-aminoisoquinoline, after proton quench. Since synthetic methodologies for the preparation of 1-aminoisoquinolines with well-defined substitution patterns are limited, a study on extending the arynic process to the reaction of 1,2-dibromo-3,4,5,6-tetramethylbenzene (**1a**) with **2a** as well as the reaction of **1a** and **1b** with 3-pyridylacetonitrile (**2b**), 2-(**2c**) and 3-(**2d**) thiopheneacetonitrile, and 2-benzimidazolylacetonitrile (**2e**) was initiated.

In other related studies,[2-4] we found that the reaction of certain haloarenes with various alkyl- and arylacetonitriles can yield either α–arylated products by the usual aryne mechanism and/or rearranged 2-arylmethylbenzonitriles by the tandem addition-rearrangement pathway. For example, haloarenes possessing one or more of the electron-donating (both inductively and mesomerically) methyl group, e.g. 1,2-dibromo-3,4,5,6-tetramethylbenzene (**1a**), 1-chloro-2,5-dimethylbenzene (**1b**) and 2-bromo-4-methylanisole (**1c**) preferentially follow the tandem addition-rearrangement pathway. In contrast, 1-bromo-2,5-dimethoxybenzene (**1f**), in which the electron-donating mesomeric effect of the two methoxy groups is counterbalanced by their electron-attracting inductive effect, preferentially chooses the aryne arylation pathway when treated with arylacetonitriles and LDA. Interestingly, both **1a** and **1b** react with crotonic acid and *N*-4-methoxyphenylcrotonamide dianions to give rearranged 2-naphthol and indane derivatives, respectively, presumably by a process which includes the tandem addition-rearrangement pathway in the key initial steps.[4] However, treatment of **1c** with these dianions supplies only 4-arylcrotonic acid derivatives by the usual aryne arylation pathway.[6] These initial studies suggest that the partitioning of the initially formed aryne-nucleophilic anion adduct between these two pathways is highly dependent not only upon the nature of both the haloarene, whose preference for the tandem addition-rearrangement pathway varies along the series **1a** ~ **1b** > **1c** > **1f**, but also on the nature of the nucleophile.

RESULTS AND DISCUSSION

To obtain more information of the role of haloarenes and lithiated nucleophiles on these competing pathways, the reaction of haloarenes (**1a-c,f**) as well as bromobenzene (**1d**) and 2-bromoanisole (**1e**) with hetarylacetonitriles (**2a-e**) was performed, and the product distributions of the rearranged product (**3**) to the aryne arylated product **4** were compiled and assessed. For ease of comparison, the product distributions (**3**:**4**) are arranged in five sets in Table 1. Each set lists the product distributions in decreasing order from the reaction of the haloarenes (**1a-f**) with a particular hetarylacetonitrile. We initially attempted to prepare 1-amino-isoquinolines by the reaction of hetarylacetonitriles (**2a-e**) with 1,2-dibromo-3,4,5,6-tetramethylbenzene (**1a**) and 1-chloro-



(eq. 1)

1	R^1	R^2	R^3	R^4	X	Y	1	R^1	R^2	R^3	R^4	X	Y
a	Me	Me	Me	Me	Br	Br	**d**	H	H	H	H	Br	H
b	Me	H	H	Me	Cl	H	**e**	MeO	H	H	H	Br	H
c	Me	H	H	MeO	Cl	H	**f**	MeO	H	H	MeO	Br	H

2	G				
a	2-pyridyl	**b**	3-pyridyl	**c**	2-thiophene	**d.**	3-thiophene	**e.**	benzimidazoyl

3,4	R^1	R^2	R^3	R^4	G		R^1	R^2	R^3	R^4	G
aa	Me	Me	Me	Me	2-pyridyl	**dc**	H	H	H	H	2-thiophene
ba	Me	H	H	Me	2-pyridyl	**ec**	MeO	H	H	H	2-thiophene
ca	MeO	H	H	Me	2-pyridyl	**fc**	MeO	H	H	MeO	2-thiophene
da	H	H	H	H	2-pyridyl	**ad**	Me	Me	Me	Me	3-thiophene
ea	MeO	H	H	H	2-pyridyl	**bd**	Me	H	H	Me	3-thiophene
fa	MeO	H	H	MeO	2-pyridyl	**cd**	MeO	H	H	Me	3-thiophene
ab	Me	Me	Me	Me	3-pyridyl	**dd**	H	H	H	H	3-thiophene
bb	Me	H	H	Me	3-pyridyl	**ed**	MeO	H	H	H	3-thiophene
cb	MeO	H	H	Me	3-pyridyl	**fd**	MeO	H	H	MeO	3-thiophene
db	H	H	H	H	3-pyridyl	**ae**	Me	Me	Me	Me	2-benzimidazoyl
eb	MeO	H	H	H	3-pyridyl	**be**	Me	H	H	Me	2-benzimidazoyl
fb	MeO	H	H	MeO	3-pyridyl	**ce**	MeO	H	H	Me	2-benzimidazoyl
ac	Me	Me	Me	Me	2-thiophene	**de'**	H	H	H	H	2-benzimidazoyl
bc	Me	H	H	Me	2-thiophene	**ee'**	MeO	H	H	H	2-benzimidazoyl
cc	MeO	H	H	Me	2-thiophene	**fe'**	MeO	H	H	MeO	2-benzimidazoyl

