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NOTE

A Vinyl Radical Cyclization Route to Hydroxycyclohexene Fused Carbocycles

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Some hydroxycyclohexene fused carbocycles derivatives were synthesized from 6-bromo-hepta-1,5-dien-4-ol derivatives using a mediator, tri-*n*-butyltin hydride (TBTH) and an initiator, azobisisobutyronitrile (AIBN) in refluxing benzene.

Keywords: Allylation, Radical cyclization, Hydroxycyclohexene fused carbocycles.

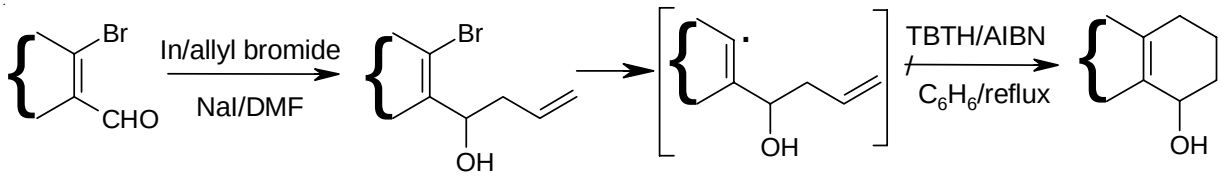
Radical reactions are now widely used in organic synthesis. However, deeper insight is still required for its application to the synthesis of the desired compounds. It is generally accepted that the rate of homolysis depends on bond dissociation energy and the homolytic cleavage of O-H bond demands higher energy than that of C-H bond [1]. Therefore to perform a radical cyclization or reduction, it is not necessary to protect a hydroxyl group and sometime radical reaction are carried out in protic solvent [2,3]. Radical induced cyclizations using tri-*n*-butyltin hydride/azobisisobutyronitrile represent alternative method for building alicyclic or heterocyclic ring. The initial step of a radical cyclization is the formation of a radical center on a molecule containing a radicophilic moiety [4]. This is the most crucial step in the process. Padwa *et al.* [5] have explored vinyl radical cyclization using N-alkenyl-7-bromo-substituted hexahydroindolinones.

There are also reports that oxidative radical cyclization of polyolefinic β-ketoester, a precursor of corresponding ketyl radical, yielded the steroid analogue *via* consecutive 6-*endo* cyclization [6a]. A similar reaction forming a steroidal skeleton from acyl radical was demonstrated by Pattenden *et al.* [6b]. However, the preparation of cyclopentenone derivatives by Heck reaction using $Pd(OAc)_2$ as catalyst was reported from our laboratory [7].

We wish to report here a TBTH/AIBN mediated cyclization of 6-bromo-hepta-1,5-dien-4-ol derivatives, which provide a highly efficient and novel route to hydroxyl cyclohexne fused carbocycles.

Indium-mediated Barbier-type allylation of bromovinyl aldehyde was reported earlier [8a-b]. We found that an allyl indium reagent *in situ* readily undergoes region selective addition to the carbonyl group of β-bromo-vinylaldehydes. Here our goal is to demonstrate an exclusive 6-*endo-trig* vinyl cyclization of 6-bromo-hepta-1,5-dien-4-ol derivatives as shown in **Scheme-I**. It is well known that a radical is commonly obtained by means of *n*-Bu_3SnH in presence of an initiator azobisisobutyronitrile.

Typical procedure of cyclization: In a mixture of compound **2a** (279 mg, 1 mmol) in super dry and degassed benzene (30 mL), a solution of AIBN (33 mg, 0.2 mmol) and TBTH (0.4 mL, 1.5 mmol) in dry and degassed benzene (20 mL) was added slowly for 2 h. After complete addition, it was refluxed for 6 h more. The solvent was removed under *vacuo* and it was diluted with saturated KF solution (50 mL) in diethylether (50 mL). It was stirred for 24 h. The organic layer was separated and washed with water. It was then filtered, dried over Na_2SO_4. And finally it was purified by column chromatograph (flash silica gel) using 10 % ethyl acetate in petroleum ether as eluent.

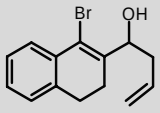
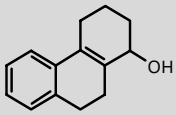
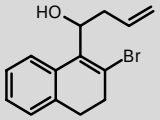
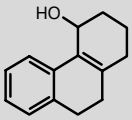
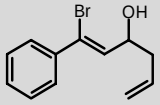
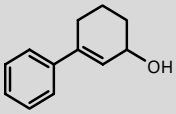
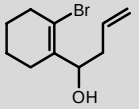
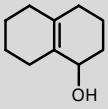
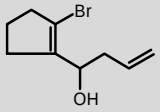
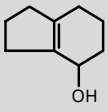
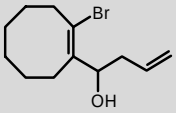
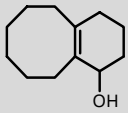


Scheme-I

The product was obtained as colourless crystalline solid, m.p. 137 °C. Yield: 124 mg, 62 %.

We exclusively got 6-*endo* product when we maintaining the concentration of the transferring reagent (n-Bu_3SnH) is 1.5 mL in 30 mL benzene. The solution of AIBN and TBTH in dry degassed benzene (20 mL) was added slowly for 2 h in the solution of compound (1 mol) in dry, degassed benzene. It was refluxed for 6 h more after complete addition. Purification of the desired product is problematic, that's why we purified the product by flash silica gel chromatography. We took a series of various types of keto compounds, open chain acetophenone (Table-1, entry 3), α-tetralone (Table-1, entry 1), cyclopentanone (Table-1, entry 5), *etc*. So we got a route to the preparation of hydroxycyclohexene fused carbocyles from these types of keto compounds as shown below in Table-1.

TABLE-1

Entry	Substrates	Products	Yield (%)	Time (h)
1	 **1a**	 **1b**	60	8
2	 **2a**	 **2b**	62	8
3	 **3a**	 **3b**	60	8
4	 **4a**	 **4b**	61	8
5	 **5a**	 **5b**	62	8
6	 **6a**	 **6b**	59	8

The structure of the compounds had been confirmed by spectroscopic and analytical data. The formation of the 6-*endo* products is a result of favourable activation enthalpy rather than activation of entropy. This region selectivity under enthalpy control is explained by conformation and electronic effects. The structure of product in one case was supported by X-ray data in case of β-tetralone as shown in Fig. 1.

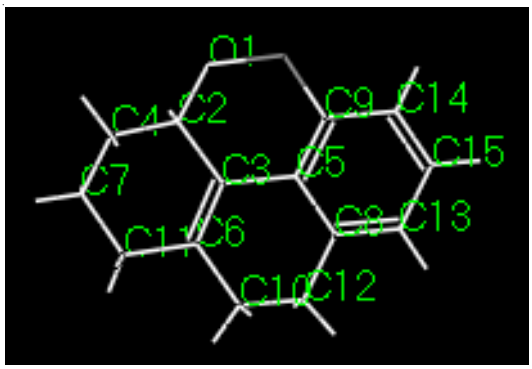


Fig. 1. ORTEP diagram

In summary, we have developed an effective TBTH/AIBN mediated protocol for the cyclization of an un activated olefin which may be useful for the construction of carbocycles. Further work is currently underway and will be reported in due courses.

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