Pergamon

Tetrahedron Letters, Vol. 37, No. 44, pp. 7893-7896, 1996

0040-4039/96 $15.00 + 0.00

PII: S0040-4039(96)01766-2

The Ene Reaction of 3-Methylene-2,3-Dihydrofuran with Aldehydes

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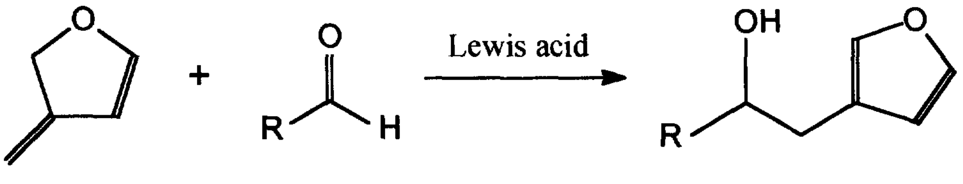
***Abstract:** The Lewis acid-promoted ene reaction of 3-methylene-2,3-dihydrofuran, 1, with aldehydes gives the corresponding alcohols in good to excellent yield.* Copyright © 1996 Elsevier Science Ltd

The preparation of furans remains an important synthetic goal due to the prominence of furans in natural products chemistry[1] and the facile manipulation of furans into other oxygenated functional groups.[2] Our serendipitous preparation of 3-methylene-2,3-dihydrofuran, 1,[3] by the Wolff-Kishner reduction of 3-furaldehyde has prompted us to consider the synthetic potential of 1 for the synthesis of furans. For example, the facile ene reaction[4] of 1 with alkenyl enophiles,[3,5] including C_{60}[6], gives 3-substituted furans in good yields. Despite the rapid isomerization of 1 to 3-methylfuran even under mildly acidic conditions (e.g. stirring with silica gel), we have found conditions that facilitate the reaction of 1 with less reactive enophiles. This paper describes our results for the ene reaction of 3-methylene-2,3-dihydrofuran with aldehydes promoted by Lewis acids.



1

2

The results for the ene reaction of 1 with various achiral aldehydes to give alcohols 2 are summarized in Table 1.[7] The highly enophilic butyl glyoxylate reacted with 1 at 0°C to give alcohol 2 ($R = CO_2(CH_2)_3CH_3$) without the need of a Lewis acid. Although benzaldehyde reacted slowly with 1 at room temperature (entry 2), the introduction of a Lewis acid (entries 3-7) gave excellent yields of 2 ($R = C_6H_5$). The lanthanide reagents Eu(fod)$_3$ and Yb(fod)$_3$ were effective catalysts[8] for the ene reaction of 1 with benzaldehyde, geranial (entry 8) and valeraldehyde (entry 10) although higher catalyst loads and longer reaction times were necessary for the less reactive aldehydes. Alkyl aluminum reagents (e.g.

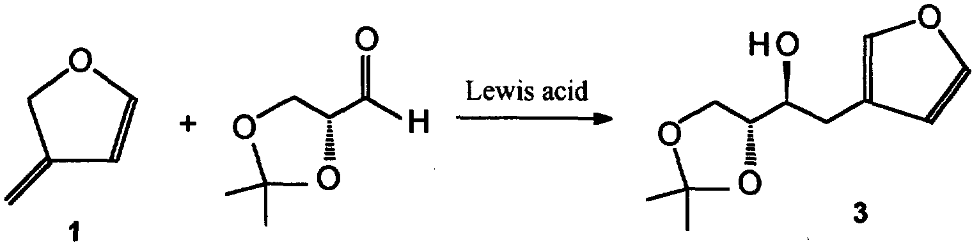
$Al(CH_3)_3$), which have been previously exploited by Snider[9] for the carbonyl-ene reaction, were effective in promoting the ene reaction of 1 with aldehydes (entries 6, 9 and 11). The use of $Al(CH_3)_3$ caused a complete reversal in the chemoselectivity of the reaction of 1 with acrolein, giving the alcohol product rather than the aldehyde product resulting from ene reaction with the carbon-carbon double bond.[5] The reaction of trimethylacetaldehyde with 1 promoted by $Al(CH)_3$ gave 3,3-dimethyl-1-(3-furyl)-2-butanol, a compound previously used in the synthesis of an antifeedant of the larvae of *Spodoptera litura* F.[10] This reaction proceeds slowly and in poor yield using other Lewis acids. Stronger Lewis acids (such as $ClAl(CH_3)_2$ and $BF_3 \cdot OEt_2$) were ineffective promoters of the ene reaction due to isomerization of 1 to 3-methylfuran (and other unidentified reactions).

Table 1. Reaction of 1 with Achiral Aldehydes.

