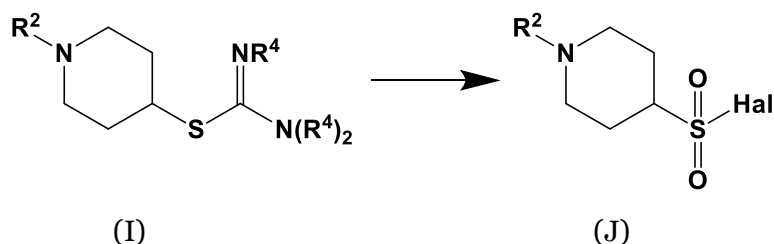


Claims

1. 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:

- R^2 is a nitrogen protecting group;
- 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; and
- Hal is Cl or Br.

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, -NO₂, -NH₂, -R²¹, -OR²¹, -NHR²¹, -N(R²¹)₂ or -N(O)(R²¹)₂, wherein each R²¹ is independently selected from a C₁-C₄ alkyl, C₁-C₄ haloalkyl, C₃-C₄ cycloalkyl or C₃-C₄ halocycloalkyl group, or any two R²¹ directly attached to the same nitrogen atom may together form a C₂-C₅ alkylene or C₂-C₅ haloalkylene group, and wherein R²⁰, 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 R² is -COOCH₂Ph.

5. The process as described in any one of claims 1 to 4, wherein each R⁴ is independently selected from hydrogen or a C₁-C₆ alkyl or C₃-C₆ cycloalkyl group, or any two R⁴ may together form a C₂-C₆ alkylene group, wherein any C₁-C₆ alkyl, C₃-C₆ cycloalkyl or C₂-C₆ alkylene group may optionally be fluoro substituted.

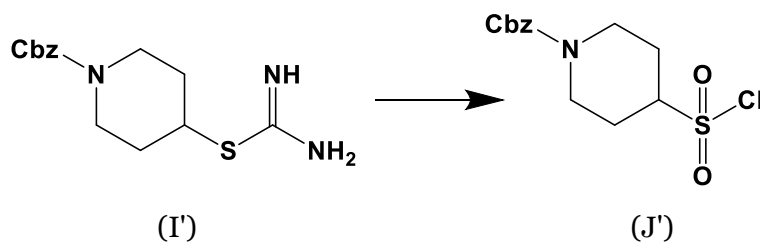
6. The process as described in any one of claims 1 to 5, wherein each R⁴ is hydrogen.

7. The process as described in any one of claims 1 to 6, wherein Hal is Cl.

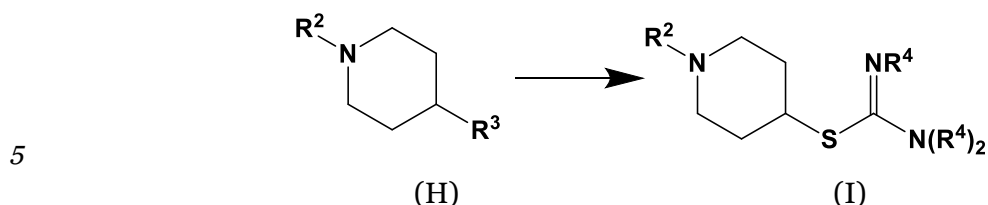
8. The process as described in any one of claims 1 to 7, wherein the process comprises the step of contacting the thiourea adduct (I) with a halogenating agent, such as N-chlorosuccinimide, to form the N-protected-4-(halosulfonyl)-piperidine (J) or the salt thereof.

9. The process as described in claim 8, wherein the thiourea adduct (I) is contacted with the halogenating agent in the presence of a carboxylic acid such as acetic acid, water, and optionally a second acid selected from HCl or HBr.

10. The process as described in claim 1 or claim 9, wherein the process comprises the step of contacting benzyl 4-(carbamimidoylthio)-piperidine-1-carboxylate (I') with a chlorinating agent to obtain benzyl 4-(chlorosulfonyl)-1-piperidinecarboxylate (J') or a salt thereof:



11. The process as described in any one of claim 1 to 10, wherein the thiourea adduct (I) or (I') is obtained by a process comprising the step of converting a N-protected-4-derivatised piperidine (H) to the thiourea adduct (I) or the salt thereof:

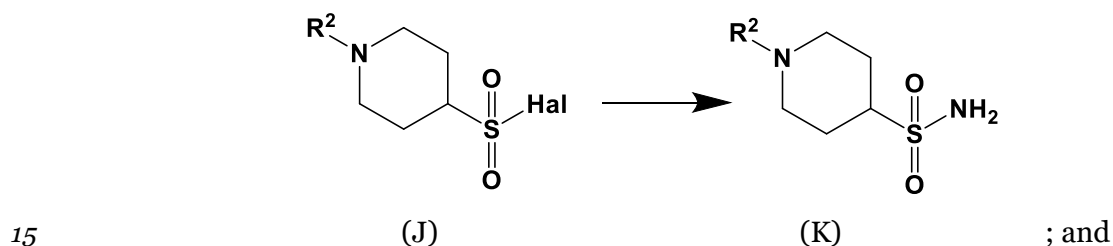


wherein:

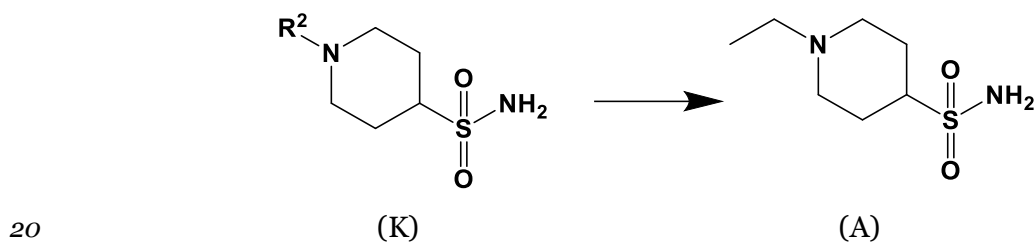
R³ is a leaving group.

- 10 12. The process as described in any one of claim 1 to 11, further comprising the steps of:

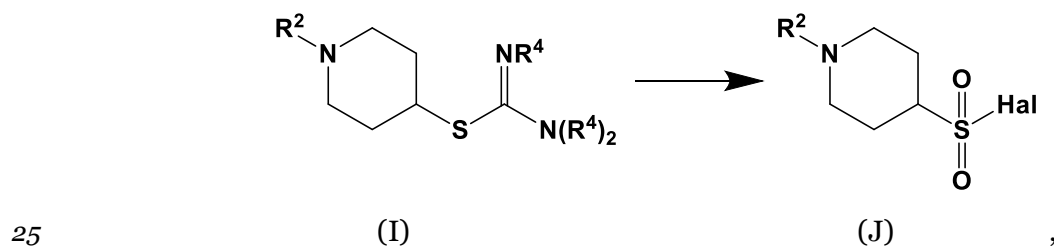
- (v) converting the N-protected-4-(halosulfonyl)-piperidine (J) or (J') to a N-protected-4-piperidinesulfonamide (K):

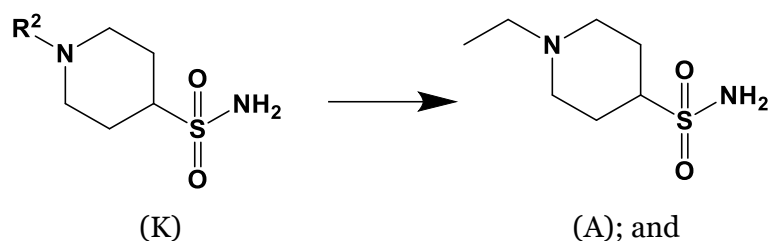


- (vi) optionally converting the N-protected-4-piperidinesulfonamide (K) to 1-ethyl-4-piperidinesulfonamide (A):

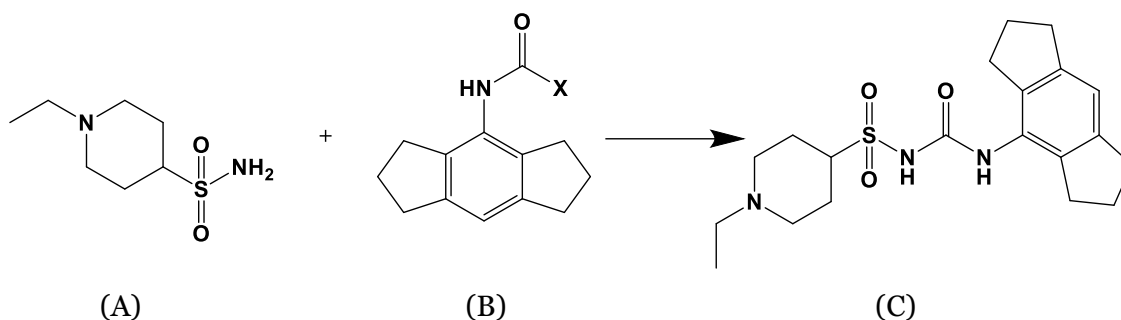


13. A process comprising the step of:
converting a thiourea adduct (I) to a N-protected-4-(halosulfonyl)-piperidine (J):





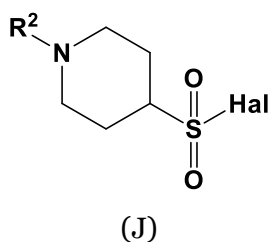
contacting the 1-ethyl-4-piperidinesulfonamide (A) with a 1,2,3,5,6,7-hexahydro-s-indacene derivative (B) in the presence of a solvent to obtain 1-ethyl-*N*-((1,2,3,5,6,7-hexahydro-s-indacen-4-yl)carbamoyl)piperidine-4-sulfonamide (C) or a salt thereof:



wherein X is a leaving group.

15. 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 14.

16. A compound, wherein the compound is:
an *N*-protected-4-(halosulfonyl)-piperidine (J) or a salt thereof:



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

17. A compound as described in claim 16, wherein R² is -COOCH₂Ph and Hal (if present) is Cl.

18. A compound as described in claim 16 or claim 17, wherein:
(i) the *N*-protected-4-(halosulfonyl)-piperidine (J) or the salt thereof is in solid form; and/or

- (ii) the N-protected-4-(halosulfonyl)-piperidine (J) or the salt thereof has a HPLC purity of $\geq 90\%$.