[Chem. Pharm. Bull.
33(5)1836—1842(1985)]

Aminohaloborane in Organic Synthesis. X.[1] A Convenient, Economical Exclusive *ortho* Substitution Reaction of *N*-Alkyl and *N*-Aminoalkyl Anilines

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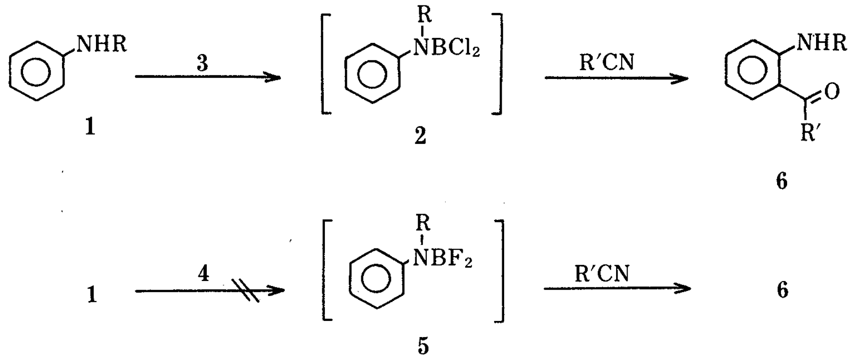
(Received August 1, 1984)

A method for *in situ* generation of boron trichloride from boron trifluoride etherate and silicon tetrachloride in the presence of triethylamine, traced by boron-11 nuclear magnetic resonance (^{11}B-NMR) spectroscopy, was successfully developed, thus eliminating the need to use expensive boron trichloride for the exclusive *ortho* substitution reaction of *N*-monoalkylanilines. The method was readily adaptable to the reaction with *N*-monoaminoalkylanilines.

Keywords——regioselective reaction; 2-acylaniline derivative; *in situ* generation of boron trichloride; ^{11}B-NMR; boron trifluoride etherate; silicon tetrachloride

Our previously described exclusive *ortho* substitution reaction of anilines derivatives[1] (**1**) proceeds due to the appropriate Lewis acidity of the intermediary anilinodichloroboranes (**2**). However, from the viewpoint of cost, the use of boron trichloride (**3**), which is much more expensive than boron trifluoride etherate (**4**), is disadvantageous. However, simple replacement of **3** with **4** was impossible, because anilinodifluoroboranes (**5**), which are hitherto unknown but would be required to give 2-acylanilines (**6**), were not generated by merely heating **1** with **4** in the absence or presence of aliphatic tertiary amines, while similar treatment of **1** with **3** readily gave **2**. In general, anilinoboranes (**7**) are obtained by treatment of **1** with **4** only in the presence of metals such as Li, Na, and Al, or ethylmagnesium bromide.[2]



$$BF_3 + ArNH_2 + \text{metal or } C_2H_5MgBr \longrightarrow \underset{7}{B(NHAr)_3}$$

3, BCl_3; **4**, $BF_3 \cdot OEt_2$ R = alkyl, aminoalkyl; R' = alkyl, aryl

Chart 1

In this work, we undertook the *in situ* generation of **3** by stepwise replacement of fluorine (F) of **4** with chlorine (Cl) from an inexpensive inorganic chloride *via* difluoroboron chloride

TABLE I. mol% of Reaction Products of *N*-Methylaniline **14**, $BF_3 \cdot OEt_2$ **4**, $SiCl_4$ **8** and Et_3N **9**, and their ^{11}B-NMR Data[a] (δ/ppm, Multiplicity and $^1J_{^{11}B,^{19}F}$/Hz)[b]

