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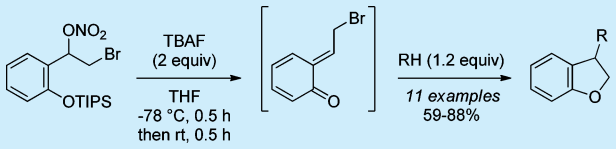
Novel Synthesis of 3-Substituted 2,3-Dihydrobenzofurans via *ortho*-Quinone Methide Intermediates Generated *in Situ*

Abdul kadar Shaikh and George Varvounis*

Section of Organic Chemistry and Biochemistry, Department of Chemistry, University of Ioannina, 451 10 Ioannina, Greece

Supporting Information

ABSTRACT: A new method is presented for the regioselective one-pot synthesis of 3-substituted 2,3-dihydrobenzofurans from 2-bromo-1-{2-[(triisopropylsilyl)oxy]phenyl}ethyl nitrate by fluoride-induced desilylation leading to *o*-quinone methide generation, Michael addition of different C, N, O, and S nucleophiles, and intramolecular 5-*exo-tet* elimination of a bromide anion. The method has potential synthetic applications in drug discovery.



Among the 2,3-dihydrobenzofurans that are substituted only at position 3, the most important biologically active representative is the prostaglandin (PG) D2 receptor antagonist[1] (Figure 1), while the 2,3-dihydrobenzofuran skeleton appears as a core element in numerous natural and synthetic pharmacologically interesting compounds.[1,2]

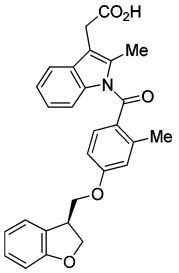


Figure 1. *N*-Benzoyl-2-methylindole-3-acetic acid derivative. An example of a biologically active 3-substituted 2,3-dihydrobenzofuran.

3-Substituted 2,3-dihydrobenzofurans have been synthesized by a variety of methods such as intramolecular aryl radical and Ullman-type cyclization, transition metal-catalyzed intramolecular C−O coupling reactions, Heck-type reactions, hydroalkoxylation and carbenoid-saturated C−H bond insertion reactions, the Parham cyclization process, intramolecular Michael-type addition, intramolecular O-to-alkene 5-*exo-trig* addition and O-to-oxirane addition, the use of benzyne intermediates, Mitsunobu type cyclodehydration reactions, cycloaddition reactions, and the application of biomimetic chemistry, as described in the review article by Bertolini and Pineschi.[2b] Since then, intramolecular aryl radical cyclization has been, by far, the most commonly employed method for the synthesis of a wide range of 3-substituted 2,3-dihydrobenzofurans.[3] A recent example to illustrate this process is the photoinduced radical reduction of 1-(allyloxy)-2-iodobenzene initiated by CuI and NaO*t*-Bu to form the corresponding aryl radical that undergoes 5-*exo-trig* radical cyclization to give the primary radical of 3-methyl-2,3-dihydrobenzofuran which traps thiophenol electrophilically, to afford 3-(phenylthiomethyl)-2,3-dihydrobenzofuran. In the absence of thiophenol, H-atom abstraction gives 3-methyl-2,3-dihydrobenzofuran.[3k]

