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An Unusual Radical Fragmentation of 8a-Cycloalkenylmethyl Wieland-Miescher Ketones Mediated by Tri-n-butyltin Hydride

Thennati Rajamannar[*a] **and Kalpattu Kuppuswamy Balasubramanian**[*b]

[a]**Centre for Agrochemical Research**
SPIC Science Foundation
110 Mount Road, Guindy
Madras 600 032, INDIA.

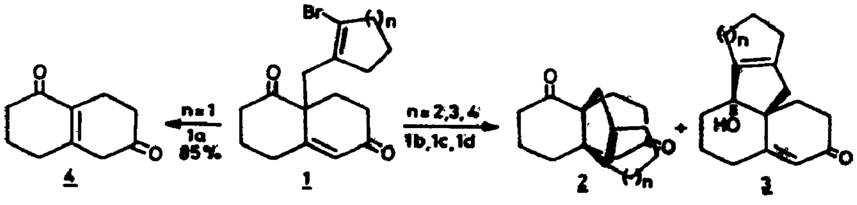
[b]**Department of Chemistry**
Indian Institute of Technology
Madras 600 036, INDIA.

Abstract: The behaviour of tri-n-butyltin hydride in poly functional molecule like Wieland-Miescher ketones, was found to be very unusual, a remarkable difference in chemoselectivity was noticed in the reductive cyclisation of cycloalkenyl bromides, resulting in the remote generation of the bromocyclopentenyl-methyl radical by a homolytic C-C bond cleavage.

The radical C-C bond formation reactions have added a new dimension to the syntheses of complex molecules.[1] The great advantage of using radical reaction is the chemo-, regio- and even a stereoselective intra and intermolecular carbon carbon bond formation apart from its high functional group tolerance.

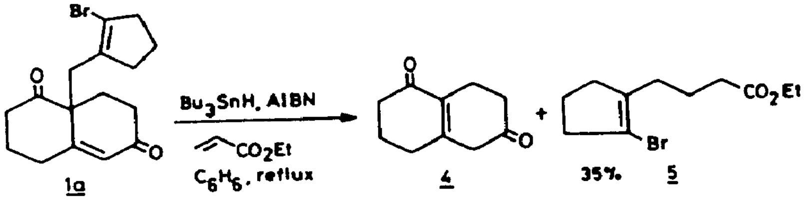
Recently we found that Wieland-Miescher ketone analogues bearing 2-bromo-1-cycloalkenylmethyl (n=2,3,4) groups are useful precursors for the synthesis of propellanes and carbocycles.[2] In an attempt to extend this reaction for the 2-bromo-1-cyclopentenylmethyl ketone 1a (n=1), we encountered an unexpected and novel fragmentation reaction (Scheme 1) which we describe in this communication.

Scheme 1



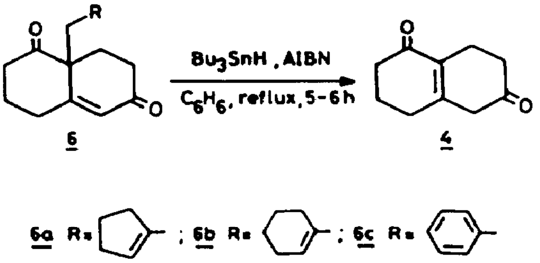
Treatment of the substrate 1a in benzene with tri-n-butyltin hydride in the presence of AIBN, led to a clean reaction, resulting in the formation of the known diketone 4 in 85% yield, which was identified on the basis of its spectral data as well as by comparison with an authentic sample.[3] The other product of this radical fragmentation reaction turned out to be the bromine intact 2-bromo-1-cyclopentenylmethyl radical, which could not be isolated in any form. However, we were able to trap it as the adduct of ethyl acrylate and isolated the adduct 5[4] in 35% yield by performing the tri-n-butyltin hydride reaction in 1a using AIBN as the radical initiator in the presence of ten fold excess of ethyl acrylate (Scheme 2).

