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SYNTHESIS OF α-METHYLENE-δ-VALEROLACTONES AND α-METHYLENECYCLOHEXANONES VIA RADICAL CYCLIZATION OF PROPIOLATES AND ACETYLENIC KETONES

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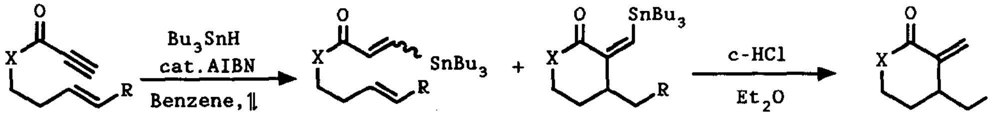
Abstract: Synthesis of α-methylene-δ-valerolactones and α-methylenecyclohexanones is readily achieved via intramolecular radical cyclization of propiolates and acetylenic ketones mediated by the addition of stannyl radicals.

Recently we reported facile synthesis of α-methylene-γ-butyrolactones and α-methylenecyclopentanones via intramolecular radical cyclizations of allylic propiolates and homoallylic acetylenic ketones mediated by the addition of stannyl radicals.[1] Two salient features are noted. First, the intermediate stannylated α-carbonylvinyl radicals are amenable to the 5-exo mode of cyclizations and Z-stannylmethylene compounds are the primary products. The trialkylstannyl group, which initiated cyclization reaction, protects products from further reactions.

We now wish to report that 6-exo cyclizations of stannylated α-carbonylvinyl radicals are also useful processes, which provide easy access to various α-methylene-δ-valerolactones and α-methylenecyclohexanones (Scheme 1).

(Scheme 1)

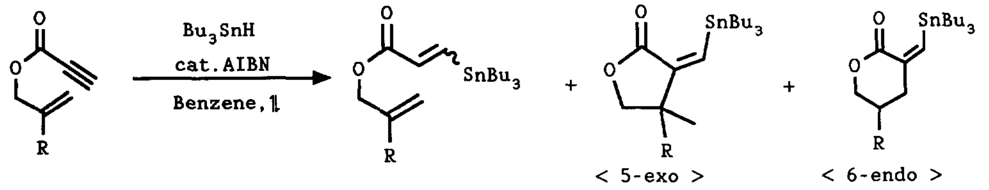


1a: X=O, R= 	2a: 19 %	3a: 41 %	4a: 70 %
1b: X=O, R= 	2b: 21 %	3b: 40 %	4b: 68 % secocrispiolide
1c: X=CH_2, R= $COOCH_3$	2c: --	3c: 82 %	4c: 73 %

For example, syringe pump addition of tributylstannane (1.2 eq.) and AIBN (0.15 eq.) over 4 hours to the propiolate 1b in boiling benzene (0.025M) resulted in the formation of 2b (21%) and 3b (40%). Upon exposure to HCl in ether, 3b was converted to (±)-secocrispiolide[2] (4b) in 68% yield. More efficient cyclization of acetylenic ketones was noted as 1c was transformed into 3c (82%) as the only product.

These examples attest to the usefulness of 6-exo mode cyclizations of stannylated α-carbonylvinyl radicals for the production of valerolactones and cyclohexanones. In certain cases, 6-endo mode is also useful for valerolactone synthesis. When the propiolate 5b was reacted with tributylstannane, only the 6-endo product 8b was isolated in low yield (15%) along with the simple addition product 6b (52%). The yield of the 6-endo product 8c was 32% from the propiolate 5c (Scheme 2). Theoretical studies on the regioselectivity of radical ring closure of related systems have been discussed by Beckwith.[3]

(Scheme 2)



5a: R= H	6a: 42 %	7a: 32 %	8a: 4 %
5b: = CH_3	6b: 52 %	7b: --	8b: 15 %
5c: = $COOCH_3$	6c: 40 %	7c: --	8c: 32 %

In these cyclizations, intermediacy of the equilibrating stannylvinyl radicals ensures the formation of acyclic products as random mixtures of E/Z isomers. However, Z-stannylvinyl radicals are expected to show greater tendency to cyclize and all cyclic products tend to be Z-isomers.

Delineation of utility of these cyclizations in the synthesis of natural products will be the subject of future studies.

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