PROCESS AND INTERMEDIATE FOR THE PREPARATION OF OXETAN-2-YLMETHANAMINE

The present invention relates to a process and intermediate for the preparation of oxetan-2-ylmethanamine, which is a key intermediate in the preparation of certain glucagon-like peptide-1 receptor agonists.

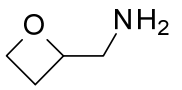
Oxetan-2-ylmethanamine is a key intermediate in the preparation of certain glucagon-like peptide-1 receptor agonists, including certain 1-[2-oxetan-2-ylmethyl]-1H-benzimidazole compounds disclosed in WO2018/109607. The process disclosed in WO2018/109607 for preparing (S)-oxetan-2-ylmethanamine is a five step process starting from (S)-2-((benzyloxy)methyl)oxirane. The first step is a ring expansion step which expands the oxirane to an oxetane. In the penultimate step, the nitrogen of the amine group is introduced using sodium azide and in the final step, the azide intermediate is reduced to provide the amine group. Azide compounds are highly toxic. Certain azide compounds also present significant physical hazards because they can be heat and shock sensitive and can explosively decompose with little input of external energy. As such, the final two steps of this process pose a significant liability and require extensive and costly safety measures.

There is a need for an improved process which is less-resource intensive, cheaper and/or facilitates more efficient production. In particular, there is a need for a process which avoids the use of toxic and hazardous azide compounds. Furthermore, there is a need for a simpler process which requires less manipulation.

The process of the present invention addresses these needs by introducing the protected nitrogen prior to the ring expansion step. The nitrogen is protected by two benzyl groups.

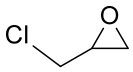
Summary

In one aspect of the present disclosure, there is provided a process for preparing a compound of the formula:

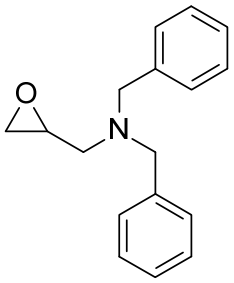


or salt thereof, comprising the steps of:

i. combining dibenzylamine and a compound of the formula:

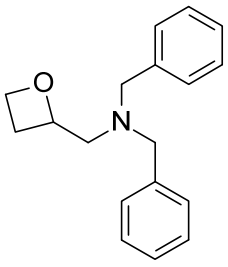


then adding a base to produce a compound of the formula:



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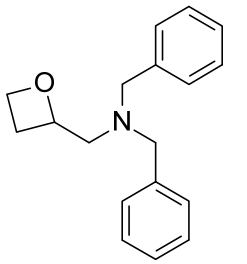
ii. taking trimethylsulfuxonium halide in the presence of a base and combining with a solution of the compound resulting from step (i) and heating to above 40°C to produce a compound of the formula:



; and

iii. deprotecting the compound resulting from step (ii).

In another aspect of the present disclosure, there is provided a compound of the formula:

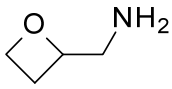


,

or salt thereof.

Description

Accordingly, in one embodiment, the present invention provides a process for preparing a compound of the formula:



Formula I

or salt thereof, comprising the steps of: