NUCLEOPHILIC SUBSTITUTION REACTIONS ON SULFUR BY n-BUTYLLITHIUM 2[1]

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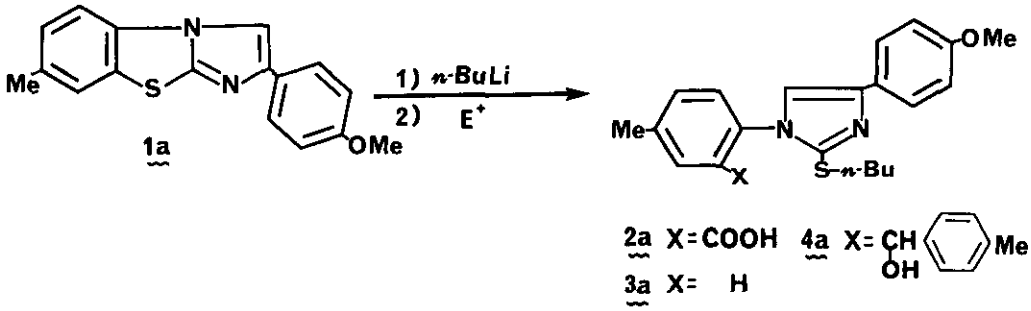
Abstract ——— The reaction of some 2-phenylimidazo[2,1-b]benzothiazoles (1) with organometal reagents (n-BuLi, n-Bu_2CuLi, i-Pr_2NLi and EtMgBr) has been investigated. Two reagents (n-BuLi and n-Bu_2CuLi) induced the nucleophilic substitution reaction on sulfur of 1 and to give the C-S bond cleaved compounds.

Previously we reported the reactions of 2-(p-methoxyphenyl)-6-methylimidazo[2,1-b]benzothiazole (1a) with n-butyl lithium (n-BuLi), followed by quenching with some electrophiles (CO_2, H_2O and p-tolualdehyde) gave the carbon-sulfur bond cleaved compounds (2a,3a and 4a) exclusively.[1]

