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Conjugate addition nitro-Mannich reaction of carbon and heteroatom nucleophiles to nitroalkenes

James C. Anderson [a,*], Andreas S. Kalogirou [a], Graham J. Tizzard [b,†]

[a] Department of Chemistry, University College London, 20 Gordon Street, London WC1H 0AJ, UK
[b] National Crystallography Service, School of Chemistry, University of Southampton, Southampton SO17 1BJ, UK

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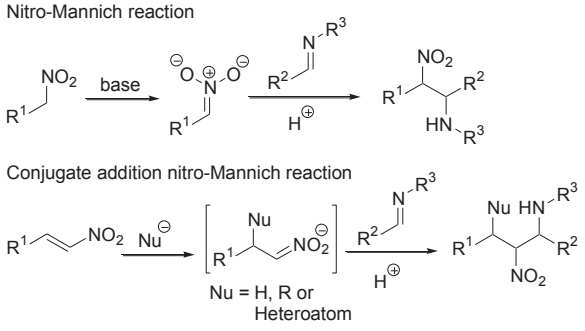
ABSTRACT

The conjugate addition nitro-Mannich reactions of ethyl-β-nitroacrylate (**1**) and β-nitrostyrene (**2**) with electron rich aromatic nucleophiles, stabilized carbanions, alcohols, amines, thiols, and diphenyl phosphine oxide were investigated. The one pot conjugate addition nitro-Mannich reaction was unsuccessful except for the addition of alkoxides to **2** in alcohol as solvent. Isolation of the conjugate addition products followed by deprotonation with ^{n}BuLi and treatment with a simple imine in the presence of TFA led to β-nitroamine derived products. Products derived from **1** spontaneously cyclised in only a few examples and on the whole led to inherently unstable products. Products derived from **2** were isolated as their trifluoroacetamides, gave good yields of single diastereoisomers for aromatic and alkoxide nucleophiles and the structures were verified by single crystal X-ray crystallography. Products derived from amine nucleophiles were isolated in low yields while sulfur nucleophiles gave poor diastereoselectivities.

1. Introduction

The nitro-Mannich reaction has emerged as a powerful method for the construction of C–C bonds with control of up to two contiguous C–N stereocentres in the β-nitroamine products (Scheme 1).[1] The product β-nitroamines have emerged as flexible synthetic building blocks due to the complimentary oxidation states of the two nitrogen atoms. They have been used in the synthesis of many nitrogen containing functional groups including α-amino carbonyls,[2,3] 1,2-diamines,[4–7] peptidomimetics,[8] natural products[9–15] and many heterocyclic small molecules.[16–28] To address the paucity of structurally diverse nitroalkanes we have developed conjugate addition nitro-Mannich protocols (Scheme 1).[29–31] The use of nitroalkenes (prepared *via* the Henry reaction) provides easy access to more structurally complex nitro coupling partners, thereby generating β-nitroamines with higher levels of functionality, which may be further manipulated to produce a range of useful intermediates. The 1,4-addition of nucleophiles to nitroalkenes generates a nitronate species, which can undergo a subsequent nitro-Mannich reaction with a suitable imine. The use of a Hantzsch ester as a hydride source and a simple chiral thiourea organocatalyst to catalyse the reductive nitro-Mannich reaction, gave access to enantio-enriched and structurally diverse β-nitroamines.[31] Enantioselective 1,4-addition of dialkylzincs to nitroalkenes generated zinc nitronates, which when reacted with an imine gave complex β-nitroamines with excellent diastereocontrol over three contiguous stereocentres.[29] Two distinct stereochemical outcomes were possible, dependent upon the choice of solvent, which dictated whether the reaction was homogeneous or heterogeneous. We extended this strategy to the addition of diorganozinc nucleophiles to ethyl-β-nitroacrylate, the products of which spontaneously lactamized in situ to give densely substituted pyrrolidin-2-ones.[26] Up to the present time, the conjugate addition nitro-Mannich methodology has been limited to the use of diorganozinc and hydride reagents. We thought that the use of more



Scheme 1.

* Corresponding author. Tel.: +44(0)2076795585; e-mail address: j.c.anderson@ucl.ac.uk (J.C. Anderson).
† Corresponding author for crystallographic results. E-mail: gjt1@soton.ac.uk.

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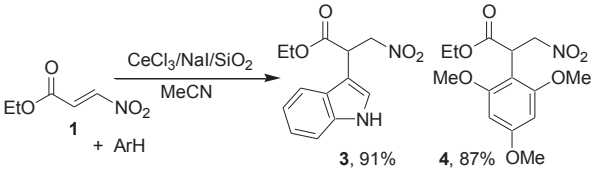
readily available carbon nucleophiles and especially heteroatom nucleophiles would greatly increase the versatility of the conjugate addition nitro-Mannich reaction.

2. Results and discussion

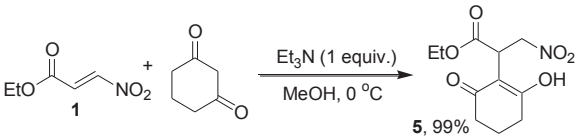
A number of heteroatom nucleophiles are known to add to nitro-alkenes. Furthermore, possible modification of the Nu group in the final products could enable further applications in target synthesis. From the large number of possible nucleophiles, we concentrated on a representative sample of carbon, oxygen, nitrogen, sulfur and phosphorus nucleophiles. The scope of nitroalkenes that could be used is potentially large, so for this investigation we selected to study the reactions of ethyl-β-nitroacrylate (**1**) and β-nitrostyrene (**2**), as we have used both of these extensively in previous studies.[26,29–31]

We investigated the 1,4-addition reactions to nitroacrylate **1** first. The addition of electron rich aromatics such as indole derivatives to **1** is known to be promoted by $CeCl_3$/NaI supported on silica.[32] There also exists an organocatalysed asymmetric protocol.[33] Synthesis of the indole addition product **3** was straightforward (91%) and the literature conditions could also be used with trimethoxybenzene to give **4** in 87% yield (Eq. 1).



