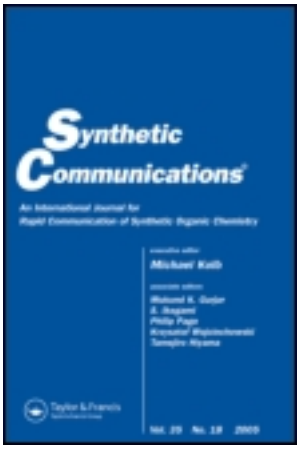

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Nitroimidazoles, Part 1. An Unexpected Reactivity During the Cyclization of 3-(4-Amino-1-benzyl-2-ethyl-1H-im Acid Methyl Ester

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Abstract: Nucleophilic substitution of the 5-bromo group in **1** by methyl 3-mercaptopropionate gave the 5-alkyl-mercapto derivative **2**. Reduction of **2** with H_2/Pd led to the amine **3**, meanwhile reduction with Fe/HOAc afforded the 5-acetamido derivative **4** and not the cyclized derivative 1,3,8-triaza-azulen-7-one **6**, as expected. Treatment of **3** with NaOMe/MeOH furnished the racemic mixture **5a** and **5b** via an unexpected reactivity.

Keywords: Cyclization, 4-nitroimidazole, nucleophilic substitution, *meso*-product

INTRODUCTION

4-Nitrohaloimidazoles are of considerable pharmacological significance, particularly as antibacterial agents,[1,2] potential radiosensitizers,[3] and in cancer chemotherapy.[4] Furthermore, because of the facile replacement of

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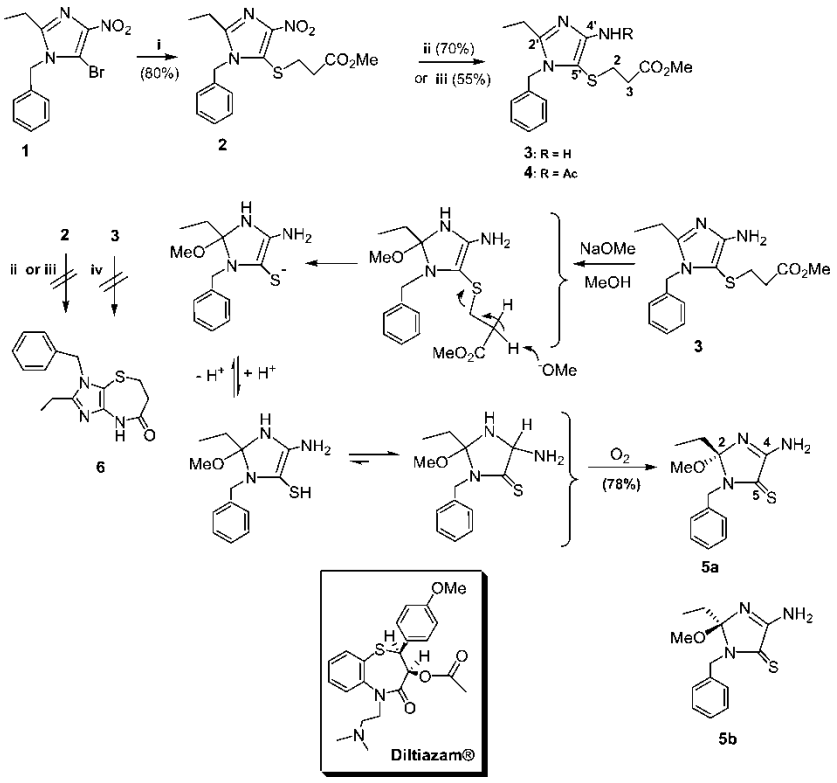
halogen[5] and the reduction of the nitro group,[5] 4-nitrohaloimidazoles are intermediates in syntheses of a variety of biologically active imidazoles. Several benzodiazepines are known as antidepressant agents. Some analogues, such as 'Diltiazam®,[6] show potent coronary vasodilatory activities as calcium antagonists. Our efforts for the synthesis of the imidazole **6** bearing thialactam, the 3-benzyl-2-ethyl-3,5,6,8-tetrahydro-4-thia-1,3,8-triaza-azulen-7-one, as a potential antitumor or coronary vasodilator agent resulted in an unexpected rearrangement of the imidazole derivative.

