Title: A PROCESS FOR SYNTHESIS OF 2, 4-DICHLORO-5- FLUOROACETOPHENONE (DCFA)

Abstract: A process for synthesis of 2,4-dichloro-5-fluoro acetophenone (DCFA) is disclosed. The process comprises first reacting 3,4-dichloronitrobenzene with potassium fluoride having bulk density in the range of 0.2 to 1.3, to form a fluorinated intermediate product, then reacting the intermediate product with chlorine to form dichlorofluorobenzene and finally acylating dichlorofluorobenzene using an acylating agent to form a mixture containing DCFA along with impurities, followed by purification and enrichment of DCFA in the mixture by melt crystallization.
A PROCESS FOR SYNTHESIS OF 2, 4-DICHLORO-5-
FLUOROACETOPHENONE (DCFA)

Field of Invention

The invention relates to a process for synthesis of 2, 4-dichloro-5-fluoroacetophenone (DCFA).

Background

2,4-dichloro-5-fluoroacetophenone (DCFA) is a valuable intermediate used in the manufacture of fluoroquinone antibiotics such as ciprofloxacin. DCFA is usually prepared from paranitrochlorobenzene (PNCB) by the process steps involving chlorination of paranitrochlorobenzene to form dichloronitrobenzene, treatment of dichloronitrobenzene with potassium fluoride to form a fluorinated product, heating the fluorinated product in an environment of chlorine gas resulting in dichlorofluorobenzene and finally acylation of dichlorofluorobenzene by an acylating agent. The overall yield of DCFA, during the process, is largely determined by the yield of the intermediate compounds, and in particular, by the yield of the fluorinated product obtained by the potassium fluoride treatment. The yield of the fluorinated product obtained by the potassium fluoride treatment, during the conventional process, has been found to be low thereby considerably impacting the yield of 2, 4-dichloro-5-fluoroacetophenone (DCFA). It has been a practice, during the conventional process to use potassium fluoride in excess of the stoichiometric quantities, to facilitate the production of the fluorinated intermediate product. When large excess of potassium fluoride is utilized for the process, the cost is increased as well as the separation and purification of the final product (DCFA) becomes cumbersome. Further, purification procedures conventionally followed result in product losses thereby further reducing the yield. It is desirable to increase the yield of the fluorinated product obtained by the potassium fluoride treatment, by minimal utilization of potassium fluoride during the process of synthesis of DCFA and by minimizing the product losses during purification procedures.
Objects of the invention

One object of the invention is to provide a process for high yield synthesis of 2,4-dichloro-5-fluoro acetophenone (DCFA)

Another object of the invention is to provide a process for synthesis of DCFA wherein the fluorination step is carried out by highly active potassium fluoride.

Yet another object of the invention is to provide a process wherein the synthesis of DCFA is carried out by using potassium fluoride obtained from potassium chloride.

A further object of the invention is to minimize the losses during procedures for purification of DCFA.

Summary of the invention

The above objects are realized by a process for synthesis of 2,4-dichloro-5-fluoro acetophenone (DCFA), the process comprising first reacting 3,4-dichloronitrobenzene with potassium fluoride having bulk density in the range of 0.2 to 1.0, to form a fluorinated intermediate product, then reacting the intermediate product with chlorine to form dichlorofluorobenzene and finally acylating dichlorofluorobenzene using an acylating agent followed by purification and enrichment of DCFA by melt crystallization from the mother liquor.

Detailed Description

Accordingly the invention provides a process for synthesis of 2,4-dichloro-5-fluoro acetophenone (DCFA)

In one embodiment, the invention provides a process for synthesis of 2,4-dichloro-5-fluoro acetophenone (DCFA), the process comprising first reacting 3,4-dichloronitrobenzene with
potassium fluoride having bulk density in the range of 0.2 to 1.3, to form a fluorinated intermediate product, then reacting the intermediate product with chlorine to form dichlorofluorobenzene and finally acylating dichlorofluorobenzene using an acylating agent to form a mixture containing DCFA along with impurities, followed by purification and enrichment of DCFA in the mixture by melt crystallization.

In another embodiment, the invention provides a process for synthesis of 2,4-dichloro-5-fluoro acetophenone (DCFA), the process comprising first reacting 3,4-dichloronitrobenzene with potassium fluoride having bulk density in the range of 0.2 to 1.3, to form a fluorinated intermediate product, then reacting the intermediate product with chlorine to form dichlorofluorobenzene and finally acylating dichlorofluorobenzene using an acylating agent to form a mixture containing DCFA along with impurities, followed by purification and enrichment of DCFA in the mixture by melt crystallization wherein the potassium fluoride has a bulk density in the range of 0.2 to 0.5.

In another embodiment, the invention provides a process for synthesis of 2,4-dichloro-5-fluoro acetophenone (DCFA), the process comprising first reacting 3,4-dichloronitrobenzene with potassium fluoride having bulk density in the range of 0.2 to 1.3, to form a fluorinated intermediate product, then reacting the intermediate product with chlorine to form dichlorofluorobenzene and finally acylating dichlorofluorobenzene using an acylating agent to form a mixture containing DCFA along with impurities, followed by purification and enrichment of DCFA in the mixture by melt crystallization wherein potassium fluoride is used in the first reaction in an amount not greater than 20% in excess of the stoichiometric amount of potassium fluoride required for the reaction.

In another embodiment, the invention provides a process for synthesis of 2,4-dichloro-5-fluoro acetophenone (DCFA), the process comprising first reacting 3,4-dichloronitrobenzene with potassium fluoride having bulk density in the range of 0.2 to 1.3, to form a fluorinated intermediate product, then reacting the intermediate product with chlorine to form dichlorofluorobenzene and finally acylating dichlorofluorobenzene using an acylating agent to form a mixture containing DCFA along with impurities, followed by purification and enrichment of DCFA in the mixture by melt crystallization wherein potassium fluoride is used in the first reaction in an amount not greater than 20% in excess of the stoichiometric amount of potassium fluoride required for the reaction.
enrichment of DCFA in the mixture by melt crystallization wherein potassium fluoride is synthesized from potassium chloride generated in the first reaction.

