

Domino reaction of lithiated allenes with nitriles†

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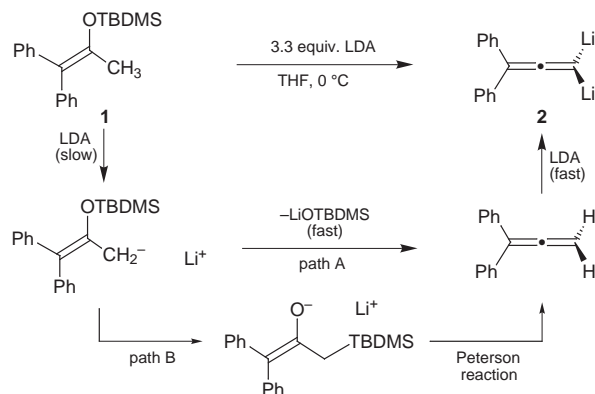
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Addition of nitriles to dilithiated allenes results in a unique domino cyclization which involves the so far highest number of nitrile molecules added to an organolithium reagent to form unambiguously characterized oligomers.

The development of domino reactions is of ongoing interest in organic synthesis.¹ Interestingly, although the base-catalyzed polymerization of nitriles has been followed for a long time and the mixtures obtained were among the first organic polymers, only a few structurally unambiguously characterized oligomers derived from multiple addition reactions of nitriles have been reported so far. In contrast, the palladium-catalyzed oligomerization of six isonitrile molecules has recently been reported.² Addition of 2 equiv. of a nitrile to an organometallic reagent has been achieved by reaction of 2,3-bis-lithiated methylbutadiene with PhCN,^{3a} by 1,4-addition of nitriles to (butadiene)zirconocene^{3b,c} and by base-induced oligomerization of glycolonitrile.^{3d} Very recently, a domino reaction initiated by addition of a Grignard reagent to a tris-nitrile has been reported.^{4a} Herein we report the addition of up to 4 equiv. of a nitrile to dilithiated allenes, a process which we believe includes a novel type of rearrangement reaction.⁵

1,1-Diphenyl-3,3-dilithioallene **2** was generated in one pot by treatment of the TBDMS enol ether **1** with an excess of LDA in THF, a reaction recently developed by us.⁶ This process presumably proceeds via a mechanism involving initial lithiation of the allyl system of the silyl enol ether, elimination of lithium silanolate and lithiation of the 1,1-diphenylallene formed (Scheme 1). The elimination could either occur directly (path A) or proceed via a O→C silyl migration/Peterson elimination sequence (path B).

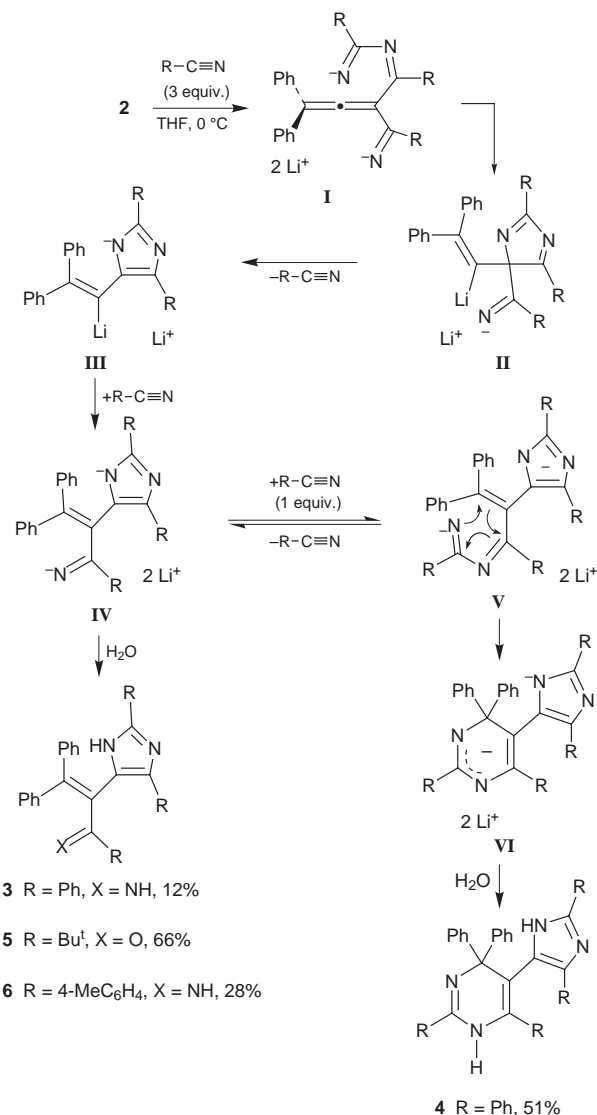
Reaction of lithiated allenes with nitriles was expected to result in formation of allenylimines. Selected examples of these compounds have recently been prepared in moderate yields by reaction of allenic aldehydes with amines.⁷ Reaction of **2** with 2.2 equiv. of PhCN resulted in a complex reaction mixture from which two products, **3** (9%) and **4** (14%) (Scheme 2), were isolated by column chromatography in low yields. Much to our surprise, FAB-MS suggested that products derived from



