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Chromatography-free, Mitsunobu-triggered heterocyclizations of salicylhydroxamic acids to 3-hydroxybenzisoxazoles

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ABSTRACT

The Mitsunobu reaction has become one of the most powerful tools to alkylate acidic pronucleophiles. A significant caveat of Mitsunobu chemistry, however, is that the reaction mixture is often plagued with purification problems owing to the phosphine oxide and hydrazine dicarboxylate by-products. In addition to the development of more readily separable Mitsunobu reagents, the product's physicochemical properties may be exploited to facilitate purification. In this regard, we present a swift and efficient preparation of 3-hydroxybenzisoxazoles by the Mitsunobu-triggered heterocyclizations of salicylhydroxamic acids, which can be isolated by an acid–base work-up. As expected, a range of functional groups was compatible with the chemistry.

Bioisosterism is the replacement of key functional groups with moieties that result in safer and/or clinically more effective drugs.[1] During our research program on the development of inhibitors of the Mcl-1 oncoprotein,[2] we explored the replacement of an arenecarboxylic acid motif, that is proposed to capture Arg263 through a salt bridge, with various bioisosteres to promote cell penetration. Bearing pK_a's of around 5,[3] 3-hydroxybenzisoxazoles represent a potential surrogate for arenecarboxylic acids. Typically, 3-hydroxybenzisoxazoles are prepared by cyclizations of the corresponding salicylhydroxamic acids with carbonyl diimidazole in refluxing THF,[4] although the range of yields associated with this chemistry would suggest it to be rather capricious. We considered if a milder and more reliable approach to these target molecules could be developed.

The Mitsunobu reaction is a powerful tool to alkylate acidic pronucleophiles through the in situ activation of primary and secondary alcohols, and occasionally tertiary alcohols, upon the reaction of a phosphine, typically triphenylphosphine (PPh_3), with an azodicarboxylate, typically diisopropyl azodicarboxylate (DIAD).[5,6] Suitable pronucelophiles exhibit pK_a's < 12, and include carboxylic acids, phenols, sulfonamides,[6] as well as various heterocycles, such as purines,[7] benzodiazepine-2,5-diones,[8] and 3-hydroxyisoxazoles.[9] The chemistry is highly versatile featuring in the construction of C—O, C—S, C—N, and C—C bonds.[6] Moreover, the reaction is mild, often occurring in under an hour at room temperature, and is tolerant of a wide range of functional groups. However, despite all these highlights, this chemistry is marred by the often problematic purification owing to the attendant phosphine oxide and hydrazine dicarboxylate generated in the reaction. Many groups, including ours, have developed alternative phosphine and azodicarboxylates to facilitate purification of the reaction mixture.[6,10–12] In parallel with this, the product's physicochemical properties may be exploited to facilitate purification. Recently, we reported on the Mitsunobu-triggered dehydration of salicylaldoximes to generate salicylonitriles via the corresponding benzisoxazoles.[13] Due to their acidities, the products were isolable by acid–base work-ups without the need for column chromatography. Herein, we present the Mitsunobu-triggered heterocyclizations of salicylhydroxamic acids to 3-hydroxybenzisoxazoles that can likewise be isolated by an acid–base work-up.

We considered that salicylhydroxamic acid carries all the elements for a successful Mitsunobu reaction, i.e. an acidic nucleophile (phenol moiety) and an alcohol (hydroxamic acid hydroxyl). Indeed, a lone report on the heterocyclization of salicylhydroxamic acid into its corresponding 3-hydroxyisoxazole by the Mitsunobu reaction exists, although no conditions, yield, nor work-up/purification were provided.[14] Furthermore, no exploration into the substrate scope was presented. In our hands, treatment of salicylhydroxamic acid **1** with 1.25 equiv of both PPh_3 and DIAD in

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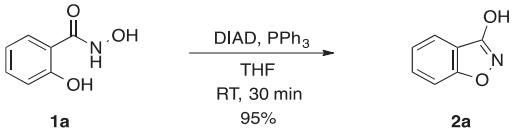
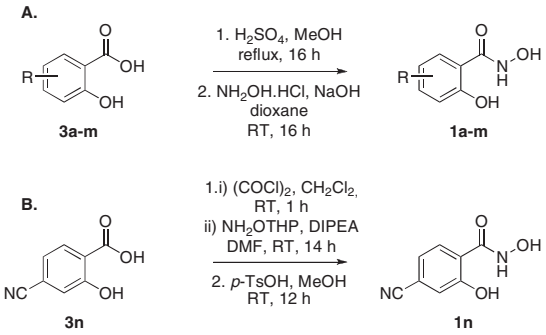


Scheme 1. Mitsunobu-triggered heterocyclization of salicylhydroxamic acid **1a**.

