Trifluoromethyl-Substituted Pyridines Through Displacement of Iodine by in situ Generated (Trifluoromethyl)copper

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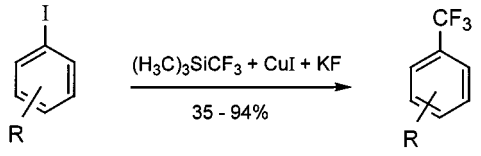
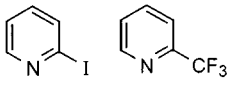
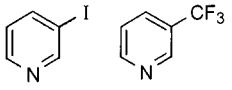
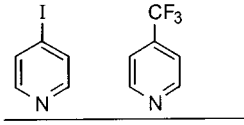
A literature method reported for iodobenzene and congeners was successfully extended to the pyridine series. 2-Iodopyridines can be converted into 2-(trifluoromethyl)pyridines almost quantitatively. In contrast, yields are moderate at best if 3- and 4-iodopyridines or 2-bromopyridines are used as the starting materials.

Fluorine plays a privileged role in life science research as a powerful modulator of bioactivity.[1−3] The trifluoromethyl group is, after single fluorine atoms, the favorite substituent in this respect. Its introduction into a given organic structure generally relies on one of two methods, both having a wide scope of applicability. One of them is the halogen exchange that trichloromethyl groups undergo when exposed to the action of anhydrous hydrogen fluoride or antimony trifluoride, in the presence or absence of antimony pentachloride, the other one is to treat a suitable carboxylic acid with sulfur tetrafluoride in a pressure vessel.[4−6] Neither method is convenient to perform in a laboratory lacking special equipment and skills. Therefore, the copper-promoted reductive coupling of aryl iodides and trifluoromethyl iodide, a modification of the well-known Ullmann reaction, was much acclaimed when reported by Y. Kobayashi et al.[7−8] More recently, T. Fuchikami et al.[9] have suggested an improved protocol where the transient trifluoromethylcopper species is generated in situ from (trifluoromethyl)trimethylsilane ("Ruppert's reagent")[10] in the presence of cuprous iodide and potassium fluoride.



For some time we have been studying systematically the site-selective lithiation of trifluoromethyl-substituted pyridines[11−12] and other heterocyclic substrates. To make the starting materials more readily available and to facilitate the identification of reaction products, we have now extended the trifluoromethyl coupling method to halopyridines. At a first stage, we have converted the three isomeric iodopyridines into the corresponding (trifluoromethyl)pyridines **1**−**3** (Table 1). The yields are moderate to good. As trifluoromethyl-substituted pyridines are quite volatile, a substantial loss of material cannot be avoided during the workup and distillative purification.

Table 1. Reaction of 2-, 3- and 4-iodopyridines with (trifluoromethyl)trimethylsilane in the presence of cuprous iodide and potassium fluoride: yields of isolated reaction products (in parentheses, yields as determined by gas chromatography)

Precursor	Product	Yield	Compd. no.
		68% (92%)	**1**
		23% (45%)	**2**
		25% (48%)	**3**

Bromoarenes are much less rapidly attacked by trifluoromethylcopper than iodoarenes and the chloro analogs are almost completely inert.[13−14] The same order of reactivity also applies to the halopyridines. As competition kinetics[15−16] have revealed, both 2- and 3-iodopyridine are consumed by trifluoromethylcopper approximately 50 times more rapidly than their bromo counterparts. Intramolecular competition experiments have qualitatively confirmed these differences in rates. When 2-chloro-6-iodopyridine, 2-bromo-6-iodopyridine and 2-bromo-6-chloropyridine were employed as the substrates, the heavier halogen was displaced exclusively (Table 2). For the same reason, 2-bromo-6-iodopyridine and 2-chloro-6-iodopyridine were found to react considerably faster than the analogous bromo com-

