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Highly diastereoselective condensation of α-nitro-esters with aldehydes catalyzed by zinc complexes of amino acids

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Abstract—Zinc complexes of amino acids efficiently catalyze the condensation between α-nitro-esters and a variety of aldehydes. An unusual domino reaction sequence leads to the diastereoselective formation of substituted isoxazoline *N*-oxides in high yields.

Nitroaldol condensation, or the Henry reaction, is one of the classical methods for carbon–carbon bond forming reactions.[1] A more specialized case of the reaction involves an α-nitro-ester as one of the reactants.[2] The reaction of α-nitro-esters with aldehydes provides three types of products depending upon the reaction conditions: (a) a Henry addition providing α-nitro-β-hydroxy esters **2**,[3] or (b) in situ dehydration of these addition products leading to α-nitroacrylates **3**,[4] or (c) the Michael addition of **1** to **3** producing 2,4-dinitroglutarates **4**.[5]

We were interested in a stereoselective nitroaldol reaction between α-nitro-esters and aldehydes. The reaction did not take place either in the presence of a Lewis acid (e.g. $ZnCl_2$) or a Lewis base (e.g. Et_3N). We then envisaged that zinc complexes of amino acids could act as dual-site (Lewis acidic and Lewis basic) catalysts for the condensation. Thus the zinc center would activate the aldehyde whereas the amino group would abstract the proton from the nitro-ester. Zinc glycinate was chosen as the preliminary catalyst. The reaction was carried out in the presence of 10 mol% zinc glycinate using methanol as the solvent. Indeed, the condensation proceeded smoothly at room temperature giving a compound which was not the expected nitroaldol, but a diastereomeric mixture of isoxazoline *N*-oxides **5**.

The two diastereomers of **5** could be separated by column chromatography, the major product being the *trans* isomer.[6] Their ratio was found to be highly dependent on the solvent chosen (Table 1). The highest selectivity was realized in DMSO as the solvent giving a single *trans* diastereomer. A small amount of water in the solvent did not hamper the reaction. However, the reaction stops halfway to give **4** (R′ = Ph; R = Me) in the presence of a large amount of water. Variation in the reaction temperature did not cause significant differences in the outcome of the reaction; comparable yields and selectivity were obtained at 0, 25 and 50°C. As expected, the concentration of the catalyst affected the rate of the reaction. The reaction was very slow when 1 mol% zinc glycinate was employed. No particular advantage was realized by increasing the catalyst

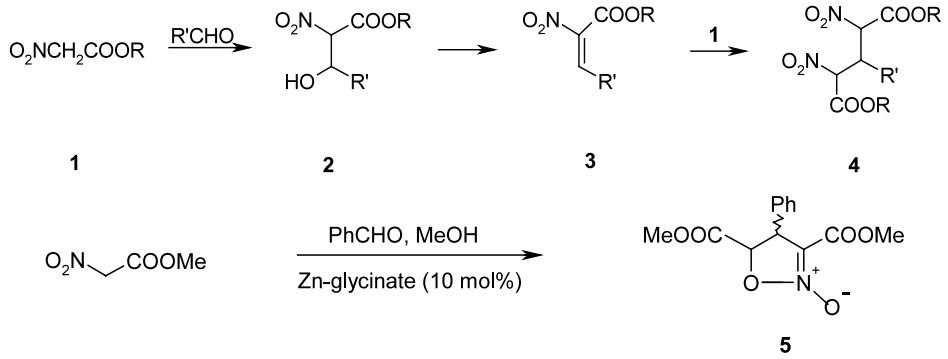

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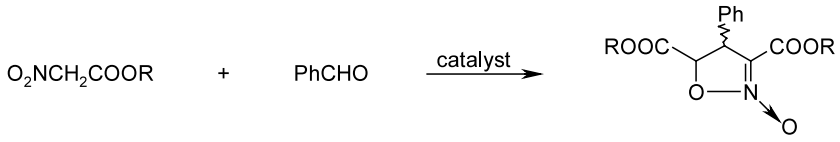
Table 1. Catalyzed condensation of α-nitro-esters with benzaldehyde



Entry	R	Solvent[a]	Time (h)	Isomeric ratio[b]	
				trans	*cis*
1	Me	MeOH	3	56	44
2	Me	CH_3CN	6	71	29
3	Me	DMF	1	92	8
4	Me	DMSO	2	>99	0
5	Et	MeOH	8	88	12
6	Et	DMSO	3	>99	0
7	^{i}Pr	MeOH	6	85	15
8	^{i}Pr	DMSO	2	>99	0

[a] All reactions were carried out at room temperature using 10 mol% of zinc glycinate as the catalyst.
[b] Estimated by HPLC.

