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Directed metalation and regioselective functionalization of 3-bromofuran and related heterocycles with NaHMDS

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ABSTRACT

A mild and regioselective functionalization protocol for 3-bromofuran and analogs has been developed. Selective metalation and functionalization of C2 can be achieved as a result of the directing effect of the adjacent electron-withdrawing bromo group. In addition, the C5 position can also be selectively functionalized by blocking the C2 position via silylation or by simply controlling the reaction temperature. These functionalized compounds bearing a C3 bromo substituent may be further elaborated by utilizing a Suzuki–Miyaura cross-coupling procedure.

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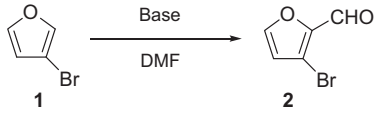
Heterocycles, such as furans, thiophenes, benzofurans and benzothiophenes are important constituents of molecules of interest in the pharmaceutical,[1] agricultural,[2] and electronics industry.[3] As a result, controlled manipulation of these heterocycles has attracted considerable interest within the synthetic community. One of the most useful strategies for the functionalization of these important heterocycles employs directed metalation protocol using bases such as *n*-BuLi or LDA.[4] In addition; Knochel has recently reported conditions using microwave irradiation for the metalation of 3-bromobenzofuran and 3-bromobenzothiophene with $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ or TMPZnCl·LiCl, respectively, as an effective method toward C2 functionalization of these heterocyles.[5]

Interest in the C2-formylation of 3-bromofuran is of synthetic value because the resulting aldehyde holds promise for further elaboration and incorporation into more complex molecular targets. The best known literature method for the formylation of 3-bromofuran with LDA gave 3-bromofurfuraldehyde in moderate yield.[6] This protocol was deemed less useful in a scale-up scenario due to the application of a strong base and the poor impurity profile of the isolated product.

In order to develop a more practical method, a study was initiated to evaluate milder bases for the metalation (LiHMDS, NaHMDS and KHMDS, Table 1) with the hope of finding a scalable procedure with a cleaner reaction profile. As a control experiment, the metalation with LDA, followed by treatment of DMF, resulted in partial conversion including the formation of several unidentified impurities at −20 or 0 °C. Reaction with LiHMDS proceeded to 65% conversion at rt, however only a 48% yield of the aldehyde **2** was obtained after purification (entry 3). This particular base was studied in other solvents, such as *n*-hexane, MTBE, and toluene (en-

Table 1
Reaction optimization for the formylation of 3-bromofuran with DMF[a]



1 2

Entry	Base	Solvent	T (°C)	Conversion (%)
1	LDA	THF	−20–0	50
2	LDA	THF	0	25
3	LiHMDS	THF	0 to rt	65 (48[b])
4	LiHMDS	*n*-Hexane	0 to rt	<10
5	LiHMDS	MTBE	0 to rt	<10
6	LiHMDS	Toluene	0 to rt	<10
7	NaHMDS	THF	0 to rt	>95[c]
8	NaHMDS	2-Me-THF	0 to rt	>95[c]
9	NaHMDS	THF	0	>95 (84)[b,e]
10	NaHMDS	2-Me-THF	0	>95 (85)[b,e]
11	KHMDS	THF	0 to rt	>95[d]
12	KHMDS	2-Me-THF	0 to rt	>95[d]

[a] 3 mmol **1**, 1.2 equiv base and 1.2 equiv DMF were used.
[b] Isolated yield.
[c] With ~20% impurities from LC/MS.
[d] With ~40% impurities from LC/MS.
[e] Order of addition does not affect the outcome (yield and purity) in this case.

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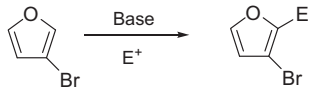
Table 2
Deprotonation of 3-bromofuran under either kinetic or thermodynamic conditions[a]



1 — 4 E=D, 5 E=TMS

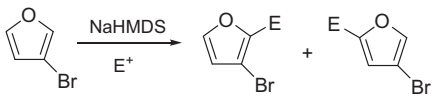
Entry	Base	T °C	Time (min)	Pdt	Pdt/s.m.[b]
1	LDA	−78	10	**4**	1/0
			30		1/0
			60		1/0
			180		1/0
2	NaHMDS	0	30	**4**	<1/10
			60		<1/10
3	NaHMDS	0	30	**5**	1/1
			60		1/1
			180		1/1

