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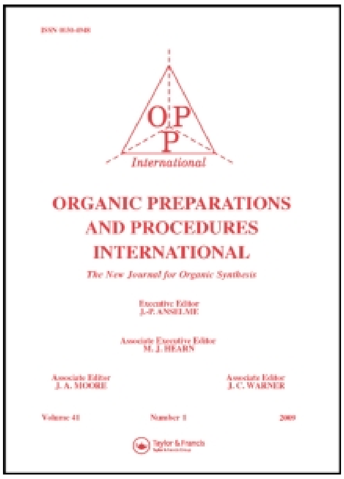

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IMPROVED PROCEDURES FOR THE BAYLIS-HILLMAN REACTION

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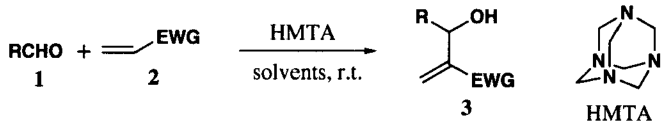
The Baylis-Hillman reaction is an atom-economical and extremely useful C-C bond forming reaction in organic synthesis.[1] Although numerous catalytic systems, such as tertiary amines,[2] phosphines,[3] $TiCl_4$ and others,[5] have been used as catalysts to mediate this reaction, 1,4-diazabicyclo[2.2.2]octane (DABCO), first introduced by Baylis and Hillman,[6] is arguably still the most widely used one. Hexamethylenetetramine (HMTA), a very inexpensive hindered tertiary amine, is a nucleophilic base. It can effectively attack the terminal carbon of activated alkenes, and thus should be a useful catalyst for the Baylis-Hillman reaction. Though, Tang *et al.* recently described one experiment using HMTA (urotropine) as promoter with dioxane-water (1:1) as solvent, to prepare 3 h in good yield (87%),[7] the scope and generality this catalyst were not tested for various aldehydes and activated olefins. The present paper describes the study of the Baylis-Hillman reaction catalyzed by hexamethylenetetramine (HMTA) and in an ionic liquid (*Scheme 1*).



a) R = 2-$NO_2C_6H_4$, EWG = CN
b) R = 2-$NO_2C_6H_4$, EWG = CO_2CH_3
c) R = 2-$NO_2C_6H_4$, EWG = $CO_2C_4H_9$-n
d) R = 2-$NO_2C_6H_4$, EWG = $CONH_2$
e) R = 3-$NO_2C_6H_4$, EWG = CN
f) R = 3-$NO_2C_6H_4$, EWG = CO_2CH_3
g) R = 4-$NO_2C_6H_4$, EWG = CN
h) R = 4-$NO_2C_6H_4$, EWG = CO_2CH_3
i) R = 4-Cl-3-$NO_2C_6H_4$, EWG = CN
j) R = 4-Cl-3-$NO_2C_6H_4$, EWG = CO_2CH_3
k) R = 2-pyridine, EWG = CO_2CH_3
l) R = 2-pyridine, EWG = $CONH_2$
m) R = 4-ClC_6H_4, EWG = CO_2CH_3
n) R = C_6H_5, EWG = CN
o) R = 3-OHC_6H_4, EWG = CN
p) R = H, EWG = CO_2CH_3
q) R = CH_3, EWG = CO_2CH_3

Scheme 1

In order to evaluate the influence of HMTA 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 HMTA. A 67% yield of **3c** was obtained when a mixture of 2-nitrobenzaldehyde (3 mmol), butyl acrylate (9 mmol), H_2O (5 mL), dioxane (5 mL) and HMTA (1 mmol) was stirred at ambient temperature. For comparison, the same reaction performed in the presence of DABCO afforded **3c** in 59% yield (*Table 1*). Encouraged by this result, we then carried out the HMTA and 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 four hours, Furthermore, the formation of Baylis-Hillman adducts could be only detected in very low yield (by TLC, GC). In contrast to the results obtained with DABCO, the reactions catalyzed by HMTA proceeded very cleanly and the yields of the desired products are high (*Table 1*).