In another embodiment, the invention provides a process for synthesis of 2,4-dichloro-5-fluoro acetophenone (DCFA), the process comprising first reacting 3,4-dichloronitrobenzene with potassium fluoride having bulk density in the range of 0.2 to 1.3, to form a fluorinated intermediate product, then reacting the intermediate product with chlorine to form dichlorofluorobenzene and finally acylating dichlorofluorobenzene using an acylating agent to form a mixture containing DCFA along with impurities, followed by purification and enrichment of DCFA in the mixture by melt crystallization wherein the melt crystallization is carried out, in a first crystallisation stage comprising charging the mixture in a crystallizer, cooling the mixture in the crystalliser, seeding the cold mixture by pure crystalline DCFA to form first purified crystals and a first mother liquor, melting the first purified crystals at a temperature above a predetermined temperature, reducing the temperature of the melt to form second purified crystals and a second mother liquor, separating the second purified crystals and the second mother liquor, slowly increasing the temperature of the second purified crystals to sweating temperature and allowing the second mother liquor to sweat off from the second purified crystals and combining the first mother liquor and the second mother liquor to form a fresh mother liquor, the melt crystallisation being continued in a further crystallization stage comprising forming further purified crystals and a further mother liquor, melting of the further purified crystals, separating the further purified crystals from the further mother liquor, slowly increasing the temperature of the further purified crystals to sweating temperature and allowing the further mother liquor to sweat off from the further purified crystals and forming further fresh mother liquor(s), till DCFA crystals are obtained in the desired yield.

In another embodiment, the invention provides a process for synthesis of 2,4-dichloro-5-fluoro acetophenone (DCFA), the process comprising first reacting 3,4-dichloronitrobenzene with potassium fluoride having bulk density in the range of 0.2 to 1.3, to form a fluorinated intermediate product, then reacting the intermediate product with chlorine to form dichlorofluorobenzene and finally acylating dichlorofluorobenzene using an acylating agent
to form a mixture containing DCFA along with impurities, followed by purification and enrichment of DCFA in the mixture by melt crystallization wherein the melt crystallization is carried out, in a first crystallisation stage comprising charging the mixture in a crystallizer, cooling the mixture in the crystallizer at a temperature in the range of about 0°C to -30°C, seeding the cold mixture by pure crystalline DCFA to form first purified crystals and a first mother liquor, melting the first purified crystals at a temperature above a predetermined temperature, reducing the temperature of the melt to form second purified crystals and a second mother liquor, separating the second purified crystals and the second mother liquor, slowing increasing the temperature of the second purified crystals to sweating temperature and allowing the second mother liquor to sweat off from the second purified crystals and combining the first mother liquor and the second mother liquor to form a fresh mother liquor, the melt crystallisation being continued in a further crystallization stage comprising forming further purified crystals and a further mother liquor, melting of the further purified crystals, separating the further purified crystals from the further mother liquor, slowing increasing the temperature of the further purified crystals to sweating temperature and allowing the further mother liquor to sweat off from the further purified crystals and forming further fresh mother liquor(s), till DCFA crystals are obtained in the desired yield.

In another embodiment, the invention provides a process for synthesis of 2,4-dichloro-5-fluoro acetophenone (DCFA), the process comprising first reacting 3,4-dichloronitrobenzene with potassium fluoride having bulk density in the range of 0.2 to 1.3, to form a fluorinated intermediate product, then reacting the intermediate product with chlorine to form dichlorofluorobenzene and finally acylating dichlorofluorobenzene using an acylating agent to form a mixture containing DCFA along with impurities, followed by purification and enrichment of DCFA in the mixture by melt crystallization wherein the melt crystallization is carried out, in a first crystallisation stage comprising charging the mixture in a crystallizer, cooling the mixture in the crystallizer at a temperature in the range of about -12°C to -15°C, seeding the cold mixture by pure crystalline DCFA to form first purified crystals and a first mother liquor, melting the first purified crystals at a temperature above a predetermined temperature, reducing the temperature of the melt to form second purified
crystals and a second mother liquor, separating the second purified crystals and the second mother liquor, slowly increasing the temperature of the second purified crystals to sweating temperature and allowing the second mother liquor to sweat off from the second purified crystals and combining the first mother liquor and the second mother liquor to form a fresh mother liquor, the melt crystallisation being continued in a further crystallization stage comprising forming further purified crystals and a further mother liquor, melting of the further purified crystals, separating the further purified crystals from the further mother liquor, slowly increasing the temperature of the further purified crystals to sweating temperature and allowing the further mother liquor to sweat off from the further purified crystals and forming further fresh mother liquor(s), till DCFA crystals are obtained in the desired yield.

In another embodiment, the invention provides a process for synthesis of 2,4-dichloro-5-fluoro acetophenone (DCFA), the process comprising first reacting 3,4-dichloronitrobenzene with potassium fluoride having bulk density in the range of 0.2 to 1.3, to form a fluorinated intermediate product, then reacting the intermediate product with chlorine to form dichlorofluorobenzene and finally acylating dichlorofluorobenzene using an acylating agent to form a mixture containing DCFA along with impurities, followed by purification and enrichment of DCFA in the mixture by melt crystallization wherein the melt crystallization is carried out, in a first crystallisation stage comprising charging the mixture in a crystallizer, cooling the mixture in the crystalliser, seeding the cold mixture by pure crystalline DCFA to form first purified crystals and a first mother liquor, melting the first purified crystals at a temperature above 20°C, reducing the temperature of the melt to form second purified crystals and a second mother liquor, separating the second purified crystals and the second mother liquor, slowly increasing the temperature of the second purified crystals to sweating temperature and allowing the second mother liquor to sweat off from the second purified crystals and combining the first mother liquor and the second mother liquor to form a fresh mother liquor, the melt crystallisation being continued in a further crystallization stage comprising forming further purified crystals and a further mother liquor, melting of the further purified crystals, separating the further purified crystals from the further mother liquor, slowly increasing the temperature of the further purified crystals
to sweating temperature and allowing the further mother liquor to sweat off from the further purified crystals and forming further fresh mother liquor(s), till DCFA crystals are obtained in the desired yield.

