Novel amine-catalysed hydroalkoxylation reactions of activated alkenes and alkynes

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Received (in Cambridge, UK) 27th September 2004, Accepted 1st November 2004
First published as an Advance Article on the web 26th November 2004
DOI: 10.1039/b414895a

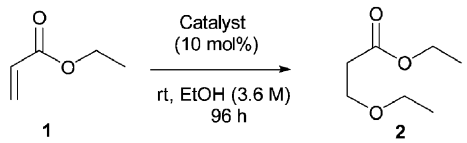
Substoichiometric loadings of DBU catalyse the efficient 1,4-addition of alcohols and non-nucleophilic amines such as pyrrole to activated alkenes; the application of this methodology in a one-pot synthesis of a natural product, and as a novel strategy for the synthesis of mono-protected 1,3-carbonyl compounds is reported.

The importance of β-hydroxycarbonyl compounds and their protected alkoxy analogues in natural product chemistry[1] and organic synthesis in general[2] is difficult to overstate. While the former class of compounds is readily prepared *via* (*inter alia*) the aldol reaction, the direct synthesis of β-alkoxycarbonyl materials is less straightforward, however, the development of an efficient *general* method for the preparation of these compounds from the Michael addition of alcohols to activated alkenes has recently begun to gather momentum with the discovery of trialkylphosphine-[3,4] and proazaphosphatrane-catalysed[5] hydroalkoxylation processes. While these catalysts generally give moderate to excellent yields of addition product (depending on the steric and electronic nature of the substrates), they are either air[3,4] or moisture[5] sensitive, often requiring solvent degassing,[4] manipulation under an inert atmosphere and removal of the catalyst/decomposition products by chromatography.

In the course of studies on the tertiary amine promoted Baylis–Hillman reaction in alcoholic media, we observed a competing hydroalkoxylation reaction of acrylamide,[6] which alerted us to the possibility of the development of a novel, convenient amine-catalysed general methodology for β-alkoxycarbonyl compound synthesis. To provide an instructive test of the scope of the reaction with respect to the Michael acceptor, screening studies were undertaken to determine the optimum amine for the hydroethoxylation of ethyl acrylate (**1**) (Table 1).

Of the amines screened, DBU proved the most efficacious hydroethoxylation catalyst. The ability of DMAP to promote the reaction where more basic, bulkier bases such as TEA and DIPEA fail strongly indicates that the role of the amine is nucleophilic in nature; addition of the catalyst to the alkene (Scheme 1) generates ammonium enolate **A**, which is protonated by the solvent to afford **B** and an ethoxide ion, the addition of which to a second molecule of **1** gives adduct **2** *via* enolate **C**. Thus the superiority of DMAP and DBU may be attributable to cation resonance stabilisation and low steric hindrance around the nucleophilic heteroatom,[8] thus maximising the concentration of **B** (and hence ethoxide ion) in solution.

Table 1 Amine-catalysed hydroethoxylation of **1**

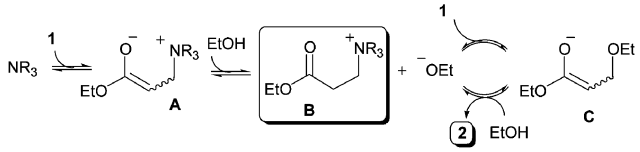


Catalyst[a]	pK_a (R_3NH^+, H_2O, 25 °C)[b]	Conversion (%)[c]
DIPEA	11.4	0
TEA	10.9	0
DABCO	8.8	0
3-HQD	9.9	8
DMAP	9.7	24
DBU	>12[d]	>98

[a] DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene, DMAP = 4-*N*,*N*-dimethylaminopyridine, 3-HQD = 3-hydroxyquinuclidine, DABCO = 1,4-diazabicyclo[2.2.2]octane, TEA = triethylamine, DIPEA = diisopropylethylamine. [b] Ref. 6. [c] Determined by ^1H NMR spectroscopy. [d] Ref. 7.