2,5-dimethylbenzene (**1b**), *since these haloarenes are suitably structured to yield requisite* ortho 6-methyl-1-cyano *intermediates.* With the exception of the reactions of **1a**, lithium diisopropylamide (LDA) was used for the generation of the nitrile anion and aryne. Since a relatively high temperature (~ 0 °C) is required for the generation of 3,4,5,6-tetramethylbenzyne from **1a** and LDA, which results in the extensive formation of intractible tars, this aryne was generated at -50 °C by the action of t-butyl -

lithium in the presence of a pre-formed hetarylacetonitrile anion, prepared by the action of KH. As shown in Table 1 and eq. 1, the reactions of **1a** (runs 1,7,13,19 and 25) and **1b** (runs 2,8,14,20, and 26) gave no 1-aminoisoquinolines, but rather supplied rearranged 2-hetarylmethyl-3,4,5,6-tetramethylbenzonitriles (**3aa-ae**) and 2-hetarylmethyl-3,6-dimethylbenzonitriles (**3ba-be**),

Table 1. Yields and Product Distributions of Rearranged Nitriles (**3**) and Aryne Arylated Nitriles (**4**)[a]

Set 1. Reaction of 1 with 2a

Run	Halo-arene	3 or 4	Yld (%) Total	Prod. Dist. 3:4
1	**1a**	**aa**	82	>95:5
2	**1b**	**ba**	b	-
3	**1c**	**ca**	70	60:40
4	**1d**	**da**	68	63:37
5	**1e**	**ea**	62	55:45
6	**1f**	**fa**	65	8:92

Set 2. Reaction of 1 with 2b

Run	Halo-arene	3 or 4	Yld (%) Total	Prod. Dist. 3:4
7	**1a**	**ab**	80	>95:5
8	**1b**	**bb**	73	>95:5
9	**1c**	**cb**	67	>95:5
10	**1d**	**db**	67	66:34
11	**1e**	**eb**	70	50:50
12	**1f**	**fb**	65	7:93

Set 3. Reaction of 1 with 2c

Run	Halo-arene	3 or 4	Yld (%) Total	Prod. Dist. 3:4
13	**1a**	**ac**	63	>95:5
14	**1b**	**bc**	90	>95:5
15	**1c**	**cc**	75	>95:5
16	**1d**	**dc**	68	>95:5
17	**1e**	**ec**	40	59:41
18	**1f**	**fc**	47	13:87

Set 4. Reaction with 1 and 2d

Run	Halo arene	3 or 4	Yld (%) Total	Prod. Dist. 3:4
19	**1a**	**ad**	81	>95:5
20	**1b**	**bd**	70	>95:5
21	**1c**	**cd**	65	87:13
22	**1d**	**dd**	41	92:8
23	**1e**	**ed**	33	43:57
24	**1f**	**ed**	46	8:92

Set 5. Reaction with 1 and 2e

Run	Halo-arene	3 or 4	Yld (%) Total	Prod. Dist 3:4
25	**1a**	**ae**	66	>95:5
26	**1b**	**be**	51	>95:5
27	**1c**	**ce**	32	21:79
28	**1d**	**de**	40	17:83
29	**1e**	**ee**	33	5:95
30	**1f**	**fe**	44	7:93

a. Product ratio **3:4** determined by integration of the ^{1}H nmr signals of the respective methylene and α--methine hydrogen atoms.

b. Major product obtained was 1-amino-3,8-di-(2-pyridylmethyl)-7-methylisoquinoline.

respectively, in fair to excellent yields. The failure of **1a** to supply 1-aminoisoquinolines may reflect the decreased acidity of the 6-methyl group engendered by the other three electron-donating methyl groups, thus obviating the crucial metalation step in the aminoisoquinoline synthesis. It may well be that the reluctance of 3- and 4-substituted hetarylacetonitriles to yield isoquinolines stems from the inability of their hetero atom, being removed from the reaction site, to provide a chelating loci for possible transition state stabilization. However, the inability of 2-thiopheneacetonitrile (**2c**) to give isoquinolines suggests that other factors, presently unknown, are involved.

