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Synthesis of $C^{\alpha\alpha}$-Unsymmetrically Disubstituted Nitroesters by Electron Transfer *C*-Alkylation of Ethyl 2-Nitropropionate Anion

Valérie Béraud[1], Patricia Perfetti[1], Christine Pfister[1], Mustapha Kaafarani[1], Patrice Vanelle[2] and Michel P. Crozet[1§*]

[1]Laboratoire de Chimie Moléculaire Organique, UMR 6517, CNRS-Universités d'Aix-Marseille I et 3, Faculté des Sciences et Techniques de Saint-Jérôme, Avenue Escadrille Normandie-Niemen, 13397 Marseille Cedex 20, France

[2]Laboratoire de Chimie Organique, UMR 6517, CNRS-Universités d'Aix-Marseille I et 3, Faculté de Pharmacie, Université de la Méditerranée, 27 Bd Jean Moulin, 13385 Marseille Cedex 5, France

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Abstract : The ethyl 2-nitropropionate anion was shown to react with six reductive alkylating agents to give new $C^{\alpha\alpha}$-unsymmetrically disubstituted nitroesters and in some cases new ethyl monosubstituted methacrylates. The *C*-alkylation was shown to proceed by the $S_{RN}1$ mechanism which was confirmed by the classical criteria for $S_{RN}1$ reaction: the electron-withdrawing group effect and classical inhibition experiments by dioxygen, *p*-dinitrobenzene, cupric chloride or TEMPO. For example, ethyl 2-methyl-2-nitro-3-*p*-nitrophenylpropionate was transformed in the corresponding amino acid.

INTRODUCTION

Alkyl nitroacetates constitute a class of valuable intermediates for the preparation of various organic molecules.[1] Some DL-aminoacids have been synthesized after carbon alkylation reaction of alkyl nitroacetates[2] and a great deal of procedures has been devoted to increase the yields of this S_N2 reaction.[3]

Several synthetic reactions have been developed to prepare $C^{\alpha\alpha}$-disubstituted nitroesters by formation of a C-C bond from ethyl 2-nitropropionate. Condensation reactions with 2-dimethylaminomethyl pyrrole,[4a] indole derivatives,[4b] acrylaldehyde,[4c] formaldehyde and acetic anhydride,[4d] acetaldehyde,[4e] triethyl orthoformate,[4f] methyl vinyl ketone,[4g] dimethylaminomethyl phenol,[4h] 4-chloromethylimidazole,[4i] phenyl vinyl sulfoxide,[4j] N,N,N-trimethyl-2,2-bis(aci-nitro)ethanaminium hydroxide,[4k] acrylonitrile,[4l] 4-hydroxy-benzyl alcohol and 4-hydroxy-3-methoxybenzyl alcohol,[4m] levoglucosenome,[4n] conjugated azoalkenes,[4o] acetoxypropene,[4p] and enones[4q] have been described in the last decades.

§ Fax: (33) 04 91 67 09 44; E-Mail: michel.crozet@LCMO.u-3mrs.fr

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By contrast, there are only two conflicting reports related to the *C*-alkylation of an α-monosubstituted nitroester anion by benzyl bromide[3b] and benzyl chloride or *p*-nitrobenzyl chloride,[4h] without studies on the mechanistic aspects of these substitution reactions. There is also an electrochemical synthesis of some disubstituted derivatives of ethyl nitroacetates presented by Evans and coworkers,[3c] but the approach employed is based on the electrochemical generation of an ethyl nitroacetate anion (electrochemically generated base, EGB) followed by nucleophilic attack on alkyl halides or Michael addition.

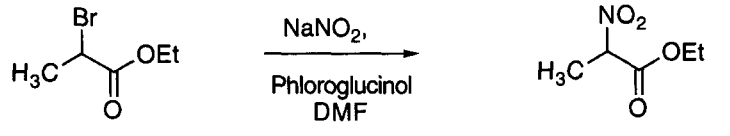
Since the initial proposal by Kornblum[5] and Russell[6] of the radical chain mechanism put forward to explain the *C*-alkylation of nitronate anions by *p*-nitrobenzyl chloride and its designation as $S_{RN}1$ by Bunnett,[7] the extensions of that reaction at sp^3 carbons attached to aromatic, aliphatic and heterocyclic systems have been studied extensively.[8,9] Otherwise, if the $S_{RN}1$ reaction of α-nitroesters with nitroparaffin salts appears to have wide applicability providing highly branched β-nitroesters,[10] the reactivity of anions of α-monosubstituted nitroesters in the $S_{RN}1$ reaction has not been studied.

With the recent interest in the study of $C^{\alpha\alpha}$-symmetrically disubstituted aminoacids,[11] which are useful building blocks in the design of conformationally restricted peptides and in continuation of our studies on the extensions of $S_{RN}1$ reaction to the preparation of compounds of biological interest,[8] we have wondered whether $C^{\alpha\alpha}$-unsymmetrically disubstituted nitroesters bearing substituents with a nitro or a quinone group could be prepared by this electron transfer reaction and used in the preparation of new α-amino acids.