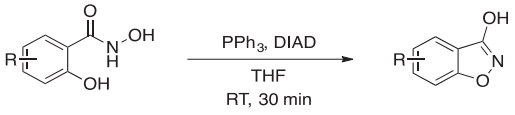
anhydrous THF at room temperature afforded 3-hydroxybenzisoxazole **2** in 95% yield, which was isolated by an acid–base extraction with no need for flash column chromatography (Scheme 1);[15] the ^{1}H and ^{13}C NMR spectra are furnished in the Supporting information. Complete conversion occurred within 30 min. Reducing the equivalents of the Mitsunobu reagents led to slightly lower conversions. The conversion was just as efficient in toluene and CH_2Cl_2, despite the poor initial solubility of **1** in these solvents. We next evaluated the tolerance of a range of functional groups to this chemistry, as described in Table 1.



Scheme 2.

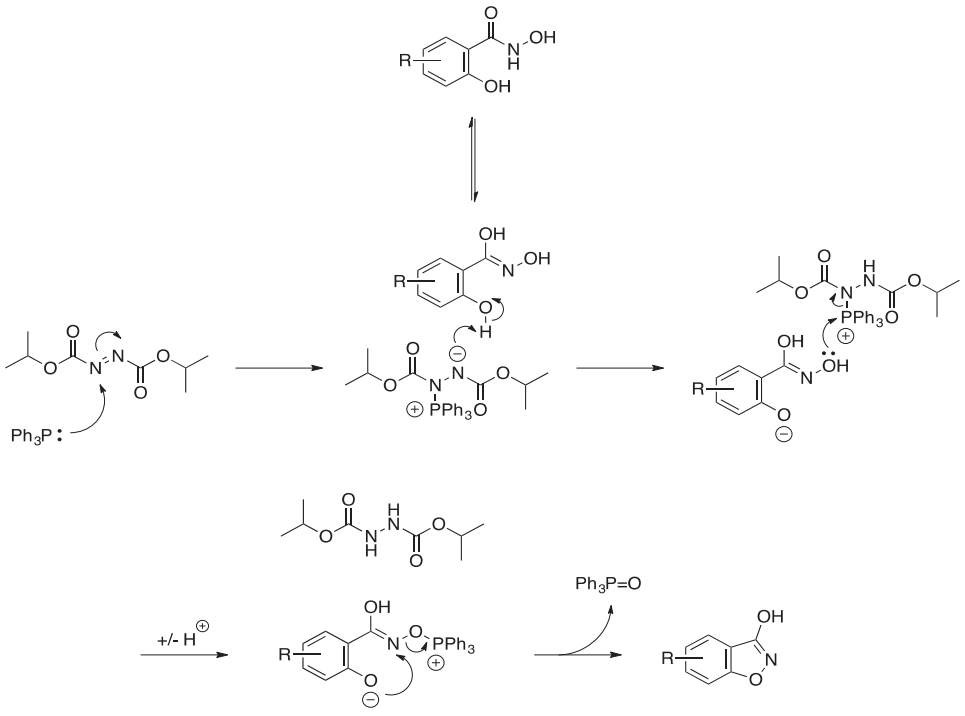
First, all but one of the salicylhydroxamic acids were prepared by a standard two-step procedure (Scheme 2A). Briefly, the appropriate salicylic acid was esterified with MeOH and concentrated

Table 1
[a]



