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Conjugate addition of a primary carbon radical to α,β-unsaturated carboxylic acids

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Abstract

Triethylborane in the presence of trace oxygen was employed simultaneously as a radical initiator and carboxyl protecting group to promote the conjugate radical addition of 2-phenethyl iodide to α,β-unsaturated carboxylic acids in good yields. © 2000 Elsevier Science Ltd. All rights reserved.

Over the last two decades, interest in free radical reactions in organic synthesis has greatly increased, with many radical reaction types now providing useful synthetic strategies.[1] Of various radical based reactions, the 1,4-addition of carbon radicals to enones represents a well known subset. While the synthetic applications of conjugate radical additions to α,β-unsaturated esters has also been studied, little work has been reported in the area of direct conjugate radical addition to α,β-unsaturated carboxylic acids.[2] As part of ongoing efforts to develop direct methods for conjugate addition to eneoic acids,[3] herein we report the direct conjugate radical addition of phenethyl iodide to α,β-unsaturated acids enhanced by triethylborane.

Employing routine conditions for effecting conjugate radical addition, a benzene solution of artemisinic acid **1** containing a low concentration of tributyltin hydride was refluxed in the presence of AIBN and 2-phenylethyl iodide. Under these conditions, the product **2** was formed in low yield (less than 5%) (Scheme 1). Triethylborane, which serves as one of several methods for the generation of radical species,[4] is an effective radical initiator for radical additions under mild conditions.[5] When a small amount of triethylborane was employed as a radical initiator in place of AIBN above, only starting material was detected. However, with 1.2 mol equivalents of triethylborane, the reaction proceeded smoothly providing **2** in 72% yield as a mixture of diastereomers (*R*:*S*=2:1).

Table 1 shows some other examples of direct conjugate radical addition to α,β-unsaturated carboxylic acids in the presence of triethylborane.[6] When the reaction was performed under standard radical addition

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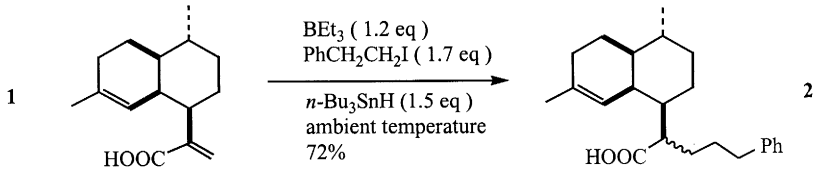
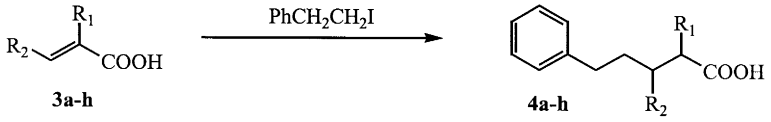


Scheme 1.

conditions (Entries 1, 3 and 5, AIBN was used as an initiator), the yields were poor (less than 15% yield). Substituents at the 2- or 3-position of the α,β-unsaturated acid gave comparable results (Entries 6, 7, 9 and 10), while the 2,3-disubstituted α,β-unsaturated carboxylic acid **3e** gave a poor yield (Entry 8) of conjugate addition product **4e**. We noted that many of the yields were moderate after chromatography despite a relatively clean TLC profile, while the isolated yield of product **2** starting from artemisinic acid **1**, a crystalline, nonvolatile acid with greater lipophilicity, was quite acceptable. Thus, purification of a simple acid was studied in greater depth to estimate the loss due to conventional purification. Entry 2 gave 71% of **4a** after flash chromatography on silica gel; however, careful quantitation of the crude reaction product by HPLC methods revealed the yield to be 80%.[7]

