

# Synthesis of nitroaryl derivatives of glycine via oxidative nucleophilic substitution of hydrogen in nitroarenes

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Dedicated to Prof. Heinz Heimgartner on the occasion of his 70<sup>th</sup> anniversary

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## Abstract

Carbanion of ethyl *N*-(1,3-dithiolan-2-ylidene)glycinate adds to activated nitroarenes mostly in *para* position to the nitro group. Subsequent oxidation of the resulting  $\sigma^H$  adducts with DDQ gave respective  $\alpha$ -nitroarylated glycine derivatives in moderate yields. The reaction of esters of chiral alcohols such as (-)-menthol or (-)-8-phenylmenthol proceeds with a moderate or high diastereoselectivity leading to enantiomerically enriched nitroarylglycines.

**Keywords:** Carbanions, nitroarenes, oxidative nucleophilic substitution of hydrogen, amino acids

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## Introduction

Synthesis of unnatural amino acids is of substantial interest since they are valuable intermediates in the construction of pharmaceutically important products such as peptidomimetics, enzyme inhibitors, etc.<sup>1,2</sup> Of particular interest are arylglycines because they are components of many pharmaceuticals e.g. Plavix<sup>3a</sup>, Cefprosil<sup>3b</sup> or Vancomycin,<sup>3c</sup> etc.

Although there are numerous methods of synthesis of arylglycines<sup>4</sup>, those that contain the nitro group in *ortho* or *para* position are not much known. Synthesis of such nitroarylated glycines are reported via the Strecker reaction,<sup>5</sup> and the base-induced Smiles rearrangement of *N*-nitrophenylsulfonyl amino acids.<sup>6</sup>

In a few earlier papers we reported synthesis of some  $\alpha$ -nitroaryl- $\alpha$ -amino acids via oxidative nucleophilic substitution of hydrogen (ONSH) in nitroarenes with carbanions of protected esters of amino acids. The ONSH reaction, a two-stage process, comprises addition of nucleophilic agents such as carbanions to nitroarenes in the *ortho* or *para* position, in relation to

the nitro group, occupied by hydrogen to form  $\sigma^H$  adducts and their subsequent oxidation by an external oxidant.<sup>7</sup> Since the addition is a reversible process and the nucleophiles (carbanions) are sensitive to oxidation, the ONSH proceeds satisfactorily only when the addition equilibrium is shifted to the adduct due to high nucleophilicity of carbanions and high electrophilicity of nitroarenes. Following this methodology, we have synthesized the  $\alpha$ -nitroaryl derivatives of alanine,<sup>8a</sup> proline,<sup>8b</sup> serine<sup>8a,8c</sup>, threonine<sup>8c</sup> and phosphoglycine.<sup>8d</sup>

In this paper we report an application of this methodology for synthesis of C-nitroarylglycines.

## Results and Discussion

We have chosen ethyl *N*-(diphenylmethylene)glycinate **1a** and ethyl *N*-(1,3-dithiolane-2-ylidene)glycinate **1b** for the precursors of protected glycine carbanions. Similar derivatives of alanine were successfully used in the ONSH reaction in nitroarenes in our early work.<sup>8a</sup> The protected glycine esters **1a** and **1b** were obtained according to the literature procedures.<sup>9,10</sup>

Preliminary experiments in which carbanion of **1a** generated by treatment of **1a** with *t*-BuOK in THF/DMF mixture at low temperature was reacted with nitrobenzene and 3-cyanonitrobenzene and subsequently oxidized with DDQ gave negative results. No ONSH products were found in the reaction mixtures. It appears that the nucleophilicity of the carbanion of **1a** is too low to form the  $\sigma^H$  adduct in a sufficient degree, even with highly electrophilic 3-cyanonitrobenzene.

Somewhat similar situation was observed earlier in ONSH with carbanion of protected alanine. The reaction proceeded satisfactorily with nitrobenzenes containing electron-withdrawing substituents but not with the less electron-deficient nitrobenzenes.<sup>8a</sup> Due to the presence of the methyl group the nucleophilicity of the carbanion of the analogously protected alanine ester is higher than that of **1a**. On the other hand the carbanion of **1b** exhibited higher nucleophilicity than that of **1a** and formed  $\sigma^H$  adducts to nitrobenzene derivatives that contain electron-withdrawing substituents. The carbanion of protected alanine esters due to their tertiary character added to nitrobenzenes only in the *para* position, whereas the secondary carbanion of **1b** can react with such nitroarenes in both *ortho* and *para* positions.

Thus, when a solution of **1b** and 4-chloronitrobenzene in a mixture of THF/DMF at -78 °C was treated with *t*-BuOK and after a few minutes DDQ was added, the expected product of ONSH **4a** was obtained in a reasonable yield of 45%. It shall be stressed that no traces of a product of nucleophilic substitution of chlorine,  $S_NAr$  were detected in the reaction mixture. Under similar conditions a series of nitrobenzene derivatives were reacted with **1b** to form products of ONSH, mainly in the *para* position. The reaction with 2-chloro, 2-bromo- and 2-cyanonitrobenzene gave two isomeric ONSH products in positions 4- and 6-, whereas 3-chloro- and 3-bromonitrobenzene reacted exclusively in position 4 (Table 1).

