

Carbanions with Two N Substituents: Nucleophilic Acyl-Group-Transfer Reagents**

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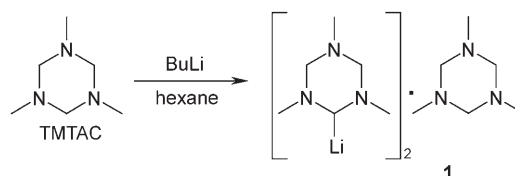
Dedicated to Professor Helge Willner on the occasion of his 60th birthday

Among the many types of carbanionic systems, those in which the carbanion is attached to a nitrogen atom are special, as they belong to the group of formally nonstabilized or even destabilized systems.^[1] This can be rationalized by the repulsive interaction of the carbanion with the adjacent nitrogen lone pair. For this reason α -lithiated amines are in general not easily accessible by direct deprotonation of amines; they are typically prepared by transmetalation,^[2] by cleavage of C–S or C–Te bonds,^[3] or by the use of α -metalated amines such as the more easily deprotonated amine–BF₃ adducts.^[4] There are only few exceptions, for example aminals of the type RMeNCH₂NMeR, which can be deprotonated at both methyl groups simultaneously by direct treatment with *t*BuLi;^[5] 1,4,7-trimethyl-1,4,7-triazacyclononane,^[6] which reacts already with *n*BuLi to give a product monolithiated at one methyl group; and *N*-methylpiperidine, which is deprotonated at the CH₃ group upon application of Schlosser's base.^[7] The difficulties of α -lithiation can also be considered in the context of the facilitated deprotonation of systems with donor-functionalized side chains,^[8] which led to noticeable possibilities in synthesis.^[9]

Our recent attempts to extend the metalation reaction of iminium chlorides with low-valent Group 13 metal halides (InCl, GaI etc.) resulting in α -metalated amines,^[10] to the metalation of formamidinium systems failed. Instead disproportionation was observed, leading to hexahalogenodimetalates and leaving the formamidinium ion unchanged.^[11] Thus, so far no carbanions with two directly attached amino functions are known, and the closest related examples are a few doubly^[12] or triply^[13] pyrazolyl-substituted carbanions.

We now report that the reaction of 1,3,5-trimethyl-1,3,5-triazacyclohexane (TMTAC) with *n*BuLi in hexane proceeds

unexpectedly smoothly, and—in contrast to the twofold terminal deprotonation of the related Me₂NCH₂NMe₂—the deprotonation in these systems occurs exclusively at a position between two N atoms (Scheme 1).



Scheme 1. Lithiation of TMTAC.

The lithiation always occurs selectively at a methylene unit regardless of the solvent (various hydrocarbon or ether solvents), temperatures (between –78 °C and ambient temperature), and which base is used (*n*-, *sec*-, or *t*BuLi). The best yields are achieved with *t*BuLi in hexane. In all cases the product obtained consists of two equivalents of a deprotonated species and one equivalent of the free base TMTAC. The reason is apparent from the crystal structure determination of this compound (Figure 1).^[14]

The chain aggregate consists of two crystallographically independent units of dimeric 2-lithio-TMTAC (Figure 2), which are alternately linked by two nitrogen atoms of a non-lithiated TMTAC molecule. The dimers are centrosymmetric aggregates, whereby the lithium atom is attached to the carbanionic center of one ring and to the two nitrogen atoms adjacent to the carbanionic C atom of the other ring. The

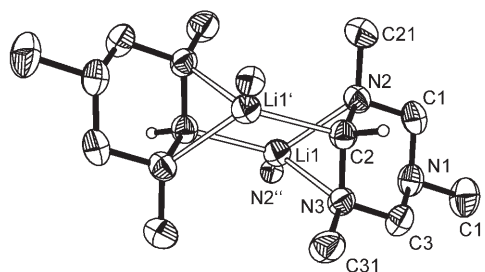


Figure 1. Structure of a dimer of 2-lithio-TMTAC in aggregate 1. Selected bond lengths [Å] and angles [°]: Li1'–C2 2.202(3), Li1–N2 2.174(3), Li1–N3 2.129(3), Li1–N2' 2.153(3), C2–N2 1.485(2), C2–N3 1.491(2); Li1'–C2–N2 67.4(1), Li1'–C2–N3 65.6(1), N2–Li1–N3 66.3(1), N2–Li1–C2' 121.2(1), N3–Li1–C2' 119.3(1).