Table 1. Baylis-Hillman Reaction Mediated by HMTA in Dioxane-water and [BuPy][BF_4]

Cmpd	Yield (%)	mp. (°C)	*lit.* mp. (°C)	Time (hrs)	Solvent
3a	85[a]	41-42	40-42[1]	24	Dioxane-water (1:1)
3a	86	41-42	40-42[1]	2	[BuPy][BF_4]
3b	82	Oil	Oil[6d]	24	Dioxane-water (1:1)
3b	81	Oil	Oil[6d]	8	[BuPy][BF_4]
3c	67[b]	Oil	Oil[7]	30	Dioxane-water (1:1)
3d	72[c]	59-60	60[5c]	16	Dioxane-water (1:1)
3d	76	59-60	60[5c]	8	[BuPy][BF_4]
3e	86	64-65	64[1]	4	[BuPy][BF_4]
3f	80	Oil	Oil[5d]	24	Dioxane-water (1:1)
3f	85	Oil	Oil[5d]	6	[BuPy][BF_4]
3g	86.5	73.5-74	72-75[7]	4	[BuPy][BF_4]
3h	78	72-73.5	71-73[7]	24	Dioxane-water (1:1)
3h	89	72-73.5	71-73[7]	4	[BuPy][BF_4]
3i	82	Oil	----	8	[BuPy][BF_4]
3j	79	84-85	----	12	[BuPy][BF_4]
3k	92	Oil	Oil[5d]	16	Dioxane-water (1:1)
3l	81.5	Oil	Oil[5c]	24	Dioxane-water (1:1)
3m	42	42-43	43-44[7]	48	Dioxane-water (1:1)
3n	39	Oil	Oil[7]	24	Dioxane-water (1:1)
3n	47	Oil	Oil[7]	24	[BuPy][BF_4]
3o	34	Oil	-----	48	Dioxane-water (1:1)
3p	62	Oil	Oil[5d]	52	Dioxane-water (1:1)
3q	74	Oil	Oil[5d]	56	Dioxane-water (1:1)

a) Only trace amounts with DABCO. b) Yield with DABCO (59%). c) Yield with DABCO (45%).

To broaden the scope of the Baylis-Hillman reaction catalyzed by HMTA, we also successfully carried out the HMTA induced Baylis-Hillman reaction of the other aldehydes with a three fold equiv. of activated alkenes. The yields reported in *Table 1* are based on the amount of aldehydes used.

