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LETTERS

Synthesis of Benzofuranones Related to Diazonamide via an Intramolecular Pummerer Reaction

Philip Magnus* and **Jennifer D. Kreisberg**

Department of Chemistry and Biochemistry, University of Texas at Austin, Austin, Texas 78712

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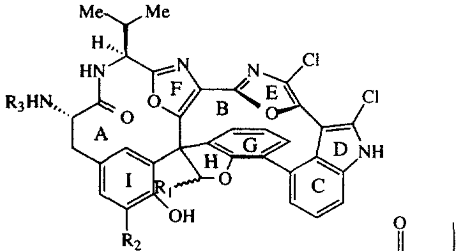
Abstract: Treatment of in situ generated 2-thiomethyl-2-chloro-2-phenylacetyl aryl esters with $SnCl_4$ (catalytic) resulted in the formation of the corresponding 3-thiomethylbenzofuran-2-ones.

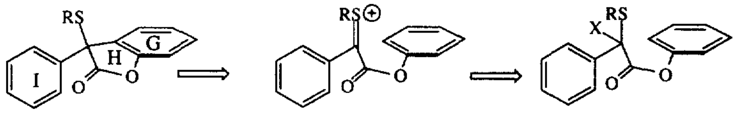
Scheme 1



1, Diazonamide A, R_1 = OH, R_2 = H, R_3 =
2, Diazonamide B, R_1 = OH, R_2 = Br, R_3 = H.
3, R_1 = O2 (acetal), R_2 = Br, R_3 = COC_6H_4Br-*p*.

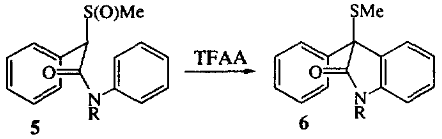
In 1991 Fenical and Clardy reported the structure of diazonamide A, **1** and diazonamide B, **2**.[1] The structures of these unusual alkaloids was inferred from the X-ray determination of the acetal **3**, which was formed by treatment of **2** with *p*-BrC_6H_4COCl/pyridine. The diazonamides were isolated from the colonial ascidian Diazona chinensis, collected from the ceilings of caves along the northwest coast of Siquijor Island in the Philippines. It was reported that **1** has potent in vitro activity against HCT-116 human colon carcinoma and B-16 murine melanoma cancer cells (IC_{50} < 15 ng/mL). The diazonamides have generated some synthetic interest,[2] and the synthesis of oxazoles and bis-oxazoles has undergone renewed interest.[3,4,5] There is a growing number of oxazole natural products with interesting biological properties, but the diazonamides are manifestly unique in their structural features.[6]

Eqn 1



4 **4a** **4b**

Eqn 2



5 **6**

We were interested in constructing the IHG-rings[7] of diazonamide with an ionizable group at the bis benzylic position, and **Eqn 1** illustrates a simple model system **4** that can be made from the closure of the sulfonium ion **4a**, which in turn is derived from the 2-thiomandelic phenyl ester **4b**. While 2-oxindoles have been made using the intramolecular Pummerer reaction, **Eqn 2**,[8,9] there are no examples of the formation of benzofuran-2-ones using this reaction. The intermolecular version of the above reaction has been reported by McKervey who showed that treatment of phenols with methyl 2-chloro-(butylthio)propionate in the presence

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of $ZnCl_2$ (2 equiv) resulted in benzofuran-2-ones.[10] Clearly, the classical Fries rearrangement reaction could be a competing process in the intramolecular Pummerer reaction as depicted in **Eqn 1**.

Scheme 2

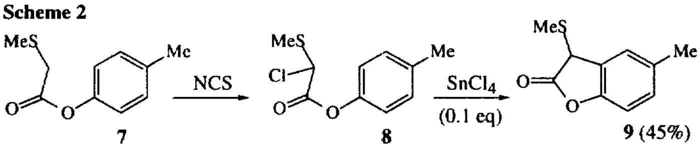
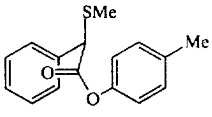
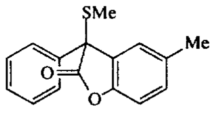
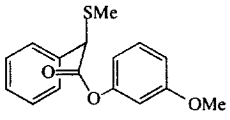
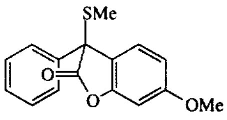
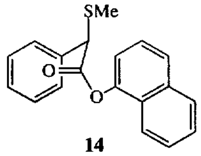
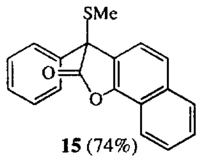
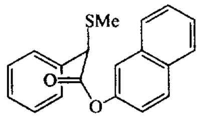
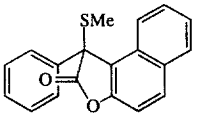
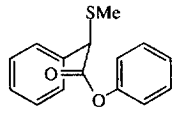
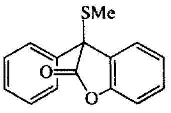
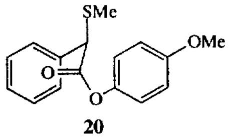
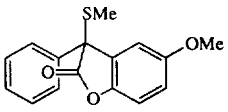
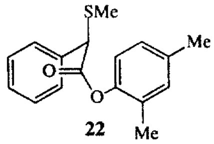
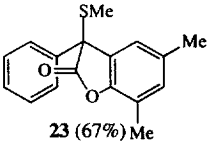


