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— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*
— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))*

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(54) Title: PROCESS FOR THE PREPARATION AND ISOLATION OF INTERMEDIATES OF CERTAIN MESOIONIC PESTICIDES

(57) Abstract: A process to produce sodium 2-(3-(trifluoromethyl)phenyl)malonate from dimethyl 2-(3-(trifluoromethyl)phenyl)malonate is disclosed.

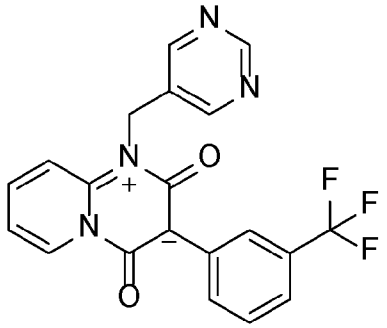
PROCESS FOR THE PREPARATION AND ISOLATION OF INTERMEDIATES OF CERTAIN MESOIONIC PESTICIDES

BACKGROUND FOR THIS DISCLOSURE

Mesoionic pesticides and methods for preparing them have been previously disclosed in, for example, WO 2009/099929 A1, WO 2011/017334 A1, WO 2011/017342 A1, WO 2011/017347 A1, WO 2012/092115 A1, WO 2013/090547 A1, WO 2017/189339 A1, and WO 2019/173173 A1. Triflumezopyrim is a mesoionic pesticide that is used against rice plant hopper, as well as other pests. Ammonium, potassium, sodium, other metal salts, and organic amine salts of 2-[3-(trifluoromethyl)phenyl]propanedioate may be used as an intermediate in the synthesis of triflumezopyrim. However, certain synthesis steps disclosed previously have one or more drawbacks for large-scale manufacture of triflumezopyrim. For example, WO 2013/090547 Example 2, located on page 38, discloses a process that, in general, includes does a saponification reaction followed by azeotropic removal of excess water in the presence of toluene to produce sodium 2-(3-(trifluoromethyl)phenyl)malonate. This process requires more operation units and longer cycle time, generates more waste, and thus limits the manufacturing capacity. Thus, there remains a need for alternative ways of preparing triflumezopyrim in high yield and high quality.

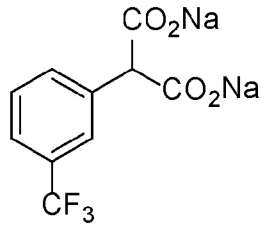
DETAIL DESCRIPTION FOR THIS DISCLOSURE

Triflumezopyrim has the following structure.

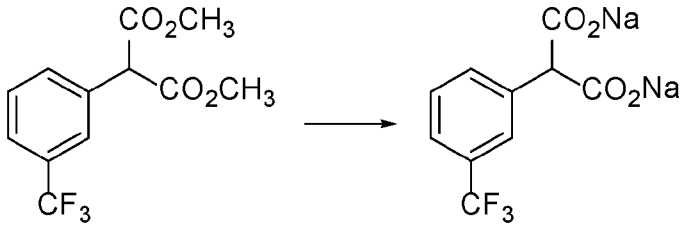


It is also known 2,4-dioxo-1-(pyrimidin-5-ylmethyl)-3-(3-(trifluoromethyl)phenyl)-3,4-dihydro-2*H*-pyrido[1,2-*a*]pyrimidin-1-ium-3-ide.

Sodium 2-[3-(trifluoromethyl)phenyl]propanedioate has the following structure (hereafter also known as "**STPP**"). It is also known as sodium 2-(3-(trifluoromethyl)phenyl)malonate (hereafter also known as "**STPM**").



In the following Scheme One:



sodium 2-(3-(trifluoromethyl)phenyl)malonate is prepared from dimethyl 2-(3-(trifluoromethyl)phenyl)malonate (hereafter also known as "**DTPM**"). **STPM** is prepared, in general, by conducting a saponification reaction followed by crystallization to obtain **STPM** in a higher yield and higher purity than the prior art. If desired, other alkyl substituents may be used such as diethyl 2-(3-(trifluoromethyl)phenyl)malonate or dipropyl 2-(3-(trifluoromethyl)phenyl)malonate, as well as mixtures of alkyl substituents with or without **DTPM**.

