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The first general synthesis of *N*-substituted 1,2-benzisoxazolin-3-ones

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Abstract

A convenient synthesis of the title compounds has been developed. Key synthetic steps include: (1) conversion of the readily available salicylic acid derivatives to the corresponding *N*-substituted salicylhydroxamic acids; (2) cyclization of the hydroxamic acids under Mitsunobu conditions to give the title compounds. © 2000 Elsevier Science Ltd. All rights reserved.

Synthesis of heterocyclic compounds has been a central and important theme in modern medicinal chemistry. During our recent structure–activity relationship studies, we became interested in the synthesis of a series of *N*-substituted benzisoxazolin-3-ones (**1**). With their good chemical stability and structural rigidity, this class of compounds may serve as a general structural motif for medicinal chemistry applications. It was surprising, however, that no general method exists for their synthesis. Direct *N*-alkylation of the known 3-hydroxy-1,2-benzisoxazole,[1] the tautomeric form of *N*-unsubstituted 1,2-benzisoxazolin-3-one, was disqualified by the predominance of *O*-alkylation,[2] while a previous attempt at the ring closure of *N*-phenyl salicylhydroxamic acids led only to degradation via Lossen rearrangement.[3,4] Herein, we would like to report a convenient and general method for the synthesis of *N*-substituted 1,2-benzisoxazolin-3-ones.

Our approach for the synthesis of the title compounds involves the use of two readily available starting materials, salicylic acids and *N*-alkyl- or *N*-arylhydroxamines, and features the use of the Mitsunobu reagent[5] for cyclodehydration. As outlined in Scheme 1, salicylic acid (**2**) was converted to the acid chloride after acetylation of the phenolic hydroxy group. The *ortho*-acetoxy acid chloride was then treated with appropriate *N*-alkyl or *N*-arylhydroxyamine to produce *N*-substituted benzohydroxamic acid **3** with concomitant removal of the neighboring acetyl group in a selective manner such that a remote acetoxy group as in **3g** and **3h** (entries 7 and 8, Table 1) was not affected under the reaction conditions. The ring closure of *o*-hydroxyhydroxamic acid **3** was the key step. The attempted cyclodehydration with carbonyldiimidazole[6] or thionyl chloride[1,4] led either to no reaction at low temperature or complex

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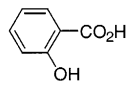
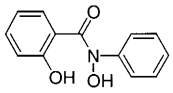
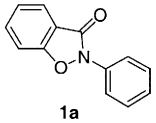
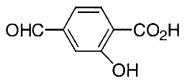
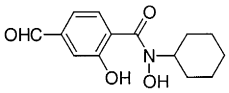
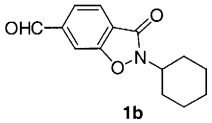
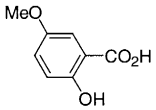
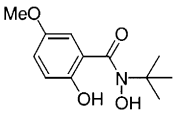
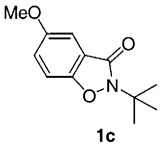
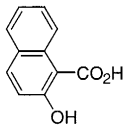
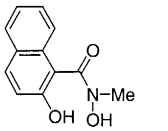
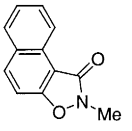
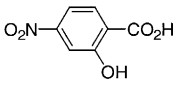
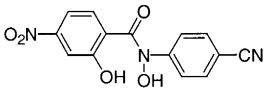
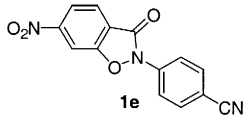
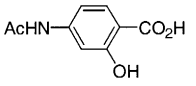
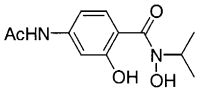
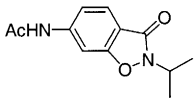
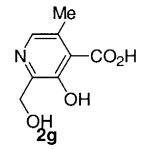
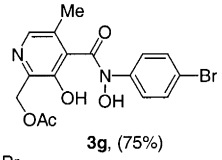
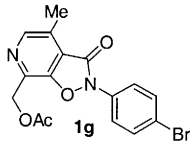
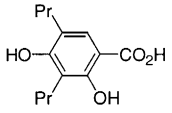
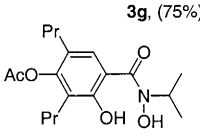
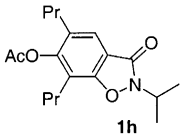
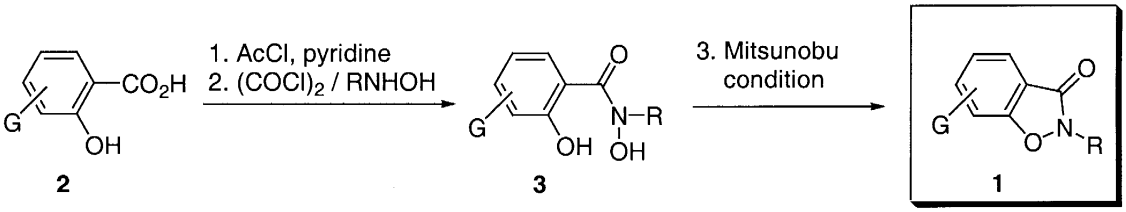
Table 1
Synthesis of *N*-substituted benzisoxazolin-3-ones from salicylic acids and hydroxamines

