The Equilibrium Between 2-Lithium-Oxazole(-Thiazole, -Imidazole) Derivatives and Their Acyclic Isomers – A Structural Investigation☆

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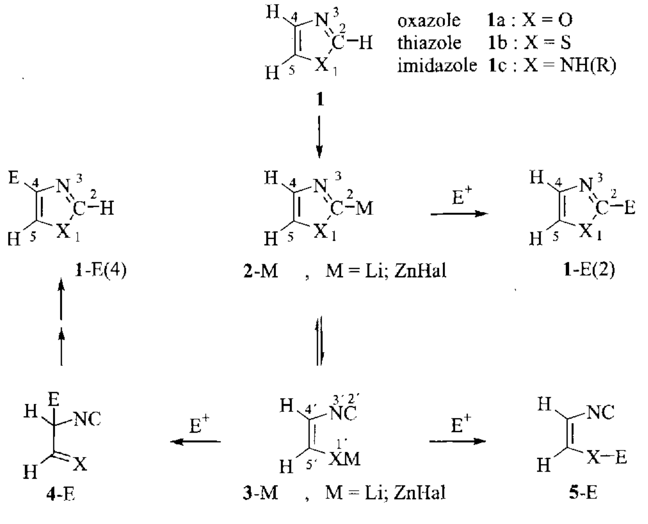
2-Metallated oxazoles, thiazoles and imidazoles are of interest for the preparation of derivatives of the respective heterocycles, and – especially in the case of metallated thiazoles – as acyllithium equivalents in organic syntheses. Metallation at C2 of these compounds, however, often leads (more so with Li-oxazoles than with Li-thiazoles and Li-imidazoles) to products derived from the acyclic isomers of the metallated heterocycles. In order to obtain more information on the positions of the relevant equilibria, we have carried out a ^{13}C-NMR study of substituted Li- and ZnCl-oxazoles, Li-thiazoles and Li-imidazoles. In the case of Li-oxazoles, the equilibrium is completely on the side of the acyclic isomers. Addition of $ZnCl_2$, however, leads to ring-closure, and, even in the case of 2-ZnCl-substituted benzoxazole, only the ring-closed isomer is observed. This demonstrates a dramatic gegenion effect on the equilibrium between two isomeric anions. In the case of Li-thiazoles, depending on the substitution pattern, either solely the ring-closed or an equilibrium with the ring-opened isomer is observed. In the series of Li-imidazoles, only the 2-lithiated benzimidazole is in equilibrium with its ring-opened isomer. The tendency of these compounds to undergo ring-opening parallels the leaving group properties of the various subunits [ROLi > RSLi > R_2NLi, and phenyl-O(S,NR)Li > vinyl-O(S,NR)Li]. The difference between the effects of Li^+ vs. $ZnCl^+$ in the (benz)oxazole series is in agreement with results of solid-state structure investigations of a 2-lithiated and a 2-zincated thiazole: in the Li compound the C–S bond is 2.9 pm longer than in the ZnCl species, indicating a more facile C–S bond cleavage with Li^+ as the gegenion.

Introduction

Metallation at C2 of oxazole (**1a**)[1], thiazole (**1b**)[2] and imidazole (**1c**)[3] (or of substituted derivatives of **1a–c**) to give **2a**-M, **2b**-M, and **2c**-M, respectively, (M = Li, ZnHal) has been a subject of interest for around three decades. This interest stems from the possible use of species of the type **2-M** as acyl (formyl) anion equivalents, and also from the synthetic access they offer to substituted heterocycles of the type **1**-E(2), see Scheme 1.

However, the chemistry involved is not as straightforward as one might have hoped, the problems encountered also being illustrated in Scheme 1. The *desired* reaction involves the formation of **1**-E(2) from **2-M** and electrophiles E^+. Complications are to be expected if a *ring-opening reaction* of **2-M** to give the acyclic **3-M** occurs. In the case of the lithiated oxazoles **2a**-Li, this reaction leads to the isocyano enolates **3a**-Li, while in the case of **2b(c)**-Li the corresponding **3b(c)**-Li should be formed. If the equilibration **2**-Li ⇌ **3**-Li is comparatively slow, reaction with E^+ leads to a mixture of products **1**-E(2)/(**4**-E + **5**-E), in a ratio equal to that of **2**-Li/**3**-Li. However, if the equilibration **2**-Li ⇌ **3**-Li is faster than (or of comparable rate to) the trapping of **2**-Li and **3**-Li with E^+, then the product ratio of cyclic **1**-E(2) to acyclic **4**-E + **5**-E also depends on the nature of E^+ and its rates of reaction with the different species present[1,2,27].

Scheme 1



The situation is even more complex if the acyclic reaction product **4**-E bears a hydrogen atom α to the –CH=X [X = O, S, NH(R)] and –N=C groups because of the acidic nature of this proton: transformation of **4**-E into the corresponding enol (or enolate) allows ring-closure to a heterocycle in which the substituent E is found at C4 [**1**-E(4)], and not at C2 [**1**-E(2)].

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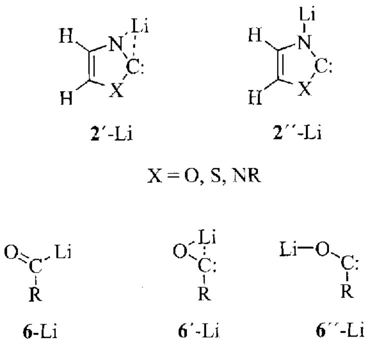
In view of these complications it is of primary interest to ascertain whether or not the various metallated heterocycles **2**-M are in equilibrium with their acyclic isomers **3**-M. Two recent publications dealing with these questions from a synthetic viewpoint prompt us to report our findings from structural studies of lithiated derivatives of the type **2**-Li, with regard to the equilibrium with their acyclic counterparts **3**-Li. Crowe, Hossner and Hughes[4] studied the equilibrium **2a**-Li $\rightleftharpoons$ **3a**-Li of some *lithiated* (substituted) oxazoles and compared the results with data for the corresponding *ZnCl* species **2a**-ZnCl and **3a**-ZnCl. The ZnCl compounds **2a**-ZnCl were employed in Pd-catalyzed coupling reactions to give oxazole derivatives of pharmaceutical interest. A short communication by Anderson and Harn had a similar objective[5]. Our principal reason for studying compounds of the type **2**-Li was to ascertain whether they show carbene character, as would be expected for an Li-bridged isomer **2′**-Li, or are even real carbenes (**2″**-Li)[6], see Scheme 2.

