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A convenient synthesis of *N*,*N*′,*N*″-trisubstituted diethylenetriamines

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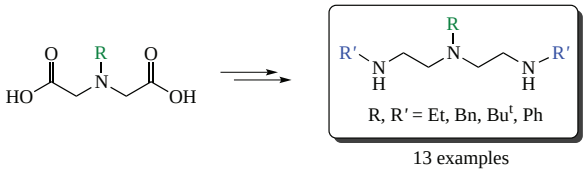
***N*,*N*′,*N*″-Trisubstituted diethylenetriamines (1,4,7-triazaheptanes) were synthesized by reduction of the relevantly substituted 2,2′-iminodiacetiamides which, in turn, were accessed from cheap reactants by the methods depending on their nature. The triamines thus obtained may be promising ligands for metal catalysts.**



Keywords: diethylenetriamines, ligands, microwave-assisted synthesis, polyamines, carboxamides, reduction, amidation.

Dedicated to Academician Irina P. Beletskaya on the occasion of her anniversary.

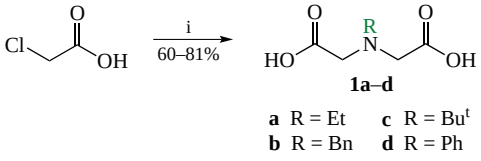
Active study of catalysis, organometallic and coordination chemistry makes the research and design of new ligand systems relevant. Ligands play a key role in accessing the desired properties of catalytically active derivatives of both transition and non-transition metals.[1,2] They allow for the 'fine' tuning of both electronic properties of the metal centre and its steric accessibility. The key factor for both the stabilization of the low-valence centre and varying the chemical properties of the complexes is the structure of the ligand. Among a fairly large set of various tridentate ligands (substituted dialkanolamines,[3] amino bisphenols,[4] pyridine-containing di-alcohols[5]), a special place is occupied by 1,4,7-trisubstituted 1,4,7-triazaheptanes (diethylenetetramines, DETAs). Diethylenetriamines $RN(CH_2CH_2NHR')_2$, or rather their dianions, are very effective ligands for controlling both the electronic properties and the steric accessibility of the metal centre. This is primarily due to the possibility of varying the substituents at three nitrogen atoms of the ligand since the substituents locate in the immediate vicinity of the metal centre in the complex. Their effect on the properties of the metal centre is difficult to underestimate. To date, in addition to being effective ligand systems,[6] these compounds are also used for the synthesis of heterocyclic systems[7] or antitumor agents[8] (see Online Supplementary Materials, Figure S1). It should be indicated that the structure of these compounds in complexes is currently limited to derivatives based on ligands containing aryl, pentafluorophenyl, tosyl, and trimethylsilyl groups at positions 1 and 7.[7–14]

The straightforward synthesis of *N*,*N*′,*N*″-trisubstituted DETAs is a serious problem. Two main strategies for their obtaining are known. (1) In triamine $HN(CH_2CH_2NH_2)_2$, initially substituents into positions 1 and 7 are introduced followed by derivatization of the central nitrogen atom. Despite its widespread use, this method is restricted to 1,7-diaryl-4-alkyl substituted DETAs[9–12] since in 1,7-dialkyl substituted DETAs selective modification of position 4 is not feasible. (2) The second method is based on the ring-opening of two *N*-tosyl/*N*-trifluoromethylsulfonyl-containing aziridine molecules with one molecule of primary amine. This method is limited by the availability of the starting aziridines.[13–16]

