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Preparation of Functional Benzofurans, Benzothiophenes, and Indoles Using Ester, Thioester, and Amide via Intramolecular Wittig Reactions

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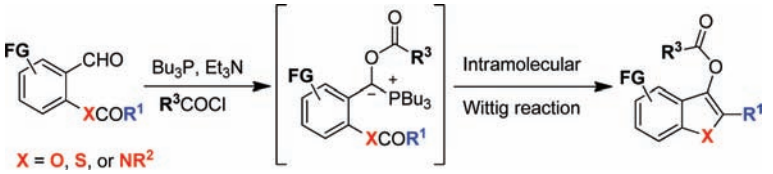
ABSTRACT



Preparation of new types of highly functional benzofurans, benzothiophenes, and indoles is realized via intramolecular Wittig reactions with the corresponding ester, thioester, and amide functionalities. The key intermediates, phosphorus ylides, presumably result from the addition of Bu_3P toward aldehydes followed by acylation and deprotonation. Synthesis of functional benzofurans directly starting from salicylic aldehyde derivatives with acid chlorides in a one-step procedure is also developed.

Benzofurans **1**,[1] benzothiophenes **2**,[1b−d,2] and indoles **3**[1,3] are important classes of heterocycles present in pharmaceuticals and many natural products. Different types of substitution patterns in these heterocycles provide new opportunities for drug discoveries and other applications in material science. However, in order to prepare new

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(4) For recent examples of benzofurans, see: (a) Guo, X.; Yu, R.; Li, H.; Li, Z. *J. Am. Chem. Soc.* **2009**, *131*, 17387. (b) Murai, M.; Miki, K.; Ohe, K. *Chem. Commun.* **2009**, 3466. (c) Shen, Z.; Dong, V. M. *Angew. Chem., Int. Ed.* **2009**, *48*, 784. (d) Pei, T.; Chen, C.-y.; DiMichele, L.; Davies, I. W. *Org. Lett.* **2010**, *12*, 4972. (e) Maimone, T. J.; Buchwald, S. L. *J. Am. Chem. Soc.* **2010**, *132*, 9990.

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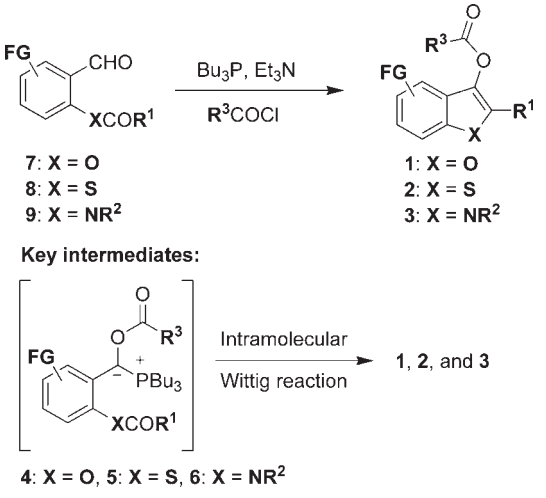
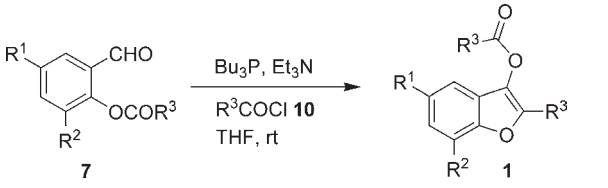
classes of these heterocycles, development of novel synthetic strategies for an efficient approach or even new methodologies is in strong demand.[1−6] The Wittig reaction has long been recognized as one of the most powerful methods to construct carbon−carbon double bonds,[7,8] and the development of new routes toward new types of Wittig reagents has attracted much attention in organic synthesis. Recently, we have reported an efficient synthesis of highly substituted furans via intramolecular Wittig reactions between ester functionalities and ylide intermediates resulting from Michael acceptors and Bu_3P.[9] We assume that it should be possible to utilize new types of phosphorus ylides **4**−**6**, which result from the addition of Bu_3P to aldehydes **7**−**9**, acylation, and then deprotonation to provide intramolecular Wittig reactions with the corresponding ester, thioester, or amide functionalities to provide functional heterocycles **1**−**3** (Scheme 1). To the best of our knowledge, there is no reported literature related to the successful generation of Wittig reagents **4**−**6** and their further applications.[10] In addition, we demonstrated the one-step procedure for the synthesis of benzofurans **1** directly starting from commercially available substituted salicylic aldehydes.