Scheme 2



2′-Li **2″**-Li

X = O, S, NR

6-Li **6′**-Li **6″**-Li

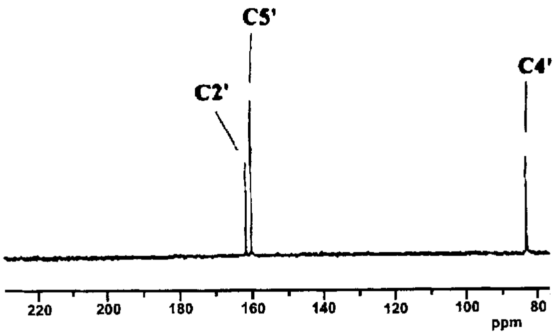
The carbene nature of the acyllithium equivalents **2″b(c)**-Li, which was demonstrated in the preceding paper[6], was suggested from the carbene-like reactivity of "real" acyllithium species **6**-Li, which behave like **6′**-Li and/or **6″**-Li, see Scheme 2. Thus, both for synthetic purposes as well as for investigations of the properties of **2**-Li, information regarding the equilibrium **2**-Li $\rightleftharpoons$ **3**-Li is of considerable interest.

Results and Discussion

2-Metallated Oxazoles **2a**-M (M = Li, ZnCl)

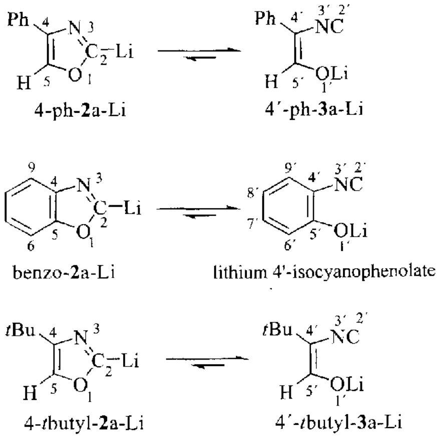
Most of the studies concerning the equilibrium **2a**-Li $\rightleftharpoons$ **3a**-Li (Scheme 1) have dealt with *reactions* of this system with electrophiles E$^+$. These have generally indicated the presence of both **2a**-Li and **3a**-Li[1,4,5]. For the reasons outlined in the introduction it is however impossible to determine the ratio of cyclic **2a**-Li to acyclic **3a**-Li solely from such trapping reactions. Therefore, we first measured the ^{13}C-NMR spectrum of lithiated oxazole in [D$_8$]tetrahydrofuran ([D$_8$]THF) between −105 and 20°C[7]. The spectrum remained the same over the whole temperature range; that recorded at −30°C is shown in Figure 1.

Figure 1. ^{13}C-NMR spectrum of lithiated oxazole in [D$_8$]THF at −30°C



Line broadening was not observed at any temperature. From the chemical shift of C2′ (for the numbering, see Scheme 1) at δ = 161.5, which corresponds to the signal of an isocyanide carbon atom, it was clear that acyclic **3a**-Li had been formed. Further signals could be attributed to the enolate α-C atom (C5′: δ = 160.0) and to the enolate β-C atom (C4′: δ = 82.8). Since other signals were not observed, it can be concluded that only the ring-opened **3a**-Li was present (95 ± 5% within the limits of error). A similar spectrum was recorded by Crowe et al.[4]. The presence of the isocyanide group was also evident from the IR spectrum of **3a**-Li in THF, giving rise to an absorption at $\tilde{\nu}$ = 2120 cm^{-1}. Other lithiated oxazoles behave similarly, as depicted in Scheme 3.

Scheme 3



4-ph-**2a**-Li 4′-ph-**3a**-Li

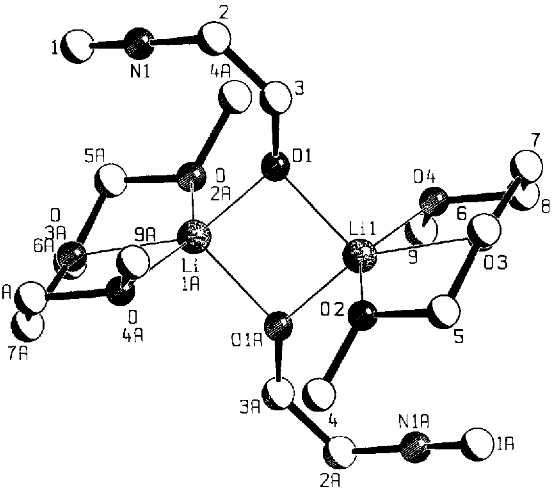
benzo-**2a**-Li lithium 4′-isocyanophenolate

4-*t*butyl-**2a**-Li 4′-*t*butyl-**3a**-Li

In the case of the 4-phenyl compound (4-Ph-**2a**-Li), only the ring-opened 4′-Ph-**3a**-Li could be detected [^{13}C NMR (−60°C): C2′ δ = 161.7, C4′ δ = 82.9, C5′ δ = 160.0 (besides the signals of the phenyl group)[7,8]]. Likewise, Fraser et al.[9] found only the ring-opened lithium 2-isocyano phenolate after lithiation of benzoxazole, leading initially to benzo-**2a**-Li (Scheme 3). This result was confirmed in the course of our studies: besides the isocyanide carbon-atom signal at δ = 165.7, only the signals of the 6 carbon atoms of the phenyl group between δ = 111.6 and 164.0 could be detected[8]. In this example, the rate of the ring-opening reaction should be enhanced by the better leaving group properties of Li phenolate as compared to Li enolate. Furthermore, the Li phenolate is thermodynamically more stable then a Li enolate. In view of the results presented in the following sections, it was perhaps rather surprising that even the 4-*tert*-butyl-**2a**-Li underwent complete ring-opening (95 ± 5%) to give the acyclic 4′-*tert*-butyl-**3a**-Li (Scheme 3): in the ^{13}C-NMR spectrum at −80°C only the signals of C2′ (δ = 163.4), C4′ (δ = 108.0) and C5′ (δ = 152.7) were observed, besides those of the *tert*-butyl group[8,10]. Considering the high affinity of Li^+ for oxygen, metal-assisted ionization undoubtedly plays a key role in facilitating the cleavage of the C2−O1 bond in lithiated oxazoles **2a**-Li. An α-elimination of RO^-Li^+, however, is only possible because of the simultaneous formation of a very stable "carbene", namely the isocyanide functionality. In "normal" α-lithiated ethers, in which case a rather unstable "normal" carbene would be formed if RO^-Li^+ is α-eliminated, cleavage of the C−O bond is observed only in the presence of strong nucleophiles such as RLi compounds[11].

From a diglyme solution we were able to crystallize the acyclic **3a**-Li as a diglyme-complexed dimer [**3a**-Li · diglyme]$_2$, see Figure 2[8]. Not surprisingly, we were unable to crystallize a ring-closed lithiated oxazole.

