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(54) Title: PROCESS FOR PRODUCING α, β-UNSATURATED ALDEHYDE COMPOUNDS

(57) Abstract: The present invention relates to a process for producing α, β-unsaturated aldehyde compounds under relatively mild reaction conditions, i.e. at a temperature lower than 115 °C.

PROCESS FOR PRODUCING α,β-UNSATURATED ALDEHYDE COMPOUNDS

TECHNICAL FIELD

The present invention relates to a process for producing α,β-unsaturated aldehyde compounds.

BACKGROUND

The following discussion of the prior art is provided to place the invention in an appropriate technical context and enable the advantages of it to be more fully understood. It should be appreciated, however, that any discussion of the prior art throughout the specification should not be considered as an express or implied admission that such prior art is widely known or forms part of common general knowledge in the field.

α,β-Unsaturated aldehyde compounds are useful compounds as perfumes, intermediates for perfumes, or raw materials for medicines or agricultural chemicals.

α,β-Unsaturated carbonyl compounds are commonly prepared by the Horner-Wadsworth-Emmons reaction, aldol or Knoevenagel condensation, Saegusa-Ito oxidation or carbonylation reactions. Among these pathways, the carbonylation reaction is of high interest, as it involves CO as a very cheap carbonylation agent. The carbonylation of alkenes is even more attractive, as alkenes are easily accessible at large scale and much cheaper than alkynes or allenes. However, the oxidative carbonylation of alkenes is scientifically challenging, mainly because of the much lower reactivity of alkenes.

With respect to the preparation of α,β-unsaturated aldehydes, the carbonylation of alkenes in the presence of metal catalysts has been mainly reported. For example, US 7141702 teaches a hydroformylation-aldol condensation process for preparing an α-substituted acrolein. A rhodium complex was used as catalyst in hydroformylation reaction. Acta Chemica Scandinavica B 40(1986) 190-195 discloses an aminomethylation reaction of alkenes. In a typical procedure, styrene was heated with paraformaldehyde and dimethylammounium chloride in acetic acid without using any metal catalyst. It was found that α,β-unsaturated aldehyde can be produced. Disadvantageously, the reaction had to be heated at 115℃ for 5h.

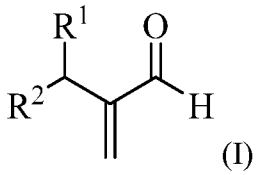
As such, there remains a need for improved process for producing α,β-unsaturated aldehyde compounds.

SUMMARY OF THE INVENTION

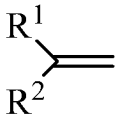
The aim of the present invention is to provide an improved process for producing α,β-unsaturated aldehyde compounds under relatively mild reaction conditions, i.e. at a temperature lower than 115 °C.

Upon diligent research, the inventors have discovered surprisedly that such an aim can be achieved by selecting a specific solvent in the reactions of alkenes with formaldehyde.

Thus, the present invention is directed to a process for producing an α,β-unsaturated aldehyde represented by general formula (I) by reacting an alkene represented by general formula (II) with formaldehyde in the presence of a compound represented by general formula (III) and a solvent being a compound represented by general formula (IV),



(I)



(II)

NHR^3R^4 (III)

$CX_m[(CF_2)_nCF_3]_{3-m}OH$ (IV)

wherein:

- R^1 and R^2, are each independently H or a hydrocarbon radical which is optionally interrupted by one or more heteroatom(s) and/or heteroatom(s) containing groups and/or which is optionally substituted with one or more functional groups;
- R^3 and R^4, are each independently H or C_1-C_4 alkyl;
- m is an integer being 0, 1 or 2;
- n is an integer from 0 to 20;
- X is H or F; and
- with the proviso that when m is 2, X is not H.

With the process according to the present invention, the reactions of alkenes with formaldehyde towards α,β-unsaturated aldehydes under mild reaction conditions, i.e. at a temperature lower than 115 °C, can be realized.

In addition, it has been found that in the specific solvent system, alkenes shows high reactivity at a low reaction temperature, i.e. at a temperature lower than 115 °C.

Other subjects and characteristics, aspects and advantages of the present invention will emerge even more clearly on reading the detailed description and the examples that follow.

DEFINITIONS

Throughout the description, including the claims, the term "comprising one" should be understood as being synonymous with the term "comprising at least one", unless otherwise specified, and "between" should be understood as being inclusive of the limits.