Further experimentation demonstrated that DBU was capable of the efficient promotion of hydroalkoxylation reactions involving primary or secondary alcohols across a range of Michael acceptors selected to probe the sensitivity of the catalyst to the steric and electronic properties of the substrate (Table 2).

Gratifyingly, the conversion of terminal and internal activated α,β-unsaturated nitriles, esters and ketones (**3–9**) to primary (**10–11**, **14** and **16–18**), secondary (**13**, **15**, and **20**) and tertiary (**19**) ethereal centres[9] respectively is possible with low catalyst loadings under mild conditions. In the absence of the amine promoter no hydroalkoxylation occurs even after extended reaction times. Although the DBU-catalysed reactions are generally slower than previously reported phosphine-promoted processes, the reaction scope is similar to the best literature systems. One of the distinct advantages associated with the use of an amine- as opposed to a phosphine-catalysed protocol is convenience; the amine catalysed reactions are carried out under an air atmosphere in non-degassed solvent, and the catalyst can be conveniently removed after reaction by means of a mild acidic workup, affording pure hydroalkoxylated products on removal of the solvent in the majority of cases.†



Scheme 1 Mechanistic rationale for the formation of **2**.

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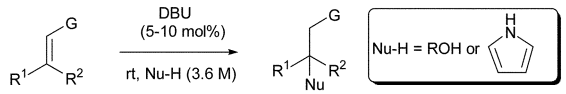
Table 2 DBU-catalysed hydroalkoxylation and hydroamination

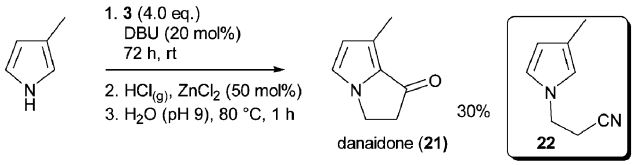


3 G = CN, R^1, R^2 = H
4 G = CN, R^1= Me, R^2 = H
5 G = CO_2Me, R^1, R^2 = H
6 G = CO_2Me, R^1= Me, R^2 = H
7 G = COMe, R^1, R^2 = H
8 G = COMe, R^1, R^2 = Me
9 G = COEt, R^1= Me, R^2 = H

10 G = CN, R^1, R^2 = H, Nu = OMe
11 G = CN, R^1, R^2 = H, Nu = O^{i}Pr
12 G = CN, R^1, R^2 = H, Nu = 1-pyrrole
13 G = CN, R^1= Me, R^2 = H, Nu = OMe
14 G = CO_2Me, R^1, R^2 = H, Nu = OMe
15 G = CO_2Me, R_1 = Me, R_2 = H, Nu = OMe
16 G = COMe, R^1, R^2 = H, Nu = OMe
17 G = COMe, R^1, R^2 = H, Nu = OEt
18 G = COMe, R^1, R^2 = H, Nu = O^{i}Pr
19 G = COMe, R^1, R^2 = Me, Nu = OMe
20 G = COEt, R^1= Me, R^2 = H, Nu = OMe

Substrate	Pronucleophile	Mol% DBU	Product	Time/h	Yield (%)[a]
3	MeOH	5	**10**	24	62
3	^{i}PrOH	5	**11**	70	86
3	Pyrrole[b]	5	**12**	24	76
4	MeOH	5	**13**	72	77
5	MeOH	5	**14**	18	79
6	MeOH	10	**15**	93	60
7	MeOH	5	**16**	3	95[c]
7	EtOH	5	**17**	3	69[c]
7	^{i}PrOH	5	**18**	8.5	97[c]
8	MeOH	10	**19**	93	49
9	MeOH	5	**20**	47	93[c]

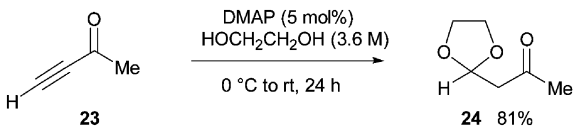
[a] Refers to isolated yield unless otherwise indicated. [b] Conditions: pyrrole (1.0 mmol), acrylonitrile (1.3 mmol), DBU (0.05 mmol), rt, air atmosphere. [c] Determined by ^{1}H NMR spectroscopy using anisole as an internal standard.



