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Synthesis of Substituted Dihydrobenzofurans via Tandem S_NAr/5-*Exo-Trig* Cyclization

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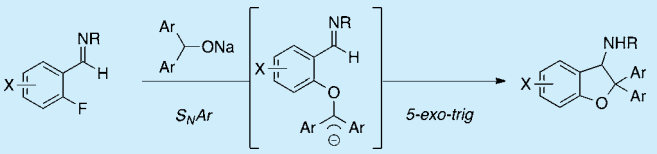
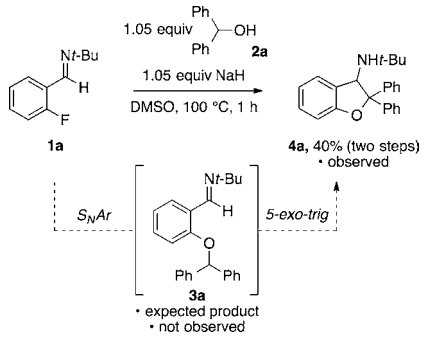
Supporting Information

ABSTRACT: A tandem S_NAr/5-*exo-trig* cyclization reaction is reported that converts *N*-alkyl- and -arylimines derived from *o*-fluorobenzaldehydes into 3-amino-2,3-dihydro-2,2-diarylbenzofurans in moderate to good yields. Diarylmethoxide coupling partners serve the dual role of nucleophile in the S_NAr step and catalytic base in the cyclization step. With a subset of the substrates, a further base-induced elimination of the 3-amino-2,3-dihydro-2,2-diarylbenzofuran to a phenolic enamine was observed.



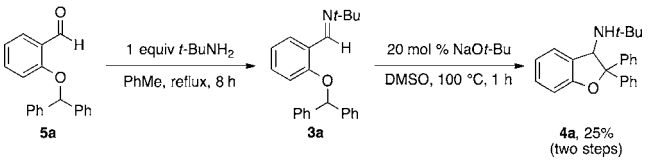
Substituted dihydrobenzofurans are prized building blocks in medical chemistry.[1] As such, a variety of strategies have been devised for their synthesis.[2] During the course of an otherwise unrelated study,[3] it was found that treatment of *N*-*tert*-butylimine **1a** with sodium diphenylmethoxide (Na-**2a**) led to an unexpected outcome. Rather than the anticipated S_NAr product **3a**, the only product that could be isolated was dihydrobenzofuran **4a** (Scheme 1). Although the identity of **4a** was initially unclear, the connectivity was eventually confirmed by analogy to X-ray crystal structures of two products in this family (vide infra).

Scheme 1. Unexpected Formation of 4a



Given the synthetic difficulty in accessing this 2,2-diaryl-3-amino substitution pattern, we sought to elucidate the mechanism and determine whether it could provide general and practical access to this class of 2,3-dihydrobenzofurans. Regarding the mechanism, specific points of interest were (1) the possible intermediacy of the expected S_NAr product **3a** and (2) the mode of cyclization. First, **3a** was independently prepared by an alternative route (Scheme 2). *O*-Alkylation of salicylaldehyde provided **5a**, and subsequent condensation with *tert*-butylamine led to imine **3a**, which was used without

Scheme 2. Independent Synthesis of 3a and Subsequent Base-Mediated 5-*Exo-Trig* Cyclization



further purification. Treatment of crude **3a** with NaO-*t*-Bu in DMSO, at 100 °C, for 1 h, gave **4a** in 25% yield over the two steps. In addition to demonstrating that **3a** is a competent intermediate, this result establishes that cyclization is base-mediated and that alkoxides are sufficiently basic for deprotonating the methine proton.[4]

This leads us to suggest a mechanistic manifold in which following the expected S_NAr reaction a subsequent deprotonation of the methine proton of the diphenylmethoxy group takes place under the basic reaction conditions.[4] The resulting carbanion then attacks the imine carbon atom in a 5-*exo-trig* fashion. Protonation of the nitrogen anion would then give the final product. To further assess the feasibility of this proposed cascade sequence, the reaction in Scheme 1 was repeated at reduced temperature (20−22 °C) under otherwise identical conditions, and reaction progress was monitored over time (Figure 1). In the early stages of reaction (10 min), S_NAr intermediate **3a** was observed. After 1 h, both **3a** and the cyclized product **4a** were detected. The amount of **1a** steadily decreased, and in the 2−4 h range, **3a** appeared to reach a steady-state concentration. In the later stages of the reaction (12 h) both **1a** and **3a** were consumed, and **4a** was the predominant species in solution. These results clearly

