Silyl-Mediated Halogen/Halogen Displacement in Pyridines and Other Heterocycles

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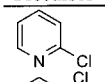
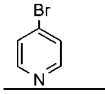
Heating with bromotrimethylsilane converts 2-chloropyridine into 2-bromopyridine and 2-chloro-6-methylpyridine into 2-bromo-6-methylpyridine. Both 2-chloropyridines and 2-bromopyridines give the corresponding iodo compound when treated with in situ generated iodotrimethylsilane. Although 3- and 4-chloropyridine are completely inert, 2,4-dichloropyridine undergoes the halogen/halogen exchange simultaneously at the 2- and 4-position. Halogen displacement takes place exclusively at the 2-position with 2,3-dichloropyridine and 2,5-dichloropyridine. In agreement with the intermediacy of *N*-trimethylsilylpyridinium salts as a prerequisite for the occurrence of halogen exchange, neither 2-fluoropyridine and 2-fluoro-6-methylpyridine nor any 2,6-dihalopyridine reacts. Finally, bromine/chlorine and iodine/chlorine substitution can also be accomplished with 2- or 4-chloroquinoline, 1-chloroisoquinoline, 2-chloropyrimidine, chloropyrazine and 2,3-dichloroquinoxaline as substrates.

Bromo- and iodopyridines are versatile starting materials for organic synthesis. The halogen may be reductively or permutationally replaced by lithium or magnesium and the organometallic intermediate converted into a functionalized derivative by reaction with a suitable electrophile.[1−3] Alternatively, the bromo- or iodopyridine may undergo substitution with in situ generated (trifluoromethyl)copper [4] or be submitted to a palladium-catalyzed Suzuki coupling.[5−7] There remains the problem of availability, however. If commercial at all, bromo and iodo compounds tend to be expensive. Therefore, we decided to explore the prospects of preparing them from low-priced chloro analogues.

A possible solution has been reported in the literature. 2,6-Dibromopyridine was obtained in a 92% yield, when 2,6-dichloropyridine was heated for several hours with a large excess of hydrogen bromide.[8] However, this method suffers from a laborious and uneconomic protocol. As we have found now, the exchange can be accomplished conveniently and at lower temperatures (90−100 °C) when bromotrimethylsilane is employed as the bromide source (Table 1). Using in situ produced iodotrimethylsilane, 2-iodopyridine was obtained from 2-chloropyridine and 2-bromopyridine (Table 1). On the other hand, 3- and 4-chloropyridine and 3- and 4-bromopyridine did not provide any well-characterized product (Table 1).

Table 1. Halogen/halogen exchange between chloro- and bromopyridines and bromotrimethylsilane or iodotrimethylsilane: yields of isolated products

Precursor	Yield	Bromo compd.	Yield	Iodo compd.
	49%[a]		57%	
	0%		–	–
	0%[b]		–	–
	–	–	72%	
	–	–	0%	
	–	–	0%[b]	

[a] The crude reaction mixture contained 59%, as determined by gas chromatography. [b] Decomposition of the starting material.

We assume *N*-(trimethylsilyl)pyridinium salts[9−11] to act as the crucial intermediates. Their existence is suggested by the very precipitate which forms instantaneously upon mixing of the reactants. Although all exchange-mediating steps are reversible, the equilibrium is continuously displaced when the volatile chlorotrimethylsilane is removed as formed.

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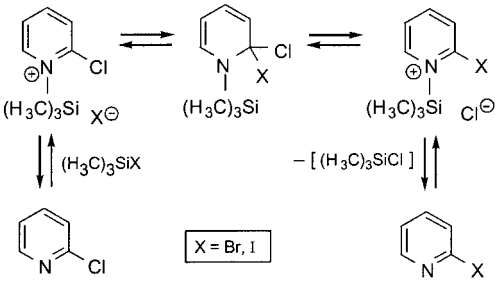
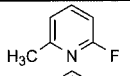
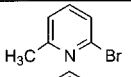
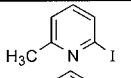
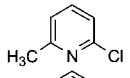
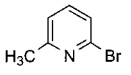
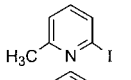
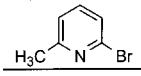
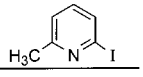


A number of findings is in agreement with this mechanism. Lacking sufficient nucleophilicity, 2-fluoropyridine, 2,6-difluoropyridine and 2-fluoro-6-methylpyridine proved to be completely inert. Fluorinated pyridines are indeed known to be less basic than their chloro- or bromo-substituted counterparts in both the gas phase [12] and in an aqueous medium.[13] No reaction occurred with 2,6-dichloro- and 2,6-dibromopyridine. We attribute this again to electron deficiency rather than to steric effects as 2-chloro-6-methylpyridine and 2-bromo-6-methylpyridine did undergo chlorine/bromine, chlorine/iodine and bromine/iodine exchange (Table 2).

