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A one-pot radical addition/fragmentation route to ketones and esters

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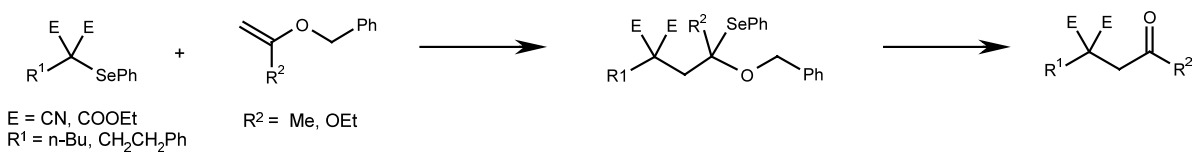
Abstract—A simple one-pot procedure has been developed that combines carbon–carbon bond formation via a radical addition to either substituted enol ethers or ketene acetals, with a subsequent fragmentation reaction to yield ketones and esters. The 'masked' methyl carbonyl radical acceptors discovered in this work are either commercially available or easily prepared in one to two steps.

The use and development of synthetic radical chemistry is due in large part to the ease and variety of carbon–carbon bond forming reactions that have been discovered.[1] The development of atom and group transfer addition reactions using electrophilic radicals has opened up a much wider range of alkene acceptors than are typically available to nucleophilic radicals.[2] In particular phenylselenomalonic esters and malononitriles were found to undergo group transfer radical additions with a number of electron rich acceptors, such as enol ethers and enamides, that had previously failed with other radical precursors.[3] An additional advantage of this method, besides the expanded scope of alkene partners, is the synthetic utility of the phenylseleno group transfer addition products.[2e] This is in contrast to tin hydride-mediated radical additions and halogen transfer radical additions which are terminated by halogen or hydride transfer.[1]

The development of reagents for use in radical chemistry that can form carbon–carbon bonds while also introducing additional functionality are of great use. One such example is allylstannanes, which have been widely used in organic synthesis.[4] A major advantage of allylstannanes is that they terminate a radical chain with an allyl group, which can be used for further synthetic elaboration. Since the synthetic utility of a carbon–carbon bond forming radical addition can be greatly enhanced when coupled to the additional introduction of other functional groups, the development of further reagents that accomplish this should be of value.

The β-fission of α-alkoxyalkyl radicals is a known process, but few examples of synthetic interest have been described.[5] There has also been a published review of related carbon–oxygen radical fragmentations.[6] Herein the one-pot conversion of enol ether and ketene acetal derivatives into ketones and esters following radical addition/fragmentation is described. A mechanistically similar reaction using acetonyltributylstannane as a radical acceptor has previously been described.[7] Advantages of the radical acceptors in this current work include their greater variety and stability, as well as the absence of tin. These reactions represent the first examples of intermolecular radical additions followed by α-alkoxyalkyl radical fragmentation to produce carbonyl compounds, as outlined in Scheme 1.



Scheme 1. Radical addition/fragmentation sequence.

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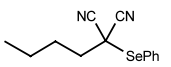
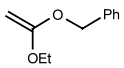
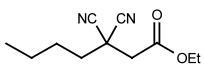
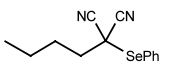
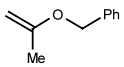
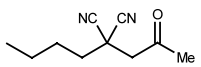
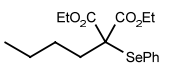
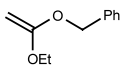
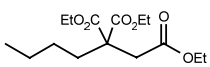
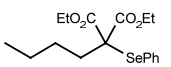
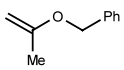
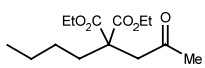
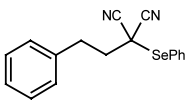
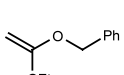
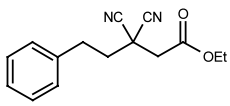
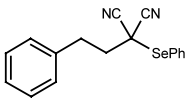
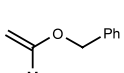
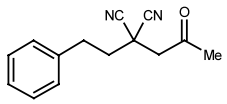
The reactions are generally carried out in either chloroform or benzene. The simplest method involves the sunlamp photolysis (65 W) of a phenylseleno radical precursor (1 EQ) with the appropriate enol ether or ketene acetal (2–5 EQ) in chloroform (0.1 M) for 17 h. Proton NMR spectrum at this time indicated complete consumption of the starting phenylseleno radical precursor, the presence of the excess acceptor, as well as the desired product. Concentration of the reaction mixture followed by column chromatography provided desired products. Alternatively reactions could be conducted in refluxing benzene (0.1 M) with added AIBN (5–10%) using the same ratio of starting materials as in the photolysis experiments. Similar results were obtained with either method. The phenylselenomalonic esters and malononitriles were made by known methods.[2e] The results are shown in Table 1.[8]

