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Annulation of the Cyclohexane Ring by Tandem Free Radical Alkylation of a Nonactivated δ-Carbon Atom–Intramolecular Carbanion Cycloalkylation

Goran Petrovic and Zivorad Cekovic*

Faculty of Chemistry, University of Belgrade, Studentski trg 16, P.O Box 158, 11000 Belgrade, Serbia, Yugoslavia

zcekovic@.chem.bg.ac.yu

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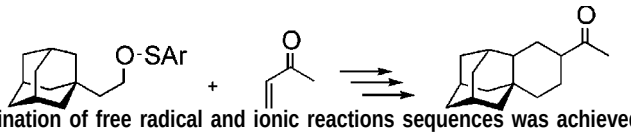
ABSTRACT

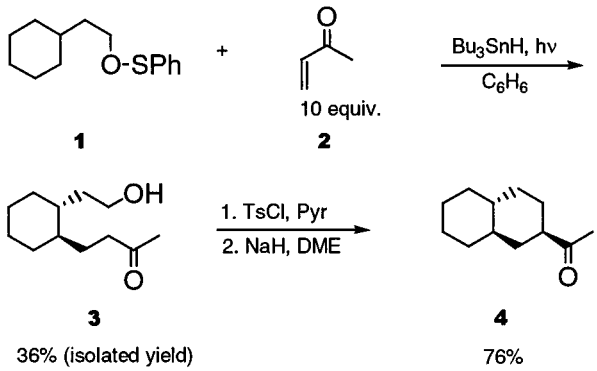


Annulation of the cyclohexane ring by a combination of free radical and ionic reactions sequences was achieved. Free radical alkylation of the remote nonactivated δ-carbon atom involves addition of δ-carbon radicals, generated by 1,5-hydrogen transfer in alkoxy radical intermediates, to radicophilic olefins, while the polar sequence involves enolate anions as intermediates which undergo a cycloalkylation reaction. Thus, the cyclohexane ring was constructed using diverse acyclic and cyclic structures as precursors of alkoxy radicals.

Recently we discovered that δ-carbon radicals, generated by 1,5-hydrogen transfer in alkoxy radical intermediates, undergo intermolecular addition to activated olefins with the introduction of a functionalized alkyl chain at a remote nonactivated carbon atom.[1−3] In these sequential free radical reactions, hydroxy compounds possessing an electron-withdrawing group at the 6-position are obtained, offering the possibility for cyclohexane ring closure by an intramolecular alkylation reaction involving enolate anions.

Herein a new method for the construction of the cyclohexane ring by free radical δ-alkylation of nonactivated carbon atoms and a subsequent anionic cyclization reaction, which could be complementary to the Robinson annulation, is described. Thus, starting from alkyl benzenesulfenate **1** as a precursor of alkoxy radicals and activated olefin **2**, annulation of cyclohexane ring **4** was achieved by a combination of a free radical sequence of reactions and an intramolecular carabanion alkylation reaction (Scheme 1).

Scheme 1



This cyclohexane ring annulation methodology was verified using various structurally different alkyl arenesulfenates as alkoxy radical precursors. Thus, substituted cyclohexane

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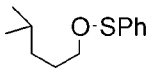
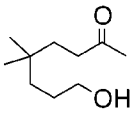
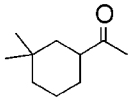
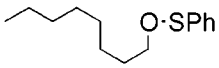
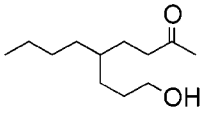
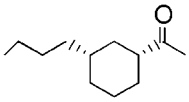
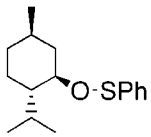
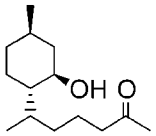
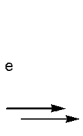
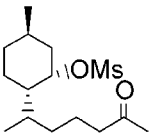
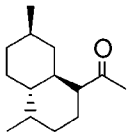
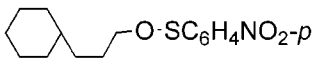
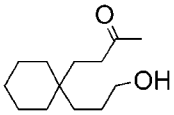
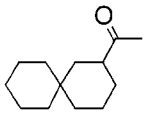
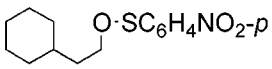
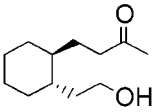
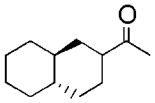
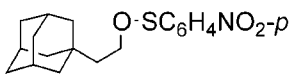
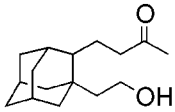
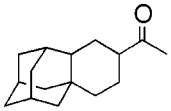
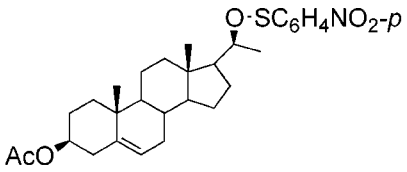
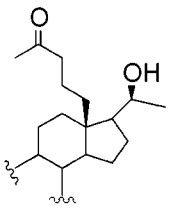
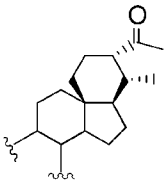
Table 1. Annulation of the Cyclohexane Ring by a Free Radical and Carbanionic Sequence of Reactions Using Methyl Vinyl Ketone as the Activated Olefin

