# A FACILE ONE-STEP SYNTHESIS OF NOVEL POLYSUBSTITUTED PYRIDINES *via* THE TANDEM-ADDITION REARRANGEMENT HETARYNE REACTION

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**Abstract** - Polysubstituted pyridines have been prepared in fair yields by a one-step reaction of heteroarene 3-bromo-2,3-dimethoxy-5-(methoxymethyl)pyridine **3** and lithio alkyl- and lithio aryl-acetonitriles *via* the heteroaryne **13** generated from **3** by LDA in THF. Most lithio arylacetonitriles **4a-f** yield rearranged products **5a-f** by the tandem-addition rearrangement pathway and a 2:1 to 3:1 mixture of normal hetaryne products **6a-f** and **7a-f**. The other nitriles **4g-l** give mixtures of the usual hetaryne products in ratios of 3:1 to 4:1, **6g-l**:**7g-l**, respectively.

## INTRODUCTION

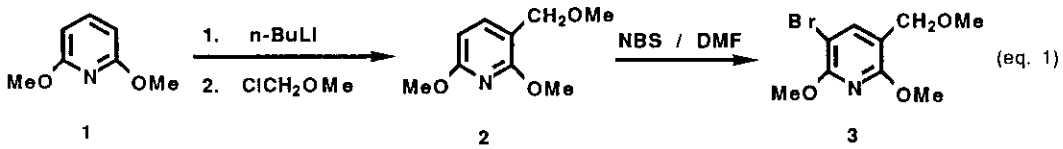
Only a few methods are presently available for the synthesis of polysubstituted pyridines since classical substitutions, which have been used with great success in aromatic systems, require more vigorous conditions and often are not regioselective. The most convenient method for the preparation of substituted pyridines is the introduction of electrophiles onto the pyridine ring by the *ortho* directed lithiation of pyridines[1] activated by halogens, hydroxy derivatives, carboxylic acid derivatives, sulfonic acid derivatives and amino groups. Our interest in the synthetic aspects of the aryne reaction[2] led us to explore the possibility of using nucleophilic additions to dehydropyridines as a useful functionalization method in the synthesis of polysubstituted pyridines. We[3] showed previously that certain 2-bromoanisoles reacted with various acetonitriles under aryne-forming conditions to yield either the expected aryne addition products and/or rearranged 3-arylmethyl-2-cyanoanisoles. The regioselective introduction of the cyano and arylmethyl functionalities was postulated to occur via the tandem-addition rearrangement aryne (TARA) mechanism.[4] This pathway was shown to compete successfully with the usual

aryne mechanism when aromatic nitriles and 2-bromoanisoles substituted with at least one electron-releasing group were used. Thus an investigation of the extension of the aryne/TARA reaction to the synthesis of polycyclic pyridines was carried out.

3-Bromo-2,6-dimethoxypyridine initially appeared to be an attractive candidate, since it could be easily prepared from the commercially available 2,6-dimethoxypyridine. However, upon treatment with arylacetonitriles and LDA it was found to give only typical hetaryne addition products. We subsequently discovered that 3-bromo-2,6-dimethoxy-5-(methoxymethyl)pyridine **3** did yield TARA products as well as typical hetaryne addition products when various nitriles were subjected to hetaryne-forming conditions, the results of which are reported herein.

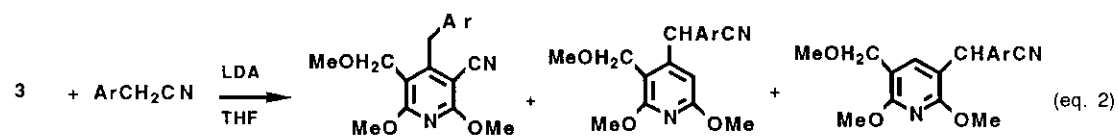
**RESULTS AND DISCUSSION**

Compound **3** was prepared by treating the commercially available 2,6-dimethoxypyridine (**1**) with n-butyllithium followed by chloromethyl methyl ether, and then brominating the 2,6-dimethoxy-3-methoxymethylpyridine (**2**) so formed with NBS in DMF (see eq. 1).




**1** **2** **3** (eq. 1)

Compound **3** was then treated with various aryl- (**4a-h**), hetaryl- (**4l,j**) and alkyl-acetonitriles (**4k,l**) and LDA in THF, and the results are shown in the Table. Of these nitriles, only the arylacetonitriles **4a-f** reacted




**4a-f** **5a-f** **6a-f** **7a-f** (eq. 2)

with **3** to give rearranged products, namely, 4-(arylmethyl)-3-cyano-2,6-dimethoxy-5-(methoxymethyl)pyridines (**5a-f**) (17-19% yield). Nmr spectroscopic analysis of these reaction mixtures revealed the absence of the other rearranged regioisomers, 3-(arylmethyl)-4-cyano-2,6-dimethoxy-5-(methoxymethyl)pyridines. These nitriles **4a-f** (eq. 2) as well as nitriles **4g-l** (eq. 3) reacted with **3** to give mixtures of the hetaryne isomeric addition products, α-(aryl)-2,6-dimethoxy-3-(methoxymethyl)-4-pyridyl- (**6a-l**) and α-(aryl)-2,6-dimethoxy-3-(methoxymethyl)-3-pyridylacetonitriles (**7a-l**) in overall yields of 31-45%. Attempts to separate these mixtures by flash chromatography or thick layer chromatography were generally unsuccessful. However, 3,4-dimethoxyphenylacetonitrile product **6g** was obtained by recrystallization of the reaction mixture containing both

