Organocatalyzed nitroaldol reaction of α-ketophosphonates and nitromethane revisited

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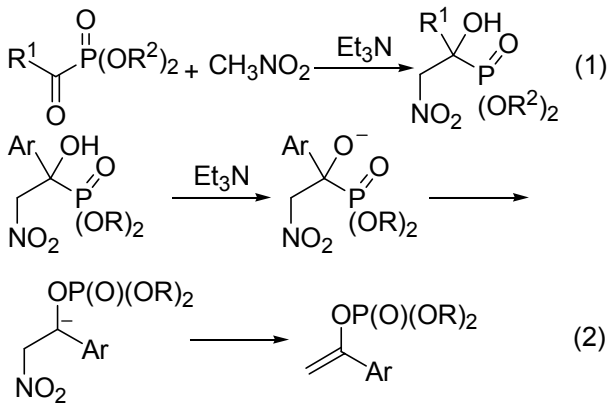
Abstract
An improved procedure for the nitroaldol reaction of α-ketophosphonates (both aryl and alkyl substituted) and nitromethane was achieved by using sterically hindered organic bases, such as DABCO, as the catalysts. Both α-aryl and α-alkyl substituted α-hydroxy-β-nitrophosphonates may be obtained in excellent yields with a simple operation and in a short reaction time.

Keywords: DABCO, α-ketophosphonate, nitromethane, Henry reaction, organocatalyst

Introduction

The nitroaldol (Henry) reaction of ketones and aldehydes has received a lot of attention in recent years.[1] Also new developments in asymmetric nitroaldol reactions further enhanced their synthetic utility.[2] The use of α-ketophosphonates as the acceptors in the nitroaldol reaction has been known for some time.[3] These nitroaldol products are of special significance due to their biological relevance. For example, through the reduction of the nitro group, the nitroaldol reaction products, α-hydroxy-β-nitrophosphonates, may be converted into β-amino-α-hydroxyphosphonates.[4] Derivatives of the latter are important analogues of α-hydroxy-β-amino acids.[5] There are several well-known natural products of significant biological activity endorsed by the α-hydroxy-β-amino acid moiety, such as the anti-cancer agent taxol.[6]

In a typical nitroaldol reaction of α-ketophosphonates, an organic base, such as triethylamine, is used as the catalyst (Eq 1).[3] Nevertheless, because of a competing rearrangement (Eq 2)[7,8] of the aryl-substituted nitroaldol product (as well as potential C-C or C-P bond cleavages[8]) initiated by the deprotonation of the product, this nitroaldol reaction is not trivial for aryl-substituted α-ketophosphonates (Eq 1, R^1 = Ar). The desired nitroaldol products are usually obtained in very poor yields.[3,8] To improve the yields, a phase-transfer catalysis, where the direct contact of the product and the base is avoided, has to be employed.[8]



Our continued interest in α-amino and α-hydroxyphosphonate derivatives[9] led us to reinvestigate this reaction. As shown in Eq 2, the rearrangement of the nitroaldol product is initiated by the deprotonation of the tertiary alcohol, we hypothesized that the use of a sterically hindered amine should be able to inhibit such a pathway, since such an amine should not able to interact with the tertiary alcohol moiety well due to steric reasons. As a support of this hypothesis, the successful preparation of diisopropyl (1-hydroxy-2-nitro-1-phenylethyl)phosphonate by using triethylamine as the catalyst[10] has been ascribed to steric effects of the large isopropyl groups.[8] To test our hypothesis, we investigated this amine-catalyzed nitroaldol reaction of α-ketophosphonates by using sterically hindered amines as the catalyst. Herein, we wish to report an efficient nitroaldol reaction of both aryl and alkyl substituted α-ketophosphonates catalyzed by DABCO.

Results and Discussion

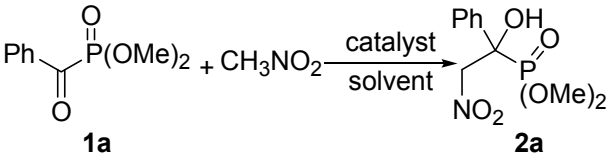
By using dimethyl benzoylphosphonate (**1a**) and nitromethane as the starting materials, we screened some readily available bulky amines, such as DABCO and quinuclidine (Fig. 1), as the catalyst for the nitroaldol reactions. The results are collected in Table 1.

Figure 1. Structure of the Catalysts.

