Boron Trifluoride Etherate Mediated Dehydrogenative Nucleophilic Addition Reaction of Aliphatic Ethers in the Presence of Acetal Affording α,β-Unsaturated Carbonyl Compounds

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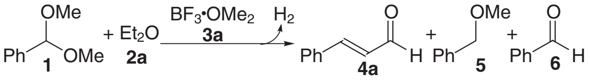
In the presence of boron trifluoride etherate, some kinds of aliphatic ethers have been found to react with benzaldehyde dimethyl acetal yielding α,β-unsaturated carbonyl compounds with evolution of H_2. In this reaction, dehydrogenation of the ether undergoes in cooperation with the acetal and BF_3, which enables the ether molecule to behave as enol ether equivalent affording crossed aldol adduct via nucleophilic attack to oxycarbenium ion electrophile formed from the acetal.

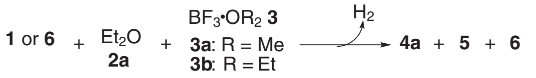
In the course of our study on the acid-mediated arylation reaction of in situ formed active oxycarbenium ion equivalents,[1] we have unexpectedly found that cinnamaldehyde (**4a**) and benzyl methyl ether (**5**) are formed and hydrogen gas[2] is evolved when benzaldehyde dimethyl acetal (**1**) is allowed to react with Et_2O (**2a**) in the presence of $BF_3 \cdot OMe_2$ (**3a**) (Scheme 1, Entry 1 in Table 1).



Scheme 1.

On the other hand, benzaldehyde (**6**) has been found inert to this reaction (Entry 2 in Table 1). Furthermore, treatment of acetal **1** with **3a** in the absence of Et_2O (**2a**) gave no adducts (Entry 3 in Table 1). Conversely, when $BF_3 \cdot OEt_2$ (**3b**) was treated with acetal **1** in the absence of **2a**, **4a** was obtained with evolution of H_2 (Entry 4 in Table 1). These results show that Et_2O does not react with **6** but reacts with the corresponding acetal (**1**) as the carbon source for **4a**.

Table 1. Reaction of acetal **1** with **2a** in the presence of $BF_3 \cdot OR_2$ (**3**) and related reaction[a]



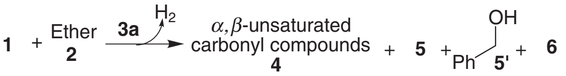
Entry	**1** or **6**	**2a**/ mmol	BF_3 Etherate	H_2[b]	Product Distribution/%[c]		
					4a	**5**	**6**
1	**1**	20	**3a**	+	12	16	72
2	**6**	20	**3a**	-	-	-	100
3	**1**	0	**3a**	-	-	2	98
4	**1**	0	**3b**	+	43	40	17

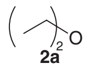
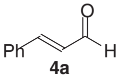
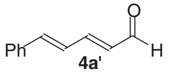
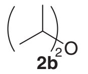
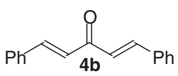
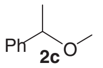
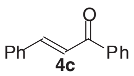
[a] Reaction conditions: acetal **1** or **6**, 2 mmol; $BF_3 \cdot OR_2$, 12 mmol; CH_2Cl_2, 20 mL; 25 °C, 3 h, under a N_2 atmosphere.
[b] Evolution of H_2 was confirmed by the aid of gas indicator tube; sign plus denotes evolution of H_2 and minus denotes not.
[c] Calculated on the basis of ^{1}H NMR spectrum.

Table 2 shows the results of the reaction of several ethers (**2**) with acetal **1** in the presence of **3a**. Acyclic ethers **2a**–**2c** have capability to react with acetal **1** giving the corresponding α,β-unsaturated carbonyl compounds (**4**) and H_2 (Entries 1–3 in Table 2). In contrast, THF (**2d**) gives no α,β-unsaturated carbonyl compounds (Entry 4 in Table 2).

The formation of α,β-unsaturated carbonyl compounds **4** from acetal **1** and saturated aliphatic ethers **2** means that ethers **2** are oxidized to enol ether equivalents in this system. In general, α,β-unsaturated carbonyl compounds are obtained by crossed aldol type condensations. Actually, treatment of benzaldehyde dialkyl acetals with vinyl ethers in the presence of Lewis acids affords cinnamaldehyde homologs.[3] Furthermore, the reaction of α-deutrated diisopropyl ether (**7**) with acetal **1** in the presence

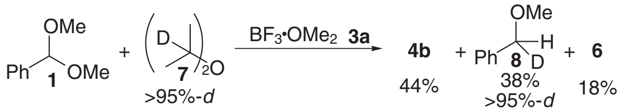
Table 2. $BF_3 \cdot OMe_2$ (**3a**) mediated reaction of acetal **1** with ethers **2**[a]



Entry	Ether	H_2[b]	Product Distribution/%[c]			
			4	**4**	**5'**	**6**
1	 **2a**	+	 **4a**	19	52	12	8
			 **4a'**	9			
2	 **2b**	+	 **4b**	59	31	8	2
3[d]	 **2c**	+	 **4c**	27	14	0	59
4	 **2d**	-	-		24	0	76

