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THE SYNTHESIS OF FUSED AND BRIDGED RING SYSTEMS BY FREE RADICAL CARBOCYCLIZATION. A GENERAL ROUTE TO MASKED 1,4-DIKETONES.

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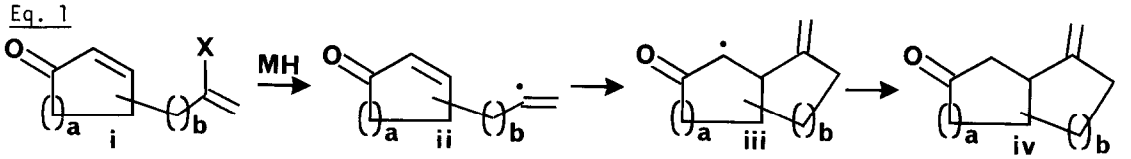
Abstract: A new method for the synthesis of fused and bridged ring systems based on intramolecular addition of a vinyl radical to α,β-unsaturated carbonyls is described. The method represents a general route to masked γ-diketones.

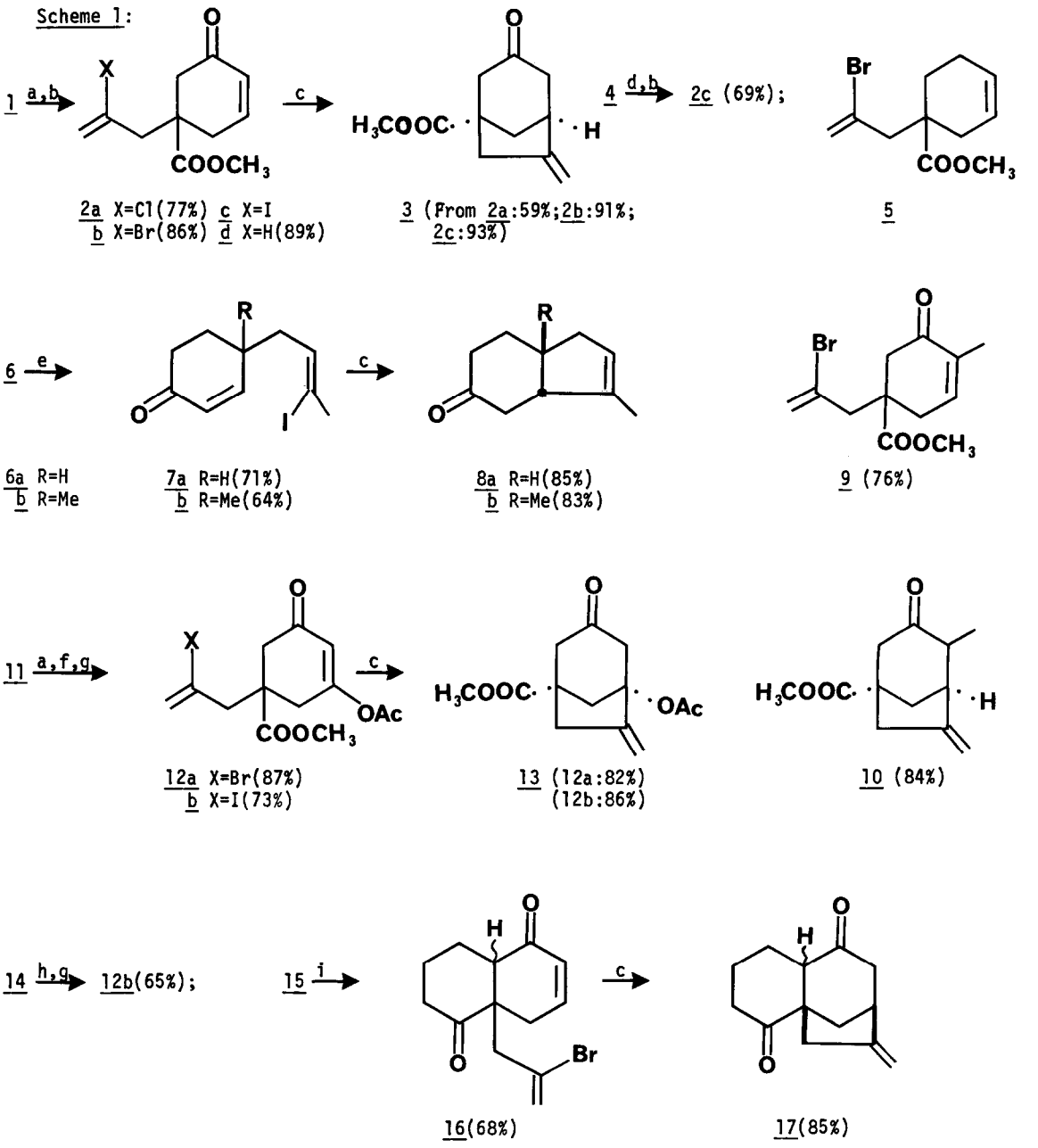
The importance of the methodology for the formation of carbocyclic rings to the synthesis of complex organic molecules has been well recognized.[1] Various ionic, concerted, and radical processes have been utilized in developing carbocyclization methods. In general, the synthetic potential of the ring forming methods has been decisively increased by invoking the principle of intramolecularity.[2] A predictable stereochemical course for such reactions is especially advantageous in the design of synthetic strategies for complex molecules. Stork has recently demonstrated for the first time a new type of annulation based on the cyclization of vinyl radicals to olefins.[3] Intramolecular addition of radicals to α,β-unsaturated carbonyl compounds, a reaction type of considerable synthetic potential in carbocyclization, has been of limited use in sythesis of natural products progenitors.[4]