Table 2. Reaction between 2-chloro-6-methylpyridine with bromo- or iodotrimethylsilane and 2-bromo-6-methylpyridine and iodotrimethylsilane: yields of isolated products

Precursor	Yield	Bromo compd.	Yield	Iodo compd.
	0%		0%	
	47%		61%	
	–	–	82%	

As demonstrated above (Table 1), chlorine can be readily displaced only from the 2-position. Therefore, 3,5-dichloropyridine and 3,5-dibromopyridine did not react at all whereas the treatment of 2,3-dichloro- and 2,5-dichloropyridine with bromo- or iodotrimethylsilane afforded 2-bromo-3-chloropyridine or 3-chloro-2-iodopyridine and 2-bromo-5-chloropyridine or 5-chloro-2-iodopyridine, exclusively (Table 3). However, halogens at the 4-position are also mobile to some extent as shown by the conversion of 2,4-dichloropyridine into 2,4-dibromopyridine (Table 3).

When moving from pyridines to benzo analogs, the reactivity increases substantially. Chlorine was readily displaced from both the 2- and 4-positions of quinolines and from the 1-position of isoquinoline (Table 4).

The exchange reaction proceeded also rapidly with 2-chloropyrimidine and 2,3-dichloroquinoxaline (Table 5). In contrast, chloropyrazine reacted only sluggishly, this presumably as a result of preferential silylation at the halogen-remote nitrogen atom. No attempt was made to prepare iodo derivatives of these diaza heterocycles for fear of poor chemical stability.

Table 3. Halogen/halogen exchange between 2,3-, 2,4- and 2,5-dichloropyridine and bromo- or iodotrimethylsilane: yields of isolated products

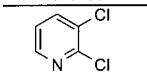
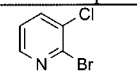
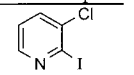
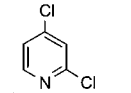
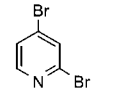
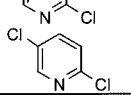
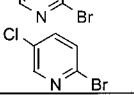
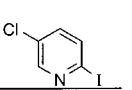
Precursor	Yield	Bromo compd.	Yield	Iodo compd.
	83%		33%	
	49%		–	–
	67%		52%	

Table 4. Halogen/halogen exchange between 2-chloroquinoline, 4,7-dichloroquinoline and 1-chloroisoquinoline and bromo- or iodotrimethylsilane: yields of isolated products

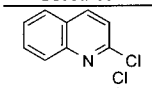
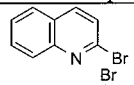
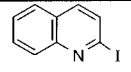
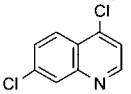
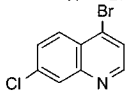
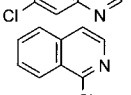
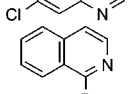
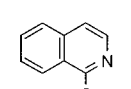
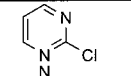
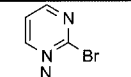
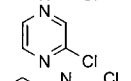
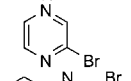
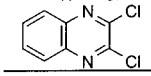
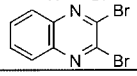
Precursor	Yield	Bromo compd.	Yield	Iodo compd.
	83%		86%	
	82%		–	–
	73%		81%	

Table 5. Chlorine/bromine exchange between chloro(benzo)diazines and bromotrimethylsilane: yields of isolated products

Precursor	Yield	Bromo compd.	Yield	Iodo compd.
	89%		–	–
	30%		–	–
	96%		–	–

Recently, we have successfully applied the new halogen/halogen displacement protocol to more complex substrates, in particular trifluoromethyl-substituted ones. These results will be communicated in a different context.

Experimental Section

General: ^{1}H and ^{13}C NMR spectra were recorded of samples dissolved in deuteriochloroform at 400 and 101 MHz, respectively. The chemical shifts listed refer to tetramethylsilane (δ = 0.00 ppm) as an internal standard. For the working routine and abbreviations, see previous publications from this laboratory.[14–16] All starting materials were commercial except 2,4-dichloropyridine, which was prepared according to a literature procedure.[17] The same holds for

the expensive 1-chloroisoquinoline.[18] The chlorine/bromine displacements were carried out in a flask to which a Dimroth condenser was vertically mounted and which was connected to a distillation bridge ending in a drying tube filled with calcium chloride. The condenser spiral was fed with +75 °C warm water to retain bromotrimethylsilane (b.p. 80 °C) but to let escape the chlorotrimethylsilane (b.p. 58 °C) formed. It was collected in a graduated trap. In this way, it was easy to monitor the progress of the reaction which was stopped as soon as the evolution of chlorotrimethylsilane had ceased. The chlorine/- and bromine/iodine displacements were performed by simply refluxing the starting material in propionitrile in the presence of chlorotrimethylsilane and excess sodium iodide.

