Pergamon

Tetrahedron Letters, Vol. 35, No. 22, pp. 3699-3702, 1994
Elsevier Science Ltd
Printed in Great Britain
0040-4039/94 $7.00+0.00

0040-4039(94)E0645-E

Radical Cyclization of β-Allenic Hydrazones. An Asymmetric Approach.

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Abstract: β-allenic hydrazones undergo hydrostannylation to afford cyclopentene derivatives and linear rearranged products depending on the substitution of the allenic and hydrazone moieties. A first example of asymmetric radical cyclization of a SAMP β-allenic hydrazone is described.

Radical cyclization reactions of allenic derivatives have not yet been extensively explored[1]. The selective addition of a radical center to an allene could generate a new radical center wich in turn could react with a suitable acceptor group within the molecule to give cyclic derivatives. In this regard several radical acceptors can be considered[2,9]. We have recently reported a novel tin mediated radical cyclization of β-allenic oxime ethers leading to five membered rings. After destannylation this reaction affords cyclopentenes bearing a protected amino group[3]. As an extention of this work we have studied related radical cyclizations using hydrazones as radical acceptors[4]. Our approach was motivated by the opportunity to make an asymmetric version of this reaction using chiral hydrazones.

We now report the results obtained with N,N dimethyl β-allenic hydrazones **1** which have been prepared in a few steps starting from the corresponding acetylenic alcohols according to figure 1.

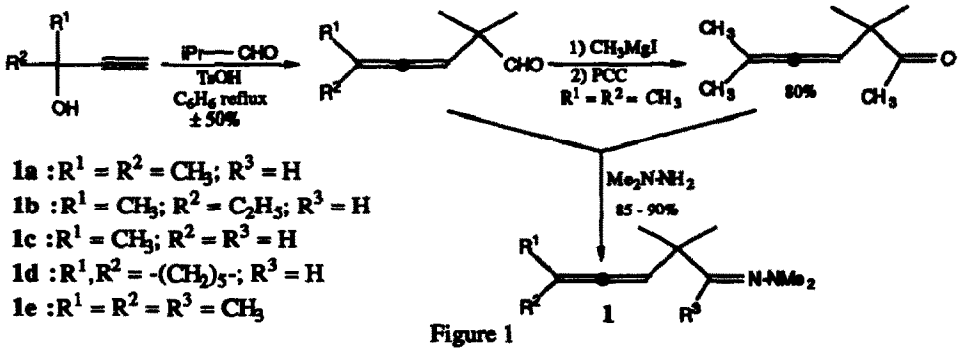
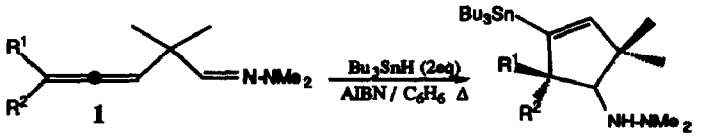


Figure 1

The addition of a benzene solution of tributyltin hydride (2eq.) and AIBN (0.2 eq.) to a 0.02M refluxing benzene solution of compounds **1a, b, c** affords exclusively the expected cyclopentenes **2a,b,c** in very good

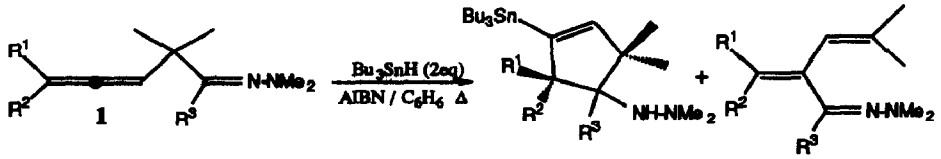
yields[5]. The cyclizations of **1b** and **1c** are diastereoselective. The trans isomer is the major isomer obtained in both cases (**2b**: 81/19; **2c**: 60/40)[6] (Figure 2).



2a (89%)
2b (77%)
2c (90%)

Figure 2

However under the same reaction conditions the hydrazone **1d** leads to a mixture of **2d** and a non cyclized product **3d**. Similar results were observed with the hydrazone **1e** but in this case, the yield of the cyclized compound **2e** is dramatically decreased and the non cyclized product **3e** is obtained as a mixture of syn and anti isomers (Figure 3).



2d (58%)
2e (16.2%)
3d (25%)
3e (57.2%)

Figure 3

The structure of compound **3d** has been determinated by X-Ray analysis[7]; both **3d** and **3e** were fully characterized by MS, ^1H and ^{13}C NMR spectrometries, IR and elemental analysis[7].

