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Controlled Synthesis of 2- and 3-Substituted Benzo[*b*]furans

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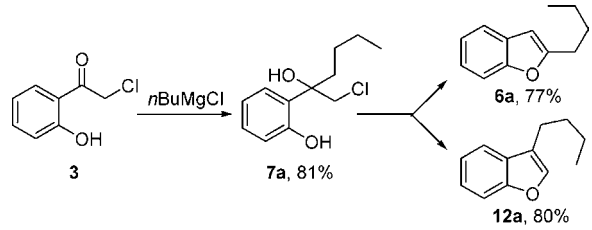
ABSTRACT



A controlled regioselective synthesis of either C-2 or C-3 substituted benzo[*b*]furans from readily accessible 1-(2-hydroxyphenyl)-2-chloroethanones is described. Addition of a range of Grignard reagents to the α-chloro ketones generates alkoxide intermediates, which can form either 2-substituted benzo[*b*]furans via a [1,2]-aryl migration or 3-substituted benzo[*b*]furans via a direct cyclization and dehydration sequence. A temperature-dependent [1,2]-aryl migration mechanism for the formation of 2-substituted benzo[*b*]furan is proposed.

Benzofurans, as a core structural motif, are ubiquitous in natural products as well as pharmaceutical compounds, such as Amiodarone and (−)-BPAP.[1] The pursuit of a general and efficient synthesis of benzo[*b*]furans that controls the introduction of substituents in a regioselective fashion has been of continued interest to synthetic organic chemists. Many existing approaches focus on the formation of the furan ring from a variety of substrates while introducing substituents at C-2 and C-3.[2] The synthesis of either 2- or 3-substituted benzo[*b*]furans from the same substrate, however, remains elusive and would have great advantages over existing protocols. Herein, we wish to report a controlled and regioselective synthesis of either C-2 or C-3 substituted benzo[*b*]furans from readily accessible 1-(2-hydroxyphenyl)-2-chloroethanones.[3]

We recently reported an efficient synthesis of 2-substituted indoles (**2**) from readily accessible 1-(2-aminophenyl)-2-chloroethanones (**1**) and commercially available organometallic reagents (Scheme 1).[4] The highly regioselective introduction of substituents at C-2 was achieved via a novel [1,2]-aryl migration mechanism. We subsequently observed that a similar migration was feasible when 1-(2-hydroxyphenyl)-2-chloroethanone (**3**) was treated with excess Grignard.[5] The [1,2]-aryl migration for this reaction happened at a slower rate compared to its nitrogen counterpart in the synthesis of indoles, thus requiring elevated temperature to facilitate the migration. The key intermediate phenoxy ketone **5** was formed cleanly and cyclized under acidic conditions to successfully generate

(1) (a) Donelly, D. M. X.; Meegan, M. J. Furans and Their Benzo Derivatives: (iii) Synthesis and Applications. In *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R., Ed.; Pergamon: New York, 1984; Vol. 4, pp 657−712. (b) Luca, L. D.; Nieddu, G.; Porcheddu, A.; Giacomelli, G. *Curr. Med. Chem.* **2009**, *16*, 1. (c) Banskota, A. H.; Tezuka, Y.; Midorikawa, K.; Matsushige, K.; Kadota, S. *J. Nat. Prod.* **2000**, *63*, 1277. (d) Punnam, S. R.; Goyal, S. K.; Kotaru, V. P. K.; Pachika, A. R.; Abela, G. S.; Thakur, R. K. *Cardiovasc. Hematol. Disord: Drug Targets* **2010**, *10*, 73. (e) Dawson, L. A.; Watson, J. M. *CNS Neurosci. Ther.* **2009**, *15*, 107. (f) Ohtsuka, T.; Aoka, Y. *Drugs Future* **2003**, *28*, 143.

(2) For recent reviews of the synthesis of benzofurans, see: Hou, X.-L.; Yang, Z.; Yeung, K.-S.; Wong, H. N. C. *Prog. Heterocycl. Chem.* **2009**, *21*, 179.