In Scheme One, **DTPM** and sodium hydroxide (NaOH) are mixed under conditions to produce **STPM**. In general, about 2 moles to about 8 moles of NaOH per mole of **DTPM**, preferably, about 2 moles to about 4 moles of NaOH per mole of **DTPM**, and more preferably, about 2 moles to about 3 moles of NaOH per mole of **DTPM** may be used. The NaOH is preferably a solution of sodium hydroxide in water of 5 to 50 weight percent (wt %) concentration, and even more preferably, a solution of sodium hydroxide in water of 10 to 40 wt % concentration.

In Scheme One, currently, temperatures from about 0 °C to about 50 °C may be used; preferably temperatures from about 5 °C to about 25 °C may be used. Currently, pressures from

about 10 kilopascals (kPa) to about 1000 kPa may be used; preferably pressures from about 50 kPa to about 150 kPa may be used, however, generally, ambient pressure is preferred.

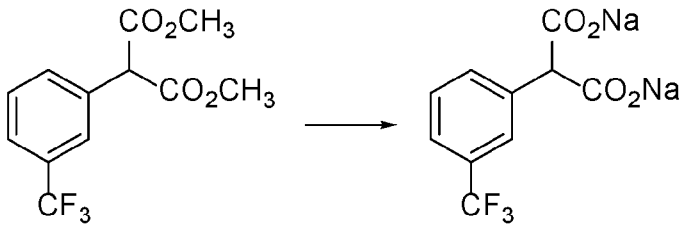
The mixing of **DTPM** and NaOH is conducted in the presence a solvent. While a variety of solvents may be used, such as, for example, nonpolar hydrocarbon solvents, polar aprotic solvents, polar protic solvents, etc., it has been discovered that using isopropyl alcohol (also known as, propan-2-ol) as a solvent provides unexpected and important benefits. The amount of solvent used is from about 1 mole to about 32 moles of solvent per mole of **DTPM**, preferably, about 1 mole to about 16 moles of solvent per mole of **DTPM**, and more preferably, about 1 mole to about 4 moles of solvent per mole of **DTPM** may be used.

Following the mixing of **DTPM** with NaOH in the presence of a solvent, preferably isopropyl alcohol, a resulting mixture comprising **STPM** is further mixed with additional solvent, preferably isopropyl alcohol, under temperatures from about 5 °C to about 20 °C, preferably from about 10 °C to about 15 °C, and pressures indicated above. These conditions promote better crystallization of **STPM** to obtain higher yield and higher purity of **STPM.**

The amount of additional solvent used is from about 1 mole to about 50 moles of solvent per mole of **STPM**, preferably, about 1 mole to about 30 moles of solvent per mole of **STPM**, and more preferably, about 1 mole to about 4 moles of solvent per mole of **STPM** may be used. It should be noted that a mixture of different solvents may be used, such as, for example, a mixture of isopropyl alcohol with water or other alcohols such as ethanol.

In light of the above and the examples below the following additional details (D) are provided.

1D. A process to produce sodium 2-(3-(trifluoromethyl)phenyl)malonate from dimethyl 2-(3-(trifluoromethyl)phenyl)malonate



said process comprising:

(1) mixing dimethyl 2-(3-(trifluoromethyl)phenyl)malonate and NaOH in a solvent, wherein said solvent comprises isopropyl alcohol, and said mixing is under temperature and pressures to produce a mixture comprising sodium 2-(3-(trifluoromethyl)phenyl)malonate; and

(2) crystallizing said mixture comprising sodium 2-(3-(trifluoromethyl)phenyl)malonate in the presence of added solvent, wherein said solvent comprises isopropyl alcohol, and said crystallizing is under temperatures and pressures to crystallize said sodium 2-(3-(trifluoromethyl)phenyl)malonate.

