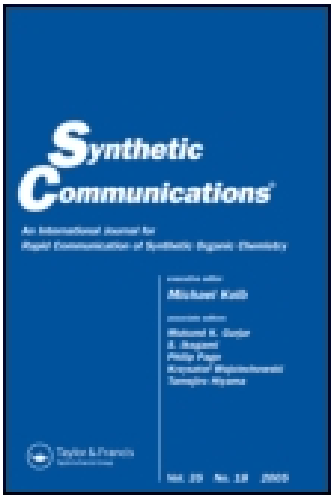


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Aeysha Sultan [a] , Abdul Rauf Raza [a] & Muhammad Nawaz Tahir [b]

[a] Ibn e Sina Block, Department of Chemistry , University of Sargodha , Sargodha , Pakistan

[b] Ibn e Haithem Block, Department of Physics , University of Sargodha , Sargodha , Pakistan

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# FREE RADICAL–MEDIATED CHEMOSELECTIVE REDUCTION OF ENONES

**Aeysha Sultan,[1] Abdul Rauf Raza,[1] and Muhammad Nawaz Tahir[2]**

[1]*Ibn e Sina Block, Department of Chemistry, University of Sargodha, Sargodha, Pakistan*

[2]*Ibn e Haithem Block, Department of Physics, University of Sargodha, Sargodha, Pakistan*

## GRAPHICAL ABSTRACT


**8a** **9a**

**Abstract** *A novel methodology has been devised for the chemoselective reduction of enones involving the use of* $^{n}Bu_3SnH$ *and azobisisobutyronitrile. The 1,4-reduction of variously substituted* α,β*-unsaturated cyclic and acyclic enones has been successfully carried out under free radical reaction conditions. The reaction has been determined to proceed via single-electron transfer.*

*[Supplementary materials are available for this article. Go to the publisher's online edition of* Synthetic Communications® *for the following free supplemental resource(s): Full experimental and spectral details.]*

**Keywords** AIBN; $^{n}Bu_3SnH$; chemoselectivity; enone; reduction; SET mechanism

## INTRODUCTION

Chemoselectivity is an important tool in organic synthesis that involves reaction of a reagent at a particular functional group. The current trends in organic synthesis focus on the development of methodologies that lead a reaction to take place precisely on a particular reaction center. Chemoselective reactions have the advantage of formation of the desired product in greater yields with minimal loss of reactants, minimal efforts, and great economy in the purification of product(s).

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Address correspondence to Abdul Rauf Raza, Ibn e Sina Block, Department of Chemistry, University of Sargodha, Sargodha 40100, Pakistan. E-mail: roofichemist2012@gmail.com

α,β-Unsaturated enones are a basic component of many medicinal and pharmaceutical products either synthetic or naturally occurring (e.g., chalcones, steroids, phytoestrogens, coumarins, certain carotenones, etc.). The chemoselective reaction on such a functional group has been a challenge for chemists for many years and the same is still the case because in many reactions attack on one group also leads to the transformation of other. Furthermore, both natural products and synthetic compounds with a variety of functional groups are vulnerable to different reagents. Thus, methodologies involving selective, mild, and neutral conditions are the demanding factor to devise chemoselective reactions on enones.

The reduction of enones has been carried out under different conditions and many efforts have been made to carry out chemoselective 1,2- and/or 1,4-reduction. The previously reported methods mostly involve the use of metals (e.g., Pd, Zn, Rh, Pt, Ni, Ir, Co) and their complexes,[1–3] but hydrides of Cu, Sn, Se, Te, and B,[4,5] sodium dithionite,[6,7] and sodium borohydride[8] have also been reported to be useful for the hydrogenation of α,β-unsaturated carbonyl compounds. Mostly these reagents have their own limitations. Negishi et al. used $KCuH_2$ for 1,4-reduction of enones. This reagent also reduces ketones and other functional groups.[9] Churchill and co-workers described Osborn complex $[(Ph_3P)CuH]_6$ under slight positive pressure of hydrogen as efficient 1,4-reductant of enone.[10,11] Jian et al. reported $Zn/NH_4Cl$ as a selective 1,4-enone reductant.[12]

