Pergamon

Tetrahedron Letters 40 (1999) 6627–6630

TETRAHEDRON
LETTERS

Diethylaminotrimethylsilane Mediated Aldol Condensation of Naked Aldehydes

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Received 7 June 1999; revised 25 June 1999; accepted 2 July 1999

Abstract: Self-aldol condensation of naked aldehydes in the presence of diethylaminotrimethylsilane with or without solvent provided unsaturated aldehydes. © 1999 Elsevier Science Ltd. All rights reserved.

Keywords: Aldehydes, Aldol reactions, Enals

Nucleophilic reactions of naked aldehydes are difficult to control affording a mixture of complicated products often because of high reactivity of formyl groups under either basic or acidic reaction condition. In order to solve such problems, aldehydes were transformed once to their stable synthones which were reacted with electrophiles.[1-3] After the reaction, the products were transformed back to aldehydes. In the case of self-aldol condensation of naked aldehydes leading to α,β-unsaturated aldehydes (enals), there are several examples employing aqueous sodium hydroxide,[4] 2,4,6-trimethylphenoxymagnesium bromide,[5] boric acid,[6] anion exchange resin[7] or electrolysis.[8] For cross aldol condensation between benzaldehyde and heptanal, ethanolic sodium hydroxide has been used.[9-11] Since enals are versatile intermediates for organic synthesis, new efforts to explore milder reaction condition are still continuing.

Recently, Ishikawa, Saito and their coworkers reported pyrrolidine with benzoic acid catalyzed self-aldol condensation of aldehydes leading to enals.[12] Their findings prompted us to report herein our independent protocol for diethylaminotrimethyisilane (Et_2NTMS)[13] mediated synthesis of enals **2** by self-aldol condensation of naked aldehydes **1** (Scheme 1).[14]

2a-f

Scheme 1

1a R = $PhCH_2$
b R = $THPO(CH_2)_3$
c R = $TBSO(CH_2)_3$
d R = $AcO(CH_2)_3$
e R = $CH_3(CH_2)_7$
f R = $CH_3(CH_2)_3$

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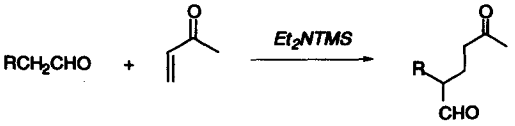
PII: S0040-4039(99)01326-X

We previously found that reaction of naked aldehydes **1** and α,β-unsaturated ketone **3** gave conjugate 1,4-addition product **4** in the presence of Et_2NTMS without solvent (Scheme 2).[15-16] For large scale preparation (10~100 mmol), addition of 10 mol% of Et_2NTMS was sufficient to provide 1,4-addition product **4**. Though the exact mechanism of the 1,4-addition reaction is yet to be discussed, Et_2NTMS may play a role as a mild base.



1 **3** **4**

Scheme 2

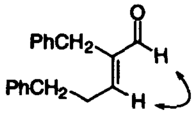
In order to expand further utility of Et_2NTMS which has been underestimated as a reagent for organic synthesis, we applied Et_2NTMS to self-aldol condensation of naked aldehydes **1**. As we expected, reaction of aldehyde **1** in the presence of Et_2NTMS without solvent except entry 2 (Table 1) gave enals **2** as a single isomer after evaporation of volatile components *in vacuo* followed by medium pressure liquid chromatography of the residue. No aqueous work up was needed. Some representative examples of the present reaction were shown in Table 1. The reaction condition is so mild that the aldehydes **1b~d** having acid or base sensitive protecting groups such as THP, TBS or Ac provided the desired enals **2b~d** (Table 1, entry 2~4). The geometry of double bond of **2** was apparent from n.O.e. enhancement between aldehydic and olefinic protons (Figure 1). Solvent effect was investigated in entry 5 by employing refluxing solutions of MeCN, CH_2Cl_2, $ClCH_2CH_2Cl$, THF or Et_2O resulting in decrease of yields (8~23%) in every case. Intermediary β-hydroxyaldehyde was isolated in 32% yield as a diastereomeric mixture (ratio = 1:1), when the reaction of hexanal was carried out at room temperature with molecular sieves 4Å powder in acetonitrile,.

Table 1 Intermolecular Self-Aldol Condensation of Various Aldehydes[a, b]

Entry	Aldehyde 1	Enal 2	Yield (%)
1	**1a** R = $PhCH_2$	**2a**	51
2	**1b** R = $THPO(CH_2)_3$	**2b**	49[c]
3	**1c** R = $TBSO(CH_2)_3$	**2c**	47
4	**1d** R = $AcO(CH_2)_3$	**2d**	44
5	**1e** R = $CH_3(CH_2)_7$	**2e**	54[d]
6	**1f** R = $CH_3(CH_2)_3$	**2f**	27

[a] Half equiv of Et_2NTMS was used unless otherwise specified.
[b] Reaction was carried out at 50 °C for 16 h.
[c] Acetonitrile was used as solvent.
[d] An equiv. of Et_2NTMS was used.