In order to extend this methodology to various reductive alkylating agents, we have examined the reactivity of ethyl 2-nitropropionate anion (**1**$^-$) with *p*-nitrobenzyl chloride (**2a**), chloromethyl nitroheterocycles (**2b-c**), halogenomethyl quinones (**2d-e**), 2,2-dinitropropane (**2f**) and α,*p*-dinitrocumene (**2g**) under conditions conducive to $S_{RN}1$ reaction (inert atmosphere, photostimulation). The $S_{RN}1$ mechanism of the *C*-alkylation has been confirmed by inhibition of this reaction. Finally, as example, the preparation of the $C^{\alpha\alpha}$-unsymmetrically disubstituted aminoacid from the the *C*-alkylation product with *p*-nitrobenzyl chloride, 2-amino-3-(4-aminophenyl)-2-methylpropionic acid (**7**), has been developed.

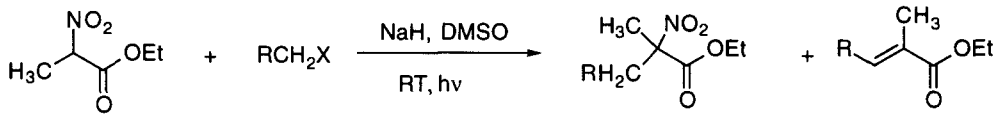
RESULTS AND DISCUSSION

Ethyl 2-nitropropionate (**1**) was prepared from commercially available and inexpensive ethyl 2-bromopropionate in 69% yield following the Kornblum procedure.[12]



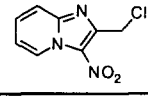
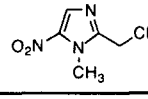
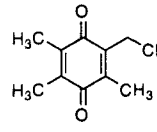
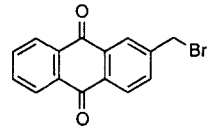
1 69 %

Ethyl 2-nitropropionate (**1**) is a relatively strong acid [pKa (H_2O) = 6.0][12] and the tetrabutylammonium salt can be prepared by using tetrabutylammonium hydroxide 40% in water. The sodium salt of **1**, prepared from ethyl 2-nitropropionate with sodium hydride in DMSO, reacts with compounds **2a-e** at room temperature to give the *C*-alkylation products **3a-e** and sometimes the ethylenic derivatives **4bce** formed by loss of nitrous acid from derivatives **3bce**. The results of the reactions of the sodium salt of **1** with **2a-e** in DMSO are summarized in Table I.



1 **2a-e** **3a-e** **4bce**

Table I. Reaction of ethyl 2-nitropropionate anion (1^-) with reductive alkylating agents 2a-e[a]

	RCH_2X	time (h.)	3%	4%
2a	*p*-$NO_2C_6H_4CH_2Cl$	3	79	-
2b[13a,b]		1.5[c] 3	44 30	5 65
2c[13c]		2[c] 4	70 36	- 57
2d[13d]		0.5 0.25[b]	14 65	- -
2e[13e]		1[c] 2[b] 3	23 20 18	4 35 32

(a) All reactions were performed by using two equivalents of **1** under argon with a 150 W fluorescent lamp. (b) These reactions were performed by using 2-nitropropane anion (5 mol %) for entrainment. (c) Reaction stopped when **4** appeared in TLC.

The *C*-alkylation derivatives (**3** + **4**) are obtained in good yields (55-95%), which are in the range of the yields observed in the $S_{RN}1$ reaction of these alkylating agents with nitronates.[13] Entrainment[8a] (a catalytic amount of a reactive nucleophile is capable of inducing the reaction of a less or nonreactive nucleophile) by 5 mol % of lithium salt of 2-nitropropane accelerates the rate of the reaction and higher yields can be obtained with quinones **2de**. The obtention of ethyl monosubstituted methacrylates **4** formed from **3** by the elimination of nitrous acid depends of the structure of the alkylating agent and shows a time-dependence. If the contact time of the reagents is lowered, the formation of these unsaturated products can be avoided and the unreacted alkylating agent recovered and reused. The ethyl monosubstituted methacrylates **4** can be isolated by column

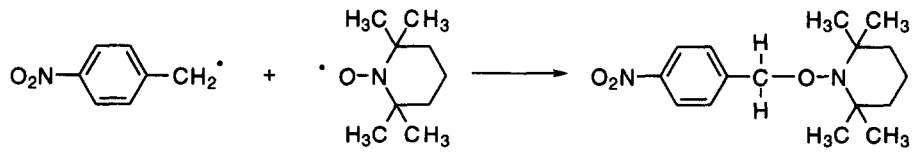
chromatography and characterized by NMR, but they are quite unstable at room temperature with daylight and gave poor elemental analyses. The stereochemistry of the double bond has been determined by NMR (NOESY) and the R and ester groups are *trans*.

