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A divergent protocol for solid-phase synthesis of highly substituted Bi-aryl furan derivatives

Yongxin Han,* Amélie Roy and André Giroux

Department of Medicinal Chemistry, Merck Frosst Centre for Therapeutic Research, Merck Frosst Canada & Co., PO Box 1005, Pointe-Claire-Dorval, Québec H9R 4P8, Canada

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Abstract

A versatile protocol for the solid-phase synthesis of highly substituted furan derivatives is discussed. This approach employs zincate **1** as the scaffold followed by sequential palladium-catalyzed cross-coupling reactions as the C–C bond-formation step. This methodology allows convenient modification of the furan core in three dimensions, giving rise to structurally diverse derivatives with overall good chemical purity and yield. © 2000 Published by Elsevier Science Ltd.

Combinatorial synthesis of small organic molecules has evolved rapidly in the last few years to become a new paradigm for contemporary drug discovery[1] and in material science.[2] While the recent emergence of various new techniques (e.g. solution phase combinatorial synthesis,[3] resin capturing and resin scavenging,[4] ion-exchange for acid-base extraction,[5] fluorous phase extraction[6] and synthesis on soluble polymers[7]) further enhances the practicality of combinatorial synthesis, solid-phase chemistry continues to enjoy its dominant role partly due to the successful adaptation of many types of organic reactions onto solid supports.[8] Our interests in exploring mild and efficient solid-phase synthesis of heterocycles such as thiophene[9] and furan[10] derivatives have led to the development of a highly divergent protocol for the preparation of 1,5-diaryl furan analogs using zincate **1** and we herein disclose our preliminary findings.

The preparation of scaffold **1** and its use for solid-phase synthesis are illustrated in Scheme 1. 3-Furanmethanol tetrahydropyranyl (THP) ether, readily available from 3-furanmethanol, was treated with *n*-BuLi in ether and then with $ZnCl_2$ in THF to afford zincate **1**. As a model study, **1** was first reacted with methyl 4-iodobenzoate in the presence of tris(dibenzylideneacetone)-dipalladium(0) (Pd_2dba_3) and triphenylarsine ($AsPh_3$) in THF/ether at rt.[11] Two coupling products were obtained in a ratio of 19:1 (**2**:**3**) (by ^1H NMR) in 90% yield. Extensive NOE experiments established the structural assignments for both **2** and **3**.

* Corresponding author. Tel: (514)-428-3301; fax: (514)-428-4900; e-mail: yongxin_han@merck.com

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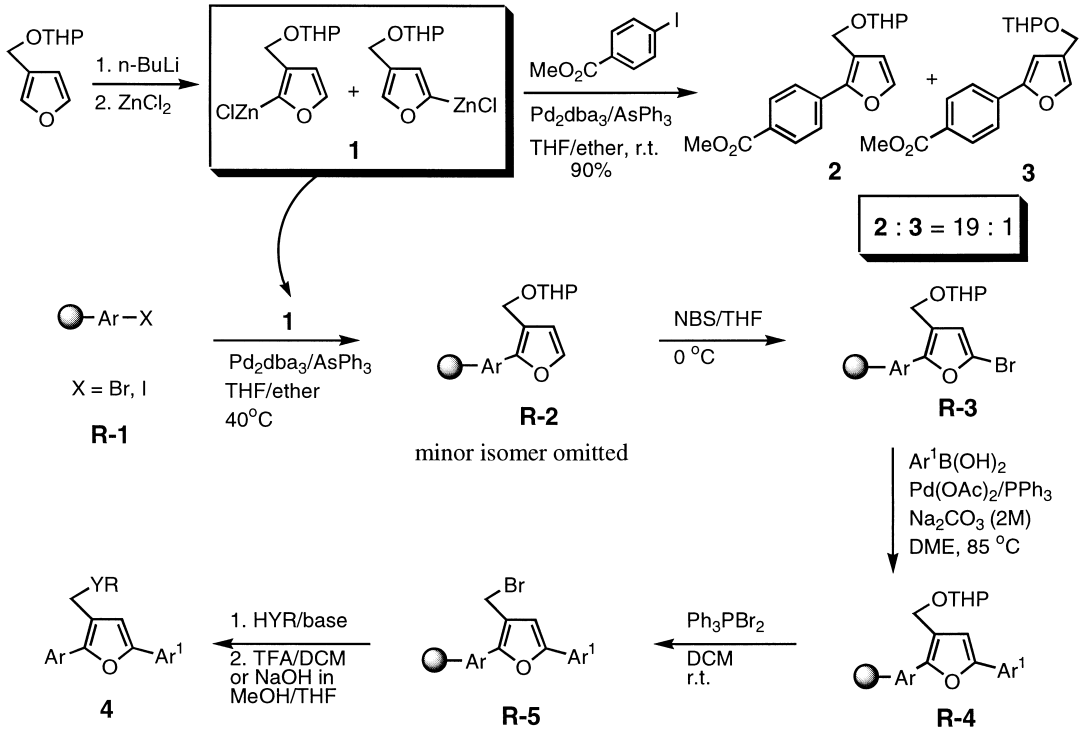
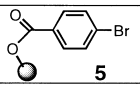
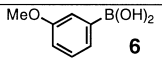
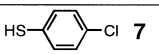
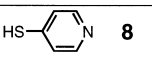
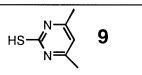
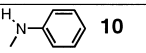
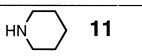
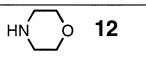
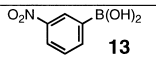
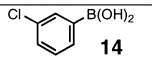
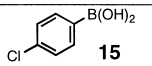
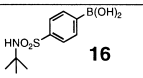
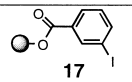
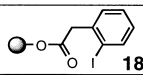
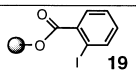