Entry	Salicylic acid (**2**)	Benzohydroxamic acid (**3**) [a]	Benzisoxazolin-3-one (**1**) [b]	Yield[c]
1	 **2a**	 **3a,** (67%)	 **1a**	90%
2	 **2b**	 **3b**, (77%)	 **1b**	85%
3	 **1c**	 **3c**, (55%)	 **1c**	87%
4	 **2d**	 **3d**, (80%)	 **1d**	92%
5	 **2e**	 **3e**, (70%)	 **1e**	78%
6	 **2f**	 **3f**, (60%)	 **1f**	88%
7	 **2g**	 **3g**, (75%)	 **1g**	82%
8	 **2h**	 **3h**, (72%)	 **1h**	92%

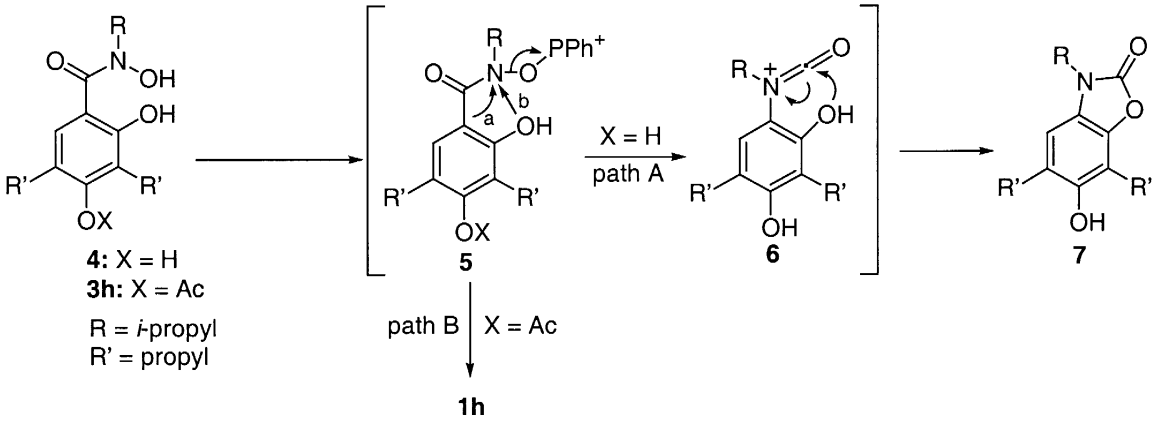
[a] *Reagents and conditions:* 1) acetylation of **2:** AcCl (2.0-3.0 equiv.), pyridine (4.0-6.0 eqiv.), 0-25 °C, 30 min; 2) preparation of acid chloride: acetylated salicylic acid (1.0 equiv.), $(COCl)_2$ (3.0 equiv.), CH_2Cl_2, 25 °C- reflux, 1 h; 3) conversion of acid chloride to **3**: acid chloride (1.0 equiv.), $RNHOH \cdot HCl$ (3.0 equiv.), 1*N* Na_2CO_3 (4.0 equiv.), CH_2Cl_2-THF (1 : 1), 25 °C, 1 h. [b] *Reagents and conditions*: Ph_3P (1.2 equiv.),$EtO_2CN{=}NCO_2Et$ (1.2 equiv), THF, 0-25 °C, 30 min. [c] Yield of isolated product.

products at elevated temperature due to competing side reactions including the Lossen degradation. Fortunately, the desired ring closure was smoothly effected with the use of the Mitsunobu reagent (Ph_3P-DEAD), affording product **1** in high yield (Scheme 1 and Table 1).[7]



Scheme 1.

