Reaction of Phosgeniminium Salts with Enolates Derived from Lewis Acid Complexes of 2′-Hydroxypropiophenones and Related β-Diketones

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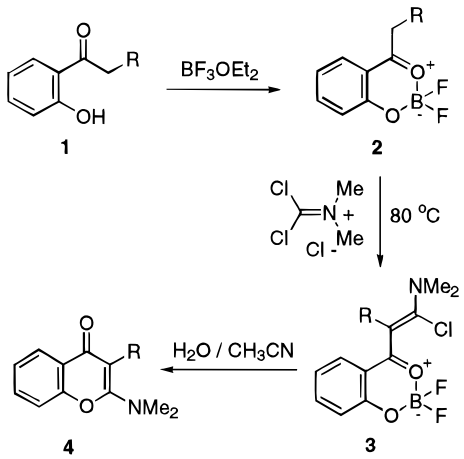
The 2-aminochromone ring system has proven to be a rich pharmacophore for use in the design of compounds with a diversity of biological effects that includes unique antiplatelet derivatives,[1] antiproliferative agents,[2] and phosphatidylinositol 3-kinase inhibitors.[3] Our interest in the utilization of this template[4,5] as well as the related 2-aminopyrone system[6] as part of our medicinal chemistry efforts led us to explore a variety of new methods for their preparation.[7] We recently reported a synthesis of 2-aminochromones (eg **4**) that involves the thermal reaction of boron difluoride complexes of 2′-hydroxyacetophenones (or 2′-hydroxypropiophenones) with phosgene iminium chloride.[4] Hydrolysis of the readily isolated complex **3** with aqueous acetonitrile (or anhydrous methanol) affords the desired 2-aminochromone **4**. This reaction is successfully performed either by preforming the boron difluoride complex **2** or through the generation of this complex *in situ* by the addition of boron trifluoride etherate to an ethylene dichloride solution of the starting 2′-hydroxyacetophenone prior to the introduction of the iminium chloride. As shown in Scheme 1, yields for the overall conversion of **1a** to **4a** in both instances are comparable (47 vs 56%). In contrast, attempts to utilize this methodology for the conversion of benzoylacetone (**6**, R′ = H) to the 6-phenyl-2-aminopyrones **7a** and **7b** were unsuccessful, providing only small amounts of the desired products (Table 2).[8]

Our desire to improve the overall efficiency of this process and expand its applicability to related ring systems (eg **7**) prompted us to examine modifications to this sequence. Having previously explored the unraveling of complex **3** to aminochromone **4**,[9] we chose to focus on the events surrounding the formation and reaction of the boron difluoride complex **2**. Presumably, heating the mixture of **2** with phosgene iminium chloride at 80 °C allows for the generation of significant equilibrium concentrations of the corresponding enol form of **2** that is continuously siphoned off as the reaction proceeds. In this note, we report that the *prior* enolization of related Lewis acid complexes of **2** with Hunig's base provides a significant improvement to this synthesis that allows for a smooth reaction with phosgene iminium chloride under mild conditions (0 °C to rt), producing excellent overall yields of the 2-aminochromone **4**.[10,11]

Scheme 1



	R	% Yield of **2**	% Yield **1** → **4**
a)	H	60	47 (56)[a]
b)	CH_3	58	23

[a] *In Situ* generation of BF_2 Complex **2**

We first examined the direct enolization and reaction of the stable boron difluoride complex **2b**. Treatment of a methylene chloride solution of **2b** with 1.2 equiv of Hunig's base at 0 °C followed by the addition of phosgene iminium chloride (0 °C to rt) produced, after a methanol quench, a 70% yield of **4b** (41% overall yield from **1b**) (Table 1). For comparison purposes, this reaction was also carried out by the *in situ* generation of **2b** and its subsequent enolization with 2.1 equiv of base, affording a 33% yield of **4b**. In an effort to improve the overall efficiency of the process, we examined the use of two alternate Lewis acids. Treatment of **1b** with boron trichloride, followed by enolization of the resultant boron dichloride complex **5** with 2.1 equiv of Hunig's base (0 °C), and reaction with phosgene iminium chloride afforded an excellent 80% overall isolated yield of 2-

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(2) Erickson, L. A.; Bonin, P. D.; Wishka, D. G.; Morris, J.; Dalga, R. J.; Williams, D. J.; Wilson, G. J.; Hoover, J. L.; Simmons, C. A.; Humphrey, S. J.; Shebuski, R. J. *J. Pharm. Exp. Ther.* **1994**, *271*, 415.