The formation of **2** and **3** deserves some comments about the mechanistic pathway of the reaction of β-allenic hydrazones with tributyltin hydride (Figure 4). The five membered products **2** originate from the initial attack of the tin radical on the digonal carbon atom of the allene. The alkyl radical so formed **4** binds to the carbon atom of the hydrazone function in a 5-exo ring closure process. When $R^3 = CH_3$ and in a less extent when $R^1,R^2 = -(CH_2)_5-$, the 5-exo cyclization and the formation of linear compounds **3** become competitive. It is well known that the presence of an alkyl substituent on C-5 slows down the 5-exo ring closure of 5-hexenyl radicals and thus allows the 6-endo mode to become predominant[8]. However in the case of **1e** this 6-endo cyclization implies the attack of the nucleophilic radical **4** on the sp^2 nitrogen atom of the hydrazone function which is far less favourable than the attack on the carbon[9]. In the case of **1d**, the 5-exo cyclization of the cyclohexyl radical **4d** is less favorable than for **4a-b** probably for steric hindrance reasons. The formation of **3** may be explained by the attack of the tin radical on the less substituted trigonal carbon of the allenic moiety. The very reactive vinyl radical[10] **5** adds to the carbon atom of the hydrazone in an unusual and new described 4-exo-mode[11,12]. This cyclization is undoubtedly facilitated by the presence of a *gem*-dimethyl group on the α carbon atom of the hydrazone function in agreement with recent similar reports in the literature[12]. The cyclobutyl aminyl radical **6** fragments immediately into **3** with subsequent loss of the tributyltin group[13].

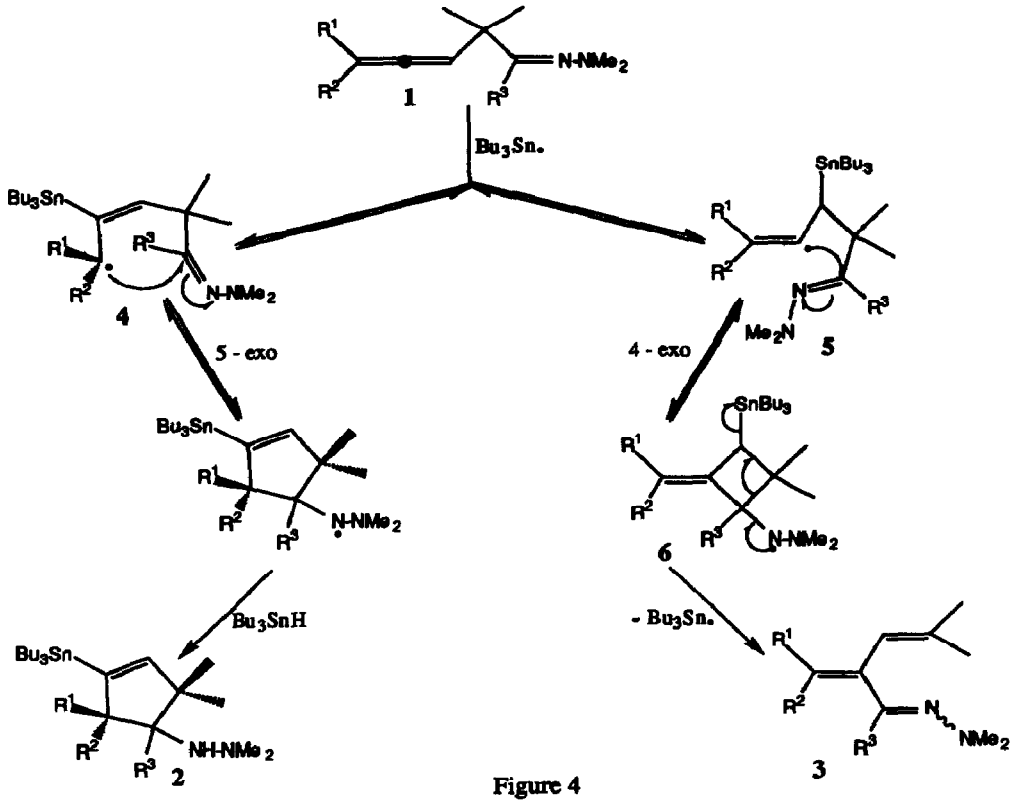


Figure 4

The control of the stereoselectivity of intermolecular radical reactions has recently attracted much attention[14]. However the intramolecular stereocontrol directed by chiral auxiliary has not yet been extensively developped[15]. So at this stage of our work, it seemed of interest to investigate the ability of a chiral hydrazone to induce asymmetry during the cyclization step. We first choose the SAMP as the chiral auxiliary. The addition of tributyltin hydride to the chiral hydrazone **7** under the experimental conditions[5] used for **1** leads exclusively to the cyclopentene hydrazine **8** with 78% yields (figure 5).

