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Short Communication

Improvement of the synthesis of diphenylmethyl 7β-(*o*-hydroxy)benzylideneamino-3-hydroxymethyl-3-cephem-4-carboxylate

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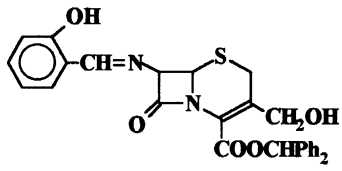
Abstract

The title product (**I**) is synthesized currently from 7-aminocephalosporanic acid, and diphenyldiazomethane (DDM) is used as a protective reagent of the acid function for further reactions. When DDM was prepared from benzophenone hydrazone by reaction with chloramine T, it was resulted impure by *p*-toluenesulfonamide, formed as side product, which cannot be removed during the final purification step carried out according to the literature procedure. Two simple methods are proposed here to obtain **I** with the suitable degree of purity necessary for a drug. © 2001 Elsevier Science S.A. All rights reserved.

Keywords: Diphenyldiazomethane; *p*-Toluenesulfonamide; Purification

1. Introduction

Diphenylmethyl - 7β - (*o* - hydroxy)benzylideneamino-3-hydroxymethyl-3-cephem-4-carboxylate (**I**) (Fig. 1) is a synthetic intermediate in the preparation of a class of cephalosporins from 7-aminocephalosporanic acid (7-ACA), such as cefixime and cefdinir [1,2].



I

Fig. 1. Diphenylmethyl-7β-(*o*-hydroxy)benzylideneamino-3-hydroxymethyl-3-cephem-4-carboxylate.

This compound was prepared by alkaline hydrolysis of 7-ACA under mild conditions, followed by protection of the amino group by formation of a Schiff base with salicylaldehyde, and of the carboxyl group by esterification with diphenyldiazomethane (DDM) [1,2]. This compound is used widely in reactions of cephalosporins because it requires mild conditions both to protect and de-protect a carboxyl group, avoiding side reactions, such as lactonization of the dihydrothiazine ring.

DDM is an unstable reagent that needs to be prepared just before use. To obtain this compound from benzophenone hydrazone, chloramine T is used currently as an oxidant in the presence of iodine, as a catalyst of the process, in aqueous solution of DMA or DMF. The resulting product is extracted of the reaction mixture with dichloromethane, purified with sodium hydrogen carbonate solution and dried. However, an accurate analysis of a sample of this material prepared for the synthesis of **I**, according to the proposed method, showed the presence of an impurity (Table 1),

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Table 1
Characterization of **I** obtained with diphenyldiazomethane (literature method)

IR [ν (cm^{-1})]		^{1}H NMR [δ (ppm)]	
Reported	Obtained	Reported	Obtained
3470	3470		2.3 (s, 3H)
	3328	3.70 (s, 2H)	3.70 (s, 2H)
	3240	4.30 (s, 2H)	4.20 (s, 2H)
1768	1760	5.15 (br, 1H)	5.20 (t, 1H)
1710	1700	5.45 (d, 1H) $J = 5$ Hz	5.31 (d, 1H) $J = 5$ Hz
1620	1620	5.71 (d, 1H) $J = 5$ Hz	5.70 (d, 1H) $J = 5$ Hz
Yields (%)		6.96 (s, 1H)	6.90 (s, 1H)
78.1	79.5	7.0–7.7 (m, 14H)	7.0–7.7 (m, 20H)
m.p. (°C)		8.80 (s, 1H)	8.80 (s, 1H)
97–98.5	95–98		

which cannot be eliminated following the literature method [3]. We did not find any report in the literature about this side product or suggestions for its elimination: in the case of cephalosporin synthesis this aspect appears important since the impurity is associated with the final drug, decreasing both the yield and melting point (m.p.); additionally it introduces an unforeseen variable and a potential toxic component into the in vivo test.

Physical–chemical parameters for **I**, such as m.p., the yield of the reaction, IR frequencies and ^{1}H NMR chemicals shift are reported in Table 1 for our sample and compared with those found in the literature [3].

Yield and m.p. overlap. However, in the IR spectrum, besides the characteristic bands of **I**, the presence of two additional bands was observed at frequencies of 3328 (ν^{as}_{NH2}) and 3240 (ν^{s}_{NH2}), not belonging to **I** and appearing typical of a NH_2 group. Moreover, in the ^{1}H NMR spectrum all the signals expected for **I** were obtained, although a signal at 2.3 ppm was registered corresponding to a methyl group (not a part of the structure of **I**), as well as a number of signals in the range of aromatic protons.

As a result there appears to be an impurity mixed to the desired product. To identify the impurity a *Variant 1* was applied in the synthesis of DDM. This compound was dissolved in *n*-hexane, where it is highly soluble, leaving a white solid, insoluble in this solvent, that was filtered and recrystallized from *n*-hexane/ethylacetate 1:1 (v/v). The residue was identified as *p*-toluenesulfonamide (PTSA), as it emerges in Table 2, by comparing with a pure sample [4,5].