Less common methods of synthesizing 3-substituted 2,3-dihydrobenzofurans are intramolecular enantioselective ring opening of 2-oxetan-3-ylphenol catalyzed by (salen)Co(III) complexes,[4a] intramolecular alkene carboacylation of [2-(allyloxy)phenyl](quinolin-8-yl)methanones initiated by quinoline-directed rhodium-catalyzed C−C σ-bond activation with $\{RhCl(C_2H_4)_2\}_2$ or $Rh(OTf)(COD)_2$,[4b] nickel-promoted Favorskii-type rearrangement of 3-bromo-2,3-dihydro-4*H*-chromen-4-ones with $NiCl_2$,[4c] intramolecular Heck−Matsuda reaction of 2-(allyloxy)benzenediazonium tetrafluoroborates with $Pd(OAc)_2$ as the catalyst in an atmosphere of CO,[4d] 5-*exo-trig* intramolecular carbolithiation of 1-[(3,3-dimethoxyprop-2-en-1-yl)oxy]-2-iodobenzene with *n*-BuLi and TMEDA and elimination of the methoxide ion,[4e] asymmetric hydrogenation of 3-methylbenzofuran at 10 bar of hydrogen in the presence of the [Ru(cyclooctadiene)(2-methylallyl)$_2$] catalyst,[4f] and intramolecular copper-promoted Sandmeyer trifluoromethylation of 2-(allyloxy)anilines in the presence of *i*-AmONO and 5-(trifluoromethyl)dibenzo[*b*,*d*]thiophenium tetrafluoroborate (Umemoto's reagent).[4g]

Although the synthesis of 3-substituted 2,3-dihydrobenzofurans *via* *o*-quinone methide (*o*-QM) intermediates is unknown, the parent compound and 2-substituted and 2,3-disubstituted derivatives have been synthesized by this method. Melumad and Breuer[5a] reported that the reaction of *o*-QM, generated *in situ* from *o*-hydroxybenzyltrimethylammonium iodide by the action of $CH_3S(O)CH_2Na$ in DMSO, with dimethyl sulfoxonium methylide, afforded the parent 2,3-dihydrobenzofuran. A similar approach was recently reported by Zhou and co-workers.[5b] Cesium carbonate was used to induce elimination of a toluene-*para*-sulfinate anion from 2-{(aryl)[(4-methylphenyl)sulfonyl]methyl}phenols to form *o*-

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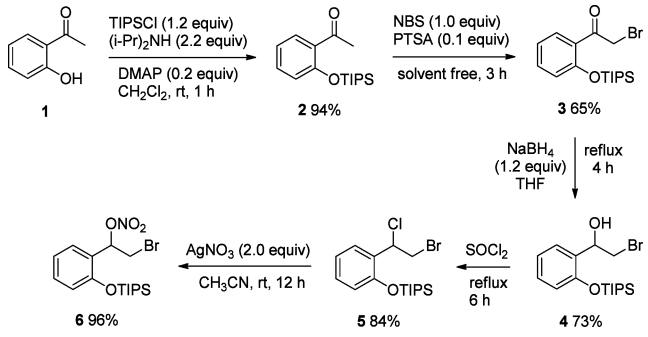
QMs which are trapped by the sulfur ylides derived, for example, from (2-ethoxy-2-oxoethyl)(dimethyl)sulfonium bromide and a base. The resulting phenoxides undergo a *trans*-elimination−cyclization process, to yield 2,3-disubstituted 2,3-dihydrobenzofurans with >20:1 *trans*/*cis* selectivity. Osyanin and co-workers[5c] used DBU to transform (2-hydroxyphenyl)-*N*,*N*,*N*-trimethylmethanaminium iodides into *o*-QMs which react with pyridinium acylmethylides to afford phenoxides that cyclize by elimination of pyridine, to give 2-substituted 2,3-dihydrobenzofurans.

Recently we have reported[6a] a new method for *o*-QM generation, via fluoride-induced desilylation of 2-(*tert*-butyldimethylsilyloxy)benzyl nitrate and elimination of a nitrate anion. The *o*-QM was trapped *in situ* by different C, N, O, and S nucleophiles leading to 2-(substituted methyl)phenols. In view of our continuing interest in substituted 2,3-dihydrobenzofurans as pharmacologically active substances and due to the lack of a versatile and efficient method of introducing variable substitution at position 3 of these compounds, we now present an application of our novel method for generating an *o*-QM and trapping with a range of nucleophiles, by using nitrate ester **6** as a precursor and incorporating into the one-pot reaction an intramolecular 5-*exo*-*tet* elimination process, to afford 3-substituted 2,3-dihydrobenzofurans. The starting material used to synthesize nitrate ester **6** is commercially available 2-hydroxyacetophenone **1** (Scheme 1). In the first

