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Synthesis and Reactivity of Boron Difluoride Complexes of N,N-Dimethylsalicylacetamide

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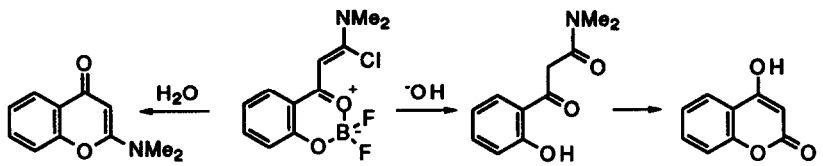
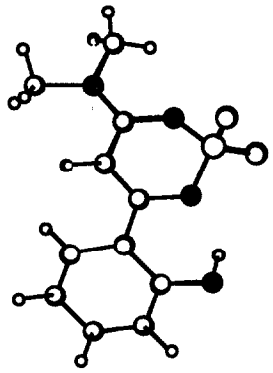
Abstract: *The synthesis and reactivity of a series of BF_2 complexes of N,N-dimethylsalicylacetamide was examined.*

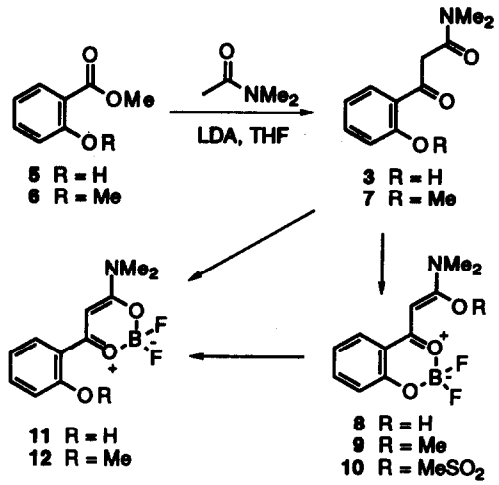
We recently reported a novel synthesis of 2-aminochromones (e.g. **1**) involving the reaction of 2'-hydroxyacetophenone-BF_2 complexes with phosgeniminium salts.[1] This procedure provides the ß-chlorovinylogous amide-BF_2 complex **2** which upon treatment with H_2O/CH_3CN affords **1** in high yield. In contrast, we found that hydrolysis of **2** under basic conditions yields N,N-dimethylsalicylacetamide (**3**) and 4-hydroxycoumarin (**4**) along with lesser amounts of **1**.[2] Since neither **3** or **4** is produced from **1** under the reaction conditions,[1] we surmised that hydroxide induced displacement of chloride (→ **8**) becomes competitive relative to the initial breakdown of the BF_2 complex of **2** as the pH of the reaction is increased. In this letter we present further insight into this process through the synthesis and study of BF_2 complexes of **3**.[3]



Treatment of methyl salicylate (**5**) with lithiodimethylacetamide (THF, 0 °C) afforded a 75% yield of ß-ketoamide **3**. Reaction of **3** with BF_3OEt_2 in *diethyl ether* resulted in the formation of **8** as a single BF_2-complex in 91% yield. When **8** was suspended in CH_3CN (rt, 24 h) the isomeric complex **11** was isolated (98%). Alternatively, **11** was formed directly from **3** in 81% yield by treatment with BF_3OEt_2 in CH_2Cl_2. The ^1H NMR's of **8** and **11** revealed that the amide portion of *both* of these molecules exist in the enol form ($CDCl_3$, δ vinyl C<u>H</u>, O<u>H</u>: **8**, 5.62, 13.15; **11**, 5.87, 9.19). Further structure proof was provided via the methylation of complexes **8** and **11** with CH_2N_2 in Et_2O to furnish the corresponding methyl ethers **9** and **12** in 99% and 92% yield, respectively.[4] BF_2-complex **12** prepared by this route and that synthesized independently from methyl 2-methoxybenzoate (**6** → **7** → **12**, 35%) proved to be spectrometrically identical. In addition, the thermodynamic complex **11** was subjected to X-ray crystallographic analysis which revealed a highly planar structure in which the phenolic hydroxyl is hydrogen bonded to the already complexed ketone carbonyl (H--O distance = 1.81 Å).[5,6,7]



11



Consistent with the proposed mechanism, subjection of the intermediate BF_2-complex **8** to basic hydrolysis afforded **3** and **4** in ratios similar with those found for the reaction of **2** under identical conditions (Table 1). As expected, no 2-aminochromone **1** was detected from either of these reactions. Conversion of **8** to mesylate **10** (Ms_2O, Et_3N, Et_2O, 51%) permitted examination of the effect of an alternative leaving group on the hydrolysis of complex **2**. Treatment of **10** with 20% H_2O/CH_3CN produced 68% of chromone **1** along with 26% of **4**. In contrast, hydrolysis of **10** with 2N NaOH gave only **3** (87%) and **4** (7%). Even the use of saturated $NaHCO_3/CH_3CN$, which afforded a 2:1 ratio of **1/3** from complex **2**,[1] gave none of **1** when applied to mesylate **10**. Given the proposed scheme for their formation, the different product ratios obtained from the hydrolyses of complexes **2** and **10** can be rationalized based on the relative effects of their chloride and mesylate groups on the addition-elimination process.[8]

