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(54) Title: CONTINUOUS FLOW LIQUID PHASE NITRATION OF ALKYL BENZENE COMPOUNDS

(57) Abstract: The invention discloses a process for continuous flow of liquid phase nitration of alkyl benzene compounds in micro-mixer and tubular reactors with better control on the product profile which comprises reacting alkyl benzene compounds with nitrating agent at a temperature range of 10 to 60 deg C.

CONTINUOUS FLOW LIQUID PHASE NITRATION OF ALKYL BENZENE COMPOUNDS

FIELD OF THE INVENTION

The invention relates to a process for continuous flow liquid phase nitration of aromatic compounds. More particularly, the invention relates to continuous flow liquid phase nitration of alkyl benzene compounds.

BACKGROUND AND PRIOR ART OF THE INVENTION

Usually nitration of organic compounds are carried out with nitric acid or nitrating acid. Nitrating acid is a colorless to light yellow or gray to reddish brown mixture of undefined stoichiometric composition of sulfuric acid and nitric acid that may generally contain some amount of dissolved sulfur trioxide (http://cameochemicals.noaa.gov/chemical/7197). The nitration agent comprises at least one nitrogen compound which is able to release the electrophilic nitryl cation (N02)+ which is deemed to be the true nitration agent (comp. Nitration, Methods and Mechanisms, Series: Organic Nitro Chemistry Series, Olah, G. A., Malhotra, R., Narang, S. C, Verlag VCH, Weinheim 1989).

Selectivity is a primary challenge in nitration reactions because usually the nitrating agent is used in excess and hence more than one nitro-derivative of the respective substrate are obtained, which affect the process viability. The undesired products thus obtained act as contaminants arid reduces the yield and purity of the desired ones. Accordingly, it is desirable to design synthetic approach that yields better selectivity of the desired isomer for example, by controlling the reaction conditions.

Aromatic and hetero aromatic compounds can be easily nitrated and often it is difficult to obtain selective introduction of only one nitro group. Hence this poses a great challenge in selective nitration of the benzene rings to yield desired isomer.

Conventionally, the aromatic nitration is a prolonged reaction that is carried out at very low temperatures predominantly using nitrating mixture comprising of concentrated nitric acid and sulfuric acid. Such processes result in mixtures of both required and non-required isomers. From this aggregated pool the required isomers has to be retrieved by employing separation methods, such as distillation, fractional crystallization; selective precipitation or chromatographic purifications etc. that adds additional cost to manufacturing process.

Further, unsubstituted aromatic compounds like benzene and naphthalene show relatively less reactivity and hence slowly react with a nitration agent which results in low yields.

The batch processes being used till now for nitration of aromatic compounds have certain limitations like long reaction time, energy, poor yields, undesired isomers, effluents, excess cost etc. which pose a constant need for improved process for nitration of aromatic compounds which have wider applications. Continuous flow synthesis could be an option but presently, there is no known continuous flow liquid phase synthesis that is feasible for nitration of aromatic compounds.

Hence the inventors have come up with a novel methodology for continuous flow liquid phase nitration which overcomes the limitations of prior art methods and provides an easy, facile, time- saving, energy efficient, environmental friendly process to synthesize nitrated alkyl benzene compounds including o-xylene with good selectivity. 4-nitro-o-xylene is known to have various applications including vitamin B12 synthesis.

OBJECTS OF THE INVENTION

The main object of the invention is to provide a process for continuous flow liquid phase nitration of alkyl benzene compounds.

Another object of the present invention is to provide a process of continuous flow liquid phase nitration of alkyl benzene compounds including o-xylene with better control on the product profile.

Another object of the present invention is to provide a process of liquid phase nitration of alkyl benzene which reduces the reaction time, zero effluent process, easily manageable and can be operated at lower temperature thus conserving time and energy.

SUMMARY OF THE INVENTION

Accordingly, the present invention provides a process for continuous flow of liquid phase nitration of alkyl benzene compounds in micromixer and tubular reactors comprising reacting alkyl benzene compounds with nitrating agent at a temperature in the range of 10 to 60 deg C for a period in the range of 30 sec to 30 min at atmospheric pressure to obtain nitro alkyl benzene.

In one embodiment of the present invention the alkyl benzene compounds are selected from the group consisting of toluenes, Xylenes, halogenated alkyl benzenes, cresols and their substituted derivatives.

