PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ^{6} **:**
C07D 311/76

A1

(11) International Publication Number: **WO 99/10335**

(43) International Publication Date: 4 March 1999 (04.03.99)

(21) International Application Number: PCT/GB98/02250

(22) International Filing Date: 28 July 1998 (28.07.98)

(30) Priority Data:

9718010.3	26 August 1997 (26.08.97)	GB
9723200.3	3 November 1997 (03.11.97)	GB

(71) Applicant *(for all designated States except US)*: ZENECA LIMITED [GB/GB]; 15 Stanhope Gate, London W1Y 6LN (GB).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: JONES, Raymond, Vincent, Heavon [GB/GB]; Zeneca Grangemouth Works, Earls Road, Grangemouth, Stirlingshire FK3 8XG (GB). RITCHIE, David, John [GB/GB]; Zeneca Grangemouth Works, Earls Road, Grangemouth, Stirlingshire FK3 8XG (GB). McCANN, Hannah, Sallie, Robertson [GB/GB]; Zeneca Grangemouth Works, Earls Road, Grangemouth, Stirlingshire FK3 8XG (GB). FIELDHOUSE, Robin [GB/GB]; Zeneca Grangemouth Works, Earls Road, Grangemouth, Stirlingshire FK3 8XG (GB). MacCORMICK, Kirstin [GB/GB]; Zeneca Grangemouth Works, Earls Road, Grangemouth, Stirlingshire FK3 8XG (GB). WHITE, Jennifer, Ann [GB/GB]; Zeneca Grangemouth Works, Earls Road, Grangemouth, Stirlingshire FK3 8XG (GB).

(74) Agents: HOUGHTON, Malcolm, John et al.; Zeneca Agrochemicals, Intellectual Property Dept., Jealotts Hill Research Station, P.O. Box 3538, Bracknell, Berkshire RG42 6YA (GB).

(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, 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 international search report.

(54) Title: PROCESS FOR PREPARING 3-ISOCHROMANONE

(57) Abstract

3-Isochromanone is prepared by contacting an *o*-xylene-α,α'-dihalide with carbon monoxide in a two-phase liquid medium, in which one phase is aqueous and the other phase is water-immiscible, in the presence of a catalyst and a hindered amine base.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania
AM	Armenia
AT	Austria
AU	Australia
AZ	Azerbaijan
BA	Bosnia and Herzegovina
BB	Barbados
BE	Belgium
BF	Burkina Faso
BG	Bulgaria
BJ	Benin
BR	Brazil
BY	Belarus
CA	Canada
CF	Central African Republic
CG	Congo
CH	Switzerland
CI	Côte d'Ivoire
CM	Cameroon
CN	China
CU	Cuba
CZ	Czech Republic
DE	Germany
DK	Denmark
EE	Estonia
ES	Spain
FI	Finland
FR	France
GA	Gabon
GB	United Kingdom
GE	Georgia
GH	Ghana
GN	Guinea
GR	Greece
HU	Hungary
IE	Ireland
IL	Israel
IS	Iceland
IT	Italy
JP	Japan
KE	Kenya
KG	Kyrgyzstan
KP	Democratic People's Republic of Korea
KR	Republic of Korea
KZ	Kazakstan
LC	Saint Lucia
LI	Liechtenstein
LK	Sri Lanka
LR	Liberia
LS	Lesotho
LT	Lithuania
LU	Luxembourg
LV	Latvia
MC	Monaco
MD	Republic of Moldova
MG	Madagascar
MK	The former Yugoslav Republic of Macedonia
ML	Mali
MN	Mongolia
MR	Mauritania
MW	Malawi
MX	Mexico
NE	Niger
NL	Netherlands
NO	Norway
NZ	New Zealand
PL	Poland
PT	Portugal
RO	Romania
RU	Russian Federation
SD	Sudan
SE	Sweden
SG	Singapore
SI	Slovenia
SK	Slovakia
SN	Senegal
SZ	Swaziland
TD	Chad
TG	Togo
TJ	Tajikistan
TM	Turkmenistan
TR	Turkey
TT	Trinidad and Tobago
UA	Ukraine
UG	Uganda
US	United States of America
UZ	Uzbekistan
VN	Viet Nam
YU	Yugoslavia
ZW	Zimbabwe

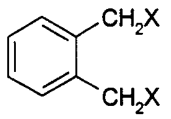
PROCESS FOR PREPARING 3-ISOCHROMANONE

This invention relates to a chemical process and more particularly to a process for preparing 3-isochromanone which is useful in the manufacture of certain agricultural products.

