

Cyclic and Acyclic Products from the Addition of 1-Aza-Allyl Anions to Dienes and α,β -Unsaturated Ketones - Regioselectivity

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Abstract: Addition of 1-aza-allyl-lithium compound **1** to isoprene at low temperature yields two regioisomeric γ,δ -unsaturated imines **3**, whereas at THF reflux temperature the cyclic regioisomeric cyclohexene derivatives **4** are formed. With 2,3-dimethylbutadiene, the acyclic products **6** are obtained. C-C-bond formation also takes place with methylvinylketone, leading to the acyclic regioisomers **7,8** from 1,2- and 1,4 attack.

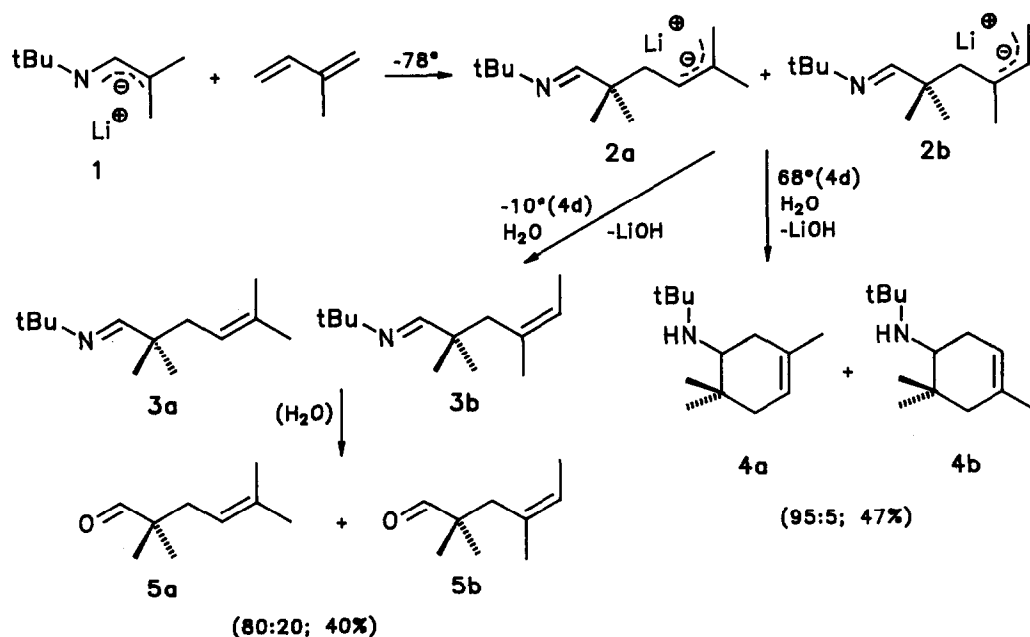
In comparison with the widespread use of enolates in organic synthesis, the application of their nitrogen analogues, the 1-aza-allyl anions, has found relatively little attention in spite of several synthetic advantages¹⁻⁴. The electronic nature of the nitrogen atom and the adjustable substituent on it are the reasons for their enhanced selectivity, which allows to conduct reactions under milder and better controlled conditions, compared to enolates. Today, the structural properties of 1-aza-allyl anions are well known, both experimentally⁵⁻⁷ and theoretically from quantum chemical calculations^{8,9}.

In this paper, we report on the reactions of the 1-aza-allyl-lithium compound **1** with simple dienes and an α,β -unsaturated carbonyl compound. In 1975, Takabe et al.¹⁰ briefly described a cycloalkenylation of lithiated *N*-isobutyldiene-*t*-butylamine with three different dienes (butadiene, isoprene and myrcene). They found cyclic and acyclic products in varying amounts as detected by glc.

Our interest in this field concentrates on the regio- and stereoselectivity of polyfunctional aza-substituted anions and their possible control in organic synthesis^{11,12}.

