Synlett T. E. Hurst et al. Letter

Metal-Free Synthesis of Dibenzoxazepinones via a One-Pot S_NAr and Smiles Rearrangement Process: Orthogonality with Copper-Catalyzed Cyclizations

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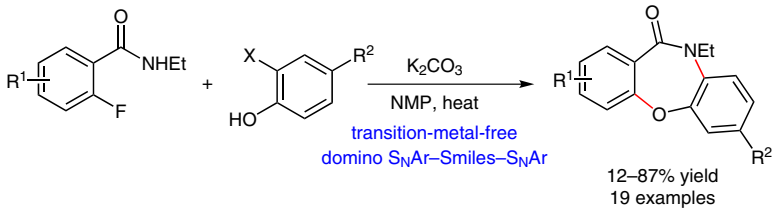

To Peter, with fond and vivid remembrance of the birth of *Synlett* and in praise of how far you have taken it.

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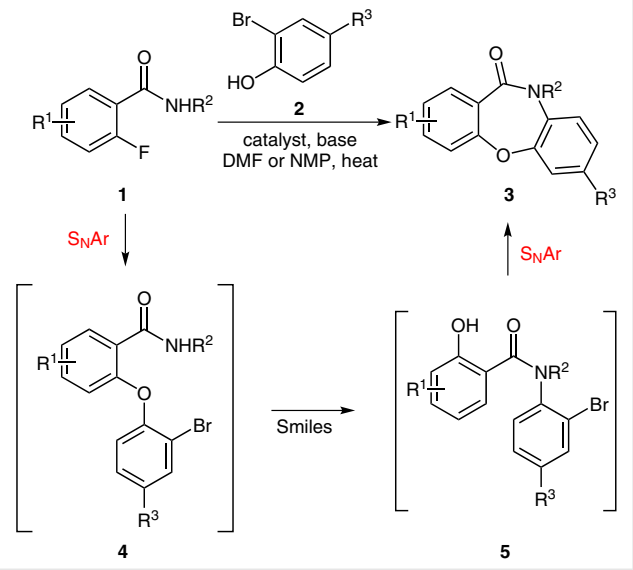
Abstract Reported is the transition-metal-free synthesis of substituted dibenzoxazepinones using a convergent domino S_NAr–Smiles rearrangement–S_NAr process. Substrate-scope investigations demonstrated the critical importance of ring electronic effects on the efficiency of the process. In addition, the orthogonality of this approach with transition-metal-catalyzed procedures was established.

Key words dibenzoxazepinones, domino reaction, Smiles rearrangement, nucleophilic aromatic substitution, heterocycles

Dibenzo[*b*,*f*][1,4]oxazepin-11(10*H*)-ones are attractive targets in synthesis due to their extensive and varied biological activity.[1] Thus, unsurprisingly, dibenzoxazepinones have received considerable attention from the synthetic community and have traditionally been synthesized via stepwise classical S_NAr and amide-formation methods.[2] More recently, dibenzoxazepinones have been prepared by the intramolecular palladium-catalyzed carbonylative coupling of 2-(2-halophenoxy)anilines[3] and by palladium-catalyzed amination of 2-(2-halophenoxy)benzoate esters.[4] All of these methods suffer from the same drawback; the reliance on multistep syntheses which require isolation of intermediates at each step. Domino reactions provide an elegant solution to such practical concerns, enabling successive transformations to occur in a single reaction vessel.[5]

A resurgence in the investigation of domino S_NAr–Smiles rearrangement processes, first disclosed by Sapegin,[6] has been spearheaded by Ma and co-workers as demonstrated in their one-pot approaches to dibenzoxazepinones[7] and related tricyclic systems.[8] Similar approaches to other fused heterocycles have also been reported.[9]

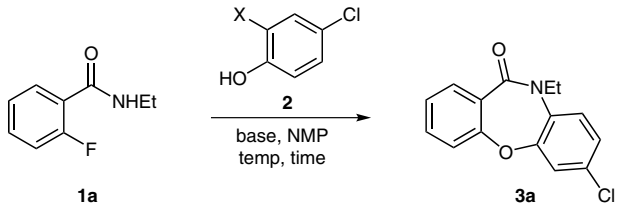
Recently, we reported a copper-catalyzed synthesis of dibenzoxazepinones from 2-iodobenzamides which involves an unexpected Smiles rearrangement.[10] During our attempts to elucidate the mechanism of this reaction, we observed that *N*-ethyl 4-methyl-2-fluorobenzamide was converted into the desired dibenzoxazepinone solely under S_NAr conditions in moderate yield. Intrigued by this result, we sought to optimize and explore the scope of this complementary process, and we now report the highly selective metal-free synthesis of dibenzoxazepinones **3** from the reaction of 2-fluorobenzamides **1** with 2-halophenols **2** (Scheme 1).



