PROCCESSES FOR THE PREPARATION OF AN NLRP3 INHIBITOR

Field of the Invention

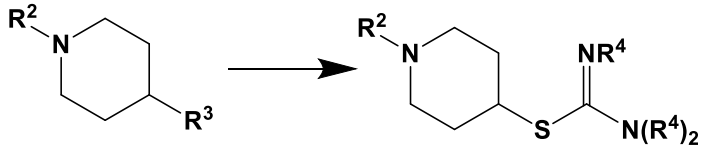
The present invention relates to intermediates and processes useful for preparing 1-ethyl-*N*-((1,2,3,5,6,7-hexahydro-s-indacen-4-yl)carbamoyl)piperidine-4-sulfonamide and salts thereof. The present invention further relates to 1-ethyl-*N*-((1,2,3,5,6,7-hexahydro-s-indacen-4-yl)carbamoyl)piperidine-4-sulfonamide 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

In one aspect, the present 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:



(H) (I)

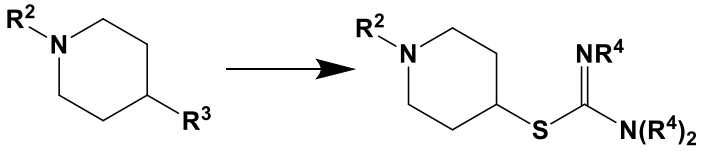
wherein:

R^2 is a nitrogen protecting group;

R^3 is a leaving group; and

each R^4 is independently selected from hydrogen or a C_1-C_{20} hydrocarbyl group, wherein each C_1-C_{20} hydrocarbyl group may be straight-chained or branched, or be or include one or more cyclic groups, wherein each C_1-C_{20} hydrocarbyl group may optionally be substituted with one or more oxo (=O) and/or one or more halo groups, and wherein each C_1-C_{20} 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 R^4 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 R^{40}, wherein each R^{40} is independently selected from a -CN, -OH, $-NH_2$, oxo (=O), =NH or C_1-C_6 hydrocarbyl group, wherein each C_1-C_6 hydrocarbyl group may be straight-chained or branched, or be or include one or more cyclic groups, wherein each C_1-C_6 hydrocarbyl group may optionally be substituted with one or more halo groups, and wherein each C_1-C_6 hydrocarbyl group may optionally include one or more heteroatoms independently selected from N, O and S in its carbon skeleton.

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



(H) (I) ;

wherein the conversion is performed in the presence of a C_3-C_5 alcohol; and wherein:

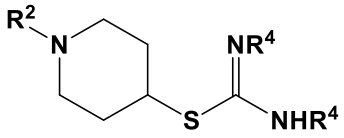
R^2 is a nitrogen protecting group;

R^3 is a leaving group; and

each R^4 is independently selected from hydrogen or a C_1-C_{20} hydrocarbyl group, wherein each C_1-C_{20} hydrocarbyl group may be straight-chained or branched, or be or include one or more cyclic groups, wherein each C_1-C_{20} hydrocarbyl group may optionally be substituted with one or more oxo (=O) and/or one or more halo groups, and wherein each C_1-C_{20} 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 R^4 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 R^{40}, wherein each R^{40} is independently selected from a -CN, -OH, $-NH_2$, oxo (=O), =NH or C_1-C_6 hydrocarbyl group, wherein each C_1-C_6 hydrocarbyl group may be straight-chained or branched, or be or include one or more cyclic groups, wherein each C_1-C_6 hydrocarbyl group may optionally be substituted with one or more halo groups, and wherein each C_1-C_6 hydrocarbyl group may optionally include one or more heteroatoms independently selected from N, O and S in its carbon skeleton.