The data shown in Table 1 also confirm and extend the notion that the **3:4** product distributions depend heavily on the nature of the haloarene and hetarylacetonitrile. For example, of the six haloarenes studied, **1a** and **1b** are the most inclined toward the rearrangement pathway since each gives rearranged products exclusively when treated with the hetarylacetonitriles (**2a-e**). In contrast,

1-bromo-2,5-dimethoxybenzene (**1f**) is the least inclined to pursue the rearrangement pathway since the **3:4** ratios from all its reaction with **2a-e** (i.e. runs 6,12,18,24, and 30) lie heavily in the direction of the aryne arylated products (**4**). The regiochemistry of the addition of α–hetarylacetonitrile anions to unsymmetric 3-methoxyarynes was assumed to occur at the 1-position in accord with the strong *meta* directing ability of the methoxy group.[7] This proposed regiochemistry was confirmed by single crystal X-ray diffractometric analysis of 2-(2-thiophenemethyl)-6-methoxy-3-methylbenzonitrile (**3cc**)[8] whose ORTEP[9] is shown in Figure 1.

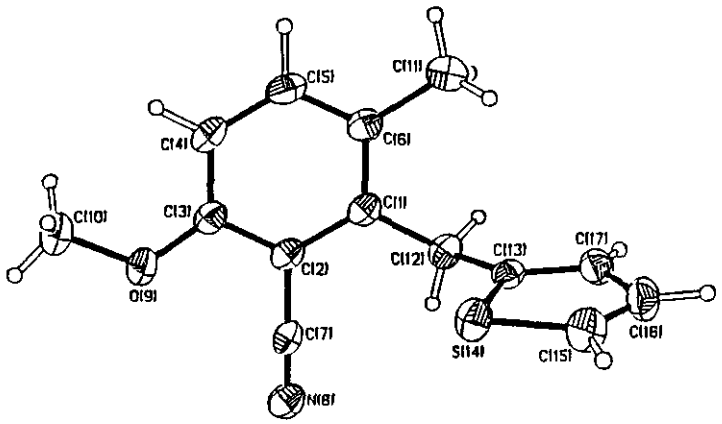
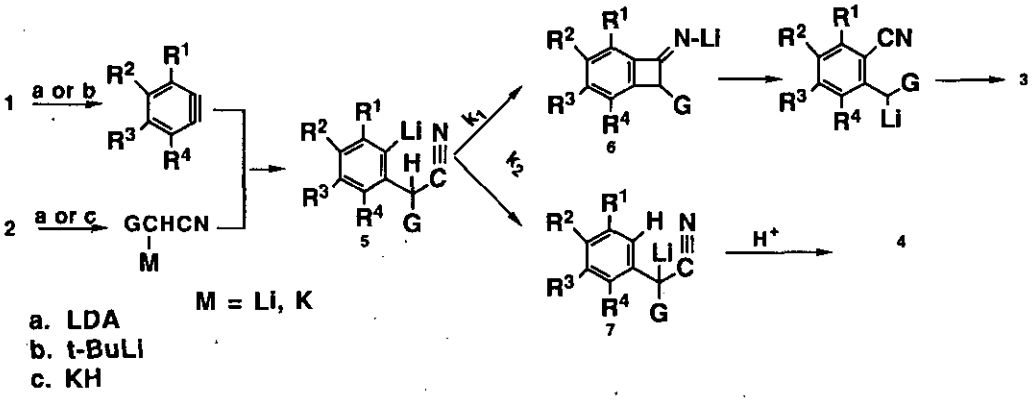


Figure 1 ORTEP of Molecule **3cc**

By determining the number of **3:4** product ratios ≥ 50:50 from the reaction of each of the three remaining haloarenes (**1c-e**) with (**2a-e**), a qualitative measure of their relative preference for the rearrangement pathway can be assessed. For example, both 2-bromo-4-methylanisole (**1c**) (runs 3,9,15,21) and bromobenzene (**1d**) (runs 4, 10, 16, 22) give four **3:4** ratios ≥ 50:50, and therefore exhibit greater propensities for the rearranged pathway than **1e**, which yields only three such ratios (runs 5,11 and 17). Of the **3:4** ratios ≥ 50:50 from the reaction of **1c** and **1d** with a particular hetarylacetonitrile (i.e. listed in a particular set), only those in set 2 (runs 9 and 10) are *significantly different (>95:5 vs 66:34, respectively). However,* this difference indicates that **1c** has a greater preference than **1d** for the rearrangement pathway. Thus from the above considerations, the preference of haloarenes for the rearrangement pathway appears to vary along the series **1a** ~ **1b** > **1c** > **1d** > **1e** >**1f**, which also parallels the variation in the net overall electron-donating ability of the ring substituents of the haloarenes.

