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A New Synthesis of 2-Substituted Pyridines via Aluminum Chloride Induced Heteroarylation of Arenes and Heteroarenes†

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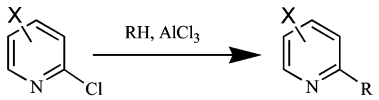

R= Aryl, Heteroaryl; X = NO_2, CN

We herein report a new synthesis of 2-(hetero)aryl-substituted pyridines via heteroarylation of arenes/heteroarenes through $AlCl_3$-induced C−C bond-forming reactions. 2-Halopyridines bearing an electron-withdrawing group were reacted with a number of (hetero)arenes to give 2-aryl/heteroaryl-substituted pyridines in good yields.

We describe here the first $AlCl_3$-induced C−C bond-forming reaction between 2-halopyridines and arenes or heteroarenes, such reactions being only known using transition-metal catalysts.

The prevalence of pyridines in nature (e.g., in the coenzyme vitamin B_6 family and in numerous alkaloids)[1] and their central role as versatile building bocks in the synthesis of natural products[2] as well as biologically active compounds[3] has led to a continued interest in the practical synthesis of pyridine derivatives, especially 2-substituted pyridines. For example, 2-arylpyridines are intermediates in the synthesis of physiologically active products, such as antitumor compounds.[4] Some simple 2-alkyl(aryl)pyridines have been identified as natural flavor compounds of cocoa,[5] tobacco,[5] and orange oil.[6] Among the diverse approaches that have been discovered for the synthesis of 2-aryl/heteroaryl pyridines, the transition-metal-catalyzed cross-couplings have proven to be an important method and are being utilized extensively. These include coupling of a 2-halopyridine with a aryl halide in the presence of (a) $(PPh_3)_4Pd$−active Zn,[7a−b] (b) lithium naphthalenide−$ZnCl_2$−$(PPh_3)_4Pd$,[7c] (c) $NiBr_2$byp−Bu_4NBF_4 under electrolysis,[7d] (d) $(PPh_3)_4Pd$, $Me_3SnSnMe_3$,[7e] or (e) $Pd(OAc)_2$ under phase-transfer conditions.[7f] Alternatively, 2-arylpyridines were prepared via Pd-catalyzed reaction of a 2-halopyridine with a variety of organometallic reagents namely ArZnCl,[8a−b] ArMnCl,[8c] $ArSi(OMe)_3$,[8d] Ar_2InCl,[8e] Ar_3Bi,[8f] ArLi,[8b] ArMgX,[8g] or $KArBF_3$.[8f] The Suzuki coupling of 2-halopyridines with arylboronic acids has been an efficient and powerful method for the preparation of 2-aryl/heteroaryl pyridines.[9] This carbon−carbon bond-forming reaction has been employed widely due to the versatile nature of this protocol, increased functional group toleration, and improved yields. Despite being quite versatile, the synthesis of 2-aryl/heteroaryl pyridine employing Suzuki cross-coupling reaction involves the use of expensive palladium catalyst and therefore may not be suitable for the large-scale preparation of these compounds. Moreover, in many cases the required boronic acids are either not available commercially or their preparations often

† DRL publication no. 459.

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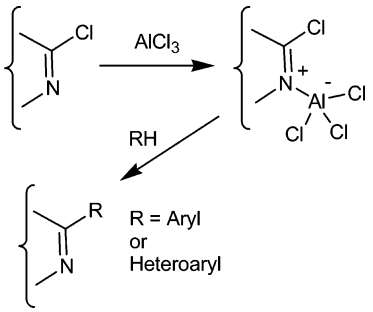
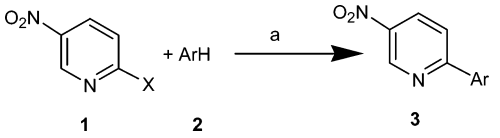


FIGURE 1. $AlCl_3$-induced C−C bond-forming reaction.

