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Mono-benzyl substituted *cis*,*cis*-1,3,5-triaminocyclohexanes

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Abstract—Unsymmetrical derivatives of the versatile molecule *cis*,*cis*-1,3,5-triaminocyclohexane (tach) have been prepared using a new metal-promoted synthesis to give the mono *N*-substituted tach ligands. This new method enables the synthesis of these molecules selectively and in good yields and purity.

Small molecules which can coordinate to metal ions and which enforce an N_3 face-capping geometry at the metal are used extensively in coordination chemistry, particularly as catalysts and biomimetic complexes. The most widely used ligands are those based on triazacyclononane, trispyrazolylborates, trisimidazoylmethanes and *cis*,*cis*-1,3,5-triaminocyclohexane (tach). Of these ligands, tach–metal complexes are attracting increased attention due to their potential application as imaging agents and metal chelating agents,[1–6] as cata- lysts for the hydrolysis of DNA[7] and peptides[8,9] and in biomimetic complexes.[10–12] Despite the wide interest in tach, there are few reports for the general synthesis of unsymmetrically *N*,*N*′,*N*″-substituted tach ligands. The existing synthetic methods tend to produce a mixture of products, which require complex separation.[13,14] Building on our previous work in which we demonstrated that *N*-substituted tach molecules acted as ligands in metal complexes,[15–17] we present here a general synthesis and characterisation of unsymmetrical *N*,*N*′,*N*″-substituted tach ligands, significantly extending the range of possible tach derivatives. To prepare N-substituted tach, we have used a simple and reliable metal-catalysed controlled hydrolysis of tri-imine derivatives of tach.

The hydrobromide salt of tach was synthesized from the corresponding *cis*,*cis*-1,3,5-cyclohexanetricarboxylic acid using the route of Brechbiel et al.[18] The reaction proceeds via a Curtius rearrangement to form a benzyl carbamate, which is then cleaved with HBr/acetic acid to yield the triamine.

The general synthesis of the unsymmetrically *N*,*N*′,*N*″-substituted tach is as follows: neutralisation of the hydrobromide salt of tach with aqueous sodium hydroxide followed by reaction with three equivalents of a benzaldehyde gave the tris-imine, **1** (Scheme 1), in excellent yield (>95%). Compound **1** was then reacted with one equivalent of $Ni(NO_3)_2{\cdot}6H_2O$ resulting in a remarkable selective hydrolysis of *two* of the three imines to afford a mono-substituted imine metal complex. This hydrolysis is highly selective for the mono-imine compound. This complex was reduced in situ using $NaBH_4$ to give the amine derivatised Ni complex **2** (Scheme 1). $[Ni(tach)_2]^{2+}$ is a by-product of the reaction (<5% yield), however, it is known that $[Ni(tach)_2]^{2+}$ is stable and it could easily be removed by extraction of **2** into THF. Compound **2** was typically isolated in >70% yield. From **2**, the mono *N*-benzylated triamino cyclohexane, **3** was produced by treatment of **2** with NaCN in H_2O to liberate the metal as $[Ni(CN)_4]^{2-}$. The *N*-benzyl derivatives of *cis*,*cis*-1,3,5-triaminocyclohexane were isolated as viscous oils in overall yields for the three steps of >55% for both derivatives (Table 1).

A demonstration of the ability of the new unsymmetrical tach molecules to be further derivatised and then act as ligands for metal ions was shown in the preparation of salicylaldehyde derivatised ligand **L** (Scheme 2). Due to the hygroscopic nature of the product it was necessary to store it under nitrogen, however complexation with $Cu(BF_4)_2{\cdot}6H_2O$ resulted in the formation of an air-stable copper complex in 70% yield, Cu^{II} **L**.

