Generation of Alkyl Radicals from Thiols via Zinc Thiolates: Application for the Synthesis of *gem*-Difluorostyrenes

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Manuscript received: January 21, 2021; Revised manuscript received: March 14, 2021; Version of record online:

Supporting information for this article is available on the WWW under https://doi.org/10.1002/adsc.202100088

Abstract: Reaction of thiols with α -(trifluoromethyl)styrenes under photocatalytic conditions leading to desulfurative allylic fluorine substitution is described. The reaction is performed by treatment of thiols with benzyl zinc chloride to generate zinc thiolates followed by visible light induced desulfurization by means of triphenylphosphine. Radicals formed after the C–S bond cleavage react with the double bond affording *gem*-difluorostyrenes.

Keywords: Fluorine; Radicals; Photocatalysis; AlkenesThiols

Free radicals are important intermediates in organic chemistry, and radical reactions have been widely used for a long time.^[1,2] Radicals are usually generated at the carbon atom connected to a certain substituent such as halogen or hydroxy group derivatized with sulfurbased reagents.^[2] Concerning cleavage of the C–S bond, various derivatives of thiols have been used in radical processes. For example, xanthates provide ample opportunities for group transfer reactions triggered by radical initiators.^[3] We have also shown that sulfides bearing a fluorinated aromatic group can be used to generate alkyl radicals.^[4] Recently, a derivatization strategy based on the conversion of the thiol group by means of an iodine (III) regent followed by photoredox initiated radical relay process was reported.^[5,6]

The generation of radicals directly from thiol was achieved by single electron oxidation with subsequent interaction of the thiyl radical with phosphines or phosphites^[7,8] (Scheme 1). The reaction is believed to proceed through short-lived neutral four-coordinate intermediate **A** (known as phosphoranyl radical^[8,9]),

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which undergoes cleavage of the C–S bond with concomitant formation of strong P=S bond. The resulting radical rapidly abstracts a hydrogen atom from the starting thiol leading to the product of reductive desulfurization (path a). Indeed, the facile hydrogen atom transfer (HAT) between thiols and alkyl radicals is a key problem for trapping of the latter radical by external π -systems (path b).^[10] Successful examples of such process were described for thiols generating electrophilic radicals (such as α -carbonyl-substituted),^[11] which may exhibit favorable selectivity profile for alkene addition *vs.* HAT.

Herein we describe a novel approach to generate alkyl radicals directly from unprotected thiols without



Scheme 1. Generation of radicals from thiols.

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their conversion into a separate organic derivative. We propose conditions allowing to switch off the side HAT pathway. This leads to intrinsically wider scope of alkyl radicals, which can be involved in C,C bond forming reactions. Our concept is based on in situ conversion of thiols to metal thiolates, which interact with a phosphine upon single electron oxidation. This would allow generation of intermediate **A** followed by its fragmentation. The absence of free thiol makes possible further productive transformations of the alkyl radical such as interaction with alkenes.

The proposed mechanistic scenario is shown in Scheme 2. First, thiols **1** are treated with benzyl zinc chloride with the formation of zinc thiolates. Indeed, the zincation of thiols is rapid, and is likely to be compatible with many functional groups by virtue of mild reactivity profile of organozincs.^[12] Interaction of the zinc thiolate with triphenylphosphine in the presence of oxidative photocatalyst generates neutral sulfur-phosphorus intermediate **A**, which gives the alkyl radical. As alkenes, we considered α -CF₃-substituted styrenes.^[13,14] After radical addition at the C=C bond, the CF₃-substituted benzyl radical **B** is reduced by the photocatalyst followed by elimination of fluoride anion affording *gem*-difluorinated products **3**.

Concerning the mechanism of radical generation, two pathways should be considered. First, the zinc thiolate may be oxidized by photocatalyst to give Scentered radical, which can interact with phosphine leading to neutral species **A**.^[8] An alternative pathway involves single electron oxidation of phosphine into phosphonium radical cation, which can then attack the thiolate with concomitant expulsion of zinc chloride cation. Phosphinyl radical cations have long been known,^[15] but only within the last few years they have found applications for the activation of alcohols and carboxylic acids,^[16] and other reactions.^[17]

Cyclohexylthiol 1a and styrene 2a were selected as model substrates and their reaction was evaluated (Table 1). The mixture of the thiol, triphenylphosphine and a photocatalyst was first treated with a tetrahydrofuran solution of benzyl zinc chloride for 10 min affording a heterogeneous system, presumably due to precipitation of zinc thiolate. Styrene 2a and a cosolvent were added to give 0.25 M solution, and the mixture was irradiated with blue LED. Among various solvent, dichloromethane gave best result with acetonitrile and DMF being inefficient (entries 2 and 3). The use of substoichiometric amount of chlorotrimethylsilane (0.25 equiv.) was essential for reproducibility. The precise role of TMSCl is not clear





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 $^{[a]}$ Determined by $^{19}\!\mathrm{F}$ NMR using $PhCF_3$ as internal standard. $^{[b]}$ Isolated yield.



at present. Presumably, the silane may scavenge fluoride anion originating from the trifluoromethyl group. In the absence of light or photocatalyst, no product was formed. Tributylphosphine was notably less efficient, while triethylphosphite did not promote the reaction at all.

