Chelated Ester Enolates as Versatile Nucleophiles for Direct Nucleophilic Attack on Aromatic Nitro Groups

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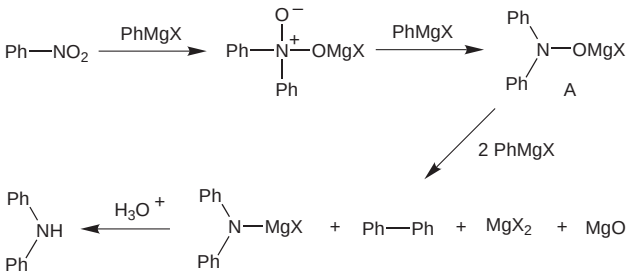
Abstract: Chelated amino acid ester enolates react with aromatic nitro compounds at the nitrogen atom. Best results were obtained with TFA-protected glycinates.

Key words: amino acids, chelates, enolates, nitroarenes

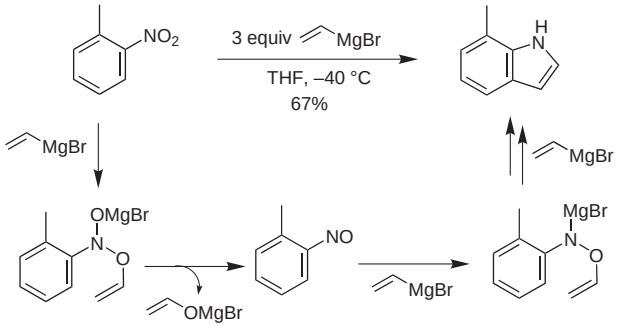
Nitro compounds play an important role as key intermediates in organic synthesis. Besides the very popular nitro aldol reaction,[1] especially the conversion of the nitro group into other functionalities is of major interest. For example, the nitro compounds can easily be reduced to either amines,[2] or nitroso, hydroxyamino and hydrazine derivatives, depending on the pH value and the reducing agent used.[3] Dehydration of nitroalkanes allows the in situ generation of nitrile oxides, reactive intermediates which undergo rapid 1,3-dipolar cycloadditions.[4] Very recently Carreira's group[5] and our group[6] reported independently about a reductive conversion of nitro groups into nitriles.

By far much less investigated, but not less interesting, are additions of C-nucleophiles to the nitro group.[7] Already in 1935, Kursanov and Solodkov investigated the reaction of nitrobenzene with an excess of phenylmagnesium chloride and obtained diphenylamine via the hydroxylamine derivative **A**, which was reduced in situ by the excess of the Grignard reagent (Scheme 1).[8] Other Grignard reagents such as allylmagnesium halides attack the nitro group also at the nitrogen,[9] and the intermediate formed can be converted into different products depending on the reaction conditions used.[10]



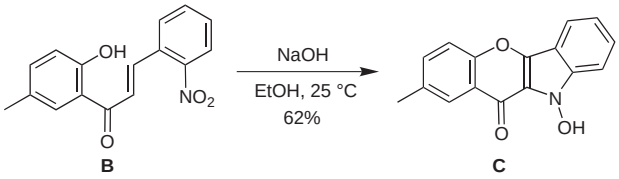
Scheme 1

Many years later Bartoli et al. reported an efficient synthesis of 7-substituted indoles by addition of vinylmagnesium bromide towards substituted nitrobenzenes.[11] Herein, the first step was a nucleophilic attack of the Grignard reagent on the oxygen (and not on the nitrogen as before) of the nitro group (Scheme 2). The labile O-alkylated intermediate formed then underwent elimination of enolate giving rise to aromatic nitroso compound.[12] This was attacked a second time by the Grignard reagent and the *O*-vinylhydroxylamine derivative formed underwent a [3,3]sigmatropic rearrangement towards the indole.



Scheme 2

In principle, nitro groups can also be attacked by enolates, as indicated by the conversion of **B** into **C** (Scheme 3).[13] But to the best of our knowledge, no other examples of such kind of additions are reported in the literature so far.



Scheme 3

For several years our group has been investigating reactions of chelated amino acid ester enolates as nucleophiles in several kinds of reactions.[14] Based on their high reactivity, these enolates react under very mild reaction conditions to a wide range of unnatural amino acids. Very recently, we reported the highly stereoselective 1,4-addition of these enolates **D** towards nitroalkenes (Scheme 4).[15] Interestingly the nitronates formed as inter-

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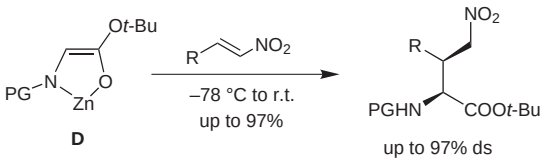
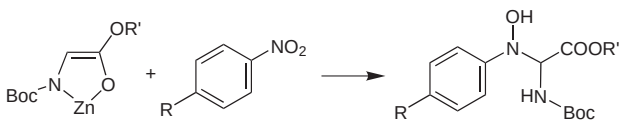
mediates could be trapped by acyl halides giving rise to nitriles[6] or different heterocycles,[16] depending on the reaction conditions and the protecting groups used.