Scheme 1. Synthesis of Highly Functional Benzofurans **1**, Benzothiophenes **2**, or Indoles **3**



Thus, the aldehyde **7a**, Bu_3P (1.5 equiv), Et_3N (2.5 equiv), and benzoyl chloride (**10a**, 1.1 equiv) reacted smoothly at room temperature within 1 h, furnishing the highly substituted benzofuran **1a** in 68% yield (Table 1, entry 1).[11] The electronic effects were observed when different aryl ester functions of **7** and the corresponding acid chlorides **10** were employed in our protocol (entries 1−5). For example, the aldehydes **7b**−**d**, which are also derived from 5-bromosalicylic aldehyde and bear an electron-withdrawing group on the aryl ester function (R^3 = *p*-BrC_6H_4, *p*-ClC_6H_4, or *m*-ClC_6H_4), proceeded efficiently with the corresponding acid chlorides **10b**−**d** within 0.5−1 h, providing **1b**−**d** in 67−76% yields (entries 2−4). However, the reaction of **7e** (R^3 = *p*-$MeOC_6H_4$) and the acid chloride **10e** took 6 h to complete, leading to the functional benzofuran **1e** in 50% yield (entry 5). Similar results were obtained when **7f**−**h**, derived from 5-chloro- or 3,5-dichlorosalicylic aldehyde, were used. The reaction of **7f** and **10b** worked nicely within 1 h, giving rise to the adduct **1f** in 70% yield (entry 6). The other aldehyde bearing an aliphatic ester function, such as **7g** or **7h**, reacted successfully with the corresponding acid chloride **10f** or **10g** within 1 or 2 h, affording the benzofuran **1g** or **1h** in 68 or 62% yield, respectively (entries 7 and 8).

Table 1. Synthesis of Benzofurans **1**[a]



entry	R^1, R^2, R^3 (**7**)	R^3 (**10**)	time (h)	yield of **1**[b] (%)
1	Br, H, C_6H_5 (**7a**)	**10a**	1	**1a**,[c] 68
2	Br, H, *p*-BrC_6H_4 (**7b**)	**10b**	0.5	**1b**, 73
3	Br, H, *p*-ClC_6H_4 (**7c**)	**10c**	0.5	**1c**, 67
4	Br, H, *m*-ClC_6H_4 (**7d**)	**10d**	1	**1d**, 76
5	Br, H, *p*-$MeOC_6H_4$ (**7e**)	**10e**	6	**1e**, 50
6	Cl, H, *p*-BrC_6H_4 (**7f**)	**10b**	1	**1f**, 70
7	Cl, Cl, CH_3 (**7g**)	**10f**	1	**1g**, 68
8	Cl, Cl, $CH(CH_3)_2$ (**7h**)	**10g**	2	**1h**, 62

[a] Reactions were performed with **7** (1.0 mmol), Bu_3P (1.5 equiv), Et_3N (2.5 equiv), and **10** (1.1 equiv) in dry THF (10 mL) under nitrogen at rt. [b] Yield of isolated products. [c] The structure of **1a** was confirmed by X-ray analysis.[12]

A two-step, controlled experiment was carried out to demonstrate the importance of the base for a successful intramolecular Wittig reaction in our preliminary studies (Scheme 2). In the absence of Et_3N, the phosphonium chloride **11**, which was formed via the 1,2-addition of Bu_3P toward **7b** followed by acylation of **10b**, can be observed in

(8) For recent examples, see: (a) O'Brien, C. J.; Tellez, J. L.; Nixon, Z. S.; Kang, L. J.; Carter, A. L.; Kunkel, S. R.; Przeworski, K. C.; Chass, G. A. *Angew. Chem., Int. Ed.* **2009**, *48*, 6836. (b) Hodgson, D. M.; Arif, T. *Org. Lett.* **2010**, *12*, 4204. (c) Okamoto, N.; Takeda, K.; Yanada, R. *J. Org. Chem.* **2010**, *75*, 7615. (d) Xu, S.; Zou, W.; Wu, G.; Song, H.; He, Z. *Org. Lett.* **2010**, *12*, 3556.

