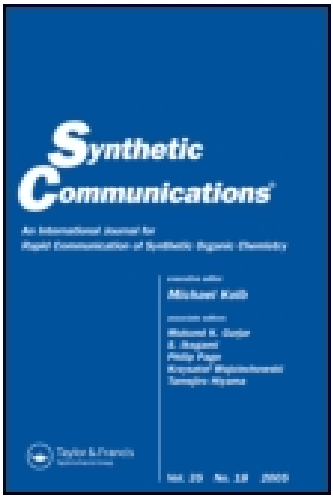

Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

The N,N,N′,N′-Tetramethylethylenediamine Mediated Baylis-Hillman Reaction

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Published online: 22 Jun 2006.

To cite this article: Sanhu Zhao & Zhaobin Chen (2005) The N,N,N′,N′-Tetramethylethylenediamine Mediated Baylis-Hillman Reaction, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 35:1, 121-127, DOI: 10.1081/SCC-200046521

To link to this article: http://dx.doi.org/10.1081/SCC-200046521

Synthetic Communications®, 35: 121–127, 2005

ISSN 0039-7911 print/1532-2432 online
DOI: 10.1081/SCC-200046521

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The N,N,N′,N′–Tetramethylethylenediamine Mediated Baylis-Hillman Reaction

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Abstract: The Baylis-Hillman reaction of aromatic aldehydes with various activated alkenes catalyzed by N,N,N′,N′–Tetramethylethylenediamine (TMEDA) in aqueous medium were reported. The efficiency of this catalyst was examined in comparison with DABCO. It was demonstrated that this amine is not only a very efficient catalyst for the Baylis-Hillman reaction, it also outperforms the most widely used catalyst DABCO.

Keywords: N,N,N′,N′–Tetramethylethylenediamine, catalyze, Baylis-Hillman reaction

INTRODUCTION

The Baylis-Hillman reaction is an atom-economical and extremely useful C-C bond-forming reaction in organic synthesis.[1] Numerous catalytic systems, such as tertiary amines,[2–7] phosphines[8,9] and chalcogenides,[10] $TiCl_4$[11] etc, were used as catalyst to mediate this reaction. 1,4-Diazabicyclo [2.2.2] octane (DABCO, **1**), first introduced by Baylis and Hillman,[12] is arguably still the most widely used one. We are surprised to find, however, that other related tertiary amines such as the very readily available N,N,N′,N′–Tetramethylethylenediamine (TMEDA, **2**) has never been used as a catalyst in this context. We now wish to report our preliminary findings that, not only

Received in Japan August 19, 2004
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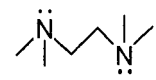
this inexpensive and user-friendly amine can be successfully used in the Baylis-Hillman reaction, it also outperforms the classical **1**.

1

1,4-diazabicyclo[2.2.2] octane (DABCO)



2

N, N, N', N'-Tetramethylethylene diamine (TMEDA)

RESULTS AND DISCUSSION

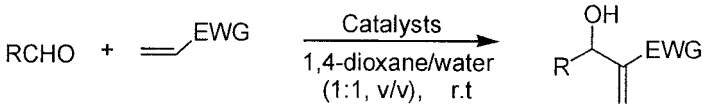
For evaluating the influence of TMEDA on the Baylis-Hillman reaction, we examined the reaction of 2-nitrobenzaldehyde with butyl acrylate in a 1 : 1(v/v) mixture of 1,4-dioxane and water in the presence of TMEDA. The good result was obtained when a mixture of 2-nitrobenzaldehyde (3 mmol), butyl acrylate (9 mmol), H_2O (5 ml), 1,4-dioxane (5 ml), and TMEDA (1 mmol) was stirred at ambient temperature. The main emphasis was here given to aromatic aldehydes, because they are harder to react in Baylis-Hillman reaction than aliphatic one.[13] For comparing the effect of TMEDA with DABCO, the similar reaction of 2-nitrobenzaldehyde with butyl acrylate in the presence of DABCO was also conducted (Table 1).

Encouraged by this result, we then carried out the TMEDA or DABCO catalyzed Baylis-Hillman coupling of 2-nitrobenzaldehyde with acrylonitrile. It was found that the reaction medium catalyzed by DABCO became dark and dirty after 4 hrs. Furthermore, the formation of Baylis-Hillman adducts could be only detected in very low yields (by TLC,GC). As compared with DABCO, the reaction medium catalyzed by TMEDA was very clean in all reaction times, and a better result (fast reaction rate, higher yield) was obtained.

