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Synthesis of tris(β,β,γ-oximinoalkyl)amines from aliphatic nitro compounds and methyl vinyl ketone

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ABSTRACT

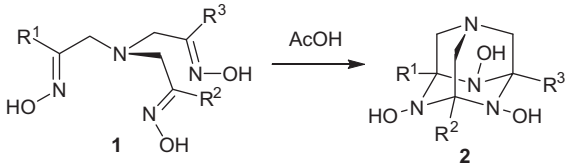
A general strategy for the assembly of previously unknown tris(β,β,γ-oximinoalkyl)amines from aliphatic nitro compounds and methyl vinyl ketone is described. The strategy involves *N,N*-bis(siloxy)enamines as key intermediates. The latter are accessible by double silylation of alkylnitro compounds. Nickel(II) and copper(II) complexes of tris(β,β,γ-oximinoalkyl)amines are prepared and structurally characterized.

Tris(β,β,β-oximinoalkyl)amines (trisoximes) **1** are prospective ligands for the design of biomimetic catalysts.[1] Also, the cyclization of the oxime groups in **1** results in the formation of 4,6,10-trihydroxy-1,4,6,10-tetraazaadamantanes **2**—derivatives of a new class of heterocage compounds with a cage isomeric to the well-known urotropine (1,3,5,7-tetraazaadamantane) (Scheme 1).[2]

Symmetrically substituted trisoximes **1**, which were prepared by the reaction of α-halooximes **3** with ammonia have been well known for more than 100 years (Scheme 2).[3] However, various functionalized and unsymmetrically substituted trisoximes became available only recently by using aliphatic nitro compounds (**ANC**s) as starting materials (Scheme 2).[4,5] The strategy of **ANC** silylation to give the corresponding *N,N*-bis(siloxy)enamines (**BENA**s) was exploited to achieve this aim. **BENA**s, similarly to α-halooximes **3**, serve as precursors for generation of highly reactive nitroso-alkenes (**NA**s). However, the use of **BENA**s allows the generation of **NA**s to be controlled more effectively and provides good selectivity during the process.[6]

In the present work we demonstrate that **BENA** can also serve as convenient precursors for currently unknown trisoximes **4**, or homotrisoximes, which contain an additional methylene group in one of the oximinoalkyl fragments compared to trisoximes **1** (Fig. 1).

The proposed scheme for the synthesis of trisoximes **4** includes the introduction of the two β-oximinoalkyl fragments and one γ-oximinoalkyl fragment to ammonia (or a synthetic equivalent of ammonia). In these approaches the introduction of β-oximinoalkyl fragments by employing **BENA**s seems to be logical, since they show high efficiency in the synthesis of common trisoximes **1**. For the introduction of the γ-oximinoalkyl substituents we conceived tandem aza-Michael reactions then oximation of the resulting aminoketone. It should be noted, that the sequence of introduction of these fragments can be varied. In accordance with this we considered several procedures for the synthesis of various homotrisoximes **4**.



Scheme 1. Cyclization of tris(β-oximinoalkyl)amines into 4,6,10-trihydroxy-1,4,6,10-tetraazaadamantanes.

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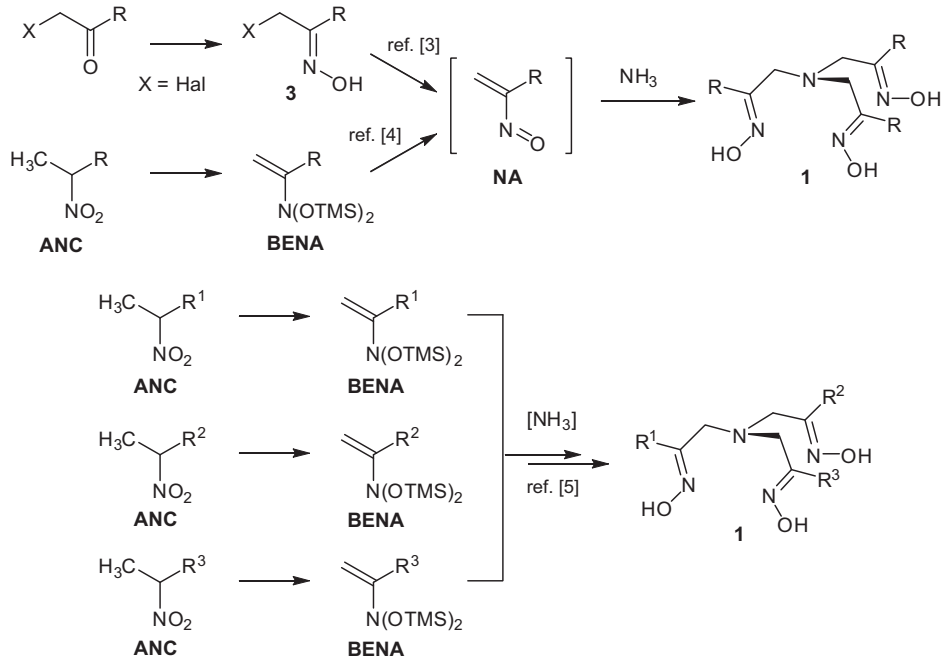


Scheme 2. Synthesis of tris(β-oximinoalkyl)amines.

