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Convenient Synthesis and Transformation of 2,6-Dichloro-4-iodopyridine

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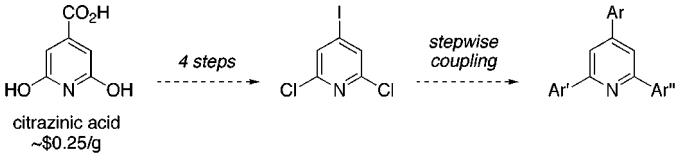
ABSTRACT

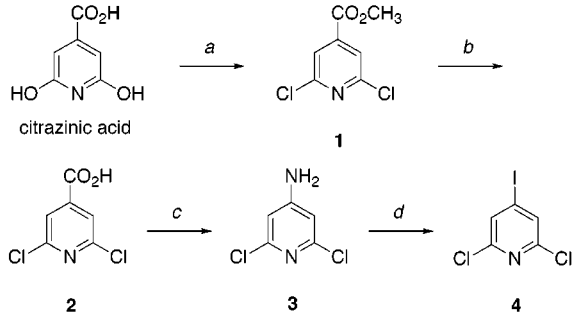


We describe a convenient scalable synthesis of 2,6-dichloro-4-iodopyridine and demonstrate its utility by stepwise elaboration to a number of 2,4,6-trisubstituted pyridines.

In the course of extending our work on arylpyridine fluorescent chemosensors,[1] we required ready access to 2,4,6-trisubstituted pyridines. While such compounds can be prepared by any of a number of condensation methods,[2,3] we were drawn to the comparative simplicity and convergence of directly installing the substituents via transition metal catalyzed coupling to a pyridine precursor. The dearth of procedures for the preparation of appropriate trihalopyridines has led us to develop a four-step, scalable synthesis of 2,6-dichloro-4-iodopyridine (**4**, Scheme 1). As described here, **4** is a versatile intermediate in the synthesis of trisubstituted pyridines. Such polysubstituted pyridines and their associated metal complexes possess interesting and useful structural, electronic, and optical properties,[4] and we anticipate this methodology will be of use to a broad range of practicing chemists.

Our synthesis of **4** begins with the inexpensive pyridine derivative citrazinic acid.[5,6] Treatment with $POCl_3$ at elevated temperature afforded the corresponding 2,6-dichloroisonicotinoyl chloride.[7] To facilitate purification, the reaction was quenched with methanol; methyl ester **1** was isolated in 76%

Scheme 1. Synthesis of 2,6-Dichloro-4-iodopyridine[a]



[a] Reagents and conditions: (a) $POCl_3$, Me_4NCl, Δ; CH_3OH, 76%; (b) LiOH, THF/H_2O, 100%; (c) $(COCl)_2$, CH_2Cl_2; NaN_3; TFA, Δ; K_2CO_3, CH_3OH, 78%; (d) $NaNO_2$, HCl; aqueous KI, 57%.

(1) Mello, J. V.; Finney, N. S. *Angew. Chem., Int. Ed.* **2001**, *40*, 1536.

(2) For authoritative treatment of pyridine synthesis, see: (a) Katritzky, A. R. *Handbook of Heterocyclic Chemistry*, 2nd ed.; Pergammon: New York, 2000. (b) *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R., Rees, C. W., Eds; Pergammon: New York, 1984; Vol. 2.

(3) For recent examples of the condensation of chalcones with acetophenone derivatives to form 2,4,6-triarylpyridines, see: (a) Chiu, C.; Tang, Z.; Ellingboe, J. *J. Comb. Chem.* **1999**, *1*, 73−77. (b) Katritzky, A. R.; Abdel-Fattah, A. A. A.; Tymoshenko, D. O.; Essawy, S. A. *Synthesis* **1999**, 2114−2118.

(4) For representative overviews, see: (a) Biradha, K.; Fujita, M. *Adv. Supramol. Chem.* **2000**, *6*, 1. (b) Long, N. J. In *Optoelectronic Properties of Inorganic Compounds*; Roundhill, D. M., Fackler, J. P., Jr., Eds.; Plenum: New York, 1999; pp 107−167. Publisher: Plenum Publishing Corp., New York. (c) Krasovitskii, B. M.; Bolotin, B. M. *Organic Luminescent Materials*; VCH: New York, 1988.

