SHORT PAPER

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An efficient benzyltriethylammonium chloride catalysed preparation of electrophilic alkenes: a practical synthesis of trimethoprim†

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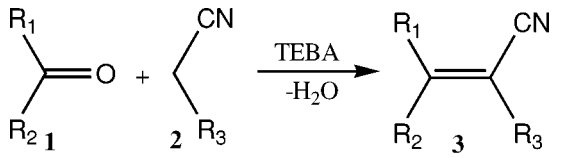
The Knoevenagel condensation of carbonyl compounds with active methylene compounds was readily carried out with benzyltriethylammonium chloride as a catalytic agent, under solvent-free conditions to produce olefinic products in high yields: the scope of this protocol is utilised for the synthesis of the antibacterial agent trimethoprim.

Keywords: benzytriethylammonium chloride, electrophilic alkenes trimethoprim

In spite of the fundamental importance in organic synthesis of the formation of carbon–carbon single or double bonds there are relatively few general methods available for effecting this process. Ever since its discovery, the Knoevenagel reaction[1] has been widely utilised in organic synthesis to produce coumarins and coumarin derivatives which are important chemicals in the cosmetic, perfume and pharmaceutical industries.[2] In the last few years, there has been a growing interest in Knoevenagal condensation products, because many of them have significant biological activity *e.g.*, tyrphostins, such as α-cyanothiocinnamide, were shown to inhibit autophosphorylation of the EGF receptor, in addition to possessing antiproliferative effects on human keratinocytes.[3] Usually the process consists of the condensation of active methylene compounds such as cyanomethyl ketones with aromatic aldehydes or ketones and proceeds *via* standard Knoevenagel reaction conditions from which benzylidene cyanomethyl ketone products can be obtained. Under homogenous conditions, weak bases[4] or Lewis acids[5] are known to catalyse this condensation. However, it can also be performed in heterogeneous media.[6-10] Most of the examples developed so far employ mainly aldehydes rather than ketones. However, there still exists a need for the development of new and mild methods of obtaining these products under conditions tolerated by sensitive functional groups, and using techniques involving easy work-up procedures (Scheme 1).



Scheme 1

In view of the current interest in catalytic processes, there is merit in developing a truly catalytic method for the stereoselective formation of *E*-olefins using inexpensive reagents. The use of such processes should increase the process's selectivity, maximise the use of starting materials, replace stoichiometric reagents with catalysts and facilitate easy separation of the final reaction mixture including the efficient recovery and reusability of the catalyst. Here we wish to report the use of a new catalytic agent, benzyltriethylammonium chloride (TEBA),[11] for C–C bond formation in heterogeneous conditions in the absence of solvent. The reaction proceeds efficiently in high yields and the olefinic products are obtained in good purity.

TEBA is one of many commonly used phase transfer catalysts in organic synthesis in general and in particular in the formation of carbenes in heterogenous systems. It has recently been used as an activator for fluorapatite as a heterogeneous catalyst of the solvent-free Knoevenagel reaction.[12] To our knowledge, however, the generality and applicability of TEBA as a catalyst for the preparation of electrophilic alkenes under solvent-free conditions is not known. To reduce the employment of ecologically-suspect solvents, we have chosen to carry out the reactions in the absence of solvent. The ability of TEBA as a neutral catalytic agent in Knoevenagel condensations was demonstrated using various aliphatic, aromatic and heterocyclic carbonyl compounds reacting with active methylene compounds such as malononitrile, ethylcyanoacetate and 2-cyanoacetamide in the presence of TEBA and the results are summarised in Table 1. These reactions lead to completion in 1h at 80°C to produce the olefinic products in 40–95% yield. Interestingly, the reaction with the more acidic malononitrile went very fast giving excellent yields whereas ethylcyanoacetate and 2-cyanoacetamide were relatively less reactive. The reaction conditions for and the corresponding yields from these three active methylene species suggest that their reactivity order is: R = CN > CO_2Et > $CONH_2$. Aromatic α,β-unsaturated aldehydes give the corresponding olefins and there was no evidence for the formation of Michael-type addition products (entry **1g** and **1h**). Moreover, the Knoevenagel reaction is strongly solvent dependent under both homogeneous and heterogeneous conditions. Thus, for example, the reaction of cinnamaldehyde with malononitrile gave 1,1-dicyano-4-phenylbuta-1,3-diene in 95% conversion after 1h (entry **1g**). When the same reaction was carried out in refluxing benzene, it required a longer reaction time (approximately 15h) and gave a poor yield of **3g**; only isobutyraldehyde (entry **1i**) afforded **3i** in low yield, probably due to the evaporation (low boiling point of this aldehyde). In the case of ketones, the condensation of acetophenone and 2-methylcyclohexanone readily occurred (entries **1l** and **1j**) but the hindered 2,6-dimethylcyclohexanone failed to react (entry **1k**). The efficacy of the reaction was studied by subjecting substrates **1e** and **1l** in 20 mmol scale under similar conditions. However, it appears that there is no significant improvement in the rate of reaction by changing experimental parameters such as prolonged time, temperature and nature of the solvent (NMP, 1,4-dioxane, toluene).

