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Lewis acid-promoted direct substitution of 2-methoxy-3-cyanopyridines by organo cuprates. Part 3: Facile preparation of nicotinamide and nicotinic acid derivatives

Alaa A.-M. Abdel-Aziz*

Department of Pharmaceutical Chemistry, College of Pharmacy, King Saud University, PO Box 2457 Riyadh 11451, Saudi Arabia

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Abstract—2-Methoxy-3-cyano-4,6-diarylpyridines were subjected to Lewis acid-promoted nucleophilic displacement reactions with various organo cuprates to afford the corresponding 2,4,6-trisubstituted nicotinonitriles. Subsequent hydrolysis of compounds **10** and **11** afforded the corresponding 2,4,6-trisubstituted nicotinic acid **22** and nicotinamide **23** derivatives, respectively. The mechanism of the displacement reaction has been studied experimentally and by molecular modeling calculations.
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The directed construction of carbon–carbon bonds has always been a central theme in synthetic organic chemistry and the structural diversity and biological importance of nitrogen-containing heterocycles have made them attractive targets for synthesis over many years and justify continuing efforts in the development of new synthetic strategies.[1,2] The pyridine motif is among the most common heterocyclic compounds found in various therapeutic agents and is a building block for the synthesis of nicotinic acid and its amide (nicotinamide) which are used in pharmaceutical formulations, as additives in food and animal feed and as brighteners in electroplating baths and stabilizers for pigmentation in cured meat.[3,4] Thus, extensive efforts have been exerted on developing methodology for the synthesis of pyridine derivatives.[5] For example, Bryce and co-workers have reported the synthesis of pyridine derivatives from furan precursors.[6] However, introduction of substituents to pyridine rings often requires long reaction times and vigorous conditions to achieve acceptable yields under conventional heating or photolysis conditions.[7] Hence, a versatile route for the synthesis of 2,4,6-trisubstituted nicotinonitrile, 2,4,6-trisubstituted nicotinamide and 2,4,6-trisubstituted nicotinic acid derivatives under mild conditions is highly desirable. In the previous papers,[8] we reported the synthesis of 4,6-diaryl-3-cyano-2-alkoxypyridines **1** and their reactions with anhydrous hydrazine or substituted amines in the presence of a Lewis acid to give the corresponding 1*H*-pyrazolo-[3,4-*b*]pyridines **2** and 2-substituted aminopyridines **3**, respectively (Scheme 1).

This Letter describes the procedures for the smooth reaction of a wide variety of alkyl and phenyl cuprates at the 2-position and/or 3-position of 2-methoxy-3-cyanopyridines **4**, **15** and **16**, leading to the preparation of compounds of medicinal interest such as nicotinamide and nicotinic acid derivatives. Our approach depends on the reaction of 2-methoxy-3-cyanopyridines with organo cuprates promoted by a Lewis acid with or without reaction of the 3-cyano group[9] to afford a new series of pyridine derivatives. To the best of our knowledge, no Lewis acid-promoted arylation or alkylation of 2-methoxy-3-cyanopyridines through regioselective C–C bond formation under mild reaction conditions has been described in the literature. Starting compound **4** was prepared according to our previous report in which α,β-unsaturated ketones were condensed with malononitirile in sodium methoxide/methanol to yield the corresponding 2-methoxy-3-cyanopyridines **4**.[8a]

Initial experiments[10] involved attempted direct substitution reactions of phenylmagnesium bromide with 2-methoxy-3-cyano-4,6-diphenylpyridine **4** in the presence of a variety of Lewis acid-additives such as $MgBr_2$,