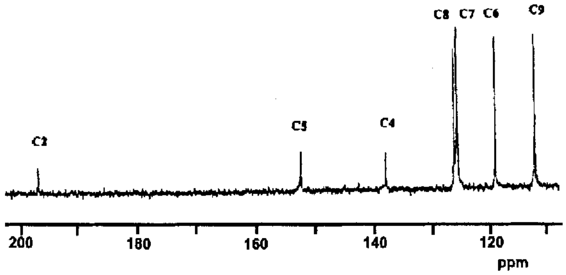
Figure 2. X-ray crystal structure of the lithium (*Z*)-2-isocyano enolate **3a**-Li [**3a**-Li · diglyme]$_2$



The two Li-enolates in the dimer [**3a**-Li · diglyme]$_2$ are connected to each other via an Li−O−Li−O four-membered ring. The diglyme molecules provide three further oxygen atoms for coordination to each Li^+ cation[12]. Figure 2 also shows the (*Z*) configuration at the enolate double bond, which is maintained in the ring-opening reaction.

The predominance of the ring-opened isomers **3a**-Li in the equilibria with the lithiated oxazoles **2a**-Li requires strong preference of the reactions of electrophiles E^+ with cyclic **2a**-Li, if the cyclic products **1**-E(2) are formed (Scheme 1). For example, this is the case in the reaction with benzaldehyde at room temperature, which occurs to some extent at C2 of **2a**-Li[1c,13,27]. At lower temperatures (down to −75°C) the reaction at C4′ of the acyclic **3a**-Li is, however, more favorable[1c]. A preference for reaction with the ring-opened isomer **3a**-Li is also observed in many other reactions of **2a**-Li ⇌ **3a**-Li with electrophiles E^+. This is the reason why Crowe et al.[4] as well as Anderson and Harn[5] introduced the *zinc* compounds **2a**-ZnCl, which – most significantly – allowed the trapping of the cyclic isomers. The question then arises as to whether the equilibrium in the case of the ZnCl species is shifted towards the side of the cyclic **2a**-ZnCl and/or whether trapping of this isomer is much faster than that of the open-chain **3a**-ZnCl. From the ^{13}C-NMR spectrum published by Crowe et al. it can be concluded that the ring-closed **2a**-ZnCl predominates in the equilibrium[4], although the authors did not assign the small but important peak at δ = 198 to the zincated carbon atom C2. As shown in Figure 3, even the C2-"zincated" benzoxazole exists exclusively as the ring-closed isomer.

Figure 3. ^{13}C-NMR spectrum of 2-ZnCl-benzoxazole in [D$_8$]THF at −10°C



The signal of C2, which is characteristic of the ring-closed structure, was observed at δ = 197.1, while the ^{13}C-NMR signals of the six-membered ring carbon atoms appeared at δ = 111.8, 118.8, 125.3, 125.5, 137.8 and 152.2. A signal of an isocyanide carbon atom ($\delta \approx$ 161) was not observed. These findings clearly demonstrate the enormous effect of different gegenions – Li^+ vs. $ZnCl^+$ – on the preferred structure adopted by two isomeric anions[14].

X-ray crystal structure investigations of 2-lithiated and 2-ZnBr-substituted 4-*tert*-butyl*thiazole* are in perfect agreement with these findings[6]: In the *lithiated* species, the C−S bond is significantly longer (176.2 pm) than in the *ZnBr* species (173.3 pm), indicating the more facile cleavage of this bond to give the ring-opened isomer in the Li^+ case. Furthermore, while Li^+ is closely bonded to N3, which leads to a carbene-type structure (**2″b**-Li, Scheme 2), $ZnBr^+$ is more closely attached to C2 instead. This corresponds to a bonding situation with more **2**-M character (Scheme 1). The ^{13}C-NMR signals of the C2 carbon atoms of such compounds confirm this situation: the signal of 2-Li-thiazole (δ = 231.5) is much closer to that of a thiazol-2-ylidene (δ = 252.0)[15] than that of the corresponding ZnBr species (δ = 198.5)[6,28].

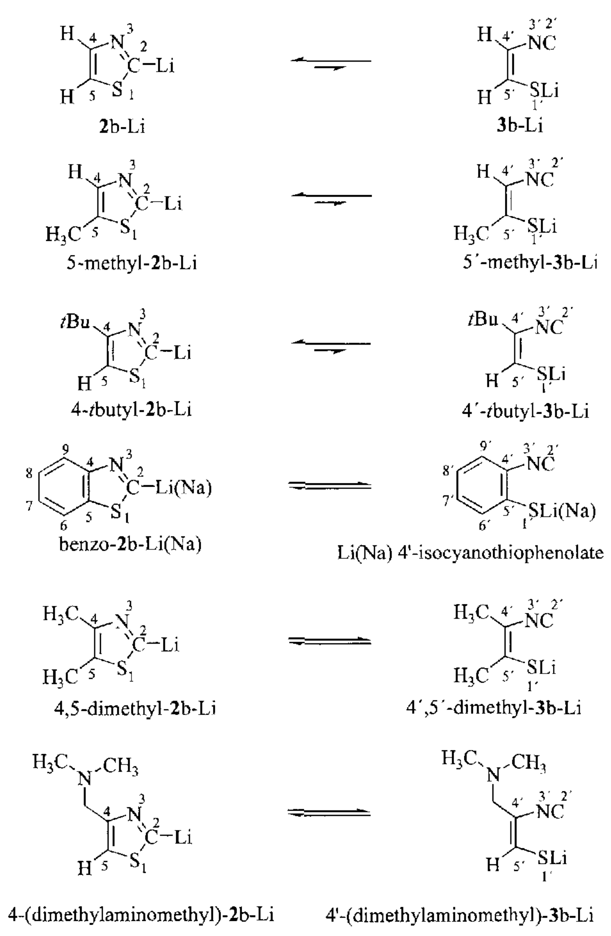
In conclusion, 2-lithiated oxazole, **2a**-Li, and its substituted derivatives isomerize very rapidly, even at low temperature (−78°C), to the more stable ring-opened lithium isocyano (ph)enolates, **3a**-Li. According to NMR measurements in the range of −105 to 20°C, the ring-opened **3a**-Li species are the only observable products (95 ± 5%). This is supported by the crystallization of [**3a**-Li · diglyme]$_2$, the structure of which was determined by X-ray crystallography. The presence of very small amounts of **2a**-Li in the equilibrium **2a**-Li ⇌ **3a**-Li are only suggested from trapping reactions with E^+, which lead to products of the type **1**-E(2)[27]. A dramatic effect of the gegenion is observed: if

Li^+ is replaced by $ZnCl^+$, instead of the acyclic isomers **3a**-ZnCl, only the ring-closed oxazole-derived **2a**-ZnCl species are detected in the ^{13}C-NMR spectrum, as indicated by Crowe et al.[4] and corroborated by reactions of such species[4,5]. The completely different behaviour of Li^+ vs. $ZnCl^+$ is in agreement with solid-state structure investigations of C2-metallated thiazoles[6,28].

2-Lithiated Thiazoles 2b-Li

Lithiated (substituted) thiazoles **2b**-Li (Scheme 4) have been used much more widely as acyl(formyl)lithium equivalents than their oxygen analogues **2a**-Li[2]. This suggests a lower tendency to undergo ring-opening to give (substituted) **3b**-Li. Most notably, Dondoni et al. have highlighted the application of lithiated (and silylated) thiazoles in stereoselective syntheses[16].