Scheme 1. General protocol for solid-phase synthesis of Bi-aryl furan analogs **4**

Having established the feasibility of the desired coupling reaction, we investigated the corresponding process on polymer supports. Thus, treating **1** with a polymer bound (Wang resin linked through a carboxylate) aryl bromide or iodide **R-1** in ether/THF at 40°C under aforementioned conditions gave resin intermediate **R-2**. Treating **R-2** with NaOMe in anhydrous THF/MeOH yielded products **2** and **3** (when **5** was used) in a ratio of 19:1, thus confirming that the coupling reaction on solid support was identical to that in solution. Reaction of **R-2** with N-bromosuccinimide (NBS) in anhydrous THF furnished resin **R-3** which was reacted with a boronic acid $Ar^1B(OH)_2$ under the standard palladium catalyzed Suzuki coupling reaction conditions (3 mol% $Pd(PPh_3)_4$ or $Pd(OAc)_2/PPh_3$, aqueous Na_2CO_3, DME, 85–90°C)[12] to afford resin **R-4**. Direct conversion of the CH_2OTHP moiety to the corresponding CH_2Br on solid support was readily achieved using the procedure described by Sonnet[13] (Ph_3PBr_2, CH_2Cl_2 at rt), giving resin **R-5**. The bromide thus obtained was first reacted with a thiol in the presence of diisopropylethylamine or with a secondary amine. The resultant resin was subjected to either a solution of 20% TFA in CH_2Cl_2 (containing 5% methyl sulfide) or aqueous NaOH in MeOH/THF at 70°C to furnish the desired product **4**. The results are summarized in Table 1.

As illustrated in Table 1, the yield and purity of this five-step solid-phase protocol provided desired products with good to excellent purity and yield. The variation in yields may be attributed to the handling of small amounts of material in the purification process. It can also be concluded that the protocol tolerates a variety of different polymer-bound aryl halides, boronic acids and nucleophiles. One exception was observed when polymer bound 2-iodobenzoate (**18**) was employed as the starting resin (entry 19). In this case, no desired product was obtained. A closer examination revealed that the solid-phase sequence terminated at resin **R-2** probably as a result

Table 1
Synthesis of diaryl furan **4** using various resins, boronic acids and nucleophiles

	Resins	Boronic acids	Nucleophiles	Product **4**		
Entry	**R-1**	$Ar^1B(OH)_2$	HYR	m/z (-APCI)	Purity (%)[a]	Yield (%)[b]
1	 **5**	 **6**	 **7**	449.3	54	63
2	**5**	**6**	 **8**	416.3	72	66
3	**5**	**6**	 **9**	445.5	40	74
4	**5**	**6**	 **10**	412.3	62	60
5	**5**	**6**	 **11**	390.4	58	58
6	**5**	**6**	 **12**	392.5	77	60
7	**5**	 **13**	**9**	460.6	92	—
8	**5**	**13**	**12**	407.5	94	64
9	**5**	 **14**	**9**	449.2	91	54
10	**5**	**14**	**12**	396.0	75	71
11	**5**	 **15**	**9**	449.2	93	62
12	**5**	**15**	**12**	396.0	86	65
13	**5**	 **16**	**9**	550.5	72	59
14	**5**	**16**	**12**	497.3	89	60
15	 **17**	**15**	**9**	449.3	68	57
16	**17**	**15**	**12**	396.1	90	42
17[c]	 **18**	**15**	**9**	463.4	67	60
18[c]	**18**	**15**	**12**	410.4	93	55
19	 **19**	--	--	--	--	--

[a]Purity was determined by integrating the TIC trace of the LC-MS spectrum and the minor isomer co-eluted with the major isomer
[b]The crude cleavage mixture was first treated with CH_2N_2 and yield was based on the isolated methyl esters (both major and minor isomers) according to initial resin loading. [c]Cleaved with 1 N NaOH in THF/MeOH at 70°C.

of steric hindrance. It is worth noting that the use of boronic acids bearing an electron withdrawing group (entries 7–14) generally gave products with superior purity under acidic cleavage conditions. This is due to the fact that the more electron-rich furan analogs decomposed slowly when subjected to the TFA cleavage conditions. This was further illustrated when Wang resin bound 2-iodophenylacetate (**17**) was employed as the starting resin (entries 17–18). In these cases, cleavage under basic conditions was necessary to avoid extensive decomposition.

