Free Radical-Mediated Acylation and Carboxylation Reactions

Sunggak Kim

Center for Molecular Design & Synthesis and Department of Chemistry, Korea Advanced Institute of Science and Technology, Daejeon 305-701, Korea
Fax: (+82)-42-869-8370, e-mail: skim@kaist.ac.kr

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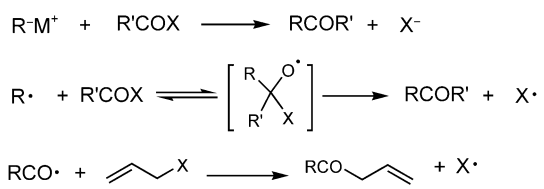
Abstract: Radical acylations to prepare carbonyl compounds are described and focus on indirect acylation approaches using sulfonyl oxime ethers under tin-mediated and tin-free conditions. The efficiency of carboxylic acid derivatives as carbonyl group radical acceptors in radical acylation and carboxylation reactions is discussed.

Keywords: acylation; aldehydes; carboxylation; C-C coupling; ketones; radicals

1 Introduction

The carbonyl group is one of the central functional groups in organic chemistry. Although there are many ways to prepare the keto group, one of the most direct and useful methods is an acylation approach involving the reaction of an organometallic reagent with a carboxylic acid derivative.[1] However, the radical version of the acylation reaction has not been well studied because additions of alkyl radicals to C=O bonds are difficult due to their reversibility and the high π bond strengths of the C=O bonds.[2] Since β-fragmentations of alkoxyl radicals are much faster than the additions of the alkyl radicals to carbonyl groups, it is anticipated that carbonyl group derivatives cannot be used as efficient radical acceptors to achieve radical-mediated acylations. Only a few carboxylic acid derivatives are effective to some extent in radical cyclizations.[3,4] Thus, the synthesis of ketones has been indirectly achieved by the use of an alkynyl,[5] a nitrile,[5] and an oxime ether group.[6] This indirect approach is attractive since the carbonyl group can be easily generated by oxidative cleavage or by hydrolysis. In the case of intermolecular acylation, the use of carbonyl group derivatives as radical acceptors is uncommon and only several reports for radical carboxylations have appeared to date.[7–9] Another useful approach for the synthesis of ketones involves the addition of acyl radicals to C=C bonds. Since acyl radicals are conveniently produced by radical carbonylation of alkyl radicals[10] or from readily available carbonyl radical precursors,[11] this approach is more general and provides powerful synthetic options for the synthesis of ketones (Scheme 1).

This account will focus on the radical acylation reactions of carboxylic acid derivatives and their



Scheme 1. Synthesis of ketones.

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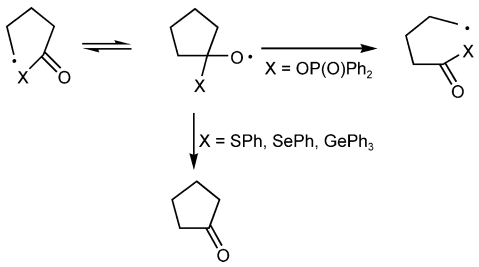
Sunggak Kim was born on March 17, 1946 in Kyungbuk province, Korea. He studied chemistry at Seoul National University, where he obtained his B.S. in 1969. After he had served in the Korean Army; he went to Canada in 1972 to receive his graduate training at McGill University in Montreal, where he did his Ph.D research with Prof. G. Just. He moved to Harvard in 1976, where he spent three years for postdoctoral studies with Professor E. J. Corey. In 1979, he returned to Korea to join the chemistry faculty at the Korea Advanced Institute of Science. He was promoted to Professor of Chemistry at KAIST in 1986. His research interests focus on the design and the development of new reactions and strategies with general utility in organic synthesis. He has developed several synthetically useful reagents including reducing, oxidizing, and coupling reagents. Although he continues his interest in new synthetic methodologies utilizing carbenes, cations, and anions, his major research emphasis in recent years has been on the development of new free radical reactions. He is the author of 200 publications. His major scientific awards include the Korea Science Prize in Chemistry (1994), the Korean Chemical Society Award for Young Chemists (1985), and the Korean Federation of Science and Technology Societies Award (1991).

synthetic equivalents along with radical carboxylation reactions but will not include radical acylation reactions involving the addition of acyl radicals to C=C bonds.

2 Intramolecular Acylation

Intramolecular radical cyclizations are much faster and more efficient than intermolecular reactions and are of great synthetic importance since they allow the synthesis of various 5- and 6-membered cyclic compounds with high regioselectivity and often high stereoselectivity.[12] Although the addition of alkyl radicals to carbonyl groups is energetically unfavorable and reversible, it is expected that intramolecular acylations would be feasible by using highly efficient leaving groups. Since readily available carboxylic esters and amides are inert to alkyl radical additions, a limited number of the carbonyl group radical acceptors such as thioesters[3] and acylgermanes[4] are available. It is noteworthy that mixed carboxylic anhydrides are good radical acceptors in radical cyclizations but fail to function as carbonyl



Scheme 2. Intramolecular acylation approach.

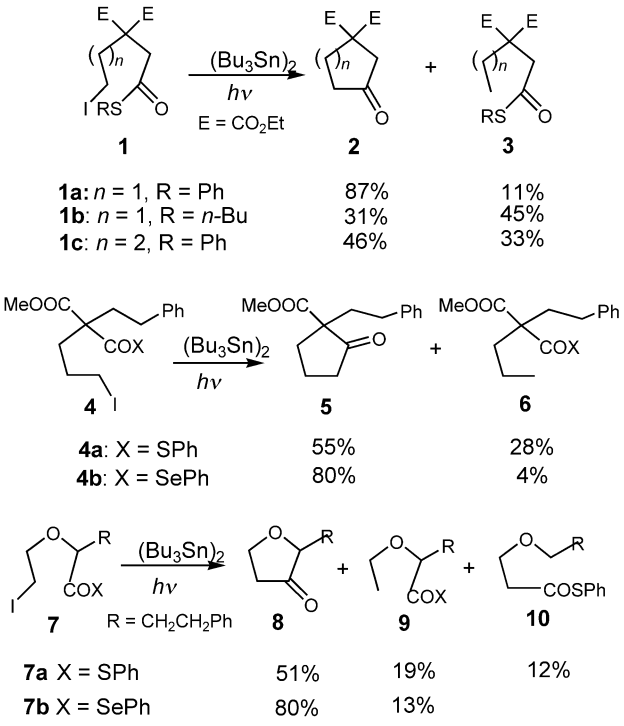
group acceptors because β-fragmentation of alkoxyl radicals cleaves the carbon-carbon bond rather than the carbon-oxygen bond (Scheme 2).[13]

Intramolecular acylations can be achieved by the combination of carboxylic acid derivatives and organometallic compounds derived from alkyl iodides and bromides but this cyclization would be troublesome due to the compatibility of the carbonyl groups with the organometallic compounds and functional group selectivity. Thus, radical-mediated intramolecular acylations are synthetically useful because radical reactions proceed without affecting various functional groups under mild and neutral conditions.