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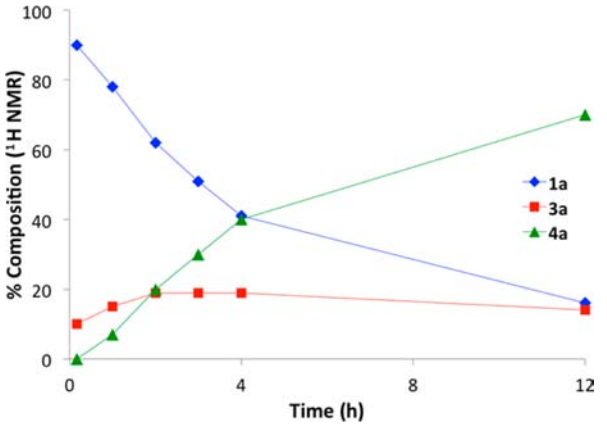


Figure 1. Reaction progress over time. The reaction was performed at room temperature (20−22 °C); conditions were otherwise identical to those in Scheme 1. The percent composition was determined by ^{1}H NMR of the crude reaction mixture.

illustrate that **3a** is a kinetically competent intermediate to provide **4a** under basic conditions.

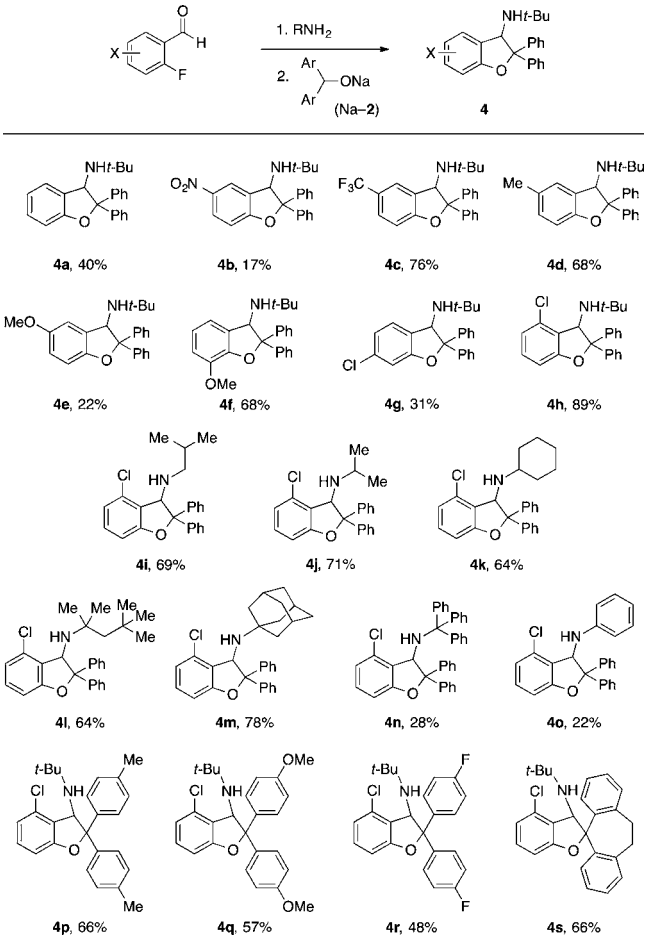
Given the potential utility of this cascade sequence, the scope of the reaction was next evaluated (Scheme 3). First, using a *tert*-butyl group on nitrogen and diphenylmethoxide as the nucleophile, a collection of *o*-fluorobenzaldehyde-derived imine electrophiles were examined (**4a**−**h**). While many different functional groups were tolerated in the transformation, yields ranged from 17% in the case of **4b** to 89% in the case of **4h**.

There was no clear relationship between the electron-donating or -withdrawing character of the aromatic substituent and the final yield. Given that S_NAr reactions are typically accelerated by electron-withdrawing groups, as was indeed the case in our earlier study,[3a] we attribute the low yields with **4b** and **4g** to unidentified decomposition pathways. In the case of **4e**, where the starting material contained a methoxy group *para* to fluoride, diphenylmethyl methyl ether was isolated as a byproduct, suggesting that an S_N2 reaction on the methoxy group contributed to undesired consumption of the starting materials. With a more hindered methoxy group in the case of **4f**, there was no evidence for this pathway being operative.