As shown in Table 1, with 20 mol % loading of DABCO in DMSO as the solvent, the desired nitroaldol product **2a** was obtained in 83% yield after reaction at room temperature for 25 h (entry 1). Under similar conditions, 60% yield of **2a** was obtained when quinuclidine was used as the catalyst (entry 2). In contrast, only 10% yield of the product could be isolated with

triethylamine catalyst, although the reaction was much faster (entry 3). Apparently, DABCO is the best one among these three catalysts. Further screening of solvents (entries 4-6) revealed DMSO is the best solvent for this reaction in terms of both reaction yield and rate (entry 1), whereas CH_2Cl_2 and toluene are also good solvents (entries 5-6).

Table 1. Screening of the amine catalysts[a]



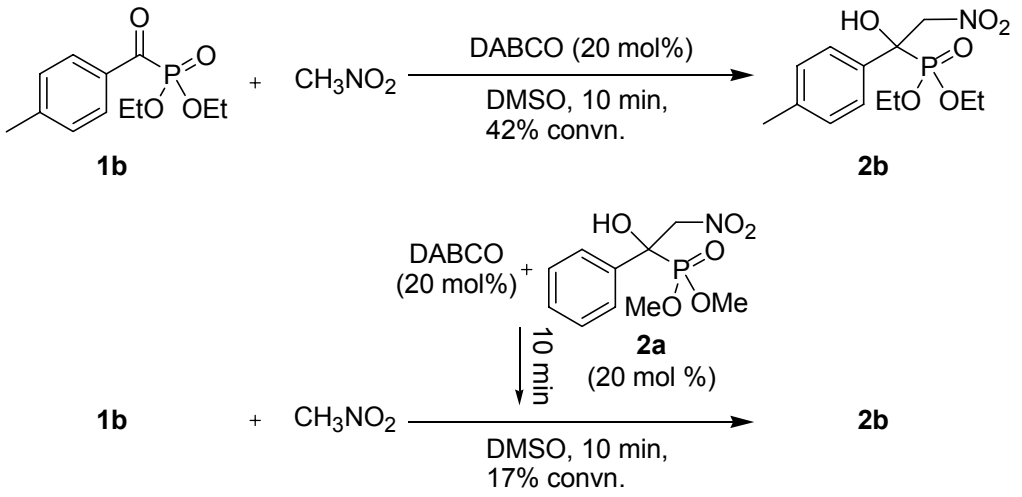
1a **2a**

Entry	Catalyst	Solvent	Time (h)	Yield (%)[b]
1	DABCO	DMSO	25	83
2	quinuclidine	DMSO	25	60
3	Et_3N	DMSO	0.75	10
4	DABCO[c]	---	48	60
5	DABCO	CH_2Cl_2	48	85
6	DABCO	toluene	48	80
7	DABCO[d]	DMSO	1.5	81
8	DABCO[d,e]	DMSO	2.0	75
9	Et_3N[f]	DMSO	0.75	15
10	DABCO[d]	*t*-BuOH[g]	5	40

[a]Unless otherwise specified, all reactions were carried out with dimethyl benzoylphosphonate (0.5 mmol), nitromethane (0.5 mL), amine (0.1 mmol) in the indicated solvent (0.5 mL) at room temperature. [b]Yield of isolated product after chromatography. [c]CH_3NO_2 (0.5 mL) was used as solvent. [d]The catalyst was added in two equal portions with an interval of 30 min. [e]0.05 mmol (10 mol %) DABCO was used. [f]With an interval of 10 min. [g]*t*-BuOH (0.5 mL) was used.

During the course of this study, we also observed that the reaction was very fast initially, but slowed down quickly afterwards. For example, with 20 mol % DABCO in DMSO, about 60% conversion may be achieved within 30 min; however, to achieve full conversion of the substrate, it takes 25 h (entry 1). Similar effects were also observed for quinuclidine. These results led us to suspect that the nitroaldol product is actually lowering the catalytic activity of DABCO (poisoning the catalyst). Indeed, control experiments verified this speculation (Scheme 1). As shown in Scheme 1, the reaction of diethyl [4-methylbenzoyl]phosphonate (**1b**) and nitromethane with DABCO (20 mol %) as the catalyst gave 42% conversion of **1b** after 10 min in DMSO (Scheme 1, upper equation). In comparison, if DABCO (20 mol %) was treated with the nitroaldol product **2a** (20 mol %) for 10 min before it was used in the above reaction, the conversion of **1b** was only 17% after 10 min (Scheme 1, lower equation). To overcome this

poisoning problem, the DABCO catalyst was intentionally added in two portions (10 mol % each) with an interval of 30 min. To our pleasure, comparable yield (81 vs. 83%) of the desired product **2a** may be obtained within just 1.5 h by using this new procedure (Table 1, entry 7). Nonetheless, reducing the loading of the catalyst to 10 mol % led to slightly inferior results (entry 8). We also tried triethylamine under these new conditions, but again poor yield (15%) was obtained (entry 9).