**Table 1.** Results of ONSH reactions of carbanion **1b** with nitroarenes **2** – **12**

Nitroarene		Product		
Z			Yield (%)	Ratio <sup>a</sup>
2-Cl	<b>2</b>	<b>2a,2b</b>	35	1:3
3-Cl	<b>3</b>	<b>3b</b>	55	<sup>c</sup>
4-Cl	<b>4</b>	<b>4a</b>	45	<sup>c</sup>
2-Br	<b>5</b>	<b>5a,5b</b>	25	3:2
3-Br	<b>6</b>	<b>6b</b>	57	<sup>c</sup>
3-F	<b>7</b>	<b>7a,7b</b>	26	1:2
3-I	<b>8</b>	<b>8a,8b</b>	52	2:15
2-CN	<b>9</b>	<b>9a,9b</b>	49	2:5
3-CN	<b>10</b>	<b>10b</b>	40	<sup>c</sup>
3-NO <sub>2</sub>	<b>11</b>	<b>11b</b>	41	<sup>c</sup>
1-NN <sup>b</sup>	<b>12</b>	<b>12a</b>	52	<sup>c</sup>

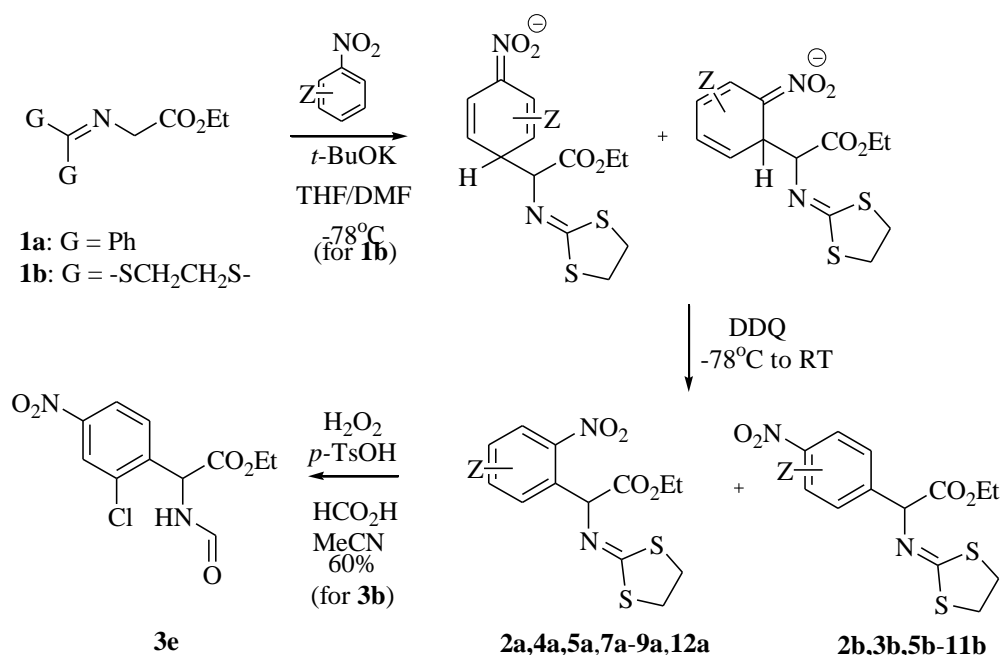
<sup>a</sup>Ratio *ortho:para* isomer established on the basis of <sup>1</sup>H NMR. <sup>b</sup>1-NN – 1-nitronaphthalene.

<sup>c</sup>Only one isomer was formed.

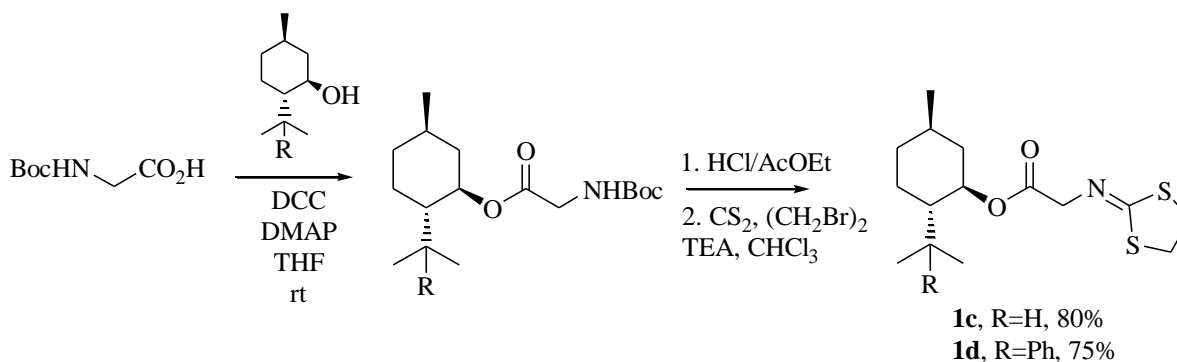
In all the cases, yields of the ONSH products were only moderate; however, taking into account the availability of the starting materials and the simplicity of the procedures this synthesis of nitroarylated glycines is of practical value. We observed serious difficulties in the separation of the isomeric ONSH products due to small differences in R<sub>f</sub> in TLC and column chromatography; thus the products were isolated and purified as mixtures *o*- and *p*-nitroarylglycinates. The composition of the mixtures was determined on the basis of <sup>1</sup>H NMR.