RESULTS AND DISCUSSION

Treatment of **1** with methyl 3-mercapto-propionate in THF with K_2CO_3 at 23°C under argon afforded, after purification, the crystalline sulfide **2** in 80% yield. Recently, Erker et al.[8,9] have reported the reduction of some thiophenes carrying a propionylthio substituent, vicinal to a nitro group, resulting in the formation of the thienothialactams. Moreover, hydrogenation[5] of **2** in the presence of a molar amount of 5% Pd/C as a catalyst in anhyd. EtOH at 23°C gave methyl ester **3** in 70% yield as oil and not the expected cyclized product **6**. The structure of **3** was confirmed by the homo- and heteronuclear NMR studies and by its mass spectrum [m/z: $C_{16}H_{21}N_3O_2S$ (319, M^+)]. The $^1H-^{13}C$ HSQC spectrum of **3** showed, unexpectedly, two methylene groups [(CH_2)-2, (CH_2)-3] as a singlet at δ_H 2.46, which are cross-linked to their carbons C-2 and C-3 at δ_C 34.0 and 32.0, respectively. Reduction[9] at 70°C for 24 h of **2** with Fe/AcOH furnished the 5-acetamido derivative **4** in 55% yield, as an oil [m/z: $C_{18}H_{23}N_3O_3S$ (361, M^+)].

In an attempt to obtain **6** by cyclization of **3**, the latter compound was stirred at 23°C h in 0.2 M NaOMe/MeOH. However, the isolated product turned out to be a racemic mixture of the **5a** and **5b** (78%) (Scheme 1). A possible mechanism for the formation of **5a,b** is depicted in Scheme 1, depending on the observation of Kulkarani et al.[10] during the reaction of sodium methoxide with 5-iodo-4-nitroimidazole. The structure **5** was assigned by NMR and mass spectra. The CH_2Ph signal in the ^1H NMR spectrum appeared as an AB system at δ_H 4.87 with a large coupling constant ($J = 14.4$ Hz), indicative of diastereotopic protons. The methylene protons of the ethyl group at C-2 showed the pattern of an ABX_3 system (δ_H 2.02 and 1.78, $J = 7.3$ Hz). The broad singlet at δ_H 6.38 was assigned to the NH_2 group, exchangable with D_2O. In the ^{13}C NMR of **6** a signal at δ_C 182.9 was assigned to the C=S group. Irradiation of the CH_2CH_3 signal at δ_H 0.61 resulted in collapsing of the two multiplets of the diastereotopic CH_2 protons at δ_H 2.02 and 1.78 into an AB-quartet (Figure 1). Furthermore, the IR spectrum of **5** showed strong absorptions at 1655 and 1235 cm^{-1}, indicative for the C=N, and C=S resonances, respectively.



Scheme 1. Reagents and conditions: (i) $SH(CH_2)_2CO_2Me$, K_2CO_3, THF, rt, 18 h, under argon; (ii) H_2/Pd-C, anhydr. EtOH, rt; (iii) Fe/AcOH, 70°C, 24 h; (iv) NaOMe/MeOH, rt, 4 h.

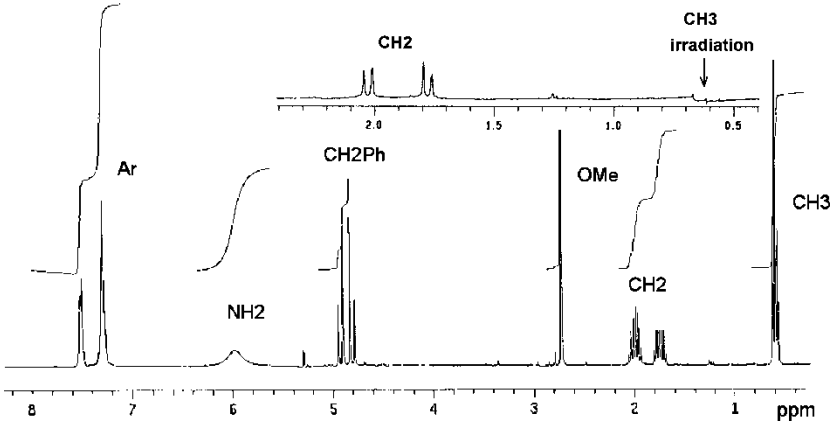


Figure 1. ^1H NMR ($CDCl_3$, 600 MHz) of **5**, showing irrradiation experiment.