involve cumbersome synthetic procedures. In our effort toward the synthesis of various heterocyclic structures,[10] we have reported a new approach toward the formation of $C_{aryl}-C_{aryl}$ bond very recently.[11a−c] In this approach, an arene or heteroarene was reacted with the appropriate heteroaryl chloride in the presence of $AlCl_3$ to generate a variety of heterocyclic compounds (Figure 1) of potential biological interest. Herein we now wish to report a novel and scalable synthesis of 2-aryl/heteroaryl pyridines using a $AlCl_3$ induced C−C bond-forming reaction. While the Friedel−Crafts alkylation and acylation have been used widely and are well documented in the literature, the present $AlCl_3$-induced heteroarylation, however, has not been exploited well in organic synthesis.[11d]

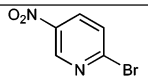
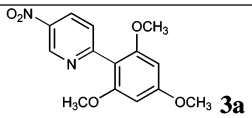
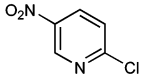
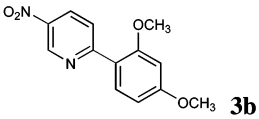
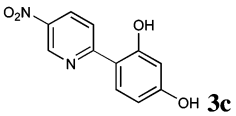
In our earlier approach for the $AlCl_3$-induced heteroarylation of arenes and heteroarenes we have utilized a heteroaryl chloride as a coupling agent that contains an −N=N−C(Cl)− moiety. We, however, did not explore the use of a heteroaryl halide containing −N=C(X)− moiety in our heteroarylation reaction. We anticipated that the development of such a methodology would be useful particularly in the synthesis of 2-aryl- and heteroaryl-substituted pyridines of medicinal as well as synthetic value. In the beginning of our study we choose commercially available 2-bromo-5-nitropyridine **1a** (**1**; X = Br) as a heteroaryl halide for the heteroarylation of 1,3,5-trimethoxybenzene **2a** (Scheme 1). Thus, a mixture of **1a** (1.26 mmol), **2a** (1.25 mmol) and $AlCl_3$ (1.51 mmol) in dichloroethane (10 mL) was stirred at room temperature for 1 h and then at 80 °C for 24h. The pyridine substrate was completely consumed after 24 h, and the desired 5-nitro-2-(2,4,6-trimethoxyphenyl)pyridine **3a** was isolated in 80% yield. We then examined the reactivity of 2-chloro-5-nitropyridine **1b** in this $AlCl_3$-induced heteroarylation reaction. The interest in using heteroaryl chlorides stems from the fact that chlorides are available

SCHEME 1[a]



[a] Reagents and conditions: (a) $AlCl_3$, dichloroethane, 50−80 °C, 12−15 h.

TABLE 1. $AlCl_3$-Induced Heteroarylation of Arenes and Heteroarenes

S.No	Reactant	Product	Yield%
1.	 **1a**	 **3a**	80
2.	 **1b**	**3a**	76
3.	**1a**	 **3b**	55
4.	**1b**	**3b**	53
5.	**1a**	 **3c**	65
6.	**1b**	**3c**	64

[a] Yield of isolated products.

in far greater number and their use is more economical. Encouragingly, the chloro derivative **1b** was found to be equally effective in this reaction affording the product **3a** in 76% yield. The results of this study are summarized in Table 1. It is evident from Table 1 that **3a** could be isolated in almost same yield regardless of the use of 2-chloro- or 2-bromopyridine (entries 1 and 2, Table 1). A similar observation was noted by Kelly and Lang in a reactivity studies of pyridine substituted with bromine and triflate in the presence of palladium catalysts.[12a] The use of relatively less electron-rich arenes[12b] such as 2,4-dimethoxybenzene (**2b**) and benzene-1,3-diol (**2c**) in place of **2a** was also examined which afforded the desired product, i.e., **3b** and **3c**, respectively, in acceptable yields (entries 3−6, Table 1). It is noteworthy that the heteroarylation of benzene-1,3-diol (**2c**) occurred at the ring carbon rather than oxygen.[12c]

