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IN SITU NMR SPECTROSCOPIC STUDIES OF ANILINE *ORTHO* ACYLATION ("SUGASAWA REACTION"): THE NATURE OF REACTION INTERMEDIATES AND LEWIS ACID INFLUENCE ON YIELD

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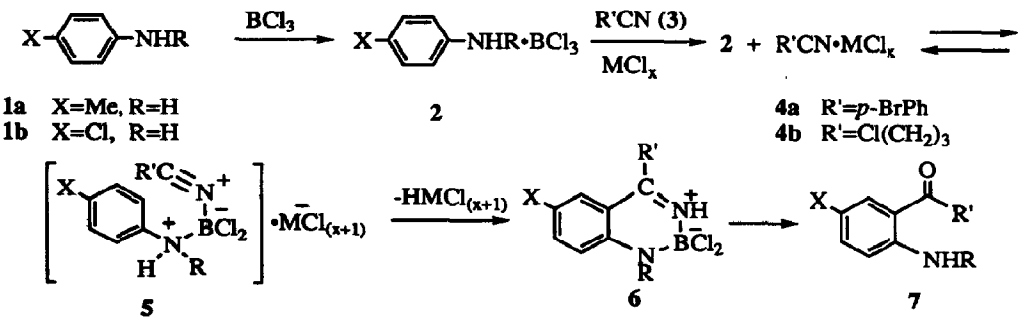
Abstract: *Ortho acylation of anilines by nitriles in the presence of BCl_3 and a second Lewis acid appear to proceed through an intermediate "supercomplex" including all four components. Yield improvements were obtained based on recognition that chloride affinity of the second Lewis acid governs supercomplex formation. Aniline protonation was found to be the cause of incomplete reaction.*

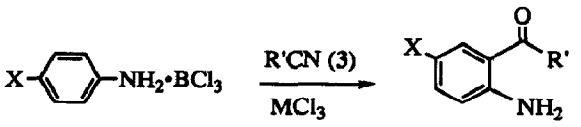
Ortho-acylated aniline derivatives **7**, Scheme 1, are versatile intermediates for many heteroaromatic compounds.[1] Generally, Friedel-Crafts reactions involving anilines suffer due to their complexation with Lewis acids. Acylation typically occurs at the aniline nitrogen, but Sugasawa has reported[2] that BCl_3 in particular is capable of leading to *ortho* C-acylation, when $AlCl_3$ is also used as an auxiliary Lewis acid. It was proposed[2b] that boron bridging led to exclusive *ortho* acylation, but a detailed mechanism was not conclusively elucidated. Using *in situ* NMR spectroscopy,[3] we observe pathway intermediates and have determined the role of auxiliary Lewis acids.

The reaction of *p*-toluidine (**1a**) and *p*-bromobenzonitrile (**3a**) in the presence of BCl_3 and $AlCl_3$ was followed using *in situ* ^{13}C NMR spectroscopy. A "supercomplex" (**5a**, Chart 1) was observed which required all four reactants for formation. Its concentration relative to binary complexes **2a** and **4a** diminished on dilution, indicating an equilibrium. As product precursor **6a** formed, **5a** receded, behaving as an intermediate. The ^{11}B signal from **5a** was identified as a relatively sharp line at 1.3 ppm, corroborating the tetrahedral, nearly symmetric environment for boron depicted in Chart 1.[4] The ^{27}Al chemical shift was identical to that reported[5] for $AlCl_4^-$. In contrast to Sugasawa's proposal,[2b] the aniline nitrogen remains protonated when **5** is derived from primary or secondary anilines, based on spin splittings,[6] especially between ^1H and ^{15}N. Other supercomplexes involving variations in aniline, nitrile or auxiliary Lewis acid were also characterized (Chart 1), and tertiary aniline examples gave supercomplexes fully analogous spectroscopically to intermediates **5**. These blocked "intermediates" did not acylate, suggesting that supercomplex deprotonation must precede C-acylation of primary or secondary anilines (Scheme 1). Ultimately, optimization[6] using $AlCl_3$ gave **7a** in 80% yield.