3-Isochromanone is a well known compound and a number of methods for its preparation are described in the chemical literature. In particular, a process is described in WO97/00850 which comprises reacting an *o*-xylene-α,α'-dihalide derivative with carbon monoxide and water in an organic solvent in the presence of a catalyst and a hydrogen halide capturing agent followed by treatment with an acid. In this process the hydrogen halide capturing agent is preferably an inorganic base. The use of amines in palladium-catalyzed carbonylation reactions are discussed in *J. Org. Chem.* [1993] 58, 1538-45 and in US 4,713,484. These references relate, however, to the alkoxycarbonylation of allylphosphates and acetates and to the preparation of carboxylic acid salts.

Thus, according to the present invention, there is provided an improved process for the preparation of 3-isochromanone which comprises contacting an *o*-xylene-α,α'-dihalide with carbon monoxide in a two-phase liquid medium, in which one phase is aqueous and the other phase is water-immiscible, in the presence of a catalyst and a hindered amine base.

The *o*-xylene-α,α'-dihalide starting material has the general formula:



where X is a halogen atom such as chlorine, bromine or iodine, especially chlorine or bromine. *o*-Xylene-α,α'-dichloride is a particularly convenient starting material.

The process of the invention is carried out in a two-phase liquid medium, one phase comprising water and the other phase conveniently comprising a water-immiscible organic solvent. Any suitable water-immiscible organic solvent may be used. Examples are saturated or aromatic hydrocarbons or halogenated derivatives thereof, such as chlorinated or fluorinated derivatives, for example methylene chloride, toluene or chloro- or fluorobenzene. Xylene is particularly convenient from a manufacturing standpoint. Where the hindered base is a liquid and water-immiscible, it may itself act as the solvent without the need to employ an additional solvent. An example of a base which may be used in this way is *N,N*-di*iso*-propylethylamine.

It may, however, be convenient to include in the two-phase liquid medium one or more other water-immiscible solvents or a water miscible solvent, provided that at least two-phases are maintained, one of which is aqueous.

Suitably the molar ratio of water:water-immiscible solvent is in the range of 1:50 to 50:1, preferably 1:1 to 10:1 and typically 1:1 to 3:1, for example about 5:2.

There will usually be a molar excess of water used in relation to the quantity of *o*-xylene-α,α'-dihalide starting material. Preferably the molar ratio of water:*o*-xylene-α-α'-dihalide will be in the range of 100:1 to 1:1 typically 20:1 to 5:1, for example about 10:1.

The carbon monoxide will normally be dispersed into the two-phase medium either at atmospheric pressure or at pressures up to 100 atmospheres, for example at from 1 to 10 atmospheres. The pressure chosen will depend on the equipment in which the reaction is carried out and the required reaction rates and yield.

Any suitable carbonylation catalyst may be used in the process of the invention, particularly Group VIII (first, second and third triads) metal catalysts, for example palladium, cobalt or iron catalysts. Especially suitable are palladium catalysts, for example palladium (0) and palladium (II) catalysts, which may be water-soluble or water-insoluble, supported on a carrier, such as carbon, silica or calcium carbonate, a polymer or other inert solid, or unsupported. Supported catalysts have the advantage of facilitating catalyst recovery and recycling. Ligands such as triphenylphosphine may be used in conjunction with certain palladium catalysts or it may be beneficial to pre-reduce the catalyst with hydrogen, or another suitable reducing agent.