2,2-Dinitropropane (**2f**) under the same conditions gave 18% yield of the *C*-alkylation product **3f** with uncharacterized by-products. α,*p*-Dinitrocumene (**2g**) was recovered unchanged after two hours at room temperature, even by entrainment with the anion of 2-nitropropane. In other reactions at higher temperatures only tars were formed. These results show that the reaction of $\mathbf{1}^-$ is very sensitive to the steric hindrance of the alkylating agent. This fact is unusual in $S_{RN}1$ reactions, which are known to give very good yields in substitution on tertiary carbon even with anions stabilized by two electron-withdrawing groups. For example, 2-bromo-2-nitropropane reacts with the anion of ethyl 2-cyanoisovalerate to give the coupling product in 73% yield.[14] 2-Chloro-2-nitropropane reacts with the anion of diethyl ethylmalonate to give the coupling product in 75% yield.[14] Dicyanoethane anion is *C*-alkylated by $O_2NC_6H_4CMe(i\text{-}Pr)Cl$ with a yield higher than 90%.[15]

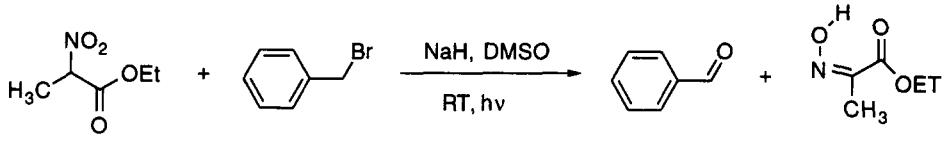
On the other hand, the addition of a radical to a nucleophile to form a radical anion is a key step in the $S_{RN}1$ sequence. Di- or tri-nitroalkane anions have been shown to fail to react with $t\text{-}Bu^\bullet$ and $(CH_3)_2NO_2C^\bullet$[16] and even *p*-nitrobenzyl radical fails to react with the anion of phenylnitroacetonitrile.[17] To explain the reactivity of electrophilic radicals, Russell has suggested[18] that the energy of activation for addition of an electrophilic radical to a nucleophile is apparently controlled by the SOMO-HOMO interaction with consequence that E* decreases as the HOMO energy increases (SOMO and LUMO constant). Inversely, E* increases as the SOMO and LUMO energies increase (HOMO constant). Compared to a primary radical as *p*-nitrobenzyl radical, the energy of the SOMO is higher for tertiary radicals as 2-nitropropyl and *p*-nitrocumyl radicals[19] and the formation of the radical anion in the reaction of these radicals with a strongly stabilized anion as $\mathbf{1}^-$ is more difficult or too difficult. That could be an explanation of the poor yields observed in the reaction of the anion of ethyl 2-nitropropionate with the crowded alkylating agents **2f** and **2g**. If this interpretation is correct, the anions of nitroesters would constitute the upper limit of stabilized tertiary anions able to react by $S_{RN}1$ mechanism with nitro alkylating agents of the *p*-nitrobenzyl chloride type and 2,2-dinitropropane type.

Another possible way to prepare ethyl 2,3-dimethyl-2,3-dinitrobutyrate (**3f**) was the reaction between ethyl 2-bromo-2-nitropropionate with lithium salt of 2-nitropropane in DMSO. This reaction failed to give **3f** and only 2,3-dimethyl-2,3-dinitrobutane has been obtained in 26% yield.

The effects of classical inhibitors[20] on the reaction of $\mathbf{1}^-$ with the *p*-nitrobenzyl chloride provide good evidence for assigning the $S_{RN}1$ mechanism. Indeed, complete inhibition was observed with cupric chloride (ligand-transfer oxidation of *p*-nitrobenzyl radical or one-electron transfer oxidation of chain carrying radical anions)[5] and *p*-dinitrobenzene (strong electron acceptor)[5] in stoechiometric quantities. The formation of **3a** strongly decreased, when bubbling dioxygen (47%), or performing the reaction in the dark (40%) or with one equivalent of TEMPO (13%). The isolation in 10% yield and the characterization by NMR of the coupling product between *p*-nitrobenzyl radical and TEMPO[21] also strongly suggests that a free radical chain process as $S_{RN}1$ mechanism is operating in this reaction.



Furthermore, the reaction of $\mathbf{1}^-$ with a "non reductive" alkylating agent as benzyl bromide leads to benzaldehyde (20%) and 2-hydroxyiminopropionic acid ethyl ester (**5**)[22] (70%) resulting of an *O*-alkylation by an S_N2 mechanism.

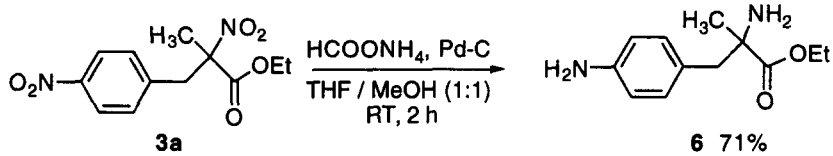


1 **5**

This result is in agreement with the experiment using benzyl chloride in DMF,[10] but in disagreement with the formation of ethyl 2-nitro-2-methyl-3-phenylpropionate in 78% yield from benzyl bromide and ethyl 2-nitropropionate under phase transfer conditions (DMF, $KHCO_3$, TEBA, 60 °C, 16 h).[3b] In our hands, these experimental conditions gave benzaldehyde (17%) and **5** (60%). Finally, the electrochemical *C*-alkylation of ethyl 2-nitropropionate anion by methyl iodide[3b] cannot be done chemically. Indeed, the reaction of tetrabutylammonium salt of ethyl 2-nitropropionate with methyl iodide in acetonitrile did not give ethyl 2-methyl-2-nitropropionate, but only **5**. In that work, the electrolyses were not performed with control potential and the electrode potential might have been negative enough to reduce methyl iodide during the electrolysis allowing an $S_{RN}1$-like process.[23]

