



Regioselective Reaction of Allylbenzotriazoles with Aldehydes and Ketones in the Presence of Lithium

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Abstract: The reactions of α - and γ -substituted allylbenzotriazoles **2**, **3** and **4** with an excess of lithium in THF at -78°C generate various allyllithiums, which react readily with aldehydes and ketones with high regioselectivity to give predominantly the branched products **5** in excellent yields.

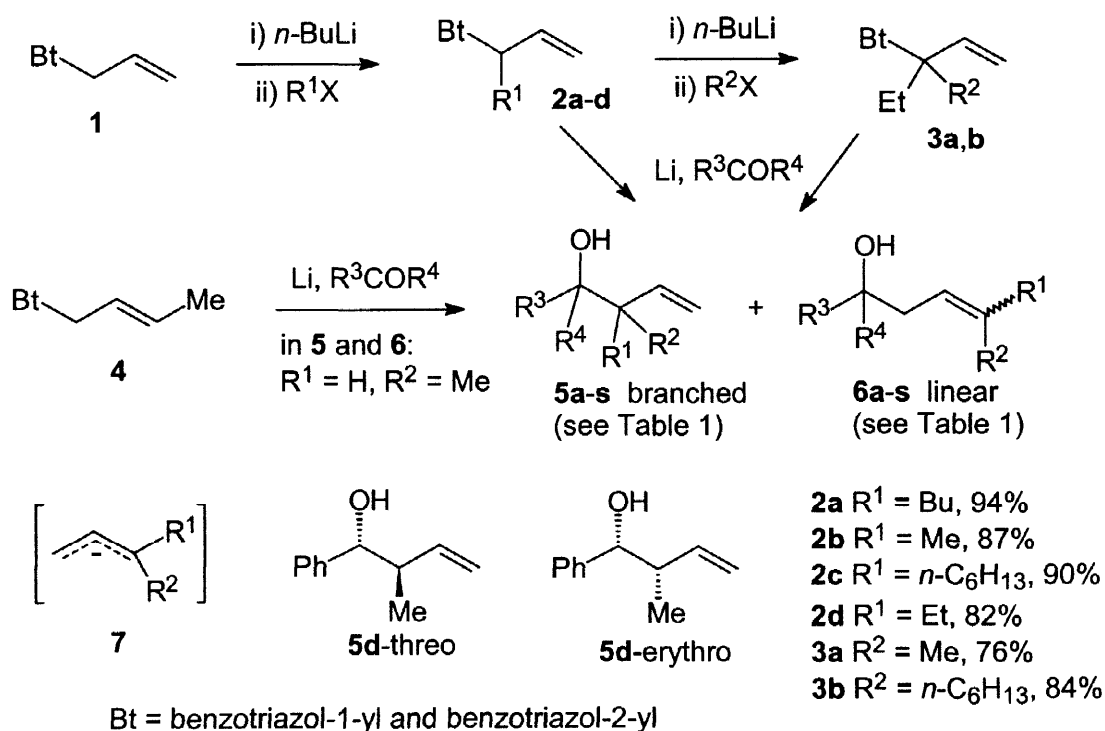
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Allylmetals are important reagents in organic synthesis, particularly their reaction with carbonyl compounds, which can be viewed as a complementary technique to the Aldol reaction.¹ Allyllithium is one of the most useful allylmetals; however, only low to moderate regioselectivity has been reported for the reaction of substituted allyllithiums with carbonyl compounds.² Therefore other metals, such as chromium³ and titanium,⁴ are used to achieve regio- and stereo-selectivity. Unfortunately, such reactions are of quite limited scope as the organometal reagents are usually prepared from the corresponding substituted allyl halides, many of which are not readily available. Cohen and co-workers developed a general and versatile method for generating allyllithiums from the reductive lithiation of phenyl thioethers;⁵ the allyllithiums formed initially⁶ were transmetalated with titanium or cerium to achieve high regioselectivity.^{6,7}