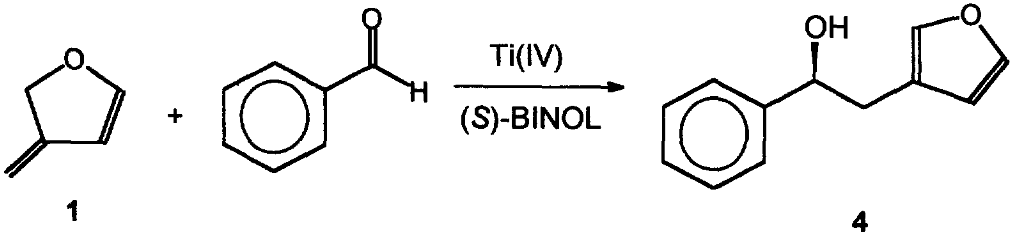
entry	R =	Lewis acid; time[a]	Yield(%)[b]
1	$CO_2CH_2CH_2CH_2CH_3$[c]	none; 1 h	85
2	C_6H_5	none; 68 h	5[d]
3	"	$Yb(fod)_3$, 0.5 mol%; 20 h	97
4	"	$Yb(fod)_3$, 0.5 mol%; 24 h	59[e]
5	"	$Eu(fod)_3$, 0.5 mol%; 48 h	92
6	"	$Al(CH_3)_3$, 1.0 equiv; 1 h	91
7	"	$Ti(OCH(CH_3)_2)_4$, 10 mol%; 20 h	94
8	(*E*)-$CH{=}C(CH_3)CH_2CH_2CH{=}C(CH_3)_2$	$Yb(fod)_3$, 2 mol%; 68 h	88
9	$CH{=}CH_2$	$Al(CH_3)_3$, 1.2 equiv; 1 h	79
10	$CH_2CH(CH_3)_2$	$Yb(fod)_3$, 1 mol%; 48 h	86
11	$C(CH_3)_3$	$Al(CH_3)_3$, 1.0 equiv; 1 h	79

a) Standard conditions: To the aldehyde (10.0 mmol) in CH_2Cl_2 (20 mL) was added 3-methylene-2,3-dihydrofuran (approximately 25 mmol; 4:1 mixture of 1:3-methylfuran) at room temperature, then the catalyst ($Yb(fod)_3$, $Eu(fod)_3$, or $Ti(OCH(CH_3)_2)_4$) was added. For entries 6, 9, and 11, trimethylaluminum (2.0 M in hexane) was added dropwise to a solution of 1 and the aldehyde at 0°C. b) Yields refer to alcohols purified by flash chromatography. c) A solution of 1 in CH_2Cl_2 was added dropwise to a solution of freshly prepared *n*-butyl glyoxylate in CH_2Cl_2. d) 57% yield of recovered benzaldehyde. e) Yield based on 3-furaldehyde for the two-step sequence with benzaldehyde in excess in the second step.

In light of the demonstrated diasteroselectivity in the ene reaction of chiral aldehydes,[3] we also have investigated the diastereoselective reactions of **1**. The ene reaction of **1** with racemic 2-phenylpropionaldehyde[11] (2 mol% Yb(fod)$_3$, 48 h) gave a 4.5:1 mixture of the diastereotopic alcohols in 78% yield.[12] The reaction of **1** and (*R*)-glyceraldehyde acetonide with either Yb(fod)$_3$ (0.5 mol%, 24 h; 99% yield) or Al(CH$_3$)$_3$ (1.2 equiv, 0°C, 1 h, 96% yield) gave high diastereoselectivity (>98% de) for the *anti* isomer **3**[13].



Guided by the successful enantioselective ene reaction of glyoxylates[14] (and other reactions[15]) that use titanium catalysts with (*R*)- or (*S*)- BINOL ligands, we have developed conditions for the asymmetric ene reaction of **1** with benzaldehyde. At this time our optimal procedure employs a catalyst prepared by mixing Ti(O-*i*-Pr)$_4$ and (*S*)-BINOL (1:2 stoichiometry; 10 mol% Ti(O-*i*-Pr)$_4$) in ether with ground molecular sieves at room temperature, followed by the addition of benzaldehyde and **1** (1.5 equiv) at 0°C, and stirring for 0.5 h. The alcohol product **4**, obtained in 98% yield and 81%ee, results from the attack by **1** on the *si*-face of benzaldehyde,[16] comparable to the stereochemical results of related reactions.[14,15]



The Lewis acid-promoted ene reaction of **1** with aldehydes provides a variety of 3-(2-alkanol)furans. The application of this reaction to the synthesis of furan[17] and related oxygenated natural products is in progress.

Acknowledgements: We gratefully acknowledge the generous financial support of Lafayette's Committee on Advanced Study and Research in the form of summer stipends under the EXCEL Scholar program to CLB and CAA and a Summer Research Fellowship to WHM.

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(*Received in USA* 1 *August* 1996; *accepted* 4 *September* 1996)