(9) (a) Kao, T.-T.; Syu, S.; Lin, W. *Org. Lett.* **2010**, *12*, 3066. (b) Chen, K.-W.; Syu, S.; Jang, Y.-J.; Lin, W. *Org. Biomol. Chem.* **2011**, *9*, 2098.

(10) To the best of our knowledge, it is the first time that the Wittig reaction of a phosphorus ylide and the thioester functionality was reported.

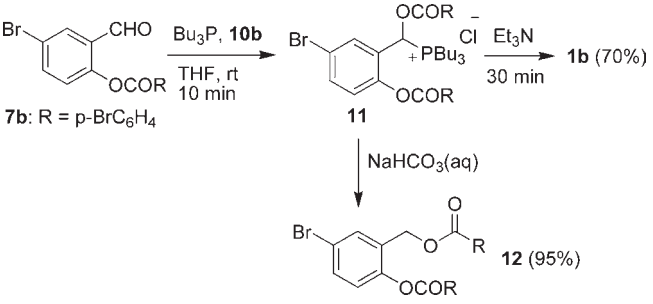
(11) In our preliminary studies, we found that the acyl group (R^1) transfer occurred, which led to two isomers when R^1 and R^3 are different (R^1 and R^3 assigned in Scheme 1). It happened in the case of benzothiophenes **2** as well. For the optimization of reaction conditions, detailed studies, and proposed reaction mechanisms for the formation of **1**−**3**, please see the Supporting Information.

(12) The CCDC number for **1a**: 808628.

(13) The structure of **11** can be confirmed by ^1H, ^{13}C, and ^{31}P NMR spectra and HRMS analysis. For the reaction progress monitored by crude ^1H NMR studies, see the Supporting Information.

the crude ^{1}H NMR study.[13] There was no formation of the desired benzofuran **1b** until Et_3N was added, and then **11** was converted into **1b** in 70% yield. Interestingly, the intermediate **11** can be purified simply by washing the crude reaction mixture with pentane. Alternatively, the intermediate can be transformed into compound **12** (95% yield) after workup with aqueous $NaHCO_3$.[13]

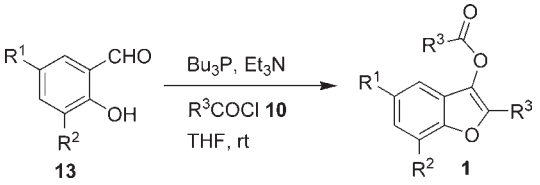
Scheme 2. Formation of the Phosphonium Chloride **11** and **12**



Furthermore, the development of a one-step procedure for the synthesis of highly functional benzofurans **1** directly starting from salicylic aldehyde derivatives **13** was realized (Table 2). It showed that the reactions of **13** and various acid chlorides **10** (2.1 equiv) in the presence of Bu_3P (1.5 equiv) and Et_3N (3.5 equiv) took place at room temperature within 0.5−24 h, leading to the corresponding adducts **1** in 27−77% yields (entries 1−12). 5-Bromosalicylic aldehyde (**13a**) worked nicely with an acid chloride, such as **10b**−**d**, leading to the corresponding benzofuran **1b**, **1c**, or **1d** in 72%, 54%, or 74% yield, respectively (entries 1−3). *p*-Methoxybenzoyl chloride (**10e**) as well as an alkanecarbonyl chloride, such as **10f** or **10h**, showed less reactivity with **13a** and gave rise to the corresponding benzofuran **1e**, **1i**, or **1j** within 5−15 h in 52%, 42%, or 62% yield, respectively (entries 4−6). In addition, the electronic effects of substituents of **13** are also significant. The reaction of *p*-bromobenzoyl chloride (**10b**) and 5-chlorosalicyclic aldehyde (**13b**) or 3,5-dichlorosalicyclic aldehyde (**13c**) proceeded efficiently within 0.5−1 h, furnishing the corresponding benzofuran **1f** or **1k** in 61% or 77% yield, respectively (entries 7 and 8). 5-Methoxysalicylic aldehyde (**13d**) reacted more slowly with **10b** to provide **1l** within 24 h in merely 27% yield (entry 9). 5-Nitrosalicyclic aldehyde (**13e**) also worked successfully not only with **10a** but also with *o*-bromobenzoyl chloride (**10i**) or **10e** within 1−5 h, affording **1m**, **1n**, or **1o** in 65%, 30%, or 48% yield, respectively (entries 10−12).

