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Tetrahedron Letters 46 (2005) 707–710

Tetrahedron Letters

Some reactions of persistent benzofuranone radicals related to the 'old' diazonamide structure

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Received 9 November 2004; accepted 17 November 2004

Abstract—The benzofuranone dimers **9** and **10/11** readily (ca. 75 °C) dissociate to the persistent radicals **16** and **17** respectively, which are stable to, dioxygen. The OMe analog **25** dissociates to form the radical **24**, which reacts with dioxygen of TEMPO to give **26**.

The original structure of diazonamide A, **1**[1] was corrected to **2** by Harran and co-workers,[2] and the total synthesis of **1** and **2** has been reported, Scheme 1.[3] Prior to the structural correction we had been interested in the formation of the central C30–C10 bond of **1** from intermediates such as **3**, **4**, and **5**. Since there have been a recent resurgence of interest in benzofuranyl radicals and their exceptional stability even toward dioxygen,[4] we report in this letter some of our own observations.

The 2-deoxy version of **3**, namely **16** is a known radical, and the precursor **6** (Scheme 2) is readily made in 27% yield by heating mandelic acid with phenol.[5] Most interestingly, it has been reported that treatment of **6** with Na/Et_2O followed by iodine gave the dimer **8/9**, which on heating at 70–75 °C dissociates to the radical **16** (blue).[6] The persistent radical[7] **16** will oxidize thiols to disulfides,[8] and exposure of **6** to sunlight and air gives the dimer **8/9** rather than peroxides.[9]

2-Oxo-2,3-dihydro-3-phenylbenzo[*b*]furan **6** and its 5-methyl analog **7** were synthesized by condensation of mandelic acid with phenol and *p*-cresol, respectively. Deprotonation of **6** with LDA/THF or sodium/Et_2O, and subsequent single electron transfer reaction (SET) with iodine produced the radical **16**, which dimerizes to give **9** (84%, mp 110–113 °C, *meso* by X-ray, Fig. 1), Scheme 2. The *dl*-form, namely **8** was not detected.[4a] The X-ray crystallographic analysis shows that the C3–C3′ bond length in **9** is 1.60 Å.

An alternative dimerization route involved reaction of **7** with 4-*N*,*N*-dimethylaminopyridine (DMAP)/CH_2Cl_2 and $TiCl_4$,[10] to produce a titanium enolate complex and further oxidation with $TiCl_4$ gave the dimers **10** and **11** (57% yield, mp 185–195 °C, ratio 6.8:1, or vice versa by ^1H NMR δ 2.24 (s) and 2.31 (s) ratio).

A dichlorobenzene solution of **10/11** became blue when it was heated to 75 °C. The blue color did not disappear when the solution was exposed to air, but vanished when the solution was cooled to room temperature. This suggests that the radical **17** exists in an equilibrium with the dimers **10/11**. Interestingly, after the solution was cooled to room temperature, the ratio of the *dl*:*meso* (or vice versa) of the recovered dimer **10/11** changed to 5:1.

The low dissociation energy[11] of the C3–C3′ bond is attributed to the steric compression in the structure of **17**. The repulsive interactions between groups are relieved when the central carbon atom passes from tetrahedral bonding to the trigonal bonding. Such steric compression induced bond weakening has been extensively observed in thermolysis reactions leading to free radicals.[12]

Treatment of **7** with sodium and $PhSSO_2Ph$ gave the sulfide **13** (87%). A dichlorobenzene solution of **13** (0.25 mol/L) started turning blue when the temperature reached 125 °C. The solution turned light yellow upon cooling, and both sulfide **13**, dimers **10/11** and

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Keywords: Diazonamide; Benzofuranyl radicals; Pummerer reaction.

