Titanium(IV) Enolates of 2-Nitrocarboxylic Esters and Their Oxidative Chlorination. A Convenient Route to α-Chloro-α-nitrocarboxylates

Dariusz Cież,* Justyna Kalinowska-Tłuścik

Faculty of Chemistry, Jagiellonian University, ul. Romana Ingardena 3, 30-060 Kraków, Poland
Fax +48(12)6340515; E-mail: ciez@chemia.uj.edu.pl

Received 23 September 2011

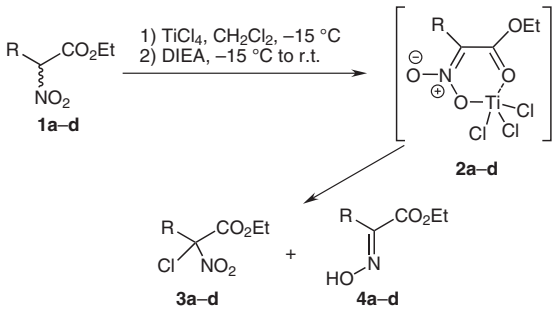
Abstract: A new method for the synthesis of 2-chloro-2-nitrocarboxylic esters from 2-nitrocarboxylates is described. The procedure consists of the oxidative chlorination of titanium(IV) enolates of 2-nitro esters in the presence of ammonium nitrate. Esters of 2-chloro-2-nitrocarboxylic acids are formed in very good to quantitative yields. Application of this method for the chlorination of α,α′-dinitrodicarboxylates leads to α,α′-dichloro-α,α′-dinitrocarboxylic esters with high *meso*-diastereoselectivity. The absence of ammonium nitrate from the reaction mixture affects the reduction of nitro groups and leads to partial transformation of 2-nitrocarboxylic esters into 2-(hydroxyimino)carboxylates.

Key words: oxidative chlorination, titanium enolates, diastereoselectivity, esters, transition states

Gem-chloro-nitro compounds have been found to be convenient reactants for the synthesis of nitro-substituted products[1] or cyclic systems that incorporate an N-O moiety into heterocyclic ring.[2] The presence of two electronegative groups bonded to the same carbon atom exerts influence not only on its CH-acidity but also on the reactivity of both substituents. Nitro groups in *gem*-halo-nitro compounds can be easily silylated giving *N*,*N*-bis(silyloxy)enamines[3] – products that attract considerable interest owing to their synthetic applications – whereas the halogen atoms can undergo various substitution reactions.[4] The synthetic potential of *gem*-chloro-nitrocarboxylic acids comes from their polyfunctional nature. Three electronegative groups bonded to the C-2 atom increases the CH-acidity of chloronitroacetates and facilitates the application of these esters in alkylation reactions,[5] α-hydroxyalkylation[6] aldol reactions,[7] deuteroexchange,[8] Michael additions,[5] and halogenation.[9]

Synthesis of 2-chloro-2-nitrocarboxylic esters can be realized in two different ways: from oximino esters and nitrosyl chloride followed by oxidation of 2-chloro-2-nitrosocarboxylates,[10] and by direct chlorination of 2-nitrocarboxylates using chlorine in water,[11] chlorine in chloroform,[12] *N*-chlorosuccinimide,[13] or sulfuryl dichloride in diethyl ether.[5,14] The described methods were applied not only for chlorination of nitroacetates but also for the syntheses of higher substituted nitrocarboxylates – 2-chloro-2-nitropropanoates and 2-chloro-2-nitrobutyrates.[11a,14] An alternative attempt to generate higher substituted 2-chloro-2-nitrocarboxylates was described by Yurtanov et al.,[5] but alkylation of chloronitroacetic esters was limited only to the reactions with methyl and ethyl iodide.