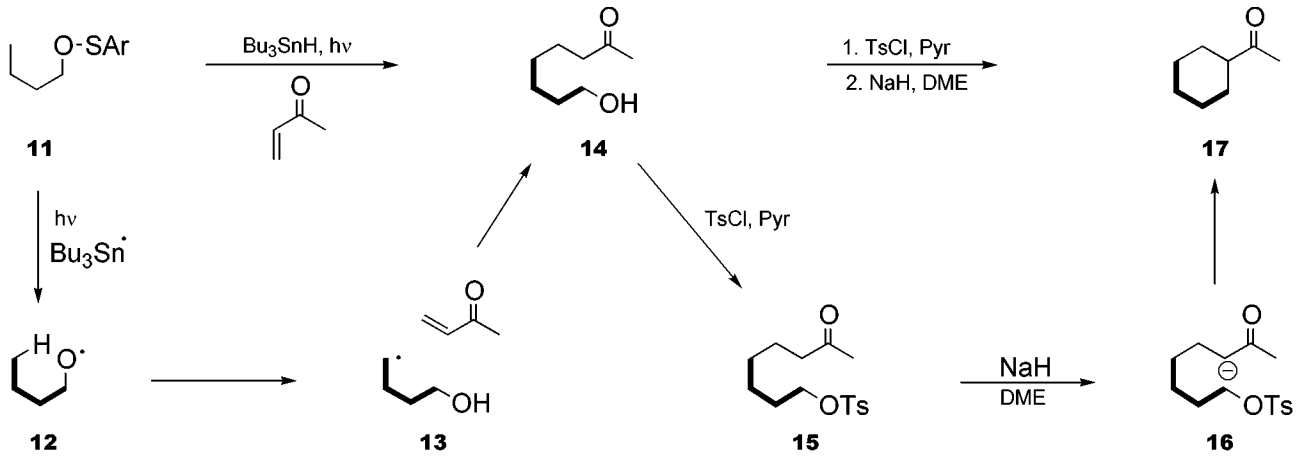
Alkyl arenesulfenates [a]	δ–Alkylated products (yields in %) [b]	Annulated (cyclic) products (yields in %) [b, c]
	 (41)	 (74) **5**
	 (35)	 (76) [d] **6**
 From (-) menthol	 (32) [e]  	 (53) [f] **7**
	 (47)	 (77) **8**
	 (36)	 (76) **4**
	 (42)	 (78) **9**
	 (27)	 (95) [g, h] **10**

[a] The alkyl benzenesulfenates were purified by destilation under reduced pressure, while the alkyl p-nitrobenzenesulfenates were purified by dry flash chromatography. [b] Isolated yields (yields by GC-analysis were 10-20% higher). [c] The hydroxyl group of the alkylated products was converted to the corresponding tosylates or mesylates (80-90% yields) and then the cycloalkylation reaction was carried out under basic condition. [d] Only the *cis*-isomer was obtained. [e] The equatorial hydroxyl group was isomerised to the axial epimer and then converted to the corresponding mesylate. [f] An elimination reaction occurs and the unsaturated compound was also formed (34%) (see Scheme 3). [g] The hydroxy ketone was converted to the corresponding mesylate before the cycloalkylation reaction. [h] During the work up procedure hydrolysis of the acetate group occurred and the product was characterized as a 3-hydroxy steroid derivative.

derivatives (**5** and **6**) were obtained by using open chain alkyl arenesulfenates and methyl vinyl ketone as an activated (radicophilic) olefin, while decaline derivative **4** was obtained from 2-cyclohexylethyl benzenesulfenate. By the appropriate selection of starting compounds, a spirobicyclohexane derivative (**8**) was prepared, and annulation of a cyclohexane ring on adamantane (**9**) and the steroid skeleton (**10**) was achieved (all results are summarized in Table 1.).