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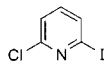
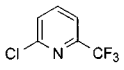
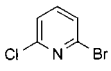
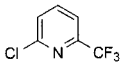
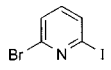
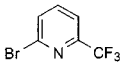
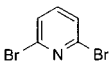
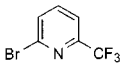
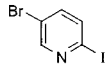
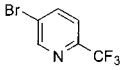
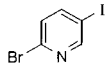
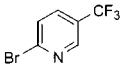
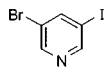
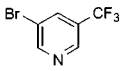
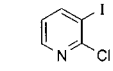
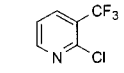
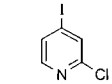
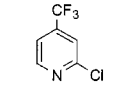
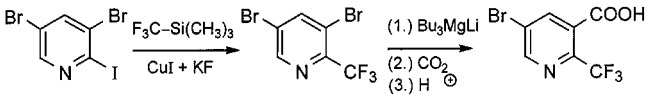
pounds 2,6-dibromopyridine and 2-bromo-6-chloropyridine (Table 2). The halogen/CF_3 exchange proceeded sluggishly or not at all if the heavy halogen occupied the 3- rather than the 2- or 4-position. The only exceptions found so far in this respect are 3-bromo-5-iodopyridine and 2-chloro-3-iodopyridine, which underwent the substitution process smoothly and efficaciously as evidenced by high yields of 3-bromo-5-(trifluoromethyl)pyridine and 2-chloro-3-(trifluoromethyl)pyridine (**8** and **9**, Table 2). Nevertheless, as the conversion of 2-bromo-5-iodopyridine into 2-bromo-5-(trifluoromethyl)pyridine (**7**) demonstrates, iodine, even if located at the unfavorable 3-position, proved to be a better leaving group than a bromine atom placed at the nucleofugally privileged 2-position (Table 2).

Table 2. Reaction of three chloroiodopyridines, four bromoiodopyridines, one dibromopyridine and one bromochloropyridine with (trifluoromethyl)trimethylsilane in the presence of cuprous iodide and potassium fluoride: yields of isolated reaction products **4**–**10** (in parentheses, yields as determined by gas chromatography)

Precursor	Product	Yield	Cpd. no.
		59% (89%)	**4**
		32% (39%)	**4**
		79% (93%)	**5**
		28% (34%)	**5**
		69% (85%)	**6**
		29% (42%)	**7**
		48% (72%)	**8**
		67% (91%)	**9**
		68% (90%)	**10**

This method tolerates the presence of more than one non-exchangeable halogen atom. 3,5-Dibromo-2-iodopyridine afforded 3,5-dibromo-2-(trifluoromethyl)pyridine (**11**) smoothly in 59% yield of isolated product (87% by gas chromatography). The bromine atom neighboring the fluorinated substituent was found to be replaced selectively when the dibromopyridine **11** was submitted to a halogen/metal interconversion, thus providing an access to the acid **12** after carboxylation and neutralization.



11 : 59% (87%) **12** : 83%

Organomagnesium or organolithium species have been generated from bromopyridines by reductive[17–19] or permutational[19–22] halogen/metal exchange as versatile intermediates for subsequent functionalization. In the same way, the trifluoromethyl-substituted congeners described above can be converted into a variety of attractive building blocks for pharmaceutical and agricultural research work.

Experimental Section

General: For laboratory routine and abbreviations, see previous publications[23–24] from this laboratory. ^1H and ^{13}C NMR spectra were recorded at 400 and 101 MHz, respectively, all samples having been dissolved in deuterochloroform. All ^{13}C signals are singlets unless the multiplicity is specified.

The gas chromatographic identification and quantification of products was performed using two 30 m long capillary columns having stationary phases of different polarity (silicon rubber and polyethylene glycol). Three distinct sets of conditions were applied: one for compounds **1**–**3** (DB-1, 50 °C; DB-WAX, 75 °C, nonane and dodecane as the internal standards, respectively), another one for compounds **4**–**5** and **7**–**11** (DB-1, 75 °C; DB-WAX, 75 °C, dodecane as the internal standard in both cases) and a final one for compound **6** (DB-1, 75 °C, dodecane; DB-WAX, 100 °C, tridecane).

Starting Materials: 2,6-, 3,6- and 3,5-Dibromopyridine are commercial. 2-Iodopyridine,[25] 3-iodopyridine,[25] 4-iodopyridine,[26] 2-chloro-3-iodopyridine,[27] 2-chloro-4-iodopyridine,[28] 5-bromo-2-iodopyridine,[29] 2-bromo-6-iodopyridine[25] and 2,3,5-tribromopyridine[30] were prepared according to literature procedures.