Scheme 1. Control experiments indicating the poisoning of the catalyst by the product.

Two plausible explanations for this special catalyst poisoning are shown in Fig. 2. In the first scenario, DABCO may deprotonate the more accessible β-hydrogen of **2a** and form a salt complex with the deprotonated nitroaldol product (Figure 2, left structure). This process is actually similar to the reaction between nitromethane and DABCO; however, the nitronate anion of nitromethane is small and able to react with the α-ketophosphonate substrate, while the nitronate anion out of the product (Fig. 2) maybe is too large to react further and thus forces DABCO out of the catalytic cycle. In the second scenario, the hydroxy group of product **2a** may form a hydrogen bond with the nitrogen atom of the DABCO (Figure 2, right structure), and the hydrogen-bonded DABCO has less reactivity as compared with free DABCO. Through an NMR study of the mixture of DABCO and pure **2a**, we were not able to identify any salt complexes or active intermediates formed by DABCO and **2a**. Furthermore, the nitroaldol reaction was also carried out in the presence of *t*-BuOH (Table 1, entry 10), which, likes **2a**, is a tertiary alcohol. As is evident from Table 1, the reaction was much slower as compared with that in DMSO (entry 7). On the basis of these observations, it seems that the second scenario is more likely. In the case of triethylamine, this hydrogen-bond complex may also have formed in the first place; however, since its size is smaller, it may get closer to **2a** to achieve the deprotonation, which leads to the rearrangement.

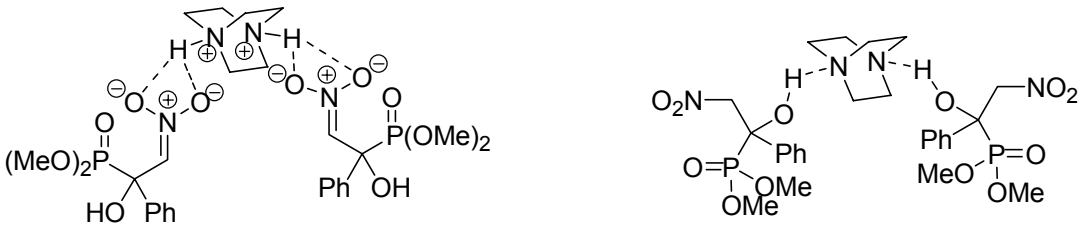
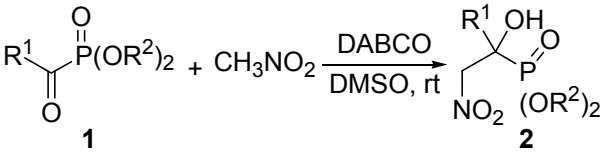


Figure 2. Plausible poisoning mechanisms.

To understand the scope and limitation of this new procedure, various α-ketophosphonate substrates were studied under these new conditions, and the results are compiled in Table 2.

Table 2. DABCO-catalyzed nitroaldol reaction of α-ketophosphonates[a]



Entry	R^1	R^2	**1**/**2**	Time (h)	Yield (%)[b]
1	Ph	Me	**a**	1.5	81
2	Ph	Et	**c**	1.5	83
3	Ph	^{i}Pr	**d**	2	79
4	4-FC_6H_4	Me	**e**	1	83
5	4-FC_6H_4	Et	**f**	1	80
6	4-FC_6H_4	^{i}Pr	**g**	2	92
7	4-ClC_6H_4	Me	**h**	1.5	79
8	4-ClC_6H_4	Et	**i**	1.5	83
9	4-ClC_6H_4	^{i}Pr	**j**	2	90
10	3-FC_6H4	Et	**k**	2	88
11	4-BrC_6H_4	Et	**l**	1.5	85
12	4-MeC_6H_4	Me	**m**	2	74
13	4-MeC_6H_4	Et	**b**	3	77
14	4-$MeOC_6H_4$	Et	**n**	2	69
15		Et	**o**	1.5	92
16	Me	Et	**p**	1	97
17	Me	^{i}Pr	**q**	1	93
18	$PhCH_2$	Et	**r**	2	81
19	$PhCH_2CH_2$	Et	**s**	1.5	96