Entry	Substrate	Product	Yield (%)	Entry	Substrate	Product	Yield[b] (%)
1	1a	2a	95	8	1h	2h	81
2	1b	2b	91	9	1i	2i	80
3	1c	2c	96	10	1j	2j	83
4	1d	2d	89	11[c]	1k	2k	89
5	1e	2e	86	12	1l	2l	94
6	1f	2f	93	13	1m	2m	91
7	1g	2g	96	14	1n	2n	91

[a] 1 equiv of **1** and 1.25 equiv of PPh_3 were dissolved in anhydrous THF (0.07 M) under an inert atmosphere at rt. After 2 min, 1.25 equiv of DIAD were added dropwise. TLC after 30 min indicated reaction was complete.
[b] Isolated yield after work-up as described in the References and notes section.
[c] General work-up modified: instead of the acidification step, the basic aqueous layer was neutralized with 1 M HCl, then the product **2k** was extracted into CH_2Cl_2.



Scheme 3. Proposed mechanism for the Mitsunobu-triggered cyclodehydrations of salicylhydroxamic acids into their corresponding 3-hydroxybenzisoxazoles.

H_2SO_4. Subsequently, the methyl ester was transformed into the corresponding salicylhydroxamic acid by treatment with NH_2OH and NaOH for 16 h. 4-Cyanosalicylhydroxamic acid (**1m**) could not be prepared by this procedure owing to transformation of the nitrile functional group into a methyl imidate. Instead, as shown in Scheme 2B, 4-cyanosalicylic acid was converted to its acid chloride via oxalyl chloride, amidated with *O*-(tetrahydropyran-3-yl)-hydroxylamine, and then the THP protecting group was subsequently removed by treatment with *p*-tosic acid in methanol to deliver the desired salicylhydroxamic acid **1m**. As can be seen in Table 1, electron-neutral, electron-rich and electron-poor salicylhydroxamates cyclized efficiently under the reaction conditions, and a variety of functional groups were compatible with the Mitsunobu chemistry. Compound **2a** was also prepared on a larger scale (5 mmol) in a similarly high-yield of 92%, indicating the chemistry is scalable. In Scheme 3, we have proposed a mechanism for this transformation. Briefly, it is postulated that the DIAD/PPh_3 betaine deprotonates the phenol of the salicylhydroxamic acid, which is followed by triphenylphosphinylation of the hydroxamic acid hydroxyl group. A subsequent intramolecular S_N2 reaction on the iminolic nitrogen by the phenolate anion then delivers the 3-hydroxybenzisoxazole.

In conclusion, we have demonstrated that heterocyclizations of salicylhydroxamic acids to their corresponding 3-hydroxybenzisoxazoles proceeds quickly and efficiently under mild conditions through an intramolecular Mitsunobu reaction. As anticipated, the chemistry is tolerant of a range of functional groups. Significantly, the products were isolable by acid–base work-ups, circumventing the often difficult purification of Mitsunobu reactions.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2016.10.045.

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15. Typical procedure: Salicylhydroxamic acid **1a** (77 mg, 0.5 mmol, 1 equiv) was dissolved in anhydrous THF (7 mL) under an inert (N_2) atmosphere. Triphenylphosphine (164 mg, 0.625 mmol, 1.25 equiv) was then added. After 2 min, DIAD (123 μL, 0.625 mmol, 1.25 equiv) was added dropwise. TLC (Hex/EtOAc, 1:3) after 30 min revealed the reaction was complete. The THF was removed in vacuo. The residue was partitioned between 0.1 M NaOH (50 mL) and CH_2Cl_2 (100 mL). The organic layer was separated, then the aqueous layer was washed a further three times with CH_2Cl_2 (100 mL). The aqueous layer was acidified with 1 M HCl (10 mL), then extracted into CH_2Cl_2 (2 × 100 mL), washed with brine (50 mL), dried (Na_2SO_4), filtered and concentrated to yield the 3-hydroxybenzisoxazole **2a**: mp = 143–146 °C; δ_H (400 MHz, d_6-DMSO) 7.09–7.17 (m, 3H, Ar), 7.29 (d, J = 7.6 Hz, 1H, Ar), 11.63 (s, 1H, OH); δ_C (100 MHz, $CDCl_3$) 156.2, 143.8, 129.4, 124.2, 122.7, 110.2, 110.1.