Table 1

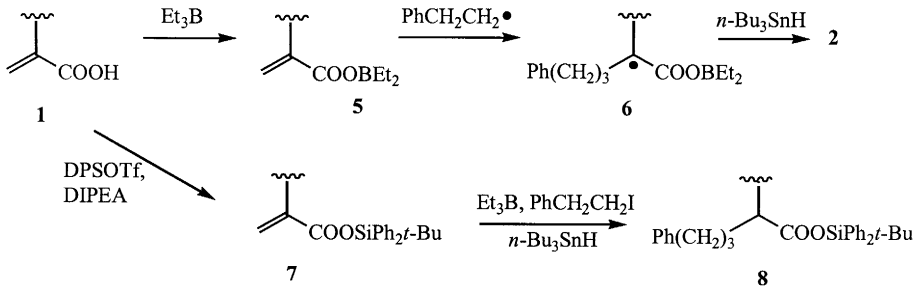


Entry	Compound	R_1	R_2	Initiator	Product	Yield%[d]
1	**3a**	H	H	AIBN[a]	**4a**	10
2	**3a**	H	H	BEt_3(1.2eq)[b]	**4a**	71(80[e])
3	**3b**	Me	H	AIBN[a]	**4b**	15
4	**3b**	Me	H	BEt_3(1.2eq)[b]	**4b**	74
5	**3c**	H	Et	AIBN[a]	**4c**	5
6	**3c**	H	Et	BEt_3(1.2eq)[b]	**4c**	60
7	**3d**	H	Me	BEt_3(1.2eq)[b]	**4d**	56
8	**3e**	Me	Et	BEt_3(1.2eq)[b]	**4e**	24
9	**3f**	H	Ph	BEt_3(1.2eq)[c]	**4f**	58
10	**3g**	H	*o*-NO_2Ph	BEt_3(1.2eq)[c]	**4g**	60

a) 1.7 eq of 2-phenethyl iodide and 1.5 eq of *n*-Bu_3SnH were used. The reaction was performed in refluxing benzene for 10 to 24 h; b) The reaction was performed in hexane at room temperature for 16 h, and the same amount of 2-phenethyl iodide and *n*-Bu_3SnH was used; c) The reaction was performed in a (1:1) mixture of hexane and benzene at 60°C for 16 h. d) Yield after silica gel chromatography; e) Yield based on HPLC analysis using calibration curves for purified products.[7]

Since alkyl radicals are generally nucleophilic, their addition to olefinic substrates would be enhanced by electron-withdrawing substituents on the olefinic linkage.[4,8] It has been reported that all acyloxydialkylboranes are monomeric, or only very loosely self-associated in dilute solution, and generally dimeric in the solid state.[9] Therefore, when an α,β-unsaturated carboxylic acid (e.g. **1**) is treated with triethylborane, an acyloxydiethylborane (e.g. **5**) should be formed leading to an expected decrease in the electron density of its olefinic moiety and an increase in the radical addition rate to **5** leading to radical **6** (Scheme 2). It therefore seems possible that in the above reactions, triethylborane serves not only as a radical initiator, but also to enhance the reactivity of the α,β-unsaturated carboxylic acid toward radical addition. If the borate ester did not exert a beneficial influence in the addition step, one might expect the silyl ester to undergo radical addition equally well. To gauge this, reaction of the diphenyl-*tert*-butylsilyl (DPS) ester of **1** (**7**)[3] was studied with catalytic Et_3B and O_2, 1.7 equiv., $PhCH_2CH_2I$ and 1.5 equiv. *n*-

Bu_3SnH (vide supra). While **8** was formed in modest yield in this case (40%), it was inferior to production of **2** via the borate ester **5** (72%).



Scheme 2.

The secondary enhancing effect of preforming the borate ester might be to protect the *n*-Bu_3SnH from reaction with the carboxyl group. In a separate experiment, **1** reacted slowly with *n*-Bu_3SnH to furnish a stannyl carboxylate (NMR). Finally, the effect of the H-atom donor was briefly examined. In principle, radical **6** could afford product **2** via a mechanism not involving *n*-Bu_3SnH. Reaction of **5**, $PhCH_2CH_2I$ and varying amounts of Et_3B (catalytic O_2) did not provide the product **2**, indicating that a H-atom donor was required in the reaction. If tris(trimethylsilyl)silane were used in place of tributylstannane in this process, product **2** was formed, but in low yield (10%).