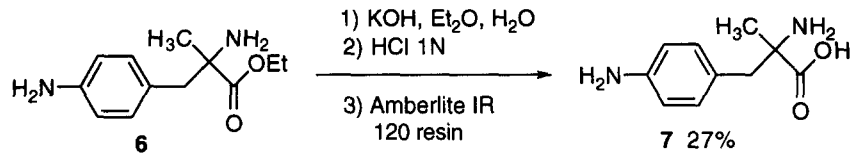
The fact that an electron-withdrawing group as a nitro or a quinone is necessary for the *C*-alkylation confirms a single electron transfer mechanism for the *C*-alkylation of ethyl 2-nitropropioniate anion by reductive alkylating agents **2a-f**. Furthermore, the formation of the oxime **5**[22] in the reaction with benzyl bromide also allows us to notice that the anion $\mathbf{1}^-$ reacts under these experimental conditions by an S_N2 mechanism as all other nitronate anions by an oxygen atom of the nitro group and not by oxygen atom of the ester group.

As example, the disubstituted nitroester **3a** was reduced[24] in the corresponding aminoester **6**:



3a **6** 71%

and after saponification of the ethyl ester group and treatment with 1N hydrochloric acid, the obtained dihydrochloride is purified by ion-exchange chromatography on Amberlite IR 120 column to give the $C^{\alpha,\alpha}$-unsymmetrically disubstituted aminoacid, 2-amino-3-(4-aminophenyl)-2-methylpropionic acid (7)[25] in 27% yield.



These reactions, when applied to nitroesters **3b-e** did not leave to the corresponding α-amino acids. Indeed they gave tars or side-products in poor yields because, for **3b-c**, amino imidazo[1,2-*a*]pyridine and amino imidazole are probably unstable in air,[26] and for **3d**, the intermediate diphenol can react with the ester group to give the nitro lactone.[27] Therefore, the instability and/or the reactivity of the intermediates during the direct transformation of the disubstituted nitroesters in the corresponding α-aminoacids is a limitation of the $S_{RN}1$ methodology, which must be considered in the chemical strategy to accede to the target molecules.

CONCLUSION

In conclusion, the ethyl 2-nitropropionate anion reacts with various reductive alkylating agents by $S_{RN}1$ mechanism to give *C*-alkylated products in good yields. These $S_{RN}1$ reactions allow the synthesis of new $C^{\alpha,\alpha}$-disubstituted nitroesters, which can be useful for the preparation of new $C^{\alpha,\alpha}$-unsymmetrically disubstituted amino acids and new ethyl monosubstituted methacrylates. Extension of this reaction to other monosubstituted nitroesters and study of the diastereoselectivity in this $S_{RN}1$ reaction by using chiral nitroesters are under active investigation in our laboratories.

EXPERIMENTAL SECTION

Melting points were determined on a Buchi capillary melting point apparatus and are uncorrected. Elemental analyses were performed by the Centre de Microanalyses of the University of Aix-Marseille 3. Both ^1H and ^{13}C NMR spectra were determined on a Bruker AC 200 spectrometer. The ^1H chemical shifts are reported as parts per million downfield from tetramethylsilane (Me_4Si), and the ^{13}C chemical shifts were referenced to the solvents peaks: $CDCl_3$ (76.9 ppm) or Me_2SO-d_6 (39.6 ppm). Absorptions are reported with the following notations: s, singlet; d, doublet; t, triplet; q, quartet; m, a more complex multiplet or overlapping multiplets. Infrared (IR) spectra were taken on a Nicolet 20-SXB infrared spectrometer of the Service de Spectrométrie Moléculaire.

The following adsorbents were used for column chromatography: silica gel 60 (Merck, particule size 0.063-0.200 mm, 70-230 mesh ASTM). TLC were performed on 5 cm x 10 cm aluminium plates coated with silica gel 60 F-254 (Merck) in an appropriate solvent.

Ethyl 2-nitropropionate (1). Sodium nitrite (3.24 g, 0.0469 mol) and phloroglucinol dihydrate (4.93 g, 0.0304 mol) were stirred in 50 ml of DMF until complete dissolution and ethyl 2-bromopropionate (3.6 ml, 0.0276 mol) was added dropwise and the mixture was stirred 3 h at room temperature. The reaction mixture was then poured into 120 ml of ice-water layered over with 30 ml of diethyl ether. After separation of the upper layer, the aqueous phase was extracted four more times with 100-ml portions of ether. The combined extracts were washed with four 100-ml portions of water and then were dried over anhydrous magnesium sulfate. The

mixture was suction-filtered, the magnesium sulfate was washed with four 25-ml portions of ether and these were combined with the filtrate. The solvent was removed under reduced pressure and the residual oil was purified by column chromatography on silica gel (eluent pentane/diethyl ether 8:2) to give **1** (2.8 g, 0.0190 mol) with 69% yield.