Suitable water-soluble palladium catalysts in the form of phoshine complexes are described, for example, by J. Kiji *et al* in *Chem. Lett.*, 957-960 (1988). Suitable water-insoluble palladium catalysts include *bis*(triphenylphosphine)palladium dichloride and tetrakis(triphenylphosphine)palladium (0) which are described by L. Cassar *et al* in *J. Organometallic Chem.*, 121 (1976), C55-56, in DE-A-2526046 and by X. Huang *et al* in *Chem. & Ind.*, 3 Sep 1990, 548. Palladium (II) catalysed carbonylation reactions are also discussed by V. Grushin *et al* in *Organometallics*, 12 (5), 1890-1901 (1993). The use of a supported carbonylation catalyst in the form of palladium-black is described by T. Ito *et al* in

Bull. Chem. Soc. Japan, 48 (7), 2091-2094 (1975). The use of soluble triphenylphosphine ligands to activate palladium catalysts is described by D. Bergbreiter *et al* in *J. Mol. Catalysis*, 74 (1992), 409-419. Typical examples of suitable catalysts are palladium chloride, dihydrotetrachloropalladium, tetrakis(triphenylphosphine) palladium (0), dichloro*bis*(triphenylphosphine) palladium (II), palladium/carbon, palladium on calcium carbonate and palladium on Montmorillonite™. Other suitable catalysts and ligands, including water soluble ones, are described in WO 97/00850. The ligands may be used in amounts up to 1000 mole equivalents of palladium, and suitably in the range of from 1 to 200 mole equivalents of palladium. The amount of palladium catalyst used may be in the range of 0.000001 to 0.5 mole equivalents of the *o*-xylene-α,α'-dihalide.

The hindered amine base will usually be one which has at least two aliphatic, preferably branched aliphatic, or cycloaliphatic groups or one in which the *N* atom is in a cycloaliphatic or aromatic ring, substituted in a manner that induces steric crowding around the *N* atom. Typically it will be of low water solubility and have a pK_a of the conjugate acid of about 10. Thus, it may be a heteroaromatic base such as pyridine or a substituted pyridine, for example 2,6-dimethylpyridine. Or it may be a secondary amine, providing it is sufficiently sterically hindered. An example of a suitable secondary amine is 2,2,6,6-tetramethylpiperidine. Preferably, however, it is a tertiary amine of formula $R^1R^2R^3N$ wherein R^1, R^2 and R^3 are independently C_{1-10} alkyl (especially C_{1-6} alkyl) C_{3-6} cycloalkyl, aryl (especially phenyl, but also pyridyl) or aryl(C_{1-4})alkyl (especially benzyl), or wherein two or three of R^1, R^2 and R^3 join together with the nitrogen atom to which they are attached to form one, two or three, 5-, 6- or 7- membered alicyclic rings optionally fused and optionally containing a second ring nitrogen atom.

Alkyl groups are straight or branched chain and, unless stated otherwise, contain from 1 to 10, especially from 1 to 6, particularly from 1 to 4, carbon atoms. Examples are methyl, ethyl, *iso*-propyl, *n*-propyl, *n*-butyl, *sec*-butyl and *tert*-butyl. Cycloalkyl groups comprise 3 to 6 carbon atoms and are optionally substituted by C_{1-6} alkyl. Examples are cyclohexyl, 2-methylcyclohexyl and 2-ethylcyclohexyl.

Suitable tertiary amines of formula $R^1R^2R^3N$ are, for example, *N,N*-di*iso*propylethylamine, *N,N*-dimethylaniline, triethylamine, *t*-butyldimethylamine, *N,N*-di*iso*propylmethylamine, *N,N*-di*iso*propyl*iso*butylamine, *N,N*-di*iso*propyl-2-ethylbutylamine, tri-*n*-butylamine, *N,N*-dicyclohexylmethylamine, *N,N*-dicyclohexylethylamine, 1,5-diazabicyclo[4.3.0]non-5-ene, 1,4-diazabicyclo[2.2.2]-octane or 2- or 4-dimethylaminopyridine.

There will usually be a molar excess of hindered amine base used in relation to the quantity of *o*-xylene-α,α'-dihalide starting material. Preferably the molar ratio of amine:*o*-xylene-α-α'-dihalide will be in the range of 10:1 to 1:1, typically 5:1 to 2:1, for example 4:1 to 2.5:1.