A similar assessment of hetarylacetonitriles (**2a-e**) can be obtained by comparing the variation of the **3:4** product ratios within each of the five sets. Accordingly, benzimidazoylacetonitrile (**2e**) has the least propensity for the rearrangement pathway since only two of the **3:4** listed in set 5 (runs 25,26) from the reaction of **2e** with the haloarenes (**1a-f**) are ≥ 50:50. In contrast, 2-thiopheneacetonitrile

(**2c**) has the greatest preference for the rearrangement pathway since its **3:4** ratios listed in set 3 are on the average higher than of the other sets. For example, it is the only one of the nitriles to react exclusively with bromobenzene through the rearrangement pathway (run 15, set 3). Next in preference for the rearrangement pathway is 3-thiopheneacetonitrile (**2d**) which reacts exclusively with **1a** and **1b** (runs 19 and 20, set 4) and predominantly with **1c** and **1d** (runs 21 and 22, set 4) via the rearrangement pathway. Similar comparisons of the pyridylacetonitriles (**2a**) and (**2b**) indicate that **2b** is more inclined toward the rearrangement pathway since it gives the rearranged products (**3ab**), (**3bb**), and (**3cb**) exclusively when treated with **1a**, **1b**, and **1c**, respectively (runs 7-9, set 2), whereas **2a** undergoes rearrangement exclusively with only **1a** and **1b** (assuming the 1-aminoisoquinoline proceeds through the rearrangement pathway) (runs 1 and 2, set 1) and yields only slightly more **3ca** than **4ca** (60:40, respectively, run 3, set 1) when treated with **1c**. Thus, the variation in preference of **2a-e** for the tandem addition-rearrangement pathway is: **2c > 2d > 2b > 2a > 2e**. A possible explanation to account for the variations of the preference of haloarenes and hetarylacetonitriles for the rearrangement pathway can be presented by considering the effect of these reactants on the competing tandem addition-rearrangement and aryne arylation pathways suggested in Scheme 1. The variation in the proclivity of haloarenes for the pathway is directly related to the



Scheme 1

rearrangement variation in the net electron-donating ability of their substituents, with the methyl substituted haloarenes (**1a** and **1b**) exhibiting the highest predilection, methoxymethyl substituted arynes (**1c**) and unsubstituted haloarene (**1d**) displaying a modest penchant, and the methoxy- (**1e**) and dimethoxyarynes (**1f**) demonstrating the lowest preference for the rearrangement pathway. This change is in accord with the relative ability of these substituents to enhance the nucleophilicity at the 2-cyclization site in adduct (**5**), and hence the rate of ring closure (k_1), the crucial step in the tandem addition-rearrangement pathway. Because of the increased distance between the aromatic ring and the α–methinyl carbon atom, the effect of aromatic ring substituents on the α–proton abstraction step

(k_2) of the aryne arylation mechanism is less pronounced. Consequently, the changes in the product ratio **3:4** as the nature of the haloarene is varied are governed by k_2.

The variation of the product distribution shown by the hetarylacetonitriles (**2a-e**) appears to be governed by the rate of α–methinyl proton abstraction, k_2. As a result, the π–excessive thiophene ring delivered to the α–methinyl carbon in adduct **5** by **2c** and **2d** represses by induction the acidity of the α–methine hydrogen atom to such an extent that the rate of proton abstraction, k_2 in **5** is significantly less than that of the competing ring closure step, k_1, resulting in **3:4** product distributions lying heavily in favor of rearranged products **3**. On the other hand, the π–deficient pyridine ring supplied to the α-carbon in adduct (**5**) by **2a** and **2b** inductively enhances the acidity and the rate of proton abstraction of that hydrogen atom to such an extent that k_2 predominates over k_1, which leads to 3:4 product ratios heavily in favor of the latter products. Benzimidazoylacetonitrile (**2e**), the most reluctant of the hetarylacetonitriles studied here to give rearranged nitriles, probably owes its recalcitrant behavior to its ability to deliver the benzimidazoyl ring to adduct (**5**), which in turn is best able to increase both the acidity and rate of abstraction of the α–methine hydrogen atom when compared to the other hetarylacetonitriles. The increased acidity engendered by the benzimidizoyl ring most likely arises by the mutual resonance stabilizing interactions between the α-lithiated carbon and the 3-nitrogen atom of the benzimidazole ring of the resulting conjugate base.

In conclusion, we have shown that the product distributions of rearranged nitriles and aryne arylated nitriles from the LDA-mediated reactions of haloarenes and hetarylacetonitriles are a function of the nature of both starting materials. The reaction of haloarenes possessing electron-releasing and acetonitriles possessing electron-withdrawing groups tends to favor rearranged nitriles, whereas reaction of haloarenes possessing electron-attracting groups and acetonitriles containing electron-releasing groups tends to favor aryne arylated nitriles.

