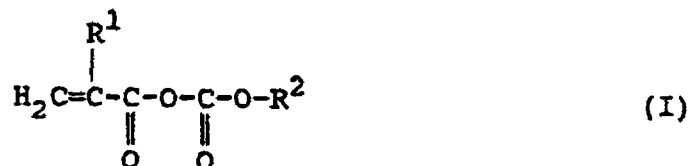


IMPROVED PROCESS FOR THE MANUFACTURE OF HIGH-
PURITY MIXED (METH)ACRYLIC ANHYDRIDES

The present invention relates to a process for
manufacturing mixed anhydrides represented by the
5 general formula (I):



in which:

- 10 - R^1 represents H or CH_3 ; and
- R^2 represents an alkyl, alkenyl, aryl, alkaryl or
aralkyl residue,
according to which process an alkali metal
(meth)acrylate of general formula (II):

15



in which:

- R^1 is as defined above; and
20 - M is an alkali metal,
is reacted with a chloroformate of general formula
(III):

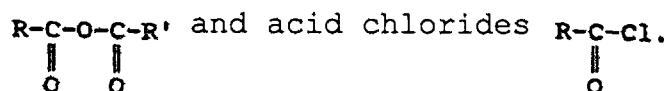


25

in which R^2 is as defined above.

Mixed anhydrides are mild acylating agents, the
use of which has been described in peptide synthesis in
place of conventional anhydrides

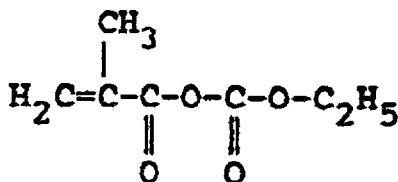
30



In addition, the only by-products generated by the mixed anhydrides of formula (I) in the acylation reactions are CO_2 and the alcohol R^2OH , which are easier to remove than (meth)acrylic acid or HCl .

5 The processess for synthesizing the non-acrylic mixed anhydrides which have been described in the literature are mostly based on the method described by Vaughan in J. Am. Chem. Soc. 73, 3547, 1951: the mixed anhydride is synthesized by equimolar reaction between
10 an alkyl chloroformate and a tertiary amine carboxylate, at low temperature (generally less than 0°), in a solvent medium (tetrahydrofuran, acetone, toluene, chloroform, etc.). Besides the need to work in a solvent medium, at very low temperature, one of the
15 main constraints of the process lies in the fact that it is necessary to separate off by filtration the trialkylammonium chloride which precipitates in the medium.

 In Bull. Chem. Soc. Jap. 1968, 41, 2521-3, Harada and Kondo describe, among the examples, the
20 synthesis of carboethoxymethacrylic anhydride:



by reaction between potassium methacrylate and ethyl
25 chloroformate, in a solvent medium (chloroform), at 0°C , in the presence of pyridine.

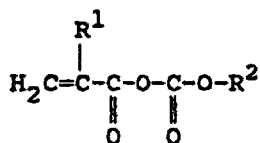
 The synthesis of carboethoxymethacrylic anhydride is also described in French patent application FR-A-2 212 340, starting with triethyl-
30 ammonium methacrylate and ethyl chloroformate in a solvent medium (acetonitrile).

 The synthesis of non-acrylic mixed anhydrides is described in German patent DE-C-1 133 727 by reaction between a carboxylate and a chloroformate in a
35 chloroformate/carboxylate molar ratio of between 0.95 and 1.10.

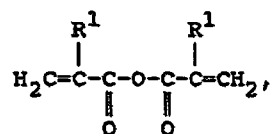
The processes described in the literature mostly relate to non-acrylic mixed anhydrides and present, depending on the case, many drawbacks, the chief ones being the use of solvents and the use of amines in stoichiometric amount relative to the carboxylic acid or in catalytic amount. The need to separate out the alkylammonium chloride by filtration also constitutes a drawback.

In most of the processes described in the literature, the reagents (II) and (III) are used in equimolar proportions or between 0.95 and 1.1. Under these conditions, it is possible to obtain a mixed

(meth)acrylic anhydride



containing little symmetrical anhydride



R^1 being as defined above. This is particularly inconvenient when it is desired to synthesize carboxyalkoxy (meth)acrylic anhydride containing very little methacrylic anhydride. The Applicant Company has discovered, surprisingly, that these problems can be solved by modifying the conditions of the reaction between compounds (II) and (III), and in particular by carrying out this synthesis with a compound (III)/compound (II) molar ratio of greater than or equal to 1.15.

