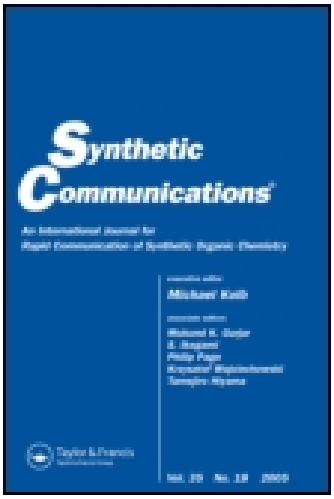

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SYNTHESIS OF TRIS(γ-OXIMINOALKYL)AMINES, NEW TRIPODAL N4 LIGANDS

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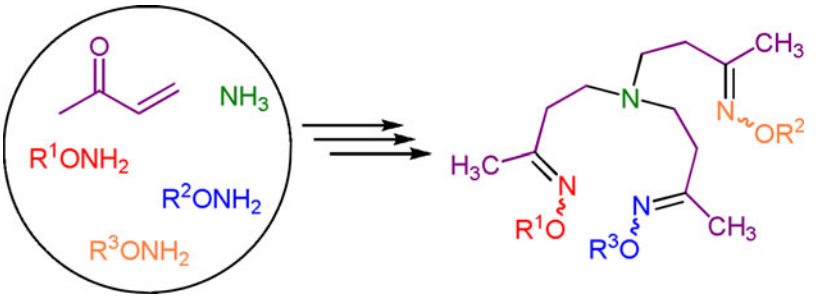
GRAPHICAL ABSTRACT



Abstract *An original approach to the synthesis of tris(γ-oximinoalkyl)amines was proposed. The suggested synthetic sequence is based on aza-Michael addition of ammonia to methyl vinyl ketone and oximation of obtained products with hydroxylamine or* O*-alkhylhydroxylamines. The tris(γ-oximinoalkyl)amines may be considered as prospective N4 tripodal ligands.*

Keywords Michael addition; oxime; tripodal ligand

INTRODUCTION

Tripodal N4 ligands play great roles in catalysis,[1] biomimetics,[2] and systems of molecular recognition and sensors.[3] Selected examples of such ligands are shown in Fig. 1.

In the present work we suggest an approach to the synthesis of a new type of N4 ligands, tris(γ-oximinoalkyl)amines **7**. The only known trimethyl substituted tris

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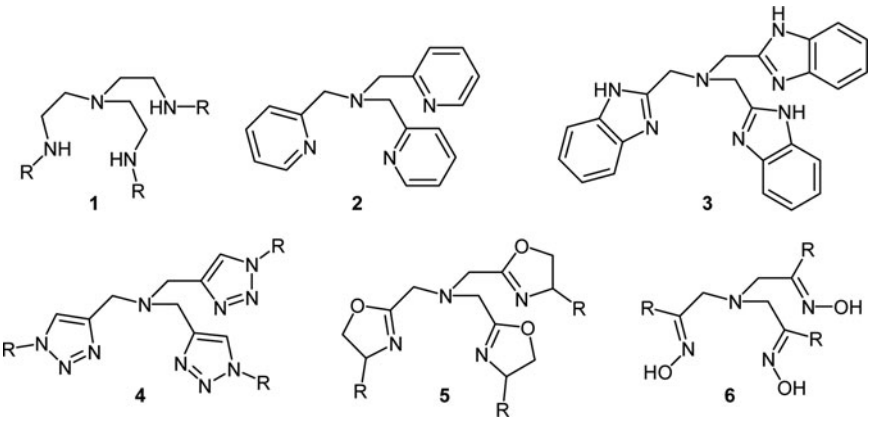
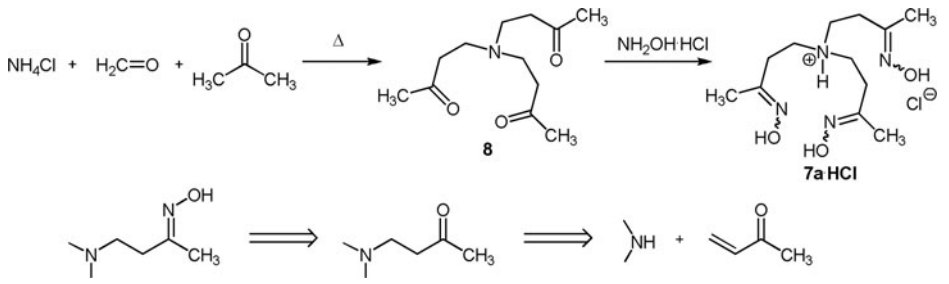


Figure 1. Selected examples of tripodal N4 ligands.



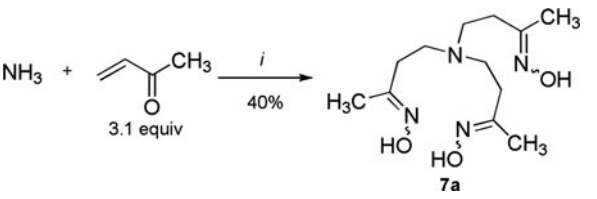
Scheme 1. Known and suggested approaches to trisoxime **8**.