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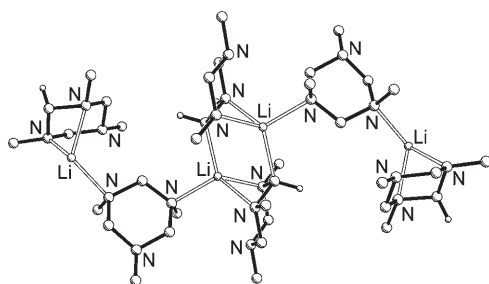


Figure 2. Structure of the chains of aggregate **1**.

fourth coordination site of these lithium atoms is saturated by a contact to a nitrogen atom of the bridging TMTAC unit. Indicative of a repulsive interaction between the carbanions and the adjacent nitrogen atoms are the C–N bond lengths (mean of four bonds: 1.489 Å), whereas the same N atoms have shorter bonds to the adjacent CH₂ groups in the ring (mean: 1.456 Å).

Compound **1** was furthermore characterized by elemental analysis and ¹H, ⁷Li, and ¹³C NMR spectroscopy. The NMR data clearly reflect the presence of lithiated and free TMTAC units in a 2:1 ratio.

It must be mentioned that the lithiation of TMTAC was used previously to prepare 2-deuterio-TMTAC; by 2-Li-TMTAC was generated in situ and quenched with D₂O.^[13] However, the reported yield of 91 % is not consistent with our findings for aggregate **1** consisting of a 2:1 mixture of lithiated and non-lithiated TMTAC.

Another interesting point was the differing regioselectivity of the deprotonation of Me₂NCH₂NMe₂ and of TMTAC with alkyl lithium reagents. Although both compounds contain a CH₂(Me)NCH₂N(Me)CH₂ unit, the aminal is deprotonated at the methyl groups, whereas TMTAC at the seemingly unfavorable methylene position between the two deactivating nitrogen atoms. This is surprising as the open-chain aminal Me₂NCH₂NMe₂ can adopt every conformation that is adopted by the corresponding unit in TMTAC. Therefore intramolecular electronic effects like the anomeric effect seem not to be dominant here.^[16]

It seemed more likely that the third N atom in TMTAC might be responsible for the observed reactivity by pre-coordinating BuLi in close proximity to the lithiation site. To test this hypothesis we carried out a lithiation reaction with the related heterocycle 1,3-dimethyl-1,3-diazacyclohexane, which should have similar conformational behavior but does not contain the third N atom. This compound can be deprotonated with *t*BuLi, and again surprisingly, the reaction occurs selectively at the position between the two N atoms, proving the irrelevance of the third N atom in TMTAC for the observed regioselectivity of lithiation.

We obtained single crystals of this lithiated product **2** cocrystallized with *t*BuLi. The molecular structure of a tetramer of **2** in these crystals is shown in Figure 3; the crystal structure containing also tetramers of *t*BuLi is displayed in Figure 4.^[12] The tetrameric aggregation motif resembles distantly the aggregation of tetrameric lithium aryls, in which the Li atoms are σ-bound to the aryl rings and

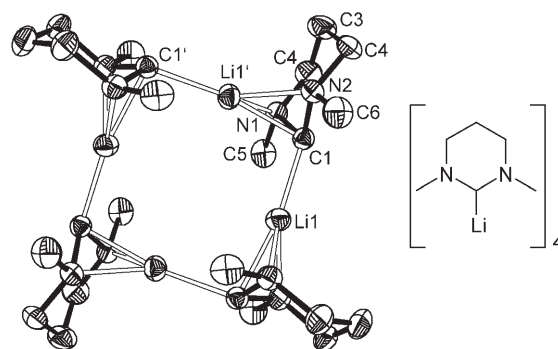


Figure 3. Structure of the tetrameric units of 2-lithio-1,3-dimethyl-1,3-diazacyclohexane in **2**. Selected bond lengths [Å] and angles [°]: C1–Li1 2.123(4), C1–Li1' 2.107(4), Li1'–N1 2.043(4), Li1'–N2 2.035(4), Li1...Li1' 3.163(5); N1–C1–N2 104.9(2), Li1–C1–N1 121.1(2), Li1–C1–N2 119.7(2), C1–N1–Li1' 71.4(2), C1–N2–Li1' 71.5(2).

