(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
5 October 2017 (05.10.2017)

WIPO | PCT

(10) International Publication Number
WO 2017/167756 A1

(51) International Patent Classification:
C07C 43/12 (2006.01) *C08G 65/00* (2006.01)
C07C 17/00 (2006.01)

(21) International Application Number:
PCT/EP2017/057319

(22) International Filing Date:
28 March 2017 (28.03.2017)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
16163098.3 31 March 2016 (31.03.2016) EP

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(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, KH, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Published:

— *with international search report (Art. 21(3))*

WO 2017/167756 A1

(54) Title: METHOD OF MAKING FLUORINE GROUP-CONTAINING AROMATIC COMPOUNDS

(57) Abstract: The invention pertains to a method of making an aromatic compound comprising a fluorine-containing group, the method comprising the following steps: Step (1): providing an aromatic compound comprising at least one aromatic ring comprising sp2-hybridized carbon atoms [compound (Ar)], and a nitrile compound comprising at least one nitrile group (-CN) bound to a fluorine-containing group (group R_f) [nitrile (F)]; Step (2): reacting the nitrile (F) with compound (Ar) under electrophilic substitution conditions followed by hydrolytic conditions so as to generate a ketone derivative comprising a group -C(O)-R_f covalently bound to a sp^2-hybridized carbon atom of an aromatic ring, wherein Rf has the meaning as indicated above [ketone (Ar)]; and Step (3): reacting ketone (Ar) with a reducing agent effective in reducing carbonyl group -C(O)-, so as to obtain an aromatic compound comprising a group -CH_2-R_f covalently bound to a sp_2-hybridized carbon atom of an aromatic ring.

Description

Method of making fluorine group-containing aromatic compounds

Cross-reference to Related Application

[0001] This application claims priority to European application No. 16163098.3 filed March 31st, 2016, the whole content of this application being incorporated herein by reference for all purposes.

Technical Field

[0002] The present invention focuses on the formation of covalent carbon-carbon bonds between aromatic moieties and fluorine-containing groups, in particular fluoroalkyl groups or fluoro(poly)oxyalkyl groups.

Background Art

[0003] Methods of binding aromatic groups and fluorine-containing groups through covalent bonds are known; nevertheless, most of the method described in the art provide for creating covalent bonds between sp^2 -hybridized carbon atoms of the aromatic moiety and heteroatoms, e.g. as (thio)ether, amine, amide, ester connecting moieties. These binding groups suffer nevertheless of being, under certain conditions, labile, and do not offer same thermal and chemical stability which the aromatic moiety or the fluorinated group can withstand.

[0004] The invention hereby provides a solution to this aim, and makes available a synthetic route towards aromatic compounds possessing a fluorine-containing group connected to the aromatic moiety through a carbon-carbon covalent bond.

Summary of invention

[0005] The invention specifically pertains to a method of making an aromatic compound comprising a fluorine-containing group, the method comprising the following steps:

Step (1): providing an aromatic compound comprising at least one aromatic ring comprising sp^2-hybridized carbon atoms [compound (Ar)], and a nitrile compound comprising at least one nitrile group (-CN) bound to a fluorine-containing group [nitrile (F)];

Step (2): reacting the nitrile (F) with compound (Ar) under electrophilic substitution conditions followed by hydrolytic conditions so as to generate

a ketone derivative comprising a group -C(O)-R_f covalently bound to a sp^2-hybridized carbon atom of an aromatic ring, wherein R_f has the meaning as indicated above [ketone (Ar)]; and

Step (3): reacting ketone (Ar) with a reducing agent effective in reducing carbonyl group -C(O)-, so as to obtain an aromatic compound comprising a group –CH_2-R_f covalently bound to a sp^2-hybridized carbon atom of an aromatic ring.

Description of embodiments

[0006] Step (1) includes providing an aromatic compound comprising at least one aromatic ring comprising sp^2-hybridized carbon atoms [compound (Ar)].

