ORGANIC LETTERS

2013
Vol. 15, No. 23
5944–5947

One-Pot Synthesis of Functionalized 2,5-Dihydrofurans via an Amine-Promoted Petasis Borono–Mannich Reaction

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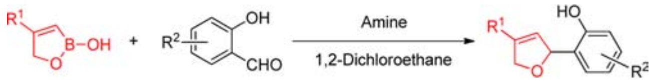
Received September 26, 2013

ABSTRACT



A series of functionalized 2,5-dihydrofurans were efficiently synthesized via an amine-promoted Petasis borono–Mannich reaction of 4-substituted 1,2-oxaborol-2(5*H*)-ols with salicylaldehydes in high yields. The process, which combines a boronic acid-based Mannich reaction and a highly efficient intramolecular S_N2 cyclization, provides a one-step and efficient route toward 2,5-dihydrofurans from simple and stable starting materials.

2,5-Dihydrofurans are a class of useful and versatile intermediates in organic syntheses. They also serve as common structural building blocks in a wide variety of bioactive natural and unnatural products.[1,2] Moreover, a large number of 2,5-dihydrofuran derivatives containing a phenolic group at the 2-position are reported to possess a diverse range of bioactivities. For instance, a new monoterpenylbenzenoid, 9,17-epoxyarnebinol (Figure 1), isolated from the stem bark of *Arnebia euchroma*, has anti-HCV and antibacterial activities.[3] Dihydroshikonofuran (Figure 1) isolated from the shikonin-free cell suspension of *Lithospermum erythrorhizon*[4] and pteleifolins C (Figure 1) isolated from *Melicope pteleifolia*, a traditional Chinese medicine,[5] also exhibit interesting biological activities. As a consequence, the development of practical synthetic routes to access such compounds is of significant interest.

Recently, several synthetic strategies for preparation of 2,5-dihydrofurans have been reported, which include RCM and Prins reactions, Ag(I)-catalyzed rearrangement–cyclization, and Pd(0)-, Au(I)-, Ag(I)-, Hg(II)-, Au(III)-, or Ru(III)-catalyzed cyclization reactions.[6–17] However, some

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10.1021/ol402782f

of these methods are still suboptimal because of the difficulty in obtaining the raw materials, use of expensive catalysts, and the harsh reaction conditions and multistep synthetic procedures. Consequently, novel efficient methods for synthesis of functionalized 2,5-dihydrofurans are much needed.

The Petasis borono–Mannich reaction is a highly versatile multicomponent reaction that utilizes readily available components capable of incorporating a wide range of functional groups into the product. This methodology allows the synthesis of a large variety of interesting molecules, including allylamines, amino acids, amino ketones, amino alcohols, amino sugars, and several types of heterocycles.[18,19] Petasis and co-workers first reported that organoboronic acids react with amines and salicylaldehydes to give amino phenols.[20] Finn and co-workers reported that a catalytic Petasis reaction of salicylaldehydes and vinylboronic acids is applicable to the preparation of 2*H*-chromenes.[21] After then, Petasis and co-workers described the synthesis of 2*H*-chromenes and 1,2-dihydroquinolines from arylaldehydes, amines, and alkenylboron compounds.[22] As far as we know, there is not any report on the Petasis reaction of multisubstituted alkenyl boronic acid. Moreover, no method for the construction of 2,5-dihydrofurans via Petasis reaction has been reported.