Scheme 4



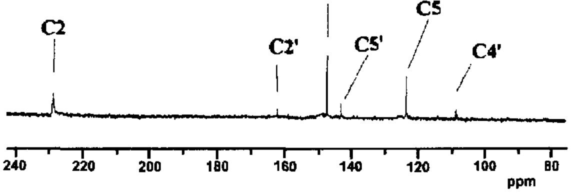
In the case of the parent lithiated thiazole **2b**-Li, only products of the ring-closed isomer **2b**-Li were trapped in reactions with electrophiles[2,16], indicating a predominance of **2b**-Li in the equilibrium with **3b**-Li. However, it was also shown that reaction of, e.g., 2-sodium benzothiazole (benzo-**2b**-Na) in ammonia with ethyl bromide, leads to a 90% yield of the ethyl thioether derived from the ring-opened sodium (2-isocyanato)thiophenolate. Thus, ring-opening does take place, at least to some degree. With other electrophiles, the ring-closed benzo-**2b**-Na was trapped.[2,16]

The ^{13}C-NMR spectrum of the parent 2-lithiothiazole, **2b**-Li, (see Scheme 4) in THF at −75[7] was consistent with the results of the trapping reactions with E^+: only the three signals of the ring-closed species were in evidence (C2: δ = 231.5, C4: δ = 141.6 and C5: δ = 117.5)[8]. Since an isocyano carbon-atom signal was clearly absent, **2b**-Li indeed dominates (95 ± 5%) in the equilibrium **2b**-Li $\rightleftharpoons$ **3b**-Li. Similarly, in the ^{13}C-NMR spectrum of lithiated 5-methylthiazole (5-methyl-**2b**-Li) (Scheme 4) in [D_8]THF at temperatures between −78 and −40°C, only the signals of the ring-closed isomer 5-methyl-**2b**-Li were observed (C2: δ = 234.6, C4: δ = 141.2, C5: δ = 131.0; the H_3C-signal was found at δ = 12.7). An isocyanide carbon-atom signal was again absent. Above −40°C, the compound decomposes readily. Also ring-closed, but thermally much more stable is the 2-lithiated 4-*tert*-butyl-**2b**-Li (Scheme 4). The signals of C2 (δ = 232.0), C4 (δ = 166.5) and C5 (δ = 110.8) are in the expected range, and an isocyanide peak is not detectable[8], not even at 35°C. The fact that the spectrum of this compound can be measured at 35°C is an indication of its thermodynamic and thermal stability. Thus, it is not surprising that 4-*tert*-butyl-**2b**-Li was the compound of choice for a solid-state structure investigation aimed at assessing carbene properties[6].

In contrast to these compounds, the ^{13}C-NMR spectrum of lithiated benzothiazole (benzo-**2b**-Li) (Scheme 4) in [D_8]THF at −75°C did not feature only the 7 sharp signals of the ring-closed compound. Instead, around 11 broadened signals were observed, which seems to support an equilibrium with the ring-opened lithium (2-isocyano)thiophenolate, as indicated above for the Na^+ species in NH_3. The prominent signals at δ = 220.8 and 157.9, were most likely attributable to C2 of the ring-closed benzo-**2b**-Li and the isocyanide C2′ of the ring-opened isomer, respectively. In the spectrum at 27°C, the signal at δ = 220.8 was not detectable[9].

The ^{13}C-NMR spectrum of the 2-lithiated 4,5-dimethylthiazole (4,5-dimethyl-**2b**-Li) (Scheme 4) provided more conclusive proof for the existence of an equilibrium, since the signals of both the ring-closed species and those of the ring-opened 4′,5′-dimethyl-**3b**-Li could be detected simultaneously, see Figure 4.

Figure 4. ^{13}C-NMR spectrum of 4,5-dimethyl-**2b**-Li and 4′,5′-dimethyl-**3b**-Li in [D_8]THF at −35°C



At −78°C, only the signals of the ring-closed 4,5-dimethyl-**2b**-Li were detected (C2: δ = 229.6, C4: δ = 147.4, C5: δ = 123.6), while at −35°C those of the acyclic 4′,5′-dimethyl-**3b**-Li (C2′: δ = 161.8, C4′: δ = 108.3, C5′: δ =

143.0) were also observed. Only the latter signals remained upon warming the THF solution to 0°C[8]. When one molar equivalent of [12]-crown-4 was added to this solution, ring-opening of the 4,5-dimethyl-**2b**-Li was only observed above 0°C. Furthermore, besides the acyclic 4′,5′-dimethyl-**3b**-Li the cyclic 4,5-dimethyl-**2b**-Li is still present – in contrast to the experiment without [12]-crown-4. These observations are consistent with metal ion assistance of such ring-opening reactions as discussed above: complexed within [12]-crown-4, Li^+ is much less to support the ring-opening reaction. They also show a decreased stability of the Li^+ enolate in the presence of [12]-crown-4.

4-(Dimethylaminomethyl)-2-lithiothiazole [4-(dimethylaminomethyl)-**2b**-Li] (Scheme 4) behaved similarly to 4,5-dimethyl-**2b**-Li: in the ^{13}C-NMR spectrum in [D$_8$]THF at −50°C, an equilibrium with the ring-opened 4′-(dimethylaminomethyl)-**3b**-Li was apparent from the following signals: C2: δ = 234.9, C4: δ = 153.8, C5: δ = 115.8 and C2′: δ = 164.8, C4′: δ = 95.6, C5′: δ = 151.5; signals of the methyl groups were observed at δ = 45.7, 59.9 and 61.4. Even on warming to 25°C, the signals of ring-closed 4-(dimethylaminomethyl)-**2b**-Li were still present.

Summarizing the results obtained for the various lithiated thiazoles **2b**-Li, one can conclude that the tendency to undergo ring-opening to give the acyclic **3b**-Li is much less pronounced than in the Li-oxazole case (**2a**-Li $\rightleftharpoons$ **3a**-Li). Consistent with this observation is the fact that *lithiated* thiazoles, **2b**-Li, are successfully used as acyl(formyl)lithium equivalents in synthesis[2,16], and that the cyclic compounds can be crystallized and examined by X-ray crystallography (e.g., 4-*tert*-butyl-**2b**-Li[6]). It should be recalled that in the case of the 2-lithiated oxazoles, **2a**-Li $\rightleftharpoons$ **3a**-Li, only crystals of a ring-opened isomer ([**3a**-Li · diglyme]$_2$, Figure 2) could be obtained. To the best of our knowledge, 2-zincated thiazoles have not previously been investigated in solution. However, as pointed our earlier, an "Li^+ vs. $ZnBr^+$ effect" with respect to ring-opening is also observed in the thiazole series: the C–S bond length in the solid-state structure of the lithiated 4-*tert*-butylthiazole (176.2 pm) indicates a more facile cleavage than in the case of the corresponding ZnBr species (173.3 pm).