Our investigations on titanium(IV) enolates provided strong evidence for a relationship between the stability of enolates derived from 2-substituted carboxylates and the substituents at the C-2 position. We noted that, in comparison with earlier investigated titanium(IV) enolates of 2-isothiocyanocarboxylates[15] and 2-azidocarboxylates,[16] titanium(IV) enolates of 2-nitro esters were very stable and unreactive. They formed easily using a 'soft enolization technique' from ethyl 2-nitrocarboxylates, titanium tetrachloride and tertiary amine, and could be stored under argon at the room temperature for many hours. According to a known procedure,[17] we prepared ethyl 2-nitropropanoate (**1a**) and transformed it into titanium(IV) enolate **2a** (Scheme 1). The enolate was stirred at room temperature and the process was monitored using TLC and gas chromatography. After 24 hours the appearance of two new products was observed, and their concentration gradually increased. The process stopped after six days and GC-MS analysis of the reaction mixture showed the presence of two main products: ethyl 2-chloro-2-nitropropanoate (**3a**) and ethyl 2-(hydroxyimino)propanoate (**4a**). The postulated structure **3a** was confirmed by IR and NMR data, which were comparable with those presented previously.[5] We also detected ethyl 2-nitropropanoate (**1a**) and estimated its concentration by gas chromatography to be 35% of the initial amount. Application of a range of 2-nitrocarboxylic esters **1b–d** gave similar results; we isolated a mixture of 2-chloro-2-nitrocarboxylate **3b–d**, 2-(hydroxyimino)carboxylic ester **4b–d** and unconsumed starting material **1b–d**.



Scheme 1 Transformation of 2-nitrocarboxylates into titanium(IV) enolates followed by oxidative chlorination at C2 and partial reduction of the nitro group

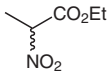
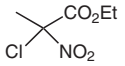
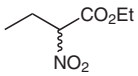
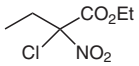
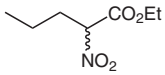
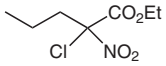
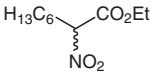
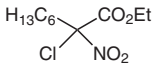
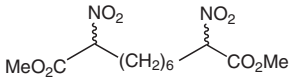
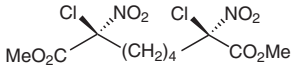
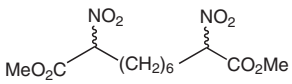
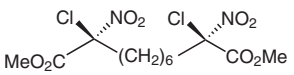
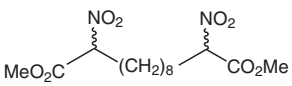
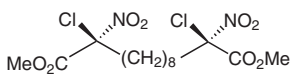
SYNLETT 2012, 23, 267–271
Advanced online publication: 03.01.2012
DOI: 10.1055/s-0031-1290081; Art ID: B17711ST

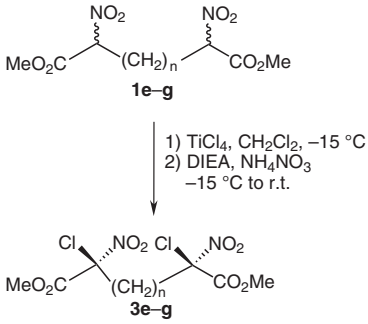
Chlorination of some arylacetic acid imides at the C-α position in the presence of titanium(IV) chloride has been observed during oxidative homocoupling of some chiral 3-(arylacetyl)-2-oxazolidinones in the presence of $TiCl_4$ and a tertiary amine.[19] There is, however, no evidence for practical application of $TiCl_4$ in efficient chlorination of CH-acids. We supposed that the formation of 2-chloro-2-nitrocarboxylates from 2-nitrocarboxylic esters was an oxidative process supported by titanium(IV), whereas 2-(hydroxyimino)esters were formed from titanium(IV) enolates as a result of reduction by titanium(III) ions. This secondary process regenerated titanium(IV), mainly as unreactive TiO_2, and the reaction stopped before all the 2-nitrocarboxylate was consumed. To examine this hypothesis, we carried out chlorination of ethyl 2-nitropropanoate (**1a**) in the presence of cerium(IV) ammonium nitrate (CAN). The solubility of CAN in dichloromethane was poor, but it was enough to oxidize Ti(III) into Ti(IV) ions. In the presence of CAN, chlorination of **1a** was realized quantitatively and we did not observe any trace of 2-(hydroxyimino)carboxylate (**4a**) as a by-product. We noted, however, that a stoichiometric amount of Ce(IV) was not needed to obtain the chlorination product in quantitative yield. Moreover, we observed release of nitric oxides in place of formation of cerium(III) salts. This observation convinced us that Ti(III) ions were oxidized to Ti(IV) by the nitro groups and not by cerium ions. Indeed, chlorination of ethyl 2-nitropropanonate (**1a**) in the presence of a stoichiometric amount of ammonium nitrate gave ethyl 2-chloro-2-nitropropanoate (**3a**) in quantitatively yield; GC analysis of the crude reaction mixture did not indicate the presence of 2-(hydroxyimino)carboxylate (**4a**). The synthesis was accompanied by emission of nitric oxide (NO), which could be formed in a redox process described by the equation: $3TiCl_3 + NO_3^- \rightarrow 2TiCl_4 + TiO_2 + NO + Cl^-$. Indeed, the reduction of nitrate (NO_3^-) to nitric oxide (NO) by Ti(III) ions has been previously reported,[20] and this process has found some applications in the field of analytical chemistry.