The $^nBu_3SnH$ is used along with azobisisobultyronitrile (AIBN, as a radical initiator) in numerous C-C bond formation reactions through dehalogenation process; however, $^nBu_3SnH$ is also a very powerful carbonyl reducing agent when used in the presence of a Lewis acid, $Ph_3PO$, AIBN, or neat in boiling MeOH.[13] Leusink et al. were the first to report the application of $^nBu_3SnH$ for 1,4-reduction of α,β-unsaturated enones under the influence of UV irradiation.[14] Later on, Hays et al. utilized $^nBu_3SnH$-catalyzed silicon-mediated conjugate reduction of enones by making use of $(^tBuO)_2$ under refluxing conditions.[15] Pattenden et al. reported the $^nBu_3SnH$/AIBN-mediated reduction of estrone as an undesired minor product during the synthesis of estrone skeleton.[16]

## DISCUSSION

In an attempt toward the free radical–mediated construction of ring D–annulated estrogens, the radical-mediated conjugate addition of δ-chloro substituted enone **1** to methyl vinyl ketone (MVK) was tried. Interestingly, instead of the desired cyclized product **2**, a conjugate adduct **3** was isolated as a minor product along with a reduced product **4** formed as major product (Fig. 1).

These unexpected results forced us to repeat the reaction under the same conditions again, which led to the same results. The reduction of the C=C bond instead of dehalogenation was a surprising fact and more interestingly the β,γ-unsaturated C=C bond was reduced rather than the α,β-unsaturated C=C under these conditions. The β,γ-unsaturated C=C is reduced preferentially because the endocyclic C=C are more reactive than exocyclic C=C because of relief of angle strain. Second, the endocyclic C=C in this particular case is less substituted (less hindered), thus making it more reactive under these reaction conditions. Third, the –I effect of the $NO_2$ group destabilizes the radical cation on the exocylic C=C whereas

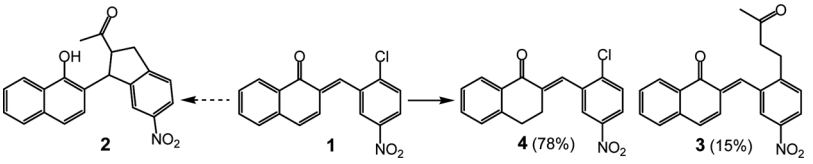



**Figure 1.** Attempted synthesis of **2** carried out by refluxing **1** in the presence of AIBN (0.1 eq), $^{n}Bu_3SnH$ (4 eq), and MVK (4 eq) in PhH for 18 h.

the radical cation on the endocyclic double bond is stabilized by fused benzene ring. Furthermore, the C=O group has no destabilization effect on the fused benzene ring. These findings led us to explore the $^{n}Bu_3SnH$ as a potential candidate for selective reduction of conjugated enones.

In the absence of MVK, with the rest of conditions being the same, the enone **4** was the exclusive product obtained. By varying the equivalents of AIBN and/or $^{n}Bu_3SnH$ it appeared that reaction went smoothly when 2 equivalents of $^{n}Bu_3SnH$ and 0.1 equivalents of AIBN were employed. Increasing the equivalents of AIBN did not affect the yield; however, decreasing equivalents of $^{n}Bu_3SnH$ reduced the yield. In the absence of AIBN no reaction was observed (Table 1). These findings suggest that AIBN is catalyzing the reaction and hence the reduction is free radical mediated.

The same reaction was applied to enones bearing δ-chloro group (**5a** and **5h**) with a single conjugated C=C bond. In this case again, the reduction of C=C bond was observed and the mass spectrum clearly indicated the presence of two peaks in 1:3, thus confirming the chlorine atom is intact. The disappearance of a singlet corresponding to $H^{1'}$ and the appearance of diastereotopy (by $H^3$ and $H^{1'}$) indicated formation of 1,4-adduct. The 1,4-addition was also supported by the $^{13}C$ NMR, which indicated the presence of C=O and appearance of two new aliphatic carbons ($C^2$ and $C^{1'}$).

