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Synthesis of 1,4-dihydro-benzo[*d*][1,3]oxazin-2-ones from phthalides via an aminolysis-Hofmann rearrangement protocol

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Abstract—A simple two-step procedure for the conversion of readily available phthalides to the corresponding benzoxazinones was developed. Initial ring-opening aminolysis to form a primary 2-hydroxymethylbenzamide, followed by reaction with bis(trifluoroacetoxy)iodobenzene (BTI) conveniently, provided a variety of 4-substituted benzoxazinones.
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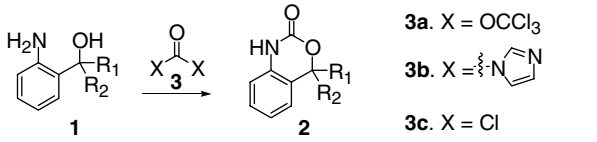
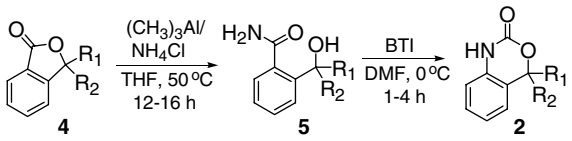
Benzoxazinones **2** (1,4-dihydro-benzo[*d*][1,3]oxazin-2-ones, Scheme 1) are an important class of compounds with a benzo-fused heterocyclic ring and form the key structural element of a variety of biologically active compounds. For example, Sustiva® (efavirenz) is a marketed human immunodeficiency virus type 1 (HIV-1) specific non-nucleoside reverse transcriptase inhibitor (NNRTI) that contains benzoxazinone core.[1] Furthermore, in a recent report a variety of other benzoxazinone derivatives were described as potent orally active nonsteroidal progesterone receptor antagonists with potential use in contraception or in the treatment of hormone-dependent cancers.[2]

In laboratory scale procedures, benzoxazinones are generally prepared from the corresponding amino alcohols **1** via reaction with phosgene derivatives such as triphosgene **3a** or 1,1′-carbonyldiimidazole **3b**. For the large-scale (15.7 kg) preparation of the heterocyclic ring system of Sustiva®, the use of the environmentally unfriendly and extremely toxic and hazardous phosgene **3c** has been reported.[3] Here, we describe an alternative procedure for the synthesis of benzoxazinone core via a two-step process involving the aminolysis of readily accessible isobenzofuran-1(3*H*)-ones (phthalides) **4**,[4] followed by a Hofmann rearrangement reaction.

The optimized procedure for the process that was developed is represented in Scheme 2. In the first step,



Scheme 1. Generally applied route for the synthesis of benzoxazinones.



Scheme 2. Synthesis of benzoxazinones **2** from phthalides **4**.

a 3-substituted phthalide **4** was reacted with an in situ prepared aluminum amide reagent. This resulted in aminolysis of the aromatic lactone ring to provide the 2-hydroxymethyl substituted benzamide derivative **5**. Subsequent Hofmann rearrangement, most likely via the isocyanate, provided the desired 4-substituted benzoxazinone **2**. The overall transformation of **4** to **2** can alternatively be visualized as insertion of an N–H into the bond between the aromatic ring and the carbonyl group.

Initially, the ring-opening aminolysis of phthalides **4** to the 2-hydroxymethyl-substituted primary benzamides **5** was investigated. Direct reaction of the phthalides with ammonia (or other primary amines) did not result in ring-opening of the relatively stable benzolactone ring.