Recently, we demonstrated that allylbenzotriazoles can be transformed into the corresponding allyllithiums by reductive cleavage of a C-N bond.⁸ As lithiated *N*-allylbenzotriazoles undergo alkylation exclusively at the position α to the benzotriazole group,⁹ various alkyl groups can be introduced at the α -position. Our preliminary results indicated that the reductive cleavage of benzotriazole gave substituted allyllithium reagents and that the reaction of these allyllithiums with electrophiles proceeded with high regioselectivity.⁸ Herein we confirm that such high regioselectivity is valid for the reaction of a number of carbonyl compounds with various α -substituted allyllithiums.

The reaction of allylbenzotriazole **1** with *n*-BuLi followed by the appropriate alkyl halide gave the α -substituted allylbenzotriazoles **2a-d** in excellent yields (Scheme 1). No further purification was needed: although **2a-d** exist as mixtures of Bt¹ and Bt² isomers, which can be separated by column chromatography on silica, the Bt¹ and Bt² isomers were shown to possess similar reactivity and therefore mixtures were always

used in the subsequent reactions. Further lithiation and treatment with alkyl halides converted **2d** into α,α -disubstituted allylbenzotriazoles **3a,b** in 76% and 84% yields, respectively.



Scheme 1

The reaction of allylbenzotriazole **2a** with an excess of lithium in the presence of 3-pentanone in THF (under Barbier-type reaction conditions) at -78°C gave, after hydrolysis with water at -78°C , branched product **5a** (α -attack) exclusively in excellent yield.¹⁰ No linear product **6a** of γ -attack was detected by GC and ^1H NMR analysis of the crude product (Table 1, Entry 1). Similarly, other reactions of allylbenzotriazoles **2a-d** with carbonyl compounds gave predominantly the branched homoallylic alcohols **5b-k** together with a small amount of the linear products **6b-k**, determined by GC and ^1H NMR analysis. The linear and branched products could not be separated by column chromatography. These results are summarized in Scheme 1 and Table 1. The α -attack products **5c-k** were formed as mixtures of two diastereomers which were identified as threo- and erythro-isomers, based on the difference in the coupling constant of the methine proton adjacent to the hydroxy group. For example, the isomer of **5d** (Scheme 1) with higher coupling constant (7.5 Hz) corresponds to the threo isomer as reported by Kimura and co-workers,¹¹ while the isomer with a smaller coupling constant (6.6 Hz), corresponds to the erythro isomer. The ratios for the regio- and stereo-selectivities shown in Table 1 were determined by GC.

It is noteworthy that α,α -disubstituted allylbenzotriazoles **3a,b** can also react with 3-pentanone under the same conditions to afford predominantly the branched homoallylic alcohols **5l,m** (Table 1). The linear product **6m** was also isolated in 10% yield, but no **6l** was detected by GC in the crude product.

Table 1. Reaction of Substituted Allylbenzotriazoles **2**, **3** and **4** with Carbonyl Compounds.