After optimization, we applied the new method for the oxidative chlorination of symmetric dimethyl α,α′-dinitrodicarboxylates **1e–g** (Scheme 2 and Table 1).[21] Starting dinitro esters **1e–g** were prepared according to the general procedure[17] and purified using column chromatography. Chlorination reactions were carried out in dichloromethane using a stoichiometric amount of ammonium nitrate as a co-oxidant. The products **3e–g** were isolated in high yields, and analysis of the spectral data confirmed their structures (Table 1).

Investigation of the obtained symmetrical α,α′-dichlorodinitrodicarboxylates **3e–g** led us to interesting conclusions on the stereochemistry of the discovered process. Although chlorination of the symmetric α,α′-dinitrodicarboxylates should lead to two different diastereoisomeric forms, NMR data of **3e–g** showed the presence only one

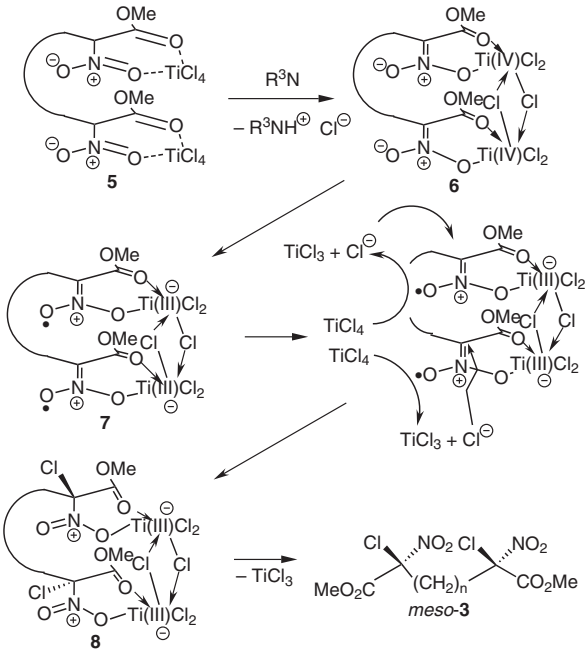
Table 1 Oxidative Chlorination of α-Nitrocarboxylic Esters in the Presence of $TiCl_4/R_3N$ with NH_4NO_3 (1 equiv) in Dichloromethane at Room Temperature

Entry	Substrate	Time (d)	Product	Physical data	Yield (%)
1	 **1a**	6	 **3a**	colorless liquid	96
2	 **1b**	6	 **3b**	colorless liquid	94
3	 **1c**	6	 **3c**	colorless liquid	94
4	 **1d**	6	 **3d**	yellowish oil	95
5	 **1e**	7	 **3e**	colorless solid mp 77–78 °C	85
6	 **1f**	7	 **3f**	colorless solid mp 45–46 °C	78
7	 **1g**	7	 **3g**	colorless solid mp 42–43 °C	82



Scheme 2 Preparation of *meso*-dichlorodinitrodicarboxylates with high diastereoselectivity