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The aluminum amide reagent Me_3Al-HNR_2·HCl, formed by mixing trimethylaluminum with an amine hydrochloride, has been reported to be useful for the aminolysis of non-cyclic esters to give primary, secondary, or tertiary amides.[5] Analogous reagents prepared in situ from DIBAL-H/NR_2·HCl[6] or from Me_2AlCl/HNR_2·HCl have been used similarly. It was reported that when NH_4Cl was used as the amine source, a threefold excess of the aluminum amide reagent was required to obtain acceptable conversion of starting material, which we also observed in the current experiments.[5] As shown in Table 1 (entries 1 and 2), aminolysis of the unsubstituted phthalide **4a** with the latter two reagents resulted in only moderate yields of the desired product. The best yield of **5a** was obtained by heating **4a** for 12–16 h at 50 °C in THF with the reagent prepared from Me_3Al/NH_4Cl. The same reaction also proceeded at ambient temperature, but did not go to completion resulting in low yield (entry 4). Despite the relative stability of the benzo-fused lactone ring, in the presence of three equivalents of the aluminum amide reagent, the aminolysis proceeded satisfactorily. The successful conditions established in entry 3 were utilized for aminolysis of the substituted phthalides **4b–f**. The isolated yields of substituted 2-hydroxymethylbenzamides **5b–f** are represented in Table 3 and are shown to be in the 71–81% range.[11]

With a series of 2-hydroxymethylbenzamide derivatives **5** now available, attention was turned to their conversion into the benzoxazinones **2**. The classical procedure for the Hofmann rearrangement converts a primary carboxamide via an isocyanate to an amine using an alkaline solution of bromine.[7] However, compounds **5** contain primary or secondary benzylic hydroxyl groups that are very labile in these standard oxidative reaction conditions. Therefore, a much milder reagent would be required for the potential rearrangement of **5** to **2** and we chose to investigate the relatively mildly oxidizing polyvalent iodine compounds.[8] As a precedent, the synthesis of a variety of benzo-fused five-membered ring 2-benzoxazolones was shown to be formed by reaction of 2-hydroxybenzamides with $PhI(OAc)_2$ in basic methanolic solution.[9] Similarly, the reaction of non-aromatic γ-hydroxybutyramides with $PhI(OCOCF_3)_2$ (BTI) provided 2-oxazolidinones in excellent yield.[10] However, the presence of sensitive benzylic hydroxyl groups and the formation of a larger six-membered ring fused to a benzene group as in **2** provide an additional challenge.

Table 1. Yield of **5a** after aminolysis of **4a** with aluminum amide reagents

Entry	Method[a]	Temperature (°C)	Yield (%)
1	DIBAL-H/NH_4Cl[b]	45	60
2	Me_2AlCl/NH_4Cl[c]	50	56
3	Me_3Al/NH_4Cl[d]	50	78
4	Me_3Al/NH_4Cl	rt	22

[a] The aluminum amide reagents were prepared in situ in THF following the reported procedure. A threefold excess of the reagent was used for each of the reactions.
[b] DIBAL-H 1.5 M in toluene.
[c] Me_2AlCl 1.0 M in hexane.
[d] Me_3Al 2.0 M in hexane.

We first examined the Hofmann rearrangement of the unsubstituted 2-hydroxymethylbenzamide **5a** with BTI in a variety of solvents. When the reaction was carried out in THF or acetone, consumption of the starting material **5a** required several hours and the desired benzoxazinone **2a** was obtained in only moderate yields (Table 2). In acetonitrile, a slight increase in reaction yield was observed. However, when the reaction was performed in DMF, starting material **5a** was consumed within 1 h and benzoxazinone **2a** could be isolated in a yield of 90%. Therefore, as standard reaction conditions for Hofmann rearrangement of α-substituted 2-hydroxymethyl-benzamides **5b–f**, we utilized 1.05 equiv of BTI in DMF at 0 °C for 1 h. The isolated yields of the corresponding benzoxazinones **2a–f** are represented in Table 3.[12]

As is demonstrated in Table 3, the selected reaction conditions provide for the successful conversion of a variety of α-substituted 2-hydroxymethylbenzamides **5a–f** to their corresponding benzoxazinones **2a–f**. The reaction occurred smoothly to provide the desired cyclic carbamates in yields of 61–90%. The unsubstituted product **2a** (entry 1) was obtained in the highest yield, possibly due to the strong nucleophilic character of the primary alcohol. Entries 2–5 show that the Hofmann rearrangement and benzoxazinone formation proceed readily with various substituted (hetero)aromatic or aliphatic groups. The reaction of the sterically hindered 3,3-disubstituted tertiary alcohol **5f** with BTI required 4 h to produce the carbamate **5f** in 61% yield. It should be noted that in some, but not all cases (seemingly especially in acidic conditions), the 2-hydroxymethylbenzamides **5** are prone to lactonization, upon which the corresponding phthalides **2** are regenerated. As this might lead to loss of material during purification of **5**, we demonstrated that the conversion of **5e** to **2e**, without column chromatographic purification of intermediate **4e**, provided a good combined yield (70%) of **2e**.