^{1}H NMR ($CDCl_3$) δ 1.31 (t, J = 7.08 Hz, 3H, CH_3CH_2O), 1.79 (d, J = 7.08 Hz, 3H, CH_3CHNO_2), 4.29 (q = J = 7.1 Hz, 2H, CH_3CH_2O), 5.22 (q, J = 7.08 Hz, 1H, CH_3CHNO_2). ^{13}C NMR ($CDCl_3$) δ 13.66 (CH_3CH_2O), 15.48 (CH_3CHNO_2), 62.83 (CH_3CH_2O), 83.10 (CH_3CHNO_2), 165.02 (C=O).

General Procedure for *C*-Alkylation of Ethyl 2-Nitropropionate

Sodium hydride 60% in mineral oil was washed with dry pentane and dry dimethylsulfoxyde (4 ml) was added to sodium hydride (1.4 mmol, 40 mg). Argon was bubbled through the suspension, then placed under a positive pressure of argon. Ethyl 2-nitropropionate (1.4 mmol, 200 mg) and the alkylating agent (0.7 mmol) were dissolved in 5 ml of dry dimethylsulfoxyde and the solution was added dropwise to the suspension of sodium hydride in dimethylsulfoxide, and the mixture irradiated with a 150 Watt lamp. The mixture was stirred at room temperature and the reaction was monitored by TLC. When the alkylating agent had disappeared, the reaction was quenched with addition of 50 ml of water, and then the mixture was extracted with diethyl ether (3 x 50 ml). The combined etheral extracts were washed with saturated aqueous sodium chloride solution (50 ml). The organic extracts were then dried over magnesium sulfate, and the solvent removed on a rotary evaporator under reduced pressure to give the crude *C*-alkylation products. Chromatography on silica gel gave the purified *C*-alkylation products. In the entrainment reaction, the lithium salt of 2-nitropropane (5 mol %, 7 mg) was added to the suspension of sodium hydride in dimethylsulfoxide before addition of the solution of ethyl 2-nitropropionate and the alkylating agent.

Ethyl 2-methyl-2-nitro-3-*p*-nitrophenyl propionate (3a). Yellow solid, mp 89 °C (ethanol), ^{1}H NMR ($CDCl_3$) δ 1.29 (t, J = 7.08 Hz, 3H, CH_3CH_2); 1.70 (s, 3H, CH_3CNO_2); 3.63 (AB, J = 14.2 Hz, $\Delta\nu$ = 39.0 Hz, 2H, CH_2-φ*p*-NO_2); 4.29 (q, J = 7.08 Hz, 2H, CH_3CH_2); 7.32 (d, J = 8.8 Hz, 2H, CHarom); 8.16 (d, J = 8.8 Hz, 2H, CHarom). ^{13}C NMR ($CDCl_3$) δ 13.74 (CH_3CH_2); 20.90 (CH_3CNO_2); 41.61 (CH_2-Ph); 63.29 (CH_2CH_3); 92.40 (CNO_2); 123.73 (CHarom.); 131.15 (CHarom.); 140.59 (Carom.); 166.64 (C=O); C-NO_2arom. (not observed). Anal. Calcd for $C_{12}H_{14}N_2O_6$: C, 51.06; H, 4.96; N, 9.82. Found: C, 51.14; H, 4.94; N, 9.83.

Ethyl 2-methyl-2-nitro-3-(3-nitroimidazo[1,2-*a*]pyridin-2-yl)propionate (3b), yellow solid, mp 142-143 °C (ethanol), ^{1}H NMR ($CDCl_3$) δ 1.32 (t, J = 6.99 Hz, 3H, CH_3CH_2); 1.99 (s, 3H, CH_3CNO_2); 4.28 (s, 2H, CH_2); 4.33 (q, J = 6.99 Hz, 2H, CH_2CH_3); 7.31 (td, J = 1,34 Hz, and 0.99 Hz, 1H, **H6**); 7.66 (ddd, J = 0.90 Hz, 1.08 Hz and 6.73 Hz, 1H, **H6**); 7.75 (ddd, J = 0.90 Hz, 1.08 Hz and 7.89 Hz, 1H, **H8**); 9.44 (ddd, J = 0.90 Hz, 1.08 Hz and 7.00 Hz, 1H, **H5**). ^{13}C NMR ($CDCl_3$) δ 13.71 (CH_3CH_2O); 21.42 (CH_3CNO_2); 35.75 (CH_2-Im.); 63.15 (OCH_2CH_3); 91.24 (C-NO_2); 116.74-118.22-127.69-131.00 (CHarom); 142.38-146.54 (Carom.); 166.67 (C=O); CNO_2arom. (not observed). Anal. Calcd for $C_{13}H_{14}N_2O_6$: C, 48.45; H, 4.38; N, 17.38. Found: C, 48.43; H, 4.31; N, 17.30.