Scheme 1 One-pot domino approach to dibenzoxazepinones **3**

Optimization of the reaction was carried out using the readily accessible *N*-ethyl 2-fluorobenzamide **1a** and commercially available 2-bromo-4-chlorophenol **2** under microwave conditions. By employing NMP as the reaction solvent, direct comparisons to our previously reported copper-catalyzed process are facilitated.[10] A brief examination of different bases and reagent stoichiometry provided the optimal conditions (Table 1, entry 4). Examination of the 2-halophenol component revealed that 2-chloro and 2-fluorophenols were equally competent in the reaction (Table 1, entries 8 and 9). However, 2-bromophenols were chosen for the bulk of this study due to their greater commercial availability and lower cost.

Table 1 Optimization Studies in the Synthesis of Dibenzoxazepinones **3a**



1a **3a**

Entry	**2** (equiv)	Base (equiv)	X	Temp (°C)	Time (h)	Yield (%)
1	1.2	K_2CO_3 (2.4)	Br	220	2	47
2	2	K_2CO_3 (3)	Br	220	1	47
3	2	K_2CO_3 (3)	Br	220	2	54
4	2	K_2CO_3 (2.1)	Br	220	2	62
5	2	Cs_2CO_3 (2.1)	Br	220	2	50
6	2	K_3PO_4 (2.1)	Br	220	2	–
7	2	DIPEA (2.1)	Br	220	2	0
8	2	K_2CO_3 (2.1)	Cl	220	2	61
9	2	K_2CO_3 (2.1)	F	200	2	57

Armed with the optimal conditions, our attention turned to examining the scope of the benzamide component (Table 2). As expected from a reaction operating under a S_NAr manifold, altering the electronic properties of the benzamide has a profound effect on the reaction efficiency.[11] For example, in comparison to our prototype substrate **3a** (Table 2, entry 1), introduction of the weakly electron-donating methyl group (**3b**, Table 2, entry 2) led to a noticeable decrease in yield. This could be effectively countered by employing the more reactive 2-fluoro-4-chlorophenol (Table 2, entry 3), which increased the yield to 67%, restoring the efficacy of the process.[12] Inclusion of the strongly electron-donating methoxy group (Table 2, entry 4) exacerbated this problem, affording dibenzoxazepinone **3c** in significantly reduced yield, which could not be improved with recourse to the alternate phenolic nucleophile (Table 2, entry 5). Additionally, 2-fluoro-5-bromobenzamide led to product in a disappointing yield of 26% (Table 2, entry 6). Fortunately, all these dibenzoxazepinones can be easily prepared in 78%, 86%, and 85% yields (for **3b**, **3c**, and **3d**, respectively) using our copper-catalyzed approach.[10]

In contrast, benzamides bearing electron-withdrawing groups proved excellent substrates (Table 2, entries 7–9). Not only were the desired products **3e**–**g** obtained in high yields, but lower temperatures were acceptable to effect the transformations. To establish the lack of any specific microwave effect,[13] a reaction using 4-cyano-2-fluorobenzamide was also performed under conventional heating conditions to give an identical yield of **3e** to that obtained under microwave irradiation. Since using microwave reactors remain a safe and convenient way to perform high temperature reactions, we adopted this technology for our study.[14]

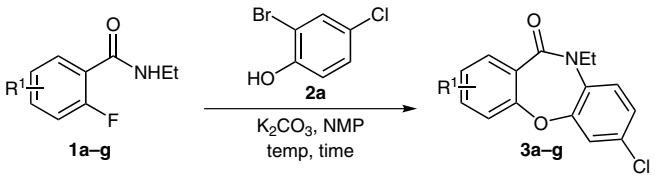
Due to its high efficiency in the reaction, and the prevalence of the CF_3 group in biologically relevant compounds,[15] trifluoromethylbenzamide **1e** was chosen as the model substrate for investigation of the scope of the phenolic coupling partner (Table 3).