As summarized in Table 1, a variety of compounds with a benzene, naphthalene and pyridine ring fused to the *N*-substituted isoxazolinone have been prepared following the general synthetic sequence outlined in Scheme 1. Several functional groups are well tolerated throughout the entire synthetic sequence. No degradation products arising from the Lossen rearrangement were observed except for substrate **4** (Scheme 2) in which the presence of the free hydroxyl group *para* to the reaction center appeared to have completely diverted the reaction course to Lossen rearrangement, giving rise to benzoxazolinone **7** as the only isolated product. This is probably because the *p*-hydroxyl group in **4** was sufficiently electron donating to force the migration of the phenyl group (path A, Scheme 2), giving the isocyanate intermediate[4] **6** that subsequently cyclized to afford **7**, whilst other aromatic substituents including the acetoxy group was generally less activating so that the attack on the nitrogen by the *ortho* hydroxyl group (path B) prevailed giving the desired benzisoxazolinones. It should be emphasized that the use of the Mitsunobu reagent must also contribute to the control of the desired pathway since as mentioned above other cyclization reagents led to the Lossen rearrangement even for substrates without a *para* hydroxyl group.



Scheme 2.

In conclusion, we have developed a convenient and general method for the synthesis of *N*-substituted 1,2-benzisoxazolin-3-ones. Noteworthy is the high efficiency and the ease with which all synthetic steps can be executed as well as the ready availability of the starting materials, which may make this method useful for combinatorial synthesis.

References

1. Boeshagen, H. *Chem. Ber.* **1967**, *100*, 594.
2. A small amount of *N*-alkylation product was obtained when a primary halide was used as the electrophile. However the desired *N*-alkylation product became essentially negligible when secondary halides was used. Similar results have been mentioned in a few patents. (a) Nagano, M.; Sakai, J.; Mizukai, M.; Nakamura, N.; Misaka, E.; Kobayashi, S.; Tomita, K. JP 79:54073772; *Chem. Abstr.* 91:211401. (b) Slawik, T.; Bien, I. PL 92:15571; *Chem. Abstr*. 94:244786.
3. (a) Kalkote, U. R.; Goswami, D. D. *Aust. J. Chem.* **1977**, *30*, 1847. (b) Sheradsky, T.; Avramovici-Grisaru, S. *Tetrahedron Lett.* **1978**, 2325.
4. For a review of the Lossen rearrangement, see: Bauer, L.; Exner, O. *Angew. Chem., Int. Ed. Engl.* **1974**, *13*, 376.
5. Mitsunobu, O.; Yamada, M. *Bull. Chem. Soc. Jpn*. **1967**, *40*, 2380.
6. Friary, R.; Sunday, B. R. *J. Heterocycl. Chem.* **1979**, *16*, 1277.
7. Typical procedure: **2h**→**3h**: 2,4-dihydroxy-3,5-dipropylbenzoic acid (**2h**) (0.48 g, 2 mmol) in CH_2Cl_2 (20 mL) was treated at 0°C with pyridine (0.96 mL, 12.0 mmol) and acetyl chloride (0.43 mL, 6.0 mmol). The reaction mixture was warmed to 25°C over 30 min and then poured into water (20 ml). The resulting biphasic mixture was stirred for 1 h, acidified with 1N HCl and extracted with ethyl acetate. The crude 2,4-diacetoxy-3,5-dipropylbenzoic acid obtained was heated with oxalyl chloride (0.52 mL, 6.0 mmol) in CH_2Cl_2 (5 mL) for 1 h. After removal of the volatiles, the acid chloride was taken up in methylene chloride (20 mL) and added to a vigorously stirred mixture of aqueous sodium carbonate (0.5N, 16 mL), *i*-PrNHOH·HCl (0.67 g, 6.0 mmol) and THF (20 mL), and then cooled at 0°C. The mixture was further stirred at 25°C for 1 h before it was acidified with 0.5N hydrochloric acid to pH 2 and extracted with ethyl acetate. The crude product was purified by chromatography on silica gel eluting with 7:3 hexane:ethyl acetate to give hydroxamic acid **3h** (0.48 g, 72%). **3h**→**1h**: To a solution of compound **3h** (0.48 g, 1.42 mmol) and triphenylphosphine (0.63 g, 1.7 mmol) in THF (20 mL) was added dropwise diethyl azodicarboxylate (0.30 g, 1.7 mmol) at 0°C. The reaction mixture was warmed to 25°C over 30 min and quenched with a 1:1 mixture of methanol:acetic acid (0.1 mL). Concentration and chromatography on silica gel eluting with 7:3 hexane:ethyl acetate gave **1h** as an oil (0.42 g, 92%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.58 (s, 1H), 4.28 (heptet, J=7.2 Hz, 1H), 2.81 (t, J=7.0 Hz, 2H), 2.68 (t, J=7.1 Hz, 2H), 2.40 (s, 3H), 1.70–1.57 (m, 4H), 1.32 (d, J=7.2 Hz, 6H), 0.99 (t, J=7.3 Hz, 3H), 0.97 (t, J=7.6 Hz, 3H). Anal. calcd for $C_{18}H_{25}NO_4$: C, 67.69; H, 7.89; N, 4.39. Found: C, 67.55; H, 7.95; N, 4.33.