Ethyl 2-methyl-3-(1-methyl-5-nitro-1H-imidazol-2-yl)-2-nitropropionate (3c), brown solid, mp 70-71 °C (ethanol). ^{1}H NMR ($CDCl_3$) δ 1.29 (t, J = 7.08 Hz, 3H, C**H**$_3$CH$_2$); 2.03 (s, 3H, C**H**$_3$CNO$_2$); 3.67 (AB, J = 16.11 Hz, $\Delta\nu$ = 20.87 Hz, 2H, C**H**$_2$); 3.96 (s, 3H, NC**H**$_3$); 4.31 (q, J = 7.08 Hz, 2H, C**H**$_2$CH$_3$); 7.91 (s, 1H, **H** Im.). ^{13}C NMR ($CDCl_3$) δ 13.63 (**C**H$_3$CH$_2$); 21.51 (**C**H$_3$CNO$_2$); 33.41 (**C**H$_3$N and **C**H$_2$Im.); 63.47 (**C**H$_2$CH$_3$); 90.67 (**C**NO$_2$); 131.99 (**C**Harom.); 146.17 (**C**arom.); 166.09 (**C**=O); **C**NO$_2$arom. (not observed). Anal. Calcd for $C_9H_{14}N_4O_6$: C, 41.96; H, 4.93; N, 19.57. Found: C, 41.81; H, 4.97; N, 19.47.

Ethyl 2-methyl-2-nitro-3-(2,4,5-trimethyl-3,6-dioxocyclohexan-1,4-dienyl)propionate (3d), yellow-orange oil, ^{1}H NMR ($CDCl_3$) δ 1.31 (t, J = 7.08 Hz, 3H, C**H**$_3$CH$_2$); 1.66 (s, 3H, C**H**$_3$CNO$_2$); 2.01 (s, 6H, C**H**$_3$); 2.03 (s, 3H, C**H**$_3$); 3.57 (AB, J = 14.64 Hz, $\Delta\nu$ = 19.59 Hz, 2H, C**H**$_2$); 4.28 (q, J = 7.08 Hz, 2H, C**H**$_2$CH$_3$). ^{13}C NMR ($CDCl_3$) δ 12.29 (2 x **C**H$_3$); 13.19 (**C**H$_3$); 13.57 (**C**H$_3$CH$_2$); 21.65 (**C**H$_3$CNO$_2$); 32.45 (**C**H$_2$CH$_3$); 63.03 (**C**H$_2$); 91.65 (**C**NO$_2$); 137.04-140.56-144.81 (**C**arom); 166.73 (**C**=O); 182.89 (**C**=O quinone).

Ethyl (9,10-dioxo-9,10-dihydroanthracen-2-yl)-2-methyl-2-nitropropionate (3e), yellow solid, mp 176 °C (cyclohexane/ethanol). ^{1}H NMR ($CDCl_3$) δ 1.33 (t, J = 7.08 Hz, 3H, C**H**$_3$CH$_2$); 1.75 (s, 3H, C**H**$_3$CNO$_2$); 3,72 (AB, J = 13.9 Hz, $\Delta\nu$ = 23.59 Hz, 2H, C**H**$_2$); 4.33 (q, J = 7.08 Hz, 2H, C**H**$_2$CH$_3$); 7.54-8.29 (m, 7H, C**H**arom.). ^{13}C NMR ($CDCl_3$) δ 14.26 (**C**H$_3$CH$_2$); 21.05 (**C**H$_3$CNO$_2$); 41.95 (**C**H$_2$); 61.21 (**C**H$_2$CH$_3$); 92.43 (**C**NO$_2$); 127.19-127.39-127.74-127.95 (**C**Harom.); 133.43-133.55 (**C**arom.); 134.16-134.21-137.70 (**C**Harom.); 139.9-141.84 (**C**arom.); 166.30 (**C**=O); 182.30 (**C**=O quinone). Anal. Calcd for $C_{20}H_{17}NO_6$: C, 65.39; H, 4.66; N, 3.81. Found: C, 65.46; H, 4.66; N, 3.82.

Ethyl 2,3-dimethyl-2,3-dinitrobutyrate (3f), oil, ^{1}H NMR ($CDCl_3$) δ 1.29 (t, J = 7.08 Hz, 3H, C**H**$_3$CH$_2$); 1.74 (s, 3H, C**H**$_3$); 1.94 (s, 3H, C**H**$_3$); 2.17 (s, 3H, C**H**$_3$); 4.21 (q, J = 7.08 Hz, 2H, C**H**$_2$CH$_3$).

Ethyl 2-methyl-3-(3-nitroimidazo[1,2-*a*]pyridin-2-yl)acrylate (4b), yellow solid, 191-192 °C (ethanol). ^{1}H NMR ($CDCl_3$) δ 1.39 (t, J = 7.2 Hz, 3H, C**H**$_3$CH$_2$); 2.49 (s, 3H, C**H**$_3$C=); 4.33 (q, J = 7.2 Hz, 2H, C**H**$_2$CH$_3$); 7.29 (td, J = 6.86 Hz and 1.03 Hz, 1H, **H**$_6$); 7.67 (ddd, J = 6.86 Hz, 1.03 Hz and 0.90 Hz, 1H, **H**$_7$); 7.84 (ddd, J = 7.89 Hz, 1.03 Hz and 0.90 Hz, 1H, H$_8$); 8.29 (s, 1H, =C**H**); 9.47 (ddd, J = 6.86 Hz, 1.03 Hz and 0.90 Hz, 1H, **H**$_5$). ^{13}C NMR ($CDCl_3$) δ 14.17 (**C**H$_3$CH$_2$); 14.89 (**C**H$_3$); 61.30 (**C**H$_2$CH$_3$); 116.63-118.36-126.36-130.92 (**C**Harom.); 127.63 (=**C**H); 139.92 (=**C**); 142.38-143.60 (**C**arom.); 165.50 (**C**=O); **C**NO$_2$arom. (not observed). Anal. Calcd for $C_{13}H_{13}N_3O_4$: C, 56.73; H, 4.76; N, 15.27. Found: C, 56.60; H, 4.82; N, 15.22.