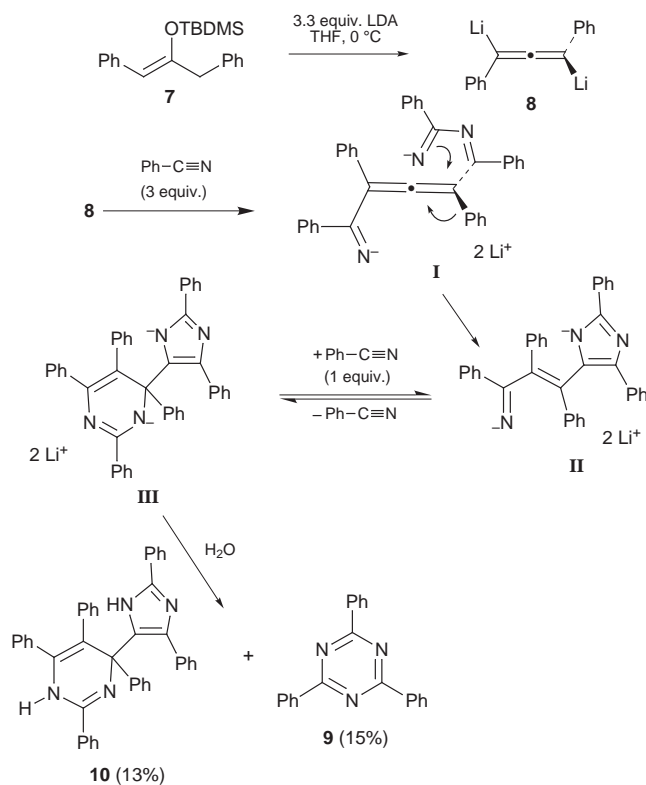
Scheme 1

reaction of the allene with three and four nitriles, respectively, had been formed. The yield of **4** was significantly improved by use of 4.5 equiv. of the nitrile. Yellow-coloured imidazole **3** and colourless 5-imidazol-5-yl-1,4-dihydropyrimidine **4** were isolated in 12 and 51% yield, respectively.[§] Similar results were obtained when 10 equiv. of PhCN were employed. Reaction of dilithioallene **2** with pivalonitrile afforded as the sole isolated product the colourless imidazole **5** (66%). The imine group was hydrolyzed during aqueous work-up to generate an α,β -unsaturated keto group. Reaction of **2** with *p*-tolunitrile gave the orange coloured imidazole **6** (28%).

Formation of the sterically crowded imidazoles **3–6** can be rationalized by the mechanism shown in Scheme 2. The



Scheme 2



terminal carbon atom of the allene dianion **2** initially reacts with two molecules of the nitrile. Presumably, the negative charge will mainly be localized at the nitrogen atoms. A third nitrile molecule is attacked (intermediate **I**) and the amidine anion thus formed attacks the terminal allene carbon atom to give intermediate **II** which contains a five-membered ring and a vinyl carbanion function. An aromatic imidazole anion (intermediate **III**) is generated next by elimination of 1 equiv. of the nitrile. The vinyl carbanion subsequently reacts with the nitrile to give intermediate **IV**. The fourth nitrile molecule is attacked by the imine anion of intermediate **IV** to generate an amidine anion (intermediate **V**). The amidine anion attacks the terminal allene carbon atom bearing the phenyl groups to give a dihydropyrimidine anion (intermediate **VI**). Aqueous work-up furnishes heterocycles **4** and **3** derived from intermediates **VI** and **IV**, respectively.

