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An improved method for preparation of cefpodoxime proxetil

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Abstract

Cefpodoxime proxetil, a third-generation cephalosporin for oral administration, was synthesized by a method based on the following sequence of reactions: acylation of 7-aminocephalosporanic acid (7-ACA) with *S*-benzothiazol-2-yl(2-amino-4-thiazolyl)(methoxyimino)thioacetate (MAEM), chloroacetylation of the cefotaxime formed with chloroacetyl chloride, esterification of the acid function with 1-iodoethyl isopropyl carbonate and final cleavage of chloroacetamide protective group by treatment with thiourea in *N*,*N*-dimethylacetamide. The developed procedure allows us to obtain better yields of cefpodoxime proxetil and to eliminate the final purification step by column chromatography, necessary during the synthesis of this antibiotic by the previously reported methods.

Keywords: Cephalosporins; 7-Aminocephalosporanic acid; Cefpodoxime proxetil; Cefotaxime; Synthesis

1. Introduction

Cefpodoxime proxetil (Fig. 1), a relatively new broad-spectrum third-generation cephalosporin, has very good in vitro activity against Gram-negative bacteria, including β-lactamase producers and many strains resistant to other oral agents. It also has activity against Gram-positive bacteria, especially streptococci. It is well tolerated and is one of the first third-generation cephalosporins to be available in oral form. This antibiotic has been used widely in the treatment of respiratory and urinary tract infections and also in the treatment of skin structure infections, acute media otitis, pharyngitis, tonsillitis and sexually transmitted diseases [1–4].

From the structural point of view, cefpodoxime proxetil has a methoxymethyl group linked to the C-3 position of the cephem nucleus and ethyl 1-(isopropoxycarbonyloxy) group linked to the acid function by an ester-type bond. Both structural characteristics are associated with its good oral absorption. At the same time, it contains a (*Z*)-2-(2-aminothiazol-4-yl)(methoxyimino)acetamido moiety linked to the C-7 position. This molecular fragment is associated with the potent activity against Gram-negative bacteria and high β-lactamase stability displayed by this antibiotic.

The best current synthetic method to prepare cefpodoxime proxetil is outlined in Scheme 1.

The 3-acetoxymethyl derivative **II** prepared by acylation of 7-aminocephalosporanic acid (7-ACA) with the acid chloride of (*Z*)-2-(2-chloroacetamido-4-thiazolyl)-2-(methoxyimino)acetic acid (CATMA) is treated with aqueous methanol in the presence of calcium chloride to give the corresponding 3-methoxymethyl derivative **III**. The chloroacetyl group of **III** is removed by treatment with thiourea in aqueous solution to afford compound **IV**. Finally, esterification of **IV** with 1-iodoethyl isopropyl carbonate (**VI**) gives the corresponding ester **VII** (cefpodoxime proxetil) [5–9].

Although this synthetic pathway allows to get good overall yields (ca. 31% from 7-ACA) it has some drawbacks:

a) The use of CATMA to introduce the (*Z*)-2-(2-aminothiazol-4-yl)(methoxyimino)acetamido moiety linked to the C-7 position increases the cost of