In another embodiment, the invention provides a process for synthesis of 2,4-dichloro-5-fluoro acetophenone (DCFA), the process comprising first reacting 3,4-dichloronitrobenzene with potassium fluoride having bulk density in the range of 0.2 to 1.3, to form a fluorinated intermediate product, then reacting the intermediate product with chlorine to form dichlorofluorobenzene and finally acylating dichlorofluorobenzene using an acylating agent to form a mixture containing DCFA along with impurities, followed by purification and enrichment of DCFA in the mixture by melt crystallization wherein the melt crystallization is carried out, in a first crystallisation stage comprising charging the mixture in a crystallizer, cooling the mixture in the crystalliser, seeding the cold mixture by pure crystalline DCFA to form first purified crystals and a first mother liquor, melting the first purified crystals at a temperature above a predetermined temperature, reducing the temperature of the melt to -8°C or less to form second purified crystals and a second mother liquor, separating the second purified crystals and the second mother liquor, slowly increasing the temperature of the second purified crystals to sweating temperature and allowing the second mother liquor to sweat off from the second purified crystals and combining the first mother liquor and the second mother liquor to form a fresh mother liquor, the melt crystallisation being continued in a further crystallization stage comprising forming further purified crystals and a further mother liquor, melting of the further purified crystals, separating the further purified crystals from the further mother liquor, slowly increasing the temperature of the further purified crystals to sweating temperature and allowing the further mother liquor to sweat off from the further purified crystals and forming further fresh mother liquor(s), till DCFA crystals are obtained in the desired yield.

In another embodiment, the invention provides a process for synthesis of 2,4-dichloro-5-fluoro acetophenone (DCFA), the process comprising first reacting 3,4-dichloronitrobenzene with potassium fluoride having bulk density in the range of 0.2 to 1.3, to form a fluorinated intermediate product, then reacting the intermediate product with
chlorine to form dichlorofluorobenzene and finally acylating dichlorofluorobenzene using an acylating agent to form a mixture containing DCFA along with impurities, followed by purification and enrichment of DCFA in the mixture by melt crystallization wherein the melt crystallization is carried out, in a first crystallisation stage comprising charging the mixture in a crystallizer, cooling the mixture in the crystalliser, seeding the cold mixture by pure crystalline DCFA to form first purified crystals and a first mother liquor, melting the first purified crystals at a temperature above a predetermined temperature, reducing the temperature of the melt to form second purified crystals and a second mother liquor, separating the second purified crystals and the second mother liquor, slowly increasing the temperature of the second purified crystals to sweating temperature and allowing the second mother liquor to sweat off from the second purified crystals and combining the first mother liquor and the second mother liquor to form a fresh mother liquor, the melt crystallisation being continued in a further crystallization stage comprising forming further purified crystals and a further mother liquor, melting of the further purified crystals, separating the further purified crystals from the further mother liquor, slowly increasing the temperature of the further purified crystals to sweating temperature and allowing the further mother liquor to sweat off from the further purified crystals and forming further fresh mother liquor(s), till DCFA crystals are obtained in the desired yield, wherein the mother liquor is sweated off the purified crystals at a temperature in the range of 30 to 40°C.

In another embodiment, the invention provides a process for synthesis of 2,4-dichloro-5-fluoro acetophenone (DCFA), the process comprising first reacting 3,4-dichloronitrobenzene with potassium fluoride having bulk density in the range of 0.2 to 1.3, to form a fluorinated intermediate product, then reacting the intermediate product with chlorine to form dichlorofluorobenzene and finally acylating dichlorofluorobenzene using an acylating agent to form a mixture containing DCFA along with impurities, followed by purification and enrichment of DCFA in the mixture by melt crystallization wherein the melt crystallization is carried out, in a first crystallisation stage comprising charging the mixture in a crystallizer, cooling the mixture in the crystalliser, seeding the cold mixture by pure crystalline DCFA to form first purified crystals and a first mother liquor, melting
the first purified crystals at a temperature above a predetermined temperature, reducing the
temperature of the melt to form second purified crystals and a second mother liquor,
separating the second purified crystals and the second mother liquor, slowly increasing the
temperature of the second purified crystals to sweating temperature and allowing the
second mother liquor to sweat off from the second purified crystals and combining the first
mother liquor and the second mother liquor to form a fresh mother liquor, the melt
crystallisation being continued in a further crystallization stage comprising forming further
purified crystals and a further mother liquor, melting of the further purified crystals,
separating the further purified crystals from the further mother liquor, slowly increasing
the temperature of the further purified crystals to sweating temperature and allowing the
further mother liquor to sweat off from the further purified crystals and forming further
fresh mother liquor(s), till DCFA crystals are obtained in the desired yield wherein the
mother liquor is sweated off the purified crystals at a temperature in the range of 33 to 34°C

The synthesis of dichlorofluorobenzene from 4-fluoro-3-chloro nitrobenzene is carried out
by following the procedure in US5227545A which is herein incorporated by reference.

The fluorinated intermediate product in the process of the invention is prepared by the
procedure as illustrated in examples 1 to 8. Further, the acylation of DCFB is carried out by
the procedure illustrated in examples 9 to 13.
The reaction scheme leading to the production of DCFA from PNCB is illustrated below.

