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Synthesis of (*Z*)-2-(2-formamido-4-thiazolyl)-2-(substituted alkoxyimino) acetic acids

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Abstract

(*Z*)-2-(2-formamido-4-thiazolyl)-2-(substituted alkoxyimino) acetic acids were synthesized by a new method based on the following sequence of reactions: treatment of the *tert*-butyl acetoacetate with sodium nitrite, alkylation of the oxime formed with an appropriate alkyl halide, halogenation of methyl α-keto group and simultaneous cleavage of *tert*-butyl ester with sulfuryl chloride, protection of the obtained acid function with diphenyldiazomethane, formation of the 2-aminothiazole ring by the Hantzsch method with thiourea, formylation of the amino group and selective final cleavage of the diphenylmethyl ester by treatment with trifluoroacetic acid and anisol. The developed procedure allows the synthesis of (*Z*)-2-(2-formamido-4-thiazolyl)-2-(substituted alkoxyimino) acetic acids, with an ester function in the alkoxyimino group employing a simple method and obtaining higher yields in comparison with the habitually used classic method.

Keywords: Cephalosporins; 7-Aminocephalosporanic acid; Synthesis; Alkoxyimino group

1. Introduction

Cephalosporins are a group of antibiotics, widely developed for their large activity spectrum and resistance to β-lactamase. They can be divided into cephalosporins of first, second and third generation. Moreover this last group of drugs displays an interesting activity towards Gram (−) bacteria, even though they do not operate the same towards Gram (+) bacteria as compounds of the first generation. Among these drugs cefixime and cefdinir are well-assessed compounds. A structural characteristic of these molecules is the presence in the 7 position of the 7-aminocephalosporanic acid (7-ACA), nucleus of a 2-aminothiazolyl moiety bounded by means of an (alkoxyimino) acetamido grouping. The heterocyclic ring is responsible of higher Gram (−) activity of this class of drugs and the *syn* configuration of the side chain can be associated to a high resistance of these drugs to hydrolytic enzymes towards the cefem ring [1–3].

The (*Z*)-2-(2-formamido-4-thiazolyl)-2-(substituted alkoxyimino) acetic acids are important synthetic intermediates in the cephalosporin chemistry. These compounds are used in the preparation of the third-generation cephalosporins by acylation of various 3-cephem nuclei [4–9] (Fig. 1).

New compounds of this class must therefore maintain the above reported structural characteristics in order to preserve activity. However the thiazolyl heterocycle is rather difficult to obtain and in this

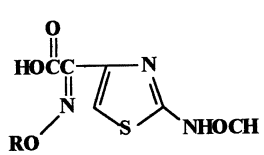

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Fig. 1. Structure of the (*Z*)-2-(2-formamido-4-thiazolyl)-2-(substituted alkoxyimino) acetic acids.

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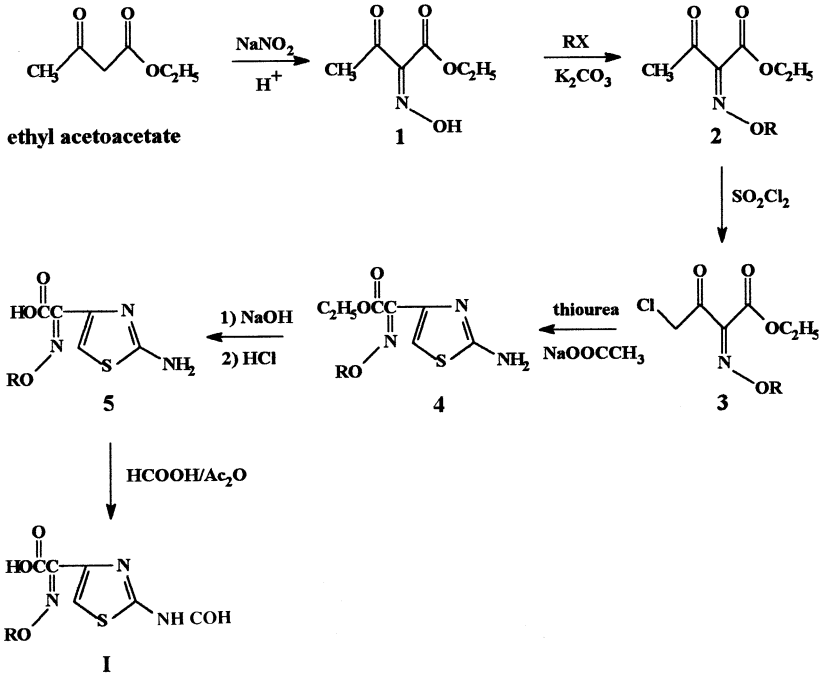


