

Straightforward Approach to Iminoxazines and Azetidinimines via 1,4-Additions of Chelated Enolates toward Nitroalkenes

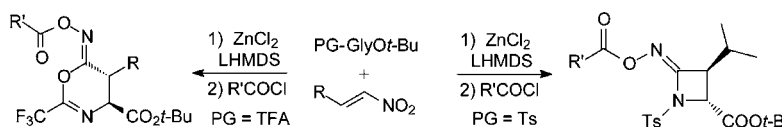
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ABSTRACT



Chelated amino acid ester enolates undergo 1,4-addition toward nitroalkenes in a highly stereoselective fashion. Trapping the nitronates formed in the addition step with chloroformates or acyl chlorides gives rise to highly reactive intermediates that directly undergo cyclization. Depending on the N-protecting group (PG) used, iminoxazines or azetidinimines are formed in a simple one-pot protocol.

Although not very often found in nature, aliphatic nitro compounds play an very 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. A straightforward approach toward a wide range of aliphatic nitro compounds is given by the 1,4-addition of suitable nucleophiles to nitroalkenes.⁴ These Michael-type additions can also be carried out in an

asymmetric version by using either chiral nitroalkenes⁵ or chiral nucleophiles.⁶ For example, Schöllkopf et al. used their bislactone ethers as chiral glycine equivalents for their synthesis of nitro-substituted amino acids,⁷ but other chiral glycine synthons can be used as well.⁸

Our group is also involved in amino acid synthesis, investigating chelated amino acid ester enolates as nucleophiles in various types of reactions.⁹ 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

[†] X-ray structure analysis.

(1) (a) Seebach, D. *Angew. Chem.* **1979**, 91, 259–278; *Angew. Chem., Int. Ed. Engl.* **1979**, 18, 239–258. (b) *Polarity Control for Synthesis*; Ho, T.-L., Ed.; John Wiley & Sons: New York, 1991.

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(3) (a) Nef, J. U. *J. Liebigs Ann. Chem.* **1894**, 280, 263–291. (b) Hassner, A.; Larkin, J. M.; Dowd, J. E. *J. Org. Chem.* **1968**, 33, 1733–1739. (c) Pinnick, H. W. *Org. React.* **1990**, 38, 655–792. (d) Ballini, R.; Petrini, M. *Tetrahedron*, **2004**, 60, 1017–1047.

(4) Reviews: (a) Barrett, A. G. M.; Graboski, G. G. *Chem. Rev.* **1986**, 86, 751–762. (b) Schäfer, H.; Seebach, D. *Tetrahedron* **1995**, 51, 2305–2324.

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(6) (a) Enders, D.; Otten, T. *Synlett* **1999**, 747–749. (b) Brenner, M.; Seebach, D. *Helv. Chim. Acta* **1999**, 82, 2365–2379. (c) Enders, D.; Adam, A.; Klein, D. *Synlett* **2000**, 1371–1384. (d) Berner, O. M.; Tedeschi, L.; Enders, D. *Eur. J. Org. Chem.* **2002**, 1877–1894. (e) Alexakis, A.; Andrey, O. *Org. Lett.* **2002**, 4, 3611–3614.

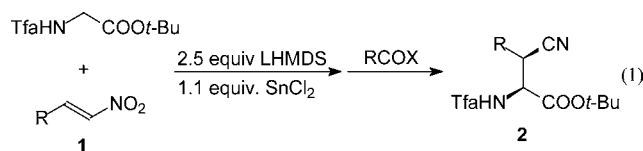
(7) (a) Schöllkopf, U.; Kühnle, W.; Egert, E.; Dyrbusch, M. *Angew. Chem.* **1987**, 99, 480–482; *Angew. Chem., Int. Ed. Engl.* **1987**, 26, 480–482. (b) Busch, K.; Groth, U.; Kühnle, W.; Schöllkopf, U. *Tetrahedron* **1992**, 48, 5607–5618.

