

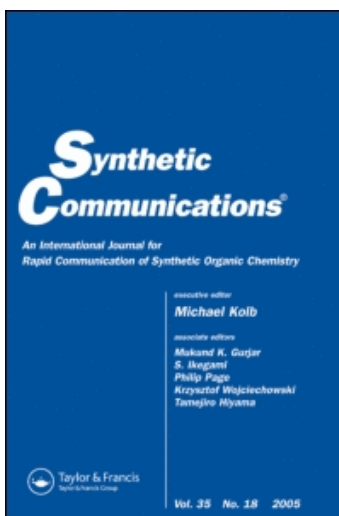
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The Aqueous Trimethylamine Mediated Baylis-Hillman Reaction

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THE AQUEOUS TRIMETHYLAMINE MEDIATED BAYLIS-HILLMAN REACTION

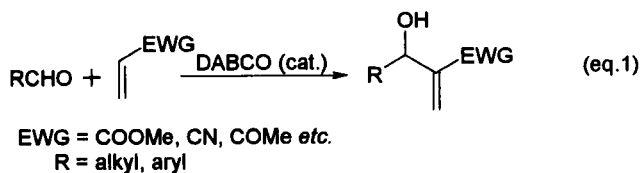
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Abstract: Aqueous trimethylamine mediated Baylis-Hillman coupling of alkyl acrylates with aldehydes is described.

The bicyclic tertiary amine (particularly DABCO) catalyzed Baylis-Hillman construction of carbon-carbon bond between the α -position of activated alkenes and aldehydes producing a useful class of multifunctional molecules (eq. 1) and applications of these molecules in a variety of stereoselective transformations have been well documented in the literature.¹ In continuation of our interest in Baylis-Hillman reaction,² we herein report the application of aqueous trimethylamine in performing the Baylis-Hillman coupling between various alkyl acrylates and aldehydes.

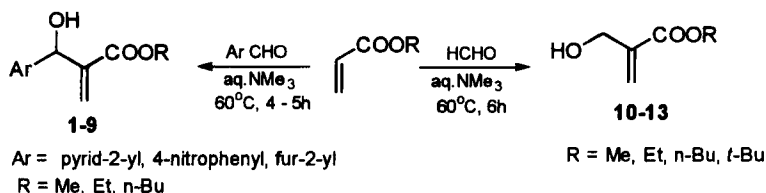
* To whom correspondence should be addressed



Though DABCO has been the most commonly used catalyst for the Baylis-Hillman reaction, organic chemists have been interested in the development of other catalysts/catalytic systems such as DMAP,³ dimethyl sulfide/TiCl₄,⁴ pyrrolizidines,⁵ phosphines⁶ *etc.* Careful literature survey reveals that Nakagawa *et al.* reported in 1995 in their European patent an aqueous trimethylamine mediated Baylis-Hillman reaction of paraformaldehyde with alkyl acrylates.⁷ With an objective to understand the scope of various amine catalysts in performing the Baylis-Hillman reaction, we have undertaken a systematic study on the efficacy of trimethylamine, the tertiary amine containing minimum number of carbon atoms, for performing the Baylis-Hillman reaction. In this direction first we examined the Baylis-Hillman reaction of 2-pyridinecarboxaldehyde with methyl acrylate in the presence of aqueous trimethylamine. The best results were obtained when a mixture of 2-pyridinecarboxaldehyde (10 mmol), methyl acrylate (30 mmol) and aqueous trimethyl amine (30% w/v) (12 mmol) was heated at 60°C for 4 hours thus providing the required methyl 3-hydroxy-2-methylene-3-(pyrid-2-yl)propanoate (**1**) in 62% yield after usual work up.^{8,9} Encouraged by the fastness of this reaction we then successfully carried out the aq.Me₃N catalyzed Baylis-Hillman coupling of representative alkyl acrylates with various reactive aldehydes (Scheme 1, Tables 1&2).⁹ However similar

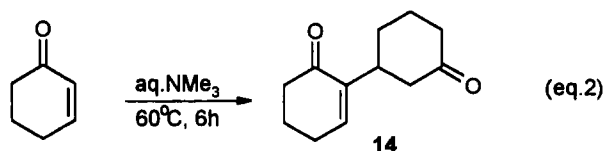
reaction of benzaldehyde and 4-chlorobenzaldehyde with methyl acrylate is extremely sluggish under these conditions.