(3) These compounds can be prepared via Friedel−Crafts acylation from corresponding phenols and nitriles. See: (a) Sugasawa, T.; Toyoda, T.; Adachi, M.; Sasakura, K. *J. Am. Chem. Soc.* **1978**, *100*, 4842. (b) Sugasawa, T.; Adachi, M.; Sasakura, K.; Kitagawa, A. *J. Org. Chem.* **1979**, *44*, 578.

(4) (a) Pei, T.; Chen, C.; Dormer, P. G.; Davies, I. W. *Angew. Chem., Int. Ed.* **2008**, *47*, 4231. (b) Pei, T.; Tellers, D.; Streckfuss, E.; Chen, C.; Davies, I. W. *Tetrahedron* **2009**, *65*, 3285.

(5) Similar [1,2]-aryl migration was observed when 1-(4-hydroxyphenyl)-2-chloroethanone was treated with excess methyl Grignard. See: Crombie, L.; Hardy, R.; Knight, D. W. *J. Chem. Soc., Perkin Trans. 1* **1985**, 1373.

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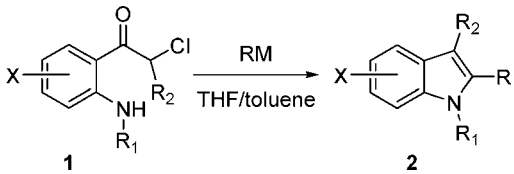
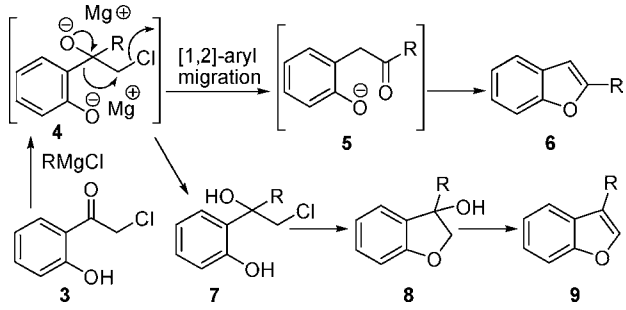
Scheme 1. Synthesis of 2-Substituted Indoles from **1** via [1,2]-Aryl Migration



2-substituted benzo[*b*]furans in moderate to good yields. Furthermore, we found that the migration process could be halted by quenching the reaction at low temperature to give the alcohol intermediate **7**. Subsequent cyclization−elimination of the alcohol intermediate **7** then allowed access to isomeric 3-substituted benzo[*b*]furans (Scheme 2). On the basis of these

Scheme 2. Proposed Mechanism for the Synthesis of 2- and 3-Substituted Benzo[*b*]furans from **3**

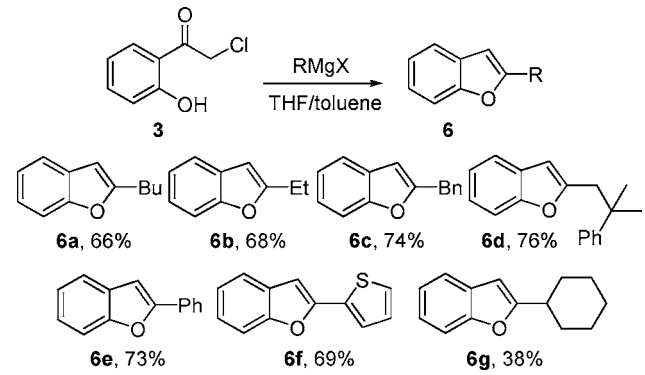


promising initial results, we believed that the reaction of 1-(2-hydroxyphenyl)-2-chloroethanones with various Grignard reagents could be developed into a versatile method for direct access to 2- and 3-substituted benzo[*b*]furans.