Table 2. IR and ^{1}H NMR Spectra of the Known Products

Product	IR (cm^{-1})	^{1}H NMR (δ)
3a	3462, 2229, 1610, 1344	8.03 (d, J = 8.06 Hz, 1H), 7.84 (d, J = 8.06 Hz, 1H), 7.73 (t, J = 7.71 Hz, 1H), 7.56 (t, 1H, J = 7.71 Hz), 6.15 (s, 1H), 6.12 (s, 1H), 5.96 (d, J = 5.56 Hz, 1H), 3.27 (br s, 1H)
3b	3449, 1714, 1530, 1352	7.96 (d, J = 8.01 Hz 1H), 7.76 (d, 1H, J = 8.01 Hz), 7.66 (t, J = 7.41 Hz, 1H), 7.48 (t, 1H, J = 7.41 Hz), 6.38 (s, 1H), 6.21 (s, 1H), 5.74 (s, 1H), 3.77 (s, 3H), 3.25 (br s, 1H)
3c	3434, 2960, 1731, 1536, 1357	8.04 (d, 1H, J = 8.05 Hz), 7.74 (d, J = 8.05 Hz, 1H), 7.60 (t, J = 7.56 Hz, 1H), 7.44 (t, J = 7.56 Hz, 1H), 5.92 (s, 1H), 5.62 (s, 1H), 5.20 (s, 1H), 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)
3d	3360, 1662, 1640, 1346	10.43 (s, 1H), 8.13 (d, J = 8.09 Hz, 1H), 7.96 (d, J = 8.09 Hz), 7.80 (t, J = 7.76 Hz, 1H), 7.76 (t, J = 7.76 Hz 1H), 6.19~6.34 (m, 2H), 5.73 (d, J = 5.52 Hz 1H), 5.53 (br s, 2H)
3e	2239, 1533, 1348	8.07 (s, 1H), 8.02 (d, J = 8.06 Hz, 1H), 7.58 (d, J = 7.71 Hz, 1H), 7.40 (t, J = 7.71 Hz, 1H), 6.03 (s, 1H), 5.93 (s, 1H), 5.27 (s, 1H), 2.84 (br s, 1H)
3f	3482,1715, 1530, 1352	8.19 (t, J = 1.01 Hz 1H), 8.07 (d, 1H, J = 8.01 Hz), 7.72 (t, J = 7.81 Hz, 1H), 7.50 (t, 1H, J = 7.81 Hz), 6.38 (s, 1H), 5.94 (s, 1H), 5.63 (s, 1H), 3.77 (s, 3H), 3.55 (br s, 1H)
3g	3424, 2865, 2229	8.26 (d, J = 8.56 Hz, 2H), 7.60 (d, J = 8.02 Hz, 2H), 6.18 (1s, 1H), 6.10 (s, 1H), 5.44 (s, 1H), 2.11 (br s, 1H)
3h	3510, 2992, 1724, 1634	8.70 (d, J = 8.76 Hz, 2H), 7.56 (d, J = 8.76 Hz, 2H), 6.40 (s, 1H), 5.88 (s, 1H), 5.64 (d, J = 5.87 Hz, 1H), 3.75 (s, 3H), 3.40 (br s, 1H)
3k	3418, 3012, 2952, 1725, 1593	8.48 (d, J = 4.82 Hz, 1H), 7.60-7.55 (m, 1H), 7.36 (d, 1H, J = 7.36 Hz), 7.15 (t, 1H, J = 6.15 Hz), 6.33 (s, 1H), 5.90 (s, 1H), 5.61 (d, 1H, J = 5.31 Hz), 4.83 (br s, 1H, OH), 3.68 (s, 3H, CH_3)
3l	3380, 1675	8.3-8.18 (m, 1H,), 7.52 (d, J = 7.6 Hz, 1H), 7.27(d, J = 8.4 Hz, 1H), 7.05-6.96 (m, 1H), 5.76 (s, 1H), 5.68 (s, 2H), 5.32 (s, 1H), 5.38 (s, 1H), 3.29 (br s, 1H)
3m	3500, 2985, 1725	7.82 (s, 2H), 7.30 (s, 2H), 6.35 (s, 1H), 5.85 (s, 1H), 5.52 (d, J = 5.82 Hz, 1H), 3.72 (s, 3H), 3.15 (d, J = 5.84, 1H)
3n	3445, 2229, 1605	7.40-7.16 (m, 5H), 6.15 (s, 1H), 6.12 (s, 1H), 5.96 (d, J = 5.56 Hz 1H), 2.87 (br s, 1H)
3p	3440, 2989, 1720, 1613	6.25 (s, 1H), 5.88 (s, 1H), 4.30 (s, 2H), 3.78 (s, 3H), 3.2 (br s, 1H)
3q	3469, 2937, 1720, 1638	6.15 (d, J = 1.5 Hz, 1H), 5.8 (d, J = 1.2 Hz, 1H), 4.76 (m, 1H), 3.70 (s, 3H), 2.9 (br s, 1H), 1.25 (d, J = 6.5 Hz, 3H).

Table 3. IR, ^1H and ^{13}C NMR Spectra and Elemental Analysis of **3i**, **3j** and **3o**

Product	IR (cm^{-1})	^1H NMR (δ)	^{13}C NMR (δ)	Elemental Analysis (Found) C	H	N
3i	3429, 2875, 2229, 1537	7.74 (s, 1H), 7.39 (m, 2H), 6.00 (s, 1H), 5.92 (s, 1H), 5.20 (s, 1H), 3.00 (br s, 1H)	74.7, 118.6, 126.0, 127.5, 129.7, 133.5, 133.9, 134.6, 142.1, 150.3	50.26	2.91	11.72
3j	3471, 1708, 1533	7.89 (s, 1H), 7.48-7.55 (m, 2H), 6.39 (s, 1H), 5.89 (s, 1H), 5.55 (s, 1H), 3.73 (s, 3H), 3.01 (br s, 1H)	54.7, 74.5, 126.0, 128.5, 128.8, 129.9, 133.5, 134.2, 143.0, 144.5, 168.6	48.21	3.56	5.12
3o	3381, 2233, 1593, 1271	7.25 (t, J = 7.86 Hz, 1H), 6.88 (d, J = 7.06 Hz), 6.80 (d, J = 7.01 Hz), 6.7 (br s, 1H), 6.10 (s, 1H), 6.04 (s, 1H), 5.90 (br s, 1H), 5.25 (s, 1H)	73.8, 113.2, 113.5, 116.0, 116.8, 118.6, 128.8, 130.2, 140.7, 156.0	68.51	5.22	7.86