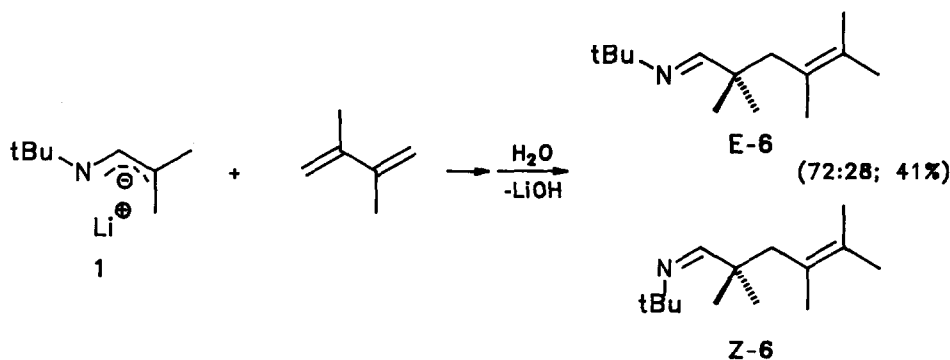
Starting from the corresponding aldimine, we prepared the 1-aza-allyl-lithium compound **1** in situ by deprotonation in THF at -78°C using lithium-diisopropylamide (LDA) as base. Isoprene was added to the

deeply colored solution of **1** at low temperature. Depending on reaction time and temperature open chain (**3**) and cyclic (**4**) products were isolated after NaHCO_3 hydrolysis and chromatographic workup¹³. Thus, at THF reflux temperature (4 days) a 95:5 mixture of **4a** and **4b** was obtained in 47% yield. At -10°C however (4 days), a 80:20 mixture of **3a** and **3b** was isolated in 40% yield; further hydrolysis during flash chromatography on wet silica gel leads to the γ,δ -unsaturated aldehydes **5a** and **5b**. Mechanistically, the formation of the cyclic products **4** takes place via a two step mechanism, involving the allyl anions **2** as key intermediates; they can be trapped at low temperature during the workup giving the imines **3**; under more severe conditions at higher temperature the anions **2** cyclize yielding the amino-cyclohexene derivatives **4**. The isolation of the acyclic products **3** is our main argument against an one-step cycloaddition mechanism of the Diels-Alder type.

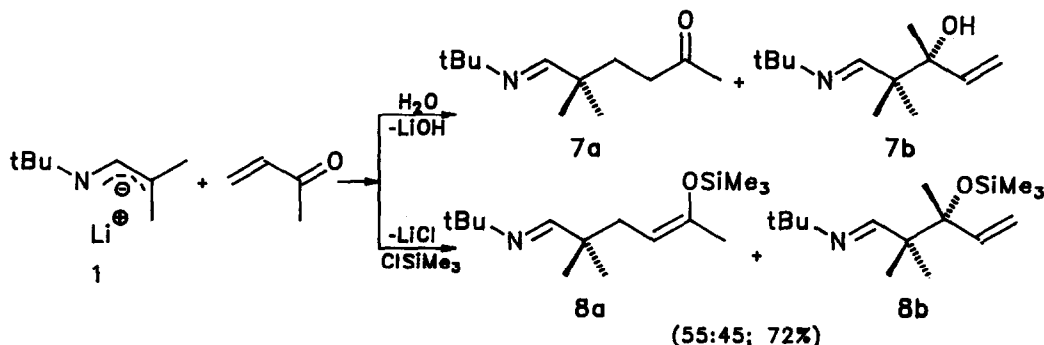


The addition of isoprene to **1** is not completely regioselective; however, the formation of the adduct **2a** with the more favorable allyl anion intermediate dominates strongly.

Reaction of **1** with 2,3-dimethylbutadiene (3 days, 50°C) yields open chain products **6** exclusively; no cyclic isomers were detected. Differing from the isoprene adducts, the imines **6** are formed as an E/Z-mixture (72:28; 41% yield); the E-isomer seems to predominate.



Other dienes (1,3-cyclohexadiene, 1,3-cyclooctadiene, cyclopentadiene, 1,4-diphenylbutadiene and anthracene) did not react even under more vigorous conditions (see however ¹⁴).



Additionally, the reaction of the oxygen analogue of isoprene, methylvinylketone, with **1** was investigated (compare ¹⁵). After addition at -78°C , warming up to room temperature, stirring for 4 days and hydrolytic workup, a reaction mixture (72%) was obtained consisting of the two regioisomers **7a,b** (55:45), resulting from 1,2- and 1,4-attack at the Michael acceptor. **7a** could be isolated by distillation, but complete separation of both isomers was not possible due to their low stability. Hydrolysis (acetate buffer, pH = 4.5) gives access to the corresponding aldehydes (compare ¹⁶). The intermediate adducts can also be trapped by trimethylsilyl chloride, which yields the siloxy compounds **8** (55:45; 72% yield). Pure **8b** was obtained after Kugelrohr distillation.