EXPERIMENTAL

General Aspects: ^1H and ^{13}C nmr spectra were measured in $CDCl_3$ solution on a WP 200-SY Bruker spectrometer. All chemical shifts are reported in parts per million downfield from internal tetramethylsilane. Infrared spectra (ir) were recovered on a Perkin-Elmer 283 grating spectrophotometer. Mass spectra (70 eV) were obtained on a Hewlett-Packard Model 5988A chromatograph/mass spectrometer. E. Merck silica gel 9385 (230-400 mesh) was used for flash chromatography. Reported boiling points are uncorrected; melting points were determined on an electrothermal apparatus and are uncorrected. All reactions were carried out in flame-dried flasks under nitrogen atmosphere. The haloarenes(**1b-e**)were obtained from Aldrich Chemical Company. Compounds (**1a**) and (**1f**) were prepared by treatment of 1,2,3,4-tetramethylbenzene with 2.2 eq. of NBS in DMF[3] and 1,4-dimethoxybenzene with 1.1 eq. of NBS in DMF.[2]

General Procedure for the Reaction of Haloarenes (1b-f) with Hetarylacetonitriles (3) and LDA. LDA was prepared in a flamed-dried flask flushed with nitrogen by adding diisopropylamine (2.1 g, 21 mmol) into a -78° C solution of n-BuLi (15 mmol, 2.5M in hexane) in THF (25 ml) under nitrogen atmosphere (using septum cap technique). After stirring the solution for 1(min at -78° C, the appropriate hetarylacetonitrile (**2**) (15 mmol) in THF (25 ml) was added over a period of 10 min, and the resulting solution was warmed to -40 °C. At that point, the haloarene (**1**) (5 mmol) was added dropwise over 5 min at -40° C, the resulting dark brown solution was stirred an additional 10 min, then was allowed to warm to room temperature. After stirring overnight, the reaction mixture was washed with saturated aqueous ammonium chloride solution, was extracted with CH_2Cl_2 (3 X 25 ml), and the combined extracts were dried (Na_2SO_4) and evaporated (rotary evaporator). The individual components in resulting residue were obtained in pure form by flash chromatography on silica gel using acetone-hexane (5:95) as eluent.

General Procedure for the Reaction of 1,2-Dibromo-3,4,5,6-tetramethylbenzene (1a) with Hetarylacetonitriles (2a-e), t-Butyllithium and Potassium Hydride. A solution of the nitrile (30 mmol) was added to a solution containing KH (3.42 g, 30 mmol) in 40 ml of THF and the resulting reddish clear solution was stirred for 15 min then cooled to -65 °C. Then to this solution was added the dibromoarene (**1a**) (2.92 g, 10 mmol in ether (90 ml) and hexane (10 ml) was added dropwise followed by the rapid addition of a solution of t-BuLi (20 mmol, 11.8 ml of 1.7 M solution in pentane), maintaining the temperature at -65 °C. The resulting solution, which turned deep red immediately upon addition of the t-BuLi, was stirred for 1 h, then was allowed to warm to room temperature where it was worked up in the same manner as that described for the reactions carried out using LDA.

The following compounds were isolated in pure form (yields shown are isolated yields).

2-(2-Pyridylmethyl)-3,4,5,6-tetramethylbenzonitrile (3aa): yield, 48%; yellow solid (from hexane), mp 93-96 °C; ^{1}H nmr ($CDCl_3$) δ 2.15 (s, 3 H), 2.22 (s, 3 H), 2.23 (s, 3 H), 2.50 (s, 3 H), 4.45 (s, 2 H), 6.96-7.01 (m, 2 H), 7.47-7.52 (m, 1 H), 8.48-8.52 (m, 1 H); ^{13}C nmr ($CDCl_3$) δ 16.38, 16.66, 17.08, 19.14, 41.33, 112.23, 118.91, 131.16, 122.33, 134.37, 136.46, 136.77, 137.46, 137.84, 141.05, 149.24, 159.24; ir ν_{max} ($CHCl_3$) 2213 cm^{-1}. Anal. Calcd for $C_{17}H_{18}N_2$: C, 81.56; H, 7.25; N, 11.19. Found: C, 81.72; H, 7.16; N, 11.19.

2-(3-Pyridylmethyl)-3,4,5,6-tetramethylbenzonitrile (3ab): yield, 63%; brown solid (from hexane), mp 104-105 °C; ^{1}H nmr ($CDCl_3$) δ 1.96 (s, 3H), 2.14 (s, 6 H), 2.51 (s, 3 H), 4.28 (s, 2 H), 7.16-7.25 (m, 2 H), 7.36 (br d, J = 7 Hz,1 H), 8.38 (br s, 1 H); ^{13}C nmr $CDCl_3$) δ 16.33, 16.46, 17.06, 19.07, 35.54, 112.25, 123.24, 133.73, 134.42, 134.86, 137.50, 141.27, 147.50, 149.45; ir ν_{max} ($CHCl_3$) 2214 cm^{-1}. Anal. Calcd for $C_{17}H_{18}N_2$: C, 81.56; H, 7.25; N, 11.19. Found: C, 81.70; H, 7.19; N, 11.21.