[a]Unless otherwise specified, all reactions were carried out with α-ketophosphonate (0.5 mmol), nitromethane (0.5 mmol), DABCO (0.1 mmol) in DMSO (0.5 mL) at room temperature. The

catalyst was added in two portions (10 mol % each) with an interval of 30 min. [b]Yield of isolated product after chromatography.

As is evident from Table 2, benzoylphosphonates with different substituents on the aromatic ring (**1a-n**) all produce the desired nitroaldol products in good to excellent yields (entries 1-14). It should be pointed out that benzoylphosphonates substituted with electron-withdrawing groups (**1e-l**), which are very difficult substrates in the traditional procedure [3], give excellent yields of the desired products (entries 4-11). The ester alkyl groups were found to have minimum influence on this reaction, since good yields were obtained with all the Me, Et, and ^{i}Pr esters (entries 1-3 and 4-6). A heteroarene-substituted α-ketophosphonate **1o** also works pretty well under these conditions (92% yield, entry 15). As expected, alkyl-substituted α-ketophosphonates (**1p-s**) are excellent substrates for this reaction (≥81% yield, entries 16-19), too. The chain-length of the alkyl group has no significant effects on the reaction.

In conclusion, we have developed an improved procedure for the nitroaldol reaction of α-ketophosphonates and nitromethane by using sterically hindered base DABCO as the organocatalyst. This method is convenient to operate and general to both aryl and alkyl-substituted α-ketophosphonates. It also paves the way for an asymmetric nitroaldol of the α-ketophosphonates substrates (by using an enantioenriched amine base[11]).

Experimental Section

General Information. Melting points were recorded on MEL-TEMP melting point apparatus in open capillaries and uncorrected. IR spectra were recorded on VECTOR 22 model Specac ATR instrument. ^{1}H and ^{13}C NMR spectra were recorded on Advanced Varian-500 (500 MHz) instrument using residual solvent as standard. TLC was performed with silica gel GF254 precoated on aluminium plates (VWR), and spots were visualized with UV. Flash column chromatography was performed on silica-gel (VWR), unless otherwise stated. Microanalyses were conducted by Atlantic Microlab, Inc (PO Box 2288, Norcross, Georgia 30091, USA). DABCO, quiniclidine and all other chemicals were purchased from Aldrich. All α-ketophosphonates were prepared using literature procedure [3,8]. Toluene was distilled from benzophenone and sodium metal, and CH_2Cl_2 and DMSO from CaH_2. All reactions were carried out at ambient temperature in oven-dried glassware.

General procedure for the nitroaldol reaction of α-ketophosphonates

To a stirred solution of the α-ketophosphonate (1, 0.5 mmol), nitromethane (0.5 mL) and dry DMSO (0.5 mL) was added DABCO (11.3 mg, 0.1 mmol) in two equal portions with an interval of 30 min at room temperature. The reaction mixture was stirred for the time as specified in Table 2 (monitored by TLC for the disappearance of the α-ketophosphonate). Then the reaction was quenched by a few drops of saturated ammonium chloride solution and extracted with ethyl

acetate (3 × 10 mL). The combined extracts were washed with brine solution (2 mL), dried over $MgSO_4$, and evaporated to give the crude product, which was purified by column chromatography over silica gel (1:2 ethyl acetate/hexane) to give the desired α-hydroxy-β-nitrophosphonate. Except for **2l**, **2n**, and **2o**, all the products are known compounds and have identical spectroscopic data as those reported [3,8]. The new compounds were fully characterized by their ^{1}H NMR, ^{13}C NMR, and IR spectra and microanalyses.

Control Experiments

Experiment A. To a stirred solution of diethyl [4-methylbenzoyl]phosphonate (**1b**, 0.1 mmol) and nitromethane (0.1 mL) in dry DMSO (0.2 mL) was added DABCO (0.02 mmol) at room temperature. The reaction mixture was stirred at this temperature for 10 min. and then was quenched with few drops of saturated ammonium chloride solution. Afterwards the reaction mixture was extracted with diethyl ether (3 x 5 mL), washed with brine (5 mL) and the solvent evaporated to give the crude products. The ^{1}H NMR of this crude product was taken and a 42 % conversion of diethyl [4-methylbenzoyl]phosphonate (**1b**) was obtained.

