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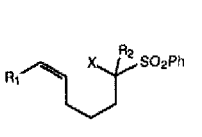
α-SULFONYL RADICAL INITIATED INTRAMOLECULAR TANDEM RADICAL CYCLIZATION

Vichai Reutrakul*, Chompoonut Poolsanong and Manat Pohmakotr

Department of Chemistry, Faculty of Science, Mahidol University,
Rama VI Road, Bangkok 10400, Thailand.

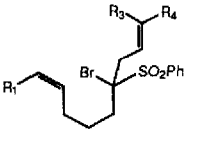
SUMMARY: Suitable derivatives of hex-5-enyl α-sulfonyl radical undergo cyclization to produce complex cyclic systems by a multiple radical chain mechanism.

The construction of cyclic compounds by free radical methods has received much attention.[1] Syntheses of natural products and potentially useful synthetic intermediates utilizing radical cyclization reactions involving nucleophilic carbon centered radical as key steps have been reported.[2] A much less developed area is the use of electrophilic carbon radical in the carbon-carbon bond formation.[3] As part of our continuing study on the chemistry of α-halosulfonyl compounds,[4] we became interested in the reaction of α-sulfonyl radical for the formation of carbon-carbon bond. There have been scattered reports on the radical cyclization of α-sulfonyl radical.[5,6] Our investigation, involving both mono- and di-substituted radical species, represents the first report on the tandem radical cyclization initiated by the α-sulfonyl radical in which the cyclization chain is neither substituted nor containing a heteroatom.[7] The preliminary investigations on the radical reactions of compounds 1 to 7 are reported herein.



1 : R_1=H ; R_2=H
2 : R_1=H ; R_2=Me
3 : R_1=Ph ; R_2=H
4 : R_1=p-MeOC$_6$H$_4$; R_2=H

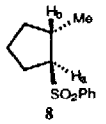
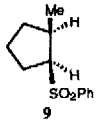
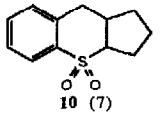
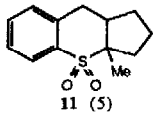
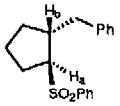
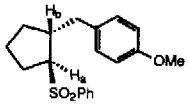
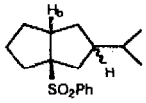
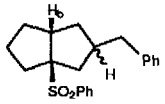
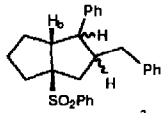
X = Br, I



5 : R_1=H ; R_3=R_4=Me
6 : R_1=H ; R_3=H ; R_4=Ph
7 : R_1=Ph ; R_3=H ; R_4=Ph

The reaction conditions-$NaCNBH_3$/Bu_3SnCl/AIBN/t-BuOH - was used for generating the radical and it was found that, in general, the α-bromosulfonyl compounds gave higher yields of the cyclized products and cleaner reaction mixtures than the corresponding α-iodosulfonyl derivatives. The results are summarized in Table 1.

Table 1 : Products of radical cyclization reaction using $NaCNBH_3$ / Bu_3SnCl / AIBN / t-BuOH[1]

Compound	Product (yield %)			
1	 **8** (22)[2]	 **9**	 **10** (7)	RP[4] (19)
2	-		 **11** (5)	RP[4] (33)
3	 **12** (39)		-	RP[4] (7)
4	 **13** (32)		-	RP[4] (6)
5	 **14** (35)		-	RP[4] (11)
6	 **15** (46)		-	RP[4] (10)
7	 **16a + 16b** (51)[3]		-	-

[1]The reactions were carried out at reflux for 4 h on 3 mmole scale with 0.024 M concentration.

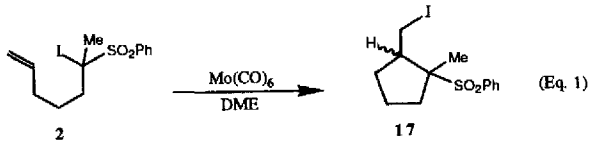
[2]Combined yield, ratio of 8:9 ca.9:1[(by NMR signals of methyl group at δ 0.98(for 8) and 1.30 (for 9)]. Pure 8 was obtained by careful PLC separation and the stereochemistry at the ring junction was determined by NMR. H_a appears at δ 3.05 (td, J_{ab} = 6.4 Hz), Me-group resonates at δ0.98 (d, J = 6.0 Hz) (Cf.ref.6b and 6g).

[3]Two isomers 16a:16b ca.1:1.2 (by PLC separation) with the same stereochemistry at the ring junction (see text).

[4]Reduction product.

The stereochemistries at the ring junctions of compounds[10] 12, 13, 14, 15 and 16 were determined by NMR. H_a proton of 12 and 13 appears at δ3.25 (td, J_{ab} = 6.0 Hz) and δ3.23 (td, J_{ab} = 6.0 Hz). The configurations of H_b proton and the phenylsulfonyl group of 14 and 15 were assigned as cis by analogy with 12, 13 and the clean quartet of H_b proton (δ3.10 for 14 and δ3.15 for 15).[11] Both isomers of 16 (16a and 16b) gave clean triplet of H_b proton at δ3.1 (16a) and δ3.05 (16b), hence the stereochemistry is assigned as indicated.

The products 10, 11, 14, 15 and 16 were originated from the tandem radical cyclization initiated by α-sulfonyl radical. It is noteworthy that in the case of compound 2, only cyclic product isolated was compound 10. Through an effort to find the suitable reaction conditions for the radical cyclization, it was found that the reaction of $Mo(CO)_6$/DME[12] with 2 (X=I) gave compound 17 in 31% yield (equation 1). This result represents the first reported case on iodine atom transfer cyclization catalyzed by such an organometallic complex.



2 17 (Eq. 1)

Further work on the refinement of the "TIN METHOD" for the tandem radical cyclization and the exploratory work on utilizing organometallic compounds to catalyze the atom transfer cyclization is in progress.

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7. The substituents and heteroatom on cyclizing chain are believed to facilitate the cyclization reaction: see ref. 6g and 2f.
8. The starting materials are conveniently prepared as follows: the monosubstitued α-halosulfones 1, 3 and 4 were prepared by the phase transfer catalytic alkylation of the α-halomethyl phenylsulfone with the appropriate bromoalkenes (TEBA/50% aq.NaOH/ benzene/24h). The dialkylated compounds 2, 5, 6 and 7 were prepared by the alkylation of the monosubstituted α-halosulfones with methyl iodide (for compound 2) and the appropriate allylic halides [LDA/THF:HMPA/-78° → RT(24h)].
9. G. Stork and P.M. Sher, J.Am.Chem.Soc., 108, 303(1986).
10. Structures of all reported compounds were rigorously established by spectral data and elemental analysis. High resolution NMR and ^{13}C spectra were recorded on a Bruker AM300.
11. Cf. G. Stork and P.M. Sher, J.Am.Chem.Soc., 105, 6765(1983).
12. Cf. (a) Ref.3; (b) T.K. Hayes, R. Villani and S.M. Weinreb, J.Am.Chem.Soc., 110, 5533 (1988).

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