In summary, we have described a simple and efficient direct radical addition of a primary alkyl iodide to α,β-unsaturated carboxylic acids enhanced by triethylborane. We have also found that the reaction proceeded smoothly with a substituent in either the α- or β-position of the acid, while α,β-disubstituted acid gave only poor yields of addition products.

Acknowledgements

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References

1. For reviews, see: (a) Giese, B. *Radicals in Organic Synthesis: Formation of Carbon–Carbon Bonds*; Pergamon Press: New York, 1986; (b) Curran, D. P. *Synthesis* **1988**, 417–439; (c) Curran, D. P. *Synthesis* **1988**, 489–513; (d) Jasperse, C. P.; Curran, D. P.; Ferig, T. L. *Chem. Rev*. **1991**, *91*, 1237–1286; (e) Motherwell, W. B.; Crich, D. *Free Radical Chain Reactions in Organic Synthesis*; Academic Press: London, 1992; (f) Fossey, J.; Lefort, D.; Sorba, J. *Free Radicals in Organic Chemistry*: John Wiley & Sons: New York, 1995; (g) Fallis, A. G.; Irina, M.; Brinza, I. M. *Tetrahedron* **1997**, *53*, 17 543–17 594; (h) Yet, L. *Tetrahedron* **1999**, *55*, 9349–9403.
2. (a) Vassen, R.; Runsing, J.; Shrf, H. D. *Chem. Ber*. **1986**, *119*, 3492–3497; (b) Adlington, R. M.; Baldwin, J. E.; Basak, A.; Kozyrod, R. P. *J. Chem. Soc., Chem. Commun*. **1983**, 944–945.
3. Vroman, J. A.; Khan, I.; Avery, M. A. *Tetrahedron Lett*. **1997**, *38*, 6173–6176.
4. For a review, see: Smadja, W. *Synlett* **1994**, 1–26.
5. Nozaki, K.; Oshima, K.; Utimoto, K. *Tetrahedron Lett*. **1988**, *29*, 1041–1044.
6. *General synthetic procedure*: The acid (5 mmol) was added to a flame dried 250 mL two-necked round bottomed flask under an atmosphere of Ar. Freshly distilled solvent (150 mL) was introduced, and a solution of triethylborane (6 mL, 1 M in hexane, 1.2 equiv.) was added. The resulting mixture was stirred for 3 h at the indicated temperature shown in Table 1.