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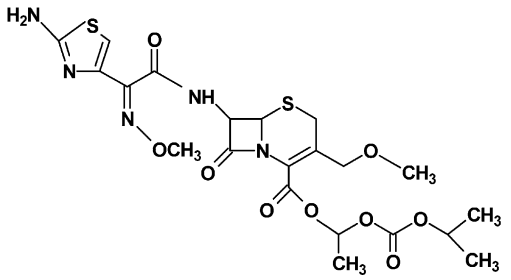
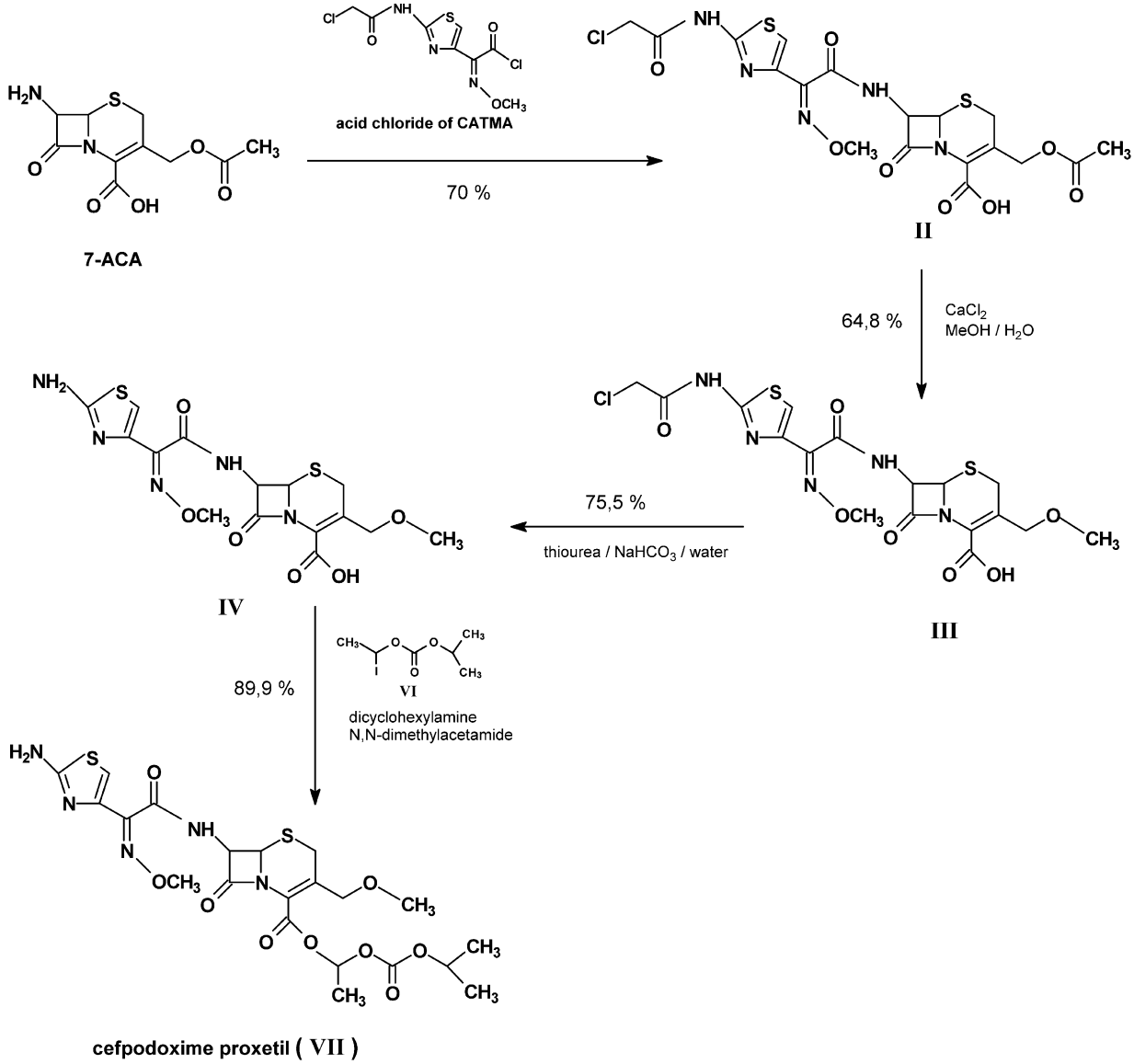


Fig. 1. Chemical structure of cefpodoxime proxetil.

the final product (cefpodoxime proxetil), because although CATMA is a commercial raw material used in cephalosporin chemistry, this compound has a high price in the market (similar to that of 7-ACA).

b) It is necessary to prepare the acylating agent (the acid chloride of CATMA) by the reaction of CATMA with phosphorous pentachloride or thionyl chloride, and it is known that acid chlorides are difficult to be purified because they are water sensitive.

c) The yield of 7-ACA acylation reaction with the acid chloride of CATMA is relatively low (70%). As a consequence, the yield of cefpodoxime proxetil and the production cost of this antibiotic become negatively affected. Additionally, the acylation with the acid chloride of CATMA must be carried out at very low temperatures ($\sim -20\,^{\circ}C$), an



Scheme 1. Synthesis of cefpodoxime proxetil as reported in the literature.

important handicap from the technological point of view.

d) The removal of the chloroacetyl group in aqueous solution causes a lot of troubles, especially the absolute necessity to purify the obtained cefpodoxime proxetil by column chromatography.

