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Facile Triphenylphosphine Deoxygenation of Benzofuran Dioxetanes, their Epoxides and Valence-Isomeric Quinone Methides

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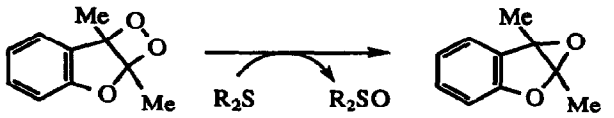
Abstract: The triphenylphosphine deoxygenation of 2,3-dimethylbenzofuran, 2,3-dimethylindole- and 2,3-dimethylindene dioxetanes 2 leads to the respective epoxides 4 through the intermediary phospholanes 3, of which the indene and indole derivatives 3d,e were detected by low-temperature NMR spectroscopy; with excess Ph_3P the benzofuran dioxetane 2a affords the benzofuran 1a, a novel process in which the resulting benzofuran epoxide 4a is in situ deoxygenated.

The chemistry of 1,2-dioxetanes, four-membered ring peroxides, has been intensively studied during the last two decades.[1] Previous work has shown that the main transformations of these highly strained molecules comprise phosphine[2] and sulfide[3] deoxygenation to the corresponding epoxides and $LiAlH_4$[4] and thiol[5] reductions to their 1,2-diols. More recently, S_N2 attack of π nucleophiles like electron-rich olefins,[6a] enamines,[6b] and heteroatom nucleophiles[6c,d] on 3,3-disubstituted dioxetanes has been reported. The toxicologically relevant 2,3-dimethylbenzofuran dioxetane, conveniently prepared by photooxygenation, gave with R_2S (R=Me and Ph) the labile benzofuran epoxide (Eq. 1), which for the first

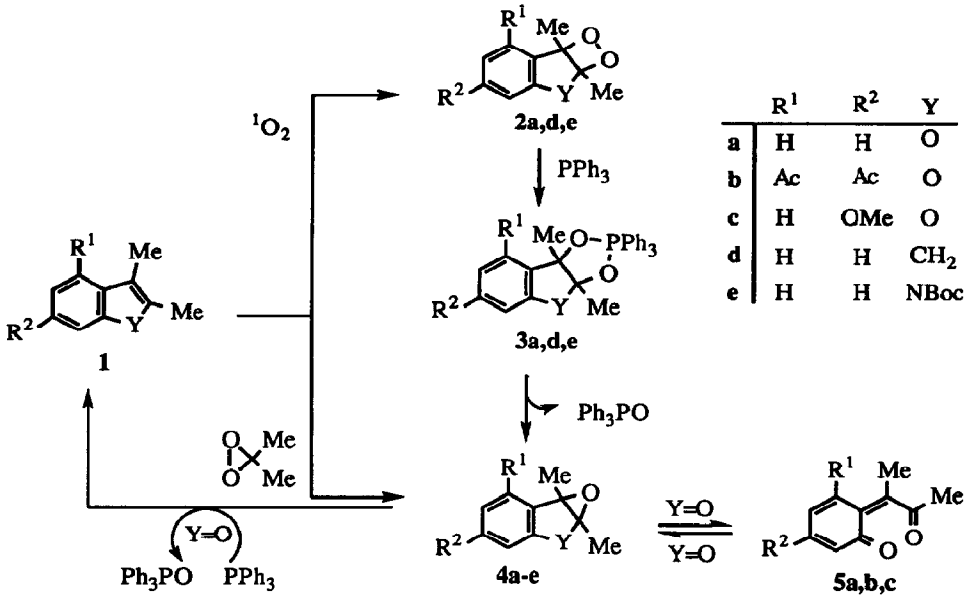


(Eq. 1)

time was detected by the NMR spectroscopy and belongs to the class of most reactive epoxides known to date. They are implicated in the high mutagenicity exhibited by the benzofuran dioxetanes in the *Salmonella typhimurium* TA100 strain (Ames test).[7]

Herein we present the unprecedented observation that the benzofuran dioxetanes are efficiently deoxygenated to their benzofurans by excess triphenylphosphine through the intermediary epoxides. The analogous indole and indene dioxetanes lead as well to the expected epoxides, but the latter are resistent towards further deoxygenation by triphenylphosphine under these conditions.