In an embodiment of the present invention the alkyl benzene compound used is o-xylene.

In another embodiment of the present invention the nitrating agent is selected from the group consisting of standard nitrating mixture (HN03: H2S04 = 40: 60), volumetric nitrating mixture (HN03: H2S04 = 50: 50) and fuming nitric acid.

Still in another embodiment of the present invention stoichiometric ratio of nitrating agent to the aromatic substrate is in the range of 1:1 to 10: 1.

Still in another embodiment of the present invention conversion of 0-xylene is in the range of 98 - 100%.

Still in another embodiment of the present invention yield of 4-nitro-o-xylene is in the range of 45 to 71 %.

DETAILED DESCRIPTION OF FIGURES:

Figure 1 depicts a typical experimental setup for continuous flow nitration of alkyl benzene compounds.

DETAILED DESCRIPTION OF THE INVENTION

To overcome the limitations of the prior art in producing nitrated alkyl benzene compounds, the current invention discloses a methodology for continuous flow liquid phase nitration of alkyl benzene compounds.

The invention discloses a process for continuous flow of liquid phase nitration of alkyl benzene compounds in micromixer and tubular reactors with better control on the product profile comprising reacting alkyl benzene compounds with nitrating agent at a temperature range of 10 to 60 deg C.

The continuous flow liquid phase nitration of alkyl benzene compounds according to the invention that may advantageously be carried out in any continuous reactor including metal reactors with high heat transfer co-efficient. The experimental setup according to the invention consists of two syringe pumps (Longer Pumps) for pumping the nitrating agent and alkyl benzene compounds to a micromixer (1ml) followed by a residence time unit. The residence time unit was made of 5 parts connected using a 4-way port for withdrawing a sample for analysis to track the reaction progress at different conditions. A constant temperature bath (Julabo, Germany) was used to maintain appropriate temperature.

A typical experimental setup used for continuous flow nitration according to the invention includes pumps for the dosing of reactants, a micromixer for the rapid and efficient mixing of these reactants, and a residence time unit, which may be either a microfluidic device with channels or a tube. The residence time unit is either immersed in a constant temperature bath. In an alternate setup the residence time unit has built-in cooling/heating systems to maintain a specific temperature. The schematic diagram of the set-up is shown in the Figure 1.

The effect of experimental parameters such as temperature (0 to 60°C), residence time (20 sec to 20 min), and nitric acid equivalents (1- 10 moles) has been investigated in the present invention. It was found that depending upon the nitrating agent and its mole ratio with the substrate, the reaction mixture was seen to be homogeneous as well as two-phase and hence the reaction regimes were different.

In an embodiment, it was observed that with the use of mixed acid nitrating agent (**$HNO3$** and H_2S0_4), at complete conversion of o-xylene, the product mixture consists of 3NOX (3-nitro-o-xylene) and 4 NOX (4-nitro-o-xylene) with the mole ratio ranging between 1.22 to 2.22 that results in more of 3NOX than the 4NOX.

However, in another embodiment, it was observed that the fuming nitric acid alone as the nitrating agent gave more yield of 4NOX than the 3NOX in less than 30 seconds residence time. Reaction being extremely exothermic and using fuming nitric acid in excess helps change the mechanism of nitration and thus avails more yield of 4NOX.

In the invention, the substrate (alkyl benzene compounds) is selected from the group consisting of toluenes, Xylenes, halogenated alkyl benzenes, cresols and their substituted derivatives etc. One preferred alkyl benzene substrate is o-xylene.

According to the invention different nitrating agents may be used to yield optimal results preferably selected from the group consisting of standard nitrating mixture ($HN0_3$: H_2S04 = 40:60), volumetric nitrating mixture (HNO_3: H_2S0_4 = 50: 50) and the fuming nitric acid.

The nitrating agent may be employed to the aromatic substrate in a stoichiometric ratio of 1:1 to 10:1 depending upon the desired isomer to be obtained.

In the invention, the reaction will be accomplished within 30 sec to 10 minutes depending upon the temperature and mole ratio of aromatic substrate to nitric acid as against the longer reaction periods of 4 to 8 hrs of the prior art processes. Therefore, the process of the present invention has the major advantage in time efficiency.The reaction temperature ranges from 10-60 deg C unlike 0 deg C as in the prior art processes, thus advantageous in terms of conserving energy.