The products of the ONSH reaction in nitroarenes can be converted into *N*-formyl derivatives of nitroarylated glycine esters via typical procedure described in our previous paper.<sup>8a</sup> This possibility was exemplified by hydrolysis of **3a** to give ethyl *N*-formyl- $\alpha$ -(2-chloro-4-nitrophenyl)glycinate **3e** in 60% yield (Scheme 1).

In order to explore possibilities of synthesis of enantiomerically enriched nitroarylglycines we have attempted the ONSH reaction with protected glycine esters of chiral alcohols. We expected that the chiral auxiliary could promote diastereoselective addition of the carbanions to nitroaromatic rings. For this purpose, we obtained *N*-Boc protected glycine esters of (-)-menthol and (-)-8-phenylmenthol. These compounds upon deprotection and the reaction with carbon disulfide and 1,2-dibromoethane were converted into the desired *N*-(1,3-dithiolane-2-ylidene)glycinates **1c** and **1d**, respectively (Scheme 2).

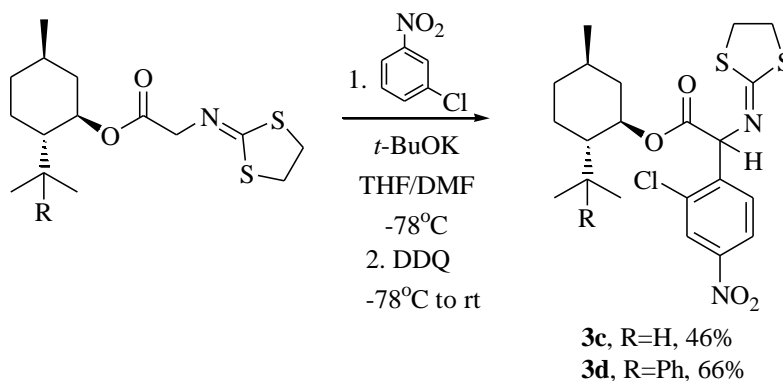


Scheme 1



Scheme 2

The ONSH reaction of **1c** with 3-chloronitrobenzene under standard conditions (treatment of a solution of the nitroarene and **1c** in THF/DMF at -78 °C with *t*-BuOK followed by oxidation with DDQ) gave the expected product of substitution in the *para* position **3c** in 46% yield. The <sup>1</sup>H NMR spectrum of this product indicates the presence of two diastereomers, observed as two sets of signals in ratio 2:1. Particularly diagnostic was the signal of the α-proton of the arylglycine that appeared as two singlets at 5.44 ppm of the major diastereomer and at 5.42 ppm for the minor one. Under the same conditions the reaction **1d** with 3-chloronitrobenzene gave, according to the <sup>1</sup>H NMR spectrum, a single diastereomer **3d** in a good yield of 66%. The signal of the proton in the α-position appeared as a singlet at 4.92 ppm.



### Scheme 3

In order to clarify the origin of the diastereoselectivity, **3d** was treated with  $t\text{-BuOK}$  in THF at  $0^\circ\text{C}$  so as to induce epimerization. The solution became immediately deep-blue indicating a formation of the nitrobenzylic carbanion. The  $^1\text{H}$  NMR spectrum of the product, isolated upon acidification and standard isolation procedure, shows presence of the additional set of signals that can be assigned to the second diastereomer. A new  $\alpha$ -proton signal at 5.35 ppm appeared, whereas in the pure diastereomer **3d** the same proton has the chemical shift of 4.92 ppm. Such an outcome suggests that the configuration of the new chiral center in **3d** was fixed at the addition stage.

These results imply that it is possible to obtain enantiomerically enriched *p*-nitroarylglycines using the procedure presented in this paper.

## Experimental Section

**General.** The carbanion precursors **1a**<sup>9</sup> and **1b**<sup>10</sup> were obtained according to the standard literature procedures. The syntheses of **1c** and **1d** were performed in the following way:

**(-)-Menthyl *N*-(1,3-dithiolan-2-ylidene)glycinate (1c).** *N*-Boc-glycine (1.68 g, 9.6 mmol), DMAP (488 mg, 4 mmol) and (-)-menthol (1.25 g, 8 mmol) were dissolved in THF (50 mL) and cooled to  $0^\circ\text{C}$  under stirring. Then a solution of DCC (2.70 g, 12.0 mmol) in THF (60 mL) was added dropwise and the resulting mixture was kept at  $0^\circ\text{C}$  for further 2 h and at rt for 20 h. The precipitated solid was filtrated and washed with diethyl ether. The solvents were evaporated and the resulting oil was purified by short column chromatography (hexane/ethyl acetate, 6:1, v/v). After evaporation of the solvents the oil obtained was treated with anhydrous 5M solution of HCl in ethyl acetate (15 mL) and stirred for 2 h at room temp. The oily residue obtained by evaporation of the solvent was treated with triethylamine, carbon disulfide and 1,2-dibromoethane in chloroform as described in [10]. Yield 2.05 g, 81% based on (-)-menthol. Yellow oil; IR (film,  $\text{CH}_2\text{Cl}_2$ )  $\nu_{\text{max}}$ : 2954, 2928, 2869, 1746, 1599, 1455, 1425, 1269  $\text{cm}^{-1}$ ;  $^1\text{H}$

NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  = 4.78 (td,  $J$  = 4.4, 10.8, 1H), 4.10 (d,  $J$  = 7.6, 2H), 3.58 – 3.64 (m, 2H), 3.44 – 3.50 (m, 2H), 2.10 – 1.95 (m, 1H), 1.94 – 1.80 (m, 1H), 1.71 – 1.71 (m, 2H), 1.55 – 1.45 (m, 1H), 1.41 – 1.37 (m, 2H), 1.12 – 0.95 (m, 2H), 0.94 – 0.87 (m, 6H), 0.76 (s, 3H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$  = 173.0, 168.9, 57.5, 46.9, 40.7, 38.1, 35.2, 34.1, 31.3, 26.2, 23.4, 23.3, 20.7, 16.3. LRMS-ESI (+): 338 [M+Na]<sup>+</sup>; Anal. calc. for C<sub>15</sub>H<sub>25</sub>NO<sub>2</sub>S<sub>2</sub>: C, 57.10; H, 7.99; N, 4.44; S, 20.33; found: C, 56.86; H, 7.86; N, 4.40; S, 20.13.

**(-)-8-Phenylmenthyl N-(1,3-dithiolan-2-ylidene)glycinate (1d)** was obtained according to the procedure for **1c** and (-)-8-phenylmenthol, **1d** was obtained in 75% yield. Yellow oil; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  = 7.35 – 7.23 (m, 4H), 7.19 – 7.07 (m, 1H), 4.89 (td,  $J$  = 4.4, 10.8, 1H), 3.62 – 3.56 (m, 2H), 3.46 – 3.40 (m, 2H), 3.24 (d,  $J$  = 18.1 Hz, 2H), 2.29 – 2.19 (m, 1H), 2.09 – 1.98 (m, 1H), 1.94 – 1.85 (m, 1H), 1.81 – 1.71 (m, 1H), 1.70 – 1.60 (m, 1H), 1.54 – 1.40 (m, 1H), 1.34 – 1.28 (m, 3H), 1.16 – 1.11 (m, 1H), 1.02 – 0.92 (m, 1H), 0.86 (d,  $J$  = 6.4 Hz, 6H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$  = 168.5, 151.7, 128.0, 127.3, 126.9, 126.3, 126.3, 125.4, 58.9, 50.3, 41.6, 39.6, 38.1, 35.2, 34.5, 31.1, 28.6, 26.4, 24.01, 21.8. LRMS-ESI (+): 392 [M+H]<sup>+</sup>.

#### General procedure for oxidative nucleophilic substitution of hydrogen in nitroarenes

To a stirred solution of **1b** (1.0 mmol) and nitroarene **2** – **12** (2.0 mmol) in THF (10 mL) and DMF (2 mL) at -78°C under argon a solution of *t*-BuOK in THF (1.3 mL, 1.0 M) was added dropwise. The dark mixture was stirred for further 30 min, treated then with DDQ (1.2 mmol) in THF (1 mL). After 5 min the cooling bath was removed and the mixture was allowed to reach room temp. and treated with acidified water. The products were extracted and finally isolated by column chromatography on silica-gel (hexane/ethyl acetate).

**Ethyl N-(1,3-dithiolan-2-ylidene)- $\alpha$ -(3-chloro-2-nitrophenyl)glycinate and ethyl N-(1,3-dithiolan-2-ylidene)- $\alpha$ -(3-chloro-4-nitrophenyl)glycinate (2a/2b)**. In ratio 1:3: yellow oil; IR (film, CH<sub>2</sub>Cl<sub>2</sub>)  $\nu_{\max}$ : 3334, 3096, 2982, 2934, 2871, 1741, 1675, 1582 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  = 8.90 – 7.85 (m, 2H+2H), 7.75 – 7.70 (m, 1H), 7.67 – 7.40 (m, 1H), 5.04 (s, 1H, *o*-), 4.98 (s, 1H, *p*-), 4.30 – 4.14 (m, 2H + 1H), 3.70 – 3.40 (m, 4H+4H+1H), 1.25 (t,  $J$  = 7.2 Hz, 3H+3H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$  = 176.3, 175.3, 168.8, 168.2, 147.3, 143.4, 132.1, 131.3, 131.2 (2C), 128.5, 128.0, 127.3, 125.7, 73.4, 69.5, 62.3, 62.2, 41.3, 38.5, 35.2, 14.1, 13.1. LRMS-ESI (+): 361 [M+H]<sup>+</sup>; Anal. calc. for C<sub>13</sub>H<sub>13</sub>ClN<sub>2</sub>O<sub>4</sub>S<sub>2</sub>: C, 43.27; H, 3.63; N, 7.76; S, 17.77; found: C, 43.57; H, 3.70; N, 7.80; S, 17.89.