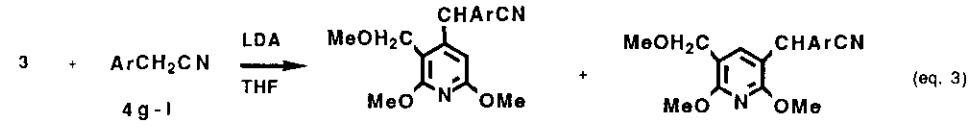
**6g** and **7g**, and the isomeric 3,4,5-trimethoxyphenylacetonitrile products **6h** and **7h** were separated from the crude reaction mixture by flash chromatography. The isomeric distribution of the major to minor isomeric hetaryne

**Table**

**Yields From Reaction of Bromopyridine 3 with Acetonitriles 4 and LDA in THF**

| Nitrile | | Rearranged Product 5 | % Yield | Hetaryne Addition Product Mixtures of 6 and 7 | % Yield |
|---|---|---|---|---|---|
| **4a** | 4-$MeOC_6H_4CH_2CN$ | **5a** | 17 | **6a + 7a** | 33 |
| **4b** | 3-$MeOC_6H_4CH_2CN$ | **5b** | 18 | **6b + 7b** | 34 |
| **4c** | 3,4-(Methylenedioxy)$C_6H_3CH_2CN$ | **5c** | 19 | **6c + 7c** | 31 |
| **4d** | 2-$FC_6H_4CH_2CN$ | **5d** | 19 | **6d + 7d** | 45 |
| **4e** | 3-$FC_6H_4CH_2CN$ | **5e** | 17 | **6e + 7e** | 34 |
| **4f** | 4-$FC_6H_4CH_2CN$ | **5f** | 18 | **6f + 7f** | 39 |
| **4g** | 3,4-$DiMeOC_6H_3CH_2CN$ | | | **6g + 7g** | 33 |
| **4h** | 3,4,5-$TriMeOC_6H_2CH_2CN$ | | | **6h + 7h** | 39 |
| **4i** | 2-Pyridylacetonitrile | | | **6i + 7i** | 29 |
| **4j** | 3-Pyridylacetonitrile | | | **6j + 7j** | 31 |
| **4k** | MeCN | | | **6k + 7k** | 44 |
| **4l** | EtCN | | | **6l + 7l** | 45 |

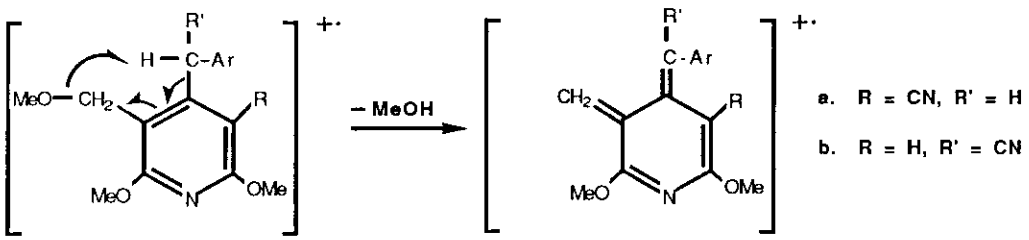
addition products were found by nmr analysis to be greater for the reactions yielding no rearranged products (i.e. 4:1, **6g-l** to **7g-l**, respectively) than those in which rearranged nitriles were also formed (i.e. 2:1-3:1, **6a-f** to **7a-f**, respectively). This indicated that the rearranged products **5a-f** were formed at the expense of the corresponding major hetaryne addition products **6a-f**.




(eq. 3)

Identification of rearranged products **5a-f** and the major hetaryne products[5] **6a-l** was accomplished by $^1H$ nmr and high resolution mass spectometric (hrms) analyses. The $^1H$ nmr spectra of **5a-f** exhibited a $-CH_2-$ resonance at $\delta$ 4.17-4.28 ppm and those of **6a-l** revealed $\alpha$-CH resonances at 5.50-5.60 ppm. In addition, the methylene hydrogens of the methoxymethyl group in **6a-l** were split by the adjacent $\alpha$-CH group into two sets of doublets. The high resolution mass spectra of the rearranged nitriles and the majority of the major hetaryne products

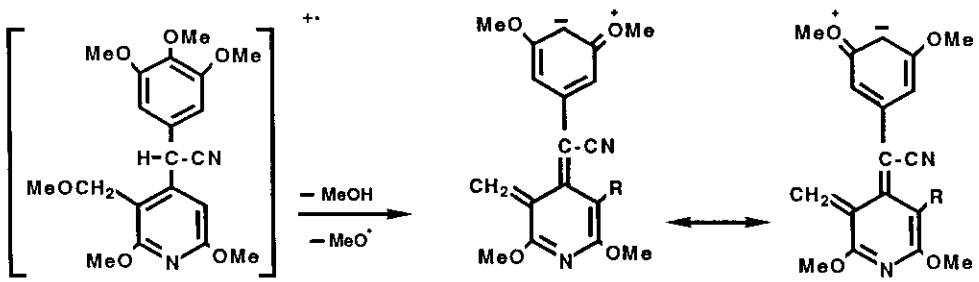
exhibited base peaks at m / z $M^+$ - 32 corresponding to the respective radical-cation **9a** and **9b** resulting from the loss of methanol between the adjacent methoxymethyl and arylmethyl substituents of the parent ions **8a** and **8b** (see Scheme 1). In addition, $M^+$ - 31 peaks, due to the loss of methoxide from the methoxymethyl group in parent **8a** were observed in the high resolution mass spectra of the rearranged products.




