Radical Reactions

Radical-Mediated γ-Functionalizations of α,β-Unsaturated Carboxylic Amides**

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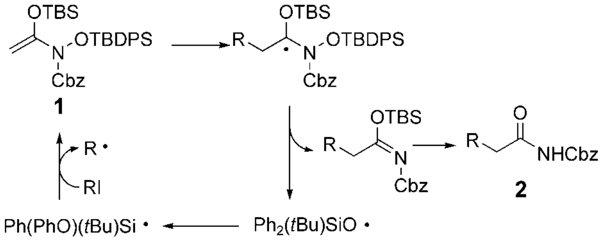
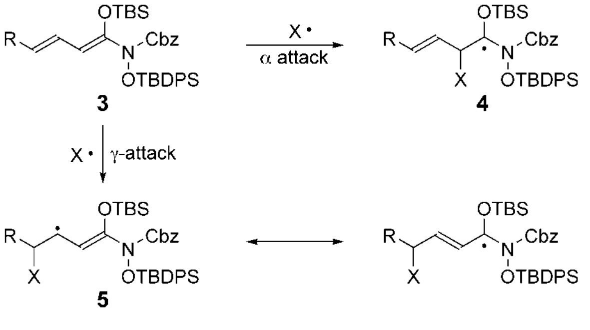
α,β-Unsaturated carbonyl compounds are important intermediates in organic synthesis.[1] Reaction of their enolate anions with various electrophiles generally affords α-functionalized products. Despite their versatility in synthetic manipulations, γ-functionalization of α,β-unsaturated carbonyl compounds, including γ-alkylation, has been often a very difficult and unresolved problem. Several methods to effect this operation have been developed over the years and include the use of γ-arylsulfonyl groups as regiospecific control elements,[2] copper dienolates,[3] and zinc bromide catalyzed alkylation of *O*-silylated dienolates.[4,5] However, these methods have their limitations in that they, most importantly, depend on the nature of the alkylation agents and dienolates. Thus, the γ-functionalization of α,β-unsaturated carbonyl compounds has been a very challenging problem.

We recently reported a radical alkylation method based on the addition of an alkyl radical to ketene *O*,*N*-acetal **1** followed by the cleavage of the N–O bond to afford the alkylated carboxylic amide **2** after aqueous workup (Scheme 1).[6,7] In this approach, the rearrangement of a silyloxy radical to a silyl radical was utilized effectively in tin-free alkylation.[8] A radical-mediated γ-functionalization approach has not, to the best of our knowledge, been reported to date and seems to be a conceptual advance to our previous finding. Therefore, we initially studied the radical-mediated γ-alkylation of α,β-unsaturated carboxylic amides. Our idea to effect γ-alkylation relies on the stability of the radical intermediates derived from α and γ attack of an alkyl radical onto diene *O*,*N*-acetal **3** (Scheme 2). The γ-alkylation would be feasible because it is evident that intermediate **5** should be more stable than intermediate **4** owing to the allylic nature of **5**.

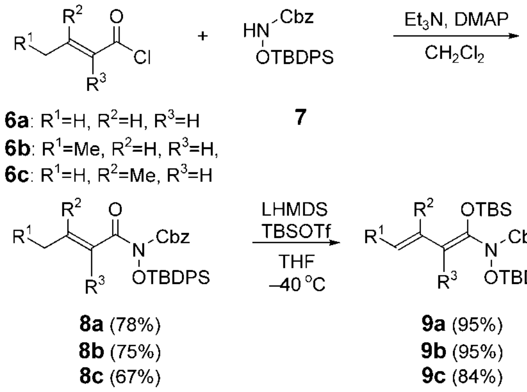


Scheme 1. Tin-free radical alkylation of carboxylic amides. Cbz = benzyloxycarbonyl, TBDPS = *tert*-butyldiphenylsilyl, TBS = *tert*-butyldimethylsilyl.



Scheme 2. Radical approach to the γ-functionalization of α,β-unsaturated carboxylic amides via **3**.

Three diene *O*,*N*-acetals **9a**, **9b**, and **9c** were prepared (Scheme 3). The coupling of acid chloride **6a** with **7** and triethylamine in the presence of a catalytic amount of 4-(dimethylamino)pyridine (DMAP) in dichloromethane at room temperature for 30 minutes gave amide **8a** in 78% yield. The amide **8a** was treated with lithium hexamethyldisilazide (LHMDS) in THF at −40 °C in the presence of *tert*-butyldimethylsilyl trifluoromethanesulfonate (TBSOTf) to afford **9a** in 95% yield. Similarly, diene *O*,*N*-acetals **9b** and **9c** were prepared in high yields. They were observed to be fairly stable to purification by silica gel column chromatography.