Run	Reaction component	Reaction products[c]								
		CH_3 | PhNH ↓ BF_3 (+18.87 q J=14) **19**	CH_3 | PhNH ↓ F_2BCl (+14.98 t J=42) **20**	CH_3 | PhNH ↓ $FBCl_2$ (+11.88 d J=68) **21**	CH_3 | PhNH ↓ BCl_3 (+10.91 s) **22**	$PhNCH_3$ | BCl_2 (−12.14 br s) **23**	CH_3 | $(PhN)_3$ | B (−6.0 br) **24**	CH_3 | $(PhN)_2$ | BCl (−10.2 br) **25**	Et_3N ↓ BF_3 (+18.93 q J=19) **10**	Et_3N ↓ F_2BCl (+14.24 t J=47) **11**
1	**4 8**									
2	**4 8 9**								37	35
3	**4 8 14**	77	19	4						
4	**4 8 9 14**		5	17	19	30	4	7	5	4
5	**4 8 9 14**	20	28	20	14	16	2			
6	**4 14**	~100								
7	**4 9 14**								~100	

Run	Reaction component	Reaction products[c]							
		Et_3N ↓ $FBCl_2$ (+10.78 d J=73) **12**	Et_3N ↓ BCl_3 (+9.64 s) **13**	$Et_3\overset{+}{N}H$ BCl_4^- (+12.12 s) **15**	Et_2O ↓ BF_3 (+18.96 s like) **4**	Et_2O ↓ F_2BCl (+15.04 t J=30) **16**	Et_2O ↓ $FBCl_2$ (+11.01 d J=57) **17**	$(EtO)_2$ | BCl (−4.0 br) **18**	Conversion (%)
1	**4 8**				82	17	1		18
2	**4 8 9**	10	1	12				5	63
3	**4 8 14**								23
4	**4 8 9 14**			7					95
5	**4 8 9 14**								80
6	**4 14**								0
7	**4 9 14**							0	

a) A solution of each component in a molar ratio of 1 except for run 5 in $CDCl_3$ was refluxed for 2 h and the yields (mol%) of the products were estimated from the ^{11}B-NMR spectra. *b*) ^{11}B-NMR spectra were recorded with a Varian XL-200 NMR spectrometer under ^{1}H decoupled conditions at 24°; external $B(OCH_3)_3$ was used as the reference; for the multiplicity, g, t, d and s mean quartet, triplet, doublet and singlet, respectively, and br means broad; from the conditions for Fourier transform (FT)-NMR measurement the estimated observational errors in δ and J values are *ca.* 0.01 ppm and 1 Hz, respectively. *c*) Assignments of ^{11}B-NMR signals of **4**, **10**, **13**, **15**, **19**, **22** and **23** were made by measuring authentic samples. For **11**, **12**, **16**, **17**, **18**, **20**, **21**, **24** and **25**, the assignments were based on the literature data[7] and the ^{1}H-NMR spectra.

(BF_2Cl) and fluoroboron dichloride ($BFCl_2$). Considering the extremely high affinity of the F anion for silicon, as noted by Kuwajima *et al.*,[3] we first used silicon tetrachloride (**8**) as a Cl source and followed the course of the transformation by using boron-11 nuclear magnetic resonance (^{11}B-NMR) spectroscopy (Table I). The ^{11}B-NMR spectrum of a solution of **4** and **8** in deuteriochloroform ($CDCl_3$) after refluxing for 2 h showed that the transformation of F of **4** into BF_2Cl and $BFCl_2$ took place in only 18% yield (run 1). However, we found that the transformation proceeded quite rapidly in the presence of one equivalent of triethylamine (**9**), forming the triethylammonium complexes of boron chlorofluoride (**11**, **12**) and trichloride (**13**, **15**), with a conversion yield of 63% (run 2). Acceleration of the transformation in the presence of **9** was also confirmed in the similar reaction of *N*-methylaniline (**14**) with a combination of **4** and **8** (runs 3 and 4). In run 4, a complex (**22**) of **3** and **14** and dichloro-*N*-methylanilinoborane (**23**) were observed at 19 and 30 mol%, respectively, although these species were not yet formed in run 3. This result can be explained by assuming that an anionically activated F anion[4)] generated from the ammonium-ate complex **10** attacks **8**, which in turn produces Cl anion, forming silicon fluorotrichloride ($SiCl_3F$). The Cl anion is transformed to give the ammonium-ate complex **11** and similar transformation follows until the ammonium complex of **3** (**13**) is produced (Chart 2).

