Regioselective Electrophilic Substution on 2,5-Bis(trimethylsilyl) 1-methylimidazole and 2,5-Bis(trimethylsilyl)thiazole

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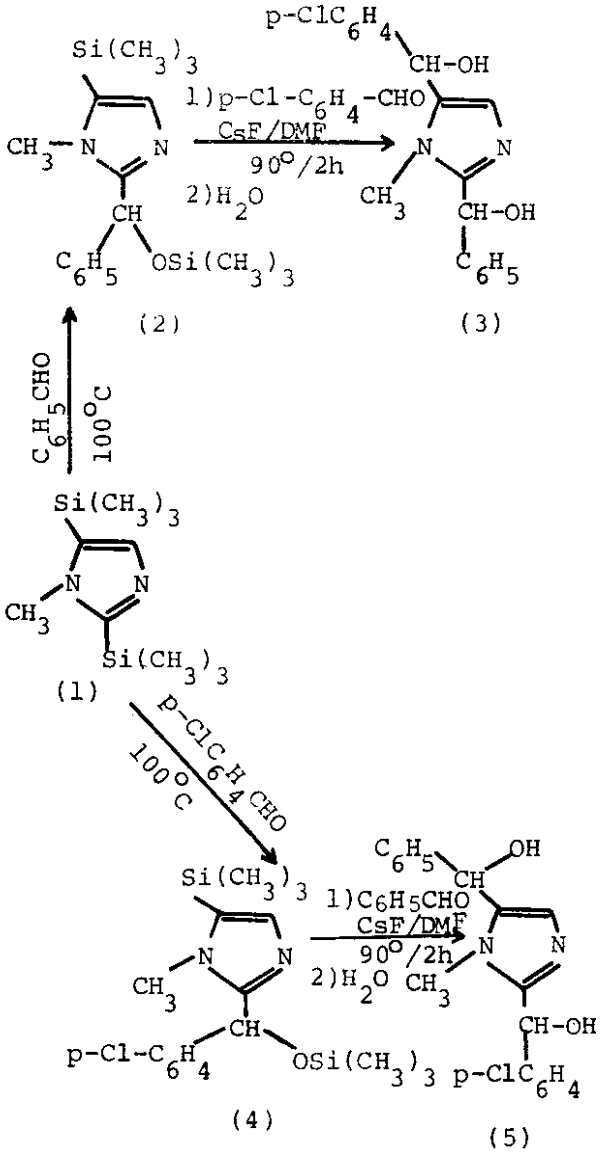
Summary: 2-as well as 3-positions of 2,5-bis(trimethylsilyl) 1-methylimidazole have been substituted selectively by reactions with aromatic aldehydes. The substitution reactions with 2,5-bis(trimethylsilyl)thiazole were not very selective.

The reactions of aryl (trimethyl) silanes with aldehydes, ketones, arylfluorides, carboxylic acids and anhydrides in the presence of catalyst like $KOC(CH_3)_3$, KF, CsF, tetramethylammonium fluoride and KOAc have been published [1] The electrophilic substitution in the presence of CsF on heteroaromatic compounds [2] have also been tried successfully. We have already reported [3] and compared the reactions of I-methyl-imidazole and thiazole derivatives in the presence of benzaldehyde with or without CsF. Whreas desilylation in imidazole derivatives at 2-position is possible without a catalyst, at 5-position it is only effective with a catalyst. This difference is less prominent in case of thiazole dervatives in which the 2-and 5-positions are attacked with little difference in reaction conditions with or without a catalyst. These results led us to attempt regioselective substitutions reaction with 2,5-bis(trimethylsilyl)-I-methylimidazole (1) and compare the results with reactions of 2,5-bis(trimethylsilyl) thiazole. (Scheme 1)

The electrophilic substitution reactions at 2-position of 2,5-bis(trimethylsily)-I-methylimidazole (1) were effected by heating with benzaldehyde at 100°C without the cleavage of trimethylisilyl-group at 5-position. The results are in accordance to the reported observations according to which the uncatalysed desilylation at α-position to a ring nitrogen depends upon the pK_{BH}^{+} values which is 7.33 [4] in case of I-methylimidazole. 1-methyl-2 [phenyl-(trimethylsilyloxy)methyl] -5-trimethylsilylimidazole (2) was identified spectroscopically and was further subjected to fluoride catalysed electrophilic substitution reaction without isolation. Reaction with p-chlorobenzaldehyde at 90°C led to replacement of 5-position also. The trimethylsilyldiether was hydrolysed further without isolation to give α^5-(p-Chlorophenyl)-1-methyl- α^2-phenyl-2,5-imidazoledimethanol (3) in good yield.

