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LANTHANIDE (III) PROMOTED ALDOL CONDENSATION OF ENONES AND ALDEHYDES¹

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Abstract: The first lanthanide (III) mediated α '-alkylation of MVK with aldehydes is described. This methodology allows the efficient preparation of a number of synthetically important hydroxyenones.

1,2- and 1,4-additions to acyclic α , β -unsaturated carbonyl systems are well precedented carbon-carbon bond forming reactions. In contrast, the aldol condensation at the saturated α -carbon of enones (α '-alkylation) is quite problematic. A number of recent studies have focused on the alkylation of the sp² α -carbon (α -alkylation),² but very little worked has been carried out on α 'alkylations of acyclic enones.^{3,4}

As shown in Scheme 1, hydroxyenones 1, 2 and 3 are key intermediates in the synthesis of a variety of natural products.⁵ Unfortunately, the laborious sequences required for the preparation of some of these hydroxyenones has limited

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their use in total synthesis. An efficient regioselective α' -alkylation protocol of methyl vinyl ketone (MVK) would be an attractive approach to this class of compounds. Herein we disclose a direct method for the aldol condensation of aldehydes with the saturated α -carbon of MVK.

Despite the important synthetic value of these aldol adducts, the direct α' alkylation of MVK has never been reported probably due to the low yield of the standard reaction. In fact, addition of the MVK lithium enolate to PhCHO at -78°C afforded only 8% of the corresponding hydroxyenone (Table 1, entry 1).

We reasoned that activation of the aldehyde with a Lewis acid prior to the addition of the MVK lithium enolate could enhance the yield. Whereas addition of TiCl₄ gave less than 4% of the desired product, when the lithium enolate of MVK was added to a solution of PhCHO and 1.3 equiv of BF₃•OEt₂, the hydroxyenone product was isolated in 22% yield. In general, these Lewis acids were too hard and lead to much decomposition of the intermediates and/or products. This prompted us to investigate softer catalysts for this condensation. CeCl₃ is a mild and selective

	Ba	j'	~	1) LDA / THF	. в.	_
		\checkmark	, СН ₃ —	2) RACHO, LnCla /THF		<u> </u>
				-78 °C		
		H3 O		10 0	n ₃ 0	ОН
Entry	R ₁	R ₂	R ₃	R ₄	LnCl ₃ /Aldehydes	Isolated
<u> </u>					<u>(mol equiv.)</u>	_Yields(%) ^(a)
1	н	н	н	C ₆ H ₅ CHO	0	8
2	н	Н	Н	C ₆ H ₅ CHO	LaCl ₃ (2)	11
3	Н	Н	н	C ₆ H ₅ CHO	$CeCl_3(2)$	47
4	Н	н	н	C ₆ H ₅ CHO	$CeCl_3(2)$	14 ^(b)
5	н	Н	Н	C ₆ H ₅ CHO	PrCl ₃ (2)	40
6	н	н	н	C ₆ H ₅ CHO	$NdCl_3(2)$	10
7	Н	н	н	C ₆ H ₅ CHO	SmCl ₃ (2)	47
8	Н	н	н	C ₆ H ₅ CHO	$EuCl_3(2)$	35
9	н	Н	Н	C ₆ H ₅ CHO	$GdCl_3(2)$	68
10	н	Н	н	C ₆ H ₅ CHO	TbCl ₃ (2)	69
11	н	Н	Н	C ₆ H ₅ CHO	DyCl ₃ (2)	68
12	Н	Н	Н	C ₆ H ₅ CHO	$HoCl_3(2)$	51
13	н	Н	Н	C ₆ H ₅ CHO	ErCl ₃ (2)	66
14	н	н	н	C ₆ H ₅ CHO	TmCl ₃ (2)	14
15	н	Н	Н	C ₆ H ₅ CHO	YbCl ₃ (2)	28
16	Н	н	Н	C ₆ H ₅ CHO	LuCl ₃ (2)	43
17	н	н	Н	CH ₃ (CH ₂) ₂ CHO	0	14
18	н	Н	Н	CH ₃ (CH ₂) ₂ CHO	TbCl ₃ (2)	52
19	н	н	Н	BnO(CH ₂) ₂ CHO	0	16
20	н	н	Н	BnO(CH ₂) ₂ CHO	TbCl ₃ (2)	60
21	н	н	н	(CH ₃) ₂ CHCHO	0	9
22	н	н	н	(CH ₃) ₂ CHCHO	TbCl ₃ (2)	38
23	н	Н	н	C ₆ H ₅ CH=CHCHO	0	18
24	н	н	н	C ₆ H ₅ CH=CHCHO	$TbCl_3(2)$	50
25	н	CH ₃	CH ₃	C6H5CHO	0	65
26	н	CH ₃	CH ₃	C ₆ H ₅ CHO	$TbCl_3(2)$	85
27	н	CH ₃	н	C6H5CHO	0	61
28	н	CH ₃	н	C ₆ H ₅ CHO	TbCl ₃ (2)	80
29	CH ₃	CH ₃	н	C ₆ H ₅ CHO	0	88
30	CH ₃	CH ₃	Н	C ₆ H ₅ CHO	TbCl ₃ (2)	91