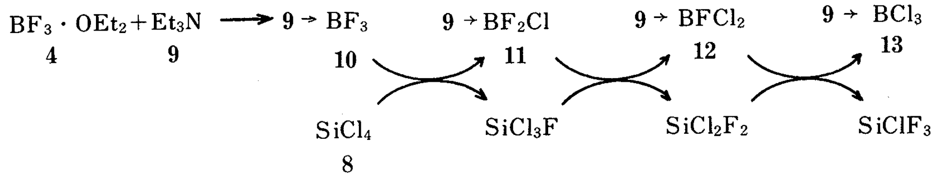
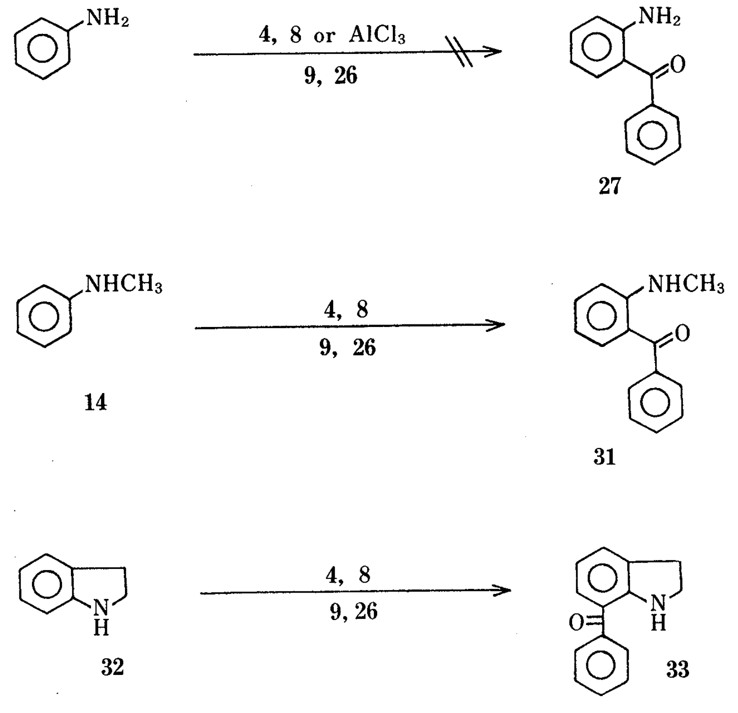


Chart 2

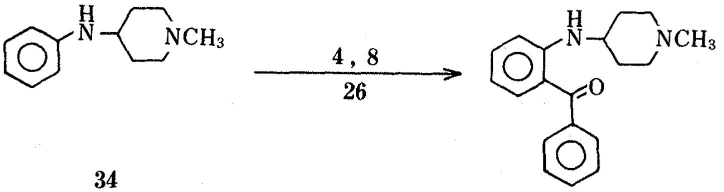
We next examined to what extent a combination of **4** and **8** or other inorganic chlorides in the presence of **9** can play the role of **3** in the reaction of anilines and benzonitrile (**26**) (Chart 3, Table II). The reaction of aniline with **26** in the presence of **4**, **8** or aluminum trichloride ($AlCl_3$) and **9** in refluxing dichloroethane did not give 2-benzoylaniline (**27**) (run 1), probably due to rapid formation of anilinoboranes such as **28**, **29** and **30**, which did not serve to direct the *ortho* substitution reaction. Of course, treatment of a preheated mixture of **14** and **4** alone with **26** did not give 2-benzoyl-*N*-methylaniline (**31**) (run 2). The ^{11}B-NMR spectrum of a solution of **14** and **4** in $CDCl_3$ in the absence or presence of **9** after refluxing for 2 h showed only the existence of complexes of boron trifluoride **19** and **10**, respectively (Table I, runs 6 and 7). However, a similar reaction in the presence of one equivalent of **8** gave **31** in 44% yield (method A, Table II, run 3). As expected, the yield of **31** was raised to 63% by