(γ-oximinoalkyl)amine **7a** was synthesized by Mannich in 1926 as hydrochloric salt by condensation of ammonium chloride with acetone and formaldehyde and further oximation of triketone **8**, but the overall yield did not exceed 1%[4a] (probably because of the labiality of **8** to intermolecular aldol reaction[4b]). Our strategy is based on the sequence of aza-Michael addition of amine to methyl vinyl ketone (MVK) and subsequent oximation of the resulting aminoketone. The main advantages of using aza-Michael reaction instead of Mannich condensation are mild conditions, short reaction times, and the possibility of *one-pot* oximation of the generated β-aminoketones after reaction. It should be noted that previously only products of cyclization of triketone **8** were isolated in reaction of methyl vinyl ketone with ammonia (Scheme 1).[5]

RESULTS AND DISCUSSION

The reaction of ammonia with MVK in methanol rapidly (10–15 min) produces unstable triketone **8**, which was oximated without isolation by addition of hydroxylamine solution. Thought the desired product **7a** is formed in moderate yield, its isolation is very simple (crystallization from reaction mixture). Also the procedure was easily scaled up for preparation of **7a** in a multigram quantity.

Application of benzylamine instead of ammonia allows a sequential introduction of γ-oximinoalkyl substituents and thus provides access to unsymmetrically



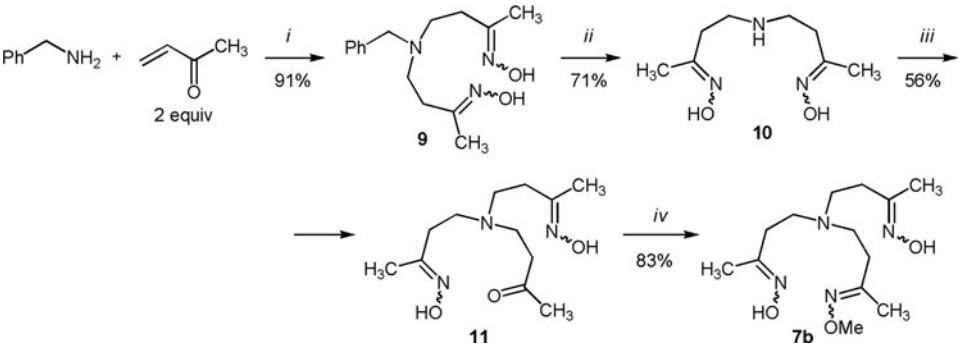
Scheme 2. MeOH, 15 min; then NH_2OH (aq., 3.1 equiv), 12 h.

substituted *O*-substituted trisoximes **7** by using *O*-alkyl hydroxylamines. Such modification of trisoxime structure may be of interest from several viewpoints. First, variation of hydrophility of ligand and hence the corresponding complexes is possible. The second point is controlling of coordination properties of ligand by deprotonation of oxime groups into oximate anion (see Ref. 2b). Finally, *O*-oxime ether bond might be useful for conjugation of trisoximes with functional molecules.[6]

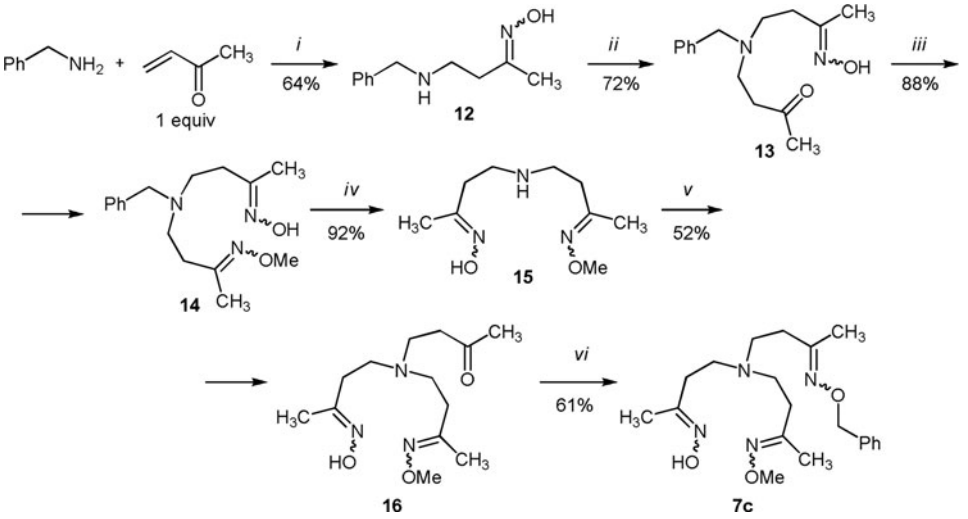
The synthesis of mono-*O*-methyl substituted trisoxime **7b** involves bis(γ-oximinoalkyl)amine **10** as key intermediate. The latter was synthesized by reaction of benzylamine with 2.2 equiv. of MVK, *one-pot* oximation, and reductive abstraction of the benzyl group. Then the secondary amine **10** was involved in the reaction with MVK to give ketone **11**, which was subsequently oximated with *O*-methylhydroxylamine to give trisoxime mono-*O*-methyl ether **7b** (Scheme 3).