We report here a new method for ring formation based on intramolecular addition of a vinyl radical to conjugated unsaturated carbonyl derivatives. This method also represents a general route to masked 1,4-diketones. The utilization of vinylogous reactivities in radical processes are difficult to realize selectively, since dimerization, disproportionation, polymerization, trapping of oxygen and α-bond cleavage often effectively compete with the hydrogen atom transfer reaction. Our approach (Eq 1) involves formation of a vinyl radical ii by trialkyltin hydride[5] mediated homolysis of a vinyl halide i, followed by an internal addition to a stereoproximal acceptor alkene moiety and a hydrogen transfer to the addend radical iii. A synthetically useful feature of this approach to carbocyclization is that chemoselectivity of an organostannane assures the compatibility of the α,β-unsaturated carbonyl moiety until homolytic cleavage. The efficiency of ring formation is enhanced by the kinetic preference of vinyl radical ii to undergo addition to an acceptor alkene moiety over transfer of the hydrogen atom from the

Eq. 1



Scheme 1:



2a X=Cl(77%) c X=I
b X=Br(86%) d X=H(89%)

3 (From 2a:59%;2b:91%; 2c:93%)

5

6a R=H
b R=Me

7a R=H(71%)
b R=Me(64%)

(a)Li, liq. NH_3-THF (4:1), -78°C, 25 min; 2,3-dihalopropene/THF, -78°C. (b)10% HCl-THF (1:2), 25°C; CH_2N_2. (c)n-Bu_3SnH, cat. AIBN, benzene, 80°C. (d)LDA, $BrCH_2C(I)=CH_2$[8b], THF, HMPA, -78°C. (e)i) LDA, $ICH_2CH=C(I)CH_3$[8c], THF, -78°C. ii) LAH, ether, 36°C, 1/2h; 2% HCl, 0°C, 10 min. (f)CH_2N_2; then (b). (g)CH_3COCl, $CHCl_3$, 61°C, 2h. (h)LDA, $BrCH_2C(I)=CH_2$, THF, HMPA, -78°C; then (b). (i)i) K, liq. NH_3-THF, t-BuOH, -78°C, 10 min; anh. LiBr/THF, -78°C, 20 min; 2,3-dibromopropene/THF, -78°C, 4h; then (b).

organostannane[6] and by effective delocalizaton of the free spin by the adjacent carbonyl group in the addend radical iii.[7]