Since the planned strategy toward the synthesis of 2-arylpyridines via $AlCl_3$-induced C−C bond formation

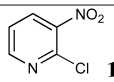
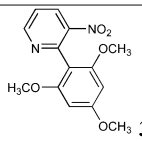
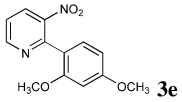
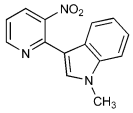
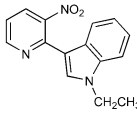
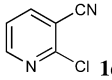
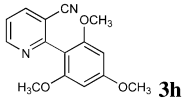
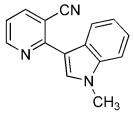
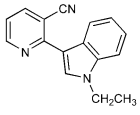
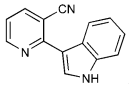
(10) For example, see: (a) Pal, M.; Rao, V. V.; Srinivas P.; Murali N.; Akhila V.; Premkumar M.; Rao, C. S.; Misra, P.; Ramesh M.; Rao Y. K. *Indian J. Chem.* **2003**, *42B*, 593−601. (b) Pal, M.; Veeramaneni, V. R.; Nagaballi, M.; Kalleda, S. R.; Misra, P.; Casturi, S. R.; Yeleswarapu, K. R. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 1639−1643. (c) Pal, M.; Madan, M.; Srinivas, P.; Pattabiraman, V. R.; Kalleda, S. R.; Akhila, V.; Ramesh, M.; Rao Mamidi, N. V. S.; Casturi, S. R.; Malde, A.; Gopalakrishnan, B.; Yeleswarapu, K. R. *J. Med. Chem.* **2003**, *46*, 3975−3984.

(11) (a) Pal, M.; Batchu, V. R.; Khanna, S.; Yeleswarapu, K. R. *Tetrahedron* **2002**, *58*, 9933−9940. (b) Pal, M.; Batchu, V. R.; Parasuraman, K.; Yeleswarapu, K. R. *J. Org. Chem.* **2003**, *68*, 6806−6809. Also see: (c) Pal, M.; Dakarapu, R.; Padakanti, S. *J. Org. Chem.* **2004**, *69*, 2913−2916. (d) For the synthesis of 2- and 4-(2,4-dihydroxyphenyl)-quinoline via condensation reaction of 2- and 4-chloroquinoline with resorcinol in the presence of $AlCl_3$, see: Kepinskaya, I. B.; Makarova, Z. S.; Koptyug, V. A. *Zh. Org. Khim.* **1980**, *16*, 1263−1268. *Chem. Abstr.* **1980,** *93*, 185326.

(12) (a) Kelly, T. R.; Lang, F. *J. Org. Chem.* **1996**, *61*, 4623−4633. (b) The use of arenes possessing a single electron-donating group such as anisole, *N*,*N*-dimethylaniline, was examined. These arenes failed to react with **1b** under the condition studied. (c) Merchant, J. R.; Kulkarni, S. D.; Venkatesh, M. S. *Indian J. Chem. Sect. B* **1980**, 914−916.