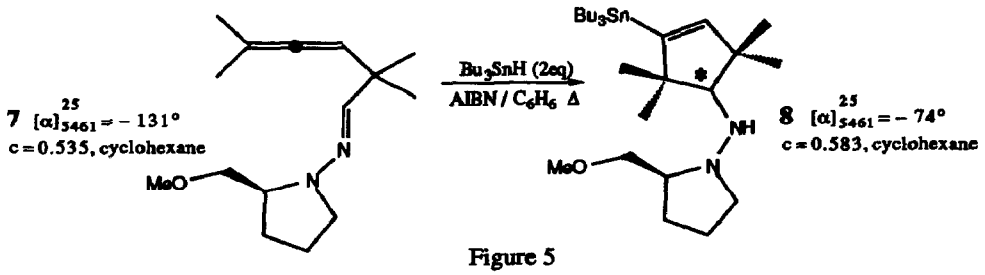


Figure 5

The diastereomeric excess estimated by ^1H NMR spectrometry is about 50%. Although this asymmetric induction is too low to be of some interest for synthetic use, it should be possible to improve the stereoselectivity by using alternate chiral auxiliaries. In this event, we are currently investigating C_2 symmetric groups which could be more efficient[16].

Acknowledgements

We thank Dr. M. Pierrot and Dr. H. Ajilou (Centre de Cristallographie, Faculté de S^t Jérôme, Marseille) for the X ray structure determination and Dr. R. Faure (Centre Régional de RMN, Faculté de S^t Jérôme, Marseille) for recording and elucidating some of the NMR spectra. We should also like to thank Professor M. Bertrand for fruitful discussions.

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5. In a typical experiment, a benzene solution of n Bu_3SnH (2eq.) and AIBN (0.2eq.) was slowly added to a 0.02M refluxing benzene solution of the hydrazone 1. The mixture was refluxing until the starting material disappeared on TLC plates. After evaporation of the solvent, the crude product was purified by flash chromatography over silicagel. Compounds 2 have spectral data (IR, ^{1}H NMR, ^{13}C NMR) and combustion analysis in agreement with the structures assigned. *Selected spectroscopic data.* **2a**: ^{1}H NMR ($CDCl_3$, TMS, 400MHz) δ 0.94 (t,J=7.3Hz,9H), 1.03 (t,J=8.2Hz,6H), 1.14 (s,3H), 1.17 (s,3H), 1.23 (s,3H), 1.3 (s,3H), 1.39 (sex,J=7.3Hz,6H), 1.62 (m,6H), 1.75 (s,1H), 2.25 (s,6H), 2.9 (s,1H), 5.65 (s,1H); ^{13}C NMR ($CDCl_3$, 100MHz) δ 151.31(C), 150.17 (CH), 73.17 (CH), 53.7 (C), 49.62 (C), 47.18 (NCH_3), 31.27 (CH_3), 30.13 (CH_3), 29.65 (CH_2), 27.78 (CH_2), 24.71 (CH_3), 23.84 (CH_3), 13.93 (CH_3), 10.23 (CH_2). Analysis Calcd. for $C_{23}H_{48}N_2Sn$ C: 58.61, H: 10.26, N: 5.94; Found C: 58.58, H: 10.32, N: 5.98.
6. The isomeric ratios were determinated by ^{1}H NMR spectrum integration.
7. Spectroscopic data for **3d**: mp: 35-40°C; ^{1}H NMR ($CDCl_3$, TMS, 400MHz) δ 1.49 (s,3H), 1.58 (m,6H), 1.81 (s,3H), 2,19 (m,2H), 2.39 (s,2H), 2.80 (s,6H), 5.78 (s,1H), 7.4 (s,1H). ^{13}C NMR ($CDCl_3$, 100MHz) δ 19.90 (CH_3), 25.35 (CH3), 26.94 (CH_2), 27.68 (CH_2), 28.13 (CH_2), 30.07 (CH_2), 32.05 (CH_2), 43.18 (C), 122.34 (CH), 127.05 (C), 133.77 (C), 135.55 (HCN), 141.54 (C). MS m/z: 220 (M^+,34), 205 (43), 176 (92). Analysis Calcd. for $C_{14}H_{24}N_2$ C: 76.31, H: 10.97, N: 12.71; Found C: 76.78, H: 10.56, N: 12.37. The X Ray data can be obtained upon request from the authors.
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(*Received in France* 9 *March* 1994; *accepted* 30 *March* 1994)