[0007] The expression "aromatic ring" is to be understood according to the usual meaning in organic chemistry, i.e. to designate unsaturated cyclic structures, possibly including heteroatoms in the cycle, having conjugated double bonds following the Hückel's rule, i.e. having 4n+2 electrons in the delocalized, conjugated p-orbital cloud.

[0008] The aromatic compound may be a mononuclear compound, i.e. including only one aromatic ring, or may be polynuclear, i.e. comprising more than one aromatic rings, which may be condensed or not condensed.

[0009] Non-limitative examples of aromatic rings are benzene, naphthalene, pyridine, pyrrole, thiophene, anthracene, biphenyl, thyazoles, tetrazoles, triazoles, indoles.

[0010] Furthermore, the aromatic compound may comprise substitutents covalently bound to the aromatic rings, whose choice is not particularly limited. In order to enhance reactivity in Step (2), aromatic compounds may comprise one or more than one electron-donating group connected to a sp^2-hybridized carbon atom of the aromatic ring. Non-limitative examples of these groups are notably hydroxyl group -OH, alkyl ether groups of formula –OR_H, with R_H being a C_1-C_6 hydrocarbon group, in particular a C_1-C_6 aliphatic group; alkyl groups of formula –R_{alk}, with R_{alk} being a C_1-C_6 alkyl group, primary or secondary amine groups, primary or secondary thioether groups.

[0011] Step (1) further includes providing a nitrile compound as above detailed [nitrile (F)].

[0012] The choice of fluorine-containing group (group R_f) is not particularly limited, provided it comprises organically-bound fluorine.

[0013] According to certain embodiment's, group R_f is selected among fluorine-containing C_1-C_{12} (hydro)carbon groups, in particular (per)fluoroalkyl groups having 1 to 12 carbon atoms.

[0014] According to other embodiments, R_f is selected from the group consisting of (per)fluoropolyoxyalkylene groups [group (R_{of})] comprising a plurality of recurring units (R_1), said recurring units having general formula: -$(CF_2)_k$ -CFZ-O-, wherein k is an integer of from 0 to 3 and Z is selected between a fluorine atom and a C_1-C_6 perfluoro(oxy)alkyl group.

[0015] According to these embodiments, nitrile (F) is generally a compound of formula:

T^B-O-R^*_f-$T^{B'}$ (I)

wherein:

R^*_f is a group (R_{of}), as above detailed;

each of T^B and $T^{B'}$, equal to or different from each other, are selected from (j) a group of any of formulae -CF_3, -CF_2Cl, -CF_2CF_3, -$CF(CF_3)_2$, -CF_2H, -CFH_2, -CF_2CH_3, -CF_2CHF_2, -CF_2CH_2F, -CFZ*CH_2OH, -CFZ*COOH, -CFZ*$COOR_h$ and –CFZ*-$CH_2(OCH_2CH_2)_k$-OH, wherein k is ranging from 0 to 10, wherein Z* is F or CF_3; R_h is a C_1-C_6 hydrocarbon chain; and (jj) a group T^{CN}, of any of formulae -CFZ*$(CH_2)_q$-CN, wherein q is zero or an integer of 1 to 3, and –CFZ*-$(CH_2)_{q'}(OCH_2CH_2)_k$-CN, with q' is zero or an integer of 1 to 3, and k is ranging from 0 to 10, Z* is F or CF_3,

with the provisio that at least one of T^B and $T^{B'}$ is a group T^{CN}, as above detailed

[0016] Group R^*_f of the compound (I) more preferably complies with formula:

-$(CF_2CF_2O)_{a'}(CFYO)_{b'}(CF_2CFYO)_{c'}(CF_2O)_{d'}(CF_2(CF_2)_zCF_2O)_{e'}$-,

wherein the recurring units are statistically distributed along the (per)fluoropolyoxyalkylene chain, wherein:

- Y is a C_1-C_5 perfluoro(oxy)alkyl group;
- z is 1 or 2;
- a', b', c', d', e' are integers ≥ 0.