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(9) Reviews: (a) Kazmaier, U. *Liebigs Ann./Recl.* **1997**, 285–295. (b) Kazmaier, U. In *Bioorganic Chemistry*; Wiley-VCH: Weinheim, 1999; pp 201–206. (c) Kazmaier, U.; Maier, S.; Zumpe, F. L. *Synlett* **2000**, 1523–1535.

formed.¹⁰ Therefore, we were interested to see if a similar behavior is also found in additions toward nitroalkenes **1** (eq 1),¹¹ because in principle the nitronates formed in the addition step should be capable of reacting with several electrophiles. During our screening of the chelating metal salt, we observed that excellent diastereoselectivities could be obtained with tin enolates, and the addition of acyl halides resulted in the formation of nitriles **2**.¹²

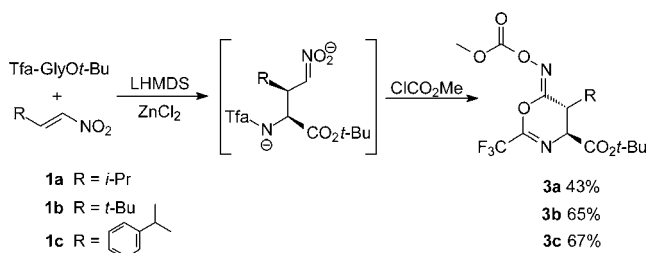
Independently, Carreira et al. recently reported on a related nitro–nitrile conversion.¹³ Our findings were surprising, because from a mechanistic point of view, the formation of nitrile oxides or their derivatives, but not the nitrile itself, is reasonable under the reaction conditions. Obviously, the tin chloride added for chelation acts also as a reducing agent.



To suppress this reduction step, we decided to switch to other chelating metals without reducing potential. We found that ZnCl₂ is superior to other salts such as MgCl₂ or TiCl₄(*Oi*-Pr)₃, especially with respect to the yield in the addition step. With the nitroalkenes **1a–c** investigated so far, the syn-configured addition product was obtained preferentially, as determined by X-ray structure analysis. Addition of methyl chloroformate to the solution of the zinc enolate indeed does not give the nitrile **2** as above but a completely different product, which was formed as a single stereoisomer (Scheme 1).¹⁴

Even with the chiral nitroalkene **1c**, which should provide four different diastereoisomers, only a single set of signals was observed in the ¹H and ¹³C NMR spectra. Surprisingly, the carbonyl group of the trifluoroacetyl (Tfa)-protecting group was missing in the ¹³C NMR, while the CF₃-carbon was nearly unchanged. We were lucky to get X-ray structures of all three reaction products **3a–c**, which clearly indicate

Scheme 1. Iminoxazine Formation via Addition/Cyclization



that the corresponding iminoxazines were formed. The structure of **3c** showing the relative configuration at all stereogenic centers is illustrated in Figure 1.¹⁵

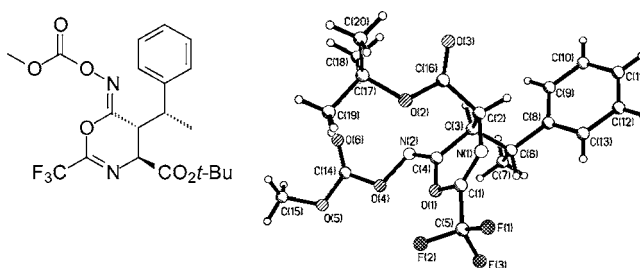


Figure 1. X-ray structure of **3c**.

The formation of the iminoxazines 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, and therefore the formation of an O-acylated species **A** is reasonable. Under the basic reaction conditions used, **A** can eliminate toward the nitrile oxide **B**, which then might undergo cyclization with the deprotonated amide giving rise to **C**, which is acylated a second time to **3**. Alternatively, the second acylation can occur earlier (pathways via **E**), and we assume this is the case, because we were not able to isolate protonated intermediate **C**. When exactly 1 equiv of chloroformate was used, no iminoxazine formation was observed, which also supports this hypothesis.

To obtain further insight into the reaction mechanism, we tried to trap the nitrile oxide intermediate **B** via [3 + 2]-cycloaddition.¹⁶ According to Huisgen et al., electronically poor aromatic aldehydes are especially suitable for this purpose.¹⁷ Unfortunately, we were not able to isolate any cycloadduct, regardless of the amount of chloroformate used.

(10) (a) Pohlman, M.; Kazmaier, U. *Org. Lett.* **2003**, *5*, 2631–2633. (b) Pohlman, M.; Kazmaier, U.; Lindner, T. J. *Org. Chem.* **2004**, *69*, 6909–6912.

