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Full Paper

Unusual Reactivity Patterns of 1,3,6,8-Tetraazatricyclo-[4.4.1.1^{3,8}]-dodecane (TATD) Towards Some Reducing Agents: Synthesis of TMEDA

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Abstract: *N,N,N´,N´*-Tetramethylethylenediamine (TMEDA) can be synthesized by simple reduction of 1,3,6,8-tetraazatricyclo-[4.4.1.1.^{3,8}]dodecane (TATD), an aminal cage type amine, with formic acid. The aminal can be converted to TMEDA in high yield very easily and in a very short time. We comment on the scope and limitations of the reduction of this aminal and propose a possible reaction mechanism.

Keywords: Aminals, TMEDA, aminal reduction, Leuckart-Wallach reaction

Introduction

Syntheses of symmetrical and unsymmetrical *N,N´*-tetrasubstituted 1,2-diamines are well known. By comparison, syntheses of trisubstituted and tetrasubstituted 1,2-diamines involving the reduction of aminals are much less well documented. Most of the methods found in literature involve the use of sodium borohydride or lithium aluminum hydride as reducing agents [1]. Despite the existence of these varied reduction methodologies and contrary to other chemical functions, none of the previously presented reduction methods can be considered general since some aminals are inactive under certain or all conditions [2]. For instance, reduction of (–)-2-phenyl-1,3-dibenzyloctahydrobenzoimidazole (**1**) with sodium boronhydride generates the triamine 2,2(–)-(*R,R*)-*N,N,N´*-tribenzyl-1,2-diamino-cyclohexane (**2**) in 79% yield [1], but the analogous reaction of 2-phenyl-1,3-bis[(4'-aza-5'-phenyl)-

pent-4'-enyl]-1,3-imidazolidine (**3**) with excess sodium boronhydride, chemoselectively generates 2-phenyl-1,3-bis[4'-aza-5'-(phenyl)-pentyl]-1,3-imidazolidine (**4**) in 98% yield, without any evidence of reduction of the 1,3-imidazolidine ring [3]. In some cases, cyclic aminal reduction depends on the substitution pattern of the imidazolidine nucleus. Thus, Salerno *et al.*, have shown that *N*-aryl or C_2-aryl-imidazoline nucleus cleavage occurs when a carbocation-iminium ion intermediate, stabilized through available electrons on nitrogen or on C_2 substituent, can be formed [4]. However, Alexakis and Andrey have reported [5] a synthesis of *N*-alkyl-2,2-bipyrrolidine in excellent yield from reduction of C_2-alkyl substituted imidazolidines with sodium borohydride, which exhibited a different scenario where a carbocation-iminium ion intermediate could be unstable.

R,R-1   **R,R-2 79%**

3   **4**

We have recently become interested in the reduction of 1,3,6,8-tetraazatricyclo[4.4.1.1.^{3,8}]dodecane (TATD, **5**). We initially chose to study the simple reduction of the aminal with sodium borohydride. The efficacy of sodium borohydride as a reducing agent in organic synthesis is apparent in the extant chemical literature [6]. However, simple addition of the aminal to a stirred solution of sodium borohydride in absolute ethanol gave no reduction product after 12 h and TATD was recovered in 99% yield. As an alternative approach, we reasoned that a better transformation might be achieved using lithium aluminum hydride, but treatment of TATD with an excess of this reducing agent followed by hydrolysis afforded only the starting aminal. Next we choose hydrogenation with Pd as a catalyst in MeOH or Raney/Ni in EtOH, but these were also found to not be good methods for the reduction of **5**, and the reduction of TATD was only achieved when formic acid was used, and the reduction product isolated in good yield was the diamine *N,N,N´,N´*-tetramethylethane-1,2-diamine (TMEDA, **6**) (Scheme 1).

Scheme 1: Reduction of TATD with formic acid.