The most likely reaction pathway follows the Hofmann rearrangement as induced by BTI, Scheme 3. Reaction of the 2-hydroxymethylbenzamide **5** with BTI leads to the formation of the rate-limiting step intermediate **6**.[8b] Breakdown of **6** leads to the formation of **7** and the isocyanate group is rapidly trapped by the free hydroxyl group to produce the intramolecular cyclization carbamate **2**.

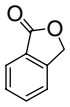
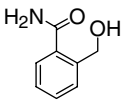
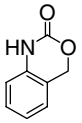
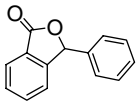
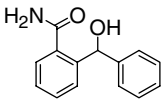
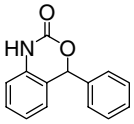
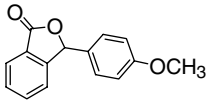
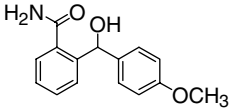
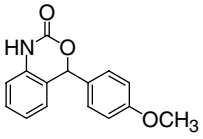
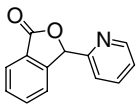
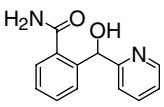
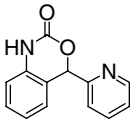
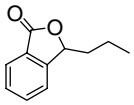
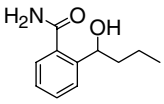
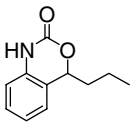
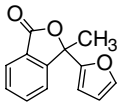
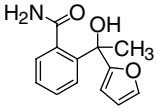
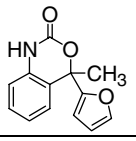
In summary, we have developed a simple two-step procedure to synthesize benzoxazinones from phthalides via

Table 2. Influence of solvent on the yield of **2a** from the reaction of **5a** with BTI

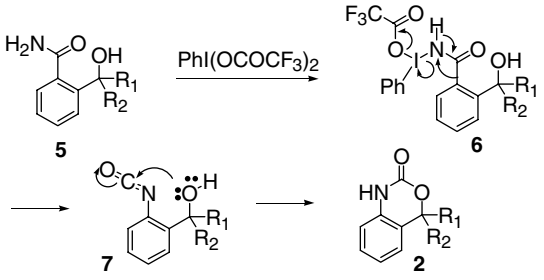
Entry	Solvent	Yield[a] (%)
1	THF	36
2	Acetone	58
3	Acetonitrile	66
4	DMF	90

[a] All reactions were carried out with 1.05 equiv BTI at 0 °C and monitored by TLC until all **5a** had been consumed.

Table 3. Synthesis of benzoxazinones **2** from phtalides **4** via 2-hydroxymethylbenzamides **5**

Entry	Phthalide[a]	2-Hydroxymethylbenzamide	Yield[b] (%)	Benzoxazinone	Time[c] (h)	Yield[c] (%)
1	**4a** 	**5a** 	78	**2a** 	1	90
2	**4b** 	**5b** 	77	**2b** 	1	78
3	**4c** 	**5c** 	81	**2c** 	1	68
4	**4d** 	**5d** 	76	**2d** 	1	70
5	**4e** 	**5e** 	80	**2e** 	1	77
6	**4f** 	**5f** 	71	**2f** 	4	61

[a] Prepared according to Ref. 4c.
[b] Isolated yield of **5** from **4**; reaction conditions: 3.0 equiv $(CH_3)_3Al/NH_4Cl$, THF, 50 °C, 12–16 h.
[c] Isolated yield of **2** from **5**; reaction conditions: 1.05 equiv BTI in DMF at 0 °C for time provided.