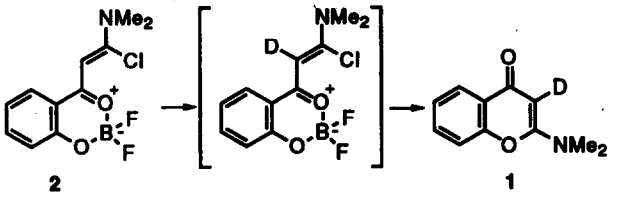
Table 1. Hydrolysis of BF_2-Complexes of N,N-Dimethylsalicylacetamide

Starting Material	Reaction Conditions[a]	Time	Products (% Yield) 1	3	4	11
8	sat $NaHCO_3$	1 h	-	62	27	-
	2N NaOH	30 min	-	77	14	-
	20 % H_2O	1 h	-	29	69	-
	1 % H_2O	1 h	-	-	-	88
10	sat $NaHCO_3$	1 h	-	66	25	-
	2N NaOH	30 min	-	87	7	-
	20 % H_2O	6 h	68	-	26	-
	1 % H_2O	35 min	84	-	trace	16

[a] All reactions run in CH_3CN at 50 °C; 1:1 v/v unless otherwise noted

Having examined the events surrounding the formation ß-keto amide **3** from the chlorovinylogous amide BF_2 complex **2**, we turned our attention to the process by which **2** is converted to 2-aminochromone **1**. Specifically, we were interested in establishing whether H_2O was essential to the success of this reaction. We found that **2** was smoothly converted to **1** in dry CH_3CN, although at a slower rate than in the presence of 20% water. This result prompted a series of ^1H NMR experiments to further define the role of H_2O. The reactions were performed in triplicate in CD_3CN (rt) with varying amounts of D_2O and monitored over time for % conversion to product. Under anhydrous conditions the reaction was 50% complete at the 50 h point.

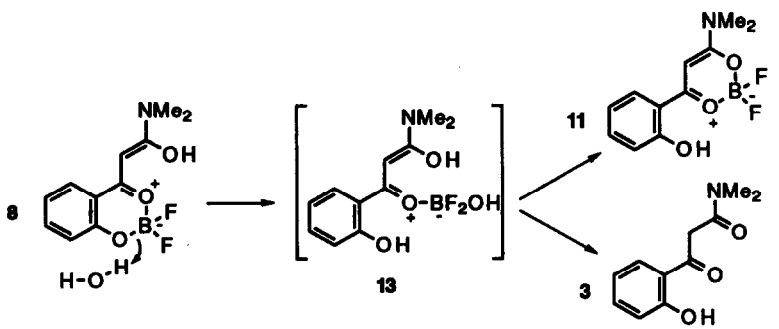
Interestingly, in the presence of 1% D_2O, that point shifted to 2 h, but with 10% D_2O the reaction was again slower with a half-life of 22 h. An additional point concerns the rate of exchange of the vinyl CH of **2**, which proved to be a faster process than the conversion to **1** as well as dependent on the % of D_2O. One possible explanation for this data relates to the intrinsic acidity of the reaction, suggesting that increasing amounts of H_2O serves as a buffer and raises the pH. Relative to use of anhydrous CH_3CN, the presence of a small quantity of H_2O may act as a catalyst for the breakage of the phenolic oxygen-boron bond. When this ^1H NMR experiment was repeated with 10% D_2O in the presence of increasing concentrations of DCl, the rate of conversion of **2** to **1** was increased, such that with 0.5M DCl the half-life was 4 h.



2 **1**

% D_2O/CD_3CN	$T_{1/2}$ (h)
0	50
0.2	9
1	2
10	22
20	22
10 (0.01M DCl)	17
10 (0.05 M DCl)	12
10 (0.5 M DCl)	4

The aqueous hydrolysis of the kinetic intermediate **8** offered an opportunity to examine the events associated with the breakdown of a BF_2-complex related to **2**. Treatment of **8** with 20% H_2O/CH_3CN (50 °C, 1 h) afforded 29% of ß-keto amide **3** along with 69% of **4**. This contrasts with the use of 1% H_2O/CH_3CN which resulted in the smooth transformation of **8** to the corresponding thermodynamic complex **11** in 88% yield.[9] As a control, complex **11** was subjected to 20% H_2O/CH_3CN at 50 °C and recovered unchanged after 1 h.[10] The use of H_2O as a catalyst to promote the opening of the boron-phenolic oxygen bond of **8** leads to **13**. This intermediate, in which the Lewis acid remains bound to the vinylogous amide carbonyl, becomes a potential branch point for the formation of complex **11** or ß-keto amide **3** (in the case where larger amounts of H_2O are present).[11] The application of this mechanistic scenario to the conversion of complex **2** to chromone **1** raises the question as to the role of the Lewis acid in the ring closure. It is possible that the relative rate differences between the 1% H_2O and 10% H_2O reactions depend on whether or not a BF_2X species remains bound to the vinylogous amide carbonyl during the cyclization step. Although the mechanistic details of this process remain largely unknown, the work presented herein provides a basis for the study of BF_2 complexes of this type.



