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Nitration of benzyl derivatives of acetylated hexaazaisowurtzitane

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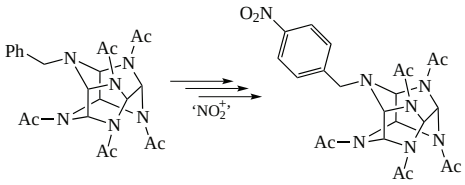
Nitration of *N*-benzylated 2,4,6,8,10,12-hexaazaisowurtzitane derivatives occurs selectively at *para*-positions of the benzyl groups. The best reagent for this reaction is ammonium nitrate in sulfuric acid.



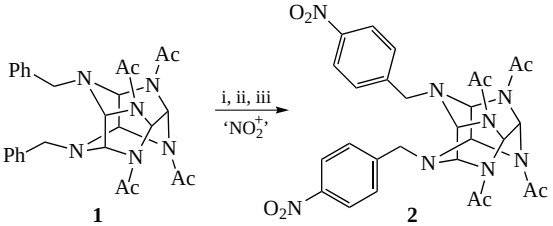
Keywords: hexaazaisowurtzitanes, cage compounds, nitration, nitrating mixtures, benzyl groups, selective reaction.

Since 2,4,6,8,10,12-hexanitro-2,4,6,8,10,12-hexaazaisowurtzitane (CL-20, HNIW) has become the new powerful explosive, the major related research has been focused on compounds suitable for industrial applications and on studying the nitration stage.[1–7] The available data on bioactivity of 2,4,6,8,10,12-hexaazaisowurtzitane derivatives and polycyclic structure allows for the assumptions that this family of chemical entities has a huge pharmacological potential.[8–11] Thus, the investigated 4,10-bis-(*p*-nitrobenzyl)-2,6,8,12-tetraacetyl-2,4,6,8,10,12-hexaazaisowurtzitane **2** exhibits the effect of allosteric stimulation of the central nervous system, acting simultaneously on GABA-ergic system, and on the cerebral cortex.[10] In addition, nitration of benzyl derivatives of 2,4,6,8,10,12-hexaazaisowurtzitane followed by reduction of the nitro group may provide an array of functional compounds with a considerable bioactivity.

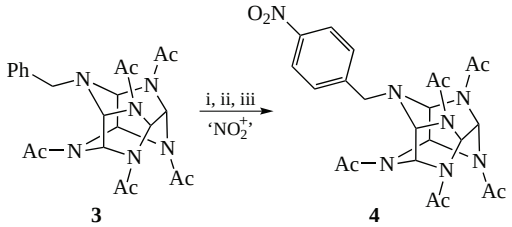
The known method for producing **2** (Scheme 1) is based on the nitration of 4,10-dibenzyl-2,6,8,12-tetraacetyl-2,4,6,8,10,12-hexaazaisowurtzitane **1** with excess fuming nitric acid at temperatures below –28 °C for 1 h. The resulting product with a yield of 60% is a mixture of isomers with a *para*-isomer **2** content of 60.2% (HPLC). Along with this, *p*-nitrobenzyl and acetyl groups are partially replaced by a nitro group. Upon the prolongation the processing, the fraction of **2** in the reaction mixture would decrease.[11]

In order to improve the yield of the target compound **2** and to reduce the amount of side products, a study of nitration of compound **1** with various nitrating agents was herein carried out. When the nitration with fuming nitric acid was performed at somewhat higher temperatures of –5 to –10 °C, the reaction proceeded vigorously producing much byproducts, the yield of the crude material did not exceed 45%, and the content of **2** was 64% (HPLC). The use of ammonium nitrate in trifluoroacetic acid as a nitrating mixture reduced the rate of the nitration process, the product yield varied from 11 to 35% subject to the temperature regime. When a stoichiometric amount of ammonium nitrate in sulfuric acid was applied at 0 °C and the reaction time was increased to 20 h, the crude product yield reached 98% with the content of **2** having been 86%. After recrystallization from acetone, the target product **2** was isolated in a yield of 72% with a purity of 93% (HPLC). Raising the temperature to 10 °C reduced the processing time to 4 h without dropping the yield of the crude product (96%), after recrystallization, the yield of the target product with a 94% purity was 69%.

We also examined the nitration of monobenzylated analogue **3**, namely, 4-benzyl-2,6,8,10,12-pentaacetyl-2,4,6,8,10,12-hexaazaisowurtzitane (Scheme 2). When the process was carried out in fuming nitric acid at –5 to –10 °C, the reaction produced a range of byproducts thus making the product isolation difficult (the target product **4** yield was not higher than 44%). The use of ammonium nitrate in trifluoroacetic acid at –10 °C provided only 37% yield of compound **4**. When the temperature was raised, the product yield declined. The use of stoichiometric amount of ammonium nitrate in sulfuric acid to obtain **4** showed the best results. At 0 °C and the exposure time of 8 h, the crude product yield was 87% with the content of **4** being 76% (HPLC). After recrystallization, the yield of compound **4** with HPLC purity of 93% was 63%. An increase in temperature to 10 °C reduced the processing time to 3 h without a significant change in the yield of the crude material (86%), while the nitro derivative



Scheme 1 *Reagents and conditions*: i, HNO_3, –5 to –10 °C; ii, NH_4NO_3/CF_3COOH, –10 °C; iii, NH_4NO_3/H_2SO_4, 0–10 °C.



Scheme 2 *Reagents and conditions*: i, HNO_3, –5 to –10 °C; ii, NH_4NO_3/CF_3COOH, –10 °C; iii, NH_4NO_3/H_2SO_4, 0–10 °C.

4 had a higher purity of 83% (HPLC). However, the use of this nitrating mixture at room temperature led to a drop in the yield to 39%, with the reaction time being no more than 1 h.

In summary, we performed a selective nitration of benzyl derivatives **1** and **3** at the *para*-position of the benzyl groups to produce compounds **2** and **4**, respectively. The yields of the target products depended largely on the nitrating mixture activity.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2022.05.019.

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