5   **6**

We specially noticed the preferential formation of the *N,N,N´,N´*-tetrasubstituted diamine, in contrast with the formation of other feasible products such as *N,N,N´*-trisubstituted ethylenediamines or *N,N´*-disubstituted ethylenediamines. The formation of **6** was confirmed by comparison of its spectroscopic data and physical contrasts with commercial samples of TMEDA (**6**). This diamine is a versatile bidentate ligand and a chelating Lewis base [7]. Many of these complexes have shown catalytic activity in oxidative coupling reactions [8], olefin polymerizations [9], oxidative carbonylation of phenol to produce diphenyl carbonate (DPC) [10], and alkyl-alkyl cross-coupling reactions [11]. In the same way, TMEDA has been used as an initiator of anionic polymerization in the synthesis of high vinyl copolymers containing styrene and butadiene [12], lithiation by alkyl-Li/TMEDA [13], reductive ring opening of many oxygen-, nitrogen-, or sulfur-containing heterocycles [14], synthesis of asymmetric hydroborating reagents [15] and diastereoselective dihydroxylation of olefins [16]. Although some methods for obtaining **6** are known [17], many of them suffer from limitations of starting material availability.

Results and Discussion

In the current study, all attempts to reduce TATD (**5**) using $NaBH_4$, $AlLiH_4$ or catalytic hydrogenation failed to yield any reaction product. We rationalized these results on the basis of the proposed mechanism for these reactions, which involves the formation of a complex between the aminal and hydride reagents, with subsequent transference of a hydride ion to an iminium ion [2]. The metallic complex formation between the aminal and the metallic compound is based in the formation of stable structures from a variety of complex hydrides [18]. A weak metal-nitrogen bond is probably responsible for the exceptional resistence of **5** towards reduction. This is due to the fact that a highly reactive aminal metal complex is required to break the non activated CH_2-nitrogen bond.

The inability of **5** to form the active species is understandable on the basis of a low nucleophilicity of nitrogen atoms in this aminal cage, evidenced by the conspicuous absence of reported metallic adducts of this macrocyclic aminal in the literature, as far as we know. In contrast, other cage type aminals, similar to urotropine (**7**), not only form complexes with metals [19] but also other products such as hexamethylenetetramine-*N*-oxide [20] and *N*-alkyltropinium [21]. In fact, a $(CH_2)_6N_4BH_3$ monoadduct has previously been isolated from direct combination of diborane and hexamine in benzene [22]. Also, higher hexamethylenetetramine-multiple borane adducts have been obtained by treatment of a chloroform solution of $(CH_2)_6N_4$ with polyboranes [23]. These facts indicate that, compared with **7**, in **5** the nucleophilic character of the four equivalent tertiary nitrogens is probably diminished and this must be the result of a difference in the pyramidal character of nitrogen. Our recent X-ray studies of adducts formed between hydroquinone and **5**, **7** and 1,3,6,8-tetraazatricyclo-[4.3.1.1^{3,8}]undecane (TATU, **8**) showed that **5** presents the weakest hydrogen bond [24]. Besides, it was determined that the bond distance depended on the sp^3 character of the nitrogen lone pair, measured as the sum of bonding angles around nitrogens, and that of these adamanzanes TATD presented the lowest sp^3 character, diminishing basicity of the macrocyclical aminal [24].

5   **8**   **7**
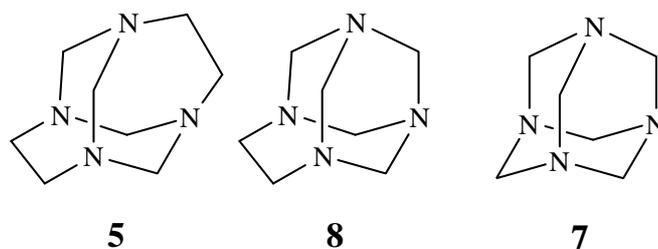
On the other hand, despite the chemical inertness seen in **5** in the presence of metallic hydrides, treatment of TATD with an excess of formic acid under Leuckart-Wallach conditions effects reduction of the aminal, and TMEDA was primarily obtained. The use of an excess in formic acid was necessary, probably to increase the reactivity of **5**.

Although a definitive mechanism for a Leuckart-Wallach type reduction has not been reported, two mechanistically distinct reaction pathways are widely recognized, involving the use of formate ester or formiate anion as hydride transfer reagent [25-27]. Thus, the first mechanistic pathway for this conversion probably involves formation of α-aminoalcohol **9**, which subsequently undergoes condensation with formic acid to give **10**. This process is repeated four times to give a tetraformate **11**, which then undergoes reductive elimination of carbon dioxide to produce **6** (Scheme 2).

Scheme 2: Possible non-ionic pathway.