2-Bromopyridine: A mixture of 2-chloropyridine (4.7 mL, 5.7 g, 50 mmol), bromotrimethylsilane (13 mL, 15 g, 0.10 mol) and propionitrile (50 mL) was heated for 100 h under reflux. The reaction mixture was then poured into a 2.0 M aqueous solution of sodium hydroxide (50 mL) to which ice (approx. 50 g) had been added. The aqueous phase was thoroughly extracted with diethyl ether (3 × 50 mL). The combined organic layers were washed with water (2 × 50 mL) and brine (50 mL), dried and the solvents evaporated. The product was isolated by distillation as a colorless liquid; b.p. 192−195 °C (ref.[19] 193.5−194 °C); n_D^{20} = 1.5715 (ref.[19] 1.5713); yield: 3.9 g (49%).

3-Chloropyridine did not react at all under such conditions, whereas 4-chloropyridine underwent slow decomposition without forming notable amounts of 4-bromopyridine. 2-Fluoropyridine was also found to be completely inert.

2-Bromo-6-methylpyridine: Analogously from 2-chloro-6-methylpyridine (5.5 mL, 6.4 g, 50 mmol); b.p. 74−75 °C/7 Torr (ref.[20] 198−201/772 Torr); n_D^{20} = 1.5816; yield: 4.1 g (47%).

2-Iodopyridine: A mixture of 2-chloropyridine (4.7 mL, 5.7 g, 50 mmol), propionitrile (50 mL), chlorotrimethylsilane (6.3 mL, 5.4 g, 50 mmol) and sodium iodide (22 g, 0.15 mol) was heated for 4 d under reflux. The reaction mixture was then poured into a 2.0 M aqueous solution of sodium hydroxide (50 mL) containing some ice (approx. 50 g). The aqueous phase was thoroughly extracted with diethyl ether (3 × 50 mL). The combined organic layers were washed with water (2 × 50 mL) and brine (50 mL), dried and the solvents evaporated. The residue was purified by distillation; b.p. 87−89 °C/10 Torr (ref.[2] 92 °C/15 Torr); n_D^{20} = 1.6361 (ref.[21] 1.6363); yield: 4.2 g (57%). The yield was raised to 7.4 g (72%) when 2-bromopyridine (4.9 mL, 7.9 g, 50 mmol) was employed as the starting material and the reflux time was shortened to 2 d (50 h).

2-Iodo-6-methylpyridine: Analogously from 2-chloro-6-methylpyridine (5.5 mL, 6.4 g, 50 mmol) and 2-bromo-6-methylpyridine (5.6 mL, 8.6 g, 50 mmol) in 61% (6.7 g) and 82% (9.0 g) yield, respectively; m.p. 10−13 °C; b.p. 115−116 °C/15 Torr; n_D^{20} = 1.6195. ^{1}H NMR: δ = 7.53 (d, J = 7.6 Hz, 1 H), 7.20 (t, J = 7.6 Hz, 1 H), 7.11 (d, J = 7.6 Hz, 1 H), 2.52 (s, 3 H) ppm. ^{13}C NMR: δ = 160.5, 137.6, 131.9, 122.5, 117.3, 24.2 ppm. C_6H_6IN (219.02): calcd. C 32.90, H 2.76; found C 32.99, H 2.68.

2-Bromo-3-chloropyridine: Analogously from 2,3-dichloropyridine (7.4 g, 50 mmol) as described above (see the preparation of 2-bromopyridine); yield: 38% (by gas chromatography: 30 m, DB-1, 150 °C; 30 m, C20M, 150 °C; undecane as an internal standard). The yield increased to 83% (8.0 g) when heating under reflux was allowed to alternate with periods of cooling to +50 °C in 60-min intervals for 70 h. The product was isolated by recrystallization; colorless needles (from hexanes); m.p. 58−59 °C (ref.[22] 59 °C).

2-Bromo-5-chloropyridine: Analogously by applying this cyclical heating-cooling protocol to 2,5-dichloropyridine (7.4 g, 50 mmol) for 20 h; colorless needles (from hexanes); m.p. 68−69 °C (ref.[23] 70−71 °C); yield: 6.4 g (67%).