2D. A process according to detail 1D wherein about 2 moles to about 8 moles of NaOH per mole of dimethyl 2-(3-(trifluoromethyl)phenyl)malonate is used.

3D. A process according to detail 1D wherein about 2 moles to about 4 moles of NaOH per mole of dimethyl 2-(3-(trifluoromethyl)phenyl)malonate is used.

4D. A process according to detail 1D wherein about 2 moles to about 3 moles of NaOH per mole of dimethyl 2-(3-(trifluoromethyl)phenyl)malonate is used.

5D. A process according to details 1D, 2D, 3D, or 4D, wherein said temperature is from about 0 °C to about 50 °C.

6D. A process according to detail 5D wherein said temperature is from about 5 °C to about 25 °C.

7D. A process according to details 1D, 2D, 3D, 4D, 5D, or 6D, wherein said pressure is from about 10 kilopascals (kPa) to about 1000 kPa.

8D. A process according to detail 7D wherein said pressure is from about 50 kilopascals (kPa) to about 150 kPa.

9D. A process according to detail 7D wherein said pressure is about ambient pressure.

10D. A process according to details 1D, 2D, 3D, 4D, 5D, 6D, 7D, 8D, or 9D, wherein the amount of solvent used is from about 1 mole to about 32 moles of solvent per mole of dimethyl 2-(3-(trifluoromethyl)phenyl)malonate when mixing with NaOH.

11D. A process according to detail 10D wherein the amount of solvent used is from about 1 mole to about 16 moles of solvent per mole of dimethyl 2-(3-(trifluoromethyl)phenyl)malonate when mixing with NaOH.

12D. A process according to detail 10D wherein the amount of solvent to used is from about 1 mole to about 4 moles of solvent per mole of dimethyl 2-(3-(trifluoromethyl)phenyl)malonate when mixing with NaOH.

13D. A process according to details 1D, 2D, 3D, 4D, 5D, 6D, 7D, 8D, 9D, 10D, 11D, or 12D, wherein said mixture comprising sodium 2-(3-(trifluoromethyl)phenyl)malonate is in the presence of additional isopropyl alcohol, and said crystalizing is conducted at a temperature from about 5 °C to about 20 °C.

14D. A process according to detail 13D wherein the additional solvent is from about 1 mole to about 50 moles of solvent per mole of sodium 2-(3-(trifluoromethyl)phenyl)malonate.

15D. A process according to detail 13D wherein the additional solvent is from about 1 mole to about 25 moles of solvent per mole of sodium 2-(3-(trifluoromethyl)phenyl)malonate.

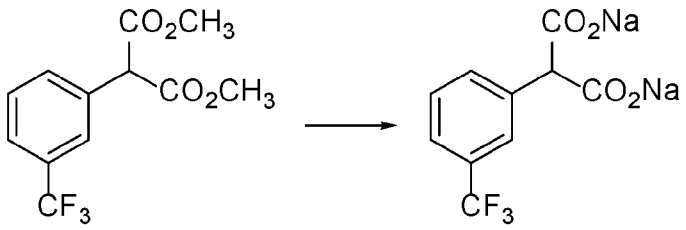
16D. A process according to detail 13D wherein the additional solvent is from about 1 mole to about 4 moles of solvent per mole of sodium 2-(3-(trifluoromethyl)phenyl)malonate.

EXAMPLES

The following examples are for illustration purposes and are not to be construed as limiting. Starting materials, reagents, and solvents that were obtained from commercial sources were used without further purification. Anhydrous solvents were purchased as Sure/Seal™ from

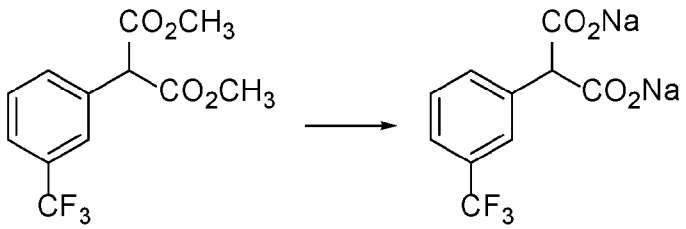
Aldrich and were used as received. Molecules are given their known names, named according to the naming program within ChemDraw (version 17.1.0.105 (19)). If such a program is unable to name a molecule, such molecule is named using conventional naming rules. ^{1}H NMR spectral data are in ppm (δ) and were recorded at 400 MHz, and ^{13}C NMR spectral data are in ppm (δ) and were recorded at 101 MHz, unless otherwise stated.