In this communication, we report on a practically universal synthetic scheme leading to *N*,*N*′,*N*″-trisubstituted DETAs with various aryl and alkyl substituents, which does not require expensive reagents. As the starting materials, we considered 2,2′-iminodiacetic acid, chloroacetic acid, amines and alcohols. For the main strategy, we chose the method that was previously[17] implemented for the preparation of substituted triethylenetetramines $N(CH_2CH_2NHR)_3$. At the first step, trisamides of nitrilotriacetic acid $N(CH_2CONHR)_3$ were obtained from the *in situ* generated acid trichloride and the corresponding amine. At the second step, the reduction of thus prepared trisamides with lithium aluminum hydride was performed.[17] Surprisingly, the synthesis of *N*,*N*′,*N*″-trisubstituted DETAs in such a logical way is currently limited to only one representative $MeN[CH_2CH_2NH(C_6H_4CF_3\text{-}m)]_2$. Initially, bis-amide was obtained from 2,2′-(*N*-methylimino)diacetic acid and the corresponding aniline in the presence of pyridine and triphenyl phosphite (74% yield), and then the bis-amide was reduced with $BH_3{\cdot}SMe_2$ (68% yield).[18]

To implement this strategy, we initially obtained four *N*-substituted iminodiacetic acids **1a–d** (Scheme 1).[19] The choice of substituents at the nitrogen atom was justified by the need to synthesize compounds containing at the central nitrogen atom both low-molecular-weight alkyl substituents and heavier substituents of the arylalkyl and aryl types.

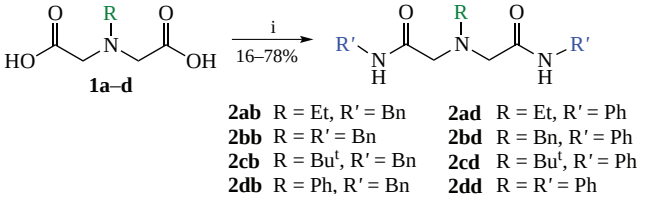
Several approaches were reviewed for the synthesis of diamides. The approach involving acid chloride was not



Scheme 1 *Reagents and conditions*: i, RNH_2, NaOH, 80 °C.

successful. In fact, treatment of acids **1a–c** with oxalyl chloride in the presence of catalytic amounts of DMF as well as with phosphorus pentachloride led to products that could not be identified. In the reaction with thionyl chloride, acid anhydrides were obtained. Also, the reaction of acids with oxalyl chloride in the presence of catalytic amounts of DMF, followed by treatment with 2,6-dimethylaniline in order to obtain diimides, afforded mixtures of hard-to-identify products (see Online Supplementary Materials, Scheme S1). The approach involving acid anhydrides was regarded as an alternative since a well-known synthesis of diacid diamides from their cyclic anhydrides was documented.[20] However, treatment of cyclic anhydride (generated *in situ* from acetic anhydride and acid **1b**) with 2,6-dimethylaniline gave only cyclic imide (see Online Supplementary Materials, Scheme S2).

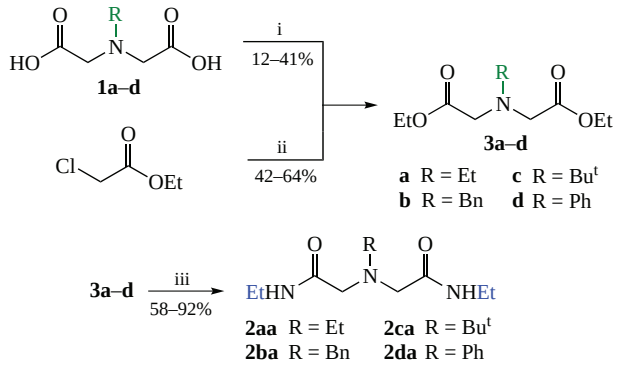
Direct synthesis from acids under microwave irradiation turned to be more successful (Scheme 2). Preparation of bis(benzyl amides) **2ab–db** and bis(phenyl amides) **2ad–dd** involved relatively high-boiling benzylamine and aniline, which was consistent with high temperature processing. Previously,[21] this approach was used for the synthesis of nitrilotriacetamides and diketopiperazines. Importantly, this procedure does not require the use of expensive starting materials and is solvent-free.