3-Chloro-2-iodopyridine: The standard protocol (see the preparation of 2-iodopyridine) was applied to 2,3-dichloropyridine (7.4 g, 50 mmol) for 2 d; yield: 33% (by gas chromatography: 30 m, DB-1, 150 °C; 30 m, C20M, 150 °C; undecane as an internal standard). The yield increased to 83% (10 g) when 2-bromo-3-chloropyridine (9.6 g, 50 mmol) was employed as the starting material and the reaction time shortened to 2 h. The product was isolated by recrystallization; colorless prisms (from hexanes); m.p. 47−49 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.28 (dd, J = 4.7, 1.5 Hz, 1 H), 7.67 (dd, J = 7.9, 1.7 Hz, 1 H), 7.24 (dd, J = 7.9, 4.7 Hz, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 101 MHz): δ = 147.9, 138.2, 136.2, 123.6, 121.5 ppm. C_5H_3ClIN (239.44): calcd. C 25.08, H 1.26; found C 25.33, H 1.31.

5-Chloro-2-iodopyridine: Analogously from 2,5-dichloropyridine (7.4 g, 50 mmol) but allowing for 4 d of reflux; colorless platelets (from hexanes); m.p. 85−87 °C; yield: 6.5 g (52%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.35 (d, J = 2.6 Hz, 1 H), 7.66 (d, J = 8.3 Hz, 1 H), 7.24 (dd, J = 8.2, 2.6 Hz, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 101 MHz): δ = 149.6, 137.5, 135.5, 132.5, 114.3 ppm. C_5H_3ClIN (239.44): calcd. C 25.08, H 1.26; found C 25.28, H 1.26.

2,4-Dibromopyridine: The standard protocol (see the preparation of 2-bromopyridine) was applied to 2,4-dichloropyridine [17] (7.4 g, 50 mmol), while 3 equiv. of bromotrimethylsilane (20 mL, 23 g, 0.15 mol) were used. The product was isolated by recrystallization; colorless needles (from hexanes); m.p. 38−39 °C (ref.[24] 38.0−38.5 °C); yield: 5.8 g (49%).

No new product was formed when 2,6-difluoropyridine, 2,6-dichloropyridine, 2,6-dibromopyridine or 3,5-dibromopyridine were treated in the same way.

2-Bromoquinoline: The standard protocol (see the preparation of 2-bromopyridine) was applied to 2-chloroquinoline (8.2 g, 50 mmol) for 4 h. The product was isolated by recrystallization; colorless needles (from acetone); m.p. 50−51 °C (ref.[25] 50−51 °C); yield: 8.6 g (83%).

2-Iodoquinoline: A mixture of 2-chloroquinoline (8.2 g, 50 mmol), chlorotrimethylsilane (6.3 mL, 5.4 g, 50 mmol) and sodium iodide (15 g, 0.10 mol) was heated to reflux for 1 d (20 h) and worked up as described in the case of 2-iodopyridine. The product was isolated by recrystallization; colorless needles (from hexanes); m.p. 53−54 °C (ref.[25] 53 °C); yield: 10.9 g (86%).

4-Bromo-7-chloroquinoline: 4,7-Dichloroquinoline (9.9 g, 50 mmol) was treated with bromotrimethylsilane (13 mL, 15 g, 0.10 mol) as described above for the preparation of 2-bromoquinoline; colorless needles (from hexanes); m.p. 102−103 °C (ref.[26] 104−105 °C); yield: 9.9 g (82%).

1-Bromoisoquinoline: Analogously from 1-chloroisoquinoline[18] (8.2 g, 50 mmol) and bromotrimethylsilane (13 mL, 15 g, 0.10 mol); colorless needles (from hexanes); m.p. 41−43 °C (ref.[27] 41.5−42.3 °C); yield: 7.6 g (73%).

1-Iodoisoquinoline: Analogously as described for the preparation of 2-iodoquinoline (see above), starting with 1-chloroisoquinoline[18] (8.2 g, 50 mmol); colorless needles (from hexanes); m.p. 75−77 °C (ref.[25] 75.5−76.5 °C); yield: 10.3 g (81%).

2-Bromopyrimidine: From 2-chloropyrimidine (5.7 g, 50 mmol) under the same conditions as described for the preparation of 2-bromoquinoline (see above); colorless needles (from pentanes); m.p. 56−57 °C (ref.[28] 55−57 °C); yield: 6.9 g (87%).

Bromopyrazine: Analogously from chloropyrazine (5.7 g, 50 mmol), although the heating under reflux had to be extended over 2 d (50 h). The colorless oil obtained after extraction was purified by distillation; b.p. 59−61 °C/10 Torr (ref.[29] 57−58 °C/9 Torr); n_D^{20} = 1.5819 (ref.[29] 1.5814); yield: 2.4 g (30%).

2,3-Dibromoquinoxaline: A mixture of 2,3-dichloroquinoxaline (2.0 g, 10 mmol) and bromotrimethylsilane (4.0 mL, 4.5 g, 30 mmol) in propionitrile (10 mL) was heated under reflux and was worked up after 50 h when no chlorotrimethylsilane was evolved any more. Crystallization of the residue from ethyl acetate afforded colorless needles; m.p. 172−174 °C (ref.[30] 171−174 °C); yield: 2.8 g (96%).

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