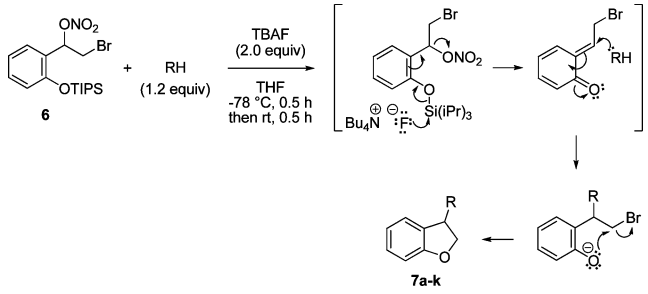
Scheme 1. Synthesis of 2-Bromo-1-{2-[(triisopropylsilyl)-oxy]phenyl}ethyl Nitrate 6 from 2-Hydroxyacetophenone 1



step of this synthesis, the hydroxy group of **1** is protected using triisopropylsilyl chloride (TIPSCl), DMAP, and $(i\text{-Pr})_2$NH in dichloromethane, to yield silyl ether **2** in 94% yield. Bromination of **2** was achieved by triturating **2** with *N*-bromosuccinimide and a catalytic amount of *p*-toluenesulfonic acid (PTSA), as reported by Stavber and co-workers,[6b] to give *α*-bromoacetophenone **3** in 65% yield. The carbonyl group of **3** was then selectively reduced by $NaBH_4$ in THF to afford alcohol **4** in 73% yield. In the next step, the hydroxy group of **4** was converted to a chloro atom by heating in $SOCl_2$ and the dihalo derivative **5** was isolated in 84% yield. Room temperature reaction of dihalo compound **5** with 2 equiv of $AgNO_3$ in acetonitrile, as reported by Lehmann and co-workers[6c] for the preparation of benzyl nitrates from benzyl bromides, afforded regioselectively nitrate ester **6** in 96% yield.

In order to determine the applicability of the aforementioned method of synthesizing regioselectively 3-substituted 2,3-dihydrobenzofurans, nitrate ester **6** (Scheme 2) was dissolved in dry THF under a nitrogen atmosphere, the temperature was lowered to −78 °C, and then the appropriate nucleophile (RH) was slowly added, over 1 min, followed by the dropwise

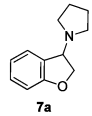
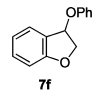
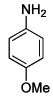
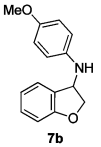
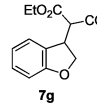
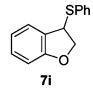
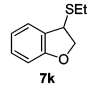
Scheme 2. Plausible Mechanism for the Synthesis of 3-Substituted 2,3-Dihydrobenzofurans



addition of TBAF at the same temperature. In the case of MeOH or 2-PrOH these solvents were added instead of THF to react also as nucleophiles. The reaction is postulated to proceed by attack of a fluoride anion onto the silyl ether, breakage of the Si−O bond, and elimination of a nitrate anion to generate the corresponding *o*-QM *in situ*. The latter is then trapped by different C, N, O, and S nucleophiles to generate Michael addition phenoxide ion intermediates that undergo intramolecular 5-*exo*-*tet* elimination of a bromide anion, to afford 3-substituted 2,3-dihydrobenzofurans **7a**−**k**. The type of nucleophiles used, the products, and the yields obtained are shown in Table 1.

In an effort to reduce by one the number of synthetic steps from 2-hydroxyacetophenone **1** to the 3-substituted 2,3-dihydrobenzofurans **7a**−**k**, we thought of reacting dihalo compound **5** with TBAF in THF at −78 °C so that fluoride Si−O bond cleavage would bring on conjugate elimination of a chloride anion (Cl instead of ONO_2 in the mechanism of the

Table 1. Synthesized 3-Substituted 2,3-Dihydrobenzofurans

entry	RH	product	yield (%)[a]	entry	RH	product	yield (%)[a]
1		 **7a**	82	6	PhOH	 **7f**	59
2		 **7b**	74	7	$CH_2(CO_2Et)_2$[c]	 **7g**	76
3	NaN_3	 **7c**	79	8		**7h**	67
4	MeOH[b]	 **7d**	88	9	PhSH	 **7i**	85
5	i-PrOH[b]	 **7e**	68	10		**7j**	80
				11	EtSH[c]	 **7k**	76

[a]Isolated yields. [b]Instead of using THF as a solvent, methanol or 2-propanol were used. [c]Sodium hydride was used to generate the anions.