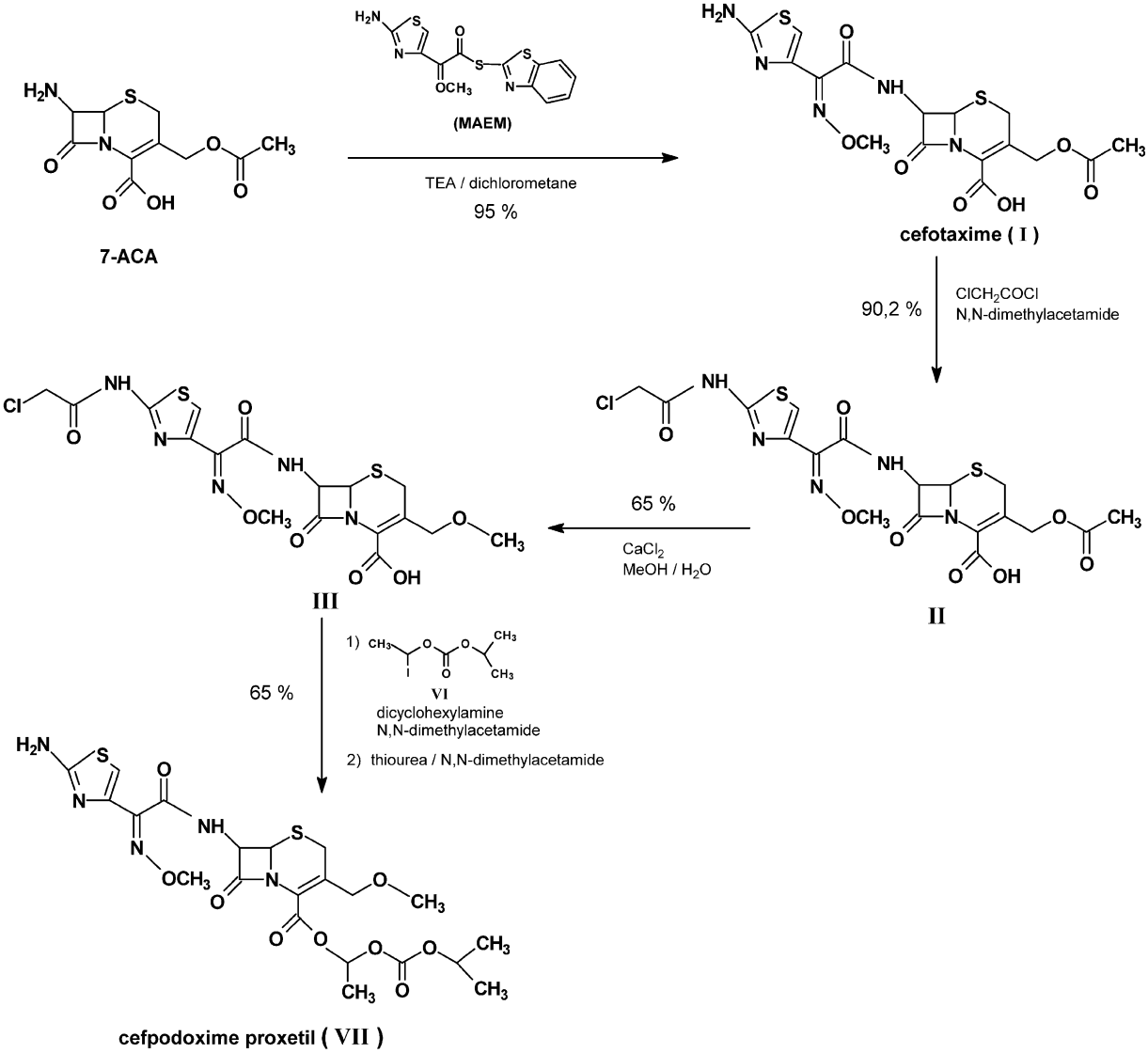
The objective of this paper is to find an alternative procedure for the synthesis of cefpodoxime proxetil in order to overcome the problems cited above.

