A Formal [4 + 4] Complementary Ambiphile Pairing Reaction: A New Cyclization Pathway for *ortho*-Quinone Methides
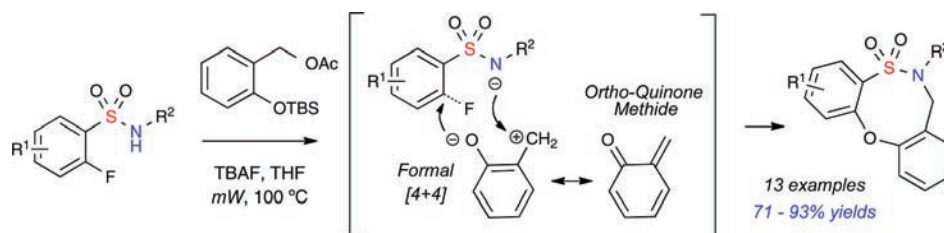
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ABSTRACT

A formal, one-pot [4 + 4] cyclization pathway for the generation of eight-membered sultams via in situ generation of an *ortho*-quinone methide (*o*-QM) is reported. The pairing of ambiphilic synthons in a complementary fashion is examined whereby *o*-fluorobenzenesulfonamides are merged with in situ generated *o*-QM in a formal [4 + 4] cyclization pathway to afford 5,2,1-dibenzooxathiazocine-2,2-dioxide scaffolds under microwave (*m*W) conditions. The method reported represents the first use of an *o*-QM in a formal hetero [4 + 4] cyclization.

The development of chemical methodologies allowing ready access to novel heterocyclic scaffolds in a minimal number of steps is a key facet of drug discovery. Single-pot, multicomponent reaction (MCR) strategies in particular have gained high value in this regard.[1] The great majority of these reactions involve the combination of reactive partners possessing single nucleophile−electrophile interactions, followed by subsequent merging in domino, cascade, or tandem pathways to produce heterocyclic moieties. In comparison, synthons containing both electrophilic and nucleophilic sites (ambiphilic synthons)[2−4] have great potential in developing new reaction pathways with high step economy[5] but remain underdeveloped. Interest in the development of chemical

methodologies for the production of diverse sultam libraries has led to the exploration of complementary ambiphile pairing (CAP) pathways as part of a general strategy for the

(1) (a) Zhu, J.; Bienayme, H.; *Multicomponent Reactions*; Wiley-VCH Verlag GmbH & Co. KGaA: Weinheim, 2005. (b) Toure, B. B.; Hall, D. G. *Chem. Rev.* **2009**, *109*, 4439–4486. (c) Sunderhaus, J. D.; Martin, S. F. *Chem.–Eur. J.* **2009**, *15*, 1300–1308.

(2) (a) Bontemps, S.; Gornitzka, H.; Bouhadir, G.; Miqueu, K.; Bourissou, D. *Angew. Chem., Int. Ed.* **2006**, *45*, 1611–1614. (b) Bontemps, S.; Bouhadir, G.; Miqueu, K.; Bourissou, D. *J. Am. Chem. Soc.* **2006**, *128*, 12056–12057. (c) Bontemps, S.; Bouhadir, G.; Dyer, P. W; Miqueu, K.; Bourissou, D. *Inorg. Chem.* **2007**, *46*, 5149–5151.

(3) Molecules containing both electrophilic and nucleophilic nodes have also been also defined as amphiphilic molecules, see: (a) Nakamura, H.; Shim, J.-G.; Yamamoto, Y. *J. Am. Chem. Soc.* **1997**, *119*, 8113–8114. (b) Nakamura, H.; Aoyagi, K.; Shim, J.-G.; Yamamoto, Y. *J. Am. Chem. Soc.* **2001**, *123*, 372–377. (c) Kimura, M.; Tamaki, T.; Nakata, M.; Tohyama, K.; Tamaru, Y. *Angew. Chem., Int. Ed.* **2008**, *120*, 5887–5889.