2-Bromo-6-chloropyridine: At 0 °C, a 2.0 M solution of isopropylmagnesium chloride (0.20 mol) in tetrahydrofuran (0.10 L) was added to 2,6-dibromopyridine (47 g, 0.20 mol) in tetrahydrofuran (0.30 L). After having been kept for 2 h at 25 °C, the mixture was treated dropwise, in the course of 45 min, with 1,1,2-trichloro-1,2,2-trifluoroethane (36 mL, 56 g, 0.30 mol) at 0 °C. After 1 h at 25 °C, diethyl ether (0.30 L) was added and the organic layer was washed with a saturated aqueous solution (2 × 0.20 L) of ammonium chloride and brine (0.2 L) before being dried, filtered and the solvents evaporated. The residue was crystallized from ethanol to give white needles; m.p. 87–88 °C (ref.[31] m.p. 87–88 °C); yield: 28.1 g (73%).

2-Chloro-6-iodopyridine: At −75 °C, butyllithium (0.15 mol) in hexanes (92 mL) was added dropwise, over 30 min, to 2-bromo-6-chloropyridine (29 g, 0.15 mol) in diethyl ether (0.20 L). After 15 min, the mixture was treated with a precooled solution of iodine (38 g, 0.15 mol) in tetrahydrofuran (0.20 L) and then kept for a further 45 min at −75 °C before being poured into a 2.0 M aqueous solution (0.10 L) of sodium thiosulfate. The organic phase was decanted, washed with brine (0.20 L), dried and the solvents evaporated. Upon recrystallization of the residue tiny white needles were obtained; m.p. 83–85 °C (ref.[32] m.p. 82–85 °C); yield: 35.8 g (84%).

2-Bromo-5-iodopyridine: As described in the preceding paragraph, 2,5-dibromopyridine (36 g, 0.15 mol) was consecutively treated with butyllithium and iodine. After the same workup of the mixture, the product was crystallized from ethanol as colorless needles; m.p. 125−126 °C (ref.[25] m.p. 124−126 °C); yield: 35.8 g (84%).

3-Bromo-5-iodopyridine: A solution of 3,5-dibromopyridine (24 g, 0.10 mol) and isopropylmagnesium chloride (0.10 mol) in tetrahydrofuran was kept for 2 h at 25 °C. At −75 °C, a precooled solution of iodine (24 g, 0.10 mol) in tetrahydrofuran (0.10 L) was added all at once. At 25 °C, the mixture was diluted with diethyl ether (0.20 L) and washed with a saturated aqueous solution (0.20 L) of ammonium chloride, a 2.0 M aqueous solution (0.10 L) of sodium thiosulfate and brine (0.20 L). Upon evaporation of the volatiles and recrystallization of the residue from ethanol, thin colorless needles were obtained; m.p. 117−118 °C; yield: 17.3 g (61%). ^{1}H NMR: δ = 8.76 (d, J = 1.8 Hz, 1 H), 8.64 (d, J = 2.0 Hz, 1 H), 8.20 (t, J = 2.0 Hz, 1 H). ^{13}C NMR: δ = 153.9, 149.4, 146.2, 121.1, 93.2. C_5H_3BrIN (283.89): calcd. C 21.15, H 1.07; found C 21.16, H 1.12.

3,5-Dibromo-2-iodopyridine: At −75 °C and under high-speed stirring (Ultraturrax, approx. 10000 rpm), butyllithium (0.15 mol) in hexanes (90 mL) and, 45 min later, pulverized iodine (38 g, 0.15 mol) were added to 2,3,5-tribromopyridine [30] (47 g, 0.15 mol) in toluene (0.30 L). After a further 2 h at −75 °C, the mixture was filtered through a pad of basic alumina (0.3 L) which was rinsed with more toluene. Recrystallization from ethanol of the residue left after evaporation of the solvents gave colorless platelets; m.p. 72−73 °C (ref.[33] m.p. 70.5 °C); yield: 43.0 g (75%). ^{1}H NMR: δ = 8.38 (d, J = 2.2 Hz, 1 H), 7.96 (d, J = 2.2 Hz, 1 H). ^{13}C NMR: δ = 149.3, 141.6, 130.4, 121.5, 120.0. $C_5H_2Br_2IN$ (362.79): calcd. C 16.55, H 0.56; found C 16.66, H 0.59.