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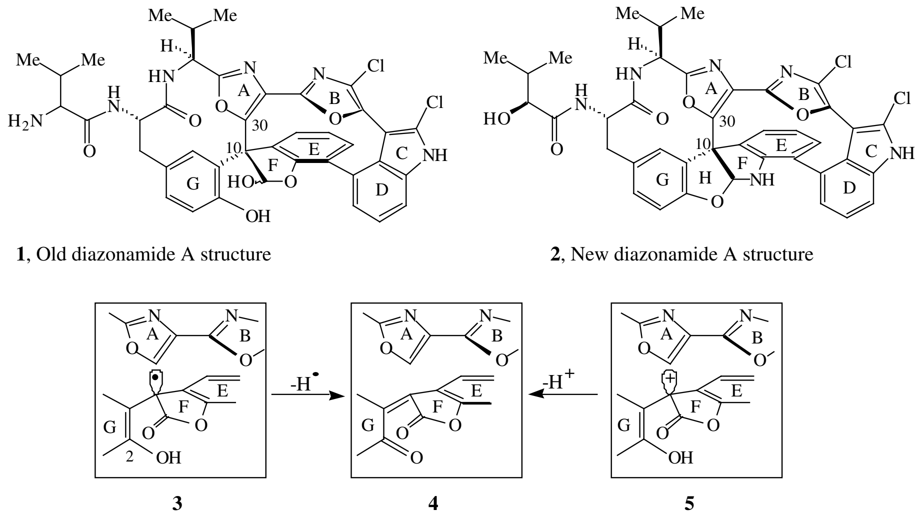
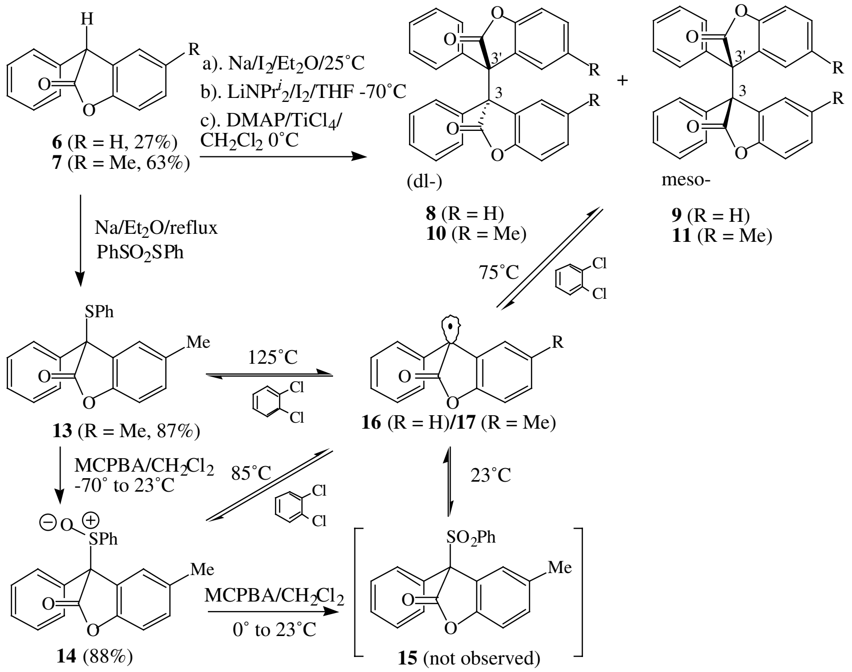
0040-4039/$ - see front matter © 2004 Published by Elsevier Ltd.
doi:10.1016/j.tetlet.2004.11.103



Scheme 1. Structures of Diazoamides.



Scheme 2.

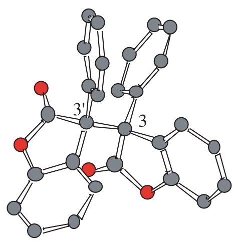
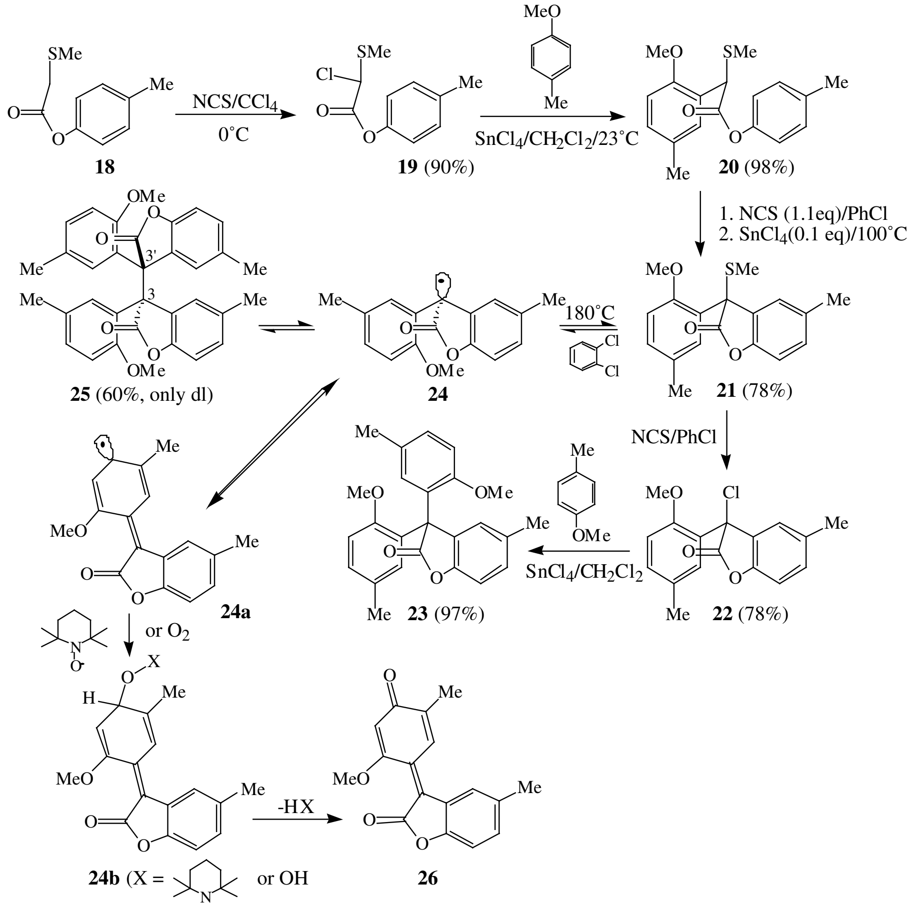


