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Generality and Mechanism of Homobenzylic-Homoallylic Hydrogenolysis of 5-Aryl-4,5-dihydro-1,3-dioxepins

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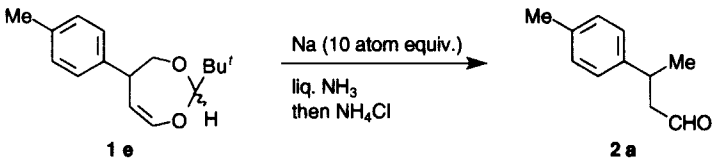
Abstract: Birch reduction of several 5-aryl-4,5-dihydro-1,3-dioxepins gave rise to 3-arylbutanal in moderate to good yields by hydrogenolytic cleavage of the homobenzylic-homoallylic carbon-oxygen bond when the benzylic-allylic carbon is tertiary. However, the reaction did not take place when the benzylic-allylic carbon is quaternary. Moreover, the reaction was found to proceed with complete racemization at the benzylic-allylic center indicating a concurrent elimination-reduction pathway to be involved.

We, recently, reported a new synthetic entry into the aromatic bisabolane sesquiterpenes by inadvertent discovery of an unprecedented hydrogenolytic cleavage reaction.[1] Thus, treatment of 2-*tert*-butyl-4,5-dihydro-5-(4-methylphenyl)-1,3-dioxepin (**1e**) under standard Birch conditions[2] using sodium in liquid ammonia furnished 3-(4-methylphenyl)butanal (**2a**), a common key intermediate of the natural products, in a satisfactory yield after quenching the reaction with ammonium chloride (**Scheme 1**). In order to extend this reaction for the synthesis of a variety of substituted butanal derivatives, we investigated the reaction using some typical substituted 5-aryl-4,5-dihydro-1,3-dioxepin derivatives[1,3,4] including a chiral substrate. We now report the results which indicate generality and mechanism of the reaction.

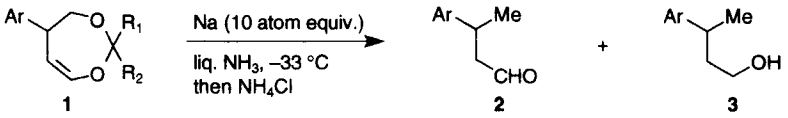


1e **2a**

Scheme 1

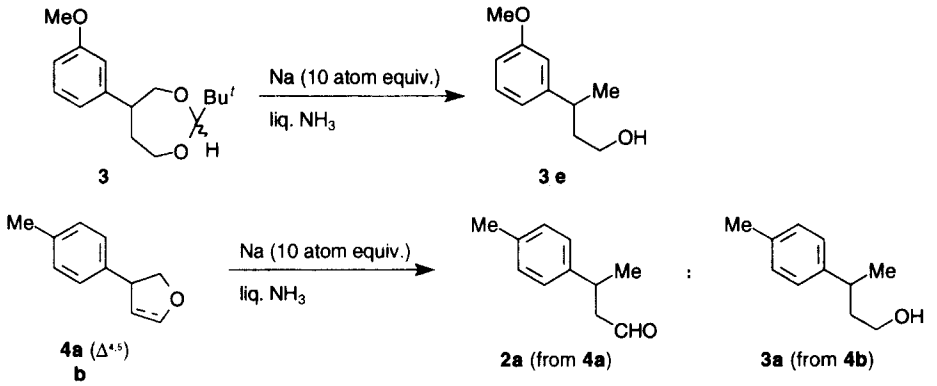
We first examined the reaction in a liquid ammonia in the presence of sodium metal using the substrates (**1**) bearing a tertiary benzylic-allylic center having a variety of 2-substituents. In all cases, a smooth hydrogenolysis occurred at the homobenzylic-homoallylic carbon-oxygen bond to give the corresponding 3-arylbutanals (**2**) in moderate to good yields, in some cases, accompanied by a minor amount of the overreduced products[4] (**3**). Virtually, the substituent(s) on C-5 aromatic ring and C-2 center did not affect on the reaction though the yields were significantly diminished in the substrates bearing no substituent on C-2 center (Entries 2~4). Addition of a proton source such as ethanol or *tert*-butanol rather made the reaction more complex and gave a bad mixture (**Table 1**).