We have begun to study the scope and limitations implicit in the intramolecular addition of a vinyl radical to an activated double bond. The convergent synthetic routes to the vinyl halide starting materials have been developed (Scheme 1). Thus, reductive alkylation of 3-methoxybenzoic acid (1) with a 2,3-dihalopropene,[8a] followed by dilute mineral acid treatment and esterification afforded the precursors of the bridged systems 2a and 2b.[9] Vinyl iodide 2c was obtained upon alkylation of 1-carbomethoxy-3-methoxy-1,4-cyclohexadiene (4) followed by treatment with acid. Alkylation of the kinetic lithium enolate of 3-ethoxy-2-cyclohexenone (6),[11] subsequent reduction and acidic work-up gave the progenitors (7) of fused systems. Intramolecular vinyl radical additions were induced by treatment of a vinyl halide with tributyltin hydride. This resulted in the regioselective exo cyclization to produce bridged (3) and fused (8) ring systems.[12] The regiochemical preference had been anticipated since: a) even a cursory inspection of models of the two possible modes for cyclization of vinyl radical ii reveals that the required disposition of reactive centers is more readily accommodated in the transition state for 1,5 ring closure[13]; b) possible modes of orbital interactions between a radical and a closed-shell molecule notwithstanding, frontier orbitals, in case of acceptor alkenes, have larger coefficients on the β-carbon.[14] Furthermore, the failure of vinyl bromide 5 to cyclize suggests that the "vicinal" orbital interaction is a SOMO-LUMO interaction.

The influence of the nature of the halide on the efficiency of carbocyclization was investigated. The results indicate: a) a vinyl chloride function is the least useful vinyl radical precursor; vinyl bromides, being less sensitive and synthetically more accessible than vinyl iodides are the vinyl radical precursors of choice. b) a major involvement of the SOMO of the tin radical with the HOMO of the vinyl halide, since both the ease of abstraction of halogens and the energies of the HOMO of the carbon-halogen bonds,[15] fall in the order I > Br > Cl.

In order to study the relationship between the substitution pattern of the acceptor alkene moiety and the mode of ring closure, substituted enones, prepared from 3-methoxy-4-methylbenzoic acid, 3,4,5-trimethoxybenzoic acid (11) and 1-carbomethoxy-3,5 dimethoxy-2,5-cyclohexadiene (14)[16] were treated with tributylstannane. Carbocyclization of the vinyl halides 9 and 12 gave only the exo cyclization products 10 and 13. This indicates the utility of activated olefins, substitute by π-electron acceptor groups as cyclization substrates that will ensure regiochemical control of ring closure.

The substantial concentration effect on the ratio of rates for the hydrogen atom transfer and carbocyclization is consistent with trends noted in alkyl radical cyclization.[17] At 0.25 M stannane concentration carbocyclization of 2a yielded only 2d (71%); 2b gave a mixture of 3 (54%) and 2d (22%); a mixture of 3 (68%) and 2d (13%) was produced from 2c. Yields of cyclized products increased with decreasing stannane concentration and eventually no hydrogenolysis product was obtained at 18 mM stannane concentration except for 2a which gave 3 (59%) and 2d (17%). The choice of solvent was briefly examined. Benzene, being inert to radical intermediates and having a sufficiently high boiling point to facilitate initiation of homolytic cleavage of a hydrogen-tin bond, proved to be the optimum solvent.

The potential utility of this annulating method in synthesis is underscored by the utilization of 13 for the preparation of a useful intermediate in the synthesis of gibberilic acid[18] and by the example presented in Scheme 2. Our approach to highly functionalized bridged bicyclic systems found in several terpenoids possessing anti-tumor and antifertility activity[19] utilizes carbocyclization of a vinyl halide for construction of the required bicyclo[3.2.1]octanone derivatives. Thus the tricyclic skeleton of (12S)-7,12-secoishwaran-12-ol was assembled by the following sequence: 1) reductive alkylation of 5-methoxy tetralone[20] (15) with 2,3-dibromopropene; 2) acid treatment to yield the enone 16; 3) organostannane initiated carbocyclization to afford the tricyclic diketone 17. Further studies on the scope and limitations of free radical carbocyclization and its application to organic synthesis are in progress.

A general procedure for vinyl radical carbocyclization is given below: A mixture of tributyltin hydride (1.1 mmol) and 5 mg of azobis (isobutyronitrile) in 10 mL of dry benzene is added dropwise to the vinyl bromide 1b (1 mmol) in 45 mL of benzene at reflux over a 1 h period, followed by heating for an additional 45 min. The residue after removal of benzene is purified by column chromatography to give the olefinic keto ester 3 (0.91 mmol) in 91% yield.

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