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Selective 4-Arylation of Pyridines by a Nonmetalloorganic Process

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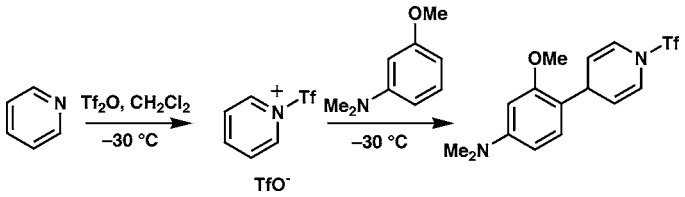
ABSTRACT

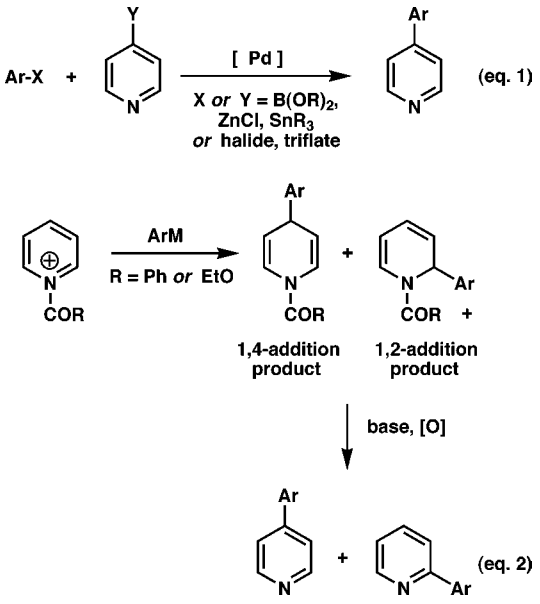


Mild and position-selective nucleophilic 4-arylation of pyridines has been accomplished by the use of triflic anhydride N-activation.

4-Arylpyridines[1] are usually prepared by one of three approaches: (1) cross-coupling reactions,[2] such as the palladium-catalyzed Suzuki reaction, Stille reaction, or Negishi reaction (Scheme 1, eq 1) starting with pyridyl halides or triflates; (2) nucleophilic addition of arylmetallic reagents to pyridinium compounds followed by rearomatization (Scheme 1, eq 2);[3] or (3) reactions that form the pyridine ring last. Herein, we report a position-selective addition of π-basic aromatic compounds directly to pyridinium compounds that have been activated by *N*-trifluoromethylsulfonation with triflic anhydride. This process depends on a method for strong electrophilic activation of pyridines that we expect will be more widely useful.

Although trifluoromethanesulfonic (triflic) anhydride in combination with 2,6-lutidine is often used as a reagent combination for the conversion of hydroxy compounds to the corresponding triflates,[4] pyridine itself or its derivatives in which the ring nitrogen is not sterically screened by 2- and 6-substituents are generally not applicable as catalysts for triflate ester formation probably because N-triflylation intervenes. The sharp difference between triflic anhydride

Scheme 1



(1) (a) Micetich, R. G. *Pyridine and Its Derivatives*, Supplement Part Two; Abramovitch, R. A., Ed.; John Wiley & Sons: New York, 1974. (b) Kartrizky, A. R., Rees, C. W., Eds.; *Comprehensive Heterocyclic Chemistry, The Structure, Reactions, Synthesis and Use of Heterocyclic Compounds*; Pergamon: New York, 1984; Vol. 2.

(2) (a) Joule, J. A.; Mills, K. *Heterocyclic Chemistry*, 4th ed.; Blackwell: UK, 2000; pp 83−84. (b) Katritzky, A. R.; Pozharskii, A. F. *Handbook of Heterocyclic Chemistry*, 2nd ed.; Pergamon: New York, 2000; p 40.

(3) (a) Comins, D. L.; Abdullah, A. H. *J. Org. Chem.* **1982**, *47*, 4315. (b) Akiba, K.; Iseki, Y.; Wada, M. *Tetrahedron Lett.* **1982**, *23*, 429. (c) Akiba, K.; Iseki, Y.; Wada, M. *Bull. Chem. Soc. Jpn.* **1984**, *57*, 1994. (d) Zhang, D.; Liorente, I.; Liebesking, L. S. *J. Org. Chem.* **1997**, *62*, 4330. (e) Joule, J. A.; Mills, K. *Heterocyclic Chemistry*, 4th ed.; Blackwell: UK, 2000; pp 66 and 96−98. (f) Katritzky, A. R.; Pozharskii, A. F. *Handbook of Heterocyclic Chemistry*, 2nd ed.; Pergamon: New York, 2000; p 210.

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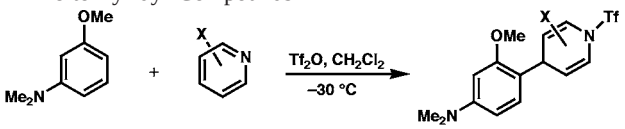
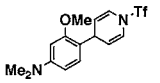
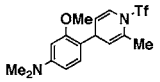
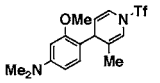
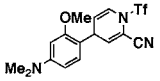
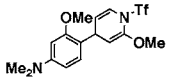
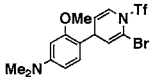
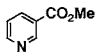
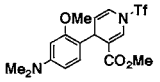
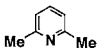
Table 1. Nucleophilic Addition of 3-Methoxy-*N*,*N*-dimethyl Aniline to Pyridyl Compounds

