

Radicals

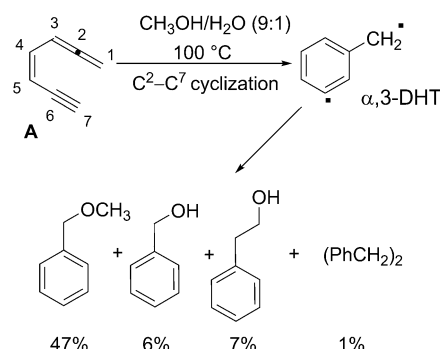
α,n -Didehydrotoluenes by Photoactivation of (Chlorobenzyl)-trimethylsilanes: An Alternative to Enyne–Allenes Cyclization**

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Chemotherapeutic agents must be able to kill tumor cells while being inactive against healthy cells. Typically, a prodrug is activated in situ by some mild mechanism and generates an aggressive intermediate that may for example, abstract hydrogen atoms from DNA and induce DNA cleavage and subsequent apoptosis. Among the few chemical classes that come close to this paradigm are highly unsaturated hydrocarbons, such as enediynes and enyne–allenes which are present in some natural compounds known as antibiotics (e.g. Neocarzinostatin or Dynemicin).^[1–4] These moieties cyclize under physiological conditions by converting two π bonds into a σ bond through the Bergman^[5] and the Myers–Saito^[5–7] reaction to give a *p*-benzyne and a $\alpha,3$ -didehydrotoluene ($\alpha,3$ -DHT), respectively.^[8]

The chemistry of heterosymmetric ($\pi^1\sigma^1$) $\alpha,3$ -DHT diradicals has been explored on simple models.^[5,9] Thus, when the enyne–allene **A** was heated at 100 °C in aqueous methanol, products from a diradical path (phenethyl alcohol and 1,2-diphenylethane) and from a polar path (methyl benzyl ether and benzyl alcohol; Scheme 1) were formed.^[6] The product distribution changed in deuterated solvents. For example, in CD₃OH [D₃]methyl benzyl ether became the exclusive product (70 % yield). The detailed mechanism and the dual polar/diradical reactivity of the DHT intermediate are still discussed.^[10] Models that mimic cyclization to DHT diradicals^[11,12] are limited to $\alpha,3$ -DHT. The $\alpha,3$ -DHT is the only isomer accessible by the Myers–Saito cyclization through the C²–C⁷ path (Scheme 1), which is in competition with the C²–C⁶ cyclization (discovered by Schmittel).^[13] Light-induced formation of $\alpha,3$ -DHT and related diradicals has been likewise reported.^[14]

It occurred to us that a double elimination process from toluene derivatives would offer a simple alternative entry to



Scheme 1. Thermal generation and reactivity of $\alpha,3$ -DHT in a MeOH/water mixture.

structures of this type, and potentially to all of the three isomeric α,n -DHTs. There is sparse indication of the generation of such intermediates from halotoluenes. These findings include the collision-induced halide elimination from gas-phase halobenzyl anions in a flow afterglow-triple quadrupole reported by Squires and co-workers,^[15] the EPR characterization of $\alpha,2$ - and $\alpha,4$ -DHTs by photolysis in a matrix of the corresponding iodobenzyl iodides reported by Sander and co-workers,^[16] and possibly the formation of a $\alpha,2$ -DHT by thermolysis of some phthalide derivatives.^[17] However, to the best of our knowledge, the generation of DHTs from aromatic compounds in solution has no precedent.

The rationale behind our choice is that electron-rich aryl chlorides have been shown to undergo heterolytic cleavage of the Ar–Cl bond upon irradiation. Phenyl cations (in the triplet state, $^3\text{Ar}^+$ having a $\pi^5\sigma^1$ structure) are thus smoothly generated (Scheme 2a).^[18,19] The efficiency depends on the nature of the substituents more than on their relative position with respect to the nucleofugal group, and is maximal when a strong electron-donating group (EDG; for example, NMe₂ and OR) is present. In neat solvents triplet phenyl cations are mainly reduced to the corresponding aromatic hydrocarbons,^[20] whereas in the presence of π -bond nucleophiles (NuE) arylation takes place with the concomitant release of the E⁺ group (Scheme 2a).