Scheme 3. Reaction pathway for the formation of benzoxazinones **2**.

an aminolysis-Hofmann rearrangement procedure. For the difficult aminolysis of the benzolactone ring, in situ prepared aluminum amide reagents were successfully employed. For the Hofmann rearrangement, BTI was selected and shown to be sufficiently mild to not oxidize the benzylic alcohol groups. Instead the hydroxyl group reacted with the intermediate isocyanate to form the desired six-membered ring benzoxazinones. The method can potentially be applied to available phthalide libraries.[4e]

Acknowledgments

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Supplementary data

Supplementary data include NMR and MS-data of compounds **5b–f** and **2b–f**. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.10.114.

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11. *General procedure: 2-Hydroxymethylbenzamide* **5a**: In a 50 mL three neck round bottom flask, 0.80 g (15.0 mmol) of dry, finely ground NH_4Cl was added followed by 10 mL of THF under a nitrogen atmosphere. The flask was immersed in an ice-water bath and 7.5 mL (15.0 mmol) of $(CH_3)_3Al$ (2.0 M in Toluene) was added dropwise. The ice-water bath was removed and the reaction mixture stirred for 2 h at room temperature. Then, 0.67 g (5.0 mmol) of phthalide **4a** was added and the reaction heated to 50 °C for 18 h upon which all starting material had disappeared (confirmed by TLC). The reaction mixture was carefully quenched by addition of water (10 mL) while maintaining the temperature at 0 °C. The mixture was partitioned between 10 mL of the aqueous phase and 20 mL of EtOAc. The aqueous phase was washed with EtOAc (3×20 mL). The organic phases were combined and dried over $MgSO_4$, filtered and concentrated by rotary evaporation. The residue was purified by flash chromatography with a solvent mixture of hexane–EtOAc (1:1) to yield 2-(hydroxymethyl)benzamide **4a** as a white solid in a yield of 78% (3.90 mmol, 0.59 g). $R_f = 0.18$. ^1H NMR (DMSO-d_6, 400 MHz) δ 4.79 (d, $J = 5.7$ Hz, 2H), 5.13 (t, $J = 5.7$ Hz, 1H), 7.30 (t, $J = 7.4$ Hz, 1H) 7.43–7.50 (m, 3H), 7.53 (d, $J = 7.6$ Hz, 1H), 7.86 (s, 1H); ^{13}C (DMSO-d_6, 100 MHz) δ 61.2, 126.5, 127.41, 127.64, 129.6, 134.9, 140.4, 170.6; LRGC-MS m/z $[M]^+$ 151. HRESIMS m/z calcd for $[C_8H_9NO_2+H]^+$ 152.0706, found 152.0703.
12. *1,4-Dihydro-benzo[d][1,3]oxazin-2-one* **2a**: In a 50 mL round bottom flask was added 2-(hydroxymethyl)benzamide **5a** (3.00 mmol, 0.454 g) and dissolved in 12 mL of DMF. The solution was cooled at 0 °C and covered with aluminum paper. To the solution, BTI (3.15 mmol, 1.35 g) was added in one portion and the resulting mixture stirred for 1 h at 0 °C and monitored by TLC which indicated disappearance of the starting material. The mixture was allowed to reach room temperature and 20 mL EtOAc was added. The organic phase was washed with $NaHSO_3$ (2×10 mL). The resulting aqueous phase was washed with EtOAc (3×10 mL). The combined organic phases were washed with brine, dried with Na_2SO_4, filtered and concentrated by rotary evaporation. The residue was purified by flash chromatography with a first wash with hexane to remove iodobenzene, and then with a mixture of hexane–EtOAc (3:1) to give benzoxazinone **2a** as a white solid in a yield of 90% (2.70 mmol, 0.403 g). $R_f = 0.47$. ^1H NMR ($CDCl_3$, 400 MHz) δ 5.35 (s, 2H), 6.90 (d, $J = 7.9$ Hz, 1H), 7.06 (t, $J = 7.4$ Hz, 1H), 7.11 (d, $J = 7.2$ Hz, 1H), 7.28 (t, $J = 7.4$ Hz, 1H), 9.15 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz), δ 68.7, 114.2, 117.8, 123.3, 124.2, 129.2, 135.5. LRGC-MS m/z $[M]^+$ 149. HRESIMS m/z calcd for $[C_8H_7NO_2+H]^+$ 150.0550, found 150.0551.