Scheme 4

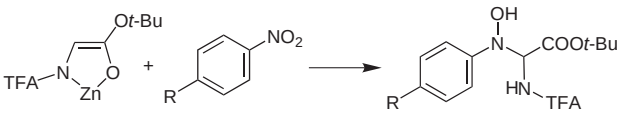
Therefore, we were interested to see what might happen with aromatic nitro compounds, for example if nucleophilic attack on the aromatic ring is possible. Based on our previous good results obtained with TFA-protected *tert*-butyl glycinate, we used enolate **1** as nucleophile in the reaction with *p*-chloro nitrobenzene **2a**, and indeed, a reaction was observed, but not at the aromatic ring system, but at the nitro group, and the *N*-arylhydroxylamine **3a** was obtained in very moderate yield (<20%). During our attempts to optimize the reaction conditions we found that increasing the amount of nucleophile to 2.5 equivalents[17] gave the expected product in a very clean reaction but only 38% yield (Table 1, entry 1). This was quite surprising, because all starting material was consumed. With respect to the structure of **3a**, one might assume that the N-hydroxylated aminal structure might be sensitive towards hydrolysis, especially under acidic conditions. Therefore we changed also the work-up protocol. Instead of hydrolyzing the reaction mixture with 1 N $KHSO_4$ (as done before) we quenched the reaction with a buffer solution (pH 6). And indeed, under these conditions the expected product could be obtained in nearly quantitative yield (entry 2). To prove the generality of this reaction, we subjected several other nitroarenes to these optimized conditions (entries 3–8).[18] The yield depends obviously on the electronic nature of the aromatic ring system. With electron-withdrawing substituents the yields were generally very high and they decrease with decreasing electron-withdrawing properties, as illustrated in the series of halogen substituted derivatives **2a**–**c**. Even with nitrobenzene the yield was good, but no reaction was observed with nitroanisole **2g**, or other 'electron-rich' nitro derivatives.

To prove the influence of the attacking nucleophile, we varied also the substitution pattern on the glycinate (Scheme 5). However, in this reaction the TFA protecting groups proved to be the best, with carbamates such as **4** the yields dropped dramatically, nearly independent of the ester used.



Scheme 5

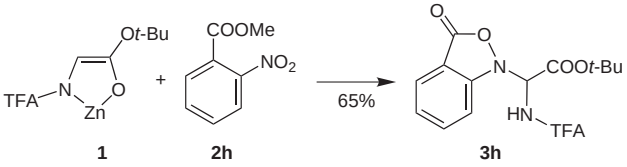
Table 1 Addition of Chelated Enolates towards Nitroarenes



Entry	Substrate	R	Product[19]	Yield (%)[a]
1	**2a**	Cl	**3a**	38[b]
2	**2a**	Cl	**3a**	95
3	**2b**	Br	**3b**	88
4	**2c**	I	**3c**	74
5	**2d**	CN	**3d**	85
6	**2e**	COOMe	**3e**	85
7	**2f**	H	**3f**	81
8	**2g**	OCH_3	**3g**	–

[a] Work-up conditions: quenching with NH_4OAc/HOAc buffer (pH 6).
[b] Work-up conditions: quenching with 1 N $KHSO_4$.

Next, we tried to trap the deprotonated **3**, formed in the addition step, by an intramolecular cyclization (Scheme 6). And indeed, if *o*-substituted nitroarene **2h** was used, the cyclization product **3h** was obtained directly as sole product.



Scheme 6

In conclusion we could show that chelated enolates are versatile nucleophiles for direct additions towards aromatic nitro groups. Applications towards the synthesis of more complex molecules and mechanistic studies are currently under investigation.