2. Results and discussion

The proposed synthetic route is as follows (Scheme 2).

In this method, the CATMA used during the acylation of 7-ACA was replaced by *S*-benzothiazol-2-yl(2-amino-4-thiazolyl)(methoxyimino)thioacetate (MAEM, also a commercial raw material used in cephalosporin chemistry) and cefotaxime (**I**) was obtained in very good yields (95%) through a rapid and efficient procedure previously developed in our laboratory [10]. In the following step, it was necessary to block the free amino group of **I** in order to carry out further replacement of acetoxy group linked to C-3 position by the methoxy group without side reactions. After evaluating some options, it was decided to effect the protection of amino function with chloroacetyl group. With this objective, a rapid and efficient procedure was developed for chloroacetylation of **I** by treatment with chloroacetyl chloride in *N*,*N*-dimethylacetamide as the reaction solvent. The chloroacetylated derivative **II** was obtained with high purity and over 90% yields.

Although it was necessary to introduce an additional synthetic step, compound **II** was prepared in 85.5% yield calculated from 7-ACA, that is to say, a yield 15.5%



Scheme 2. Synthesis of cefpodoxime proxetil by the developed procedure.

higher than that of the previously reported procedure. It is known that in cephalosporin synthesis, the cost of the final product (in this case cefpodoxime proxetil) depends almost exclusively on the mass relationship between 7-ACA and the final product, because the 7-ACA price is many times higher than the price of the auxiliary reagents used during the synthetic procedures. Thus, whereas less 7-ACA quantity is needed to obtain a mass unity of the final product, more economic is the synthetic method. The use of MAEM in place of CATMA during the acylation step provides an additional economic benefit, because MAEM price is two or three times lesser than the price of CATMA in the market. From the technological point of view, the use of MAEM to prepare cefpodoxime proxetil improves the synthetic process because it is not necessary to obtain and purify the acylating agent, and the acylation step can be carried out at room temperature, thus avoiding the necessity of using very low temperatures (as in the case of CATMA).

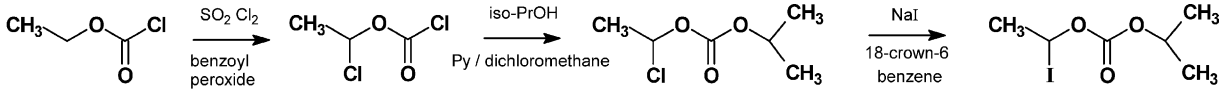
Following the developed synthetic procedure, in the next step the 3-methoxymethyl derivative **I** was obtained from **II** in 65% yield by reaction with aqueous methanol in the presence of calcium chloride as catalyst, according to the method reported in the literature [6,8].

The 1-iodoethyl isopropyl carbonate (**VI**) was synthesized from ethyl chloroformate through the following sequence of reactions (Scheme 3): radical chlorination with sulfuryl chloride, alcoholysis of the 1-chloroethyl chloroformate formed with isopropyl alcohol to obtain **V** and final halogen exchange by treatment of **V** with sodium iodide in the presence of a catalytic amount of 18-crown-6 ether. The resulting yield was the same as reported and no changes were introduced to the described method [8,9].

Another objective of this work was to overcome the problems found during the elimination of the chloroacetyl protective group of compound **III**. In the reported procedure (Scheme 1), this process is effected before the esterification of the acid function with **VI**. Although relatively high yields are reported (75.5%), we found that it is very difficult to isolate the resulting compound **IV**. During the purification procedure, it is necessary to dissolve **IV** by treatment with concentrated hydrochloric acid in order to remove reaction by-products. Further addition of sodium hydrogen carbonate (to precipitate **IV**) produces a vigorous evolution of CO_2 and the formation of a gummy precipitate difficult to handle. In consequence, poor yields are obtained and at the end of the process an additional purification step by column chromatography is necessary to obtain cefpodoxime proxetil of a suitable purity.

