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Synthesis of 2,3-disubstituted benzofurans on solid-support

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ABSTRACT

A library of 2,3-disubstituted benzofuran scaffold was developed by using intramolecular Wittig olefination and Friedel–Crafts acylation.

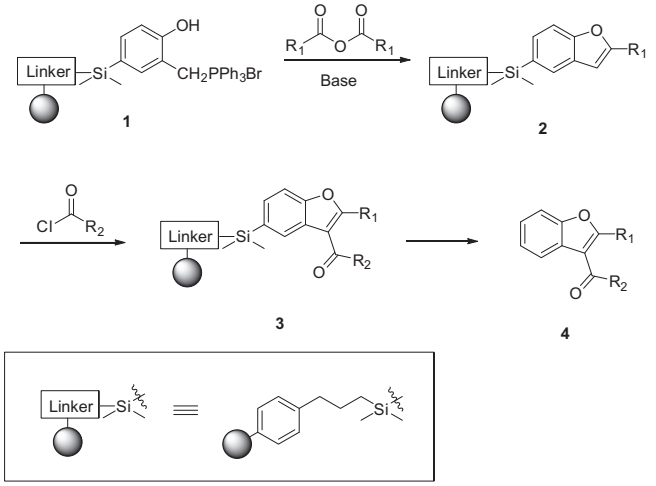
Aiming at supplying the library of small molecule ligands as the chemical tools for understanding biological mechanisms, we developed a solid-phase synthesis of benzofuran derivatives. We selected benzofuran as the key structural motif not only because of its frequent appearance in numerous natural or unnatural compounds of biological significance,[1] but also because it would make the appropriate next step for our on-going efforts of building bicyclic heterocycle libraries in continuation from our previous indole library synthesis.[2]

Intramolecular Wittig olefination[3] protocol is one of the most widely used methods for constructing benzofurans and, however, its utility on solid-support has not been validated yet in the previously reported benzofuran library syntheses.[4] We were thus prompted at developing the synthesis of 2,3-disubstituted benzofurans by utilizing intramolecular Wittig olefination on solid-support.

We designed the general synthetic scheme featuring the intramolecular Wittig olefination followed by the Friedel–Crafts acylation[5] and it is depicted in Scheme 1. The synthesis would involve the acid anydrides for R_1 introduction and the acyl chlorides for R_2 variation. We envisioned that the commercial abundance of both R_1 and R_2 sources would provide the competitive advantage of our synthetic strategy over other known methods.

With all these perspectives, we set out our synthesis by treating the commercially available (4-methoxyphenyl) dimethylsilylpropyl polystyrene **5** (0.83 mmol/g) with BBr_3 to liberate phenol **6**. A $Zn(NO_3)_2$-catalyzed electrophilic aromatic substitution of **6** with paraformaldehyde[6] gave rise to the formation of the benzyl alcohol **7**, and the desired key phosphonium intermediate **8** was obtained by treating **7** with triphenylphosphine hydrogen bromide in refluxing acetonitrile, as shown in Scheme 2. The progress of the reactions was monitored by FT-IR spectroscopy using KBr plates.

In order to examine the viability of the on-bead phosphonium salt **8** for the subsequent Wittig olefination, we synthesized a 2,3-disubstituted benzofuran target on solid-support as a model study as summarized in Scheme 3. O-Alkylation of **8** with propionic anhydride was successfully accompanied by the subsequent intramolecular Wittig olefination in the presence of triethylamine in refluxing toluene[7] for 24 h to afford the desired 2-ethylbenzofuran **9**. Compound **9** was then elaborated on C-3 by a Friedel–Crafts acylation using *p*-anisoyl chloride and tin(IV) chloride to produce the on-bead benzofuran **10**. Finally, the benzofuran **11** was re-



Scheme 1. General synthetic strategy for benzofuran library synthesis on solid-support.