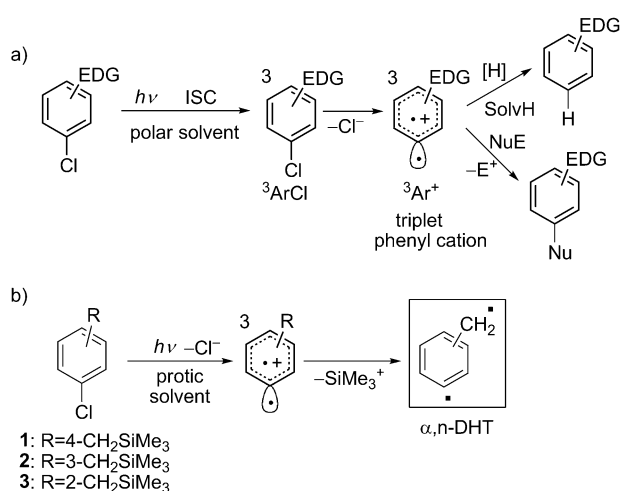
We reasoned that introducing an electrofugal group in the benzylic position would cause a second cleavage in the cation and generate the same DHTs which are formed from the enyne–allenes cycloaromatization (Scheme 2b). (Chlorobenzyl)trimethylsilanes (**1–3**) appeared to be suitable models for testing the hypothesis, since the CH₂SiMe₃ group facilitates initial Cl[–] loss (as an electron donor, comparable to

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Scheme 2. Photogeneration of triplet phenyl cations (a) and of α,n -DHTs (b). ISC = intersystem crossing.

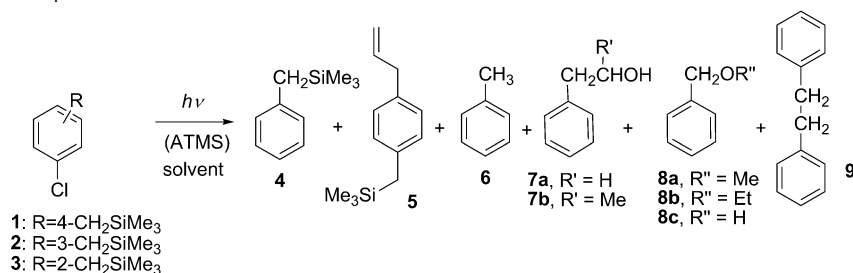
a OMe)^[21] and then should split off the SiMe₃⁺ cation, a process promoted by the electron-deficient nature of the π system^[22] in triplet phenyl cations.

The likelihood of a heterolytic cleavage of the C_{Ar}–Cl bond in these aromatic derivatives was first checked computationally. Calculations carried out in bulk MeOH at the CPCM-UB3LYP/6-311 + G(2d,p)//UB3LYP/6-311 + G(2d,p) level of theory for **1–3** clearly supported the hypothesis. Thus, excitation of the silane to the triplet state resulted in the heterolytic cleavage of the C_{Ar}–Cl bond (see the Supporting Information for further details).

The diagnostic arylation reaction in the presence of π -bond nucleophiles could be used to prove the intermediacy of triplet phenyl cations (Scheme 2a). If the expected process delivers DHT intermediates, then end products such as those depicted in Scheme 1 would be expected.

