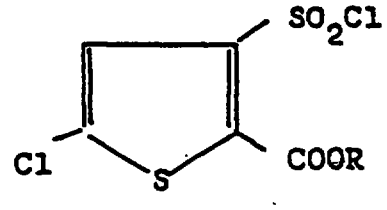
The invention relates to a process for the preparation of 5-chloro-3-chlorosulphonylthiophene-2-carboxylic acid esters.

Alkyl 5-chloro-3-chlorosulphonylthiophene-2-carboxylates (5-CCT) are intermediates in the preparation of pharmaceutically active substances. Thus, for example, US patent 4,801,591 describes substances which lower blood fat whose preparation starts from 5-CCT. Chlortenoxicam (6-chloro-4-hydroxy-2-methyl-3-(pyridin-2-ylcarbamoyl)-2H-thieno(2,3-e)-1,2-thiazine 1,1-dioxide), an antirheumatic described in US patent 4,180,662, can also be prepared from 5-CCT.

British patent application A-2 159 156 describes a process for the preparation of alkyl 3-chlorosulphonyl-thiophene-2-carboxylates substituted by methyl or halogen, wherein alkyl 5-chloro-3-aminothiophene-2-carboxylates, which are not easily obtainable, are diazotised and the diazonium chlorides formed are then reacted with SO_2 to give the sulphonyl chlorides. This process is laborious, however, and gives unsatisfactory yields.

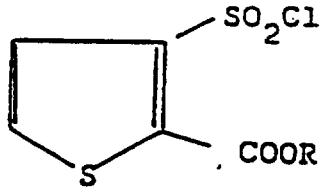
European Patent Application A-0 245 835 discloses, inter alia, the halogenation of 2-(alpha-alkoxyimino)ethylthiophenes, but these compounds, with the (alkoxyimino)ethyl radical, have an electron-donating substituent which facilitates the halogenation.

The present invention relates to a process for the preparation of 5-chloro-3-chlorosulphonylthiophene-2-carboxylic acid esters of the formula



I

in which R is C_1-C_4-alkyl,
characterised in that a compound of the formula



II

in which R is as defined above, is chlorinated by the introduction of chlorine gas in the presence of activated iron.

One method of activating the iron consists in suspending 0.1 to 1.0 mol, preferably 0.2 - 0.4 mol of metallic iron in the form of powder or borings, per mol of compound II, in 0.5 - 5 l, preferably in 1 - 3 l of an organic solvent which is inert under the reaction conditions, for example methylene chloride or carbon tetrachloride, or in mixtures of such solvents, methylene chloride being preferred. The iron is activated by the introduction of approx. 100 - 500 g, preferably of about 200 - 300 g of chlorine gas per mol of iron. The chlorine gas is introduced with vigorous stirring of the iron suspension, over a period of 1 - 5, preferably of 2 - 3 hours, at a temperature of about 10 - 50°C, preferably 24 - 28°C.

Another method of activation consists in placing approximately the same amounts of iron as described above in a reaction flask and leaving it to stand for 12 to 48 hours, preferably for 24 hours, under a chlorine gas atmosphere. However, it is preferable to activate the iron in a solvent suspension.

If the iron has been activated in a solvent suspension, the alkyl 3-chlorosulphonylthiophene-2-carboxylates (CT) are chlorinated by dissolving the CT in the same solvent or solvent mixture in which the metallic iron has been suspended, namely in about 0.3 - 5 l of solvent per mol of CT, preferably in 0.5 to 1 l of solvent per mol of CT, and mixing this solution rapidly with the iron suspension. The CT are chlorinated, with stirring, by the introduction of approx. 5 - 50 g of chlorine gas per hour and per mol of CT, preferably of

15 - 35 g per hour and per mol of CT, at a temperature of about 20 to 50°C, preferably at a temperature of 30 to 32°C. The course of the reaction is monitored by analysis, preferably by gas chromatography. After the formation of 50 - 70%, preferably 62 - 65% of the monochloro compound, the reaction mixture is poured on to iced water and the phases are separated. The organic phase is dried and evaporated.

If the iron has been activated under a chlorine gas atmosphere, the CT is preferably dissolved in 2 - 4 l of one of the above-mentioned solvents or solvent mixtures and the course of the subsequent chlorination is as described above. The total amount of solvent used is the same in both the possible methods of activation.