In exactly the same manner (1) was first heated with p-chlorobenzaldehyde to give 1-methyl-2[p-chlorophenyl(trimethylsilyloxy)methyl]-5-trimethylsilylimidazole (4) which was then reacted with benzaldehyde in the presence of nucleophilic catalyst and later on hydrolysed to yield α^2-(p-Chlorophenyl)-1-methyl- α^5-phenyl-2,5-imidazoledimethanol (5), an isomer of (3). Both (3) and (5) were identified spectroscopically and their purity confirmed by C,H,N, analysis.

The reactions with thiazole derivative, on the other hand were not



Scheme 1

very selective. 2,5-bis(trimethylisilyl) thiazole when treated with benzaldehyde at 100°C for 24 hrs. gave only 60% substitution at 2 position and three other undnown compounds along with some unreacted benzaldhyde (as checked by G.C. and NMR). It was attempted to purify 2[(phenyltrimethylsilyloxy)methyl] 5-trimethylsilylthiazole by vacuum distillation but most of the compound decomposed. The failure of selective substitution in case of thiazole is in accordance to previous observations according to which pK_{BH^+} values of thiazole [4] at 2 as well as 5-position are not much different, hence the uncatalysed reactions are less selective as compared to imidazole-derivatives. CsF-catalysed reactions of bis -thiazolederivative with aromatic aldehydes also gave unsatisfactory results. It was expected from H/D-exchange rate constants [5] which are nearly the same for 2 as well as 5-positions . All other attempts to carry out selective substitution reaction on trimethyisilylthiazole derivatives were unsuccessful.

Experimental

The melting points were taken on Buechi SMP 20 with silicone oil bath and are uncorrected. ^{1}H-NMR spectra were recorded on Varian A.60, 60 MHz and IR spectra were taken with perkin Elmer spectrophotometer 457. For gas chromatographic data. Hewlett packard 5700 A with flame ionization indicator (FID) was used. Nitrogen (30 ml/min.) was employed as carrier gas. Column used was OVA, ChromosorbW, glass tube 2.3 mm ,ϑ 2mm. Temperature kept was 100-300°C and rate of heating was 16°/min. Mass spectra were recorded by Varian MAT 711 mass spectrometer.

1-methyl-2[phenyl(trimethylsilyloxy)methyl] 5-trimethylsilylimidazole (2).

A round bottomed flask with side arm (closed with a quickfit cap bearing a rubber septum) equiped with a gas inlet adapter bearing a stopcork, and a magnetic bar was heated on a burner. During cooling it was evacuated and then filled with pure nitrogen. The process was repeated three times and flask was cooled to room temp. 2,5-bis(trimethylsilyl) 1-methylimidazole (1) (1.13g,5m mole)

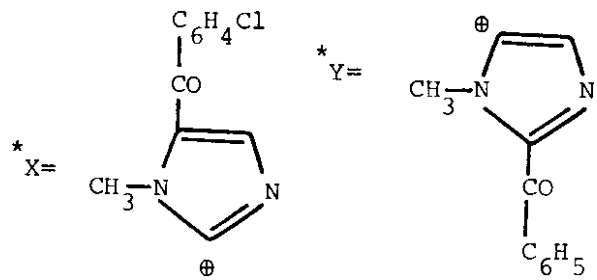
was weighed in the flask under nitrogen and benzaldehyde (0.51 ml, 5m mole) was injected. The reaction was followed gas-chromatographically. The reaction mixture was heated to 100°C for 1½ hr. till the gas-chromatogram showed 95% of new product (2). NMR (of unpurified product in $CDCl_3$) 0.1 (s, 9H, O-Si$(CH_3)_3$), 0.27 [s, 9H, C^5-Si$(CH_3)_3$], 3.43 (s, 3H, C^1-H-CH_3), 6.23 (s, 1H, CH-OSi), 7.08 (s, 1H, C^4), 7.37 (s, 5H, C_6H_5).