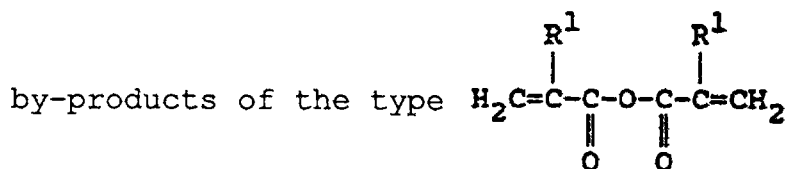
A subject of the present invention is thus a process for preparing a high-purity mixed (meth)acrylic anhydride (I), by reaction between the abovementioned compounds (II) and (III), characterized in that the said reaction is carried out in an aqueous medium and in the absence of amines, the chloroformate (III)/alkali metal (meth)acrylate (II) molar ratio being at least equal to 1.15.

In general, the reaction is carried out with compounds (II) and (III) in which:

- R^2 is chosen from C_1 - C_{40} alkyl, C_2 - C_{40} alkenyl, phenyl, phenyl (C_1 - C_{40} alkyl) and (C_1 - C_{40} alkyl) phenyl residues; and
- M represents Na or K.

The mixed anhydrides of formula (I) in which R^2 represents C_1 - C_{40} alkyl, such as ethyl, n-propyl, isopropyl, n-butyl or isobutyl, are of particular interest and constitute a family of preferred mixed anhydrides of the invention. These are mild acylating agents which can very advantageously replace methacrylic anhydride or (meth)acryloyl chloride which generate methacrylic acid or hydrochloric acid in acylation reactions.

In the process of the present invention, the chloroformate (III)/alkali metal (meth)acrylate (II) molar ratio can be between 1.15 and 2, preferably between 1.5 and 1.7, in order to limit the formation of



for example. At and above 1.15, a substantial improvement in the selectivity and yields are observed; thus, when the synthesis of carboethoxymethacrylic anhydride is carried out by reaction between sodium methacrylate and ethyl chloroformate, a reduction in the formation of methacrylic anhydride and by-products is observed. Moreover, a high molar ratio is favourable in terms of selectivity, but is penalizing with respect to the production efficiency.

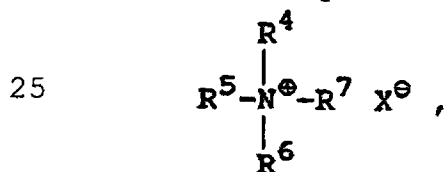
The reaction according to the present invention is advantageously carried out at a temperature of between -10 and $+30^\circ\text{C}$, preferably between $+10$ and $+20^\circ\text{C}$.

In accordance with one specific embodiment of the present invention, the alkali metal (meth)acrylate (II) is prepared in aqueous solution by neutralizing (meth)acrylic acid with the hydroxide MOH, the MOH/(meth)acrylic acid molar ratio being between 1 and 1.5, in particular between 1 and 1.1, and the water/alkali metal (meth)acrylate (II) weight ratio being between 1.5 and 7, in particular between 1.5 and 2, after which the chloroformate (III) is reacted with the alkali metal (meth)acrylate (II).

In accordance with one particularly advantageous characteristic of the present invention, the reaction between the alkali metal (meth)acrylate (II) and the chloroformate (III) is carried out in the presence of a phase-transfer catalyst, dissolved or fixed to a polymeric support such as a styrene-divinylbenzene copolymer or a crosslinked polyvinylpyridine resin and used in particular in a proportion of from 0.001 to 0.02 mol, in particular from 0.005 to 0.01 mol, per mole of alkali metal (meth)acrylate (II).

The phase-transfer catalyst is advantageously chosen from quaternary ammonium salts, phosphonium salts and crown ethers.

