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New Entry to γ-Butyrolactams by Free Radical Cyclization of N-Allyl-α-chloro-α-(methylthio)acetamides. Formal Total Synthesis of (±)-Pseudoheliotridane

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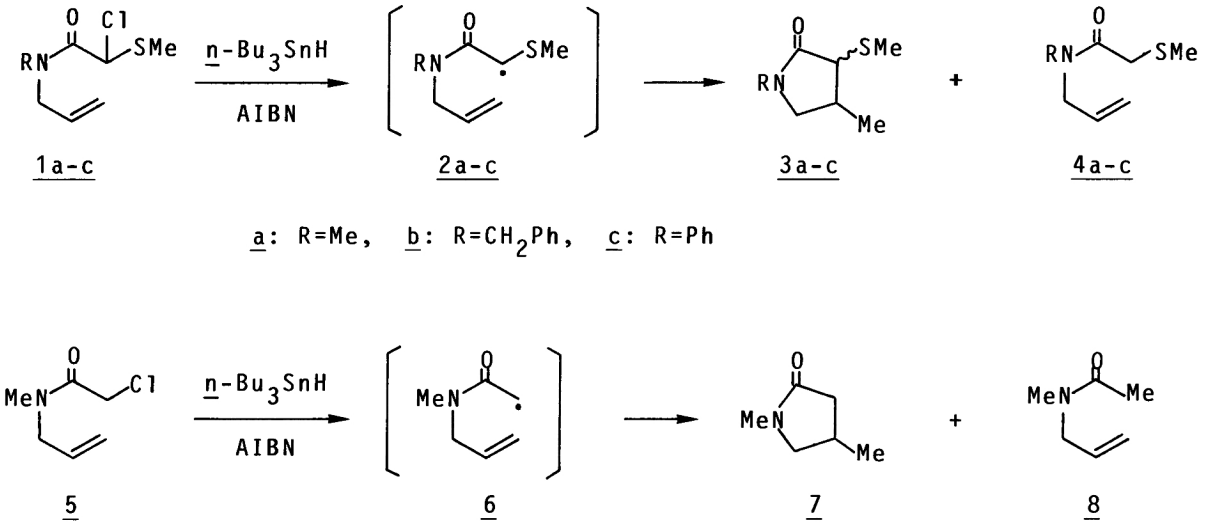
Tributyltin hydride-azobisisobutyronitrile induced radical cyclization of N-allyl-α-chloro-α-(methylthio)acetamides afforded γ-butyrolactams. This method was applied to the formal total synthesis of (±)-pseudoheliotridane.

Free radical cyclization is rapidly becoming an important synthetic method for cyclic compounds.[1,2] Although a number of radical species capable of ring closure with unsaturated bonds have been discovered so far, the use of sulfur-substituted radicals has received little attention.[3] Here, we wish to demonstrate the usefulness of the methylthio-substituted α-carbamoyl radical (2) as an initiator for radical olefin cyclization which provides a new route to γ-butyrolactams.

In a typical experiment, a mixture of tributyltin hydride (n-Bu_3SnH) (1.1 equiv.) and a catalytic quantity of azobisisobutyronitrile (AIBN) in benzene was injected over 30 min into a 0.06 M solution of the chloride (1a)[4] in refluxing benzene, and refluxing was continued for 2 h. Evaporation of the solvent followed by flash chromatography on silica gel (benzene:ethyl acetate=4:3) gave 1,4-dimethyl-3-methylthiopyrrolidin-2(1H)-one (3a) in 68% yield as a mixture of two stereoisomers (trans:cis=69:31) (vide infra) [δ ($CDCl_3$, 300 MHz) 1.15 (d, J=6.7 Hz, CMe for cis), 1.22 (d, J=6.8 Hz, CMe for trans), 2.23 (s, SMe for trans), 2.26 (s, SMe for cis), 2.87 (3H, s, NMe)], along with the reduction product (4a) (16%). This result is in sharp contrast to a similar treatment of the chloride (5) which gave only a 24% yield of the cyclized product (7)[5] together with the reduction product (8) (39%). It is generally accepted that the stabilized radicals are less reactive than the less stabilized radicals in the olefin cyclizations. This is,



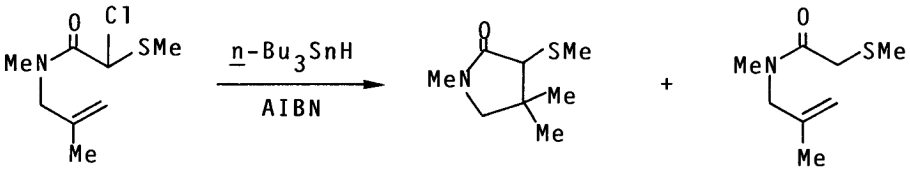
Scheme 1.

however, in conflict with our results, since the radical (2) flanked by a pair of capto-dative substituents[6] is expected to be more stable than the primary one (6).

Assignment of trans-stereochemistry for the major isomer of the cyclization product (3a) was made on the basis of the thermodynamic consideration. Thus, treatment of the mixture of 3a with sodium ethoxide in refluxing ethanol resulted in an increase in the amount of the major isomer [δ 2.23 (s, SMe)] at the expense of the minor one [δ 2.26 (s, SMe)] (87:13 by ^{1}H-NMR).[7] Earlier studies on the cyclizations of 1-substituted hex-5-enyl radicals have revealed that relatively stabilized radicals afford predominantly the trans products, while less stabilized radicals give cis-rich products.[8] This is the case for the cyclization of 2.