2-Phenylethyl iodide (8.5 mmol, in 5 mL hexane) was added followed by the addition of a 0.1 mL solution of triethylborane via a syringe containing a trace of oxygen. A solution of *n*-Bu_3SnH (2.2 g, 1.5 equiv. in 40 mL hexane) was then slowly added via a syringe pump over a period of 10 h, and the reaction mixture was stirred for an additional 6 h. Following evaporation of the solvent, the residue was dissolved in 10 mL of ether, and a 10 mL solution of saturated KF was added. The mixture was stirred overnight, filtered and washed with ether. The ether solution was combined, concentrated to 20 mL, and stirred with 2N NaOH for 1 h. The layers were separated, and the aqueous layer was washed with ether (3×30 mL), and neutralized with 1N HCl. The aqueous layer was extracted with ether, and the combined ether extracts were washed with brine and water, and then dried over $MgSO_4$. Concentration and silica gel flash chromatography of the residue gave the desired product. Known compounds had physical and spectroscopic properties in accord with literature reports, and new compounds gave satisfactory analytical data. Compound **4c**: IR (KBr) 3400–2500, 1707, 1603 1456 1077 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.27 (2H, m), 7.17 (3H, m), 2.61 (2H, t, J=8.4 Hz), 2.33 (2H, d, J=6.8 Hz), 1.87 (1H, m), 1.61 (2H, m), 1.23 (2H, m), 0.97 (3H, t, J=7.2 Hz); ^{13}C NMR ($CDCl_3$) δ 179.8, 141.9, 128.2 (3C), 125.7 (2C), 45.2, 34.4, 33.8, 30.6, 24.2, 14.1. Compound **4e**: IR (KBr): 3400–2500, 1708, 1603, 1495, 1379 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.27 (2H, m), 7.16 (3H, m), 2.85 (1H, q, J=7.0 Hz), 2.59 (2H, t, J=8.2 Hz), 1.69 (1H, m), 1.53 (2H, m), 1.26 (2H, m), 0.95 (3H, q, J=7.02 Hz); ^{13}C NMR ($CDCl_3$): δ 180.2, 142.2, 128.2 (3C), 125.2 (2C), 60.4, 35.4, 33.8, 30.7, 24.2, 20.9, 14.0. Compound **4g**: IR (KBr) 3450–2500, 1699, 1601, 1346, 1250 cm^{-1}; ^1H NMR ($CDCl_3$): δ 8.14 (2H, m), 7.13–7.37 (7H, m), 3.10 (1H, m), 2.90 (1H, m), 2.65–2.79 (3H, m), 2.05 (1H, t, J=8.2 Hz), 1.92 (1H, m); ^{13}C NMR ($CDCl_3$): δ 180.5, 146.7, 146.4, 140.6, 129.6 (2C), 128.5 (2C), 128.3 (2C), 126.2, 123.6 (2C), 45.9, 37.5, 33.2, 24.3.

7. *General analytical procedure*: A Waters chromatography system (Waters, Milford, MA, USA) equipped with two 510 programmable pumps with a Rheodyne 7725I injector and a 486 tunable UV detector at 216 nm was used to quantitate the compounds. The column selected was a Phenomenex 250×4.6 mm, reversed phase C-18 IBO-SIL silica column with 5 micron particle size (Phenomenex, Torrance, CA, USA). All injections were performed using a 20 μL loop and at a flow rate of 1 mL/min. The chromatographic system was controlled using the 2010 Millennium chromatography (Waters, Milford, MA, USA) manager software (version 2.10) loaded on a Digital Venturis computer (Digital, Maynard, MA, USA). The mobile phase was prepared by mixing HPLC grade acetonitrile (Fisher Scientific, Fair Lawn, NJ, USA) and nanopure water (Barnstead, Neuton, MA, USA) in a 70:30 ratio. The two solvents were premixed then filtered and degassed in a water vacuum assembly for about 5 min. To a clean, dry 10 mL volumetric flask was added an accurately weighed sample (approximately 40 mg) of the compound, which was then dissolved in 1 mL of acetonitrile and diluted to 10 mL with the mobile phase to make a stock solution. Four calibration standards were prepared by diluting the stock solution with the mobile phase. The calibration curve was generated by plotting the logarithm of area under the curve versus the logarithm of concentration. Regression analysis was performed on the data points using the Cricket Graph software Version 1.3.2 (Cricket Graph, Malvern, PA, USA). The equation of the regression line was used to quantitate unknown control samples.
8. Curran, D. P.; Qi, H.; Porter, N. A.; Su, Q.; Wu, W. *Tetrahedron Lett*. **1993**, *34*, 4489–4492; For Lewis acid enhanced reactivity of α,β-unsaturated esters and amides, see: Urabe, H.; Yamashita, K.; Suzuki, K.; Kobayashi, K.; Sato, F. *J. Org. Chem*. **1995**, *60*, 3576–3577. For the use of BEt_3 for intramolecular cyclization, see: Clive, D. J.; Postema, M. H. D. *J. Chem. Soc., Chem. Commun*. **1993**, 429–430.
9. Yalpani, M.; Boese, R.; Seevogel, K.; Kster, R. *J. Chem. Soc., Dalton Trans*. **1993**, 47–50.