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 thiourea adduct (I) or a salt thereof:



(I)

wherein:

R^2 is a nitrogen protecting group; and

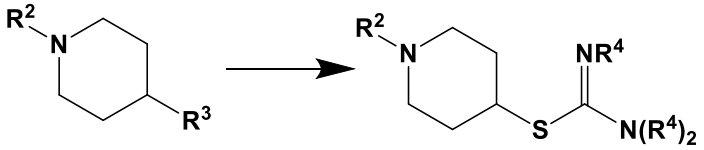
each R^4 is independently selected from hydrogen or a C_1-C_{20} hydrocarbyl group, wherein each C_1-C_{20} hydrocarbyl group may be straight-chained or branched, or be or include one or more cyclic groups, wherein each C_1-C_{20} hydrocarbyl group may optionally be substituted with one or more oxo (=O) and/or one or more halo groups, and wherein each C_1-C_{20} 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 R^4 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 R^{40}, wherein each R^{40} is independently selected from a -CN, -OH, $-NH_2$, oxo (=O), =NH or C_1-C_6 hydrocarbyl group, wherein each C_1-C_6 hydrocarbyl group may be straight-chained or branched, or be or include one or more cyclic groups, wherein each C_1-C_6 hydrocarbyl group may optionally be substituted with one or more halo groups, and wherein each C_1-C_6 hydrocarbyl group may optionally include one or more heteroatoms independently selected from N, O and S in its carbon skeleton.

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 (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 C_1-C_{20} hydrocarbyl group. More typically a hydrocarbyl group is a C_1-C_{15} hydrocarbyl group. More typically a hydrocarbyl group is a C_1-C_{10} 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 (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

Claims

1. 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:



(H) (I)

wherein:

R^2 is a nitrogen protecting group;

R^3 is a leaving group; and

each R^4 is independently selected from hydrogen or a C_1-C_{20} hydrocarbyl group, wherein each C_1-C_{20} hydrocarbyl group may be straight-chained or branched, or be or include one or more cyclic groups, wherein each C_1-C_{20} hydrocarbyl group may optionally be substituted with one or more oxo (=O) and/or one or more halo groups, and wherein each C_1-C_{20} 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 R^4 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 R^{40}, wherein each R^{40} is independently selected from a -CN, -OH, $-NH_2$, oxo (=O), =NH or C_1-C_6 hydrocarbyl group, wherein each C_1-C_6 hydrocarbyl group may be straight-chained or branched, or be or include one or more cyclic groups, wherein each C_1-C_6 hydrocarbyl group may optionally be substituted with one or more halo groups, and wherein each C_1-C_6 hydrocarbyl group may optionally include one or more heteroatoms independently selected from N, O and S in its carbon skeleton.

2. The process as described in claim 1, wherein R^2 is a nitrogen protecting group that may be removed by catalytic hydrogenolysis.

3. The process as described in claim 1 or claim 2, wherein R^2 is $-CH_2R^{20}$ or $-COOCH_2R^{20}$, wherein R^{20} is an aryl or heteroaryl group, wherein the aryl or heteroaryl group is monocyclic, bicyclic or tricyclic, wherein the aryl or heteroaryl

group may optionally be substituted with one or more substituents independently selected from halo, -CN, -OH, -NO_2, -NH_2, -R^{21}, -OR^{21}, -NHR^{21}, -$N(R^{21})_2$ or -$N(O)(R^{21})_2$, wherein each R^{21} is independently selected from a C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_3-C_4 cycloalkyl or C_3-C_4 halocycloalkyl group, or any two R^{21} directly attached to the same nitrogen atom may together form a C_2-C_5 alkylene or C_2-C_5 haloalkylene group, and wherein R^{20}, including any optional substituents, contains from 1 to 20 carbon atoms.

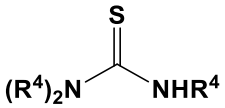
4. The process as described in any one of claims 1 to 3, wherein R^2 is -$COOCH_2Ph$.

5. The process as described in any one of claims 1 to 4, wherein R^3 is a sulfonate leaving group such as -OMs.

6. The process as described in any one of claims 1 to 5, wherein each R^4 is independently selected from hydrogen or a C_1-C_6 alkyl or C_3-C_6 cycloalkyl group, or any two R^4 may together form a C_2-C_6 alkylene group, wherein any C_1-C_6 alkyl, C_3-C_6 cycloalkyl or C_2-C_6 alkylene group may optionally be fluoro substituted.

7. The process as described in any one of claims 1 to 6, wherein each R^4 is hydrogen.

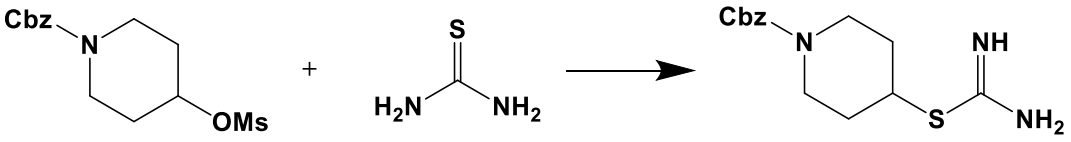
8. The process as described in any one of claims 1 to 7, wherein the process comprises the step of contacting the N-protected-4-derivatised piperidine (H) with reagent (I-X):



(I-X)

optionally in the presence of a base and/or a solvent.