Prior art example: Preparation of sodium 2-[3-(trifluoromethyl)phenyl]propanedioate from 1,3 -dimethyl 2-[3-(trifluoromethyl)phenyl]propanedioate



The procedure in Example 2, located on page 38 of WO 2013/090547 A1, was recreated in order to determine the purity of the product, sodium 2-[3-(trifluoromethyl)phenyl]propanedioate, produced by this two-step procedure. This was done because the purity was not specified in the example. The yield obtained in conducting this procedure was 80% and the purity was 87.3%.

Example One: Preparing sodium 2-(3-(trifluoromethyl)phenyl)malonate (hereafter "STPM") from dimethyl 2-(3-(trifluoromethyl)phenyl)malonate (hereafter "DTPM")



To a 250 mL jacketed reactor was charged 25% sodium hydroxide (17.51 g, 109 mmol) and propan-2-ol (7.5 mL, 98 mmol). This reaction mixture was cooled to 10-15 °C. A mixture of dimethyl 2-(3-(trifluoromethyl)phenyl)malonate (15 g, 49.7 mmol, **hereafter "DTPM"**) and propan-2-ol (7.5 mL, 98 mmol) at 10-15 °C was slowly added (about 30 minutes) while maintaining the temperature of the reaction mixture between 10-15 °C. After this addition, the

reaction mixture was stirred at 15 °C for 30 minutes. The reaction mixture was then warmed to 21-23 °C and stirred for one hour until analysis by HPLC showed that the reaction was complete.

The reaction mixture was then cooled to 15 °C and propan-2-ol (45 mL, 589 mmol) was slowly added while stirring at 15 °C over 30 minutes. The resulting slurry was stirred for an additional one hour at 15 °C. Afterwards, propan-2-ol (60 mL, 785 mmol) was slowly added over 20 minutes at 15 °C and was stirred for three hours at 15 °C. The slurry was cooled to 5 °C and stirred for one hour. The slurry was filtered. The resulting solid was washed with propan-2-ol; the white filter cake was dried under nitrogen (N_2)/vacuum for 30 minutes and then was dried under vacuum at 40 °C for 48 hours. The product, sodium 2-(3-trifluoromethyl)phenyl)malonate (14.3 g, 46.9 mmol, 94% yield) was obtained as a white solid (95.78 wt % purity).

The procedure as in Example One was conducted four other times except that instead of using propan-2-ol, a different solvent selected from methanol, ethanol, 1-propanol, and *n*-butanol, was used.

A summary of the results of prior art example, the results of Example One, and the results of using the procedures of Example One with different solvents, is disclosed in Table One.

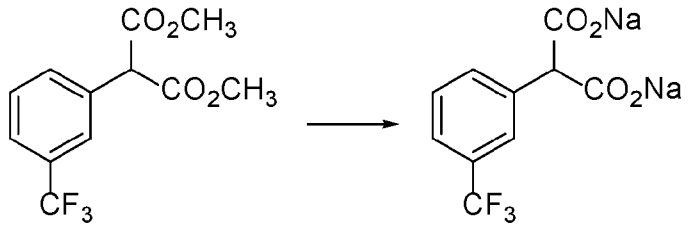
TABLE ONE

Solvent Example	DTPM amount (mmols)	NaOH amount (mmols)	Solvent Amount (mmols)	Yield % STPM	Purity % STPM
Methanol	49.7	109	1472	50	94.1
Ethanol	49.7	109	1472	84	93.3
1-Propanol	49.7	109	1472	66	94.2
Propan-2-ol	49.7	109	1472	94	97.0
n-Butanol	49.7	109	1472	61	89.5
Toluene	49.7	114		80	87.3

As can be seen from Table One, propan-2-ol is much better than the prior art example which is a two-step process with toluene as the solvent. In fact, the yield was 14% better, and the purity was almost 10% better. Furthermore, propan-2-ol provides much better yields and purity than any of the other solvents (methanol, ethanol, 1-propanol, or *n*-butanol).