Turning to the experiment, the photoreactivity of **1** (0.025 M) at $\lambda = 254$ nm was examined (see Table 1, 1 h irradiation). The course of the reaction depended on the choice of medium. In ethyl acetate or acetonitrile less than 23 % of the reagent was consumed and the only product was the dechlorinated benzyltrimethylsilane **4**. In protic methanol, the consumption was almost complete (the quantum yield was one of the highest among aryl chlorides, $\Phi_{-1} = 0.71$)^[19a,23] and, apart from a little **4**, only silicon- and chlorine-free products were formed, that is, toluene (**6**), phenethyl alcohol **7a**, benzyl ether **8a**, and dibenzyl **9**

Table 1: Photoreactivity of compounds **1–3**.^[a]

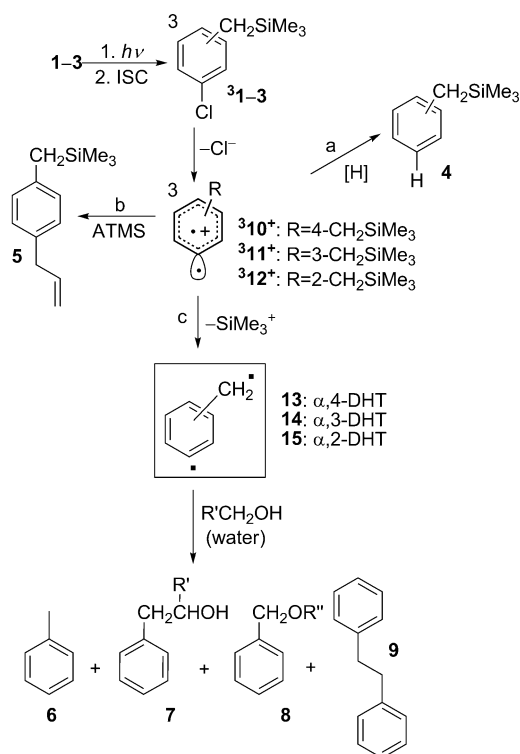


Entry	Halide	Solvent	Φ_{-1} ^[b]	Conv. [%]	4	5	6	Yield [%] 7	8	9	DHT/ cation ^[c]
1	1	CH ₃ COOEt (MeCN)	–	23 (20)	51 (37)	–	–	–	–	–	0
2	1	MeOH	0.71	91	4	–	2	7a: 39	8a: 2	13	14.0
3	1	MeOH/H ₂ O (4:1)	0.73	100	2	–	4	7a: 39	8a: 4	14	31.5
4	1	EtOH	–	46	14	–	6	7b: 27	8c: 2	11	3.14
5	1	EtOH/H ₂ O (2:1)	–	100	1	–	3	7b: 21	8b: <1	10	38
6	1	MeOH, ATMS (0.2 M)	–	100	6	14 ^[d]	2	7a: 20	8b: 2	10	1.60
7	1	MeOH, ATMS (1 M)	–	100	2	35 ^[d]	7	–	8c: 2	–	0.19
8	2	MeOH	0.90	98	44	–	2	7a: 11	8a: 11	<1	0.54
9	2	MeOH/H ₂ O (4:1)	0.82	100	18	–	5	7a: 14	8a: 38; 8c: 20	2	4.39
10	2	CD ₃ OH/H ₂ O (4:1)	–	92	[D ₁]-4: 16	–	[D ₁]-6: 2	[D ₃]-7a: 2	[D ₃]-8a: 44; [D ₁]-8c: 19	<1	4.19
11	2	EtOH	–	80	69	–	4	7b: 11	8b: 5	1	0.30
12	2	EtOH/H ₂ O (2:1)	–	100	22	–	4	7b: 17	8b: 12; 8c: 21	3	2.59
13	3	MeOH	0.56	91	61	–	8	7a: 13	8a: 4	–	0.41
14	3	MeOH/H ₂ O (4:1)	0.27	98	23	–	7	7a: 25	8a: 4; 8c: 2	4	1.83
15	3	EtOH	–	74	69	–	9	7b: 6	8b: 1	<1	0.23
16	3	EtOH/H ₂ O (2:1)	–	98	19	–	4	7b: 13	8b: 1; 8c: 1	1	1.05

[a] Irradiation conditions: 0.025 M of the substrate in the chosen solvent irradiated at $\lambda = 254$ nm (four lamps) for 1 h. Yields were based on consumed **1–3** and determined by GC/MS analysis. [b] The decomposition quantum yields (Φ_{-1}) of **1–3** (10^{–2} M) were determined by irradiation at $\lambda = 254$ nm. [c] Ratio between DHT-derived products and phenyl cation adducts. [d] A partial secondary desilylation of **5** to the corresponding 4-allyltoluene has been observed.