2-(2-Thiophenemethyl)-3,4,5,6-tetramethylbenzonitrile (3ac): yield, 63%; brown oil; ^{1}H nmr ($CDCl_3$) δ 2.22 (s, 3H), 2.25 (s, 6 H), 2.49 (s, 3 H), 4.40 (s, 2 H), 6.73-6.75 (m, 1 H), 6.80-6.87 (m, 1 H), 7.01 (d, J = 5 Hz,1 H); ^{13}C nmr ($CDCl_3$) δ

16.41, 17.12, 19.07, 32.93, 111.72, 118.57, 123.57, 124.98, 126.59, 133.56, 134.68, 137.53, 138.71, 141.12, 142.00: ir ν_{max} ($CHCl_3$) 2212 cm^{-1}. Anal. Calcd for $C_{16}H_{17}NS$: C, 75.24; H, 7.24; N, 5.48. Found: C, 75.19; H, 7.11; N, 5.34.

2-(3-Thiophenemethyl)-3,4,5,6-tetramethylbenzonitrile (3ad): yield, 70%; thick oil; ^1H nmr ($CDCl_3$) δ 2.19 (s, 3H) 2.21 (s, 3 H), 2.24 (s, 3 H), 2.49 (s, 3 H), 4.22 (s, 2 H), 6.79 (s, 1 H), 6.91 (d, J = 5 Hz, 1 H), 7.21 (d, J = 5 Hz, 1 H). Anal. Calcd for $C_{16}H_{17}NS$: C, 75.24; H, 7.24; N, 5.48. Found: C, 75.28; H, 7.22; N, 5.41.

2-(2-Benzimidazoylmethyl)-3,4,5,6-tetramethylbenzonitrile (3ae): yield, 66%; mp 249-254 °C (from hexane); ^1H nmr ($CDCl_3$) δ 2.14 (s, 3H), 2.16 (s, 3 H), 2.34 (s, 3 H), 2.45 (s, 3 H), 4.53 (s, 2 H), 7.13-7.18 (m, 2 H), 7.46 (m, 2 H); ir ν_{max} ($CHCl_3$) 3384, 2214 cm^{-1}. Anal. Calcd for $C_{19}H_{19}N_3$: C, 78.86; H, 6.61; N, 14.52. Found: C, 79.01; H, 6.71; N, 14.34.

2-(3-Pyridylmethyl)-3,6-dimethylbenzonitrile (3bb): yield, 51%; brown liquid; ^1H nmr ($CDCl_3$) δ 2.17 (s, 3H), 2.45 (s, 3 H), 4.19 (s, 2 H), 7.07-7.36 (m, 4 H), 8.30-8.40 (m, 2 H); ^{13}C nmr ($CDCl_3$) δ 19.34, 20.51, 34.93, 114.28, 117.45, 123.38, 128.58, 133.77, 134.60, 135.03, 135.51, 140.32, 147.75, 149.55; ir ν_{max} ($CHCl_3$) 2217 cm^{-1}. Anal. Calcd for $C_{15}H_{14}N_2$: C, 81.04; H, 6.34; N, 12.06. Found: C, 81.01; H, 6.51; N, 12.30.

2-(2-Thiophenemethyl)-3,6-dimethylbenzonitrile (3bc): yield, 58%; yellow oil, bp 170-175 °C / 1 torr; ^1H nmr ($CDCl_3$) δ 2.32 (s, 3 H), 2.51 (s,3 H), 4.37 (s, 2 H), 6.76-6.77(m, 1 H), 6.85-6.90 (m, 1 H), 6.70-7.12 (m, 2 H), 7.26 (d, J = 8 Hz, 1 H); ^{13}C nmr ($CDCl_3$) δ 19.25, 20.57, 32.28, 113.85, 117.44, 123.86, 125.33, 126.71, 128.45, 134.55, 140.18, 141.14, 141.92; ir ν_{max} ($CHCl_3$) 2217 cm^{-1}. Anal. Calcd for $C_{14}H_{13}NS$: C, 73.92; H, 5.76; N, 6.16. Found: C, 73.82; H, 5.86; N, 6.44.

2-(3-Thiophenemethyl)-3,6-dimethylbenzonitrile (3bd):. yield, 58%; thick liquid; ^1H nmr ($CDCl_3$) δ 2.26 (s, 3 H), 2.51 (s,3 H), 4.20 (s, 2 H), 6.81-7.26 (m,5 H), 7.49-7.51 (m, 2 H); ir ν_{max} ($CHCl_3$) 2218 cm^{-1}. Anal. Calcd for $C_{14}H_{13}NS$: C, 73.92; H, 5.76; N, 6.16. Found: C, 73.92; H, 5.96; N, 6.54.

