

A convenient synthesis of crystalline 4-ethyl-2,3-dioxopiperazine-1-carboxamido-*p*-hydroxyphenylacetyl chloride using triphosgene

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Abstract : The crystalline 4-ethyl-2,3-dioxopiperazine-1-carboxamido-*p*-hydroxyphenylacetyl chloride was prepared in 97.6% yield when triphosgene was reacted with D(-)-2-[(4-ethyl-2,3-dioxo-1-piperazineyl)-carbonylamino]-2-(4-hydroxyphenyl)acetic acid (HO-EPCP) in methylene dichloride at 0-5 °C in the presence of triethylamine (TEA). This new method without using chlorinating agent such as phosgene, diphosgene, phosphorus oxychloride or oxalyl chloride enjoys a number of advantages in that the reaction is carried out under mild conditions and is clean.

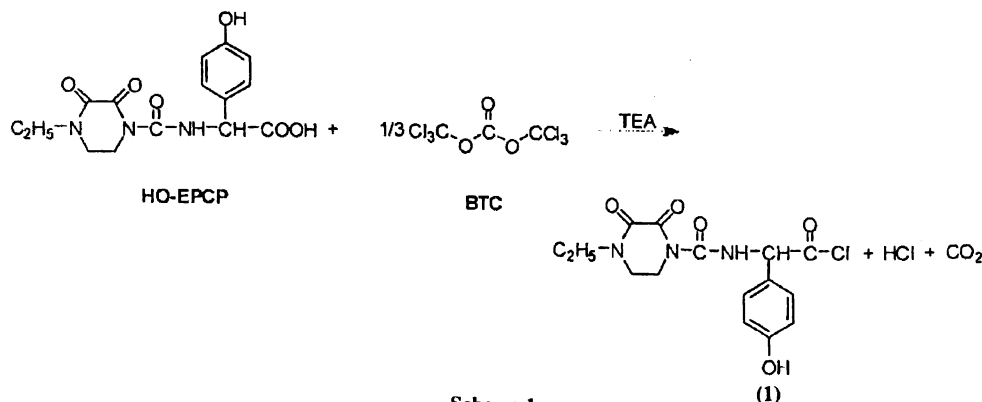
Keywords : 4-Ethyl-2,3-dioxopiperazine-1-carboxamido-*p*-hydroxyphenylacetyl chloride, D(-)-2-[(4-ethyl-2,3-dioxo-1-piperazineyl)-carbonylamino]-2-(4-hydroxyphenyl)acetic acid, triphosgene.

Introduction

The salerom of Cephalosporin which is the most important antibiotics in China account for 40% of that of anti-infective drug in the world at present. 4-Ethyl-2,3-dioxopiperazine-1-carboxamido-*p*-hydroxyphenylacetyl chloride **1** is an important synthetic intermediate for the Cephalosporin type compound¹ which is excellent in antibacterial activity against not only gram-positive but also gram-negative bacteria, and low in toxicity, and has a broad antibacterial spectrum². It has been reported that **1** has been prepared by the reaction of D(-)-2-[(4-ethyl-2,3-dioxo-1-piperazineyl)carbonylamino]-2-(4-hydroxyphenyl)acetic acid (HO-EPCP) with a suitable chlorinating agent such as phosgene, diphosgene, phosphorus oxychloride or oxalyl chloride³. However, in those procedures, **1** was not isolated as a crystalline product but directly introduced

into the next step reaction in the form of the reaction mixture. So some impurities will inevitably be introduced into the following reactions, even to final product. Moreover, due to those chlorinating agents, which are highly toxic and irritant gas or liquid, it is difficult to operate in the experiment or factory and is harmful to the health of the operator and environment. Therefore, the need of a new and mild synthetic method for **1** become urgent. In this study BTC was selected as chlorinating agent owing to its high boiling point and since it is solid, it is easy to store and transport.

Triphosgene [bis(trichloromethyl)carbonate, BTC] (m.p. 79-80 °C, b.p. 205-207 °C; only slight decomposition to phosgene occurs at its boiling point) is known to react with acid to produce acyl chlorides⁴. Herein the convenient synthesis of **1** using triphosgene was reported.