* Tel.: +966 562947305; fax: +966 14676220; e-mail: alaa_moenes@yahoo.com

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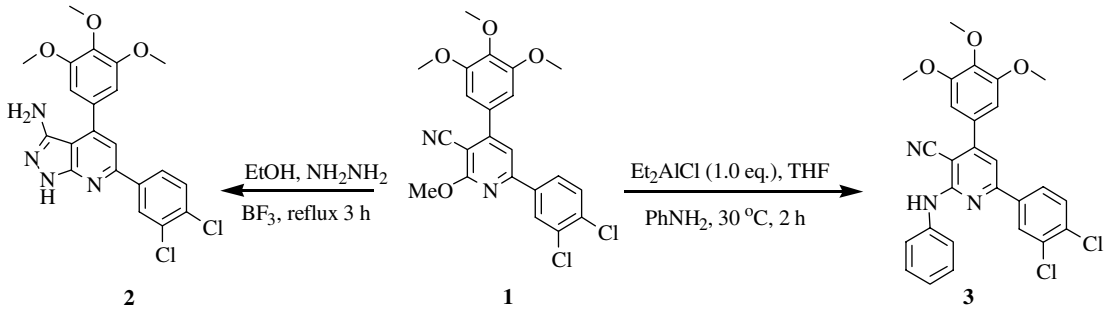


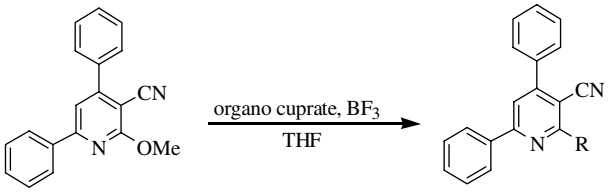
Scheme 1. Lewis acid-promoted reaction of aniline or hydrazine with the 2-methoxypyridine.

$FeCl_3$, $ZnCl_2$, $AlCl_3$ or $SnCl_4$ in THF at ambient temperature. The reactions, however, did not proceed under any of the conditions and the recovered starting material was obtained. Next, we examined the same type of reaction employing other Lewis acids. Whereas the reactions with Et_2AlCl and CuI gave the desired substituted product **12**, but in low yield, the use of $BF_3{\cdot}Et_2O$ had a dramatic effect on the rate and smoothly brought about formation of target compound **12** in almost quantitative yield under mild conditions (Table 1, entry 8). Furthermore, the nature of the solvent also affected the reaction yield. Solvents such as diethyl ether and methylene chloride afforded low yields, while the result of the reaction in THF was completely in contrast with that in toluene and benzene (disfavored nucleophilic attack), that is, THF gave arylated product, exclusively.

We were delighted to find that comparable results were obtained in the reaction employing organo cuprates containing alkyl or aryl moieties. The results from our survey are summarized in Table 1. Treatment of 2-methoxy-3-cyanopyridine **4** with cuprate reagents in the presence of $BF_3{\cdot}Et_2O$[8,11] was found to give excellent yields of 2-alkyl or 2-aryl-3-cyanopyridines, while reaction with a combination of Grignard reagent and $BF_3{\cdot}Et_2O$[12] resulted in generally lower yields.[13] This method is versatile enough to permit the introduction of a range of alkyl and aryl groups at the 2-position of the pyridine moiety. Thus, 2-methoxy-3-cyanopyridine was treated with a mixture of cyclohexylmethylmagnesium bromide (4.0 equiv), CuCN (4.4 equiv) and LiCl (8.8 equiv) in the presence of $BF_3{\cdot}Et_2O$ (2.0 equiv) at 20 °C to give 2-cyclohexylmethyl-3-cyanopyridine **14**, regioselectively, in 98% yield without any substitution at the 3-position of pyridine (Table 1, entry 10). It is noteworthy that the observed nucleophilic displacement was highly dependent on the nature of the Lewis acid, and the tendency for formation of the target product correlated approximately with the acidity of the conjugate base formed.[8b]

The generality of this reaction was examined using various starting materials containing different electronic moieties such as nitro and methoxy groups as shown