Table 1. Birch Reduction of 5-Aryl-4,5-dihydro-1,3-dioxepins (**1**)



		Substrate				Product (**2**)			Product (**3**)	
Entry		R_1	R_2	Ar		Ar	(%)		Ar	(%)
1	a:	H	H	4-Me	a:	4-Me	(67)	a:	4-Me	(6)
2	b:	H	H	H	b:	H	(49)			
3	c:	H	H	4-MeO	c:	4-MeO	(54)			
4	d:	H	H	2-NHAc	d:	2-NHAc	(49)			
5	e:	*t*-Bu	H	4-Me	a:	4-Me	(70)	a:	4-Me	(8)
6	f:	*t*-Bu	H	4-MeO	c:	4-MeO	(66)			
7	g:	*t*-Bu	H	3-MeO	e:	3-MeO	(61)			
8	h:	*t*-Bu	H	2-MeO	f:	2-MeO	(82)			
9	i:	Me	Me	4-Me	a:	4-Me	(81)			
10	j:	$-(CH_2)_4-$		4-Me	a:	4-Me	(78)			
11	k:	$-(CH_2)_5-$		4-Me	a:	4-Me	(70)	a:	4-Me	(8)
12	l:	$-(CH_2)_5-$		4-MeO	c:	4-MeO	(61)			

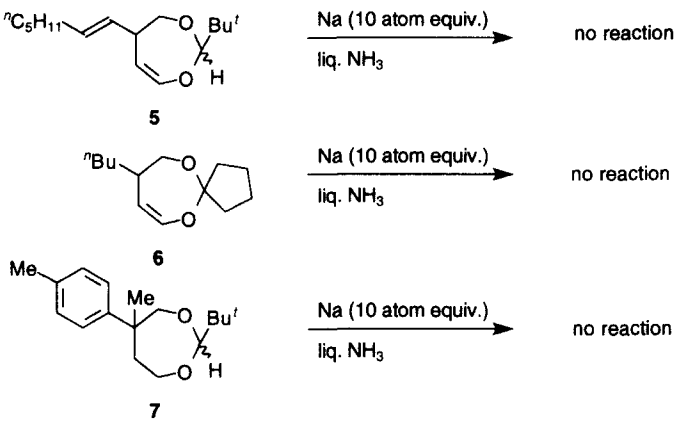
Interestingly, the tetrahydrooxepin (**3**) as well as the 3-aryl-2,3-dihydrofuran[5] (**4a**) and 3-aryltetrahydrofuran (**4b**) furnished the corresponding cleavage products, **3e**, **2a** and **3a**, indicating that neither the homoallylic double bond nor the dioxepin ring is essential for the reductive cleavage (**Scheme 2**).



Scheme 2

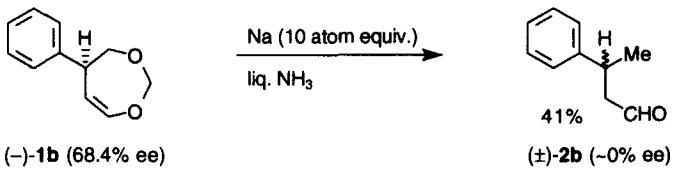
However, the reaction did not proceed without presence of 5-aryl group since the substrates, **5** and **6**, bearing 5-alkenyl[6] or 5-alkyl group in place of 5-aryl group were found to be inert under the same conditions.

Moreover, the reaction did not occur at all with the 5,5-disubstituted tetrahydrooxepin substrate[7] (**7**) even though 5-aryl group existed (**Scheme 3**).