The cyclizations of the chlorides (1b) and (1c) also gave the lactams (3b) (80%) and (3c) (90%) along with the reduction products (4b) (12%) and (4c) (8%), respectively.[9]

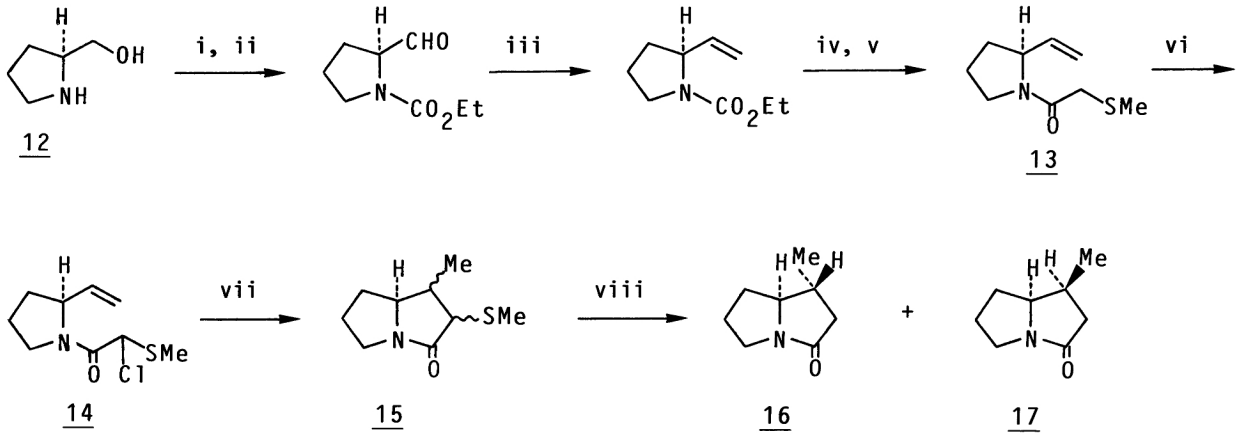
The 5-exo cyclization of the N-methallyl system (9) proceeded similarly, giving the pyrrolidinone (10) (68%) together with the reduction product (11) (15%). None of the 6-endo cyclization product was detected in the reaction mixture. In some cases, internal olefin substitution leads to enhanced endo cyclization for steric reason.[10] The present example is a rare case of the exclusive formation of the exo-cyclization product.[11]



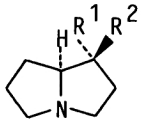
9 10 11

Scheme 2.

Finally, we applied this method to the synthesis of a pyrrolizidine ring system. Thus, treatment of the chloride (14), which was prepared from L-prolinol (12) as outlined in Scheme 3, with n-Bu_3SnH and AIBN gave the hexahydro-3H-pyrrolizin-3-one (15) in 60% yield together with the reduction product (13) (24%). The lactam (15) was shown to be a mixture containing two or more diastereoisomers by ^{1}H-NMR spectroscopy. Desulfurization of the compound (15) with Raney nickel afforded, in 80% yield, the 1α-methyl-lactam (16) [δ 1.16 (d, J=6.6 Hz, Me)], whose ^{1}H-NMR spectrum (300 MHz) showed it to contain a trace amount (<5%) of the corresponding 1β-methyl isomer (17) [δ 0.98 (d, J=7 Hz, Me)]. Chromatographic separation of these isomers and their reduction leading to (±)-pseudoheliotridane (18) and (±)-heliotridane (19), respectively, have been described in the literature.[12]



12 13 14 15 16 17



18: R^1=Me, R^2=H
19: R^1=H, R^2=Me

Scheme 3. i, $ClCO_2Et$, 4 M NaOH (91%); ii, DMSO, $(COCl)_2$, Et_3N, CH_2Cl_2, -60 °C (90%); iii, $Ph_3\overset{+}{P}MeBr^-$, $NaCH_2S(O)Me$, DMSO (83%); iv, KOH, $NH_2NH_2\cdot H_2O$, $(CH_2OH)_2$, reflux; v, $MeSCH_2COCl$, Et_3N, Et_2O (iv and v, total 60%); vi, NCS, $CHCl_3$ (quant.); vii, n-Bu_3SnH, AIBN, C_6H_6, reflux; viii, Raney Ni (W-2), EtOH, reflux.

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4) The chlorides (1) were prepared by acylation of the corresponding allylamines with α-(methylthio)acetyl chloride and Et_3N in diethyl ether followed by treatment of the resultant amides (4) with N-chlorosuccinimide (NCS) in CCl_4.

5) IR (CCl_4): 1690 cm^{-1}, ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 1.13 (3H, d, J=6.7 Hz, CMe), 2.01 (1H, dd, J=16.0, 6.4 Hz, one of $COCH_2$), 2.35-2.54 (1H, m, CHMe), 2.55 (1H, dd, J=16.0, 8.6 Hz, one of $COCH_2$), 2.83 (3H, s, NMe), 2.96 (1H, dd, J=9.6, 5.9 Hz, one of NCH_2), 3.49 (1H, dd, J=9.6, 7.7 Hz, one of NCH_2). This compound was identical with that obtained by desulfurization (Raney Ni) of 3a.

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7) For analogous isomerizations of 3-methylthio-4-substituted pyrrolidin-2-ones, see H. Ishibashi, M. Ikeda, H. Maeda, K. Ishiyama, M. Yoshida, S. Akai, and Y. Tamura, J. Chem. Soc., Perkin Trans. 1, in press.

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