(entry 2). Going to a MeOH/H₂O mixed solvent ($\Phi_{-1}=0.73$) caused a further decrease in the yield of **4** and the formation of some benzyl alcohol **8c** (entry 3). In ethanol the reaction was slower than in methanol and led to an analogous product mixture (**6**, **7b**, **8b**, **9**; entry 4). The addition of water to the solvent (entry 5) caused a marked increase in the fraction of DHT-derived products to essentially the same value as that obtained in MeOH/H₂O. In contrast, in the presence of allyltrimethylsilane (ATMS) some of the allylated **5** was formed,^[19a] the yield of which increased with an increase in the ATMS concentration (entries 6 and 7).

The above results fit nicely with the presence of cation $^3\mathbf{10}^+$ and the $\alpha,4$ -DHT **13** as intermediates (Scheme 3). The efficiency of the $\mathbf{1} \rightarrow ^3\mathbf{10}^+$ conversion is affected, as one may expect, by the polarity of the medium. The fate of the cation $^3\mathbf{10}^+$ depends on the competition between reaction with the



Scheme 3. Generation of α,n -didehydrotoluenes **13–15** from silanes **1–3**.

solvent (H abstraction) and desilylation to **13**, which is highly favored in water. The other products result from the loss of the SiMe₃ group as well as that of chlorine, that is, via **13**. The role of the first cationic intermediate $^3\mathbf{10}^+$ on the way to **13** is further supported by the concentration-dependent trapping by ATMS.

The examination was extended to the other isomeric (chlorobenzyl)silanes. The solvent dependence with the *meta*-substituted **2** (quite efficient reaction, $\Phi_{-1}=0.90$; Table 1, entry 8) was larger than with **1**. Reduction to **4** was the main process in alcohols, but DHT-derived compounds (**6–9**) accounted for one-third to one-fourth of the products in neat alcohols (entries 8 and 11). The addition of water (which

has a marginal effect on the quantum yield, $\Phi_{-1}=0.82$ in MeOH/H₂O) reversed the distribution with the latter products predominating four to one in MeOH/H₂O and three to one in EtOH/H₂O (entries 9 and 12). Gratifyingly, their distribution closely corresponds to that obtained by cycloaromatization of enyne–allenes (compare the thermally induced cyclization of (*Z*)-1,2,4-heptatrien-6-yne (**A**) in MeOH/water 9:1 mixture, Scheme 1).^[6] Irradiation of **2** in a CD₃OH/H₂O mixture led to an increased yield of [*D*₃]-**8a** (from 38 to 44%) at the expense of [*D*₃]-**7a** (from 14 to 2% yield), thus supporting a primary isotope effect^[6] and the key role of hydrogen abstraction by DHT **14** (entry 10).

The *ortho*-substituted **3** was the least reactive of the series and water in this case decreased the photoreactivity (compare $\Phi_{-1}=0.56$ in MeOH and $\Phi_{-1}=0.27$ in aqueous methanol; entries 13 and 14). Reduction to **4** was the main process in neat alcohol, but the presence of water markedly increased the formation of DHT-derived products **6–9** (entries 13–16).

The above results fully support the contention that DHTs are smoothly photogenerated from all of the three isomeric (chlorobenzyl)trimethylsilanes. The main mechanistic features are detailed in Scheme 3. Thus, derivatives **1–3** heterolitically cleave via the triplet state to afford the triplet phenyl cations $^3\mathbf{10}^+ \rightarrow ^3\mathbf{12}^+$ (Scheme 3), just as other chlorobenzenes having electron-donating substituents^[19a] with a convenient quantum yield in protic solvents (Φ_{-1} 0.56–0.90 in MeOH), as predicted by calculations. Desilylation producing DHTs does not occur in nonprotic solvents (see Table 1, entry 1 and Scheme 3, path a), but ion stabilization favors this process in protic solvents, thereby resulting in DHTs with a structure-dependent efficiency.