Aldehyde derived 1-aza-allyl-lithium compounds like **1** are obviously interesting synthetic building blocks; their special reactivity allows not only addition to carbonyl compounds ("directed aldol reaction" ²),

but also to simple dienes, a reaction type, which is not known from enolate analogues. Key step in these reactions is the intermediate formation of a stabilized allylic anion species, which under the reaction conditions does not react with dienes and methylvinylketone. Therefore, anionic polymerization as a side reaction is not observed. Sometimes however, the low stability of some of the aldehydes requires special care during workup and purification.

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- All compounds were completely characterized by spectroscopic methods and gave satisfactory C,H,N analyses. For example:
4a: colorless liquid b.p. 65 °C/1.5 Torr. ¹H-NMR (300 MHz, CDCl₃): δ= 0.80 (s, 3H, CH₃), 0.90 (s, 3H, CH₃), 1.05 (s, 9H, C(CH₃)₃), 1.59 (s, 3H, C=C-CH₃), 1.65-1.75 (m, 1H, J=7.40 Hz, J=18.02 Hz, HC=C-C-H), 1.75-1.85 (m, 2H, C=CH-CH₂), 2.12-2.22 (m, 1H, J=4.6 Hz, J=17.58 Hz, HC=C-C-H), 2.40 (dd, 1H, J=7.70 Hz, J=5.20 Hz, N-C-H), 5.22-5.27 (m, 1H, C=C-H).
¹³C-NMR (90.56 MHz, CDCl₃): δ= 21.97 (CH₃), 23.38 (CH₃), 28.17 (C=C-CH₃), 30.53 (C(CH₃)₃), 32.86 (CH₃-C-CH₂), 39.19 (CH₂), 39.43 (CH₂), 50.48 (C(CH₃)₃), 54.39 (N-C-H), 120.1 (C=C-H), 131.9 (C=C-H). IR ν_{N-H} 3400-3200 cm⁻¹.
5a: colorless liquid b.p. 55 °C/6 Torr. ¹H-NMR (300 MHz, CDCl₃): δ= 1.02 (s, 6H, C(CH₃)₂), 1.58 (s, 3H, C=C-CH₃), 1.67 (s, 3H, C=C-CH₃), 2.12 (d, 2H, J=7.70 Hz, CH₂), 5.05 (t, 1H, J= 7.80 Hz, C=C-H), 9.45 (s, 1H, O=C-H). ¹³C-NMR (75.47 MHz, CDCl₃): δ= 21.07 (C(CH₃)₂), 25.87 (C=C-CH₃), 35.52 (CH₂), 46.55 (OHC-C-(CH₃)₂), 118.7 (CH=C-CH₃), 134.6 (CH=C-CH₃), 206.3 (CHO). IR ν_{C=O} 1720 cm⁻¹.
8b: lightgreen oil b.p. 60 °C/0.01 Torr (Kugelrohr distillation). ¹H-NMR (300 MHz, CDCl₃): δ= 0.07 (s, 9H, Si(CH₃)₃), 0.90 (s, 6H, C(CH₃)₂), 1.12 (s, 9H, C(CH₃)₃), 1.23 (s, 3H, C-CH₃), 5.00-5.10 (m, 2H, J=17.5 Hz, J=11.0 Hz, CH=CH₂), 5.90 (dd, 1H, J=17.8 Hz, J=10.4 Hz, CH=CH₂), 7.64 (s, 1H, N=C-H). ¹³C-NMR (75.47 MHz, CDCl₃): δ= 2.34 (Si(CH₃)₃), 20.43 (C(CH₃)₂), 22.12 (CH₃), 29.73 (C(CH₃)₃), 45.88 (C(CH₃)₂), 56.42 (C(CH₃)₃), 79.78 (CH₃-C-OSi), 113.6 (CH=CH₂), 142.8 (CH=CH₂), 164.2 (N=C-H). IR ν_{C=N} 1660 cm⁻¹.
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