

New Synthesis of Pinacols By Oxidative Coupling Mediated by 1,2-Disulfides as Dehydrogenating Reagents under Irradiation

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A new procedure for the synthesis of pinacols is established by way of oxidative coupling reaction of benzylethers with a thiyl radical, a hydrogen acceptor, generated from disulfide under UV irradiation.

Thiols are generally considered hydrogen donors and their corresponding thiyl radicals play important roles not only in chemical but also in biological areas because of their characteristic behaviors.¹ For example, addition reactions to the unsaturated carbon bonds in chemistry, and the well known "repair reactions" toward targeted carbon-centered radicals in biology.²

The abstraction of hydrogen by thiyl radicals is also well known and several examples concerning cleavage of carbon-hydrogen bonds by thiyl radicals have already been introduced. Further, the absolute rate constants were reported for the reversible hydrogen-transfer process in several cases.³

In synthetic organic reactions, however, there are only a few that reported the use of thiyl radical as dehydrogenating reagent,⁴ and hardly any attention has been turned to this matter for a while. Therefore with the consideration that dehydrogenation by thiyl radical would provide a useful tool in developing new reactions, a new type of pinacol coupling reactions involving carbon-hydrogen bond cleavage step by the thiyl radical was now studied.

Concerning pinacol coupling reactions, there are two quite different approaches: namely, a) reductive coupling of aldehydes and ketones;⁵ and b) oxidative dimerization of alcohol or ether via dehydrogenation step.⁶ In contrast to intensive studies on pinacol coupling reactions by reductive way,⁵ the oxidative coupling method has never been turned up except for the coupling reaction of alcohols and the corresponding trimethylsilylether using di-*tert*-butyl peroxide.⁶ Then, the study on the pinacol coupling reaction of benzylethers via dehydrogenation with thiyl radicals was focused in order to find a new possibility in synthetic reaction.

At first, disulfides were tried as a source of thiyl radicals because they were mildly generated under UV irradiation and were safer and easier to handle compared with other radical sources such as peroxides.⁶

After screening various disulfides, small aliphatic disulfides such as diethyl disulfide were found to react smoothly with benzyl *tert*-butyldimethylsilyl (TBS) ether and the result looked favorable as seen in Table 1. On the other hand, thiyl radicals which were generated from aromatic disulfides such as diphenyl or dipyridyl disulfides were non-reactive. These indicated that the labile thiyl radicals were highly reactive in the dehydrogenation step while the stable aromatic radicals were not. In addition, the thiols that have low boiling points were supposed to have assisted the reaction since they existed in equilibrium in the above-mentioned step of hydrogen abstrac-

Table 1.

$\text{Ph-CH}_2\text{-OTBS} + \text{Disulfide (2 equiv)} \xrightarrow[\text{Et}_2\text{O, rt, 3 h}]{h\nu} \text{Pinacol Product}$				
Entry ^{a,b}	Disulfide	Yield ^c /%	Conv. ^d /%	d.r. ^e
1	PyS-SPy	n.d.	-	-
2	PhS-SPh	n.d.	-	-
3	^t BuS-S ^t Bu	17	20	49 : 51
4	ⁿ BuS-S ⁿ Bu	56	59	49 : 51
5	EtS-SEt	67	68	46 : 54
6	MeS-SMe	57	59	49 : 51

The photochemical reactions were performed in a Pyrex flask with a 100 W immersion type high pressure mercury lamp (UVL-100HA-50P type, Riko Corp.). ^a0.1 mol dm⁻³ Concentration based on starting material. ^bSolvents were degassed by freeze-pump-thaw method and purged with Ar. ^cYields were determined by ¹H NMR analysis (500 MHz or 400 MHz) using triphenylmethane as an internal standard. ^dConversion yields. ^edl : *meso*

tion by thiyl radicals, and the volatility of thiols shifted the equilibrium to the right. Also, the non-reacted diethyl disulfide and the resulted products of ethanethiol can easily be removed after the reaction, which was an advantage.

In order to optimize the reaction conditions, the effect of solvents was carefully examined as cage effect by solvents had been known to affect reactivity of the radical reaction. Here, transparency of the solvents⁷ was also necessary for the photoreaction. In consequence, solvents such as petroleum ether, acetonitrile and diethyl ether turned out to be quite useful, and among which, diethyl ether was the best (Table 2, Entry 8).

