

ALKYL RADICAL GENERATION BY REDUCTION OF A KETONE TOSYLHYDRAZONE

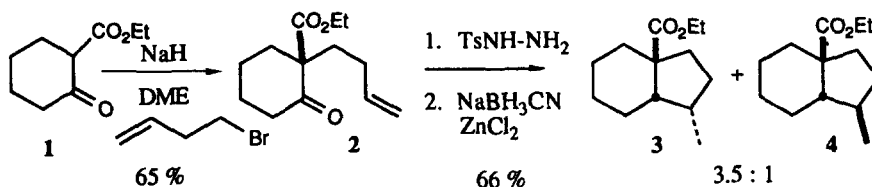
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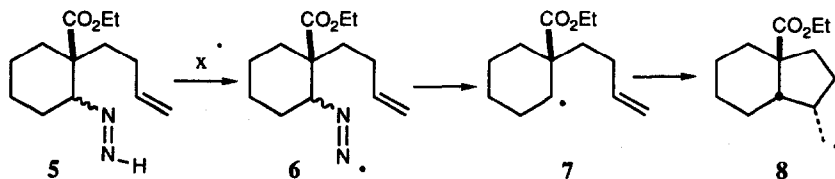
Abstract: Reduction of the tosylhydrazone of ketone **2** with NaBH₃CN / ZnCl₂ leads to a 3.5 : 1 mixture of **3** and **4**. It is suggested that this reaction proceeds by radical chain decomposition of an intermediate monoalkyl diazene.

Free radical cyclization is now a well-established method for ring construction.² In the bulk of the published work, cyclization is initiated by reduction of a halide or alcohol derivative. We now report that a *ketone* can be used as the starting functionality for a free radical cyclization, via reduction^{3, 4} of the derived tosylhydrazone.

Ketone **2** was prepared by alkylation of β -keto ester **1** with 4-bromo-1-butene. Condensation with *p*-toluenesulfonyl hydrazine, followed by reduction of the crude tosylhydrazone with NaBH₃CN in the presence of ZnCl₂ then led to cyclized esters **3** and **4**, which run together on TLC, as a 3.5:1 mixture. The reduced but uncyclized ester was not observed.



The predominance of the *endo* methyl isomer is uniquely typical⁵ of a free radical cyclization. Following the accepted mechanism,⁶ the monoalkyl diazene **5** would be an intermediate in the reduction of the tosylhydrazone to the corresponding hydrocarbon. Hydrogen atom abstraction (perhaps by molecular oxygen, although the reductions were run under an atmosphere of dry N₂) would then initiate cyclization. The monoalkyl diazene **5** could donate a hydrogen atom to radical **8**, thus maintaining a free radical chain mechanism.



There are reports⁷ of the oxidation of *hydrazine* derivatives to the corresponding hydroperoxides and thus to the alcohols. It would seem plausible that those reactions are proceeding also by radical decomposition of the monoalkyl diazenes, with the alkyl radicals so formed being trapped, perhaps by molecular oxygen.⁸

Experimental: A mixture of ketone 2 (576 mg, 2.56 mmol) and tosylhydrazine (584 mg, 3.13 mmol) in THF (4 mL) was heated to reflux for 16 h. The reaction mixture was cooled to room temperature, and ZnCl₂ (501 mg, 3.58 mmol) followed by NaBH₃CN (222 mg, 3.58 mmol) were added. After 12 h at reflux, the reaction was quenched by 10% aqueous NaHCO₃ (4 mL) and partitioned between ethyl acetate and, sequentially, 5% aqueous HCl, saturated aqueous Na₂SO₄ and water. The combined organic extracts were dried (Na₂SO₄) and concentrated, and the residue was purified by silica gel chromatography to give 353 mg (66% from 2) of the mixture of 3 and 4 as a colorless oil, TLC R_f (10% EtOAc / petroleum ether) = 0.72. ¹H NMR (major, δ): 4.04 (q, J=7.2 Hz, 2H), 2.04-1.49 (m, 11H), 1.25-1.19 (m, 3H), 1.17 (t, J=7.2 Hz, 3H), 0.81 (d, J=6.6 Hz, 3H); (minor) 4.07 (q, J=7.1 Hz, 2H), 2.04-1.49 (m, 11H), 1.25-1.19 (m, 3H), 1.18 (t, J=7.1 Hz, 3H), 0.90 (d, J=5.6 Hz, 3H). ¹³C NMR (major, δ): u: 179.0, 60.2, 60.0, 31.1, 29.4, 28.0, 24.6, 22.5, 21.5; d: 45.0, 36.3, 15.2, 14.1; (minor): u: 177.5, 54.9, 52.2, 36.5, 34.1, 30.9, 23.7, 23.2, 20.4; d: 48.4, 33.8, 21.1, 19.4. MS (m/z, %): 210.1647 (14), 182(6), 168 (14), 165 (8), 155 (22), 137 (100), 127 (12), 121 (42), 109 (9).

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