(3) Vlahos, C. J.; Matter, W. F.; Hui, K. Y.; Brown, R. F. *J. Biol. Chem.* **1994**, *269*, 5241.

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(7) Ermili, A.; Mazzei, M.; Roma, G.; Cacciatore, C. *Farmaco Ed. Sci.* **1977**, *32*, 375. Ermili, A.; Balbi, A.; Di Braccio, M.; Roma, G. *Farmaco Ed. Sci.* **1977**, *32*, 713. Ermili, A.; Roma, G.; Mazzei, M.; Balbi, A.; Di Braccio, M.; Schianterelli, P.; Cadel, S. *Farmaco Ed. Sci.* **1974**, *29*, 225. Gammill, R. B.; Nash, S. A.; Mizsak, S. A. *Tetrahedron Lett.* **1983**, *24*, 3435. Bantick, J. R.; Suschitzky, J. L. *J. Heterocycl. Chem.* **1981**, *18*, 679.

(8) The preformed BF_2 complex of **6** was reacted with either phosgene iminium chloride or 4-(dichloromethylene)morpholinium chloride under the conditions outlined in Table 2. In both examples, the bulk of the unreacted BF_2 compex of **6** was recovered along with small amounts of **7a** or **7b**. Moreover, in the reaction producing **7b**, the 4-morpholine iminium salt appeared to decompose at the high temperature required for reaction.

(9) Morris, J.; Fang, Y.; Wishka, D. G.; Han, F. *Tetrahedron Lett.* **1993**, *34*, 3817.

(10) For the reaction of enol borinates with Eschenmoser's salt, see: Hooz, J.; Bridson, J. N. *J. Am. Chem. Soc.* **1973**, *95*, 602.

(11) For the enolization and subsequent aldol reaction of related titanium and boron complexes of β-hydroxy ketones, see: Luke, G. P.; Morris, J. *J. Org Chem.* **1995**, *60*, 3013.

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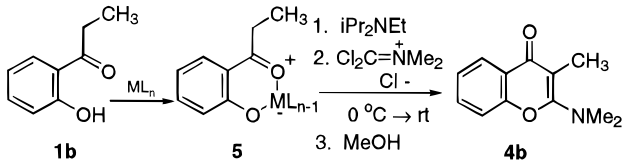
Table 1

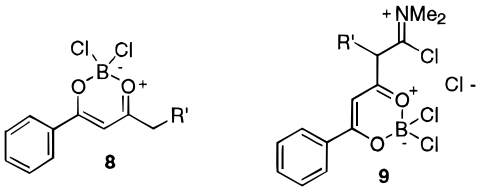


ML_n	equiv of iPr_2NEt	% yield **1b** → **4b**
BF_3OEt_2	1.2[a]	41
BF_3OEt_2	2.1	33
BCl_3	2.1	80
$TiCl_4$	2.1	84

[a] Enolization accomplished using preformed BF_2 complex **2b**.

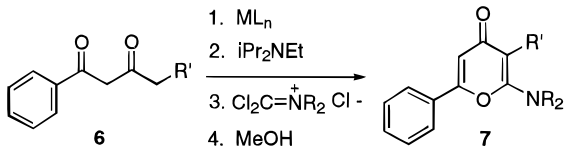
aminochromone **4b**. Similar results (84% yield) were obtained through the use of titanium tetrachloride as a substitute Lewis acid in this process.

