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Synthesis of aminopyridines via an unprecedented nucleophilic aromatic substitution of cyanopyridines

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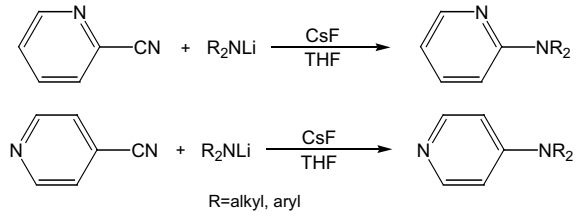
Abstract—The direct reaction of 2- and 4-cyanopyridines with lithium amides affords good yields of the corresponding aminopyridines via displacement of cyanide. Addition of CsF accelerates the reaction and can lead to significantly higher yields.

While the study of carbon–carbon bond activation has received much attention, it has led to only limited synthetic success.[1] Recently it has been shown that the C–CN bond of benzonitriles can be broken by various nickel complexes.[2] Furthermore, catalytic activation of a C–CN bond has been employed by us in cross-coupling chemistry.[3] Recently we described the nickel-catalyzed amination of benzonitriles with lithium amides promoted by cesium salts.[3a] It was initially observed that reaction of 2- and 4-cyanopyridine with lithium amides proceeded smoothly and in good yield in the presence of a nickel catalyst and CsF additive. Through control reactions it was discovered that the amination of 2- and 4-cyanopyridine also proceeded to a small extent in the absence of catalyst and additive. Further study of this reaction showed that addition of the nickel catalyst without CsF failed to improve the uncatalyzed yield. Addition of CsF without the nickel catalyst, however, led to high yields of the desired amination product.

While a variety of substitution reactions of halogens on halopyridines are known,[4] the corresponding substitution of cyanide ion from cyanopyridines is not. The scope of this amination reaction is illustrated in Table 1 and Scheme 1. Lithium amides prepared from secondary amines react with 2- and 4-cyanopyridines in moderate to good yields. For example, reaction of 4-cyanopyridine (2.0 mmol) with lithium pyrrolidide (4.0 mmol, prepared in situ from pyrrolidine and *n*-BuLi) and CsF (3.0 mmol) in THF at 65 °C for 2 h led to the formation



Scheme 1. Amination of 2- and 4-cyanopyridine by lithium amides.

of 4-pyrrolidinopiperidine (1.6 mmol).[5] Attempts to couple primary amines in this same manner led to mixtures of secondary and tertiary amination products due to addition of the amine to multiple cyanopyridines. 2-Cyanopyridine reacts with lithium amides more slowly than 4-cyanopyridine to give the corresponding aminopyridine. 3-Cyanopyridine, however, does not react to give any amination products.[6] In most cases complete conversion of the limiting reagent, 2- or 4-cyanopyridine, was observed even when the yield of aminopyridine was low. The fate of the balance of cyanopyridine is unclear, although it is reasonable to suspect it may lie in oligomerized products.[7]

Amidine formation, illustrated in Scheme 2, is immediate upon addition of lithium amide to a solution of cyanopyridine as evidenced by a sudden color change of the reaction mixture.[8] Whether this is a true intermediate in the amination reaction is unknown.

The role of the additive in this reaction is twofold. In most cases, addition of CsF leads to a sharp increase in rate of reaction. In some cases, especially with 2-cyanopyridine, addition of CsF also leads to a large

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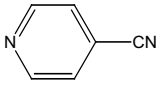
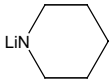
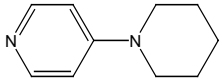
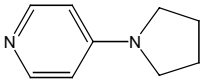
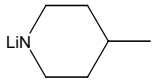
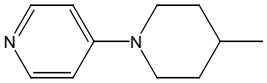
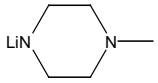
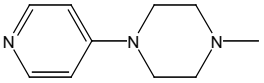
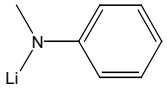
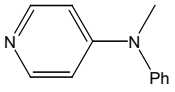
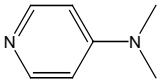
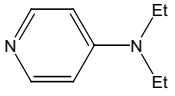
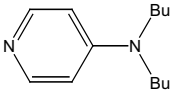
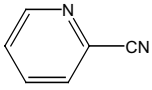
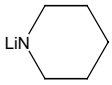
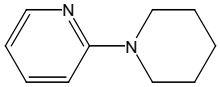
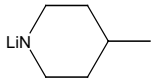
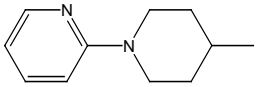
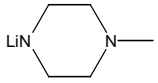
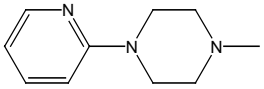
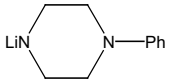
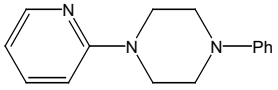
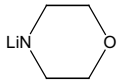
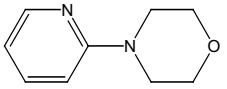
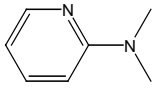
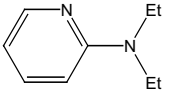
Table 1. Amination of 2- and 4-cyanopyridine with lithium amides[a]