Under the optimized conditions, a series of thiols were combined with CF_3 -susbtituted styrenes (Scheme 3). The reaction worked with thiols generating primary and secondary alkyl radicals. Various functional groups such as ester, PMP-protected hydroxy group, and phosphite were tolerated. Notably, ethyl ester of *N*-benzoylated cysteine also gave the expected product **3k** with acidic N–H fragment remaining unaffected. The styrene component may contain halogen (products **3q**, **r**) and a boryl group (3 x). The reaction was typically complete within 4 hours. However, for 1-naphthyl-substituted alkene, 24 hours of irradiation were required. The decreased reactivity of this substrate may be attributed to the steric effect of the 1-naphthyl group, which attenuates conjugative stabilization of radical forming at the radical addition step. The reaction was unsuccessful with 4-methoxy-substituted styrene 1 furnishing an inseparable mixture of the expected product and the hydroalkylation by-product (sequential addition of the cyclohexyl and hydrogen atom at the double bond). This is presumably associated with electron-donating effect of the MeO-group disfavoring SET reduction of radical B (see Scheme 2), which instead undergoes hydrogen atom transfer.



^[a] Small amount of DMF was added to dissolve the intermediate zinc thiolate. ^[b] Reaction time 24 h using 60W LED.

Scheme 3. Synthesis of difluorinated styrenes 3. Isolated yields are shown. ^[a] Small amount of DMF was added to dissolve the intermediate zinc thiolate. ^[b] Reaction time 24 h using 60 W LED.

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Concerning the mechanism of the alkyl radical formation, the pathway involving the oxidation of the phosphine seems to be more probable for the following reasons. Measurement of oxidation potentials suggested that triphenylphosphine (+0.78 V vs. SCE) is oxidized more readily than the zinc thiolate (cyclohexylSZnCl, +1.48 V vs. SCE). Moreover, ethyl phosphite P(OEt)₃, which is known to react with thiyl radicals,^[8] was ineffective under our conditions (Table 1, entry 6). In further agreement, the Stern-Volmer studies demonstrated fluorescence quenching of the iridium photocatalyst by triphenylphosphine, but not by the zinc thiolate.

In summary, a mechanistic scenario for the generation of alkyl radicals from thiols under the conditions excluding undesired hydrogen atom transfer is described. This is achieved by using an organozinc reagent to completely remove the thiol hydrogen. The phosphine serves as a recipient of sulfur, thereby providing driving force for the cleavage of the carbonphosphorus bond.

Experimental Section

Reaction of Thiols with α-trifluoromethyl Styrenes (General Procedure)

Photocatalyst (Ir[dF(CF₃)ppy]₂(dtbpy))PF₆ (1.4 mg, 0.25 mol%) and triphenyl phosphine (262 mg, 1.0 mmol, 2.0 equiv.) were placed in a tube (Duran cat. no 261351155, Roth cat. no K248.1, outside diameter = 12 mm). The tube was evacuated and filled with argon. Thiol 1 (0.67 mmol 1.33 equiv.) was added followed by benzyl zinc chloride (1.9 M in THF, 350 µL, 0.67 mmol, 1.33 equiv.), and the mixture was stirred for 10 minutes at room temperature. Then, Me₃SiCl (16 µL, 0.125 mmol, 0.25 equiv.), dichloromethane (1.5 mL) and styrene 2 (0.50 mmol) were successively added [for 3d, DMF] (200 µL) was added as a co-solvent to mitigate low solubility of the corresponding zinc thiolate]. The tube was closed with a screw cap and irradiated for 4 hours by a 450 nm LED chip (Hontiey royal blue 100 W) operated at 40 Watt for 3 a-s, u-x or for 24 hours operated at 60 Watt for 3t. The distance between LED chip and the reaction tube was 1 cm. The reaction temperature was maintained in a range of 15-20 °C by a cooling bath. For the work-up, the mixture was poured into water (10 mL) and extracted with hexanes (4×4 mL). The combined organic phases were dried over Na₂SO₄, filtered, concentrated, and the residue was purified by column chromatography on silica gel.

Acknowledgements

This work was supported by the Russian Science Foundation (project 20-13-00112).

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UPDATES

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Adv. Synth. Catal. 2021, 363, 1-6

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