SCHEME 1



In the $AlCl_3$-moderated acylation of *p*-chloroaniline (1b) by 4-chlorobutyronitrile (3b), yields were initially disappointing in spite of attempts to develop the reaction. It seemed that the equilibrium leading to supercomplexes 5 had to be shifted, and that chloride transfer from boron might be critical. Variation of the auxiliary Lewis acid indeed indicated that its chloride affinity[9] was a key factor. For *p*-chloroaniline (1b), the level of the 4-chlorobutyronitrile (3b) supercomplex, relative to 1:1 BCl_3 complex 2b, was systematically increased for the series 5b-5b". The level of 5b was somewhat less that that of 2b for $AlCl_3$, while $GaCl_3$ shifted the 5b':2b' ratio to about 10:1 and $SbCl_5$ gave 5b":2b > 20:1. Gallium chloride furthermore markedly increased the yield[10] of 2-(4-chlorobutyryl)-4-chloroaniline, 7b, from 45 to 72% (Table 1). Milder conditions than with $AlCl_3$ were possible, as indicated by results for cyclopropane carbonitrile and 1b. With $GaCl_3$, yield improvement for aniline itself was moderate, but acylations of p-toluidine were almost unaffected. Table 2 summarizes trials using several auxiliary Lewis acids of high chloride affinity;[9] $GaCl_3$ performed best in our hands.[11] The antimony chloride performed poorly; decomposition was evident in preparations of 5b" even at room temperature. Silver triflate was not effective for chloride abstraction in this reaction (Table 2).



2 7

TABLE 1

ACYLATION YIELD[10] COMPARISONS USING ALUMINUM *vs* GALLIUM CHLORIDES

2, X=	Cl	H	Me	Cl	H	Cl
3, R'=	$Cl(CH_2)_3$	$Cl(CH_2)_3$	$Cl(CH_2)_3$	*c*-C_3H_5	*c*-C_3H_5	Ph
$AlCl_3$	45%	53%	67%	30-40%[a]	71%	23%
$GaCl_3$	72%	70%	71%	74%[b]	82%	41%

a. 15-20% cyclopropyl ring opening
b. 4% cyclopropyl ring opening

TABLE 2

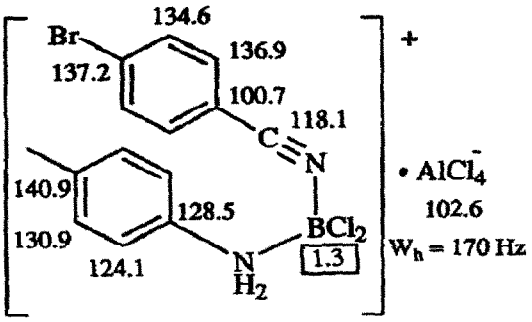
CONDITIONS AND YIELDS (FROM NITRILE 3b) FOR SEVERAL AUXILIARY LEWIS ACIDS

Cl^- abstractor	$GaCl_3$	$InCl_3$	$AlCl_3$	$FeCl_3$	$SbCl_5$	AgOTf
Conditions[a]	c,26h,80°	c,4h,132°	c,4h,132°	t,17h,96°	t,5h,78°	c,7h,100°
Yield	72%	63%	45%	44%	26%	24%

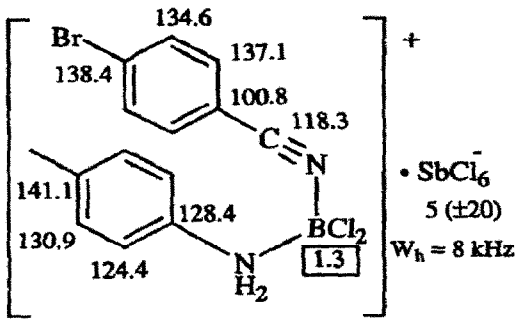
a. All trials used 1.1 mol BCl_3, 1.2 mol aux. Lewis acid, 1.0 mol 3b and 1.5 mol 1b; solvents: c = chlorobenzene, t = toluene