The process gives a better control on the selectivity of 3-nitro-o-xylene and 4-nitro o-xylene. The process of the invention has better control on the product profile and the 4-nitro-o-xylene so produced has various applications including vitamin B12 synthesis. Yield of 4 nitro o-xylene obtained according to the process of the invention varies between 35% to 60%.It is zero effluent process when fuming nitric acid is used as nitrating agent.

The extent of conversion in any reaction depends upon the concentration of substrates, catalyst and the temperature. For the case of two phase reactions, additional effect of interfacial mass transfer followed by reaction is seen. In general, nitration carried out using mixed acids is catalyzed by the presence of sulfuric acid. It helps generation of nitronium ions and also abstracts water that gets generated in the nitration reaction. For the systems where only fuming nitric acid is used, it is an autocatalytic reaction where the excess fuming nitric acid acts as catalyst. Thus the rates of generation of nitronium ions in both the cases is different and thus governs the selectivity of isomers. Moreover aromatic nitration being exothermic it is necessary to have high heat removal rates that help avoid byproducts. In conventional approach of batch or semi-batch mode, reaction is done in a very slow manner (either by adding one of the reactants slowly to the other and by doing it at very low temperatures) to avoid generation of heat, which reduces the yield of the desired product. In the present invention, (i) use of fuming nitric acid that give s different rate for generation of nitronium ions, (ii) efficient micromixing followed by (iii) the reaction in a tubular reactor having very high heat transfer area helps to control the reaction temperature in a better manner and thus allows to achieve higher yield of the desired product at lower residence time and lower temperatures. For the case of nitrations using mixed acids, still the process can be improved by using micromixers followed by flow reactors so that one can achieve better yield.

The process of liquid phase nitration is easily manageable, facile and environmental friendly.4-nitro-o-xylene is an important raw material used for the synthesis of pharmaceutical intermediates. It is the important raw materials of the chemical synthesis for producing vitamin B_2 and it can be used for producing 3, 4-dimethyl-aniline.

Following examples are given by way of illustration therefore should not be construed to limit the scope of the invention.

EXAMPLES

The experiments were performed for the continuous flow nitration of o-xylene using different nitrating agents and later optimized for the highest yield at lab scale. A few batch experiments were also performed for benchmarking and comparison. The details of the experimental procedure are given as follows.

Experimental set-up and experimental procedure

O-xylene as well as the nitrating agent were maintained at room temperature in closed bottles. Two different nitrating mixtures containing sulphuric acid i.e. HN03: H2S04 = 40:60 (v/v) and 50:50 (v/v) were prepared at low temperature. Fuming nitric acid was used as it is (density = 1.5 g/cc) and was maintained at the room temperature in closed bottles. The composition of the organic phase was characterized by extracting the organic phase from quenched reaction mixture in another organic substrate viz. toluene, o-xylene etc. and then analysis by Gas Chromatography (HP-5 column).

Batch Experiment

1. Experiment was carried out by adding o-xylene to nitrating agent (a mixture of $HN0_3$ and H_2S0_4) at 0 °C. The mole ratio of o-xylene to nitric acid to sulphuric acid was 1:1:1. The addition time was 6 min and the reaction when monitored for 2 hours showed 14% conversion and 5% dinitro derivatives of o-xylene with 46% 3NOX (3-nitro-o-xylene) and 54% 4NOX (4-nitro-o-xylene) in the mononitro composition.

2. Experiment was carried out by adding 10 ml of o-xylene to nitrating agent (a mixture of **HNO3** and H_2SO_4) at 0°C. The mole ratio of o-xylene to nitric acid to sulphuric acid was 1:2:2. The addition time was 6 min and the reaction when monitored for 2 hours and 45 minutes showed 18% conversion and 4.2% dinitro derivatives of o-xylene with 47% 3NOX (3-nitro-o-xylene) and 53% 4NOX (4-nitro-o-xylene) in the mononitro composition.

3. Experiment was carried out by adding 10 ml of o-xylene to nitrating agent (a mixture of HNO_3 and H_2SO_4) at 0 °C. The mole ratio of o-xylene to nitric acid to sulphuric acid was 1:3:3. The addition time was 6 min and the reaction when monitored for 2 hours and 45 minutes showed 19% conversion and 3.9 % dinitro derivatives of o-xylene with 46% 3NOX(3-nitro-o-xylene) and 54% 4NOX (4-nitro-o-xylene) in the mononitro composition.