Scheme 1. Method A for the synthesis of **I**.

paper new synthetic pathways are explored both to increase the yields and to decrease the number of the synthetic steps.

Current synthetic methods to prepare **I** are outlined in Schemes 1 (Method A) and 2 (Method B) [10–14].

In both methods the oxime **1** is the common intermediate, obtained from ethyl acetoacetate by treatment with sodium nitrite in acetic acid.

In Method A the oxime **1** is alkylated with an alkyl halide in the presence of potassium carbonate as a catalyst. The methyl group of **2** is then halogenated with sulfuryl chloride or bromine. The reaction of the halogenated derivative **3** with thiourea afforded the 2-aminothiazole ring, according to the conditions of Hantzsch method. In the next step the alkaline hydrolysis of the ester group of **4** occurs in the presence of sodium hydroxide. Finally the amino function of (**5**) is protected by formylation with a mixture of acetic anhydride–formic acid to give **I**.

According to Method B the halogenated derivative (**6**) is synthesized from the oxime **1**. The formation of the 2-aminothiazole ring is a similar reaction to that previously described. The glyoxalate **8** is prepared by treatment of **7** with sodium hydrogen sulfite and it is formylated with a mixture of acetic anhydride–formic acid. From the formylated glyoxalate (**9**), by means of alkaline hydrolysis, was finally obtained the acid form (**10**). Into this last compound was then introduced a substituted alkoxyimino group, using an alkoxyamine obtained by treatment of a substituted *N*-alkoxyphthalimide (**12**) with 100% hydrazine hydrate [15,16].

Method A is much less complex and the yields are higher than in Method B. Nevertheless, Method A cannot be used when the alkoxyimino group to be introduced contains an ester function as substituent, because the treatment with sodium hydroxide causes the simultaneous hydrolysis of the two ester groups of the molecule. In this case a product with two acid functions with similar reactivity would be obtained. This acid function would compete during the acylation reaction with cephalosporanic nucleus and the formation of side products would take place. This situation causes a reduction of the yields and the degree of purity of the resulting cephalosporins.

