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Smooth photogeneration of α,*n*-didehydrotoluenes (DHTs)*

Stefano Protti, Davide Ravelli, Maurizio Fagnoni, and Angelo Albini‡

PhotoGreen Lab, Department of Chemistry, University of Pavia, via Taramelli 12, 27100 Pavia, Italy

Abstract: Irradiation of the three isomeric (chlorobenzyl)trimethylsilanes in methanol–water generates the corresponding didehydrotoluenes (DHTs). The process involves expulsion of a chloride ion to give the triplet phenyl cation and ensuing elimination of the trimethylsilyl cation. This straightforward generation of DHT intermediates overcomes a shortcoming of previous methodology (cycloaromatization of enyne-allenes), which is limited to the *meta*-isomer, and opens the path for understanding the chemistry (and possibly the biological action) of these unusual intermediates.

Keywords: diradicals; didehydrotoluenes; phenyl cations; photochemistry.

INTRODUCTION

The high energy of excited states facilitates those reactions that involve deep-seated molecular or skeletal transformations. In particular, high-energy intermediates are photochemically generated under mild conditions that have no parallel in thermal chemistry. Intermediates that can be generated include radicals, ions, carbenes, but also highly unsaturated species, such as cumulenes (an important example being the generation of didehydroazepines (DHTs) from phenyl azides via singlet nitrene [1]), *ortho*-quinodimethanes [2], and many others. For the two last mentioned intermediates, photochemical generation is practically the only significant approach for DHTs, and one of the best choices for *ortho*-quinodimethanes.

A possible application is based on molecules that contain two moieties that serve different purposes (or a single one that serves both of them). The first moiety (**A** in Fig. 1) forms a complex with a target molecule or site **C**, while the second one is susceptible of photochemical activation (**B**). Irradiation generates an intermediate able to form or to cleave a bond in the neighboring structure. In this way, a weak interaction (the formation of a complex) "guides" the formation of a strong one, involving the covalent attachment of the entire "tag" to the original location. As mentioned, this occurs under mild conditions, not otherwise obtained, that may allow, for example, the use of these probes in living cells. Relevant examples of this principle include photochemical labeling [3a], imaging [3b], photoinduced drug release [4], "green" synthesis [5], and more.

Photogeneration of other classes of intermediates is less well known and offers scope for further exploration of the peculiar advantages of this approach.

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‡Corresponding author: E-mail: angelo.albini@unipv.it

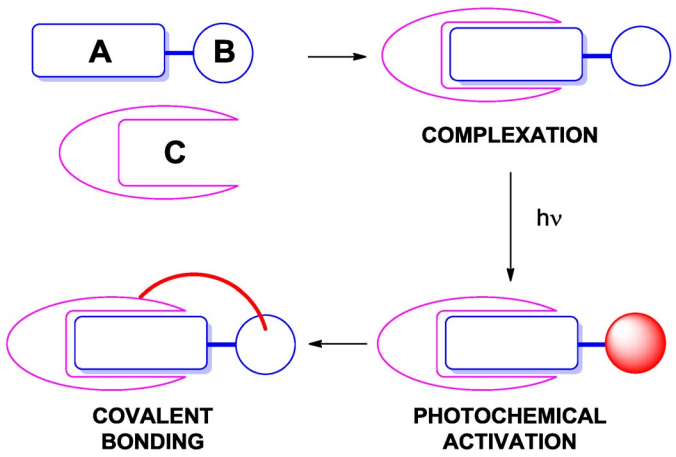
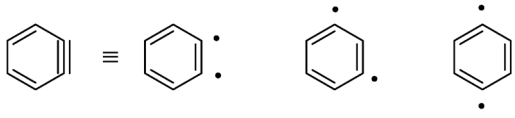


Fig. 1 From weak interaction to covalent bond via photochemical activation (see text).

A fitting example is that of benzynes that are commonly generated by base- or metal-induced elimination, although few examples of photochemical generation are also known [6,7]. The name alludes to the presence of a triple bond in such a structure, but obviously this is no realistic picture and the name of didehydrobenzene (C_6H_4) seems better suited for these intermediates (the *ortho*-isomers) and for the *meta*- and *para*-isomers (Chart 1, top part). All of them are generally indicated by a diradical formula. *p*-Benzynes became of considerable interest in recent years in view of their capability to cleave double-strand DNA, and they are quite exclusively formed by the Bergman cyclization of enediyne derivatives (Scheme 1a) [7].