worked well it was of interest to test the generality and scope of this process by conducting further experiments and then comparing its merit with other methods especially those catalyzed by transition metal complexes or salts. We therefore focused on the reaction of other 2-chloropyridine derivatives such as 2-chloro-3-nitropyridine **1c** and 2-chloro-3-cyanopyridine **1d** with various arenes and heteroarenes.[13] The isolated yields of products after column chromatography are shown in Table 2. Based on the results summarized in Table 2 it is evident that the heteroarylation reaction proceeds well in the presence of various aryl or heteroaryl reactants. Unlike the transition-metal-catalyzed reactions, no homocoupled products, i.e., bipyridyl or biaryl derivatives, were isolated in the present case. Generally, electron-rich arenes afforded better yields of products (entries 1 and 5, Table 2) than those having fewer electron-donating groups. This is in contrast to the palladium-catalyzed cross-coupling process where an electron-rich aryl halide furnished lower yields of product.[14] Additionally, the presence of a group at the C-3 position of 2-halopyridine ring afforded a lower yield of product in the Pd-catalyzed reaction due to a possible steric hindrance.[7e] This trend was not observed in the present $AlCl_3$-mediated synthesis of 2-arylpyridines (entry 1, Table 1 vs entry 1, Table 2). With these efficient conditions in hand for the reaction with electron-rich arenes, we then investigated the reaction of nitrogen containing heteroarenes. Due to our long-term interest in the synthesis of a variety of indole derivatives[11b,c,15] we employed a few indoles as heteroarenes in this $AlCl_3$-induced C−C bond-forming reaction. Both 2-chloro-3-nitropyridine **1c** and 2-chloro-3-cyanopyridine **1d** were reacted with N-protected indoles, e.g., *N*-methyl- and *N*-ethylindole separately and the corresponding 3-(2-pyridyl)indoles were isolated in moderate yields (entries 3, 4 and 6, 7, Table 2). The reaction, however, was also successful when indole without N-protection was used (entry 8, Table 2) indicating that the N-protection was not a prerequisite for successful heteroarylation of indoles. It is noteworthy that 3-(2-pyridyl)-indoles, useful synthetic precursors for indole alkaloids, were prepared via a Pd(0)-catalyzed heteroarylation of 3-indolylzinc derivatives earlier.[16] The method however, required a complicated preparation of 3-indolylzinc derivative, i.e., (1-silyl-3-indolyl)zinc which was generated from 3-bromo-1-(*tert*-butyldimethylsilyl)indole by halogen−metal exchange with *t*-BuLi followed by transmetalation of the resulting 3-lithioindole with $ZnCl_2$. The present $AlCl_3$-mediated heteroarylation of indoles therefore is a straightforward process in comparison of the Pd(0)-catalyzed heteroarylation of 3-indolylzinc derivative. Moreover, although the successful Friedel−Crafts acylation of indole is an indirect method[17] (as the method involves N-protection, acylation, and N-deprotection

TABLE 2. $AlCl_3$-Induced Heteroarylation of Arenes and Heteroarenes

S.No	Reactant	Product	Conditions	Yield%
1.	 **1c**	 **3d**	DCE, 24h	74
2.	**1c**	 **3e**	DCE, 24h	41
3.	**1c**	 **3f**	DCE, 24h	42
4.	**1c**	 **3g**	DCE, 24h	44
5.	 **1d**	 **3h**	DCE, 24h	66
6.	**1d**	 **3i**	DCE, 24h	48
7.	**1d**	 **3j**	DCE, 24h	50
8.	**1d**	 **3k**	DCE, 24h	48

[a] Yield of isolated products.