[a] Reaction was conducted on 3 mmol substrate with 1.2 equiv base, then quenched with 5.0 equiv electrophile (D_2O or TMSCl). After 1 h, the reaction was quenched with 3 mL NH_4Cl (sat.) aqueous solution and 3 mL water.
[b] The ratio of product and starting material in the crude organic layer was determined by ^1H NMR spectroscopy.

tries 4–6). This solvent study indicated THF as the best medium. When NaHMDS was explored in both THF and 2-Me-THF, the best results were generated at 0 °C. Remarkably, with this variant both the conversion (>95%) and isolated yield (84%) were far superior to other bases. Although 2-Me-THF was a preferred solvent in terms of work-up and ease of scale-up, THF was selected for this study because of the commercial availability of NaHMDS in THF solution and the sufficiently high yields obtained under these conditions. The formylation of 3-bromofuran with NaHMDS and DMF in THF was optimized with this system and these conditions were adopted as our standard metalation protocol for the functionalization of 3-bromofuran and related analogs.

Interestingly, the reaction of 3-bromofuran and NaHMDS with a compatible electrophile provided a reaction mixture with nearly 100% conversion and correspondingly high yields (Table 1, entries 9 and 10). However, under similar metalation conditions, when a more reactive electrophile was used for trapping, incomplete conversion was observed (Table 2, entries 2 and 3). These results could be rationalized by considering an equilibrium between **1** and metalated species. Thus, quenching this mixture with a reactive electrophile such as D_2O resulted in less than 10% conversion whereas in the case of a less reactive electrophile such as DMF the complete conversion was achieved. Quenching the anion with TMSCl allowed only 50% conversion to be attained due to competitive silylation with the base. In contrast, with a stronger base such as LDA, complete metalation occurred with quantitative formation of the deuterated product **4**.

Table 3
Functionalization of 3-bromofuran



1 — a — b

Entry	Electrophile	E	T °C	Yield	a/b
1	DMF	CHO	0	**2** (84%)	1/0
2	PhCON(OMe)Me	PhCO	0	**6** (83%)	1/0
3	Ph_2CO	Ph_2COH	0	**7** (84%)	1/0
4	*t*-BuCOPh	*t*-BuC(OH)Ph	0	**8** (88%)	1/0
5[a]	*t*-Bu_2CO	*t*-Bu_2COH	rt	**9** (67%)	3/1

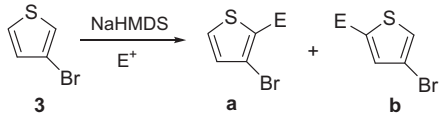
[a] An 87% yield based on reacted starting material. The reaction was carried out at rt for 15 h.

All previously reported functionalization reactions of 3-bromofuran, including the aforementioned formylation, utilized direct metalation approaches with LDA or *n*-BuLi.[6,7] Evaluation of the scope of our methodology on 3-bromofuran with various electrophiles was undertaken (Table 3). To our delight, the reaction at 0 °C proceeded smoothly with most electrophiles to give only the corresponding C2 substituted products (**2a**, **6a**, **7a**, and **8a**) in good to excellent yield with none of the C5 isomer detected. Interestingly, two regioisomeric products (**9a** and **9b**) were obtained when a very sterically hindered ketone was used as the electrophile (entry 5). The electron-withdrawing bromo substituent greatly enhances the acidity at C2, which leads to preferential reaction at this site.[8] For most electrophiles, increasing the steric bulk did not affect the reaction rate and only formed the desired C2 functionalized product. However, with the extremely hindered electrophile *t*-Bu_2CO, the reaction was much slower even at ambient temperature and two regioisomeric products (**9a** and **9b**) were produced as a 3:1 mixture.

Next we extended the protocol to 3-bromothiophene (Table 4). Traditionally, functionalization of 3-bromothiophene is straightforward and gives products in higher yield. However, in most cases LDA and lower temperatures were generally the most utilized conditions.[9] Employing the NaHMDS-mediated functionalization of 3-bromothiophene at 0 °C, afforded products **10, 11**, **12**, and **13** with excellent yields. Also, with this substrate, reaction at C5 was also observed and appears to correlate with the steric nature of the electrophile. In the ketone series, from Ph_2CO to *t*-Bu_2CO, the product distribution indicated that the bulkier electrophile preferred to react at the less hindered C5 position. Thus, in the reaction with *t*-Bu_2CO as electrophile, only C5 substituted product **14b** was obtained after 15 h at rt.