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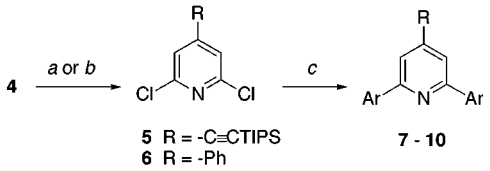
yield after passage through a plug of silica gel to remove colored impurities. Saponification then provided acid **2** in quantitative yield without purification.

Transformation to **3** was effected by conversion to the acyl azide, thermal Curtius rearrangement, and hydrolysis of the resulting trifluoroacetamide to provide 2,6-dichloro-4-aminopyridine (**3**).[8] While this method for converting **2** to **3** is nominally three steps, it requires only a single extractive workup and the steps can thus be carried out in rapid succession. **3** was converted directly to **4** by diazotization and reaction with potassium iodide,[9] providing **4** in reasonable yield and excellent purity after trituration with acetone. This short sequence of reactions allows for preparation of **4** in ~35% overall yield, requires no chromatography beyond a single filtration through a plug of silica gel, and has allowed the routine preparation of 5−10 g quantities of this intermediate. Unlike many 4-halopyridines, we have found **4** to be stable for several months at room temperature if protected from light.

The value of **4** for our purposes is its ready transformation to fluorophores such as **7**−**10** (Scheme 2, Table 1). Selective

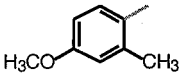
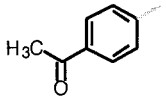
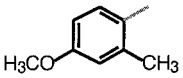
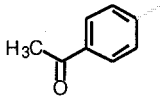
Scheme 2. Selective Reaction of the 4-Iodo Substituent[a]



[a] Reagents and conditions: (a) catalytic $PdCl_2(PPh_3)_2$, catalytic CuI, Et_2NH, TIPSC≡CH, THF, 100%; (b) PhZnCl, catalytic $Pd(PPh_3)_4$, THF, 98%; (c) $ArB(OH)_2$, catalytic $Pd_2(dba)_3/P(tBu)_3$, Cs_2CO_3, THF, Δ. See Table 1 for structures and yields of **7**−**10**.

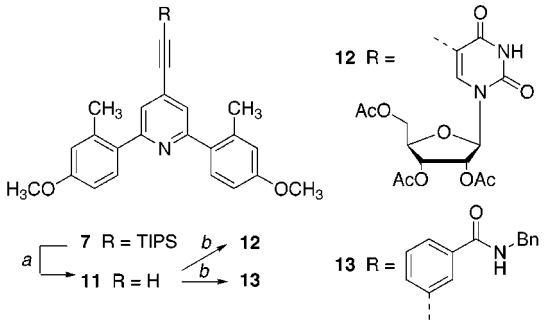
Pd-catalyzed coupling of the iodide to either triisopropylsilylacetylene or phenylzinc chloride provides the corresponding monocoupled products (**5**, **6**) in excellent yield.[10,11] Subsequent condensation with arylboronic acids under

Table 1. Symmetrical Trisubstituted Pyridines

dichloride	product	R	Ar	yield (%)
5	**7**	-C≡CTIPS		98
5	**8**	-C≡CTIPS		77
6	**9**	-Ph		82
6	**10**	-Ph		65

slightly more forceful conditions leads to trisubstituted pyridines in fair to excellent yield.[12,13] While steric hindrance appears to have little influence, the electron-deficient boronic acids couple less efficiently. In the case of **7**, further elaboration leads to interesting functionalized fluorophores such as **12** and **13** (Scheme 3), which are suitable for

Scheme 3. Elaboration of **7** to Novel Fluorophores[a]



[a] Reagents and conditions: (a) TBAF, THF, 69%; (b) ArI, catalytic $PdCl_2(PPh_3)_2$, catalytic CuI, Et_2NH, THF (**12**, 40%; **13**, 92%).

immobilization on solid support or incorporation into oligonucleotides.