9. The process as described in any one of claims 1 to 8, wherein the process comprises the step of contacting benzyl 4-((methylsulfonyl)oxy)piperidine-1-carboxylate (H') with reagent (I-Xb) in a solvent to obtain benzyl 4-(carbamimidoylthio)-piperidine-1-carboxylate (I') or a salt thereof:

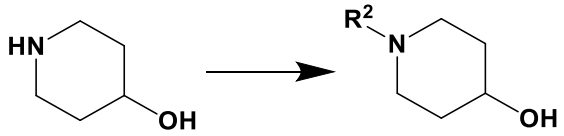


(H') (I-Xb) (I')

10. The process as described in any one of claims 1 to 9, wherein the thiourea adduct (I) or (I') is obtained as a methanesulfonic acid salt.

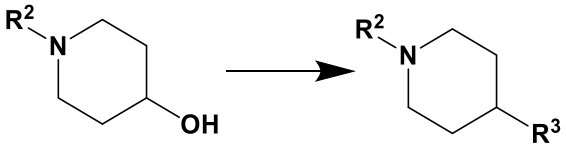
11. The process as described in any one of claims 1 to 10, wherein the N-protected-4-derivatised piperidine (H) or (H') is obtained by the steps of:

(i) converting 4-hydroxy piperidine (F) to a N-protected-4-hydroxy piperidine (G):



(F) (G) ; and

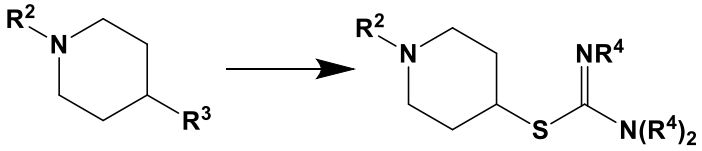
(ii) converting the N-protected-4-hydroxy piperidine (G) to the N-protected-4-derivatised piperidine (H):



(G) (H) .

12. A process comprising the step of:

converting a N-protected-4-derivatised piperidine (H) to a thiourea adduct (I):



(H) (I) ;

wherein the conversion is performed in the presence of a C_3-C_5 alcohol;

and wherein:

R^2 is a nitrogen protecting group;

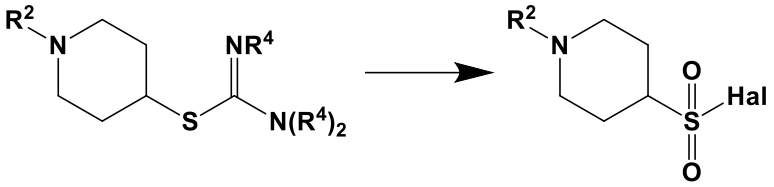
R^3 is a leaving group; and

each R^4 is independently selected from hydrogen or a C_1-C_{20} hydrocarbyl group, wherein each C_1-C_{20} hydrocarbyl group may be straight-chained or branched, or be or include one or more cyclic groups, wherein each C_1-C_{20} hydrocarbyl group may optionally be substituted with one or more oxo (=O) and/or one or more halo groups, and wherein each C_1-C_{20} 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 R^4 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 R^{40}, wherein each R^{40} is independently selected from a -CN, -OH, $-NH_2$, oxo (=O), =NH or C_1-C_6 hydrocarbyl group, wherein each C_1-C_6 hydrocarbyl group may be straight-chained or branched, or be or include one or more cyclic groups, wherein each C_1-C_6 hydrocarbyl group may optionally be substituted with one or more halo groups, and wherein each C_1-C_6 hydrocarbyl group may optionally include one or more heteroatoms independently selected from N, O and S in its carbon skeleton.