of the possible diastereoisomers. X-ray crystal structure determination carried out on **3g** showed that the prepared product appeared only in the *meso* form.[18] The observed diastereoselectivity cannot be explained on the basis of a simple model of chlorination of the titanium(IV) enolates.[19] It seems apparent that titanium(IV) enolates of 2-nitrocarboxylates form more complex, three-dimensional structures in the solution, which undergo chlorination via a highly ordered transition state. The precise reaction mechanism remains unclear. Taking into consideration the tentative mechanism suggested by Matsumura et al. for the highly *dl*-diastereoselective oxidative couplings of arylacetic acid derivatives,[22] we assumed that a similar intermediate complex is involved in the chlorination process (Scheme 3). In contrast to arylacetic acid derivatives, 2-nitrocarboxylates such as **5** coordinate titanium(IV) chloride with the nitro group. Proton abstraction gives an enolate **6**, which is subsequently oxidized by titanium(IV) ions to a radical **7**. The low reactivity of this radical comes from its resonance stabilization and is manifested in significantly longer reaction times (up to one week) needed for the transformation of **7** into the chlorinated product **3**. In contrast to the previously investigated 2-isothiocyanatocarboxylates,[15] the formed nitro-radical **7** does not undergo oxidative coupling, probably due to electrostatic repulsion between the electron-rich oxygen atoms of the two nitro groups. The intermediate **7** can be reduced by Ti(III) species to 2-(hydroxyimino)carboxylates **4**[23] or oxidized by Ti(IV) and chlorinated at C-2, furnishing 2-chloro-2-nitrocarboxylic ester **8** (as a titanium(III) complex). Formation of the 2-(hydroxyimino)carboxylates **4** takes place only in the absence of co-oxidant (CAN or NH_4NO_3) and involves an intramolecular reaction between Ti(III) ion and coordinated by a Ti(III) nitro group. We suppose that this mechanism could be responsible for the highly stereoselective formation of (*E*)-2-(hydroxyimino)carboxylic esters **4**. The stereochemical effects of the chlorination process were not evident for simple 2-nitrocarboxylates but became apparent during chlorination of symmetric α,α′-dinitrodicarboxylates. Attack of chlorine anions on the coordinated ligands from the opposite sides of the dimeric intermediate led to *meso*-substituted α,α′-dichlorodinitrodicarboxylates **3e**–**g**.



Scheme 3 A tentative reaction mechanism for the highly diastereoselective C-2 chlorination, giving the *meso*-derivatives **3e**–**g** exclusively

We assumed that the dimeric transition state **6** is a key structure before oxidation of the enolate to the radical intermediate **7** and reasoned that inhibiting the formation of complex **6** should have a significant effect on the oxidative chlorination process. To this end, we prepared (4*R*)-4-ethyl-3-(2-nitropropanoyl)-1,3-oxazolidin-2-one (**9b**) and 3-*O*-(2-nitropropionyl)-1,2;4,5-di-*O*-cyclohexylidene-D-fructopyranose (**10b**; Figure 1). The synthesized imide **9b** and ester **10b** easily formed titanium(IV) enolates but no chlorination products were detected. Moreover, reduction of **9b** and **10b** to derivatives of 2-(hydroxyimino)propanonic acid, which is usually observed for methyl and ethyl nitrocarboxylates in the absence of ammonium nitrate, was completely inhibited. Under these conditions, after six days, we recovered unchanged starting material. The oxidative chlorination was restrained, probably due either to steric repulsion between the large groups or to the formation of different titanium(IV) complexes than those depicted in Scheme 3. This experiment has shown that the described redox processes observed for titanium(IV) enolates strongly depend on the structure of the starting 2-nitrocarboxylates.

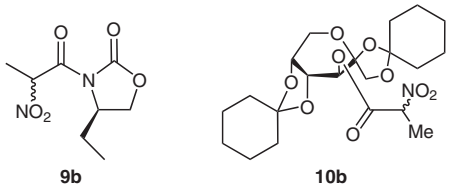


Figure 1 Structures of 2-nitropropionylimide **9b** and ester **10b**, which form titanium(IV) enolates but do not undergo oxidative chlorination

The developed, novel method for the oxidative chlorination of 2-nitrocarboxylates under very mild conditions is an alternative tool for the efficient preparation of 2-chloro-2-nitrocarboxylic esters. Application of ammonium nitrate as a co-oxidant leads to the formation of chlorination products in nearly quantitatively yields. The procedure can be applied to various methyl and ethyl esters of 2-nitrocarboxylic acids, provided that the starting ester bears a substituent at the C-2 position.[25] The method can be also employed for chlorination of α,α′-dinitrodicarboxylates, giving the appropriate α,α′-dichloro-α,α′-dinitrodicarboxylates in high yields with very high *meso*-diastereoselectivity.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

Acknowledgment

This work was supported by the Polish Ministry of Science and Higher Education (Grant No. N N204 310037) and the research was carried out with equipment purchased with financial support of the European Regional Development Fund in the framework of the Polish Innovation Economy Operational Program (contract no. POIG.02.01.00-12-023/08).

References and notes

(1) (a) Tyrkov, A. G.; Sukhenko, L. T. *Pharm. Chem. J.* **2002**, *36*, 14. (b) Jahn, U.; Rudakov, D. *Org. Lett.* **2006**, *20*, 4481. (c) Hansen, H. M.; Longbottom, D. A.; Ley, S. V. *Chem. Commun.* **2006**, 4838.

