An Unprecedented, Tandem Aldol−Grob Reaction Sequence

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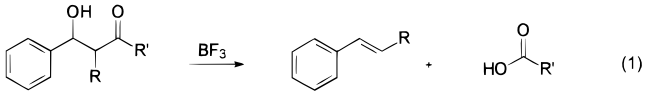
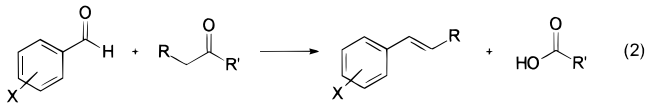
Aldol chemistry has been extensively investigated since the self-condensation of acetone was reported by Kane in 1838.[1] The initial product of the aldol condensation is a *β*-hydroxy carbonyl compound, which is often transformed into the corresponding α,*β*-unsaturated derivative[2] or a 1,3-diol.[3] All these products have proven to be valuable intermediates in the syntheses of a wide variety of natural products.[4] Although many acids and bases can be utilized, new boron reagents have been developed for use in mixed aldol condensations because of their ability to efficiently control the stereochemistry of the reactions.[5] During the course of an investigation involving the stereoselective synthesis of 1,3-diols starting from *β*-hydroxy ketones,[6] we discovered an unprecedented boron trifluoride-initiated cleavage reaction that resulted in the formation of (*E*)-1-arylalkenes and carboxylic acids (eq 1).[7] Since *β*-hydroxy



(1)

ketones are often prepared via acid-catalyzed aldol reactions, we reasoned that the reaction sequence would be more synthetically useful if it could be carried out in a tandem fashion starting from aromatic aldehydes and appropriate ketones.

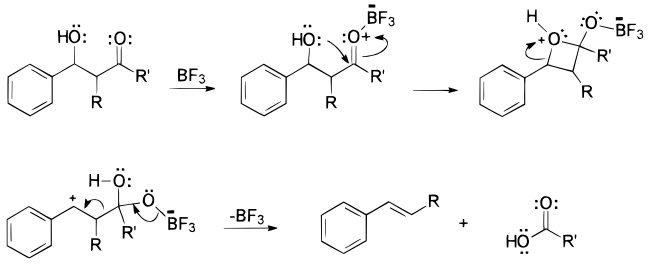
We wish to report an unprecedented, tandem Aldol−Grob sequence involving the reaction of ketones with aromatic aldehydes in nonnucleophilic solvents in the presence of boron trifluoride. The reaction affords the corresponding (*E*)-1-arylalkene (eq 2) and provides a versatile one-pot alternative to the Wittig, Heck, Peterson, and related syntheses.[8]



(2)

1 2 3 4

Scheme 1



Readily available and inexpensive starting materials are utilized, and the reaction conditions should tolerate a variety of functional groups. The reaction may also be viewed as a new route to carboxylic acids as well as a new method for cleaving ketones. The overall sequence is rather remarkable since the reaction conditions appear to be ideal for a straightforward dehydration resulting in the formation of α,*β*-unsaturated ketones. Apparently, the combination of a powerful Lewis acid and a nonnucleophilic solvent are keys to this unexpected behavior and, ultimately, to the success of the reaction.

Although a detailed study of the reaction mechanism has not yet been completed, the consistent formation of (*E*)-alkene products,[9,10] as well as the fact that aromatic aldehydes appear to be required, would point toward the intermediacy of a carbocation derivative. Hydrogen and carbon NMR analyses reveal the expected olefinic and carboxylic acid resonances prior to hydrolysis. A reasonable mechanism would involve the formation of the mixed aldol followed by the formation and subsequent nonsynchronous ring opening of a lactol as shown in Scheme 1. The proposed fragmentation is reminiscent of two-step Grob[11] fragmentations that have been reported for *N*-halo-α-amino acids[12] and cyclobutane hemiacetals[13] as well as the acid-catalyzed fragmentation of *β*-hydroxy acetals.[14,15] Grob fragmentations have been reported in numerous syntheses including the preparation of medium-sized carbocycles,[16] hormones,[17] pharmaceuticals,[18] and carbohydrates.[19]

We examined the effect of various acids on the reaction sequence in order to ascertain which would be most efficient. The results are summarized in Table 1, and they reveal that the formation of the alkene product is common to all the acids examined. However, the rates of product formation vary rather dramatically. Interestingly, *p*-toluenesulfonic acid monohydrate was the only acid that afforded the aldol product in moderate yields. We conclude that boron trifluoride is the most effective of the acids studied in achieving the new tandem condensation−cleavage sequence.

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(10) Isomeric mixtures of *syn*- and *anti*-*β*-aryl-*β*-hydroxy ketones consistently yield (*E*)-alkenes.