(4) Molecules containing both electrophilic and nucleophilic nodes have been also defined as amphoteric molecules by Yudin, see: (a) Yudin, A.; Hili, R. *J. Am. Chem. Soc.* **2009**, *131*, 16404–16406. (b) Yudin, A.; Hili, R. *Angew. Chem., Int. Ed.* **2008**, *120*, 4188–4191.

(5) Wender, P. A.; Verma, V. A.; Paxton, T. J.; Pillow, T. H. *Acc. Chem. Res.* **2008**, *41*, 40–49.

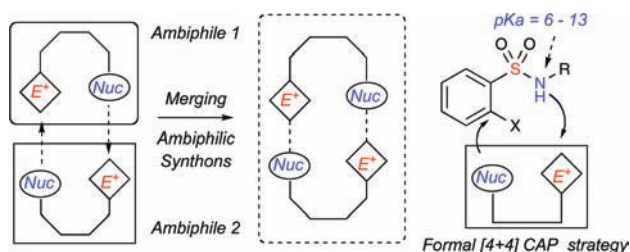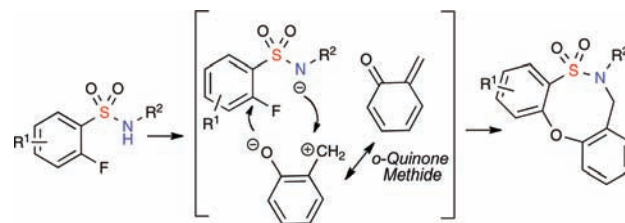production of benzofused sultams in a facile manner (Figure 1).

Figure 1. Pairing strategies for benzofused sultam synthesis.

At the heart of the titled method is the complementary pairing of two ambiphilic synthons, *o*-fluorobenzenesulfonamides and *ortho*-quinone methide (*o*-QM) in a formal, one-pot [4 + 4] approach to afford the novel 5,2,1-dibenzooxathiazocine-2,2-dioxide ring system. This route augments a recently reported [4 + 3] epoxide cascade strategy developed in our laboratory and others using the ambiphilic character of *o*-fluorobenzenesulfonamides for the synthesis of benzofused sultams.[6]

Quinone methides are reactive intermediates that have been known for more than 50 years[7] and are extensively utilized in biological processes.[8] In addition to their use in nature, they also have great synthetic potential. In particular, *o*-QMs are highly versatile intermediates as they can serve as Michael acceptors or dienes in cycloaddition reactions. A number of natural products as well as biologically active heterocycles have been accessed utilizing in situ generated *o*-QMs.[9] The overwhelming majority of cases involves the utilization of *o*-QMs as dienes in hetero Diels−Alder reactions. Recently, elegant use of acyl-anion Michael additions into *o*-QMs has been reported for the generation of α-aryl ketones.[10] However, in spite of numerous reports of aza-Michael reactions of *o*-QMs in biological systems, the exploitation of these pathways in the synthesis of heterocycles is limited to reports of the dimerization of orthoquinone methides (*o*-QMs).[11] In contrast, the utilization of *o*-QMs as ambiphiles in hetero [4 + 4] cyclizations has not been reported in the literature.

The aforementioned dibenzooxathiazocine ring system represents a new subclass within sultams that have not been reported to date. Sultams are a class of non-natural heterocycles that have gained prominence in recent years due to their activity against a wide spectrum of biological targets.[12,13] Their acyclic precursors, sulfonamides, are highly versatile synthons due to the tunability of the SO$_2$NH pK_a.[14] In this regard, *o*-fluorobenzenesulfonamides are particularly attractive due to the highly electron-withdrawing nature of the SO$_2$ functionality, in conjunction with the *o*-fluoro substituent, which imparts enhanced electrophilicity at the *ortho*-carbon as well as attenuated acidity/nucleophilicity of the sulfonamide NH (Scheme 1). The ability of *o*-fluoroben-

Scheme 1. Pairing *o*-Fluorobenzenesulfonamides and *o*-QMs in a Formal [4 + 4] Reaction

zenesulfonamides to undergo facile nucleophilic aromatic substitution (S$_N$Ar) reactions[6,15] at the *ortho*-carbon allows for their potential pairing with *o*-QMs in CAP strategies for production of benzofused sultams. This pairing entails an aza-Michael addition at the exo methylene *o*-QM carbon and subsequent interception of the nucleophilic phenoxy by *o*-fluorobenzenesulfonamides via an S$_N$Ar reaction in a formal [4 + 4] cyclization pathway (Scheme 1).