The invention provides a process for obtaining DCFA in high purity and yield. The process of the invention uses potassium fluoride having a bulk density in the range of 0.2 to 1.3. Advantageously, potassium fluoride used in the process of the invention has a bulk density in the range of 0.2 to 0.5. More advantageously, the density of potassium fluoride is 0.5 g/cc. The potassium fluoride used in the process of the invention is obtained either from potassium fluoride that is commercially available or from potassium fluoride that is generated from the potassium chloride by-product formed during the potassium fluoride treatment. Advantageously, the potassium fluoride has a moisture content in the range of 200 to 3000 ppm. More advantageously, the moisture content of potassium fluoride is less than 600 ppm. The process of fluorination is advantageously carried out in the presence of a phase transfer catalyst. More advantageously, the phase transfer catalyst concentration is in the range of 0.1 to 10 % w/w. Still more advantageously, the phase transfer catalyst concentration is 3%. The fluorination is usually carried out in DMSO solvent, onium salt could be chosen from quaternary ammonium salt, quaternary phosphonium salt, quaternary phosphazenium salt and amidophosphonium salts. Some examples of onium salts are triethy dodecyl ammonium halide, trimethyl dodecyl halides, ethylmethyl dodecyl halides.
The hydrocarbon radical of the onium group can vary from C1 - C22 or a mixture thereof. The tetraalkylphosphonium salt of the present invention has a branched alkyl chain containing 9 or more carbon atoms in total. The branched alkyl chain containing 9 or more carbon atoms in total is preferably a branched alkyl chain containing 9 to 100 carbon atoms in total, more preferably a branched alkyl chain containing 12 to 50 carbon atoms in total, further preferably a branched alkyl chain containing 16 to 36 carbon atoms in total. If the tetraalkylphosphonium salt has a branched alkyl chain containing less than 9 carbon atoms in total, on the other hand.

Specific examples of the branched alkyl chain containing 9 or more carbon atoms in total include, for example, 2-butyloctyl group, 2-hexyldecy group, 2-octyldodecyl group, 2-decyltetradecyl group, 2-dodecylhexadecyl group, 2-tetradecyloctodecyl group, 2-hexadecylicosyl group, 3,5,5-trimethylhexyl group, 3,7-dimethyloctyl group, 3,7,11,15-tetramethylhexadecyl group and so forth. Preferred are branched alkyl chains branching at the 2-position such as 2-butyloctyl group, 2-hexyldecy group, 2-octyldodecyl group, 2-decyltetradecyl group, 2-dodecylhexadecyl group, 2-tetradecyloctodecyl group and 2-hexadecylicosyl group. 2-Hexadecylicosyl group is more preferred. Further, the alkyl group may have an unsaturated bond (double bond or triple bond) or a substituent such as an ester group, an amide group, an ether group or a phenylene group as a partial structure.

Some examples of phosphonium compounds are tetrapenyl phosphonium halide, ethyltriphenyl phosphonium halides or a mixture thereof. Some examples of amidophosphonium are tetrakis (dimethylamido)phosphonium halide, diethyl dimethylamidophosphonium halide etc. Example of Another group of catalyst can be chosen from guanidinium salt of the type, hexamethyl guanidinium halide, pentaethy methyl guanidinium halide, hexaethylguanidinium halides or with mixed substituents. The anion A- of the phase transfer catalyst can be chosen from halides, carbonates, sulphates, nitrate, acetates, phenolates, sulfides etc.

Advantageously, the DCNB: DMSO ratio is in the range of 1:0.3 to 1:5. More advantageously, the ratio is 1:0.6.
The acylation of dichlorofluorobenzene in the process of the invention is usually carried out by acetyl chloride. Advantageously, a DCFB: acetylchloride ratio (by w/w) of 1:0.4 to 1:1 is maintained during the acylation. More advantageously, the DCFB: acetyl chloride ratio is 1:0.55. DCFB: AlCl$_3$ ratio (by w/w) is advantageously maintained in the range of 1:1.5 to 1:2.2. More advantageously, the DCFB: AlCl$_3$ ratio is maintained at 1:1.8. The acetylation temperature is advantageously maintained in the range of 80° C to 130° C. More advantageously, the acetylation temperature is maintained in the range of 90-115° C. Still more advantageously, the acetylation temperature is maintained in the range of 110-115° C. The activation temperature during addition of acetyl chloride can vary from 10° C to 50° C, preferably in the range of 20° C to 40° C, more preferably in the range of 25-35° C. Further, the AlCl$_3$ built up in quenching water can vary from 8% AlCl$_3$ solution to 12% AlCl$_3$ solution.

The crude DCFA product prepared by the process of the invention can be extracted with halogenated solvents like ethylene dichloride, chlorobenzene. The concentration of the solvent may vary from 0 - 50% with respect to the starting material.

The process of the invention also involve purification of a mixture containing DCFA and impurities, by melt crystallization. The melt crystallization can include various crystallization stages involving introduction of impure DCFA into a crystallizer, cooling, seeding, separation of purified crystals and the mother liquor and slowly increasing the temperature of the purified crystals to sweating temperature. During sweating, the mother liquor adhered to the purified crystals are sweated off. Fresh DCFA crystals are formed from the mother liquor collected after each stage of crystallization and the crystals are separated from the fresh mother liquor formed during each time and sweated off to obtain highly pure DCFA crystals. Advantageously, the purified crystals are sweated off at a temperature in the range of 30 to 40° C. The melt crystallization is continued for enrichment of purified DCFA crystals till the desired yield of DCFA is obtained. Advantageously DCFA is obtained in a yield greater than 95%.

The invention is further illustrated by way of the following non-limiting examples.
Example 1: Fluorination of 3,4-dichloronitrobenzene (3,4-DCNB):

using KF in 10% excess
3,4-dichloronitrobenzene (150 g, 0.78 mol), Dimethylsulphoxide (97 gm) and Tetrabutylammonium Bromide (TBAB) (4.5 g, 3 %) was added in 1-lit round bottom flask fitted with a scraper blade and overhead stir. 70ml toluene was added and the reaction mixture was heated to 120-125 °C to remove water azeotropically. After removal of water significantly below 600 ppm level spray dried KF (49.84g, 0.858 mol) was added. Then the reaction mixture was heated to 180 °C for 5 hrs under intense stirring.
% Conversion = 99.26 % by GC
The reaction mixture was filtered to remove KCl and unreacted KF and was washed twice by 50ml DMSO. DMSO was recovered by distillation under reduced pressure to give brown colored 3-chloro, 4-fluoro nitrobenzene crude product as syrupy liquid (yield 129.7 g). The composition by GC % area is as follows.