A typical solid-phase protocol for making product **4** (Entry 1, Table 1) is illustrated. To a solution of 3-furanmethanol tetrahydropyranyl ether (2.68 g, 14.9 mmol) in ether (8 mL) at 0°C was added *n*-BuLi (7.35 mL, 2 M in hexanes) dropwise over 5 min. After stirring at rt for 30 min, the mixture was cooled to 0°C and $ZnCl_2$ (1M in THF, 14.7 mL, 14.69 mmol) was added. The resultant mixture was allowed to warm to rt for 10 min. The zincate solution thus generated was cannulated to a receiving flask containing resin **5** (5.05 g, 0.97 mmol/g) suspended in 15 mL of anhydrous THF under N_2. To this mixture was added a suspension (mixed using ultrasonic bath) of Pd_2dba_3 (201 mg, 0.219 mmol) and $AsPh_3$ (269 mg, 0.88 mmol) in THF (3 mL). The mixture was shaken on an orbital shaker at 37°C overnight under N_2 and then filtered. The residual resin was washed thoroughly and dried under high vacuum to give resin **R-2**. To a suspension of the dried resin **R-2** (5.21 g, 0.88 mmol/g) in 50 mL of THF cooled to 0°C was added *N*-bromosuccinimide (2.14 g, 12.03 mmol) and the suspension was gently stirred at 0°C for 1 h and filtered. The resin was washed sequentially with THF, H_2O/THF (1:1 v), H_2O, THF, CH_2Cl_2 and MeOH, and then dried under high vacuum to yield resin **R-3**. A suspension of resin **R-3** (3.0 g, 0.826 mmol/g) and 3-methoxyphenylboronic acid (1.18 g, 7.74 mmol) in DME (30 mL) was flushed with a stream of N_2 for 5 min and to the suspension was added aqueous Na_2CO_3 (3.23 mL, 2 M), H_2O (3.23 mL), PPh_3 (169 mg, 0.645 mmol) and $Pd(OAc)_2$ (29 mg, 0.129 mmol). The mixture was heated to reflux for 6 h and filtered when hot. The residual resin (**R-4**) was washed sequentially with DMF, DMF/H_2O, H_2O, DMF, CH_2Cl_2 and MeOH. After drying under high vacuum, a portion of **R-4** (1 g, 0.81 mmol/g) was reacted with PPh_3Br_2 (1.06 g, 2.52 mmol) in CH_2Cl_2 (10 mL) for 90 min. The mixture was filtered, and the resin was washed with CH_2Cl_2, EtOAc and Et_2O, and then dried under vacuum to furnish resin **R-5**. A portion of **R-5** (100 mg, 0.82 mmol) in DMF (1 mL) was treated with a solution of *p*-chlorothiophenol (0.43 mL, 1 M in DMF) in the presence of *N*-diisopropylethylamine (74 μL, 0.43 mmol) for 1 h. The mixture was filtered and the residual resin was washed thoroughly and dried. This resin was finally treated with a solution of 20% (v) TFA in CH_2Cl_2 (1 mL) containing 5% methyl sulfide for 20 min and filtered. The filtrate was collected and concentrated to give 29 mg of crude product **4** (Ar = 4-carboxyphenyl, Ar^1 = 3-methoxyphenyl, Y = S, R = 4-chlorophenyl) which was treated with excess diazomethane. The corresponding methyl ester was purified by column chromatography to yield 24 mg of the final product (63% overall based on original resin loading).[14]

In summary, we have developed a general and efficient solid-phase protocol for the construction of highly substituted furan derivatives. The commercial availability of aryl halides, boronic acids and nucleophiles thus will allow for the construction of a vast array of structurally diverse furan derivatives.

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14. ^{1}H NMR (300 MHz, acetone-d_6) δ 8.11 (1H, s), 8.08 (2H, d, $J=8$ Hz), 7.90 (2H, d, $J=8$ Hz), 7.43–7.29 (7H, m), 7.03 (1H, s), 4.39 (2H, s), 3.90 (3H, s), 3.86 (3H, s). ^{13}C NMR (75 MHz, acetone-d_6) δ 166.8, 161.1, 154.0, 149.1, 135.6, 135.4, 133.0, 132.5, 132.1, 130.9, 130.7, 130.3, 129.8, 129.7, 126.4, 122.5, 117.2, 114.7, 111.2, 110.1, 55.6, 52.4.