We first explored the generality of the controlled synthesis of 2-substituted benzo[*b*]furans by adding different Grignard reagents to 1-(2-hydroxyphenyl)-2-chloroethanone (**3**), and the results are summarized in Scheme 3. Reaction of **3** with *n*BuMgCl at 55 °C for 1 h followed by treatment with HCl/IPA at 70 °C for 10 min formed 2-butylbenzo[*b*]furan (**6a**) in 66% isolated yield (condition **A**). Similar to *n*BuMgCl, other primary alkyl Grignard reagents reacted with **3** to form 2-substituted benzo[*b*]furans in good yields. For example, 2-ethylbenzo[*b*]furan (**6b**), a key intermediate in the synthesis of Benziodarone,[6] a vasodilator, was easily prepared in 68% isolated yield from **3** and EtMgCl under condition **A**. Under the same conditions, bulky Grignard 2,2-dimethyl-2-phenylethyl magnesium bromide led to formation of 2-substituted benzo[*b*]-furan **6d** in 76% yield. Introduction of aromatic substituents, such as a phenyl (**6e**) or thien-2-yl (**6f**) group, to C-2 of benzo[*b*]furan using corresponding aromatic Grignard reagents also worked well. When the secondary Grignard cyclohexyl magnesium bromide was used, 2-cyclohexylbenzo[*b*]furan (**6g**) was obtained in only 38% isolated yield.

(6) Buu Hoi, N. P.; Beaudet, C. *US Patent*, 1961, 3041042.

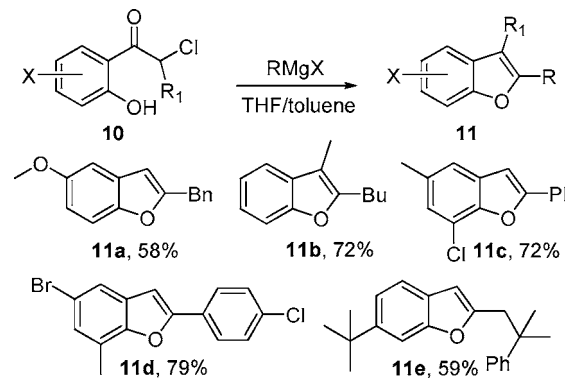
Scheme 3. Synthesis of 2-Substituted Benzo[*b*]furans **6** from Ketone **3** under Condition **A**[a,b]



[a] Condition **A**: A solution of ketone **3** (1.0 mmol) in 2.0 mL of THF/toluene (1:1 v/v) was mixed with the Grignard reagent (3.0 mmol) at −10 °C. The cold bath was removed, and the mixture was stirred at room temperature for 30 min and then at 55 °C for 1 h, cooled to room temperature, quenched with 1.2 mL of 5 M HCl/IPA, and heated at 70 °C for 10 min. [b] All reactions were carried out without optimization. Yields refer to isolated material based on ketone **3**.

Having successfully prepared a range of 2-substituted benzo[*b*]furans **6** from ketone **3** employing various RMgX reagents, we decided to extend this methodology to substituted ketones **10**. Under condition **A**, a series of 2-substituted benzo[*b*]furans **11** were readily synthesized in moderate to good yields (Scheme 4). It was found that neither electron-donating nor electron-

Scheme 4. Synthesis of 2-Substituted Benzo[*b*]furans **11** from Ketone **10** under Condition **A**[a,b]



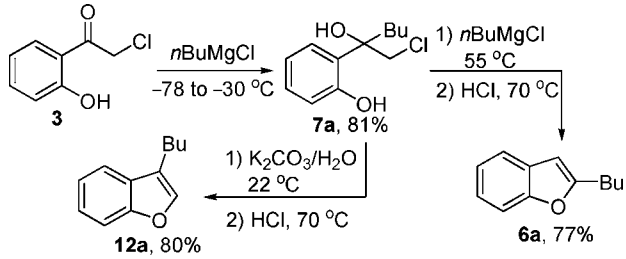
[a] Reaction conditions: ketone **10** (1.0 mmol) in 2.0 mL of THF/toluene (1:1 v/v) and Grignard (3.0 mmol) were reacted under condition **A**. [b] All reactions were carried out without optimization. Yields refer to isolated material based on ketone **10**.

withdrawing substituents on the aromatic ring had much impact on the transformation. For instance, 2-benzyl-5-methoxybenzo[*b*]furan (**11a**) and 6-*t*-butyl-(2,2-dimethyl-2-phenyl)ethylbenzo[*b*]furan (**11e**), with electron-donating groups on the phenyl ring, were prepared in 58% and 59% yield, respectively. In addition, ketones with electron-withdrawing Cl and Br substituents on the phenyl ring also reacted with Grignard reagents in good yields. Under the identical conditions, 2,3-

disubstituted benzo[*b*]furan **11b** was prepared in 72% isolated yield from ketone **10b** (R_1 = Me, X = H) and *n*BuMgCl.