DIDEHYDROBENZENE ISOMERS (C_6H_4)



DIDEHYDROTOLUENE ISOMERS (C_7H_6)

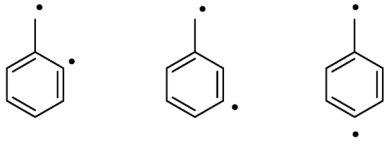
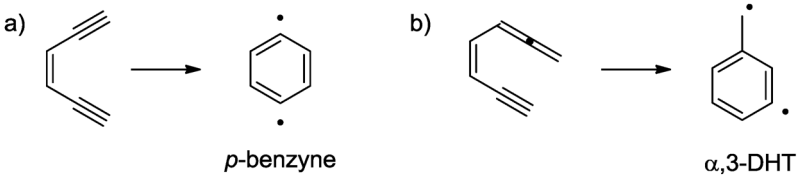


Chart 1



Scheme 1 Known routes for the generation of (a) *p*-benzynes and (b) α,3-DHTs by cycloaromatization reactions.

A related case is that of DHTs (C_7H_6), which differ from the previous ones for being σ,π- rather than σ,σ-diradicals (Chart 1, bottom part). Actually, only the α,3-isomer has been generated in solution, via a Myers–Saito cycloaromatization process of the corresponding enyne-allene (Scheme 1b) [7]. The aggressive intermediates produced by both Bergman and Myers–Saito rearrangements have become of interest for the development of new anticancer drugs, alternative to the natural enediyne antitumorals dynemicin A, neocarzinostatin (Chart 2), and esperamicins [8]. Indeed, the starting polyene moieties are present in natural compounds endowed with cytostatic action. It is assumed that this activity is due to the DNA cleavage in tumor cells caused by the in situ smooth formation of diradicals. These antitumorals are typical examples of molecules containing both a flat accepting moiety which may have a complexing role and the chemically active part. Moreover, simple molecules that are models for the active moiety have been synthesized and mechanistically investigated [9].

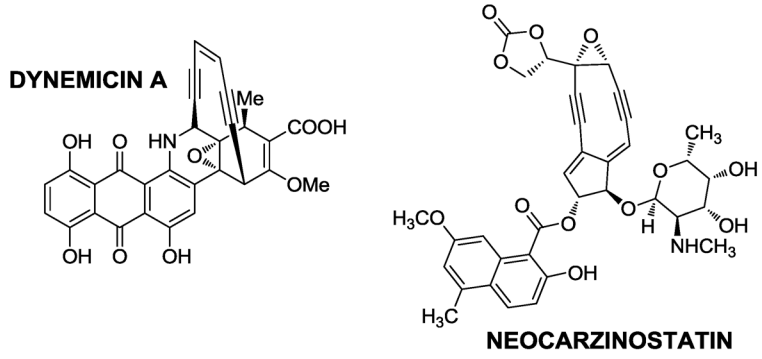
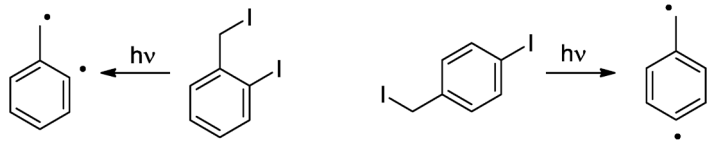


Chart 2

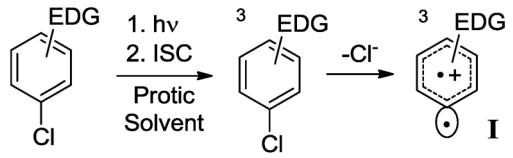
AN ALTERNATIVE APPROACH

Synthesis of the precursors for existing methodology is nontrivial and invites exploration of simpler approaches. Photochemistry offers such an approach, based upon ready access to high-energy intermediates, for example, via elimination reactions. This applies also to this case; as a matter of fact, photochemically induced elimination is the elective method for the generation of DHTs in matrix, where both *o*- and *p*-DHTs have been generated by photolysis of the corresponding iodobenzyl iodides. This method relies on the subsequent fragmentation of two C–I bonds and cannot be transferred to solution, obviously, since there is no way to avoid that the first intermediate reacts before it undergoes the second photochemical cleavage (Scheme 2) [10].



Scheme 2 Photogeneration of DHTs in matrix.