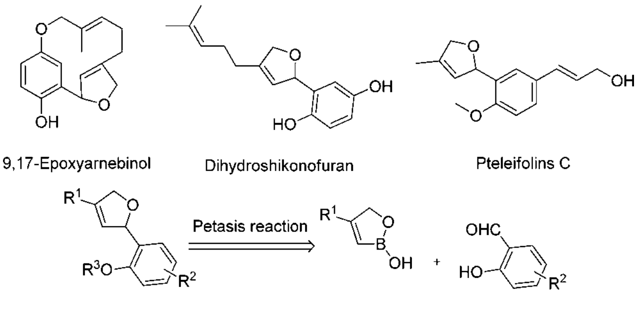
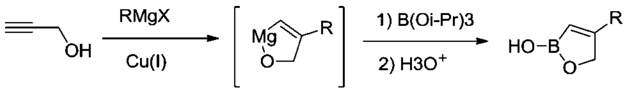
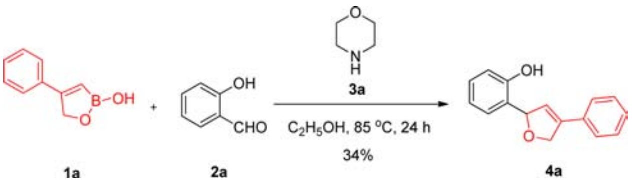


Figure 1. Biologically active natural products with 2,5-dihydrofuran unit, which might be synthesized via Petasis reaction.

Scheme 1



Scheme 2



Here in we report an efficient one-step synthetic route toward 2,5-dihydrofuran derivatives via an amine-promoted Petasis borono–Mannich reaction of 4-substituted 1,2-oxaborol-2(5*H*)-ols with salicylaldehydes.

The synthesis of 4-substituted 1,2-oxaborol-2(5*H*)-ols was reported previously by our group.[23] They can be easily prepared through copper-catalyzed carbomagnesation of propargyl alcohol, followed by the transmetalation of magnesium to boron in a one-pot procedure (Scheme 1).

4-Phenyl-1,2-oxaborol-2(5*H*)-ol **1a**, salicylaldehyde **2a**, and morpholine **3a** were first chosen for a model reaction. As shown in Scheme 2, the reaction took place after the mixture was heated in C_2H_5OH at 85 °C for 24 h. The isolated product was characterized as 2-(4-phenyl-2,5-dihydrofuran-2-yl)phenol (**4a**), which is composed of a 2,5-dihydrofuran core. The effect of different solvents, the temperature, and reaction time were then optimized, and the results are summarized in Table 1. As shown in Table 1, the reaction is very sensitive to solvents; 1,2-dichloroethane was found to be the best solvent of the reaction (Table 1, entry 6). We then noticed that the yield decreased with fall of temperature (Table 1, entries 6, 13, and 14), and the best reaction time was found to be 24 h as both decreased (Table 1, entries 15 and 16) and increased (Table 1, entry 17) reaction times led to decreased yields.

With the optimized reaction conditions in hand, we studied whether using a range of other amines would yield a better result. The results are summarized in Table 2. Structurally different amines were tested (Table 2, entries 1–11), and we determined that, with electron-rich secondary amines such as cyclic amine and dibenzylamine, moderate to good yields could be afforded (73–90%). However, *N*-ethylbenzylamine, *N*-methylbenzylamine, and diethylamine gave lowered yields (61%, 58%, and 56%, respectively) (Table 2, entries 4–6).

When amines with a bulky steric hindrance were used as catalyst, no product was given (Table 2, entries 7, 8, and 10).

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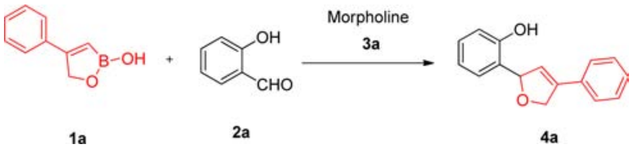
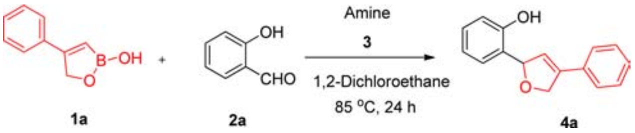
Table 1. Optimization of Reaction Conditions



entry	solvent	temp (°C)	time (h)	yield[b] (%)
1[a]	C_2H_5OH	85	24	34
2	Toluene	85	24	52
3	DMF	85	24	21
4	H_2O	85	24	64
5	$(CH_3)_2CHOH$	85	24	31
6	$ClCH_2CH_2Cl$	85	24	90
7	$HOCH_2CH_2OH$	100	24	29
8	DMSO	100	24	14
9	$(CF_3)_2CHOH$	60	24	62
10	CH_2Cl_2	50	24	26
11	CH_3CN	85	24	40
12	1,4-dioxane	90	24	50
13	$ClCH_2CH_2Cl$	60	24	55
14	$ClCH_2CH_2Cl$	40	24	6
15	$ClCH_2CH_2Cl$	85	6	79
16	$ClCH_2CH_2Cl$	85	12	86
17	$ClCH_2CH_2Cl$	85	48	87