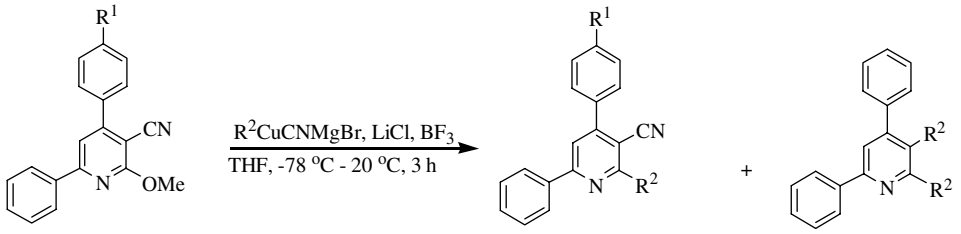
Table 1. The BF_3-promoted direct substitution of 2-methoxy-3-cyanopyridines by alkyl and phenyl cuprates[a]



Entry	Compd	Organo cuprate	R	**5–14**[b] (%)
1	**5**	MeCuCNLi, LiCl[c]	Me	93
2	**6**	EtCuCNLi, LiCl[d]	Et	96
3	**7**	*i*-PrCuCNMgBr, LiCl	*i*-Pr	89
4	**8**	*n*-BuCuCNLi, LiCl[e]	*n*-Bu	92
5	**9**	*i*-BuCuCNMgBr, LiCl	*i*-Bu	86
6	**10**	*t*-BuCuCNMgBr, LiCl	*t*-Bu	77
7	**11**	1-AdamantylCuCNMgBr, LiCl	1-Adamantyl	69
8	**12**	PhCuCNMgBr, LiCl	Ph	86
9	**13**	$PhCH_2CuCNMgBr$, LiCl	$PhCH_2$	92
10	**14**	*c*-$C_6H_{11}CH_2CuCNMgBr$, LiCl	*c*-$C_6H_{11}CH_2$	98

[a] The reaction was performed using Grignard reagent (4.0 equiv), CuCN (4.4 equiv) and $BF_3{\cdot}Et_2O$ (2.0 equiv) in the presence of LiCl (8.8 equiv) at −78 °C to 20 °C for 3 h, unless otherwise stated.
[b] Total yield after column chromatographic separation.
[c] MeLi (4.0 equiv) was used.
[d] EtLi (4.0 equiv) was used.
[e] *n*-BuLi (4.0 equiv) was used.

Table 2. Effects of electronic and steric factors on the direct substitution of 2-methoxy-3-cyanopyridines by alkyl and phenyl cuprates[a]



R^1 = H (**4**), NO_2 (**15**), MeO (**16**) **10,12,17–20** **21**

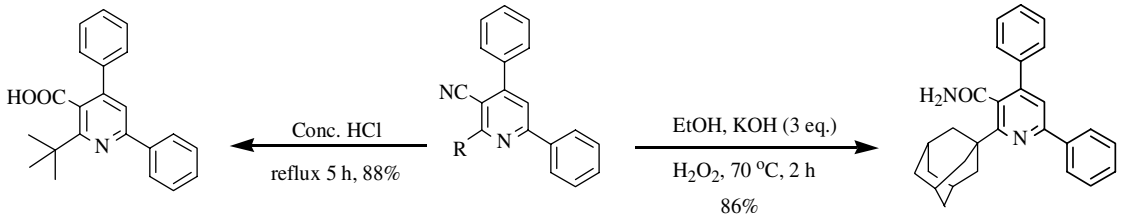
Entry	Compd	R^1	R^2	**10**,**12**,**17**–**20**[b] (%)	**21**[b] (%)
1	**12**	H	Ph	86[c]	0
2	**10**	H	*t*-Bu	77[c]	0
3	**17**	NO_2	Ph	61	30
4	**18**	NO_2	*t*-Bu	80	0
5	**19**	MeO	Ph	97	0
6	**20**	MeO	*t*-Bu	89	0

[a] The reaction was performed using Grignard reagent (4.0 equiv), CuCN (4.4 equiv) and $BF_3{\cdot}Et_2O$ (2.0 equiv) in the presence or absence of LiCl (8.8 equiv) at −78 °C to 20 °C, for 3 h, unless otherwise stated.
[b] Total yield after column chromatographic separation.
[c] Data were taken from Table 1.