WE CLAIM

1. A process to produce sodium 2-(3-(trifluoromethyl)phenyl)malonate from dimethyl 2-(3-(trifluoromethyl)phenyl)malonate



said process comprising:

(1) mixing dimethyl 2-(3-(trifluoromethyl)phenyl)malonate and NaOH in a solvent, wherein said solvent comprises isopropyl alcohol under temperatures and pressures to produce a mixture comprising sodium 2-(3-(trifluoromethyl)phenyl)malonate; and

(2) crystallizing said mixture comprising sodium 2-(3-(trifluoromethyl)phenyl)malonate in the presence of a solvent wherein said solvent comprises isopropyl alcohol under temperatures and pressures to crystallize said sodium 2-(3-(trifluoromethyl)phenyl)malonate.

2. A process according to claim 1 wherein about 2 moles to about 8 moles of NaOH per mole of dimethyl 2-(3-(trifluoromethyl)phenyl)malonate is used.

3. A process according to claim 1 wherein about 2 moles to about 4 moles of NaOH per mole of dimethyl 2-(3-(trifluoromethyl)phenyl)malonate is used.

4. A process according to claim 1 wherein about 2 moles to about 3 moles of NaOH per mole of dimethyl 2-(3-(trifluoromethyl)phenyl)malonate is used.

5. A process according to any of the previous claims 1, 2, 3, or 4, wherein said temperature is from about 0 °C to about 50 °C.

6. A process according to claim 5 wherein said temperature is from about 5 °C to about 25 °C.

7. A process according to any of the previous claims 1, 2, 3, 4, 5, or 6, wherein said pressure is from about 10 kilopascals (kPa) to about 1000 kPa.

8. A process according to claim 7 wherein said pressure is from about 50 kilopascals (kPa) to about 150 kPa.

9. A process according to claim 7 wherein said pressure is about ambient pressure.

10. A process according to any of the previous claims 1, 2, 3, 4, 5, 6, 7, 8, or 9, wherein the amount of solvent used is from about 1 mole to about 32 moles of solvent per mole of dimethyl 2-(3-(trifluoromethyl)phenyl)malonate when mixing with NaOH.

11. A process according to claim 10 wherein the amount of solvent used is from about 1 mole to about 16 moles of solvent per mole of dimethyl 2-(3-(trifluoromethyl)phenyl)malonate when mixing with NaOH.

12. A process according to claim 10 wherein the amount of solvent to used is from about 1 mole to about 4 moles of solvent per mole of dimethyl 2-(3-(trifluoromethyl)phenyl)malonate when mixing with NaOH.

13. A process according to any of the previous claims 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12, wherein said mixture comprising sodium 2-(3-(trifluoromethyl)phenyl)malonate is in the presence of additional isopropyl alcohol, and said crystalizing is conducted at a temperature from about 5 °C to about 20 °C.

14. A process according to claim 13 wherein the additional solvent is from about 1 mole to about 50 moles of solvent per mole of sodium 2-(3-(trifluoromethyl)phenyl)malonate.

15. A process according to claim 13 wherein the additional solvent is from about 1 mole to about 25 moles of solvent per mole of sodium 2-(3-(trifluoromethyl)phenyl)malonate.

16. A process according to claim 13 wherein the additional solvent is from about 1 mole to about 4 moles of solvent per mole of sodium 2-(3-(trifluoromethyl)phenyl)malonate.

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2023/072301

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07C51/41 C07C51/43 C07C57/58
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, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2013/090547 A1 (DU PONT [US]) 20 June 2013 (2013-06-20) cited in the application page 24, line 28 - page 26, line 35; example 2 -----	1-16

☐ 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

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2023/072301

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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