Keywords: Triaminocyclohexane; Nickel; Biomimetic.
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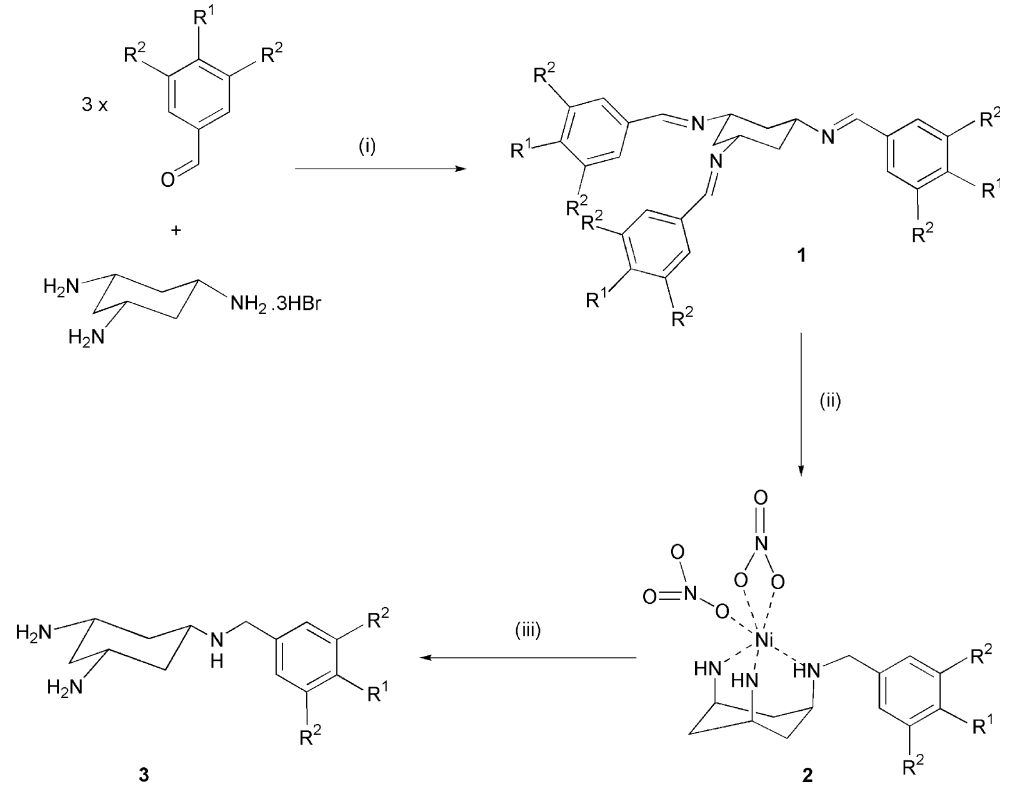
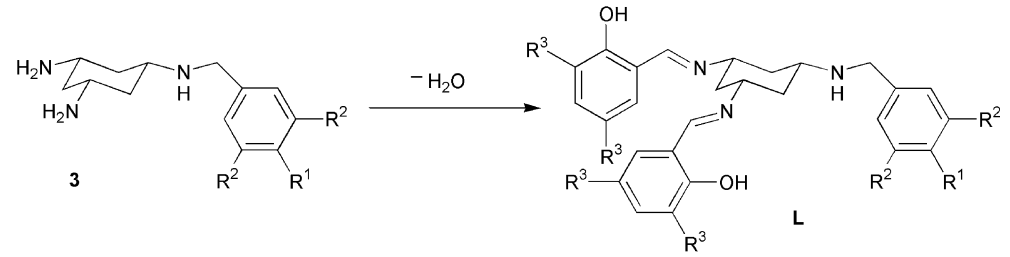


Scheme 1. Synthetic route to the new N_3O_2 donor ligands (**1a**, **2a**, **3a**; $R^1 = H$, $R^2 = OMe$: **1b**, **2b**, **3b**; $R^1 = {}^tBu$, $R^2 = H$). Conditions: (i) Et_2O, $NaOH/H_2O$, (ii) $Ni(NO_3)_2{\cdot}6H_2O$, $NaBH_4$ in MeOH, (iii) NaCN in H_2O.

Table 1. Summary of derivatives prepared and yields obtained of new unsymmetrically *N*,*N*′,*N*″-substituted tach species

Compound	Number	Substitution pattern	Yield/%
cis,*cis*-1,3,5-Tris(benzylidene amino)cyclohexane	**1a**	$R^1 = H$, $R^2 = OMe$	97
	1b	$R^1 = {}^tBu$, $R^2 = H$	96
1-[Benzylamino]-3,5-(diaminocyclohexane)$Ni(NO_3)_2$	**2a**	$R^1 = H$, $R^2 = OMe$	73
	2b	$R^1 = {}^tBu$, $R^2 = H$	92
1-(Benzylamino)-3,5-diaminocyclohexane	**3a**	$R^1 = H$, $R^2 = OMe$	89
	3b	$R^1 = {}^tBu$, $R^2 = H$	63



Scheme 2. Synthetic route to the new N_3O_2 donor ligand (**L**, where $R^1 = H$, $R^2 = OMe$, $R^3 = {}^tBu$). Conditions: 2 equiv of 3,5-di-^{t}Bu-salicylaldehyde, $-H_2O$.

In summary, we have prepared a novel *N*-benzyl substituted *cis*,*cis*-1,3,5-triaminocyclohexane molecules using a new synthesis, which selectively produces the mono substituted species. The route has the potential to accommodate a wide range of functional groups and offers an alternative to tosylation procedures, which result in low-yielding deprotection steps limiting the functional groups present in the target molecule, without the use of further protective group strategies. Moreover, the general strategy allows for acid-sensitive functional groups to be included in the benzyl moiety.

Acknowledgements

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Supplementary data

Synthetic and characterization details for the compounds **1a**, **1b**, **2a**, **2b**, **3a**, **3b**, **L** and Cu^{II} **L** are available as supplementary data in the online version at doi: 10.1016/j.tetlet.2005.07.112.

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