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Aldol Reaction of Aromatic Acetals with Cyclic and Acyclic Alkyl Enol Ethers by Electrogenerated Acid (EG Acid) as a Catalyst

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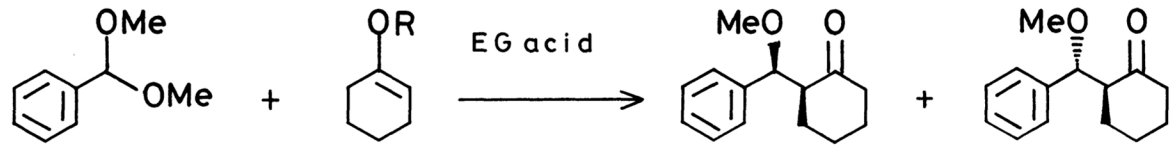
Aldol reaction of aromatic acetals with alkyl enol ethers proceeds efficiently with electrogenerated acid (EG acid) independently prepared in an MeCN-$NaClO_4$/Bu_4NClO_4-(Pt) system.

The directed aldol reaction with enolates has well been utilized in the selective carbon-carbon bond formation.[1] In contrast to a bewildering array of reports dealing with metal enolates or enol silyl ethers as a nucleophilic counter part, alkyl enol ethers have found limited use due in part to their low reactivity toward carbonyl functions.[2] However, the current interest in providing an alternative access to valuable α,β-unsaturated aldehydes from easily available enol ethers has led to the development of new acid catalysts such as $TrClO_4$,[3] Montmorillonite Clay K-10,[4] and Lewis acids.[5] In this regard, the electrogenerated acid (EG acid) is also an attractive catalyst owing to its high oxygenophilic ability.[6] We report here an EG acid-catalyzed aldol reactions of aromatic acetals with alkyl enol ethers.

The EG acid prepared in the anodic compartment of a divided cell was used and the effect of the solvent-electrolyte system was firstly examined. Thus, potentiality of the EG acid was assayed by the reaction of 1-methoxy-1-cyclohexene (**2a**) and benzaldehyde dimethyl acetal (**1a**). As shown in entry 1 of Table 1, the best result was provided by the EG acid of an MeCN-$NaClO_4$/Bu_4NClO_4 system. $LiBF_4$, $NaPF_6$, and $NaSbF_6$ can be used as a source of EG acid in the same electrolysis medium (entries 4-6), while Et_4NOTs is not effective at all.

Prior to the present work, we have reported that the EG acid-catalyzed aldol reaction of enol silyl ether **2b** and **1a** yielded a 86:14 mixture of erythro/threo (e/t) isomers **3**.[7] It is of interest to note that the product ratio changes from 86/14 to 35/65 when alkyl enol ether **2a** is employed. In addition, the aldol reaction of 2-furfuryl aldehyde dimethyl acetal (**1d**) with **2a** gave 61:39 e/t ratio, a rather low selectivity compared with 93:7 e/t ratio[7] obtained with **2b**. These results imply a different reaction pathway from that of an acyclic transition state suggested in the reaction of enol silyl ether **2b**. Although the mechanism is not clear yet, it is likely that the present reaction would partially proceed by a mechanism involving cyclic transition states similar to that proposed to the aldol reaction of metal enolates.[8]



1a 2a R = Me 2b R = $SiMe_3$ 3 erythro 3 threo

Table 1. The Effect of Electrolytes[a)]

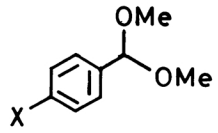
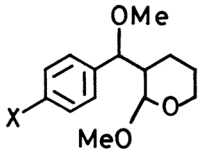
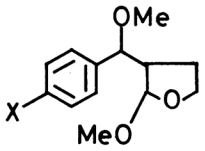
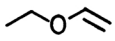
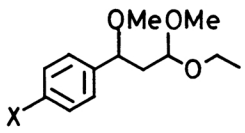
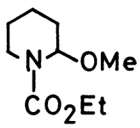
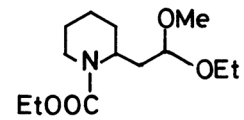
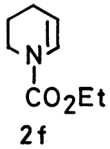
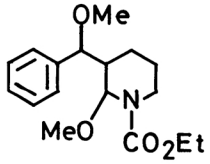
Entry	Electrolyte	Yield of 3/%	Erythro/Threo[b)]
1	$NaClO_4/Bu_4NClO_4$	95	35/65
2	$LiClO_4$	94	34/66
3	Bu_4NClO_4	82	38/62
4	$LiBF_4$	50	38/62
5	$NaPF_6$	44	47/53
6	$NaSbF_6$	43	38/62
7	Et_4NOTs	-	-