4. Experiment was carried out by adding 10 ml of o-xylene to fuming nitric acid as the nitrating agent at 0 °C. The mole ratio of o-xylene to fuming nitric acid was 1:1. The addition time was 1 min and the reaction when monitored for 2 hours showed 15% conversion and 1.9 % dinitro derivatives of o-xylene with 39% 3NOX (3-nitro-o-xylene) and 61% 4NOX (4-nitro-o-xylene) in the mononitro composition.

Example 1: Continuous flow experiments

Reaction of O-Xylene with nitrating mixture (60:40 v/v, 68% HNO_3 & H_2SO_4 respectively) was carried out with AmAR micro mixer followed by residence time tube. The collected samples were quenched with a fixed quantity of ice cold water (10 to 30 ml). A known quantity of toluene was used to extract the samples. To make samples free of residual nitric acid each sample was washed two times with water and then salt solution. Trace quantity of water was removed by passing organic phase from the bed of sodium sulphate penta hydrate. The samples were analyzed using gas chromatography with an HP5 capillary column and an FID detector.

Nitration of o-xylene with fuming nitric acid Continuous flow process

1. With 1:1 mole ratio of the o-xylene to fuming nitric acid, at 40°C, the conversion was only 46.7% with almost 9.3% dinitro products, 61.6% 3-NOX and 38.3% 4NOX at a residence time of 20 minutes.
2. With 1:2 mole ratio of the o-xylene to fuming nitric acid, at 40°C, the maximum conversion was 69% with selectivity of 8.1% dinitro products and 91.9% for mono-nitro derivatives at a residence time of 10 minutes. The mono-nitro isomers were seen to have a composition of 51.7% 3-NOX and 48.3% 4NOX.
3. With 1:3 mole ratio of the o-xylene to fuming nitric acid, at 40 °C, the maximum conversion was 97% with selectivity of 9.6% dinitro products and 90.4% for mono-nitro derivatives at a residence time of 10 minutes. The mono-nitro isomers were seen to have a composition of 49.6% 3-NOX and 50.4% 4NOX.
4. With 1:2 mole ratio of the o-xylene to fuming nitric acid, at 40°C, the maximum conversion was 83% with selectivity of 10.7% dinitro products and 89.3% for mono-nitro derivatives at a residence time of 20 minutes. The mono-nitro isomers were seen to have a composition of 47.5% 3-NOX and 52.5% 4NOX.
5. With 1:4 mole ratio of the o-xylene to fuming nitric acid, at 10°C, the conversion was 38%, 54% and 73% and selectivity of 8.3%, 7.47% and 8.73% dinitro products at a residence time of 0.5, 1 and 2 minutes, respectively. The mono-nitro isomers were seen to have a composition of 47.8% 3-NOX and 52.2% 4NOX.

6. With 1:4 mole ratio of the o-xylene to fuming nitric acid, at 20°C, the conversion was 96%, 98% and 99% and selectivity of 6.5%, 7.1% and 14.1% dinitro products at a residence time of 0.5, 1 and 2 minutes, respectively. The mono-nitro isomers were seen to have a composition of 51.4% to 52% 3-NOX and 47.9 to 52.2% 4NOX.

7. With 1:4 mole ratio of the o-xylene to fuming nitric acid, at 20 °C, the conversion was 99.6% and selectivity of 17.3% dinitro products at a residence time of 10 minutes. The mono-nitro isomers were seen to have a composition of 47.8% 3-NOX and 52.2% 4NOX.

8. With 1:4 mole ratio of the o-xylene to fuming nitric acid, at 30°C, the conversion was 98.6% and selectivity of 20.6% dinitro products at a residence time of 10 minutes. The mono-nitro isomers were seen to have a composition of 48.1% 3-NOX and 51.9% 4NOX.

9. With 1:6 mole ratio of the o-xylene to fuming nitric acid, at 10°C, the conversion was 98.7% and selectivity of 15.99 and 20.3% dinitro products at a residence time of 0.5 and 1 minutes, respectively. The mono-nitro isomers were seen to have a composition of 46.3% 3-NOX and 53.7% 4NOX.