Protonated anilines were evident in ^{13}C NMR spectra of unheated reaction mixtures, and their concentrations typically grew as reactions were heated. Unless an overcharge of aniline was used, reactions stopped with considerable unreacted anilinium salt present.[12] We found no more than minor amounts of trichloroborazines blamed by Sugasawa for primary aniline reaction incompleteness,[2b,13] and there was no evidence of primary or secondary anilinodichloroboranes acting as intermediates.

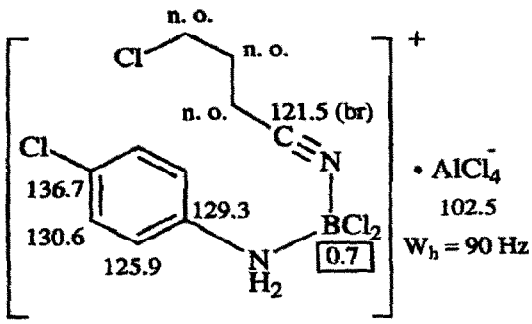
CHART 1



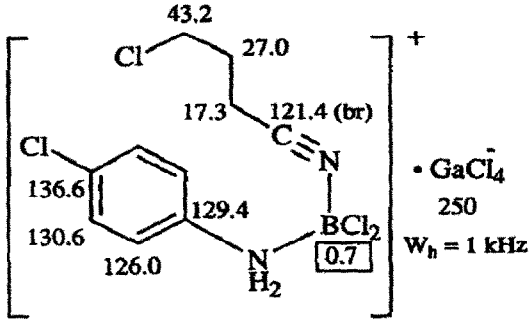
5a



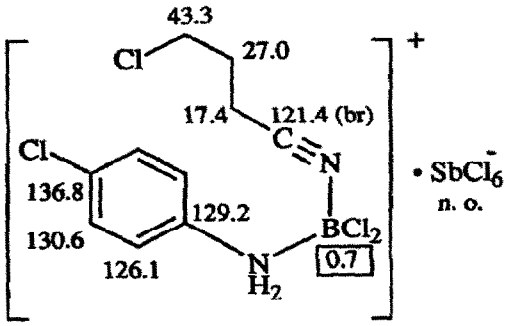
5a'



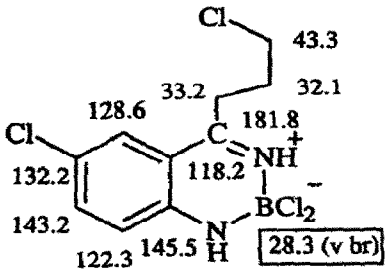
5b



5b'



5b''



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In summary, selection of an auxiliary Lewis acid based on its affinity for chloride ion enhances performance of the Sugasawa reaction,[2] particularly for electron-poor aniline derivatives. The structure of a complex involving all four reactants has been characterised using *in situ*, multinuclear NMR spectroscopy. The proposed supercomplex adequately accounts for the selectivity (and success) of the acylation *via* deprotonation and then cyclization at the aniline *ortho* position. Finally, reaction incompleteness is seen as due to buildup of protonated anilines rather than formation of chloroborazines.[2b,13]

ACKNOWLEDGEMENT

We thank Mr. R.A. Reamer of these laboratories for helpful discussions of the NMR experiments.