5   **5-H⁺**   **9**

9   **10**   **11**   **6**
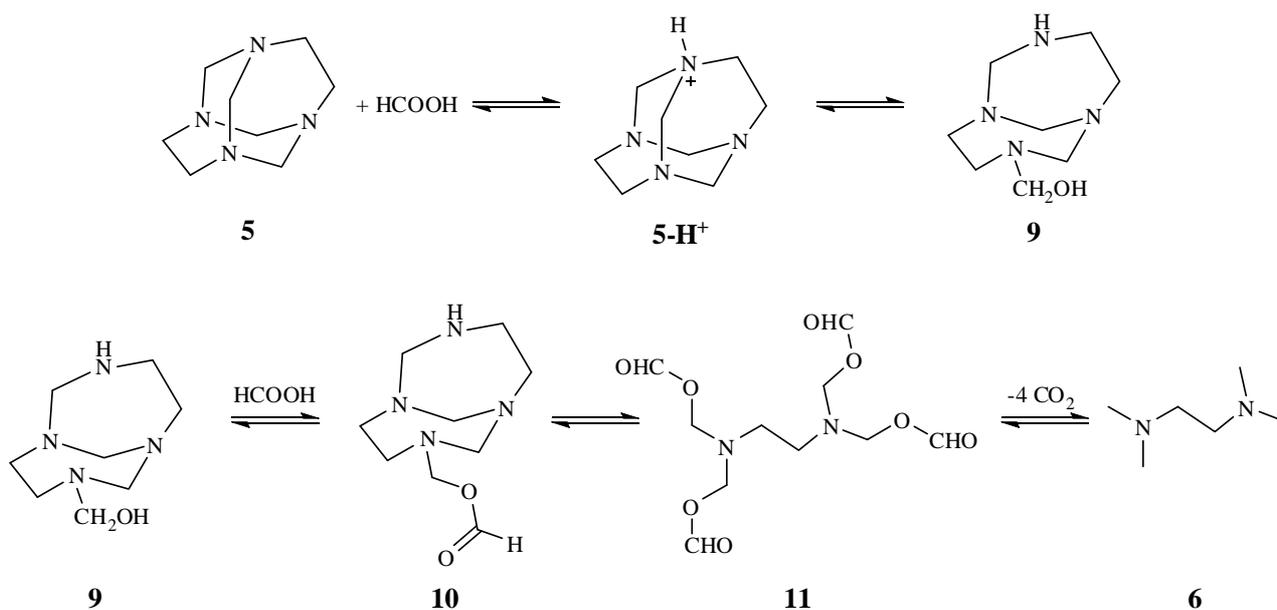
According to the proposed mechanism, formation of **6** could be expected to have occurred by direct reaction between ethylenediamine, formaldehyde and formic acid, whereupon the formation of intermediates type α-aminoesters must be facilitated. In fact, evidence for the presence of **5** and methylolamine intermediates, such as **9**, has been previously provided by NMR spectra of an ethylenediamine/formaldehyde mixture [28]. In order to test this prediction, we decided to use ethylenediamine and formaldehyde as starting materials. To our initial surprise, when we mixed these reagents with formic acid, at the same temperature and for the same time reported for **5** only the starting materials were observed in the crude reaction mixtures. This result is in accordance with the observed direct alkylation to form symmetrically tetrasubstituted diamines using formaldehyde and formic acid, the so called Eschweiler–Clarke methylation [25]. Thus, our experiment suggested that,

not only is the formation of **6** due to the direct reduction of TATD (**5**) but also the absence of a crypto radical type mechanism.

Although a more in depth study of the reaction mechanism is required, most of the above experiments provide evidence that the alternative ionic mechanism is more probable. An ionic mechanism of this transformation may be considered to involve initial protonation of **5** with formic acid to generate **5-H⁺**. This intermediate could then experience a ring opening process to produce 3-methylene-1,6,8-triaza-3-azoniabicyclo-[4.4.1]undecane (**12**), with both species being in equilibrium. The formiate anion can react with either the protonated aminal **5-H⁺** or the carbocation-iminium ion **12** to give 3-methyl-1,3,6,8-triazabicyclo[4.4.1]undecane (**13**, Scheme 3). The presence of an excess of formic acid suggests that both ionic species can be present in the reaction mixture. However, although it is known that the formation of open species is favoured in the ring-chain tautomeric equilibrium of aminals under acid conditions [29-30], the lifetime of aliphatic iminium ions in an aqueous solution is quite short [31].