**Ethyl N-(1,3-dithiolan-2-ylidene)- $\alpha$ -(2-chloro-4-nitrophenyl)glycinate (3b)**. Yellow oil; IR (film, CH<sub>2</sub>Cl<sub>2</sub>)  $\nu_{\max}$ : 3335, 3130, 2981, 2934, 2870, 1740, 1676, 1581, 1252 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  = 8.26 (d,  $J$  = 2.2 Hz, 1H), 8.14 (ddd,  $J$  = 0.4, 2.2, 8.6 Hz, 1H), 7.85 (d,  $J$  = 8.6 Hz, 1H), 5.44 (s, 1H), 4.22 (qd,  $J$  = 1.9, 7.2 Hz, 2H), 3.70 – 3.30 (m, 4H), 1.23 (t,  $J$  = 7.2 Hz, 3H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$  = 176.3, 168.2, 147.6, 124.7, 134.3, 130.6, 124.4, 122.0, 71.2, 62.2, 38.4, 35.3, 14.0. LRMS-ESI (+): 361 [M+H]<sup>+</sup>; Anal. calc. for C<sub>13</sub>H<sub>13</sub>ClN<sub>2</sub>O<sub>4</sub>S<sub>2</sub>: C, 43.27; H, 3.63; N, 7.76; S, 17.77; found: C, 43.60; H, 3.71; N, 7.49; S, 17.80.

**Ethyl N-(1,3-dithiolan-2-ylidene)- $\alpha$ -(5-chloro-2-nitrophenyl)glycinate (4b)**. Yellow oil; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  = 8.03 (d,  $J$  = 8.8 Hz, 1H), 7.91 (dd,  $J$  = 0.4, 2.7 Hz, 1H), 7.44 (dd,  $J$

= 2.4, 8.8 Hz, 1H), 5.73 (s, 1H), 4.18 (q,  $J = 7.2$ , 2H), 3.68 – 3.50 (m, 4H), 1.23 (t,  $J = 7.2$  Hz, 3H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta = 177.2, 167.9, 146.2, 140.4, 135.0, 130.4, 128.8, 126.2, 70.6, 62.2, 38.2, 35.2, 13.9$ . LRMS-ESI (+): 361  $[\text{M}+\text{H}]^+$ ; Anal. calc. for  $\text{C}_{13}\text{H}_{13}\text{ClN}_2\text{O}_4\text{S}_2$ : C, 43.27; H, 3.63; N, 7.76; S, 17.77; found: C, 43.60; H, 3.71; N, 7.49; S, 17.80.

**Ethyl *N*-(1,3-dithiolan-2-ylidene- $\alpha$ -(3-bromo-2-nitrophenyl)glycinate and ethyl *N*-(1,3-dithiolan-2-ylidene)- $\alpha$ -(3-bromo-4-nitrophenyl)glycinate (5a/5b).** In ratio 3:2 yellow oil;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta = 7.90$  (d,  $J = 1.7$  Hz, 1H, *o*-), 7.81 (d,  $J = 8.4$  Hz, 1H, *o*-), 7.78 (dd,  $J = 1.1, 8.0$  Hz, 1H, *p*-), 7.63 (dd,  $J = 1.1, 8.0$  Hz, 1H, *p*-), 7.61 (dd,  $J = 1.7, 8.4$  Hz, 1H, *o*-), 7.39 – 7.36 (m, 1H, *p*-), 5.04 (s, 1H, *p*-), 5.00 (s, 1H, *o*-), 4.22 – 4.19 (m, 2H+2H), 3.70 – 3.55 (m, 2H+2H), 3.55 – 3.40 (m, 2H+2H), 1.26 (t,  $J = 7.2$  Hz, 3H, *o*-), 1.24 (t,  $J = 7.2$  Hz, 3H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ):  $\delta = 177.2, 177.0, 168.7, 168.0, 150.1, 150.3, 143.2, 134.4, 133.4, 131.9, 131.5, 129.2, 127.7, 126.7, 114.6, 113.1, 73.2, 69.5, 62.3, 62.2, 38.5, 38.4, 35.4, 35.3, 14.0, 13.9$ . LRMS-ESI (+): 405, 407  $[\text{M}+\text{H}]^+$ ; Anal. calc. for  $\text{C}_{13}\text{H}_{13}\text{BrN}_2\text{O}_4\text{S}_2$ : C, 38.53; H, 3.23; N, 6.91; S, 15.82; found: C, 38.78; H, 3.31; N, 7.01; S, 15.43.