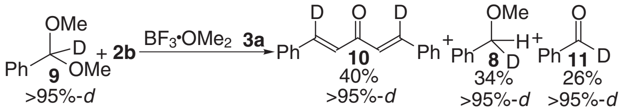
[a]Reaction conditions: acetal **1**, 0.5 mmol; **3a**, 3 mmol; **2**, 5 mmol; 25 °C, 3 h, under a N_2 atmosphere. [b,c]See footnotes b and c in Table 1. [d]CH_2Cl_2 (5 mL) was added as solvent.

of **3a** have been found to afford α,β-unsaturated carbonyl compound **4b** and α-monodeutrated benzyl methyl ether (**8**) (Scheme 2). This result indicates that the α-hydrogen (deuterium) of ethers are oxidatively eliminated as a hydride (deuteride), and a part of the hydrides (deuterides) behave as reductant of acetal **1** to form benzyl methyl ethers **5** and **8**.



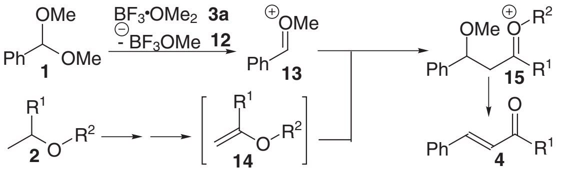
Scheme 2.

In addition, the fact that the reaction of α-deutrated acetal **9** with ether **2b** gave β-deutrated α,β-unsaturated carbonyl compound (**10**) and **8** shows that the hydride source in this reaction is α-hydrogen in the ethers and α-hydrogen of acetal does not function as a hydride such as the acid mediated Cannizzaro reaction[4] (Scheme 3).



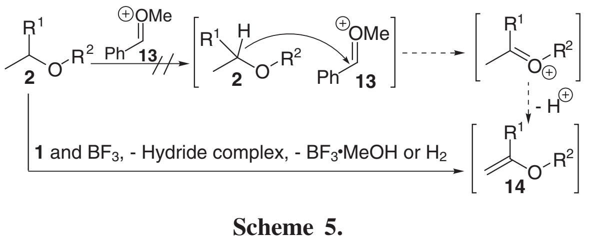
Scheme 3.

Consequently, saturated aliphatic ethers **2** are found to be dehydrogenatively transformed and to react as an equivalent of enol ether species **14** with the electrophile such as oxycarbenium ion **13** to afford α,β-unsaturated carbonyl compound **4** (Scheme 4).



Scheme 4.

On the other hand, there remains the specification of the reaction route where ether **2** is dehydrogenated to behave like enol ether species **14** (Scheme 5). One of possible two routes is the hydride abstraction from ether **2** by oxycarbenium ion **13** followed by proton release. The other is the hydride abstraction by dissociated BF_3 followed by proton release.



Scheme 5.

Inadequacy of the former route is ascertained on the basis of the fact of evolution of H_2. Direct capture of hydride from alkyl ether **2** by oxycarbenium ion **13** to give benzyl methyl ether (**5**) is inconsistent with the formation of H_2. The evolution of H_2 is only explained by the existence of a hydride complex to react with a proton source. In addition, if the reaction proceeded via the former route, **5** should be produced more than α,β-unsaturated carbonyl compounds **4**. Thus, formation of α,β-unsaturated carbonyl compounds **4** more than benzyl methyl ether (**5**) also indicates inadequacy of the former route (Entries 2, 3 in Table 2).

In the latter route, dissociated BF_3 abstracts hydride from aliphatic ether **2**. However, if dissociated BF_3 by itself were able to abstract hydride, enol formation should be generally observed in other $BF_3 \cdot OEt_2$ solutions. So, in this step, hydride abstraction from aliphatic ether **2** by dissociated BF_3 probably achieves in cooperation with proton abstraction by an ate complex of BF_3, i.e., hydride complex or F_3B^-–OMe (**12**), which is formed via the reaction of BF_3 and acetal **1**. As a result of abstraction of proton and hydride, $BF_3 \cdot MeOH$ or H_2, and hydride complex are formed. The hydride complex reacts with proton source to generate H_2 or attacks oxycarbenium ion **13** to form **5**. Consequently, oxidative transformation of ether **2** is suggested to undergo via the latter route. Distinguished difference in reactivity of acetal **1** and **6** strongly supports the involvement of **12** in this reaction.

To the best of our knowledge, the formation of α,β-unsaturated carbonyl compounds from ethers and acetals has never been reported. As the only one related reaction, Arulraj and Alphonse have reported the self-condensation of benzaldehyde dialkyl acetals catalyzed by $BF_3 \cdot OEt_2$, where cinnamaldehyde derivatives are formed via disproportionative crossed aldol condensation of an oxycarbenium ion formed from acetal and an enolate equivalent also generated from the alkoxy moiety in acetal.[5] In their report, the carbon source of cinnamaldehyde is only restricted to acetals and possibility of ether to react is never considered. On these bases, the addition reaction of aliphatic ether as enol ether species reported herein is extraordinary unique reaction behavior.

Conclusively, anomalous conversion behavior of saturated aliphatic ethers reacting as equivalents of enol ether species in cooperation with acetal and boron trifluoride etherate is disclosed. Further work on clarification of the determining factors for transformation of ethers into active enol ether equivalent species, the reaction mechanism, the scope of the reaction, and the limitation of ethers to this reaction is currently being undertaken.

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