**8** **9**

Scheme 1

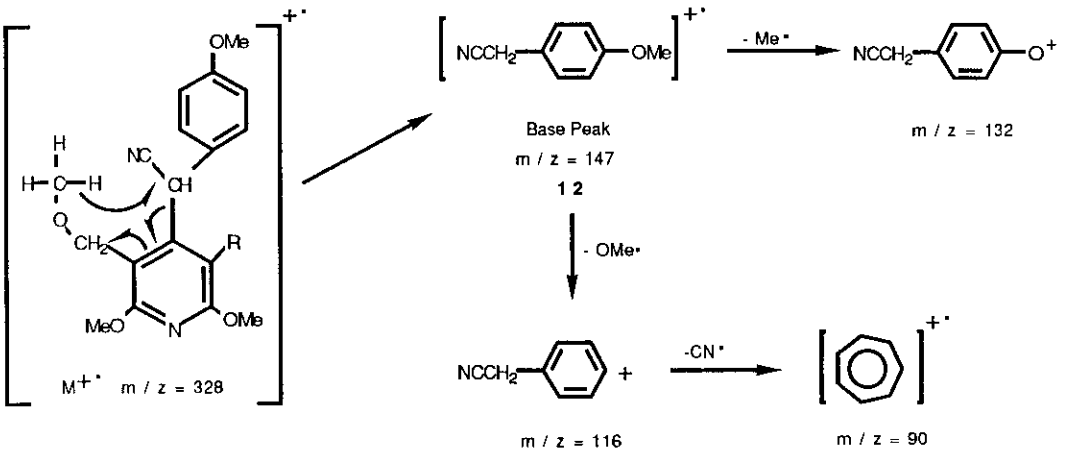
However, the mass spectrum of α-3,4-dimethoxy- (**6g**) and α-3,4,5-trimethoxyphenyl (**6h**) nitrile products




**10** **11a** **11b**

Scheme 2

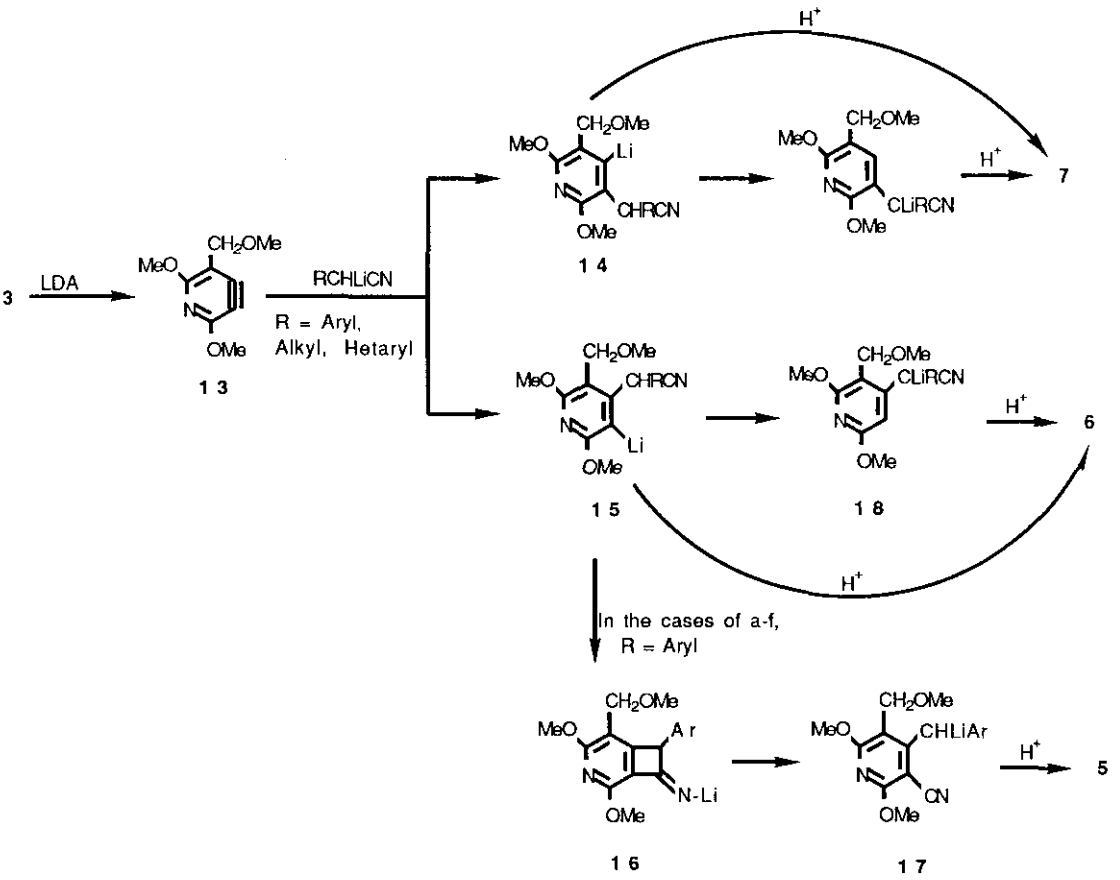
exhibit base peaks at $M^+$- 63 resulting from the loss of methanol as described previously in Scheme 1, and the loss of the 4-methoxy group from the α- aryl moiety. The fragmentation pattern of the parent ion **10** of **6h** and the resonance stabilization by the remaining methoxy groups of the resulting $M^+$ - 63 m / z ion **11a** and **11b** are shown as a typical example in Scheme 2. Interestingly, the base peak of the 4-methoxy product **6b** occurred at m / z 147.0680 ($C_9H_9NO$) corresponding to the 4-methoxyphenylacetonitrile cation-radical which was likely formed by a hydrogen rearrangement-fragmentation as shown in Scheme 3. Subsequent fragmentation of **12** gave the expected peaks at 132 (loss of methyl), 116 (loss of methoxy), and 90 (loss of CN). The $M^+$ - 63 peak for **6b** was not observed since no one more methoxy group on the α- aryl was available for resonance stabilization of this ion.




Scheme 3

Similar arylacetonitrile fragmentation patterns were observed in the mass spectra of several of the hetaryne addition products, but their intensities were considerably less than those observed in **6b**, reflecting the partitioning of the parent ion into these two aforementioned fragments. Interestingly, the mass spectrum of the one isolated minor hetaryne addition isomer **7h** revealed that the parent ion was the base peak (the intensity of its $M^{+\cdot}$ 32 peak is very small) which is consistent with its proposed structure in which the methoxymethyl and arylmethyl groups are not on adjacent ring carbon, but rather separated from each other by one carbon.