Investigations commenced with the production of an array of 2° *o*-fluorobenzenesulfonamides under modified Schotten−Baumann conditions. *o*-QMs can be formed in situ from 2-hydroxybenzyl alcohol derivatives under basic conditions.[7] Accordingly, a mixture of 2-fluorobenzenesulfonamide **1c** was mixed with 2-hydroxy benzyl alcohol in the presence of anhydrous K$_2$CO$_3$ (3.0 equiv) in DMF and was subjected to microwave irradiation (*m*W) at 140 °C for 30 min (Scheme 2). The sulfonamide starting material was completely consumed to afford a compound that was highly visible on TLC under UV irradiation. Characterization of the product revealed the novel tricyclic sultam **2c** containing the dibenzooxathiazocine ring system. However, the overall yield of the reaction was modest possibly due to inefficient

(6) (a) Rolfe, A.; Samarakoon, T. B.; Hanson, P. R. *Org. Lett.* **2010**, *12*, 1216–1219. (b) Cleator, E.; Baxter, C. A.; O'Hagan, M.; O'Riordan, T. J. C.; Sheen, F. J.; Stewart, G. W. *Tetrahedron Lett.* **2010**, 1079–1082.

(7) For a comprehensive review on *o*-QM see: (a) Rokita, S. E. *Quinone Methides. Wiley Series of Reactive Intermediates in Chemistry and Biology*; John Wiley & Sons, Inc.: Hoboken, NJ, 2009; Vol. 1. (b) Van De Water, R. W.; Pettus, T. R. R. *Tetrahedron* **2002**, *58*, 5367–5404. (c) Pettus, T. R. R.; Selenski, C. *Sci. Synth.* **2006**, *28*, 831–872.

(8) Wolkenberg, S. E.; Boger, D. L. *Chem. Rev.* **2002**, *102*, 2477–2495.

(9) (a) Bender, C. F.; Yoshimoto, F. K.; Paradise, C. L.; De Brabander, J. K. *J. Am. Chem. Soc.* **2009**, *131*, 11350–11352. (b) Lumb, J.-P.; Choong, K. C.; Trauner, D. *J. Am. Chem. Soc.* **2008**, *130*, 9230–9231. (d) Selenski, C.; Pettus, T. R. R. *J. Org. Chem.* **2004**, *69*, 9196–9203.

(10) Mattson, A. E.; Scheidt, K. A. *J. Am. Chem. Soc.* **2007**, *129*, 4508–4509.

(11) (a) Pisova, N.; Soucek, M. *Collect. Czech. Chem. Commun.* **1982**, *47*, 838–842. (b) Wang, P.; Wang, Y.; Hu, W.; Liang, X. *Eur. J. Org. Chem.* **2009**, *13*, 2055–2058. (c) Rosenau, T.; Bömdorfer, S. In *Quinone Methides. Wiley Series of Reactive Intermediates in Chemistry and Biology*; John Wiley & Sons, Inc.: Hoboken, NJ, 2009; Vol. 1, p 180.

(12) (a) Drews, J. *Science* **2000**, *287*, 1960–1964. (b) Scozzafava, A.; Owa, T.; Mastrolorenzo, A.; Supuran, C. T. *Curr. Med. Chem.* **2003**, *10*, 925–953.

(13) Jiménez-Hopkins, M.; Hanson, P. R. *Org. Lett.* **2008**, *10*, 2223–2226.

(14) (a) Rayabarappu, D. R.; Zhou, A.; Jeon, K.; Samarakoon, T.; Rolfe, A.; Siddiqui, H. *Tetrahedron* **2009**, *65*, 3180–3188. (b) Zhou, A.; Hanson, P. R. *Org. Lett.* **2009**, *11*, 531–534.