| Product 5/6 | Starting material | R ¹ | R ² | R ³ | R ⁴ | Total GC yield % ^a | Ratio of 5/6 | 5: Threo/ erythro |
|----------------|----------------------|--|--|---|--|----------------------------------|--------------|----------------------|
| a | 2a | Bu | H | Et | Et | 99 (75) | >99/1 | - |
| b | 2a | Bu | H | -(CH ₂) ₅ - | | 98 (78) | 89/9 | - |
| c | 2b | Me | H | Et | <i>n</i> -C ₉ H ₁₉ | 79 (80) | 94/6 | <i>b</i> |
| d | 2b | Me | H | Ph | H | 94 (87) | 85/15 | 60/40 |
| e | 2b | Me | H | <i>n</i> -C ₈ H ₁₇ | H | 99 (95) | 94/6 | 54/46 |
| f | 2c | <i>n</i> -C ₆ H ₁₃ | H | Et | <i>n</i> -C ₉ H ₁₉ | 100 (89) | 97/3 | <i>b</i> |
| g | 2c | <i>n</i> -C ₆ H ₁₃ | H | Ph | H | 98 (88) | 97/3 | 66/34 |
| h | 2c | <i>n</i> -C ₆ H ₁₃ | H | Ph(CH ₂) ₂ | H | 95 (76) | 88/12 | 52/48 |
| i | 2c | <i>n</i> -C ₆ H ₁₃ | H | <i>t</i> -Bu | H | 99 (74) | 84/16 | <i>b</i> |
| j | 2c | <i>n</i> -C ₆ H ₁₃ | H | (CH ₂) ₅ CH | H | 94 (77) | 82/18 | <i>b</i> |
| k | 2d | Et | H | C ₄ H ₉ CHC ₂ H ₅ | H | 82 (73) | 85/15 | 83/17 |
| l | 3a | Et | Me | Et | Et | (87) | >99/1 | - |
| m | 3b | Et | <i>n</i> -C ₆ H ₁₃ | Et | Et | (99) | 89/10 | - |
| n | 4 | H | Me | Et | <i>n</i> -C ₉ H ₁₉ | 86 (70) | 94/4 | <i>b</i> |
| o | 4 | H | Me | <i>n</i> -C ₈ H ₁₇ | H | 98 (84) | 96/4 | 52/48 |
| p | 4 | H | Me | Ph | H | 98 (86) | >99/1 | 65/35 |
| q | 4 | H | Me | Ph | Me | 93 (81) | 94/6 | 56/44 |
| r | 4 | H | Me | Ph(CH ₂) ₂ | H | 99 (78) | 89/11 | 54/46 |
| s | 4 | H | Me | <i>n</i> -C ₅ H ₁₁ | H | 99 (90) | >99/1 | 70/30 |

^a Isolated yields in parenthesis. ^b The two diastereomers were not separable by GC.

We prepared *N*-(γ -methylallyl)benzotriazole (**4**) (an isomer of **2b**) from crotyl bromide and compared its regioselectivity with **2b**. As shown in Table 1, the reactions of **4** with benzaldehyde, nonaldehyde and dodecanone gave the same products with a similar regioselectivity as for **2b**. These results suggest that both starting materials **2b** and **4** go through a common intermediate **7** (Scheme 1) and the addition to electrophiles occurs at the more substituted carbon, giving mainly the terminal alkene. Comparing all of the results in Table 1, better regioselectivity was generally observed with the ketones than with the aldehydes. The regioselectivity

was slightly lower with increased branching of the aldehydes, probably due to the steric effects. The stereoselectivity remains low, as previously reported for allyllithiums.^{2a,5}

In conclusion, we report the first example of the generation of allyllithiums from allylbenzotriazoles in the presence of lithium, and their reactions with ketones and aldehydes with high regioselectivity. This methodology has advantages over other reported methods using lithium: (i) high regioselectivity can be achieved without transmetallation or use of a catalyst, (ii) easy accessibility to various α -substituted allyllithiums that otherwise are not readily obtained, and (iii) the main byproduct, benzotriazole, can be washed away by a basic aqueous solution, which avoids the use of acid generally used in the work-up of other methods.

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10. General procedure: Lithium (25 mmol, 30% dispersion in mineral oil) was washed twice with THF under argon. THF (5 mL) was added and the suspension was cooled to -78 °C. A solution of the appropriate allylbenzotriazole (5 mmol) and electrophile (5 mmol) in THF (25 mL) were added to the lithium suspension over 1 h and kept another 1-4 h before being quenched with water (15 mL) at the same temperature. After ether extraction, the crude product was purified by flash column chromatography on silica gel. All of the homoallylic alcohols prepared gave satisfactory ¹H and ¹³C NMR spectra, and novel products gave satisfactory microanalyses or HRMS.
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