2-(2-Benzimidazoylmethyl)-3,6-dimethylbenzonitrile (3be): yield, 51%; mp 258-260 °C (from hexane); ^1H nmr ($CDCl_3$) δ 2.43 (s, 3 H), 2.47 (s, 3 H), 4.48 (s, 2 H), 7.07-7.24 (m, 4 H), 7.49-7.51 (m, 2 H); ir ν_{max} ($CHCl_3$) 3220, 2215 cm^{-1}. Anal. Calcd for $C_{17}H_{15}N_3$: C, 78.13; H, 5.79; N, 16.08. Found: C, 78.12; H, 5.86; N, 16.44.

2-(3-Pyridylmethyl)-6-methoxy-3-methylbenzonitrile (3cb): yield, 46%; thick liquid; ^1H nmr ($CDCl_3$) δ 2.16 (s, 3 H). 3.89 (s, 3 H), 4.18 (s, 2 H), 6.79 (d, J = 9 Hz, 1 H)), 7.13-7.41 (m, 3 H), 8.39-8.57 (m, 2 H); ir ν_{max} ($CHCl_3$) 2223 cm^{-1}. Anal.Calcd for $C_{15}H_{14}N_2O$: C, 75.61; H, 5.92; N, 11.02. Found: C, 75.92; H, 5.86; N, 10.88.

2-(2-Thiophenemethyl)-6-methoxy-3-methylbenzonitrile (3cc): yield, 38%; thick liquid; ^1H nmr ($CDCl_3$) δ 2.28 (s, 3 H), 3.88 (s, 3 H), 4.32 (s, 2 H), 6.74-6.87 (m, 3 H), 7.08-7.11 (m, 1 H), 7.24-7.31 (m, 1 H); ir ν_{max} ($CHCl_3$) 2223 cm^{-1}. Anal. Calcd for $C_{14}H_{13}NOS$: C, 69.12; H, 5.39; N, 5.76. Found: C, 68.99; H, 5.36; N, 5.88.

2-(3-Thiophenemethyl)-6-methoxy-3-methylbenzonitrile (3cd): yield, 35%; thick liquid; ^{1}H nmr ($CDCl_3$) δ 2.58 (s, 3 H), 3.47 (s, 3 H), 4.12 (s, 2 H), 6.58 (d, J = 8 Hz, 1 H), 7.01-7.44 (m, 3 H), 7.77 (s, 1 H); ir ν_{max} ($CHCl_3$) 2223 cm^{-1}. Anal. Calcd for $C_{14}H_{13}NOS$: C, 69.12; H, 5.39; N, 5.76. Found: C, 69.12; H, 5.35 N, 5.78.

2-(2-Thiophenemethyl)benzonitrile (3dc): yield, 36%, thick liquid; ^{1}H nmr ($CDCl_3$) δ 4.36 (s, 2 H), 6.89-6.43 (m, 2 H), 7.15-7.64 (m, 5 H); ^{13}C nmr ($CDCl_3$) δ 34.17, 112.11, 117.57, 124.42, 125.89, 126.84, 126.97, 129.57, 132.65, 132.87, 140.88, 143.86 ; ir ν_{max} ($CHCl_3$) 2233 cm^{-1}. Anal. Calcd for $C_{12}H_9NS$: C, 72.35; H, 4.55; N, 7.03. Found: C, 72.31; H, 4.56; N, 7.12.

2-(3-Thiophenemethyl)benzonitrile (3dd): yield, 40%, thick liquid; ^{1}H nmr ($CDCl_3$) δ 4.19 (s,2 H), 6.93-7.02 (m, 2 H), 7.23-7.63 (m, 5 H); ^{13}C nmr ($CDCl_3$) δ 34.80, 112.29, 117.83, 122.3, 125.93, 128.71, 127.97, 129.70, 132.78, 138.71, 144.30; ir ν_{max} ($CHCl_3$) cm^{-1}. Anal. Calcd for $C_{12}H_9NS$: C, 72.35; H, 4.55; N, 7.03. Found: C, 72.46; H, 4.76; N, 4.44.

2-(2-Benzimidazoyl)-3-methoxyphenylacetonitrile (4ce): yield, 25%; thick liquid: ^{1}H nmr ($CDCl_3$) δ 3.62 (s, 3 H), 5.62 (s, 1 H), 6.81-7.20 (m, 9H). Anal. Calcd for $C_{16}H_{13}N_3O$: C, 72.99; H, 4.98; N, 15.96. Found: C, 70.72; H, 5.06; N, 16.17.

α-(2-Pyridyl)-2,5-Dimethoxyphenylacetonitrile (4fa): yield, 39%; thick liquid; ^{1}H nmr ($CDCl_3$) δ 3.73 (s, 3 H), 3.81 (s, 3 H), 4.33 (s, 2 H), 6.76 (d, J = 9 Hz, 1 H), 6.98-7.05 (m, 2 H), 7.45-7.49 (m, 2 H), 8.44-8.48 (m, 1 H). Anal. Calcd for $C_{15}H_{14}N_2O_2$: C, 70.85; H, 5.55; N, 11.02. Found: C, 70.72; H, 5.46; N, 11.17.