We had hoped to extend the utility of **4** by transforming **5** and **6** to 4,6-disubstituted-2-chloropyridines (**14**−**17**, Scheme 4, Table 2). However, under the numerous conditions tried, differentiation of the chlorine atoms was modest at best.[14] While subsequent conversions of **14** and **16** to **18** and

(5) The preparation of **4** from 2,6-dichloro-4-aminopyridine has been previously described. We have found the reported procedures for the synthesis and transformation of this key intermediate difficult to reduce to practice and have thus devised the approach presented here. See: Talik, T.; Plazek, E. *Rocz. Chem.* **1959**, *33*, 387, and references therein.

(6) Complete experimental and spectroscopic details are provided in the Supporting Information.

(7) Henegar, K. E.; Ashford, S. A.; Baughman, T. A.; Sih, J. C.; Gu, R.-L. *J. Org. Chem.* **1997**, *62*, 6588.

(8) Pfister, J. R.; Wymann, W. E. *Synthesis* **1983**, 38.

(9) It is necessary to stir **3** in cold hydrochloric acid for several hours prior to diazotization in order to obtain an acceptable yield. See Supporting Information for details.

(10) For a recent review, see: (a) Sonogashira, K. In *Metal-Catalyzed Cross Coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: New York, 1998; Chapter 5. (b) Negishi, E.-i. In *Metal-Catalyzed Cross Coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: New York, 1998; Chapter 1.

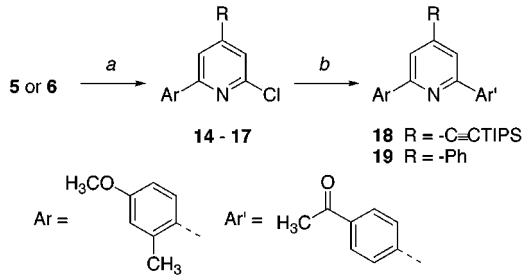
(11) For recent examples of the chemoselective cross-coupling of chloroiodo- and bromoiodopyridines, see: (a) Baxter, P. N. W. *J. Org. Chem.* **2000**, *65*, 1257−1272. (b) Loren, J. C.; Siegel, J. S. *Angew. Chem., Int. Ed.* **2001**, *40*, 754−757. For representative earlier examples of the cross-coupling of halopyridines, see: (c) Zhang, H.; Chan, K. S. *Tetrahedron Lett.* **1996**, *37*, 1043−1044. (d) Lohse, O.; Thevenin, P.; Waldvogel, E. *Synlett* **1999**, 45−48.

(12) The combination of $Pd_2(dba)_3$ and P^tBu_3 consistently provided the best yields of dicoupled products. See: (a) Old, D. W.; Wolfe, J. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **1998**, *120*, 9722−9723. (b) Littke, A. F.; Fu, G. C. *Angew. Chem., Int. Ed. Engl.* **1997**, *37*, 33387-3388. (c) Wolfe, J. P.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **1999**, *38*, 2413−2416. (d) Littke, A. F.; Dai, C.; Fu, G. C. *J. Am. Chem. Soc.* **2000**, *122*, 4020−4028.

(13) For reviews, see: (a) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457−2483. (b) Suzuki, A. *J. Organomet. Chem.* **1999**, *576*, 147.

(14) The reactions proceed cleanly, with residual starting material and decoupled products as the other major components of the reaction mixture.

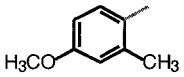
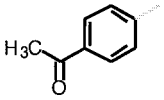
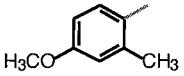
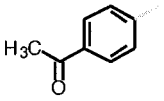
Scheme 4. Selective Coupling of the Chloro Substituents[a]



[a] Reagents and conditions: (a) limiting $ArB(OH)_2$, catalytic $PdCl_2(PPh_3)_2$, Cs_2CO_3, THF, Δ; (b) $ArB(OH)_2$, catalytic $Pd_2(dba)_3$/$P(tBu)_3$, Cs_2CO_3, THF, Δ (**18**, 79%; **19**, 57%). See Table 2 for structures and yields of **14**−**17**.

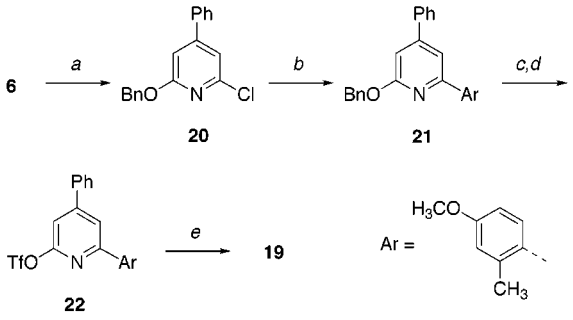
19, respectively, proceed in acceptable yield, an alternative approach to pyridine derivatives with unique substituents at positions 2, 4, and 6 was clearly desirable.