(13) (a) All the arenes, heteroarenes, and 2-chloropyridines are available commercially. (b) Typical procedure for the synthesis of **3d**: A mixture of 2-chloro-3-nitropyridine **1c** (0.20 g, 1.26 mmol), 1,3,5-trimethoxybenzene (0.21 g, 1.25 mmol), and $AlCl_3$ (0.20 g, 1.51 mmol) in dichloroethane (10 mL) was stirred at 25 °C for 1 h under a nitrogen atmosphere. The reaction mixture was then stirred at 75−80 °C for 24 h. After completion, the mixture was poured into ice-cold water (100 mL), stirred for 10 min, and then extracted with chloroform (3 × 30 mL). The organic layers were collected, combined, washed with water (2 × 30 mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum. The residue was purified by column chromatography using ethyl acetate−petroleum ether to afford the expected product as a light yellow solid: mp 170−172 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.90−8.87 (dd, J = 1.4, 1.4 Hz, 1H), 8.28−8.23 (dd, J = 1.4, 1.7 Hz, 1H), 7.43−7.37 (m, 1H), 6.20 (s, 2H), 3.85 (s, 6H, OCH_3), 3.70 (s, 3H, OCH_3); ν_{max} (KBr, cm^{-1}) 1526, 1418, 1355; Mass (CI method, isobutane) 291 (M^++1), 261 (M^+-30, 100%); ^{13}C NMR (50 MHz, $CDCl_3$) 162.3 (2C), 158.2, 152.3, 148.9, 147.3, 131.7, 122.0, 107.9, 90.9 (2C), 55.7 (OCH_3), 55.3 (2C, OCH_3); HPLC 99.10%, Inertsil ODS 3V (250 × 4.6 mm), mobile phase 0.01 M KH_2PO_4/acetonitrile, 0/40, 5/40, 30/70, 40/70, 45/40, 50/40, 1.0 mL/min, 210 nm, retention time 11.1 min.

(14) It has been observed that the yields of cross-coupled products in a palladium-catalyzed reaction are higher when phenyl bromide is substituted with electron-withdrawing groups. These groups make aryl bromide more electron deficient and thus facilitate the oxidative addition to Pd(0). For phenyl bromides substituted with electron-donating groups, the desired coupled products were obtained in much lower yields. For related studies, see ref 7e.

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process to limit polymerization) the present process however can be carried out without any N-protection.

The heteroarylation of arenes and heteroarenes were usually carried out at 75−80 °C as no reaction was observed at lower temperature. The duration of the reaction was 24 h. An attempt to reduce the reaction time failed as the reaction ended up with either lesser yield of products or recovery of the starting materials.

The strategy developed here was to synthesize 2-arylpyridines using cheaper as well as commercially available raw materials in order to make the process amenable for the scale-up synthesis of this class of compounds. The strategy worked well for electron rich arenes and was extended to heteroarenes such as indoles. Both arenes and indoles participated in the reaction through their Friedel−Crafts active positions. The electron-withdrawing substituents were tolerated on the pyridyl ring. In other words the presence of electron-withdrawing groups perhaps facilitated the heteroarylation reaction by increasing the electron deficiency in the pyridyl ring. The role of the electron-withdrawing group was further supported by the observation that 2-chloropyridine did not react with the electron rich arene **2a** under the reaction condition employed.[18] From the viewpoint of mechanism of the reaction, this electron deficiency, however, did not prevent the complexation of $AlCl_3$ with the nitrogen of 2-chloropyridine moiety that is followed by a nucleophilic attack at the adjacent chlorine bearing carbon atom. It is evident that the nucleophilicity of the reacting arenes or heteroarenes is crucial in such cases and therefore the reaction proceeds smoothly with electronrich arenes or heteroarenes leading to the formation of **3**.

(18) No product was detected in the reaction mixture even after 4 days.

In conclusion, we have demonstrated for the first time that 2-halopyridines could be utilized as an efficient heteroarylating agent for arenes and heteroarenes in the presence of $AlCl_3$ in a one-pot reaction. 2-Halopyridine derivatives are commercially available or can be readily made. The process does not involve the use of expensive catalysts or complex ligands. Unlike the transition-metal-catalyzed reactions no homocoupled products were isolated as byproducts. The methodology therefore has advantages over the transition-metal-mediated synthesis especially in the large-scale preparation of 2-aryl- or heteroarylpyridines. The process could be viewed as a useful alternative to the Suzuki coupling reactions (when applied to a similar type of C−C bond formation reaction) as preparations of required boronic acids are often cumbersome. Since the bond-forming reaction between Csp^2-centers allows the preparation of a range of polyfunctional heterocycles of pharmaceutical and agrochemical interest we believe that the present methodology despite having few limitations would find practical applications in organic as well as medicinal chemistry.

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Supporting Information Available: Characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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