Next, various *N*-alkyl and -aryl groups were tested on the imine electrophile by varying the amine coupling partner (**4i**−**o**). 2-Chloro-6-fluorobenzaldehyde was used as the electrophile since it is relatively inexpensive and typically gave clean reactions. It was found that imines derived from primary (**4i**), secondary (**4j** and **4k**), and tertiary (**4h** and **4l**−**n**) amines all provided moderate to high yields. The reaction also proceeded with an *N*-phenyl group (**4o**), albeit in lower yield. Notably, the *N*-trityl group in **4n** is a common amine protecting group, which offers the possibility for further synthetic elaborations. *N*-Tosyl,[5] -Boc,[6] -allyl, and -*p*-methoxyphenyl groups were ineffective.

Lastly, the scope of nucleophiles was examined using the *N*-*tert*-butylimine derived from 2-chloro-6-fluorobenzaldehyde (**4p**−**s**). Four diarylmethanols were tested, and all participated in the reaction and provided moderate to good yields of the desired products. Electron-donating substituents on the aryl rings appear to have an adverse effect on the yield, possibly by increasing the pK_a of the methine proton and thus suppressing deprotonation. By intramolecularly tethering the two aromatic rings, spirocycle-containing compound **4s** could

Scheme 3. Substrate Scope[a,b]



[a]General procedure. Step 1: *o*-fluorobenzaldehyde (10.0 mmol), amine (1.00 equiv), toluene, reflux (140−150 °C, Dean−Stark apparatus), 8 h. Step 2: crude product from step 1 (assumed to be 10.0 mmol), NaH (1.05−1.50 equiv), diarylmethanol (1.05 equiv), DMSO, 100 °C, 1 h. See the Supporting Information for further details. [b]Isolated yield over two steps.

be accessed. Penta-1,4-dien-3-ol, the divinyl analogue of diphenylmethanol, was unreactive in the S_NAr step for reasons that remain unclear.[3a] Benzyl alcohol, on the other hand, was reactive as a nucleophile in the S_NAr step, but attempts to induce the subsequent cyclization were unsuccessful.

In some cases, the entire S_NAr/cyclization sequence required only 1.05 equiv of sodium diarylmethoxide (**2**), consistent with excess **2** (or another anionic species) serving as a catalytic Brønsted base in the cyclization step. In many cases, however, an additional portion of NaH was required to fully convert the S_NAr intermediate (e.g., **3a**), which could often be observed by ^{1}H NMR, into the final 3-amino-2,3-dihydro-2,2-diarylbenzofuran product. The connectivity of products **4h** and **4n** was confirmed by X-ray crystallography (Figure 2).

With two subclasses of starting materials, (1) imine substrates containing a halogen atom *ortho* or *para* to the fluoride leaving group and (2) pyridyl-substituted imines, a phenolic enamine byproduct was observed (Table 1). Single-crystal X-ray crystallography of one representative byproduct, **6u**, confirmed the structure of this class of byproducts (Figure

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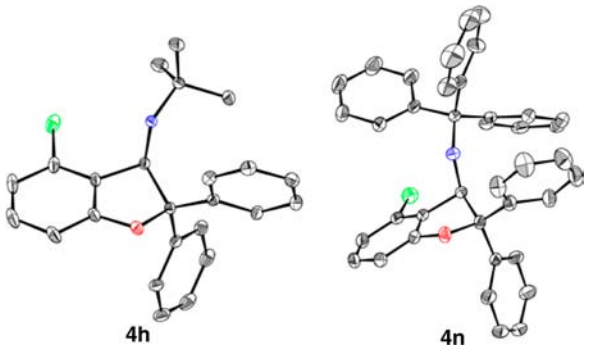
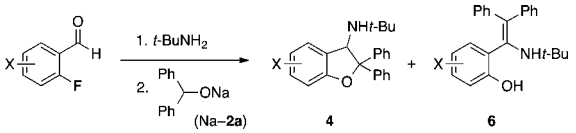
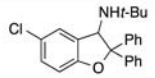
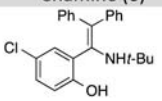
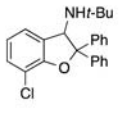
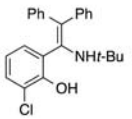
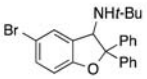
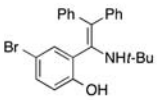
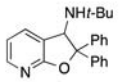
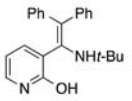
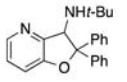
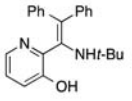


Figure 2. X-ray crystal structures of **4h** and **4n**. 50% probability ellipsoids. Hydrogen atoms omitted for clarity. CCDC 1058167 (**4h**) and 1058169 (**4n**).[7]