(2) (a) Kunetsky, R. A.; Dilman, A. D.; Ioffe, S. L.; Struchkova, M. I.; Strelenko, Y. A.; Tartakovsky, V. A. *Org. Lett.* **2003**, *5*, 4905. (b) Kunetsky, R. A.; Dilman, A. D.; Struchkova, M. I.; Belyakov, P. A.; Tartakovsky, V. A.; Ioffe, S. L. *Synthesis* **2006**, 2265.

(3) Kunetsky, R. A.; Dilman, A. D.; Struchkova, M. I.; Belyakov, P. A.; Korlyukov, A. A.; Ioffe, S. L.; Tartakovsky, V. A. *Mendeleev Commun.* **2007**, *17*, 108.

(4) (a) Al-Khalil, S. I.; Bowman, W. R.; Gaitonde, K.; Marley, N. A.; Richardson, G. D. *J. Chem. Soc., Perkin Trans. 2* **2001**, 1557. (b) Khisamutdinov, G. K. h.; Lyapin, N. M.; Nikitin, V. G.; Slovetskii, V. I.; Fainzil'berg, A. A. *Russ. Chem. Bull.* **2009**, *58*, 2178.

(5) Yurtanov, A. I.; Baidildaeva, S. K.; Chekhlov, A. N.; Zefirov, N. S. *Russ. Chem. Bull.* **1994**, *43*, 816.

(6) (a) Martynov, I. V.; Kruglyak, Yu. L.; Makarov, S. P. *Zh. Obshch. Khim.* **1963**, *33*, 3382. (b) Yurtanov, A. I.; Martynov, I. V. *Bull. Acad. Sci. USSR, Div. Chem. Sci.* **1989**, *38*, 2497.

(7) (a) Yurtanov, A. I.; Martynov, I. V. *Bull. Acad. Sci. USSR, Div. Chem. Sci.* **1989**, *38*, 2497. (b) Martynov, I. V.; Stoyankova, E. V.; Yurtanov, A. I. *Zh. Org. Khim.* **1982**, *18(9)*, 1849.

(8) Martynov, I. V.; Zavel'skii, V. O.; Kovalenko, S. V.; Yurtanov, A. I. *Dokl. Chem.* **1983**, 269.

(9) (a) Plewa, M. J.; Wagner, E. D.; Jazwierska, P.; Richardson, S. D.; Chen, P. H.; McKague, A. B. *Environ. Sci. Technol.* **2004**, *38*, 62. (b) Martynov, I. V.; Postnova, L. V.; Bikkineev, R. Kh.; Yurtanov, A. I. *Zh. Org. Khim.* **1984**, *20(8)*, 1724.

(10) Kissinger, L. W.; Ungnade, H. E. *J. Org. Chem.* **1958**, *23*, 1517.

(11) (a) Macbeth, A. K.; Traill, D. *J. Chem. Soc.* **1925**, 896. (b) Adolph, H. G.; Oersterling, R. E.; Sitzmann, M. *J. Org. Chem.* **1968**, *33*, 4296.

(12) Brintzinger, H.; Janecke, J. *Chem. Ber.* **1950**, *83*, 103.

(13) Amrollah-Madjdabadi, A.; Beugelmans, R.; Lechevallier, A. *Synthesis* **1986**, 828.

(14) Yurtanov, A. I.; Adkhamova, Z. M.; Baidildaeva, S. K. *Russ. Chem. Bull.* **1992**, *41(5)*, 891.

(15) Cież, D. *Tetrahedron* **2007**, *63*, 4510.

(16) Cież, D. *Org. Lett.* **2009**, *11*, 4282.

(17) Kornblum, N.; Blackwood, R. K.; Powers, J. W. *J. Am. Chem. Soc.* **1957**, *79*, 2507.

(18) Crystallographic data (excluding structure factors) for the structure of **3g** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 843131. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 (1223)336033 or e-mail: deposit@ccdc.cam.ac.uk

(19) Kise, N.; Kumada, K.; Terao, Y.; Ueda, N. *Tetrahedron* **1998**, *54*, 2697.

(20) (a) Burns, E. A. *Anal. Chim. Acta* **1962**, *26*, 143. (b) Al-Wahid, A.; Townshend, A. *Anal. Chim. Acta* **1986**, *186*, 289. (c) Yang, F.; Troncy, E.; Francur, M.; Vinet, B.; Vinay, P.; Czaika, G.; Blaise, G. *Clin. Chem.* **1997**, *43*, 657. (d) Baezzat, M. R.; Parsaeian, G.; Zare, M. A. *Quim. Nova* **2011**, *34*, 607.