As the process is carried out in a two-phase system, it may be advantageous to include a phase transfer catalyst. By the term "phase transfer catalyst" is meant a substance which, being at least partly present in or wetted by a first (usually organic) phase, promotes reaction between a reactant in the first phase and a reactant which it transfers to the first phase from a second (usually aqueous but sometimes solid) phase. After reaction, the phase transfer catalyst is released for transferring further reactant. Phase transfer catalysts are reviewed by E. V. Dehmlow in *Angewante Chemie* (International Edition), 13 (3), 170 (1974). Other reviews are by Jozef Dockx in *Synthesis* (1973), 441-456 and by C. M. Starks in *JACS.*, (93) 1, Jan 13 1971, 195-199.

Suitably the phase transfer catalyst is a quaternary ammonium or phosphonium salt preferably containing bulky organic groups, usually alkyl or aralkyl groups, to make it soluble in the organic phase. It is preferred that the phase catalyst is a tetraalkyl or aralkyl (eg benzyl) trialkyl ammonium or phosphonium salt in which the total number of carbon atoms attached to each nitrogen or phosphorus atom is at least 4. There is little advantage in the number being above 70. It is especially preferred that the number should be in the range of from 16 to 40.

Examples of quaternary ammonium salts are: tetramethylammonium chloride, cetyltrimethylammonium bromide, dicetyldimethylammonium chloride, octyltributylammonium bromide, trioctylmethylammonium chloride (available as Aliquat™ 336), benzyldimethyllaurylammonium chloride, benzyltriethylammonium chloride, dilauryldimethylammonium chloride, tetrabutylammonium bromide and dieicosyldimethylammonium chloride. Examples of quaternary phosphonium salts are cetyltripropylphosphonium bromide and triphenylethylphosphonium bromide. Other phase transfer catalysts which may be suitable include crown ethers and polyethylene glycol variants. If used, the phase transfer catalyst may be present in an amount ranging from 0.001 to 0.5 mole equivalents of the *o*-xylene-α,α'-dihalide.

The process may be carried out at any suitable temperature within a range of from 20°C to 120°C, preferably from 60°C to 100°C, typically from 70°C to 90°C, for example at about 70°C.

After reaction is complete, the reaction mixture is filtered and the aqueous and organic phases separated. 3-Isochromanone in the aqueous phase can be isolated by solvent extraction, for example using dichloromethane, and evaporation of the solvent. 3-Isochromanone in the organic phase can be extracted by the addition of aqueous base to form a salt of the corresponding hydroxy acid. The aqueous layer is separated and the 3-isochromanone regenerated by suitable pH adjustment. Where the palladium catalyst is soluble in the organic phase, the organic layer is retained for recycling and reuse.

When using a palladium catalyst which is soluble in the aqueous phase, the organic phase is separated for isolation of the 3-isochromanone and the aqueous phase is acidified and the palladium catalyst extracted into an organic solvent. The palladium catalyst is recovered for recycling and reuse by extraction of the organic layer with aqueous base. A two-phase carbonylation process of this type using a water-soluble palladium catalyst is described by C Kohlpaintner in *J. Mol. Catalysis A: Chem.* 116 (1997) 259-267.

The use of a supported palladium catalyst has the advantage that it can be filtered from any reaction mixture using known technology, thereby facilitating its recycling and reuse.

3-Isochromanone is useful, *inter alia*, as an intermediate in the manufacture of agricultural products, especially fungicides of the strobilurin type, for example, those described in EP-A-278595.

The invention is illustrated by the following Examples in which :

g = grammes

mmol = millimoles

M = molar

gc = gas chromatography

ODCX = *o*-xylene-α,α'-dichloride

MR = molar ratio

Act = actual

$[(CH_3)_2CH]_2NC_2H_5$ = *N,N*-di*iso*propyl ethylamine (Hünig's base)

Ph_3P = triphenylphosphine

ml = millilitres

°C = degrees centigrade

mp = melting point

rpm = revolution per minute

DCM = dichloromethane

Wt = weight

Str = strength

$(Ph_3P)_2PdCl_2$ = dichloro*bis* (triphenylphosphine) palladium (II)

Pressures recorded in 'bar.g' units are gauge measurements, not absolute. Thus, for example, 4 bar.g is equivalent to 5 bar absolute.

EXAMPLES 1 TO 5

The following general procedure was used.

