Site-Selective Trifluoroacetylation of Dimethylamino-Substituted Pyridines and Its Use as a Building Block for Trifluoromethyl-Containing Heterocycles

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Trifluoroacetyl pyridine derivatives are conveniently prepared and applied to the synthesis of trifluoromethyl-substituted pyrazolo[4,3-*c*]pyridine derivatives.

Key words trifluoroacetylation; dimethylaminopyridine; trifluoromethyl; pyrazolo[4,3-*c*]pyridine

Trifluoromethyl ketones are of considerable current interest due to their ability to act as potent enzyme inhibitors and their importance as synthetic intermediates.[1)] Acylation of aromatic compounds with electrophilic trifluoroacetylating reagents is an efficient route to aromatic trifluoromethyl ketones[1)] and successful extension of this reaction to heterocycles including pyrrole, indole, and thiophene is reported.[1)] However, pyridines are electron deficient and generally resistant to electrophilic substitution reactions, such as Friedel–Crafts acylation.[2)] To the best of our knowledge, trifluoroacetylation of pyridines has not been reported previously.

Trifluoroacetylation of three *N*,*N*-dimethylamino-substituted pyridines (**1a**—**c**) was carried out. Thus reaction of 4-(dimethylamino)pyridine (**1a**) with trifluoroacetic anhydride (TFAA) in refluxing benzene led exclusively to the 3-trifluoroacetyl derivative (**2a**) in high yield. The yield and percent conversion of **1a** into **2a** were dependent on the ratio of **1a** to TFAA (Table 1). The yield was optimized when a 2 : 1 ratio of **1a** to TFAA was used. Trifluoroacetylation occurs at position 6 in 3-(dimethylamino)pyridine (**1b**), but the yield of **2b** is poor (38%). From 2-(dimethylamino)pyridine (**1c**), a 5-trifluoroacetyl derivative (**2c**) was obtained in 81% yield. Under similar conditions, pyridine did not undergo trifluoroacetylation. It is reported that trifluoroacetylation of methyl-substituted pyridines occurred at the methyl group and resulted in the formation of trifluoroacetonyl pyridines.[3)]

The presence of the *ortho*-substituents of the dimethylamino and trifluoroacetyl groups could make **2a** a useful building block for trifluoromethyl-containing heterocycles, because it is known that the *N*,*N*-dimethylamino group, which is activated by an *ortho*-trifluoroacetyl group, leads to a leaving group and undergoes an aromatic nucleophilic substitution reaction with several nucleophiles in *N*,*N*-dimethyl-2,4-bistrifluoroacetyl-1-naphthylamine.[4)] Thus the utility of **2a** as a trifluoromethyl building block is demonstrated in the reactions with hydrazines to give pyrazolo[4,3-*c*]pyridine derivatives (**3a**—**c**). Pyrazolopyridines constitute a medicinally important class of heterocyclic compounds because of their biological activity and structural relationship to indoles and azaindoles.[5)]

Treatment of **2a** with 3 equivalents of hydrazine·HCl in butanol under reflux for 20 h afforded the 3-trifluoromethylpyrazolo[4,3-*c*]pyridine (**3a**) in 88% yield. It was found that the hydrochloride salt is necessary for this reaction. Under similar conditions, phenylhydrazine·HCl yielded condensed pyridine (**3b**) in 42% yield and the starting material (**2a**) was recovered in 30% yield. In the case of methylhydrazine, its hydrochloride salt was not commercially available. We devised the addition of pyridine·HCl to allow the smooth reaction of **2a** with methylhydrazine and the yield of **3c** was 77%.

The structural determination of **2a**—**c** and **3a**—**c** was performed by spectral data.[6)] The position of trifluoroacetylation of **1a**—**c** was determined by the nuclear Overhauser effect (NOE) and the coupling constants of the pyridine protons. The coupling constant between the pyridine hydrogens of **2a** is 6.4 Hz, which is consistent with the 3,4-disubstituted pyridine. The 2,5-disubstituted pyridines (**2b** and **2c**) have coupling constants of 8.8 and 9.1 Hz, respectively. The structures of **3a**—**c** were also confirmed by NOEs between the 7-H and protons of the *N*-substituent.

In summary, this work describes the trifluoroacetylation of dimethylaminopyridines with TFAA, which has practical potential because of the ready availability of the starting materials and reagents and the ease of manipulation. Our method also demonstrated the novel compound **2a** to be a potential building block for the synthesis of trifluoromethyl-containing heterocycles.[7)] Furthermore, the present method is experimentally simple, convenient, and useful for the synthesis of 3-trifluoromethylpyrazolo[4,3-*c*]pyridines which are not easily obtained by other methods.[5)]

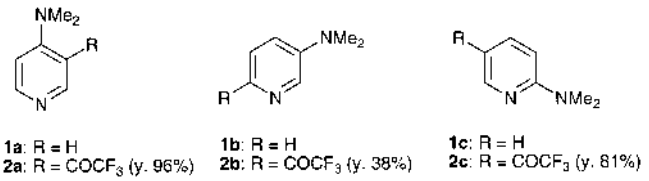

Fig. 1

Table 1. Trifluoroacetylation of DMAP (**1a**) with TFAA[a)]

Entry	**1a** (mol)	TFAA (mol)	Additive (mol)	Reaction time (h)	Yield of **2a** (%)[b)]
1	2	1	—	20	96[c)]
2	1	1	—	20	37
3	1	1	Pyridine (1)	20	39
4	1	2	—	20	26[d)]
5	2	1	—	3	89[c)]
6	2	1	—	6	96[c)]

a) The reactions were carried out on a 5-mmol scale in refluxing benzene (8 ml). *b*) Isolated yields of pure products. *c*) The yield was based on TFAA. *d*) The yield was based on **1a**.

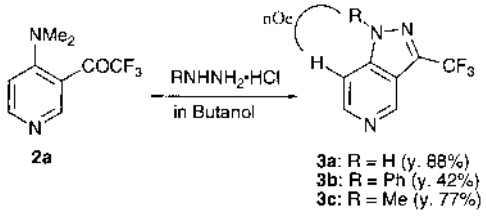

Chart 1

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References and Notes

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6) Selected data for **2a**: oil; MS *m/z*: 218 (M^+, 36%), 149 (100%); IR (Neat) cm^{-1}: 1690; ^{1}H-NMR ($CDCl_3$) δ: 2.89 (6H, s), 6.74 (1H, d, J=6.4 Hz), 8.24 (1H, d, J=6.4 Hz), 8.73 (1H, d, J=1.5 Hz); ^{13}C-NMR ($CDCl_3$) δ: 42.81 (CH_3), 109.52 (CH), 113.60 (C), 116.36 (CF_3, $^1J_{CF}$=292.2 Hz), 151.80 (CH), 152.34 (C, $^3J_{CF}$=5.2 Hz), 155.74 (CH), 179.33 (C, $^2J_{CF}$=34.7 Hz). **3a**: mp 216 °C (AcOEt); MS *m/z*: 187 (M^+, 100%); IR (Nujol) cm^{-1}: 1620, 2300—3200 (br); ^{1}H-NMR ($CDCl_3$) δ: 6.80 (1H, d, J=6.1 Hz), 7.66 (1H, d, J=6.1 Hz), 8.33 (1H, s), 13.35 (1H, br s, NH); ^{13}C-NMR ($CDCl_3$) δ: 104.14 (CH), 114.84 (C), 119.92 (CF_3, $^1J_{CF}$=267.9 Hz), 132.61 (C, $^2J_{CF}$=39.3 Hz), 141.84 (CH), 141.88 (C), 142.49 (CH).
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