Alkyl arenesulfonates **11** were used as precursors of alkoxy radicals **12**.[1,4] The alkylation of the nonactivated δ-carbon atom was carried out by irradiation of the alkyl arenesulfenates in the presence of tributyltin hydride and 10 molar

Scheme 2



equiv of methyl vinyl ketone as the activated olefin **2**.[5] The δ-carbon radicals **13**, generated by 1,5-hydrogen transfer in the alkoxy radical **12**,[6] undergo intermolecular addition to give δ-alkylated products **14** (Scheme 2).[1,7] Products of the free radical alkylation at the δ-carbon atom were isolated and fully characterized.

The hydroxyl group in the alkylated products **14** was converted to the corresponding toluenesulfonate or methanesulfonate ester **15** by reaction with sulfonyl chlorides in pyridine.[8] In the next step, the sulfonate esters were reacted with sodium hydride in DME under equilibrium conditions and converted to the corresponding ketone enolate anions **16**. In the presence of a suitably disposed sulfonate leaving group, an intramolecular alkylation takes place and cyclohexane ring **17** is formed with an exocyclic electron-withdrawing group.[9] We propose that 8-*endo*-cycloalkylation, with the formation of the cyclooctane ring, could also occur if the formation of the enolate anion is performed under kinetic conditions.[10]

Cycloalkylation reaction of the open chain or cyclic sulfonate esters **15** with appropriate positions and stereochemical orientation of the reacting centers is a favorable reaction. However, when the stereochemical relations are not suitable for intramolecular alkylation, an elimination occurs as a side reaction to give unsaturated products.

The importance of stereochemistry in the cycloalkylation reaction was observed in the reaction of the enolate anion **18**, derived from a compound obtained by δ-alkylation of (−)-menthyl benzenesulfenate with methyl vinyl ketone. Possesing an equatorial leaving group, the enolate anion **18** does not undergo a substitution reaction but rather undergoes an elimination reaction to give the unsaturated compound.[11] To carry out the cycloalkylation reaction, the hydroxyl group in the δ-alkylated product obtained from (−)-menthyl benzenesulfenate was epimerized to the axial position (via the *p*-nitrobenzoate ester).[12] The enolate anion **19**, derived from the corresponding keto-methanesulfonate with an axial leaving group, undergoes intramolecular substitution to give the bicylic product **7**. However, in addition to the bicyclic product **7**, the unsaturated compound **20** was also formed as a product of the elimination reaction (yields of 53% and 34%,

(4) Beckwith, A. L. J.; Hay, B. P.; Williams, G. M. *J. Chem. Soc., Chem. Commun.* **1989**, 1202.

(5) **Typical experiment:** A solution of 3-cyclohexylpropyl-*O*-*p*-nitrobenzenesulfenate ester (0.15 g; 0.51 mmol), methyl vinyl ketone (0.35 g; 5.1 mmol; 10 equiv excess), and tributyltin hydride (0.16 g; 0.55 mmol) in benzene (40 mL) was irradiated at rt with visible light (xenon lamp 250 W, $\lambda > 300$ nm or by UV lamp) for 1 h in an argon atmosphere. After reaction was completed, the benzene was evaporated and the residual oil was dissolved in ether (50 mL) and washed with an aqueous NaF solution (0.5 g in 10 mL). The ethereal solution was separated and the aqueous solution extracted with ether (2 × 20 mL). The ethereal solutions were dried (anhydrous Na_2SO_4), and by evaporation of the ether, an oily alkylation product was obtained, which was dissolved in toluene and purified by dry flash chromatography using petroleum ether:acetone 95:5 as eluent. 4-[(3-Hydroxypropyl)cyclohexyl]butan-2-one was obtained as a pale yellow oil (50 mg; 47% yield). IR (film): 3405, 1713, 1596, 1519, 1459, 1416, 1358, 1339, 1164, 1057, 1018, 964, 918, 852, 822 cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz) δ: 0.91 (t, $J = 7.2$ Hz, 2H), 1.21−1.61 (m, 14H), 1/93 (s, broad, 1H), 2.16 (s, 3H), 2.29−2.38 (m, 2H), 3.61 (t, $J = 6.4$ Hz, 2H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ: 210.01, 63.52, 37.71, 35.58, 33.92, 3252, 30.42, 29.88, 27.67, 26.92, 26.27. 26.09, 21.41. The hydroxy ketone was converted to the corresponding tosylate which was treated with sodium hydride in DME to give 1-spiro[5.5]undec-2-ylethanone (**8**) as a colorless oil (10 mg; 77% yield). IR (film): 1709, 1451, 1372, 1354, 1270, 1236, 1189, 1164, 964, 903, 843 cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz) δ: 0.89−1.90 (m, 18H), 2.13 (s, 3H), 2.50 (tt, $J_{aa} = 12.2$ Hz, $J_{ae} = 3.4$ Hz, 1H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ: 212.84 (C), 46.68 (CH), 41.82, 38.75, 35.83 (CH_2), 32.65 (C), 32.14, 28.71 (CH_2), 27.93, (CH_3), 26.78, 21.47. 20.67 (CH_2). MS (CI): 195 (M + 1) 100%.