A suggested mechanism is shown in Scheme 2. The initial radical **2** is formed either by photolytic cleavage of the C–SePh bond or by abstraction by AIBN from radical precursor **1**. Radical **2** then adds to radical acceptor **3** to give α-alkoxyalkyl radical **4**. Radical **4** has two distinct paths to desired product **6**, it can either fragment directly or abstract the phenylseleno group to give group transfer addition product **5**. Addition product **5** can then reform radical **4** which then fragments to desired product. The final fragmentation provides the benzyl radical **7** which can then abstract the phenylseleno group from **5** and continue the chain. All the postulated steps are known radical reactions.[2e,5,6,9]

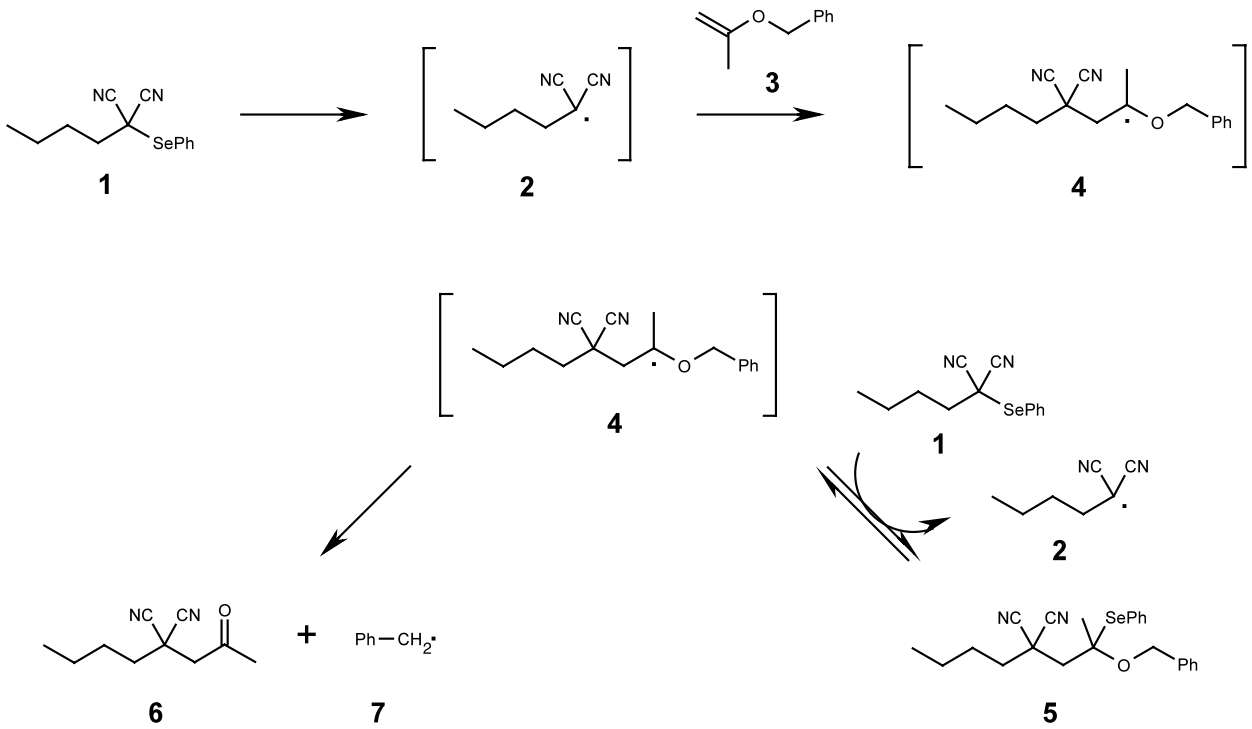
Evidence that the benzyl radical does indeed carry the chain was provided by isolation of benzylphenyl selenide (from entry 5) in essentially the same yield (53%) as the desired product. Preliminary evidence that radical **4** undergoes group transfer prior to fragmentation was obtained by monitoring the reaction by proton NMR at various time points during the reaction. A proton NMR spectrum of the reaction mixture after 2 h revealed a significant decrease of starting selenide and about a 3 to 1 ratio of suspected group transfer addition product to desired product. Proton NMR spectra taken at later reaction times revealed the disappearance of the peaks belonging to the group transfer addition product with a coincident increase in the desired product. Isolation of **5** from the reaction mixture was achieved by flash chromatography. A proton NMR spectrum of the isolated product was consistent with product **5**, and showed diastereotopic protons that corresponded to benzylic protons based on chemical shift.