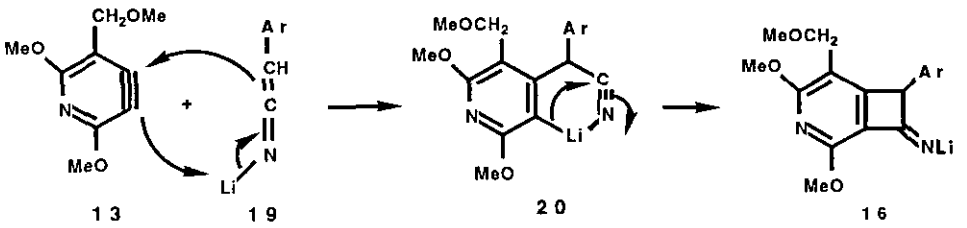
The results of this investigation can be explained in terms of both the hetaryne mechanism and the tandem-addition rearrangement hetaryne (TARA) mechanism as shown in Scheme 4. Thus the lithionitriles add mainly to the 4-position of the hetaryne **13** yielding adduct **15** and to a lesser extent to the 3-position yielding adduct **14**. The greater preponderance of the former as compared to the latter indicates that the inductive effect of the methoxy group is more important than the chelating effect of the methoxymethyl group in influencing the direction of addition to **13**. In all cases, adducts **14** and **15** were transformed into **7** and **6**, respectively, by the usual aryne mechanism. However, the adducts **15** where R = aryl proceed in part to rearranged products **5** via the TARA pathway. The two methoxy groups in **15** facilitate the cyclization to the azabenzocyclobutanimine **16** since the two groups are in the proper position to increase the electron density and hence nucleophilicity of the 3-lithiated intermediate through their strong electron-releasing resonance effect. The failure of alkylacetonitriles to undergo the TARA reaction most likely reflects the destabilizing effect of the α-alkyl groups in the corresponding rearranged ion. Further, the absence of rearranged products in the reactions of **3** and pyridyl-acetonitriles (**4l, j**), 3,4-dimethoxy- (**4g**), and 3,4,5-trimethoxy- (**4h**) phenylacetonitriles may be due




Scheme 4

to a greater tendency for the corresponding adducts to undergo α-hydrogen lithium exchange to give **18** . This α-hydrogen lithium exchange may be favored due to the resulting α-anion stabilization by the respective pyridyl, 3-methoxy, and 3,5-dimethoxy groups.

Upon further reflection, we believe that the results of the rearrangement process may be better accommodated by postulating that the bicyclic intermediate **16** is formed by a non-concerted [2+2] cycloaddition as shown in Scheme 5. Thus, hetaryne **13** and the N-lithiated ketenimine (**19**) add to yield the lithium chelated intermediate **20** which then cyclizes to **16.** The lithium chelation imposes a geometric constraint that facilitates its collapse to **16**. A similar [2+2] pathway has been suggested for the reactions of arynes with O-silylated enolates.[6] Even though the lithation of arylacetonitriles **3a-f** were carried out in the presence of excess LDA at -78 °C prior to aryne formation at -40 °C, they likely underwent only monolithiated. under these conditions. For example,

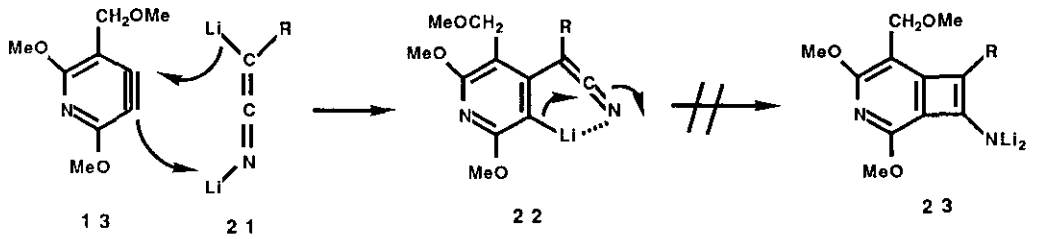



13 19 20 16

Scheme 5

Crowley and coworkers[7] have shown by $^{13}C$ nmr spectroscopy that phenylacetonitrile is only monolithiated in the presence of excess lithium bis-trimethylsilylamide.

The initially formed lithiated solutions of alkylacetonitriles **4k,l** and pyridylacetonitriles **4g,h** (unlike those of the arylacetonitilres **4a-h**) changed prior to aryne formation. A colorless solid precipitated from the former solutions, whereas the latter solutions rapidly darkened to a deep red color. Both of these processes are indicative of dilithiation. West,[8] for example, has shown that acetonitrile or propionitrile in the presence of 2 equiv of t-butyllithium yield a THF insoluble dilithiated species. Further, he found that these species exist as ketenimine derivatives, R(Li)CH=C=N-Li (**21**). Accordingly, the failure of these dilithiated species to yield rearranged product might reflect their reluctance to participate in [2+2] cycloadditions rather than inability to supply stabilizing groups to the rearranged carbanion as suggested in the original TARA mechanism. As shown in Scheme 6, the formation of the dilithiated benzocyclobutenimine (**23**) from intermediate **22** would be unlikely if due to the high energy content of the anti-aromatic species **23**. Presently, we do not understand why arylnitriles




13 21 22 23

Scheme 6

**4g** and **4h** (which normally give rearranged products in other systems) fail to give rearranged compounds with aryne **3**. Although the yields of **5a-f** from this reaction are poor, the method does provide a convenient way of synthesizing penta-substituted pyridines with unique substitution patterns. Also, the cyano and arylmethyl groups introduced by the TARA reaction are suitably configured after suitable modification for subsequent cyclization to important heterocyclic ring systems. For example, we have shown that 2-cyanodiarylmethanes provided by the

TARA reaction of arylacetonitriles and 2-bromo-4-methylanisole upon successive treatment with LDA and benzaldehydes can be readily converted into *cis*-3,4-diarylisochroman-1-ones.[9] Further, we have demonstrated that the aromatic compounds possessing the same ortho difunctionality as that found in **6a-i** can be cyclized to synthetically valuable 4-substituted isochroman-3-ones.[10] Thus the hetaryne addition products produced in this study should provide access to heretofore unknown 6-azaisochroman-3-ones.