Scheme 2



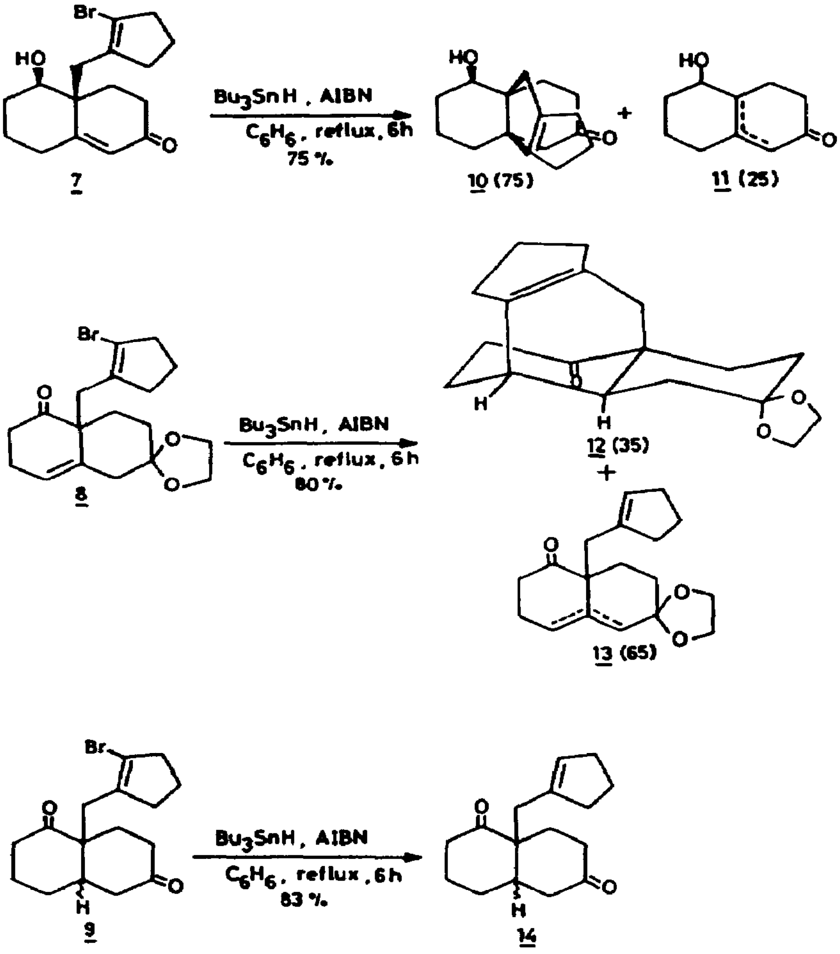
In order to establish the generality of this fragmentaion reaction we have synthesised various Wieland-Miescher ketone analogues 6a-6c, which on treatment under typical reaction conditions cleanly furnished the product 4 in yields of 72%, 75% and 82% respectively (Scheme 3). It is noteworthy that, when the reaction was carried out with tri-n-butyltin hydride in the absence of AIBN, after 6h the starting material was recovered unchanged.

Scheme 3



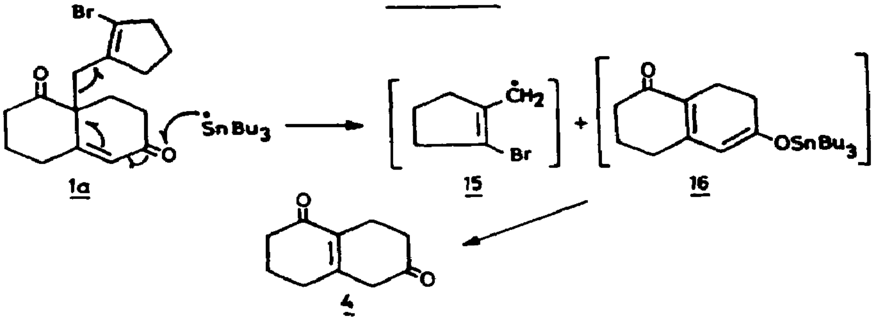
With a view to get some insight into the mechanism of this fragmentation, we investigated the behaviour of related compounds 7[5], 8[6] and 9[7], which were synthesised by extending the literature procedures. The results of the tri-n-butyltin hydride reaction of 7, 8 and 9 depicted in the Scheme 4, reveal that all the three functionalities present in 1a are essential to realise this fragmentation. While the hydroxy enone 7 underwent a similar radical fragmentation, but in poorer yield (19%), neither the ketal 8 nor the dihydro derivative 9 led to any products of fragmentation. It can be conceived from our results, that the initial attack of the tri-n-butyltin radical is on the enone carbonyl, resulting in the remote generation of the 2-bromo-1-cyclopentenylmethyl

Scheme 4



radical by a homolytic C-C bond cleavage Scheme 5.

Scheme 5



The reducing ability of tri-n-butyltin hydride was found to differ in HMPA[8] or in the presence of some additives like tetra-n-butyl-ammonium halides[9], resulting in the chemoselective reduction of the carbonyl function in the presence of halides. A few cases of formation of cyclic ehters during the tri-n-butyltin hydride reduction of the chloro ketones[10] are known, wherein, the initial attack was reported to be at the ketonic carbonyl. Though tri-n-butyltin hydride has till now been reported to be highly chemoselctive for the reduction of carbon halogen bond, our present work has shown that in a polyfunctional molecule like Wieland-Miescher ketone 1a, the generation of cyclopentenyl radical from the bromide is difficult there by altering the site selectivity towards the enone carbonyl and this fragmentation reaction was found to be general for Wieland-Miescher ketones bearing an allyl moiety at 8a position.

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4. All compounds reported have been thoroughly characterised. Data for the compound 5: ^{1}H NMR (CDCl$_3$, 400 MHz): δ : 4.06(q, J=7.33 Hz, 2H); 2.55(m, 2H); 2.23(t, J=7.81 Hz, 2H); 2.22(m, 2H); 2.13(t, J=7.32 Hz, 2H); 1.86 (m, 2H); 1.69 (pent, J=7.81 Hz, 2H); 1.19(t, J=7.33 Hz, 3H). ^{13}C NMR (CDCl$_3$, 100 MHz): δ : 173.49(s), 139.86(s), 116.62(s), 60.30(t), 39.92(t), 33.73(t), 33.60(t), 29.17(t), 22.39(t), 21.70(t), 14.25(q).
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