Scheme 3. Preparation of diene *O*,*N*-acetals. AIBN = azobisisobutyronitrile, DMAP = 4-(dimethylamino)pyridine, LHMDS = lithium hexamethyldisilazide, TBSOTf = *tert*-butyldimethylsilyl trifluoromethanesulfonate, V-70 = 2,2′-azobis(4-methoxy-2,4-dimethylvaleronitrile).

Irradiation of a solution of **9a** (1.5 equiv), iodoacetophenone (1.0 equiv) and hexamethylditin (1.1 equiv) in benzene at 300 nm for 3 h gave **10a** in 79% yield after isolation by silica gel column chromatography without the formation of

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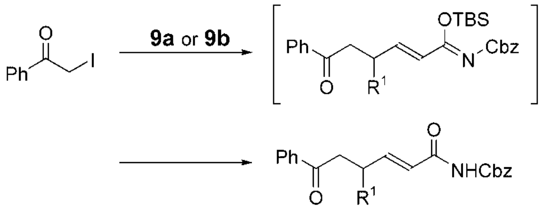
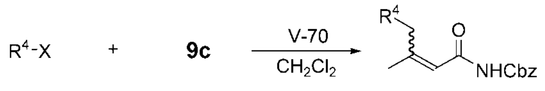
the α-alkylation product (Scheme 4). Encouraged by this result, we studied the tin-free γ-alkylation of **9a** based on the previously reported rearrangement of a silyloxy radical into a silyl radical.[9] Reaction of **9a** with iodoacetophenone with azobisisobutyronitrile (AIBN) as the initiator in benzene at 80 °C for 3 h afforded **10a** in 57 % yield. Apparently, the low yield resulted from thermal decomposition of **9a** to some extent. When the reaction was carried out with V-70 (2,2′-azobis(4-methoxy-2,4-dimethylvaleronitrile)) as the initiator in dichloromethane at 30 °C for 10 h, the reaction cleanly afforded **10a** in 86 % yield. Also, employing **9b** in the reaction under the same conditions gave **10b** in 72 % yield. To determine the efficiency and scope of the present method, we performed additional experiments with several different alkyl iodides and bromides and with **9a** and **9b** as substrates. As shown in Table 1, alkyl iodides and bromides bearing an α-electron-withdrawing group underwent clean γ-alkylations under tin-free conditions. Notably, the monosubstituted diene *O*,*N*-acetal **9b** gave comparable results to **9a**. When further reactions were also carried out with **9c**, derived from senecioic acid, similar results were obtained, which confirms the generality of the present method (Scheme 5).[10] We consider the exclusive formation of γ-alkylation products under tin-free radical conditions with no indication of the formation of α-alkylation products to be of synthetic importance. However, this method proved to be limited with respect to nucleophilic alkyl radicals. Irradiation of a benzene solution of **9b** with an equimolar mixture of 4-phenoxybutyl iodide and hexamethylditin at 300 nm for 10 h gave the desired γ-alkylation product (25 %) together with the dimerized product (31 %) and the starting iodide (11 %), thus indicating that the addition of a nucleophilic alkyl radical onto electron-rich **9b** is slow and inefficient.



$(Me_3Sn)_2$ (1.1 equiv), C_6H_6, hν, 3 h **10a**: R^1=H, 79%
AIBN (0.2 equiv), C_6H_6, 80 °C, 3 h **10a**: R^1=H, 57%
V-70 (0.2 equiv), CH_2Cl_2, 30 °C, 10 h **10a**: R^1=H, 86%; **10b**: R^1=Me, 72%

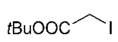
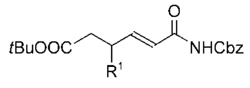
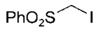
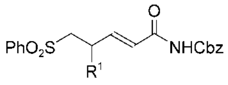
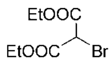
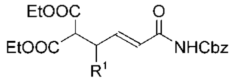
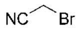
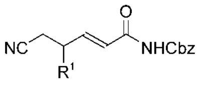
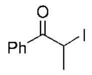
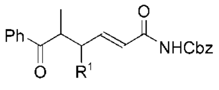
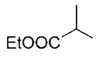
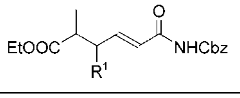
Scheme 4. Formation of γ-functionalized products **10a** and **10b**.