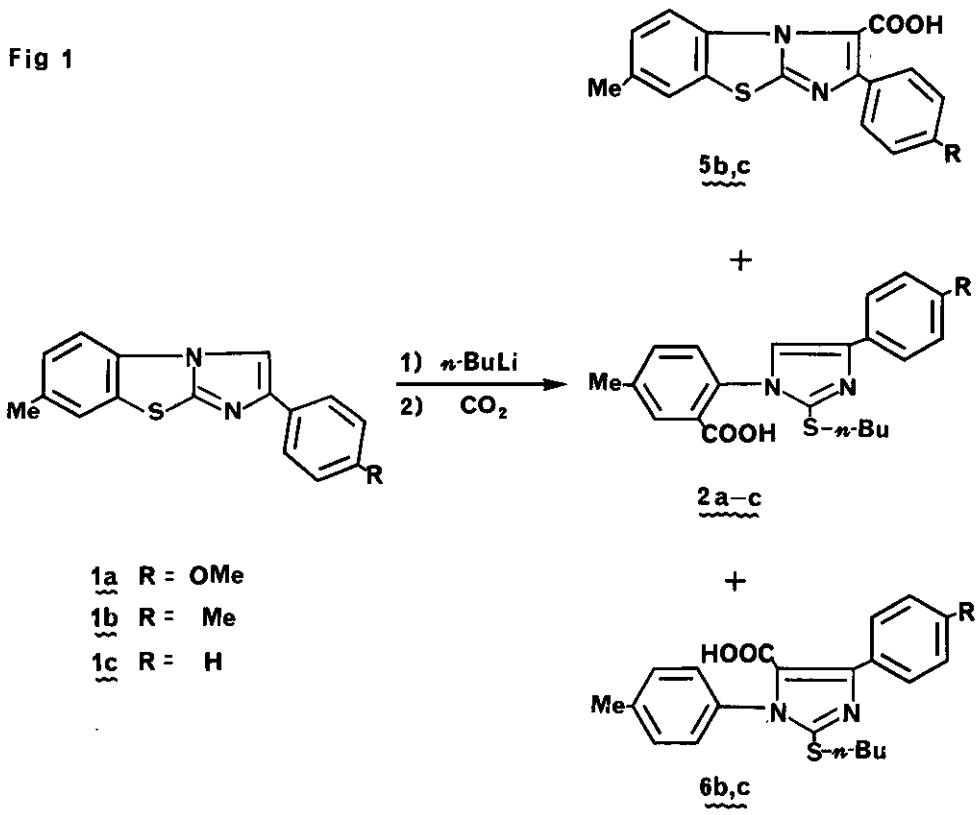


The application of this reaction to the derivatives of 1a gave some different results. In this paper, we describe the reaction of 2-(p-methylphenyl)-6-methylimidazo[2,1-b]benzothiazole (1b)[2] and 2-phenyl-6-methylimidazo[2,1-b]benzothiazole (1c)[3] with n-BuLi and the reaction of 1a with other organometal reagents.

Compound 1b was allowed to react with 1 equiv of n-BuLi in tetrahydrofuran (THF) for 30 min at -70°C under argon. The reaction mixture was quenched with carbon dioxide (CO_2) at -60°C to give three products differed from the result of the reaction of 1a and n-BuLi, which gave only C-S bond cleaved product (2a).[1] In addition to the major product (2b, 32%), the C-S bond cleaved

compounds, 3-carboxy-2-(p-methylphenyl)-6-methylimidazo[2,1-b]benzothiazole (5b, 16%) and 5-n-butylthio-1,3-di-(p-methylphenyl)-2-carboxyimidazole (6b, 18%) were obtained. The reaction of 1c with n-BuLi and CO_2 also afforded 2c (50%), 5c (23%) and 6c (21%) and these results were summarized in Fig.1.

Fig 1

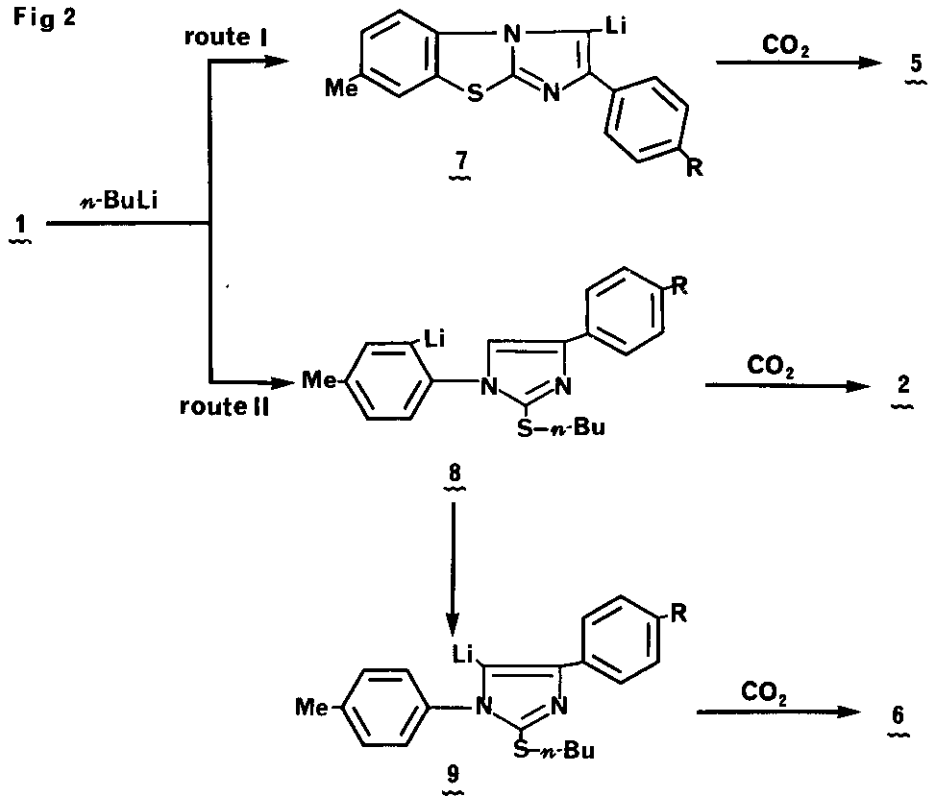


1a R = OMe
1b R = Me
1c R = H

A plausible mechanism for the reaction of 1 and n-BuLi may be described as shown in the Fig 2. Compound 1 would be lithiated at two positions (route I and II). In the case of route I, 1 would be directly lithiated at 3-position to yield lithiated intermediate 7, which would be quenched with CO_2 to give carboxylated compound 5. In route II, intermediate 8, in which the C-S bond is cleaved and benzene ring is lithiated, on quenching with CO_2 could afford 2. On the other hand, gradual lithiation of imidazole ring (9) from phenyl ring (8) followed by quenching with CO_2 would yield 6.