Varying the position of the chloro group in the enone also resulted in the formation of a reduced product with the halogen atom intact. The reaction was tried by varying the ring size of enones; however, no significant difference in yields was observed. Interestingly, the yield was quite poor (21%) for enone **5d**. The poor yield in this case can be rationalized from the fact that the hydroxyl proton can be easily substituted by $^{n}Bu_3SnH$ under free radical conditions. Because there is a competition between the 1,4-addition and the substitution of hydroxyl proton with $^{n}Bu_3Sn$, the

**Table 1.** Synthesis of **4** via Fig. 1

| | Equivalent to 1 | | | | |
|---|---|---|---|---|---|
| Entry | AIBN | $(BzO)_2$ | $^{n}Bu_3SnH$ | Solvent (time) | Yield of **4** (%) |
| 1 | 0.1 | — | 0.5 | THF (16 h) | 23 |
| 2 | 0.1 | — | 1 | THF (16 h) | 43 |
| 3 | 0.1 | — | 2 | PhH (8 h) | 82 |
| 4 | 0.1 | — | 4 | PhH (18 h) | 85 |
| 5 | 1 | — | 2 | 8 h | 74 |
| 6 | — | 0.1 | 2 | 8 h | — |

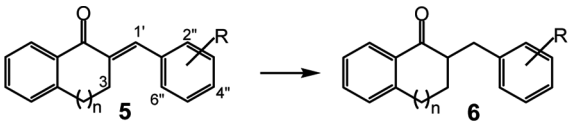
effective available concentration of the $^{n}Bu_3Sn$ radical is reduced, which results in an overall decrease in the yield of 1,4-reduced product.

The reduction of unsubstituted enone **5a** afforded the ketone **6a** in reasonable yield. The enone **5e** afforded product **5a** with C-Br reduction instead of C=C reduction. The inability of radical to cause dehalogenation in the case of chloro-substituted enone(s) was attributed to the stronger C-Cl bond, which was not cleaved under free radical conditions, whereas the bromo-substituted enone **5e** followed the course as predicted for any alkyl and/or aryl halide along with formation of reduced ketone **6a** as trace product. When furyl substituted enones (**5g** and **5i**) were employed, no reaction was observed at all (Fig. 2). It would be due to the formation of a highly resonance stabilized radical cation at O of oxole ring.

After the successful studies on the reduction of cyclic enones, variously substituted acyclic enones were subjected to free radical–mediated reduction. The disappearance of *trans* coupling and appearance of two sets of triplets (in most of the cases) in the aliphatic region indicated the formation of a reduced product. The mass spectra were in agreement with the expected product in all cases (Fig. 3).

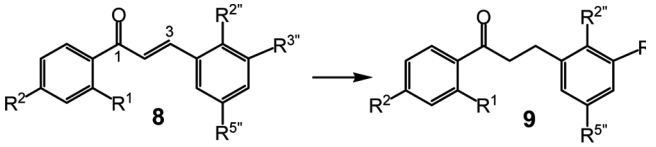
The changes in the bond length of $C^8$–$C^9$ ($C^2$–$C^{1'}$) observed in the x-ray diffraction for **4, 8a**, and **9a** are represented in Table 2. See also Fig. 4.

The role of AIBN in the $^{n}Bu_3SnH$-mediated reaction makes it obvious that the reaction is free radical mediated. The reaction mixture was boiled (digested) in HCl,




| Entry | n | $R^{2''}$ | $R^{3''}$ | $R^{4''}$ | $R^{5''}$ | Product (% yield) |
|---|---|---|---|---|---|---|
| **5a** | 0 | H | H | H | H | **6a** (53) |
| **5b** | 0 | Cl | H | H | $NO_2$ | **6b** (72) |
| **5c** | 0 | H | H | Cl | H | **6c**(72) |
| **5d** | 0 | H | OH | H | H | **6d** (21) |
| **5e** | 0 | Br | H | H | H | **5a** (82)+**6a** (8) |
| **5f** | 0 | H | H | $NO_2$ | H | **6f** (46) |
| **5g** | 0 | 2-furyl | | | | - |
| **5h** | 1 | Cl | H | H | H | **6h** (68) |
| **5i** | 1 | 2-furyl | | | | - |

**Figure 2.** Reduction of cyclic enones under free radical conditions by refluxing **5a–i** with AIBN (0.1 eq) and $^{n}Bu_3SnH$ (2 eq) in PhH for 8 h.