## EXPERIMENTAL

**General Aspects**. Melting points were determined on an electrothermal apparatus and are uncorrected. Ir spectra were recorded on a Perkin-Elmer 283 grating spectrophotometer. High field (200 MHz) proton and carbon-13 spectra were taken on a IBM-Bruker WP 200-SY spectrometer. Nmr spectra were run in $CDCl_3$ solution and chemical shifts were related to $Me_4Si$. High resolution mass spectra were obtained from the Midwest Center for Mass Spectrometry. E. Merck silica gel 9385 (230-400 mesh) was used for flash chromatography. Tetrahydrofuran (THF), diisopropylamine, 2,6-dimethoxypyridine, and the acetonitriles were purchased from Aldrich Chemical Co. and were dried and distilled before use. n-BuLi and chloromethyl methyl ether were purchased also from Aldrich Chemical Co. and used as received.

**Synthesis of Bromoarene 3.** To a stirred solution of 2,6-dimethoxypyridine (0.2 mol, 26.4 ml) in 250 ml of THF was added slowly a solution of 84 ml of 2.5 M n-BuLi at -78 °C. The mixture was stirred and allowed to warm to 10° C. After stirring for 30 min it was cooled to -78 °C and quenched by the dropwise addition of chloromethyl methyl ether (16 g, 0.2 mmol) after which the resulting solution was allowed to warm to room temperature. After the THF was evaporated (rotary evaporator), the residue was dissolved in 100 ml of methylene chloride, and the methylene chloride solution was washed with water, dried ($Na_2SO_4$), and concentrated under reduced pressure to give 33.2 g (96% yield) of 2,6-dimethoxy-3-(methoxymethyl)pyridine (**2**) as a colorless liquid, bp 100-101 °C (0.15 torr); $^1$H nmr ($CDCl_3$) δ 3.33 (s, 3H, $-CH_2OC\underline{H}_3$), 3.86 (s, 3H, $OCH_3$), 3.90 (s, 3H, $OCH_3$), 4.32 (s, 2H, $C\underline{H}_2OCH_3$), 6.25 (d, $J$ = 6.8, 1H, $C_5$-Ar-H), 7.46 (d, $J$ = 6.8 Hz, 1H, $C_4$-Ar-H). A 13.7g (0.075 mol) of **2** was then added to 50 ml of DMF, to which was then added N-bromosuccinimide (13.5 g, 0.076 mol) at room temperature. After the resulting mixture was stirred for 1 h, water (75 ml) was added, and the milky suspension was extracted with methylene chloride (2 X 100 ml). The combined methylene chloride extracts were washed with water, dried ($Na_2SO_4$), and concentrated under reduced pressure to yield a thick oil, which was distilled in a Kugelrohr apparatus (120-125 °C, 0.5 Torr) to yield 19.1 g (97%) of **3**. Recrystallization of **3** from hexane gave white crystals, mp 52-53 °C; $^1$H nmr ($CDCl_3$) δ 3.37 (s, 3H, $-CH_2OC\underline{H}_3$), 3.92 (s, 3H, $OCH_3$), 3.97 (s, 3H, $OCH_3$), 4.32 (s, 2H, $C\underline{H}_2OCH_3$), 7.69 (s, 1H, Ar-H); ir ($CHCl_3$) $\nu_{max}$ 1592, 1476, 1398, 1324, 1265 cm$^{-1}$.

General Procedure for the Reaction of 3 with Aryl-, Alkyl-, and Heterylacetontriles and LDA in THF. In a flame-dried flask flushed with nitrogen, LDA (30 mmol) was prepared by adding diisopropylamine (30 mmol) into a solution of n-BuLi (30 mmol, 2.5 M in hexane) in THF (50 ml) at -78 °C, the appropriate acetonitrile (10 mmol) in THF (50 ml) was added dropwise over 20 min. The reaction mixture was stirred at -78° C and then allowed to warm to -40 °C, and the solution was allowed to warm to room temperature slowly over a period of 2 h. The resulting dark reddish solution was then quenched with absolute ethanol, the THF was evaporated under reduced pressure, and the residue was extracted with methylene chloride (2 X 50 ml). The combined extracts were washed with brine, dried ($Na_2SO_4$), and concentrated (rotary evaporator) to provide an oil which was purified by flash column chromatography using a mixture of hexane/acetone (19:1) as the eluent.

3-Cyano-2,6-dimethoxy-4-(4'-methoxybenzyl)-5-(methoxymethyl)pyridine (**5a**): White solid (acetone/ hexane); mp 115-119 °C; $^1$H nmr ($CDCl_3$) δ 3.36 (s, 3H, $-CH_2OCH_3$,), 3.76 (s, 3H, $OCH_3$), 4.01 (s, 3H, $OCH_3$), 4.04 (s, 3H, $OCH_3$), 4.20 (s, 2H, $-CH_2Ar$), 4.39 (s, 2H, $-CH_2OCH_3$,, 6.82 (d, $J$ = 7.1 Hz, 2H, Ar-H), 7.11 (d, $J$ =7.1 Hz, 2H, Ar-H); ir ($CHCl_3$) $\nu_{max}$ 2221 cm$^{-1}$ (CN); hrms, m / z M$^+$ calcd for $C_{18}H_{20}N_2O_4$ 328.1418, obsd 328.1428; $^{13}$C nmr ($CDCl_3$) δ 35.42, 54.10, 54.19, 54.93, 55.01, 58.04, 64.19, 88.77, 111.16, 113.74, 115.39, 129.01, 129.27, 157.76, 158.08, 163.94, 164.47.