**Ethyl *N*-(1,3-dithiolan-2-ylidene)- $\alpha$ -(2-bromo-4-nitrophenyl)glycinate (6b).** Yellow oil;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta = 8.43$  (d,  $J = 2.3$  Hz, 1H), 8.18 (dd,  $J = 2.3, 8.6$  Hz, 1H), 7.84 (d,  $J = 8.6$  Hz, 1H), 5.44 (s, 1H), 4.22 – 4.18 (m, 2H), 3.70 – 3.64 (m, 1H), 3.64 – 3.50 (m, 3H), 1.22 (t,  $J = 7.2$  Hz, 3H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ):  $\delta = 168.0, 147.7, 144.3, 130.8, 127.6, 123.0, 122.5, 122.0, 73.5, 62.2, 38.4, 35.4, 14.0$ . LRMS-ESI (+): 405, 407  $[\text{M}+\text{H}]^+$ ; Anal. calc. for  $\text{C}_{13}\text{H}_{13}\text{BrN}_2\text{O}_4\text{S}_2$ : C, 38.53; H, 3.23; N, 6.91; S, 15.82; found: C, 38.78; H, 3.31; N, 7.01; S, 15.43.

**Ethyl *N*-(1,3-dithiolan-2-ylidene)- $\alpha$ -(4-fluoro-2-nitrophenyl)glycinate and ethyl *N*-(1,3-dithiolan-2-ylidene)- $\alpha$ -(2-fluoro-4-nitrophenyl)glycinate (7a/7b).** In ratio ca. 1:2 yellow oil; IR (film,  $\text{CH}_2\text{Cl}_2$ )  $\nu_{\text{max}}$ : 3087, 2982, 2934, 2871, 1744, 1581, 1534  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta = 8.10 - 7.70$  (m, 3H+3H), 5.61 (s, 1H, *o*-), 5.33 (s, 1H, *p*-), 4.36 – 4.16 (m, 2H + 2H), 3.70 – 3.40 (m, 4H+4H), 1.25 (t,  $J = 7.2$ , 3H+3H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta = 176.2, 175.8, 168.1, 167.4, 162.1, 160.8, 131.9, 130.6, 120.8, 120.6, 120.2, 119.5, 111.3, 111.1, 71.1, 67.1, 64.4, 62.3, 38.5, 35.8, 35.5, 24.7, 14.0, 13.0$ . LRMS-ESI (+): 345  $[\text{M}+\text{H}]^+$ ; Anal. calc. for  $\text{C}_{13}\text{H}_{13}\text{FN}_2\text{O}_4\text{S}_2$ : C, 45.34; H, 3.80; N, 8.13; S, 18.62; found: C, 45.65; H, 3.70; N, 8.01; S, 18.43.

**Ethyl *N*-(1,3-dithiolan-2-ylidene)- $\alpha$ -(4-iodo-2-nitrophenyl)glycinate and ethyl *N*-(1,3-dithiolan-2-ylidene)- $\alpha$ -(2-iodo-4-nitrophenyl)glycinate (8a/8b).** In ratio ca. 1:7.5 yellow oil; IR (film,  $\text{CH}_2\text{Cl}_2$ )  $\nu_{\text{max}}$ : 3093, 2980, 2932, 2867, 1738, 1579, 1523, 1463  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta = 8.68$  (d,  $J = 2.0$  Hz, 1H, *p*-), 8.35 (dd,  $J = 1.2, 9.5$  Hz, 1H, *o*-), 8.21 (dd,  $J = 2.0, 8.8$  Hz, 1H, *p*-), 8.00 – 7.91 (m, 1H, *o*-), 7.76 (d,  $J = 8.8$  Hz, 1H, *p*-), 7.61 (d,  $J = 9.5$  Hz, 1H, *o*-), 5.66 (s, 1H, *o*-), 5.39 (s, 1H, *p*-), 4.30 – 4.14 (m, 2H+2H), 3.70 – 3.50 (m, 4H+4H), 1.25 (t,  $J = 7.2$  Hz, 3H+3H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta = 176.6, 168.2, 168.0, 158.2, 147.5, 147.4, 142.7, 142.5, 134.2, 134.0, 133.2, 132.4, 131.8, 130.2, 123.3, 98.4, 92.7, 62.7, 62.2, 41.3, 38.5, 38.3, 35.4, 35.2, 14.0$  (2C); LRMS-ESI (+): 453  $[\text{M}+\text{H}]^+$ ; Anal. calc. for  $\text{C}_{13}\text{H}_{13}\text{IN}_2\text{O}_4\text{S}_2$ : C, 34.52; H, 2.90; N, 6.19; S, 14.18; found: C, 35.00; H, 3.01; N, 6.07; S, 13.89.