As used herein, the terminology "(C_n-C_m)" in reference to an organic group, wherein n and m are both integers, indicates that the group may contain from n carbon atoms to m carbon atoms per group.

The articles “a”, “an” and “the” are used to refer to one or to more than one (i.e., to at least one) of the grammatical object of the article.

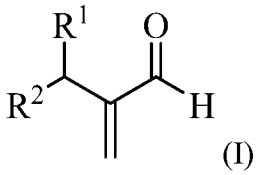
The term “and/or” includes the meanings “and”, “or” and also all the other possible combinations of the elements connected to this term.

It is specified that, in the continuation of the description, unless otherwise indicated, the values at the limits are included in the ranges of values which are given.

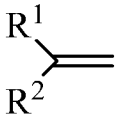
Ratios, concentrations, amounts, and other numerical data may be presented herein in a range format. It is to be understood that such a range format is used merely for convenience and brevity and should be interpreted flexibly to include not only the numerical values explicitly recited as the limits of the range, but also all the individual numerical values or sub-ranges encompassed within that range as if each numerical value or sub-range is explicitly recited.

DETAILS OF THE INVENTION

The present invention provides a process for producing an α,β-unsaturated aldehyde represented by general formula (I) by reacting an alkene represented by general formula (II) with formaldehyde in the presence of a compound represented by general formula (III) and a solvent being a compound represented by general formula (IV),



(I)



(II)

NHR^3R^4 (III) $CX_m[(CF_2)_nCF_3]_{3-m}OH$ (IV)

wherein:

- R^1 and R^2, are each independently H or a hydrocarbon radical which is optionally interrupted by one or more heteroatom(s) and/or heteroatom(s) containing groups and/or which is optionally substituted with one or more functional groups;
- R^3 and R^4, are each independently H or C_1-C_4 alkyl ;
- m is an integer being 0, 1 or 2;
- n is an integer from 0 to 20 ;
- X is H or F; and
- with the proviso that when m is 2, X is not H.

In some embodiments, R^1 and R^2 are each independently H, an aryl or a heteroaryl.

As used herein, the term "aryl" means a monocyclic or bicyclic aromatic hydrocarbon radical of 6 to 10 ring atoms which is optionally substituted independently with one to four substituents, preferably one, two, or three substituents selected from alkyl, alkenyl, alkynyl, aryl, halo, nitro, cyano, hydroxy, alkoxy, amino, mono-alkylamino, di-alkylamino and heteroalkyl.

As used herein, the term " heteroaryl" means a monocyclic or bicyclic radical of 5 to 12 ring atoms having at least one aromatic ring containing one, two, or three ring heteroatoms selected from N, O, or S, the remaining ring atoms being C, with the understanding that the attachment point of the heteroaryl radical will be on an aromatic ring. The heteroaryl ring is optionally substituted independently with one to four substituents, preferably one or two substituents, selected from alkyl, aryl, halo, nitro, cyano, hydroxy, alkoxy, amino, acylamino, mono-alkylamino, di-alkylamino, heteroalkyl, More specifically the term heteroaryl includes, but is not limited to, pyridyl, furanyl, thienyl, thiazolyl, isothiazolyl, triazolyl, imidazolyl, isoxazolyl, pyrrolyl, pyrazolyl, pyridazinyl,

pyrimidinyl, benzofuranyl, tetrahydrobenzofuranyl, isobenzofuranyl, benzothiazolyl.

In a preferred embodiment, R^1 is H and R^2 is an aryl. Non-limiting examples of the alkene represented by general formula (II) can be styrene or styrene substituted with alkyl, phenyl, halo or alkoxy. Said alkyl can be a C_1-C_6 straight or branched chain alkyl. Preferably, C_1-C_6 straight chain alkyl can be selected from the group consisting of methyl, ethyl, 1-propyl, n-butyl and n-pentyl. Preferably, C_1-C_6 branched chain alkyl can be isobutyl. Said alkoxy preferably can be a C_1-C_6 alkoxy and more preferably methoxy or ethoxy. Said halo can be F, Cl, Br or I. The halo can be preferably in para position.

In another preferred embodiment, R^1 and R^2 are each independently an aryl. Non-limiting examples the alkene represented by general formula (II) can be ethene-1,1-diyldibenzene.