Finally, the suggested strategy was employed for the synthesis of trisoxime **7c** bearing *O*-methyl- and *O*-benzyl oxime ethers and one oxime group (Scheme 4). To achieve this benzylamine was involved in reaction with equimolar amount of MVK and the resulting aminoketone was treated with hydroxylamine. The resulting secondary amine **12**[7] was alkylated with the second molecule of MVK and oximated with *O*-methylhydroxylamine to give bis-oxime ether **14** in good yield. Subsequent hydrogenolysis of **14**, alkylation with a third molecule of MVK, and oximation with *O*-benzylhydroxylamine furnished the desired unsymmetric di-*O*-substituted trisoxime **7c**.

The identity and purity of all products were confirmed by ^1H and ^{13}C NMR, high-resolution mass spectrometry (HRMS), and elemental analysis data. The oxime-containing products were obtained as dynamic mixtures of *E*/*Z* isomers. The configuration of the C=N double bond in the oxime groups was determined



Scheme 3. (*i*) neat, 15 min, then NH_2OH (aq., 2.2 equiv), MeOH; (*ii*) H_2 (1 atm), Pd/C (10%), MeOH; (*iii*) MVK (1.2 equiv), MeOH; *iv*: NH_2OH (aq.,1.2 equiv), MeOH.



Scheme 4. (*i*) Neat, 10 min, then NH_2OH (aq., 1.0 equiv), MeOH; (*ii*) MVK (1.2 equiv); (*iii*) $MeONH_2$•HCl (1.2 equiv), K_2CO_3 (1.2 equiv), MeOH; (*iv*) H_2 (1 atm), Pd/C (10%), MeOH; (*v*) MVK (1.2 equiv); and (*vi*) $PhCH_2ONH_2$•HCl (1.2 equiv), K_2CO_3 (1.2 equiv), MeOH.

as described in previous works,[8] and isomeric composition of obtained compounds refers to products after isolations.

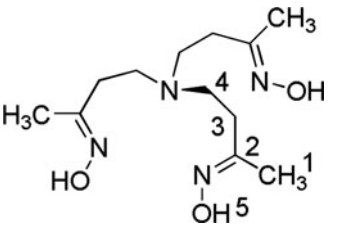
CONCLUSION

An efficient scalable *one-pot* procedure for preparation of trisoxime **7a** from ammonia, MVK, and hydroxylamine was developed. The suggested approach was extended to the synthesis of unsymmetrically substituted ethers of tris(γ-oximinoalkyl)amines.

EXPERIMENTAL

4-{Bis[3-(hydroxyimino)butyl]amino}-2-butanone Oxime (7a)

Methyl vinyl ketone (1 ml, 12.3 mmol) was added to a solution of ammonia in methanol (2 M, 2 ml, 4 mmol) with vigorous stirring. The reaction mixture was stirred for 15 min and then the solution of hydroxylamine in methanol (0.75 ml of 50% aqueous solution, 12.3 mmol dissolved in 5 ml of methanol) was added. The reaction mixture was kept overnight at 2–5 °C and then for 72 h at −20 °C. White precipitate was filtered, washed with Et_2O, and dried in vacuum (0.25 mm Hg). Yield: 435 mg (40%).



White solid, mp 116–123 °C, mixture of isomers with ratio of *E* and *Z* fragments 1.2:1.

^{1}H (300 MHz, DMSO-d_6): δ = 1.73 and 1.76 [2 s, 9 H, (1), *E* and *Z* fragments], 2.23 and 2.37 [2 m, 6 H, (3), *E* and *Z* fragments], 2.60 [m, 6 H, (4)], 10.16 and 10.22 [2 s, 2 H, (6), *Z* and *E* fragments]. ^{13}C (75 MHz, DMSO-d_6): δ = 13.7 and 20.3 [(1), *E* and *Z* fragments], 26.0, 26.1, 33.3, and 33.4 [(3), *Z, Z, E,* and *E* fragments], 48.7, 48.8 and 50.0 (4), 154.6 and 154.9 (2). HRMS (+ve): For $C_{12}H_{25}N_4O_3$ [MH+] calculated *m/z*: 273.1921. Found: 273.1923. Elemental analysis for $C_{12}H_{24}N_4O_3$ calculated: C, 52.92; H, 8.88; N, 20.57. Found: C, 52.89; H, 8.91; N, 20.46.

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SUPPORTING INFORMATION

Full experimental detail and ^{1}H and ^{13}C NMR spectra for this article can be accessed on the publisher's website.

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