REFERENCES

1. One application, to the synthesis of a HIV RT inhibitor, is presented in the following letter.

2.(a) Sasakura, K.; Terui, Y.; Sugasawa, T. *Chem. Pharm. Bull.* **1985**, *33*, 1836 and references therefrom;
(b) Sugasawa, T.; Toyoda, T.; Adachi, M.; Sasakura, K. *J. Am. Chem. Soc.* **1978**, *100*, 4842

3. Spectra were obtained using Bruker Instruments WM-250 and AM-400 spectrometers in 1,1,2,2,-tetrachloroethane (TCE), with CD_2Cl_2 added for lock. Proton and ^{13}C shifts were referenced internally to $CHDCl_2/CD_2Cl_2$, at 5.32 and 53.8 ppm, respectively. Other shift references, all external, were: ^{11}B, $BF_3{\bullet}OEt_2$ in CD_2Cl_2; ^{15}N, CH_3NO_2 in TCE with CD_2Cl_2 lock: 379.6 ppm (*cf* Levy, G.C.; Lichter, R.L. *Nitrogen-15 Nuclear Magnetic Resonance Spectroscopy*, Wiley, New York, 1979, pp 32-3). ^{27}Al and ^{71}Ga, M^{+++} in DCl/D_2O, prepared from MCl_3 and D_2O; ^{121}Sb, $SbCl_6^{-}{\bullet}^{+}NEt_4$ in CD_2Cl_2. No corrections were made for solvent in ^{11}B, ^{27}Al, ^{71}Ga and ^{121}Sb shift calibrations.

4. Nöth, H.; Wrackmeyer, B. *Nuclear Magnetic Resonance Spectroscopy of Boron Compounds*, Vol. 14 of *NMR Basic Principles and Progress*, P. Diehl, E. Fluck and R. Kosfeld, eds., Springer Verlag, Berlin, 1978, pp 82-3, 385-91.

5. Akitt, J.W.; *Prog. NMR Spectrosc.* 1989, *21*, 1: on p. 65 the median of several reported values is given as 102.6 ± 0.6 ppm.

6. Examples: 5.5 hz from *NH* to *NCH*$_3$ in a 3a-N-methyl-aniline complex; 3 hz (t) from *ortho*-^{13}C to *NH*$_2$ in **5a**; $^1J_{NH}$ = 73.$_6$ Hz (INEPT[7] t, 1,0,-1 @ δ_N 72 ppm) in **5b**.

7. Morris, G.A.; Freeman, R. *J. Am. Chem. Soc.* 1979, *101*, 760

8. A slurry of **2a** (20% excess) in chlorobenzene was added in portions to **3a** and $AlCl_3$ refluxing in the same solvent. After 3 hours reaction time, the aminobenzophenone was obtained in 80% yield after aqueous workup.

9. Baaz, M.; Gutman, V. "Lewis Acid Catalysts in Non-aqueous Solutions," Ch. 5 in *Friedel-Crafts and Related Reactions*, G.A. Olah, ed., Interscience, N.Y. 1963, v 1, pp 367-97.

10. Yields of products **7** based on nitriles **3** with anilines **1** in excess. Procedure: To 11 mmol BCl_3 (1M in CH_2Cl_2) was added 15 mmol of **1** in 1,1,2,2-tetrachloroethane at 0°C. Ten mmol **3** and 12 mmol $AlCl_3$ or $GaCl_3$ were added and resultant mixtures stirred 5 h at 100°C, removing CH_2Cl_2. Products **7** were obtained after aqueous workup.

11. As reported,[2] BCl_3 appears uniquely required. Combined use of Al and Ga chlorides gave no *ortho* acylation.

12. A ^{15}N INEPT[7] NMR spectrum at the end of one reaction of **1b** and **3b** showed two approximately equal, major components: **1b**$\bullet H^+$: δ_N 55.$_4$ ppm, $^1J_{NH}$ 75.$_6$ Hz (q, 1,1,-1,-1: specific for NH_3^+), and **6b**: δ_N 140.$_2$, $^1J_{NH}$ 84.$_8$ Hz (d, 1,-1), aniline N; δ_N 179.$_4$, $^1J_{NH}$ 87.$_5$ Hz (d, 1,-1), iminium N.

13. Treatment of **2a** with triethylamine at room temperature led to slow but substantial formation of the corresponding trichloroborazine.

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