In the reaction of *o*-hydroxybenzaldehyde with active methylene compound (entry **1m**), the first formed Knoevenagel

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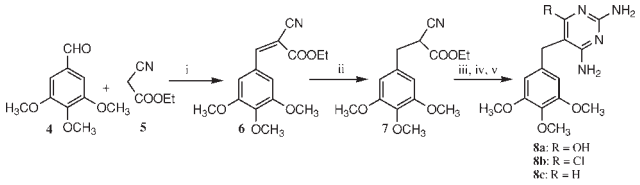
Table 1 TEBA-catalysed Knoevenagel condensation under solvent-free conditions

Entry[a]	R_1	R_2	R_3	Yield/% b	m.p. or b.p.(mmHg)/°C
a	C_6H_5	H	CN	85	82–83[4c]
b	C_6H_5	H	$CONH_2$	75	122–123[4c]
c	*p*-$NO_2C_6H_4$	H	COOEt	85	168–169[6b]
d	3-OCH_3-4-OHC_6H_3	H	CN	92	131–132[5a]
e	3-OCH_3-4-OHC_6H_3	H	$CONH_2$	78	205–206[5a]
f	C_4H_3O (furyl)	H	COOEt	90	93–94[6b]
g	C_6H_5CH=CH-(E)	H	CN	95	127–128[6b]
h	C_6H_5CH=CH-(E)	H	COOEt	90	116–117[6b]
i	C_3H_7 (^{i}Pr)	H	CN	40	20 (0.03)[6b]
j	-$(CH_2)_4$-CH(CH_3)-		CN	55	100 (1)[14]
k	-CH(CH_3)-$(CH_2)_3$-CH(CH_3)-		CN	–	–
l	C_6H_5	CH_3	CN	65	91–92[6b]
m	*o*-OHPh	H	COOEt	75	133–135[6bc]

[a]All the products were characterized by comparison of their m.p or bp, IR and ^{1}HNMR spectra with those of authentic samples. [b]Yields of pure isolated products. [c]The reaction product is characterized by its transformation to 2-oxo-2H-1-benzopyran-3-carboxylic acid ethyl ester (see ref. 13).

condensation product underwent further transformations as a result of nucleophilic attack by the phenolate ion on the cyano group, which is held in a stereochemically favourable position by the olefinic bond. Thus, ethyl 2-imino-2*H*-1-benzopyran-3-carboxylate is formed in 85% yield. The iminolactone thus obtained led us to conclude that the initial product possessed adjacent hydroxyl and cyano groups (*E* configuration, for the condensation with ethyl cyanoacetate). The resulting iminolactone hydrolysed in cold dilute hydrochloric acid to ethyl 2—oxo-2*H*-1-benzopyran-3-carboxylate.[13]

The viability of this strategy is illustrated in a practical synthesis of trimethoprim, a widely used broad spectrum antibacterial agent. The synthetic route to the desired target (Scheme 2) involves the condensation of benzaldehyde (**4**) with ethylcyanomalonate (**5**) in the presence of TEBA as a catalyst for 1h to give the olefinic product (**6**) in 95% yield. The double bond was then reduced to afford compound (**7**). Conversion of **7** into the target compound **8c** was carried out essentially by the three step synthetic sequence reported in the literature[12] involving (iii) guanidine nitrate, (iv) PCl_5-$POCl_3$, (v) Pd/C.