| Entry | $R^1$ | $R^2$ | $R^{2''}$ | $R^{3''}$ | $R^{5''}$ | % Yield of **9** |
|---|---|---|---|---|---|---|
| **8a** | H | H | Cl | H | $NO_2$ | 64 |
| **8b** | Cl | Cl | Cl | H | H | 62 |
| **8c** | Cl | Cl | OMe | H | H | 71 |
| **8d** | Cl | Cl | OMe | OMe | H | 78 |

**Figure 3.** Reduction of acyclic enones under free radical conditions by refluxing **8a–d** with AIBN (0.1 eq) and $^n Bu_3SnH$ (2 eq) in PhH for 4 h.

and $Na_2S$ was added to this solution. The resulting mixture was heated to boiling to exclude excess of $H_2S$. Upon cooling, dull brown precipitates were produced, which indicated the presence of SnS, and greenish-yellow-colored filtrate upon concentration afforded a dull yellow solid, which indicated the presence of $SnS_2$.[17] The presence of both Sn[II] and Sn[IV] ions favor the SET mechanism (Fig. 5).

## EXPERIMENTAL

The thin-layer chromatography (TLC) was carried out on precoated silica gel (0.25-mm-thick layer over Al sheet, Merck) with fluorescent indicator. The spots were visualized under ultraviolet lamps (365 and 254 nm λ) of 8 W power or a $KMnO_4$ dip upon heating. The compounds were purified either on a glass column packed with silica gel (0.6–0.2 mm, 60-Å mesh size, Merck) or by crystallization. All solutions were concentrated under reduced pressure (25 mm of Hg) on a rotary evaporator (Laborota 4001, Heidolph) at 35–40 °C. Melting points were determined using a MF-8 (Gallenkamp) instrument and are reported uncorrected. The infrared (IR)-spectra were recorded on Prestige 21 spectrophotometer (Shimadzu) as KBr discs. The electrospray ionization mass spectrometry (ESI MS) and electron impact mass spectrometry (LR EIMS) were carried out on a MAT312 machine. The $^1H$ and $^{13}C$ NMR were recorded on a Bruker Avance DPX300 spectrometer using tetramethylsilane (TMS) as internal standard. The x-ray data for the single crystal

**Table 2.** Selected bond lengths of **4**, **8a**, and **9a** Å

| Bond | **4** | **8a** | **9a** |
|---|---|---|---|
| $O^1$–$C^7$ | 1.222(3) | 1.215 (5) | 1.218 (5) |
| $C^8$–$C^9$ | 1.518(3) | 1.406 (5) | 1.461 (6) |

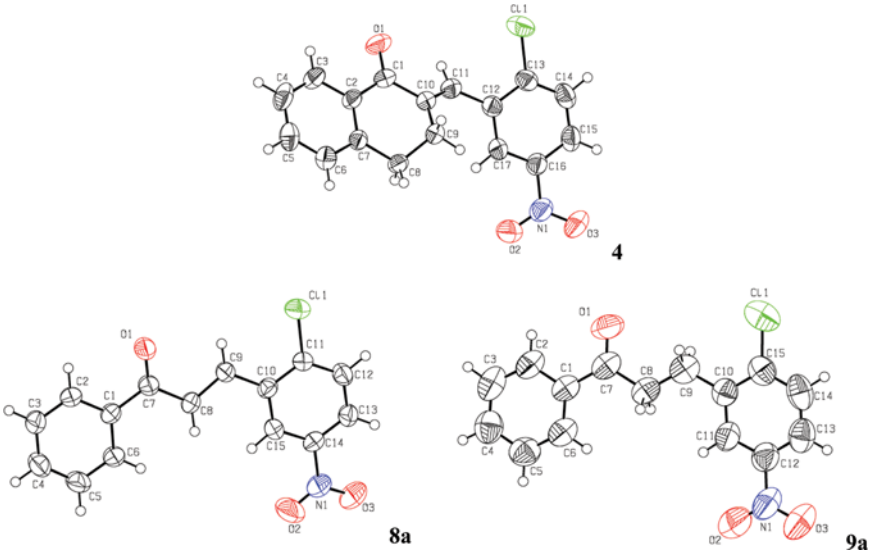



**Figure 4.** ORTEP diagram of reduced product **4** (top), acyclic enone **8a** (bottom left), and ketone **9a** (bottom right). (Figure is provided in color online.)

were collected on a Bruker Kappa Apex II CCD diffractometer using graphite monochromated ($\lambda_{MoK\alpha} = 0.7107$ Å) as radiation source.