Contrary to the Myers–Saito cyclization, wherein the two radical centers are formed simultaneously, the radical centers are formed sequentially with the present approach. Thus, desilylation competes with other reactions at the phenyl cation stage (H abstraction from the solvent, more efficient with EtOH than with MeOH; addition to alkenes). A protic, nonreducing solvent such as water obviously shifts the balance toward DHT formation. Solvent-assisted desilylation of $^3\mathbf{10}^+$ in a protic solvent is extremely fast as judged from the competition with ATMS trapping (see below). These generalizations are valid throughout the series, but the size of the effect depends on the substrate structure and conditions. In neat MeOH, desilylation to give DHT competes with reaction at the cation level, thus resulting in product ratios of 14, 0.54, and 0.41 for the *para*-, *meta*-, and *ortho*-substituted isomers, respectively (Table 1). These values increase to 31.5, 4.4, and 1.8 in MeOH/H₂O (4:1), but decrease when an efficient trap such as ATMS is present for $^3\mathbf{10}^+$. Isomeric DHTs exhibit a partially different chemistry, as judged from the different distribution of the products arising from them (**6** to **9**). Thus, with $\alpha,4$ - and $\alpha,2$ -DHTs hydrogen atom abstraction to yield **6**,^[24] **7**, and **9** predominates, whereas with the $\alpha,3$ -DHT derivative the large proportion of the polar addition product **8** points to nucleophilic addition.^[25]

Although this point requires further investigation, it is tempting to attribute this difference to the fact that the lowest-energy state of $\alpha,3$ -DHT is a singlet, whereas the lowest-energy state is a triplet for the other two isomers.^[15]

In conclusion, we have presented a new photochemical approach to α,n -DHTs and it is based on the fragmentation of easily available (chlorobenzyl)silanes in mixed aqueous solutions, thus overcoming the limitation of their generation from enyne-allenes. In the latter approach, aromaticity is achieved at the same time as diradical formation, whereas in the present approach the starting substrate is aromatic and is transformed into the final intermediate through a double elimination process by absorption of a photon.

Contrary to the Myers–Saito protocol, which is valid only for $\alpha,3$ -DHT, all isomers are generated in this way, thus allowing appreciation of the varied chemical behavior of these intermediates. Notice further that the photochemical mode of activation allows the spatial and temporal control of the reaction.^[14]

Additional work is currently ongoing in our lab to gain more insights into the generation of the three α,n -DHT isomers and their reactivities.

Experimental Section

General procedure for the irradiation of compounds **1–3**: A solution of the (chlorobenzyl)silane **1–3** (0.025 M), in the chosen medium was purged with nitrogen in quartz tubes and irradiated using 4 Hg lamps (15 W, emission centered at $\lambda = 254$ nm) for 1 h. The solution was then analyzed using GC/MS analysis. The photoproducts were identified by comparison with authentic samples, and quantified by using calibration curves. Quantum yields were measured by irradiation of a 10^{-2} M solution of the (chlorobenzyl)silanes **1–3** at $\lambda = 254$ nm (1 Hg lamp, 15 W).

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- [1] *Enediyne Antibiotics as Antitumor Agents* (Eds.: D. B. Borders, T. W. Doyle), Marcel Dekker, New York, **1995**.
- [2] M. Gredičak, I. Jerič, *Acta Pharm.* **2007**, *57*, 133–150.
- [3] U. Galm, M. H. Hager, S. G. Van Lanen, J. Ju, J. S. Thorson, B. Shen, *Chem. Rev.* **2005**, *105*, 739–758.
- [4] A. L. Smith, K. C. Nicolaou, *J. Med. Chem.* **1996**, *39*, 2103–2117.
- [5] K. K. Wang, *Chem. Rev.* **1996**, *96*, 207–222.
- [6] A. G. Myers, P. S. Dragovich, E. Y. Kuo, *J. Am. Chem. Soc.* **1992**, *114*, 9369–9386.
- [7] R. Nagata, H. Yamanaka, E. Okazaki, I. Saito, *Tetrahedron Lett.* **1989**, *30*, 4995–4998.