Table 2.

$\text{Ph-CH}_2\text{-OTBS} + \text{EtS-SEt (2 equiv)} \xrightarrow[\text{Solvent, rt, 3 h}]{h\nu} \text{Pinacol Product}$				
Entry ^a	Solvent ^b	Yield ^c /%	Conv. ^d /%	d.r. ^e
1	Benzene	58	69	47 : 53
2	Toluene	48	59	47 : 53
3	P.E.	69	74	48 : 52
4 ^f	P.E.	53	82	48 : 52
5	Hexane	60	66	49 : 51
6	CH ₃ CN	68	76	45 : 55
7	Et ₂ O	67	68	46 : 54
8 ^f	Et ₂ O	70	95	48 : 52
9	THF	53	62	45 : 55
10	MeOH	23	66	43 : 57
11	EtOH	47	67	49 : 51

The photochemical reactions were performed in a Pyrex flask with a 100 W immersion type high pressure mercury lamp (UVL-100HA-50P type, Riko Corp.). ^a0.1 mol dm⁻³ Concentration based on starting material. ^bSolvents were degassed by freeze-pump-thaw method and purged with Ar. ^cYields were determined by ¹H NMR analysis (500 MHz or 400 MHz) using triphenylmethane as an internal standard. ^dConversion yields. ^edl : *meso* ^f0.25 mol dm⁻³ Concentration based on starting material.

Table 3.

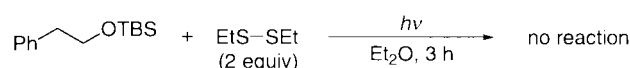
Entry ^{a,b}	R ₁	R ₂	Time /h	Yield ^c (%) ^d	d.r.
1	TBS	<i>o</i> -Me	5	59 (60)	45 : 55
2	TBS	<i>m</i> -Me	4	66	49 : 51
3	TBS	<i>p</i> -Me	5	80	47 : 53
4	TBS	<i>o</i> -MeO	8	61 ^e	44 : 56
5	TBS	<i>m</i> -MeO	5	76	45 : 55
6	TBS	<i>p</i> -MeO	6	78	47 : 53
7	TBS	<i>p</i> -Cl	3	26 (47)	49 : 51
9	TBS	<i>p</i> -Br	3	9 (23)	47 : 53
10	TBS	<i>p</i> -Ph	8	79 (82)	50 : 50
11	TBS	<i>p</i> -CF ₃	5	77 ^e	49 : 51
12	TBS	<i>p</i> - ^t Bu	4	80 ^e	47 : 53
14	Me	H	3	78 (88)	49 : 51
15	Et	H	3	76	50 : 50

The photochemical reactions were performed in a Pyrex flask with a 100 W immersion type high pressure mercury lamp (UVL-100HA-50P type, Riko Corp.). ^a0.25 mol dm⁻³ Concentration based on starting material.

^bSolvents were degassed by freeze-pump-thaw method and purged with Ar. ^cYields were determined by ¹H NMR analysis (500 MHz or 400 MHz) using triphenylmethane as an internal standard. ^dConversion yields.

^eIsolated yields.

With those results in mind, the influence of the substituents on aromatic rings was checked (Table 3). At first, location of the substituents on aromatic rings was examined and better results were obtained in the coupling reactions of *para*-substituted derivatives compared with those of *ortho*- or *meta*-substituted ones. Next, effects of various substituents at *para* position were then examined and satisfactory results were obtained when either electron-donating or electron-withdrawing group was introduced except in the case of halogens which induced self decomposition under irradiation.



Finally, limitations of this coupling reaction were studied. Then, it was found that no coupling products were detected, when 2-phenylethyl TBS ether was employed as a substrate. In the case of benzyl TBS ether in toluene (Table 2, Entry 2), coupling product originated from toluene was not detected either. These results suggest that the selective C–H activation by thiyl

radical takes place only at benzylic position of ethers to afford the corresponding coupling product under mild conditions.

Thus, a new method for the synthesis of pinacols was developed via an oxidative step of C–H activation by thiyl radicals derived from 1,2-disulfide under UV irradiation.

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