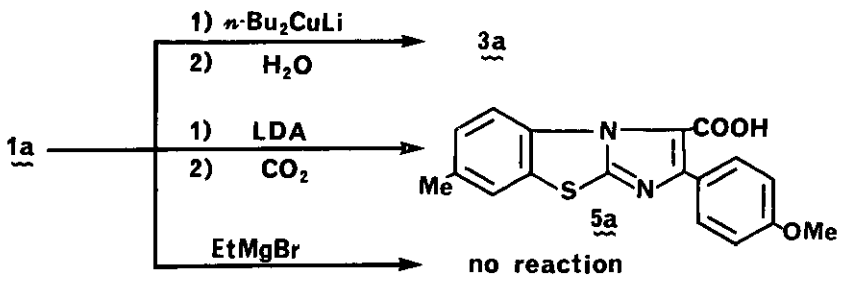
Among these reactions, only 1a gave one product 2a in high yield. This result seemed to be induced by electron donating effect of methoxy group.

Fig 2



Next, we tried the reaction of 1a with other organometal reagents as shown in Fig. 3. The treatment of 1a with 1 equiv of lithium dibutylcuprate (n-Bu_2CuLi) in THF at -70°C for 30 min under argon, followed by quenching with H_2O gave the C-S bond cleaved compound (3a, 80%) similarly to the reaction of 1a with n-BuLi.[1] The reaction of 1a with 1 equiv of lithium diisopropyl amide (LDA) in THF at -50°C under argon, followed by quenching with CO_2 gave 5a (38%). Ethyl magnesium bromide could not react with 1a under usual reaction conditions.

Fig 3



EXPERIMENTAL

Melting points were taken on a Yanaco MP-3 melting point apparatus and are uncorrected. ^{1}H-Nmr spectra were obtained on a JEOL JNM-FX 90 (90 MHz) and JEOL GX-500 (500 MHz) spectrometer with TMS as an internal standard. Ir spectra were obtained on a Hitachi 270-30 Infrared spectrometer. EI mass spectra were obtained on a Hitachi M-80 spectrometer and FAB mass spectra were obtained on a JEOL JMS-DX300 spectrometer. Elemental analyses for C,H, and N were performed on a Yanagimoto CHN Corder MT-3 and those for S were performed on a Metrohm 660 conductometer by the Measurement Division in this Laboratories. In general, organic extract was dried over $MgSO_4$ and solvent was evaprated under reduced pressure.

Reaction of 2-(p-Methylphenyl)-6-methylimidazo[2,1-b]benzothiazole (1b) with n-Butyllithium and CO_2.

To a solution of 1b (1.39 g, 5.0 mmol) in THF (50 ml) was added n-BuLi (5.0 mmol) at -70°C under argon and the reaction mixture was stirred at the same temperature for 30 min. The resulted yellow solution was saturated with CO_2 at -60°C and the mixture was stirred at that temperature for 30 min and then allowed to warm up to room temperature. The reaction mixture was concentrated and water (50 ml) was added to the residue. The mixture was exstracted with AcOEt (50 ml x3). The organic layer was retained for further examination. The aqueous layer was acidified with 1N-HCl (5.2 ml) and extracted with AcOEt (50 mlx3). The extract was washed with sat. NaCl aq. solution, dried and evaporated to give a half solid, which was stirred with toluene (5 ml). The crystals were collected by filtration and washed with toluene (2 ml) to give 5b (250 mg, 16%). The filtrate was combined with the organic layer obtained above and the combine was concentrated. The residue was column chromatographed on silica-gel. Initially, 6b (340 mg, 18%) was eluted with a mixture of toluene-ether (9:1) and then 2b (600 mg, 32%) was eluted with ether.