Attempts to form aldehydes by this reaction methodology with radical precursor **8** and benzylvinyl ether as the radical acceptor failed to provide desired aldehyde **10**. Instead the only isolated product was the group transfer addition product **9** in 75% yield (Scheme 3). Further photolysis of **9** (up to 96 h, 65 W sunlamp) failed to provide any aldehyde and provided only recovered starting material. Numerous reaction conditions have been attempted to convert group transfer addition product **9** to desired aldehyde, but none have

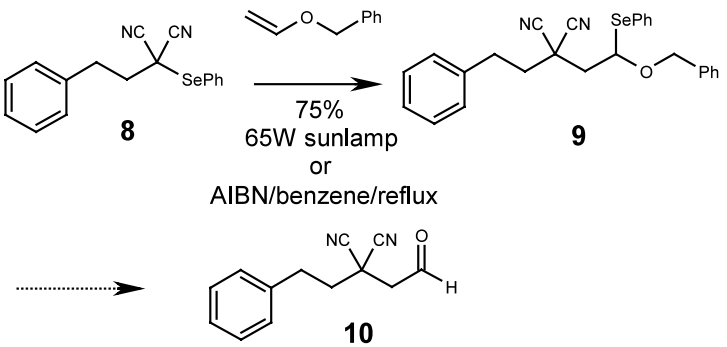
Table 1. Radical addition/fragmentation results

entry	radical precursor	acceptor	method[a]	product	yield(%)
1			A		69
2			B		50
3			A		62
4			A		71
5			A		55
6			B		76

[a]Method A: 65 W sunlamp irradiation, chloroform, 12–17 h. Method B: AIBN, benzene, reflux, 16 h.



Scheme 2. Radical addition/fragmentation mechanism.



Scheme 3. Radical addition to benzylvinyl ether.

been successful. Proton NMR spectra of these reactions have shown the conversion of **9** into new products and efforts are underway to isolate and characterize these products. Work is also continuing to try and find conditions that cleanly form aldehyde products.

The radical precursors chosen for this study were phenylselenomalonic esters and malononitriles due to their known good behavior in radical additions to enol ethers, as well as the hoped for ability to isolate their group transfer addition products for further study. But a much wider class of radical precursors as well as radicals are known to add to enol ethers, and it is hoped that the scope of partners for this reaction will expand with further research.[10] Currently radical acceptors are being investigated that should provide access to amides and pyruvates. A simple intermolecular radical addition/fragmentation reaction has been developed which gives direct access to ketones and esters. Since these carbonyl groups are central to organic synthesis, both as final products and for further synthetic transformations, this method should be found useful. Additionally, by the appropriate choice of radical acceptor one can obtain the carbonyl group desired without having to undertake functional group interconversions. An added advantage of the radical acceptors described in this work are their ease of preparation and in the case of **3** its commercial availability.[11] The availability of other substituted enol ethers by known chemistry should allow for ready access to a wide variety of ketones in addition to methyl.[12]