EXPERIMENTAL

General

Melting points are uncorrected. NMR spectra are at 300 and 600 MHz (^{1}H) and at 62.9 MHz (^{13}C) with TMS as internal standard and on δ scale in ppm. The signal assignments for protons were verified by selective proton decoupling or by COSY spectra. Heteronuclear assignments were verified by ^{1}H–^{13}C correlation spectroscopy (COSY)[11] or heteronuclear multiple quantum coherence (HMQC) experiments.[12] IR spectra (KBr disks) were measured with an FTIR Bomen MB-120 spectrophotometer. 3-Nitrophenol (NBOH) or glycerol were used in the EI and FAB mass measurements as matrices. Some molecular ions were detected by doping the sample with Na^+ ions.

3-(1-Benzyl-2-ethyl-4-nitro-1*H*-imidazol-5-ylsulfanyl)propionic Acid Methyl Ester (2)

A suspension of potassium carbonate (0.90 g, 8.05 mmol) and methyl 3-mercaptopropionate (0.47 g, 3.91 mmol) was stirred in dry THF (20 mL) under argon at rt. To this suspension, **1** (1.0 g, 3.22 mmol) was added slowly and was stirred for 18 h, until the disappearance of the starting material as monitored by TLC. The mixture was poured into ice water, and the precipitate filtered off and recrystallized from EtOH to give **2** (0.90 g, 80%), mp: 94–95°C. ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.36–7.26 (m, 3H, Ar); 6.95 (d, 2H, $J = 7.1$ Hz, Ar); 5.33 (s, 2H, CH_2Ph); 3.62 (s, 3H, OMe); 3.12 [t, 2H, $J = 6.8$ Hz, (CH_2)-2]; 2.65 (q, 2H, $J = 7.5$ Hz, CH_2CH_3); 2.53 [t, 2H, $J = 6.8$ Hz, (CH_2)-3]; 1.26 (t, 3H, CH_2CH_3). ^{13}C NMR ($CDCl_3$): δ 171.4 (C═O); 150.5 (C-2′); 134.8 (C-4′); 129.2, 128.3, 125.9, (Ar); 124.1 (C-5′); 51.9 ($COCH_3$); 47.6 (CH_2Ph); 34.2, 31.4 (C-2, C-3); 21.2 (CH_2CH_3); 11.2 (CH_2CH_3). MS (70 eV, EI): m/z 349 (M^+): elemental analysis calcd. (%) for $C_{16}H_{19}N_3O_4S$ (349.4): C, 55.00; H, 5.48; N, 12.03; found: C, 54.75; H, 5.08; N, 11.92.

Reduction of 2

a) with H_2/Pd: A solution of **2** (0.50 g, 1.43 mmol) in anhyd. EtOH (10 mL) was hydrogenated in the presence of 5% palladium oxide (0.60 g) on charcoal at atmospheric pressure and rt until the absorption of H_2 has ceased. The catalyst was filtered and the filtrate was concentrated to give an oily product (0.32 g) that was identified as 3-(4-amino-1-benzyl-2-ethyl-1*H*-imidazol-5-ylsulfanyl)-propionic acid methyl ester (**3**) (70%). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.33–7.25 (m, 3H, Ar); 6.98 (d, 2H, $J = 7.0$ Hz, Ar); 5.13 (s, 2H, CH_2Ph); 4.05 (br s., 2H, NH_2); 3.56 (s, 3H, OMe); 2.55 (q, 2H,

$J = 7.6$ Hz, CH_2CH_3); 2.47 [s, 4H, (CH_2)-2, (CH_2)-3]; 1.28 (t, 3H, CH_2CH_3). ^{13}C NMR ($CDCl_3$): δ 172.1 (C=O); 151.6 (C-2′); 148.8 (C-5′); 137.0 (C-4′); 128.7, 127.4, 125.8 (Ar); 51.6 ($COCH_3$); 46.3 (CH_2Ph); 34.0, 32.0 (C-2, C-3); 20.8 (CH_2CH_3); 11.6 (CH_2CH_3). MS (70 eV, EI): m/z 320 (MH^+). Analysis calcd. for $C_{16}H_{21}N_3O_3S$ (319.43): C, 60.16; H, 6.63; N, 13.15; found: C, 60.01; H, 6.57; N, 12.92.

