Alkyllithium-Mediated Anomalous Trimerization of 2,6-Xylyl Isocyanide

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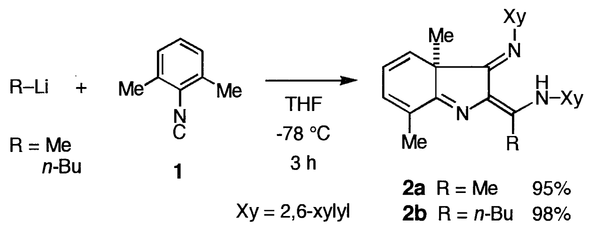
The reaction of alkyllithium with 2,6-xylyl isocyanide led to the trimerization of the isocyanide to afford an indole derivative. The anomalous reaction pattern provided inference about the structural features of the intermediate organolithium species.

Isocyanides undergo insertion into metal–alkyl bonds to furnish (alkaneimidoyl)metal compounds; e.g., the reaction of *tert*-alkyl isocyanide with alkyllithium furnishes an (alkaneimidoyl)lithium intermediate, which has found successful synthetic applications.[1] Unlike with carbon monoxide, the successive multiple occurrence of this elementary process is possible with isocyanides, leading to the formation of oligomers[2] and polymers.[3] Alkaneimidoyl complexes of the transition, lanthanide, and actinide series have been the subject of intense research.[4,5] Most of them adopt a η^2-bonding mode. In contrast, the structural features of alkaneimidoyl complexes of main group elements have received little attention.[6] η^1-Bonding through a C–Li linkage has been conventionally assumed for (alkaneimidoyl)lithium intermediates. We now report the alkyllithium-mediated anomalous trimerization of aryl isocyanide, which infers the bonding properties of the intermediate organolithium species.

2,6-Xylyl isocyanide (**1**, 0.50 mmol) was treated with methyllithium (0.50 mmol) in THF at -78 °C. The color of the solution changed from yellow to red, and after 3 h became dark blue with quantitative conversion of the isocyanide. The dark blue color disappeared the instant a drop of water was added to the mixture, and after chromatography, 0.16 mmol of an indole derivative **2a** was obtained (95% based on **1**). When 0.25 mmol of methyllithium was used under otherwise identical conditions, 0.078 mmol of **2a** was produced and half of **1** remained unreacted. Therefore, it is likely that the lithio derivative of **2a** traps two more equivalents of methyllithium, which are inert toward the free isocyanide (**1**) probably due to the steric reason. The skeletal arrangement of the anomalous product **2a** was deduced as depicted below on spectroscopic grounds.[7] Three molecules of **1** and one methyl group coming from methyllithium constitute **2a**. Recrystallization from CH_2Cl_2–MeCN provided single crystals suitable for an X-ray crystallographic analysis, which finally established the exact structure of **2a** (Figure 1).[8] The location of the double bonds was assigned on the basis of the bond distances. The hydrogen atom H1 found on a difference electron density map, together with N1, C5, C6, C7, and N3 forms a 6-membered cyclic geometry, indicating the presence of an N3•••H1 hydrogen bond [N3–H1 = 2.00(2) Å, N1–H1–N3 = 138(2)°]. The use of butyllithium instead of methyllithium furnished an analogous indole **2b** as well. However, a complex mixture was obtained when other aryl isocyanide having no substituents at the *o*-positions was reacted with alkyllithium.



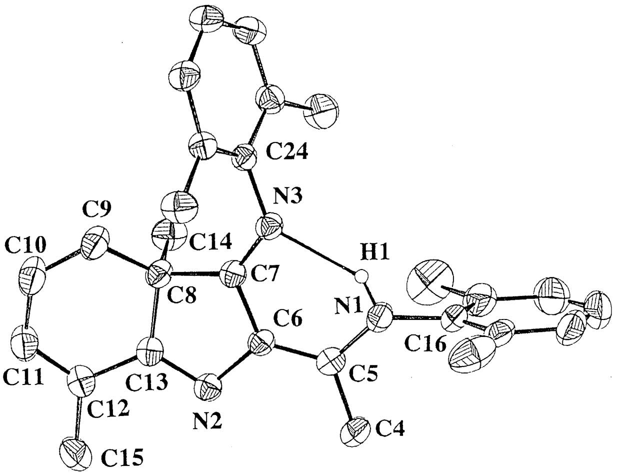
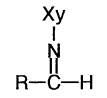


Figure 1. Molecular structure of **2a** with the hydrogen atoms except H1 omitted for clarity (35% probability thermal ellipsoids). The selected bond distances (Å): N1–H1, 0.93(2); N1–C5, 1.357(2); C5–C6, 1.369(2); C6–C7, 1.456(2); N3–C7, 1.288(2); N2–C6, 1.404(2); N2–C13, 1.299(2); C7–C8, 1.534(2); C8–C9, 1.497(3); C8–C13, 1.514(2); C9–C10, 1.340(3); C10–C11, 1.446(3); C11–C12, 1.349(3); C12–C13, 1.447(3).