a) Electrolyses were carried out in a divided cell.
b) Determined by ^1H NMR at 500 MHz.[9)]

The EG acid-catalyzed reaction of alkyl enol ethers is not applicable to acetals of aliphatic aldehydes. Furthermore, we have found that the EG acid is superior to other acid-catalysts such as $TrClO_4$[10)] (electrochemically prepared one: 71% yield, e/t = 36/64) and Ph_3SiClO_4[10)] (82% yield, e/t = 34/66). In order to clarify the potentiality of EG acid as an acid-catalyst, we examined a variety of aldol reactions. As exemplified in Table 2, the homologations of aromatic aldehyde acetals are easily achievable by using a catalytic amount of the EG acid. In contrast to the aldol reaction of enol ether **2a** prepared from ketone, adducts of dihydropyran and its analogues are usually produced as a form of acetals, which never underwent further addition of enols. As shown in entry 10, the reaction of N,O-acetal **1e** with ethyl vinyl ether (**2e**) gave the corresponding adducts in good yield. Interestingly, the enamine **2f** prepared from N,O-acetal **1e** is useful as a nucleophilic substrate in this aldol reaction (entry 11). The products obtained from vinyl ether **2e** are valuable intermediates in the synthesis of cinnamaldehyde derivatives.[4)]

Typical procedure is as follows. A solution of $NaClO_4$ (240 mg, 2.0 mmol)

Table 2. The reaction of Acetals **1** with enol ethers **2**

Entry	Acetals 1	Enol Ethers 2	Products 4	Yield of 4 / %	
					
1	X = H 1a	2b	X = H 4a	87	
2	OMe 1b		OMe 4b	96	
3	t-Bu 1c		t-Bu 4c	89	
					
4	1a	2d	X = H 4d	45	
5	1b		OMe 4e	53	
6	1c		t-Bu 4f	53	
					
7	1a	2e	X = H 4g	51	
8	1b		OMe 4h	62	
9	1c		t-Bu 4i	72	
10	 1e		 4j	62	a)
11	1a	 2f	 4k	70	

a) A ca. 1:2 mixture of acetal and aldehyde was obtained.

and Bu_4NClO_4 (680 mg, 2.0 mmol) in dry MeCN (20 ml) was divided into two exact halves and each of them was added to both compartments of an H-type divided electrolysis cell. The mixture was electrolyzed under a constant applied voltage of 20 V with two platinum electrodes (1.5 cm^2 x 2) at room temperature. The electrolysis was continued until 1.5 F/mol (based on $NaClO_4$ in the anodic room) of electricity was consumed. From the anolyte was taken 1 ml of aliquot which was then added to a solution of benzaldehyde dimethyl acetal (**1a**, 148 mg, 1.0 mmol) and 1-methoxy-1-cyclohexene (**2a**, 134 mg, 1.2 mmol) in CH_2Cl_2 (3ml) at -78 °C. The mixture was stirred for 20 min and quenched with aqueous $NaHCO_3$. The product was extracted with AcOEt and the extracts were washed with brine and dried (Na_2SO_4). Concentration followed by purification by column chromatography (SiO_2, Hexane:AcOEt) gave 155 mg (71%, e/t = 36/64) of the desired **3a**.

The present procedure based on the EG acid-catalyst is highly beneficial in terms of short reaction time (usually 20-30 min) at low temperature (-78 to -60 °C), high yields, and reasonable material balance at the starting[5] (the reaction is achievable with a slight excess enol ethers).

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