The broad reaction scope of our protocol was demonstrated by further studies disclosed in Table 3. The intramolecular Wittig reactions with the thioester function in compounds **8** were successful, and a wide variety of functional benzothiophenes **2** (17−60% yields) can be readily prepared at 50 °C within 6−24 h (entries 1−8).[11] Similarly, poor results were given when the steric hindrance was present in **8d** or **8f** (R^3 = *o*-ClC_6H_4 or *o*-BrC_6H_4) in comparison with those of **8b**,**c** or **8e** (entries 2−6).

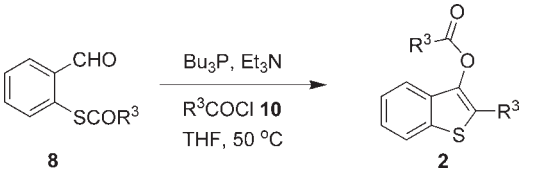
Table 2. Direct Synthesis of Benzofurans **1** from **13**[a]



entry	R^1, R^2 (**13**)	R^3 (**10**)	time (h)	yield of **1**[b] (%)
1	Br, H (**13a**)	*p*-BrC_6H_4 (**10b**)	1	**1b**, 72
2	**13a**	*p*-ClC_6H_4 (**10c**)	1	**1c**, 54
3	**13a**	*m*-ClC_6H_4 (**10d**)	1	**1d**, 74
4	**13a**	*p*-$MeOC_6H_4$ (**10e**)	6	**1e**, 52
5	**13a**	CH_3 (**10f**)	5	**1i**, 42
6	**13a**	cyclohexyl (**10h**)	15	**1j**, 62
7	Cl, H (**13b**)	**10b**	1	**1f**, 61
8	Cl, Cl (**13c**)	**10b**	0.5	**1k**, 77
9	MeO, H (**13d**)	**10b**	24	**1l**, 27
10	NO_2, H (**13e**)	C_6H_5 (**10a**)	1	**1m**, 65
11	**13e**	*o*-BrC_6H_4 (**10i**)	2	**1n**, 30
12	**13e**	**10e**	5	**1o**, 48

[a] Reactions were performed with **13** (1.0 mmol), Bu_3P (1.5 equiv), Et_3N (3.5 equiv), and **10** (2.1 equiv) in dry THF (10 mL) under nitrogen at rt. [b] Yield of isolated products.

Table 3. Synthesis of Benzothiophenes **2**[a]



entry	R^3 (**8**)	R^3 (**10**)	time (h)	yield of **2**[b] (%)
1	C_6H_5 (**8a**)	**10a**	10	**2a**, 58
2	*p*-ClC_6H_4 (**8b**)	**10c**	6	**2b**, 55
3	*m*-ClC_6H_4 (**8c**)	**10d**	6	**2c**, 60
4	*o*-ClC_6H_4 (**8d**)	**10j**	9.5	**2d**, 47
5	*p*-BrC_6H_4 (**8e**)	**10b**	8	**2e**, 51
6	*o*-BrC_6H_4 (**8f**)	**10i**	24	**2f**, 17
7	2-furyl (**8g**)	**10k**	7	**2g**, 23
8	$CH(CH_3)_2$ (**8h**)	**10g**	18	**2h**, 42

[a] Reactions were performed with **8** (0.3 mmol), Bu_3P (1.5 equiv), Et_3N (1.7 equiv), and **10** (1.5 equiv) in dry THF (1.5 mL) under nitrogen. [b] Yield of isolated products.