Scheme 3: Proposed mechanism for the formation of **6**.
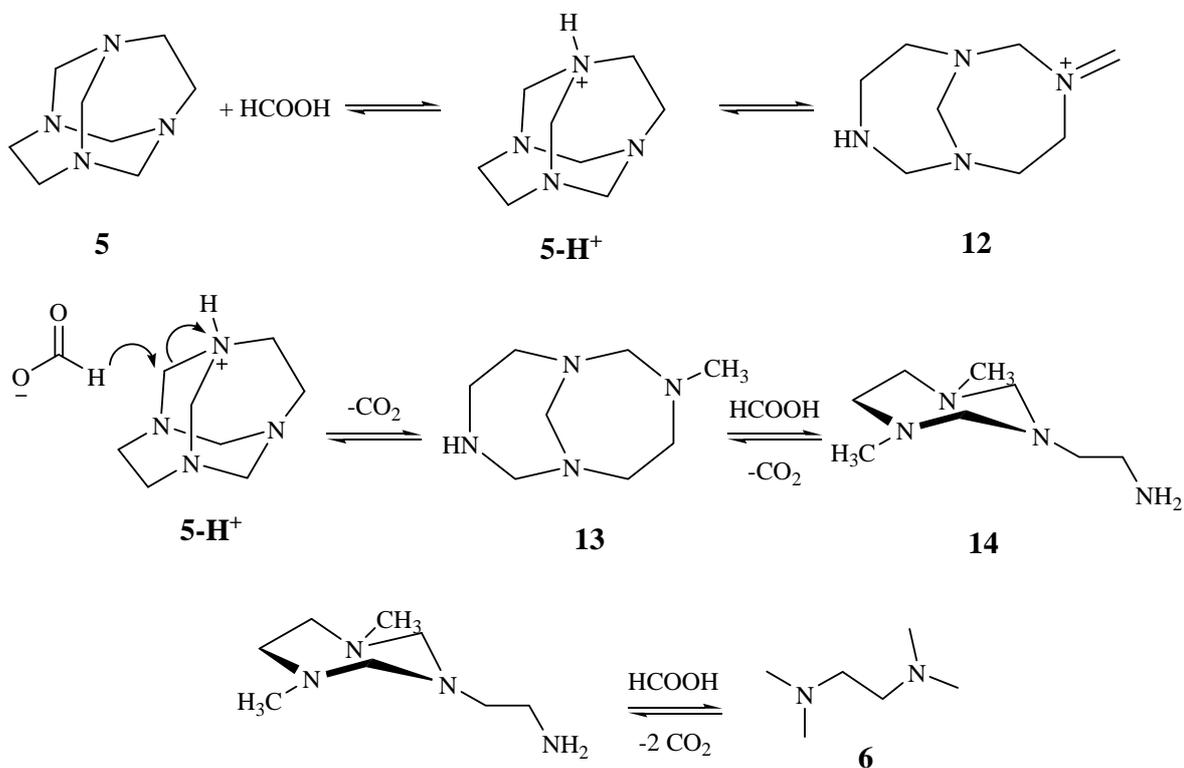
To resolve this mechanistic puzzle, theoretical calculations using the Gaussian 98 computational package [32] were performed for these tautomeric forms. Their structures were optimized using the density functional theory (DFT) at the B3LYP level of theory and a 6-31G(d) basis set. The results suggested that formiate anions react with **5-H⁺**, which is more stable than **12** (ΔE 15.83 kcal mol^{-1}). Thus, the protonated form of **5** undergoes the hydride ion migration from the formiate anion to give **13**. This structure is in full agreement with some products obtained for the TATD (**5**), such as 3,8-di(2-aryl-1-azenyl)-1,3,6,8-tetraazabicyclo[4.4.1]undecanes **15** [33]. In the next steps, the reaction of **13** with three molar equivalents of formic acid leads to **6** (Scheme 3). The preferential alkylation in the

ring opening of intermediate **13** to form **6** could be explained by assuming that **13** undergoes ring opening reaction to yield **14** instead of **16** or **17**, due to he presence of the additional stability of seven members (**14**) rather than a ten member cyclic system (i.e. **16** and **17**).