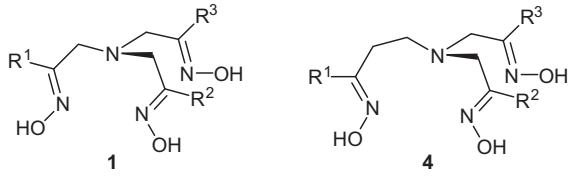


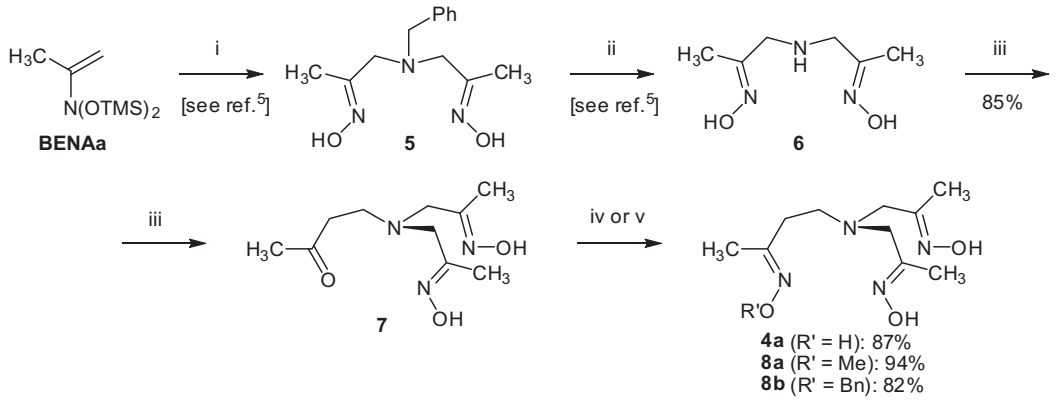
Figure 1. Tris(β-oximinoalkyl)amines and their homologues.

The first route (Scheme 3) involves the synthesis of bis(β-oximinoalkyl)amine **6** according to a literature protocol, followed by its reaction with methyl vinyl ketone (MVK). Subsequent oximation of the keto-group in aminoketone **7** by treatment with hydroxylamine in methanol furnished the desired trimethylsubstituted homotrisoxime **4a**. The use of *O*-methyl- or *O*-benzylhydroxylamines in the oximation step provided the corresponding homotrisoximes **8a** and **8b** in high yields.

However, attempts to extend this approach to a range of other α,β-unsaturated ketones [mesityl oxide $CH_3C(=O)CH=C(CH_3)_2$ and benzylideneacetone $CH_3C(=O)CH=CHPh$] were unsuccessful. No noticeable conversion of amine **6** was observed in these experiments, probably, due to the higher steric hindrance of the employed ketones compared to MVK. Furthermore, the reaction of bisoxime **6** with acrolein gave a complex mixture of unidentified compounds.

The second route to homotrisoximes **4** is based on an inverted sequence of oximinoalkyl fragment introduction (a γ-oximinoalkyl fragment followed by two β-oximinoalkyl fragments, Scheme 4). The action of MVK with sodium azide furnished azidoketone **9**,[7] which was then transformed into the corresponding oxime by treatment with hydroxylamine. The azido group in **9** was reduced into primary amine by catalytic hydrogenation over palladium.[5] The target homotrioximes **4a** and **4b** were obtained by addition of BENA**a** or BENA**b** to β-aminooxime **11** in MeOH (Scheme 4).

Finally, it was demonstrated that the strategy could be employed for the synthesis of unsymmetrically substituted homotrisoximes (e.g., **4c**). For this aim, mono(β-oximinoalkyl)amine **12** was prepared according to the literature procedure.[5] Aza-Michael reaction of oxime **12** with MVK, followed by oximation of the



Scheme 3. Reagents and conditions: (i) 0.45 equiv $BnNH_2$, CH_2Cl_2, then MeOH; (ii) 1 atm H_2, Pd/C (10%); (iii) 1.2 equiv MVK, MeOH; (iv) 1.5 equiv NH_2OH, MeOH; (v) 1.2 equiv $R'ONH_2{\cdot}HCl$, 1.2 equiv K_2CO_3, MeOH.