ORGANIC
LETTERS

2005
Vol. 7, No. 9
1715−1718

Highly Stereoselective Additions of Tin Enolates to Nitroalkenes and Subsequent Conversion of the Nitro Group into a Nitrile

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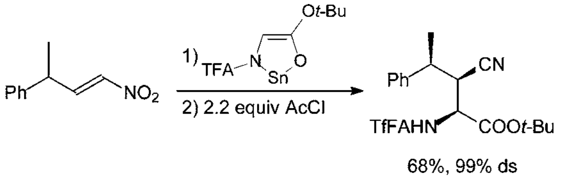
Received January 20, 2005

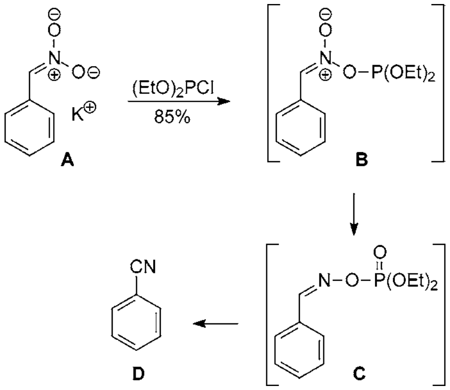
ABSTRACT



Sn-chelated glycine ester enolates are efficient nucleophiles for highly stereoselective 1,4-additions toward nitroolefins and subsequent reductions of the nitronate intermediates formed, giving rise to amino acid nitriles.

Although rarely found in nature, aliphatic nitro compounds play an enormously important role as synthetic intermediates. These chemical chameleons can react as carbonyl equivalents with inverted polarity (Umpolung)[1] and can be converted into a wide range of other functionalities.[2] For example, Nef reactions provide the corresponding aldehydes,[3] while stepwise reductions give rise to nitrones, oximes, hydroxylamines, and amines. Nitriles can be obtained from nitro compounds in general via oxime intermediates and subsequent elimination of water. The required oximes can either be provided in a stepwise protocol using a Nef reaction and subsequent addition of hydroxylamine to the derived aldehyde[4] or by direct reduction using a mixture of $Sn(SPh)_2$/$PhSH/NEt_3$.[5] Direct conversion of nitro compounds into the corresponding nitriles can be carried out using $Sn(SPh)_4$ in the presence of PBu_3 and DEAD.[6] Another interesting direct conversion was described by Mukaiyama in 1962.[7] In their reaction of deprotonated α-nitrotoluene **A** with chlorodiethyl phosphite they did not obtain the expected nitrile oxide but the nitrile **D**, probably via rearrangement of the phosphite intermediate **B** into the phosphate **C** and subsequent elimination (Scheme 1). Very recently, Carreira et al. reported a similar protocol using benzyl bromide and thionyl chloride.[8]

Scheme 1. Nitrile Formation from Nitro Compounds



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10.1021/ol050129j CCC: $30.25

A straightforward approach toward a wide range of aliphatic nitro compounds is provided by the 1,4-addition of suitable nucleophiles to nitroalkenes.[9]

These Michael-type additions can also be carried out in an asymmetric version by using either chiral nitroalkenes[10] or chiral nucleophiles.[11] For example, Schöllkopf et al. used their bislactim ethers as chiral glycine equivalents in their synthesis of nitro-substituted amino acids,[12] but other chiral glycine synthons can be used as well.[13]

Our group is also involved in amino acid synthesis, investigating chelated amino acid ester enolates as nucleophiles in various types of reactions.[14] Very recently, we reported on highly stereoselective Michael additions of these chelated enolates toward α,β-unsaturated esters and subsequent ring-closing reactions of the enolate intermediates formed.[15] Therefore, we were interested to see if a similar behavior is also found in additions toward nitroalkenes (Figure 1) because, in principle, the nitronates formed in the addition step should be capable of reacting with several electrophiles.