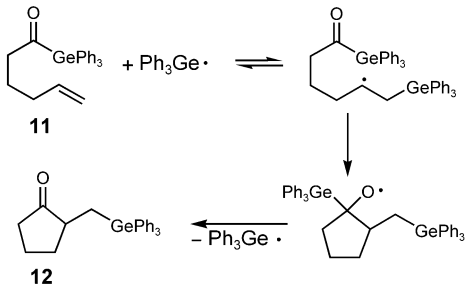
2.1 Radical Cyclization of Thio- and Selenoesters

Thio- and selenoesters have been widely used as precursors of acyl radicals[11] but their use as carbonyl group radical acceptors has not been well studied.[14] The use of a thioester group as the carbonyl group radical acceptor is based on our assumption that β-elimination of the phenylsulfanyl radical should be irreversible, thereby shifting the equilibrium to the forward direction, even though the reverse reaction is favorable in the cyclization step.[3]

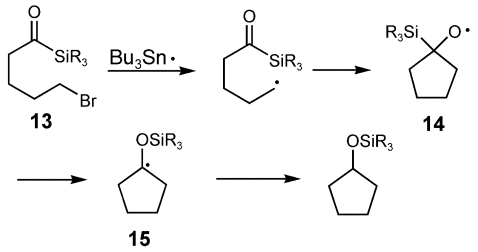
When a solution of **1a** and hexabutylditin in benzene was irradiated at 300 nm, the cyclopentanone **2a** was isolated in 87% yield along with the direct reduction product **3a** (11%), although it is somewhat surprising that **3a** was isolated because there was no source to provide hydrogen atoms for the direct reduction. For most of the cases observed with thioesters, considerable amounts of the direct reduction products are isolated and the 6-*exo* cyclization gives more reduction products than the 5-*exo* cyclization. *S*-Phenyl thioester **1a** is a better radical acceptor than *S*-alkyl thioester **1b** towards alkyl radicals. In addition, β-cleavage of the carbon-carbon bond from the alkoxyl radical in **7a** is observed to some extent. Furthermore, the use of phenyl selenoesters **4b** and **7b** reduces the direct reduction products **6b** and **9b** considerably and obviates the problem of β-cleavage of the carbon-carbon bond because β-elimination of the phenylseleno group is much faster than that of the phenylsulfanyl group, thus providing more cyclized products.



Scheme 3. Radical cyclizations of thio- and selenoesters.



Scheme 4. Radical cyclization of an acylgermane.

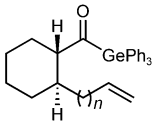
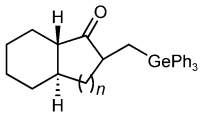
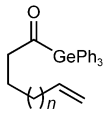
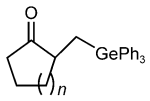
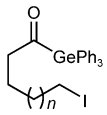


Scheme 5. Cyclization of acylsilanes.

2.2 Radical Cyclization of Acylgermanes

Kiyooka first reported the intramolecular acylation reactions of acylgermanes.[4] Photolysis of the alkenyl acylgermane **11** with a UV lamp provided cyclopentanone **12** in 92% yield. Curran studied the radical cyclization of acylgermanes in detail and found that acylgermanes are excellent carbonyl group radical acceptors in intramolecular cyclizations.[15a] Mechanistically, the acylgermane behaves as the radical acceptor and the β-fragmentation occurs with cleavage of the carbon-germanium bond but not with cleavage of carbon-carbon bond. Since the germyl radical propagates the radical chain by abstraction or addition, this reaction occurs by a unimolecular chain transfer process (Scheme 4).

Table 1. Photochemical cyclizations of acylgermanes.

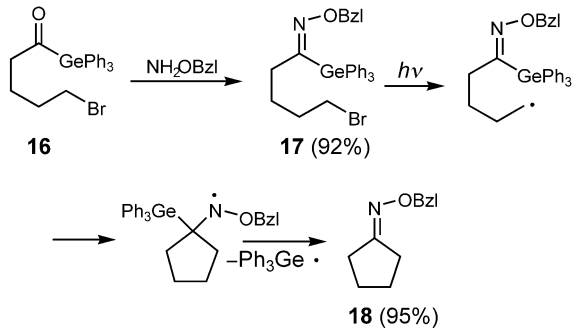
Substrate	Product
	
n = 1 n = 2	75% 65%
	
n = 1 n = 2	92% 86%
	
n = 1 n = 2	90% 87%

Approximate rate constants for 5-*exo* and 6-*exo* cyclizations of primary alkyl radicals to acylgermanes are 7×10^6 $s^{-1}$and 2×10^6 s^{-1}at 80 °C, respectively.[15a,16] As shown in Table 1, 5-*exo* and 6-*exo* cyclizations of the acylgermanes under photolytic conditions proceed cleanly, yielding cyclopentanones and cyclohexanones in high yields but 7-*exo* cyclizations do not occur.

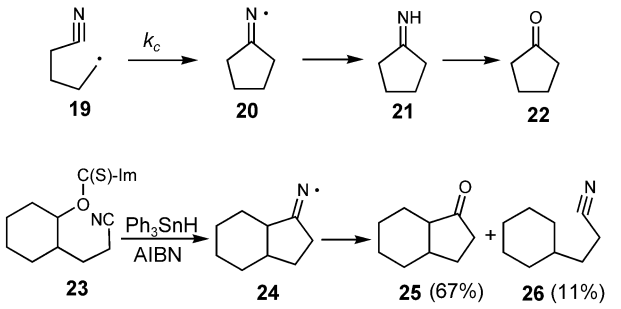
Acylstannanes are expected to be equally useful as carbonyl group acceptors but acylsilanes do not behave like acylgermanes (Scheme 5). In the cyclization of acylsilanes **13**, alkoxyl radical **14** does not undergo β-fragmentation to give a cyclopentanone but instead a radical-Brook rearrangement to give **15**.[17]

2.3 Radical Cyclization of Acylgermane Oxime Ethers

The efficiency of C=N bonds as radical acceptors has been recognized in recent years.[18] According to kinetic studies, C=N bonds are much better radical acceptors than C=C bonds and C=O bonds.[19] Curran used acylgermanes oxime ethers and hydrazones to generate C=N bonds after cyclizations, which is an indirect way to provide ketone groups (Scheme 6).[6] Condensation of acylgermanes with *O*-benzylhydroxylamine or *N,N*-



Scheme 6. Preparation and cyclization of an acylgermane oxime ether.

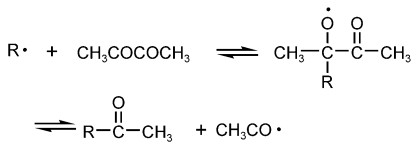


Scheme 7. Radical cyclization of nitriles.

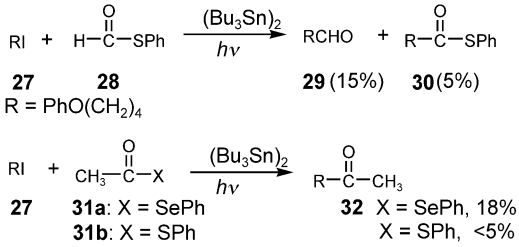
dimethylhydrazone provides acylgermane oxime ethers and hydrazones. Thus, treatment of acylgermane **16** with *O*-benzylhydroxylamine gave the acylgermane oxime ether **17** in 92% yield. Radical cyclization of **17** under photolytic initiation afforded the cyclopentanone oxime ether **18** in 95% yield but failed when phenyl selenide was used as a precursor. This problem can be overcome by adding hexabutylditin or by using triphenyltin hydride and AIBN. The cyclization rate constant for the 5-*exo* addition of primary alkyl radicals to the acylgermane oxime ethers is approximately $10^7\ s^{-1}$ at 80 °C, indicating that they are better radical acceptors than the parent acylgermanes.[6]

2.4 Radical Cyclization of Nitriles

Cyclization of the 4-cyanobutyl radical **19** using a nitrile group as a radical acceptor provides ketone **22** because the primary imine **21** is easily hydrolyzed *in situ* to form the ketone. According to kinetic studies by Ingold,[20] the 4-cyanobutyl radical **19** has cyclization rate constants of $4.0 \times 10^3\ s^{-1}$ at 25 °C and $4.0 \times 10^4\ s^{-1}$ at 80 °C. Thus, the cyclization is relatively slow and nitriles are modest radical acceptors. Another problem associated with cyclizations of nitriles is derived from the tendency for β-fragmentation of the resulting iminyl radicals. For instance, radical cyclization of **23** with Ph_3SnH/AIBN gave cyclic ketone **25** along with nitrile **26** due to β-fragmentation of the iminyl radical **24** and subsequent H-atom abstraction by the cyclohexyl radical.[5]



Scheme 8. Radical acetylation of hydrocarbons.