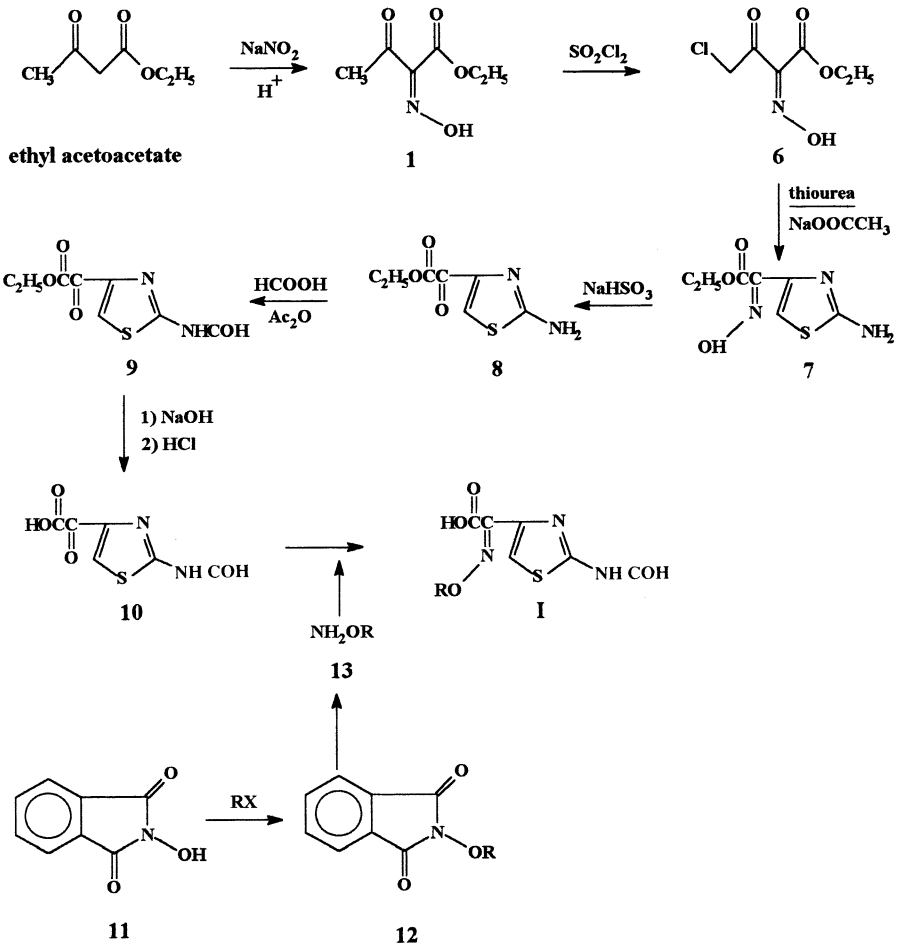
Method B can be used for the introduction of the alkoxyimino group with an ester function but the yields of reaction are much lower and it implies the execution of many reaction steps.

The objective of this paper is to find an alternative method for the synthesis of (*Z*)-2-(2-formamido-4-thiazolyl)-2-(substituted alkoxyimino) acetic acids, with an ester function in the alkoxyimino group (**I**). We wanted to develop a new synthetic pathway, which applies the advantages of the method A over the method B to prepare **I**.

2. Chemistry

The proposed synthetic pathway is as follows (Scheme 3):

In this method the ethyl acetoacetate used in Methods A and B as starting material was replaced by



Scheme 2. Method B for the synthesis of **I**.

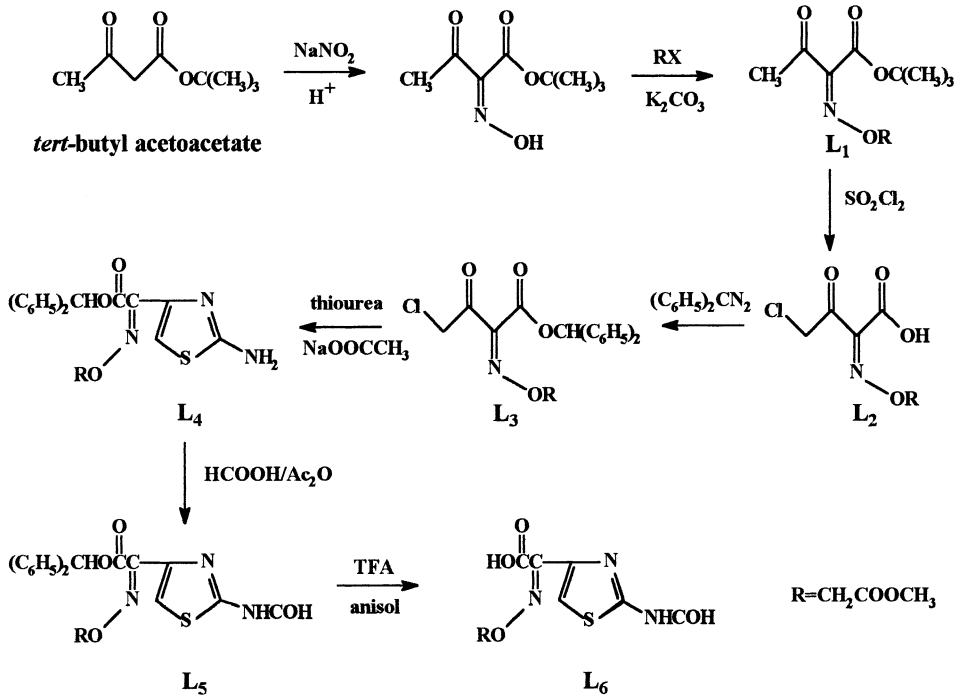
tert-butyl acetoacetate. This compound reacts with sodium nitrite in acid medium to produce the oxime, which was alkylated with an appropriate alkyl halide. The ester function in the alkoxyimino group was formed and the intermediate $\mathbf{L_1}$ was obtained [4,5]. The methyl group adjacent to the keto carbonyl group was halogenated with sulfuryl chloride in acetic acid. In these conditions the simultaneous cleavage of the *tert*-butyl ester furnished the acid ($\mathbf{L_2}$) [4,5].