In the present work, the reaction sequence was reversed and compound **III** was esterified by treatment with **VI** in *N*,*N*-dimethylacetamide in the presence of dicyclohexylamine. The low polarity of the resulting ester allowed the extraction of this compound from reaction mixture with ethyl acetate and the elimination of the impurities (dicyclohexylammonium iodide and dicyclohexylamine in excess) by washing with water and diluted hydrochloric acid, respectively. In consequence, it was not necessary to isolate the ester and after removing the organic solvent, it was possible to effect the direct cleavage of the chloroacetyl protective group by reaction with thiourea in *N*,*N*-dimethylacetamide. The use of an organic solvent to effect the deprotection allowed to overcome all the problems found when carrying this reaction in aqueous solution (as reported in the literature). The cefpodoxime proxetil formed was extracted from the reaction mixture with ethyl acetate and after evaporation of the solvent, the residue was crystallized with isopropyl ether to give the pure antibiotic as was demonstrated by ^{1}H NMR and ^{13}C NMR spectroscopy. This result made an additional purification of the product by column chromatography unnecessarily, which is an advantage in comparison with the reported method.

On the other hand, the overall yield calculated from 7-ACA was 36.2%. It means that from 100 g of 7-ACA, it was possible to obtain 11 g more of cefpodoxime proxetil in comparison with the synthetic route reported in the literature consulted. It is also possible to affirm that the different procedure used in the first step (synthesis of compound **II** from 7-ACA) and the reversing of the reaction sequence (synthesis of compound **VII** from **II**) improve the process for the preparation of this antibiotic, both from the economic and technological point of view. Another advantage that results from the present research is the possibility to use the same raw materials (7-ACA and MAEM) in the synthesis of both antibiotics (cefotaxime and cefpodoxime proxetil).



ethyl chloroformate **V** **VI**

Scheme 3. Synthesis of 1-iodoethyl isopropyl carbonate (**VI**).

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 and 62.5 MHz, respectively, on a Bruker AC 250F spectrometer, using either deuterated dimethylsulfoxide (DMSO-d_6) or deuterated chloroform ($CDCl_3$) as solvent and tetramethylsilane (TMS) as an internal standard.

The mass spectra (MS) were recorded in a quadrupolar mass spectrometer TRIO 1000 (Fisons Instruments) based on the electronic impact technique with EI = 70 eV and DMK 400 V.

Thin-layer chromatography (TLC) was performed on pre-coated plates of silica gel GF-254 (Merck). 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 (3:1). The chromatograms were visualized in a Camag UV–Vis lamp with a wavelength of 254 nm.

The synthesis of each compound was confirmed by comparison of registered ^{1}H NMR spectra with the ^{1}H NMR data reported in the literature consulted [8]. In the particular case of compound **V**, the mass spectrum was also used with the same purpose.

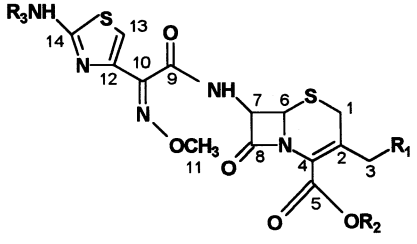
In Fig. 2, the base structures of the synthesized compounds are shown with an arbitrary numeration of carbon atoms, in order to support the assignment of ^{13}C NMR chemical shifts given below for each compound.