Success was also achieved in the application of this methodology for the preparation of the corresponding 6-phenyl-2-aminopyrones (Table 2). Enolization of the boron dichloride complex generated from benzoylacetone and boron trichloride at −78 °C with 2.1 equiv of Hunig's base, followed by treatment with phosgene iminium chloride, afforded a 47% yield of **7a**. Increasing the amount of base to 3.1 equiv produced a significant increase in the yield of this reaction to 84%. The apparent need for an additional 1 equiv of Hunig's base in this conversion can be rationalized by consideration of the relative acidities of the two complexes present before and after reaction with the iminium salt. The initial product intermediate complex **9** would be expected to have a pK_a on the order of a β-dicarbonyl system, significantly lower than the pre-enolate complex **8**.[12] A comparable yield (91%) was obtained in the reaction to produce the corresponding 3-methyl derivative **7c**. The use of the less soluble 4-morpholine iminium salt[4] with **6** (R′ = H) in this process afforded a somewhat lower yield (54%) of the desired 2-aminopyrone **7b**.[6]



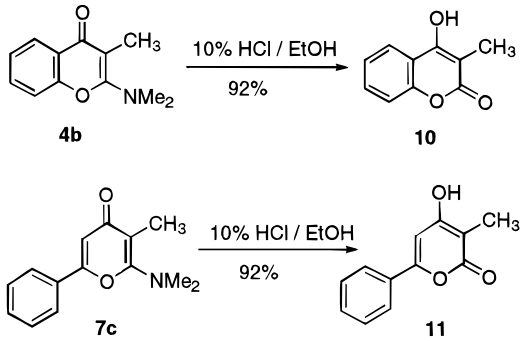
A useful extension of this methodology can be found in the synthesis of two other classes of medicinally active derivatives, the 4-hydroxycoumarins and 4-hydroxy-2-pyrones.[13] Hydrolysis of 3-methyl-2-aminochromone **4b** and 3-methyl-2-aminopyrone **7c** with 10% aqueous hydrochloric acid/ethanol afforded **10** and **11**, respectively, in high yield (Scheme 2). In summary, reaction of phosgeniminium salts with enolates derived from Lewis acid complexes of 2′-hydroxypropiophenones and related β-diketones provides an improved strategy for the synthesis of 2-aminochromones, 2-aminopyrones, and related derivatives.

Table 2



	NR_2	R′	ML_n	equiv of iPr_2NEt	iminium salt reaction conditions	% yield **7**
(a)	NMe_2	H	BF_3OEt_2	0	70 °C, 24 h $Cl(CH_2)_2Cl$	trace
	NMe_2	H	BCl_3	2.1	−78 °C → rt CH_2Cl_2	47
	NMe_2	H	BCl_3	3.1	−78 °C → rt CH_2Cl_2	84
(b)	4-morpholine	H	BF_3OEt_2	0	80 °C, 3 h $Cl(CH_2)_2Cl$	2
	4-morpholine	H	BCl_3	3.1	−40 °C → rt $Cl(CH_2)_2Cl$	54
(c)	NMe_2	CH_3	BCl_3	3.1	−78 → 0 °C CH_2Cl_2	91

Scheme 2



Experimental Section

IR spectra were taken as a Nujol mull. ^1H and ^{13}C NMR spectra were obtained in $CDCl_3$ (unless otherwise indicated) at 300 MHz and 75 MHz, respectively. Column (flash) chromatography was performed with Merck silica gel 60 (230−400 mesh).

Representative Experimental: 2-(Dimethylamino)-6-phenyl-4*H*-pyran-4-one (7a). A solution of benzoylacetone (**6**, R′ = H) (1.62 g, 10 mmol) in 30 mL of CH_2Cl_2 at 0 °C was treated with 11 mL (11 mmol, 1 M in CH_2Cl_2) of BCl_3. After stirring for 1 h, the solution was cooled to −78 °C and treated with 5.4 mL (31 mmol) of iPr_2EtN. After stirring 1 h, the mixture was treated with phosgene iminium chloride (1.80 g, 12 mmol) and stirred 15 min at −78 °C, 2 h at 0 °C, and 30 min at rt. The mixture was cooled to 0 °C and diluted with 20 mL of MeOH and stirred for 3 h at rt. The volatiles were removed *in vacuo*, and the residue was partitioned between 50 mL of saturated $NaHCO_3$ and 4 × 25 mL of CH_2Cl_2. The combined organics were concentrated *in vacuo*, and the material was chromatographed over 150 g of silica gel, eluting with 4% MeOH/CH_2Cl_2 to afford 1.80 g (84%) of **7a**: mp 157−158 °C; ^1H NMR δ 3.09 (s, 6H), 5.35 (d, J = 1.9 Hz, 1H), 6.53 (d, J = 1.9 Hz, 1H), 7.47 (m, 3H), 7.69 (m, 2H); ^{13}C NMR δ 37.5, 88.7, 109.0, 125.2, 128.9, 130.6, 131.4, 158.3, 163.4, 179.5. Anal. Calcd for $C_{13}H_{13}NO_2$: C, 72.54; H, 6.09; N, 6.51. Found: C, 72.29; H, 6.05; N, 6.47.