4, $BF_3 \cdot OEt_2$; **8**, $SiCl_4$; **9**, Et_3N; **26**, PhCN;
28, $(PHNH)_2BCl$; **29**, $(PhNH)_3B$; **30**, $(PhNBCl)_3$

Chart 3

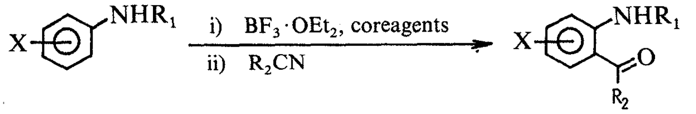
adding one equivalent of **9** (run 4). Our originally reported method using **3** gave **31** in 87% yield, so the extent of substitution of **3** by **4** was as high as 72% with the cooperation of **8** and **9**. Similarly, the reaction of indoline (**32**) with **26** in the presence of **4** and **8** gave 7-benzoylindoline (**33**) in 60% yield, but the yield could be raised to 83% by adding **9**, so that the result was comparable with that of the method using **3**[5] (80%).

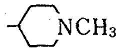
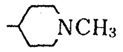
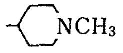


34 **35**

Chart 4

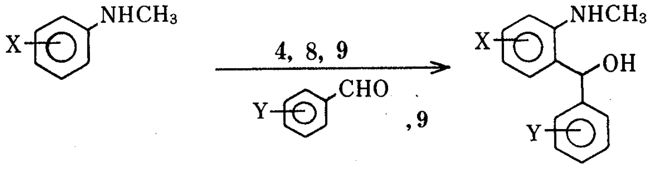
Table II. Reaction of *N*-Alkyl and *N*-Aminoalkylanilines with Nitriles Using Boron Trifluoride Etherate and Coreagents



Run	X	R_1	R_2	Coreagents	Method	Yield[a] (yield by using BCl_3)
1	H	H	Ph	$SiCl_4$ or $+Et_3N$ $AlCl_3$	B	0 (63)[6]
2	H	CH_3	Ph	None	A	0
3	H	CH_3	Ph	$SiCl_4$	A	44
4	H	CH_3	Ph	$SiCl_4+Et_3N$	A	63[b] (87)[6]
5	H		Ph	$SiCl_4$	A	95 (99)[1]
6	H		Ph	$SiCl_4$	B	79
7	H		Ph	$AlCl_3$	A	69
8	H		Ph	$TiCl_4$	A	34
9	H		Ph	PCl_5	A	49
10	H		CH_3	$SiCl_4$	B	85 (95)[1]
11	4-Cl		2-F–Ph	$SiCl_4$	A	81 (99)[1]
12	4-Cl		Ph	$SiCl_4$	A	82 (99)[1]
13	4-OCH_3		Ph	$SiCl_4$	B	53 (56)[1]
14	4-CH_3		Ph	$SiCl_4$	A	90[c] (95)
15	H	$-(CH_2)_2N(Et)_2$	Ph	$SiCl_4$	A	73 (88)[1]

a) Isolated yields based on aniline used; unchanged anilines were recovered in inversely related yields. *b*) Yield was raised to 73% when two moles of $BF_3 \cdot OEt_2$ and coreagents were used. *c*) Oil, IR ν_{max}^{film} cm^{-1}: 3280 (NH), 1620 (C=O). ^{1}H-NMR ($CDCl_3$) δ: 1.4—3.7 (m, aliph. H), 2.16 (s, C–CH_3), 2.34 (s, NCH_3), 6.6—7.6 (m, arom. H).