Scheme 2 One-pot synthesis of danaidone.

The putative hydroalkoxylation mechanism (Scheme 1) suggested that pronucleophiles of suitable acidity other than alcohols could also participate in this type of addition reaction. This was verified *via* the observation of a novel and efficient nucleophile-catalysed *N*-cyanoethylation of pyrrole (pK_a = 16.5) to give **12** in good yield (Table 2).

To demonstrate the potential synthetic utility of these catalytic processes we have utilised a DBU-catalysed cyanoethylation reaction as a key step in a novel, *one-pot* synthesis of the Monarch butterfly pheromone danaidone[10] (**21**) (Scheme 2).‡ Addition of 3-methylpyrrole to acrylonitrile catalysed by DBU gave intermediate **22** (Scheme 2), which underwent subsequent electrophilic cyclisation in the presence of added HCl–$ZnCl_2$. The resultant iminohydrochloride was hydrolysed to give the natural product in 30% yield after chromatography. This concise strategy compares favourably with previously reported multistep-syntheses of this biologically relevant compound.[11]



Scheme 3 DMAP-promoted one-pot alkynone dihydroalkoxylation.

Given the wide scope of the alkene hydroalkoxylation processes summarised in Table 2, the possibility of developing a novel dihydroalkoxylation reaction of alkynones was intriguing, not least because the products of such reactions would be synthetically useful mono-protected 1,3-dicarbonyl compounds. Treatment of terminal alkyne **23** with ethylene glycol in the presence of 5 mol% DMAP[12] gave smooth conversion to acetal **24**, which was isolated in high yield after chromatography (Scheme 3). To our knowledge this is the first example of a nucleophile-promoted dihydroalkoxylation reaction to be reported.[13]

In summary, it has been found that tertiary nucleophilic amines such as DBU and DMAP catalyse the efficient hydroalkoxylation of activated alkenes under mild conditions. The reaction scope with respect to both the olefin and the alcohol is comparable to previously reported phosphine-catalysed reactions, while the air-stability, commercial availability, ease of removal and low cost[14] of DBU make it an attractive alternative to phosphine-based systems. Preliminary efforts to expand the synthetic potential of these processes have led to the discovery of efficient analogous catalytic hydroamination (involving pyrrole) and alkynone dihydroalkoxylation reactions. It thus seems likely that considerable potential exists for further scope expansion with respect to both the pronucleophilic and electrophilic components. Investigations along these lines are in progress in our laboratory.

We would like to thank Dr. John O'Brien for NMR spectra and the Irish Research Council for Science Engineering and Technology (IRCSET) for financial support.

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Notes and references

† Representative procedure (Table 2): To a solution of the Michael acceptor (1.8 mmol) in alcohol (500 μL) in a 1 mL reaction vessel was added DBU (0.09 mmol) *via* a syringe. After stirring for the time indicated in Table 2 the solution was diluted with ether (30 mL) and washed with sat. NH_4Cl (2 × 15 mL). The organic extracts were dried ($MgSO_4$) and the solvent removed to afford the spectroscopically pure adduct. The products can be further purified by column chromatography, although this is necessary only in cases involving recalcitrant substrates such as **6** and **8**.
‡ One-pot synthesis of danaidone (**21**): DBU (33 μL, 0.22 mmol) was added to a magnetically stirred solution of 3-methylpyrrole (89 mg, 1.10 mmol) in acrylonitrile (290 μL, 4.40 mmol) *via* a syringe. The reaction vessel was fitted with a stopper and the resulting solution stirred at rt until complete conversion of 3-methylpyrrole was achieved (72 h). Excess acrylonitrile was removed *in vacuo* and both anhydrous ether (2.0 mL) and anhydrous $ZnCl_2$ (75 mg, 0.55 mmol) were added. Dry HCl gas was passed through the resulting mixture with precipitation of a yellow solid. The vessel was fitted with a stopper and allowed to stand for 12 h at rt, after which time the ether was decanted and a solution of the iminohydrochloride salt in H_2O (2 mL) was basified to pH 8–9 (Na_2CO_3) and stirred at 80 °C for 1 h. After allowing the reaction vessel to cool, the mixture was extracted with CH_2Cl_2 (3 × 20 mL), the organic layers were separated, dried ($MgSO_4$) and the solvent removed *in vacuo* to give a brown oil, which was purified by column chromatography (gradient: 1 : 1 CH_2Cl_2 : hexane to 2 : 1 CH_2Cl_2 : EtOAc) to give **21** (44 mg, 30%). Mp (66–68 °C, lit.[11c] 68–70 °C); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.34 (s, 3H), 3.07 (t, 2H, J = 6.2 Hz), 4.23 (t, 2H, J = 6.3 Hz), 6.32 (d, 1H, J = 1.3 Hz), 6.89 (d, 1H, J = 1.3 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 189.0, 129.2, 122.0, 121.2, 116.9, 41.3, 39.1, 10.6.