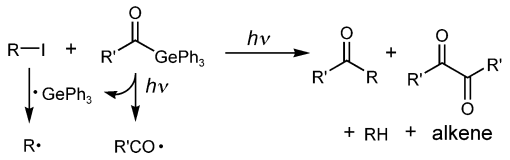
Scheme 9. Intermolecular acylation of thio- and selenoesters.

3 Intermolecular Acylation Reactions

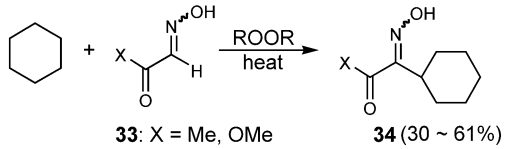
Intermolecular acylation reactions have not been actively investigated, mainly due to the difficulty of the addition step, the limitation of the carbonyl group acceptors, and several competing side reactions. In fact, no successful methods for intermolecular acylations are available so far. For successful intermolecular acylations, it will be the most important to develop highly efficient carbonyl group radical acceptors.

The first radical acylation was reported by Bentrude,[21] in which biacetyl was utilized as the carbonyl group acceptor (Scheme 8). Reaction of cyclohexane with biacetyl in the presence of benzoyl peroxide at reflux gave cyclohexyl methyl ketone in 32 – 69% yield. However, there have been no reports for radical acetylation of alkyl iodides. Based on our previous results,[3] intermolecular acylation reactions using thio- and selenoesters were briefly studied.[22] A radical reaction of thioester **28** with iodide **27** in the presence of hexabutylditin at 300 nm provided aldehyde **29** in 15% yield along with thioester **30** (5%). When the reaction was carried out with selenoester **31a** under the same conditions, methyl ketone **32** was isolated in 18% yield, whereas a trace amount of **32** was observed using thioester **31b**. Curran also investigated intermolecular acylations of alkyl iodides with acylgermanes under photolytic conditions (Scheme 10).[23] The reaction is initiated by photolytic cleavage of acylgermanes to acyl radicals and triphenylgermyl radical, providing low yields of ketones along with diketones, alkanes, and alkenes *via* bimolecular combination of acyl radicals and alkyl radicals.

The fundamental problems associated with intermolecular addition of alkyl radicals onto carbonyl groups cannot be easily solved. Therefore, the feasibility of C=N bonds as radical acceptors was investigated. Previously, intermolecular addition of alkyl radicals to oxime ethers was reported (Scheme 11).[24] Especially,



Scheme 10. Bimolecular reaction of alkyl iodides with acylgermanes.



Scheme 11. Ketoximes from aldoximes.

oxime ethers **33**, activated by ketone and ester groups, react with alkyl radicals to give oxime ethers **34** in moderate yield.[24a]

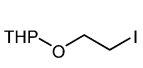
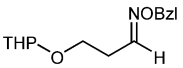
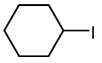
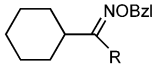
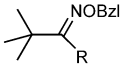
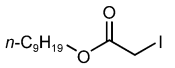
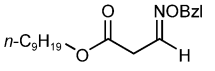
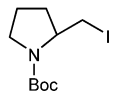
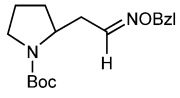
3.1 Relative β-Elimination Rates of Leaving Groups from Aminyl Radicals

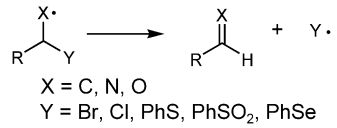
To develop a highly efficient radical acceptor containing the C=N bond, two important features should be considered. First, the acceptor must be very reactive toward alkyl radicals for the fast addition of alkyl radicals to the acceptor. In this regard, it is desirable to introduce an electron-withdrawing group to the radical acceptor for nucleophilic alkyl radicals. Second, highly efficient and fast β-elimination would be essential for the success of this approach. The ease of β-elimination depends on both (i) the strength of the σ-bond broken (C–Y) and (ii) the nature of the π-bond formed (C=X) (Scheme 12). It is expected that β-fragmentation would be faster when the bond broken is weaker and the bond formed becomes stronger. The relative β-elimination rates of leaving groups from aminyl radicals are in the order of PhSe > $PhSO_2$ > PhS ~ Br.[25] However, the order of Br > PhSe > PhS > $PhSO_2$ > Cl is observed for β-eliminations from alkyl radicals. In this study, it is of interest that a phenylsulfonyl group is a much better leaving group than a phenylsulfanyl group when the phenylsulfonyl group is eliminated from the aminyl radical.

3.2 Radical Reaction of Sulfonyl Oxime Ethers

Sulfonyl oxime ethers have been developed as carbonyl equivalent radical acceptors for an indirect radical acylation approach. This novel acylation approach involves the additions of alkyl radicals to C=N bonds and subsequent fast and irreversible β-elimination of the phenylsulfonyl radicals to afford oxime ethers **37** which

Table 2. Synthesis of oxime ethers from alkyl iodides.

Substrate	Product	Yield [%]
		93
		R = H, 91 R = Me, 87
		R = H, 85 R = Me, 15
		72
		95

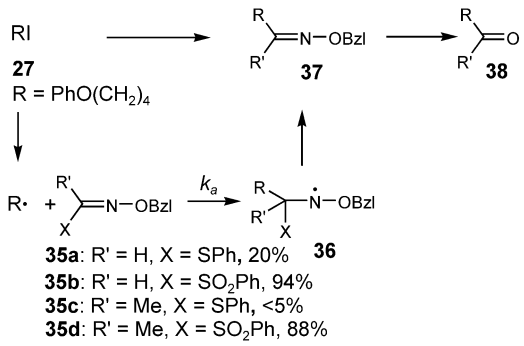


Scheme 12. β-Elimination rates of leaving groups.

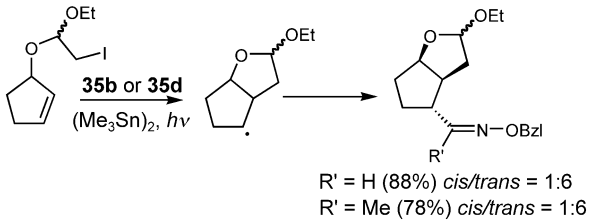
can be readily converted into carbonyl compounds **38** (Scheme 13).[22] The presence of a phenylsulfonyl group is essential for the success of this approach. Phenylsulfanyl oxime ethers **35a** and **35c** are not effective, suggesting that the introduction of an electron-withdrawing group onto the iminyl carbon would not only lower the energy of LUMO of a radical acceptor but also increase the electron density of the iminyl carbon, thereby raising the rate of the addition reaction. Approximate rate constants for intermolecular additions of primary alkyl radicals to phenylsulfonyl oxime ethers have been determined as $k_a = 9.6 \times 10^5\ s^{-1}$ at 25 °C for **35b** and $k_a = 7.3 \times 10^4\ s^{-1}$ at 80 °C for **35d**, indicating that the additions are very fast and highly efficient.[26]

Thus, the addition of an alkyl radical to **35b** is much faster than the radical allylation reaction. As shown in Table 2, this reaction works well with primary, secondary, and sterically hindered tertiary alkyl iodides. In the case of sterically hindered *t*-butyl iodide, it works well with **35b** but only a very low yield of the oxime ether is isolated with **35d**, apparently due to steric reasons. Furthermore, the efficiency of this acylation approach is shown in the cyclization-acylation sequence, which cannot be achieved by conventional methods and can be applicable to prostaglandin synthesis (Scheme 14).