Acknowledgment

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(17) Probably, attack of the glycine nucleophile occurs according to Scheme 2 and one equiv of the enolate is necessary to reduce the nitro group. Attempts to trap the oxidized glycine species are currently under investigation.
(18) **Additions of Chelated Enolates towards Nitroarenes – General Procedure.**
The base used for enolate formation was prepared directly before use. In a Schlenk flask HMDS (428 mg, 2.65 mmol) was dissolved in THF (2 mL) under N_2. Then, *n*-BuLi (1.6 M, 1.64 mL, 2.63 mmol) was added dropwise at –20 °C and the mixture was allowed to stir at r.t. for 10 min. After cooling at –78 °C a solution of $ZnCl_2$ (187 mg, 1.38 mmol, dried previously in vacuo with a hot-air gun) was added with the amino acid derivative (1.25 mmol) in THF (3 mL). The suspension was stirred for further 30 min at –78 °C to form the chelated ester enolate. After that the nitroarene (0.5 mmol) was added in THF (1 mL). The solution was allowed to warm to r.t. overnight before it was diluted with Et_2O (10 mL) and hydrolyzed in an ice bath with NH_4OAc/HOAc buffer (pH 6, 10 mL). The layers were separated and the aqueous layer was extracted twice with Et_2O. The combined organic layers were dried (Na_2SO_4) and the solvent was evaporated in vacuo. The crude product was purified by flash chromatography (silica, hexane–EtOAc).
(19) **Selected Spectroscopic and Analytical Data.**
***tert*-Butyl [(4-Chlorophenyl)(hydroxy)amino][(trifluoroacetyl)amino]acetate (3a).**
Compound **3a** was obtained from **2a** (79 mg, 0.5 mmol) as a colorless solid; yield 175 mg (0.47 mmol, 95%); mp 101 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.40 (s, 9 H), 5.68 (d, *J* = 7.9 Hz, 1 H), 5.90 (s, 1 H), 7.14 (d, *J* = 8.8 Hz, 2 H), 7.23 (d, *J* = 8.8 Hz, 2 H), 7.56 (d, *J* = 7.6 Hz, 1 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 27.8, 72.6, 84.8, 115.6 (q, $J_{C,F}$ = 286.1 Hz), 118.2, 128.7, 128.8, 147.4, 157.3 (q, $J_{C,F}$ = 37.2 Hz), 164.7. HMRS (CI): *m/z* $[M]^+$ calcd for $C_{14}H_{16}N_2O_4F_3Cl$: 368.0751. Found: 368.0746. Anal. Calcd for $C_{14}H_{16}N_2O_4F_3Cl$ (368.77): C, 45.59; H, 4.38; N, 7.59. Found: C, 45.28; H, 4.30; N, 7.57.
***tert*-Butyl [(4-Bromophenyl)(hydroxy)amino][(trifluoroacetyl)amino]acetate (3b).**
Compound **3b** was obtained from **2b** (51 mg, 0.25 mmol) as a colorless solid; yield 91 mg (0.22 mmol, 88%); mp 98 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.39 (s, 9 H), 5.68 (d, *J* = 8.0 Hz, 1 H), 6.16 (br s, 1 H), 7.06 (d, *J* = 8.5 Hz, 2 H), 7.35 (d, *J* = 8.5 Hz, 2 H), 7.56 (d, *J* = 7.0 Hz, 1 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 27.8, 72.5, 84.9, 114.3, 116.2, 118.5, 131.7, 147.9, 157.4 (q, $J_{C,F}$ = 38.5 Hz), 165.0.
HMRS (CI): *m/z* $[M]^+$ calcd for $C_{14}H_{16}N_2O_4F_3Br$: 412.02. Found: 412.0247. Anal. Calcd for $C_{14}H_{16}N_2O_4F_3Br$ (413.19): C, 40.69; H, 3.90; N, 6.78. Found: C, 40.82; H, 3.80; N, 6.76.
***tert*-Butyl [(4-Cyanophenyl)(hydroxy)amino][(trifluoroacetyl)amino]acetate (3d).**
Compound **3d** was obtained from **2d** (104 mg, 0.70 mmol) as a colorless solid; yield 215 mg (0.60 mmol, 85%); mp 151 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.35 (s, 9 H), 5.80 (d, *J* = 7.5 Hz, 1 H), 6.32 (s, 1 H), 7.31 (d, *J* = 9.0 Hz, 2 H), 7.56 (d, *J* = 8.5 Hz, 2 H), 7.67 (d, *J* = 7.0 Hz, 1 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 27.8, 71.8, 85.1, 105.4, 116.2, 116.6, 119.0, 133.1, 152.9, 157.4 (q, $J_{C,F}$ = 39.9 Hz), 164.1. HMRS (CI): *m/z* $[M]^+$ calcd for $C_{15}H_{16}N_3O_4F_3$: 359.1093. Found: 359.1082. Anal. Calcd for $C_{15}H_{16}N_3O_4F_3$ (359.34): C, 50.14; H, 4.50; N, 11.69. Found: C, 50.18; H, 4.55; N, 11.53.
Methyl 4-[{2-*tert*-Butoxy-2-oxo-1-[(trifluoroacetyl)amino]ethyl}(hydroxy)amino]benzoate (3e).
Compound **3e** was obtained from **2e** (18 mg, 0.10 mmol) as a colorless solid; yield 33 mg (84.1 μmol, 85%); mp 114 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.35 (s, 9 H), 3.86 (s, 3 H), 5.84 (d, *J* = 7.6 Hz, 1 H), 6.30 (br s, 1 H), 7.25 (d, *J* = 8.5 Hz, 2 H), 7.67 (d, *J* = 7.6 Hz, 1 H), 7.94 (d, *J* = 8.5 Hz, 2 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 27.8, 51.9, 72.0, 84.8, 115.5 (q, $J_{C,F}$ = 286.1 Hz), 115.5, 124.4, 130.7, 153.0, 157.1, 164.5, 166.9. HMRS (CI): *m/z* $[M]^+$ calcd for $C_{16}H_{19}N_2O_6F_3$: 392.1195. Found: 392.1201. Anal. Calcd for $C_{16}H_{19}N_2O_6F_3$ (392.37): C, 48.98; H, 4.89; N, 7.14. Found: C, 49.17; H, 4.87; N, 7.10.