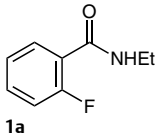
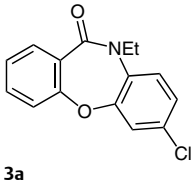
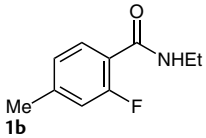
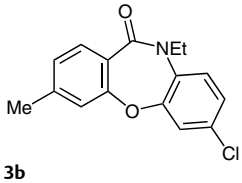
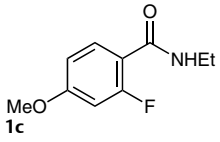
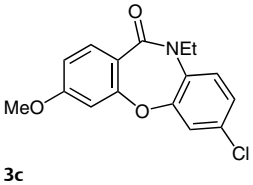
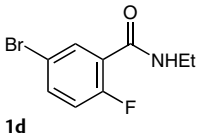
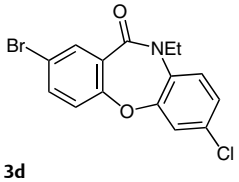
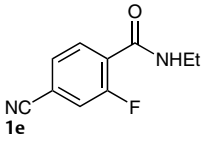
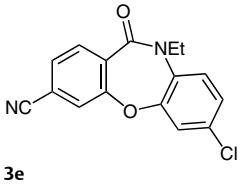
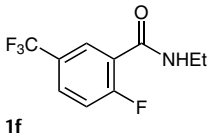
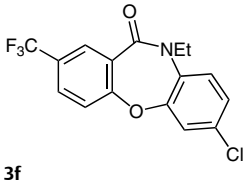
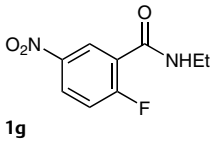
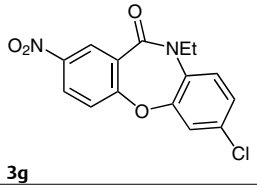
As observed previously,[10] the electronic character of the substituent on the phenol component is an important factor in determining whether high yields of products are obtained. Particularly good substrates are heavily halogenated phenols and electronically deficient heterocycles (Table 3, entries 4, 5, 8), which are known to be effective participants in Smiles rearrangement processes.[6–10,16] Substituents which modulate either the nucleophilicity of the phenol (Table 3, entry 6) or lessen the stability of the putative Meisenheimer intermediate[17] (Table 3, entries 1, 2, 7) decrease the efficiency of the reaction.

Cognizant of the potential convolution of metal-catalyzed coupling and S_NAr methods,[18] we were keen to examine the orthogonality of our current method with our previously disclosed copper-catalyzed process.[10] To test this hypothesis, 2-bromo-4-trifluoromethyl-6-fluorobenzamide (**4**) was prepared (Scheme 2) via the effective D*o*M strategy.[19] Thus, taking advantage of the synergistic directing ability of the two halogens, addition of 3-bromo-5-fluoro-trifluoromethylbenzene to LDA under inverse metalation conditions, followed by inverse quench onto dry ice gave the desired acid, which was readily converted into amide **4** under standard conditions (see Supporting Information).

Gratifyingly, treatment of **4** under the optimal S_NAr conditions delivered 1-bromo-dibenzoxazepinone **5** as the major product albeit in 26% yield, whilst the application of our copper-catalyzed method[10] led chemoselectively to the 1-fluoro derivative **7** as the sole product. Further derivatization of **5** and **7** was accomplished by either Suzuki–Miyaura cross-coupling (for **5**) or S_NAr reactions (for **7**) to afford 1-substituted dibenzoxazepinones **6** and **8a**–**c**, respectively. It is challenging to prepare these compounds directly, as sterically congested amides perform poorly in the Smiles rearrangement.[10]