The scheme we propose here is based again on elimination reactions, but involves a single photochemical act leading to the consecutive splitting of two groups of opposite polarity [11]. Serendipitously, the scheme involves the co-exploitation of two general reactions we have been separately investigating in the last few years, namely, the heterolytic C–Cl bond cleavage in aromatic halides

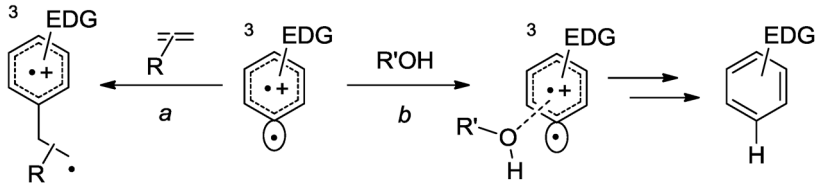


Scheme 3 Photogeneration of triplet phenyl cations **I**.

(Scheme 3) and the photoinduced electron transfer (PET) oxidation of benzyl derivatives (see below) [12].

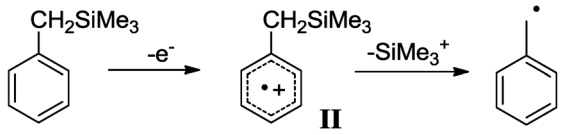
As for the first reaction, aromatic halides undergo efficient intersystem crossing (ISC), and the chemistry generally proceeds via the triplet state. These compounds suffer a solvent-dependent fragmentation, particularly when bearing an electron-donating ring-substituent. This occurs as a homolytic process in apolar or moderately polar solvents, but as a heterolytic cleavage in protic solvents [13].

This reaction offers a convenient entry to phenyl cations, intermediates that are practically nonaccessible through thermal methods [14]. On the contrary, these are conveniently generated photochemically, with the additional advantage that the triplet state is arrived at, since the reaction involves the triplet halide. This is important because, in contrast to the singlet that is an unselective electrophile with a $\pi^6\sigma^0$-structure, the $\pi^5\sigma^1$-configuration of the triplet (**I**) makes it a diradical rather than a localized cation (Scheme 3), allowing it to react with π-bond nucleophiles. Trapping of a triplet phenyl cation by an alkene indeed leads to a distonic diradical (Scheme 4, path *a*). On the other hand, with σ-nucleophiles there is no way to accommodate the two parallel electrons [15,16], and in such a case a weakly stabilized complex is formed. This increases the lifetime of the triplet cation and allows for further reactions. In most solvents, the process actually occurring is the other general reaction of these intermediates, reduction (Scheme 4, path *b*) [15].



Scheme 4 Reactions of triplet phenyl cations with alkenes (path *a*) and σ-nucleophiles (path *b*).

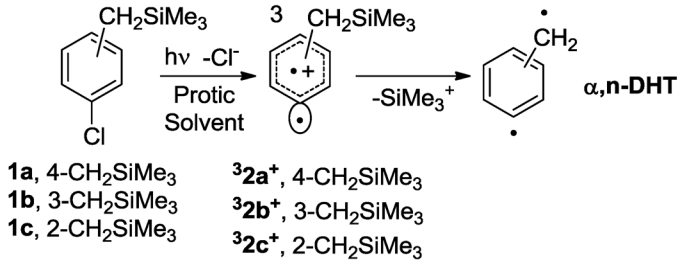
The first step of the proposed scheme is thus the photogeneration of a stabilized (e.g., in water or water-containing solvents) triplet phenyl cation. Then, an electrofugal group is required. Actually, cations are known to be split off from benzylic radical cations (e.g., **II**), particularly under the assistance of a nucleophilic solvent [17]. In turn, the latter intermediates are conveniently generated upon single electron transfer from a benzene derivative to an excited sensitizer [12,18]. The π^5-nature of radical cations favors the fragmentation of benzylic substituents (e.g., a trimethylsilyl cation) suitably aligned with the π-cloud to form benzyl radicals (Scheme 5). Now, the π^5-structure of the benzylic radical cation is remarkably analogous to that of the benzene π-moiety of triplet phenyl cation, which differs only for the σ-part (compare structures **I** and **II** in Schemes 3 and 5, respectively). We surmised that the vacancy in the π-cloud could have the same effect towards the group in the α-position, thus causing in cations the occurrence of the same fragmentation as in radical cations.