The 2-aminothiazole ring cannot be formed with the main acid function in free form because the yield of reaction is very low or null. For this reason the temporary protection of this acid group was carried out through the formation of diphenylmethyl ester by treatment of $\mathbf{L_2}$ with diphenyldiazomethane to obtain the $\mathbf{L_3}$ compound. Diphenyldiazomethane was obtained using sodium hydroxide instead of sodium hydrogen carbonate [17]; this change allows the preparation of a very pure reagent, avoiding the presence of *p*-toluenesulfonamide, which is completely eliminated in these conditions; this fact in turn avoids side reactions that decrease the yield of $\mathbf{L_3}$.

This is the most important step of the proposed method, because the formation of diphenylmethyl ester facilitates the formation of 2-aminothiazole ring with good yields, as well as allowing the introduction of a protective group in the carboxyl group, which can be eliminated without affecting the alkoxyimino group.

The following step was the formation of 2-aminothiazole ring by means of the Hantzsch method by treatment of $\mathbf{L_3}$ with thiourea in the presence of sodium acetate as basic catalyst. The reaction was carried in a mixture of tetrahydrofuran–water [4,5,14], because these conditions guarantee the almost exclusive obtainment of the *syn* isomer, the only one that has biological activity, and allows an easy separation of the desired product ($\mathbf{L_4}$). The formylation of the amino function, in a mixture of anhydride acetic–formic acid [18], afforded $\mathbf{L_5}$.

Finally the cleavage of the diphenylmethyl group of $\mathbf{L_5}$ was obtained with an excess of trifluoroacetic acid in the presence of anisole [18]. The stability of the alkyl ester alkoxyimino group in acid medium in this case facilitates the selective liberation of the main acid function.



Scheme 3. Method developed for the synthesis of (*Z*)-2-(2-formamido-4-thiazolyl)-2-(methoxycarbonylmethoxyimino) acetic acid.

The compound **L_6** was thus obtained with a high degree of purity and good yields (> 70–80% in the last steps). The hydrolysis of **L_5** is an important step of the overall reaction, because the free form of the acid (**L_6**) allows soft conditions to obtain a series of derivatives by acylation without degrading the cephalosporanic nucleus.

The developed technique was also used with success for the synthesis of an analog of **L_6**, having an ethyl ester in the alkoxyimino group. This method could be used in the preparation of similar alkyl esters, as well as for other derivatives of **I** that contain functional groups unstable in a basic medium.

The following chart shows, in a comparative form, the yields obtained in the synthesis of this type of compound by Methods A and B, as well as for the developed method.

	Alkoxyimino group of **I** (R)	Yield (%)
Method A[9]	OCH_2COOH	12.3
Method B[9]	$OCH_2COOC_2H_5$	5.9
Developed variant	OCH_2COOCH_3	15.4
Developed variant	$OCH_2COOC_2H_5$	14.6

Total yields are calculated on the basis of the ethyl and *tert*-butyl acetoacetate used as initial substances.