Table 1. Substrates That Formed Phenolic Enamine Byproduct[a]



entry	dihydrobenzofuran (**4**)	phenolic enamine (**6**)	combined yield (%)	ratio (**4**:**6**)
1[b]	 **4t**	 **6t**	74	1.3:1
2[b]	 **4u**	 **6u**	74	1.7:1
3[b]	 **4v**	 **6v**	87	6.3:1
4[c]	 **4w**	 **6w**	17	4.7:1
5[c]	 **4x**	 **6x**	55	0.7:1

[a]The general procedure is the same as in Scheme 3. See the Supporting Information for further details. [b]The two compounds, **4** and **6**, were isolated as a mixture after two steps following purification by silica gel column chromatography. The combined yield was calculated from the mass of the mixture. The product ratio was determined by ^{1}H NMR analysis, and analytically pure samples of each compound for characterization were obtained by PTLC. [c]The two compounds, **4** and **6**, were isolated by column chromatography. The combined yield is the sum of the two individual yields, and the ratio was determined by dividing the isolated masses.

3). Byproduct formation was found to be promoted by additional base and extended reaction times, consistent with a base-mediated elimination of the 2,3-dihydrobenzofuran

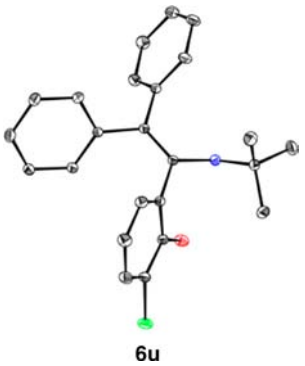
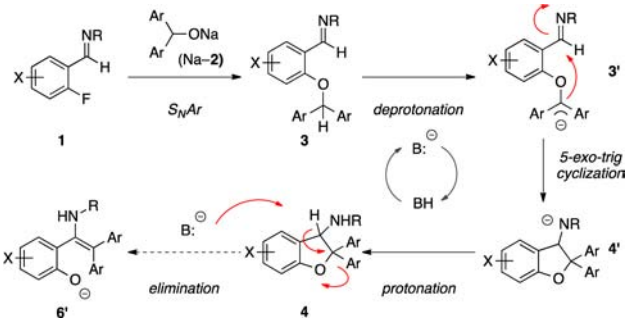


Figure 3. X-ray crystal structure of **6u**. 50% probability ellipsoids. Hydrogen atoms omitted for clarity. CCDC 1058168 (**6u**).[7]

product. The amount of byproduct was highest in the cases of chloride-containing compounds (entries 1 and 2). The fact that the phenolic enamine byproduct was not observed with more strongly electron-withdrawing groups (**4b** and **4c**) or other chloride-containing isomers (**4g** and **4h**) suggests that the electronic properties of the aromatic ring are crucial for the favorability of this pathway and/or the stability of the resulting byproducts.

A mechanistic proposal for the S_NAr/5-*exo-trig* cyclization reaction and subsequent elimination is shown in Scheme 4. As

Scheme 4. Proposed Reaction Mechanism for Tandem S_NAr/5-*Exo-Trig* Cyclization and Subsequent Elimination



alluded to above, in the first step, an S_NAr reaction between sodium diarylmethoxide (Na-**2**) and the *o*-fluorobenzaldehyde imine starting material **1** leads to intermediate **3**. Next, deprotonation of the methine proton with a Brønsted base generated in situ provides stabilized anion **3′**. This intermediate undergoes 5-*exo-trig* cyclization to provide **4′**, which is protonated to form **4**. With some products, a base-mediated formal elimination then converts **4** to **6′**.

In conclusion, a tandem S_NAr/5-*exo-trig* cyclization reaction is described, which provides an expedient route to 3-amino-2,3-dihydro-2,2-diarylbenzofurans from *o*-fluorobenzaldehyde imine and diarylmethanol starting materials. The reaction was found to tolerate a variety of functional groups on the aryl rings of the *o*-fluorobenzaldehyde imine electrophile and diarylmethanol nucleophile. Primary, secondary, and tertiary *N*-alkyl substituents on the imine were all compatible, as was an *N*-phenyl group. In several cases, a further base-mediated elimination of the dihydrobenzofuran products yielded phenolic enamine byproducts.

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■ ASSOCIATED CONTENT

Supporting Information

Experimental details, NMR spectra of new compounds, and X-ray data for compounds **4h**, **4n**, and **6u** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(7) CCDC 1058167 (**4h**), 1058169 (**4n**), and 1058168 (**6u**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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