# **Radical** Alkylations of Alkyl Halides and Unactivated C–H Bonds Using Vinyl Triflates

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**Abstract:** Radical alkylations of activated alkyl iodides and bromides were achieved using vinyl triflates in the presence of hexadimethyltin, whereas those of unactivated C–H bonds using vinyl triflates proceeded cleanly under tin-free conditions.

Key words: alkylation, radical reaction, ketone, vinyl triflate

Alkylation is one of the most important and fundamental organic reactions for the formation of carbon-carbon bonds and is routinely performed with metal enolates and alkylating agents.<sup>1</sup> Despite extensive studies of radical reactions during last three decades, radical-mediated alkylations of carbonyl compounds have not been well studied, mainly due to inefficiency of intermolecular radical reactions. To solve this problem, one of the most attractive approaches is to develop highly efficient radical acceptors.<sup>2</sup> The radical acceptors should possess both an activating group and an eliminating group to generate a carbonyl group, and such compounds include: stannyl enolates,<sup>3</sup> Obenzyl enols,<sup>4</sup> and *O-tert*-alkyl enols.<sup>5</sup> In this regard, we reported two approaches to achieve radical alkylations of carbonvl compounds using ketene N.O-acetals (Scheme 1, equation 1)<sup>6</sup> and *tert*-butyl ketene enol ethers as acceptors (Scheme 1, equation 2).<sup>7</sup>



Scheme 1

As part of our continued interest in radical alkylations, we have studied the feasibility of using vinyl sulfonates as radical acceptors. Although vinyl sulfonates are very useful functional groups for the formation of carbon–carbon bonds via cross-coupling reactions,<sup>8</sup> their synthetic usefulness has not been well studied, probably due to the difficulties involved in their preparation. Vinyl sulfonates

SYNLETT 2010, No. 11, pp 1647–1650 Advanced online publication: 04.06.2010 DOI: 10.1055/s-0029-1219960; Art ID: U02610ST © Georg Thieme Verlag Stuttgart · New York are accessible by two methods involving: the sulfonylation of enolates with sulfonic anhydrides,<sup>9</sup> and gold-catalyzed addition of sulfonic acids to alkynes.<sup>10</sup> In the radical reaction of vinyl sulfonates, we have been interested in the feasibility of  $\beta$ -cleavage of the oxygen–sulfonyl (O– SO<sub>2</sub>R<sup>2</sup>) bond (Scheme 2, equation 1), even though a similar  $\beta$ -cleavage of the O–SO<sub>3</sub><sup>-</sup> bond was reported in anionic transannular, self-terminating radical cyclizations (Scheme 2, equation 2).<sup>11</sup> The success of the present approach depends very much on the efficiency of the addition of an alkyl radical to the vinyl sulfonates and on the  $\beta$ -cleavage of the O–SO<sub>2</sub>R bond.



Scheme 2 Alkylation of RI with vinyl sulfonate 3

The key feature in our initial approach is the  $\beta$ -elimination of intermediate **1** to yield a carbonyl compound, along with liberation of an ethanesulfonyl radical (equation 1 and Scheme 2).<sup>12</sup> Second, thermal decomposition of the ethanesulfonyl radical followed by iodine atom transfer from an alkyl iodide to an ethyl radical would generate the alkyl radical for the chain-propagation reaction. Another important issue is the addition of the ethanesulfonyl radical to vinyl sulfonate **3**, which should be slower than thermal conversion of the ethanesulfonyl radical into the ethyl radical. Finally, it is noteworthy that the present approach can be performed under tin-free conditions.

We began our studies with vinyl sulfonate 3. When 3 was treated with ethyl iodoacetate and AIBN in toluene for two hours,  $\alpha$ -ethanesulfonyl ketone **5** was isolated in 78% yield, which indicates two important results (Scheme 3). First, β-elimination of O–SO<sub>2</sub>Et occurred smoothly. Second, the addition of the ethanesulfonyl radical to vinyl sulfonate 3 is much faster than thermal decomposition of the ethanesulfonyl radical. To achieve radical alkylation of vinyl sulfonates, the reaction was performed in the presence of hexamethylditin (1.2 equiv) under thermal and photochemically initiated conditions. Treatment of 3 with ethyl iodoacetate and AIBN in toluene at 80 °C for two hours generated a mixture of the addition product 5 and the desired product 6 that was isolated in a ratio of 4:3. When the reaction was repeated under photochemically initiated conditions (300 nm), a similar result was obtained. Apparently, the addition of the ethanesulfonyl radical to the vinyl sulfonate competed with quenching of the ethanesulfonyl radical with hexamethylditin.