% conversion by GC = 99.26 %
% product by GC method = 98.85 %
% unreacted DCNB = 0.743 %
% High boiler = 0.40 %

Examples-2: Fluorination of 3,4-dichloronitrobenzene (3,4-DCNB) using KF in 20% excess
3,4-dichloronitrobenzene (150 g, 0.78 mol), Dimethylsulphoxide (97 gm) and Tetrabutylammonium Bromide (TBAB) (4.5 g, 3 %) was added in 1-lit round bottom flask fitted with a scraper blade and overhead stir. 70ml toluene was added and the reaction mixture was heated to 120-125 °C to remove water azeotropically. After removal of water significantly below 700 ppm level spray dried KF (54.28 g, 0.936mol) was added. Then the reaction mixture was heated to 180 °C for 5 hrs under intense stirring.
% Conversion = 99.31 % by GC
The reaction mixture was filtered to remove KCl and unreacted KF and was washed twice by 50ml DMSO. DMSO was recovered by distillation under reduced pressure to give brown colored 3-chloro, 4-fluoro nitrobenzene crude product as syrupy liquid (yield 127.9g). The composition by GC % area is as follows.

<table>
<thead>
<tr>
<th>% conversion by GC</th>
<th>99.31 %</th>
</tr>
</thead>
<tbody>
<tr>
<td>% product by GC method</td>
<td>98.13 %</td>
</tr>
<tr>
<td>% unreacted DCNB</td>
<td>0.59 %</td>
</tr>
<tr>
<td>% High boiler</td>
<td>1.23 %</td>
</tr>
</tbody>
</table>

Example-3: Fluorination of 3,4-dichloronitrobenzene (3,4-DCNB) using KF in 30% Excess

3,4-dichloronitrobenzene (150 g, 0.78 mol), Dimethylsulphoxide (97 gm) and Tetrabutylammonium Bromide (TBAB) (4.5 g, 3 %) was added in 1-lit round bottom flask fitted with a scraper blade and overhead stir. 70ml toluene was added and the reaction mixture was heated to 120-125 °C to remove water azeotropically. After removal of water significantly below 650 ppm level spray dried KF (58.81 g, 1.014mol) was added. Then the reaction mixture was heated to 180 °C for 5 hrs under intense stirring.

% Conversion = 99.43 % by GC

The reaction mixture was filtered to remove KCl and unreacted KF and was washed twice by 50ml DMSO. DMSO was recovered by distillation under reduced pressure to give brown colored 3-chloro, 4-fluoro nitrobenzene crude product as syrupy liquid (yield 128.9 g). The composition by GC % area is as follows.

<table>
<thead>
<tr>
<th>% conversion by GC</th>
<th>99.43 %</th>
</tr>
</thead>
<tbody>
<tr>
<td>% product by GC method</td>
<td>97.12 %</td>
</tr>
<tr>
<td>% unreacted DCNB</td>
<td>0.51 %</td>
</tr>
<tr>
<td>% High boiler</td>
<td>2.26 %</td>
</tr>
</tbody>
</table>
Examples-4: Fluorination of 3,4-dichloronitrobenzene (3,4-DCNB) at high temperature

3,4-dichloronitrobenzene (150 g, 0.78 mol), Dimethylsulphoxide (97 gm) and Tetrabutylammonium Bromide (TBAB) (4.5 g, 3 %) was added in 1-lit round bottom flask fitted with a scraper blade and overhead stir. 70ml toluene was added and the reaction mixture was heated to 120-125 °C to remove water azeotropically. After removal of water significantly below 700 ppm level spray dried KF (49.84g, 0.858mol, density < 0.8 g/cc) was added. Then the reaction mixture was heated to 200 °C for 5 hrs under intense stirring.

% Conversion = 99.73 % by GC

The reaction mixture was filtered to remove KCl and unreacted KF and was washed twice by 50ml DMSO. DMSO was recovered by distillation under reduced pressure to give brown colored 3-chloro, 4-fluoro nitrobenzene crude product as syrupy liquid (yield 130.1 g). The composition by GC % area is as follows.

% conversion by GC = 99.73 %
% product by GC method = 96.38 %
% unreacted DCNB = 0.23 %
% High boiler = 3.31%

Examples-5: Fluorination of 3,4-dichloronitrobenzene (3,4-DCNB) using excess of Solvent

3,4-dichloronitrobenzene (150 g, 0.78 mol), Dimethylsulphoxide (200 gm) and Tetrabutylammonium Bromide (TBAB) (4.5 g, 3 %) was added in 1-lit round bottom flask fitted with a scraper blade and overhead stir. 70ml toluene was added and the reaction mixture was heated to 120-125 °C to remove water azeotropically. After removal of water significantly below 600 ppm level spray dried KF (49.84g, 0.858mol) was added. Then the reaction mixture was heated to 180 °C for 5 hrs under intense stirring.

% Conversion = 98.94 % by GC

The reaction mixture was filtered to remove KCl and unreacted KF and was washed twice by 50ml DMSO. DMSO was recovered by distillation under reduced pressure to give
brown colored 3-chloro, 4-fluoro nitrobenzene crude product as syrupy liquid (yield 127.39 g). The composition by GC % area is as follows.

% conversion by GC = 98.94 %
% product by GC method = 98.17 %
% unreacted DCNB = 1.02 %
% High boiler = 0.67 %

Example 6: Synthesis of 4-fluoro-3-chloro nitrobenzene on a lab scale

3,4-dichloronitrobenzene (150 g, 0.78 mol), Dimethylsulphoxide (97 gm) and TetrabutylammoniumBromide (TBAB) (4.5 g, 3 %) were added in 1 liter round bottom flask fitted with a scraper blade and overhead stirrer. 70ml toluene was added and heated to 125°C to remove water from the reaction mixture azeotropically. After removal of water significantly below 700 ppm level spray dried KF (49.84g, 0.858 mol) was added. Then the reaction mixture was heated to 180°C for 5 hrs under intense stirring.