Interestingly, the intramolecular Wittig reaction can occur with an amide functionality in compounds **9** under our optimized reaction conditions (Table 4). The reactions of amides **9a**−**f** and an acid chloride (**10a** or **10c**) or Ac_2O (**10j**) in the presence of Bu_3P and Et_3N proceeded smoothly

(14) For other methods for the preparation of similar derivatives of the indole **3c**, see: (a) Choy, P. Y.; Lau, C. P.; Kwong, F. Y. *J. Org. Chem.* **2011**, *76*, 80. (b) Liu, Q.; Li, G.; Yi, H.; Wu, P.; Liu, J.; Lei, A. *Chem.*−*Eur. J.* **2011**, *17*, 2353. A selected literature for the Wittig reaction of a phosphorus ylide and the amide functionality, see:(c) Lu, Y.; Arndtsen, B. A. *Org. Lett.* **2009**, *11*, 1369.

Table 4. Synthesis of Indoles **3**[a]

9 **3**

entry	R^1, R^2 (**9**)	R^3 (**10**)	time (h)	yield of **3**[b] (%)
1	Bn, C_6H_5 (**9a**)	C_6H_5 (**10a**)	20	**3a**,[c] 75
2	**9a**	*p*-ClC_6H_4 (**10c**)	38	**3b**,[c] 70
3	**9a**	CH_3 (**10j**)[d]	24	**3c**, 65
4	Bn, *p*-$NO_2C_6H_4$ (**9b**)	**10a**	24	**3d**,[c,e] 73
5	Bn, *p*-ClC_6H_4 (**9c**)	**10a**	20	**3e**, 71
6	Bn, *p*-$MeOC_6H_4$ (**9d**)	**10a**	24	**3f**, 65
7	allyl, C_6H_5 (**9e**)	**10a**	24	**3g**, 63
8	CH_3, C_6H_5 (**9f**)	**10a**	80	**3h**, 70

[a] Reactions were performed with **9** (0.5 mmol), Bu_3P (1.5 equiv), Et_3N (1.7 equiv), and **10** (1.5 equiv) in dry toluene (1.0 mL) under nitrogen. [b] Yield of isolated products. [c] The structures of **3a**, **3b**, and **3d** were confirmed by X-ray analysis.[15] [d] Ac_2O was used. [e] 2.0 equiv of Bu_3P was used.

at 80 °C within 20−80 h, giving rise to the corresponding indoles **3a**−**h** in 63−75% yields (entries 1−8).[14] Remarkably, the acyl group (R^2CO−) transfer did not happen during the reaction, and therefore, the installation of different substitution patterns (R^2 and R^3) in **9** can be successfully accomplished.[11] In addition, not only the benzylic group (R^1 of **9a**−**9d**) but also other groups such as the allyl group (R^1 of **9e**) or the methyl group (R^1 of **9f**) can be tolerated under our reaction conditions. Furthermore, all the results showed that the reactivity of the intramolecular Wittig reaction with the amide functionality was lower than that of the thioester functionality (Tables 3 and 4).

In conclusion, we have developed a general procedure for novel synthesis of new types of benzofurans **1**, benzothiophenes **2**, and indoles **3**. The reaction conditions are mild, and numerous acid chlorides **10** can be applied successfully to afford **1**−**3**. The reaction mechanism is proposed to undergo the 1,2-addition of Bu_3P toward **7**, **8**, or **9** followed by acylation with an acid chloride **10**, deprotonation by Et_3N, and finally an intramolecular Wittig reaction of **4**, **5**, or **6**. In addition, the efficient synthesis of **1** directly starting from commercially available **13** makes our protocol an attractive approach. Further studies and the extensions of this work in the preparation of other heterocycles are currently underway.

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Supporting Information Available. General experimental procedures, compound characterization data, and X-ray and NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

(15) The CCDC numbers for **3a**, **3b**, and **3d** are 808629, 809083, and 809082, respectively.