In a third preferred embodiment, R^1 is H and R^2 is a naphthyl. Non-limiting examples of the alkene represented by general formula (II) can be 2-vinylnaphthalene.

In some embodiments, R^1 and R^2 are each independently H or an alkyl. Non-limiting examples the alkene represented by general formula (II) can be C_1-C_{20} linear alkenes with a terminal double bond, such as 1-octene, 1-decene and 1-dodecene.

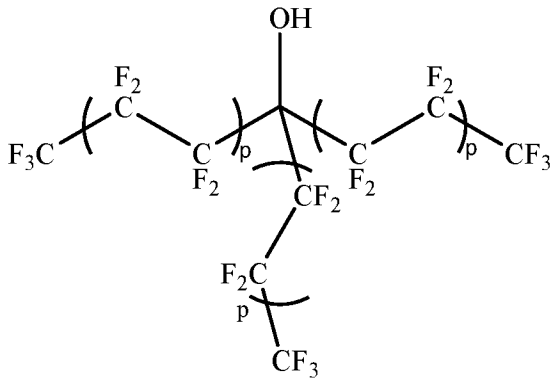
As previously expressed, the solvent is a compound represented by general formula (IV).

$$CX_m[(CF_2)_nCF_3]_{3-m}OH \quad (IV)$$

wherein:

- m is an integer being 0, 1 or 2;
- n is an integer from 0 to 20 ;
- X is H or F; and
- with the proviso that when m is 2, X is not H.

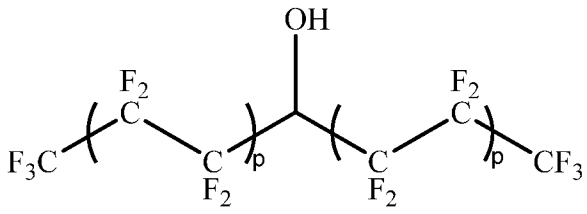
In a preferred embodiment, m are 0. The solvent in this embodiment can be a compound having the following general formula (V).



(V)

wherein p is an integer from 0 to 10.

In another preferred embodiment, X is H, m is 1. The solvent in this embodiment can be a compound having the following general formula (VI).



(VI)

wherein p is an integer from 0 to 10.

Non limitative examples of the compound having the following general formula (VI) is hexafluoroisopropanol(HFIP).

According to the process of the present invention, formaldehyde can be introduced in the form of an aqueous solution. The concentration of formaldehyde in the aqueous solution can be from 35% to 55% and preferably from 35% to 40%. In a preferred embodiment, the aqueous solution of formaldehyde can be formalin.

Advantageously, the molar ratio of the alkene represented by general formula (II) to formaldehyde can be from 1:2 to 1:6 and preferably 1:2 to 1:4.

The C_1-C_4 alkyl in the compound represented by general formula (III) can be straight or branched and preferably straight.

In some embodiments, R^3 and R^4 can be both H. In this embodiment, the compound represented by general formula (III) is ammonia.

In some embodiments, R^3 is H and R^4 is a C_1-C_4 alkyl group. In this embodiment, the compound represented by general formula (III) is a primary amine.

In some embodiments, R^3 and R^4 are both C_1-C_4 alkyl groups. In this embodiment, the compound represented by general formula (III) is a secondary amine. The two alkyl groups can be same or different and preferably same. Advantageously, both alkyl groups are methyl.

According to the process of the present invention, the compound represented by general formula (III) can either be introduced as a pure chemical or be introduced in the form of an aqueous solution. The concentration of the compound represented by general formula (III) in the aqueous solution can be from 30% to 45% and preferably from 35% to 40%.

Advantageously, the molar ratio of the alkene represented by general formula (II) to the compound represented by general formula (III) can be from 1:1 to 20:1 and preferably 1:1 to 10:1.

Advantageously, the weight ratio ratio of the alkene represented by general formula (II) to the solvent can be from 1: 10: o 1: 200 and preferably 1: 10: o 1: 50.

As previously expressed, the reactions of the alkenes represented by general formula (II) with formaldehyde can be carried out under mild reaction conditions. The reaction temperature can be lower than 110 ℃, preferably lower than 100 ℃, more preferably lower than 90 ℃ and most preferably lower than 80 ℃. Advantageously, the reaction temperature can be in the range of 20 ℃ to 60 ℃ and preferably in the range of 30 ℃ to 50 ℃.