## Representative Procedure for the Synthesis of Enones

A solution of acetophenone (0.88 mL, 0.9 g, 7.53 mmol, 1 eq) and 2-chloro-5-nitrobenzaldehyde (1.40 g, 7.53 mmol, 1 eq) in EtOH was added to a refluxing solution of KOH (0.42 g, 7.53 mmol, 1eq) in EtOH (25 mL), and resulting reaction

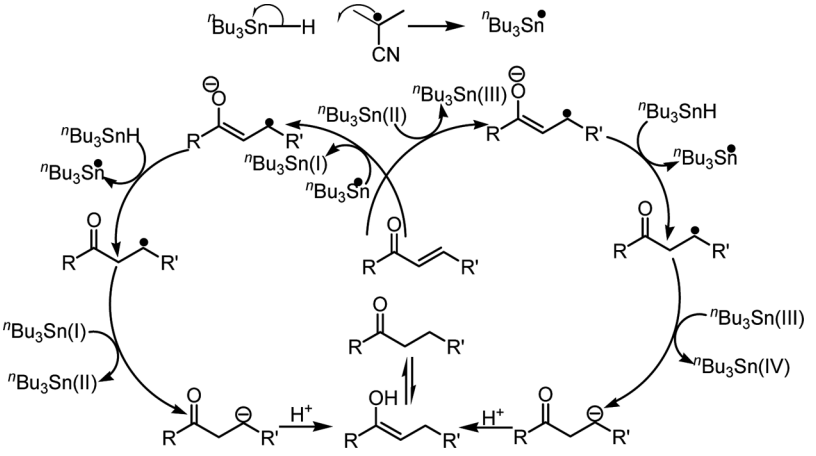


**Figure 5.** Mechanism of radical-mediated enone reduction.

mixture was refluxed for 3 h. After the completion of the reaction, the solvent was evaporated under reduced pressure, and the concentrate was acidified with aq. HCl (15 mL). The reaction mixture was partitioned between $H_2O$ (15 mL) and $CH_2Cl_2$ ($3 \times 25$ mL), and the combined organic extract was dried over anhydrous $Na_2SO_4$, filtered, and concentrated under reduced pressure to afford the enone **8a** as off-white crystalline solid (1.78 g, 82%).

### Acetophenone (0.88 mL, 0.9 g); 2-chloro-5-nitrobenzaldehyde (1.4 g)

Off-white crystalline solid **8a** (1.78 g, 82%); $R_f$: 0.59 (EtOAc/petrol 1:1); Mp: 173 °C; IR (KBr): $\upsilon_{max}$ ($cm^{-1}$) 1676 (C=O), 1512 (N=O), 682 (C-Cl); UV-vis ($CHCl_3$): $\lambda_{max} = 346$ nm (log $\varepsilon = 4.68318\ cm^{-1}\,M^{-1}$); LR EIMS ($m/z$): 287, 289 $[M]^+$(23, 7%), 105 $[PhCO]^+$ (78%), 77 $[Ph]^+$ (100%); ESI HRMS (amu): 310.0954, 312.0926 $[M + Na]^+$ (found in 3:1) for 310.0247, 312.0217; $^1$H NMR (300 MHz, $CDCl_3$): δ (ppm) 7.58 (3H, t, $J = 7.2$ Hz, $H^{3''} + H^{4''}$), 7.66–7.69 (2H, m, $H^{2''}$), 7.68 (1H, d, $J = 15.9$ Hz, $H^2$), 8.10 (1H, d, $J = 7.2$ Hz, $H^{3'}$), 8.19 (1H, d, $J = 15.9$ Hz, $H^3$), 8.23 (1H, dd, $J = 7.2$, 2.4 Hz, $H^{4'}$), 8.65 (1H, d, $J = 2.4$ Hz, $H^{6'}$); $^{13}$C NMR (75 MHz, $CDCl_3$): δ (ppm) 122.6 ($C^{3'}$), 125.1 ($C^{4''}$), 127.0 ($C^2$), 128.7 (2×, $C^{2''}$ or $C^{3''}$), 128.9 (2×, $C^{2''}$or $C^{3''}$), 131.3 ($C^3$), 132.0 ($C^{1''}$), 133.5 ($C^3$), 134.9 ($C^{1'}$), 137.0 ($C^{2'}$), 138.0 ($C^{6'}$), 146.8 ($C^{5'}$), 189.4 ($C^1$).