The Baylis-Hillman reaction is very sluggish[2] and several attempts have been made to accelerate this reaction by using nitrogen base,[7] high pressure,[8] ultrasound,[9] microwave irradiation[10] and changing reaction medium such as using supercritical CO_2,[11] water,[12] aqueous medium,[5d] and poly(ethyleneglycol).[13] In spite of the number of significant improvements made to the Baylis-Hillman reaction resulting from these modifications, there still remains a need for identifying new solvents. It is well known that polar solvents, such as methanol, accelerate the Baylis-Hillman reaction by stabilizing the polar reactive intermediate. This has led to the use of ionic liquids to facilitate the reaction. A recent report has described acceleration of the DABCO-catalysed Baylis-Hillman in an ionic liquid, 1-butyl-3-methyimidazolium hexafluorophosphate ([bmim][PF_6]).[14] It was later shown that the imidazolium salts are deprotonated under basic conditions, to generate reactive nucleophiles.[15] The low yields reported in the ionic liquid [bmim][PF_6] result from the reaction between the aldehyde and the reactive nucleophiles under basic conditions. Therefore, the development of efficient ionic liquids is still a desirable goal.

The present work reports that the Baylis-Hillman reaction could be carried out rapidly and cleanly in N-butylpyridinium tetrafluoroborate ([BuPy][BF_4]). The recycling and re-use of the reactive medium in the Baylis-Hillman reaction of 2-nitrobenzaldehyde with methyl acrylate were also demonstrated. Firstly, in order to compare the reaction rates in ionic liquid [BuPy][BF_4] with conventional solvents, the condensation between 2-nitrobenzaldehyde and acrylonitrile in the presence of hexamethylenetetramine (HMTA) and DABCO was carried out in ethanol, dioxane/H_2O (1:1,v/v) and [BuPy][BF_4]. The results are shown in *Table 1*. Indeed, the rate of reaction of 2-nitrobenzaldehyde with acrylonitrile in the ionic liquid [BuPy][BF_4] was found to be much higher than in the other media.

Hu *et al.*[5d] have reported that the Baylis-Hillman reaction was rapid in dioxane/H_2O (1:1,v/v) and they believed that the Baylis-Hillman reaction sequence involved charged transition states and intermediates could be stabilized by polar solvents such as water through intermolecular charge-dipole interactions as well as hydrogen-bonding interactions. Now in the [BuPy][BF_4] with 1mmol HMTA, the reaction was faster than in dioxane/H_2O (1:1, v/v). The reason for the reactivity increase in ionic solvent could eventually result from the effect of the solvent on the reaction equilibrium, due to stronger stabilization of the zwitterionic intermediate. Encouraged by this result, we next examined some other Baylis-Hillman reactions catalyzed by HMTA in the [BuPy][BF_4] (*Table 1*). The versatility of the [BuPy][BF4] as a solvent for Baylis-Hillman reaction was further strengthened when a variety of aromatic aldehydes were allowed to react with Michael acceptors such as methyl acrylate and acrylonitrile at room temperature to give the corresponding adducts respectively, in good to excellent yields and in short reaction times. To evaluate the possibility of recycling the ionic liquid used for the reaction, methyl acrylate (9 mmol) was added to a magnetically stirred solution of 2-nitrobenzaldehyde (3 mmol) and HMTA (1 mmol) in the [BuPy][BF_4](10 mL), the reaction proceeds smoothly and cleanly. After stirring for 8 h, the reaction mixture was first diluted with dichloromethane, washed twice with 10% citric acid, and then concentrated under pressure. The product in the ionic liquid solution was extracted with ethyl ether (2 x 20 mL). Then the combined ethereal extract was concentrated to dryness *in vacuo* followed by flash chromatographic purification of the Baylis-Hillman adduct. Then methyl acrylate, 2-nitrobenzaldehyde and HMTA were added to the recycled [BuPy][BF_4]. The recovered ionic liquid was used three times and the yields ranged from 78 to 82%.

In conclusion, we have demonstrated that the inexpensive, readily available and user-friendly hexamethylenetetraamine can be used as a new and efficient catalyst for the Baylis-Hillman reaction; in addition, the simple modification to the classical condition using the ionic liquid [BuPy][BF_4] as reaction medium proved to be successful in converting a variety of aromatic aldehydes to their corresponding Baylis-Hillman products.

EXPERIMENTAL SECTION

All glassware were oven-dried and cooled in a desiccator (P_2O_5, desiccant) prior to use. Commercially available reagents were purchased from Aldrich and used without further purification. The ionic liquid N-butylpyridinium tetrafluorobroate ([BuPy][BF_4]) was prepared following reported procedures.[16] All melting points were recorded using capillary melting point apparatus and are uncorrected. The IR spectra were determined neat or as KBr pellets on a Shimadzu FTIR-8300 Spectrophotometer, ^1H NMR and ^{13}C NMR spectra were acquired in CD Cl_3 on a DRX300 NMR Spectrometer using TMS as an internal standard. The elemental analyses were performed at the Institute of Chemistry, Chinese Academy of Sciences. Analytical thin layer chromatography (TLC) was carried out using MN Kieselgel G/UV254 (Art.816320) glass backed plates. All the compounds except **3i**, **3j** and **3o**, are known and their spectral data were identical with those previously reported.