Scheme 1



We also successfully carried out the aqueous trimethylamine induced Baylis-Hillman reaction of paraformaldehyde with various alkyl acrylates thus providing a simple synthesis of alkyl 2-(hydroxymethyl)prop-2-enoates (**10-13**) in good yields (Scheme 1, Tables 1&2).⁹ Alkyl 2-(hydroxymethyl)prop-2-enoates are important precursors for the synthesis of α -bromomethylacrylates and α -methylene- γ -butyrolactones.¹⁰

Attempted Baylis-Hillman reaction of cyclohex-2-en-1-one with paraformaldehyde in presence of aq. Me_3N was not clean. However, cyclohex-2-en-1-one undergoes Michael type self dimerization in the presence of aqueous trimethylamine (30% w/v) (1.2 equivalents) to provide 2-(3-oxocyclohex-1-yl)cyclohex-2-enone (**14**) in 35% yield (eq. 2, Table 2).^{11, 12}



In conclusion, we have demonstrated the application of aqueous trimethylamine (which is readily available and cheap) as an alternative catalyst

Table 1: Aqueous trimethylamine mediated Baylis-Hillman reaction^{a,b,c}

Aldehyde	COOR	Time (h)	Product	Yield ^d (%)
2-pyridinecarboxaldehyde	COOMe	4	1 ¹²	62
	COOEt	4	2 ¹²	66
	COOBu ⁿ	4	3	74
4-nitrobenzaldehyde	COOMe	5	4 ¹²	56
	COOEt	5	5	59
	COOBu ⁿ	5	6	58
2-furaldehyde	COOMe	5	7 ¹²	30
	COOEt	5	8	33
	COOBu ⁿ	5	9 ¹²	35
paraformaldehyde	COOMe	6	10 ¹²	52
	COOEt	6	11 ¹²	66
	COOBu ⁿ	6	12	62
	COOBu ^t	6	13 ¹²	64

a) all reactions of aromatic aldehydes were carried out on a 10 mmol scale of the aldehyde with 30 mmol of alkyl acrylate and 12 mmol of aqueous trimethylamine (30% w/v) at 60°C. b) all reactions in the case of HCHO were carried out on a 100 mmol scale of HCHO with 200 mmol of alkyl acrylate and 120 mmol of aqueous trimethylamine (30% w/v) at 60°C. c) all products (except **4**) were obtained as either colorless (**1**, **2**, **10-13**) or pale yellow oils (**3**, **5-9**, **14**); compound **4** was obtained as pale yellow crystals. d) yields of the isolated pure products after silica gel column chromatography (5% ethyl acetate in hexanes) (**1-9**) or distillation under reduced pressure (**10-13**) based on the aldehydes.

Table 2: Spectral Data of the Compounds 1-14^a

Product	IR (cm ⁻¹)	¹ H NMR (CDCl ₃ , 200 MHz)	¹³ C NMR (CDCl ₃ , 50 MHz)
1 ¹³	3371, 1720, 1631	δ 3.73 (s, 3H), 4.80 (b, 1H, D ₂ O washable), 5.62 (s, 1H), 5.96 (s, 1H), 6.35 (s, 1H), 7.22 (m, 1H), 7.41 (m, 1H), 7.66 (m, 1H), 8.54 (m, 1H)	δ 51.52, 71.94, 121.11, 122.37, 126.38, 136.62, 141.61, 148.05, 159.68, 166.26
2 ¹³	3368, 1714, 1631	δ 1.24 (t, 3H, J = 7.5 Hz), 4.19 (q, 2H, J = 7.5 Hz), 4.82 (b, 1H, D ₂ O washable), 5.62 (s, 1H), 5.95 (s, 1H), 6.36 (s, 1H), 7.21 (m, 1H), 7.42 (m, 1H), 7.67 (m, 1H), 8.54 (m, 1H)	δ 13.84, 60.55, 72.12, 121.14, 122.40, 126.29, 136.64, 141.93, 148.09, 159.79, 165.90
3 ¹³	3387, 1716, 1631	δ 0.88 (t, 3H, J = 7.0 Hz), 1.20-1.45 (m, 2H), 1.50-1.75 (m, 2H), 4.10 (t, 2H, J = 6.7 Hz), 4.80 (bs, 1H, D ₂ O washable), 5.60 (s, 1H), 5.93 (s, 1H), 6.34 (s, 1H), 7.14-7.48 (m, 2H), 7.61-7.76 (m, 1H), 8.53 (m, 1H)	δ 13.57, 19.02, 30.47, 64.59, 72.28, 121.20, 122.52, 126.54, 136.76, 142.01, 148.17, 159.77, 166.12
4 ¹⁴	3512, 1699, 1628	δ 3.25 (d, 1H, J = 5.8 Hz, D ₂ O washable), 3.75 (s, 3H), 5.63 (d, 1H, J = 5.8 Hz), 5.86 (s, 1H), 6.39 (s, 1H), 7.57 (d, 2H, J = 8.6 Hz), 8.21 (d, 2H, J = 8.6 Hz)	δ 52.04, 72.15, 123.45, 126.90, 127.38, 141.18, 147.29, 148.83, 166.27
5 ¹³	3487, 1711, 1630	δ 1.26 (t, 3H, J = 6.8 Hz), 3.33 (d, 1H, J = 6.0 Hz, D ₂ O washable), 4.19 (q, 2H, J = 6.8 Hz), 5.62 (d, 1H, J = 6.0 Hz), 5.84 (s, 1H), 6.39 (s, 1H), 7.57 (d, 2H, J = 8.4 Hz), 8.20 (d, 2H, J = 8.4 Hz)	δ 13.87, 61.16, 72.18, 123.40, 126.64, 127.38, 141.38, 147.23, 148.94, 165.81
6 ¹³	3485, 1711, 1630	δ 0.90 (t, 3H, J = 7.0 Hz), 1.19-1.74 (m, 4H), 2.73 (b, 1H, D ₂ O washable), 4.12 (t, 2H, J = 6.5 Hz), 5.62 (s, 1H), 5.85 (s, 1H), 6.38 (s, 1H), 7.56 (d, 2H, J = 8.5 Hz), 8.19 (d, 2H, J = 8.5 Hz)	δ 13.40, 18.90, 30.28, 64.94, 72.22, 123.35, 126.56, 127.29, 141.32, 147.21, 148.84, 165.81