3-Cyano-2,6-dimethoxy-4-(3'-methoxybenzyl)-5-(methoxymethyl)pyridine (**5b**): Thick oil; $^1$H nmr ($CDCl_3$) δ 3.36 (s, 3H, $-CH_2OCH_3$,), 3.77 (s, 3H, $OCH_3$), 4.01 (s, 3H, $OCH_3$), 4.04 (s, 3H, $OCH_3$), 4.20 (s, 2H, $-CH_2Ar$), 4.39 (s, 2H, $-CH_2OCH_3$), 7.09 (d, $J$ = 8.0 Hz, 2H, 3' and 5' Ar-H), 7.13 (d, $J$ = 8.0 Hz, 2H, 2' and 6' Ar-H); ir ($CHCl_3$) $\nu_{max}$ 2220 cm$^{-1}$ (CN); hrms, m / z M$^+$ calcd for $C_{18}H_{20}N_2O_4$ 328.1418, obsd 328.1324.

3-Cyano-2,6-dimethoxy-4-(3',4'-methylenedioxybenzyl)-5-(methoxymethyl)pyridine (**5c**): White needles (acetone / hexane); mp 129-130 °C; $^1$H nmr ($CDCl_3$) δ 3.36 (s, 3H, $-CH_2OCH_3$), 4.01 (s, 3H, $OCH_3$), 4.04 (s, 3H, $OCH_3$), 4.18 (s, 2H, $-CH_2Ar$), 4.38 (s, 2H, $-CH_2OCH_3$), 5.91 (s, 2H, $-OCH_2-$), 6.65-6.70 (m, 3H, Ar-H); ir ($CHCl_3$) $\nu_{max}$ 2220 cm$^{-1}$ (CN); hrms, m / z M$^+$ calcd for $C_{18}H_{18}N_2O_5$ 342.1211, obsd 342.1219; $^{13}$C Nmr ($CDCl_3$) δ 36.03, 54.31, 54.40, 58.28, 64.35, 89.01, 100.11, 108.18, 108.81, 111.41, 115.49, 121.58, 130.81, 146.22, 147.79, 157.52, 164.13, 164.83.

3-Cyano-4-(2'-fluorobenzyl)-2,6-dimethoxy-5-(methoxymethyl)pyridine (**5d**): White crystals (acetone / hexane); mp 65-66 °C; $^1$H nmr ($CDCl_3$) δ 3.30 (s, 3H, $-CH_2OCH_3$), 4.01 (s, 3H, $OCH_3$), 4.04 (s, 3H, $OCH_3$), 4.27 (s, 2H, $-CH_2Ar$), 4.32 (s, 2H, $-CH_2OCH_3$), 6.96-7.03 (m, 4H, ArH); ir ($CHCl_3$) $\nu_{max}$ 2222 cm$^{-1}$ (CN); hrms, m / z *calcd for (M$^+$ - MeOH) 284.0957, obsd 284.1011*; $^{13}$*C nmr* ($CDCl_3$) δ 29.24, 54.31, 54.40, 58.18, 64.27, 89.33, 111.84, 114.95, 115.39, 124.15, 128.41, 129.45, 129.51, 156.36, 162.87, 164.03, 164.59.

3-Cyano-4-(3'-fluorobenzyl)-2,6-dimethoxy-5-(methoxymethyl)pyridine (**5e**): Light yellow thick oil; $^1$H nmr ($CDCl_3$) δ 3.33 (s, 3H, $-CH_2OCH_3$), 4.01 (s, 3H, $OCH_3$), 4.03 (s, 3H, $OCH_3$), 4.24 (s, 2H, $-CH_2Ar$), 4.35 (s, 2H, $CH_2OCH_3$), 6.86-7.21 (m, 4H, ArH); ir ($CHCl_3$) $\nu_{max}$ 2221 cm$^{-1}$ (CN); hrms, m / z calcd M$^+$ for $C_{17}H_{17}N_2O_3F$ 316.1219, obsd 312.1100.

3-Cyano-4-(4'-fluorobenzyl)-2,6-dimethoxy-5-(methoxymethyl)pyridine (**5f**): White crystals (acetone / hexane); mp 92-93 °C; $^1$H nmr ($CDCl_3$) δ 3.33 (s, 3H, $-CH_2OCH_3$), 4.01 (s, 3H, $OCH_3$), 4.03 (s, 3H, $OCH_3$), 4.24 (s, 2H, $-CH_2Ar$), 4.35 (s, 2H, $-CH_2OCH_3$), 6.86-7.21 (m, 4H, ArH); ir ($CHCl_3$) $\nu_{max}$ 2220 cm$^{-1}$ (CN); hrms, m / z calcd M$^+$ for $C_{17}H_{17}N_2O_3F$ 316.1219, obsd 316.1217; $^{13}$C nmr ($CDCl_3$) δ 35.61, 54.31, 54.42, 58.24, 64.37, 88.95, 111.41, 115.11, 115.55, 129.86, 130.03, 132.79, 157.28, 159.12, 164.15, 164.71.

α-(3'-Methoxyphenyl)-2,6-dimethoxy-3-(methoxymethyl)-4-pyridylacetonitrile (**6a**): Thick oil; $^1$H nmr ($CDCl_3$) δ 3.42 (s, 3H, $-CH_2OCH_3$), 3.45 (s, 3H, OMe), 4.28 (d, $J$ = 10.0 Hz, 1H, $CH_2$-Ar), 4.39 (d, $J$ = 10.0 Hz, 1H, $CH_2$-Ar), 5.59 (s, 1H, CH-CN) , 5.97 (s, 1H, Ar-H), 6.42 (s, 1H, Ar-H), 6.76-6.84 (m, 3H, Ar-H); ir ($CHCl_3$) $\nu_{max}$ 2244 cm$^{-1}$ (CN); hrms, m / z M$^+$ calcd for $C_{18}H_{20}N_2O_4$ 328.1418, obsd 328.1432.