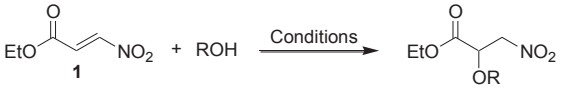
(1)

The attempted addition of some stabilized nucleophiles derived from Meldrum's acid, malononitrile and diethyl malonate under neutral conditions, with a variety of amines and NaH were all unsuccessful. By analogy to an example in the literature though 1,3-cyclohexanedione in the presence of Et_3N led to the addition product **5** in nearly quantitative yield (Eq. 2).[34]



(2)

The 1,4-addition of oxygen nucleophiles to nitroalkenes is well documented,[35] so the corresponding additions of alcohols to nitroacrylate **1** were investigated (Eq. 3). Addition of a solution of MeONa in MeOH (0.10 M) to a solution of nitroacrylate at rt, gave only degradation of the starting material (baseline on TLC). This result was attributed to base-catalysed polymerization. Reversing the addition mode led to the formation of the 1,4-addition product **6** in 62% yield, after quenching with AcOH and aqueous workup (entry 2, Table 1). Performing the same reaction at −78 °C gave **6** in an improved 80% yield (entry 3). Furthermore, when nitroacrylate **1** was refluxed in MeOH for 24 h, **6** was isolated in 85% yield (entry 4). It was found that activation of the nitroacrylate **1** under acidic conditions was ineffective in promoting the conjugate addition of alcohols. Other simple alcohols EtOH and BnOH when refluxed with **1** gave the corresponding addition products **7** and **8** in 89% and 62% yield, respectively (entries 5 and 6). Reaction with phenol was unsuccessful (entries 7–10) as was attempts at the 1,4-addition of H_2O/hydroxide ion.



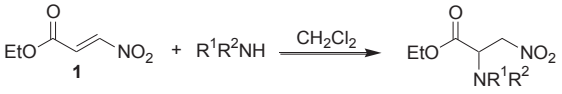
(3)

Table 1
1,4-addition of ROH to nitroacrylate **1**

Entry	ROH/conditions	Compound	Yield/%[a]
1	MeONa/MeOH added to **1**, rt	—	—
2	**1** added to MeONa/MeOH, rt	**6**	62
3	**1** added to MeONa/MeOH, −78 °C	**6**	80
4	MeOH, reflux	**6**	85
5	EtOH, reflux	**7**	89
6	BnOH, 100 °C	**8**	62
7	PhOH/PhMe, rt	—	—
8	PhOH/PhMe, reflux	—	—
9	PhOH/PhMe, K_2CO_3 (0.3 equiv), rt	—	—
10	PhOH, melt (70 °C)	—	—

[a] Isolated yields.

The 1,4-addition of nitrogen nucleophiles was subsequently investigated. Simply mixing nitroacrylate **1** with simple substituted amines in most cases gave fast and clean reactions (Eq. 4, Table 2). Reactions with hydrazine and ammonia were unsuccessful, as was reaction with oxazolidin-2-one, which was surprising as it is known to add to simple nitroalkenes quite readily.[36]



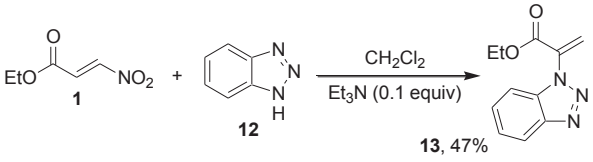
(4)

Table 2
1,4-addition of substituted amines to nitroacrylate **1**

Entry	R^1R^2NH (equivs.)	T/°C	t/h	Compound	Yield/%[a]
1	*p*-MeOPhNH$_2$ (1.8)	rt	24	**9**	98
2	Morpholine (1.2)	rt	1	**10**	98
3	BnNH$_2$ (1.1)	0	1	**11**	81

[a] Isolated yields.

In a similar manner the 1,4-addition of 1*H*-benzotriazole (**12**) was attempted, but gave no reaction. In the presence of catalytic Et_3N (0.1 equiv) product **13**, derived from elimination of HNO_2 from the desired addition product, was isolated in 47% yield (Eq. 5). Elimination of HNO_2 from nitroalkanes under basic or acidic conditions has been reported and in this case is exacerbated by the acidifying effect of the ester group.[37]



(5)

The conjugate addition of a sulfur and a phosphorus nucleophile was also investigated. Despite following the literature precedent with 1-propanethiol,[38] treatment of nitroacrylate **1** with 1-butanethiol in the presence of catalytic Et_3N led to consumption of starting material over 24 h, but again gave elimination of HNO_2 to give **14** in 38% yield (Eq. 6). Repeating the reaction in the absence of base, with 1-butanethiol (1.00 equiv), in EtOH, at rt, was much faster (consumption of starting material in 10 min), but again failed to provide the desired product. Only a baseline spot was