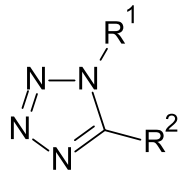
New process for the manufacture of tetrazole derivatives

The invention relates in particular to a new process for the manufacture of tetrazole derivatives.

Tetrazoles are a class of heterocycles with a wide range of applications in medicinal chemistry and in material sciences and versatile methods to synthesize tetrazoles through safe protocols is highly desirable. Typical procedures use either toxic metals, expensive reagents, harsh reaction conditions and may lead to the formation of dangerous and highly toxic hydrazoic acid (HN_3) or explosive sublimates. As such, procedures involving azides including NaN_3, $TMSN_3$, $Al(R)_2N_3$, $Sn(R)_2N_3$ or free HN_3 have not found broad practical application in organic synthesis, due to the associated safety concerns.

The applicant has surprisingly found that these problems can be solved and tetrazole derivatives be prepared using a flow chemistry, three components reaction as described below.

In one aspect, the present disclosure thus relates in particular to a process for the preparation of a compound of formula (I)



(I)

wherein

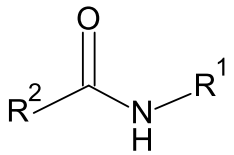
R^1 is alkyl, cycloalkyl, aryl, arylalkyl, alkyloxy, alkenyl, alkynyl, heterocyclyl or heteroaryl, all optionally substituted with one to three substituents independently selected from halogen, hydroxyl, alkyl, haloakyl, hydroxyalkyl, cycloalkyl, halocycloalkyl, hydroxycycloalkyl, alkoxy and cyano;

R^2 is $-CH_2-X$ or aryl optionally substituted with one to three substituents independently selected from halogen, hydroxyl, alkyl, haloakyl, hydroxyalkyl, cycloalkyl, halocycloalkyl, hydroxycycloalkyl, alkoxy and cyano;

or R^1 and R^2 together form alkylene; and

X is halogen, aryloxy, alkyoxycarbonyl, haloalkyl, hydroxyl, mesyl, tosyl, alkoxy, alkylamino or dialkylamino, wherein aryloxy is optionally substituted with one to three substituents independently selected from halogen, hydroxyl, alkyl, haloakyl, hydroxyalkyl, cycloalkyl, halocycloalkyl, hydroxycycloalkyl, alkoxy and cyano;

comprising the flow chemistry, three components reaction of a compound of formula (II)



(II)

wherein R^1 and R^2 are as defined above;

with trimethylsilyl azide ($TMSN_3$) and a chlorinating agent in acetonitrile.

The continuous process of the disclosure can for example be done in microreactors. It offers many benefits such as enhanced heat- and mass transfer characteristics, operation at lower reactor volumes, operation at high temperature/pressure and tighter control of process parameters. The continuous process of the disclosure can in particular be use in large reactors for large scale production.

In the process of the disclosure, synthetic intermediates can be generated and consumed in situ (make & consume approach), which eliminates the need to store toxic, reactive, or explosive intermediates and thus makes the synthetic protocol safer. A particularly attractive feature of the present process is the ability to operate without having a head-space where HN_3 (bp=37°C) may accumulate and/or condense. Consequently, the continuous process of the disclosure mitigates process safety risk associated to azide chemistry.

It was found in particular that acetonitrile is the ideal solvent for the reaction of the disclosure in regards of kinetics and solubility of starting material, intermediates and product.

$POCl_3$ was found to be the best chlorinating agent in terms of kinetics, solubility and general reaction performance although other.

Attempts to use an alternative azide source in a biphasic liquid/liquid system failed and the organic soluble $TMSN_3$ was selected for the reaction of the disclosure.

Figure 1 represents an exemplary reactor setup suitable for running the process of the invention.

In the present description the term “alkyl”, alone or in combination, signifies a straight-chain or branched-chain alkyl group with 1 to 8 carbon atoms, particularly a straight or branched-chain alkyl group with 1 to 6 carbon atoms and more particularly a straight or branched-chain alkyl group with 1 to 4 carbon atoms. Examples of straight-chain and branched-chain C1-C8 alkyl groups are methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert.-butyl, the isomeric pentyls, the isomeric hexyls, the isomeric heptyls and the isomeric octyls, particularly methyl, ethyl, propyl, butyl and pentyl. Particular examples of alkyl are methyl, ethyl, isopropyl, butyl, isobutyl, tert.-butyl and pentyl.

The term “cycloalkyl”, alone or in combination, signifies a cycloalkyl ring with 3 to 8 carbon atoms and particularly a cycloalkyl ring with 3 to 6 carbon atoms. Examples of cycloalkyl are cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl, cycloheptyl and cyclooctyl. A particular cycloalkyl is cyclopropyl.

The term “alkoxy” or “alkyloxy”, alone or in combination, signifies a group of the formula alkyl-O- in which the term "alkyl" has the previously given significance, such as methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy, sec-butoxy and tert.-butoxy. Particular examples of “alkoxy” are methoxy and ethoxy.

The term “alkylene”, alone or in combination, signifies a linear saturated divalent hydrocarbon group of 1 to 7 carbon atoms or a divalent branched saturated divalent hydrocarbon group of 3 to 7 carbon atoms. Examples of alkylene groups include methylene, ethylene, propylene, 2-methylpropylene, butylene, 2-ethylbutylene, pentylene, hexylene, in particular pentylene.

The term “oxy”, alone or in combination, signifies the -O- group.

The terms “halogen” or “halo”, alone or in combination, signifies fluorine, chlorine, bromine or iodine and particularly fluorine, chlorine or bromine, more particularly chlorine. The term “halo”, in combination with another group, denotes the substitution of said group with at least one halogen, particularly substituted with one to five halogens, particularly one to four halogens, i.e. one, two, three or four halogens.