% Conversion = 99 % by GC

The reaction mixture was filtered to remove KCl and unreacted KF and was washed twice by 50ml DMSO. DMSO was distilled under reduced pressure to give brown colored 3-chloro-4-fluoronitrobenzene crude product as syrupy liquid (yield 129.7 g). The composition by GC % area is as follows.

% conversion by GC 99.3%
% product by GC method 97%
% unreacted DCNB 0.7%
% High boiler 3%

Example 7: Synthesis of 4-fluoro-3-chloro nitrobenzene from 3, 4-dichloronitobenzene on a plant scale using DMSO as solvent

The synthesis was carried out in a stainless steel reactor SS 316 was provided having diameter of 300 mm, height of 450 mm and possessing pitched blades diameter of 110 mm. The stainless steel reactor was also provided with variable speed motor and mechanical seal.
Into the stainless steel reactor, 6 kg of 3, 4-DCNB of specific gravity 1.45 was added and melted at a temperature of 42°C. To the molten 3, 4-DCNB, 3 liters of toluene and 4.2 kg of DMSO (DMSO level less than 0.65% of 3, 4-DCNB and water content less than 2000ppm) were added to obtain a reaction mass. The reaction mass was refluxed at a temperature of 120°C followed by the application of vacuum around 300 mm to 500 mm of Hg to remove moisture present in 3, 4-DCNB azeotropically. The vacuum was continued till the required moisture level of the reaction mass was less than 500 ppm. After removal of moisture from the reaction mass, 1.99 kg of spray dried potassium fluoride (bulk density less than 0.6) and 120 grams of catalyst (TBAB) were added and mixed properly at a temperature of 130°C to 140°C to obtain a reaction mixture. The moisture was again removed from the reaction mixture by vacuum distillation till the required moisture level of the reaction mixture was less than 350 ppm and finally distilling out the toluene completely from the reaction mixture. The reaction mixture was further heated to a temperature of 170°C to 185°C for 3 to 5 hrs. The sample reaction mixture was taken at every hour and checked on G.C for conversion of 3, 4-DCNB to 4-fluoro-3-chloro nitrobenzene. Heating of the reaction was stopped when about 96% or more of 3, 4-DCNB is converted to 4-fluoro-3-chloro nitrobenzene.

G.C Results: % product formation was around 85 % and Unreacted starting material 8 % & 7% byproduct.

**Example 8: Synthesis of 4-fluoro-3-chloro nitrobenzene from 3, 4-dichloronitobenzene on a plant scale using DMSO and acetone as solvents.**

The synthesis was carried out in a stainless steel reactor SS 316 was provided having diameter of 300 mm, height of 450 mm and possessing pitched blades diameter of 110 mm. The stainless steel reactor was also provided with variable speed motor and mechanical seal. Into the stainless steel reactor, 6 kg of 3, 4-DCNB of specific gravity 1.45 was melted at a temperature of 42°C. To the molten 3, 4-DCNB, 3 liters of toluene and 4.2 kg of DMSO (DMSO level less than 0.65% of 3, 4-DCNB and water content less than 2000ppm) were added to obtain the reaction mass. The reaction mass was refluxed at a temperature of 120°C followed by the application of vacuum around 300 mm to 500 mm of Hg to remove...
moisture present in 3, 4-DCNB azeotropically. The vacuum was continued till the required moisture level of the reaction mass was less than 500 ppm. The reaction mass of 3, 4-DCNB and DMSO mixture was carefully filled in an air tight container and kept under nitrogen pressure. In same stainless steel reactor, 2 kg of KF and 1.5 liters of acetone was taken and mixed to obtain a second reaction mass. The second reaction mass was heated at a temperature of 90°C to remove acetone. At the end, vacuum of around 730 mm of Hg was applied to the second reaction mass. The second reaction mass was heated till it was completely dry and heating was continued for one hour. The reaction mass of 3, 4-DCNB and DMSO mixture was added to the second reaction followed by addition of 120 grams of catalyst (TBAB) to obtain a reaction mixture. The reaction mixture was heated to a temperature of 130°C to 140°C. The moisture is again removed from the reaction mixture by vacuum distillation till the required moisture level of the reaction mixture was less than 350 ppm and finally distilling out the toluene completely from the reaction mixture. The reaction mixture was further heated to a temperature of 170°C to 185°C for 3 to 5 hrs. The sample reaction mixture was taken at every hour and checked on G.C for conversion of 3, 4-DCNB to 4-fluoro-3-chloro nitrobenzene. Heating of the reaction mixture was stopped when about 95% or more of 3, 4-DCNB is converted to 4-fluoro-3-chloro nitrobenzene.

Example 9: Synthesis of 2, 4-dichloro-5-fluoro acetophenone (DCFA) from 2, 4-dichloro Fluorobenzene (DCFB)

Into a four necked RB flask of 1 L capacity equipped with an over head stirrer, a glass condenser and an addition funnel, 250 gm (1.5 mol) DCFB and 297 gm (2.22 mol) AlCl3 were added and the suspension was stirred at 30-35°C. Then 125 gm (1.57 mol) acetyl chloride was added drop wise within two hours maintaining the temperature at 30-35°C. After complete addition of acetyl chloride, the mixture was heated quickly to 110-120°C for 5-6 hrs. The reaction kinetics was monitored by taking samples every two hrs. After the reaction was stopped the crude reaction mixture was cooled to ambient temperature. Then the mixture was quenched using 1 kg of ice and 500 ml water maintaining the temperature below 50°C. The organic layer thus formed was extracted with 200 ml of DCM thrice and combined all the extracts for evaporation. After evaporation of DCM, 297.5g of brown product was obtained with the following composition.
% conversion of DCFB by GC area = 75% (25% DCFB as solvent)
DCFA = 67%
% selectivity = 92%
% Isomer by GC method = 4.5%
% DCFB = 25%
% HB = 3%