Scheme 5 Benzyl radicals from the one electron oxidation of benzylsilanes.

DHTs FROM (CHLOROBENZYL)TRIMETHYLSILANES

On this basis, the following plan was formulated for the generation of a DHT through a single excitation step. In a protic solvent the heterolytic aryl–chlorine bond cleavage is efficient, the triplet cation is stabilized, and benzylic fragmentation, again favored by the protic solvent, should give the desired intermediate. A trimethylsilyl group is the obvious choice for the role of leaving cation. Furthermore, the reasoning is independent from the relative position of nucleo- and electrofugal groups and thus holds for all of the isomers (Scheme 6). With this plan in mind, the photochemistry of the three (chlorobenzyl)trimethylsilanes (**1a**–**c**) was studied through a combined computational and experimental approach.

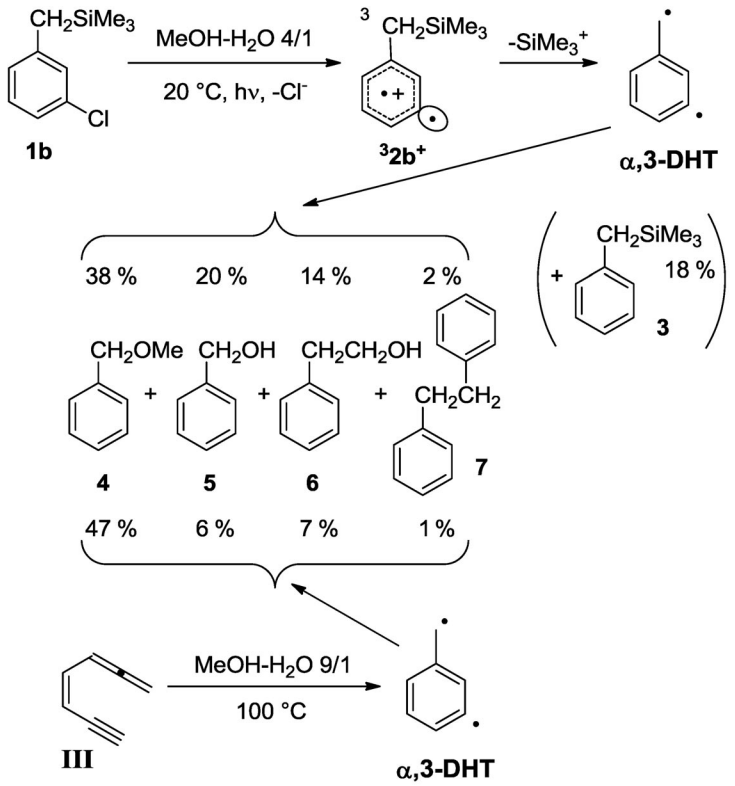


Scheme 6 Generation of α,*n*-DHT isomers by irradiation of (chlorobenzyl)trimethylsilanes (**1a–c**).

Summarily, density functional theory (DFT) calculations at the UB3LYP/6-311G+(2d,p) level of theory supported that excitation of these benzyl silanes in a polar medium and efficient ISC caused polarization of the C–Cl bond and fragmentation in the triplet state [11], initiating a process that ultimately led to DHTs.

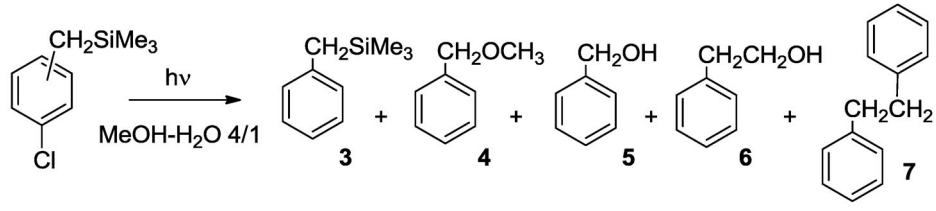
In the experiment, 0.025 M solutions of the (chlorobenzyl)silanes **1a–c** were purged with nitrogen in quartz tubes and irradiated using 4 Hg lamps (15 W, emission centered at λ = 254 nm) for 1 h. The photoproducts formed were identified by comparison with authentic samples by using gas chromatography/mass spectrometry (GC/MS) analysis. Quantum yields were measured by irradiation of a 10^{-2} M solution of the above compounds by irradiation by a 15 W, 254 nm lamp.

