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Synthesis of sterically hindered ketones from aldehydes via *O*-silyl oximes

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ABSTRACT

A mild and efficient method to synthesize sterically hindered ketones from aldehydes via *O*-silyl oximes was developed. Treatment of *O*-triphenylsilylated oximes with alkyl iodides in the presence of triethyl borane afforded the corresponding ketones.

The synthesis of ketones has attracted considerable attention from the synthetic community due to their great importance as building blocks for the preparation of pharmaceutically useful compounds.[1] Ketones are widely used in the chemical industry as useful synthetic intermediates for the preparation of fine chemicals in the fields of pharmaceuticals, fragrances, and agrochemicals.[2] They are also present in a wide range of natural products and are useful as flavoring agents.[3] Consequently, different methodologies have been developed for the preparation of ketones,[4] including a one-pot preparation from aldehydes using *N*-*tert*-butylphenylsulfinimidoyl chloride,[4a] palladium-catalyzed oxidative coupling of trialkylamines with aryl iodides,[4b] and (*N*-heterocyclic carbene)-Pd complex-catalyzed anaerobic oxidation of secondary alcohols.[4c] Recently, the sodium nitrite-catalyzed aerobic oxidative deoximation of ketoximes and aldoximes has also been reported.[5] However, these methods are generally limited to the synthesis of less sterically hindered ketones. Therefore, there is still a need for synthetic routes, which can be used to synthesize sterically hindered ketones. Most of the recently developed methods for the synthesis of sterically hindered ketones have been developed by Lockhart and co-workers[6] starting with arylstannanes and aroyl chlorides. Other reported methods include the rhodium-catalyzed oxidative arylation of aldehydes[7] and the carbonylative Suzuki–Miyaura cross-coupling of sterically hindered *ortho*-disubstituted aryl iodides with aryl boronic acids.[8]

As a part of our ongoing research, we previously developed a novel method of synthesizing aryl ketones by means of an indium-mediated Friedel–Crafts acylation.[9] In this Letter, we report a method for the preparation of sterically hindered ketones from aldehydes via *O*-silyl oximes (Scheme 1).

Scheme 1. Synthesis of ketones from O-silylated oximes.

O-(Triphenylsilyl)benzaldoxime (**1a**) was synthesized from benzaldehyde via benzaldoxime using a known protocol.[10] A reaction of **1a** was carried out with *t*-butyl iodide (2.0 equiv) and triethyl borane (1.0 equiv) in toluene at 90 °C affording the product **3** in poor yield (Table 1, entry 1). During the course of our investigation, a variety of reactions were carried out using different equivalents of reactants (entries 1–6). After several attempts, the best result was obtained with 8.0 equiv of *t*-butyl iodide and 5.0 equiv of triethyl borane in toluene at 90 °C (entry 4). We also performed the reaction in various solvents. The reaction in benzene afforded a comparable yield (entry 8). Although the yield of product **3** was reduced slightly when the reaction was performed in toluene at reflux (entry 7), the reaction was best performed in toluene (entry 4). The reaction was very sluggish in dichloromethane or diethyl ether even after prolonged reaction times (entries 10–12). The O-silylated benzaldoximes **1b** and **1c** were also investigated while maintaining the other optimized conditions, but in both

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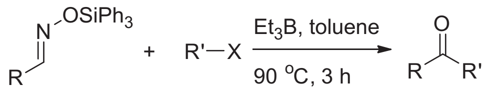
Table 1
Synthesis of *t*-butyl phenyl ketone **3** under various reaction conditions

Entry	^{t}BuI (equiv)	Et_3B (equiv)	Solvent	Time (h)	Temp. (°C)	Yield[a] (%)
1	2.0	1.0	Toluene	12	90	28
2	3.0	2.0	Toluene	12	90	49
3	5.0	5.0	Toluene	4	90	78
4	8.0	5.0	Toluene	3	90	85
5	10.0	5.0	Toluene	3	90	84
6	10.0	10.0	Toluene	3	90	85
7	8.0	5.0	Toluene	3	110	83
8	8.0	5.0	Benzene	5	80	75
9	8.0	5.0	THF	10	66	63
10	8.0	5.0	CH_2Cl_2	24	40	39
11	8.0	5.0	CH_2Cl_2	24	25	10
12	8.0	5.0	Et_2O	24	34	25

[a] Isolated yield.