2-(Trifluoromethyl)pyridine (1): Potassium fluoride (6.4 g, 0.11 mol) and cuprous iodide (21 g, 0.11 mol) were thoroughly mixed and flame-heated under gentle shaking and at reduced pressure (1 Torr) during some 30 min until a greenish color appeared. 2-Iodopyridine [25] (21 g, 0.10 mol), (trifluoromethyl)trimethylsilane (15 mL, 14 g, 0.10 mol), anhydrous *N*,*N*-dimethylformamide (0.10 L) and anhydrous *N*-methylpyrrolidone (0.10 L) were added and the slurry, which eventually became a brown solution, was vigorously stirred for 6 h at 25 °C before being poured into 6.4 M aqueous ammonia (0.20 L). The product was then extracted with diethyl ether (3 × 0.10 L). The combined organic layers were washed with 6.4 M aqueous ammonia (3 × 50 mL), 1.0 M hydrochloric acid, a saturated aqueous solution (0.10 L) of sodium hydrogen carbonate and brine (0.10 L), dried and the solvents evaporated. Upon distillation, a colorless oil was collected; b.p. 138−140 °C (ref.[34] b.p. 139−140 °C); n_D^{20} 1.4183 (ref.[34]: n_D^{20} 1.418); yield: 10.0 g (68%). ^{1}H NMR: δ = 8.74 (d, J = 4.7 Hz, 1 H), 7.89 (tm, J = 7.8 Hz, 1 H), 7.70 (d, J = 7.9 Hz, 1 H), 7.50 (ddm, J = 7.4, 4.8 Hz, 1 H). ^{13}C NMR: δ = 150.1, 148.4 (q, J = 35.0 Hz), 137.5, 126.5, 121.6 (q, J = 274 Hz), 120.2.

The same reaction conditions and workup protocol were applied to the preparation of the (trifluoromethyl)pyridines **2**−**11**.

3-(Trifluoromethyl)pyridine (2): From 3-iodopyridine[25] (21 g, 0.10 mol); colorless oil; b.p. 110−114 °C (ref.[34] b.p. 113−115 °C); n_D^{20} 1.4145 (ref.[34]: n_D^{20} 1.415); yield: 3.4 g (23%). ^{1}H NMR: δ = 8.91 (s, 1 H), 8.81 (d, J = 4.8 Hz), 7.94 (d, J = 8.0 Hz), 7.88 (dd, J = 7.9, 4.9 Hz). ^{13}C NMR: δ = 153.3, 146.9 (q, J = 4.0 Hz), 133.1 (q, J = 3.0 Hz), 127.8 (q, J = 33.0 Hz), 123.5 (q, J = 273 Hz), 123.5.

4-(Trifluoromethyl)pyridine (3): From 4-iodopyridine [26] (21 g, 0.10 mol); colorless oil; b.p. 105−106 °C (ref.[34] b.p. 110−113 °C); n_D^{20} 1.4147 (ref.[34]: n_D^{20} 1.415); yield: 3.6 g (25%). ^{1}H NMR: δ = 8.82 (d, J = 5.1 Hz, 1 H), 7.53 (d, J = 5.2 Hz, 1 H). ^{13}C NMR: δ = 150.5, 138.3 (q, J = 34.0 Hz), 122.3 (q, J = 273 Hz), 119.2.

2-Chloro-6-(trifluoromethyl)pyridine (4): From 2-chloro-6-iodopyridine (24 g, 0.10 mol); white needles (from hexanes); m.p. 28−29 °C; b.p. 77−78 °C/23 Torr; yield: 10.7 g (59%). ^{1}H NMR: δ = 7.9 (m, 1 H), 7.64 (d, J = 7.5 Hz, 1 H), 7.55 (d, J = 8.1 Hz, 1 H). ^{13}C NMR: δ = 152.0, 148.3 (q, J = 36.0 Hz), 140.0, 127.6, 120.6 (q, J = 274 Hz), 119.0. ^{19}F NMR: δ = −68.6 (s). $C_6H_3ClF_3N$ (181.54): calcd. C 39.70, H 1.67, N 7.72; found C 39.21, H 1.55, N 7.59.