α-(4'-Methoxyphenyl)-2,6-dimethoxy-3-(methoxymethyl)-4-pyridylacetonitrile (**6b**): Thick oil; $^1$H nmr ($CDCl_3$) δ 3.35 (s, 3H, $-CH_2OCH_3$), 3.75 (s, 3H, OMe), 3.93 (s, 6H, 2 OMe), 4.39 (d, $J$ = 10.0 Hz, 1H, $-CH_2OCH_3$,), 5.59 (d, $J$ = 10.0 Hz, 1H, $-CH_2OCH_3$,), 5.56 (s, 1H, CH-CN), 6.48 (s, 1H, Ar-H), 6.34-7.25 (m, 4H, Ar-H); ir ($CHCl_3$) $\nu_{max}$ 2246 cm$^{-1}$ (CN); hrms, m / z M$^+$ calcd for $C_{18}H_{20}N_2O_4$ 328.1418, obsd 328.1424.

α-(3',4'-Methylenedioxyphenyl)-2,6-dimethoxy-3-(methoxymethyl)-4-pyridylacetonitrile (**6c**): Thick oil; $^1$H nmr ($CDCl_3$) δ 3.34 (s, 3H, $-CH_2OCH_3$), 3.90 (s, 3H, $OCH_3$), 3.93 (s, 3H, $OCH_3$), 4.33 (d, $J$ = 12.0 Hz, 1H, $-CH_2OCH_3$), 4.53 (d, $J$ = 12.0 Hz, 1H, $-CH_2OCH_3$), 5.59 (s, 1H, CH-CN), 5.93 (s, 1H, 2H, $-O-CH_2-O$), 6.43 (s,1H, Ar-H), 6.76-7.78 (m, 3H, Ar-H); ir ($CHCl_3$) $\nu_{max}$ 2246 cm$^{-1}$ (CN); m / z M$^+$ calcd for $C_{18}H_{18}N_2O_5$ 342.1211, obsd 342.1219.

α-(2'-Fluorophenyl)-2,6-dimethoxy-3-(methoxymethyl)-4-pyridylacetonitrile (**6d**): Light yellow thick liquid; $^1$H nmr δ 3.36 (s, 3H, $-CH_2OCH_3$), 3.92 (s, 3H, $OCH_3$), 3.98 (s, 3H, $OCH_3$), 4.38 (d, $J$ = 8.6 Hz, 1H, $-CH_2OCH_3$), 4.42 (d, $J$ = 8.6 Hz, 1H, $-CH_2OCH_3$), 5.68 (s, 1H, CH-CN), 6.38 (s, 1H, Ar-H), 7.03-7.20 (m, 4H, Ar-H); ir ($CHCl_3$) $\nu_{max}$ 2244 cm$^{-1}$ (CN); hrms m / z M$^+$ calcd for $C_{17}H_{17}N_2O_3F$ 316.1219, obsd 316.1212.

α-(3'-Fluorophenyl)-2,6-dimethoxy-3-(methoxymethyl)-4-pyridylacetonitrile (**6e**): Light yellow thick liquid; $^1$H nmr δ 3.36 (s, 3H, $-CH_2OCH_3$), 3.92 (s, 3H, $OCH_3$), 3.98 (s, 3H, $OCH_3$), 4.38 (d, $J$ = 8.6 Hz, 1H, $-CH_2OCH_3$), 4.42 (d, $J$ = 8.6 Hz, 1H, $-CH_2OCH_3$), 5.68 (s, 1H, CH-CN), 6.38 (s, 1H, Ar-H), 7.03-7.20 (m, 4H, Ar-H); ir ($CHCl_3$) $\nu_{max}$ 2244 cm$^{-1}$ (CN); hrms m / z M$^+$ calcd for $C_{17}H_{17}N_2O_3F$ 316.1219, obsd 316.1212.

α-(4'-Fluorophenyl)-2,6-dimethoxy-3-(methoxymethyl)-4-pyridylacetonitrile (**6f**): Light yellow thick liquid; $^1$H nmr δ 3.33 (s, 3H, -$CH_2OCH_3$), 3.90 (s, 3H, $OCH_3$), 3.93 (s, 3H, $OCH_3$), 4.36 (d, *J* = 10.0 Hz, 1H, -$CH_2OCH_3$), 4.51 (d, *J* = 10.0 Hz, 1H, -$CH_2OCH_3$), 5.65 (s, 1H, CH-CN), 6.37 (s, 1H, Ar-H), 7.04-7.08 (m, 2H, Ar-H), 7.28-7.33 (m, 2H, Ar-H); ; ir ($CHCl_3$) $\nu_{max}$ 2245 cm$^{-1}$ (CN); hrms m / z M$^+$ calcd for $C_{17}H_{17}N_2O_3F$ 316.1219, obsd 316.1213.

