

PROCESSES FOR THE PREPARATION OF AN NLRP3 INHIBITOR

Field of the Invention

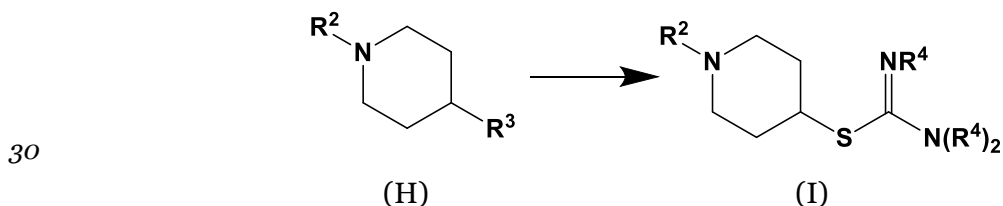
The present invention relates to intermediates and processes useful for preparing 1-ethyl-*N*-((1,2,3,5,6,7-hexahydro-s-indacen-4-yl)carbamoyl)piperidine-4-sulfonamide and salts thereof. The present invention further relates to 1-ethyl-*N*-((1,2,3,5,6,7-hexahydro-s-indacen-4-yl)carbamoyl)piperidine-4-sulfonamide and salts thereof when prepared by such processes and to associated pharmaceutical compositions and uses for the treatment and prevention of medical disorders and diseases, most especially by NLRP3 inhibition.

Background

1-Ethyl-*N*-((1,2,3,5,6,7-hexahydro-s-indacen-4-yl)carbamoyl)piperidine-4-sulfonamide is disclosed in WO 2019/008025 A1 as an NLRP3 inhibitor (see Example 6). However, there is a need to provide improved processes for preparing 1-ethyl-*N*-((1,2,3,5,6,7-hexahydro-s-indacen-4-yl)carbamoyl)piperidine-4-sulfonamide and salts thereof. In particular, there is a need to provide efficient processes that are suitable for large scale synthesis and which, for example, avoid costly chromatographic or high temperature techniques, avoid or minimise the use of expensive or environmentally unfriendly reagents, and/or avoid the generation of hazardous by-products. There is also a need to provide 1-ethyl-*N*-((1,2,3,5,6,7-hexahydro-s-indacen-4-yl)carbamoyl)piperidine-4-sulfonamide and salts thereof, and intermediates on route to such a compound, in a higher yield and/or with a higher purity compared to prior art processes, especially on a large scale. The present invention solves the aforementioned problems.

Summary

The disclosure provides a process of preparing a thiourea adduct (I) or a salt thereof, the process comprising the step of converting a *N*-protected-4-derivatised piperidine (H) to the thiourea adduct (I) or the salt thereof:



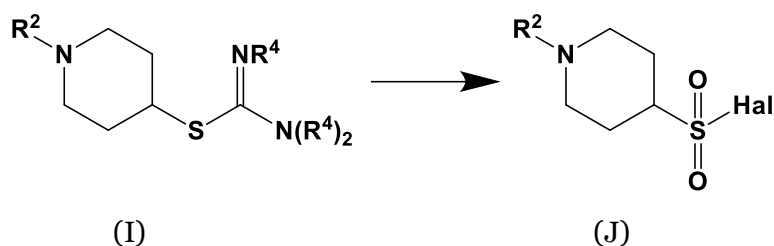
wherein:

R² is a nitrogen protecting group;

R³ is a leaving group; and

each R⁴ is independently selected from hydrogen or a C₁-C₂₀ hydrocarbyl group, wherein each C₁-C₂₀ hydrocarbyl group may be straight-chained or branched, or be or include one or more cyclic groups, wherein each C₁-C₂₀ hydrocarbyl group may optionally be substituted with one or more oxo (=O) and/or one or more halo groups, and wherein each C₁-C₂₀ hydrocarbyl group may optionally include one or more heteroatoms independently selected from N, O and S in its carbon skeleton, or wherein any two or more R⁴ may, together with the atom or atoms to which they are attached, form a 3- to 16-membered heterocyclic group, wherein the heterocyclic group may be monocyclic, bicyclic or tricyclic, and wherein the heterocyclic group may optionally be substituted with one or more halo groups and/or one or more groups R⁴⁰, wherein each R⁴⁰ is independently selected from a -CN, -OH, -NH₂, oxo (=O), =NH or C₁-C₆ hydrocarbyl group, wherein each C₁-C₆ hydrocarbyl group may be straight-chained or branched, or be or include one or more cyclic groups, wherein each C₁-C₆ hydrocarbyl group may optionally be substituted with one or more halo groups, and wherein each C₁-C₆ hydrocarbyl group may optionally include one or more heteroatoms independently selected from N, O and S in its carbon skeleton.