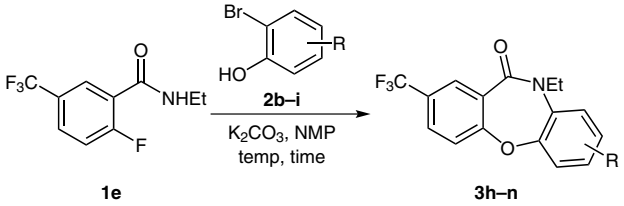
Table 2 Synthesis of Compounds **3a–g**. Variation of Benzamide Substituents



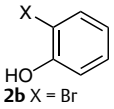
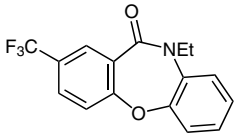
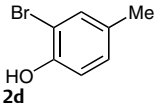
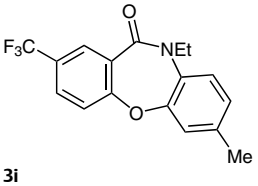
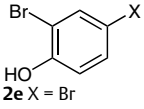
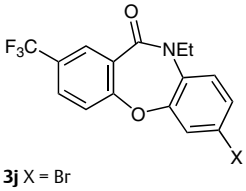
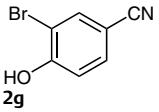
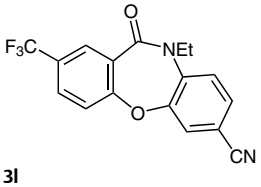
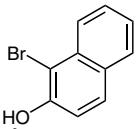
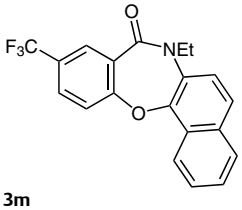
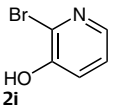
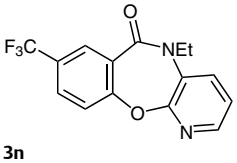
Entry	Amide **1**	Product **3**	Temp (°C)	Time (h)	Yield (%)
1	 **1a**	 **3a**	220	2	62
2	 **1b**	 **3b**	220	2	40
3	**1b**	**3b**	220	2	67[a]
4	 **1c**	 **3c**	220	2	14
5	**1c**	**3c**	220	2	19[a]
6	 **1d**	 **3d**	220	2	26
7	 **1e**	 **3e**	150	2	82 (84)[b]
8	 **1f**	 **3f**	150	2	78
9	 **1g**	 **3g**	150	2	70

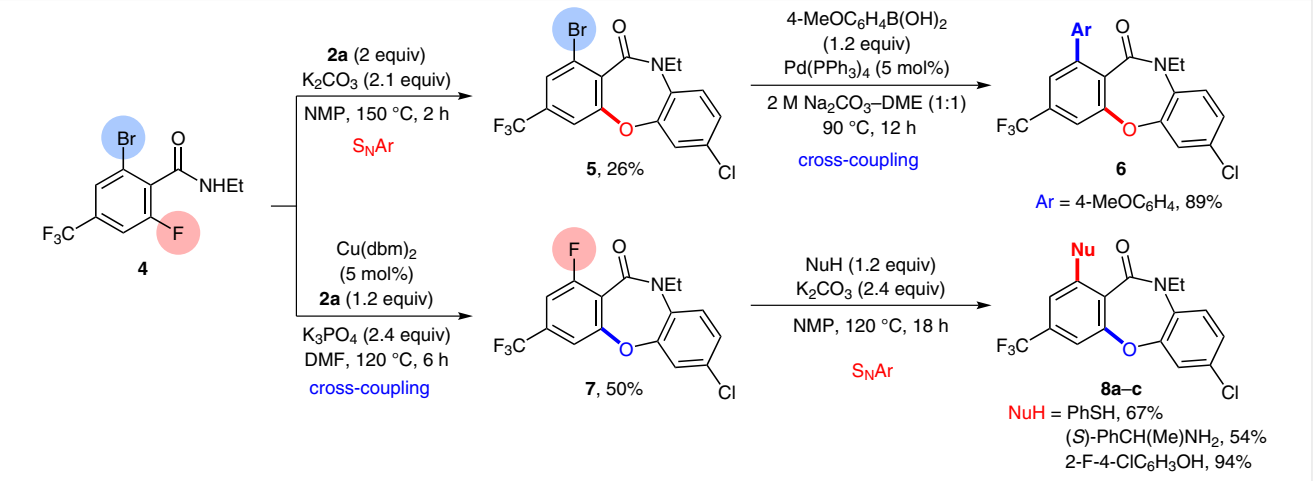
[a] 2-Fluoro-4-chlorophenol was used instead of 2-bromo-4-chlorophenol.
[b] Yield in parentheses refers to a reaction carried out under conventional heating.