2-(Dimethylamino)-3-methyl-6-phenyl-4*H*-pyran-4-one (7c): yield, 0.63 g (91%) from 0.54 g (3.05 mmol) of **6** (R′ = CH_3); mp 115−118 °C; ^1H NMR δ 2.02 (s, 3H), 3.06 (s, 6H); 6.66 (s, 1H), 7.47 (m, 3H), 7.72 (m, 2H); ^{13}C NMR δ 10.6, 40.5, 103.9, 108.8, 125.2, 129.0, 130.6, 131.8, 158.3, 163.2, 181.1; IR 1643 cm^{-1}. Anal. Calcd for $C_{14}H_{15}NO_2$: C, 73.34; H, 6.59; N, 6.11. Found: C, 73.13; H, 6.62; N, 6.05.

2-(Dimethylamino)-3-methyl-4*H*-1-benzopyran-4-one (4b): yield, 0.50 g (80%) from 0.46 g (3.07 mmol) of **1b**; mp 98−100

(12) The related use of 3 equiv of Hunig's base for the conversion of **1b** to **4b** had no effect on the overall yield of this reaction.

(13) For example, see: Thaisrivongs, S.; Tomich, P. K.; Watenpaugh, K. D.; Chong, K.-T.; Howe, W. J.; Yang, C.-P.; Strohbach, J. W.; Turner, S. R.; McGrath, J. P.; Bohanon, M. J.; Lynn, J. C.; Mulichak, A. M.; Spinelli, P. A.; Hinshaw, R. R.; Pagano, P. J.; Moon, J. B.; Ruwart, M. J.; Wilkinson, K. F.; Rush, B. D.; Zipp, G. L.; Dalga, R. J.; Schwende, F. J.; Howard, G. M.; Padbury, G. E.; Toth, L. N.; Zhao, Z.; Koeplinger, K. A.; Kakuk, T. J.; Cole, S. L.; Zaya, R. M.; Piper, R. C.; Jeffrey, P. *J. Med. Chem.* **1994**, *37*, 3200, and references cited therein.

°C (lit.[4] 102−102.5 °C); ^{1}H NMR δ 2.09 (s, 3H), 3.09 (s, 6H), 7.31 (t, J = 8.3 Hz, 2H), 7.53 (d, J = 7.8 Hz, 1H), 8.17 (d, J = 7.9 Hz, 1H); ^{13}C NMR δ 11.2, 40.3, 99.0, 116.4, 122.3, 124.2, 125.6, 131.8, 153.3, 163.1, 178.1; IR 1611,1551 cm^{-1}. Anal. Calcd for $C_{12}H_{13}NO_2$: C, 70.92; H, 6.45; N, 6.89. Found: C, 71.03; H, 6.46; N, 6.62.

4-Hydroxy-3-methyl-6-phenyl-2*H*-pyran-2-one (11). To a solution of 292.6 mg (1.28 mmol) of **7c** in 10 mL of ethanol at rt was added 2 mL of 10% aqueous HCl. The mixture was heated to reflux for 4 h, allowed to cool to rt, and the ethanol was evaporated *in vacuo*. The resulting slurry was cooled to 0 °C and filtered. The solids were washed with H_2O and Et_2O and dried under high vacuum to afford 238 mg (92%) of **11**: mp 270−273 °C; ^{1}H NMR δ 1.85 (s, 3H), 6.71 (s, 1H), 7.52 (m, 3H), 7.75 (m, 2H), 11.36 (s, 1H); ^{13}C NMR δ 8.6, 97.8, 98.4, 125.0, 129.1, 130.5, 131.1, 156.5, 164.2, 164.8; IR 2924, 2855, 1615, 1567 cm^{-1}. Anal. Calcd for $C_{12}H_{10}O_3$: C, 71.28; H, 4.98. Found: C, 71.20; H, 5.07.

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