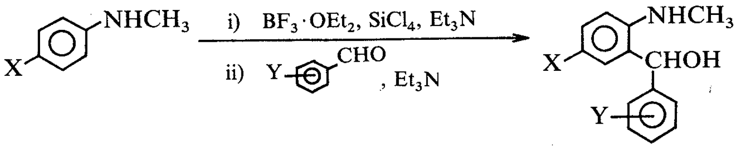
Next, we tried applying this method to *N*-(1-methyl-4-piperidinyl)aniline (**34**), which contains an aliphatic tertiary amine group (Chart 4). 2-Benzoylaniline (**35**) was obtained in 95% yield without adding **9**; the yield was close to that of the original method shown in run 5, Table II. Moderately effective reaction promotors in addition to **8** were $AlCl_3$, $TiCl_4$ and PCl_5. When nitriles having a boiling point under 150 °C or *N*-monoaminoalkylanilines bearing substituents vulnerable to Lewis acid were used, a solution of an aniline, **4**, **8** and a nitrile in dichloroethane was refluxed (method B). Table II summarizes our results and shows that a combination of **4** and **8** in the presence of **9** can practically replace **3** in the exclusive *ortho* acylation reaction of *N*-monoalkylanilines. The new method was also used to obtain *N*-methyl-2-(α-hydroxybenzyl)aniline (**36**) from *N*-methylanilines and benzaldehydes, though the yield was somewhat lower than that in the original method[6] (Chart 5, Table III).



36

Chart 5

TABLE III. Reaction of *N*-Alkylaniline and Benzaldehyde Using Boron Trifluoride Etherate, Silicon Tetrachloride and Triethylamine

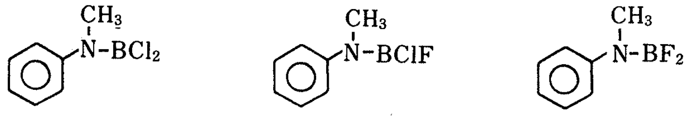


Run	X	Y	Ratio of **6**, **2**, **7**, and **8**	Reaction time (h)	Yield[a] % (yield by using BCl_3)
1	H	H	1:1.2:1.2:1.2	5	49
2	H	H	1:1.2:1.2:0.5	5	71 (84)[6]
3	H	2-NO_2	1:1.2:1.2:0.5	23	87 (97)[6]
4	H	4-OCH_3	1:1.2:1.2:0.5	5	54 (84)[6]
5	NO_2	2-F	1:1.2:1.2:0.5	22	40 (73)

a) Isolated yields based on aniline used; unchanged anilines were recovered in inversely related yields.

In this case, the use of a half equivalent of **9** gave a better yield of **36**. This may be explained by the result that a $CDCl_3$ solution of **14**, **4**, **8** and **9** in a ratio of 1 : 1 : 1 : 0.5 after refluxing for 2 h (Table I, run 5) contained only a small amount of tris-*N*-methylanilinoborane (**24**) and no detectable chloro-bis-(*N*-methylanilino)borane (**25**), both of which were observed in larger amounts in a similarly treated solution of **14**, **4**, **8** and **9** in a ratio of 1 : 1 : 1 : 1 (run 4). Thus, **24** and **25** are not useful reaction species for the desired reaction.

Our new method makes possible the convenient and economical exclusive *ortho* substitution reaction of *N*-alkyl and *N*-aminoalkylanilines by using a combination of **4** and **8** with or without **9** instead of the expensive reagent **3**. Further study is needed to determine whether the actual reaction species is only **23** or includes the hypothetical anilinochlorofluoroborane (**37**) and anilinodifluoroborane (**38**), which may be formed from the observed intermediaries BCl_2F and BF_2Cl.