- As examples of quaternary ammonium salts



mention may be made of those in which:

- R^4 to R^7 each represent C_1 - C_{40} alkyl, such as CH_3 , C_2H_5 , C_4H_9 , C_8H_{17} and $\text{C}_{16}\text{H}_{33}$, or aryl such as phenyl, or aralkyl such as benzyl;
 - X represents one from among Cl, Br, I, OH and HSO_4 ;
- and, in particular, tetramethylammonium chloride, benzyltrimethylammonium chloride, benzyltri-n-butylammonium chloride, tetra-n-butylammonium chloride, tetra-n-butylammonium bromide,

methyltrioctylammonium bromide and tetra-n-butylammonium hydrogen sulphate;

- as examples of phosphonium salts, mention may be made of $(C_4H_9)_4P^{\oplus}Cl^{\ominus}$, $(C_4H_9)_4P^{\oplus}Br^{\ominus}$, $(C_8H_{17})_3C_2H_5P^{\oplus}Cl^{\ominus}$,
5 $(C_4H_9)_3C_6H_5P^{\oplus}Cl^{\ominus}$; and
- as examples of crown ethers, mention may be made of 18-crown-6 and dibenzoyl-18-crown-6.

Working in the presence of a phase-transfer catalyst increases the reaction substantially (3 to 5
10 hours as opposed to 15 hours without catalyst).

The reaction according to the invention is generally carried out with stirring in a thermostatically-controlled jacketed reactor while rigorously controlling the temperature. The crude
15 reaction mixture separates out into two phases by settling if the stirring is stopped (or into three phases if a phase-transfer catalyst is used, fixed to a polymeric support). The reaction progress is monitored by regularly taking samples of the aqueous phase and
20 assaying the residual alkali metal (meth)acrylate (II). The reaction is considered as complete when the degree of conversion of the alkali metal (meth)acrylate (II) is greater than 95%.

At the end of the reaction, the phases of the
25 two-phase or three-phase reaction mixture are separated by settling at room temperature, advantageously washed with water (amount: 20 to 100% of the weight of the organic phase, preferentially 30 to 40%) at room temperature, the organic phase containing the mixed
30 anhydride (I) and the excess chloroformate (III) then being stripped off under vacuum at a temperature of less than or equal to 35°C. The mixed anhydride is thus obtained in very high purity.

It is necessary to introduce at least one
35 polymerization inhibitor into the reaction medium, in a proportion of from 500 to 5000 ppm, in particular from 500 to 1000 ppm, relative to the alkali metal

(meth)acrylate (II) - or to its precursor (meth)acrylic acid - in order to overstabilize the latter.

As examples of polymerization inhibitors, mention may be made of hydroquinone methyl ether, hydroquinone, phenothiazine and di-tert-butyl-para-cresol.

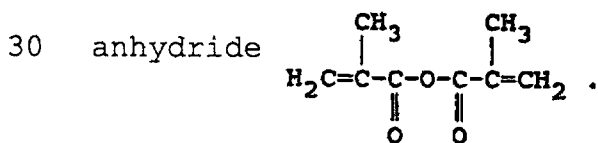
The examples which follow illustrate the present invention without, however, limiting its scope. In these examples, the percentages are given on a weight basis except where otherwise indicated.

EXAMPLE 1

408 g of an aqueous 26.5% sodium methacrylate solution, into which are introduced 900 mg of hydroquinone methyl ether, are introduced into a jacketed reactor whose temperature is maintained with the aid of a circulation of water thermostatically adjusted to 20°C; next, 162.8 g of ethyl chloroformate (ethyl chloroformate/sodium methacrylate molar ratio: 1.5:1) are introduced over 5 minutes.

The heterogeneous mixture is stirred for 15 hours. The phases are then separated by settling at room temperature. The organic phase is dried over calcium sulphate and the volatiles are then stripped off under vacuum at a temperature of less than 35°C, in order to remove the excess chloroformate.

153 g of product are thus obtained (yield: 96.7%) in a carboethoxymethacrylic anhydride NMR purity of 95%, the remaining 5% consisting of methacrylic



EXAMPLES 2 to 5

Example 1 is repeated, modifying the temperature and the ethyl chloroformate/sodium methacrylate molar ratio.

The results are reported in Table 1.