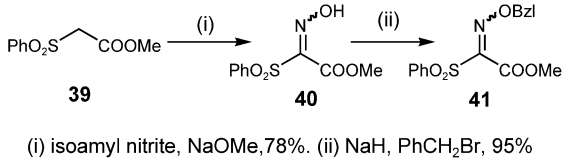
This free radical acylation approach can be extended for the synthesis of α-keto esters and ketones using

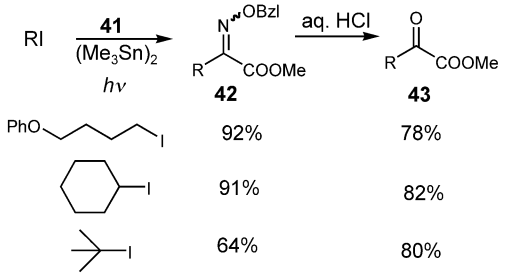


Scheme 13. Radical reaction of phenylsulfanyl and phenylsulfonyl oxime ethers **35**.

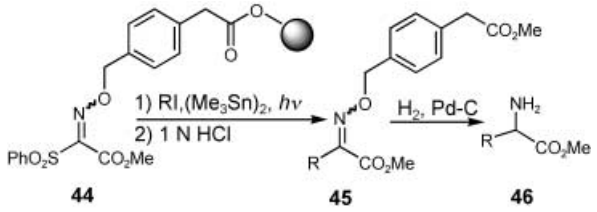


Scheme 14. Tandem cyclization and acylation sequence.



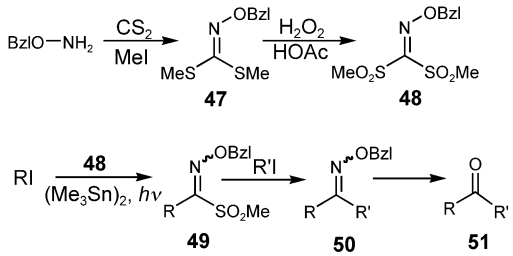


Scheme 15. Preparation of **41** and α-keto esters.



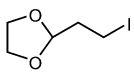
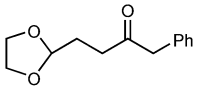
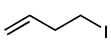
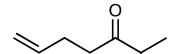
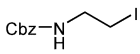
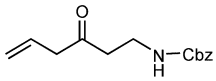
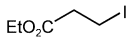
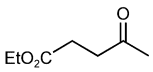
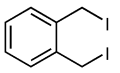
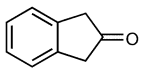
Scheme 16. Preparation of α-amino esters *via* radical acylation on a solid support.

methoxycarbonyl oxime ether **41**[28] and bis-methanesulfonyl oxime ether **48**,[29] respectively (Schemes 15 and 17). The oxime ether **41** can be conveniently prepared from readily available **39** by a two-step sequence involving nitrosation of **39** and subsequent benzylation



Scheme 17. Preparation of ketones *via* sequential radical acylation.

Table 3. Synthesis of ketones from alkyl iodides.

RI	R'I	RCOR'	Yield [%]
n-C_5H_{11}I	$Ph(CH_2)_2$I	*n*-C_5H_{11}CO$(CH_2)_2$Ph	70
n-C_5H_{11}I		*n*-C_5H_{11}COCH(CH3)2	52
$PhCH_2$I			63
			55
			56
	MeI		68
			65

of oxime **40**. Compound **41** is somewhat more reactive and effective than **35b**. For instance, radical reaction of *t*-butyl iodide with **41** gave *t*-butyl oxime ester in 64% yield, whereas the use of **35d** gave *t*-butyl oxime ether in 15% yield (Table 2). Radical reactions of **41** with a variety of structurally different alkyl iodides work well, usually yielding high yields of the corresponding oxime ester **42**. Furthermore, the synthesis of α-keto esters can be performed on a solid support (Scheme 16).[30] Using Wang resin and attachment through a modified benzyl oxime ether **44**, radical reactions with alkyl iodides gave the oxime ester **45** in modest yields (22–50%) after detachment from the resin. Oxime ester **45** was further transformed to α-amino esters **46**.

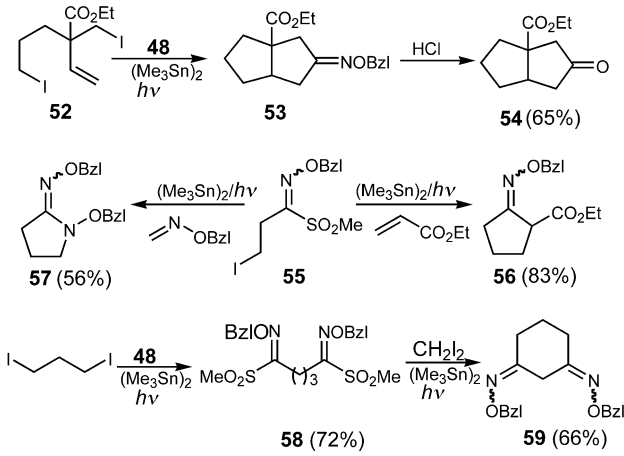
In free radical-mediated ketone synthesis *via* a sequential radical acylation approach, the bis-methanesulfonyl oxime ether **48** is used as a carbonyl equivalent geminal radical acceptor.[29] Compound **48** can be prepared from *O*-benzylhydroxylamine in a two-step sequence. Treatment of *O*-benzylhydroxylamine with carbon disulfide and methyl iodide gave the bis-meth-

ylthio oxime ether **47**, which was oxidized with hydrogen peroxide in acetic acid to give **48** as a stable crystalline solid. The approximate rate constant for the intermolecular addition of a primary alkyl radical onto **48** is $k_a = 1.7 \times 10^6\ s^{-1}$ at 80 °C, indicating that **48** is a better radical acceptor than **35b**.[31]

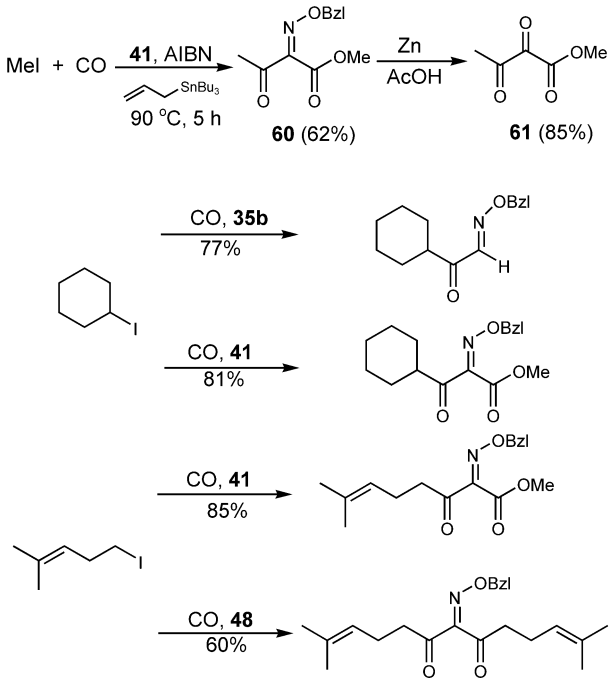
The synthesis of ketones can normally be carried out by a three-step, one-pot procedure. Treatment of an alkyl iodide with **48**, hexamethylditin in ethanol and irradiation at 300 nm for 3 h followed by the addition of another alkyl iodide and hexamethylditin with an additional irradiation at 300 nm afforded ketoxime **50** *via* **49**. Compound **50** was further hydrolyzed under acidic conditions to yield the unsymmetrical ketone **51**. As shown in Table 3, this method works well with primary alkyl iodides but somewhat less effectively with secondary iodides and can be applied to prepare unsymmetrical acyclic ketones as well as cyclic ketones. Even stable allylic and benzylic radicals react smoothly with **48**. In addition, it is noteworthy that an oxime ether group can be converted into both a carbonyl group and an amino group.[32]

Several interesting variations are shown in Scheme 18. Radical acylation of diiodide **52** with **48** furnishes **53** through cyclization followed by acylation or *vice versa*. Similarly, a tandem sequence involving intermolecular addition to acrylic ester or *O*-benzylformaldoxime followed by cyclization onto the sulfonyl oxime ether group provides the oxime ester **56** and iminolactam **57**, respectively.[33] Diiodopropane does not give the cyclobutanone oxime but yields bis-oxime **58**. Subsequent tandem radical addition and cyclization with diiodomethane completes a [3 + 1 + 1 + 1] annulation sequence to give **59** in good yield.