According to the process of the present invention, the reaction time is not particularly limited. The preferred reaction time can be from 20 to 120 h.

The process of the present invention may comprise following steps:

a) mixing formaldehyde, a compound represented by general formula (III) and a solvent being a compound represented by general formula (IV) to obtain a mixture;

b) adding an alkene represented by general formula (II) to the mixture obtained in step a) to obtain a reaction mixture;

c) maintaining the reaction mixture obtained in step b) under proper reaction temperature and proper reaction time to obtain an α,β-unsaturated aldehyde represented by general formula (I).

The α,β-unsaturated aldehyde represented by general formula (I), the alkene represented by general formula (II), the compound represented by general formula (III), the compound represented by general formula (IV), the reaction temperature and the reaction time are as defined above.

An aspect of the present invention also provides a composition comprising:

(i) formaldehyde,

(ii) an alkene represented by general formula (II),

(iii) a compound represented by general formula (III), and

(iv) a compound represented by general formula (IV).

The composition may optionally comprises an α,β-unsaturated aldehyde represented by general formula (I).

The α,β-unsaturated aldehyde represented by general formula (I), the alkene represented by general formula (II), the compound represented by general formula (III) and the compound represented by general formula (IV) are as defined above.

The following examples are included to illustrate embodiments of the invention. Needless to say, the invention is not limited to describe examples.

EXPERIMENTAL PART

Materials

- Dimethylamine (DMA) aqueous (38wt% aqueous, reagent grade), cas:100-42-5, Merck
- Formalin (37 wt% aqueous, reagent grade), cas: 124-40-3, Merck
- Dodecene (reagent grade), cas: 112-41-4, Aladin
- Decene (reagent grade), cas: 872-05-9, Aladin
- Octene (reagent grade), cas:111-66-0, Aladin
- Styrene (reagent grade), cas: 100-42-5, Aladin
- Hexafluoroisopropanol(HFIP) (reagent grade), cas: 920-66-1, Aladin
- AcOH (reagent grade), cas: 64-19-7, Aladin
- Toluene (reagent grade), cas: 108-88-3, Aladin
- MeOH (reagent grade), cas: 67-56-1, Aladin
- $MeNO_2$ (reagent grade), cas: 75-52-5, Aladin
- CF_3CH_2OH (reagent grade), cas: 75-89-8, Aladin
- 1-Methyl-3-vinylbenzene (reagent grade), cas: 100-80-1, Aladin
- 1-Methyl-2-vinylbenzene (reagent grade), cas: 611-15-4, Aladin
- 4-Vinyl-1,1'-biphenyl (reagent grade), cas: 2350-89-2, Aladin
- 1-(Tert-butyl)-4-vinylbenzene (reagent grade), cas: 1746-23-2, Aladin

- Vinylnaphthalene (reagent grade), cas: 827-54-3, Aladin
- 1,1-Diphenylethylene (reagent grade), cas:530-48-3, Aladin
- Fluoro-4-vinylbenzene (reagent grade), cas:405-99-2, Aladin
- Chloro-4-vinylbenzene (reagent grade), cas:1073-67-2, Aladin
- Chloro-2-vinylbenzene (reagent grade), cas: 2039-87-4, Aladin
- Chloro-3-vinylbenzene (reagent grade), cas: 2039-85-2, Aladin
- Bromo-3-vinylbenzene (reagent grade), cas: 2039-86-3, Aladin

Examples 1-7: Preparation of 2-benzyl-propenal in the presence of DMA in different solvents

General procedure of Examples 1-7

A round-bottom flask was charged with HCHO (8 mmol, 37 wt%, formalin), dimethylamine (DMA) solution (2 mmol, 38 wt% aqueous) and solvent (0.1M with respect to styrene). Then, styrene (208 mg, 2 mmol, 1 equiv.) was added at 30℃ and the reaction mixture was stirred under atmospheric pressure(1 bar) at 30℃ for 20h. After completion of the reaction, the mixture was filtrated and analyzed using an Agilent 7890 GC equipped with an HP-5 capillary column bearing 5 wt% phenyl groups (length 30 m; inner diameter 0.25 mm). Analytical methods were adjusted for the different mixtures depending on the boiling point and polarity of the reagents and products. In all the methods, the injector temperature was set at 250 °C, the detector temperature was 300 °C and the sample injection volume was 1 uL. The calibration of the gas chromatography was performed using dodecanol as an internal standard.