2-Bromo-6-(trifluoromethyl)pyridine (5): From 2-bromo-6-iodopyridine (28 g, 0.10 mol); white needles; m.p. 45−46 °C (from hexanes); b.p. 95−96 °C/30 Torr; yield: 17.9 g (79%). ^{1}H NMR: δ = 7.76 (t, J = 7.9 Hz, 1 H), 7.70 (d, J = 7.7 Hz, 1 H), 7.66 (dd, J = 7.7, 1.0 Hz, 1 H). ^{13}C NMR: δ = 148.7 (q, J = 36.0 Hz), 142.4, 139.6, 131.4, 120.5 (q, J = 274 Hz), 119.4. ^{19}F NMR: δ = −68.6 (s). $C_6H_3BrF_3N$ (225.99): calcd. C 31.89, H 1.34, N 6.20; found C 31.61, H 1.34, N 6.27.

5-Bromo-2-(trifluoromethyl)pyridine (6): From 5-bromo-2-iodopyridine (28 g, 0.10 mol); colorless needles; m.p. 40−41 °C (from hexanes); b.p. 76−78 °C/25 Torr; yield: 15.6 g (69%). ^{1}H NMR: δ = 8.79 (d, J = 1.9 Hz, 1 H), 8.02 (dd, J = 8.3, 1.9 Hz, 1 H), 7.59 (d, J = 8.3 Hz, 1 H). ^{13}C NMR: δ = 151.3, 146.6 (q, J = 35.0 Hz), 140.0, 124.0, 121.7, 121.3 (q, J = 274 Hz). ^{19}F NMR: δ = −68.4 (s). $C_6H_3BrF_3N$ (225.99): calcd. C 31.89, H 1.34, N 6.20; found C 31.75, H 1.40, N 6.24.

2-Bromo-5-(trifluoromethyl)pyridine (7): From 2-bromo-5-iodopyridine (28 g, 0.10 mol); colorless needles; m.p. 43−44 °C (from hexanes); b.p. 98−99 °C/50 Torr; yield: 6.7 g (29%). ^{1}H NMR: δ = 8.66 (s, 1 H), 7.80 (dd, J = 8.5, 2.5 Hz, 1 H), 7.66 (d, J = 8.4 Hz, 1 H). ^{13}C NMR: δ = 147.1 (q, J = 4.0 Hz), 145.9, 135.3 (q, J = 3.0 Hz), 128.3, 126.0 (q, J = 33.0 Hz), 123.1 (q, J = 273 Hz). ^{19}F NMR: δ = −63.0 (s). $C_6H_3BrF_3N$ (225.99): calcd. C 31.89, H 1.34, N 6.20; found C 32.12, H 1.33, N 6.30.

3-Bromo-5-(trifluoromethyl)pyridine (8): From 3-bromo-5-iodopyridine (28 g, 0.10 mol); colorless needles; m.p. 35−36 °C (from hexanes); b.p. 65−66 °C/25 Torr; yield: 10.8 g (48%). ^{1}H NMR: δ = 8.89 (s, 1 H), 8.82 (s, 1 H), 8.08 (s, 1 H). ^{13}C NMR: δ = 154.4, 144.8 (q, J = 4.0 Hz), 135.8 (q, J = 3.0 Hz), 128.0 (q, J = 34.0 Hz), 122.6 (q, J = 273 Hz), 120.7. ^{19}F NMR: δ = −63.0 (s). $C_6H_3BrF_3N$ (225.99): calcd. C 31.89, H 1.34, N 6.20; found C 31.79, H 1.46, N 6.15.