8 **13** **11** **3**

Acknowledgement: We thank Professors E. Vedejs and S.E. Denmark and Drs. S.P. Tanis and M.D. Ennis for useful discussions.

References and Notes

1. Morris, J.; Wishka, D.G.; Fang, Y. *J. Org. Chem.* **1992**, *57*, 6502-6508.
2. N,N-Dimethylsalicylacetamide (**3**) is readily converted to 4-hydroxycoumarin (**4**) under both basic and acidic conditions (faster under acidic conditions); see ref. 1.
3. Related BF_2 complexes: (a) Cram, D.J. *J. Am. Chem. Soc.* **1949**, *71*, 3953. (b) Schiemenz, G.P.; Schmidt, U. *Justus Liebigs Ann. Chem.* **1982**, 1509. (c) Daniel, D.S.; Heseltine, D.W., US Patent 3,567,439. (d) VanAllan J.A.; Reynolds, G.A. *J. Heterocycl. Chem.* **1969**, *6*, 29. (e) Reynolds, G.A.; VanAllan, J.A. *J. Heterocycl. Chem.* **1969**, *6*, 375. (f) Reynolds, G.A.; VanAllan, J.A.; Seidel, A.K. *J. Heterocycl. Chem.* **1979**, *16*, 369. (g) Chow, Y.L.; Ouyang, X. *Can. J. Chem.* **1991**, *69*, 423.
4. A typical ^1H NMR of **8** usually showed < 10% of complex **11**. However, methyl ether **9** was always free of **12** by ^1H NMR, indicating that **8** was originally isolated pure.
5. Single-Crystal Structure Determination: $C_{11}H_{12}O_3NBF_2$. Space group : $P2_1/c$ cell parameters: $a=6.716(6)Å$, $b=8.333(6)Å$, $c=21.659(18)Å$, $\beta=111.30°(5)$. Molecular weight = 275.119, Z=4, calculated density = 1.898g/cm^3. A clear, cubic-shaped crystal was selected and mounted on a glass fiber. The data were collected on Simens P1 X-ray diffractometer controlled by a Harris computer, at low temperature (-130°C), with graphite-monochromatized Cu$K\alpha$ radiation [(Cu$K\alpha$)=1.5405Å]. All 1955 unique reflections were measured to a $2\theta_{max}$ of 132° for Laue group 2/m; 1783 intensities were >3σ. The structure was solved by direct methods, using MULTAN80 (Main, Fiske, Hull, Lessinger, Germain, Declercq, & Woolfson, 1980). The trial solution obtained all 18 nonhydrogen atoms. Least squares refinement included all coordinates, and anisotropic thermal parameters for nonhydrogen atoms, isotropic thermal parameters for all hydrogen atoms. In the final refinement cycle, all shifts were <0.11σ for nonhydrogen atoms, <0.50σ for hydrogen atoms. R=0.042, S=3.01, Rw=0.115. The *CRYM* system of computer programs was used (Duchamp, 1984).
6. For an X-ray crystallographic analysis of the BF_2 complex of an N,N-dialkylsalicylamide, see: Kliegel, W.; Tajerbashi, M.; Rettig, S.J.; Trotter, J. *Can. J. Chem.* **1989**, *67*, 1636.
7. Since the amide portion of the kinetic complex **8** exists in the enol form, it is probable that the hydroxyl of this molecule is similarly hydrogen bonded to the ketone carbonyl. For examples of carbonyls doubly coordinated by two main group Lewis acids or hydrogen bonds, see: Sharma, V.; Simard, M.; Wuest, J.D. *J. Am. Chem. Soc.* **1992**, *114*, 7931 and references cited therein.
8. (a) Avramovitch, B.; Rappoport, Z. *J. Am. Chem. Soc.* **1988**, *110*, 911. (b) Rappoport, Z.; Topol, A. *J. Chem. Soc. Perkin Trans. II* **1975**, 863. (c) *Ibid.* **1972**, 1823.
9. The respective byproducts (other than **1**) which are produced from the hydrolysis of mesylate **10** are consistent with this result. The use of 1% H_2O afforded a 16% recovery of complex **11** whereas under the 20% H_2O conditions, only 4-hydroxycoumarin (**4**) was observed (Table 1).
10. Even after 3 days at 50 °C (20% H_2O/CH_3CN), a 1.3:1 ratio of **11/4** was observed.
11. A crossover experiment was performed to shed some light on whether the BF_2 species may undergo complete dissociation from the vinylogous amide during the conversion of **8** to **11**. An equimolar amount of **8** and N,N-dimethyl-4-methoxysalicylacetamide (**14**) were stirred for 3 days (CH_3CN, rt) to afford a 2:1 mixture of **11** and the corresponding thermodynamic BF_2-complex of **14** (along with a 1:2 mixture of **3/14**). In a separate control experiment, no crossover was found between **11** and **14**.

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