b) with iron/HOAc: To a stirred suspension of **2** (0.40 g, 1.14 mmol) in glacial HOAc (10 mL) and water (1.0 mL) at 70°C was added iron powder (0.60 g) in small portions. The reaction mixture was heated at 70°C for 24 h, filtered hot, and then cooled down. No precipitate was formed, instead the solution was evaporated to dryness and the residue was partitioned between water (20 mL) and $CHCl_3$ (3×20 mL). The combined organic extracts were dried (Na_2SO_4), filtered, and evaporated to dryness to give syrup. The syrup was poured on flash SiO_2 column (6 g), using $CHCl_3$–MeOH (4 : 1) as eluent, and the produce was tentatively identified as 3-(4-acetamido-1-benzyl-2-ethyl-1*H*-imidazol-5-ylsulfanyl)propionic acid methyl ester (**4**) (0.20 g, 55%). ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.95 (br s., 1H, NH); 7.55–7.25 (m, 3H, Ar); 7.00 (d, 2H, $J = 6.0$ Hz, Ar); 5.26 (s, 2H, CH_2Ph); 3.70 (s, 3H, OMe); 2.61 (q, 2H, $J = 7.5$ Hz, CH_2CH_3); 2.57, 2.46 [2d, 4H, $J = 6.5$ Hz, (CH_2)-2, (CH_2)-3]; 1.28 (t, 3H, CH_2CH_3). ^{13}C NMR ($CDCl_3$): δ 172.4 (C=O); 169.4 (NH*C*OMe); 150.4 (C-2′); 141.5 (C-5′); 136.5 (C-4′); 128.9, 127.7, 125.9 (Ar); 51.9 ($COCH_3$); 46.8 (CH_2Ph); 33.9, 32.6 (C-2, C-3); 29.6 (NHCO*Me*); 21.2 (CH_2CH_3); 11.5 (CH_2CH_3). MS (70 eV, FAB) ($C_{18}H_{23}N_3O_3S$): m/z 384 $(MNa)^+$.

Reaction of 3 with Sodium Methoxide

A solution of **3** (0.30 g, 0.94 mmol) in 0.2 M NaOMe solution (10 mL) was stirred at rt for 4 h. The solution was neutralized with HOAc and then evaporated to dryness. The residue was partitioned between water (10 mL) and $CHCl_3$ (3×10 mL), and the combined organic extracts were dried (Na_2SO_4), filtered, and evaporated to give a solid that was identified as the racemic mixture (*R*),(*S*)-4-amino-1-benzyl-2-ethyl-1,2-dihydro-2-methoxyimidazol-5-thione (**5**) (0.19 g, 78%), mp: 136–137°C decomp. ν_{max} (cm^{-1}): 3360, 3250 (NH); 1655 (C=N), 1580, 1517, 1513, 1505, 1350 (Ar, C-N); 1235 (C=S). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.51 (m, 2H, Ar); 7.32–7.20 (m, 3H, Ar); 6.38 (br s., 2H, NH_2); 4.87 (AB q, 2H, $J = 14.4$ Hz, 2H, CH_2Ph); 2.75 (s, 3H, OMe) 2.02 (dt, 1H, $J = 7.3$ Hz, CH_2CH_3, diastreotopic protons); 1.78 (dt, $J = 7.3$ Hz, CH_2CH_3, diastereotopic protons); 0.61 (t, 3H, CH_2CH_3). ^{13}C NMR ($CDCl_3$): δ 182.9 (C=S); 158.2 (C-5); 129.1, 128.5, 128.1 (Ar); 114.7 (C-2); 49.6 (OMe), 48.1 (CH_2Ph); 30.5 (CH_2CH_3); 7.2 (CH_2CH_3). MS: m/z (FAB) (264) (MH^+). Anal. calcd. for $C_{13}H_{17}N_3O_S$ (263.36): C, 59.29; H, 6.51; N, 15.96. Found: C, 59.08; H, 6.43; N, 15.68.

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