Ethyl 2-methyl-3-(1-methyl-5-nitro-1H-imidazo-2-yl)acrylate (4c), brown solid, 63-64 °C (ethanol). ^{1}H NMR ($CDCl_3$) δ 1.37 (t, J = 7.08 Hz, 3H, C**H**$_3$CH$_2$); 2.43 (d, J = 1.70 Hz, 3H, C**H**$_3$C=);

4.03 (s, 3H, NC**H3**); 4.32 (q, *J* = 7.08 Hz, 2H, C**H2**CH3); 7.38 (m, 1H, **H**C=); 8.12 (s, 1H, **H** Im.). ^{13}C NMR ($CDCl_3$) δ 14.18 (**C**H3CH2); 14.78 (**C**H3); 33.18 (**C**H3N); 61.62 (**C**H2CH3); 120.18 (=**C**H); 133.29 (**C**Harom.); 139.75 (=**C**); 147.43 (**C**arom.); 167.30 (**C**=O); 187.08 (**C**ImNO2).

Ethyl (9,10-dioxo-9,10-dihydroanthracen-2-yl)-2-methylacrylate (4e), yellow solid, mp 165 °C (ethanol / dichloromethane). ^1H NMR ($CDCl_3$) δ 1.38 (t, *J* = 7.08 Hz, 3H, C**H3**CH2O); 1.76 (s, 3H, C**H3**); 4.32 (q, *J* = 7.08 Hz, 2H, OC**H2**CH3); 7.61-8.34 (m, 8H, C**H**arom. + **H1**). ^{13}C NMR ($CDCl_3$) δ 14.26 (**C**H3CH2 + **C**H3); 61.22 (**C**H2CH3); 127.17-127.22-127.46-127.98 (**C**Harom.); 132.68 (=**C**H); 133.43-133.58 (**C**arom.); 134.13-134.21-134.70 (**C**Harom.); 139.95-141.89 (**C**arom.); 166.30 (**C**=O); 182.30 (**C**=O quinone).

Inhibited reaction of *p*-nitrobenzyl chloride with ethyl 2-nitropropionate anion.

The procedure was similar to that for previous reaction, except that the inhibitor was added to the solution of nucleophile prior to substrate addition. All the reactions were carried out with 200 mg (1.36 mmol) of ethyl 2-nitropropionate, 120 mg (0.68 mmol) of *p*-nitrobenzyl chloride and 40 mg (1.36 mmol) of sodium hydride in 9 ml of dimethylsulfoxyde during 3 h.

Inhibition by molecular oxygen. Molecular oxygen was bubbled into the solution during 15 mn before addition of *p*-nitrobenzyl chloride. After work up and purification **3a** was isolated in 47% yield.

Reaction in the dark. The described procedure was followed, except that the reaction flask was wrapped with aluminium foil. After work up and purification **3a** was isolated in 40% yield and 8% of *p*-nitrobenzyl chloride were recovered.

Inhibition by TEMPO. With one equivalent of TEMPO (106 mg), **3a** was isolated in 13% yield with 2,2,6,6-tetramethyl-1-(4-nitrobenzyloxy)piperidine in 10% yield. With 0.1 equivalent of TEMPO (11 mg), **3a** was isolated in 47% yield.

2,2,6,6-Tetramethyl-1-(4-nitrobenzyloxy)piperidine. ^1H NMR ($CDCl_3$) δ 1.17 (s, 6H,C**H3**); 1.21 (s, 6H, C**H3**); 1.25 (m, 6H, 3xC**H2**); 4.93 (s, 2H, C**H2**Ph*p*-NO2); 7.50 (d, *J* = 8.78 Hz, 2H, C**H**arom.); 8.20 (d, *J* = 8.78 Hz, 2H, C**H**arom.).

Inhibition by *p*-dinitrobenzene. With one equivalent of *p*-dinitrobenzene (115 mg), only traces of **3a** were detected. With 0.1 equivalent of *p*-dinitrobenzene (12 mg), **3a** was isolated in 74% yield.

Inhibition by $CuCl_2$. With one equivalent of anhydrous $CuCl_2$ (92 mg), only traces of **3a** were detected. With 0.1 equivalent of $CuCl_2$. 2 H_2O, **3a** was isolated in 33% yield.

Reaction of ethyl 2-nitropropionate with benzyl chloride. The procedure was similar to that for general procedure, except that sodium hydride (3.4 mmol, 82 mg) was suspended in dimethylsulfoxyde (5 ml) and ethyl 2-nitropropionate (3.4 mmol, 500 mg) and benzyl chloride (1.7 mmol, 215 mg) were dissolved in 5 ml of dimethylsulfoxyde. The reaction mixture was stirred at room temperature during 24 h. The mixture was extracted with dichloromethane. Chromatography on silica gel (pentane-ether 9:1, then pentane-ether 5:5) gave **5** in 36% yield, benzyl chloride in 18% yield and benzaldehyde in 44% yield.