Scheme 4

To obviate the problems involved in the direct addition process, we searched for possible ways to induce facile decomposition of alkylsulfonyl radicals to alkyl radicals. It is well known that the highly reactive trifluoromethanesulfonyl radical undergoes decomposition spontaneously at room temperature to generate a trifluoromethyl radical along with liberation of sulfur dioxide.<sup>13</sup> Fuchs reported the radical-mediated alkynylations, alkenylations, and allylations of unactivated C–H bonds using the corresponding trifluoromethyl sulfone (triflone; Scheme 4).<sup>13</sup>

Radical-mediated alkylations of alkyl iodides and bromides were carried out using two vinyl triflates, 7 and 9. The reaction of benzyl iodoacetate with vinyl triflate 7 and hexamethylditin (0.5 equiv) in benzene under irradiation at 300 nm for five hours afforded  $\alpha$ -alkylated product 8 in 75% yield (Scheme 5, equation 1). When the reaction was repeated with vinyl triflate 9 under similar conditions, the desired  $\alpha$ -keto ester 10 was isolated in 66% yield along with recovery of the starting material (27%; Scheme 5, equation 2). Additional experimental results are summarized in Table 1. Using vinyl triflate 7,  $\alpha$ -iodo esters and ketones worked well, yielding the corresponding 1,4-dicarbonyl compounds (entries 2-4). Iodomethylphenylsulfone and diethyl bromomalonate both smoothly underwent alkylations in good yields (entries 1 and 5). In the case of vinyl triflate 9, the reaction did not go to completion after five hours, and gave lower yields in most cases. Apparently, 9 is a more electron-deficient radical acceptor than 7, so the rate of addition of an electrophilic alkyl radical to 9 is reduced. Furthermore, the present method reaches a limit with nucleophilic radicals. For instance, when 4-phenoxybutyl iodide was treated with 9 and hexamethylditin under irradiation at 300 nm for five hours, the reaction did not proceed well, yielding the desired product (19%) and the reduction product (42%)along with recovered starting material (27%; Scheme 6). The low efficiency of the nucleophilic alkyl radical reaction was not expected and the reason is not clear at present.

We next studied the feasibility of radical alkylations of unactivated C–H bonds using vinyl triflates **7** and **9**. Radical-mediated chlorocarbonylation<sup>14</sup> and acylation of unactivated C–H bonds,<sup>15</sup> along with Fuchs approach,<sup>13</sup>

PhO(CH<sub>2</sub>)<sub>4</sub>—I  $\xrightarrow{9, (Me_3Sn)_2}$   $\xrightarrow{0}_{\text{benzene}}$   $\xrightarrow{0}_{\text{R}}$   $\xrightarrow{0}_{\text{CO}_2\text{Et}}$  + R—H 300 nm (19%) (42%) R = PhO(CH<sub>2</sub>)<sub>4</sub>



Scheme 6

#### Scheme 5

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were reported previously. Furthermore, dimethylzincmediated radical reactions involving C-H bond cleavage have been recently investigated by Tomioka.<sup>16</sup> Our investigations were based on Fuchs approach (Scheme 7),<sup>13</sup> and required that the reaction proceeds via hydrogen atom abstraction from C-H bonds by the highly electrophilic trifluoromethyl radical to generate 13. Addition of radical 13 to vinyl triflate 11 followed by elimination of the adduct radical 14, would provide carbonyl compound 15 along with liberation of a trifluoromethanesulfonyl radical. Fragmentation of the trifluoromethanesulfonyl radical to the trifluoromethyl radical and sulfur dioxide propagates the chain. This approach is attractive because it not only avoids the use of highly toxic organotin compounds, but also introduces a  $\beta$ -carbonyl group to the unactivated C-H bonds in a single step. Reaction of 9 in refluxing tetrahydrofuran in the presence of AIBN initiator for nine hours gave the desired  $\alpha$ -keto ester in 65% yield (Scheme 8). Table 2 summarizes some experimental results using vinyl triflates 7 and 9 and illustrates the efficiency and scope of the present method. The method was quite general and worked well with cyclic and acyclic ethers (entries 1 and 2), cyclic and acyclic alkanes (entries 3-5), and tetrahydrothiophene (entry 6). The yields ranged from 54 to 78%. Similar results were also obtained with vinyl triflate 7 (entries 7–9).<sup>17,18</sup>



