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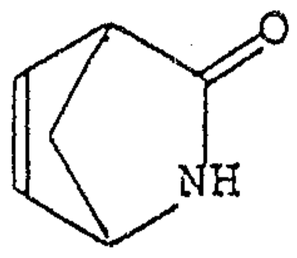
(54) Titre : PROCEDE D'OBTENTION DE 2-AZABICYCLO[2.2.1]HEPT-5-EN-3-ONE
(54) Title: PROCESS FOR THE PRODUCTION OF 2-AZABICYCLO[2.2.1]HEPT-5-EN-3-ONE

(57) Abrégé/Abstract:
A process for producing 2-azabicyclo[2.2.1]hept-5-en-3-one is disclosed by a Diels-Alder reaction of cyclopentadiene and methanesulfonyl cyanide followed by hydrolytic cleavage of the methanesulfonyl group.

## ABSTRACT OF THE DISCLOSURE

A process for producing 2-azabicyclo[2.2.1]hept-5-en-3-one is disclosed by a Diels-Alder reaction of cyclopentadiene and methanesulfonyl cyanide followed by hydrolytic cleavage of the methanesulfonyl group.

This invention relates to a process for the production of (±)-2-azabicyclo[2.2.1]hept-5-en-3-one having the formula:



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2-Azabicyclo[2.2.1]hept-5-en-3-one is a bicyclic lactam which is useful as a starting material for the synthesis of carboxylic nucleoside analogues [S. Daluge and R. Vince, J. Org. Chem., Vol. 43, (1978), page 2311]. Such nucleoside analogues are of interest because of their antiviral and chemotherapeutic properties as potential anti-tumor agents. A known synthesis of 2-azabicyclo[2.2.1]hept-5-en-one starts from 1,3-cyclopentadiene, which with chlorosulfonylisocyanate in a 1,2 addition forms a bicyclic N-chlorosulfonyl-β-lactam, which is rearranged into the corresponding 1,4-addition product and provides the target compound in poor yield (27.5 percent) by hydrolytic cleavage of the N-chlorosulfonyl group [J.R. Malpass and N.J. Tweddle, J. Chem. Soc. Perkin I, (1977), page 874].

Another known synthesis is based on the Diels-Alder reaction of cyclopentadiene with p-toluenesulfonyl cyanide. In this case, a tosyl-azanorbornadiene results first, which is converted by acid or alkaline hydrolysis into the target compound [J.C. Jagt and A.M. van Larsen, J. Org. Chem., Vol. 39, (1974), page 564; S. Daluge and R. Vince, loc. cit.]. Drawbacks of this process are the explosiveness of p-toluenesulfonyl cyanide and the unfavorable quantitative ratio of the product to the by-product p-tolylsulfinyl-p-tolylsulfone. Moreover, the cyclopentadiene is used in great excess and needs to be distilled off prior to the hydrolysis.

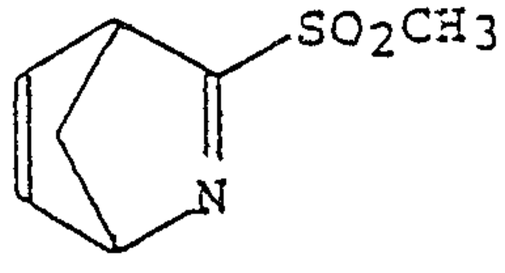
The object of the invention is to provide a process for the production of 2-azabicyclo[2.2.1]hept-5-en-3-one, which, starting from favorably priced feedstock, yields the desired product in a simple manner and in good yield without large amounts of waste.

Accordingly, the invention involves a process for the production of 2-azabicyclo[2.2.1]hept-5-en-3-one in which 1,3-cyclopentadiene is reacted with methanesulfonyl cyanide in a Diels-Alder reaction to form 3-methanesulfonyl-2-azabicyclo[2.2.1]hepta-2,5-diene and then the latter is hydrolyzed to 2-azabicyclo[2.2.1]hept-5-en-3-one.

Preferably the hydrolysis is performed in the presence of an acid. A carboxylic acid is preferably used as the acid, most preferably acetic acid. The Diels-Alder reaction is preferably performed in a solvent at a temperature of -50° to +100°C, more preferably at a temperature of -20° to +40°C. Preferred solvents include halogenated aliphatic and aromatic hydrocarbons, aromatic hydrocarbons, and acyclic or cyclic ethers, with dichloromethane being most preferred. Preferably the 3-methanesulfonyl-2-azabicyclo[2.2.1]hepta-2,5-diene is hydrolyzed without previously being isolated.

Another aspect of the invention provides the novel intermediate (±)-3-methanesulfonyl-2-azabicyclo[2.2.1]hepta-2,5-diene.

It has now been found that cyclopentadiene in stoichiometric amounts or in slight excess can react smoothly with methanesulfonyl cyanide to form the corresponding Diels-Alder adduct 3-methanesulfonyl-2-azabicyclo[2.2.1]hepta-2,5-diene having the formula:

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which can be hydrolyzed easily to 2-azabicyclo[2.2.1]hept-5-en-3-one. Methanesulfonyl cyanide can be produced according to a known process from methanesulfonyl chloride or sodium methanesulfonate [M.S.A. Vrijland, Org. Synth., Coll. Vol. VI, pages 727 to 730].

