Tin-free radical alkylation of ketones *via N*-silyloxy enamines

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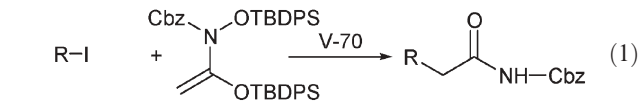
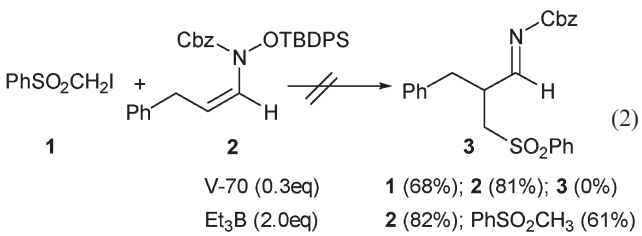
The radical alkylation of ketones is achieved by their conversion into corresponding *N*-silyloxy enamines, followed by a radical reaction with alkyl halides bearing electron-withdrawing groups.

Despite the synthetic importance of alkylating carbonyl compounds, radical alkylations have not been well studied.[1] Previously, we reported a novel radical alkylation of carboxylic amides, involving a cleavage of the N–O bond along with a radical rearrangement of a silyloxy radical into a silyl radical to achieve tin-free conditions (eqn. 1).[2] To extend our previous finding to the alkylation of aldehydes and ketones, we initially prepared *N*-silyloxy unsaturated carbamate **2** (eqn. 2).[3] When **2** was treated with iodophenylsulfonyl methane (**1**) under various radical conditions, surprisingly, the desired product was not obtained, and methyl phenyl sulfone was isolated, along with the recovery of the starting material in most cases. At present, we have no explanation as to why no reaction occurs.



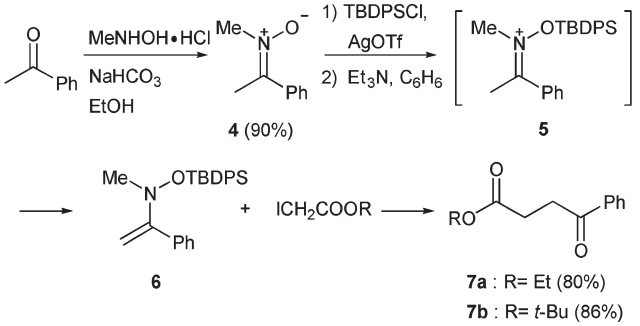
(1)



(2)

Our next approach involves the use of *N*-silyloxy enamine **6**, and is outlined in Scheme 1. Treatment of *N*-methyl nitrone **4**[4] with *tert*-butyldiphenylsilyl chloride (TBDPSCl) and silver triflate[5], followed by the addition of triethylamine, afforded **6** *via* the intermediate **5**. As we expected, **6** was hydrolytically, thermally and photochemically labile, undergoing extensive decomposition upon chromatographic separation and with standing, requiring the use of Et_3B to initiate the radical reaction.[6] Treatment of **6** with ethyl iodoacetate in the presence of Et_3B (0.5 equiv.) in benzene for 1 h at room temperature gave the corresponding ketone, **7a**, in 80% yield. A similar result was also obtained with *tert*-butyl iodoacetate.

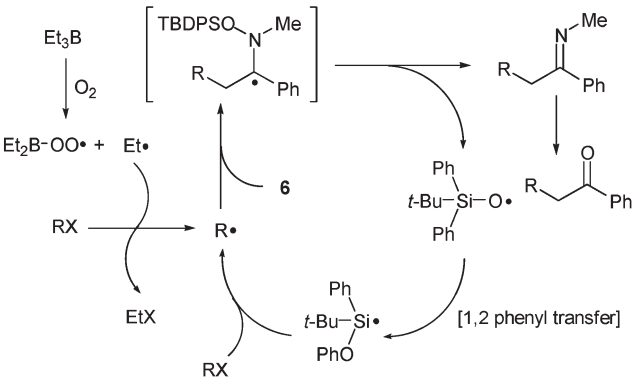
The present approach is based on three important steps involving (i) initiation of the radical reaction by iodine atom



Scheme 1

transfer from an alkyl iodide to the ethyl radical, (ii) the addition of an alkyl radical onto **6**, followed by the homolytic bond cleavage of the N–O bond to generate an imine to provide a ketone product, and (iii) a radical rearrangement of a silyloxy radical into a silyl radical to propagate the radical chain reaction (Scheme 2).[7]

Experimental results, using diethyl bromomalonate as a radical precursor, are listed in Table 1.† *N*-Silyloxy enamines derived from symmetrical ketones underwent clean radical reactions to give the corresponding ketones in high yields (Table 1, entries 1–3). Regioselective alkylation of unsymmetrical ketones is very important and depends highly on the regioselective formation of *N*-silyloxy enamines in this approach. Deprotonation of *N*-silyloxy immonium salt **8**, derived from 3-methyl-2-butanone, with triethylamine occurred at the less substituted carbon, yielding **9** exclusively. A radical reaction using **9** under the same conditions provided ketone **10** in a regioselective manner (eqn. 3). Similarly, regioselective alkylation was achieved with unsymmetrical ketones (Table 1, entries 4–7). Furthermore, it is noteworthy that the alkylation of 2-methylcyclohexanone was stereoselective, yielding