10. With 1:10 mole ratio of the o-xylene to fuming nitric acid, at 0 °C, the conversion was 98.9% and selectivity of 45.3 and 48.5% dinitro products at a residence time of 0.5 and 1 minutes, respectively. The mono-nitro isomers were seen to have a composition of 28.7% to 34.3 % 3-NOX and 71.32 to 65.62% 4NOX, respectively.

11. With 1:4 mole ratio of the o-xylene to fuming nitric acid, at 20 °C, the conversion was 98.7% and selectivity of 4.3 and 3.9% dinitro products at a residence time of 0.33 and

0.94 minutes, respectively. The mono-nitro isomers were seen to have a composition of 52.4% 3-NOX and 47.3% 4NOX.

12. Upon carrying out the reaction in a ¼" o.d. SS316 tube at a residence time of 0.94 minutes, with 1:4 mole ratio of the o-xylene to fuming nitric acid, at 20 °C, the conversion was 98.9% and selectivity of 11.9% dinitro products. The mono-nitro isomers were seen to have a composition of 52.4% 3-NOX and 47.6% 4NOX.

Experiments were carried out with nitrating mixture comprising 50:50 (V\) ratio of HNO_3 and H_2SO_4.

These are the examples with mixed acids. The mole ratio mentioned in the examples is of the organic substrate and nitric acid. It has been mentioned that the nitrating mixture has 50:50 v/v ratio of nitric to sulfuric acid.

1. With 1:1 mole ratio of the o-xylene to nitric acid, with 20 minutes residence time, upon changing the temperature from 0 °C to 70 °C, the conversion increased from 3.3% to 77.8% and selectivity of dinitro products increased from 0.55% to 4.64%. The mono-nitro isomers were seen to have a composition of 53.4% to 59.8% 3-NOX and 40.25% to 46.7% 4NOX.
2. With 1:2 mole ratio of the o-xylene to nitric acid, with 20 minutes residence time, upon changing the temperature from 40 °C to 60 °C, the conversion increased from 18.9% to 94% and selectivity of dinitro products increased from 4.2% to 12.14%. The mono-nitro isomers were seen to have a composition of 57.9% to 58.8% 3-NOX and 41.12% to 42.1% 4NOX.

3. With 1:3 mole ratio of the o-xylene to nitric acid, with 20 minutes residence time, at 40°C and 50°C, the conversion was 94.6% while the selectivity of dinitro products increased from 24.2% to 41.5%. The mono-nitro isomers were seen to have a composition of 50.7% and 52.5% of 3-NOX and 49.3% to 47.5% of 4NOX.

4. With 1:2 mole ratio of the o-xylene to nitric acid, with 30 minutes residence time, at 40°C, the conversion was 92.8% while the selectivity of dinitro products was 9.5%. The mono-nitro isomers were seen to have a composition of 58.2% for 3-NOX and 41.8% for 4NOX.

5. With 1:2 mole ratio of the o-xylene to nitric acid, with 29 minutes residence time, at 50 °C, the conversion was 94.5% while the selectivity of dinitro products was *24.3%*. The mono-nitro isomers were seen to have a composition of 53% for 3-NOX and 47% for 4NOX.

Experiments were carried out with nitrating mixture comprising 40:60 (v/v) ratio of HNO_3 and H_2SO_4.

These are the examples with mixed acids. The mole ratio mentioned in the examples is of the organic substrate and nitric acid. It has been mentioned that the nitrating mixture has 40:60 v/v *ratio of nitric to sulfuric acid.*

1. With 1:2 mole ratio of the o-xylene to nitric acid at 40 °C, 99% conversion was observed with 27% selectivity for the dinitro products in 20 minutes. The mono-nitro isomers were seen to have a composition of *56.5%* 3-NOX and 43.5 % 4NOX.

2. With 1:3 mole ratio of the o-xylene to nitric acid at 40 °C, 99% conversion was observed with 60% selectivity for the dinitro products with residence time of 17

minutes. The mono-nitro isomers were seen to have a composition of 39.3% 3-NOX and 60.66 % 4NOX.

3. With 1:4 mole ratio of the o-xylene to nitric acid at 40 °C, 99% conversion was observed with 97.2% selectivity for the dinitro products with residence time of 20 minutes. The mono-nitro isomers were seen to have a composition of 19.3% 3-NOX and 80.7 % 4NOX.