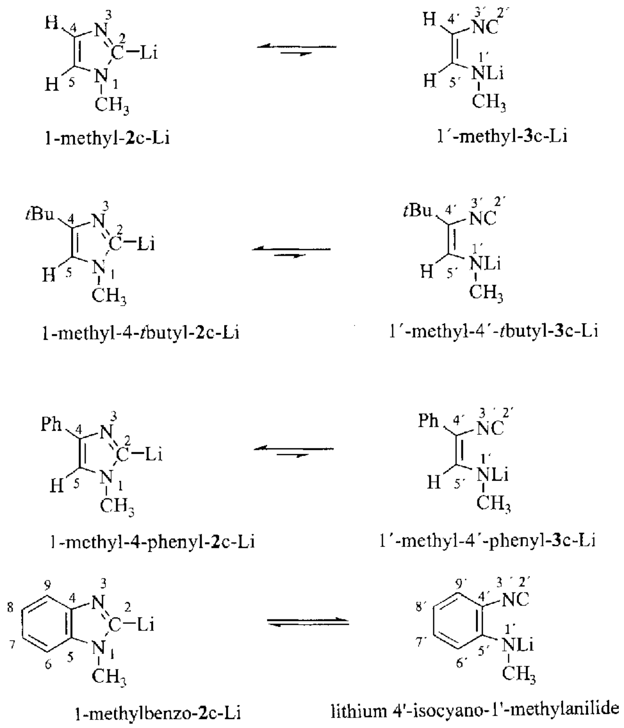
The difference in the tendency to undergo ring-opening between 2-lithiated oxazoles **2a**-Li and 2-lithiated thiazoles **2b**-Li parallels the behaviour of α-lithiated ethers and α-lithiated thioethers: α-lithiated ethers are carbenoids with a pronounced tendency to undergo cleavage of the $R^1R^2C(Li)-OR^3$ bond in the presence of nucleophiles[11]. In contrast, a similar carbenoid behaviour is observed only in a very few special cases in the α-lithiated thioether series, $R^1R^2C(Li)-SR^3$[11].

No example of carbenoid behaviour in the case of α-lithiated amines $R^1R^2C(Li)-NR_2$ has yet been reported[17]. The implications of this for 2-lithiated imidazoles, **2c**-Li, and their possible isomerization to the corresponding acyclic products, **3c**-Li, (Scheme 1) is discussed in the next section.

2-Lithiated Imidazoles 2c-Li

Deprotonation of *N*1-substituted imidazoles **1c** at C2 to give **2c**-Li, followed by reaction with an electrophile E^+, is a known reaction[3], even though the deprotonation of **1c** is more difficult to achieve than that of oxazoles (**1a**) and especially that of thiazoles (**1b**). Frazer et al.[9] recorded the ^{13}C-NMR spectrum of 2-lithium-1-methylimidazole (1-methyl-**2c**-Li) (Scheme 5).

Scheme 5



In view of the results discussed in the sections on 2-metallated oxazole(s) **2a**-M (M = Li, ZnCl) and 2-lithiated thiazole(s) **2b**-Li, we wondered whether the ^{13}C shift of C2, as published by these authors, was in fact correct: C2 (δ = *171.5*), C4 (δ = 129.1), C5 (δ = 118.9)[9]. Therefore, we recorded the ^{13}C-NMR spectrum of **2c**-Li once again {in [D$_8$]THF in the presence of some diethyl ether between −20 and 60(!)°C}. We confirmed the shifts for C4 (δ = 128.5) and C5 (δ = 115.0), but the C2 signal was detected at δ = *201.6*[8] (and not at δ = *171.5*[9]). The CH_3 group was observed at δ = 35.8. This showed quite clearly that only the ring-closed species **2c**-Li was present, especially since an isocyanide carbon-atom signal was completely absent.

With the results of the Li-thiazole (**2b**-Li) section in mind, it is not surprising that 4-*tert*-butyl-2-lithio-1-methylimidazole (4-*tert*-butyl-1-methyl-**2c**-Li, Scheme 5) exhibits a similar ^{13}C-NMR spectrum: C2 (δ = 195.9), C4 (δ = 154.0) and C5 (δ = 114.2)[8]. The ^{13}C-NMR spectrum remained unchanged after leaving the [D$_8$]THF solution to stand at 20°C for one week. Thus, the ring-closed 4-*tert*-butyl-1-methyl-**2c**-Li is very stable, and being the only compound detectable in the ^{13}C-NMR spectrum (95 ± 5%), it was possible to grow crystals of this compound and to determine their structure by X-ray crystallography[6].

^{13}C-NMR investigations of 2-lithio-1-methyl-4-phenylimidazole (1-methyl-4-phenyl-**2c**-Li) (Scheme 5) confirmed this tendency: up to 20°C, besides the signals of the aforementioned ring-closed isomer (C2: δ = 200.9, C4: δ = 142.8, C5: δ = 116.5) only the signals of the methyl and phenyl groups could be detected[8].

An exception is the benzo compound 2-lithio-1-methylbenzimidazole (1-methylbenzo-**2c**-Li) (see Scheme 5), for which a ^{13}C-NMR spectrum with 16 lines was observed. This is indicative of an equilibrium between ring-closed 1-CH_3-benzo-**2c**-Li and the ring-opened isomer lithium 2-isocyano-*N*-methylanilide (Scheme 5). The signal of C2 of the ring-closed 1-methylbenzo-**2c**-Li was observed at δ = 216.1, while the isocyanide carbon atom C2′ of the ring-opened lithium 2-isocyano-*N*-methylanilide appeared at δ = 158.4[8]. The existence of an equilibrium between the ring-closed and the ring-opened isomers in this particular example of a lithiated imidazole is due to an *N-lithiated aniline* being a much better leaving group than an *N-lithiated enamine*. Similarly, an acyclic **3c**-Li with an *N-lithiated aniline* group is more stable than with an *N-lithiated enamine* group.

In conclusion, 2-lithiated imidazoles **2c**-Li (and substituted derivatives thereof) are generally much more stable towards ring-opening than their Li-thiazole (**2b**-Li) and especially their Li-oxazole (**2a**-Li) analogues. Only in the case of the 2-lithiated benzimidazole, 1-methylbenzo-**2c**-Li, was partial ring-opening observable by ^{13}C-NMR spectroscopy.

The ^{13}C-NMR Shift of C2 in 2-Lithiated Thiazoles and Imidazoles

Since 2-*lithiated* oxazoles **2a**-Li could not be observed by ^{13}C-NMR spectroscopy because of the equilibrium being far on the side (95 ± 5%) of the ring-opened isomers **3a**-Li, we have to restrict ourselves to the C2 atoms of 2-lithiated thiazoles **2b**-Li and 2-lithiated imidazoles **2c**-Li. In Table 1, the lowest and the highest ^{13}C-chemical shifts of the C2 atoms in several **2b**-Li's and **2c**-Li's are listed, together with the $\Delta\delta$ values with respect to the ^{13}C shifts of the C2 atoms in the corresponding non-lithiated thiazoles **1b** and imidazoles **1c**, respectively.