α-(3-Pyridyl)-2,5-Dimethoxyphenylacetonitrile (4fb): yield, 42%; thick liquid; ^{1}H nmr ($CDCl_3$) δ 3.74 (s, 3 H), 3.76 (s, 3 H), 5.54 (s, 1 H), 6.81 (s, 2 H), 6.94 (s, 1 H), 6.23-7.27 (m, 1 H), 7.66-7.72 (m, 1 H), 8.50-8.60 (m, 2 H); ^{13}C nmr ($CDCl_3$) δ 34.17, 112.11, 117.57, 124.42, 125.89, 126.84, 126.97, 129.57, 132.65, 132.87, 140.88, 143.86; ir ν_{max} ($CHCl_3$) 2243 cm^{-1}. Anal. Calcd for $C_{15}H_{14}N_2O_2$: C, 70.85; H, 5.55; N, 11.02. Found: C, 70.82; H, 5.66; N, 11.12.

α-(2-Thienyl)-2,5-Dimethoxyphenylacetonitrile (4fc): yield, 44%; thick liquid; ^{1}H nmr ($CDCl_3$) δ 3.74 (s, 3 H), 3.81 (s, 3 H), 5.73 (s, 1 H), 6.83 (s, 2 H), 6.84-7.30 (m, 4 H); ir ν_{max} ($CHCl_3$) 2243 cm^{-1}. Anal. Calcd for $C_{14}H_{13}NO_2S$: C, 64.86; H, 5.05; N, 5.40. Found: C, 64.82; H, 5.06; N, 5.44.

α-(3-Thienyl)-2,5-Dimethoxyphenylacetonitrile (4fd): yield, 44%; thick liquid; ^{1}H nmr ($CDCl_3$) δ 3.72 (s, 3 H), 3.81 (s, 3 H), 5.75 (s, 1 H), 6.84 (s, 2 H), 6.81-7.32 (m, 4 H); ir ν_{max} ($CHCl_3$) 2242 cm^{-1}. Anal. Calcd for $C_{14}H_{13}NO_2S$: C, 64.86; H, 5.05; N, 5.40. Found: C, 64.87; H, 5.06; N, 5.34.

2-(2-Benzimidazoylmethyl)-3,6-dimethoxybenzonitrile (4fe): yield, 42%, yellow solid, mp 176-178 °C (from hexane); ^{1}H nmr ($CDCl_3$) δ 3.67 (s, 3 H), 3.82 (s, 3 H), 5.73 (1 H), 6.83 (s, 2 H), 7.02 (s, 1 H), 7.16-7.24 (m, 2 H), 7.48-7.53 (m, 2 H); ^{13}C nmr ($CDCl_3$) δ 34.33, 55.60, 55.87, 112.16, 114.30, 114.71, 118.70, 123.42, 124.02, 131.52, 134.81, 148.41, 149.02, 149.97,

153.78; ir ν_{max} ($CHCl_3$) cm^{-1}. Anal. Calcd for $C_{17}H_{15}N_3O_2$: C, 69.61; H, 5.15; N, 14.33. Found: C, 69.82; H, 5.16; N, 14.21.

ACKNOWLEDGEMENTS

This work was sponsored in part by grants from the Welch Foundation, Houston, TX and the donors of the Petroleum Research Foundation, administered by the American Chemical Society. We also thank Marcus Hansen and Hy Ly for performing flash chromatographic separations of some of the reaction mixtures.

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8. $C_{14}H_{13}NOS$, formula weight: 243.3. Triclinic, space group $P\bar{1}$, a = 7.718 (2), b = 8.591 (2), c = 10.057 (2) Å, α = 94.09 (2), β = 105.33 (2), γ = 99.02 (2)^{o}, V = 630.7 (3) Å^3, Z = 2, D_c = 1.281 g·cm^{-3}, R = 0.034, Rw = 0.057 for 1397 observed reflections [$I \geq 3\sigma(I)$]. Intensity data were collected on a *Nicolet R3m/v* diffractometer with graphite-monochromated Mo-$K\alpha$ radiation, $3.5 \leq 2\theta \leq 44.0$, $\theta/2\theta$ scan. The structure was solved by direct methods using *SHELXTL-Plus* program package (G. M. Sheldrick, *Structure Determination Software Packages*, Siemens Analytical X-Ray Instruments, Inc., USA, 1990) and anisotropically refined for all non-H atoms by full-matrix least-squares analysis. Sites of H-atoms, except methyl H's, were refined. Maximum and minimum residuals on final difference Fourier maps: 0.15 and -0.21 *e*/ Å^3, respectively.

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Received, 12th March, 1992