Scheme 2 Regeants and conditions: (i) TEBA, 85°C, 1h, 95%; (ii) 10%Pd-C/H_2, EtOAc, 2.5h, 90%; (iii) guanidine nitrate, Na/MeOH, reflux, 12h; (iv) PCl_5-$POCl_3$, reflux, 4h; (v) 10%Pd-C/H_2, AcOH-H_2O.

In conclusion, the simple procedure, the good yield, and the fairly mild conditions of this method for the stereoselective preparation of *E* olefins will frequently offer significant advantages over the previous methods, and this approach should be of further utility in synthetic organic chemistry.

Experimental

Products were characterised by comparison of their physical data m.p, IR, NMR and mass spectra with those prepared accordance with the literature procedures. IR spectra were recorded on a Perkin Elmer IR- 683 or 1310 spectrometer. ^{1}HNMR spectra were recorded on varian FT-200MHz (Gemini) in $CDCl_3$. Chemicals shifts are reported in parts per million (δ) relative to tetramethylsilane (δ 0.0) as an internal standard. Mass spectra were recorded under electron impact at 70eV on Finnigan Mat 1020B mass spectrometer. Melting points were recorded on Buchi 535 and are uncorrected. Column chromatography was performed on silica gel (60–120 mesh) supplied by Acme Chemical Co. (India). Thin-layer chromatography was performed on Merck 60 F-254 silicagel gel plates. Reagents and solvents were of analytical grade or were purified by standard procedures prior to use.

General procedure: To a mixture of the carbonyl compound **1a–m** (10 mmol) and active methylene compound **2** (10 mmol) was added benzyltriethylammonium chloride (2 mmol) at room temperature. After being stirred for 5min, the resulting mixture was heated at 80°C in a preheated oil bath for 1h (monitored by TLC, EtOAc:hexane, 1:9 v/v). It was then stirred and allowed to cool to room temperature when it solidified. On completion, the reaction mixture was poured into water and extracted with Et_2O (2 × 25ml), dried over Na_2SO_4 and concentrated *in vacuo*. The crude product thus obtained was purified by recrystallization or column chromatography to afford pure olefinic products **3a–m** in 40–95% yields (Table 1).

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13 *2-Imino-2H-1-benzopyran-3-carboxylic acid ethyl ester:* m.p. 133–135°C before and after crystallization from ethanol; IR (KBr) 3320 (NH), 1675 (C=N) cm^{-1}. *2-Oxo-2H-1-benzopyran-3-carboxylic acid ethyl ester:* m.p. 91–93°C crystallization from ethanol (lit m.p. 92–94°C, E. C. Horning, M.G. Horning and D.A. Dimming, *Organic Syntheses Collect.* Vol. III, p165; Wiley: New York, 1955); IR (KBr) 1765 (C=O), 1610 (C=C) cm^{-1}. Data for **6**: m.p. 46–48°C; ^{1}H NMR ($CDCl_3$): 1.33–1.45 (t, 3H, J = 7.0), 3.89 (s, 9H), 4.29–4.42 (q, 2H, J = 7.0), 7.26 (s, 2H), 8.05 (s, 1H, CH=). **7**: colourless thick syrup; ^{1}H NMR ($CDCl_3$): 1.23–1.36 (t, 3H), 3.11–3.20 (m, 2H), 3.61–3.70 (m, 1H), 3.85 (S, 3H), 3.95 (s, 6H), 4.18–4.34 (m, 2H), 6.45 (s, 2H). **8**: Colourless crystals. m.p. 196–198°C (EtOH), lit. 197–199°C, M. Smal, H.T. Andrew Cheung and P.E Davies, *J. Chem. Soc. Perkin. Trans 1*; 1986, 747. ^{1}HNMR (Me_2SO-d_6): 3.55 (s, 2H), 3.66 (s, 3H), 3.75 (s, 6H), 5.72 (br s, 2H), 6.08 (br s 2H), 6.55 (s, 2H), 7.55 (s, 1H).

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