All the listed materials were charged to a 100ml round-bottom flask and stirred at 650rpm. A continuous stream of carbon monoxide was bubbled through the reaction mixture whilst heating to 70°C. The reaction mixture was maintained at this temperature and sampled at intervals for analysis of the levels of o-xylene-α,α'-dichloride and 3-isochromanone present.

When the reaction was adjudged complete, the reaction mixture was filtered through a No. 3 sintered glass funnel and the residue washed with xylene (20ml) and in some cases water (5ml). The aqueous and organic layers of the filtrate were separated. Water (25ml) was added to the aqueous layer precipitating a fine white or pink solid. The product was extracted from the aqueous layer with DCM (2x25ml). Samples of the funnel residue, the organic and aqueous layers and the DCM extract were submitted for quantitative gc analysis.

EXAMPLE 1 (1% catalyst, 2.2% Ph_3P)

Materials	Act Wt(g)	Str (%)	100% Wt	M Wt	mmol	MR
ODCX	7.0	100	7.0	175.06	39.90	1
$[(CH_3)_2CH]_2NC_2H_5$	21.88	99	21.66	129.25	167.60	4.2
$(Ph_3P)_2PdCl_2$	0.2888	97	0.2801	701.89	0.399	0.01
Ph_3P	0.2326	99	0.2303	262.29	0.878	0.022
H_2O	7.182	100	7.182	18	399.0	10
Xylene	17.29	98	16.94	106.17	159.6	4

Total chemical yield of all detected 3-isochromanone by quantitative gc analysis was 68%.

EXAMPLE 2 (0.1% catalyst, 50% Ph_3P)

Materials	Act Wt(g)	Str (%)	100% Wt	M Wt	mmol	MR
ODCX	7.0	100	7.0	175.06	39.90	1
$[(CH_3)_2CH]_2NC_2H_5$	21.88	99	21.66	129.25	167.60	4.2
$(Ph_3P)_2PdCl_2$	0.0289	97	0.0280	701.89	0.039	0.001
Ph_3P	5.29	99	5.237	262.29	20	0.5
H_2O	7.182	100	7.182	18	399.0	10
Xylene	17.29	98	16.94	106.17	159.6	4

Total chemical yield of all detected 3-isochromanone by quantitative gc analysis was 51%.

EXAMPLE 3 (0.1% catalyst, 10% Ph_3P)

Materials	Act Wt(g)	Str (%)	100% Wt	M Wt	mmol	MR
ODCX	7.0	100	7.0	175.06	39.90	1
$[(CH_3)_2CH]_2NC_2H_5$	21.88	99	21.66	129.25	167.60	4.2
$(Ph_3P)_2PdCl_2$	0.0289	97	0.0280	701.89	0.039	0.001
Ph_3P	1.057	99	1.0465	262.29	100	0.1
H_2O	7.182	100	7.182	18	399.0	10
Xylene	17.29	98	16.94	106.17	159.6	4

Total chemical yield of all detected 3-isochromanone by quantitative gc analysis was 37 %

EXAMPLE 4 (0.3% catalyst, 25% Ph_3P)

Materials	Act Wt(g)	Str (%)	100% Wt	M Wt	mmol	MR
ODCX	7.0	100	7.0	175.06	39.90	1
$[(CH_3)_2CH]_2NC_2H_5$	21.88	99	21.66	129.25	167.60	4.2
$(Ph_3P)_2PdCl_2$	0.0866	97	0.0840	701.89	0.1197	0.003
Ph_3P	2.58	99	2.557	262.29	250	0.25
H_2O	7.182	100	7.182	18	399.0	10
Xylene	17.29	98	16.94	106.17	159.6	4

Total chemical yield of all detected 3-isochromanone by quantitative gc analysis was 67%.