We also successfully carried out the TMEDA-induced Baylis-Hillman reaction of the other aldehydes with activated alkenes, as shown in Table 1. Considering the results presented in Table 1, it was observed that the use of stoichiometric amounts of TMEDA as a promoter not only reduces the reaction time but also gives a high yield.

In conclusion, we have demonstrated that the rather inexpensive, readily available and user-friendly N,N,N′,N′−Tetramethylethylenediamine **2** can be used as a new and efficient catalyst for Baylis-Hillman reaction. Its activity is even superior to that of the most widely used catalyst DABCO **1**. Further investigation in optimizing the reaction conditions is being actively pursued in our laboratory.

Table 1. TMEDA and DABCO mediated the Baylis-Hillman reactions



1 **2** **3**

Entry	R	EWG	Cat.	Time (h)	Product	Yield (%)[a]
1	2-$O_2NC_6H_4$	$COOC_4H_9$	DABCO	36	**3a**	59
2	2-$O_2NC_6H_4$	$COOC_4H_9$	TMEDA	12	**3a**	68
3	2-$O_2NC_6H_4$	CN	DABCO	8	**3b**	N/A[b]
4	2-$O_2NC_6H_4$	CN	TMEDA	8	**3b**	90
5	2-$O_2NC_6H_4$	$CONH_2$	DABCO	36	**3c**	45
6	2-$O_2NC_6H_4$	$CONH_2$	TMEDA	12	**3c**	70.5
7	2-$O_2NC_6H_4$	$COOCH_3$	TMEDA	10	**3d**	86
8	2-pyridin	$COOCH_3$	TMEDA	8	**3e**	91
9	2-pyridin	$CONH_2$	TMEDA	10	**3f**	78
10	4-ClC_6H_4	$COOCH_3$	TMEDA	36	**3g**	62
11	4-$O_2NC_6H_4$	$COOCH_3$	TMEDA	8	**3h**	89.5
12	C_6H_5	CN	TMEDA	48	**3i**	61
13	4-OHC_6H_4	CN	TMEDA	72	**3j**	56
14	CH_3	$COOCH_3$	TMEDA	72	**3k**	27

[a]Isolated yield based on aldehyde.
[b]Only trace amount of product was detected and its yield not determined.

EXPERIMENTAL

All melting points were recorded by capillary melting point apparatus and uncorrected. The IR spectra were determined on an IR-408 Infrared Spectrometer by dispersing samples in KBr disks. ^1H NMR spectra were measured on a DRX300 NMR Spectrometer with $CDCl_3$ as solvent. Analytical thin-layer chromatography (TLC) was carried out using MN Kieselgel G/UV_{254} (Art. 816320) glass-backed plates. All products are already reported in the literature.[6,13–17]

General Procedure

A solution of aromatic aldehyde (3 mmol) and activated alkene (9 mmol) in 10 mL of 1,4-dioxane/water (1 : 1, v/v) was stirred at room temperature in the presence of DABCO (1 mmol) or TMEDA (1 mmol) and the reaction progress was monitored by TLC. Upon completion, the reaction mixture was acidified dropwise with 1.5N aqueous HCl, then partitioned with ether

(50 mL) and water (30 mL). The organic phase was washed with brine (2 × 30 mL), dried over anhydrous Na_2SO_4, and removal of solvent on a rotary vacuum evaporator afforded the crude product. The crude product obtained after work-up was purified by flash column chromatography on silica gel (300–400 mesh).

3-Hydroxy-2-methylene-3-(2-nitrophenyl) propanoic acid, n-butyl ester (3a). This compound was prepared in the same manner as that described above, the crude material obtained on workup was purified by column chromatography. Elution with petroleum ether-ethyl acetate (5 : 1) afforded pure product **3a** as a pale yellow oil; IR (neat): ν (cm^{-1}) 3434 (OH), 2960, 1731(C═O), 1536, 1357; ^{1}H NMR(300 MHz, $CDCl_3$): δ 8.04 (d, 1H, J = 8.05 Hz, Ar), 7.74(d, J = 8.05 Hz,1H, Ar), 7.60 (t, J = 7.56 Hz, 1H, Ar), 7.44(t, J = 7.56 Hz, 1H, Ar), 5.92(s, 1H), 5.62(s, 1H), 5.20(s, 1H, CHOH), 4.10(t, 2H), 2.62(br s, 1H, OH), 1.12–1.36(m, 4H), 0.94(t, J = 7.4 Hz, 3H, CH_3).