In this chart it can be observed that in the developed variant total yields were obtained more than 2.5 times higher than those achieved by Method B. The yield is only a little higher than that in the classic Method A, but this method does not allow the use of reactants with a function ester in the alkoxyimino group, which undergoes unrequired hydrolysis.

3. Experimental

Melting points (m.p.) were determined using the Gallenkamp capillary apparatus with a system of measurement and temperature control. ^{1}H NMR and ^{13}C NMR spectra were recorded at 250 MHz and 62.5 MHz, respectively, on a Bruker AC 250F spectrometer, using Me_2SO-d_6 as a solvent and tetramethylsilanne (TMS) as an internal standard.

Thin layer chromatography (TLC) was carried out in pre-coated plates of Merck silica gel 60 F_{254}. In the development of chromatograms two mobile phases were used (FM A) ethyl acetate–ethanol–water–formic acid (60:25:15:1)) and (FM B) ethyl acetate–*n*-hexane (1:1). The chromatograms were revealed in a Camag UV–Vis lamp with a wavelength of 254 nm. Evaporation of organic solvent was carried out in vacuum (rotating evaporator). Anhydrous sodium sulfate was always used as a drying agent.

The developed procedure is exemplified with the obtaining of (*Z*)-2-(2-formamido-4-thiazolyl)-2-(methoxycarbonylmethoxyimino) acetic acid (**L_6**).

3.1. Synthesis of diphenyldiazomethane

Benzophenone hydrazone (10.78 g, 55 mmol) and iodine (2.2 ml, 1% w/v) were stirred in *N*,*N*-dimethylacetamide (55 ml) and water (5 ml). A solution of chloramine T (15.5 g, 55 mmol) in *N*,*N*-dimethylacetamide (55 ml) and water (5 ml) was then added slowly over 30 min at 20°C. The mixture was stirred for 15 min before partition between dichloromethane (110 ml) and 5% sodium hydroxide solution (275 ml). The dichloromethane layer was washed with water (1 × 100 ml and 3 × 50 ml), dried and made up to 200 ml in a volumetric flask.

3.2. Quantitative determination of diphenyldiazomethane

Diphenyldiazomethane solution (10 ml) was exactly measured and the solvent was evaporated until dryness at reduced pressure. The obtained residue was dissolved with 10 ml of 1,2-dichloroethane, cooled down to 0–5°C and glacial acetic acid was added until the total fading of the breakup. The content of diphenyldiazomethane was determined by measurement of the nitrogen volume that came off during the reaction to afford 8.70 g (81.53%) of diphenyldiazomethane.

3.3. tert-Butyl-2-methoxycarbonylmethoxyimino-3-oxo-butyrate (**L_1**)

To a solution of *tert*-butyl-acetoacetate (25 g, 158 mmol) in glacial acetic acid (25 ml) was added a solution of sodium nitrite (11.45 g, 166 mmol) in 20 ml of water under ice-cooling. During the addition, the reaction temperature was maintained below 15°C. After addition, the mixture was stirred at 15°C for 30 min. After removal of the acid and the water under reduced pressure, the residue was dissolved in ethyl acetate (50 ml), and washed with 5% sodium hydrogen carbonate solution (2 × 10 ml). The separated organic layer was washed with brine, dried and evaporated.

The residue was dissolved in ethyl acetate (45 ml) and dimethylformamide (45 ml) and methyl chloroacetate (16.5 g, 152 mmol) and potassium carbonate (12 g, 152 mmol) were added at room temperature (r.t.) with stirring. An additional amount of anhydrous potassium carbonate (10.5 g, 76 mmol) was added 30 min later. After stirring at r.t. for 15 h, the mixture was poured into ice-water (100 ml) and extracted with ethyl acetate (50 ml). The organic phase was washed with water (3 × 25 ml), dried and evaporated until dryness to give 33.6 g (82%) of **L_1** as a reddish oil. TLC (FM A): 0.87; ^{1}H NMR δ (ppm) 1.40 (9H, s, $C(CH_3)_3$), 2.23 (3H, s, CH_3CO), 3.62 (3H, s, $COOCH_3$), 4.86 (2H, s, OCH_2R); ^{13}C NMR δ (ppm) 25.08 (CH_3CO), 27.64 ($R(CH_3)_3$), 51.83 (COO^*CH_3), 71.93 (OCH_2R), 84.18 ($^*C(CH_3)_3$), 150.65 (C=N–OR), 159.41 (COOR), 168.46 ($^*COOC(CH_3)_3$), 192.70 (CH_3 *COR)