EXAMPLE 5 (Reduced base charge)

Materials	Act Wt(g)	Str (%)	100% Wt	M Wt	mmol	MR
ODCX	7.0	100	7.0	175.06	39.90	1
$[(CH_3)_2CH]_2NC_2H_5$	15.63	99	15.47	129.25	119.7	3.0
$(Ph_3P)_2PdCl_2$	0.2888	97	0.2801	701.89	0.399	0.01
Ph_3P	0.2326	99	0.2303	262.29	0.878	0.022
H_2O	7.182	100	7.182	18	399.0	10
Xylene	17.29	98	16.94	106.17	159.6	4

Total chemical yield of all detected 3-isochromanone by quantitative gc analysis was 91%

EXAMPLE 6

To a 100ml round-bottom flask were charged *o*-xylene-α,α'-dichloride (7.07g, 0.0404 moles), *N,N*-di*iso*propylethylamine (21.4g, 0.164 mol), xylene (17.16g, 0.16 mol), deionised water (7.2g, 0.4 mol), palladium on Montmorillonite™ catalyst (0.2g, 0.04mmol approx) and triphenylphosphine (0.26g, 9.8 x 10^{-4} mol). Carbon monoxide was bubbled through the reaction mixture via syringe needle slowly and continuously. The temperature of the reaction mixture was raised to 70°C and held at 70°C with vigorous agitation for 30 hours. A sample tested by qualitative gc analysis showed less than 1% area starting material and 51.2% area 3-isochromanone. The reaction mixture was cooled to room temperature and the supported palladium on Montmorillonite™ catalyst was filtered off. The filtrate layers were separated and analysis quantitative by gc analysis showed 36.8% yield 3-isochromanone in the organic layer and 5% yield 3-isochromanone in the aqueous layer.

EXAMPLE 7

o-Xylene-α,α'-dichloride (7.07g, 0.0404 mol), *N,N*-di*iso*propylethylamine (21.4g, 0.164mol), palladium on Montmorrilonite™ catalyst (2.0g, 0.4mmol approx), xylene (17.16g, 0.16 mol), deionised water (7.2g, 0.4 mol) and triphenylphosphine (2.6g, 9.8×10^{-3} mol) were charged to a 100ml round bottom flask and carbon monoxide bubbled through via a syringe needle. The reaction mixture was heated to 70°C while bubbling carbon monoxide through slowly and held at 70°C for 5 hours. A sample tested by qualitative gc analysis showed less than 1% area starting material and 59.9% area 3-isochromanone. After 20 hours the reaction mixture was cooled to room temperature and the supported palladium on Montmorrilonite™ was filtered off. The filtrate layers were separated and analysed by quantitative gc analysis which showed the organic layer contained 48% yield 3-isochromanone and the aqueous layer contained 11.6% yield 3-isochromanone

EXAMPLE 8

To a 100ml round bottom flask were charged, *o*-Xylene-α,α'-dichloride (7.07g, 0.0404 mol), *N,N*-di*iso*propylethylamine, (21.4g, 0.164 mol), palladium on Montmorillonite™ catalyst recycled from Example 7 (2.0g, 1%) xylene (17.16g, 0.16 moles) deionised water (7.2g, 0.4 mol) and triphenylphosphine (2.6g, 9.8×10^{-3} moles). Carbon monoxide was bubbled through the reaction mixture via a syringe needle and the mixture was heated to 70°C, with slow continuous carbon monoxide bubbling, and vigorous agitation for 20 hours. Qualitative gc analysis showed less than 1% area starting material present and 62% area isochromanone. The reaction mixture was cooled to room temperature and the supported palladium catalyst filtered off. The filtrates were separated into organic and aqueous phases, weighed and submitted for quantitative isochromanone strength by gc analysis. The results showed 47.7% yield of 3-isochromanone in the organic phase and 11.7% yield in the aqueous phase. The Palladium/Montmorrilonite™ solids filtered off were used in Example 9.

EXAMPLE 9

The procedure used was the same as for Example 8 but using palladium/Montmorrilonite™ catalyst recycled from Example 8. The qualitative gc analysis after 20 hours showed less than 1% area starting material and 44.1% area 3-isochromanone. The organic phase contained 48.6% yield 3-isochromanone and the aqueous phase contained 7.5% yield 3-

isochromanone by quantitative gc analysis. The palladium/Montmorillonite™ solids filtered off were used in Example 11.

EXAMPLE 10

The procedure used was the same as for Example 8 but using palladium/Montmorillonite™ catalyst recycled from Example 9. The qualitative gc analysis after 20 hours showed less than 1% area starting material and 44.7% area 3-isochromanone. The organic phase contained 52.3% yield 3-isochromanone and the aqueous phase contained 9.4% yield 3-isochromanone by quantitative gc analysis.