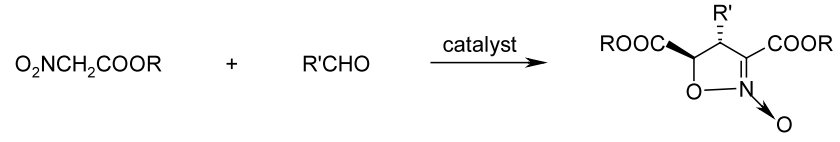
concentration from 10 to 20 mol%. A very significant effect on the stereochemical outcome was seen when the size of the ester group was changed, thus ethyl and isopropyl esters resulted in much higher selectivity even in MeOH as the solvent (Table 1).

As we had predicted at the outset of the investigation, zinc glycinate does indeed act as a dual-site catalyst. Both the amino group (for the abstraction of protons) and the zinc atom (as the Lewis acid center) are prerequisites for the catalysis. This was evident from the fact that neither zinc acetate nor sodium glycinate catalyzed the reaction. The following domino reaction sequence provides the pathway to isoxazoline *N*-oxide as the end product. The first step is the expected nitroaldol reaction. The resulting product then undergoes dehydration to the corresponding nitroacrylate. A second equivalent of the nitro-ester then undergoes Michael addition yielding a dinitroglutamate. Substitution of nitrite ion by the oxygen atom of the nitronate ion subsequently provides the isoxazoline *N*-oxide.[7]

Having optimized the reaction parameters, we then examined the reaction with a variety of aldehydes. All the reactions were over within 3 h at room temperature. Consistently high yields were obtained in all cases (Table 2). It is interesting to note that structural variation in the aldehydes had little influence on the reaction rates or yields. The present reaction is thus not only mechanistically interesting, but is a preparative procedure for a variety of isoxazolines. Some of these compounds (entries 1, 2, 4–8) have been obtained earlier, via a different protocol.[6]

We were curious to know whether the use of homochiral amino acids would impart any enantioselectivity to the reaction. For this purpose, zinc prolinate, zinc valinate and zinc phenylglycinate were prepared and

Table 2. Synthesis of *trans*-3,5-bis(alkoxycarbonyl)-4-substituted isoxazoline *N*-oxide



Entry	R	Aldehyde[a]	Time (h)	Yield (%)[b]	Mp (°C)
1	Me	Benzaldehyde	2	88	97 (lit.[6] 96)
2	Et	Benzaldehyde	3	80	76 (lit.[6] 74)
3	^{i}Pr	Benzaldehyde	2	79	75
4	Me	4-Tolualdehyde	2	78	100 (lit.[6] 98)
5	Me	4-Chlorobenzaldehyde	2	77	150 (lit.[6] 148)
6	Me	4-Methoxybenzaldehyde	2	86	104 (lit.[6] 94)
7	Me	4-Nitrobenzaldehyde	2	77	176 (lit.[6] 177)
8	Me	1-Naphthaldehyde	2	79	163 (lit.[6] 164)
9	Me	2-Furaldehyde	1	66	103
10	Me	Cyclohexanecarboxaldehyde	2	86	83

[a] All the reactions were carried out using 10 mol% zinc glycinate in DMSO.
[b] Yield of isolated and purified *trans*-isomer.

examined as the catalysts. Unfortunately, no significant enantioselectivity was provided by any of these, although all catalyzed the reaction efficiently. Efforts are now in progress to design an enantioselective catalyst for this transformation.

In conclusion, we have shown that α-nitro-esters can be efficiently condensed with a variety of aldehydes in the presence of zinc complexes of amino acids as the catalysts. The products were the outcome of a domino reaction sequence resulting in isoxazoline *N*-oxides. The protocol should prove to be a valuable tool for the diastereoselective synthesis of a variety of substituted isoxazoline *N*-oxides and their derivatives.

Typical experimental procedure: To a solution of nitro-ester (4 mM) in DMSO (5 ml), zinc glycinate (0.4 mM) and aldehyde (2 mM) were added. The resulting solution was stirred at room temperature until TLC analysis indicated the disappearance of starting materials. The reaction mixture was diluted with water (20 ml) and extracted with dichloromethane. The extract was washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The resulting product was purified by flash chromatography using hexane/ethyl acetate (4:1) as the eluent and then crystallized from the same combination of solvents. All the compounds provided satisfactory analytical data.[8]

Acknowledgements

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7. Kaji, E.; Zen, S. *Chem. Pharm. Bull.* **1980**, *28*, 479.
8. *trans*-3,5-Bis(methoxycarbonyl)-4-phenyl-4,5-dihydroisoxazole *N*-oxide: ^{1}H NMR δ 3.75 (s, 3H), 3.88 (s, 3H), 4.85 (d, $J=2.2$ Hz, 1H), 4.95 (d, $J=2.9$, 1H), 7.32–7.44 (m, 5H); ^{13}C NMR δ 52.4, 52.5, 53.1, 78.6, 108.8, 126.8, 128.6, 129.2, 137.6, 158.4, 168.4; MS m/z 279 (M^+), 261, 248, 116 (base peak). Anal. Calcd for $C_{13}H_{13}NO_6$: C, 55.91; H, 4.70; N, 5.02. Found: C, 55.72; H, 4.60; N, 5.00.