Experiment B. A mixture of dimethyl [1-hydroxy-1-phenyl-2-nitroethyl]phosphonate (**2a**, 0.02 mmol) and DABCO (0.02 mmol) was stirred in dry DMSO (0.2 mL) for 10 min at room temperature. To this mixture were added diethyl [4-methylbenzoyl]phosphonate (**1b**, 0.1 mmol) and nitromethane (0.1 mL) while stirring. After 10 min., the reaction was quenched with few drops of saturated ammonium chloride solution. Then the reaction mixture was worked up as described above. The ^{1}H NMR of the crude product indicated that the conversion of diethyl [4-methylbenzoyl]phosphonate (**1b**) was only 17%.

Diethyl [1-(4-bromophenyl)-1-hydroxy-2-nitroethyl]phosphonate (2l). White needles, mp 110-112 ºC; IR (neat): ν_{max} 3173, 1558, 1486, 1420 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.20 (t, J = 6.5 Hz, 3H), 1.30 (t, J = 6.5 Hz, 3H), 3.85-3.90 (m, 1H), 3.98-4.01 (m, 1H), 4.14-4.18 (m, 2H), 4.52-4.55 (br s, 1H), 5.02 (dd, J_1 = 4.0, J_2 = 13.5 Hz, 1H), 5.12 (dd, J_1 = 7.0, J_2 = 12.5 Hz, 1H), 7.48-7.54 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 16.5 (t), 64.7 (d), 64.9 (d), 75.40 (d, J_{CP} = 163.6 Hz), 79.9 (d), 123.3, 128.1 (d), 131.9 (d), 134.6. Anal. Calcd. for $C_{12}H_{17}BrNO_6P$: C, 37.72; H, 4.48; N, 3.67. Found: C, 37.85; H, 4.60; N, 3.68.

Diethyl [1-hydroxy-1-(4-methoxyphenyl)-2-nitroethyl]phosphonate (2n). White needles mp 92-94 ºC; IR (neat): ν_{max} 3200, 1604, 1550, 1510, 1443, 1421, 1392 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.17 (t, J = 7.00 Hz, 3H), 1.31 (t, J = 7.00 Hz, 3H), 3.76-3.86 (m, 4H), 3.92-4.00 (m, 1H), 4.11-4.19 (m, 2H), 4.35 & 4.38 (2s, 1H), 5.017 (dd, J_1 = 4.0, J_2 =13.5 Hz, 1H), 5.15 (dd, J_1 = 7.5, J_2 = 13.5 Hz, 1H), 1H), 6.92 (d, J = 8.5 Hz, 2H), 7.52 (dd, J_1 = 2.5, J_2 = 8.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 16.5 (t), 55.5, 64.3 (d), 64.8 (d), 75.4 (d, J_{CP} = 166.0 Hz), 80.1 (d), 114.2 (d), 127.0, 127.6 (d), 160.1 (d). Anal. Calcd. for $C_{13}H_{20}NO_7P$: C, 46.85; H, 6.05; N, 4.20. Found: C, 47.10; H, 6.21; N, 4.20.

Diethyl [1-hydroxy-2-nitro-1-(thiophen-2-yl)ethyl]phosphonate (2o). White needles, mp 76-78 ºC; IR (neat): ν_{max} 3210, 1561, 1410, 1390 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.24 (t, J = 7.00 Hz, 3H), 1.32 (t, J = 7.00 Hz, 3H), 3.92-3.99 (m, 1H), 4.03-4.09 (m, 1H), 4.17-4.22 (m,

2H), 5.02-5.02 (m, 3H), 7.01-7.03 (m, 1H), 7.14-7.15 (m, 1H), 7.33-7.34 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 16.5 (q), 64.8 (d), 65.1 (d), 74.7 (d, J_{CP} = 169.7 Hz), 80.3 (d), 125.9 (d), 126.8 (d), 127.6 (d), 139.6 (d). Anal. Calcd. for $C_{10}H_{16}NO_6PS$: C, 38.83; H, 5.21; N, 4.53. Found: C, 39.04; H, 5.31; N, 4.57.

Acknowledgements

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