in Table 2. The presence of an electron-withdrawing group on 4-phenylpyridine such as nitro **15** led to a decrease in the yield of the target product and the appearance of 3-phenylpyridines when using phenyl cuprate as a nucleophile, which may be attributable to the increase of electrophilic character of the pyridine ring (Table 2, entry 1 vs 3). On the other hand, 4-phenylpyridine **16** containing electron-donating groups such as methoxy resulted in the formation of only one product in which the 2-position of pyridine was regioselectively substituted with phenyl without any effect on the 3-position (Table 2, entry 3 vs 5). Moreover, due to steric reasons, the formation of 3-substituted pyridine derivatives was completely inhibited when highly hindered *tert*-butyl cuprate was used as the nucleophile (Table 2, entries 2 and 4 vs 3). Structural variation in the organo cuprates affected the yields of the product. Increasing the bulkiness of the organo cuprate from phenyl to *tert*-butyl influences the reaction products (Table 2, entries 3 and 4). It is clear that steric factors can significantly affect the chelate structures, which might play a crucial role in the substitution step.

The products thus obtained are useful precursors for the preparation of nicotinamide and nicotinic acid derivatives of medicinal interest.[3g,h,14] The versatility of the methodology was demonstrated by two representative routes for nicotinamide and nicotinic acid, as outlined in Scheme 2. Thus, 2-methoxy-3-cyanopyridine **4** was converted into its 2-*tert*-butyl and 2-(1-adamantyl) derivatives, **10** and **11**,[15] followed by conventional transformation into 2-*tert*-butylnicotinic acid **22** and 2-(1-adamantyl)nicotinamide **23**,[16] respectively. As shown in Scheme 2, acid hydrolysis of 3-cyanopyridine **10** with concd HCl for 5 h gave 2-*tert*-butylnicotinic acid **22**, while oxidative conversion of 3-cyanopyridine **11** with MnO_2 or hydrolysis with KOH/absolute ethanol in the presence of H_2O_2 resulted in exclusive formation of 2-(1-adamantyl)nicotinamide **23** in a concerted manner.

Mechanistically, it is reasonable to assume that the first step in the reaction may involve coordination of BF_3 with the pyridine through various models including two open models M-**1** and M-**2** and two cyclic models M-**3** and M-**4** (Fig. 1). It is clear from the relative energy calculations that M-**1** is more favored than M-**2**, M-**3** and M-**4** by 16, 28, and 25 kcal/mol,[17] respectively. The above coordination facilitates substitution of the methoxy group by the organo cuprate reagent. A preliminary investigation of the reaction mechanism to



22 R= *t*-Bu (**10**), 1-adamantyl (**11**) **23**

Scheme 2. Preparation of nicotinamide and nicotinic acid derivatives.

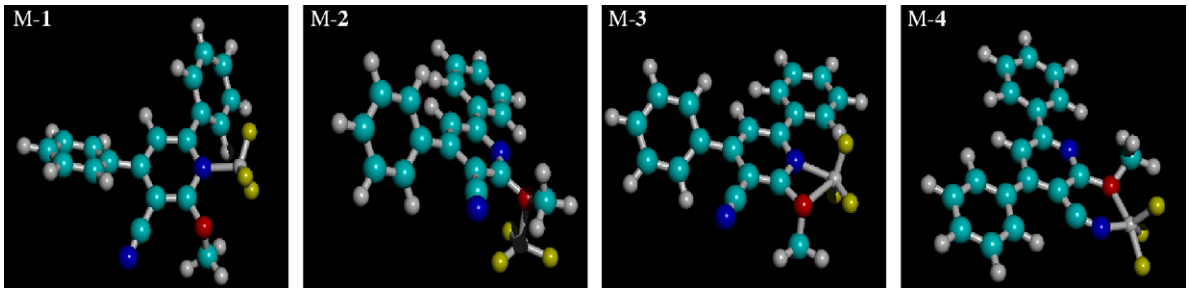
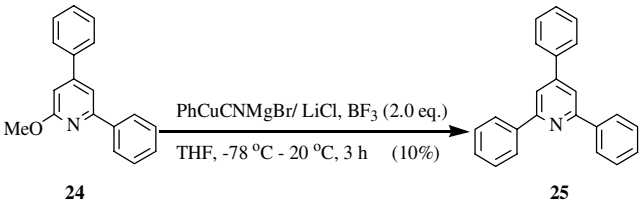