Table 2
Synthesis of ketones using *O*-silylated oximes



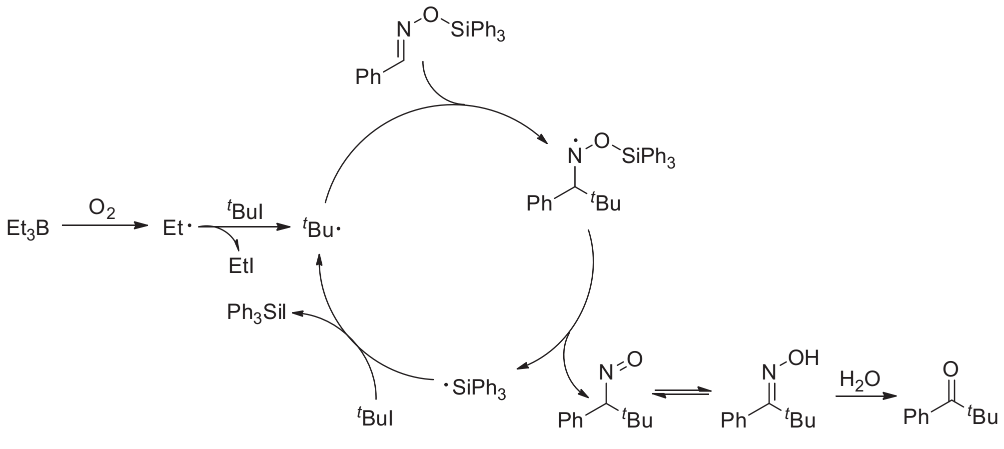
Entry	R	R′-X	Time (h)	Yield (%)[a]
1	Ph	^{i}Pr-I	5	73
2	Ph	Cyclohexyl-I	5	71
3	Ph	Adamantyl-I	12	45
4	Ph	^{t}Bu-Br	10	16
5	*p*-MeO-Ph	^{t}Bu-I	3	89
6	*p*-Me-Ph	^{t}Bu-I	4	85
7	*p*-F-Ph	^{t}Bu-I	7	72
8	*o*-MeO-Ph	^{t}Bu-I	3	87
9	^{i}Pr	^{i}Pr-I	5	69
10	^{i}Pr	^{t}Bu-I	5	78
11	^{t}Bu	^{t}Bu-I	4	82

[a] Isolated yield.

cases, the product **3** was obtained in less than 10% yield with recovering unreacted starting materials.

On the basis of the above observations, various *O*-(triphenylsilyl)oximes were subjected to the optimized reaction conditions to determine the scope and limitations of the reaction. The results are summarized in Table 2. Reactions with secondary iodides afforded good yields, while the reaction with adamantyl iodide gave a poor yield (entries 1–3). Replacement of *t*-butyl iodide with *t*-butyl bromide resulted in a drastic drop in yield from 85% to 16% (entry 4). A general trend was observed that aromatic oximes with an electron-donating group gave higher yields than those with an electron-withdrawing group (entries 5–7). A *ortho*-substituted aromatic aldehyde also reacted well to produce the corresponding sterically demanding ketone in high yield (entry 8). The reaction performed equally well with aliphatic oximes (entries 9–10). The method was also applicable to highly sterically hindered ketones. For example, the reaction proceeded efficiently even with the highly sterically hindered *O*-(triphenylsilyl) neopentyl oxime and *t*-butyl iodide to afford a high yield of the corresponding ketone (entry 11).

Radical additions to oxime ethers have become important synthetic tools because of their high reactivity and unique properties that provide selectivity in many organic transformations.[11] Natio's group has extensively investigated triethyl borane-induced intermolecular carbon radical addition to oxime ethers.[11a–c] Clive has reported an intramolecular radical cyclization of iodo *O*-trityl oximes in the presence of diphenyl diselenide and Hunig's base to produce cyclic oximes.[12] We attempted to determine whether triethyl borane was acting as a free radical initiator in the present reaction. Controlled experiments were performed to reveal the mechanism of the transformation. First, a reaction was carried out in carefully degassed solvent under argon. Then, the reaction did not proceed whereas the reaction was well performed under air atmosphere. Second, a reaction was executed under air atmosphere in the presence of TEMPO as radical scavenger. In this case, 1.0 equiv of *O*-silyl oxime, 8.0 equiv of ^{t}BuI and 5.0 equiv of TEMPO were taken and finally 5.0 equiv of triethyl borane was added. The reaction did not proceed at all. On the basis of the above observations, it was con-



Scheme 2. A plausible reaction mechanism for conversion of O-triphenylsilylated oximes with alkyl iodides in the presence of triethyl borane into the corresponding ketones.

cluded that the reaction proceeds via a radical pathway. This radical reaction proceeds in the presence of triethyl borane/oxygen generates a ^{t}Bu radical, which attacks the electrophilic C=N to yield the corresponding a nitrogen-centered radical. The N-centered radical undergoes β-silyl fragmentation to yield the corresponding nitroso compound and a silyl radical. The nitroso compound isomerizes to the oxime which is hydrolyzed to produce the corresponding ketone during workup (Scheme 2).

In summary, we have developed a method for the synthesis of ketones including sterically hindered ketones under neutral conditions. The present method provides an easy access to sterically hindered ketones and can be applied to a wide variety of ketone syntheses.

Typical procedure for ketone synthesis

To a stirred solution of *O*-triphenylsilyl oxime (0.25 mmol) and *t*-butyl iodide (368 mg, 2.0 mmol) in toluene at 90 °C was added triethyl borane (1.25 mL, 1.0 M solution in hexane, 1.25 mmol) under air atmosphere. The resulting mixture was stirred until the starting material was consumed. The reaction mixture was washed with saturated sodium bicarbonate solution, and the product was extracted into ethyl acetate. The organic layer was dried over $MgSO_4$ and was evaporated under reduced pressure to afford a residue, which was purified by silica gel column chromatography.

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