The hydrolysis of the Diels-Alder adduct can be performed both under acid and basic catalysis. Preferably an acid is used as the catalyst. Especially preferred are carboxylic acids, such as lower aliphatic carboxylic acids, especially acetic acid.

The Diels-Alder reaction is performed preferably in a solvent at a temperature of -50° to +100°C. A reaction temperature of -20° to +40°C is especially preferred. As the solvent basically all solvents are suitable which do not themselves react with one of the reactants or the Diels-Alder adduct. Preferably the solvent is a halogenated aliphatic or aromatic hydrocarbon, such as dichloromethane, 1,2-dichloroethane or chlorobenzene, an aromatic hydrocarbon, such as benzene, toluene or xylene, or an acyclic and cyclic ether, such as diethyl ether, diisopropyl ether, methyl-tert-butyl ether or tetrahydrofuran. Especially preferred is dichloromethane. The cyclopentadiene itself can be used as the solvent, by using it in excess.

The Diels-Alder adduct 3-methanesulfonyl-2-azabicyclo[2.2.1]hepta-2,5-diene can be isolated in the usual way and optionally be mildly purified, but because of its low stability, it is preferably subjected directly to hydrolysis without isolation.

The following Examples illustrate the performance of the process according to the invention.

Example 1

(±)-3-Methanesulfonyl-2-azabicyclo[2.2.1]hepta-2,5-diene

7.93 g of cyclopentadiene (120 mmol) was added to a solution of 10.51 g of methanesulfonyl cyanide (100 mmol) in 30 ml of dichloromethane over 5 minutes at -20°C. The colorless solution was stirred for another 2 hours at room

temperature and then the solvent was distilled off, and the Diels-Alder adduct remains as yellowish solid. Properties of the compound were:

Melting Point: 52° to 53°C

$^1$H-NMR ($CDCl_3$, 300 MHz): $\delta$ 2.10 (d, J=8Hz, 1H)
2.28 (d, J=8Hz, 1H)
3.15 (s, 3H)
4.45 (m, 1H)
5.47 (m, 1H)
6.89 (m, 2H)

## Example 2

### (±)2-Azabicyclo[2.2.1]hept-5-en-3-one

A solution of 2.55 g of cyclopentadiene (38.6 mmol) in 10 ml of dichloromethane cooled to -20° was added to a solution of 3.61 g of methanesulfonyl cyanide (97 percent, 33.3 mmol) in 30 ml of dichloromethane over 5 minutes. In this step the reaction temperature fluctuated between 17° and 22°C. The colorless solution was stirred for another 2 hours at room temperature and then mixed with 6 ml of acetic acid. 60 ml of water was added over 1 minute and the mixture was neutralized with 30 percent sodium hydroxide solution (pH=8). The phases were separated and the aqueous phase was extracted three times each with 25 ml of dichloromethane. The combined organic phases were dried on $MgSO_4$, filtered and evaporated to dryness. The colorless solid residue was dried at 30°C/300 mbar. The yield was 2.54 g, corresponding to 70 percent of theory, relative to the methanesulfonyl cyanide. The purity (GC) was about 100 percent. The product had a melting point of 50° to 53°C.

THE EMBODIMENTS OF THE INVENTION IN WHICH AN EXCLUSIVE PROPERTY OR PRIVILEGE IS CLAIMED ARE DEFINED AS FOLLOWS:

1. A process for the production of 2-azabicyclo[2.2.1]hept-5-en-3-one, which comprises reacting 1,3-cyclopentadiene with methanesulfonyl cyanide in a Diels-Alder reaction to form 3-methanesulfonyl-2-azabicyclo[2.2.1]hepta-2,5-diene and then hydrolyzing the latter compound to form 2-azabicyclo[2.2.1]hept-5-en-3-one.

2. A process according to Claim 1, wherein the hydrolysis is performed in the presence of an acid.

3. A process according to Claim 2, wherein the acid is a carboxylic acid.

4. A process according to Claim 3, wherein the carboxylic acid is acetic acid.

5. A process according to Claims 1, 2, 3 or 4, wherein the Diels-Alder reaction is performed in a solvent at a temperature of from -50° to +100°C.

6. A process according to Claims 1, 2, 3 or 4, wherein the Diels-Alder reaction is performed in a solvent at a temperature of from -20° to +40°C.

7. A process according to Claim 5, wherein the solvent is a halogenated aliphatic hydrocarbon, a halogenated aromatic hydrocarbon, an aromatic hydrocarbon, an acyclic ether or a cyclic ether.

8. A process according to Claim 6, wherein the solvent is a halogenated aliphatic hydrocarbon, a halogenated aromatic hydrocarbon, an aromatic hydrocarbon, an acyclic ether or a cyclic ether.

9. The process according to Claim 7 or 8,

wherein the solvent is dichloromethane.

10. A process according to Claim 1, 2, 3, 4, 7 or 8, wherein 3-methanesulfonyl-2-azabicyclo[2.2.1]hepta-2,5-diene is hydrolyzed without previously being isolated.

11. (±)-3-Methanesulfonyl-2-azabicyclo[2.2.1] hepta-2,5-diene.