[0017] Most preferably, group R^*_f complies with formula:

$-(CF_2CF_2O)_{a''}(CF_2O)_{b''}(CF_2(CF_2)_zCF_2O)_{c''}-$, wherein:

- z is 1 or 2;
- a", b", c" are integers ≥ 0.

[0018] Group (R_{of}) is generally selected so as to possess a number averaged molecular weight of 500 to 6000, preferably of 750 to 5000, even more preferably of 1000 to 4500.

[0019] Nitriles (F) can be notably synthetized according to methods known in the art.

[0020] According to certain embodiments, the method of the invention comprises a preliminary step of manufacturing the nitrile (F) by reaction of a compound comprising a fluorine-containing group (group R_f) and further comprising a $-CH_2I$ group [organic iodide (F)] by reaction with a metal cyanide, e.g. KCN.

[0021] Reactivity of compounds comprising a $-CH_2I$ group towards cyanides has been notably described in **KEMP, D.S., et al.** Chimica Organica. : N. Zanichelli, 1983. p.Ch. 3,4,6,7. and in **CHAMBERS, R., et al.** Fluorine in Organic Chemistry. BLACKWELL PUBLISHING, 2004. p.Chapt. 4.

[0022] It is to be outlined that a fundamental prerequisite of this method is that there has to be at least 1 $-CH_2-$ group in α position to the iodine atom, i.e. separating the same from fluorinated groups of $-CF_2-$ type, since substitution reactions by $-CN^{(-)}$ upon a halide alpha to a $-CF_2-$ will not proceed with any significant yield due to the high electronegativity of the fluorine atom.

[0023] According to other embodiment's the method of the invention comprises a preliminary step of manufacturing the nitrile (F) by reaction of a compound comprising a fluorine-containing group (group R_f) and further comprising an amide group of formula $-C(O)-NH_2$ [amide (F)].

[0024] Transformation of the amide group of amide (F) into nitrile group can be effected through methods known in the art, notably by dehydration, e.g. in the presence of P_2O_5 , in the presence of PCl_3, in the presence of trifluoroacetic acid anhydride, or any other suitable dehydrating agent.

[0025] The amide (F) can be provided starting from any of carboxylic acids, acyl halides, alkyl esters according to techniques known in the art.

[0026] In particular, the provision of nitriles (F), as above detailed, in particular wherein R_f is a (per)fluoropolyoxyalkylene group [group (R_{of})], as above detailed, has been notably described in **WO 2012/138457** , starting from a precursor possessing acyl fluoride groups, which is converted into an ester via reaction with an appropriate alcohol, which is subsequently concerted into an amide (F) via reaction with ammonia, which is finally dehydrated to nitrile, as above detailed.

[0027] Similar teachings can be found notably in **US 3810874** (see in particular Ex. 5), in **US 4647413** (see in particular column 5, line 40) and in **US 5545693** (see in particular Experiment 3).

[0028] Step (2) is generally carried out in the presence of a solvent. The solvents most indicated for this Step (2) are generally ethereal solvents, more particularly anhydrous ethyl ether or anhydrous THF.

[0029] Generally, this Step (2) is carried out in the presence of a combination of a Lewis acid catalyst and hydrogen chloride. The choice of the Lewis acid is not particularly limited, and Chlorine-containing Lewis acids are generally used, including notably $AlCl_3$ and $ZnCl_2$, preferably $ZnCl_2$. Typically, HCl is added through bubbling anhydrous hydrogen chloride in the reaction medium.

[0030] Step (2) is generally understood to first involve the formation of an aromatic imine hydrochloride followed by the acid hydrolysis of the said imine hydrochloride to the desired aromatic ketone.

[0031] The imine hydrochloride is generally separated from the reaction mixture by crystallization in anhydrous conditions, and generally at low temperature (e.g. around 0°C). The imine hydrochloride can be recovered by standard techniques (filtration, decantation), possibly rinsed for removal of acids and other residues, and hydrolysed to the ketone in the presence of water at a temperature of 60°C or more, generally in boiling water.

[0032] The ketone (Ar) can be so recovered, e.g. by precipitation or by phase separation.

[0033] In Step (3), the ketone (Ar) is contacted with a reducing agent effective in reducing carbonyl group -C(O)-, so as to obtain an aromatic compound comprising a group $–CH_2-R_f$ covalently bound to a sp^2-hybridized carbon

atom of an aromatic ring.

[0034] Reduction of the carbonyl group -C(O)- can be effected notably through (*a*) Clemmensen Reduction or the (*b*) Wolff-Kishner reduction.

[0035] According to embodiment (a), reducing agent is a combination of a Zinc/Mercury amalgam and hydrochloric acid.

[0036] According to embodiment (b), reducing agent is hydrazine, which is used in combination with a base; in this case, Step (3) comprises a first step of reacting the ketone (Ar) with hydrazine in the presence of a base, so as to obtain corresponding hydrazone, wherein the carbonyl group –C(O)- has been transformed into a group of formula $–C(=N-NH_2)-$; and a second step of decomposing the said hydrazone at temperatures of 100°C or more, preferably of about 170-190°C.

[0037] Should the disclosure of any patents, patent applications, and publications which are incorporated herein by reference conflict with the description of the present application to the extent that it may render a term unclear, the present description shall take precedence.

[0038] The invention will be now be described in more detail with reference to the following examples, whose purpose is merely illustrative and not intended to limit the scope of the invention.

[0039] **Preparative Example 1**

[0040] *1.1 Synthesis of the nitrile (F) via iodide route*

[0041] In a round bottomed flask equipped with a thermometer, dripping funnel a magnetic stir bar and a reflux condenser, 1.3 molar equivalents of KCN (with respect to the alkyl iodide molar equivalents) are suspended in a polar aprotic solvent chosen from CH_3CN, DMSO, DMF, Diglyme and the dishomogeneous suspension is heated to 75°C with vigorous stirring. Optionally, Crown ether 18-6 (0.3 molar eq. vs. KCN) may be added). Then the appropriate fluorine-containing organo-iodide precursor is slowly dripped in the solution and let stir for at least 5 hours following the complete addition of the fluorine-containing organo-iodide. The reaction progress may be followed by 1H-NMR observing the up-field shift of $–\underline{CH_2}I$ to $–\underline{CH_2}CN$ from 4.2 ppm to 3.5 ppm.

[0042] Following complete conversion of the iodide, the crude reaction mixture is

filtered and, diluted in CH_2Cl_2 and washed 2 times in distilled H_2O. The lower, orgainc layer is collected, dried over $MgSO_4$, filtered and the solvent is evaporated under reduced pressure at 60°C.

[0043] *1.2 Reaction of the nitrile (F) with the aromatic compound*

[0044] In a round bottomed flask equipped with a thermometer, dripping funnel a magnetic stir bar and a reflux condenser, one places 1 molar equivalent of the anhydrous compound along with 1.1 molar equivalents of anhydrous nitrile (F) synthesised in 1.1. The solvents most indicated for the reaction are anhydrous ethyl ether or anhydrous THF. Also present in the reaction flask is 0.25molar eq. of finely powder, anhydrous $ZnCl_2$. The flask is vigorously stirred and cooled to 0°C and a steady stream of anhydrous HCl is bubbled into the stirred solution at a rate of ca. 0.5 NL/h for 2 hrs. Following this initial reaction phase, the stream of HCl is stopped and the crude reaction mixture is let stir for 10-12 hrs. The crude reaction mixture becomes pale orange during this reaction phase. Again bubble a steady stream of anhydrous HCl, at 0°C with stirring at a rate of 0.5 NL/h for 2 hrs and let the reaction mixture stir for a further 15 hrs always at 0°C. Stopper the reactor al leave it stand at 0°C for 48 hrs. A bulky orang-yellow precipitate of the imine hydrochloride is formed. Filter the solvent (ether or THF) and wash the solid with 2 30 mL portions of dry ether or THF. Filter the solvent and transfer the solid hydrochloride to a second flask containing 300 mL (ca. 300 mL H_2O/eq of starting nitrile). Boil the aqueous solution for 2 hours, let the hydrolysed mixture cool to about 60°C, add decolorizing charchoal and boil the solution for 1 hr. Filter the hot, carbon-containing crude mixture, and extract the wet charcoal with a 100 ml portion of hot H_2O. Filter the washing and add the filtrate to the main product. Let the aqueous solution cool overnight and collect the precipitate (solid if the staring nitrile (F) is a fluoro-alkyl nitrile, an oil if the starting nitrile is a (per)fluoropolyoxyalkylene group-containing nitrile (F). The ketone formation is confirmed by FT-IR at the typical stretching frequency of 1754 cm^{-1}.