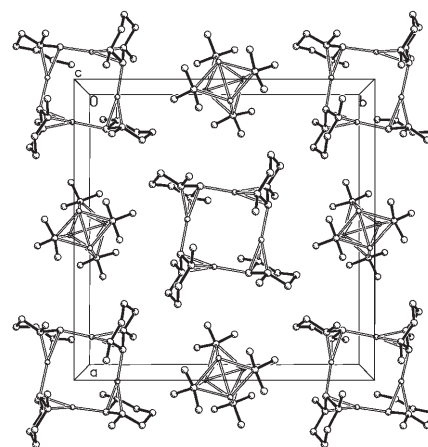


Figure 4. Structure of the cocrystallized **2** and *t*BuLi, including the (*t*BuLi)₄ units.

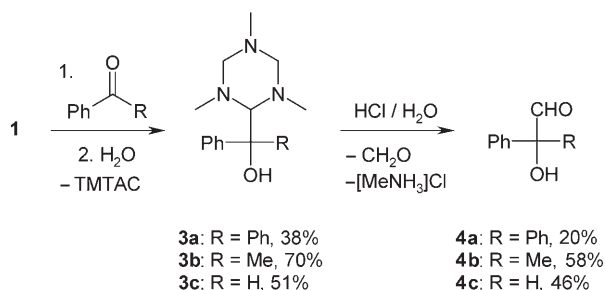
simultaneously interacting with the π systems of other monomers.^[17]

The carbanionic C atom of the 1,3-dimethyl-1,3-diazacyclohexan-2-yl ring is bound to a lithium atom ($d(\text{C1}–\text{Li1}) = 2.123(4)$ Å). The two N atoms of this ring form bonds to another Li atom ($d(\text{Li1}'–\text{N}) = 2.043(4)$ and $2.035(4)$ Å). This second Li atom is also close to the carbanionic C atom of this ring, and with a Li–C distance of 2.107(4) Å it is even closer than the atom Li1. This distance is at the low end of the range of Li–C distances in α-lithiated amines (2.101–2.375 Å).^[15] Each lithium atom is thus four-coordinate but has far from tetrahedral coordination geometry. The structures in the *t*BuLi tetramers are very similar to those found in pure *t*BuLi.^[16]

Compound **2** was further characterized by quenching it with D₂O, and the resulting 2-deuterio-1,3-dimethyl-1,3-diazacyclohexane was identified by NMR and MS spectra. This experiment indicates that the ring structure is behind the regioselectivity of the lithiation of TMTAC to give **1**, although we cannot present a detailed mechanism.

Compound **1** is related to the dialkoxymethylolithium compounds^[20] and the Corey–Seebach reagents, the 2-lithio-

1,3-dithianes,^[17] which are the examples par excellence of the umpolung principle.^[18] Like these dithianes, **1** can be used as a nucleophilic transfer reagent for acyl groups, which makes it a highly useful compound in organic synthesis. We have demonstrated this protocol by reacting **1** with several electrophiles (Scheme 2).



Scheme 2. Nucleophilic acylation of carbonyl compounds with **1**.

Hydrolytic workup under acidic conditions leads to the expected degradation of the polyaminal-type system, the TMTAC ring, and liberation of the acylated product. This is remarkable as this method does thus not require mercury- or thallium-containing reagents for liberation of the aldehyde—a notable advantage over the classical Corey–Seebach method in terms of preparative ease and ecological issues. The further development of Corey–Seebach reagents is a topic currently studied by Degl’Innocenti, Policino, and Capperucci, who employed silyl heterocycles as formyl anion equivalents.^[23]

To show that the intermediate products, the hydroxy-methyl derivatives of TMTAC, can be isolated as stable compounds, we crystallized the product of the reaction of **1** with benzophenone after careful hydrolysis: 2-(hydroxydiphenylmethyl)-1,3,5-trimethyl-1,3,5-triazacyclohexane (**3a**). Its molecular structure in the crystal is shown in Figure 5. In a further test reaction of **1** with bromodiphenylmethane, no addition of a TMTAC function could be observed, but the reductive coupling of Ph_2CHBr gave 1,1,2,2-tetraphenylethane in 72 % yield.