Scheme 7 Radical alkylation of unactivated C-H bonds



#### Scheme 8

In conclusion, we have observed the  $\beta$ -cleavage of oxygen–sulfonyl bonds together with the formation of the carbonyl group. The reaction was applied to achieve the radical alkylation of alkyl iodides and bromides bearing  $\alpha$ -electron-withdrawing groups and, using vinyl triflate acceptors, to unactivated C–H bonds.

 Table 1
 Radical Alkylation of Carbonyl Compounds using Vinyl



 $^a$  Reagents and conditions:  $(Me_3Sn)_2$  (0.5 equiv), benzene, 300 nm, 5 h.

<sup>b</sup> Yield of isolated product. The numbers in the parenthesis indicate the yield of recovered starting material.
 <sup>c</sup> E = CO<sub>2</sub>Et

**Table 2**Radical Alkylation of Carbonyl Compounds Using Vinyl<br/>Triflates 7 and  $9^a$ 



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Table 2Radical Alkylation of Carbonyl Compounds Using VinylTriflates 7 and 9<sup>a</sup> (continued)



<sup>a</sup> The reaction was carried out using AIBN as initiator at reflux for 9 h. <sup>b</sup> Yield of isolated product.

<sup>c</sup> A 3:2 mixture of the two compounds was obtained.

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## **References and Notes**

- (a) House, H. O. Modern Synthetic Reactions; Benjamin, W. A., Ed.; Menlo Park: CA, **1972**, Chap. 9. (b) Caine, D. In Comprehensive Organic Synthesis; Trost, B. M.; Fleming, I.; Pattenden, G., Eds.; Pergamon: Oxford, **1991**, Vol. 3, 1–63. (c) Seebach, D. Angew. Chem. Int. Ed. **1988**, 27, 1624.
- (2) Kim, S. In *Radicals in Organic Synthesis*, Vol 2.; Renaud, P.; Sibi, M., Eds.; Wiley-VCH: Weinheim, **2001**, 1–21.
- (3) (a) Watanabe, Y.; Yoneda, T.; Ueno, Y.; Toru, T. *Tetrahedron Lett.* **1990**, *31*, 6669. (b) Miura, K.; Fujisawa, H.; Saito, D.; Hosomi, A. Org. Lett. **2001**, *3*, 2591.
- (4) Roepel, M. G. Tetrahedron Lett. 2002, 43, 1973.
- (5) (a) Perkins, M. J.; Roberts, B. P. J. Chem. Soc., Perkin Trans. 1975, 2, 77. (b) Dang, H.-S.; Franchi, P.; Roberts, B. P. Chem. Commun. 2000, 499. (c) Fielding, A. J.; Franchi, P.; Roberts, B. P.; Smits, T. M. J. Chem. Soc., Perkin Trans. 2002, 2, 155.
- (6) (a) Kim, S.; Lim, C. J.; Song, C.; Chung, W.-j. J. Am. Chem. Soc. 2002, 124, 14306. (b) Kim, S.; Lim, C. J. Angew. Chem. Int. Ed. 2004, 43, 5378. (c) Song, H.-J.; Lim, C. J.; Lee, S.; Kim, S. Chem. Commun. 2006, 2893.
- (7) Kim, S.; Lee, J. Y. Synlett 2008, 49.