[0045] *1.3 (a) Clemmensen Reduction*

[0046] A first step is the correct preparation of the Zn/Hg amalgam needed for the

reduction. 1 eq. of Zn wool or powder are placed in a 1 L Erlenmeyer flask and covered with a 10-15% solution of NaOH. The flask is gently warmed with occasional stirring until hydrogen is evolved. The NaOH is them immediately poured off. It may be necessary to dilute flask contents with H_2O in order to moderate the vigour of the reaction. The Zn is repeatedly washed with distilled H_2O until neutral pH. The washed Zn is then covered with a 1% solution of $HgCl_2$ and it is moderately stirred for 60 min. The solution is poured away and the amalgamated Zn is washed 2 times with 100 ml of distilled H_2O. The amalgamated Zn/Hg is then covered with 100 mL of concentrated aqueous HCl and 20 mL of H_2O. This is the Zn/Hg amalgam ready for the Clemmensen Reduction. The ketone to be reduced (0.35 eq vs. the starting Zn employed) is added to the amalgam in a round bottomed flask equipped with a thermometer, a dripping funnel or solid dispenser, a magnetic stir bar and a reflux condenser. Once the addition is completed a steady stream of HCl gas is bubbled in the solution at 0.5 NL/h and the reduction is followed by following the disappearence of the carbonyl stretching (FT-IR) typically at 1754 cm^{-1}.

[0047] *1.3 (b) Wolff-Kishner Reduction*

[0048] One eq. of the ketone, obtained in step 2, to be reduced is placed in a dripping funnel which is connected to a round-bottomed flask equipped with a thermometer, a magnetic stir bar and a reflux condenser. Two eq. of commercial 85% hydrazine hydrate are placed in the round bottomed flask along with 150 ml of diethylene glycol and 3 eq of KOH. The mixture is heated to reflux and the ketone is dripped in the reducing medium. The mixture is refluxed for 1 hr following complete addition of the ketone. The hydrazone generated, is decomposed in situ by first distilling away H_2O and excess H_2NNH_2 and then reheating to 170° - 190°C which is the typical hydrazone decomposition temperature. *In situ* decomposition of the hydrazone may be followed by gas evolution (N_2) through a bubble counter. Reaction time for complete hydrazone decomposition ranges from 3 to 5 hrs. The resulting hydrazone decomposition product is the desired alkane and it is typically obtained in 75 – 85% molar yield *vs.* the starting ketone.