*3.1. 7β-[2-(2-Aminothiazol-4-yl)-(Z)-2-methoxyiminoacetamido]-3-acetoxymethyl-3-cephem-4-carboxylic acid) (**I**) (cefotaxime)*

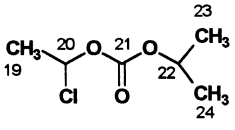
A suspension of 7-ACA (62.9 g, 231 mmol) in dichloromethane (755 ml) was cooled to 5–10 °C and with stirring triethylamine (TEA) (71 ml, 513 mmol) followed by MAEM (89.6 g, 256 mmol) were added. The mixture was stirred for 1 h at room temperature and then extracted twice with water (320 and 160 ml). The combined extracts were adjusted to pH 2.9 by the addition of 6 M hydrochloric acid (ca. 47 ml). The mixture was cooled to 0–5 °C and the resulting precipitate was separated by filtration, washed successively with cold water (60 ml), cold ethanol (60 ml), diethyl ether (2 × 80 ml) and dried to obtain **I** (100 g, 95% yield). TLC (FM A) 0.74; m.p.; ^{1}H NMR (DMSO-d_6) δ (ppm): 1.99 (3H, s, $OCOCH_3$); 3.23 and 3.45 (1H, Abq, H-2); 3.84 (3H, s, $NOCH_3$); 4.76 and 4.98 (1H, ABq, CH_2O); 5.01 (1H, d, H-6); 5.6 (1H, dd, H-7); 6.73 (1H, s, thiazol); 7.28 (2H, s, NH_2); 9.61 (1H, d, NHCO); ^{13}C NMR (DMSO-d_6) δ (ppm): C-1, 25.37; C-2, 112.17; C-3, 64.50; C-4, 134.87; C-5, 163.06; C-6, 57.34; C-7, 58.07; C-8, 164.00; C-9, 162.21; C-10, 149.06; C-11, 61.88; C-12, 142.57; C-13, 109.02; C-14, 168.47; C-15, 170.55; C-16, 20.74.

*3.2. 7β-[2-(2-Chloroacetamidothiazol-4-yl)-(Z)-2-methoxyiminoacetamido]-3-acetoxymethyl-3-cephem-4-carboxylic acid (**II**)*

To a solution of **I** (58.5 g, 128 mmol) in *N*,*N*-dimethylacetamide (295 ml), chloroacetyl chloride (15.4 ml, 193 mmol) was added, keeping the temperature between 5 and 10 °C. The mixture was stirred for 1 h at room temperature and then poured into ice water. The resulting precipitate was collected by filtration and washed successively with water (30 ml), ethanol (30 ml), diethyl ether (2 × 30 ml) and dried to obtain **II** (61.6 g, 90.2%). TLC (FM A) 0.83; m.p. 177–178 °C; ^{1}H NMR (DMSO-d_6) δ (ppm): 2.05 (3H, s, CH_3COO); 3.51 and 3.65 (2H, Abq, H-2); 3.92 (3H, s, $NOCH_3$); 4.40 (2H, s, CH_2Cl); 4.60 and 5.0 (2H, Abq, CH_2O); 5.19



Base structure for compounds I, II, III and VII



Compound V

Compound	I	II	III	VII
R_1	$OCOCH_3$ 15 16	$OCOCH_3$ 15 16	OCH_3 16	OCH_3 16
R_2	H	H	H	$(CH_3)COC(O)OCH(CH_3)_2$ 19 20 21 22 23 and 24
R_3	H	$COCH_2Cl$ 17 18	$COCH_2Cl$ 17 18	H

Fig. 2. Base structures for synthesized compounds.

(1H, d, H-6); 5.85 (1H, dd, H-7); 7.48 (1H, s, thiazol); 9.74 (1H, d, NHCO); 12.95 (1H, s, $NHCO_{chloroacetyl}$); ^{13}C NMR (DMSO-d_6) δ (ppm): C-1, 25.73; C-2, 123.51; C-3, 62.66; C-4, 126.33; C-5, 162.78; C-6, 57.41; C-7, 58.57; C-8, 163.71; C-9, 162.52; C-10, 148.49; C-11, 62.14; C-12, 141.62; C-13, 114.57; C-14, 157.89; C-15, 170.18; C-16, 20.53; C-17, 165.34; C-18, 42.16.

