Ring Opening Reaction of Epoxides under Aryl Acetylene/ZnBr$_2$/DIEA Conditions

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Recently, we have reported the usefulness of ZnBr$_2$/DIEA (N,N-diisopropylethylamine) combination for the in situ generation of zinc acetylide species from terminal acetylenic compounds. We applied the system to the reactions with N-tosylimines, activated quinolinium salts, and carboxylic acid chlorides.

The alkynylation of epoxide via ring opening with metal acetylide is an important carbon-carbon bond forming reaction. However, this useful reaction suffers from some intrinsic limitations including low yields and regioselectivity. Recently, several new methods have been suggested in order to solve these problems. Lithium acetylide in the presence of BF$_3$ etherate or Et$_2$AlCl$_2$ titanium acetylide, trimethylgallium-catalyzed lithium acetylide in the presence of LiClO$_4$ all afford better yields than the classical methods. The ring opening reaction of epoxide with these reagent combinations proceeded at the least hindered position without a special substituent which control the approach of the metal acetylide by chelation with the special substituent.

Recently, regioselective ring opening of epoxide with lithium alkynyl trimethylaluminiun are complex in the presence of BF$_3$ etherate was reported. In these respects, we decided to examine the feasibility of the alkynylation of epoxide with ZnBr$_2$/DIEA system.

Initially, we tried the reaction of styrene oxide (1a) and phenylacetylene (2a) in the presence of ZnBr$_2$ (2.0 equiv) and DIEA (1.2 equiv) in acetonitrile at room temperature and obtained 3a in 64% yield. This compound was generated by the attack of zinc acetylide at the benzylic position of 1a. With reduced amounts of ZnBr$_2$ or DIEA the yield of 3a was reduced dramatically. Encouraged by the results, we examined other entries and the results are summarized in Table 1. The reaction of 1a and 4-ethynyltoluene (2b) or 1-ethyl-4-methoxybenzene (2c) gave the same type of compounds, 3b and 3c, in 59 and 58% yields, respectively. In the reactions of 1a and 2a-c (entries 1-3) we could not find the other plausible regioisomers at all.

However, the reaction with propylene oxide (1b) showed somewhat different results. The only isolable compound was 3d in the reaction of 1b and 2a (entry 4). This compound must be generated by the attack of the zinc acetylide to propionaldehyde, which was produced by the Meinwald rearrangement of propylene oxide. Similarly, the reaction of cyclohexene oxide (1c) and 2a produced 3f via the intermediary cyclopentanecarboxaldehyde, which was also produced by the Meinwald rearrangement of 1c.

As well documented in the literature, the regioselectivity of the ring opening reaction of epoxides with C-nucleophiles is very sensitive to electronic as well as steric effects. Although limited to some representative epoxides, we could draw an important conclusion from the aryl acetylene/
ZnBr₂/DIEA system toward epoxides. This system showed somewhat Lewis acidic nature when we consider the S,S-like pathway for the formation of 3a-c regioselectively and the involvement of the Meinwald rearrangement for the formation of 3d-g. It is very interesting to note that the in situ generated zinc acetylide sustain its reactivity even in such acidic conditions.

As shown in Scheme 1, the activation of 1a with ZnBr₂ or zinc acetylide (vide infra, Figure 1) weakened the carbon-oxygen bond and produced the corresponding carbocatonic species. When the carbocation intermediate was stable enough, zinc acetylide reacted with the carbocation immediately to give the product (for 3a-c). Whereas when the carbocation intermediate was relatively unstable, Meinwald rearrangement occurred instantaneously to give the corresponding aldehyde, which reacted with the acetylide to give the product (for 3d-g). The transfer of acetylide to the carbocation intermediate could occur via either ways (Figure 1): (i) activation with zinc acetylide and intramolecular transfer, (ii) activation with zinc bromide and intermolecular transfer of acetylide from zinc acetylide. However, we do not have any definitive evidence for this. This type of characteristics of the reagents system can be applied for the allylation of epoxide during the multi-step synthesis efficiently although limited to aryl acetylenes and the chemical yields of products were moderate.

Experimental Section

Typical experimental procedure for the synthesis of 3a.

To a stirred solution of 1a (120 mg, 1.0 mmol) in acetonitrile (3 mL) was added 2a (123 mg, 1.2 mmol), ZnBr₂ (450 mg, 2.0 mmol), and DIEA (155 mg, 1.2 mmol) successively at room temperature. The reaction mixture was stirred for 3 h at room temperature. After the usual aqueous workup and column chromatographic purification process (hexanes/ether, 10:1) we obtained 3a as clear oil, 143 mg (64%). The structures were confirmed by comparison with the reported data for 3a. Spectroscopic data of the other compounds 3b, 3c, 3f, and 3g are as follows.

Compound 3b: clear oil; IR (film) 3390, 2924, 2337, 1693 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz) δ 1.96 (br s, 1H), 2.34 (s, 3H), 3.84 (br t, 2H), 4.07 (t, J= 6.9 Hz, 1H), 7.11 (d, J= 7.8 Hz, 2H), 7.24–7.47 (m, 7H); ¹³C NMR (CDCl₃, 75 MHz) δ 21.42, 42.05, 67.73, 84.92, 87.36, 119.93, 127.41, 127.98, 128.69, 129.02, 131.63, 138.12, 138.25; ESIMS m/z 237.12 (M⁺+H).

Compound 3c: clear oil; IR (film) 3310, 2222, 1604, 1508, 1250 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz) δ 2.02 (br s, 1H), 3.79 (s, 3H), 3.81 (d, J= 6.9 Hz, 2H), 4.05 (t, J= 6.9 Hz, 1H), 6.83 (d, J= 8.7 Hz, 2H), 7.23–7.46 (m, 7H); ¹³C NMR (CDCl₃, 75 MHz) δ 21.42, 24.05, 67.73, 84.92, 87.36, 113.87, 115.13, 127.36, 127.96, 128.66, 131.38, 138.20, 159.46; ESIMS m/z 253.11 (M⁺+H).

Compound 3f: clear oil; IR (film) 3371, 2951, 2866, 2229 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz) δ 1.45-1.74 (m, 6H), 1.79-1.90 (m, 2H), 1.94 (d, J= 4.8 Hz, 1H), 2.22–2.35 (m, 1H), 4.47 (dd, J= 6.6 and 4.8 Hz, 1H), 7.28–7.44 (m, 7H); ¹³C NMR (CDCl₃, 75 MHz) δ 25.73, 25.77, 28.39, 28.91, 46.34, 66.81, 84.87, 89.67, 122.75, 128.25, 128.29, 131.67; ESIMS m/z 201.12 (M⁺+H).

Compound 3g: clear oil; IR (film) 3379, 2951, 2866, 2233 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz) δ 1.45-1.92 (m, 8H), 2.21–2.32 (m, 1H), 2.34 (s, 3H), 4.45 (dd, J= 6.6 and 5.1 Hz, 1H), 7.10 (d, J= 8.1 Hz, 2H), 7.31 (d, J= 8.1 Hz, 2H); ¹³C NMR (CDCl₃, 75 MHz) δ 21.44, 25.74, 25.77, 28.38, 28.91, 46.39, 66.85, 84.99, 88.95, 119.66, 129.00, 131.56, 138.40; ESIMS m/z 215.15 (M⁺+H).

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References and Notes