Table 1

Example	2	3	4	5
Ethyl chloroformate/sodium methacrylate molar ratio	1.5	1.5	1.5	3
Temperature (°C)	5	25	35	15
Reaction time (h)	30	8	7	24
Degree of conversion of the sodium methacrylate (%)	81	90.3	97.4	98.5
<u>Composition of the organic phase separated out by settling (% by weight)</u>				
• ethyl chloroformate	39.7	29	22.5	63
• carboethoxymethacrylic anhydride	55	63	65	35
• methacrylic anhydride	5	7	11	2
• ethanol	< 1	< 1	1	
• water	0.3	0.2	0.1	
<u>Composition of the organic phase stripped of volatiles (% by weight)</u>				
• carboethoxymethacrylic anhydride	91	90	85.5	94.5
• methacrylic anhydride	9	10	14.5	5.5

EXAMPLE 6

5 The process is performed in the same apparatus as in Example 1.

445.1 g of aqueous 33.2% sodium methacrylate solution stabilized with 1.2 g of hydroquinone methyl ether are loaded in. 8.8 g of tetra-n-butylammonium
 10 bromide (0.02 mol/mole of sodium methacrylate) are then introduced. Next, 193.2 g of ethyl chloroformate are introduced with stirring and while maintaining the temperature of the medium at 20°C (ethyl chloroformate/sodium methacrylate molar ratio = 1.3).

15 The reaction mixture is left stirring while controlling the temperature at 20°C. The reaction progress is monitored by assaying the residual sodium methacrylate in the aqueous phase separated out by settling (the phases of the mixture separate out by
 20 settling as soon as the stirring is stopped). After reaction for 3 hours, the degree of conversion of the sodium methacrylate is greater than 99%. The reactor is then emptied, the phases of the reaction mixture are

separated by settling at room temperature, the organic phase is washed with 57 g of water and the washed organic phase is separated out by settling.

234.5 g of crude washed product are thus recovered, which product is stabilized with 0.02 g of di-tert-butyl-para-cresol. The excess chloroformate is removed under vacuum using a rotary evaporator at a temperature of less than 35°C.

198 g of carboethoxymethacrylic anhydride are obtained, the NMR purity of which is indicated, with the yield, in Table 2 below.

EXAMPLES 7, 8 (comparative) and 9 (comparative)

Example 6 is repeated, varying the ethyl chloroformate/sodium methacrylate molar ratio.

The results are reported in Table 2.

Table 2

EXAMPLE	6	7	8 (comp.)	9 (comp.)
Ethyl chloroformate/sodium methacrylate molar ratio	1.3	1.15	1.05	1.1
<u>Composition of the final product (% by weight)</u>				
• carboethoxymethacrylic anhydride	93.5	90	65	80
• methacrylic anhydride	5.5	9	19	10
• $\text{C}_2\text{H}_5\text{-O-C-O-C}_2\text{H}_5$ O	1	1	2	2
• $\text{C}_2\text{H}_5\text{-O-C-O-C-O-C}_2\text{H}_5$ O O			8	5
• ethyl methacrylate			6	3
Yield of carboethoxymethacrylic anhydride relative to the sodium methacrylate	85.5	80		

When the chloroformate/methacrylate molar ratio is less than 1.15, poor selectivity towards carboxyethoxymethacrylic anhydride is observed. It is

manifestly impossible to obtain a product of good purity below this molar ratio.

EXAMPLE 10

5 The process is performed in the same apparatus as in Example 1.

309.3 g of an aqueous 33.5% sodium methacrylate solution stabilized with 0.8 g of hydroquinone methyl ether are loaded in. 192 g of toluene are then introduced, followed by 0.02 mol of tetra-n-
10 butylammonium bromide per mole of sodium methacrylate. 125.1 g of ethyl chloroformate are then introduced with stirring, while controlling the temperature of the medium at 15°C (ethyl chloroformate/sodium methacrylate molar ratio: 1.2).

15 The reaction progress is monitored as in Example 3. After reaction for 4 hours, the degree of conversion of the sodium methacrylate is greater than 99%. The phases of the crude product are then separated out by settling but not washed, and stripped of
20 volatiles under vacuum at a temperature of less than 35°C.

The NMR analysis of the product stripped of volatiles is as follows:

• carboethoxymethacrylic anhydride.....	95.5%
25 • methacrylic anhydride.....	4.5%

The yield of carboethoxymethacrylic anhydride is 87.5%.