Table 2. Monocoupling of Dichloropyridines

dichloride	product	R	Ar	yield (%)
5	**14**	-C≡CTIPS		58
5	**15**	-C≡CTIPS		34
6	**16**	-Ph		49
7	**17**	-Ph		29

Such an alternative is provided by nucleophilic aromatic substitution (Scheme 5). Heating **6** with sodium benzyloxide

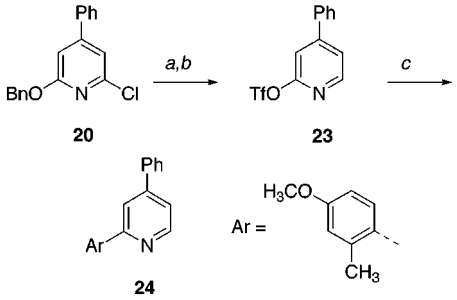
Scheme 5. Stepwise Transformation of **6**[a]



[a] Reagents and conditions: (a) BnOH, DMF, NaH, Δ, 95%; (b) $ArB(OH)_2$, catalytic $Pd_2(dba)_3$/$P(tBu)_3$, Cs_2CO_3, THF, Δ, 93%; (c) H_2, Pd/C, THF; (d) Tf_2O, Py, 0 °C, 85% over two steps; (e) $ArB(OH)_2$, catalytic $Pd(OAc)_2$/BINAP, Cs_2CO_3, THF, Δ, 85%.

in DMF cleanly provides the corresponding monoether **20** in excellent yield,[15] and subsequent arylation proceeds smoothly to provide **21**. Hydrogenolysis of the benzyl group and conversion to the corresponding triflate (**22**) sets the stage for a second arylation. With slightly modified coupling conditions,[16] **19** can now be obtained in much improved yield (64% over four steps vs 28% via **16**). A further advantage of intermediate **20** is that it may be simultaneously dechlorinated and debenzylated, providing convenient access to 2,4-biarylpyridines such as **24** (Scheme 6).[17]

Scheme 6. Synthesis of 2,4-Biarylpyridines[a]



[a] Reagents and conditions: (a) H_2, Pd/C, EtOH; (b) Tf_2O, Py, 0 °C, ∼60% over two steps; (c) $ArB(OH)_2$, catalytic $Pd(OAc)_2$/BINAP, THF, Δ, 88%.

In conclusion, we have described a convenient procedure for the multigram preparation of 2,6-dichloro-4-iodopyridine (**4**). We have further shown that **4** is a versatile precursor to both di- and trisubstituted pyridines and that fully differentiated 2,4,6-trisubstituted pyridines can be readily prepared. In light of the facility with which halopyridines undergo nucleophilic substitution and the number of commercially available boronic acid coupling partners, we anticipate that ready access to **4** will allow convenient preparation of a wide range of new pyridine derivatives.

Acknowledgment. The authors thank the National Science Foundation for support of this research (CHE-9876333) and the departmental NMR facilities (CHE-9709183) and Jennifer Davis for assistance in manuscript preparation.

Supporting Information Available: Complete experimental details. All relevant spectroscopic data, including ^1H NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(15) For representative examples of S_NAr monosubstitution of dihalopyridines, see ref 7 and the following: (a) Testaferri, L.; Tiecco, M.; Tingoli, M.; Bartoli, D.; Massoli, A. *Tetrahedron* **1985**, *41*, 1373−1384. (b) Murata, N.; Sugihara, T.; Kondo, Y.; Sakamoto. *Synlett* **1997**, 298−300.

(16) Pd-catalyzed amination of certain pyridyl triflates has been shown to require a chelating bisphosphine ligand: Arterburn, J. B.; Rao, K. V.; Ramdas, R.; Dible, B. R. *Org. Lett.* **2001**, *3*, 1351−1354.

(17) The pyridone formed upon dechlorination and debenzylation of **20** is prone to over-reduction, although this problem is not observed in the hydrogenolysis of **21**.