Investigations into the effect of reaction temperature on the product regioselectivity were carried out for 3-bromothiophene **3** with DMF and *t*-BuCOPh (Table 4, entries 1–3 and 6–8). A significant temperature effect was observed which manifested itself with increased C5 substitution with increasing temperature. In both cases, the C2 substituted product predominated at −20 °C, with the ratios of **10a:10b** and **13a:13b** at 34:1 and 10:1, respectively. Surprisingly, when the reaction was carried out at rt the product distribution reversed itself, and the major product was the C5 functionalized product. Notably, these results indicated that the regioselectivity could be controlled simply by altering the reaction temperature. We decided to probe the reversibility of the reaction. To this end, the isolated C2 substituted product **13a** was treated with NaHMDS in THF at rt. Under thermodynamic conditions, **13a** was completely converted to the C5 isomer **13b**. However, when **13b** was treated with NaHMDS in THF at rt, then cooled to

Table 4
Functionalization of 3-bromothiophene

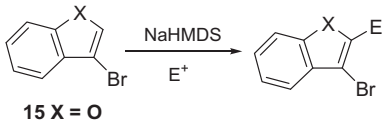


3 — a — b

Entry	Electrophile	E	T °C	Yield	a/b
1	DMF	CHO	−20	**10** (88%)	34/1
2	DMF	CHO	0	**10** (77%)	12/1
3	DMF	CHO	rt	**10** (64%)	1/5
4	PhCON(OMe)Me	PhCO	0	**11** (94%)	3/1
5	Ph_2CO	Ph2COH	0	**12** (93%)	7/1
6	*t*-BuCOPh	*t*-BuC(OH)Ph	−20	**13** (96%)	10/1
7	*t*-BuCOPh	*t*-BuC(OH)Ph	0	**13** (92%)	4/1
8	*t*-BuCOPh	*t*-BuC(OH)Ph	rt	**13** (95%)	0/1
9[a]	*t*-Bu_2CO	*t*-Bu_2COH	rt	**14** (69%)	0/1

[a] a 90% yield based on reacted starting material. The reaction was carried out at rt for 15 h.

Table 5
Functionalization of 3-bromobenzofuran and 3-bromobenzothiophene

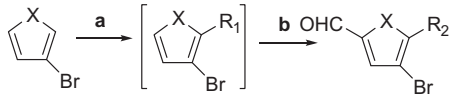


15 X = O
16 X = S

Entry	S.m.	Electrophiles	E	Yield
1	**15**	DMF	CHO	**17** (61%)
2	**15**	PhCON(OMe)Me	PhCO	**18** (86%)
3	**15**	Ph_2CO	Ph_2COH	**19** (60%)
4	**15**	*t*-BuCOPh	*t*-BuC(OH)Ph	**20** (78%)
5[a]	**15**	*t*-Bu_2CO	*t*-Bu_2COH	**21** (59%)
6[b]	**16**	DMF	CHO	**22** (88%)
7	**16**	PhCON(OMe)Me	PhCO	**23** (81%)
8	**16**	Ph_2CO	Ph_2COH	**24** (92%)
9	**16**	*t*-BuCOPh	*t*-BuC(OH)Ph	**25** (75%)

[a] a 76% yield based on reacted starting material.
[b] LiHMDS was used instead of NaHMDS.

Table 6
Selective formylation on five-position of 3-bromofuran and 3-bromothiophene



1 X = O
3 X = S

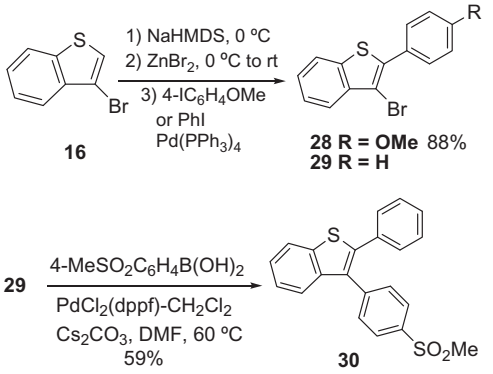
Entry	S.m.	NaHMDS	Electrophiles	R_2	Yield(%)
1[b]	**3**	a) 1.1 equiv b) 1.5 equiv	a) 1.2 equiv TESCl b) 1.4 equiv DMF	TES **26**	75
2[b]	**3**	a) 1.1 equiv b) 1.5 equiv	a) 1.2 equiv TMSCl b) 1.4 equiv DMF	H **10b**	50
3[a]	**1**	a) 3.2 equiv b) 0.7 equiv	a) 1.5 equiv TIPSCl b) 3.0 equiv DMF	TIPS **27**	67