Example 8: Preparation of 2-benzyl-propenal in HFIP without DMA

General procedure of Examples 8 is same as Example 6. But DMA was not charged.

Example 9: Preparation of 2-benzyl-propenal in HFIP without HCHO

General procedure of Examples 9 is same as Example 6. But HCHO was not charged.

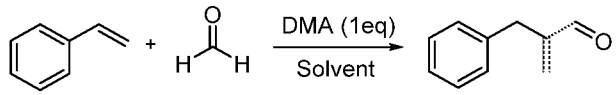
Example 10:

General procedure of Examples 10 is same as Example 6. But dimethylamine aqueous solution was replaced by pure diethylamine.

Example 11:

General procedure of Examples 11 is same as Example 6. But dimethylamine aqueous solution was replaced by pure dibutylamine.

Table 1



1 eq 4 eq A

EX	Solvent	Conversion /%	Selectivity /%	
			A	Others[a]
1	AcOH	<5	0	0
2	Toluene	<5	0	0
3	MeOH	<5	0	0
4	$MeNO_2$	<5	0	0
5	CF_3CH_2OH	<5	0	0
6	HFIP	100	78	22
7[b]	HFIP-THF	<5	0	0
8	HFIP	0	0	0
9	HFIP	0	0	0
10	HFIP	83	64	36
11	HFIP	96	56	44

[a] Others are N-methyl-3-phenylpropan-1-amine, bis(3-phenylpropyl)amine, N-methyl-bis(3-phenylpropyl)amine; [b] DMA-THF solution instead of aqueous DMA solution, trioxane instead of formalin, HFIP : THF (5:2 volume ratio).

The conversion and selectivity of Examples 1-11 are summarized in Table 1. It can be seen that at room temperature (such as 30℃), the reactivity of styrene in pure HFIP is higher than other solvents. At the same time, high conversion and selectivity of 2-benzyl-propenal can be acheived under the mild condition.

Examples 12-26: Preparation of α,β-unsaturated aldehydes in HFIP from different alkenes.

General procedure of Examples 12-26 is same as Example 6. The alkenes, reaction time, reaction temperature and results are summarized in Table 2.

Table 2

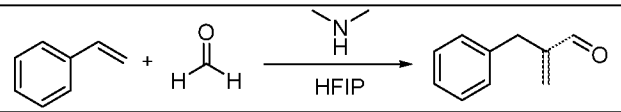
EX	Reactant (alkene)	Product (α,β-unsaturated aldehyde)	Reaction time	Reaction temperature	Yield (%)
12	1-methyl-3-vinylbenzene	2-(3-methylbenzyl)acrylaldehyde	24h	30°C	71
13	1-methyl-2-vinylbenzene	2-(2-methylbenzyl)acrylaldehyde	24h	30°C	72
14	4-vinyl-1,1'-biphenyl	2-(4-Ph-benzyl)acrylaldehyde	24h	30°C	85
15	1-(tert-butyl)-4-vinylbenzene	2-(4-tBu-benzyl)acrylaldehyde	15h	30°C	76
16	2-vinylnaphthalene	2-(naphthalen-2-ylmethyl)acrylaldehyde	24h	30°C	80
17	1,1-diphenylethylene	2-benzhydrylacrylaldehyde	24h	30°C	78
18	1-fluoro-4-vinylbenzene	2-(4- fluoro -benzyl)acrylaldehyde	25h	30°C	82

19	1-chloro-4-vinylbenzene	2-(4- chloro - benzyl)acrylaldehyde	48h	30°C	81
20	1-chloro-2-vinylbenzene	2-(2- chloro - benzyl)acrylaldehyde	84h	30°C	81
21	1-chloro-3-vinylbenzene	2-(3- chloro - benzyl)acrylaldehyde	84h	30°C	28
22	1-bromo-3-vinylbenzene	2-(3- bromo - benzyl)acrylaldehyde	84h	30°C	43
23	styrene	2-benzylacrylaldehyde	24h	30°C	71
24	1-octene	2-methylenenonanal	51h	50°C	43
25	1-decene	2-methyleneundecanal	66h	50°C	44
26	1-dodecene	2-methylenetridecanal	66h	50°C	40

Examples 27-29: Preparation of 2-benzyl-propenal with different Styrene : HCHO : DMA ratios.

General procedure of Examples 27-29 is same as Example 6. The results are summarized in Table 3.