Scheme 2

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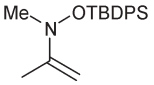
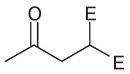
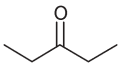
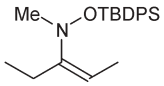
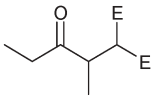
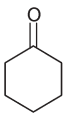
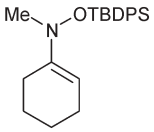
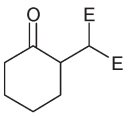
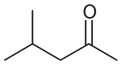
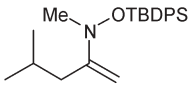
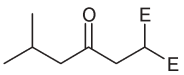
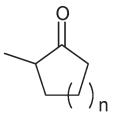
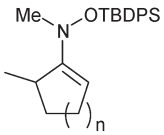
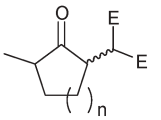
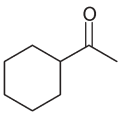
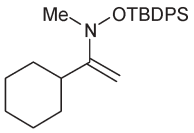
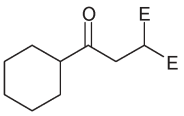
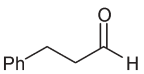
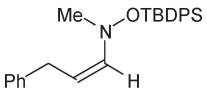
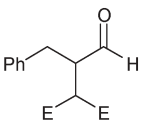
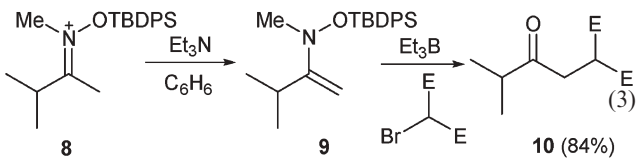
Table 1 Radical alkylation of carbonyl compounds with diethyl bromomalonate[a]

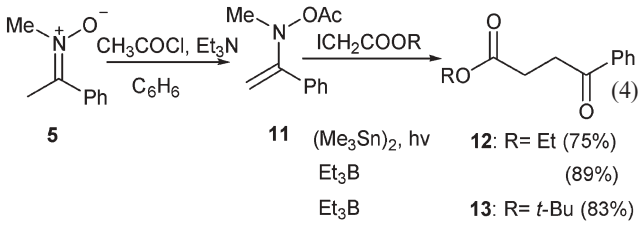
Entry	Substate	Enamine	Product	Yield (%)
1				76
2				84
3				95
4				72
5 6				n = 1: 90[b] n = 2: 87[c]
7				84
8				60[d]

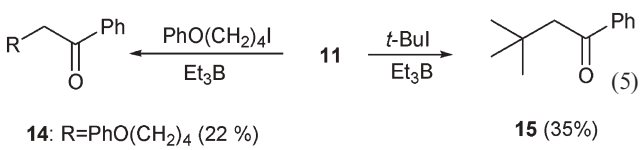
[a] E = COOEt. [b] *syn* : *anti* = 6 : 4. [c] *anti* only. [d] Solvent was CH_2Cl_2.

trans-disubstituted cyclohexanone exclusively (Table 1, entry 6), whereas that of 2-methylcyclopentanone was not stereoselective (Table 1, entry 5).



The reaction could be performed with *N*-acyloxy enamine **11** (eqn. 4). **11** was conveniently prepared by treatment of nitrone **5** with acetyl chloride and triethylamine. **11** was also thermally and hydrolytically labile but photochemically quite stable. Thus, the radical reaction could be performed under photochemically initiated conditions. Irradiation of a benzene solution of **11**, ethyl iodoacetate and hexamethylditin at 300 nm for 3 h afforded ketone **12** in 75% yield. When the same reaction was repeated using Et_3B as an initiator for 1 h, the desired ketone was isolated in 89% yield. Apparently, the methyl radical, generated from decarboxylation of the acyloxy radical, abstracts an iodine atom from the alkyl iodide to produce an alkyl radical.[8] The present approach reaches a limit with nucleophilic alkyl radicals due to the nature of electron-rich enamine radical acceptors. The radical reaction of **11** with phenoxybutyl iodide under similar conditions gave a small amount of the desired product, **14**, along with recovery of most of the starting material (71%) (eqn. 5). A similar result was also obtained with *tert*-butyl iodide.





In conclusion, we have developed a new tin-free radical alkylation of aldehydes and ketones *via* *N*-silyloxy enamines. Further extension of the present approach to secondary amines *via* nitrones is under way. We thank the Center for Molecular Design and Synthesis (CMDS) and the BK21 program for financial support.

Notes and references

† Typical procedure (Table 1, entry 1): To a stirred solution of *N*-methyl dimethyl nitrone (26 mg, 0.30 mmol) and AgOTf (85 mg, 0.33 mmol) in dry benzene (1.5 mL) was added, successively, TBDPSCl (86 μL, 0.33 mmol) and NEt_3 (46 μL, 0.33 mmol) at room temperature under N_2. After being stirred for 30 min at room temperature, the reaction mixture separated into a clear solution and a black precipitate. The clear solution was transferred to another flask containing diethyl bromomalonate (48 mg, 0.20 mmol), and then Et_3B (1.0 M in THF, 100 μL, 0.10 mmol) was added. The reaction mixture was exposed to open air and stirred at room temperature for 3 h. The solvent was then evaporated and the residue purified by column chromatography (silica gel, hexane/AcOEt = 5 : 1) to afford the desired product (33 mg, 76%).

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