EXAMPLE 11

30 Example 6 is repeated, using potassium methacrylate instead of sodium methacrylate and working at 10°C.

The composition of the final product (% by weight) is as follows:

• carboethoxymethacrylic anhydride.....	93%
35 • methacrylic anhydride.....	6%

• $\begin{array}{c} \text{C}_2\text{H}_5-\text{O}-\text{C}-\text{O}-\text{C}_2\text{H}_5 \\ \\ \text{O} \end{array}$	1%
--	----

EXAMPLES 12 to 14

Example 6 is repeated, working at 10°C and varying the nature of the phase-transfer catalyst, which is introduced in an amount of 0.01 mol/mole of sodium methacrylate.

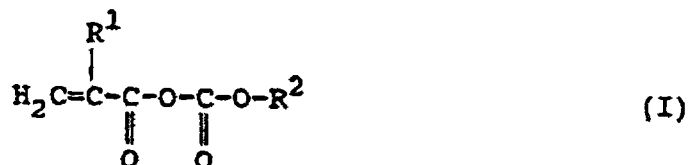
The results are reported in Table 3.

TABLE 3

Example	12	13	14
Phase-transfer catalyst	$(\text{Bu})_4\text{P}^{\oplus}\text{Br}^{\ominus}$	$(\text{Bu})_3\text{C}_6\text{H}_5\text{P}^{\oplus}\text{Cl}^{\ominus}$	$(\text{CH}_3)(\text{C}_8\text{H}_{17})_3\text{N}^{\oplus}\text{Br}^{\ominus}$
Yield of final product (relative to the sodium methacrylate converted) (%)	94	97	99.5
Degree of conversion of the sodium methacrylate greater than 98.5% after...	4.5 h	3 h	1.5 h
<u>Composition of the final product</u> (% by weight) • carboethoxy-methacrylic anhydride • methacrylic anhydride • $\text{C}_2\text{H}_5\text{O}-\text{C}(=\text{O})-\text{O}-\text{C}_2\text{H}_5$	94 4 2	94 6 	96 3 1

CLAIMS

1. Process for manufacturing a high-purity (meth)acrylic anhydride, represented by the general
5 formula (I):



in which:

- 10 - R^1 represents H or CH_3 ; and
- R^2 represents an alkyl, alkenyl, aryl, alkaryl or aralkyl residue,
according to which process an alkali metal (meth)acrylate of general formula (II):

15



in which:

- R^1 is as defined above; and
20 - M is an alkali metal,
is reacted with a chloroformate of general formula (III):



25

- in which R^2 is as defined above,
characterized in that the said reaction is carried out
in an aqueous medium and in the absence of amines, the
chloroformate (III)/alkali metal (meth)acrylate (II)
30 molar ratio being at least equal to 1.15.



2. Process according to Claim 1, characterized in that the reaction is carried out with compounds (II) and (III) in which:
- R^2 is chosen from C_1 - C_{40} alkyl, C_2 - C_{40} alkenyl, phenyl, phenyl (C_1 - C_{40} alkyl) and (C_1 - C_{40} alkyl) phenyl residues; and
 - M represents Na or K.
3. Process according to either of Claims 1 and 2, characterized in that the chloroformate (III)/alkali metal (meth)acrylate (II) molar ratio is between 1.15 and 2, preferably between 1.5 and 1.7.
4. Process according to one of Claims 1 to 3, characterized in that the reaction is carried out at a temperature of between -10 and $+30^\circ\text{C}$, preferably between $+10$ and $+20^\circ\text{C}$.
5. Process according to one of Claims 1 to 4, characterized in that the alkali metal (meth)acrylate (II) is prepared in aqueous solution by neutralizing (meth)acrylic acid with the hydroxide MOH, the MOH/(meth)acrylic acid molar ratio being between 1 and 1.5 and the water/alkali metal (meth)acrylate (II) weight ratio being between 1.5 and 7, after which the chloroformate (III) is reacted with the alkali metal (meth)acrylate (II).
6. Process according to Claim 5, characterized in that the MOH/(meth)acrylic acid (II) molar ratio is between 1 and 1.1 and the water/alkali metal (meth)acrylate (II) weight ratio is between 1.5 and 2.
7. Process according to one of Claims 1 to 6, characterized in that the reaction between the alkali metal (meth)acrylate (II) and the chloroformate (III) is carried out in the presence of a phase-transfer catalyst, dissolved or fixed to a polymeric support and used in particular in a proportion of from 0.001 to 0.02 mol, in particular from 0.005 to 0.01 mol, per mole of alkali metal (meth)acrylate (II).
8. Process according to Claim 7, characterized in that the phase-transfer catalyst is chosen from



quaternary ammonium salts, phosphonium salts and crown ethers.