[a] Silylation conducted at rt for 23 h, then warmed to 40 °C after charging with DMF.
[b] Silylation at 0 °C for 2 h and formylation at 0 °C for 1 h.

0 °C and stirred at this temperature for 6 h, no trace of **13a** was observed.

Application of the standard metalation conditions to 3-bromobenzofuran[10] and 3-bromobenzothiophene[11] is illustrated in Table 5. Here, where there was only one position for deprotonation and functionalization, the reactions provided good to excellent yields for most cases. The only incomplete reaction was observed with *t*-Bu_2CO, resulting in a 59% yield of alcohol **21** (Table 5, entry 5).

In addition to the results shown in Tables 3 and 4, we were interested in developing a more general regioselective functionalization method for C5. Taking advantage of the pK_a differential between C2 and C5, we chose to employ a strategy in which the C2 position was initially blocked with a silyl group, followed by further functionalization of the C5 position with an electrophile of choice.[9(h), 12] The results of the one-pot procedure were shown in Table 6. The corresponding aldehydes **26** and **10b** were obtained in good yield (entries 1 and 2). In the case of **10b**, unsilylated product was isolated due to liability of the TMS protecting group during acidic work-up. For 3-bromofuran, where the pK_a of the C5 C–H bond is closer to that of the base, the metalation–formylation procedure had to be carried out at an elevated temperature (40 °C) for 24 h to drive the reaction to completion. As a result, TIPSCl was used to protect the C2 position due to the partial reactivity of TMSCl and TESCl with NaHMDS. Application of these conditions resulted in a 67% yield of **27**.



Scheme 1. Application of the metalation-cross-coupling protocol toward the synthesis of bisfunctionalized heterocycles.

One of the features that made this advanced metalation protocol so appealing is that the C3 bromo substituent remains a potential site for further functionalization. In order to broaden the synthetic potential of our current metalation reaction, we decided to explore a Negishi/Suzuki–Miyaura double cross-coupling strategy (see Scheme 1) to prepare the corresponding diarylated heterocycle **30**.[13] Under this scenario, the organosodium species originally formed from metalation of the bromoheterocycle would be converted to the corresponding zinc halide intermediate for use in a palladium-catalyzed cross-coupling prior to a second coupling at the remaining aryl halide site. This strategy requires selectivity of the more reactive iodoarene coupling partner over the C3 bromo substituent on the parent heterocycle.

In an initial experiment, 3-bromobenzothiophene was metalated at C2 via the standard conditions with NaHMDS and subsequently converted to the corresponding organozinc species by treatment with $ZnBr_2$. Gratifyingly, the Negishi cross-coupling was achieved by the reaction of 4-iodoanisole or iodobenzene in the presence of 5 mol % $Pd(PPh_3)_4$ to afford **28** and **29**, respectively, in high yield. A second cross-coupling with **29** utilizing the Suzuki–Miyaura protocol was performed with the boronic acid coupling partner providing the diarylbenzothiophene **30** in a 59% yield.[14] Thus, the weaving of our metalation procedure into a two-step protocol utilizing a sequential Negishi/Suzuki–Miyaura cross-coupling protocol resulted in a concise and efficient synthesis of **30**, further demonstrating the utility of our methodology.

In conclusion, we have demonstrated an efficient and mild method for regioselective functionalization of 3-bromofuran and analogs using NaHMDS as a base at mild temperatures. This method accommodates a variety of synthetically useful electrophiles and is more amenable to scale-up than existing procedures using LDA or *n*-BuLi. Furthermore, this protocol illustrated its practical benefits in an extended application to molecular targets.

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Supplementary data

Supplementary data (experimental and spectroscopic data) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.10.158.

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