The present approach can be further extended to the synthesis of vicinal tricarbonyl compounds by combining sulfonyl oxime ether chemistry with radical carbonylation reactions.[34] When methyl iodide was treated with phenylsulfonyl oxime ether **41** in the presence of allyltributyltin and AIBN in a pressurized vessel of CO at 90 °C for 5 h, **60** was isolated in 62% yield. In this thermally induced radical chain reaction, allyltin serves as the radical chain carrier which traps the phenylsulfonyl radical. The competing reactions involving the addition of acyl radicals to allyltin and the direct addition of alkyl radicals to **41** do not interfere with this reaction, suggesting that the addition of acyl radicals to sulfonyl oxime ether **41** is much faster than the competing reactions. This three-component coupling reaction comprised of RX, CO, and phenylsulfonyl oxime ether **41** can be successfully carried out with other sulfonyl oxime ethers **35b** and **48** and some experimental results are shown in Scheme 19. Reported deoximation methods appeared not to be applicable to acylated oxime ethers and zinc in acetic acid is effective for the deoximation of acylated oxime ethers to vicinal tricarbonyl compounds.



Scheme 18. Tandem reactions of bis-sulfonyl oxime ether **48**.

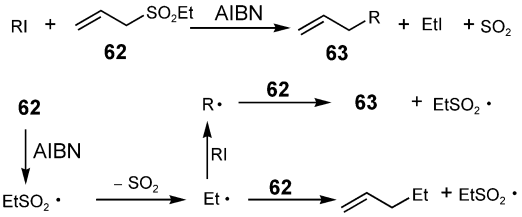


Scheme 19. Synthesis of vicinal acylated oxime ethers.

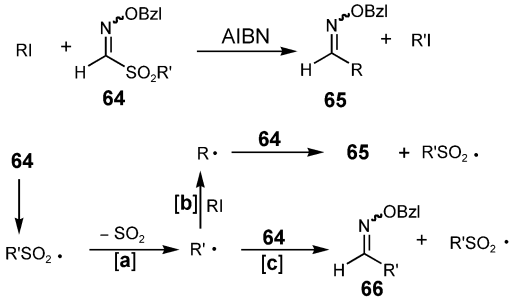
The free radical acylation approaches appear to be highly useful for the synthesis of a variety of carbonyl compounds and have great synthetic potential because the present methods succeed in complex molecules under mild conditions, where more conventional methods would be inappropriate.

4 Tin-Free Radical Acylation Approach using Sulfonyl Oxime Ethers

Recent advances in radical reactions have greatly benefited from the efficiency of organotin reagents as radical mediators. However, organotin reagents are



Scheme 20. Mechanism of tin-free radical allylation.



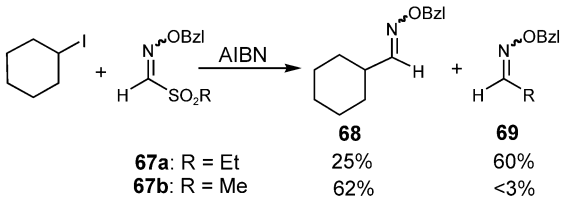
Scheme 21. Tin-free radical acylation of alkyl iodides.

highly toxic, and it is difficult to remove organotin residues from the reaction products. These disadvantages have proven to be a serious barrier to industrial applications. Among several approaches including the use of polymer-supported organotin reagents and organosilanes,[35] organosulfone-mediated tin-free radical reactions are very attractive because this approach completely eliminates the organotin reagents and uses readily available organosulfone groups as mediators.[36]

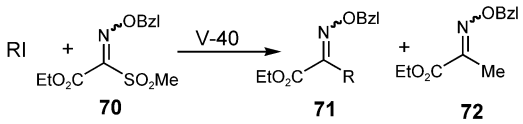
Organosulfone-mediated carbon-carbon bond forming reactions including radical allylation, vinylation, and alkynylation were developed by Zard.[37] The success of tin-free allylation is based on three important factors.[38] First, alkylsulfonyl radicals undergo thermal decomposition to give alkyl radicals along with liberation of sulfur dioxide. Second, sulfonyl radicals add reversibly to olefins. Finally, alkyl radicals abstract iodine atoms from alkyl iodides to generate more stable alkyl radicals. As shown in Scheme 20, the initially generated ethanesulfonyl radical from **62** undergoes thermal decomposition to form an ethyl radical, which abstracts an iodine atom from an alkyl iodide. The alkyl radical reacts with allyl sulfone **62** to give allylated product **63**. Direct addition of the ethyl radical onto **62** is not a serious problem because the iodine atom transfer process is normally much faster than the direct addition process.

4.1 Tin-Free Radical Acylation Approach from Alkyl Iodides

Our approach is largely based on Zard's tin-free radical allylation reaction [38] and involves thermal decomposition of an alkylsulfonyl radical (path **a**) and subsequent iodine atom transfer (path **b**) as outlined in



Scheme 22. Radical reaction of cyclohexyl iodide with methane- and ethanesulfonyl oxime ether.



Scheme 23. Synthesis of oxime esters from alkyl iodides.

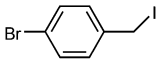
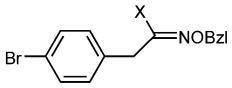
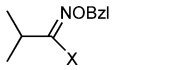
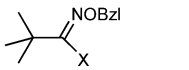
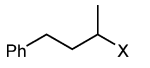
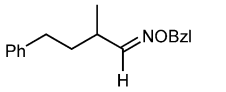
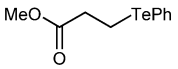
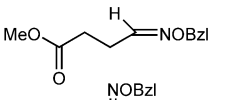
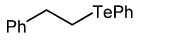
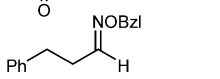
Scheme 21.[39] The problem associated with the tin-free radical acylation approach is derived from a fast addition of an alkyl radical onto sulfonyl oxime ether **64** to afford oxime ethers **65** and **66**.[26] Since the direct addition of the alkyl radical onto sulfonyl oxime ether **64** (path **c**) would compete with iodine atom transfer (path **b**) in the radical acylation approach, the efficient iodine atom transfer is a key factor for the success of this approach.

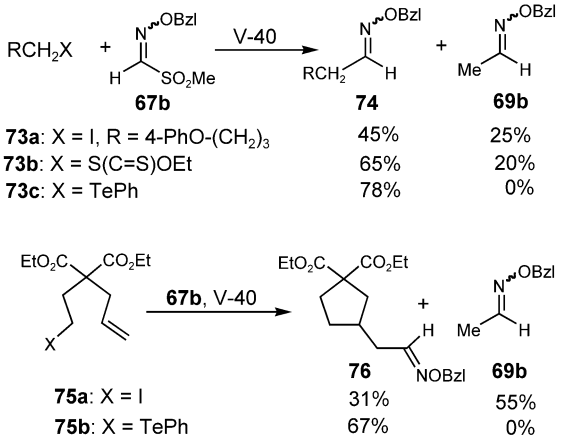
When the efficiency of the iodine atom transfer was studied with **67a**, a 25 : 60 mixture of two oxime ethers **68** and **69** was obtained (Scheme 22). It is evident that the addition of the ethyl radical onto **67a** is more than two times faster than iodine atom transfer from cyclohexyl iodide to the ethyl radical. Although **68** is increased to 48% along with 21% of **69a** by using a large excess amount of cyclohexyl iodide (5 equivs.), the serious problem involving the formation of **69** cannot be solved, indicating that **67a** is not suitable for tin-free radical acylation of secondary alkyl iodides.