Acknowledgements

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8. All reported compounds were characterized by ^{1}H (300 MHz) and ^{13}C (75 MHz) NMR in $CDCl_3$, IR, HRMS, and melting point. The data for products in Table 1 are provided below. **Entry 1**: ^{1}H NMR δ 4.29 (2H, q, $J=7.2$ Hz), 2.96 (2H, s), 2.04 (2H, m), 1.69 (2H, m), 1.46 (2H, m), 1.33 (3H, t, $J=7.2$ Hz), 0.98 (3H, t, $J=7.3$ Hz). ^{13}C NMR δ 166.77, 115.24 (2C), 62.66, 41.42, 37.54, 34.25, 27.77, 22.32, 14.40, 13.99. IR (neat) 2922, 2254, 1736, 1237 cm^{-1}. HRMS calcd for $C_{11}H_{16}N_2O_2$ 208.1212, found 208.1213. **Entry 2**: mp 72–76°C. ^{1}H NMR δ 3.12 (2H, s), 2.27 (3H, s), 2.00 (2H, m), 1.66 (2H, m), 1.46 (2H, m), 0.97 (3H, t, $J=7.3$ Hz). ^{13}C NMR δ 200.08, 115.08 (2C), 48.96, 36.80, 32.77, 29.56, 27.36, 21.96, 13.64. IR (neat) 3433, 2959, 2929, 2254, 1719, 1181 cm^{-1}. HRMS calcd for $C_{10}H_{14}N_2O$ 178.1106, found 178.1100. **Entry 3**: ^{1}H NMR δ 4.20 (4H, q, $J=7.1$ Hz), 4.12 (2H, q, $J=7.1$ Hz), 2.95 (2H, s), 1.98 (2H, m), 1.26 (13H, m), 0.89 (3H, t, $J=7.0$ Hz). ^{13}C NMR δ 170.97 (2C), 170.84, 61.86 (2C), 60.99, 56.01, 37.95, 33.22, 26.84, 23.20, 14.48, 14.37 (2C), 14.18. IR (neat) 2961, 2936, 1736, 1266, 1201, 1030 cm^{-1}. HRMS calcd for $C_{15}H_{27}O_6$ $(M+H)^+$ 303.1808, found 303.1808. **Entry 4**: ^{1}H NMR δ 4.19 (4H, q, $J=7.1$ Hz), 3.11 (2H, s), 2.16 (3H, s), 2.01 (2H, m), 1.31 (2H, m), 1.24 (6H, t, $J=7.1$ Hz), 1.14 (2H, m), 0.87 (3H, t, $J=7.0$ Hz). ^{13}C NMR δ 205.29, 170.95 (2C), 61.44 (2C), 55.34, 45.91, 33.08, 30.37, 26.86, 22.85, 14.00 (2C), 13.87. IR (neat) 2961, 1732, 1199 cm^{-1}. HRMS calcd for $C_{14}H_{24}O_5$ 272.1624, found 272.1628. **Entry 5**: mp 73–76°C. ^{1}H NMR δ 7.30 (5H, m), 4.29 (2H, q, $J=7.2$ Hz), 3.03 (2H, m), 3.00 (2H, s), 2.32 (2H, m), 1.33 (3H, t, $J=7.2$ Hz). ^{13}C NMR δ 166.27, 138.08, 128.93 (2C), 128.42 (2C), 127.09, 114.55 (2C), 62.39, 41.02, 39.10, 33.72, 31.74, 14.02. IR (neat) 3022, 1740, 1216, 755 cm^{-1}. HRMS calcd for $C_{15}H_{16}N_2O_2$ 256.1211, found 256.1206. **Entry 6**: mp 89.0–90.3°C. ^{1}H NMR δ 7.28 (5H, m), 3.13 (2H, s), 3.02 (2H, m), 2.30 (2H, m), 2.24 (3H, s). ^{13}C NMR δ 200.23, 138.63, 129.31 (2C), 128.83 (2C), 127.44, 115.16 (2C), 49.26, 39.00, 33.09, 32.08, 29.93. IR (neat) 3029, 2930, 2250, 1721, 1364. HRMS calcd for $C_{14}H_{14}N_2O$ 226.1106, found 226.1103.
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