

Ring Opening Reaction of Epoxides under Aryl Acetylene/ZnBr₂/DIEA Conditions

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Recently, we have reported the usefulness of ZnBr₂/DIEA (*N,N*-diisopropylethylamine) combination for the *in situ* generation of zinc acetylide species from terminal acetylenic compounds.¹ We applied the system to the reactions with *N*-tosylimines,^{1a} activated quinolinium salts,^{1b} and carboxylic acid chlorides.^{1c}

The alkylation of epoxide *via* ring opening with metal acetylide is an important carbon-carbon bond forming reaction.²⁻⁴ However, this useful reaction suffers from some intrinsic limitations including low yields and regioselectivity.² Recently, several new methods have been suggested in order to solve these problems. Lithium acetylide in the presence of BF₃ etherate^{3a} or Et₂AlCl,^{3b,3c} titanium acetylides,^{3d,3e} trimethylgallium-catalyzed lithium acetylide in the presence of LiClO₄^{3f} all afford better yields than the classical methods. The ring opening reaction of epoxide with these reagent combinations proceeded at the least hindered position²⁻⁴ without a special substituent which control the approach of the metal acetylide by chelation with the special substituent.⁵ Recently, regioselective ring opening of epoxide with lithium alkynyl trimethylaluminium ate complex in the presence of BF₃ etherate was reported.^{4c} In these respects, we decided to examine the feasibility of the alkylation of epoxide with ZnBr₂/DIEA system.¹

Initially, we tried the reaction of styrene oxide (**1a**) and phenylacetylene (**2a**) in the presence of ZnBr₂ (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 ZnBr₂ 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-ethynyl-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.

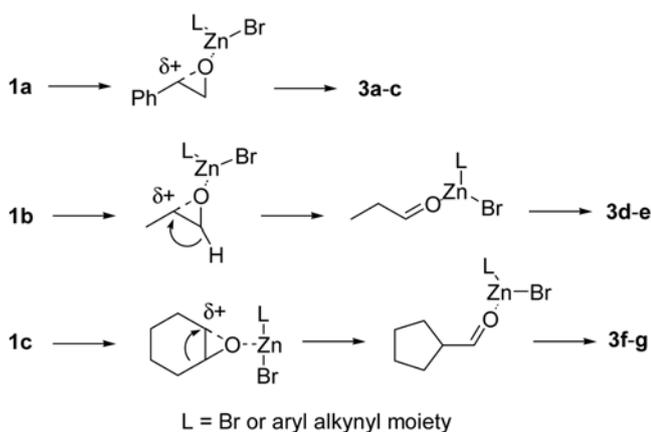
However, the reaction with propylene oxide (**1b**) showed somewhat different results. The only isolable compound was **3d** in the reaction of **1b** and **2a** (entry 4). This compound must be generated by the attack of the zinc acetylide to propionaldehyde, which was produced by the Meinwald rearrangement⁶ of propylene oxide. Similarly, the reaction of cyclohexene oxide (**1c**) and **2a** produced **3f** *via* the

Table 1. The reaction of epoxides **1a-c** and aryl acetylenes **2a-c**

Entry	Epoxide	Acetylene	Conditions	Product (% yield)
	$\mathbf{1a-c} + \text{Ar-C}\equiv\text{C-H} \xrightarrow[\text{CH}_3\text{CN, rt, 3-8 h}]{\text{ZnBr}_2 (2 \text{ equiv}), \text{DIEA} (1.2 \text{ equiv})} \mathbf{3a-g}$			
1			rt, 3 h	3a (64) ^{3h}
2	1a		rt, 6 h	3b (59) ⁷
3	1a		rt, 5 h	3c (58) ⁷
4		2a	rt, 8 h	3d (49) ^{8a}
5	1b	2b	rt, 8 h	3e (44) ^{8b}
6		2a	rt, 7 h	3f (40) ⁷
7	1c	2b	rt, 7 h	3g (42) ⁷

intermediacy 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.^{2,5b} Although limited to some representative epoxides, we could draw an important conclusion from the aryl acetylene/



Scheme 1

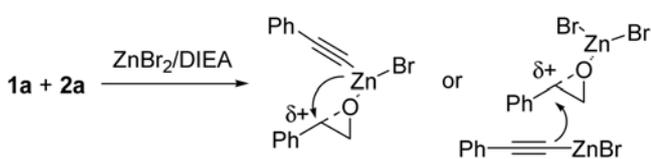


Figure 1

ZnBr₂/DIEA system toward epoxides. This system showed somewhat Lewis acidic nature when we consider the S_N1-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-c** with ZnBr₂ or zinc acetylide (vide infra, Figure 1) weakened the carbon-oxygen bond and produced the corresponding carbocationic 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 alkylation 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**,^{3h} **3d**,^{7a} **3e**.^{7b} 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) 3410, 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 42.01, 55.23, 67.71, 84.61, 86.61, 113.87, 115.13, 127.36, 127.96, 128.66, 133.12, 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, 5H); 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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