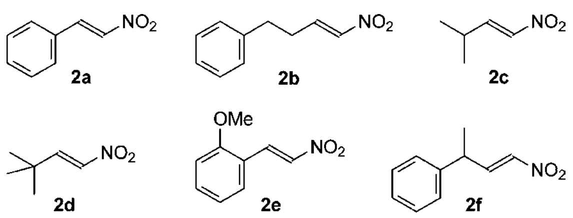
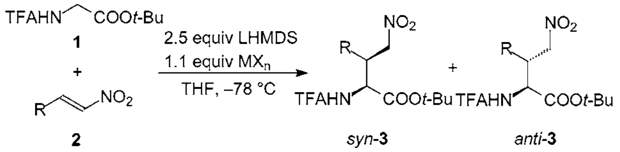


Figure 1. Nitroolefins used in Michael additions.

We started our investigations with commercial nitrostyrene **2a** using TFA-protected glycine ester **1** as the nucleophile, because the zinc enolate of this ester was superior to all other combinations in previous Michael additions[14] and palladium-catalyzed allylations as well.[16] And indeed, the zinc enolate showed a high reactivity. After 2 h at −78 °C, the nitroalkene was completely consumed and the expected product was obtained in high yield as a diastereomeric mixture with moderate selectivity (Table 1, entry 1).

Table 1. Additions of Chelated Enolates toward Nitroolefines



entry	substrate	product	MXn	yield (%)	ratio *syn*/*anti*
1	**2a**	**3a**	$ZnCl_2$	88	30:70
2	**2a**	**3a**	$SnCl_2$	58	98:2
3	**2a**	**3a**	CuI	64	82:18
4	**2a**	**3a**	$TiCl(O\textit{i}\text{-}Pr)_3$	86	79:21
5	**2a**	**3a**	$MgCl_2$	82	75:25
6	**2a**	**3a**		73	87:13
7	**2b**	**3b**	$ZnCl_2$	96	33:67
8	**2b**	**3b**	$SnCl_2$	71	78:28
9	**2c**	**3c**	$ZnCl_2$	68	68:32
10	**2c**	**3c**	$SnCl_2$	56	93:7
11	**2d**	**3d**	$ZnCl_2$	60	93:7
12	**2d**	**3d**	$SnCl_2$	15	95:5
13	**2e**	**3e**	$ZnCl_2$	86	9:91
14	**2e**	**3e**	$SnCl_2$	68	96:4
15	**2f**	**3f**	$ZnCl_2$	92	89:7:4
16	**2f**	**3f**	$SnCl_2$	77	>99:<1

To improve this selectivity, we varied the reaction parameters such as the protecting groups, the substitution pattern of the nitroalkene and the metal salts (Table 1). Surprisingly, all other metal salts gave rise to the opposite diastereomer. As determined by X-ray structure analysis[17] the *syn*-isomer is formed preferentially. With respect to selectivity $SnCl_2$ was the metal salt of choice, albeit with this salt the yield was moderate (entry 2). Other metal salts such as CuI (entry 3) or the lithium enolate per se (entry 6) gave good results, while with $TiCl(O\text{-}\textit{i}\text{-}Pr)_3$ (entry 4) and $MgCl_2$ (entry 5) the selectivity was lower. Our further investigations therefore focused mainly on zinc chloride, giving the highest yield, and tin chloride, giving the highest selectivity.

Via nitro aldol reactions, we synthesized a wide range of linear (**2b**) as well as branched aliphatic (**2c**, **2d**) and substituted aromatic nitroalkenes (**2e**) including chiral compound **2f** (Figure 2) and subjected them to our reaction conditions. Interestingly, with linear substrates such as **2b** the yields obtained were better, but the selectivity dropped

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(17) For X-ray data, please see the Supporting Information.

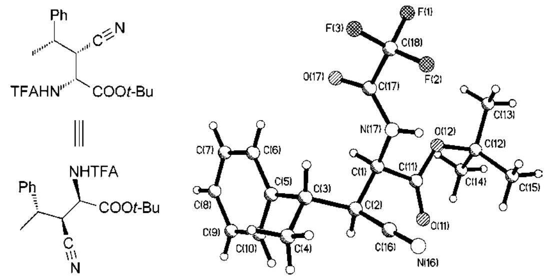


Figure 2. ORTEP plots of **4f**.