The crude 5-CCT can be purified by conventional methods such as recrystallisation, column and partition chromatography, extraction and the like. It is preferably recrystallised from diisopropyl ether.

The starting compound of the chlorination, namely the CT, is known in the literature. Its preparation is described for example in US patent 4,028,373.

Example

Methyl 5-chloro-3-chlorosulphonylthiophene-2-carboxylate

In a 20 l four-necked flask, 96 g of iron powder (1.71 mol) (Baker, reduced with H_2, at least 96%) were suspended in 12 l of absolute methylene chloride. 440 g of chlorine gas were introduced over a period of 2 to 3 hours, with vigorous stirring, the temperature being between 24 and 28°C. 1.44 kg (5.98 mol) of methyl 3-chlorosulphonylthiophenecarboxylate were then dissolved in 5 l of absolute methylene chloride and added rapidly. 100 to 200 g of chlorine gas per hour were introduced at a temperature of 30 to 32°C, with stirring, and the course of the reaction was monitored by means of gas chromatography. After the formation of 62 to 65% of the monochloro compound, the reaction mixture was poured on

to 24 l of iced water and stirred vigorously for 15 min. After phase separation, the organic phase was dried and the residue was evaporated under vacuum at a bath temperature of 40°C.

The residue was taken up in 1.5 l of diisopropyl ether, the mixture was filtered and the filtrate was cooled to -30 to -35°C. It was seeded with the monochloro compound and then left to crystallise for approx. 15 to 30 min. The crystals were filtered off with suction, washed with 0.5 l of diisopropyl ether at -30°C and dried in a vacuum cabinet at 25°C.

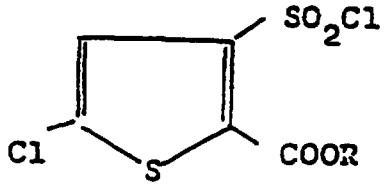
Yield: 800 g of monochloro compound (48.7%)

GC: 95% of monochloro compound, remainder unchlorinated and dichlorinated product

M.p.: 50 - 52°C

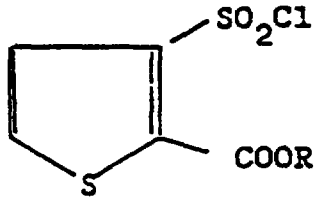
Claims

1. Process for the preparation of 5-chloro-3-chlorosulphonylthiophene-2-carboxylic acid esters of the formula



I

in which R is C_1-C_4-alkyl,
characterised in that metallic iron is activated with chlorine gas and a compound of the formula



II

in which R is as defined above, is chlorinated by the introduction of chlorine gas in the presence of the activated iron.

2. Process according to Claim 1, characterised in that the metallic iron is activated with chlorine gas under a chlorine gas atmosphere.

3. Process according to Claim 1 or Claim 2, characterised in that the metallic iron is activated under a chlorine gas atmosphere for about 12 to 48 hours, preferably for about 24 hours.

4. Process according to Claim 1, characterised in that the metallic iron is activated with chlorine gas in a solvent suspension, 0.1 to 1.0 mol, preferably 0.2 - 0.4 mol of metallic iron, per mol of compound II, being suspended in 0.5 to 5 l, preferably in 1 - 3 l of an organic solvent which is inert under the reaction conditions, such as methylene chloride or carbon tetrachloride, or in mixtures of such solvents, and the iron being activated by the introduction of 100 - 500 g

* C L M S *

of chlorine gas per mol of iron, preferably of 200 - 300 g, for 1 - 5 hours, preferably for 2 - 3 hours.

5. Process according to one of Claims 1 to 4, characterised in that the course of the chlorination reaction of the compound II is monitored by analysis, preferably by gas chromatography.

6. Process according to one of Claims 1, 4 or 5, characterised in that the activation of the iron and the chlorination of the compound of formula II are carried out in the same solvent or solvent mixture.

7. Process according to one of Claims 1 to 6, characterised in that the compound of formula II is chlorinated by the introduction of 5 - 50 g of chlorine gas per hour and per mol of compound II, preferably of 15 - 35 g/hour per mol of compound II, at 20 to 50°C, preferably at 30 - 32°C, until 50 - 70%, preferably 62 - 65% of the monochloro compound has been formed, and the reaction mixture is then poured on to iced water.

* C L M S *