3.4. 4-Chloro-2-methoxycarbonylmethoxyimino-3-oxobutyric acid (**L_2**)

To a solution of **L_1** (33.6 g, 130 mmol) in glacial acetic acid (33 ml) was added sulfuryl chloride (77 g, 570 mmol) at 58–60°C in 3.5 h. After an additional hour, the reaction mixture was cooled and evaporated. The residue was dissolved in ethyl acetate (130 ml) and the organic layer was washed with brine (3 × 30 ml). After being dried, the solvent was evaporated in vacuum. The resulting solid was collected by filtration and recrystallized with isopropyl ether (30 ml) and dried at 40°C in a stove to afford 10 g (32.5%) of **L_2**. TLC (FM A) 0.48; m.p. 133–134°C (d); ^{1}H NMR δ (ppm) 3.66 (3H, s, CH_3), 4.79 (2H, s, OCH_2R), 4.92 ($ClCH_2R$); ^{13}C NMR δ (ppm) 45.66 ($ClCH_2R$), 51.94 (CH_3), 72.13 (OCH_2R), 150.00 (C=N–OR), 160.81(COOH), 168.48 ($^*COOCH_3$), 186.50 ($ClCH_2^*COR$).

3.5. Diphenylmethyl-4-chloro-2-methoxycarbonylmethoxyimino-3-oxo-butirate (**L_3**)

To a solution of diphenyldiazomethane (15 mmol) in dichloromethane was added **L_2** (3.2 g, 13.5 mmol) in small portions under ice cooling. The mixture was stirred at r.t. for 30 min. After removal of the solvent under reduced pressure, the residue was rinsed with *n*-hexane. The resulting solid was collected by filtration, washed with *n*-hexane and dried at 40°C in a stove to give 5.1 g (93.8%) of **L_3**. TLC (FM B) 0.82; m.p. 92–93°C; ^{1}H NMR δ (ppm) 3.70 (3H, s, CH_3), 4.90 (2H, s, OCH_2R), 5.05 ($ClCH_2R$), 7.03 (1H, s, $CH(C_6H_5)_2$), 7.3–7.5 (10H, m, aromatics); ^{13}C NMR δ (ppm) 45.82 ($ClCH_2R$), 52.00 (CH_3), 72.54 (OCH_2R), 78.81 ($CH(C_6H_5)_2$), 148.09 (C=N–OR), 158.60 ($^*COOCH(C_6H_5)_2$), 168.26 ($^*COOCH_3$), 186.14 ($ClCH_2^*COR$).

3.6. Diphenylmethyl-(Z)-2-(2-amino-4-thiazolyl)-2-(methoxycarbonylmethoxyimino) acetate (**L_4**)

To a stirred solution of **L_3** (5.0 g, 12.4 mmol) in tetrahydrofuran (25 ml) and water (25 ml) were added thiourea (1.9 g, 25 mmol) and sodium acetate (5.1 g, 67.17 mmol). After being stirred at 40°C for 4 h, the mixture was extracted with ethyl acetate (125 ml). The separated organic layer was washed with brine (3 × 50 ml), dried and evaporated to give a 4.9 g (93%) of **L_4** as