[a] The reaction was performed with 4-phenyl-1,2-oxaborol-2(5*H*)-ol **1a** (1.0 mmol), salicylaldehyde **2a** (1.0 mmol), and morpholine **3a** (1.0 mmol) in C_2H_5OH (4 mL) at 85 °C for 24 h. [b] All yields were determined by ^1H NMR.

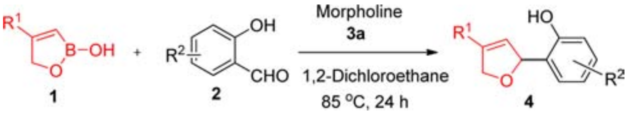
Table 2. Choice of Structure and Loading of Amines

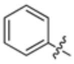
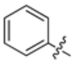
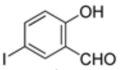
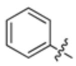
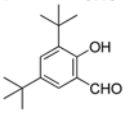
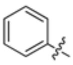
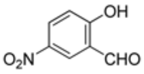
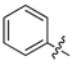
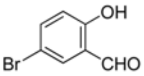
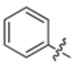
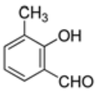
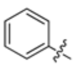
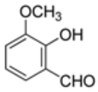
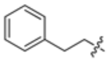
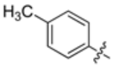
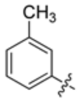
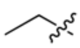


entry	amines (equiv)	yield[b] (%)
1[a]	piperidine (1.0)	65
2	pyrrolidine (1.0)	73
3	dibenzylamine (1.0)	83
4	*N*-ethylbenzylamine (1.0)	61
5	*N*-methylbenzylamine (1.0)	58
6	diethylamine (1.0)	56
7	diisopropylamine (1.0)	n.d.
8	diphenylamine (1.0)	n.d.
9	*N*-methylaniline (1.0)	15
10	benzhydrylamine (1.0)	n.d.
11	morpholine (1.0)	90
12	morpholine (0.5)	80
13	morpholine (0.3)	77
14	morpholine (0.1)	40

[a] The reaction was performed with 4-phenyl-1,2-oxaborol-2(5*H*)-ol **1a** (1.0 mmol), salicylaldehyde **2a** (1.0 mmol), and amine **3** (1.0 mmol) in 1,2-dichloroethane (4 mL) for 24 h at 85 °C. [b] All yields were determined by ^1H NMR.

Table 3. Substrate Scope[a]



entry	R^1	**2**	product	yield (%)[b]
1		**2a**	**4a**	85
2			**4b**	74
3			**4c**	82
4			**4d**	83
5			**4e**	89
6			**4f**	85
7			**4g**	79
8		**2a**	**4h**	68
9		**2a**	**4i**	90
10		**2a**	**4j**	92
11		**2a**	**4k**	71
12		**2a**	**4l**	76

[a] The reaction was performed with 4-substituted 1,2-oxaborol-2(5*H*)-ols 1 (1.0 mmol), salicylaldehydes **2** (1.0 mmol), and morpholine **3a** (1.0 mmol) in 1,2-dichloroethane (4 mL) at 85 °C for 24 h. [b] Isolated yields.

Having identified morpholine **3a** as a suitable amine for the reaction, we next examined the effect of catalyst loading. It is found that a gradual decrease of loading of the amine led to gradual lowering of the yield (Table 2, entries 11–14).