Under these conditions, irradiation of (3-chlorobenzyl)trimethylsilane (**1b**) in apolar or even in a polar, nonprotic, solvent such as acetonitrile gave benzyltrimethylsilane with low efficiency. Shifting to MeOH increased the quantum yield to 0.90 and to a MeOH–H_2O 4/1 mixture to 0.82, silicon-free products being predominant in the latter case. Actually, the compounds obtained (benzyl methyl ether **4**, benzyl alcohol **5**, phenethyl alcohol **6**, and bibenzyl **7**) were the same formed (and in about the same ratio) as those obtained from the cycloaromatization of enyne-allene **III** (Scheme 7). This is consistent with the idea that heterolytic C–Cl bond cleavage gives phenyl cation **2b**$^+$ in the triplet state. This is stabilized by water (actually, the only reaction from this intermediate is reduction to benzyltrimethylsilane **3**, now a minor product), that also favors desilylation to the DHT. As when generated by cycloaromatization, the last intermediate leads to the formation mainly of C–O bonds (**4**, **5**; via the so-called "ionic mechanism") and, to a minor extent, of C–C bonds (**6**, **7**; reasonably via radical coupling) [19].



Scheme 7 Product distribution obtained upon irradiation of silane **1b** and enyne-allene **III**.

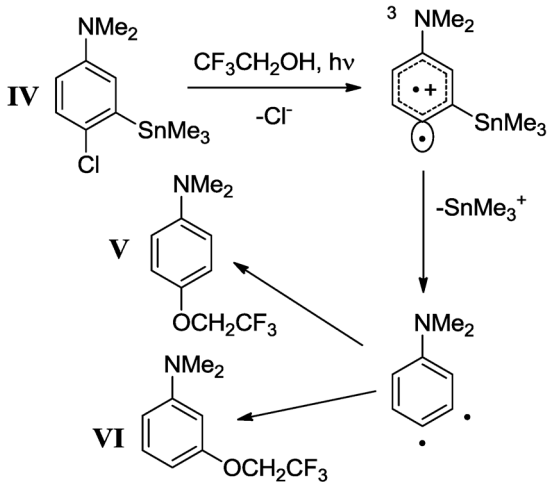
As mentioned above, our surmise was that a DHT could be formed by this path from all of the three isomeric chlorobenzylsilanes **1a–c**. Actually, irradiation of both the 2- and the 4-chlorobenzyl derivatives in MeOH–H_2O 4/1 gave products attributable to the intermediacy of the corresponding DHTs, in this case with a predominance of the radical coupling type products (**6**,**7**). The desilylation appeared to be less efficient with the *ortho*-derivative, from which an important amount of the benzylsilane **3** remained under these conditions (Scheme 8).



1a	2	4	0	39	14
1b	18	38	20	14	2
1c	23	4	2	25	4

Scheme 8 Photochemical reaction of the three isomeric chlorobenzylsilanes **1a–c** in aqueous methanol.

It may be added that in the meantime a related case of generation of a didehydro*benzene* via a related double heterolysis process has been likewise discovered, further documenting the varied chemistry stemming from phenyl cations (Scheme 9) [20]. In fact, irradiation of stannylated aniline **IV** in an ion-stabilizing, non-nucleophilic medium such as 2,2,2-trifluoroethanol, caused the consecutive elimination of the nucleofugal chloride anion and of the electrofugal Me_3Sn^+ group. As a result, the two isomeric trifluoroethyl ethers **V** and **VI** were formed upon solvent addition onto the didehydrobenzene intermediate [20].



Scheme 9 Generation of a substituted didehydro*benzene* from the photolysis of a stannylated chloroaniline.

CONCLUSION

In conclusion, both computation and experiment support that α,*n*-DHTs are accessible via a double elimination process from (chlorobenzyl)trimethylsilanes, potentially a general process that contrasts with the limited scope of the presently used cycloaromatization. This is an important challenge, because the preliminary experiments presented here suggest that isomeric DHTs exhibit a differentiated chemistry, with varied contributions of the "ionic" and "radical" paths. It is hoped that this develops into a large-scope method and makes available a variety of these intermediates. This would help in rationalizing their chemical behavior [21] and exploit their versatility through the judicious choice of structure and conditions. These species may find application in synthetic chemistry as well as the photoactivated moiety for labeling biological molecules or for specific drug release.

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