EXAMPLE 11

o-Xylene α,α'-dichloride (7.10g, 41mmol), *N,N*-di*iso*propylethylamine (21.40g, 164mmol), dichloro*bis*(triphenylphosphine)palladium (II) (286.3mg, 0.4mmol), water (7.2g, 400mmol), xylene (20ml, 160mmol) and triphenylphosphine (238.4mg, 0.9mmol) were charged to a 100ml three-necked round bottomed flask with stirring. After degassing (x 3) under vacuum, a steady flow of carbon monoxide was bubbled through the reaction mixture whilst heating to 70°C. The reaction mixture was maintained at 70°C, with carbon monoxide bubbling through and vigorously stirred (650 rpm) for 24 hours, before sampling for qualitative gas chromatographic analysis. This showed the ratio of 3-isochromanone to starting material to be > 99:1 by area percent. The reaction mixture was cooled to ambient temperature, filtered and washed with xylene (10ml). The filtrates were separated to give an organic solution and an aqueous phase. The total quantitative yield of 3-isochromanone by gc analysis (organic and aqueous phases) was 78.8%.

EXAMPLES 12 TO 21

o-Xylene-α,α'-dichloride (14.0g, 0.08 mol), *N,N*-di*iso*propylethylamine (31.35g, 0.24 mol) palladium(II) chloride catalyst (0.148g, 0.8 mmol), *o*-xylene (34.0g, 0.32 mol), water (14.4g, 0.8 mol) and triphenylphosphine (1.0g, 4.0mmol) were charged to a 300ml Inconel ™ autoclave. The vessel was then purged with carbon monoxide gas three times (at 5 bar.g) before finally pressurising to approximately 4 bar.g. The contents of the reaction vessel were then briskly agitated (approximately 900rpm) and heated to 70°C. Once at temperature, the reaction mixture was stirred at 70°C for 3 to 4 hours, maintaining the pressure at approximately 4 bar.g, and the rate of uptake of carbon monoxide gas was noted. The reaction was adjudged complete approximately when no further carbon monoxide was seen to be consumed. The reaction mixture was then rapidly cooled to below 40°C and sampled to test for the presence of starting material by gc.

Water (33g) and sodium hydroxide (27.4g at 47% strength) were charged in one portion to the open autoclave, which was then sealed and purged with carbon monoxide gas three times (at 5 bar.g) before being finally pressurised to 1 bar.g. The reaction mixture was then stirred at 60°C, under approximately 1 to 2 bar.g (CO pressure) for approximately 1 hour. The reaction mixture was then transferred to a hot separator (in air) and the aqueous and organic phases separated at 60°C. The aqueous phase was drawn off for further work-up by being added cautiously to a stirred solution of xylene and concentrated hydrochloric acid at 60°C (in air). The mixture was then stirred for 1 hour at 60°C before being separated to give an a aqueous waste stream and a xylene solution containing the product, 3-isochromanone. The xylene solution was recycled by recharging direct to the reaction vessel for use in Example 13.

The same method was used for Examples 13 to 21 except that the ODCX, triphenylphosphine and water were charged to the autoclave containing the organic phase recycled from the previous Example. The only difference between the nine 'recycled' Examples was that additional *N,N*-di*iso*propylethylamine base was added in Example 17. Yields of 3-isochloromanone obtained were as follows:

Example	Yield (%)
12	88.7
13	90.7
14	90.3
15	83.5
16	78.4
17*	71.6
18	76.4
19	67.2
20	64.0
21	50.8

* *N,N*-di*iso*propylethylamine (0.08moles) added at this cycle

EXAMPLE 22

o-Xylene-α,α'-dichloride (14.7g, 80mmol), *N,N*-di*iso*propylethylamine (31.4g, 240mmol), liquid dihydrotetrachloropalladium (H_2PdCl_4) catalyst (0.3723g, 0.8mmol), *o*-xylene (34.0g, 320 mmol), water (14.4g, 800mmol) and triphenylphosphine (0.93g, 4.0 mmol) were charged to a Parr autoclave. The autoclave was purged three times at 5 bar.g with carbon monoxide gas before being finally pressurised to 4 bar.g. The reaction mixture was heated to 70°C and maintained at this temperature with stirring for 4½ hours. The pressure was maintained at 4 bar.g with carbon monoxide. The reaction was deemed to be complete when no further carbon monoxide was seen to be consumed.