3-Hydroxy-2-methylene-3-(2-nitrophenyl) propanenitrile (3b). This compound was prepared in the same manner as that described above, the crude material obtained on workup was purified by column chromatography. Elution with petroleum ether-ethyl acetate (7 : 1) afforded pure **3b** as a yellow solid; mp 41°C; IR (KBr): ν (cm^{-1}) 3462.0 (OH), 2229.6, 1610.5, 1344.3; ^{1}H NMR (300 MHz,$CDCl_3$): δ 8.03 (d, J = 8.06 Hz, 1H, Ar), 7.84 (d, J = 8.06 Hz, 1H, Ar), 7.73 (t, J = 7.71 Hz, 1H, Ar), 7.56 (t, 1H, J = 7.71 Hz, Ar), 6.15 (s, 1H), 6.12 (s, 1H), 5.96 (d, J = 5.56 Hz 1H, CHOH), 3.27 (br s, 1H, OH).

3-Hydroxy-2-methylene-3-(2-nitrophenyl) propionamide (3c). This compound was prepared in the same manner as that described above, the crude material obtained on workup was purified by column chromatography. Elution with petroleum ether-ethyl acetate (3 : 1) afforded pure **3c** as a yellow crystal; mp 59°C; IR (KBr): ν (cm^{-1}) 3360 (OH), 1662, 1640, 1346.2; ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.43(s, 1H, OH), 8.13(d, J = 8.09 Hz, 1H, Ar), 7.96(d, J = 8.09 Hz, 1H, Ar), 7.80(t, J = 7.76 Hz, 1H, Ar), 7.76 (t, J = 7.76 Hz 1H, Ar), 6.19 ∼ 6.34(m, 2H), 5.73(d, J = 5.52 Hz 1H, CHOH), 5.53(br s, 2H, NH_2).

3-Hydroxy-2-methylene-3-(2-nitrophenyl) propanoic acid, methyl ester (3d). This compound was prepared in the same manner as that described above, material obtained on workup was purified by column chromatography, Elution with petroleum ether-ethyl acetate (9 : 2) afforded pure **3d** as a yellow oil; IR (neat): ν (cm^{-1}) 3449.4 (OH), 1714.1(C═O), 1530.9, 1352; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.96 (d, J = 8.01 Hz 1H, Ar), 7.76 (d, 1H, J = 8.01 Hz, Ar), 7.66 (t, J = 7.41 Hz, 1H, Ar), 7.48(t, 1H, J = 7.41 Hz, Ar), 6.38(s, 1H), 6.21(s, 1H), 5.74(s, 1H, CHOH), 3.77(s, 3H, CH_3), 3.25(br s, 1H, OH).

3-Hydroxy-2-methylene-3-(pyridin-2-yl) propanoic acid, methyl ester (3e). This compound was prepared in the same manner as that described above, the crude material obtained on workup was purified by column

chromatography. Elution with petroleum ether-ethyl acetate (9 : 2) afforded pure **3e** as a yellow oil; IR (neat): ν (cm^{-1}) 3418 (OH), 3012, 2952, 1725(C═O), 1593. ^1H NMR (300 MHz,$CDCl_3$): δ 8.48(d, $J = 4.82$ Hz, 1H, pyridine), 7.60–7.55(m, 1H, pyridine), 7.36(d, 1H, $J = 7.36$ Hz, pyridine), 7.15(t, 1H, $J = 6.15$ Hz, pyridine), 6.33(s, 1H), 5.90(s, 1H), 5.61(d, 1H, $J = 5.31$ Hz, CHOH), 4.83(br s, 1H, OH), 3.68(s, 3H, CH_3).

3-Hydroxy-2-methylene-3-(pyridin-2-yl) propionamide (3f). This compound was prepared in the same manner as that described above, the crude material obtained on workup was purified by column chromatography. Elution with petroleum ether-ethyl acetate (5 : 2) afforded pure **3f** as a pale yellow oil; IR (neat): ν (cm^{-1}) 3380 (OH), 1675; ^1H NMR (300 MHz, CD_3Cl_3): δ 8.3–8.18(m, 1H, pyridine), 7.52(d, $J = 7.6$ Hz, 1H, pyridine), 7.27(d, $J = 8.4$ Hz, 1H, pyridine), 7.05–6.96(m, 1H, pyridine), 5.76(s, 1H), 5.68(s, 2H, NH_2), 5.32(s, 1H), 5.38(s, 1H, CHOH), 3.29(br s, 1H, OH).