In one aspect, the present disclosure provides a process of preparing a N-protected-4-(halosulfonyl)-piperidine (J) or a salt thereof, the process comprising the step of converting a thiourea adduct (I) to the N-protected-4-(halosulfonyl)-piperidine (J) or the salt thereof:

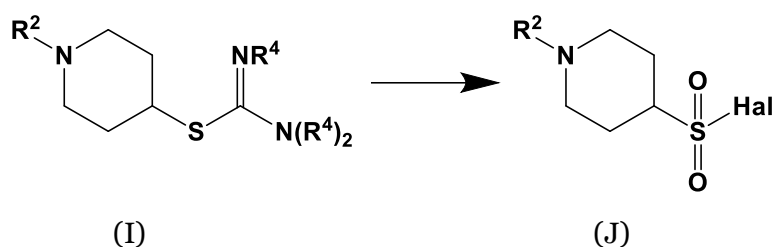


wherein:

R² is a nitrogen protecting group;

each R⁴ is independently selected from hydrogen or a C₁-C₂₀ hydrocarbyl group, wherein each C₁-C₂₀ hydrocarbyl group may be straight-chained or branched, or be or include one or more cyclic groups, wherein each C₁-C₂₀ hydrocarbyl group may optionally be substituted with one or more oxo (=O) and/or one or more halo groups, and wherein each C₁-C₂₀ hydrocarbyl group may optionally include one or more heteroatoms independently selected from N, O and S in its carbon skeleton, or wherein any two or more R⁴ may, together with the atom or atoms to which they are attached, form a 3- to 16-membered heterocyclic group, wherein the heterocyclic group may be monocyclic, bicyclic or tricyclic, and wherein the heterocyclic group may optionally be substituted with one or more halo groups and/or one or more groups R⁴⁰, wherein each R⁴⁰ is independently selected from a -CN, -OH, -NH₂, oxo (=O), =NH or C₁-C₆ hydrocarbyl group, wherein each C₁-C₆ hydrocarbyl group may be straight-chained or branched, or be or include one or more cyclic groups, wherein each C₁-C₆ hydrocarbyl group may optionally be substituted with one or more halo groups, and wherein each C₁-C₆ hydrocarbyl group may optionally include one or more heteroatoms independently selected from N, O and S in its carbon skeleton; and
Hal is Cl or Br.

In another aspect, the present disclosure provides a process comprising the step of:
converting a thiourea adduct (I) to a N-protected-4-(halosulfonyl)-piperidine (J):



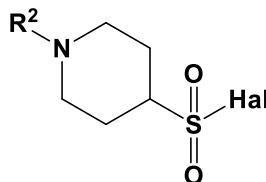
wherein the conversion is performed in the presence of a C₃-C₅ alcohol;
and wherein:
R² is a nitrogen protecting group;

each R⁴ is independently selected from hydrogen or a C₁-C₂₀ hydrocarbyl group, wherein each C₁-C₂₀ hydrocarbyl group may be straight-chained or branched, or be or include one or more cyclic groups, wherein each C₁-C₂₀ hydrocarbyl group may optionally be substituted with one or more oxo (=O) and/or one or more halo groups, and wherein each C₁-C₂₀ hydrocarbyl group may optionally include one or more heteroatoms independently selected from N, O and S in its carbon skeleton, or wherein any two or more R⁴ may, together with the atom or atoms to which they are attached, form a 3- to 16-membered heterocyclic group, wherein the heterocyclic group may be monocyclic, bicyclic or tricyclic, and wherein the heterocyclic group may optionally be substituted with one or more halo groups and/or one or more groups R⁴⁰, wherein each R⁴⁰ is independently selected from a -CN, -OH, -NH₂, oxo (=O), =NH or C₁-C₆ hydrocarbyl group, wherein each C₁-C₆ hydrocarbyl group may be straight-chained or branched, or be or include one or more cyclic groups, wherein each C₁-C₆ hydrocarbyl group may optionally be substituted with one or more halo groups, and wherein each C₁-C₆ hydrocarbyl group may optionally include one or more heteroatoms independently selected from N, O and S in its carbon skeleton; and
Hal is Cl or Br.

In another aspect, the present disclosure provides 1-ethyl-N-((1,2,3,5,6,7-hexahydro-s-indacen-4-yl)carbamoyl)piperidine-4-sulfonamide or a salt thereof, prepared by or preparable by a process as described herein.

In another aspect, the present disclosure provides a compound, wherein the compound is:

an N-protected-4-(halosulfonyl)-piperidine (J) or a salt thereof:



(J)

wherein R² is a nitrogen protecting group and Hal is Cl or Br.

In the context of the present specification, a “hydrocarbyl” substituent group or a hydrocarbyl moiety in a substituent group only includes carbon and hydrogen atoms but, unless stated otherwise, does not include any heteroatoms, such as N, O or S, in its carbon skeleton. A hydrocarbyl group/moiety may be saturated or unsaturated
5 (including aromatic), and may be straight-chained or branched, or be or include cyclic groups wherein, unless stated otherwise, the cyclic group does not include any heteroatoms, such as N, O or S, in its carbon skeleton. Examples of hydrocarbyl groups include alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl and aryl groups/moieties and combinations of all of these groups/moieties. Typically a hydrocarbyl group is a C₁-C₂₀
10 hydrocarbyl group. More typically a hydrocarbyl group is a C₁-C₁₅ hydrocarbyl group. More typically a hydrocarbyl group is a C₁-C₁₀ hydrocarbyl group. A “hydrocarbylene” group is similarly defined as a divalent hydrocarbyl group.

An “alkyl” substituent group or an alkyl moiety in a substituent group may be linear
15 (i.e. straight-chained) or branched. Examples of alkyl groups/moieties include methyl, ethyl, *n*-propyl, *i*-propyl, *n*-butyl, *i*-butyl, *t*-butyl and *n*-pentyl groups/moieties. Unless stated otherwise, the term “alkyl” does not include “cycloalkyl”. Typically an alkyl group