(15) Penso, M.; Albanese, D.; Landini, D.; Lupi, V.; Tagliabue, A. *J. Org. Chem.* **2008**, *73*, 6686–6690.
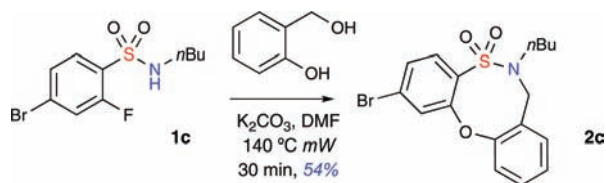
generation of the *o*-QM intermediate as well as potential dimerzation/trimerization of the *o*-QM.[16]

Investigations were then focused on alternate methods of *o*-QM generation. Interestingly, exposure of **1c** to the *o*-acetoxybenzyl acetate of *o*-hydroxybenzyl alcohol afforded the desired product in increased yields. Attention was then turned to the conditions reported by Rokita and co-workers.[7a] Accordingly, microwave irradiation of the sulfonamide in the presence of TBAF and *o*-silyloxy benzyl acetate in THF at 100 °C for 30 min furnished the desired product in 90% yield (Table 1, entry 3). In this latter result, the fluoride anion

Table 1. Substrate Scope of *o*-QM Mediated [4 + 4] Reaction
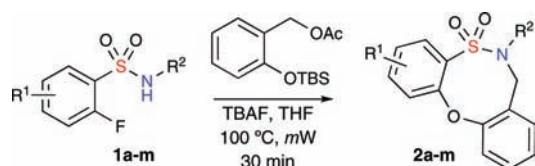
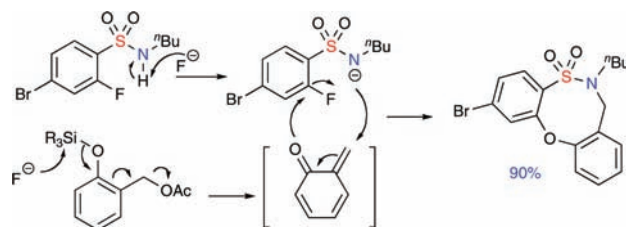| entry	pdt	R¹	R²	yield (%)[a]
1	**2a**	H	2-OMe Bn	71
2	**2b**	H	2,3-Cl CH₂Ph	73
3	**2c**	4-Br	*n*Bu	90
4	**2d**	4-Br	*i*Bu	91
5	**2e**	4-Br	PMB	82
6	**2f**	4-Br	cyclopropyl	81
7	**2g**	4-Br	propargyl	94
8	**2h**	5-Cl	allyl	94
9	**2i**	5-Cl	PMB	71
10	**2j**	5-Cl	3-F Bn	93
11	**2k**	5-Cl	2-OMe Bn	87
12	**2l**	4-Br	(iPr)CHCO₂Me	93
13	**2m**	4-Br	(iBu)CHCO₂Me	77

[a] Isolated yield after column chromatography.

serves to desilylate the silyl-protected phenol functionality thus generating the phenoxy anion, which further continues on the cascade pathway to produce the pivotal *o*-QM intermediate. In addition, it also serves as the base to produce the sulfonylamide intermediate required for the desired reaction to take place (Scheme 3).

The substrate scope was next investigated. A variety of sulfonamides were subjected to the above conditions and

were found to proceed smoothly to afford the desired sultam in excellent yields (Table 1). The optimized reaction protocol was found to tolerate a range of substituents on the N atom including alkyl, propargyl, and benzyl functionalities. Pleasingly, the reaction protocol was found to tolerate Cl and Br atoms on the aromatic ring. Halide substitution was important, as this would allow for functionalization of these scaffolds for library production via transition metal-catalyzed coupling reactions.