Figure 1. Chem 3D representation of **9** from X-ray coordinates.

diphenyldisulfide were present. Oxidation of the sulfide **13** with 1.1 equiv of *m*-CPBA produced the sulfoxide **14** in 88% yield. Formation of the radical **17** (blue color) was observed when **14** was heated to 85 °C in dichlorobenzene. Upon cooling the solution again became light yellow, and both **14** and **10/11** were isolated. Oxidation of the sulfide **13** with 2.5 equiv of *m*-CPBA or sulfoxide **14** with 1.2 equiv of *m*-CPBA (from −70 to 23 °C) gave only the dimers **10/11**, and none of the sulfone **15** was observed.

To examine the 2-oxy version of Scheme 2 we treated **18** with *N*-chlorosuccinimide (NCS) at 0 °C in CCl_4 to give **19**, which was treated with *p*-methylanisole and $SnCl_4$ to give **20** in 98% yield, Scheme 3. It was notable that the intermolecular Pummerer reaction took place preferentially to the intramolecular reaction.[13] After treatment of **20** with NCS/PhCl for 2 h the mixture was filtered,



Scheme 3.

and a catalytic amount of $SnCl_4$ was added and the solution was heated to 100 °C. After 10 min the lactone **21** (IR 1798 cm^{-1}) was isolated in 78% yield. Treating the ester **20** with 2 equiv of *N*-chlorosuccinimide, followed by heating at 100 °C, gave the chlorolactone **22** (IR 1814 cm^{-1}) in 78% yield. It was possible to generate the chlorolactone **22** directly from the lactone **21** by heating it with NCS in chlorobenzene.

The benzofuran-2-one **21** was heated in degassed dichlorobenzene, and at 160 °C (internal temperature) a slight blue-green color appeared, which intensified when the temperature reached 180 °C. The solution of the *bis*-benzylic radical **24** remained green upon cooling to about 80 °C, then turned pale yellow below this temperature. The pale yellow solution could be re-heated and the green color would re-appear at 80 °C. From this reaction the dimer **25** was isolated in 40–60% yields. While the radical **24** can dimerize in two forms, *meso* and *dl*, only the *dl*-dimer was detected, and its structure was determined by X-ray, Figure 2 (C3–C3′ bond is 1.622 Å).

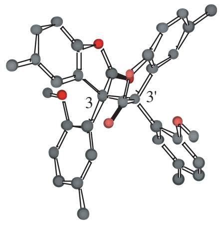


Figure 2. Chem 3D representation of **25** from X-ray coordinates.

When the dimer **25** (20 mg) was heated in chlorobenzene at 120 °C in the presence of TEMPO the orange oxidation product **26** (7 mg) was isolated. Heating **25** in the presence of air also produced small amounts (<5%) of **26**. Presumably, the resonance form **24a** intercepts TEMPO or dioxygen to give **24b**, which leads to **26**.

Finally, to examine the cationic pathway in Scheme 1, we treated **22** in CH_2Cl_2 with $SnCl_4$ in the presence of *p*-methylanisole to give the lactone **23** (97%). All attempts to trap either the radicals **16**, **17**, and **24**, or cation (from **22**) with simple oxazoles failed.

Acknowledgements

The National Institutes of Health (CA 50512), Robert A. Welch Foundation, Merck Research Laboratories and Novartis are thanked for their support of this research.

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