Figure 1. Plausible coordination models of BF_3 with 2-methoxy-3-cyanopyridines as calculated by PM3 semi-empirical molecular orbital calculations in THF.



Scheme 3. Lewis acid-promoted arylation of the 2-methoxypyridine.

determine the behavior of the Lewis acid (coordination model) in this process and the role of the nitrile moiety at the 3-position of pyridine, an experiment (Scheme 3) was carried out ranging the temperature from −78 °C to 20 °C over 3 h. Thus, arylation of 2-methoxy-4,6-diphenylpyridine **24** lacking a cyano group using the phenyl cuprate reagent afforded 2,4,6-triphenylpyridine **25** in 10% isolated yield along with 85% recovered starting material.[18] It is evident that the electrophilicity of the reacting pyridines is crucial in such cases, and therefore, the reaction proceeds smoothly with 2-methoxy-3-cyanopyridine **4**, leading to the formation of **12**. In contrast, substitution of the methoxy group of 2-methoxypyridine **24** was incomplete, perhaps due to the increased π-electron density compared with 2-methoxy-3-cyanopyridine **4**. This result proves the importance of the nitrile moiety, which accelerates the reaction rate via an electronic effect through increasing the electrophilicity of the pyridine ring and may be involved in coordination with the Lewis acid. On the basis of these observations, a possible reaction mechanism may depend on the electrophilic behavior of the pyridine core and the coordination model M-**1** which facilitates substitution of the methoxy group.

In conclusion, we have successfully explored an efficient new methodology for the synthesis of 2,4,6-trisubstituted nicotinonitriles from the parent 2-methoxy-3-cyanopyridines by their reaction with organo cuprates under mild conditions in the presence of BF_3 as a Lewis acid. Using this method, we have successfully synthesized pure nicotinonitrile, nicotinamide and nicotinic acid derivatives, which can serve as potential precursors of medicinal interest. The mechanism of the direct substitution of 2-methoxy-3-cyanopyridines has been studied in which model M-**1** was the active complex in this reaction which was augmented by the presence of a cyano group at the 3-position of pyridine.