3-Hydroxy-2-methylene-3-(4-chlorophenyl) propanoic acid, methyl ester (3g). This compound was prepared in the same manner as that described above, the crude material obtained on workup was purified by column chromatography. Elution with petroleum ether-ethyl acetate (7 : 3) afforded pure **3g** as a white solid; mp 42°C, Lit,[15] 42°C; IR (KBr): ν (cm^{-1}) 3500 (OH), 2985, 1725; ^1H NMR (300 MHz,$CDCl_3$): δ 7.82(s, 2H, Ar), 7.30(s, 2H, Ar), 6.35(s, 1H), 5.85(s, 1H), 5.52(d, $J = 5.82$ Hz, 1H,CHOH), 3.72(s, 3H, CH_3), 3.15(d, $J = 5.84$,1H,OH).

3-Hydroxy-2-methylene-3-(4-nitrophenyl) propanoic acid, methyl ester (3h). This compound was prepared in the same manner as that described above, the crude material obtained on workup was purified by column chromatography. Elution with petroleum ether-ethyl acetate (5 : 1) afforded pure **3h** as a yellow solid; mp 73°C, Lit.[13] 73–74°C; IR (KBr): ν (cm^{-1}) 3510 (OH), 2992, 1724, 1634, 1359; ^1H NMR (300 MHz, $CDCl_3$): δ 8.70(d, $J = 8.76$ Hz, 2H, Ar), 7.56(d, $J = 8.76$ Hz, 2H, Ar), 6.40(s, 1H), 5.88(s, 1H), 5.64(d, $J = 5.87$ Hz, 1H, CHOH), 3.75(s, 3H, CH_3), 3.40(br s, 1H, OH).

3-Hydroxy-2-methylene-3-phenylpropanenitrile (3i). This compound was prepared in the same manner as that described above, the crude material obtained on workup was purified by column chromatography. Elution with petroleum ether-ethyl acetate (4 : 1) afforded pure **3i** as a yellow oil; IR (neat): ν (cm^{-1}) 3445.0 (OH), 2229.5, 1605.8, 1340.3; ^1H NMR (300MHz, $CDCl_3$): δ 7.40–7.16 (m, 5H, C_6H_5), 6.15 (s, 1H), 6.12 (s, 1H), 5.96 (d, $J = 5.56$ Hz 1H,CHOH), 2.87 (br s, 1H, OH).

3-Hydroxy-2-methylene-3-(4-hydroxyphenyl) propanenitrile (3j). This compound was prepared in the same manner as that described above, the crude material obtained on workup was purified by column chromatography. Elution with petroleum ether-ethyl acetate (5 : 1) afforded pure **3j** as a colourless oil; IR (neat): ν (cm^{-1}) 3460.0 (OH), 2228.5, 1620; ^1H NMR (300 MHz, $CDCl_3$): δ 7.42 (d, $J = 8.40$ Hz, 2H, Ar), 6.75 (d, $J = 8.06$ Hz,

2H, Ar), 6.05 (s, 1H), 5.80(s, 1H), 4.75 (s, 1H,CHOH), 4.52 (s, 1H), 3.64 (br s, 1H, OH).

3-Hydroxy-2-methylene-butanoic acid, methyl ester (3k). This compound was prepared in the same manner as that described above, material obtained on workup was purified by column chromatography. Elution with petroleum ether-ethyl acetate (4 : 1) afforded pure **3k** as a yellow oil; IR (neat): ν (cm^{-1}) 3469.4 (OH), 1714.1(C═O), 1630.9; ^1H NMR (300 MHz,$CDCl_3$): δ 6.20 (d, $J = 1.35$ Hz, 1H,C═CH), 5.83 (d, 1H, $J = 1.1$ Hz, C═CH), 4.59 (m, 1H, CH), 3.79(s, 3H, OCH_3), 2.70 (s, 1H, OH), 1.35(d, $J = 6.42$ Hz, 3H, CH_3) .

ACKNOWLEDGMENTS

The present work was supported by the Natural Science Foundation of China (30000112); Laboratory of Organic Solid, Chinese Academy of Sciences, and The Returned Student Science Foundation of Shanxi Province of China.

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