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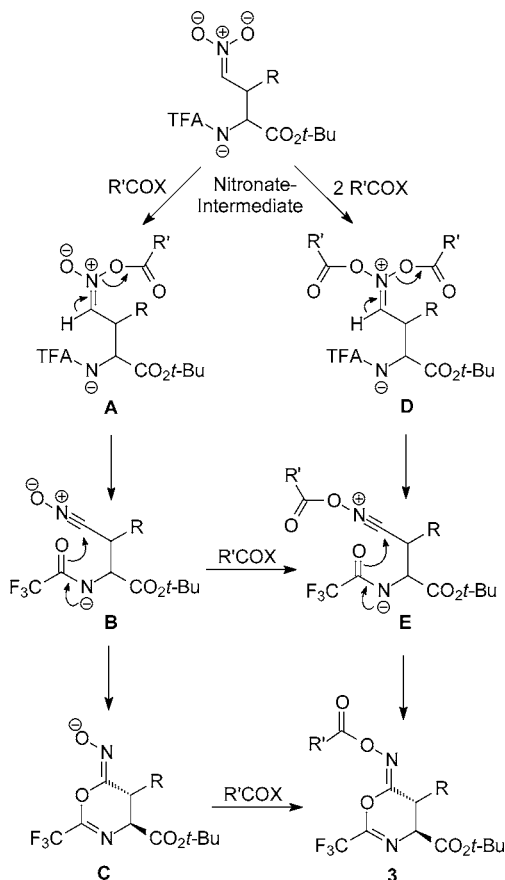
(14) **General Procedure for Iminoxazine Formation.** The base used for enolate formation was prepared directly before use. In a Schlenk flask, a solution of HMDs (0.6 mL, 2.8 mmol) was dissolved in THF (3.5 mL) under argon. *n*-BuLi (1.6 M, 1.4 mL, 2.24 mmol) was added slowly at –78 °C, and the mixture was stirred for 30 min. In a second Schlenk flask, TFA-protected *tert*-butyl glycinate (100 mg, 0.88 mmol) and ZnCl₂ (132 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 stirring 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. Over a period of 1 h, the solution was warmed to room temperature, during which time the solution's color changed from yellow to deep red. The solution was diluted with EtOAc (10 mL) and hydrolyzed with 1 M KHSO₄ (10 mL). The layers were separated, and the aqueous layer was extracted twice with EtOAc. The combined organic layers were dried (Na₂SO₄), and the solvent was evaporated in vacuo. The crude product was purified by flash chromatography (silica, hexanes/EtOAc).

(15) Crystal data for **3c**: C₂₀H₂₃F₃N₂O₆, *M* = 444.91, triclinic, *a* = 9.944(2), *b* = 11.382(2), *c* = 20.847(4) Å, α = 94.94(3)°, β = 94.25(3)°, γ = 110.75(3)°, space group *P*-1, *V* = 2184.2(7) Å³, *Z* = 4, *D* = 1.353 Mg/m³, μ(Mo Kα) = 0.116 mm^{–1}, *F*(000) = 930, 13 744 reflections collected, 6407 independent [*R*(int) = 0.0281], final *R* indices [*I* > 2σ(*I*): *R*₁ = 0.0384, *wR*₂ = 0.1013].

(16) Reviews on [3 + 2] cycloadditions of nitrile oxides: (a) Huisgen, R. In *1,3-Dipolar Cycloaddition Chemistry*; Padwa, A., Ed.; Wiley: New York, 1984; Vol. 1, pp 1–176. (b) Kozikowski, A. P. *Acc. Chem. Res.* **1984**, *17*, 410–416.

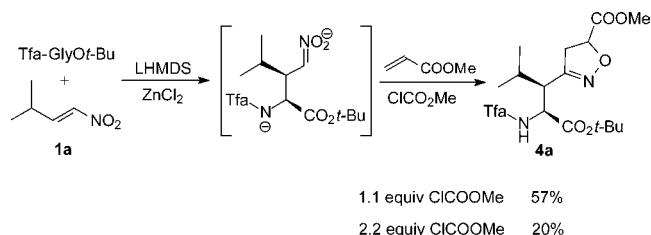
(17) Huisgen, R.; Mack, W. *Chem. Ber.* **1972**, *105*, 2805–2814.