ADVANTAGES OF THE INVENTION

- Process has high yield and selectivity for preferred isomer.
- Process is energy and time efficient hence scalable.
- Process is easily manageable, facile and environmental friendly.

We claim

1. A process for continuous flow of liquid phase nitration of alkyl benzene compounds in micromixer and tubular reactors comprising reacting alkyl benzene compounds with nitrating agent at a temperature in the range of 10 to 60 deg C for a period in the range of 30 sec to 30 min at atmospheric pressure to obtain nitro alkyl benzene.

2. The process according to claim 1, wherein, the alkyl benzene compounds are selected from the group consisting of toluenes, Xylenes, halogenated alkyl benzenes, cresols and their substituted derivatives.

3. The process according to claim 2, wherein, the alkyl benzene compound used is o-xylene.

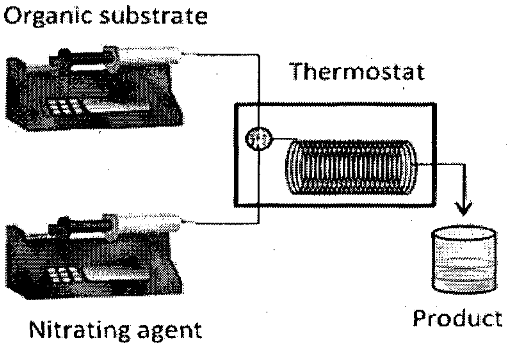
4. The process according to claim 1, wherein, the nitrating agent is selected from the group consisting of standard nitrating mixture (HN03: H2S04 = 40: 60), volumetric nitrating mixture (HN03 : H2S04 = 50: 50) and fuming nitric acid.

5. The process according to claim 1, wherein stoichiometric ratio of nitrating agent to the aromatic substrate is in the range of 1:1 to 10: 1.

6. The process according to claim 1, wherein conversion of 0-xylene is in the range of 98 - 100%.

7. The process according to claim 1, wherein yield of 4-nitro-o-xylene is in the range of 45 to 71 %.

Figure 1:



INTERNATIONAL SEARCH REPORT

International application No
PCT/IN2014/000488

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07C201/08 C07C205/06
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

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.
Y	WO 2013/054181 A1 (COUNCIL SCIENT IND RES [IN]; KULKARNI AMOL ARVIND [IN]; JOSHI RAMESH A) 18 April 2013 (2013-04-18) page 3, line 19 - page 4, line 16; page 4, line 21 - page 5, line 22; page 7, lines 1-15; examples, e.g. Example 3, Examples 5-7 -----	1-7
Y	US 4 021 498 A (ALEXANDERSON VERNER ET AL) 3 May 1977 (1977-05-03) column 2, lines 32-44; column 2, line 57-65; column 3, lines 19-43; column 3, line 51 - column 4, line 22; examples, e.g. Example 2; claims, e.g. claims 1, 6-8 ----- -/-	1-7

☒ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

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Date of the actual completion of the international search 28 October 2014	Date of mailing of the international search report 07/11/2014
Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Authorized officer Sen, Alina

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	ANTES ET AL: "Analysis and Improvement of Strong Exothermic Nitrations in Microreactors", CHEMICAL ENGINEERING RESEARCH AND DESIGN, PART A, INSTITUTION OF CHEMICAL ENGINEERS, XX, vol. 81, no. 7, August 2003 (2003-08), pages 760-765, XP022536535, ISSN: 0263-8762, D0I: 10.1205/026387603322302931 page 760, left-hand column, line 4 from the bottom to page 762, left-hand column, line 5 from the bottom; Figures 1, 3 and 4 -----	1-7
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Y	CARA E. BROCKLEHURST, HANSJÖRG LEHMANN, LUIGI LA VECCHIA: "Nitration Chemistry in Continuous Flow using Fuming Nitric Acid in a Commercially Available Flow Reactor", ORGANIC PROCESS RESEARCH & DEVELOPMENT, vol. 15, no. 6, 29 April 2011 (2011-04-29), pages 1447-1453, XP002731734, D0I: 10.1021/op200055r page 1450, Scheme 3; page 1451, Table 2; page 1450, right-hand column starting from "The third nitration...." to page 1451, left-hand column, "12 g of >97% purity material (after crystallization) was prepared over 19 min at a production rate of 39g/h. -----	1-7

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
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