(continued)

Table 2. Continued

7	3445, 1720, 1633	δ 3.05 (d, 1H, J = 6.0 Hz, D ₂ O washable), 3.77 (s, 3H), 5.59 (d, 1H, J = 6.0 Hz), 5.94 (s, 1H), 6.24-6.36 (m, 2H), 6.39 (s, 1H), 7.38 (s, 1H)	δ 51.90, 66.67, 107.09, 110.29, 126.52, 139.63, 142.23, 154.21, 166.41
8 ¹³	3433, 1712, 1633	δ 1.27 (t, 3H, J = 7.6 Hz), 3.29 (b, 1H, D ₂ O washable), 4.21 (q, 2H, J = 7.6 Hz), 5.58 (s, 1H), 5.92 (s, 1H), 6.22-6.43 (m, 3H), 7.38 (s, 1H)	δ 13.88, 60.85, 66.72, 106.98, 110.24, 126.10, 139.90, 142.11, 154.33, 165.93
9	3439, 1714, 1633	δ 0.92 (t, 3H, J = 6.8 Hz), 1.22-1.50 (m, 2H), 1.52-1.74 (m, 2H), 3.07 (d, 1H, J = 6.8 Hz, D ₂ O washable), 4.17 (t, 2H, J = 6.8 Hz), 5.58 (d, 1H, J = 6.8 Hz), 5.92 (s, 1H), 6.24-6.45 (m, 3H), 7.37 (s, 1H)	δ 13.51, 18.97, 30.43, 64.74, 66.80, 107.00, 110.28, 126.11, 139.94, 142.14, 154.40, 166.02
10 ¹⁴	3422, 1718, 1637	δ 1.99 (s, 1H, D ₂ O washable), 3.79 (s, 3H), 4.34 (s, 2H), 5.85 (s, 1H), 6.27 (s, 1H)	δ 51.55, 61.02, 125.01, 139.36, 166.58
11 ¹⁴	3427, 1712, 1639	δ 1.31 (t, 3H, J = 6.8 Hz), 2.24 (s, 1H, D ₂ O washable), 4.20 (q, 2H, J = 6.8 Hz), 4.32 (s, 2H), 5.82 (s, 1H), 6.25 (s, 1H)	δ 13.97, 60.68, 61.63, 124.88, 139.82, 166.24
12 ^{13,14}	3437, 1714, 1635	δ 0.95 (t, 3H, J = 7.2 Hz), 1.31-1.59 (m, 2H), 1.61-1.83 (m, 2H), 2.06 (bs, 1H, D ₂ O washable), 4.19 (t, 2H, J = 6.6 Hz), 4.33 (s, 2H), 5.82 (s, 1H), 6.25 (s, 1H)	δ 13.48, 19.03, 30.47, 61.74, 64.53, 124.84, 139.78, 166.27
13 ¹⁴	3427, 1709, 1639	δ 1.51 (s, 9H), 2.08 (s, 1H, D ₂ O washable), 4.28 (s, 2H), 5.74 (s, 1H), 6.15 (s, 1H)	δ 27.95, 62.03, 81.14, 124.21, 141.01, 165.59
14 ¹³	1711, 1670	δ 1.46-2.14 (m, 6H), 2.16-2.54 (m, 8H), 2.88-3.10 (m, 1H), 6.69 (t, 1H, J = 4.0 Hz)	δ 22.45, 24.81, 25.77, 30.28, 37.27, 38.45, 40.93, 46.14, 141.48, 144.18, 198.11, 210.85

a) IR spectra were recorded on a JASCO-FT-IR model 5300 spectrometer using samples as neat liquids (compounds 1-3, 5-14) or as KBr disk (compound 4). ¹H and ¹³C NMR spectra were recorded on a Bruker-AC-200 spectrometer using tetramethylsilane (TMS, $\delta = 0$) as an internal standard.

for the Baylis-Hillman reaction of reactive aldehydes and formaldehyde with various alkyl acrylates.