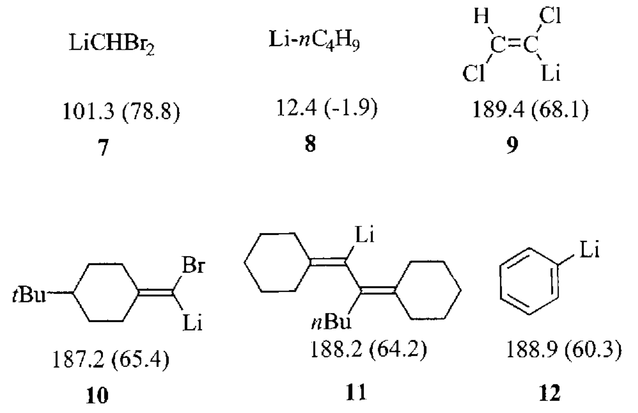
Table 1. ^{13}C-chemical shift ranges of various **2b**-Li's and **2c**-Li's; $\Delta\delta$-^{13}C values with respect to the non-lithiated thiazoles **1b** and imidazoles **1c**; the values for the lithiated benzo derivatives are underlined[8]

	δ (C2) [ppm]	$\Delta\delta$ (C2) [ppm]
2b-Li	220.8–234.9	66.8–83.1
1-CH_3-**2c**-Li	195.9–216.1	59.0–72.5

Which compounds provide an appropriate comparison? Scheme 6 gives some examples of Li compounds, studied by Seebach et al.[18a], and of the ^{13}C shifts of their α-C-atoms.

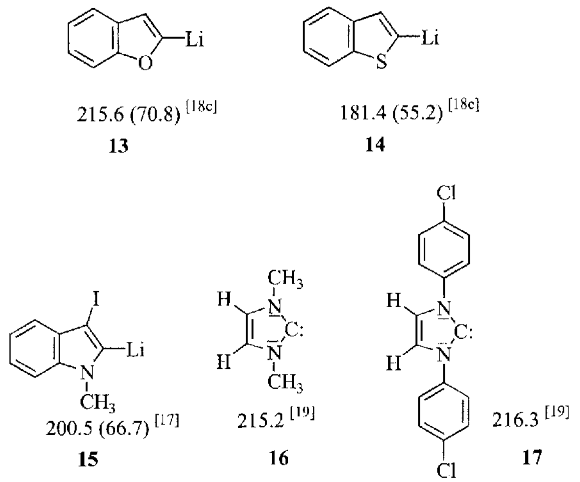
While there is a strong downfield shift in "sp^3"-hybridized carbenoids such as **7**, as compared to non-carbenoid sp^3 compounds (**8**), there is little difference in shift between carbenoid **9**, **10** and non-carbenoid vinylic compounds **11** [as well as phenyllithium (**12**)]. Apparently, the downfield shift in the vinylic Li compounds **9**–**11**, as well as in **12**, is esentially determined by the polarization of the π-bond(s) caused by the C−M σ bond[18a,b].

Scheme 6. ^{13}C-chemical shifts of the α-C atoms [δ and $\Delta\delta$(H,Li) values (the latter in parentheses)] of various lithium carbenoids and lithium compounds[18]



A comparison of 2-lithiated benzofuran **13**[18c] with 2-Li-benzothiophene **14**[18c] and the 2-Li-1-methylindole **15**[17] leads to a similar conclusion (Scheme 7).

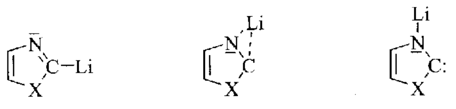
Scheme 7. ^{13}C-chemical shifts of the α-C atoms [δ and $\Delta\delta$(H,Li) values (the latter in parentheses)] of lithium compounds and δ values of the carbene C atoms of stable carbenes



Apparently, the different heteroatoms (O, S, N−CH_3) do not give rise to markedly different ^{13}C shifts. Even the carbene C atoms of imidazolidenes such as **16** and **17**[19] show signals in the same range of those of **13**, **14** and **15**, and of the lithiated thiazoles **2b**-Li and the lithiated imidazoles 1-methyl-**2c**-Li (see Table 1).

Thus, the ^{13}C-NMR results discussed in this section lead to the conclusion that the downfield shifts of the C2 atoms in 2-lithiated thiazoles **2b**-Li and 2-lithiated imidazoles **2c**-Li (see Table 1) are in the range expected for compounds of this structural type. However, from the ^{13}C-NMR data alone it is not possible to decide conclusively whether one is dealing with a lithiated heterocycle **2**-Li, a bridged species with carbene character **2′**-Li, or a carbene **2″**-Li (see Scheme 8). For such a distinction to be made it is necessary to acquire additional information from solid-state structural investigations[6].

Scheme 8



2-Li 2'-Li 2''-Li

X = $\bar{S}$ and $\bar{N}$-CH_3, respectively

Summary

The use of 2-lithiated oxazoles **2a**-Li, thiazoles **2b**-Li and imidazoles **2c**-Li in the synthesis of substituted heterocycles and as acyl(formyl)lithium equivalents relies on the predominance of the cyclic isomers **2a**(**b**, **c**)-Li in the equilibrium with the acyclic isomers **3a**(**b**, **c**)-Li. In reactions with electrophiles E^+, the latter species lead to undesired products. Since it is impossible to determine the ratio **2a**(**b**, **c**)-Li/**3a**(**b**, **c**)-Li simply by trapping reactions with E^+, we studied the propensity of these compounds to undergo ring-opening by means of ^{13}C-NMR spectroscopy. In the case of the Li-oxazoles, **2a**-Li, only the acyclic isomers **3a**-Li were observed (95 ± 5%). An X-ray crystal structure analysis of [**3a**-Li · diglyme$]_2$ was consistent with the NMR studies. The existence of 2-lithiated oxazoles **2a**-Li thus rests only on the assumption that they are trapped by certain electrophiles E^+ from the equilibrium **2a**-Li $\leftrightharpoons$ **3a**-Li to give the cyclic products **1**-E(2) (in low yields)[27]. Depending on the substitution pattern, Li-thiazoles are either ring-closed (**2b**-Li) or are in equilibrium with the acyclic isomer **3b**-Li. As far as Li-imidazoles **2c**-Li are concerned, only in the case of the 2-lithiated benzimidazole could the acyclic isomer be detected. These findings reflect the leaving-group properties of the relevant subunits involved in the ring-opening reactions: (i) ROLi > RSLi > R_2NLi, and (ii) aryl –O(S,NR)Li > vinyl–O(S,NR)Li. Whether these compounds are normal C2-lithiated heterocycles **2**-Li, bridged species (N–C by Li^+) with carbene character **2'**-Li, or carbenes **2''**-Li, cannot be determined merely from the ^{13}C-chemical shifts of the C2 atoms of the cyclic **2b**-Li and **2c**-Li. A dramatic effect of the gegenion on the equilibrium **2a**-M $\rightleftharpoons$ **3a**-M is observed, i.e., when M = Li is replaced by M = ZnCl: even in the benzoxazole case only the *ring-closed* species is observed in the ^{13}C-NMR spectrum. This is very significant for synthetic purposes[4,5,28].