Clearly the precursors and conditions of these reactions can be further optimized. The most suitable cyclic (poly)-

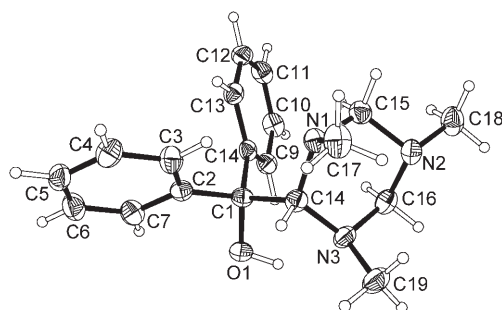


Figure 5. Molecular structure of **3a**. Selected bond lengths [Å] and angles [°]: C1–C2 1.531(2), C1–C14 1.583(2), C1–O1 1.422(2); O1–C1–C14 106.1(1), C2–C1–C14 110.9(1).

aminal system would be easily lithiated in the correct position and also efficiently cleaved under acidic conditions to liberate the corresponding acylated compound. We are currently working on these aspects as well as studying the reaction mechanism, for which a complex-induced proximity effect^[24] seems likely.

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- [14] Crystal structure determinations. **1**: $\text{C}_{18}\text{H}_{24}\text{Li}_2\text{N}_3$, triclinic, $P\bar{1}$, $a = 9.092(1)$, $b = 11.037(1)$, $c = 12.942(1)$ Å, $\alpha = 77.92(1)$, $\beta = 82.23(1)$, $\gamma = 80.92(1)^\circ$, $V = 1247.0(2)$ Å³, $Z = 2$, $\rho_{\text{calcd}} = 1.064$ g cm⁻³, $\lambda = 0.71073$ Å, $2\theta_{\text{max}} = 55.8^\circ$, $T = 192(2)$ K, $\mu = 0.067$ mm⁻¹. 16280 measured and 5934 independent reflections ($R_{\text{int}} = 0.067$). 269 parameters, $R_1 = 0.053$ for 3387 reflections with $F_o > 4\sigma(F_o)$ and $wR_2 = 0.145$ for all 5934 data. Max./min. residual electron density $-0.18/0.20$ e Å⁻³. **2**: $\text{C}_9\text{H}_{20}\text{Li}_2\text{N}_3$, tetragonal, $I\bar{4}$, $a = 17.460(2)$, $c = 8.2195(14)$ Å, $V = 2505.8(6)$ Å³, $Z = 4$, $\rho_{\text{calcd}} = 0.976$ g cm⁻³, $\lambda = 0.71073$ Å, $2\theta_{\text{max}} = 50.0^\circ$, $T = 153(2)$ K, $\mu = 0.055$ mm⁻¹. 10172 measured and 2219 independent reflections ($R_{\text{int}} = 0.039$). 130 parameters, $R_1 = 0.052$ for 1881 reflections with $F_o > 4\sigma(F_o)$ and $wR_2 = 0.145$ for all 2219 data. Max./min. residual electron density $-0.15/0.23$ e Å⁻³. **3**: $\text{C}_{19}\text{H}_{25}\text{N}_3\text{O}$,

- monoclinic, $P2_1/n$, $a = 9.009(4)$, $b = 9.489(4)$, $c = 19.599(9)$ Å, $\beta = 92.5(9)^\circ$, $V = 1673.9(13)$ Å³, $Z = 4$, $\rho_{\text{calcd}} = 1.236$ g cm⁻³, $\lambda = 0.71073$ Å, $2\theta_{\text{max}} = 50.0^\circ$, $T = 153(2)$ K, $\mu = 0.078$ mm⁻¹. 13 043 measured and 2951 independent reflections ($R_{\text{int}} = 0.043$). 215 parameters, $R_1 = 0.042$ for 2393 reflections with $F_o > 4\sigma(F_o)$ and $wR_2 = 0.094$ for all 2951 data. Max./min. residual electron density $-0.22/0.18$ e Å⁻³. Programs: a) SHELXTL 6.10, Bruker-AXS X-Ray Instrumentation Inc., Madison, WI, 2000; b) G. M. Sheldrick, SHELXL-93, *Program for Crystal Structure Refinement*, Universität Göttingen, 1993. CCDC-632841 (1), CCDC-632842 (2), and CCDC-632843 (3a) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
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