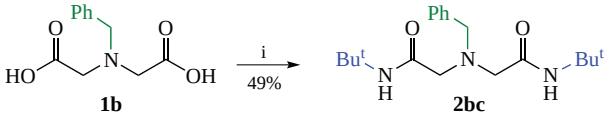
Scheme 2 *Reagents and conditions*: i, R′NH_2, microwave irradiation, 220 °C, 20 min.

The method involving diesters was suitable for the preparation of *N*,*N*′-diethyl bis-amides **2aa–da**. The synthesis should be carried out in two stages since the direct reaction of ethylamine and acid is hindered by the low boiling point of this amine. At the first step, the esterification of the corresponding diacids **1a–d** with ethanol was accomplished (Scheme 3). Although the yields of diesters **3a–d** were from low to moderate, the low cost of the starting reagents makes this approach acceptable. Alternatively, these esters can be obtained from the corresponding amines and ethyl chloroacetate.[22] The resulting diethyl diesters **3** were treated with a water–alcohol solution of ethylamine to afford *N*,*N*′-diethyl bis-amides **2aa–da** in good yields.

Direct synthesis from acids employing coupling reagents (dicyclohexylcarbodiimide and hydroxybenzotriazole hydrate, popular in peptide synthesis[23]) was good for the preparation of bis-amide **2bc** with *tert*-butyl groups at terminal nitrogen atoms



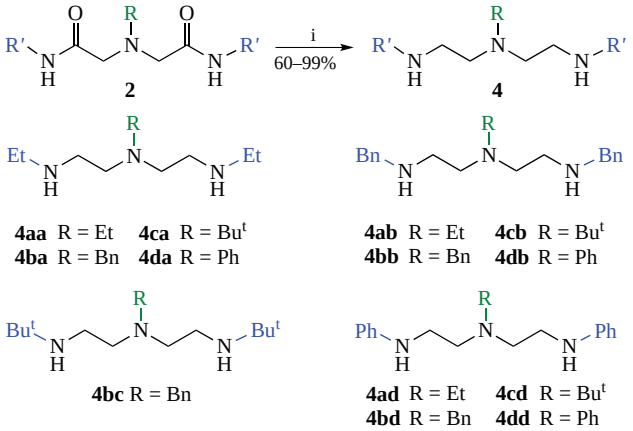
Scheme 3 *Reagents and conditions*: i, EtOH, H_2SO_4, reflux; ii, RNH_2, K_2HPO_4, MeCN; iii, $EtNH_2$, EtOH/H_2O, 3 days.



Scheme 4 *Reagents and conditions*: i, Bu^tNH_2, DCC, HOBT, THF/DMF, 2 days.

(Scheme 4). Apparently, such bis(*tert*-butyl amides) cannot be accessed by the approaches outlined in Schemes 2, 3.

The resulting amides of type **2** were readily reduced with lithium aluminium hydride in diethyl ether (Scheme 5). When THF was tried as a solvent, the reduction was incomplete. The yields of *N*,*N*′,*N*″-trisubstituted DETAs **4aa–da**, **4ab–db**, **4bc** and **4ad–dd** were high in all cases. Their structures were confirmed by ^{1}H and ^{13}C NMR spectroscopy, HRMS and elemental analysis.



Scheme 5 *Reagents and conditions*: i, $LiAlH_4$, Et_2O, 3–14 days.

In conclusion, an almost universal scheme has been herein developed for the synthesis of *N*,*N*′,*N*″-trisubstituted DETAs (1,4,7-trisubstituted 1,4,7-triazaheptanes) based on the reduction of *N*-substituted (iminobis)acetamides. The access to the latter is dependent on the nature of the substituents at the terminal nitrogen atoms. Diamides with lower alkyl substituents should be obtained from low-boiling amines and diethyl diesters of 2,2′-iminodiacetatic acid. Diamides with aryl and arylalkyl substituents can be synthesized from high-boiling amines in a straightforward way under microwave irradiation. Diamides with *tert*-butyl substituents on the terminal nitrogen atoms can be accessed only with the use of special coupling reagents.

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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.2023.02.003.

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