This problem can be solved using methanesulfonyl oxime ether **67b**. When cyclohexyl iodide was treated with **67b** in refluxing heptane in the presence of AIBN, **68** was isolated in 62% yield along with a trace amount of methyl oxime ether **69b**, indicating that the iodine atom transfer process is much faster than the direct addition process. Thus, **67b** obviates the problem we have faced with secondary alkyl iodides. As shown in Table 4, the results obtained with **67b** are quite satisfactory, yielding the corresponding oxime ethers in high yield (65 – 80%). The present approach can be further extended to the synthesis of the α-oxime ester **71**, a synthetic equivalent of α-keto ester, using **70**. When the reaction is carried out under the same conditions, **71** is obtained in good yields without the formation of **72**.

Primary alkyl iodides do not work well with **67b** and **70**. Due to a small energy difference between a methyl radical and a primary alkyl radical, iodine atom transfer competes with the direct addition of the methyl radical onto **67b**. Treatment of 4-phenoxybutyl iodide (**73a**) with an equimolar amount of **67b** in *tert*-butylbenzene at

Table 4. Synthesis of oxime ethers from alkyl iodides and tellurides.

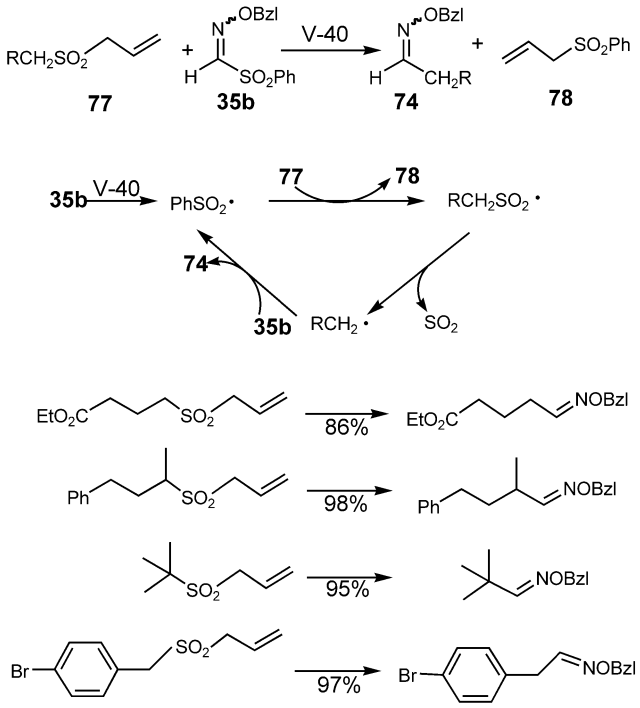
Substrate	Product	Yield [%]
		X = H, 80 X = CO_2Et, 73
		X = H, 67 X = CO_2Et, 64
		X = H, 71 X = CO_2Et, 64
		X = I, 67 X = TePh, 77
		71
		76



Scheme 24. Radical reaction of **67b** with alkyl iodide, xanthate, and phenyl telluride.

140 °C for 30 h gave a 45:25 mixture of the desired oxime ether **74** and **69b**, showing the inefficiency of **67b**. A similar result was obtained with alkyl xanthate **73b**.

The problem of slow iodine atom and xanthate group transfers can be solved by using alkyl phenyl tellurides (Scheme 24). Organic tellurides have been utilized to generate alkyl and acyl radicals.[40,41] Gratifyingly, reaction of phenyl telluride **73c** with **67b** and V-40 in *tert*-butylbenzene at 140 °C for 24 h gave **74** in 78% yield without any indication of the formation of **69b**. The reaction was also successful with secondary alkyl as well as primary alkyl tellurides. When a sequential radical reaction involving cyclization and acylation sequence was examined with **75b**, the desired oxime ether **76** was obtained in 67% yield, whereas the use of iodide **75a** gave **76** in 31% yield along with **69b** (55%), demonstrating the efficiency of phenyl telluride group as a radical precursor.



Scheme 25. Tin-free radical acylation of alkyl allyl sulfones.

4.2 Tin-Free Radical Acylation of Alkyl Allyl Sulfones

Since the tin-free radical acylation approach using methanesulfonyl oxime ether **67b** does not work with primary alkyl iodides and xanthates, alternative radical precursors are needed to accommodate all the structurally different substrates including primary alkyl substrates. It was found that alkyl allyl sulfones are highly efficient and reliable radical precursors for the generation of primary alkyl radicals under tin-free radical conditions and for the formation of carbon-carbon bonds.[42–44]

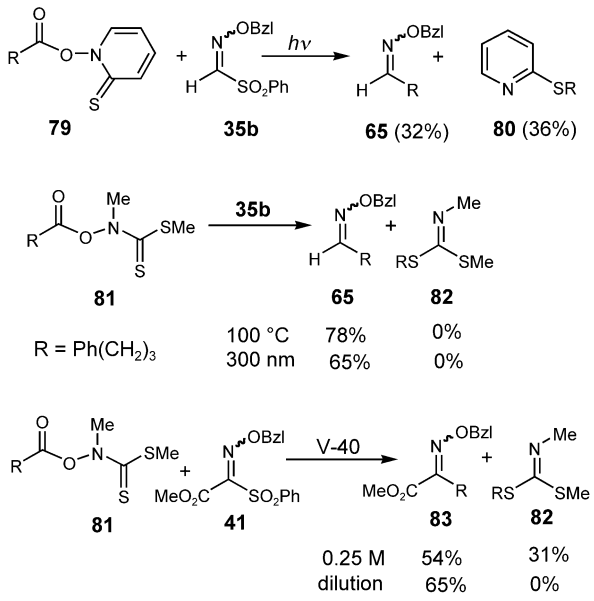
As shown in Scheme 25, the addition of a phenylsulfonyl radical onto alkyl allyl sulfone **77** would produce an alkylsulfonyl radical along with the formation of phenyl allyl sulfone (**78**). Although the alkylsulfonyl radical would add to **77** and **78**, the former is a degenerate process and the latter produces the phenylsulfonyl radical. Thus, both reactions do not interfere with the desired process. Since the addition of an alkyl radical onto **77** and **78** is relatively slow, the alkyl radical, generated from thermal decomposition of the alkylsulfonyl radical, should preferentially add to phenylsulfonyl oxime ether **35b** along with regeneration of the phenylsulfonyl radical for propagation of a radical chain reaction.

Reaction of allyl sulfone **77** with **35b** (1.5 equivs.) and V-40 (0.2 equivs.) as initiator in chlorobenzene at 110 °C proceeded cleanly and was complete within 6 h, yielding **74** in high yield, indicative of clean generation of the primary alkyl radical under tin-free conditions.[43] This method is highly efficient for radical acylation of a variety of structurally different substrates. For example, it always works well not only with reactive primary and secondary alkyl radicals but also with stable benzylic radicals. Furthermore, alkyl allyl sulfones could be efficiently utilized in tin-free radical-mediated cyanation, vinylation, and allylation. [44]

4.3 Tin-Free Radical Acylation of Thiohydroxamate Esters

Since *O*-acylthiohydroxamates were introduced in radical chemistry by Barton,[45] they have been widely utilized as useful radical precursors of alkyl and aminyl radicals. Further applications of the radical chemistry of *O*-acylthiohydroxamates **79** led to the formation of carbon-carbon bonds using sulfonyl cyanides[46] and activated olefins.[47] Highly reactive trapping agents are required because the alkyl radical can attack the thiocarbonyl group of **79** concurrently.