Claims

1. A method of making an aromatic compound comprising a fluorine-containing group (group R_f), the method comprising the following steps:
   Step (1): providing an aromatic compound comprising at least one aromatic ring comprising sp^2-hybridized carbon atoms [compound (Ar)], and a nitrile compound comprising at least one nitrile group (-CN) bound to a fluorine-containing group (group R_f) [nitrile (F)];
   Step (2): reacting the nitrile (F) with compound (Ar) under electrophilic substitution conditions followed by hydrolytic conditions so as to generate a ketone derivative comprising a group -C(O)-R_f covalently bound to a sp^2 -hybridized carbon atom of an aromatic ring, wherein R_f designates a fluorine-containing group [ketone (Ar)]; and
   Step (3): reacting ketone (Ar) with a reducing agent effective in reducing carbonyl group -C(O)-, so as to obtain an aromatic compound comprising a group $–CH_2$-R_f covalently bound to a sp^2-hybridized carbon atom of an aromatic ring.
2. The method of claim 1, wherein group R_f is selected among fluorine-containing C_1-C_{12} (hydro)carbon groups, in particular (per)fluoroalkyl groups having 1 to 12 carbon atoms.
3. The method of claim 1, wherein group R_f is selected from the group consisting of (per)fluoropolyoxyalkylene groups [group (R_{of})] comprising a plurality of recurring units (R_1), said recurring units having general formula: -$(CF_2)_k$ -CFZ-O-, wherein k is an integer of from 0 to 3 and Z is selected between a fluorine atom and a C_1-C_6 perfluoro(oxy)alkyl group.
4. The method of Claim 3, wherein nitrile (F) is a compound of formula:
   T^B-O-R^*_f-$T^{B'}$ (I)
   wherein:
   R^*_f is a group (R_{of}), as above detailed;
   each of T^B and $T^{B'}$, equal to or different from each other, are selected from (j) a group of any of formulae -CF_3, -CF_2Cl, -CF_2CF_3, -$CF(CF_3)_2$, -CF_2H, -CFH_2, -CF_2CH_3, -CF_2CHF_2, -CF_2CH_2F, -CFZ*CH_2OH, -CFZ*COOH, -CFZ*$COOR_h$ and –CFZ*-$CH_2(OCH_2CH_2)_k$-OH, wherein k is ranging from 0 to 10, wherein Z* is F or CF_3; R_h is a C_1-C_6 hydrocarbon chain; and

(jj) a group T^{CN}, of any of formulae -CFZ*$(CH_2)_q$-CN, wherein q is zero or an integer of 1 to 3, and –CFZ*-$(CH_2)_{q'}(OCH_2CH_2)_k$-CN, with q' is zero or an integer of 1 to 3, and k is ranging from 0 to 10, Z* is F or CF_3,
with the provisio that at least one of T^B and $T^{B'}$ is a group T^{CN}, as above detailed

5. The method according to anyone of the preceding claims, wherein said method comprises a preliminary step of manufacturing the nitrile (F) by reaction of a compound comprising a fluorine-containing group (group R_f) and further comprising a $–CH_2I$ group [organic iodide (F)] by reaction with a metal cyanide.
6. The method according to anyone of Claims 1 to 4, wherein said method comprises a preliminary step of manufacturing the nitrile (F) by reaction of a compound comprising a fluorine-containing group (group R_f) and further comprising an amide group of formula $–C(O)-NH_2$ [amide (F)].
7. The method according to anyone of the preceding claims, wherein Step (2) is carried out in the presence of a solvent selected from ethereal solvents, more particularly anhydrous ethyl ether or anhydrous THF.
8. The method according to anyone of the preceding claims, wherein Step (2) is carried out in the presence of a combination of a Lewis acid catalyst and hydrogen chloride.
9. The method according to anyone of the preceding claims, wherein in Step (3), reduction of the carbonyl group -C(O)- is effected through (*a*) Clemmensen Reduction or (*b*) Wolff-Kishner reduction.
10. The method according to Claim 9, wherein the reduction is a (a) Clemmensen reduction, and wherein reducing agent is a combination of a Zinc/Mercury amalgam and hydrochloric acid.
11. The method according to Claim 9, wherein the reduction is a (b) Wolff-Kishner reduction, and wherein reducing agent is hydrazine, which is used in combination with a base.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2017/057319

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07C43/12 C07C17/00 C08G65/00
ADD.

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)
C07C C08G

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 practicable, search terms used)

EPO-Internal, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2007/075804 A1 (3M INNOVATIVE PROPERTIES CO [US]) 5 July 2007 (2007-07-05) claims 1-24	1-11
A	WO 89/02884 A1 (MERCK PATENT GMBH [DE]) 6 April 1989 (1989-04-06) claim 1	1-11

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

☒ See patent family annex.

* Special categories of cited documents :

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Date of the actual completion of the international search	Date of mailing of the international search report
13 April 2017	25/04/2017

Name and mailing address of the ISA/	Authorized officer
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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2017/057319

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