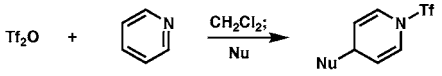


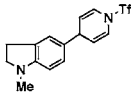
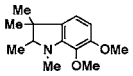
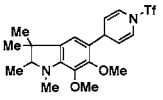
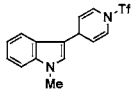
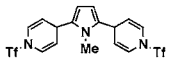
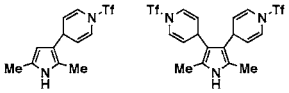
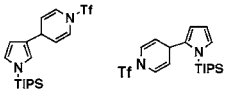
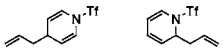
entry	substrate	product	yield %
1			86
2			68
3			78
4			57
5			70
6			58
7			76
8			No addition product
9			No reaction
10			No reaction

and other common sulfonic acid derivatives, e.g., 4-toluenesulfonyl chloride, which often are used in combination with pyridine, is testimony to the powerful electron-withdrawing effect of the CF_3 group and the great electrophilicity of triflic anhydride. We expected that the reaction of triflic anhydride with pyridine and its derivatives could provide an excellent means of activation that could lead to nucleophilic attack predominantly at the 4-position because of the bulk of the CF_3SO_2 group and resulting steric screening at positions 2 and 6. Also, as mentioned above, the strong electron-withdrawing character of the CF_3SO_2 group should provide powerful activation. Indeed, we found that pyridine and triflic anhydride readily react at −30 °C to form an *N*-triflyl cation that combines readily with neutral π-basic aromatic compounds to form 4-arylated products.

Treatment of pyridine or a variety of substituted pyridines with 0.95 equiv of triflic anhydride in CH_2Cl_2 at −30 °C for 5 min followed by the addition of 1 equiv of 3-methoxy-*N*,*N*-dimethylaniline and a further 30 min reaction time at −30 °C afforded a series of *N*-triflyl-4-aryldihydropyridines in good yield, as summarized in Table 1. The speed of the coupling reaction at −30 °C confirms the high reactivity of the *N*-triflylpyridine cations. As indicated in Table 1, neither a 2-cyano substituent (entry 4) nor a 3-methoxycarbonyl substituent (entry 7) interferes with the coupling process. The coupling reaction of 2-bromopyridine (entry 6) is noteworthy because the bromine substituent of the product can be used for further coupling reactions, giving rise to the possibility of tandem coupling processes. Substitution of the 4-position of pyridine or at the 2- and 6-positions prevents coupling (entries 8−10).

Table 2. Addition of Other Nucleophiles to Pyridine



entry	nucleophile	product	yield %
1			84
2			56
3			67
4			38%, unstable
5			21 : 49
6			34 : 17
7			21 : 34
8	TMSCN		25

To explore further the range of this coupling reaction, other electron-rich aromatic substrates have been investigated as the nucleophilic partner with pyridine in the presence of triflic anhydride, and results are shown in Table 2.

When *N*-methylindoline was used as the nucleophile under the usual coupling conditions, the addition linkage occurred between the pyridine 4-position and the 5-position of the indoline to give the coupling product in 84% yield (entry 1). The more highly substituted indoline shown in Table 2, entry 2, also underwent regioselective coupling with pyridine, as did *N*-methylindole (entry 3). The two pyrrole derivatives shown in entries 4 and 5 underwent selective coupling at

(4) Stang, P. J.; Hanack, M.; Subramanian, L. R. *Synthesis* **1982**, 85.

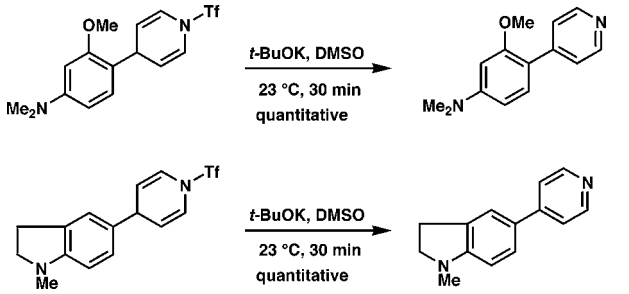
the 4-position of the triflylpyridine cation. However, the reactions were more complex due to the formation of a 2:1 product in the case of entry 4 and a mixture of 1:1 and 2:1 product in the case of entry 5. In the case of *N*-triisopropylsilylpyrrole, the expected 4−3 coupling product was formed, but surprisingly the 4−2 coupling also resulted (entry 6).

We have also investigated the reaction of the *N*-triflylpyridinium cation with two nonaromatic nucleophiles (Table 2, entries 7 and 8). Allyltri-*n*-butylstannane coupled to the *N*-triflyl pyridinium ion to give a mixture of 2- and 4-allylated dihydropyridine triflamides (entry 7), evidently because the small steric size of the allyl terminus (CH_2) minimized the steric screening effect of the CF_3SO_2 group. Also, in entry 8 is recorded the unexpected finding that trimethylsilylcyanide yielded only the triflamide of 2-cyanodihydropyridine.

The conversion of the 4-arylation products to 4-arylpyridines has been studied under a number of different reaction conditions.[5] It has been found that 1.5 equiv of KO*t*-Bu in dimethyl sulfoxide is a very satisfactory reagent for this transformation, as indicated in Scheme 2. The reaction was complete at room temperature in 30 min and gave quantitative yields.

(5) Unsuccessful reaction conditions included Et_3N, CH_2Cl_2; Bu_4NF, THF, reflux; NaOMe, MeOH, reflux; and MnO_2, MeC_6H_{11}, reflux.

Scheme 2



In summary, a simple and regioselective nucleophilic 4-arylation of pyridines has been developed. We believe that this method is admirably suited to the synthesis of a variety of biologically interesting molecules and naturally occurring alkaloids, as well.

Supporting Information Available: Experimental procedures and characterization data for 4-arylpyridines. This material is available free of charge via the Internet at http://pubs.acs.org.

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