Figure 1



2a

n.O.e. : 16 %

Cross aldol condensation was also possible between decanal **1e** and aromatic aldehydes **5a~c** (Scheme 3) in refluxing acetonitrile (MeCN) to give *E*-β-aryl-α,β-unsaturated aldehydes **6a~c** as major isomers (Table 2). Naturally, anisaldehyde **5c** having electron donating group afforded lower yields (Table 2, entry 4). In these reactions, addition of 4Å molecular sieves powder was effective. Different from self-aldol condensation, the reaction without solvent gave poor yield (entry 3, Table 2). *E*-geometry of the major isomers were determined by n.O.e. experiments.

Scheme 3

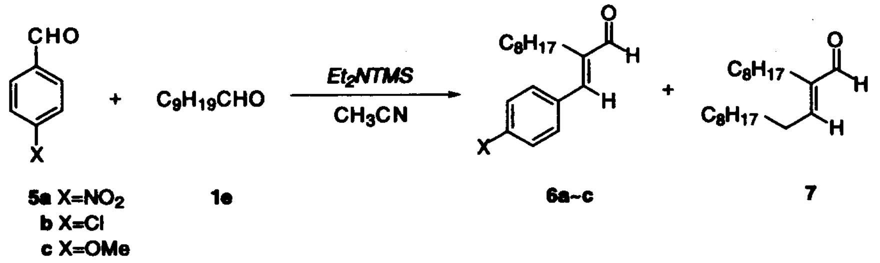
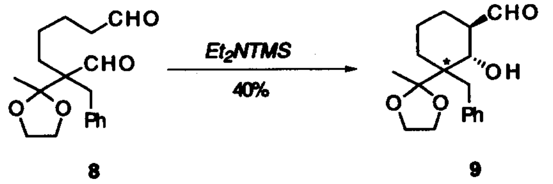


Table 2 Intermolecular Cross Aldol Condensation[a, b, c]

Entry	Arylaldehyde 5	Yield (%)		
		E-6	*Z*-6	7
1	**5a** X = NO_2	81	10	—
2	**5b** X = Cl	60	—	—
3	**5b** X = Cl	25[d]	—	—
4	**5c** X = MeO	20	2[e]	41

[a] Molecular sieves powder 4Å (100 mg / 2 mmol of arylaldehyde) was added.
[b] Two equivalents of Et_2NTMS was used.
[c] The resulting slurry was refluxed for 20~24 h.
[d] The reaction was carried out without solvent and MS 4Å.
[e] Anisaldehyde **5c** was recovered in 78% yield.

Intramolecular aldol condensation of dialdehyde **8** in refluxing solution (0.05 M concentration) of Et_2NTMS gave a six-membered aldol product **9** as a single diastereomer in 40% yield (Scheme 3).[17] Unsaturated aldehyde was not obtained.



Scheme 4

When a solution of an equivalent amount of decylaldehyde **1e** and Et_2NTMS in deuteriochloroform was stand overnight at room temperature, formation of diethylaminoenamine of **1e** was observed in NMR spectrum [δ 5.85 ppm (d, *J* 13.8 Hz) and 4.18 ppm (dt, *J* 13.8 and 7 Hz), ratio: **1e** : enamine=1 : 1.3]. On the other hand, no deuterium exchange of α-protons of **1e** was observed with **1e**, Et_2NTMS and D_2O in NMR tube. These results suggest that the present aldol condensation proceeds *via* an enamine pathway. Detailed mechanistic considerations will be reported in due course.

In summary, novelty of the present reaction as well as simplicity of operation opened a new entry to aldol condensation of naked aldehydes **1** under milder reaction condition.[18]

Acknowledgments

This work was supported by a Grant-in-Aid for Scientific Research (No. 09640630 for H. H.) from the Ministry of Education, Science, Sports and Culture, Japan.

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17 The relative stereochemistry of quaternary carbon can not be determined at this stage.

18 Typical experimental procedure is as follows: A stirred mixture of hydrocinamaldehyde (130 μl, 1 mmol) and Et_2NTMS (95 μl, 0.5 mmol) was heated at 50 °C for 16 hr under nitrogen atmosphere. The resulting mixture was evacuated *in vacuo* and the residue was separated by medium pressure liquid chromatography (eluent: n-haxane:ethyl acetate = 5:1) to give enal **1a** (68 mg, 51%).