Sodium hydroxide solution (60.3g at 21 % strength) was charged to a separate jacketed reaction vessel which was evacuated and filled with a carbon monoxide atmosphere. Carbon monoxide was bubbled through the caustic solution while heating to 60°C. The Parr autoclave was evacuated and the solution hydroxide solution charged from the separate jacketed vessel by vacuum displacement. The mixture was stirred for 1 hour at 60°C and 1 bar.g pressure before separating the organic (63.76g) and aqueous layers. The aqueous layer was added to a stirred mixture of *o*-xylene (42.5g) and concentrated hydrochloric acid (20.3g at 36% strength). This mixture was stirred at 70°C for one hour before separating the organic layer (50.72g xylene solution) and aqueous layer (96.08g). Analysis of the xylene solution indicated a yield of 76.42% of 3-isochromanone (50.72g at 17.84g 3-isochromanone).

CLAIMS

1. A process for the preparation of 3-isochromanone which comprises contacting an *o*-xylene-α,α'-dihalide with carbon monoxide in a two-phase liquid medium, in which one phase is aqueous and the other phase is water-immiscible, in the presence of a catalyst and a hindered amine base.

2. A process according to claim 1 in which the *o*-xylene-α,α'-dihalide is *o*-xylene-α,α'-dichloride.

3. A process according to claim 1 or 2 in which in the two-phase medium, one phase comprises water and the other phase comprises a water-immiscible solvent.

4. A process according to claim 3 in which the molar ratio of water:water-immiscible solvent is in the range of 1:50 to 50:1.

5. A process according to claim 3 in which the molar ratio of water:o-xylene-α,α'-dihalide is in the range of 100:1 to 1:1.

6. A process according to any one of the preceding claims in which the amine base is an amine of formula $R^1R^2R^3N$ wherein R^1,R^2 and R^3 are independently C_{1-10} alkyl, C_{3-6} cycloalkyl, aryl or aryl(C_{1-4})alkyl or wherein two or three of R^1, R^2 and R^3 join together with the nitrogen atom to which they are attached to form one, two or three, 5-, 6- or 7- membered alicyclic rings optionally fused and optionally containing a second ring nitrogen atom.

7. A process according to any one of the preceding claims in which the molar ratio of amine base:*o*-xylene-α,α'-dihalide is in the range of 10:1 to 1:1.

8. A process according to any one of the preceding claims in which the catalyst is a palladium catalyst.

9. A process according to any one of the preceding claims in which the catalyst is present in the amount of 0.000001 to 0.5 mole equivalents of the *o*-xylene-α,α'-dihalide.

10. A process according to any one of the preceding claims in which there is present a phase transfer catalyst.

11. A process according to any one of the preceding claims which is carried out at a temperature of from 20°C to 200°C.

INTERNATIONAL SEARCH REPORT

Inter onal Application No
PCT/GB 98/02250

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D311/76

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	EP 0 834 497 A (IHARANIKKEI CHEMICAL INDUSTRY ;SAGAMI CHEM RES (JP)) 8 April 1998	1-11
Y	& WO 97 00850 A cited in the application ---	1-11
Y	EP 0 222 460 A (STAUFFER CHEMICAL CO) 20 May 1987 see the whole document -----	1-11

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search 18 September 1998	Date of mailing of the international search report 02/10/1998
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Authorized officer Goetz, G

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inte. ional Application No
PCT/GB 98/02250

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0834497 A	08-04-1998	JP 9278771 A	28-10-1997
		JP 9278772 A	28-10-1997
		JP 9067364 A	11-03-1997
		JP 9328452 A	22-12-1997
		WO 9700850 A	09-01-1997
EP 0222460 A	20-05-1987	US 4668816 A	26-05-1987
		AU 6498486 A	14-05-1987
		BR 8605581 A	18-08-1987
		CA 1258870 A	29-08-1989
		JP 62114930 A	26-05-1987
		US 4761499 A	02-08-1988
		US 4713484 A	15-12-1987