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Effect of pH on the reaction outcome between tetraacetyl hexaazaisowurtzitane and aldehydes

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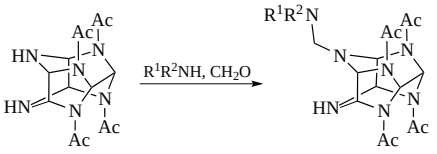
2,6,8,12-Tetraacetyl-2,4,6,8,10,12-hexaazaisowurtzitane was subjected to *N*-aminomethylation under various conditions, which afforded new derivatives of aminal nature. The highest yields were achieved when the reactions were carried out in a weak-alkali medium.



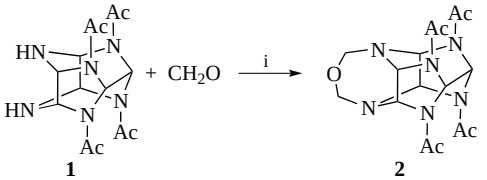
Keywords: hexaazaisowurtzitanes, formaldehyde, aldehydes, *N*-aminomethylation, acetals, aminals, cage compounds.

Ever since the synthesis of the most powerful chemical explosive CL-20, the main interest for 2,4,6,8,10,12-hexaazaisowurtzitane derivatives has been focused on compounds suitable for defense applications and on nitration reaction progress features.[1–5] In the meantime, compounds of this family possess high bioactivity[6,7] and can probably find application in our everyday routine as medicinal drugs. Therefore, it is equally important to solve the problem of incorporating active functional substituents into the hexaazaisowurtzitane molecule. The principal substrate for the study on the reactivity of hexaazaisowurtzitanes was 2,6,8,12-tetraacetyl-2,4,6,8,10,12-hexaazatetracyclo-[5.5.0.0^{5,9}.0^{3,11}]dodecane (TAIW) **1** whose structure offers the challenge to investigate amino group hydrogen substitution reactions. The most studied are acylation reactions when the substitution of one or two hydrogen atoms depends on the spatial structure of the acyl group being inserted. For instance, mono-derivatives are chiefly formed with acid chlorides that have bulky substituents at the *ortho*- and *meta*-positions of the benzyl group.[8–10] The literature[11] describes 3,5,9,11-tetraacetyl-14-oxa-1,3,5,7,9,11-hexaazapentacyclo[5.5.3.0^{2,6}.0^{4,10}.0^{8,12}]pentadecane **2** prepared *via* the reaction between TAIW **1** and formaldehyde (Scheme 1), which creates prerequisites for the design of more complex structures.

The in-depth study into the synthesis conditions for product **2** demonstrated that the most expedient was to use acetonitrile as the solvent, in which case its hydration was admissible to 50%, while the pH value had to be from 2 to 4.5.[12] Those conditions ensured that the yield of product **2** was more than 95%, with the reaction time of no more than 30 min. As the pH was raised above 4.5, the yield was decreased due to fast decomposition of the target product to the starting TAIW, while at pH > 8 decomposition of both the starting and target compounds took place. The effect of pH on the addition of other aldehydes has not been studied so far.

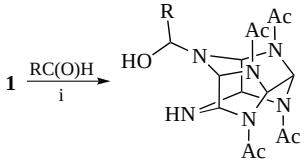
In this work, we found that the reactions between **1** and acetaldehyde, propanal or butanal furnished the corresponding *N*-(1-hydroxyalkyl) derivatives **3a–c** (Scheme 2). It is worth noting that for tetracenes, polycyclic amines, the reaction with formaldehyde gave products of aminal nature.[13] The reaction rate was low, and by the time the decomposition of the framework products began, so large amount of the initial TAIW **1** was detected in the reaction mixture. When the reaction was carried out in weak-acid and weak-alkali media, the yields of the products were the highest although moderate (see Scheme 2). It is also of note that the formation rate of the product in the weak-alkali medium was somewhat higher (reaction time 72 h) than in the weak-acid (96–108 h) or neutral medium (no less than 168 h). The similar attempted reaction with aromatic aldehydes (benzaldehyde, salicylic aldehyde and vanillin) under different conditions did not bring about the target products, which could be due to spatial hindrances.

The results obtained from the reaction with the aldehydes led us to suggest that compound **1** could be also engaged into the *N*-aminomethylation reaction (Scheme 3). Formaldehyde was chosen as the carbonyl constituent for this purpose since higher aldehydes C_2–C_4 were expected to provide very low yields. The use of benzylamine in the *N*-aminomethylation reaction under various conditions resulted in 4-(*N*-benzylaminomethyl)-2,6,8,12-tetraacetyl-2,4,6,8,10,12-hexaazaisowurtzitane **4a** in 1.6% (pH 3.5), 13.2% (pH 8) and 6.4% (pH 10) yields, with the principal byproduct (>85%) being 1,3,5-tribenzyl-1,3,5-triazacyclohexane. In the case of using morpholine as the amine component, the reaction proceeded slowly, the initial compounds prevailed, the target 4-morpholinomethyl-2,6,8,12-tetraacetyl-



1 **2**

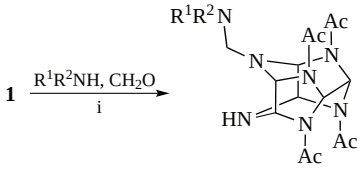
Scheme 1 *Reagents and conditions*: i, MeCN or MeCN/H_2O, pH 2–4 or 5, room temperature, 30 min.



3a–c

3a–c	R	Yield (%) at pH					
		1	4	5	7	8	10
a	Me	18	22	28	16	43	17
b	Et	7	5	9	7	14	6
c	Pr	2	4	8	7	12	1

Scheme 2 *Reagents and conditions*: i, MeCN, room temperature, 72–168 h.



4a,**b**

4a,**b**	R^1, R^2	Yield (%) at pH		
		4	8	10
a	R^1 = Bn, R^2 = H	2	13	6
b	$R^1 + R^2 = (CH_2)_2O(CH_2)_2$	4	17	9

Scheme 3 *Reagents and conditions*: i, MeCN, room temperature, 72–168 h.

2,4,6,8,10,12-hexaazaisowurtzite **4b** was obtained in 3.8% (pH 4), 16.8% (pH 8) and 8.9% (pH 10) yields.

In summary, 2,6,8,12-tetraacetyl-2,4,6,8,10,12-hexaazaisowurtzitane **1** was demonstrated to be engaged in the nucleophilic addition reaction with different aldehydes. The reaction with formaldehyde furnished pentacyclic 3,5,9,11-tetraacetyl-14-oxa-1,3,5,7,9,11-hexaazapentacyclo[5.5.3.$0^{2,6}$.$0^{4,10}$.$0^{8,12}$]-pentadecane, while the reactions with alkanals C_2–C_4 resulted in the addition of the 1-hydroxyalkyl substituent to only one nitrogen atom, whereas aromatic aldehydes did not react. The *N*-aminomethylation of TAIW **1** with morpholine and benzylamine afforded monosubstituted products of aminal nature. The yields of the products were somewhat higher in weak-alkali media due to the low basicity of the starting compound.

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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.2022.05.018.

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