Reaction of PhCN with the dianion of 1,3-diphenyl-1,3-dithioallene **8** (formed *in situ* by reaction of silyl enol ether **7** with 3.3 equiv. of LDA) afforded after hydrolytic work-up a mixture of 2,4,6-triphenyltriazine **9**⁸ (formed by trimerization of the nitrile) and imidazole **10** (a 1:4 product). The formation of **10** can be explained by a reaction sequence similar to that leading to oligonitrile **4** (Scheme 3). This reaction seems to involve migration of a phenyl rather than a phenylimino group.

It is noteworthy that all carbon atoms of the allene system are involved sequentially in the reaction leading to cyclic oligonitrile **4**. The intramolecular attack of the amidine anion on the terminal (rather than on the central) allene carbon atom and the subsequent rearrangement reaction (**I**→**IV**, Scheme 2) are surprising. However, this process can be explained by the stability of the aromatic imidazole anion formed. Steric hindrance seems to be the reason that no addition of a fourth nitrile molecule takes place for **5** and **6**. Interestingly, treatment of the dianion of 2-methylbenzimidazole or of amide derived dianions with 4.5 equiv. of PhCN resulted in addition of only 1 equiv. of the nitrile to the dianion rather than in formation of an

open-chained oligonitrile.⁹ This striking difference to the reaction of the allene dianion **2** suggests that the addition of the imine anion to the nitrile is a reversible process which becomes irreversible when the amidine anion generated can undergo a consecutive reaction to form a more stable intermediate (such as **IV** and **VI** in Scheme 2).[¶] It is noteworthy that the number of nitrile molecules added to the dianion does not depend on the number of equivalents of the nitrile employed in the reaction. Therefore, there is some relationship between the reaction reported and self-assembly processes.

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Notes and References

† Regioselective reactions of ambident dianions, Part 5. For Part 4, see ref. 5(d).

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§ Preparation of imidazole **4**. To a THF solution (40 ml) of silyl enol ether **1** (1.80 g, 5.6 mmol) was added a THF solution of LDA which was prepared by addition of BuⁿLi (1.6 M in hexane) to a THF solution (20 ml) of Prⁱ₂NH (3.3 equiv.) at 0 °C. The solution was stirred at 20 °C for 6 h during which time the color of the solution became deep red. A THF solution (10 ml) of PhCN (2.58 ml, 4.5 equiv.) was added at 0 °C by syringe. After stirring for 10 h at 20 °C, water (20 ml) was added to the deep purple solution and the colour changed to yellow. The reaction mixture was extracted (Et₂O–THF = 1:1) and the combined organic layers were dried (MgSO₄), filtered and the solvent was removed *in vacuo* to give imidazole **4** (1.73 g, 51%) after purification by column chromatography (silica gel, Et₂O–light petroleum = 1:1) as a colorless solid, mp 146–150 °C; δ_H([²H₈]THF, 200 MHz) 6.75–8.20 (m, 30 H, Ar), 8.75 (br, 1 H, NH), 10.68 (br, 1 H, NH); δ_C([²H₈]THF, 50 MHz) 107.20 (C, CPh₂), 125.27, 125.76, 125.87, 126.06, 126.26, 127.12, 127.30, 127.50, 128.02, 128.08, 128.17, 128.30, 128.68, 128.90, 129.21, 129.76, 129.92, 130.86 (CH, Ph), 132.15, 132.19, 136.43, 136.73, 137.37, 138.19 (C, Ph, =CCPh₂), 145.67, 148.50, 148.78 (C, C=CN), 150.65, 150.78 (C, CN₂); ν_{max}(KBr)/cm⁻¹ 3495 (br), 3395 (br), 3060 (m), 3029 (m), 2923 (w), 1640 (s), 1598 (m), 1578 (m), 1524 (s), 1496 (m), 1446 (m), 1395 (s), 1370 (m), 1178 (m), 1072 (m), 1028 (m), 697 (s); *m/z* (FAB) 605 (100%, M⁺+1); Calc. for C₄₃H₃₂N₄: C, 85.41; H, 5.33; N, 9.26. Found.: C, 85.17; H, 5.61; N, 9.62%.

¶ The reactions cited in refs. 3(a)–(d) involve only a single addition of each nucleophilic center to a nitrile molecule since the imine anions formed are intramolecularly trapped to form stable dianionic systems. In contrast, in ref. 4, a second nitrile group is attacked by the initially formed imine anion. Thus, in the third step of the reaction, a stable anion could be formed.

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