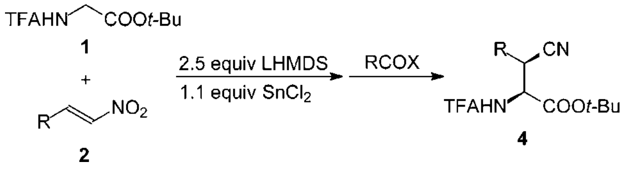
(entries 7 and 8), while introduction of steric hindrance using the branched nitroalkenes **2c** and **2d** had the opposite effect (entries 9−12). With these substrates both metal salts gave the same stereoisomer, and the best selectivities were obtained with **2d**. The dramatic drop in the yield of the tin enolate (entry 12) indicates that tin enolates are more sensitive toward steric hindrance in comparison to zinc enolates. A similar observation was made by using the ortho-substituted aromatic aldehyde **2e**, giving both high yield and selectivity with the zinc enolate (entry 13). Depending on the metal salt used, both diastereomeric products can be obtained by this protocol.

Next we investigated reactions of chiral nitroalkenes such as **2f** to investigate the possibility of controlling the stereochemical outcome of this reaction. In principle, four different diastereomers can be obtained. In the reaction of **2f** with the zinc enolate (entry 14) three of the isomers could be detected by GC and NMR, while the tin enolate gave the same major diastereomer (2,3-syn-3,4-syn isomer) exclusively (entry 15), as determined by X-ray structure analysis.[16] Using nitroalkene **2c** we investigated also the influence of the *N*-protecting groups and found that many protecting groups (Ac, Bz, Boc, Z) can be used, giving relatively good yields (50−78%) but no significant selectivity.

With this highly stereoselective protocol in hand, we next tried to trap the nitronate intermediate directly with electrophiles, generating even more complexity. Unfortunately this is not a trivial issue, because nitronates as ambident nucleophiles cannot only react at the α-C but also at the oxygen.[1,2] Although we investigated several protocols reported in the literature,[18] we were not able to react deprotonated **3f** with either aldehydes or alkyl halides. Therefore, we decided to use more reactive acyl halides or chloroformates as electrophiles (Table 2).

First of all, we quenched the reaction with 1.1 equiv of methyl chloroformate (entry 1) and observed the formation of a new product in 40% yield. The yield could be increased to 65% by raising the amount of chloroformate to 2.2 equiv (entry 2).[19] Surprisingly, the same product was obtained by using acetyl chloride (entry 3). NMR studies indicated that the acylation agent was not incorporated into the product. Instead nitrile **4f** was formed, as confirmed by X-ray structure analysis.[16] Herein also the syn-syn product was formed exclusively (Figure 2).

Table 2. Amino Acid Nitriles from Nitroolefins

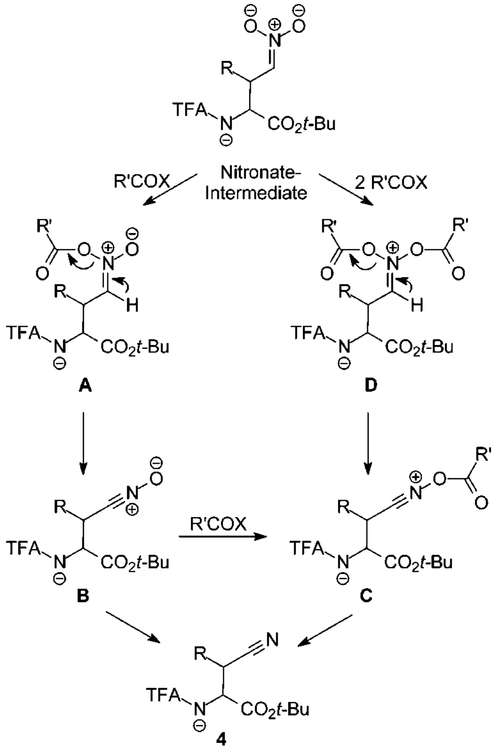


entry	substrate	product	RCOX (equiv)	yield (%)
1	**2f**	**4f**	MeOCOCl (1.1)	40
2	**2f**	**4f**	MeOCOCl (2.2)	65
3	**2f**	**4f**	AcCl (2.2)	68
4	**2c**	**4c**	MeOCOCl (1.1)	36
5	**2c**	**4c**	MeOCOCl (2.2)	66
6	**2c**	**4c**	AcCl (2.2)	35
7	**2c**	**4c**	BzCl (2.2)	68
8	**2c**	**4c**	TsCl (2.2)	