9. Process according to one of Claims 1 to 8, characterized in that, at the end of the reaction, the phases of the two-phase reaction mixture, or of the three-phase reaction mixture if the catalyst is fixed to a polymeric support, are separated out by settling at room temperature, advantageously washed with water at room temperature and the organic phase containing the mixed anhydride (I) and the excess chloroformate (III) is then stripped of volatiles under vacuum at a temperature of less than or equal to 35°C.

10. Process according to one of Claims 1 to 9, characterized in that at least one polymerization inhibitor is introduced into the reaction medium, in a proportion of from 500 to 5000 ppm, in particular from 500 to 1000 ppm, relative to the alkali metal carboxylate [sic] (II), or to its precursor (meth)acrylic acid.

11. Process according to Claim 10, characterized in that the polymerization inhibitor is chosen from hydroquinone methyl ether, hydroquinone, phenothiazine and di-tert-butyl-para-cresol.



PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION

International Bureau

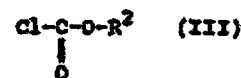
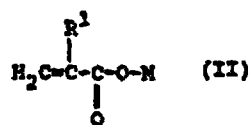
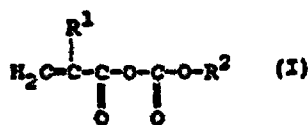
INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International patent classification ⁶ : C07C 68/02, 69/96	A1	(11) International publication number: WO 99/38837 (43) International publication date: 5 August 1999 (05.08.99)
(21) International application number: PCT/FR99/00164 (22) International filing date: 28 January 1999 (28.01.99) (30) Data relating to the priority: 98/01,155 2 February 1998 (02.02.98) FR (71) Applicant (for all designated States except US): ELF ATOCHEM S.A. [FR/FR]; 4/8, cours Michelet, F-92800 Puteaux (FR). <i>ELF</i> (72) Inventors; and (75) Inventors/Applicants (US only): PAUL, Jean-Michel [FR/FR]; 30, rue de Queleu, F-57070 Metz (FR). RIONDEL, Alain [FR/FR]; 74, rue Nationale, F-57600 Forbach (FR). FABIS, Frédéric [FR/FR]; 27 bis, rue d'Hérouville, F-14000 Caen (FR). RAULT, Sylvain [FR/FR]; 5, rue Pierre Cingal, F-14370 Moult (FR). (74) Representative: RIEUX, Michel; Elf Atochem S.A., Dépt. Propriété Industrielle, Cours Michelet, La Défense 10, F-92091 Paris la Défense Cedex (FR).		(81) Designated states: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO Patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian Patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European Patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI Patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published With the International Search Report.

As printed

(54) Title: IMPROVED METHOD FOR MAKING MIXED HIGH PURITY (METH)ACRYLIC ANHYDRIDES

(54) Titre: PROCEDE PERFECTIONNE DE FABRICATION D'ANHYDRIDES (METH)ACRYLIQUES MIXTES DE HAUTE PURETE



(57) Abstract

The invention concerns a method consisting in making a mixed (meth)acrylic anhydride of formula (I) by reacting an alkaline (meth)acrylate of formula (II) and a chloroformate of formula (III), carrying out said reaction in an aqueous medium and in the absence of amines, the mol ratio chloroformate (III)/alkaline (meth)acrylate (II) being at least equal to 1.15. R¹ represents H or CH₃; R² represents an alkyl, alkenyl, aryl, alkaryl or aralkyl residue; and M is an alkaline metal.

(57) Abrégé

On fabrique un anhydride (méth)acrylique mixte de formule (I) en faisant réagir un (méth)acrylate alcalin de formule (II) et un chloroformiate de formule (III) et, selon l'invention, on effectue ladite réaction en milieu aqueux et en l'absence d'amines, le rapport molaire chloroformiate (III)/(méth)acrylate alcalin (II) étant au moins égal à 1,15. R¹ représente H ou CH₃; R² représente un reste alkyle, alcényle, aryle, alkaryle ou aralkyle; et M est un métal alcalin.