1 Representative examples: (*a*) I. Paterson, D. Y.-K. Chen, M. J. Coster, J. L. Aceña, J. Bach, K. R. Gibson, L. E. Keown, R. M. Oballa, T. Trieselmann, D. J. Wallace, A. P. Hodgson and R. D. Norcross, *Angew. Chem., Int. Ed.*, 2001, **40**, 4055; (*b*) M. A. Calter and W. Liao, *J. Am. Chem. Soc.*, 2002, **124**, 13127; (*c*) K. C. Nicolaou, A. Ritzén and K. Namoto, *Chem. Commun.*, 2001, 1523.

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3 For PBu_3-catalysed addition of primary alcohols to Michael acceptors under high pressure see: (*a*) G. Jenner, *Tetrahedron Lett.*, 2001, **42**, 4807; (*b*) G. Jenner, *Tetrahedron*, 2002, **58**, 4311.

4 For PMe_3-catalysed addition of alcohols to Michael acceptors at atmospheric pressure see: I. C. Stewart, R. G. Bergman and F. D. Toste, *J. Am. Chem. Soc.*, 2003, **125**, 8696.

5 For $P(RNCH_2CH_2)_3N$-catalysed addition of alcohols to enones see: P. B. Kisanga, P. Illankumaran, B. M. Fetterley and J. G. Verkade, *J. Org. Chem.*, 2002, **67**, 3555.

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8 DBU is an efficient Baylis–Hillman reaction catalyst: V. K. Aggarwal and A. Mereu, *Chem. Commun.*, 1999, 2311.

9 Previously catalytic hydroalkoxylation of trisubstituted Michael acceptors such as mesityl oxide required either tributylphosphine at high pressures (800 MPa) or proazaphosphatranes at elevated temperatures (50–70 °C), see refs. 3 and 5.

10 (*a*) N. Boppré, *Naturwissenschaften*, 1986, **73**, 17; (*b*) J. B. Harbourne, *Nat. Prod. Rep.*, 2001, **18**, 361.

11 (*a*) J. Meinwald and Y. Meinwald, *J. Am. Chem. Soc.*, 1966, **88**, 1305; (*b*) E. Roeder, H. Wiedenfeld and T. Bouranel, *Liebigs Ann. Chem.*, 1985, 1708; (*c*) S. Rajaraman and L. Jimenez, *Tetrahedron*, 2002, **58**, 10407.

12 DBU can also catalyse this reaction, however we found that the less basic DMAP afforded cleaner (albeit slower) conversion of **23**.

13 For an example of the synthesis of compounds such as **24** from alkynones in low yield using a Pd(II)-mediated process in the presence of diols see: T. Hosokawa, T. Ohta and S.-I. Murahashi, *J. Chem. Soc., Chem. Commun.*, 1983, 848.

14 The relative cost g^{-1} (Aldrich 2003/2004 catalogue - based on 25 g price) of DBU, PMe_3 and triisobutylphosphatrane is 1 : 12.3 : 13.0.