23 **37** **38**

Chart 6

Experimental

Melting points were determined on a Yanagimoto micromelting apparatus and are uncorrected. Infrared (IR) spectra were recorded in $CHCl_3$ solution on a Hitachi 260-10 IRS spectrophotometer. Wave numbers are expressed in reciprocal centimeters. NMR spectra were taken in $CDCl_3$ solution on a Varian EM-390 or T-60 spectrophotometer. Chemical shifts are expressed as δ values (parts per million) from tetramethylsilane. Column chromatography was conducted using silica gel (E. Merck, 70—230 mesh ASTM) and aluminum oxide (E. Merck, Standardisiert). Silica gel GF and aluminum oxide F254 (E. Merck) were used for analytical thin-layer chromatography (TLC). In cases where the products were isolated by solvent extraction, the procedure generally followed was to extract the aqueous layer with two to three portions of the indicated solvent, then to wash the organic layer with saturated $NaCl–H_2O$ or H_2O and dry it over Na_2SO_4 or $MgSO_4$.

Method A——To a stirred solution of an *N*-alkyl- or *N*-aminoalkylaniline (2 mmol) in dichloroethane (10 ml), BF_3OEt_2 (2 × 1.2 mmol) and $SiCl_4$ (2 × 1.2 mmol) were added successively at room temperature, and the turbid solution was refluxed in the presence or absence of triethylamine (2 × 1.2 mmol) for 2 h. After concentration of the solution under normal pressure, a nitrile (2 × 2 mmol) was added to the resulting syrup and the mixture was heated at 150 °C (bath temperature) for 2 h. After cooling, 6 N HCl (5 ml) was added and the mixture was heated at 100 °C for 20 min. After cooling, the mixture was washed with ether. The acidic layer was alkalized with K_2CO_3 and the mixture was extracted with CH_2Cl_2. The extract was purified on SiO_2 (3 g) using CH_2Cl_2 and CH_2Cl_2 containing 3% CH_3OH, giving the corresponding *N*-alkyl or *N*-aminoalkyl-2-acylaniline. From the polar fraction, *N*-alkyl- or *N*-aminoalkylaniline was recovered.

Method B——To a stirred solution of an *N*-alkyl- or *N*-aminoalkylaniline (2 mmol) in dichloroethane (10 ml), BF_3OEt_2 (2 × 1.2 mmol), $SiCl_4$ (2 × 1.2 mmol) and a nitrile (2 × 2 mmol) were added successively and the turbid solution was refluxed in the presence or absence of triethylamine (2 × 1.2 mmol) for 20 h. Work-up as described above gave *N*-alkyl or *N*-aminoalkyl-2-acylaniline.

7-Benzoylindoline (33)——To a stirred solution of indoline (357 mg, 3 mmol) in dichloroethane (10 ml), triethylamine (0.5 ml, 3 × 1.2 mmol), BF_3OEt_2 (0.44 ml, 3 × 1.2 mmol) and $SiCl_4$ (0.43 ml, 3 × 1.2 mmol) were added successively and the turbid solution was refluxed for 2 h. After concentration of the solution, benzonitrile (0.62 ml, 3 × 2 mmol) was added to the residue and the mixture was heated at 150 °C for 5 h. After work-up analogous to the above, the extract was purified on SiO_2 (4.6 g) using CH_2Cl_2. From the eluate, **33** (555 mg, mp 124—125 °C, ether–petroleum ether, lit.[5] mp 121—125 °C, 83%) was obtained.

***N*-Methyl-2-(α-hydroxybenzyl)anilines (36)**——To a stirred solution of an *N*-methylaniline (2 mmol) in dichloroethane (10 ml), triethylamine (2 × 0.5 mmol), BF_3OEt_2 (2 × 1.2 mmol) and $SiCl_4$ (2 × 1.2 mmol) were added successively at room temperature, and the solution was refluxed for 2 h. After cooling, a solution of a benzaldehyde (2 mmol) and triethylamine (2 × 2 mmol) in dichloroethane (3 ml) was added and the solution was stirred at room temperature for the period indicated in Table III. After addition of ice and 2 N HCl, the mixture was washed with ether and the acid layer was alkalized with K_2CO_3 then extracted with CH_2Cl_2. Recrystallization of the extract or purification on a Lobar column B, $CHCl_3$: EtOAc = 10 : 1, gave **36**.

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