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Table 1. Reaction of 5-Nonanone and 2-Chlorobenzaldehyde in the Presence of Various Acids[a]

entry	acid[c]	alkene[b] (%)	aldol products[d] (%)
1	BF_3	74	trace
2[e]	BCl_3	trace	0
3[e]	BBr_3	trace	0
4[e]	$AlCl_3$	30	0
5[e]	$TiCl_4$	9	0
6[e]	$ZnCl_2$	trace	0
7	*p*-tolyl-$SO_3H{\cdot}H_2O$	32	60
8[e]	CF_3CO_2H	<5	trace
9[e]	$C_7F_{15}CO_2H$	trace	<5

[a] Reaction carried out in refluxing CCl_4 for 2 h using 10% excess 2-chlorobenzaldehyde. [b] Isolated yields of (*E*)-1-(2-chlorophenyl)-1-pentene. [c] Excess BF_3 bubbled into reaction mixture (entry 1). Three equivalents of acid utilized (entries 2−9). [d] α,β-Unsaturated ketone. [e] GC/MS analysis revealed unreacted starting material remaining.

Table 2. Reaction of 5-Nonanone with 3-Chlorobenzaldehyde in Various Solvents[a]

entry	solvent	time[b] (h)	*T* (°C)	yield[c] (%)
1	ether	12	rt	0
2	hexane	2.5	68−70	89
3	CCl_4	6	76−77	91
4	CH_2Cl_2	3	40	75
5	toluene	4	110	84

[a] Reactions were carried out using 30% molar excess of aldehyde. [b] Reaction time required to obtain optimum yield. [c] Isolated yields of (*E*)-1-(3-chlorophenyl)-1-pentene.

We then examined the reaction of 5-nonanone with 3-chlorobenzaldehyde in the presence of boron trifluoride in various solvents. The results are summarized in Table 2. The most significant observation is that a nonnucleophilic solvent is required for the reaction to take place. A donor solvent such as ethyl ether completely inhibits the formation of product. Apparently, the Lewis acidity of boron trifluoride is moderated sufficiently by complexation to ethyl ether such that it is ineffective as an aldol catalyst. In fact, in ethyl ether, 5-nonanone and 3-chlorobenzaldehyde were recovered unchanged after 12 h. The yield of (*E*)-1-(3-chlorophenyl)-1-pentene was significantly lower in CH_2Cl_2 than in the other nonnucleophilic solvents studied. It is possible that the polar nature of CH_2Cl_2 enhances the polymerization of the styrene product under the reaction conditions. The use of hexane, CCl_4, and toluene leads to excellent results. The only appreciable difference in these solvents is an enhanced reaction rate when hexane is used. For safety and economic reasons, we conclude that hexane is the ideal solvent for the reaction. Representative reactions are summarized in Table 3.

Table 3. Reaction of Aldehyde 1 with Ketone 2 in the Presence of BF3[a]

entry	aldehyde, X =	ketone	*T* (h)	product (**3**), X =, R =	yield (%)	(*E*/*Z*)[c]
1	H	BuCOBu	1	H, Pr	78	97:3
2	*o*-Cl	BuCOBu	4	*o*-Cl, Pr	91	98:2
3	*p*-CH_3	BuCOBu	2.5	*p*-CH_3, Pr	66	98:2
4	*m*-Cl	BuCOBu	2.5	*m*-Cl,Pr	89	95:5
5	*m*-Cl	MeCOBu	2.5	*m*-Cl,Pr	52	98:2
6	*o*-Cl	PhCOBu	4	*o*-Cl, Pr	50	96:4

[a] Reactions were carried out in hexane at reflux. [b] All products exhibited physical and spectral characteristics in accord with literature values. [c] Isomer ratios were determined by integration of nonoverlapping signals in the ^1H NMR spectrum.

Several features of this reaction make it synthetically useful: (1) The starting materials are readily available and inexpensive. (2) The reaction is stereoselective and the yields of (*E*)-alkenes are very good. (3) Moderate reaction temperatures and nonnucleophilic solvents are effective. (4) The reactions are relatively rapid. (5) The initial results indicate that methylene groups react more efficiently than methyl groups, which permits the use of readily available methyl ketones. (6) The reaction may provide a useful alternative to the Baeyer−Villiger,[20] Wittig, Heck, Peterson, and related reactions.

The synthesis of (*E*)-1-phenyl-1-pentene is representative: a small excess of BF_3 was bubbled into a solution of 5-nonanone (4.26 mmol) in hexane (10 mL). The reaction flask was flushed with nitrogen to remove excess BF_3. Benzaldehyde (5.54 mmol) was then added to the reaction mixture and the solution heated to reflux for 1 h. The reaction was quenched with distilled water (10 mL), the product extracted into ether (3 × 10 mL), and the combined ether layers dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure and the product isolated by flash chromatography (silica gel using hexanes as the eluant) to yield 0.49 g (78%) of (*E*)-1-phenyl-1-pentene.

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Supporting Information Available: Compound characterization (6 pages).

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(20) As a representative example, 84% of pentanoic acid was isolated from the reaction of 5-nonanone and benzaldehyde in the presence of BF_3.