When decarboxylative acylation approaches from carboxylic acids were carried out with *O*-acylthiohydroxamates **79** and **35b** at 300 nm for 3 h, a mixture of oxime ether **65** and pyridyl sulfide **80** was obtained in a roughly 1 : 1 ratio. Thus, the key feature for the success of this approach is to reduce the rate of the alkyl radical additions onto the thiocarbonyl group to suppress the formation of **80**.

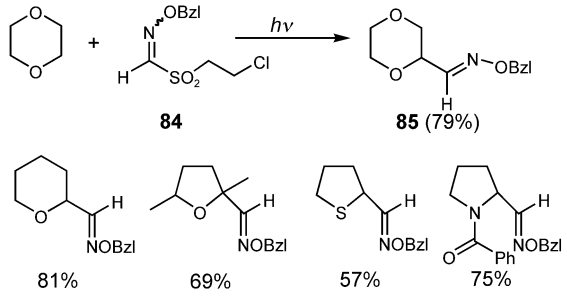


Scheme 26. Decarboxylative acylation of thiohydroxamate esters.

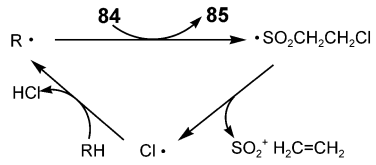
A new thiohydroxamate ester well suited for our purpose was developed.[48] Thiohydroxamate esters **81** were obtained in high yields by treatment of acid chlorides with *N*-methylhydroxydithiocarbamate in the presence of triethylamine or by using the Misunobu reaction, and were quite stable. When **81** was treated with **35b** in heptane at 100 °C using V-40 as an initiator, **65** was obtained exclusively without the formation of **82**. Furthermore, a similar result was obtained under photolytic conditions. Primary and secondary aliphatic carboxylic acids work well, yielding the corresponding oxime ethers in high yields. Sterically hindered tertiary carboxylic acids undergo the decarboxylative acylation cleanly. The reactions require 10 h and thermal conditions give somewhat higher yields than photochemical conditions. When the reaction was repeated with methoxycarbonyl oxime ether **41** under thermal conditions, the desired oxime ester **83** was isolated in 54% yield along with a significant amount of the rearranged product **82**. The problem of the formation of the rearranged product could be solved by the addition of **81** into **41** with a syringe pump.

4.4 Tin-Free Radical Acylation of C–H Bonds

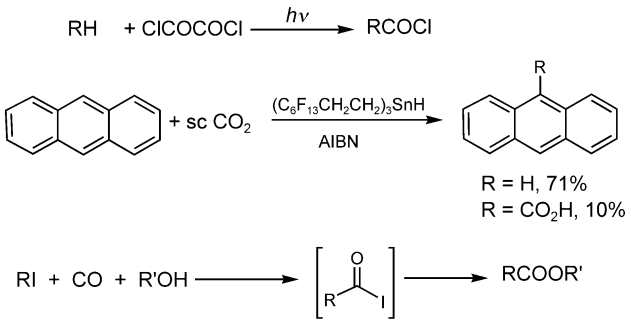
Radical acylation of C–H bonds can be achieved by using 2-chloroethylsulfonyl oxime ether **84**.[49] When a solution of **84** in dioxane was irradiated at 300 nm for 12 h, the desired oxime ether **85** was isolated in 79% yield (Scheme 27). This reaction can be carried out under thermal conditions. This approach involves an alkyl radical addition to **84** followed by β-elimination of 2-chloroethylsulfonyl radical which undergoes thermal decomposition to generate the chlorine atom along with



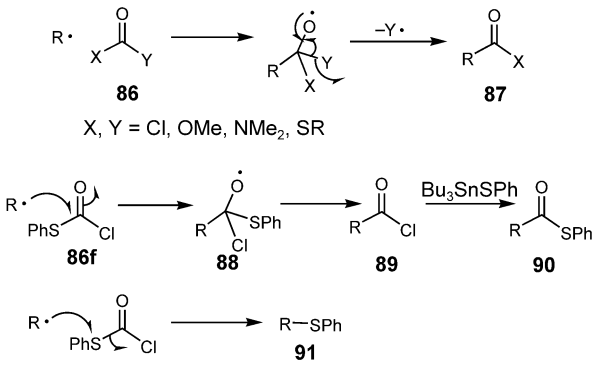
Scheme 27. Radical acylation of C–H bonds with **84**.



Scheme 28. Plausible mechanism for the radical acylation of C–H bonds.



Scheme 29. Radical carboxylation approaches.



Scheme 30. Radical carboxylation of *S*-phenyl chlorothioformate.

the liberation of sulfur dioxide and ethylene. Finally, the chlorine atom abstracts hydrogen atom from dioxane to produce the alkyl radical (Scheme 28). This approach is attractive because it not only avoids the use of highly toxic organotin compounds and strong acidic or basic conditions but also allows to introduce an oxime ether group to α-carbon to the heteroatom with cleaving C–H bonds in a single step. Furthermore, the present approach works with unactivated tertiary and benzylic C–H bonds to introduce the oxime ether group but fails with unactivated secondary and primary alkyl C–H bonds.

5 Radical Carboxylation

Since a free radical-mediated carboxylation reaction was reported by Kharasch in 1940s,[7] no significant progress in this area was made in the following 50 years. Direct radical carboxylation of alkyl radicals with carbon dioxide is an extremely difficult process because decarboxylation is a greatly favored process. Recent studies on the direct free radical carboxylation in supercritical CO_2 resulted in limited success.[50] An indirect radical carboxylation approach involving carbonylation and iodine atom transfer has recently been developed (Scheme 29).[51]

Table 5. LUMO energy of **86** and chemical yields of **87.**

	Carbonyl derivative	LUMO energy [eV]	Product **87**	Yield [%]
86a	$ClCONMe_2$	0.1377	$RCONMe_2$	0
86b	$ClCO_2Me$	0.0039	RCO_2Me	0
86c	$COCl_2$	–0.7740	RCOCl	0
86d	$C(O)(SPh)_2$	–1.0911	RCOSPh	31
86e	ClC(O)SMe	–1.1810	RCOSMe	32
86f	ClC(O)SPh	–1.3863	RCOSPh	60

5.1 Radical Carboxylation with S-Phenyl Chlorothioformate

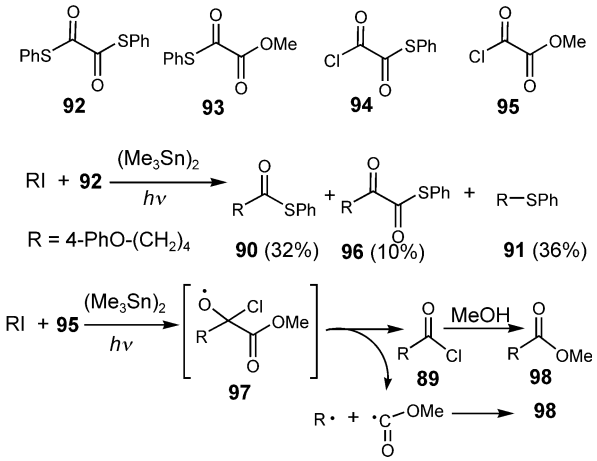
It is expected that the success of alkyl radical additions to C=O bonds would depend very much on the nature of the substituent of the carbonyl derivatives **86**, which would be closely related to the LUMO energy of **86** (Scheme 30).[8]

Since nucleophilic alkyl radicals would react more rapidly with radical acceptors having a lower LUMO energy, AM1 calculations of several carbonyl derivatives were performed (Table 5) and *S*-phenyl chlorothioformate (**86f**) shows the lowest LUMO energy among the carbonyl derivatives tested in this study. When the radical carboxylation reactions were carried out with 4-phenoxybutyl iodide, carbonyl derivative **86**, and hexabutylditin at 300 nm, *S*-phenyl chlorothioformate (**86f**) gave the best result, although bis-thiophenyl carbonate (**86d**) and *S*-methyl chlorothioformate (**86e**) were effective to some extent. Phosgene, **87a**, and **87b** were totally ineffective. The present result suggests that the LUMO energy is a very important factor in predicting and designing the radical reactions.