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8. This molecule is known in the literature and was prepared *via* the DABCO catalyzed coupling of 2-pyridinecarboxaldehyde with methyl acrylate in CHCl₃ for 3 days in 94% yield. See: Bode, M.L.; Kaye, P.T. *J. Chem. Soc., Perkin Trans. 1*, **1993**, 1809.
9. *Preparation of molecule 1 (Representative procedure):* A mixture of pyridine-2-carboxaldehyde (10 mmol, 1.071 g), methyl acrylate (30 mmol, 2.583 g) and aqueous trimethylamine (30% w/v) (12 mmol, 2.36 mL) was heated at 60°C for 4

hours. The reaction mixture was then cooled to room temperature, layers separated and the aqueous layer was extracted with ether (3 × 10 mL). The combined organic layer was dried over anhydrous sodium sulfate, concentrated and silica gel column chromatography (5% ethyl acetate in hexanes) of the crude product thus obtained, has provided 1.196 g (62%) of methyl 3-hydroxy-2-methylene-3-(pyrid-2-yl)propanoate (1) as a colorless oil.

10. a) Masuyama, Y.; Nimura, Y.; Kurusu, Y. *Tetrahedron Lett.*, **1991**, *32*, 225. b) Drewes, S.E.; Loizou, G.; Roos, G.H.P. *Synth. Commun.*, **1987**, *17*, 291.
11. *Preparation of molecule 14*: A mixture of cyclohex-2-en-1-one (20 mmol, 1.923 g) and aqueous trimethylamine (30% w/v) (24 mmol, 4.72 mL) was heated at 60°C for 6 hours. Usual work up followed by silica gel column chromatography (10% ethyl acetate in hexanes) has provided 0.680 g (35%) of 14 as pale yellow oil.
12. These molecules are known, and their spectral data (IR, ¹H and/or ¹³C NMR) are reported in the literature. Spectral data of these molecules are agreement with the literature data. For molecule 1, see: Foucaud, A.; El Guemmout, F. *Bull. Soc. Chim. Fr.*, **1989**, 403. For molecule 2, see: ref: 8. For molecule 4, see: ref: 15. For molecules 7 and 9, see: Fort, Y.; Berthe, M.C.; Caubere, P. *Tetrahedron*, **1992**, *48*, 6371. For molecule 10, see: ref: 10b. For molecule 11, see: ref: 16. For molecule 13, see: Novarro, C.; Castaing, M.D.; Colombani, D.; Maillard, B. *Synth. Commun.*, **1993**, *23*, 1025. For molecule 14, see: Mubarak, M.S.; Pagel, M.; Marcus, L.M.; Peters, D.G. *J. Org. Chem.*, **1998**, *63*, 1319.
13. Elemental analysis of selected products:[#].@

Product	Mol. Formula	Found (Calcd.) (%)		
		C	H	N
1	C ₁₀ H ₁₁ O ₃ N	62.01 (62.17)	5.77 (5.74)	7.28 (7.25)
2	C ₁₁ H ₁₃ O ₃ N	63.98 (63.76)	6.36 (6.32)	6.73 (6.76)
3	C ₁₃ H ₁₇ O ₃ N	66.62 (66.36)	7.27 (7.28)	5.99 (5.95)
5	C ₁₂ H ₁₃ O ₅ N	57.19 (57.37)	5.24 (5.22)	5.56 (5.58)
6	C ₁₄ H ₁₇ O ₃ N	60.45 (60.21)	6.10 (6.14)	5.03 (5.02)
8	C ₁₀ H ₁₂ O ₄	61.51 (61.22)	6.13 (6.16)	---
12	C ₈ H ₁₄ O ₃	60.84 (60.74)	8.95 (8.92)	---
14	C ₁₂ H ₁₆ O ₂	74.66 (74.97)	8.34 (8.39)	---

Elemental analysis is furnished for either unknown molecules or the known molecules whose spectral data is not fully reported in the literature.

@ Recorded on a Perkin-Elmer 240C-CHN analyzer.

14. Compound 4: m.p.: 72-73°C (lit.¹⁵ 74°C); Compound 10: b.p.: 71-72°C/2mm; Compound 11: b.p.: 78-80°C/2mm (lit.¹⁶ 65-70°C/1mm); Compound 12: b.p.: 80°C/0.5mm; Compound 13: b.p.: 76°C/0.5mm.
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