**Ethyl *N*-(1,3-dithiolan-2-ylidene)- $\alpha$ -(3-iodo-2-nitrophenyl)glycinate and ethyl *N*-(1,3-dithiolan-2-ylidene)- $\alpha$ -(3-iodo-4-nitrophenyl)glycinate (9a/9b).** In ratio ca. 1:1.5 yellow oil;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 7.95 – 7.20 (m, 3H+3H), 5.04 (s, 1H, *o*-), 4.99 (s, 1H, *p*-), 4.28 – 4.14 (m, 2H + 2H), 3.70 – 3.56 (m, 2H+2H), 3.55 -3.40 (m, 2H+2H), 1.25 (t,  $J$  = 7.2 Hz, 3H+3H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 176.4, 175.4, 168.7, 168.5, 168.1, 148.2, 147.1, 143.3, 133.5, 132.8, 131.2, 130.1, 128.4, 127.0, 125.6, 125.2, 124.6, 70.7, 69.5, 62.1, 38.4, 35.1, 14.0 (2C). LRMS-ESI (+): 453  $[\text{M}+\text{H}]^+$ ; Anal. calc. for  $\text{C}_{14}\text{H}_{13}\text{N}_3\text{O}_4\text{S}_2$ : C, 47.85; H, 3.73; N, 11.96; S, 18.25; found: C, 48.10; H, 3.82; N, 11.84; S, 17.97.

**Ethyl *N*-(1,3-dithiolan-2-ylidene)- $\alpha$ -(2-cyano-4-nitrophenyl)glycinate (10b).** Yellow oil; IR (film,  $\text{CH}_2\text{Cl}_2$ )  $\nu_{\text{max}}$ : 3086, 2982, 2935, 2236, 1738, 1582, 1536, 1354  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 8.34 (d,  $J$  = 0.4 Hz, 1H), 8.11 (d,  $J$  = 8.2 Hz, 1H), 7.92 (dd,  $J$  = 0.4, 8.2 Hz, 1H), 5.76 (s, 1H), 4.18 (q,  $J$  = 7.2 Hz, 2H), 3.75 – 3.40 (m, 4H), 1.22 (t,  $J$  = 7.2 Hz, 3H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 177.4, 167.5, 138.2, 136.3, 131.7, 128.3, 116.5, 113.0, 70.6, 62.3, 38.3, 35.2, 13.9. LRMS-ESI (+): 374  $[\text{M}+\text{Na}]^+$ ; Anal. calc. for  $\text{C}_{14}\text{H}_{13}\text{N}_3\text{O}_4\text{S}_2$ : C, 47.85; H, 3.73; N, 11.96; S, 18.25; found: C, 47.90; H, 3.70; N, 11.80; S, 17.83.

**Ethyl *N*-(1,3-dithiolan-2-ylidene)- $\alpha$ -(2,4-dinitrophenyl)glycinate (11b).** Yellow oil;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 8.98 (d,  $J$  = 4.2 Hz, 1H), 8.48 (ddd,  $J$  = 0.4, 2.4, 8.7 Hz, 1H), 8.20 (d,  $J$  = 0.4, 8.7 Hz, 1H), 5.82 (s, 1H), 4.19 (q,  $J$  = 7.2 Hz, 2H), 3.75 – 3.45 (m, 4H), 1.22 (t,  $J$  = 7.2 Hz, 3H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 178.1, 167.3, 148.2, 147.3, 139.6, 132.1, 127.5, 120.2, 70.5, 62.6, 38.3, 35.3, 13.9. LRMS-ESI (+): 372  $[\text{M}+\text{Na}]^+$ ; Anal. calc. for  $\text{C}_{13}\text{H}_{13}\text{N}_3\text{O}_6\text{S}_2$ : C, 42.04; H, 3.53; N, 11.31; S, 17.27; found: C, 43.20; H, 3.70; N, 11.71; S, 17.43.

**Ethyl *N*-(1,3-dithiolan-2-ylidene)- $\alpha$ -(1-nitro-2-naphthyl)glycinate (12b).** Yellow oil;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 8.01 (d,  $J$  = 8.7 Hz, 1H), 7.93 – 7.85 (m, 1H), 7.83 – 7.78 (m, 1H), 7.67 – 7.58 (m, 3H), 5.31 (s, 1H), 4.20 (dq,  $J$  = 1.8, 7.2 Hz, 2H), 3.69 – 3.41 (m, 4H), 1.22 (t,  $J$  = 7.2 Hz, 3H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 178.8, 168.3, 133.5, 131.4, 128.7, 128.1, 127.7, 127.3, 125.4, 124.3, 122.1, 69.3, 62.3, 38.5, 35.5, 13.9. LRMS-ESI (+): 377  $[\text{M}+\text{H}]^+$ ; Anal. calc. for  $\text{C}_{17}\text{H}_{16}\text{N}_2\text{O}_4\text{S}_2$ : C, 54.24; H, 4.28; N, 7.44; S, 17.04; found: C, 54.46; H, 4.70; N, 7.30; S, 17.44.