Table 3

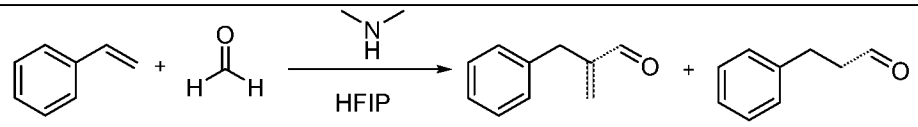


EX	Styrene : HCHO : DMA /mmol	Solvent	Conv /%	Selectivity /%
27	2:4:4	HFIP	99	48
28	2:4:8	HFIP	100	54
29	2:8:2	HFIP	100	78

Examples 30-34: Preparation of 2-benzyl-propenal with different DMA catalytic amounts.

General procedure of Examples 30-34 is same as Example 6. The results are summarized in Table 4.

Table 4

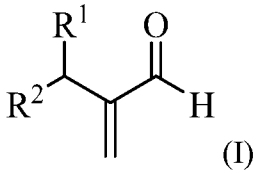


EX	DMA (eq.)	Time/h	Conversion /%	Selectivity /%		
				A	B	Other[a]
30	1	20	100	78	0	22
31	0.4	20	96	84	0	16
32	0.2	54	96	87	0	13
33	0.1	115	80	80	6	14
34	0.05	115	54	42	42	16

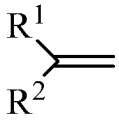
[a]Others are mainly *N*-methyl-3-phenylpropan-1-amine, bis(3-phenylpropyl)amine and *N*-methyl-bis(3-phenylpropyl)amine.

CLAIMS

1. A process for producing an α,β-unsaturated aldehyde represented by general formula (I) by reacting an alkene represented by general formula (II) with formaldehyde in the presence of a compound represented by general formula (III) and a solvent being a compound represented by general formula (IV),



(I)



(II)

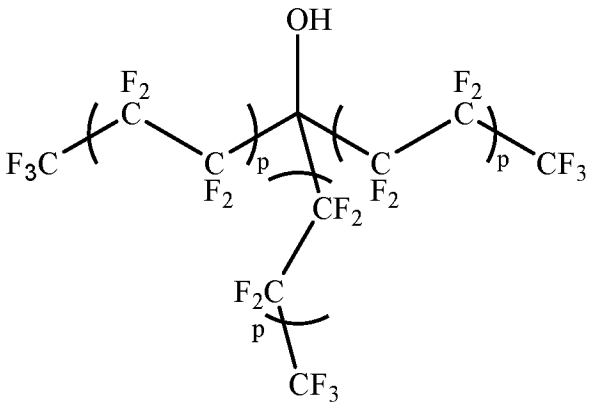
NHR^3R^4 (III)

$CX_m[(CF_2)_nCF_3]_{3-m}OH$ (IV)

wherein:

- R^1 and R^2, are each independently H or a hydrocarbon radical which is optionally interrupted by one or more heteroatom(s) and/or heteroatom(s) containing groups and/or which is optionally substituted with one or more functional groups;
- R^3 and R^4, are each independently H or C_1-C_4 alkyl.
- m is an integer being 0, 1 or 2;
- n is an integer from 0 to 20 ;
- X is H or F; and
- with the proviso that when m is 2, X is not H.

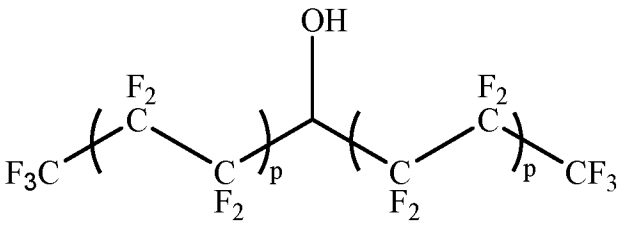
2. The process according to Claim 1, wherein the solvent is a compound having the following general formula (V),



(V)

wherein p is an integer from 0 to 10.

3. The process according to Claim 1, wherein the solvent is a compound having the following general formula (VI),



(VI)

wherein p is an integer from 0 to 10.

4. The process according to any one of Claims 1 to 3, wherein R^1 and R^2 are each independently H, an aryl or a heteroaryl.