In marked contrast to the cases of RLi–*tert*-alkyl isocyanide,[1] R_2Zn–2,6-xylyl isocyanide[9] and $RSmX_2$–2,6-xylyl isocyanide,[2c,10] neither the mono insertion product **3** nor the double insertion product **4** was obtained at all even when the reaction was quenched with water at an earlier stage. The lithio derivative of **2a** was prepared by treatment of **2a** with butyllithium. However, regeneration of the isocyanide (**1**) was not observed, being suggestive of the irreversibility of this trimerization.



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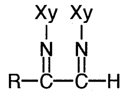

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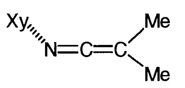

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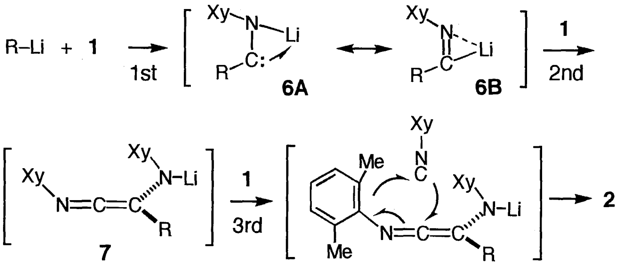
The coupling of carbenes with isocyanides to yield ketenimines has been documented well.[11] It has been also reported that N-(2,6-xylyl)ketenimine **5** reacts with 2,6-xylyl isocyanide (**1**) to afford an indole via formal [4+1] cycloaddition.[12,13] Furthermore, the direct formation of an analogous indole derivative by the reaction of a metal carbene complex with aryl isocyanide is known.[14] On the basis of these precedents, it would be reasonable to presume the following mechanism for the formation of **2**; initial coupling of alkyllithium with **1** yields a transitory η^2-(alkaneimidoyl)lithium **6**.[15] Besides **6 B**, a carbene-like resonance form (**6 A**) is viewed as an important contributor to the description of the (alkaneimidoyl)lithium. The subsequent coupling with the second equivalent of **1**, presumably carbene-like one, affords the ketenimine intermediate **7**. The third incorporation of **1** via formal [4+1] cycloaddition furnishes the indole skeleton. A related discussion of the carbenoid character of (η^2-acyl)thorium complexes has been given, based upon the formation of indole analogs in the reactions with aryl isocyanides.[16]



In conclusion, the facile formation of the anomalous product **2** by alkyllithium-mediated trimerization of **1** infers the structural features of the transient organolithium species. Assumption of an aminocarbene character for the initial coupling product, and a ketenimine structure for the second coupling product accounts for the present reaction pattern on analogy with the organic and organometallic precedents.

References and Notes

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7 **2a**: yellow powder: ^{1}H NMR (CDCl$_3$) δ 1.24 (s, 3H), 2.10 (s, 3H), 2.13 (s, 3H), 2.18 (s, 3H), 2.20 (s, 3H), 2.25 (s, 3H), 2.28 (s, 3H), 5.62–5.80 (m, 2H), 5.94–6.01 (m, 1H), 6.90–7.12 (m, 7H); ^{13}C NMR (CDCl$_3$) δ 14.7, 16.2, 18.3, 18.4, 18.8, 19.6, 26.1, 58.5, 122.9, 123.0, 123.7, 125.7, 126.8, 127.38, 127.45, 127.8, 128.0, 128.1, 128.3, 130.8, 132.2, 136.1, 136.5, 137.7, 146.7, 152.7, 167.1, 172.6. Found: C 81.84, H 7.55, N 10.17%. Calcd for $C_{28}H_{31}N_3$: C 82.11, H 7.63, N 10.26%.

8 Crystal data for **2a**: $C_{28}H_{31}N_3$, $M = 409.6$, orthorhombic, space group *Pbca* (no. 61), $a = 13.814(5)$, $b = 36.808(8)$, $c = 9.151(2)$ Å, $Z = 8$, $V = 4653(2)$ Å^3, $\rho_{calcd} = 1.17$ g/cm^3, $Cu_{K\alpha}$, $\lambda = 1.54178$ Å, $\mu = 4.55$ cm^{-1}, $T = 293$ K, 4497 reflections measured, 3891 independent, 3563 [$F > 1.0\sigma(F)$] included in the refinement, anisotropical refinement for non-hydrogen atoms by full-matrix least-squares with a program package CrystanG (Mac Science), 384 parameters, $R = 0.054$, $R_W = 0.062$, isotropic refinement for the hydrogen atom H1, refinement with isotropic thermal parameters calculated from those of the bonded atoms for other hydrogen atoms.

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15 Although the monomeric η^2-bound structure was depicted for **6**, other aggregated forms are also possible.

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