(54) Title: CONTINUOUS FLOW SYNTHESIS OF DITHIOESTER COMPOUNDS

FIG. 1

(57) Abstract: The present technology relates to methods of producing various dithioester-containing compounds via continuous flow reactors. Dithioesters are an important class of compounds in synthetic chemistry, having numerous applications in pharmaceutical, applied, and other chemical industries. For example, reversible addition-fragmentation chain transfer (RAFT) polymerization is one of the most effective and versatile methods for providing living characteristics to radical polymerization.
INTERNATIONAL SEARCH REPORT

PCT/US2014/027356

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - C07C 327/36 (2014.01)
USPC - 558/230

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)
IPC(8) - C07C 327/36 (2014.01)
USPC - 558/230

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
CPC - C07C 327/36 (2014.09)

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
PatBase, Orbit, STN, PubChem, Google Scholar

C. DOCUMENTS CONSIDERED TO BE RELEVANT

<table>
<thead>
<tr>
<th>Category</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
</tr>
</thead>
</table>

Further documents are listed in the continuation of Box C.

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
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"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

Date of the actual completion of the international search: 25 August 2014

Date of mailing of the international search report: 11 SEP 2014

Name and mailing address of the ISA/US
Mail Stop PCT, Attn: ISA/US, Commissioner for Patents
P.O. Box 1450, Alexandria, Virginia 22313-1450
Facsimile No. 571-273-3201

Authorized officer: Blaine R. Copenheaver
PCT Helpdesk: 571-272-4300
PCT OSP: 571-272-7774
This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.:
   because they relate to subject matter not required to be searched by this Authority, namely:

2. Claims Nos.:
   because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. Claims Nos.:
   because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

This International Searching Authority found multiple inventions in this international application, as follows:

Claims 1-39, 41-43, 46, 48, 51-53, and 57 have been analyzed subject to the restriction that the claims read on the formula (IV) as described in the Lack of Unity of Invention (See Extra Sheet). The claims are restricted to a method comprising: reacting a first solution comprising a compound of Formula \( \text{II} \) with a second solution comprising a compound of Formula \( \text{III} \) in a continuous flow reactor, to produce a compound of Formula IV, wherein \( R1 \) is a substituted or unsubstituted alkyl; \( R2, R3, \) and \( R4 \) are independently -H; \( Z+ \) is a cationic group, wherein \( Z^+ \) is \( \text{Li}^+ \); and \( LG \) is a leaving group, wherein \( LG \) is a halogen group.

See Extra Sheet

1. As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

   1-44 and 46-57 as they read on the elected species (See Extra Sheet).

4. No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

**Remark on Protest**

- The additional search fees were accompanied by the applicant’s protest and, where applicable, the payment of a protest fee.

- The additional search fees were accompanied by the applicant’s protest but the applicable protest fee was not paid within the time limit specified in the invitation.

- No protest accompanied the payment of additional search fees.
Claims 1-44 and 46-57 have been analyzed subject to the restriction that the claims read on the formula (IV) as described in the Response to the Invitation to Pay Additional Fees, and Where Applicable, Protest Fee dated 18 July 2014. The claims are restricted to a method comprising: reacting a first solution comprising a compound of Formula II, with a second solution comprising a compound of Formula III in a continuous flow reactor, to produce a compound of Formula IV, wherein R1 is substituted or unsubstituted aryl, R2 is substituted or unsubstituted alkyl, R3 is hydrogen, R4 is -CO2R, wherein R is substituted or unsubstituted alkyl, Z+ is Mg+, and LG is halogen.

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees need to be paid.

Group I+: claims 1-57 are drawn to methods to produce a compound of formula IV, and intermediates thereof.

The first invention of Group I+ is restricted to a method comprising: reacting a first solution comprising a compound of Formula II, with a second solution comprising a compound of Formula III in a continuous flow reactor, to produce a compound of Formula IV, wherein R1 is a substituted or unsubstituted alkyl; R2, R3, and R4 are independently -H; Z+ is a cationic group, wherein Z+ is LiI; and LG is a leaving group, wherein LG is a halogen group. It is believed that claims 1-39, 41-43, 46, 48, 51-53, and 57 read on this first named invention and thus these claims will be searched without fee to the extent that they read on the above embodiment.

Applicant is invited to elect additional formula(e) for each additional compound to be searched in a specific combination by paying an additional fee for each set of election. An exemplary election would be a method comprising: reacting a first solution comprising a compound of Formula II, with a second solution comprising a compound of Formula III in a continuous flow reactor, to produce a compound of Formula IV, wherein R1 is a substituted or unsubstituted alkyl; R2, R3, and R4 are independently -H; Z+ is a cationic group, wherein Z+ is LiI; and LG is a leaving group, wherein LG is a halogen group. Additional formula(e) will be searched upon the payment of additional fees. Applicants must specify the claims that read on any additional elected inventions. Applicants must further indicate, if applicable, the claims which read on the first named invention if different than what was indicated above for this group. Failure to clearly identify how any paid additional invention fees are to be applied to the "+" group(s) will result in only the first claimed invention to be searched/examined.

The inventions listed in Groups I+ do not relate to a single general inventive concept under PCT Rule 13.1, because under PCT Rule 13.2 they lack the same or corresponding special technical features for the following reasons:

The Groups I+ formulae do not share a significant structural element responsible for the reaction, requiring the selection of alternatives for the compound variables R1, R2, R3, R4, Z+, and LG.

The Groups I+ share the technical features of a method comprising: reacting a first solution comprising a compound of Formula II, with a second solution comprising a compound of Formula III in a continuous flow reactor, to produce a compound of Formula IV, and intermediates thereof. However, these shared technical features do not represent a contribution over the prior art.

Specifically, US 2004/0186302 to Bollinger et al. teach a method comprising: reacting a first solution comprising a compound of Formula II, with a second solution comprising a compound of Formula III in a continuous flow reactor, to produce a compound of Formula IV, wherein R1 is unsubstituted aryl; R2, R3, and R4 are independently unsubstituted alkyl or aryl group; Z+ is a cationic group; and LG is a leaving group (see Para. [0077], ...cumyl chloride obtained was extracted into 50 ml of heptane, and the heptane solution was admired with an excess of anhydrous potassium bicarbonate...The heptane solution including cumyl chloride was added to 250 ml of an aqueous sodium dithiobenzoate solution...removing the heptane, 41 g of cumyl dithiobenzoate were obtained...); and a method comprising: reacting a first solution comprising a compound of Formula I with carbon disulfide or a solution thereof, in a continuous flow reactor, to produce a compound of Formula II, wherein R1 is unsubstituted aryl; and Z+ is a cationic group (see Para. [0079], phenylmagnesium bromide solution in diethyl ether were added to 35 g of carbon disulfide in 150 ml of tetrahydrofuran...a violet oil which contained dithiobenzonic acid were obtained. Dithiobenzoic acid contained in the oil was removed by extraction with 2% sodium hydroxide...).

The inventions listed in Groups I+ therefore lack unity under Rule 13 because they do not share a same or corresponding special technical feature.

<End Box III: Observations where unity of invention is lacking>