3.3. 7β-[2-(2-Chloroacetamidothiazol-4-yl)-(Z)-2-methoxyiminoacetamido]-3-methoxymethyl-3-cephem-4-carboxylic acid (*III*)

To a solution of **II** (26.0 g, 49 mmol) and sodium hydrogen carbonate (4.1 g, 49 mmol) in water (80 ml), methanol (170 ml, 4.2 mol) and calcium chloride dihydrate (375 g, 2.55 mol) were added. The mixture was stirred for 75 min. at 70 °C and then poured into 500 ml of ice water. The mixture was acidified with 37% hydrochloric acid (10 ml) and extracted with ethyl acetate (2 × 500 ml). The extracts were combined and the organic layer was extracted with 10% potassium hydrogen phosphate aqueous solution (350, 150 and 100 ml). The aqueous layers were combined and extracted with ethyl acetate (2 × 500 ml) after acidification with concentrated hydrochloric acid. The organic extracts were combined, washed with brine (100 ml) and dried over anhydrous sodium sulfate. The mixture was filtered and the filtrate was concentrated under reduced pressure to about 1/5 of the initial volume to yield a precipitate. The mixture was allowed to stand at room temperature for 3 h. The resulting precipitate was separated by filtration, washed with ethyl acetate (30 ml) and dried to give **III** (16 g, 65% yield). TLC (FM A) 0.69; m.p. 208–210 °C; ^1H NMR (DMSO-d_6) δ (ppm): 3.25 (3H, s, CH_3O); 3.51 and 3.62 (2H, Abq, H-1); 3.92 (3H, s, $NOCH_3$); 4.20 (2H, s, CH_2Cl); 4.40 (2H, s, CH_2O); 5.20 (1H, d, H-6); 5.84 (1H, dd, H-7); 7.48 (1H, s, thiazol); 9.75 (1H, d, NHCO); 12.95 (1H, s, $NHCO_{chloroacetyl}$); ^{13}C NMR (DMSO-d_6) δ (ppm): C-1, 25.53; C-2, 125.39; C-3, 69.95; C-4, 126.14; C-5, 163.00; C-6, 57.59; C-7, 58.51; C-8, 163.62; C-9, 162.52; C-10, 148.48; C-11, 62.13; C-12, 141.64; C-13, 114.57; C-14, 157.85; C-16, 57.40; C-17, 165.32; C-18, 42.15.

3.4. 1-Chloroethyl isopropyl carbonate (*V*)

To a solution of ethyl chloroformate (140 ml, 1.47 mol) and sulfuryl chloride (130 ml, 1.61 mol) was added benzoyl peroxide (0.5 g, 2 mmol). The mixture was refluxed for 7.5 h and it was distilled at atmospheric pressure to give 1-chloroethyl chloroformate (boiling range 119–140 °C). To a solution of the resulting 1-chloroethyl chloroformate in dichloromethane (675 ml) isopropyl alcohol (134 ml, 1.74 mol) was added, under cooling (0–5 °C) and with stirring. Pyridine (78 ml, 0.96 mol) was added dropwise to the solution over 20 min and the mixture was stirred for 30 min at the same temperature. The reaction mixture was washed successively with water (170 ml), brine (170 ml) and 5% potassium hydrogen sulfate aqueous solution (170 ml), and the organic layer dried over anhydrous sodium sulfate. The solvent was removed and the resulting liquid distilled under reduced pressure at 55 mmHg to give **V** (fraction boiling between 92 and 94 °C) (113.2 g, 46.2%). ^1H NMR ($CDCl_3$) δ (ppm): 1.34 (6H, m, $(CH_3)_2$); 1.84 (3H, d, CH_3); 4.95 (1H, sept, CHO); 6.44 (1H, q, OCHCl); ^{13}C NMR (DMSO-d_6) δ (ppm): C-19, 21.60 and 21.55; C-20, 84.30; C-21, 152.22; C-22, 73.26; C-23 and C-24, 25.16.