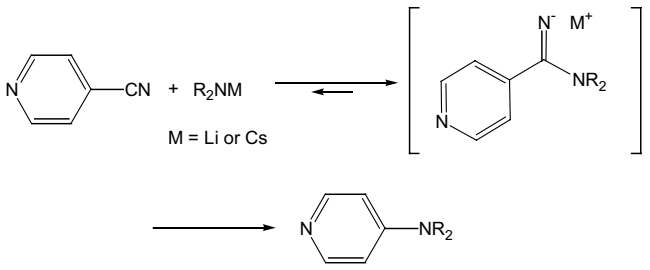
Entry	Cyanopyridine	Amide	Product	Yield[b], % (time)[c]	
				W/CsF	W/out CsF
1				85 (2)	92 (4)
2				80 (2)	29 (27)
3				98 (2)	98 (5)
4				44 (1.5)	42 (1.5)
5				28 (2.5)	31 (2.5)
6		$LiNMe_2$		79 (22)	42 (22)
7		$LiNEt_2$		66 (2)	56 (<20)[d]
8		$LiNBu_2$		74 (2)	58 (6)
9				65 (<23)[d]	23 (23)
10				60 (<29)[d]	23 (29)
11				74 (47)	34 (95)
12				87 (4)	54 (8)
13				69 (<48)[d]	22 (<48)[d]
14		$LiNMe_2$		52 (6)	82 (<29)[d]
15		$LiNEt_2$		24 (6)	0 (6)

[a] All reactions were carried out with stoichiometries, catalyst loadings, etc., as illustrated in the representative procedures.[12,13]

[b] Chemical yields are by GC analysis using an internal reference standard and based on cyanopyridine. Starting cyanopyridine and amidine intermediate adduct were consumed in all cases.

[c] Reaction time indicates the time required for full conversion of the cyanopyridine or amidine intermediate by GC analysis.

[d] The actual time needed for full conversion of cyanopyridine or amidine intermediate was not determined in this run.



Scheme 2. Formation of the amidine.

increase in yield. The amount of CsF necessary was optimized at 1.5 equiv based on cyanopyridine. Yields of amination product and rates of reaction drop significantly with use of less CsF; below 0.25 equiv no enhancements are observed. Other alkali metal salts, such as Cs_2CO_3 and KF, are also effective in increasing the rate and yield of this reaction.[9] It appears that exchange of counterions between the amide and additive creates a more reactive amide, although there are cases where having no modifier in the reaction actually gave better results (entry 14).

Polarity of the solvent also plays a role in this reaction. Polar solvents such as THF, DME, and 1,4-dioxane gave similar, good yields of amination products. Less polar solvents such as $^{i}Pr_2O$ and toluene gave low yields even at long reaction times.

There are distinct advantages of this direct reaction between lithium amides and cyanopyridines versus the increasingly common Ni and Pd catalyzed amination of aryl halides.[10] Obviously, cost savings arise from eliminating the need for transition-metal catalysts. It should also be noted that cyanopyridines are significantly less expensive than the corresponding halopyridines.[11]

In conclusion, the direct substitution of 2- and 4-cyanopyridine with lithium amides through a novel uncatalyzed activation of a C–C bond provides a simple and cost-effective method for preparation of aminopyridines.

Acknowledgements

The author would like to thank J. A. Miller (DSM Pharma Chemicals) and Professor B. M. Trost (Stanford University) for helpful discussions concerning this work.