Example 10: Preparation of 2, 4-dichloro-5-fluoro acetophenone (DCFA) from 2, 4-dichloro Fluorobenzene (DCFB) using 5% excess of Acetyl Chloride

Into a four necked RB flask of 1-lit capacity equipped with over head stirrer, a glass condenser and addition funnel, DCFB (250 g, 1.51 mol) and AlCl3 (297 g, 2.22 mol) were added. The suspension was stirred at room temperature. Acetyl chloride (125 g, 1.60 mol) was added drop wise within two hours by maintaining the temperature 30-35°C. After complete addition of acetyl chloride the mixture was quickly heated to 110-120°C for 5-6 hrs. The reaction kinetics was monitored by taking samples every two hrs. After the reaction was stopped the crude reaction mixture was cooled to ambient temperature. Then the reaction mixture was quenched using 1 kg ice and 500 ml water maintaining the temperature below 50°C. The aqueous layer thus obtained was extracted with 200 ml of DCM thrice and combined all the extracts for evaporation. After the evaporation of DCM, 294.5g of brown product was obtained with the following composition.

% Conversion of DCFB by GC = 75% (25% DCFB as solvent)
% DCFA = 67%
% Selectivity by GC = 92%
% Isomer = 4.5%
% DCFB = 25%
% H. B. = 03%

Example 11: Preparation of 2, 4-dichloro-5-fluoro acetophenone (DCFA) from 2, 4-dichloro Fluorobenzene (DCFB) using 15% excess of Acetyl Chloride
Into a four necked RB flask of 1-lit capacity equipped with over head stirrer, a glass condenser and addition funnel, DCFB (250 g, 1.51 mol) and AlCB (297 g, 2.22 mol) were added. The suspension was stirred at room temperature. Acetyl chloride (135.4 g, 1.73 mol) was added drop wise within two hours by maintaining the temperature 30-35°C. After complete addition of acetyl chloride the mixture was quickly heated to 110-120°C for 5-6 hrs. The reaction kinetics was monitored by taking samples every two hrs. After the reaction was stopped the crude reaction mixture was cooled to ambient temperature. Then the reaction mixture was quenched using 1 kg ice and 500 ml water maintaining the temperature below 50°C. The aqueous layer thus obtained was extracted with 200 ml of DCM thrice and combined all the extracts for evaporation. After the evaporation of DCM, 297.2g of brown product was obtained with the following composition.

| % Conversion of DCFB by GC | = 76.4 % (23.6% DCFB as solvent) |
| % DCFA                  | = 68.3 % |
| % Selectivity by GC     | = 91.8 % |
| % Isomer                | = 4.5 % |
| % DCFB                  | = 23.6 % |
| % H. B.                 | = 4.32 % |

**Example 12: Preparation of 2, 4-dichloro-5-fluoro acetophenone (DCFA) from 2, 4-dichloro Fluorobenzene (DCFB) using 10% excess of AlCl3**

Into a four necked RB flask of 1-lit capacity equipped with over head stirrer, a glass condenser and addition funnel, DCFB (250 g, 1.51 mol) and AlCl3 (322 g, 2.41 mol) were added. The suspension was stirred at room temperature. Acetyl chloride (125 g, 1.60 mol) was added drop wise within two hours by maintaining the temperature 30-35°C. After complete addition of acetyl chloride the mixture was quickly heated to 110-120°C for 5-6 hrs. The reaction kinetics was monitored by taking samples every two hrs. After the reaction was stopped the crude reaction mixture was cooled to ambient temperature. Then the reaction mixture was quenched using 1 kg ice and 500 ml water maintaining the
temperature below 50°C. The aqueous layer thus obtained was extracted with 200 ml of DCM thrice and combined all the extracts for evaporation. After the evaporation of DCM, 298.8g of brown product was obtained with the following composition.

% Conversion of DCFB by GC = 76% (24% DCFB as solvent)
% DCFA = 68.64%
% Selectivity by GC = 91.5%
% Isomer = 4.5%
% DCFB = 24%
% H. B. = 4.1%

Example 13: Preparation of 2, 4-dichloro-5-fluoro acetophenone (DCFA) from 2, 4-dichloro Fluorobenzene (DCFB) at low temperature

Into a four necked RB flask of 1-lit capacity equipped with over head stirrer, a glass condenser and addition funnel, DCFB (250 g, 1.51 mol) and AlCB (322 g, 2.41 mol) were added. The suspension was stirred at room temperature. Acetyl chloride (125 g, 1.60 mol) was added drop wise within two hours by maintaining the temperature 30-35°C. After complete addition of acetyl chloride the mixture was quickly heated to 80-85°C for 7-8 hrs. The reaction kinetics was monitored by taking samples every two hrs. After the reaction was stopped the crude reaction mixture was cooled to ambient temperature. Then the reaction mixture was quenched using 1 kg ice and 500 ml water maintaining the temperature below 50°C. The aqueous layer thus obtained was extracted with 200 ml of DCM thrice and combined all the extracts for evaporation. After the evaporation of DCM, 291.39g of brown product was obtained with the following composition.

% Conversion of DCFB by GC = 66% (34% DCFB as solvent)
% DCFA = 55.3%
% Selectivity by GC = 85%
% Isomer = 5.8%
% DCFB = 34%
Example 14: Melt Crystallization of 2, 4-dichloro-5-fluoroacetophenone (DCFA)

DCFA synthesized by example 4 was subjected to melt crystallization. As the product is obtained from the crystallizer the first eutectic mixture comprising DCFB is distilled followed by a part of the distillate being added to the next batch of the feed and another part being used as raw material in the acylation step. The second eutectic mixture comprising a composition similar to the feed (crude mixture) is added to the next batch of feed. The product then obtained contains DCFA with 99% purity. Thus the product obtained is partially recycled and enhances the yield. Also as against prior art only a portion (about 20%) is subjected to elevated temperatures and thus decomposition and subsequent loss of DCFA is minimized. The process results in increase in yield of DCFA by about 6-8%.