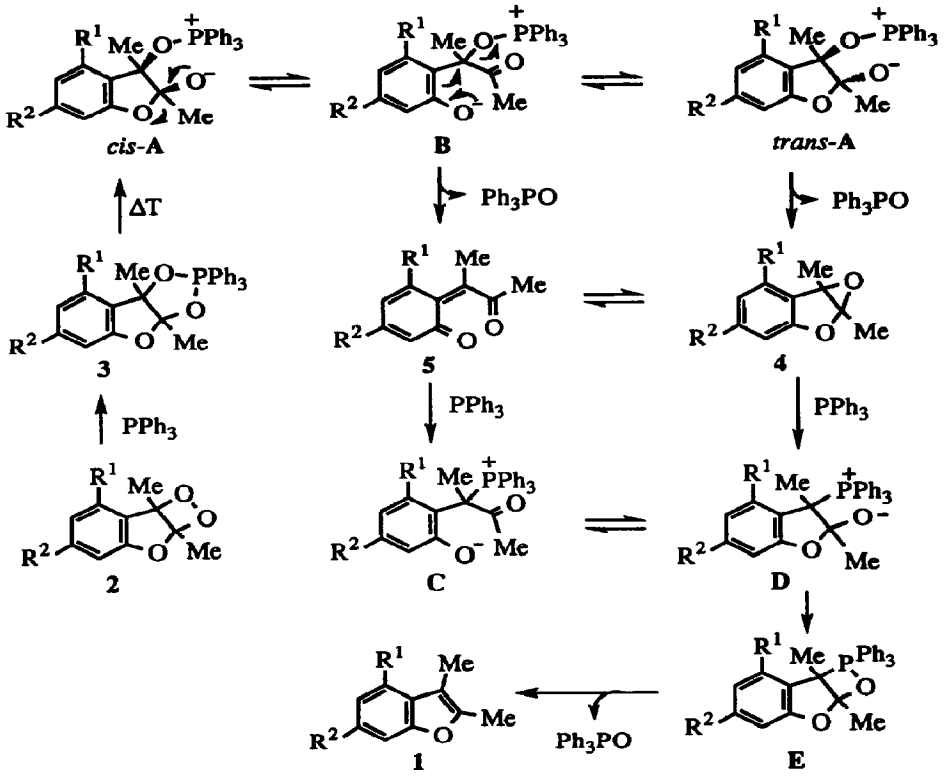
The reaction of benzofuran dioxetane **2a** with ca. three equivalents of Ph_3P at -78 °C in $CDCl_3$ afforded within 5 min the corresponding benzofuran **1a** (Scheme 1). A reasonable mechanism for the formation of the



Scheme 1

benzofuran **1a** is offered in Scheme 2, in which first biphilic insertion[2b] of Ph_3P into the peroxide bond generates the labile phospholane **3a**. The latter leads on P-O bond scission to the intermediate *cis*-**A**, which opens up to **B**, reclosure generates *trans*-**A**. Elimination of Ph_3PO from the intermediate **B** by nucleophilic attack of the ambident phenoxide ion at the benzylic carbon affords the corresponding quinone methide **5a**, while backside attack of the alkoxide ion in intermediate *trans*-**A** leads to the epoxide **4a** (Scheme 2). Subsequent nucleophilic addition of Ph_3P to benzofuran epoxide **4a** or the quinone methide **5a** gives on loss of Ph_3PO the benzofuran **1a** by trespassing the intermediates **C**, **D** and **E** (Scheme 2). Unfortunately, neither the initial phospholane **3a** nor the phosphaoxetane **E** could be detected by NMR spectroscopy even at -100 °C.

To show that in the novel phosphine deoxygenation **2a** → **1a** the epoxide **4a** and quinone methide **5a** intervene, the authentic benzofuran epoxides **4a**[7a] and **4b**[8] and the quinone methide **5c**[9a] were prepared by dimethyldioxirane oxidation of the corresponding benzofurans **1a-c** and both treated at -60 °C with Ph_3P (1.1 equiv.). Indeed, within five minutes, the corresponding benzofurans **1a-c** were produced quantitatively (Scheme 1). In contrast, usually, the deoxygenation of epoxides by Ph_3P to the corresponding olefins requires much higher temperatures (ca. 80 °C[10]). These control experiments unequivocally establish that the Ph_3P deoxygenation of the dioxetanes **2** proceeds through the epoxides **4** and/or quinone methides **5**. Since we showed previously[9] that the epoxides **4a-c** and the quinone methides **5a-c** are in equilibrium with one another, irrespective of whether one starts from the epoxides **4** or its valence-isomeric quinone methide **5**, the same phosphaoxetane intermediate serves as precursor to the deoxygenated benzofuran **1** (Scheme 2). Although the particular phosphaoxetanes **E** are not known, such labile species have been spectrally observed