General Procedure of the Baylis-Hillman Reactions.- A solution of the aldehyde (3 mmol) and of the activated alkene (9 mmol) in 10 mL of dioxane/water (1:1, v/v) was stirred for 16 to 56 h at room temperature in the presence of HMTA (1 mmol); the progress of the reaction was monitored by TLC. Upon completion, the reaction mixture was neutralized by the dropwise addition of 1.5 N aqueous HCl, then partitioned with ether (50 mL) and water (30 mL). The organic phase was washed with brine (2 x 30 mL), dried over anhydrous Na_2SO_4. 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).

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REFERENCES

1. D. Basaviah, A. J. Rao and T. Satyanarayana, *Chem. Rev.*, **103**, 811 (2003).

2. a) S. E. Drewes and G. H. P. Roos, *Tetrahedron*, **44**, 4653 (1988). b) D. Basavaiah, P. D. Rao and R. S. Hyma, *Tetrahedron*, **52**, 8001 (1996). c) P. Langer, *Angew. Chem. Int. Ed.*, **39**, 3049 (2000). d) V. K. Aggarwal and A. Mereu, *Chem. Commun.*, 2311 (**1999**).

3. a) M. M. Rauhut and H. Currier (American Cyanamide Co.) *US Patent* 3, 074, 999 (1963); *Chem. Abstr.*, **58**, 11224a (1963). b) Y. M. A. Yamada and S. Ikegami, *Tetrahedron Lett.*, **41**, 2165 (2000).

4. M. Taniguchi, T. Hino and Y. Kishi, *Tetrahedron Lett*, **27**, 4767 (1986).

5. a) D. J. Maher and S. J. Connon, *Tetrahedron Lett.*, **45**, 1301 (2004). b) N. T. McDougal and S. E. Schaus, *J. Am. Chem. Soc.*, **125**, 12094 (2003). c) C. Yu and L. Hu, *J. Org. Chem.*, **67**, 219 (2002). d) C. Yu, B. Liu and L. Hu, *J. Org. Chem.*, **66**, 5413 (2001). e) K. Y. Lee, J. M. Kim and J. N. Kim, *Tetrahedron*, **59**, 385 (2003).

6. A. B. Baylis and M. E. D. Hillman, *German Patent* 2,155,113 (1972); *Chem. Abstr.*, **77**, 34174q (1972).

7. J. Cai, Z. Zhou, G. Zhao and C. Tang, *Organic Lett.*, **4**, 4723 (2002). P. R. Krishna, E. R. Sekhar and V. Kannan, *Synthesis*, 857 (**2004**). R. O. M. A. de Souza, B. A. Meireles, L. C. S. Aguiar and M. L. A. A. Vasconcellos, *Synthesis*, 1595 (**2004**).

8. J. S. Hill and N. S. Isaacs, *Tetrahedron Lett.*, **27**, 5007 (1986).

9. F. Coelho, W. P. Almeida, D. Veronese, C. R. Mateus, E. C. S. Lopes, R. C. Rossi, G. P. C. Silveira and C. H. Pavam, *Tetrahedron*, **58**, 7437 (2002).

10. M. K. Kundu, S. B. Mukherjee, N. Balu, R. Padmakumar and S. V. Bhat, *Synlett*, 444 (**1994**).

11. P. M. Rose, A. A. Clifford, and C. M. Rayner, *Chem. Commun.*, 968 (**2002**).

12. J. Augé, N. Lubin, and A. Lubineau, *Tetrahedron Lett.*, **35**, 7947 (1994).

13. S. Chandrasekhar, C. Narsihmulu, B. Saritha, and S. S. Sultana, *Tetrahedron Lett.*, **45**, 5865 (2004).

14. J. N. Rosa, C. A. M. Afonso and A. G. Santos, *Tetrahedron*, **57**, 4189 (2001).

15. V. K. Aggarwal, I. Emme and A. Mereu, *Chem. Commun.*, 1612 (**2002**)

16. G. S. Owens, and M. M. Abu-Omar, *J. Mol. Catal. A: Chem.*, **187**, 215 (2002).

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