Example 15: Purification of crude DCFA product in lab scale crystalliser

A crude product mixture containing DCFA 63gm, DCFB 26gm, DCFA isomer 5gm, higher boiler 5gm and tar 1gm was charged in a lab scale crystallizer at temperature 30°C in such a way that the inner tube is dipped significantly into the crude product mixture. The temperature of the liquid was slowly reduced to temperature below 4°C by circulating cool liquid and seeding was done with pure DCFA crystalline powder (0.5gm). Finally, the temperature was reduced to temperature -15°C and mixture was kept for 7 hours at -15°C for formation of significant amounts of crystal. The residual liquid was drained out after crystal formation was nearly complete. The crystals thus obtained were melted at temperature above 20°C and stored for recycle in the second batch. Similarly, second batch was conducted and the final melts of two batches were mixed together and charged at room temperature. Then the temperature was slowly reduced to 12°C and seeding was completed at this temperature. Finally the temperature was reduced to -8°C and crystallization was conducted for 7 hrs.

After completion of crystallization the mother liquor was drained out and the temperature of the inner tube was slowly increased to sweating temperature of about 34°C over a period of 10 hrs. The collected mother liquor was again recycled in consecutive batches. This process was repeated couple of times to obtain a yield of more than 50% by sweating. Further the
residual liquid was subjected to distillation at temperature not more than 90°C to remove DCFB and the crystallization was repeated to finally obtain more than 95% w/w yield of DCFA.

**Example 16: Purification of crude DCFA product in an SS crystallizer**

A crude mixture containing 73gm DCFA, 5gm DCFA-isomer, 18gm DCFB, 2gm high boiler and tar 2gm was charged in a SS crystallizer. The temperature of the liquid was brought down to 25°C by circulating cool liquid slowly and further seeding with DCFA crystals at the cooled temperature. After seeding, the temperature was slowly reduced to -15°C for 8hrs. Then the mother liquor was drained out at -15°C and the crystallizer was slowly heated to temperature about 33-34°C for sweating (3°C temperature raise every one hour). Finally the product with purity of 99.2%, containing DCFB 0.8% or less was obtained.

The process of the invention results in high yield synthesis of DCFA from PNCB. DCFA synthesized during the process is isolated and purified by melt crystallization from the mother liquor resulting in continuous enrichment of DCFA in the crystals that are repeatedly formed and by continuous removal of impurities.

Apart from enabling high yield synthesis of DCFA, the process of invention provides DCFA having high purity. Owing to the use of potassium fluoride in near stoichiometric quantities (not greater than 20% in excess of the stoichiometric quantity), residual potassium fluoride is minimized and thereby contamination of the product is reduced. This enables easier separation and purification of DCFA. Further, DMSO used during the potassium fluoride treatment can be recovered and reused with reduced water content. Furthermore, the reaction waste is reduced and process efficiency is increased leading to overall reduction in the cost. During the process of the invention, the decomposition of DCFA is avoided. Further, the purification procedures as followed in the method of the invention is simple, cheaper and high yield producing, compared to purification procedures conventionally followed.
While considerable emphasis has been placed herein on the particular features of the preferred embodiment and the improvisation with regards to it, it will be appreciated the various modifications can be made in the preferred embodiments without departing from the principles of the invention. These and the other modifications in the nature of the invention will be apparent to those skilled in art from disclosure herein, whereby it is to be distinctly understood that the foregoing descriptive matter is to interpreted merely as illustrative of the invention and not as a limitation.
Claims:

1. A process for synthesis of 2,4-dichloro-5-fluoro acetophenone (DCFA), the process comprising first reacting 3,4-dichloronitrobenzene with potassium fluoride having bulk density in the range of 0.2 to 1.3, to form a fluorinated intermediate product, then reacting the intermediate product with chlorine to form dichlorofluorobenzene and finally acylating dichlorofluorobenzene using an acylating agent to form a mixture containing DCFA along with impurities, followed by purification and enrichment of DCFA in the mixture by melt crystallization.

2. The process as claimed in claim 1 wherein the potassium fluoride has a bulk density in the range of 0.2 to 0.5.

3. The process as claimed in anyone of the claims 1 and 2 wherein the melt crystallization is carried out, in a first crystallisation stage comprising charging the mixture in a crystallizer, cooling the mixture in the crystalliser, seeding the cold mixture by pure crystalline DCFA to form first purified crystals and a first mother liquor, melting the first purified crystals at a temperature above a predetermined temperature, reducing the temperature of the melt to form second purified crystals and a second mother liquor, separating the second purified crystals and the second mother liquor, slowly increasing the temperature of the second purified crystals to sweating temperature and allowing the second mother liquor to sweat off from the second purified crystals and combining the first mother liquor and the second mother liquor to form a fresh mother liquor.

4. The process as claimed in claim 3 wherein the melt crystallization is continued, with the fresh mother liquor, in a further crystallization stage.

5. The process as claimed in claim 3 wherein the further crystallization stage comprise forming further purified crystals and a further mother liquor, melting of the further purified crystals, separating the further purified crystals from the further mother liquor, slowly increasing the temperature of the further purified
crystals to sweating temperature and allowing the further mother liquor to sweat off from the further purified crystals.

6. The process as claimed in anyone of the claims 3 to 5 wherein the mixture is cooled at a temperature in the range of around 0°C to -30°C

7. The process as claimed in anyone of the claims 3 to 6 wherein the mixture is cooled at a temperature in the range of around -12°C to -15°C

8. The process as claimed in anyone of the claims 3 to 7 wherein the first purified crystals are melted at a temperature above 20°C

9. The process as claimed in anyone of the claims 3 to 7 wherein the second purified crystals are formed at a temperature not greater than -8°C.

10. The process as claimed in anyone of the claims 3 to 9 wherein the mother liquor is sweated off the purified crystals at a temperature in the range of 30 to 40°C.

11. The process as claimed in anyone of the claims 3 to 10 wherein the mother liquor is sweated off the purified crystals at a temperature in the range of 33 to 34°C

12. The process as claimed in anyone of the claims 3 to 11 wherein DCFA crystals are obtained in a yield greater than 95%