a clear yellow solid. TLC (FM B) 0.35; m.p. 143–144°C; ^{1}H NMR δ (ppm) 3.70 (3H, s, CH_3), 4.75 (2H, s, OCH_2R), 6.80 (1H, s, aminothiazole), 7.03 (1H, s, $CH(C_6H_5)_2$), 7.3–7.5 (12H, m, $(C_6H_5)_2 + NH_2$); ^{13}C NMR δ (ppm) 51.73 (CH_3), 70.91 (OCH_2R), 78.34 ($CH(C_6H_5)_2$), 109.90 (C-5 aminothiazole), 140.54 (C-4 aminothiazole), 147.27 (C=N–OR), 161.28 (*COOCH-$(C_6H_5)_2$), 168.89 (C-2 aminothiazole), 169.32 (*COO-CH_3).

*3.7. Diphenylmethyl-(Z)-2-(2-formamido-4-thiazolyl)-2-(methoxycarbonylmethoxy imino) acetate (**L_5**)*

A mixture of acetic anhydride (4 ml, 42.3 mmol) and formic acid 99% (1.6 ml, 42.4 mmol) was stirred at 40°C for 1 h. To the mixture was added L_4 (4.5 g; 10.59 mmol) and the reaction mixture was stirred at r.t. for 3 h. The obtained solution was stirred with *n*-hexane (15 ml) and ethyl acetate (15 ml). The resulting precipitate was collected by filtration, washed with *n*-hexane and dried at 40°C in a stove to afford 3.7 g (77.1%) of **L_5**. TLC (FM B) 0.45; m.p. 143–144°C; ^{1}H NMR δ (ppm) 3.70 (3H, s, CH_3), 4.80 (2H, s, OCH_2R), 7.05 (1H, s, $CH(C_6H_5)_2$), 7.3–7.5 (12H, m, $(C_6H_5)_2 + NH_2$), 8.5 (1H, s, HCO), 12.60 (1H, s, NH); ^{13}C NMR δ (ppm) 51.77 (CH_3), 71.10 (OCH_2R), 78.57 ($CH(C_6H_5)_2$), 115.94 (C-5 aminothiazole), 139.50 (C-4 aminothiazole), 146.85 (C=N–OR), 157.32 (C-2 aminothiazole), 160.14 (CHO), 160.98 (*COOCH), 169.20 (*$COOCH_3$).

*3.8. (Z)-2-(2-Formamido-4-thiazolyl)-2-(methoxycarbonylmethoxyimino)acetic acid (**L_6**)*

To a solution of **L_5** (3.5 g 7.73 mmol) in 10 ml of dichloromethane were added anisole (4.8 ml, 43.94 mmol) and trifluoroacetic acid (14 ml, 182.93 mmol) under ice cooling. After 30 min at the same temperature, the mixture was poured into isopropyl ether. The resulting solid was collected by filtration, washed with isopropyl ether and dried at 40°C in stove to give 1.9 g (85.7%) of **L_6.** TLC (FM A) 0.58; m.p. 159–160°C (d); ^{1}H NMR δ (ppm) 3.68 (3H, s, CH_3), 4.78 (2H, s, OCH_2R), 7.55 (1H, s, aminothiazole), 8.52 (1H, s, HCO), 12.63 (1H, s, NH); ^{13}C NMR δ (ppm) 51.69 (CH_3), 70.87 (OCH_2R), 115.42 (C-5 aminothiazole), 140.12 (C-4 aminothiazole), 148.12 (C=N–OR), 157.08 (C-2 aminothiazole), 160.05 (CHO), 163.13 (COOH), 169.37 (*$COOCH_3$).

4. Conclusions

A method for the synthesis of (*Z*)-2-(2-formamido-4-thiazolyl)-2-(substituted alkoxyimino) acetic acids (**I**) was developed by means of which derivatives of this type, containing alkoxyimino substituted by methyl or ethyl esters, as side chain, were synthesized. Yields were higher than those described in Method B. This procedure could be useful for obtaining other similar compounds in the alkoxyimino groups that contain functional groups sensitive to the alkaline hydrolysis and that cannot usually be prepared by traditional Method A.

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