α-(3',4'-Dimethoxyphenyl)-2,6-dimethoxy-3-(methoxymethyl)-4-pyridylacetonitrile (**6g**): White solid (acetone / hexane); mp 84-85 °C; $^1$H nmr ($CDCl_3$) δ 3.37 (s, 3H, -$CH_2OCH_3$,), 3.83 (s, 3H, $OCH_3$), 3.84 (s,3H, $OCH_3$), 3.90 (s, 3H, $OCH_3$), 3.95 (s, 3H, $OCH_3$), 4.40 (d, *J* = 8.0 Hz, 1H, -$CH_2OCH_3$), 4.54 (d, *J* = 8.0 Hz, 1H, -$CH_2OCH_3$), 5.61 (s, 1H, CH-CN), 6.41 (s, 1H, Ar-H), 6.34-7.25 (m, 3H, Ar-H); ir ($CHCl_3$) $\nu_{max}$ 2240 cm$^{-}$; hrms m / z calcd M$^+$ for $C_{19}H_{22}N_2O_5$ 358.1523, obsd 358.1522; $^{13}$C nmr ($CDCl_3$) δ 37.37, 53.33, 53.63, 55.57, 57.68, 64.16, 101.31, 108.33, 110.75. 111.14, 118.43, 119.96, 126.34, 148.86, 149.21, 149.45, 161.46, 162.79.

α-(3',4',5'-Trimethoxyphenyl)-2,6-dimethoxy-3-(methoxymethyl)-4-pyridylacetonitrile (**6h**): Thick oil; $^1$H nmr ($CDCl_3$) δ 3.38 (s, 3H, -$CH_2OCH_3$), 3.82 (s, 6H, 2 $OCH_3$), 3.84 (s, 3H, $OCH_3$), 3.91 (s, 3H, $OCH_3$), 3.95 (s, 3H, $OCH_3$), 4.40 (d, *J* = 10.0 Hz, 1H, -$CH_2OCH_3$), 4.54 (d, *J* = 10.0 Hz, 1H, -$CH_2OCH_3$), 5.59 (s, 1H, CH-CN), 6.38 (s, 1H, Ar-H), 6.58 (s, 2H, Ar-H); ir ($CHCl_3$) $\nu_{max}$ 2240 cm$^{-1}$; hrms, m / z calcd M$^+$ for $C_{20}H_{24}N_2O_6$ 388.1628, obsd 388.1653; $^{13}$C nmr ($CDCl_3$) δ 37.37, 53.33, 53.63, 55.57, 57.68, 64.16, 101.31, 108.33, 110.75. 111.14, 118.43, 119.96, 126.34, 148.86, 149.21, 149.45, 161.46, 162.79.

α-(2'-Pyridyl)-2,6-dimethoxy-3-(methoxymethyl)-4-pyridylacetonitrile (**6i**): Light yellow thick liquid; $^1$H nmr ($CDCl_3$) δ 3.28 (s, 3H, $CH_2OCH_3$), 3.85 (s, 3H, $OCH_3$), 3.89 (s, 3H, $OCH_3$), 4.32 (d, *J* = 12.0 Hz, 1H, -$CH_2OCH_3$), 4.50 (d, *J* = 12.0 Hz, 1H, -$CH_2OCH_3$), 5.67 (s, 1H, CH-CN), 6.33 (s, 1H, Ar-H), 7.20-7.29 (m, 1H, Ar-H), 7.66 (m, 1H, Ar-H), 8.49-8.58 (m, 2H, ArH); ir($CHCl_3$) $\nu_{max}$ 2240 cm$^{-1}$(CN); m / z M$^+$ calcd for $C_{16}H_{17}N_3O_3$ 299.3291, obsd 299.3288; $^{13}$C nmr ($CDCl_3$) δ 40.76, 53.39, 53.63, 57.68, 64.24, 101.37, 108.74, 118.29, 122.14, 123.02, 137.23, 148.12, 149.71, 154.03, 161.48, 162.76.

α-(3'-Pyridyl)-2,6-dimethoxy-3-(methoxymethyl)-4-pyridylacetonitrile (**6j**): Thick oil, $^1$H nmr ($CDCl_3$) δ 3.28 (s, 3H, -$CH_2OCH_3$), 3.86 (s, 3H, $OCH_3$), 3.90 (s, 3H, $OCH_3$), 4.45 (d, *J* = 12.0 Hz, 1H, $CH_2OCH_3$), 4.50 (d, *J* = 12.0 Hz 1H, $CH_2OCH_3$ ), 5.67 (s, 1H, CH-CN), 6.33 (s, 1H, Ar-H), 7.20-7.30 (m, 1H, Ar-H), 7.66 (m, 1H, Ar-H), 8.49-8.58 (m, 2H, Ar-H); ir ($CHCl_3$) $\nu_{max}$ 2240 cm$^{-1}$; m / z M$^+$ calcd for $C_{16}H_{17}N_3O_3$ 299.3291, obsd 299.3279.

2,6-Dimethoxy-3-(methoxymethyl)-4-pyridylacetonitrile (**6k**): Thick oil, $^1$H nmr ($CDCl_3$) δ 3.23 (s, 3H, -$CH_2OCH_3$), 3.71 (s, 2H, $CH_2CN$), 3.81 (s, 3H, $OCH_3$), 3.84 (s, 3H, $OCH_3$), 4.34 (s, 2H, $CH_2OCH_3$), 6.33 (s, 1H, Ar-H); ir ($CHCl_3$) $\nu_{max}$ 2240 cm$^{-1}$; m / z M$^+$ calcd for $C_{11}H_{14}N_2O_3$ 222.2434, obsd 222.2439.

α-Methyl-2,6-dimethoxy-3-(methoxymethyl)-4-pyridylacetonitrile (**6l**): Thick liquid ; $^1$H nmr ($CDCl_3$) δ 1.60 (d, $J$ = 7.2 Hz, 3H, $CHCH_3$), 3.34 (s, 3H, -$CH_2OCH_3$), 3.92 (s, 3H, $OCH_3$), , 3.95 (s, 3H, $OCH_3$), 4.25 (q, $J$ = 7.2 Hz, 1H, $CHCH_3$), 4.47 (s, 2H, $CH_2OCH_3$), 6.49 (s, 1H, Ar-H); ir ($CHCl_3$) $\nu_{max}$ 2240 cm$^{-1}$ (CN); hrms, m / z M$^+$ calcd for $C_{12}H_{16}N_2O_3$ 236.1157, obsd 236.1163.

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