TABLE 1

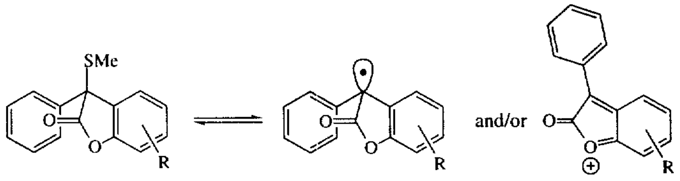
Esters	Conditions	Product (yield)
 **10**	1. *N*-chlorosuccinimide/CCl_4 (ca. 2h). 2. $SnCl_4$ (0.1 equiv)/CCl_4 reflux/5.5h.	 **11** (65%)
 **12**	As above, but heated for 2h.	 **13** (70%)
 **14**	As above, but heated for 1.5h.	 **15** (74%)
 **16**	As above, but heated for 0.5h.	 **17** (80%)
 **18**	As above, but heated for 12h.	 **19** (66%)
 **20**	As above, but heated for 12h.	 **21** (69%)
 **22**	As above, but heated for 5h.	 **23** (67%)

Initially, we examined the intramolecular Pummerer reaction *via* the sulfoxide derivative of **7**, and found that under the usual Pummerer reaction conditions[11] of trifluoroacetic anhydride, only trace amounts of the lactone **9** (υ_{max} 1805 cm^{-1}) were formed, along with substantial amounts of *p*-cresyl glyoxylate derivatives. Consequently, the alternative procedure outlined in **Scheme 2** was studied. Treatment of the ester **7**[12] with *N*-chlorosuccinimide in CCl_4 gave **8**, which was immediately exposed to $SnCl_4$ (0.1 equiv) to give **9** (45%). Initially, we had used stoichiometric amounts of either $ZnCl_2$ or $SnCl_4$, and this resulted in the formation of **9** in very low yields with considerable amounts of decomposition. The use of $SnCl_4$ in catalytic amounts (0.1 equiv) resulted in much less decomposition. **TABLE 1** lists seven examples of the synthesis of benzofuranones derived from 2-thiomethyl-2-phenylacetyl esters. In each case the corresponding esters were treated with *N*-chlorosuccinimide/CCl_4 to give the 2-chloro-adducts (aliquot analyzed by ^1H NMR), followed by exposure to $SnCl_4$ (0.1 equiv) for the times indicated to give the benzofuranones **11**, **13**, **15**, **17**, **19**, **21** and **23** respectively in yields ranging from 65% to 80%. The ^1H NMR and IR spectra of the crude products did not indicate the presence of any Fries-type rearrangement by-products.

Representative Experimental: *N*-Chlorosuccinimide (59 mg, 0.48 mmol, 1.0 eq) was added to a stirred solution of **14** (147 mg, 0.48 mmol, 1.0 eq) in CCl_4 (6 mL). The solution was stirred at 25 °C until the ^1H NMR spectrum of an aliquot showed complete chlorination (ca. 1.5 h). The mixture was filtered through a pad of glass wool into a dry flask, heated to reflux and $SnCl_4$ (47 µL, 0.048 mmol, 0.01 eq) was added dropwise. After heating the mixture for 1.5 hr the solution was cooled to 25 °C and quenched with 2N HCl (2 mL), and extracted with dichloromethane (2 x 5 mL). The combined extracts were dried ($MgSO_4$) and concentrated *in vacuo* to yield 110 mg of a crude residue. Chromatography over silica gel eluting with 10% Et_2O/petroleum ether gave **15** (107 mg, 74% of a crystalline solid).

Currently, we are studying the transformations of 3-thiomethylbenzofuranones into radical and cationic species, as depicted in equation 3, for the formation of carbon-carbon bonds at the bis-benzylic position.

Eqn 3



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References and Footnotes

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7. For clarity we have chosen to designate the rings of the diazonamides as A,B etc.
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11. For a recent review of the Pummerer reaction see:- Padwa, A.; Gunn, Jr. D. E.; Osterhout, M. H. *Synthesis* **1997**, 1353. Applications of the Pummerer reaction in the synthesis of indole alkaloids. Magnus, P.; Gallagher, T.; Brown, P.; Pappalardo, P. *Acc. Chem. Res.* **1984**, *17*, 35.
12. The esters **7** (87%), **10** (92%), **12** (75%), **18** (85%) and **20** (90%) were synthesized by DCC mediated coupling of the corresponding phenols and acids. Whereas, esters **14** (67%), **16** (86%) and **22** (67%) were synthesized using EDC as the coupling reagent.