Scheme 2

in the Wittig olefination reaction.[11] Consequently, they may be considered as *bona fide* intermediates also in the Ph_3P deoxygenation **2** → **1**, but the remaining dipolar structures **A** through **D** in Scheme 2 have been included for mechanistic convenience. As an analogy, the deoxygenation of a benzoxepin by nucleophilic attack of Ph_3P on the corresponding valence-isomeric quinone methide is cited.[12]

A different situation was encountered for the 2,3-dimethylindene and 2,3-dimethylindole dioxetanes **2d,e** (Scheme 1). Thus, treatment of the dioxetanes **2d,e** with Ph_3P at -20 °C in $CDCl_3$ gave within 20 min the phospholanes **3d,e**, which could be directly observed by low-temperature NMR spectroscopy in that the resonances of the phospholanes **3d,e** appeared at the expense of the characteristic dioxetane signals.[13] Related dioxetane-derived phospholanes have been previously reported[2b], but the indole derivative **3e** is new. On warm-up, the phospholanes **3d** (20 °C) and **3e** (40 °C) gave on Ph_3PO extrusion the respective epoxides **4d,e**; however, the latter did not deoxygenate to the indene **1d** and indole **1e** even with excess Ph_3P. As expected, in the presence of Ph_3P the indene epoxide **4e**[14] persists at room temperature, but the indole epoxide **4e**[15] deteriorates into a complex , intractable mixture.

Except for the very labile benzofuran-derived phospholanes **3a-c** (not detected spectrally even at -100 °C), direct evidence for the biphilic insertion products **3d,e** has been provided. The facile ring-opening of the benzofuran-based phospholanes **3a-c** to the dipolar intermediates **B** with concomitant Ph_3PO elimination to the epoxides **4a-c** and/or quinone methides **5a-c** appears to be responsible why the phospholanes **3a-c** could not be detected even at -100 °C. Moreover, in view of the fact that these benzofuran epoxides **4a-c**, unlike the indene and indole derivatives **4d,e** , are towards nucleophiles the most reactive epoxides known to date,[9] they are deoxygenated by the Ph_3P nucleophile to the original benzofurans **1a-c** through the intermediary phosphaoxetanes **E** (Scheme 2). The propensity of benzofuran dioxetanes to be deoxygenated to the benzofurans by excess Ph_3P at subambient temperature is unprecedented.

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13. **3d**: ^1H NMR (200 MHz, $CDCl_3$, -40 °C): δ = 1.35 (s, 9 H, Boc), 1.51 (s, 3 H, CH_3), 1.58 (s, 3 H, CH_3), 7.02 - 7.60 (m, 19 H).- ^{13}C NMR (50 MHz, $CDCl_3$, -40 °C): δ = 17.4 (q, CH_3), 19.5 (q, $C(\underline{C}H_3)_3$, 21.5 (q, CH_3), 79.3 (s, ^2J (C,P) = 32 Hz, $\underline{C}OPPh_3$), 80.6 (s, ^2J (C,P) = 27 Hz, $\underline{C}OPPh_3$), 82.5 (s, $\underline{C}(CH_3)_3$), 122.1 - 133.2 (aromatic signals overlap), 144.1 [s, ^1J (C,P) = 118 Hz, PPh_3 (*i*-C)], 144.5 [s, ^1J (C,P) = 118 Hz, PPh_3 (*i*-C)], 151.9 (s, C=O). **3e**: ^1H NMR (200 MHz, $CDCl_3$, -40 °C): δ = 1.52 (s, 3 H, CH_3), 1.58 (s, 3 H, CH_3), 3.27 (AB, *J* = 11.2 Hz), 7.01 - 7.46 (m, 19 H).- ^{13}C NMR (50 MHz, $CDCl_3$, -40 °C): δ = 17.2 (q, CH_3), 17.7 (q, CH_3), 35.6 (t), 82.7 (s, ^2J (C,P) = 31 Hz, $\underline{C}OPPh_3$), 84.9 (s, ^2J (C,P) = 33 Hz, $\underline{C}OPPh_3$), 121.3 - 137.9 (aromatic signals overlap).
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