**(-)-Menthyl *N*-(1,3-dithiolan-2-ylidene)- $\alpha$ -(2-chloro-4-nitrophenyl)glycinate mixture of diastereomers in ratio 2:1 (3c).** Yellow oil; IR (film,  $\text{CH}_2\text{Cl}_2$ )  $\nu_{\text{max}}$ : 3130, 2955, 2928, 2870, 1738, 1584, 1526, 1455  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 8.24 (d,  $J$  = 2.2, 1H), 8.15 – 8.10 (m, 1H), 7.88 (d,  $J$  = 8.6, 2H), 5.44 (s, 1H, diast.1), 5.42 (s, 1H, diast.2), 4.73 – 4.58 (m, 1H), 3.73 – 3.38 (m, 4H), 1.94 – 1.86 (m, 1H), 1.56 – 1.43 (m, 1H), 1.43 – 1.39 (m, 1H), 1.39 – 1.19 (m, 1H), 1.09 – 0.90 (m, 2H), 0.91 – 0.82 (m, 6H), 0.82 – 0.76 (m, 1H), 0.75 – 0.69 (m, 3H), 0.60 – 0.56 (m, 1H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 167.5, 147.6, 142.8, 134.4, 134.2, 130.6, 124.7, 124.3, 121.9, 121.8, 71.5, 71.0, 46.9, 46.8, 46.7, 40.4, 40.2, 38.3, 35.3(2C), 34.0, 31.4, 31.3, 26.9, 26.1, 26.0, 23.3, 23.2, 21.9, 20.7, 20.6, 16.2, 16.0. LRMS-ESI (+): 493  $[\text{M}+\text{Na}]^+$ ; Anal. calc. for  $\text{C}_{21}\text{H}_{27}\text{ClN}_2\text{O}_4\text{S}_2$ : C, 53.55; H, 5.78; N, 5.95; S, 13.61; found: C, 53.81; H, 5.73; N, 5.67; S, 13.88.



**(-)-8-Phenylmenthyl N-(1,3-dithiolan-2-ylidene)- $\alpha$ -(2-chloro-4-nitrophenyl)glycinate (3d).** Yellow oil; IR (film, CH<sub>2</sub>Cl<sub>2</sub>)  $\nu_{\max}$ : 3130, 2955, 2928, 2870, 1738, 1584, 1526, 1455 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  = 8.21 (d,  $J$  = 2.3, 1H), 8.07 (ddd,  $J$  = 0.3, 2.3, 8.6, 1H), 7.62 (d,  $J$  = 8.6, 1H), 7.32 – 7.21 (m, 4H), 7.18 – 7.05 (m, 1H), 4.92 (s, 1H), 4.88 (td,  $J$  = 4.4, 10.8 Hz, 1H), 3.69 – 3.65 (m, 1H), 3.60 – 3.54 (m, 1H), 3.52 – 3.47 (m, 1H), 3.45 – 3.40 (m, 1H), 1.95 – 1.88 (m, 1H), 1.74 – 1.68 (m, 1H), 1.58 – 1.48 (m, 1H), 1.31 (s, 3H), 1.23 (s, 3H), 1.12 – 1.07 (m, 1H), 1.06 – 0.96 (m, 1H), 0.80 (d,  $J$  = 6.4, 6H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$  = 175.2, 167.3, 150.7, 147.3, 142.4, 134.2, 130.7, 127.8, 126.6, 125.3, 125.0, 124.2, 121.6, 70.6, 50.2, 40.7, 40.0, 38.3, 35.0, 34.1, 30.9, 26.7, 26.3, 26.0, 21.4. LRMS-ESI (+): 547 [M+H]<sup>+</sup>; Anal. calc. for C<sub>27</sub>H<sub>31</sub>ClN<sub>2</sub>O<sub>4</sub>S<sub>2</sub>: C, 59.27; H, 5.71; N, 5.12; S, found: C, 59.30; H, 5.70; N, 5.01.

**Hydrolysis of 3a.** Reaction was performed according typical procedure using **3a** as a substrate, *N*-formyl derivative was obtained in 60% yield.<sup>8a</sup>

**Ethyl N-formyl- $\alpha$ -(2-chloro-4-nitrophenyl)glycinate (3e).** Oil; IR (film, CH<sub>2</sub>Cl<sub>2</sub>)  $\nu_{\max}$ : 3318, 3103, 2980, 2927, 1745, 1681, 1527 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  = 9.01, (d,  $J$  = 2.6, 1H), 8.27 (dd,  $J$  = 2.3, 10.3 1H), 8.14 (dd,  $J$  = 2.3, 8.5, 1H), 7.20 (d,  $J$  = 8.5, 1H), 6.39 (d,  $J$  = 5.2 Hz, 1H), 5.96 (d,  $J$  = 6.2 Hz, 1H), 4.30 – 4.19 (m, 2H), 1.22 (t,  $J$  = 7.2 Hz, 3H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$  = 168.6, 160.1, 141.3, 134.5, 131.3, 125.4, 122.2, 53.5, 13.9. LRMS-ESI (+): 309 [M+Na]<sup>+</sup>; Anal. calc. for C<sub>11</sub>H<sub>11</sub>ClN<sub>2</sub>O<sub>4</sub>S<sub>2</sub>: C, 46.09; H, 3.70; N, 9.77; found: C, 46.31; H, 3.70; N, 9.80.

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