5. The process according to any one of Claims 1 to 4, wherein R^1 is H and R^2 is an aryl.

6. The process according to any one of Claims 1 to 5, wherein R^1 and R^2 are each independently an aryl.

7. The process according to any one of Claims 1 to 6, wherein R^1 is H and R^2 is a naphthyl.

8. The process according to any one of Claims 1 to 3, wherein R^1 and R^2 are each independently H or an alkyl.

9. The process according to any one of Claims 1 to 8, wherein R^3 and R^4 are both C_1-C_4 alkyl groups and preferably methyl.

10. The process according to any one of Claims 1 to 9, wherein the molar ratio of the alkene represented by general formula (II) to formaldehyde is 1:2 to 1:6 and preferably 1:2 to 1:4.

11. The process according to any one of Claims 1 to 10, wherein the molar ratio of the alkene represented by general formula (II) to the compound represented by general formula (III) is from 1:1 to 20:1 and preferably 1:1 to 10:1.

12. The process according to any one of Claims 1 to 11, wherein the reaction temperature is in the range of 20 ℃ to 60 ℃ and preferably in the range of 30 ℃ to 50 ℃.

13. The process according to any one of Claims 1 to 12, wherein the reaction time is from 20 to 120 h.

14. The process according to any one of Claims 1 to 13, comprising the steps of:

a) mixing formaldehyde, a compound represented by general formula (III) and a solvent being a compound represented by general formula (IV) to obtain a mixture;

b) adding an alkene represented by general formula (II) to the mixture obtained in step a) to obtain a reaction mixture;

c) maintaining the reaction mixture obtained in step b) under proper reaction temperature and proper reaction time to obtain an α,β-unsaturated aldehyde represented by general formula (I);

wherein:

- the α,β-unsaturated aldehyde represented by general formula (I), the alkene represented by general formula (II), the compound represented by general formula (III) and the compound represented by general formula (IV) are as defined in Claim 1;

- the reaction temperature is defined in Claim 12, and
- the reaction time is defined in Claim 13.

15. A composition comprising:

(i) formaldehyde,

(ii) an alkene represented by general formula (II),

(iii) a compound represented by general formula (III),

(iv) a compound represented by general formula (IV), and

(v) optionally an α,β-unsaturated aldehyde represented by general formula (I),

wherein the α,β-unsaturated aldehyde represented by general formula (I), the alkene represented by general formula (II), the compound represented by general formula (III) and the compound represented by general formula (IV) are as defined in Claim 1.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CN2021/139863

A. CLASSIFICATION OF SUBJECT MATTER

C07C 47/20(2006.01)i; C07C 45/00(2006.01)i

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)

C07C47/-;C07C45/-

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)

CNABS;CNTXT;DWPI;VEN;USTXT;EPTXT;JPTXT;CJFD;REGISTRY;CAPLUS:formaldehyde?, formalin, aldehyde?, alpha, dimethylamine, DMA, beta, unsaturated,alkene

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 4433174 A (STANDARD OIL CO INDIANA) 21 February 1984 (1984-02-21) the whole document	1-15
A	US 4335264 A (DU PONT) 15 June 1982 (1982-06-15) the whole document	1-15
A	US 4496770 A (BASF AG) 29 January 1985 (1985-01-29) the whole document	1-15
A	WO 2005063668 A1 (COUNCIL SCIENT IND RES) 14 July 2005 (2005-07-14) the whole docment	1-15
A	CN 108495837 A (EASTMAN CHEMICAL COMPANY) 04 September 2018 (2018-09-04) the whole document	1-15
A	CN 108495835 A (EASTMAN CHEMICAL COMPANY) 04 September 2018 (2018-09-04) the whole document	1-15
A	CN 110325497 A (BASF SE) 11 October 2019 (2019-10-11) the whole document	1-15

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

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
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"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
16 September 2022	**27 September 2022**
Name and mailing address of the ISA/CN **National Intellectual Property Administration, PRC** **6, Xitucheng Rd., Jimen Bridge, Haidian District, Beijing** **100088, China** Facsimile No. **(86-10)62019451**	Authorized officer **MENG,Chao** Telephone No. **+86-010-62084582**

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	MANNINEN, Kalle et al. "Trapping an intermediate with styrene and 2-phenylbicyclo[2.2.1]hept-2-ene in the Polonovski demethylation reaction" *ChemInform,* Vol. 18, No. 2, 31 December 1987 (1987-12-31), ISSN: 0931-7597, Abstract 115	1-15

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
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