### Representative Procedure for Free Radical Mediated Reduction of Enones

A solution of $nBu_3SnH$ (0.70 mL, 0.77 g, 2.66 mmol, 2 eq) in PhH (5 mL) was added like drops over a period of 25 min to a refluxing solution of enone **8a** (0.25 g, 1.33 mmol, 1 eq) and AIBN (0.025 g, 0.13 mmol, 0.1 eq) in PhH (10 mL). The resulting solution was refluxed for 4 h under $N_2$. The reaction was quenched with saturated aq. solution of $NH_4Cl$. The solvent was evaporated in vacuo, and tributyltin salts were precipitated by the addition of brine to the concentrate followed by addition of acetone. The salts were filtered off, and the resulting solution was partitioned between $H_2O$ (25 mL) and $CH_2Cl_2$ ($3 \times 25$ mL). The organic extract was dried over anhydrous $Na_2SO_4$, filtered, and concentrated under reduced pressure to afford the reduced product **9a** as off-white crystalline solid (0.16 g, 64%).

### Enone 8a (0.25 g)

Time 4 h; off-white crystalline solid **9a** (0.16 g, 64%); $R_f$: 0.67 (EtOAc/petrol 1:1). Mp: 141 °C; IR (KBr): $\upsilon_{max}$ ($cm^{-1}$) 1685 (C=O), 1538 (N=O), 695 (C-Cl); UV-vis ($CHCl_3$): $\lambda_{max} = 299.7$ nm (log $\varepsilon = 4.32599\ L\,cm^{-1}\,M^{-1}$); LR EIMS ($m/z$): 289, 301 $[M]^+$ (4, 1), 105 $[PhCO^+]$ (100%), 77 $[Ph^+]$ (92%); ESI HRMS (amu): 312.0479, 314.0432 [M + Na] (found in 3:1) for 312.0412, 314.0382; $^1$H NMR (300 MHz, $CDCl_3$): δ (ppm) 3.27 (2H, t, $J = 6.8$ Hz, $H^3$), 3.35 (2H, t, $J = 6.8$ Hz, $H^2$), 7.45–7.63 (5H, m, $H^{2''}$-$H^{4''}$), 7.95 (1H, d, $J = 7.2$ Hz, $H^{3'}$), 8.15–8.21 (1H, m, $H^{4'}$), 8.60 (1H, d, $J = 2.4$ Hz, $H^{6'}$); $^{13}$C NMR (75 MHz, $CDCl_3$): δ (ppm) 17.8 ($C^3$), 35.9 ($C^2$), 122.1 ($C^{1''}$), 123.5 ($C^{4''}$) 126.4 (2×, $C^{2''}$ or $C^{3''}$), 127.1 (2×, $C^{2''}$ or $C^{3''}$), 130.0 ($C^{3'} + C^{1'}$), 130.9 ($C^{4'}$), 135.0 ($C^{6'}$), 138.9 ($C^{2'}$), 142.9 ($C^{5'}$), 196.5 ($C^1$).

## CONCLUSION

In conclusion, $^{n}Bu_3SnH$ has been evaluated as a potential candidate toward chemoselective 1,4-reduction of enones. These findings suggest that the free radical–mediated reduction can take place easily under neutral conditions. The combination of $^{n}Bu_3SnH$ and AIBN makes this the reagent of choice for chemoselective 1,4-reduction of enones with substituents sensitive to pH changes. Furthermore, the chloro groups are not affected under these conditions, but the same cannot be claimed for bromine.

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