Scheme 3

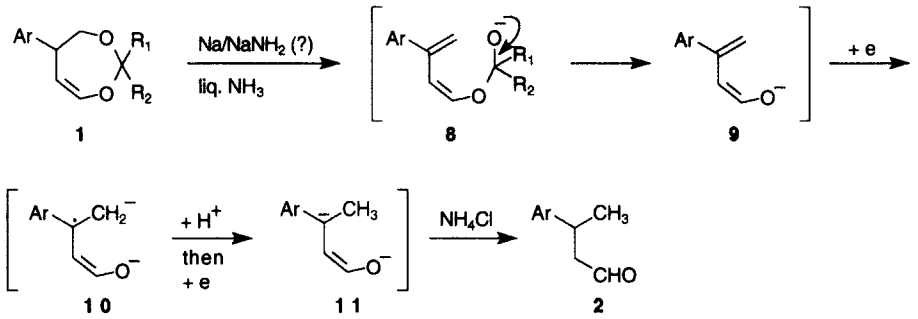
More interestingly, when the optically active substrate[8] [(–)-**1b**] (68.4% ee)[8,9] was subjected to the same reaction conditions, the original chiral integrity was lost completely during the reaction to afford the racemic aldehyde[9] [(±)-**2b**] (**Scheme 4**).



Scheme 4

Taking these results into account, we assume that the hydrogenolytic reaction occurred through a concurrent elimination-reduction pathway. Namely, the homoallylic oxygen bond was first cleft presumably by sodium amide present in a reaction medium to generate sequentially **8** and **9**, the latter of which was then reduced to a dianion (**11**) *via* a radical anion (**10**) by sequential one-electron reduction, proton abstraction from ammonia by forming an amide ion (or from the liberated carbonyl compound by forming an enolate ion), and one-electron reduction. Finally, acid workup led to a formation of a 3-arylbutanal (**2**) from the dianion (**11**) by protonation. When the reaction was carried out in the presence of sodium amide, prepared in the same reaction medium, in place of sodium metal, a 3-aryl-2-butenal could be isolated as a *E/Z*-mixture which may be generated from a conjugated enolate (**9**) by protonation (Ar=3- or 4-methoxyphenyl, R_1=*tert*-butyl, R_2=H) (**Scheme 5**).

In conclusion, we have shown that 5-aryl-4,5-dihydro-1,3-dioxepins can be reductively cleft at the homobenzylic-homoallylic oxygen bond *via* an elimination-reduction pathway only when the benzylic-allylic center is tertiary though the allylic double bond not always to be essential.



Scheme 5

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2. A pertinent review, see: Rabideau, P. W.; Marcinow, Z. *Org. React.* **1992**, *42*, 1.
3. 5-Aryl-4,5-dihydro-1,3-dioxepins were prepared by Heck reaction between the aromatic iodides and 2-substituted-4,7-dihydro-1,3-dioxepins. cf. Heck, R. F. *Org. React.* **1982**, *27*, 345; Heck, R. F. *Palladium Reagents in Organic Synthesis*; Academic Press: New York, 1985.
4. A typical procedure: To a stirred solution of **1i** (113 mg, 0.518 mmol) in liq. NH_3 (15 ml) and THF (1 ml) was added sodium metal (119 mg, 5.18 m atom) portionwise at –33 °C. After having faded blue color (~1 h), NH_4Cl was added and the mixture was left until most of NH_3 had evaporated. The residue was dissolved in water and extracted with ether. After usual workup, a crude product was purified on a silica gel column (10 g, elution with 10:1 v/v hexane-Et_2O) to give the aldehyde (**2a**) (68 mg, 81%) as a colorless oil.
5. Larock, R. C.; Baker, B. E. *Tetrahedron Lett.* **1988**, *29*, 905.
6. cf. Takano, S.; Samizu, K.; Ogasawara, K. *J. Chem. Soc., Chem. Commun.* **1993**, 1032; Takano, S.; Samizu, K.; Ogasawara, K. *Synlett* **1993**, 785.
7. Prepared from 4-methylphenylacetonitrile in 6 steps employing standard procedure.
8. Koga, Y.; Sodeoka, M.; Shibasaki, M. *Tetrahedron Lett.* **1994**, *35*, 1227.
9. Determined by HPLC (Chiralcel OD, elution with 1:50 v/v *i*-PrOH-hexane).

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