11a: R^4= CH_2COPh, X=I **12a**: 81% (*E*/*Z*=1:5)
11b: R^4= $CH(CO_2Et)_2$, X=Br **12b**: 85% (*E*/*Z*=1:4.5)

Scheme 5. γ-Functionalization of senecioic acid derivative **9c**.

Table 1: Tin-free radical γ-alkylations.[a]

Entry	Substrate	Product	Yield [%][b] **10a**	**10b**
1			77	74
2			64	71
3			75	82
4			77	73
5			79	65[c]
6			85	74[d]

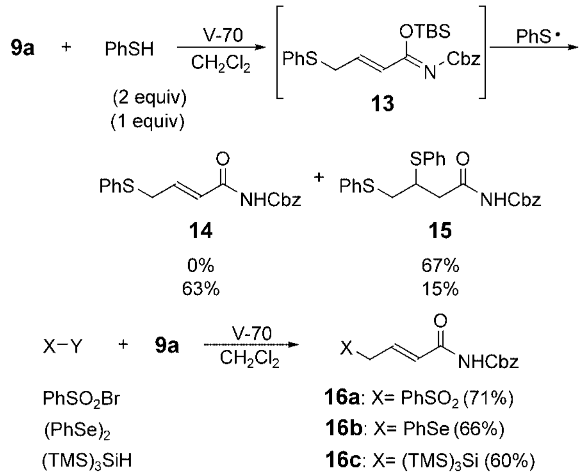
[a] The reaction was carried out with V-70 as the initiator in CH_2Cl_2 at 30 °C for 10 h. [b] Yield of isolated product. [c] *syn*/*anti* = 2.5:1. [d] *syn*/*anti* = 1:1.

Subsequently, the possibility of the γ-addition of several synthetically useful hetero groups, such as phenylsulfanyl and phenylsulfonyl, to **9a** was examined. It is known that the phenylsulfenylation and phenylselenylation of α,β-unsaturated carbonyl compounds occurs exclusively at the α position,[11] whereas trimethylsilylation of α,β-unsaturated aldimines occurs at the γ position.[12] Based on our previous rationale, the addition of the phenylsulfanyl radical to **9a** at the γ position could be anticipated. When the radical-mediated reaction was carried out with **9a** and thiophenol under the same conditions, phenylsulfenylation occurred exclusively at the γ position. Reaction of **9a** with 2 equivalents of thiophenol in dichloromethane in the presence of V-70 as the initiator gave **15** in 67 % yield because of further addition of the phenylsulfanyl radical to **13**, whereas a 63:15 mixture of **14** and **15** was isolated when 1 equivalent of thiophenol was used. The reaction of phenylsulfonyl bromide, diphenyl diselenide, and tris(trimethylsilyl)silane gave γ-addition products in high yields (Scheme 6).

In conclusion, we have developed the first radical-mediated γ-functionalization of α,β-unsaturated carboxylic amides via diene *O*,*N*-acetals under tin-free conditions to give a synthetically useful process. Further studies to expand this strategy to the α,β-unsaturated aldehydes and ketones are underway.

Experimental Section

Typical procedure: A solution of iodoacetophenone (49 mg, 0.2 mmol), **9a** (176 mg, 0.3 mmol), and V-70 (12 mg, 0.04 mmol) in dichloromethane (1 mL; 0.2 M in iodide) was degassed with nitrogen for 10 min, and the solution was then stirred at 30 °C under nitrogen for 10 h. The solvent was evaporated under reduced pressure and the residue was purified by silica-gel column chromatography with EtOAc/hexane (1:3) as the eluant to give **10a** (58 mg, 86 %). ^1H NMR ($CDCl_3$, 400 MHz): δ = 2.65–2.71 (m, 2H), 3.15 (t, J =



Scheme 6. γ-Addition of hetero groups to diene *O,N*-acetal **9a**.

7.1 Hz, 2H), 5.16 (s, 2H), 6.89 (d, $J=15.4$ Hz, 1H), 7.21 (dt, $J=15.4$ Hz, 6.9 Hz, 1H), 7.34–7.95 ppm (m, 11H); ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta=26.7$, 36.6, 67.9, 122.0, 128.0, 128.4, 128.7 (C 2), 133.3, 134.3, 134.9, 136.6, 149.5, 151.5, 165.5, 198.1 ppm; IR (polymer): $\tilde{\nu}=$ 3292, 1764, 1687, 1648, 1523, 1204, 1049, 746, 698 cm^{-1}; HRMS: calcd for $C_{20}H_{19}NO_4$: 337.1314, found: 337.1324.

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