Table 3 Synthesis of Compounds **3h–n**: Variation of Phenol Substituents



1e **3h–n**

Entry	2-Halophenol	Product	Temp (°C)	Time (h)	Yield (%)
1	 **2b** X = Br	 **3h**	180	2	24
2	**2c** X = F	**3h**	150	3	37
3	 **2d**	 **3i**	180	4	21
4	 **2e** X = Br	 **3j** X = Br	150	2	87
5	**2f** X = F	**3k** X = F	150	2	64
6	 **2g**	 **3l**	150	2	37
7	 **2h**	 **3m**	180	4	45
8	 **2i**	 **3n**	150	2	84



Scheme 2 Chemoselective synthesis and derivatization of 1-bromo- and 1-fluoro-dibenzoxazepinones **5** and **7**.

Considered together, these results provide complementary methods for the synthesis of 1-substituted dibenzoxazepinones, which are difficult to access by current methods.[10,20]

In summary, we have described a general, highly chemoselective, and metal-free domino approach for the construction of dibenzoxazepinones from 2-fluorobenzamides and 2-halophenols. Furthermore, we have demonstrated the orthogonality[21] of this methodology with our copper-catalyzed process and the tandem application of both of these methods in the synthesis of challenging 1-substituted dibenzoxazepinones.[10,20,22]

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Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0034-1378839.

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General Procedure – Reaction of 2-Fluorobenzamides with 2-Bromophenols

A sealable tube (10 mL) was charged with the 2-fluorobenzamide (1.00 mmol), the 2-bromophenol (2.00 mmol), and K_2CO_3 (0.290 g, 2.10 mmol). NMP (3 mL) was added, and the tube was sealed. The heterogeneous reaction mixture was heated to 150 °C, 180 °C, or 220 °C for 2–4 h under microwave irradiation (Biotage Initiator Microwave operating at 400 W). After cooling to r.t., the reaction mixture was partitioned between 2 M HCl (20 mL) and EtOAc (3 × 20 mL). The combined organics were washed with 2 M NaOH (2 × 20 mL) and sat. brine (20 mL), dried over $MgSO_4$, subjected to filtration, and concentrated in vacuo. The crude product was purified by flash chromatography on silica gel, eluting with EtOAc–hexanes (1:19 to 1:5) to deliver the title compound.

***N*-Ethyl 7-Chlorodibenz[*b*,*f*][1,4]oxazepin-11(10*H*)-one (3a)**

The reaction of *N*-ethyl 2-fluorobenzamide (**1a**, 0.167 g, 1.00 mmol) with 2-bromo-4-chlorophenol (**2a**, 0.415 g, 2.00 mmol) at 220 °C for 2 h gave **3a** as a colorless solid (0.170 g, 62%); mp 124–126 °C. IR (film): 1645, 1607 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.89 (dd, *J* = 1.7, 7.8 Hz, 1 H), 7.48 (dt, *J* = 1.5, 7.8 Hz, 1 H), 7.32 (d, *J* = 2.3 Hz, 1 H), 7.28 (s, 1 H), 7.26 (d, *J* = 7.3 Hz, 1 H), 7.22–7.18 (m, 2 H), 4.17 (q, *J* = 7.1 Hz, 2 H), 1.40 (t, *J* = 7.1 Hz, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.7 (C), 160.1 (C), 154.9 (C), 133.6 (C), 133.3 (CH), 132.0 (CH), 130.9 (C), 126.6 (C), 125.9 (CH), 124.5 (CH), 123.7 (CH), 121.9 (CH), 119.5 (CH), 44.2 (CH_2), 13.6 (Me). LRMS (EI): *m/z* (%) = 273/275 (58/19) [M^+], 238 (100), 210 (24), 195 (26), 139 (15), 105 (10), 84 (13). HRMS (EI): *m/z* calcd for $C_{15}H_{12}ClNO_2^+$: 273.0557; found: 273.0563.