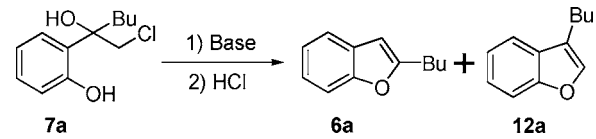
In contrast to the facile [1,2]-aryl migration in the reaction of 1-(2-aminophenyl)-2-chloroethanones (**1**) with Grignard at below −40 °C,[4] the reaction of 1-(2-hydroxyphenyl)-2-chloroethanone (**3**) with Grignard *n*BuMgCl needed 12 h at ambient temperature or 1 h at 50 °C to complete the [1,2]-aryl migration. 2-Butylbenzo[*b*]furan (**6a**) was isolated in 66% yield exclusively after heating the alkoxide intermediate for 1 h at 55 °C followed by HCl-mediated benzofuran ring formation (Scheme 3). There was no migration observed below −30 °C, and in fact, alcohol **7a** could be isolated in 81% yield after the reaction was quenched with MeOH at −30 °C. Treatment of **7a** with 2.5 equiv of Grignard at 55 °C facilitated [1,2]-aryl migration to form 2-butylbenzo[*b*]-furan (**6a**) in 77% isolated yield as a single regioisomer after subsequent cyclization and dehydration (Scheme 5).

Scheme 5. Synthesis of Benzofuran **6a** and **12a** from **3** via Alcohol **7a**



The sluggishness of the [1,2]-aryl migration of alkoxide **4** at low temperature prompted us to explore another reaction pathway toward the synthesis of 3-substituted benzo[*b*]furan via a ring-closure−elimination sequence, namely, direct cyclization of alcohol and subsequent dehydration (Scheme 2). While the use of *n*BuMgCl as base led to exclusive [1,2]-aryl migration and the formation of 2-butylbenzo[*b*]furan (**6a**), use of *n*BuLi led to formation of a mixture of 2- and 3-butylbenzo[*b*]furans (**6a** and **12a**) at both ambient temperature and 55 °C (Table 1). It appeared that the weakly nucleophilic magnesium alkoxide in **4** disfavored the direct cyclization of **4** to **12a** when compared to the [1,2]-aryl migration leading to **6a**. Similarly, when alcohol **7a** was mixed with 5 M aqueous NaOH solution at room temperature in MeOH, followed by addition of HCl in IPA, a mixture of **6a** and **12a** was obtained. A quick screen of bases showed that a mild aqueous base was key to the direct cyclization of alchol **7a** with little competition from the [1,2]-aryl migration. While no reaction occurred when pyridine was used in THF, a slow but selective direct cyclization to **12a** was observed with triethylamine in THF. Use of a saturated aqueous K_2CO_3 solution led to increased cyclization and decreased [1,2]-aryl migration. Finally, 2 M aqueous K_2CO_3 with nBu$_4$NHSO$_4$ was identified as the optimum conditions to achieve clean cyclization with little [1,2]-aryl migration. After dehydration under acidic conditions, 3-butylbenzo[*b*]-furan (**12a**) was isolated in 80% yield from **7a** (Scheme 5).

Table 1. Impact of Base and Counter Ion on the Direct Cyclization vs [1,2]-Aryl Migration of Alcohol **7a**[a]