2-Chloro-3-(trifluoromethyl)pyridine (9): From 2-chloro-3-iodopyridine [27] (24 g, 0.10 mol); colorless needles; m.p. 38−39 °C (from hexanes); b.p. 75−76 °C/30 Torr; yield: 12.3 g (67%). ^{1}H NMR: δ = 8.59 (dd, J = 4.8, 1.3 Hz, 1 H), 8.04 (dd, J = 7.8, 1.9 Hz, 1 H), 7.41 (dd, J = 7.4, 4.8 Hz, 1 H). ^{13}C NMR: δ = 152.4, 149.1, 136.7 (q, J = 5.0 Hz), 125.5 (q, J = 33.0 Hz), 122.2 (q, J = 273 Hz), 122.1. ^{19}F NMR: δ = −64.3 (s). $C_6H_3ClF_3N$ (181.54): calcd. C 39.70, H 1.67, N 7.72; found C 39.38, H 1.80, N 7.72.

2-Chloro-4-(trifluoromethyl)pyridine (10): From 2-chloro-4-iodopyridine[28] (24 g, 0.10 mol); colorless oil; m.p. −19 to −18 °C; b.p. 146−147 °C; n_D^{20} 1.4493; d_4^{20} 1.411; yield: 12.2 g (67%). ^{1}H NMR: δ = 8.61 (d, J = 5.1 Hz, 1 H), 7.58 (dq, J = 1.5, 0.8 Hz, 1 H), 7.47 (dm, J = 5.1 Hz, 1 H). ^{13}C NMR: δ = 152.7, 151.0, 141.1 (q, J = 35.0 Hz), 122.1 (q, J = 273 Hz), 120.7 (q, J = 4.0 Hz), 118.2 (q, J = 3.0 Hz). ^{19}F NMR: δ = −65.3 (s). $C_6H_3ClF_3N$ (181.54): calcd. C 39.70, H 1.67; found C 39.82, H 1.87.

3,5-Dibromo-2-(trifluoromethyl)pyridine (11): From 3,5-dibromo-2-iodopyridine (36 g, 0.10 mol); colorless needles; m.p. 22−24 °C (from pentanes); b.p. 68−69 °C/2 Torr; yield: 18.0 g (59%). ^{1}H NMR: δ = 8.67 (d, *J* = 1.8 Hz, 1 H), 8.2 (m, 1 H). ^{13}C NMR: δ = 148.3, 144.8, 144.6 (q, *J* = 35.0 Hz), 123.7, 120.9 (q, *J* = 275 Hz), 118.4. ^{19}F NMR: δ = −66.5 (s). $C_6H_2Br_2F_3N$ (304.89): calcd. C 23.64, H 0.66, N 4.59; found C 23.60, H 0.73, N 4.69.

5-Bromo-2-trifluoromethyl-3-pyridinecarboxylic Acid (12): Butyllithium (20 mmol) in hexanes (12 mL) and butylmagnesium chloride (10 mmol) in tetrahydrofuran (8.0 mL) were mixed at 0 °C. At −75 °C, 3,5-dibromo-2-(trifluoromethyl)pyridine (7.6 g, 25 mmol) in precooled tetrahydrofuran (40 mL) was added to the slurry. After stirring for 15 min at −75 °C, the mixture was poured onto an excess of freshly crushed dry ice. After evaporation of the volatiles, the residue was partitioned between diethyl ether (0.10 L) and a 2.0 M aqueous solution (3 × 0.10 L) of sodium hydroxide. The combined alkaline layers were washed with diethyl ether (2 × 50 mL), acidified with 20% hydrochloric acid to pH 1 and extracted with diethyl ether (3 × 50 mL). Evaporation of the solvent and crystallization of the solid left behind afforded colorless needles; m.p. 152 −153 °C (from ethyl acetate); yield: 5.6 g (83%). ^{1}H NMR: δ = 8.82 (d, *J* = 2.2 Hz, 1 H), 8.31 (d, *J* = 2.2 Hz, 1 H). ^{13}C NMR: δ = 165.7, 151.6, 143.8 (q, *J* = 36.0 Hz), 140.9, 130.1, 123.6, 121.1 (q, *J* = 275 Hz). ^{19}F NMR: δ = −54.6 (s). $C_7H_3BrF_3NO_2$ (270.00): calcd. C 31.14, H 1.12, N 5.19; found C 31.30, H 1.14, N 5.28.

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