Reaction of 4-phenoxybutyl iodide with **86f** and hexabutylditin in benzene at 300 nm for 10 h afforded *S*-phenyl thioate **90** in 60% yield along with 4-phenoxybutane (15%) and 4-phenoxybutyl phenyl sulfide (**91**) (8%) due to homolytic substitution by the alkyl radical at the sulfur atom. The present approach involves an alkyl radical addition to C=O bond to generate alkoxy radical **88** which undergoes β-fragmentation to afford acid chloride **89**, which reacts with tri-*n*-butyltin phenylmercaptide to provide **90**. As shown in Table 6, for most of the cases observed, the reaction affords the *S*-phenyl thioates in moderate yield and sterically hindered tertiary alkyl iodides give similar results.

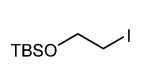
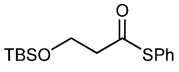
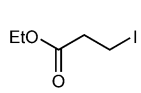
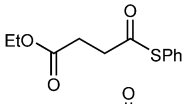
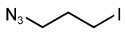
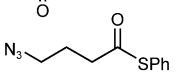
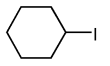
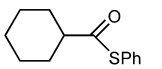
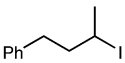
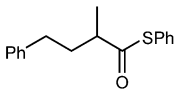
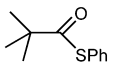
5.2 Radical Carboxylation with Oxalic Acid Derivatives

Kharasch reported the radical carboxylation of hydrocarbons using oxalyl chloride as a carboxyl group radical acceptor under photochemical and peroxide-initiated



Scheme 31. Radical carboxylation of alkyl iodides.

Table 6. *S*-Phenyl thioates from alkyl iodides and **86f**.

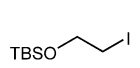
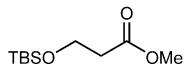
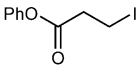
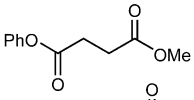
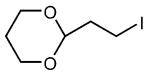
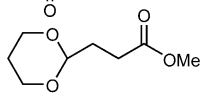
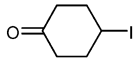
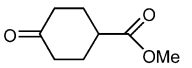
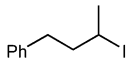
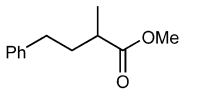
RI	Product	Yield [%]
		55 (5)[a]
		44 (11)[a]
		48 (9)[a]
		56
		53
		49

[a] Sulfide product **91**.

conditions.[7] In this reaction, the addition of an alkyl radical to oxalyl chloride would be followed by β-elimination of chlorocarbonyl radical, indicating that oxalyl chloride is a good radical acceptor toward alkyl radicals.

To perform radical carboxylation of alkyl iodides, the effectiveness of several oxalyl derivatives like 1,2-dicarbonyl and/or carboxyl group radical acceptors was investigated. When a solution of 4-phenoxybutyl iodide (1.0 equiv.), **92** (1.5 equivs.) and hexamethylditin (1.2 equivs.) in benzene (0.3 M in iodide) was irradiated at 350 nm for 20 h, *S*-phenyl thioate **90** was isolated in 32% yield along with phenyl sulfide **91** (36%) and α-ketothioate **96** (10%). Furthermore, **93** and **94** were unsuccessful, yielding several products. The best results were obtained with methyl oxalyl chloride (**95**) as a

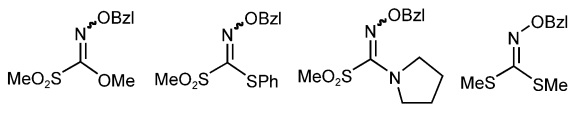
Table 7. Carboxylic methyl esters from alkyl iodides and **95**.

RI	Product	Yield [%]
		80
		73
		59
		67
		74

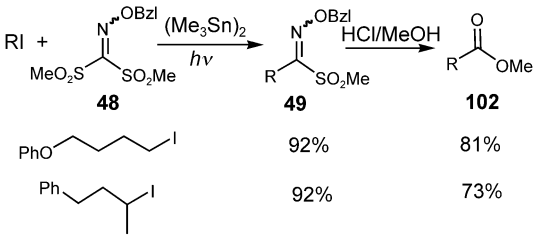
carboxyl radical acceptor. Treatment of 4-phenoxybutyl iodide with **95** (3.0 equivs.) and hexamethylditin (1.2 equivs.) in benzene at 350 nm for 20 h followed by addition of thiophenol and triethylamine afforded *S*-phenyl thioate **90** (67%) along with methyl ester **98** in 15% yield. When the reaction mixture was treated with excess methanol, the corresponding methyl esters were isolated in good yields. The reaction would proceed *via* intermediate **97**, from which the β-elimination of the methoxycarbonyl radical would occur to yield acid chloride **89**. As shown in Table 7, the reaction works well with various alkyl iodides.

5.3 Radical Carboxylation with Bis-methanesulfonyl Oxime Ether

Based on our previous results,[29] it is expected that alkyl radical additions to bis-methanesulfonyl oxime ether **48** should afford sulfonyl oxime ether **49** which can be hydrolyzed to the corresponding carboxylic acids under acidic conditions. Furthermore, MeO- and PhS-substituted sulfonyl oxime ethers (**99**, **100**) can act as carboxyl radical acceptors. When the radical reactions were performed, the reaction worked reasonably well with **99** and **100** but **101** and **47** were totally ineffective, indicating that the present radical reaction is very



Scheme 32. Chemical yield of radical reaction with 4-phenoxybutyl iodide.



Scheme 33. Synthesis of carboxylic methyl esters from alkyl iodides.

sensitive to the substituent attached to the oxime ether group (Scheme 32).

Radical reaction of alkyl iodides with **48** and hexamethylditin at 300 nm gave alkyl sulfonyl oxime ethers **49** in high yields. This method works well with primary, secondary, and tertiary alkyl and benzylic iodides. The phenylsulfonyl oxime ethers were hydrolyzed with methanolic HCl to give the corresponding methyl esters **102**. This approach is an indirect way to achieve free radical carboxylation involving alkyl radical additions to C=N bonds.

6 Conclusion

Since radical acylation reactions involving additions of alkyl radicals onto carbonyl group radical acceptors are fundamentally difficult to achieve due to the very strong π bond strengths of carboxyl groups, alternative approaches involving the additions of acyl radicals to carbon-carbon double bonds have been developed. Radical acylations with sulfonyl oxime ethers provide a new route to aldehydes, ketones, and α-keto esters under mild conditions through the reactions described above. Based on these reactions, several useful transformations such as tandem reactions and carbonyl insertions can be performed, which cannot be achieved by conventional methods. Furthermore, the availability of these methods to convert the products into the corresponding amines will make these methods more attractive for synthetic manipulations. Tin-free radical acylations using methanesulfonyl oxime ethers as efficient traps or using allyl alkyl sulfones as precursors will be synthetically useful for industrial applications to synthesize new drugs and other bio-related products. The difficulty of direct carboxylation of alkyl radicals can be solved by using *S*-phenyl chlorothioformate and methyl oxalyl chloride as carboxyl group acceptors. The free radical acylation and carboxylation approaches will find useful applications for the synthesis of a variety of carbonyl compounds and have great synthetic potential because these methods proceed under mild conditions, where more conventional methods would be inappropriate.

Acknowledgements

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