14   **15**

16   **17**
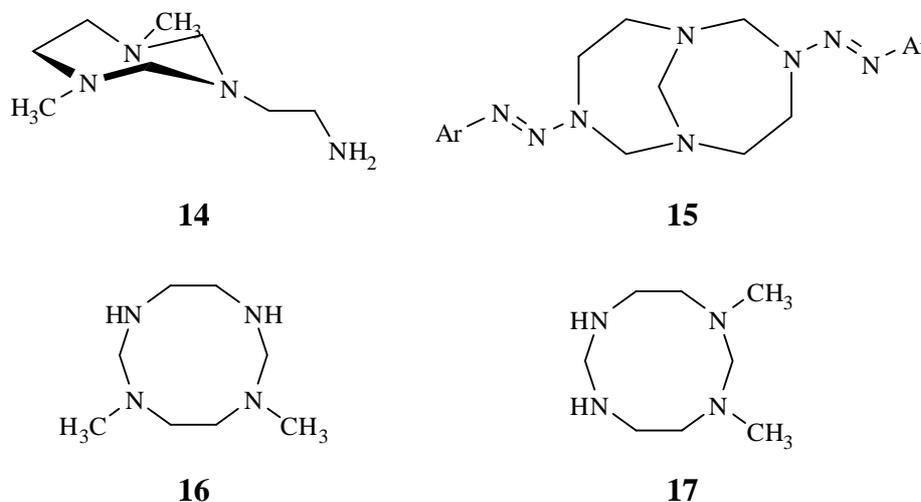
Conclusions

In summary, we have found a novel synthetic approach for the synthesis of TMEDA. We have demonstrated that the reduction mechanism with formic acid does not follow a crypto-radical pathway, and proposed a mechanism involving a protonated aminal. This method is efficient, time-saving and uses a simple aminal cage as the starting product. Additionally, we offered an explanation to chemical inertia of TATD toward $NaBH_4$, $LiAlH_4$ and catalytic hydrogenation.

Experimental

General

1,3,6,8-Tetraazatricyclo[4.4.1.1^{3,8}]dodecane (TATD, **5**) was prepared following the procedure described in literature [34]; formic acid was purchased from Merck and used as received. Melting points were determined on an Electrothermal apparatus and are uncorrected. IR spectra were measured as KBr pellets at 292 K on a Perkin-Elmer Paragon FT-IR instrument. ^{1}H- and ^{13}C-NMR spectra were obtained on a Varian XL 300 spectrometer with standard pulse sequences, operating at 299.993 MHz for ^{1}H and at 75.489 MHz for ^{13}C, respectively. The solvent used was D_2O. EIMS were run on a Shimadzu 9020 mass spectrometer at 70 eV. Carbon, nitrogen and hydrogen analysis were performed on a Carlo Erba 1106 elemental analyzer.

Reduction of TATD with formic acid

A solution of **5** (1g, 5.95 mmol) in 98% formic acid (10 mL) was refluxed with constant agitation for 10 h. Progress of the reaction was monitored by CCD (silica gel, 40:10 EtOH-NH₄OH). The reaction mixture was allowed to cool down and then treated with a solution of 10 % hydrochloric acid

(200 mL). The aqueous solution was evaporated to dryness under vacuum. The residue (142 g) was redissolved in H_2O (200 mL) and made alkaline (pH = 12) with a 25% NaOH solution, and then concentrated under reduced pressure. The distillate was then treated with an excess of hydrochloride acid; after ethanol addition, the hydrochloride precipitated as a colorless crystalline solid with a yield of 70%; m.p. 275 ^{o}C; IR ν_{max}: 2982, 2623-2457, 1342 cm^{-1}; ^{1}H-NMR δ: 3.06 (s, 12 H, Me-N), 3.74 (s, 4H, N,CH$_2$-CH$_2$-); MS m/z (20 eV) 116 (M+, 10), 58 (100); Anal. Calcd for $C_6H_{18}N_2Cl_2$: C, 38.10; H, 9.59; N, 14.82; Cl, 37.49. Found: C, 38.08; H, 9.56; N, 14.88; Cl, 37.48.

Acknowledgements

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Sample Availability: Samples of compound **6** are available from the authors**.**