IMIDAZO[2,1-b]BENZOTHIAZOLE. NUCLEOPHILIC SUBSTITUTION REACTION ON SULFUR BY n-BUTYL LITHIUM

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Abstract — The nucleophilic substitution reaction on sulfur of 2-(p-methoxyphenyl)-7-methylimidazo[2,1-b]benzothiazole by n-butyl lithium affords the C-S bond cleaved compound in excellent yield.

Nucleophilic substitution reactions on sulfur by organolithium compounds have been reported.1-3 The nucleophilic cleavage of S-S bond by organolithium compounds is well known.1 However, there are few reports on the similar nucleophilic cleavage of C-S bond.3

We now present an example of the nucleophilic substitution reaction on sulfur of 2-(p-methoxyphenyl)-7-methylimidazo[2,1-b]benzothiazole 1 by n-butyl lithium(n-BuLi).

1 was treated with n-BuLi in tetrahydrofuran at -70°C, and then quenched with carbon dioxide below -60°C. An oil 3a was obtained as the sole product, which was purified by silica gel chromatography (toluene : ethyl acetate = 7 : 3) as a yellow oil (96% yield); MS: m/z 396 (M+); Anal. Calcd. for C22H24N2O3S; 396.1507; C,66.64; H,6.10; N,7.07; S,8.09. Found: 396.1497; C,66.80; H,6.09; N,7.10; S,8.14; IR: ν max 3400cm⁻¹(OH), 1700cm⁻¹(=C=O); ¹H NMR (90MHz,CDCl₃,TMS): δ 0.76(3H,t,CH₃), 1.00-1.60(4H,m,CH₂CH₂), 2.46(3H,s,CH₃), 2.96(2H,t,CH₂), 3.77(3H,s,CH₂O), 6.40(1H,s,OH), 6.81 and 7.60 (4H,ABq,JAB=10Hz, aromatic protons of p-methoxyphenyl group), 7.10(1H,s, an aromatic proton of imidazole ring), 7.17 (1H,d,Jab = 8Hz,Ha), 7.43 (1H,dd,Jab = 8Hz, Jbc = 2Hz,Hb), 7.98 (1H,d,Jbc = 2Hz,Hc).

Based on these spectral data, 3a was determined as 2-n-butylthio-1-(2-carboxy-4-methylphenyl)imidazole.

The intermediate 2 was quenched with water to give 2-n-butylthio-4-(p-methoxyphenyl)imidazole 3b (98% yield) as an oil; MS: m/z 352 (M⁺); ¹H NMR (90MHz,CDCl₃,TMS): δ 0.88(3H,t, CH₃), 1.08-1.80(4H,m,CH₂CH₂), 2.40(3H,s,CH₃), 3.12(2H,t,CH₂), 3.80(3H,s,CH₂O), 6.90, and 7.74(4H, ABq, JAB=10Hz, aromatic protons of p-methoxyphenyl group), 7.24(5H,s, aromatic protons of p-tolyl group and imidazole ring). 3b was treated with Raney-Ni to give 4-(p-methoxyphenyl)-1-(p-methyl-
n-BuLi in THF at -70°C

\[
\begin{align*}
1 & \quad \text{Me} \\
& \quad \text{N} \\
& \quad \text{S} \\
& \quad \text{R} \\
\downarrow & \\
2 & \quad \text{Me} \\
& \quad \text{N} \\
& \quad \text{S-}n\text{-Bu} \\
\end{align*}
\]

\[
\begin{align*}
3a & \quad X = \text{COOH} \\
3b & \quad X = \text{H} \\
3c & \quad X = \text{CH}_3\text{OH} \\
\end{align*}
\]

phenyl)imidazole 4 (69% yield); mp 127-129°C; MS: m/z 264 (M⁺); 'H NMR (90MHz, CDCl₃, TMS): δ 2.40 (3H, s, CH₃), 3.84 (3H, s, OCH₃), 6.96 and 7.78 (4H, ABq, JAB = 10Hz, aromatic protons of p-methoxyphenyl group), 7.45 (1H, d, J₂₄ = 2Hz, an aromatic proton at 4-position of imidazole ring), 7.85 (1H, d, J₂₄ = 2Hz, an aromatic proton at 2-position of imidazole ring). The disappearance of n-butyl hydrogens and the appearance of one hydrogen at 2-position of imidazole ring in the 'H NMR spectra support that n-butyl group was located on sulfur and n-butylthio group was attached to 2-position of imidazole ring. 4 was also obtained from 1 by treatment with Raney-Ni in 91% yield. 2 was quenched with p-tolualdehyde to give 3c (94% yield), an oil. Further work on this reaction is now in progress.

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REFERENCES AND NOTES

4) 1 was prepared from p-methoxyphenacyl bromide and 2-amino-6-methylbenzimidazole in 56% yield by the known method.5

5) E.Ochiai and T.Nishizawa, Yakugaku Zasshi, 1940, 60, 132.

6) 3C; 1H NMR (90MHz,CDCl₃,TMS): δ 0.90(3H,t,CH₃), 1.10-1.90(4H,m,CH₂CH₂), 2.28(3H,s,CH₃), 2.48(3H,s,CH₃), 3.16(2H,t,CH₂), 3.84(3H,s,OCH₃), 5.62(1H,s,CH), 6.72-7.80(12H,m,aromatic protons); MS: m/z 472(M⁺).

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