2-n-Butylthio-1-(2-carboxy-4-methylphenyl)-4-(p-methylphenyl)imidazole (2b): An oil. Ir ν_{max}^{KBr} 1715cm^{-1} (C=O); ^{1}H nmr (90 MHz, $CDCl_3$, TMS): δ 0.74 (3H, t, CH_3), 1.0-1.64 (4H, m, CH_2CH_2), 2.28 (3H, s, CH_3), 2.44 (3H, s, CH_3), 2.92 (2H, t, CH_2), 7.07 and 7.57 (4H, ABq, J_{AB}=10Hz, aromatic protons of p-methylphenyl group), 7.16 (1H, s, a proton of imidazole ring), 7.17(1H, d, J=10Hz), 7.41 (1H, dd, J=10Hz,2Hz), 7.97 (1H, d, J=2Hz); ms(EI): m/z 380(M)$^+$; Anal. Calcd. for $C_{22}H_{24}N_2O_2S$; C, 69.45; H, 6.36; N, 7.36; S, 8.43. Found: C, 69.37; H, 6.27; N, 7.34; S, 8.34.

3-Carboxy-2-(p-methylphenyl)-6-methylimidazo[2,1-b]benzothiazole (5b): mp 172-173°C. Ir ν_{max}^{KBr} 3460cm^{-1} (OH), 1690cm^{-1} (C=O); ^{1}H nmr (90 MHz, DMSO-d_6, TMS): δ 2.35 (3H, s, CH_3), 2,42 (3H, s, CH_3), 7.24 and 7.64 (4H, ABq, J_{AB}=10Hz, aromatic protons of p-methylphenyl group), 7.35 (1H, dd, J=10Hz, 2Hz), 7.84 (1H, d, J=2Hz), 8.63 (1H, d, J=10Hz); ms(FAB): m/z 322(M+H)$^+$.

2-n-Butylthio-1,4-di-(p-methylphenyl)imidazole-5-carboxylic Acid (6b): mp 158-160°C (decomp.). Ir: ν_{max}^{KBr} 3456cm^{-1} (OH), 1676cm^{-1} (C=O): ^{1}H nmr (500M Hz, DMSO-d_6): δ 0.86 (3H, t, CH_3), 1.33 (2H, m, CH_2), 1.62 (2H, m, CH_2), 2.34 (3H, s, CH_3), 2.38 (3H, s, CH_3), 3.15 (2H, t, CH_2), 7.21 (4H, m, aromatic protons neighboring on two methyl groups), 7.30 (2H, m, aromatic protons of 4-phenylring), 7.69 (2H, m, aromatic protons of 1-phenyl ring); ms(FAB): m/z 381(M+H)$^+$; Anal. Calcd. for $C_{22}H_{24}N_2O_2S$; C, 69.45; H, 6.36; N, 7.36. Found: C, 69.72; H, 6.34; N, 7.52.

Reaction of 2-Phenyl-6-methylimidazo[2,1-b]benzothiazole (1c) with n-BuLi and CO_2.

Treatment of 1c (1.32 g, 5.0 mmol) with n-BuLi (5.0 mmol) and CO_2 in the same manner as the above reaction afforded 2c (907 mg, 50%), 5c (350 mg, 23%) and 6c (366 mg, 21%).

2-n-Butylthio-1-(2-carboxy-4-methylphenyl)-4-phenylimidazole (2c): An oil. ^{1}H Nmr (90 MHz, $CDCl_3$, TMS): δ 0.76 (3H, t, CH_3), 1.0-1.6 (4H, m, CH_2CH_2), 2.45 (3H, s, CH_3), 2.95 (2H, t, CH_2), 7.16 (1H, s, a proton of imidazole ring), 7.0-7.6 (5H, m), 7.6-7.8 (2H, m), 7.96 (1H, d, 2Hz); ms(EI): m/z 366(M)$^+$.

3-Carboxy-6-methyl-2-phenylimidazo[2,1-b]benzothiazole (5c): mp 194-195°C (decomp.). Ir ν_{max}^{KBr} 3464 cm^{-1} (OH), 1702cm^{-1} (C=O); ^{1}H nmr (90 MHz, DMSO-d_6): δ 2.40 (3H, s, CH_3), 7.36 (1H, dd, J=2Hz, 10Hz), 7.20-7.60 (3H, m), 7.60-7.88 (2H,m), 7.84 (1H, d, J=2Hz), 8.64 (1H, d, J=10Hz); ms(FAB): m/z 309(M+H)$^+$.