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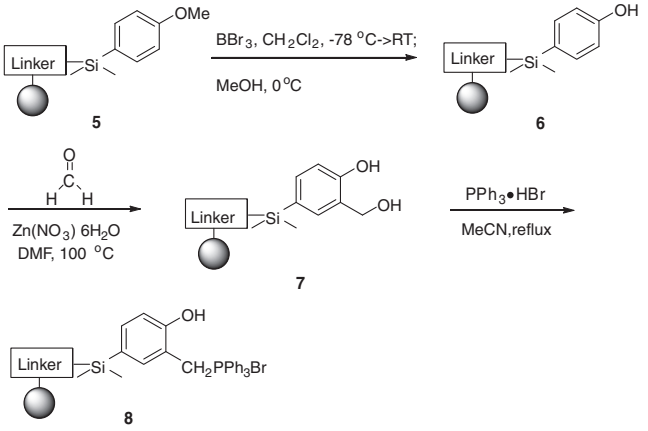
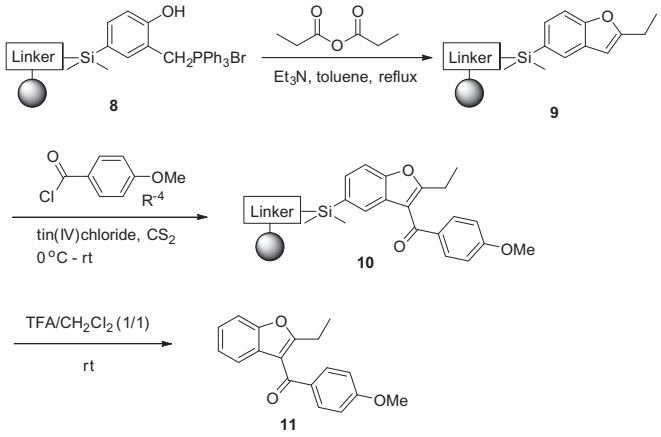


Scheme 2. Synthesis of the phosphonium intermediate on solid-support.



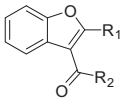
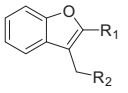
Scheme 3. Synthesis of a 2-ethyl-3-(4-methoxybenzoyl)benzofuran on solid-support.

leased from the solid-support by TFA-assisted cleavage during 10 h. The overall yield during six-steps was 7% and the structure of **11** was fully confirmed by ^{1}H NMR and HRMS.

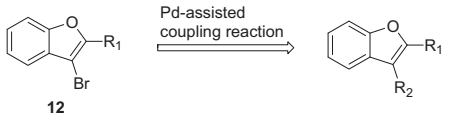
Encouraged by the success in the model experiment, we applied the developed protocol to the synthesis of a benzofuran library with variations on C-2 and C-3. Totally, nine additional compounds of the benzofuran scaffold were prepared in the same manner and they are shown below in Table 1.

In conclusion, we developed a solid-supported synthetic protocol featuring intramolecular Wittig reaction and Friedel–Crafts acylation for the benzofuran library synthesis. We believe this protocol provides an easy access to the synthesis of benzofuran scaffolds by using commercially abundant acid anhydrides and acid chlorides. We are currently examining halogenation on C-3 of the on-bead benzofurans such as **12** for Pd-assisted C–C coupling strategy aiming at expanding the diversity of the benzofuran compound library, as shown in Scheme 4 and it will be reported in due course.

Table 1
Benzofuran scaffolds synthesized using solid-support

Scaffold	Entry	R1	R2	Yield[a] (%)
	**1a**	Me	4-MeO–Ph–	5
	1b	Me	$PhCH_2CH_2$–	4
	1c	Me	Propyl	3
	1d	Et	4-MeO–Ph–	7
	1e	Et	$PhCH_2CH_2$–	5
	1f	Et	Propyl	3
	1g	Bu	4-MeO–Ph–	4
	1h	Bu	$PhCH_2CH_2$–	4
	1i	Bu	Propyl	3
	**1j**	Et	4-MeO–Ph–	3

[a] Six-step overall yields from the (4-methoxyphenyl) dimethylsilylpropyl polystyrene resin.



Scheme 4. Pd-assisted C–C coupling strategy for C-3 variation on the benzofuran scaffold.

Acknowledgment

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