- (8) (a) Ritter, K. Synthesis 1993, 735. (b) Roth, G. P.; Fuller, C. E. J. Org. Chem. 1989, 54, 4899. (c) Pridgen, L. N.; Huang, G. K. Tetrahedron Lett. 1998, 39, 8421. (d) Limmert, M. E.; Roy, A. H.; Hartwig, J. F. J. Org. Chem. 2005, 70, 9364.
- (9) (a) Huffman, M. A.; Yasuda, N. *Synlett* **1999**, 471.
  (b) Baxter, J. M.; Steinhubel, D.; Palucki, M.; Davies, I. W. *Org. Lett.* **2005**, *7*, 215.
- (10) Cui, D.-M.; Meng, Q.; Zheng, J.-Z.; Zhang, C. Chem. Commun. 2009, 1577.
- (11) (a) Wille, U. J. Am. Chem. Soc. 2002, 124, 14. (b) Wille, U. Org. Lett. 2000, 2, 3485.
- (12) (a) Kim, S.; Kim, S. Bull. Chem. Soc. Jpn. 2007, 80, 809.
  (b) Kim, S.; Kim, S.; Otsuka, N.; Ryu, I. Angew. Chem. Int. Ed. 2005, 44, 6183. (c) Kim, S.; Lim, C. J. Angew. Chem. Int. Ed. 2002, 41, 3265.
- (13) For alkynylations, see: (a) Gong, J.; Fuchs, P. L. J. Am. Chem. Soc. 1996, 118, 4486. (b) Gong, J.; Fuchs, P. L. Tetrahedron Lett. 1997, 38, 787. For alkenylations, see:
  (c) Xiang, J.; Fuchs, P. L. J. Am. Chem. Soc. 1996, 118, 11986. (d) Xiang, J.; Jiang, W.; Gong, J.; Fuchs, P. L. J. Am. Chem. Soc. 1997, 119, 4123. (e) For allylation, see: Xiang, J.; Evarts, J.; Rivkin, A.; Curran, D. P.; Fuchs, P. L. Tetrahedron Lett. 1998, 39, 4163.
- (14) (a) Kharasch, M. S.; Brown, H. C. J. Am. Chem. Soc. 1942, 64, 329. (b) Tabushi, I.; Hamuro, J.; Oda, R. J. Org. Chem. 1968, 33, 2108.
- (15) (a) Bentrude, W. G.; Darnall, K. R. J. Am. Chem. Soc. 1968, 90, 3588. (b) Citterio, A.; Filippini, L. Synthesis 1986, 473. (c) Kim, S.; Kim, N.; Chung, W.-j.; Cho, C. H. Synlett 2001, 937.
- (16) Akindele, T.; Yamada, K.-I.; Tomioka, K. *Acc. Chem. Res.* 2009, *42*, 345; and references cited therein.
- (17) Typical procedure for radical alkylation of a carbonyl compound: A solution of iodomethyl phenylsulfone (56 mg, 0.2 mmol), vinyl triflate **7** (76 mg, 0.3 mmol), and hexamethylditin (33 mg, 0.1 mmol) in benzene (1 mL; 0.2 M in iodide) was degassed with nitrogen for 10 min, and the solution was then irradiated in a photochemical reactor (300 nm) for 5 h. The solvent was evaporated under reduced pressure and the residue was purified by silica gel column chromatography (EtOAc–hexane, 1:10) to give 1-phenyl-3-(phenylsulfonyl)propan-1-one (38 mg, 69%) as a colorless oil. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz):  $\delta$  = 3.45–3.49 (m, 2 H), 3.52–3.56 (m, 2 H), 7.42–7.46 (m, 2 H), 7.55–7.57 (m, 3 H), 7.63–7.64 (m, 1 H), 7.88–7.94 (m, 4 H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz):  $\delta$  = 31.3, 51.0, 127.9 (C2), 128.0 (C2), 128.7 (C2), 129.4 (C2), 133.7, 133.9, 135.8, 139.0, 195.3
- (18) Typical procedure for radical alkylation of an unactivated C–H bond: A solution of vinyl triflate **9** (76 mg, 0.3 mmol) and AIBN (5 mg, 0.03 mmol) in THF (1 mL) was degassed with nitrogen for 10 min, and the solution was heated at reflux (80 °C) for 9 h under nitrogen. The solvent was evaporated under reduced pressure and the residue was purified by silica gel column chromatography (EtOAc–hexane, 1:50) to give **16** (41 mg, 65%) as a colorless oil. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz):  $\delta = 1.33$  (t, J = 7.2 Hz, 3 H), 1.48–1.55 (m, 1 H), 1.84–1.92 (m, 2 H), 2.06–2.14 (m, 1 H), 2.94 (dd, J = 16.5, 5.7 Hz, 1 H), 3.10 (dd, J = 16.5, 7.1 Hz, 1 H), 3.67–3.73 (m, 1 H), 3.80–3.85 (m, 1 H), 4.29 (q, J = 7.2 Hz, 2 H), 4.26–4.32 (m, 1 H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz):  $\delta = 13.9, 25.4, 31.4, 45.1, 62.4, 67.9, 74.3, 160.8, 192.6$