3.5. 1-Iodoethyl isopropyl carbonate (*VI*)

To a solution of **V** (5.1 g, 30.6 mmol) in benzene (50 ml) were added, at room temperature, sodium iodide (10 g, 66.7 mmol) and 18-crown-6 ether (0.25 g, 0.95 mmol), and the mixture was refluxed with stirring during 12 h. The mixture was washed with water (3 × 15 ml) followed by 5% sodium thiosulfate aqueous solution (10 ml). The organic layer was dried over anhydrous sodium sulfate and after filtration, the filtrate was concentrated in vacuo to give **VI** (6.7 g, 85%). ^1H NMR ($CDCl_3$) δ (ppm): 1.32 (6H, m, $(CH_3)_2$); 2.15 (3H, d, CH_3); 4.85 (1H, sept, CHO); 6.70 (1H, q, OCHCl).

3.6. 1-(Isopropoxycarbonyloxy)ethyl-7β-[2-(2-aminothiazol-4-yl)-(Z)-2-methoxyiminoacetamido]-3-methoxymethyl-3-cephem-4-carboxylate (*VII*) (cefpodoxime proxetil)

To a solution of **III** (2.0 g, 3.97 mmol) in *N*,*N*-dimethylacetamide (10 ml), dicyclohexylamine (0.9 ml, 4.52 mmol) was added, followed by **VI** (1.3 g, 5.04 mmol) under cooling (0–5 °C). The mixture was stirred for 45 min at the same temperature and ethyl acetate (50 ml) was added. The mixture was washed successively with water (15 ml), 1 M hydrochloric acid aqueous solution (15 ml) and brine (15 ml). The organic layer was dried over anhydrous sodium sulfate and the solvent was removed by vacuum distillation to give an oil (2.4 g).

The oil was dissolved in *N*,*N*-dimethylacetamide (20 ml), thiourea (0.61 g, 1.97 mmol) was added and the resulting solution was stirred for 3 h at room temperature. The mixture was poured into 5% sodium hydrogen carbonate aqueous solution (50 ml) and extracted with ethyl acetate (75 ml). The organic layer was washed successively with 10% potassium bisulfate aqueous solution (25 ml) and brine (25 ml), and dried over anhydrous sodium sulfate. After filtration, the solvent was removed under reduced pressure and the residue was stirred with isopropyl ether (25 ml). The resulting precipitate was separated by filtration, washed with

isopropyl ether (10 ml) and dried to give **VII** (1.44 g, 65%). TLC (FM A) 0.33; m.p. 98–103 °C; ^{1}H NMR (DMSO-d_6) δ (ppm): 1.25 (6H, m, $(CH_3)_2$); 1.49 (3H, d, CH_3CH); 3.20 (3H, s, CH_2OCH_3); 3.52 and 3.65 (2H, AB, q, H-2); 3.83 (3H, s, $NOCH_3$); 4.15 (2H, s, CH_3OCH_2); 4.82 (1H, m, $OCH(CH_3)$); 5.20 (1H, m, H-6); 5.85 (1H, m, H-7); 6.74 (1H, s, thiazol); 6.81 and 6.87 (1H, 2q, $OCH(CH_3)O$); 7.25 (2H, s, NH_2); 9.62 (1H, m, NHCO); ^{13}C NMR (DMSO-d_6) δ (ppm): C-1, 25.71; C-2, 123.57; C-3, 69.68; C-4, 128.48 and 128.82; C-5, 159.48; C-6, 57.72; C-7, 58.70; C-8, 163.97; C-9, 162.89; C-10, 148.89; C-11, 61.82; C-12, 142.45; C-13, 108.89; C-14, 168.32; C-16, 57.38; C-19, 18.87 and 19.03; C-20, 91.58 and 91.94; C-21, 152.76; C-22, 72.53; C-23 and C-24, 21.25.

4. Conclusions

The use of MAEM as starting material for preparing cefpodoxime proxetil allowed to obtain better yields during the synthesis of this antibiotic. Previous esterification of the chloroacetylated derivative **III**, followed by cleavage of the chloroacetyl protective group, allowed to eliminate the drawbacks of the classic route of synthesis, especially the final purification of cefpodoxime proxetil by column chromatography.

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