

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

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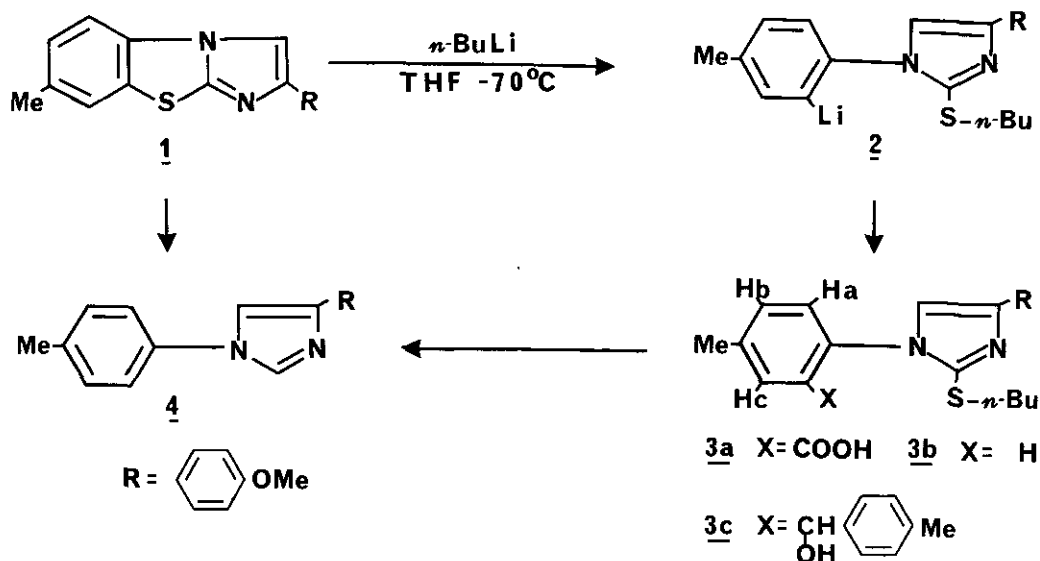
Abstract — The nucleophilic substitution reaction on sulfur of 2-(p-methoxyphenyl)-7-methylimidazo[2,1-b]benzothiazole by n-butyl lithium affords the C-S bond cleaved compound in excellent yield.

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**⁴ 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: $\nu_{\text{max}}^{\text{neat}}$ 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, OCH₃), 6.40 (1H, s, OH), 6.81 and 7.60 (4H, ABq, J_{AB} = 10Hz, aromatic protons of p-methoxyphenyl group), 7.10 (1H, s, an aromatic proton of imidazole ring), 7.17 (1H, d, J_{ab} = 8Hz, Ha), 7.43 (1H, dd, J_{ab} = 8Hz, J_{bc} = 2Hz, Hb), 7.98 (1H, d, J_{bc} = 2Hz, Hc). Based on these spectral data, **3a** was determined as 2-n-butylthio-1-(2-carboxy-4-methylphenyl)-4-(p-methoxyphenyl)imidazole.

The intermediate **2** was quenched with water to give 2-n-butylthio-4-(p-methoxyphenyl)-1-(p-methylphenyl)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, OCH₃), 6.90, and 7.74 (4H, ABq, J_{AB} = 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-



phenyl)imidazole 4 (69% yield); mp 127-129°C; MS: m/z 264(M^+); ^1H NMR (90MHz, CDCl_3 , TMS): δ 2.40(3H, s, CH_3), 3.84(3H, s, OCH_3), 6.96 and 7.78(4H, ABq, $J_{AB} = 10\text{Hz}$, aromatic protons of p-methoxyphenyl group), 7.45 (1H, d, $J_{24} = 2\text{Hz}$, an aromatic proton at 4-position of imidazole ring), 7.85(1H, d, $J_{24} = 2\text{Hz}$, 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 ^1H 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 3c⁶ (94% yield), an oil. Further work on this reaction is now in progress.

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REFERENCES AND NOTES

- 1) J.F. Biellman and J.B. Ducep, *Org. Reactions*, 1982, Vol. 27, p.1.
- 2) 2a) R.G. Micetich, *Can. J. Chem.*, 1970, **48**, 2006. 2b) K. Goda, R. Okazaki, K. Akiba and N. Inamoto, *Tetrahedron Lett.*, 1976, **20**, 181. 2c) K. Goda, R. Okazaki, K. Akiba and N. Inamoto, *Bull. Chem. Soc. Jpn.*, 1978, **51**, 260.

- 3) 3a) G.A.Wildshut, H.J.T.Boss, L.Brandsma and J.F.Arens, Monatsh. Chem., 1967, 98, 1043. 3b) D.Seebach, Chem. Ber., 1972, 105, 487. 3c) M.Hisaoka, K.Akiba and N.Inamoto, Bull.Chem.Soc.Jpn., 1975, 48, 3274. 3d) K.Akiba, Y.Ohara and N.Inamoto, ibid., 1982, 55, 2976.
- 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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