References and notes

1. For recent reviews, see: (a) Jun, C.-H.; Moon, C. W.; Lee, D.-Y. *Chem. Eur. J.* **2002**, *8*, 2422; (b) Milstein, D.; Rybtchinski, B. *Angew. Chem., Int. Ed.* **1999**, *38*, 870, and references cited therein.
2. (a) Garcia, J. J.; Jones, W. D. *Organometallics* **2000**, *19*, 5544; (b) Abla, M.; Yamamoto, T. *J. Organomet. Chem.* **1997**, *532*, 267; (c) Morvillo, A.; Turco, A. *J. Organomet. Chem.* **1981**, *208*, 103.
3. (a) Miller, J. A.; Dankwardt, J. W.; Penney, J. M. *Synthesis* **2003**, *11*, 1643; (b) Miller, J. A.; Dankwardt, J. W. *Tetrahedron Lett.* **2003**, *44*, 1907; (c) Miller, J. A. *Tetrahedron Lett.* **2001**, *42*, 6991.
4. Dunn, A. D.; Norrie, R. *J. Heterocycl. Chem.* **1987**, *24*, 85, and references therein.
5. These results were obtained by GC analysis of a reaction sample (containing tridecane as an internal standard) quenched in a mixture of 1 M sodium citrate (aq) and MTBE.
6. Nucleophiles preferentially react with the 2- and 4-positions of pyridine electrophiles, see: (a) Sugimori, A.; Furihata, T.; Mikayama, S.; Yoshida, M.; Nakanishi, Y. *Bull. Chem. Soc. Jpn.* **1982**, *55*, 2906; (b) Wagenknecht, P. S.; Penney, J. M.; Hembre, R. T. *Organometallics* **2003**, *22*, 1180; (c) Le Gall, E.; Gosmini, C.; Nédélec, J.-Y.; Périchon, J. *Tetrahedron* **2001**, *57*, 1923; (d) Ref. 4.
7. Polymerization, oligomerization, and cyclotrimerization of organonitriles are known to occur in the presence of various metal salts, see: Kabanov, V. A.; Zubov, V. P.; Kovaleva, V. P.; Kargin, V. A. *J. Polym. Sci. C* **1964**, *4*, 1009.
8. Stability of the cyanopyridine amidines toward aqueous workup is variable, in contrast to amidines derived from simple benzonitriles, making quantification of the amidine concentration during the course of the reaction troublesome.
9. For example the reaction of lithium 1-methylpiperazide with 2-cyanopyridine (entry 11) in the presence of various modifiers shows: CsF (74% yield, 47 h), Cs_2CO_3 (48% yield, 71 h), KF (72% yield, 71 h), no modifier (34% yield, 94 h).
10. For recent reviews, see: (a) Hartwig, J. F. *Angew. Chem., Int. Ed.* **1998**, *37*, 2046; (b) Muci, A. R.; Buchwald, S. L. *Top. Curr. Chem.* **2002**, *219*, 131.
11. 2003–2004 Aldrich prices for 2-cyanopyridine ($13/mol), 2-chloropyridine ($16/mol), 2-bromopyridine ($68/mol), 2-iodopyridine ($2500/mol).
12. Representative procedure with CsF: (4-pyrrolidinopyridine, entry 2). A 0 °C solution of pyrrolidine (0.334 mL, 0.284 g, 4.0 mmol, Aldrich) in 4 mL of THF was treated with *n*-butyllithium (1.6 mL, 4.0 mmol, 2.5 M in hexanes) and allowed to warm to room temperature for 15 min. The reaction solution was cooled to 0 °C and a solution of 4-cyanopyridine (0.244 g, 2.0 mmol) and tridecane (0.244 mL, 0.184 g, 1.0 mmol, internal GC standard) in THF (1 mL) was added. After warming to room temperature the entire reaction mixture was added to solid cesium fluoride (0.456 g, 3.0 mmol) and heated to 65 °C for 2 h. A sample was withdrawn and quenched in a mixture of 1 M sodium citrate (aq) and MTBE. GC analysis of the organic phase of the hydrolyzed reaction sample showed the presence of 1.6 mmol (80% yield) of 4-pyrrolidinopyridine.
13. Representative procedure without CsF: (4-piperidinopyridine, entry 1). A 0 °C solution of piperidine (0.396 mL, 0.341 g, 4.0 mmol, Aldrich) in 4 mL of THF was treated with *n*-butyllithium (1.6 mL, 4.0 mmol, 2.5 M in hexanes) and allowed to warm to room temperature for 15 min. The reaction solution was cooled to 0 °C and a solution of 4-cyanopyridine (0.244 g, 2.0 mmol) and tridecane (0.244 mL, 0.184 g, 1.0 mmol, internal GC standard) in THF (1 mL) was added and the mixture was heated to 65 °C for 4 h. A sample was withdrawn and quenched in a mixture of 1 M sodium citrate (aq) and MTBE. GC analysis of the organic phase of the hydrolyzed reaction sample showed the presence of 1.83 mmol (92% yield) of 4-piperidinopyridine.