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Experimental Section

Manipulations and reactions of organometallic compounds were carried out under dry argon (Messer-Griesheim 99.998%). Syringes and flasks were oven-dried at 100°C and flushed with argon on cooling. – ^1H- and ^{13}C-NMR spectra were recorded with Bruker AC 300 and Bruker AM 400 spectrometers. For the spectra of the lithium compounds, NMR tubes (Wilmad) were oven-dried (100°C) and argon-flushed. The NMR tubes were sealed with special 7-mm spectra (Aldrich). For the description of the NMR spectra, the following abbreviations are used: s = singlet, bs = broad singlet, d = doublet, dd = double doublet, t = triplet, q = quartet, m = multiplet, mc = centered multiplet, bm = broad multiplet, *J* = coupling constant [Hz]. – Infrared spectra were recorded with a Beckman IR-33-spectrometer. – Mass spectra were obtained by electron-impact ionization with a Varian CH-7A mass spectrometer. – Melting points were measured with a Kofler apparatus (Reichert, Vienna) and are not corrected. – Ethers used for organometallic reactions were pre-dried with KOH (one week) and then refluxed over K/benzophenone until the solution was blue. [D_8]Tetrahydrofuran (Merck, 99.5%), diglyme and [12]-crown-4 were kept over molecular sieves (4 Å) in order to remove residual traces of water. Methyllithium (1.6 M in diethyl ether; Aldrich) and *n*-butyllithium (1.6 M in *n*-hexane; Aldrich) were used without further purification.

Oxazoles, Thiazoles, Imidazoles and Their Metallated Derivatives. – *Oxazoles:* Oxazole (**1a**) (98%) was purchased from Aldrich and used without further purification.

Lithiation of Oxazole (**1a**): **1a** was lithiated in [D_8]THF with one mol-equiv. of *n*-butyllithium/*n*-hexane (1.6 M) at –75°C.

4-Phenyloxazole: 4-Phenyl-**1a** was obtained from α-(formyl)acetophenone and ammonium acetate by a two-step procedure, as described by Rickborn et al.[20].

Lithiation of 4-Phenyloxazole: 4-Phenyl-**1a** was lithiated in [D_8]THF with one mol-equiv. of *n*-butyllithium/*n*-hexane (1.6 M) at –75°C.

Benzoxazole: Benzo-**1a** was purchased from Aldrich and distilled under vacuum prior to use.

Lithiation of Benzoxazole: Benzo-**1a** was lithiated in [D_8]THF with one mol-equiv. of *n*-butyllithium/*n*-hexane (1.6 M) at –75°C.

4-tert-Butyloxazole: 4-*tert*-Butyl-**1a** was synthesized according to a procedure described by Kondrat'eva and Huang[21].

Lithiation of 4-tert-Butyloxyazole: 4-*tert*-Butyl-**1a** was lithiated in [D_8]THF with one mol-equiv. of methyllithium/diethyl ether (1.6 M) at –75°C.

Thiazoles: Thiazole (**1b**) (99%) was purchased from Aldrich and used without further purification.

Lithiation of Thiazole: Thiazole (**1b**) was lithiated in [D_8]THF with one mol-equiv. of *n*-butyllithium/*n*-hexane (1.6 M) according to a procedure described by Dondoni et al.[2f].

4,5-Dimethylthiazole: 4,5-Dimethyl-**1b** was purchased from Lancaster Synthesis and used without further purification.

Lithiation of 4,5-Dimethylthiazole: 4,5-Dimethyl-**1b** was lithiated in [D_8]THF with one mol-equiv. of *n*-butyllithium/*n*-hexane (1.6 M) according to a procedure described by Dondoni et al.[2f].

Benzothiazole: Benzo-**1b** was purchased from Janssen and purified by vacuum distillation prior to use.

Lithiation of Benzothiazole: Benzo-**1b** was lithiated in [D_8]THF with one mol-equiv. of *n*-butyllithium/*n*-hexane (1.6 M)[2f].

5-Methylthiazole: 5-Methyl-**1b** was purchased from Aldrich and used without further treatment.

Lithiation of 5-Methylthiazole: 5-Methyl-**1b** was lithiated in [D_8]THF with one mol-equiv. of *n*-butyllithium/*n*-hexane (1.6 M) according to a procedure described by Dondoni et al.[2f].

4-tert-Butylthiazole: 4-*tert*-Butyl-**1b** was prepared and lithiated as described in ref.[6].

4-[(Dimethylamino)methyl]thiazole: 4-[(Dimethylamino)methyl]-**1b** was prepared as described in ref.[6]. The lithiation was carried out using the same procedure as in the case of the other thiazoles[2f].

Imidazoles. – 1-Methylimidazole: 1-Methyl-**1c** was purchased from Merck, dried over molecular sieve (4 Å), deoxygenated, and stored under argon.

Lithiation of 1-Methylimidazole: 1-Methyl-**1c** was lithiated in [D$_8$]THF with one mol-equiv. of methyllithium in diethyl ether (1.6 M) at 0°C.

4-tert-Butyl-1-methylimidazole: 4-*tert*-Butyl-1-methyl-**1c** was prepared as described in ref.[6].

Lithiation of 4-tert-Butyl-1-methylimidazole: 4-*tert*-Butyl-1-methyl-**1c** was lithiated in [D$_8$]THF with one mol-equiv. of methyllithium in diethyl ether (1.6 M) at 0°C.

1-Methyl-4-phenylimidazole: 1-Methyl-4-phenyl-**1c** was prepared as described in ref.[6].

Lithiation of 1-Methyl-4-phenylimidazole: 1-Methyl-4-phenyl-**1c** was lithiated in [D$_8$]THF with one mol-equiv. of methyllithium in diethyl ether (1.6 M) at 0°C.

1-Methylbenzimidazole: 1-Methylbenzo-**1c** was prepared as described in ref.[6].

Lithiation of 1-Methylbenzimidazole: 1-Methylbenzo-**1c** was lithiated in [D$_8$]THF with one mol-equiv. of methyllithium in diethyl ether (1.6 M) at 0°C.

^{13}C-NMR Spectra: In the following, additional information concerning the ^{13}C-NMR spectra of some of the compounds mentioned in the "Results and Discussion" section are given.

4-Ph-**2a**-Li $\rightleftharpoons$ 4′-Ph-**3a**-Li. (at −60°C): δ = 120.5, 123.3, 128.8, 137.0 (phenyl carbon atoms).