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(12) Martin, F. S.; Dodge, A. J. *Tetrahedron Lett.* **1991**, *26*, 3017.

respectively). It is well-known that the intramolecular cycloalkylation reaction is less favorable when the leaving group (i.e., sulfonate ester group) is attached to a secondary carbon atom and the elimination of the leaving group becomes a serious side reaction.[11]

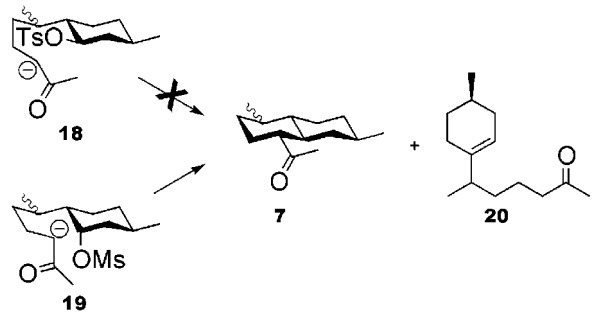
The 1,3-disubstituted cyclohexane derivative **6** obtained by the described sequence of reactions from an open chain nonbranched alkyl benzenesulfenate, such as *n*-octyl benzenesulfenates, has *cis*-stereochemistry because the "axial" interaction of the substituents disfavor the transition state leading to *trans*-1,3-disubstituted cyclohexane derivatives. One stereoisomer, **4**, was also obtained in the annulation of the cyclohexane ring starting from 2-(cyclohexyl)ethyl *p*-nitrobenzenesulfenate and methyl vinyl ketone because the addition of the intermediary cyclohexane-centered radical (of type **13**) to the methyl vinyl ketone preferentially takes place from the equatorial side to give the *trans* diequatorial intermediary product, which upon cycloalkylation gives the *trans*-decaline derivative **4** (see Scheme 1 and Table 1.).

Annulation of a cyclohexane ring into the steroid skeleton was realized by the free radical alkylation of the C-18 angular methyl group of pregnene-20β-*O*-*p*-nitrobenzenesulfenate derivative by methyl vinyl ketone followed by the intramolecular alkylation of the intermediary keto mesylate. Thus, ring E was constructed and the 18,20-ethanopregnene **10** derivative was obtained in 25.6% overall yield (Table 1).

The intermediary products of the free radical δ-alkylation, the tosylates and mesylates, as well as the products of annulation were completely characterized.

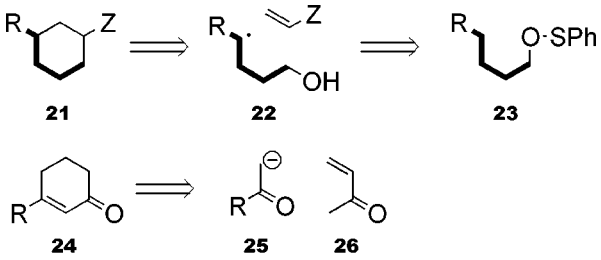
The described sequence of free radical and carbanion reactions offers a new method for annulation of a cyclohexane ring which requires two fragments: an activated olefin (i.e., Michael acceptor) and a four-carbon-atom chain, **22**, with a proalkoxy radical functional group, preferably alkyl

Scheme 3



arenesulfenates **23** (Scheme 3). The cyclohexane derivatives, **21**, formed by applying this methodology contain only an exocyclic electron-withdrawing group. Herein the presented method could be complementary to the Robinson annulation of the cyclohexenone ring,[14] **24**, which also requires two fragments: conjugated and saturated ketones **26** and **25** and two procarbanionic carbon atom (Scheme 4).

Scheme 4



Supporting Information Available: General experimental procedures and full characterization for compounds **5**, **6**, and **8**. This material is available free of charge via the Internet at http://pubs.acs.org.

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