To prove the generality of this process we subjected other nitroalkenes such as **2c** to these reaction conditions. The results obtained were similar (entries 5−7) demonstrating that other acyl halides can be used as well. The best results so far were obtained with benzoyl chloride (entry 7). Trifluoroacetic anhydride gave a mixture of Michael adduct **3c** and nitrile **4c**, and tosyl chloride failed completely (entry 8).

The formation of the nitrile was unexpected and we had to think about a possible reaction mechanism (Scheme 2). It is known that aliphatic nitro compounds are preferentially *O*-acylated,[18] and therefore the formation of a *O*-acylated

Scheme 2. Mechanistic Proposal for Nitrile Formation



species **A** is reasonable. Under the basic reaction conditions used **A** can eliminate HOAc giving nitrile oxide **B** which somehow must be reduced to the nitrile. Alternatively, **B** can be acylated a second time giving **C**, which then undergoes reduction to the nitrile. In principle, **C** should also be accessible via the diacylated intermediate **D**.

Probably the reduction of **C** is easier as indicated by the higher yields obtained with an excess of acylating agent. But what is the reducing agent? As mentioned previously, nitrile formation is not observed in reaction of zinc enolates, and therefore, we assumed that Sn(II) might be responsible.

To prove this possibility we repeated the reaction of the zinc enolate with **2f** but added 1.1 equiv of $SnCl_2$ prior to chloroformate addition. Indeed, nitrile **4f** was obtained in 80% yield and identical selectivity as reported in Table 1 (entry 15). In this case, the zinc enolate is responsible for the high yield, and the tin chloride is responsible for the reduction step.

In conclusion, we have shown that tin-chelated amino acid enolates are good nucleophiles for stereoselective Michael additions toward nitroalkenes. If the reaction is quenched with acyl halides, the tin can also act as a reducing agent giving direct access to nitriles in a one-pot protocol.

Acknowledgment. This work was supported by the Deutsche Forschungsgemeinschaft and by the Fonds der Chemischen Industrie. We also thank Prof. M. Veith and Dr. V. Huch (University of the Saarland) as well as Dr. F. Rominger (University of Heidelberg) for X-ray structure analyses.

Supporting Information Available: Analytical and spectroscopic data of all new compounds **3** and **4** as well as X-ray data of **3a**, **3f**, and **4f**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(19) **General Procedure for Michael Additions and Nitrile Formation.** The base used for enolate formation was prepared directly before use. In a Schlenk flask a solution of HMDS (0.6 mL, 2.8 mmol) was dissolved in THF (3.5 mL) under argon. *n*-BuLi (1.6 M, 1.4 mL, 2.24 mmol) was added slowly at −78 °C, and the mixture was stirred for 30 min. In a second Schlenk flask TFA-protected *tert*-butyl glycinate (100 mg, 0.88 mmol) and $SnCl_2$ (185 mg, 0.97 mmol) were dissolved in THF (2 mL), and the mixture was cooled to −78 °C. The freshly prepared base solution was added slowly, and after the solution was stirred for 30 min the corresponding nitroalkene (1.0 mmol) was added in THF (1.1 mL). The solution was allowed to warm to room temperature overnight. After the reaction mixture was cooled to 0 °C, methyl chloroformate (0.15 mL, 1.94 mmol) was added. During 1 h, the solution was warmed to room temperature before it was diluted with EtOAc (10 mL) and hydrolyzed with 1 M $KHSO_4$ (10 mL). The layers were separated, and the aqueous layer was extracted twice with EtOAc. The combined organic layers werde dried (Na_2SO_4), and the solvent was evaporated in vacuo. The crude product was purified by flash chromatography (silica, hexanes/EtOAc).