Ethyl 2-hydroxyiminopropionate (5), white solid, 92-93 °C (ethanol), ^1H NMR ($CDCl_3$) δ (ppm) 1.35 (t, *J* = 7.08 Hz, 3H, C**H3**CH2); 2.11 (s, 3H, C**H3**C=N); 3.41 (q, *J* = 7,08 Hz, 2H, C**H2**CH3).

^{13}C RMN ($CDCl_3$) δ (ppm) 10.42 (**C**H_3); 14.00 (**C**H_3CH_2); 61.79 (**C**H_2CH_3); 149.29 (**C**=N); 163.69 (**C**=O). IR: 3245 (Solid), 3282 (Solution in CCl_4 with no change with dilution). Anal. Calcd for: $C_5H_9NO_3$: C, 45.80; H, 6.87; N, 10.69. Found: C, 45.72; H, 6.90; N, 10.72.

Reduction of ethyl 2-methyl-2-nitro-3-*p*-nitrophenylpropionate (3a).

Ethyl 2-methyl-2-nitro-3-*p*-nitrophenylpropionate **3a** (2.12 mmol, 0.6 g) was dissolved in 25 ml of a 50 / 50 mixture of dry tetrahydrofuran and dry methanol. This solution was placed under a positive pressure of argon and 10% palladium on coal (0.144 g) and ammonium formate (21.3 mmol, 1.34 g) were added. The mixture was stirred until all starting **3a** had been consumed (2h, TLC). The mixture was diluted with ethyl ether, filtered and the filtrate was evaporated *in vacuo* to yield the crude amine. Column chromatography on silica gel (dichloromethane then ethanol) gave 330 mg (1.49 mmol) of ethyl 2-amino-3-(4-aminophenyl)-2-methylpropionate **6** in 71% yield.

Ethyl 2-amino-3-(4-aminophenyl)-2-methylpropionate (6). Colorless syrup, ^1H NMR ($CDCl_3$) δ 1.19 (t, *J* = 7.08 Hz, 3H, C**H**$_3$CH$_2$O); 1.29 (s, 3H, C**H**$_3$CNH$_2$); 2.78 (AB, *J* = 13.42 Hz, Δν = 67.99 Hz, 2H, C**H**$_2$-Ph); 2.70 (s, 4H, 2xN**H**$_2$); 4.07 (q, *J* = 7.08 Hz, 2H, OC**H**$_2$CH$_3$); 6.50 (d, *J* = 8.3 Hz, 2H, 2xC**H**arom); 6.36 (d, *J* = 8.3 Hz, 2H, 2xC**H**arom). ^{13}C NMR ($CDCl_3$) δ 13.86 (**C**H_3CH_2); 26.07 (CH_3CNH_2); 45.59 (**C**H_2Ph); 58.41 (**C**H_2CH_3); 60.64 (**C**NH_2); 114.64 (**C**Harom.); 125.67 (**C**arom.NH_2); 130.43 (**C**Harom.); 145.13 (**C**arom.); 176.75 (**C**=O).

Saponification of ethyl 2-amino-3-(4-aminophenyl)-2-methylpropionate (6).

The aminoester **6** (0.68 mmol, 0.15 g) was dissolved in 5 ml of ether-water mixture (50 : 50) and two equivalents of potassium hydroxide (1.35 mmol, 76 mg) were added. The reaction mixture was stirred two hours at room temperature until all starting **6** had been consumed (TLC). The solvent was evaporated under reduced pressure and the solid residue was dissolved in water and the solution was acidified at pH = 1 to be used in the following step of purification.

Obtention of 2-amino-2-methyl-3-(4-aminophenyl)propionic acid (7).

The Amberlite IR 120 (plus) ion-exchange resin was washed twice with a 1N solution hydrochloric acid and then washed with distilled water until pH was 7. The solution of the hydrochloride of 2-amino-3-(4-aminophenyl)-2-methylpropionic acid obtained from 0.3 g of aminoester **6** was put down on ion-exchange resin and was washed with distilled water until pH was 7. The resin was washed with a 5 M solution of aqueous ammonia and the obtained solution was evaporated under reduced pressure to give 0.1 g (0.51 mmol) of amino acid **7** with 27% yield for the two steps.

2-Amino-2-methyl-3-(4-aminophenyl)propionic acid (7). white solid, mp 295 °C. ^1H NMR (D_2O) δ 1.41 (s, 3H, C**H**$_3$CNH$_2$); 2.91 (AB, *J* = 15 Hz, Δν = 67.03 Hz, 2H, C**H**$_2$-Ph); 6.70 (d, *J* = 8.3 Hz, 2H, C**H**arom); 6.96 (d, *J* = 8.3 Hz, 2H, C**H**arom). ^{13}C NMR (D_2O-dioxane) δ 22.20 (**C**H_3CNH_2); 41.89 (**C**H_2Ph); 61.20 (**C**NH_2); 116.71 (**C**Harom.); 124.94 (**C**arom.NH_2); 130.86 (**C**Harom.); 145.42 (**C**arom.); 176.34 (**C**=O).

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