Under the optimized conditions, the substrate scope of the reaction was surveyed (Table 3). Employment of various salicylaldehydes **2** with electron-donating or electron-withdrawing substituents on the aryl ring did not affect the reaction performance (Table 3, entries 1–7). Moreover, a salicylaldehyde bearing a bulky C2-substituent could also afford the desired product in a good yield of 82%

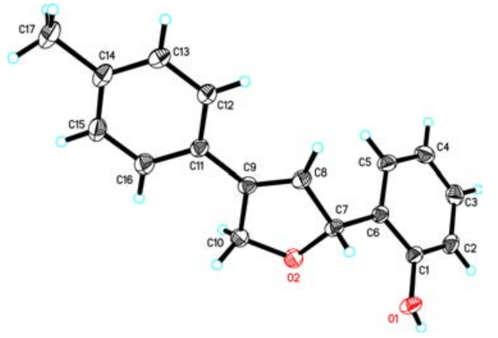
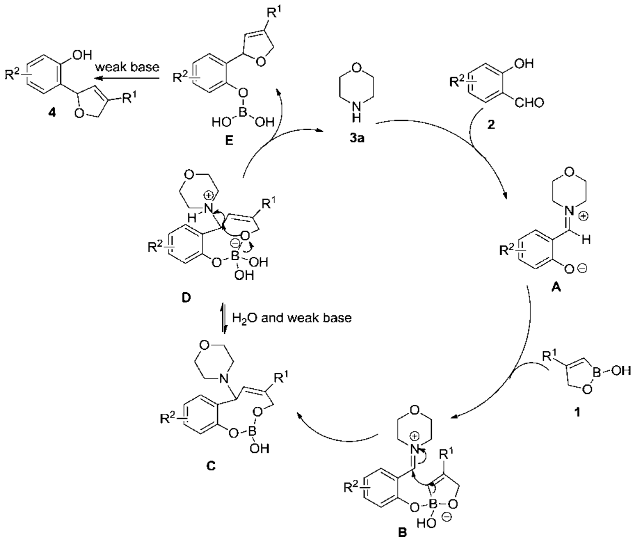


Figure 2. X-ray crystal structure of **4i**.

Scheme 3. Proposed Mechanism of the Reaction



(Table 3, entry 3). Then, reactions were carried out with a variety of differently substituted **1**. The presence of electron-donating aryl R^1 substituents on **1** gave the highest yield (Table 3, entries 9 and 10), whereas alkyl R^1 substitutions led to slightly decreased yields (Table 3, entries 11 and 12). The structure of **4i** was confirmed by X-ray single-crystal diffraction (Figure 2).

A possible mechanism for the formation of functionalized 2,5-dihydrofurans was then proposed as depicted in Scheme 3. Initially, a nucleophilic addition of amine **3a** to salicylaldehydes **2** produces the key iminium intermediate **A**. Coordination between the oxygen anion of phenolate and the boron atom of **1** leads to the formation of a tetracoordinate borate intermediate **B**. Subsequently, the alkenyl carbanion moiety of boronic acids favorably attacks the iminium ion, affording **C**. Then, after hydration of intermediate **C** to afford **D**, an intramolecular S_N2 reaction takes place, generating **E** and the recyclable amine **3a**. Finally, hydrolysis of **E** gives rise to the cyclizated product **4** through loss of a molecule of $B(OH)_3$ in the presence of a weak base.

In summary, we have developed an efficient and one-step synthesis of functionalized 2,5-dihydrofurans via an amine-promoted Petasis borono-Mannich reaction of 4-substituted 1,2-oxaborol-2(5*H*)-ols with salicylaldehydes. This approach represents a novel promising route to preparing 2,5-dihydrofuran derivatives, broadening the scope of the Petasis reaction. Further application of the reaction in the construction of various other heterocycles is in progress.

Acknowledgment. We are grateful to the Chinese Academy of Science, Chinese Natural Science Foundation (Nos. 21372077, 20802088, 91017006, 90917017), for their financial supports.

Supporting Information Available. Experimental details and characterization for all new compounds, and crystal structure data (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.