(21) **Oxidative chlorination of α-nitrocarboxylic esters; representative synthesis of 3e**: A solution of dimethyl 2,7-dinitrooctanedioate[24] (**1e**; 1.08 g, 3.69 mmol) in CH_2Cl_2 (40 mL) was cooled under argon to –15 °C and $TiCl_4$ (0.90 mL, 1.55 g, 8.16 mmol, 2.2 equiv) was added in one portion. The reaction mixture was stirred for 20 min, then DIEA (1.41 mL, 1.05 g, 8.16 mmol, 2.2 equiv) in CH_2Cl_2 (4 mL) was added dropwise to form the orange titanium(IV) enolate. The ice bath was removed and the solution was gradually warmed to r.t. Fine pulverized ammonium nitrate NH_4NO_3 (0.59 g, 7.38 mmol, 2 equiv) was added and the flask was protected against moisture. The reactants were stirred for 7 days, then the solution was poured into concentrated aqueous NH_4Cl (60 mL), stirred, and the lower organic layer was separated and dried with anhydrous $MgSO_4$. The crude product isolated after evaporation of CH_2Cl_2 and purified by column chromatography (silica gel, 230–400 mesh; $CHCl_3$–MeOH, 30:1) to give **3e** (1.13 g) as a colorless solid. Mp = 77–78 °C. TLC: R_f = 0.70 (Merck silica gel 60; $CHCl_3$–MeOH, 30:1). Anal. Calcd for $C_{10}H_{14}Cl_2N_2O_8$: C, 33.26; H, 3.91; N, 7.76. Found: C, 33.41; H, 3.99; N, 7.59. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 3.90 (s, 6 H, OCH_3), 2.63 (m, 2 H, CH_aH_b), 2.48 (m, 2 H, CH_aH_b), 1,67 (m, 2 H, CH_cH_d), 1.35 (m, 2 H, CH_cH_d). ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 163.1 (COOMe), 101.5 (C-NO_2), 54.7 (OCH_3), 38.3 (CH_2), 22.6 (CH_2). IR (ATR): 2959, 1756, 1566, 1436, 1343, 1264, 1242, 1179, 1103, 1010 cm^{-1}. GC/MS (EI): *m/z* (%) = 268 (6) [$M^+ - NO_2 - NO_2 - H$], 238 (32) [$M^+ - NO_2 - NO_2 - CH_3OH$], 236 (41) [$M^+ - Cl - COOCH_3 - OCH_3$], 209 (9) [$M^+ - H - C(Cl)(NO_2)COOCH_3$], 168 (100) [$M^+ - NO_2 - NO_2 - Cl - Cl - OCH_3$]

(22) Matsumura, Y.; Nishimura, M.; Hiu, H.; Watanabe, M.; Kise, N. *J. Org. Chem.* **1996**, *61*, 2809.

(23) Reduction of the radical intermediate **7** with Ti(III) ions gives only one isomer of two possible 2-(hydroxyimino) esters. Based on the analysis of the NMR spectra measured for by-product **4a**, we have determined its structure as ethyl (*E*)-2-(hydroxyimino)propanoate. Indeed, our assignment

has been confirmed by the literature data. Stereoselective formation of (*E*)-2-(hydroxyimino)carboxylates indicates that the nitro group loses an oxygen atom adjacent to the ester group during reduction. This observation is very helpful for investigation of the transition state. For NMR data of ethyl (*E*)-2-(hydroxyimino)propanoate, see: (a) Lampeka, R. D.; Silva, T. Yu.; Skopenko, V. V. *Zh. Obshch. Khim.* **1989**, *59*, 1252. (b) Pitts, M. R.; Harrison, J. R.; Moody, C. J. *J. Chem. Soc., Perkin Trans. 1* **2001**, 955. (c) For NMR data of ethyl (*Z*)-2-(hydroxyimino)propanoate, see: Beraud, V.; Perfetti, P.; Pfister, C.; Kaafarani, M.; Vanelle, P.; Crozet, M. P. *Tetrahedron* **1998**, *54*, 4923.

(24) Reinheckel, H.; Czech, H. *Z. Chem.* **1978**, *18*, 214.

(25) Oxidative chlorination of ethyl nitroacetate does not lead to the expected ethyl chloronitroacetate but gives, instead, ethyl chloro(hydroxyimino)acetate as a main product.