TABLE 1. LnCl₃ mediated α '-alkylations of enones and aldehydes

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(a) Isolated yield based on the starting aldehydes.⁶

(b) Cerium enolate of MVK was used.

reagent for the 1,2-reduction of and 1,2-addition to α , β -unsaturated carbonyl compounds.⁷ Although the mechanistic details of these reactions have not been fully elucidated, it is thought that activation of the substrate may be a result of coordination to CeCl₃. In fact, when a THF solution of MVK lithium enolate was

added to a THF solution of PhCHO•CeCl₃ complex at -78°C, the aldol product was isolated in 47% yield after purification by flash chromatography.⁸ Of the Lanthanide (III) reagents used in Table 1, GdCl₃, TbCl₃, DyCl₃ and ErCl₃ gave higher yields of the aldol adduct than LaCl₃, NdCl₃, TmCl₃. It is important to point out that this method for the direct α '-alkylation of MVK with aldehydes provides a facile synthesis of a class of hydroxyenones which are not easy to prepare otherwise. For example, this procedure constitutes an efficient method for the preparation of the pentamycin intermediate 1 (Scheme 1). 1 was prepared in one step and much higher overall yield than a previously reported multistep procedure (Table 1, entry 19).^{5b}

In order to gain a better understanding of the role of LnCl₃ in this reaction, we next turned our attention to the nature of the enolate. Cerium enolates generated from CeCl₃ and lithium enolates are known to facilitate the aldol condensations of readily enolizable ketones with sterically hindered aldehydes.⁹ In fact, if the α'-alkylation in this case is a result of the cerium enolate of MVK adding to the aldehyde, then transmetallation of the lithium to the cerium enolate followed by addition of the aldehyde should theoretically give yields similar to or higher than the original method. However, addition of PhCHO to a suspension of the cerium enolate of MVK and CeCl₃ at -78°C) resulted in a lower yield of the corresponding hydroxyenone (14%, Table 1, entry 4). Similar results were observed in the cases of GdCl₃, TbCl₃, DyCl₃, and ErCl₃. This points to a possible transition state where the lithium enolate adds to the Ln(III) coordinated aldehyde.

In summary, we have described the first direct and practical method for the preparation of synthetically useful hydroxyenones from MVK and the corresponding aldehydes in the presence of LnCl₃.¹⁰ Studies are currently underway in our laboratories in order to elucidate the mechanism of this process.

Further optimization of the reaction yields as well as the enantioselective version will be reported in due course along with applications of this methodology to the synthesis of several natural products.

Typical procedure for the aldol reaction: To a solution of diisopropylamine (658 mg, 6.5 mmol) in dry THF (50 mL) was added n-BuLi (1.6M in hexane, 4.4 mL, 7 mmol) and the solution was stirred at -78 °C for 20 min. To this solution was added a solution of MVK (456 mg, 6.5 mmol) in THF (150 mL) and the solution was stirred for 30 min at -78°C. Dry TbCl₃ (2.65 g, 10 mmol) was added to a solution of benzaldehyde (531 mg, 5 mmol) in dry THF (200 mL), and the resulting suspension was vigorously stirred for 5 min at -78 °C. The solution of the lithium enolate was transferred via cannula to the benzaldehyde suspension and the mixture was stirred for 20 min at -78°C. The reaction was quenched with H₂O (1 mL), diluted with EtOAc, washed with brine, dried over Na₂SO₄, concentrated in vacuo and the residue was purified by flash column chromatography with 15% EtOAc-hexane ($R_f = 0.52$ in 30% EtOAc-hexane) to give the hydroxyenone 2 as a colorless oil (608 mg, 69% yield). IR (neat): 3448, 3028, 2360, 1676, 1612, 1492, 1452, 1400, 1190, 1054, 968 cm⁻¹; ¹H NMR (CDCl₃, 200 MHz): δ 7.17-7.45 (m, 5 H), 5.88 (dd, J = 9.7, 1.7 Hz, 1 H), 5.80-5.95 (m, 1 H), 5.12-5.24 (m, 1 H), 3.40 (d, J = 3.0 Hz, 1 H), 2.98 (d, J = 3.4 Hz, 1 H), 2.95 (br. s, 1 H); ¹³C NMR (CDCl₃, 50 MHz): δ 201.31, 143.47, 137.28, 130.29, 129.23 (2C), 128.38, 126.35 (2C), 70.53, 48.55; MS (m/z, relative intensity): 176 (M+, 6), 149 (14), 131 (11), 105 (100), 97 (27); exact mass calculated for C₁₁H₁₂O₂ (M⁺): 176.0837; found 176.0839.

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