Scheme 2. Postulated Reaction Mechanism for Iminoxazine Formation



However, if methyl acrylate was added together with the chloroformate to the primary Michael adduct, the required isoxazoline **4a** was formed (Scheme 3).¹⁸ Under optimized

Scheme 3. Trapping the Nitrile Oxide Intermediate B



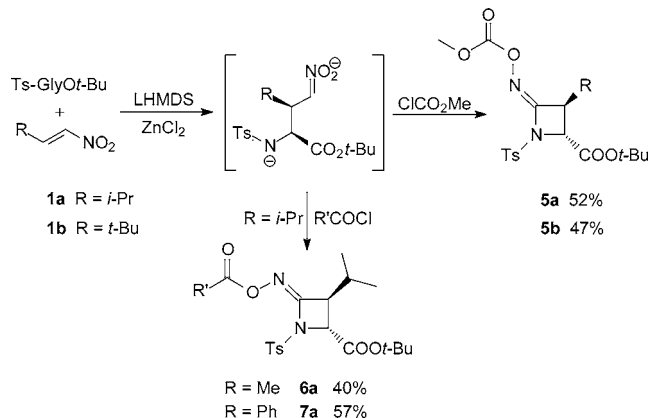
conditions, when 1.1 equiv of chloroformate was used, **4a** was obtained exclusively in 57% yield, while with 2.2 equiv of chloroformate, the standard conditions for iminoxazine formation, the yield was reduced to 20% and **2a** was the major product. This clearly supports the reaction mechanism

(18) **Formation of Isoxazoline 4a.** The reaction was carried out as described in the general procedure for iminoxazine formation. After the Michael addition, the reaction mixture was cooled to 0 °C, and then methyl chloroformate (0.08 mL, 0.97 mmol) and methyl acrylate (0.80 mL, 8.80 mmol) were added. After the mixture was stirred for 1 h, the workup was carried out as described.

proposed, and we assume that the formation of **3** proceeds via pathway B → E.

At this point another interesting question arose: what would happen if an N-protecting group, which cannot undergo such a cyclization as the TFA derivatives, were used? To explore this option, we also investigated the addition of N-tosylated enolates toward nitroalkenes under the same reaction conditions. Indeed, no iminoxazine formation was observed in this case, but a comparable cyclization took place, giving rise to four-membered azetidinimine **5**, an aza analogue of the β -lactams (Scheme 4). It should be

Scheme 4. Azetidinimine Formation via Addition/Cyclization



mentioned that these cyclization reactions are not limited to the use of chloroformates; other acyl chlorides can be used as well. For example, with acetyl and benzoyl chloride, the corresponding acylated derivatives **6a** and **7a** were obtained from **1a** in comparable yield. This is also true for the formation of the iminoxazines **3**.

Again, no intermediates could be isolated, but the formation of the highly strained four-membered ring clearly indicates that these intermediates are highly reactive and, without a suitable reaction partner, probably undergo side reactions or decompose. The identity of the azetidinimine ring system could be confirmed by X-ray structure analysis of **5b** (Figure 2).¹⁹

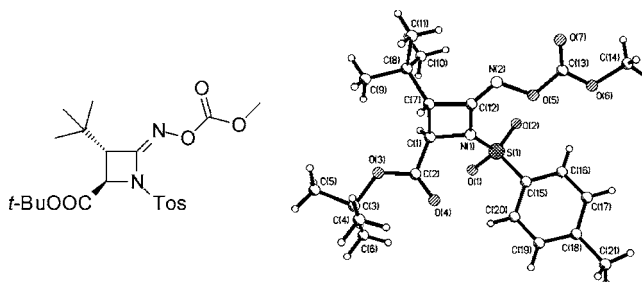


Figure 2. X-ray structure of **5b**.

In conclusion, we have shown that chelated ester enolates are suitable nucleophiles for 1,4 additions toward nitroalkenes

and that the intermediates formed are highly reactive and undergo clean cyclization toward rather unusual heterocycles such as iminooxazines and azetidinimines. The reactions probably proceed via nitrile oxide intermediates. Further investigations, especially concerning synthetic applications, are currently in progress.

(19) Crystal data for **5b**: $C_{21}H_{30}N_2O_7S$, $M = 454.53$, monoclinic, $a = 9.368(2)$, $b = 26.230(5)$, $c = 10.295(2)$ Å, $\alpha = \gamma = 90^\circ$, $\beta = 96.40(3)^\circ$, space group $P2(1)/n$, $V = 2513.9(9)$ Å³, $Z = 4$, $D = 1.201$ Mg/m³, $\mu(\text{Mo K}\alpha) = 0.168$ mm⁻¹, $F(000) = 968$, 3905 independent reflections collected, final R indices [$I > 2\sigma(I)$]: $R_1 = 0.0638$, $wR_2 = 0.1290$.

Acknowledgment. This work was supported by the Deutsche Forschungsgemeinschaft and by the Fonds der Chemischen Industrie.

Supporting Information Available: Analytical and spectroscopic data of all new compounds **3–7** as well as X-ray data of **3c** and **5b**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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