Scheme 1

Results and discussion

The 4-ethyl-2,3-dioxopiperazine-1-carboxamido-*p*-hydroxylacetyl chloride **1** was conveniently prepared in 97.6% yield when triphosgene was reacted with HO-EPCP in methylene dichloride at 0–5 °C in the presence of triethylamine (TEA) (Scheme 1).

The triphosgene-mediated reaction for the synthesis of **1** outlined here enjoys a number of advantages over the existing methods in that the reaction is carried out under mild, safe and clean conditions.

Other organic bases such as *N,N*-dimethylformamide, imidazole and pyridine may substitute for triethylamine (TEA) in this reaction⁵, however, we were in favor of triethylamine because of its good reactivity and the easy isolation of its hydrochloride salt from organic solvents.

There are another two reactive groups (phenolic hydroxyl and secondary amidocyanogen) other than carboxyl in the structure of HO-EPCP, therefore, a second even third chlorocarbonyl group may be introduced. In order to prepare **1** in high yield and good purity, the control of reaction conditions is very important.

Table 1. The results of element analysis

Element	Practical (%)	Theoretical (%)
C	46.89	47.34
H	4.81	4.86
N	12.83	12.75
O	24.32	24.28

Experimental

All glassware for this reaction must be oven-dried prior to use. A 250 ml, three-necked, round-bottomed flask was equipped with a mechanical stirrer, thermometer, and a 250 ml dropping funnel, containing anhydrous methylene dichloride 50 ml, was charged with HO-EPCP 6.6 g (0.02 mol) and triphosgene 2 g (0.0067 mol). The dropping funnel was charged with 5 ml (0.36 mol) of trimethylamine. The reaction mixture was cooled to 0 °C in an ice-water bath with stirring and the triethylamine is added slowly to the reaction mixture over 30 min. After the addition is complete, the reaction mixture was stirred in the ice-water bath for 2.5 h. The resulting white granular precipitate was removed by vacuum filtration. The filtrate was concentrated by rotary evaporation at 25 °C to give 6.9 g

(97.6%) of 4-ethyl-2,3-dioxopiperazine-1-carboxamido-*p*-hydroxylacetyl chloride **1**.

The spectral and physical properties of 4-ethyl-2,3-dioxopiperazine-1-carboxamido-*p*-hydroxylacetyl chloride (**1**) are as follows : m.p. 118~120 °C; IR (KBr) : 3431, 1789, 1716, 1682, 1614, 1517, 1472, 1188 cm⁻¹; ¹H NMR (CDCl₃) : δ_H 11.72 (1H, s, —OH), 7.20 (2H, d, ArH), 6.90 (2H, d, ArH), 5.31 (1H, d, —CONH—), 4.02 (1H, d, >CH—), 3.52~3.54 (4H, m, $\text{—CH}_2\text{—CH}_2\text{—}$), 3.07 (2H, q, $\text{—CH}_2\text{—CH}_3$), 1.37 (3H, t, $\text{>N—CH}_2\text{—CH}_3$).

Proton NMR spectra were obtained at 300 MHz using a Bruker DRX-300 NMR spectrometer, and chemical shift values (δ) are given in ppm. IR spectra were recorded on a Shimadzu FTIR-8400s spectrometer in KBr with absorption in cm⁻¹. The purity was determined on a Shimadzu SPD-10AVP HPLC (column : Dikma Technologies, Diamonsil 5 μm C 18 250 \times 4.6 mm). Melting point was taken on a YRT-3 melting-point apparatus and was uncorrected.

The results of element analysis were gained by using a Varioel Element analytical instrument from Deutschland Elementar Co. The resulting was showed in the Table 1.

Triphosgene was purchased from Shanxi Huizhihai Biochem Co. Ltd., HO-EPCP was purchased from Shanxi Jiaocheng Tianyuan Chemical Industry Co. Ltd. The other chemicals used were of A.R. grade.

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