- [8] I. Alabugin, B. Breiner, M. Manoharan, *Adv. Phys. Org. Chem.* **2007**, *42*, 1–33.
- [9] A. G. Myers, C. A. Parrish, *Bioconjugate Chem.* **1996**, *7*, 322–331.
- [10] M. E. Cremeens, T. S. Hughes, B. K. Carpenter, *J. Am. Chem. Soc.* **2005**, *127*, 6652–6661.
- [11] I. A. Maretina, *Russ. J. Gen. Chem.* **2008**, *78*, 223–257.
- [12] M. Kar, A. Basak, *Chem. Rev.* **2007**, *107*, 2861–2890.
- [13] M. Schmitt, C. Vavilala, M. Emin Cinar, *J. Phys. Org. Chem.* **2012**, *25*, 182–197.
- [14] a) B. Breiner, K. Kaya, S. Roy, W.-Y. Yang, I. V. Alabugin, *Org. Biomol. Chem.* **2012**, *10*, 3974–3987, and references therein; b) I. V. Alabugin, W.-Y. Yang, R. Pal, *CRC Handbook of Organic Photochemistry and Photobiology*, 3rd ed. (Eds: A. Griesbeck, M. Oelgemöeller, F. Ghetti), CRC, Boca Raton, **2012**, pp. 549–592; c) A. Polukhtine, G. Karpov, D. R. Pandithavidana, A. Kuzmin, V. V. Popik, *Aust. J. Chem.* **2010**, *63*, 1099–1107.
- [15] P. G. Wenthold, S. G. Wiershke, J. J. Nash, R. R. Squires, *J. Am. Chem. Soc.* **1994**, *116*, 7378–7392.
- [16] P. Neuhaus, S. Henkel, W. Sander, *Aust. J. Chem.* **2010**, *63*, 1634–1637.
- [17] U. E. Wiersum, T. Nieuwenhuis, *Tetrahedron Lett.* **1973**, *14*, 2581–2584.
- [18] P. J. Stang in *Dicordinated Carbocations* (Eds: Z. Rappoport, P. J. Stang), Wiley, New York, **1997**, p. 451.
- [19] a) V. Dichiarante, M. Fagnoni, *Synlett* **2008**, 787–800, and references therein; b) S. Lazzaroni, D. Dondi, M. Fagnoni, A. Albini, *J. Org. Chem.* **2008**, *73*, 206–211; c) S. Lazzaroni, D. Dondi, M. Fagnoni, A. Albini, *J. Org. Chem.* **2010**, *75*, 315–323.
- [20] V. Dichiarante, M. Fagnoni, A. Albini, *Green Chem.* **2009**, *11*, 942–945.
- [21] C. Hansch, A. Leo, R. W. Taft, *Chem. Rev.* **1991**, *91*, 165–195.
- [22] a) R. Tacke, H. Linoh, *The Chemistry of Organic Silicon Compounds* (Eds.: S. Patai, Z. Rappoport), Wiley, Chichester, **1989**, pp. 1143–1206; b) J. P. Dinnocenzo, S. Farid, J. L. Goodman, I. R. Gould, S. L. Mattes, W. P. Todd, *J. Am. Chem. Soc.* **1989**, *111*, 8973–8975; c) We thank a referee for making this point.
- [23] M. Freccero, M. Fagnoni, A. Albini, *J. Am. Chem. Soc.* **2003**, *125*, 13182–13190.
- [24] The formation of toluene has been reported for the Myers–Saito cyclization of **A** only in the presence of good H-donors, such as 1,4-cyclohexadiene. See Ref. [6].
- [25] An alternative view is that the cations $^3\text{10}^+ - ^3\text{12}^+$ abstract a hydrogen atom and the resulting radical cation split off SiMe_3^+ . However, the nature and distribution of the products obtained do not fit with the intermediacy of the benzyl radical (as suggested by a referee), which would be the common intermediate from either of the three precursors, even if it is difficult to exclude any contribution by this path.