Benzo-**2a**-Li $\rightleftharpoons$ lithium 2-isocyanophenolate (at −80°C): δ = 165.7 (C2′), 111.6, 117.3, 121.6, 128.1, 130.6, 164.0 (phenyl carbon atoms).

4-*t*-Butyl-**2a**-Li $\rightleftharpoons$ 4′-*t*-butyl-**3a**-Li (at −80°C): δ = 14.9 (CH$_3$), 16.9 [C(CH$_3$)$_3$].

4-*t*-Butyl-**2b**-Li $\leftrightharpoons$ 4′-*t*-butyl-**3b**-Li (at −80°C): δ = 31.0 (CH$_3$), 34.6 [C(CH$_3$)$_3$].

4,5-Dimethyl-**2b**-Li $\rightleftharpoons$ 4′,5′-dimethyl-**3b**-Li (at −35°C): δ = 11.1 (CH$_3$), 12.4 (CH$_3$). At 0°C in the presence of [12]-crown-4: δ = 12.2 (CH$_3$), 14.2 (CH$_3$), 15.1 (CH$_3$), 107.7 (C4′), 124.3 (C5), 143.0 (C5′), 147.4 (C4), 162.2 (C2′), 227.0 (C2).

4-*t*-Butyl-1-methyl-**2c**-Li $\leftrightharpoons$ 4′-*t*-Butyl-1′-methyl-**3c**-Li (at −20°C): δ = 31.7 (CH$_3$), 37.4 [C(CH$_3$)$_3$].

1-Methyl-4-phenyl-**2c**-Li $\leftrightharpoons$ 1′-methyl-4′-phenyl-**3c**-Li (at −75°C): δ = 36.0 (CH$_3$), 124.8, 125.4, 128.5, 137.9 (phenyl carbon atoms).

1-Methylbenzo-**2c**-Li $\rightleftharpoons$ lithium 2-isocyano-*n*-methylanilide (at −75°C): δ = 27.9 (CH$_3$), 33.5 (CH$_3$), 93.7, 102.2, 102.9, 107.9, 108.9, 116.1, 118.5, 118.8, 119.6, 138.2, 147.3, 148.4 (phenyl carbon atoms).

*2-ZnCl-Substituted Benzoxazole (Benzo-**2a**-ZnCl):* Benzoxazole (benzo-**1a**) was lithiated in [D$_8$]THF at −75°C as described above. The ^{13}C-NMR spectrum at this temperature showed only the signals of the ring-opened lithium 2-isocyanophenolate. To this solution, a solution of ZnCl$_2$ (3.0 mol-equiv.) in diethyl ether was added at −75°C. After warming to −10°C, the ^{13}C-NMR spectrum was recorded.

*Crystals of [**3a**-Li-diglyme]$_2$:* 0.07 g (1.0 mmol) of oxazole (**1a**) in 1 ml of THF was deprotonated with 1.1 mmol of *n*-butyllithium in hexane at −78°C. After 15 min at this temp., 2 ml of *n*-hexane was added, resulting in precipitation of **3a**-Li. After removal of the solvent, the solid was dissolved in 2.2 ml of diglyme. Crystals suitable for an X-ray crystal structure determination were formed after 12 h at 5°C.

*Crystal Structure of [**3a**-Li-diglyme]$_2$:* $C_{18}H_{32}Li_2O_8$, M_r = 418.34, crystal size 0.18 ± 0.25 ± 0.28 mm, triclinic space group $P1$, a = 770.6(1), b = 879.0(1), c = 976.7(1) pm, α = 70.33(1), „ = 80.90(1), γ = 69.63(1)°, V = 583.4(1) $\cdot$ 10^{-30} m^3, Z = 1, $D_{\text{calcd.}}$ = 1.191 mg/m^3, data collection with an Enraf-Nonius CAD4 diffractometer using Cu-K_α radiation, 2Θ range: 8–120°, scan mode: $\omega/2\theta$, T = 193(2) K; 1823 collected reflections, index ranges: $0 \leqslant h \leqslant 8$, $-9 \leqslant k \leqslant 9$, $-10 \leqslant l \leqslant 10$, 1674 were unique ($R_{\text{int}}$ = 0.0162). Solution by direct methods (SHELXTL-PLUS)[22], full-matrix least-squares refinement on F^2 (SHELXL-93)[23], non-hydrogen atoms aniosotropic, solvent hydrogen atoms with common isotropic temperature factors on calculated positions, the other hydrogen atoms isotropic; wR_2 = 0.1276 (1674 reflections, on F^2, parameters for the weighting scheme calculated by the program: 0.0711, 0.2355), extinction parameter: 0.150(8), conventional R = 0.0453 for 1594 reflections with $I > 2\sigma(I)$, goodness-of-fit (F^2) = 1.060, 161 parameters; extremes of the final difference Fourier synthesis: 0.318 and −0.204 $\cdot$ 10^{30} e/m^3. The structure possesses crystallographic inversion symmetry. Parts of the structure are disordered. All calculations were performed on a DEC 3000/300X[24–26].

☆ Dedicated to Professor Dr. *D. Seebach* on the occasion of his 60th birthday.

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[26] Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-100380. Copies of the data can be obtained free of charge on application to The Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: int. code +44(1223)336033, e-mail: deposit@chemcrys.cam.ac.uk].

[27] A referee has suggested, that the *cyclic* products **1**-E(2) might (also) be formed from the *acyclic* isocyano enolates **3a**-Li if the electrophiles E^+ first react with the carbon atom of the isocyanide group, and then ring closure occurs. Although one cannot exclude this pathway rigorously at the moment, it cannot be the prefered one, as especially shown in the section on "2-Metalated Oxazoles **2a**-M (M = Li, ZnCl)": the *acyclic* Li^+ compounds **3a**-Li, which dominate the equilibrium **2a**-Li $\rightleftharpoons$ **3a**-Li, react with electrophiles E^+ to give almost exclusively *acyclic* reaction products. It is only in the case of the *cyclic* **2a**-ZnHal (as well as **2b**-Li, **2c**-Li), that the reaction with E^+ leads to high yields of cyclic **1**-E(2).

[28] Notes added in proof (June 23, 1997): [28a] In the meantime, F. Bosold has been able to crystallize [**2**-ZnCl-benzoxazole·2 THF]$_2$ and to determine its solid-state structure. The C2–O1 (C2–N3) bonds are only slightly longer (2.2 and 1.9 pm, respectively) than in (55) oxazoles, in agreement with a structural type **2a**-ZnCl. – [28b] Theoretical calculations of **2a**-Li(ZnCl) and **3a**-Li(ZnCl) are in agreement with the experimental results of this work: **2a**-Li is 15.2 kcal/mol *less* stable than **3a**-Li, while **2a**-ZnCl is 11.8 kcal/mol *more* stable than **3a**-ZnCl (H. Hermann).

[97072]