To the best of our knowledge, the ring system produced has not been reported in the literature. The structure of these unique heterocycles was confirmed via X-ray crystallography (Figure 2). The method reported herein represents the first
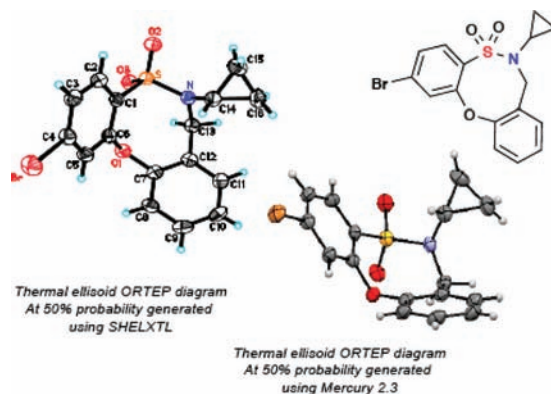

Figure 2. ORTEP diagram of **2f**.

instance of the use of an *o*-QM in a formal hetero [4 + 4] cyclization pathway to generate a heterocycle.

To expand the method, application of the *o*-QM-mediated [4 + 4] CAP strategy was investigated with amino ester-derived *o*-fluorobenzenesulfonamides. Treatment of both and valine- and leucine-derived substrates, **2l** and **2m**, under the above conditions gratifyingly afforded the desired product in excellent yields (Table 1, entries 12 and 13). These results enhance the scope of the method and allow for further elaboration of the scaffolds in library efforts. X-ray data also confirmed the source of the unique upfield ¹H NMR shifts of the MeO group in entries 12 and 13 which were found to be at 2.28 and 2.40 ppm, respectively, most likely due to shielding from the aromatic ring system in these conformationally rigid systems (Figure 3).
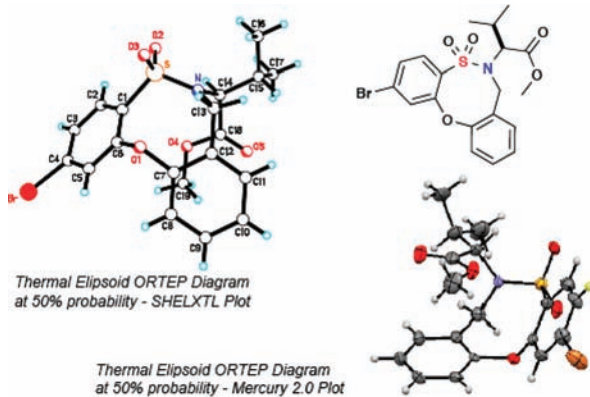
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(16) Heating at 110 °C in DMF for 12 h under reflux resulted in poor conversion and low product yields.

Figure 3. ORTEP diagram of **2l**.

In the last two entries (12 and 13), a 6:1 and a 3.7:1 mixture of inseparable products are seen in the ¹H NMR spectra, which have been tentatively assigned as N−C14 rotamers. Evidence of this lies in the fact that the ¹H, ¹³C, ¹H/¹H COSY, ¹H/¹³C HSQC, and DEPT all showed the existence of a set of peaks that was almost identical to that of the major product albeit with a change in chemical shift values and matching the expected structure of the product. The ¹H NMR shifts for the MeO group in **2l**-minor and **2m**-minor are 3.52 and 3.72 ppm, respectively (compared with 2.28 and 2.40 in the major isomers, respectively, as stated above). In contrast, the ¹H NMR shifts for the diastereotopic *gem*-dimethyl groups in the **2l**-minor rotamer are at 0.75 and 0.02 ppm due to shielding by the aromatic ring system (as opposed to 1.10 and 0.98 ppm in the **2l**-major rotamer).

In conclusion, a one-pot, complementary ambiphile-pairing (CAP) reaction has been developed to produce 5,2,1-dibenzooxathiazocine-2,2-dioxides in a formal [4 + 4] cyclization pathway under *m*W conditions. This report represents the first instance of the generation of 5,2,1-dibenzooxathiazocine-2,2-dioxide scaffolds and the first reported method utilizing in situ generated *o*-QM in a formal hetero [4 + 4] cyclization process. This method is suitable to library production and diversity-oriented synthesis. Efforts along these lines and additional applications of CAP strategies are currently in order and will be reported in due course.

Supporting Information Available: Experimental details and spectral charactization for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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