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10. Typical procedure is as follows: a solution of **4** (0.47 mmol) in THF (2.2 mL) and $BF_3{\cdot}Et_2O$ (134 mg, 0.94 mmol) was added to a suspension of LiC1 (175 mg, 4.13 mmol; dried at 150 °C for 1 h under reduced pressure), CuCN (185 mg, 2.07 mmol) and organo metal reagent (1.88 mmol) in THF (9.9 mL) which had been stirred at −78 °C under nitrogen for 30 min. The mixture was then stirred at 20 °C for an additional 3 h. The reaction was quenched by the addition of saturated NH_4Cl aq (1.4 mL) and EtOAc (100 mL) was added. The whole was washed with (i) satd NH_4Cl aq (20 mL × 3), (ii) brine (45 mL × 3), dried (Na_2SO_4) and evaporated in vacuo followed by chromatography on silica gel (hexane–EtOAc (9:1 to 6:4)) to afford compounds **5**–**14** (Table 1).
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13. For comparison, 2-methoxy-3-cyano-4,6-diphenylpyridine was treated with *n*-BuMgBr and $PhCH_2MgBr$ (4.0 equiv) and $BF_3{\cdot}Et_2O$ (1.5 equiv) in THF at −78 °C to 20 °C (10 h) to give the 2-substituted products in 55% and 38% yields, respectively.
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15. Spectroscopic data for 2-*tert*-butyl-3-cyano-4,6-diphenylpyridine (**10**). Yield 77%; pale yellow crystals, mp 175–176 °C (ethanol). IR (KBr): *v* 2971 (aromatic CH), 2219 (CN), 1608, 1587 (C═N, C═C) cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6, δ ppm): 1.05 (s, 9H, *t*-Bu), 7.12–7.45 (m, 10H, Ph-H), 7.71 (s, 1H, Pyr-H). Analysis found: C, 84.50; H, 6.39; N, 9.01. Calcd for $C_{22}H_{20}N_2$: C, 84.58; H, 6.45; N, 8.97. Spectroscopic data for 2-(1-adamantyl)-3-cyano-4,6-diphenylpyridine (**11**). Yield 69%; white crystals, mp 198–199 °C (MeCN). IR (KBr): *v* 2983 (aromatic CH), 2216 (CN), 1608, 1587 (C═N, C═C) cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6, δ ppm): 1.47 (s, 6H, adamantane-H), 1.51 (d, 3H, $J = 12.0$ Hz, adamantane-H), 1.67 (d, 3H, $J = 12.1$ Hz, adamantane-H), 2.06 (s, 3H, adamantane-H), 7.19–7.50 (m, 10H, Ph-H), 7.69 (s, 1H, Pyr-H). Analysis found: C, 85.98; H, 6.70; N, 7.14. Calcd for $C_{28}H_{26}N_2$: C, 86.12; H, 6.71; N, 7.17.
16. Spectroscopic data for 2-*tert*-butyl-4,6-diphenylnicotinic acid (**22**). Yield 88%; white crystals, mp 183–184 °C (methanol). IR (KBr): *v* 3321 (carboxyl OH), 2960 (aromatic CH), 1721 (carboxyl C═O), 1606, 1571 (C═N, C═C) cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6, δ ppm): 1.11 (s, 9H, *t*-Bu), 7.30–7.66 (m, 10H, Ph-H), 8.11 (s, 1H, Pyr-H), 12.15 (s, 1H, OH). Analysis found: C, 79.68; H, 6.46; N, 4.15. Calcd for $C_{22}H_{21}NO_2$: C, 79.73; H, 6.39; N, 4.23. Spectroscopic data for 2-(1-adamantyl)-4,6-diphenylnicotinamide (**23**). Yield 86%; white crystals, mp 211–212 °C (ethanol). IR (KBr): *v* 3431, 3254, 3145 (NH_2), 2991 (aromatic CH), 1685 (C═O), 1610, 1584 (C═N, C═C) cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6, δ ppm): 1.51 (s, 6H, adamantane-H), 1.64 (d, 3H, $J = 12.0$ Hz, adamantane-H), 1.72 (d, 3H, $J = 12.1$ Hz, adamantane-H), 2.12 (s, 3H, adamantane-H), 6.10 (s, 2H, NH_2), 7.26–7.43 (m, 10H, Ph-H), 7.98 (s, 1H, Pyr-H). Analysis found: C, 82.24; H, 6.78; N, 6.66. Calcd for $C_{28}H_{28}N_2O$: C, 82.32; H, 6.91; N, 6.86.
17. Initial structures for complexes M-**1**, M-**2**, M-**3** and M-**4** were constructed using the HyperChem program version 5.1.[19] The MM+[20] (calculations in vacuo, bond dipole option for electrostatics, Polak-Ribiere algorithm, RMS gradient of 0.01 kcal/Å mol) conformational searching in torsional space was performed. Energy minima were determined by a semi-empirical method PM3[21] and AM1[22] (as implemented in HyperChem 5.1). The PM3 semi-empirical calculations were performed in the presence of one molecule of THF which gave good results compared with AM1 semi-empirical calculations.
18. A study of the detailed substitution reactions and mechanism with 2-methoxy-4,6-diphenylpyridine **24** on experimental and theoretical levels will be the subject of a separate paper.
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