Evidently in the previous papers the final washing with a sodium hydrogen carbonate solution was inefficient because PTSA, formed as a by-product of DDM, was not eliminated completely and still contaminated **I** when the protection of the acid function in the cephem nucleus was carried out in a subsequent step.

Although *Variant 1* allows the precipitation of PTSA, a more practical way was developed for its removal (*Variant 2*). It consists in washing the final solution of DDM with a sodium hydroxide solution, since PTSA forms soluble salts in diluted alkaline solution.

The effectiveness of these procedures was verified by carrying out the synthesis of **I** with DDM obtained by means of the two purification variants.

2. Synthesis of DDM

Benzophenone hydrazone (10.78 g, 55 mmol) and iodine (2.2 ml; 1% w/v) were dissolved in 60 ml aqueous DMA (1:10, v/v). A solution of chloramine T (15.5 g, 55 mmol) in the same solvent 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% (w/v) sodium hydrogen carbonate solution (275 ml). The dichloromethane layer was washed with water (1×100 ml and 3×50 ml), dried on anhydrous sodium sulfate and made up to 200 ml.

Variant 1. After drying, the final solution was evaporated under reduced pressure until dryness. The residue was treated with *n*-hexane (30 ml) and the obtained suspension filtered. The separated solid was washed with *n*-hexane (30 ml) three times. The filtrates were combined and adjusted to a final volume of 200 ml with *n*-hexane.

Variant 2. At the end of the reaction, dichloromethane and sodium hydroxide solution 5%

Table 2
Characterization of the impurity and comparison with pure PTSA

	^{1}H NMR [δ (ppm)]	EM (m/z)		m.p. (°C)	
	Obtained	Reported	Obtained	Reported	Obtained
CH_3	2.30 (s, 3H)	171 (M^+)	171 (M^+)	135–137	133–135
NH_2	7.27 (s, 2H)	155	155		
H (3.5)	7.36 (d, 2H)	91	91		
H (2.6)	7.71 (d, 2H)	65	65		
		39	39		

Table 3
Results of the synthesis of **I** with purified DDM

Comp.	Yield (%)	m.p. (°C)
Reported [2]	78.1	97–98.5
I (with DDM without purification)	79.5	95–98
I (with DDM purified with *n*-hexane)	67.4	123–125
I (with DDM purified with 5% NaOH)	65.1	125–127

(275 ml) were added. Then the procedure was similar to the one described above.

3. Diphenylmethyl-7β-(*o*-hydroxy)benzylideneamino-3-hydroxymethyl-3-cephem-4-carboxylate (I)

A suspension of 7-ACA (9.0 g, 33 mmol) in 120 ml water/methanol 1:1(v/v) was added dropwise to 7 ml of 10 M sodium hydroxide solution at −20°C. The mixture was stirred at −20°C for 25 min and the pH adjusted to pH 7.5 with conc. HCl. The solution was then added to salicylaldehyde (4.6 ml, 44 mmol) at 15°C. Stirring was continued at this temperature for 1 h, then pH was adjusted to 4.0–4.5 with 1 M HCl and a solution of DDM (7.85 g, 4.0 mmol) in ethyl acetate (43 ml) was added (*Note 1*). The mixture was stirred for 1 h and the pH was kept in this range. The resulting mixture was extracted with ethyl acetate (275 ml). The separated organic layer was washed with brine (2 × 200 ml), dried and evaporated under reduced pressure until dryness. The residue was triturated in the presence of *n*-hexane (20 ml), washed with *n*-hexane (3 × 20 ml) and dried at 40°C during 1 h.

Note 1: To prepare this solution, the starting point was the DDM solution in *n*-hexane or dichloromethane. The solvent was evaporated under reduced pressure and the residue was dissolved in ethyl acetate (50 ml).

The results are shown in Table 3.

When applying the two variants it can be noted that the yield of the reaction decreased with respect to the reference value, while the melting point of the product increased.

The IR spectra of the **I**, obtained with purified DDM, lack the bands corresponding to the amino group of PTSA. In the ^{1}H NMR spectrum the disappearance of the signal at 2.3 ppm was also observed, as well as a reduction in the total number of protons of the aromatic region (6). It was confirmed that through both variants it was possible to remove PTSA from DDM and, as a consequence, the presence of this impurity in **I**. Examination of the differences between the yields without and with purification of DDM suggest that the impurity represented an important share of the final product, as suggested by the large increase of the m.p. of the final product.

We concluded that the reported method for preparing DDM from the oxidation of benzophenone hydrazone with chloramine T needs purification according to either variants in order to obtain cephalosporanic derivatives with a better degree of purity. According to our results, the best melting point of **I** is 125–127°C and not 97–98.5°C, as reported [2].

The notable increase of the m.p. suggests a higher purity of the final product, and this fact represents an important contribution both because the final drug is purified from a potential toxic compound and because the improvement is obtained using a very simple method.

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