2-n-Butylthio-1-(p-methylphenyl)-4-phenylimidazole-5-carboxylic Acid (6c): mp 162-163°C (decomp.) (from toluene). Ir ν_{max}^{KBr} 3480cm^{-1} (OH), 1676cm^{-1} (C=O); ^{1}H nmr (500 MHz, DMSO-d_6, TMS): δ 0.86 (3H, t, CH_3), 1.35 (2H, m, CH_2), 1.62 (2H, m, CH_2), 2.39 (3H, s, CH_3), 3.16 (2H, t, CH_2), 7.23 and 7.31 (4H, m, aromatic protons of tolyl group), 7.35, 7.41 and 7.79 (5H, m, aromatic protons of 4-phenyl group). Ms(FAB): m/z 367(M+H)$^+$; Anal. Calcd. for $C_{21}H_{22}N_2O_2S$; C, 68.83; H, 6.05; N, 7.64; S, 8.75. Found: C, 68.83; H, 5.83; N, 7.55; S, 8.81.

Reaction of 1a with $(n\text{-}Bu)_2CuLi$.[4]

To a solution of CuI (0.9 g, 4.7 mmol) and THF (50 ml), n-BuLi (9.4 mmol) was added dropwise at -70°C under argon and the mixture was stirred at that temperature for 30 min. To the mixture, 1a (1.38 g, 4.7 mmol) was added and then the mixture was stirred at the same temperature for 1 h. To the reaction mixture, 33% AcOH (3 ml), toluene (100 ml) and water (100 ml) were

successively added. The organic part was separated, washed with water, dried and concentrated to give an oil, which was purified by silica-gel column chromatography (benzene) to afford 2-n-butylthio-4-(p-methoxyphenyl)-1-(p-methylphenyl)imidazole (3a, 1.33 g, 80.6%). The spectral properties of this compound were identical in all respects with those of authentic sample.[1]

Reaction of 1a with Lithium Diisopropyl Amide (LDA) and CO_2.

To a mixture of diisopropylamine (0.5 g, 4.9 mmol) in THF (10 ml), n-BuLi (4.7 mmol) was added at -78°C and then 1a (1.38 g, 4.7 mmol) and THF (40 ml) were added. The mixture was stirred for 1.5 h at -50°C and saturated with CO_2. The solution was allowed to warm up to room temperature and to stand overnight. The mixture was concentrated and to the residue water (100 ml) and AcOEt (50 ml) were added. The mixture was stirred for 1 h and the insoluble material was removed by filtration. The aqueous solution was separated , washed with AcOEt (50 ml), acidified with dil. HCl and extracted with AcOEt. The extract was washed with sat. NaCl aq. solution, dried and concentrated to give crystals, which were washed with ether and dried to afford 3-carboxy-2-(p-methoxyphenyl)-6-methylimidazo[2,1-b]benzothiazole (5a, 610 mg, 38%), mp 162-165°C (decomp.). Ir ν_{max}^{KBr} 3460cm^{-1} (OH), 1674cm^{-1} (C=O); ^{1}H nmr (500 MHz, DMSO-d_6, TMS):δ 2.42 (3H, s, CH_3), 3.82 (3H, s, OCH_3), 7.00 (2H, m), 7.34 (1H, d, J=8.5Hz), 7.71 (2H, m), 7.83 (1H, s), 8.61 (1H, d, J=8.5Hz); ms(FAB): m/z 338(M+H)$^+$; Anal. Calcd. for $C_{18}H_{14}N_2O_3S_3$; C, 63.89; H, 4.17; N, 8.28. Found: C, 63.73; H, 4.27; N, 8.16.

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REFERENCES

1) T.Mase and K.Murase, Heterocycles, 1984, 22(5), 1013.

2) 1b was prepared from 2-amino-6-methylbenzothiazole and p-methylphenacylbromide by the known method.[5]

3) 1c was prepared from 2-amino-6-methylbenzothiazole and phenacylbromide by the known method.[5]

4) G.H.Posner, Org. Reactions, 1975, 22, 253.

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

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