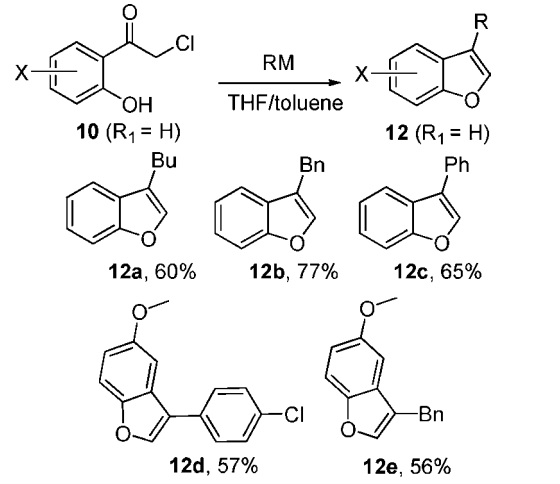


entry	base	solvent	**6a**[b]	**12a**[b]
1[c]	*n*BuMgCl, 2.0 M	THF	100	0
2[c]	*n*BuLi, 2.5 M	THF	52	48
3[c,e]	*n*BuLi, 2.5 M	THF	22	78
4[d]	NaOH, 5.0 M in water	MeOH	32	68
5[d]	pyridine	THF	0	0
6[d]	Et_3N	THF	9	91
7[d,f]	K_2CO_3, saturated in water	THF	7	93
8[d,f]	K_2CO_3, 2.0 M in water	THF	2	98

[a] Alchol **7a** (0.50 mmol) and base were mixed in 1.0 mL of solvent at room temperature for 12 h, and HCl/IPA was added (5 M, 1.0 mL) and heated at 70 °C for 10 min. [b] Regioisomeric ratio determined by HPLC. [c] Base, 2.0 mmol. [d] Base, 5.0 mmol. [e] Reaction was run at 55 °C for 1 h before addition of HCl. [f] Reaction was run with nBu$_4$NHSO$_4$ (0.1 mmol).

With the optimized conditions identified, several 3-substituted benzo[*b*]furans were successfully synthesized employing the three-step sequence.[7] Hence, treatment of ketones **10** with a variety of Grignard reagents at below −30 °C generated the crude alcohol intermediates, which cyclized upon treatment with 2 M aqueous K_2CO_3 and nBu$_4$NHSO$_4$. Finally, dehydration of the cyclized intermediate using 5 M HCl/IPA led to 3-substituted benzo[*b*]furans **12** (condition **B**). As shown in Scheme 6, 3-butylbenzo[*b*]furan (**12a**),

Scheme 6. Synthesis of 3-Substituted Benzo[*b*]furans from **10**[a,b]



[a] Condition **B**: A solution of ketone **10** (1.0 mmol) in 2.0 mL of THF/toluene (1:1 v/v) was mixed with the Grignard reagent (2.5 mmol) at −78 °C, slowly warmed to −30 °C over 30 min, quenched with cold MeOH, and warmed to room temperature, and 2 M aqueous HCl was added. The separated organic layer was stirred with 2.0 mL of 2 M aqueous K_2CO_3 and 0.10 mmol nBu$_4$NHSO$_4$ for 12 h; the aqueous layer was removed; and 1.0 mL of 5 M HCl/IPA was added and heated at 70 °C for 10 min. [b] All reactions were carried out without optimization. Yields refer to isolated material based on ketone **10**.

3-benzylbenzo[*b*]furan (**12b**), and 3-phenylbenzo[*b*]furan (**12c**) were isolated in 60%, 77%, and 65% yield, respectively. In addition, ketones with methoxy substitution on the phenyl ring also reacted to form the 3-substituted benzo[*b*]-furan **12d** and **12e** in good yields.

In summary, we have discovered and developed a versatile method for the regioselective synthesis of either 2- or 3-substituted benzo[*b*]furans from a single chloroketone starting material. The reaction proceeds via a unique [1,2]-aryl rearrangement followed by intramolecular condensation to form the 2-substituted benzo[*b*]furan under condition **A**. Under condition **B**, the reaction goes through the same alkoxide intermediate but directly cyclizes and dehydrates to form the corresponding 3-substituted benzo[*b*]furan. The method allows easy control of the introduction of substituents at the C-2 or C-3 position of the benzo[*b*]furan and tolerates various substitution patterns in the substrates. It provides rapid access to a variety of structurally useful benzo[*b*]furans and hence could serve as a versatile tool for the modular synthesis of benzo[*b*]furan-containing medicinal agents.

(7) 3-Substituted benzofurans can also be prepared from compound **3** via formation of 2,3-dihydro-1-benzofuran-3-one. For reaction of 2,3-dihydro-1-benzofuran-3-one with Grignard reagents, see: Stoermer, B. *Chem. Ber.* **1915**, *48*, 68**.**

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Supporting Information Available: Experimental procedure, spectroscopic and analytical data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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