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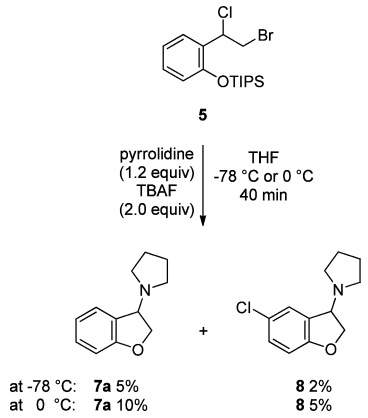
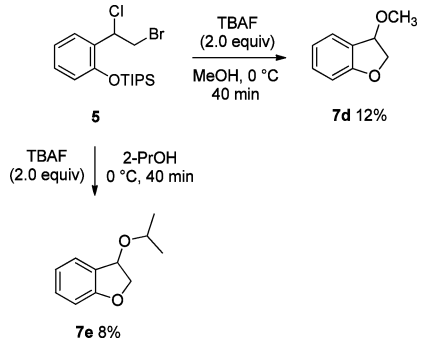
Scheme 2) and *o*-QM generation which, in the presence of pyrrolidine, would undergo Michael addition followed by intramolecular 5-*exo-tet* elimination of the bromide anion, to afford **7a**. To our surprise, this reaction instead of giving solely **7a**, a second product, 1-(5-chloro-2,3-dihydro-1-benzofuran-3-yl)pyrrolidine **8**, was also isolated (Scheme 3). In the first

Scheme 3. Synthesis of 1-(2,3-Dihydrobenzofuran-3-yl)-pyrrolidine 7a and Its 5-Chloro Derivative 8 from [2-(2-Bromo-1-chloroethyl)phenoxy](triisopropyl)silane 5



experiment at −78 °C, **7a** and **8** were isolated by SiO_2 column chromatography in 5% and 2% yield, respectively. When the reaction was repeated at 0 °C followed by stirring at rt for 40 min, **7a** and **8** were isolated by column chromatography in 10% and 5% yield, respectively. At present we are not in a position to suggest a plausible ionic or radical mechanism for the formation of **8**. Repeating this reaction and using instead of THF and pyrrolidine either MeOH or 2-PrOH, to act as both solvents and nucleophiles at 0 °C, afforded compounds **7d** and **7e** in only 12% and 8% yields, respectively (Scheme 4). No chlorination products were detected in these two reactions.

Scheme 4. Synthesis of 3-Methoxy (or Isopropoxy)-2,3-dihydrobenzofurans 7d,e from [2-(2-Bromo-1-chloro-ethyl)phenoxy](triisopropyl)silane 5



In conclusion, we have presented a new one-pot regioselective synthesis of 3-substituted 2,3-dihydrobenzofurans from 2-bromo-1-{2-[(triisopropylsilyl)oxy]phenyl}ethyl nitrate via *o*-QM generation *in situ* and Michael addition of different C, N, O, and S nucleophiles to give a phenoxide anion intermediate which undergoes intramolecular 5-*exo-tet* elimination of a bromide anion. *o*-QM is formed from the nitrate ester by a fluoride anion nucleophilic cleavage of the silyloxy *σ*-bond using *n*-tetrabutylammonium fluoride whereby the phenoxide anion intermediate undergoes conjugate elimination of a nitrate anion.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures for all reactions and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: gvarvoun@cc.uoi.gr.

Notes

The authors declare no competing financial interest.

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