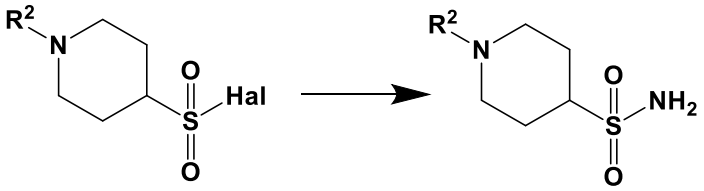
13. The process as described in claim 12, further comprising the steps of:

converting a thiourea adduct (I) to a N-protected-4-(halosulfonyl)-piperidine (J):



(I) (J) ;

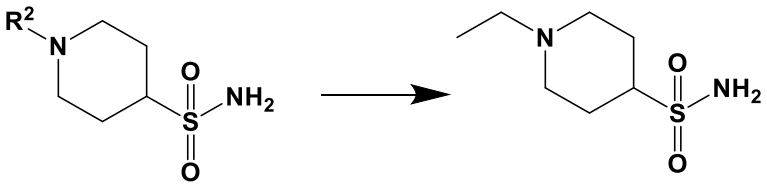
converting a N-protected-4-(halosulfonyl)-piperidine (J) to a N-protected-4-piperidinesulfonamide (K):



(J) (K)

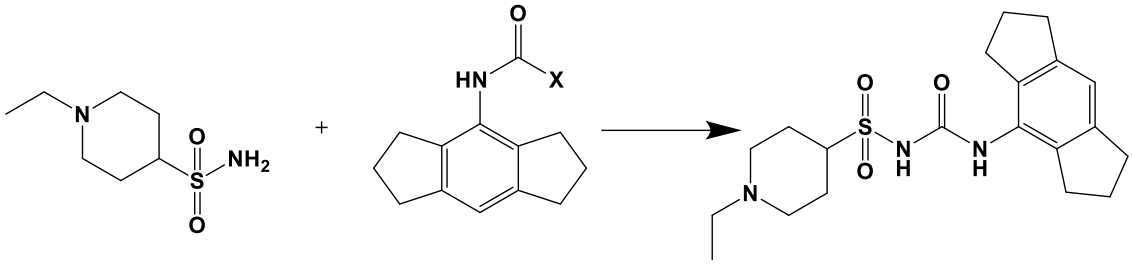
wherein the conversion comprises the steps of (1) forming a solution of ammonia in a solvent, and (2) adding the N-protected-4-(halosulfonyl)-piperidine (J) to the solution formed in step (1);

converting a N-protected-4-piperidinesulfonamide (K) to 1-ethyl-4-piperidinesulfonamide (A):



(K) (A); and

contacting the 1-ethyl-4-piperidinesulfonamide (A) with a 1,2,3,5,6,7-hexahydro-*s*-indacene derivative (B) in the presence of a solvent to obtain 1-ethyl-*N*-((1,2,3,5,6,7-hexahydro-s-indacen-4-yl)carbamoyl)piperidine-4-sulfonamide (C) or a salt thereof:

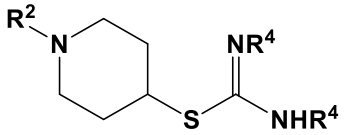


(A) (B) (C)

wherein X is a leaving group; and
Hal is Cl or Br.

14. 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 according to claim 13.

15. A thiourea adduct (I) or a salt thereof:



(I)

wherein:

R^2 is a nitrogen protecting group; and

each R^4 is independently selected from hydrogen or a C_1-C_{20} hydrocarbyl group, wherein each C_1-C_{20} hydrocarbyl group may be straight-chained or branched, or be or include one or more cyclic groups, wherein each C_1-C_{20} hydrocarbyl group may optionally be substituted with one or more oxo (=O) and/or one or more halo groups, and wherein each C_1-C_{20} 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 R^4 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 R^{40}, wherein each R^{40} is independently selected from a -CN, -OH, $-NH_2$, oxo (=O), =NH or C_1-C_6 hydrocarbyl group, wherein each C_1-C_6 hydrocarbyl group may be straight-chained or

branched, or be or include one or more cyclic groups, wherein each C_1-C_6 hydrocarbyl group may optionally be substituted with one or more halo groups, and wherein each C_1-C_6 hydrocarbyl group may optionally include one or more heteroatoms independently selected from N, O and S in its carbon skeleton.

16. The thiourea adduct (I) or the salt thereof as described in claim 15, wherein R^2 is $-COOCH_2Ph$ and each R^4 is hydrogen.