α^5-(p-Chlorophenyl)1-methyl- α^2-phenyl-2,5-imidazoledimethanol, (3)

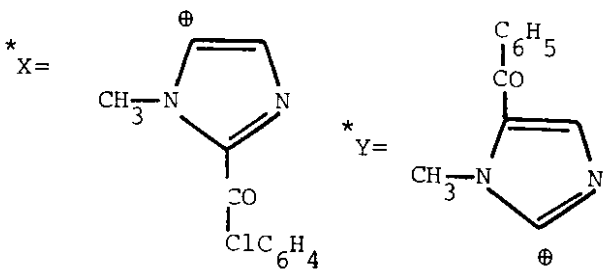
The unpurified product (2) was further subjected to fluoridecatalysed electrophilic substitution reaction with p-chlorobenzaldehyde. CsF (0.15 g, 1 m mole) and p-chlorobenzaldehyde (0.7 g, 5m mole) were added in the flask containing (2) under nitrogen. The reactions mixture was slowly heated to 90°C for 2 hr. and finally stirred at room temperature for further 1 hr. 0.1 ml water was injected in order to hydrolyse the diether and the mixture strirred for ½ hr. at R.T. Finally 100 ml water was added, brown crystals filtered, washed with ether and recrystallised from methanol. Yield 1.15 g (7%) mp 213-214°C. NMR (D_6-DMSO), 3.5(s, 3H, NCH_3) 5.77 (s, 1H, CH OH) 5.93 (s, 1H, CH OH), 6.35(s, 1H, C^4-H), 7.40 (s, 5H, C_6H_5), 7.50 (s, 4H, ClC_6H_4). Mass spectrum m/z (rel. intensities %) 328 (100 M^+), 311 (22, M-OH^+), 251 (43, M-Ph^+), 219 (12, X^*), 217 (9, M-$ClC_6H_4^+$), 203 (20), 185 (65, Y^*), 171 (15), 139 (13, ClC_6H_4 - C^+ = O) 111, (17, $ClC_6H_4^{\bullet+}$) 105 (35, Ph-C^+ = O), 77 (51, Ph^+), $C_{18}H_{17}N_2O_2Cl$ (328.85). Calc: C 65.74, H 5.21, N 8.52, Obs: C 65.39, H 5.31, N 8.35.

2[p-Chlorophenyl(trimethylsilyloxy) methyl]-1-methyl-5-trimethylsilyl-imidazole (4)

2,5-Bis(trimethylsilyl)1-methylimidazole (1) (1.13 g, 2 m mole) was reacted with p-chloro-benzaldehyde (0.7 g, 5 m mole) as for the preparation of (2) for 2 hours at 100°C. The gas-chromatogram showed 99.2%



of the product (4), NMR of the unpurified product ($CDCl_3$), 0.08 (s, 9H, OSi $(CH_3)_3$), 0.27 (s, 9H, C^5-Si$(CH_3)_3$), 3.43 (s, 3H, N-CH_3), 6.17 (s, 1H, CH-OSi), 7.07 (s, 1H, C^4-H), 7.33 (s, 4H, ClC_6H_4).



α^2-(p-chlorophenyl)1-methyl-α^5-phenyl-2,5-imidazoledimethanol (5)

The unpurified product (4) was treated with benzaldehyde (0.5 ml 5 mole), CsF (0.15 g, 1 m mole) and DMF (5 ml) under nitrogen at 90°C for 2 hours 0.1 ml water was added and mixture stirred for ½ hours. Finally 100 ml water was added, brown

crystals were washed with ether and recrystallised from ethanol. Yield 1.0 g (63%) mp. 204-205°C. NMR (D_6-DMSO) 3.47 (s, 3H, CH_3N), 5.77 (s, 1H, CH-OH) 5.90 (s, 1H, CHOH) 6.30 s, 1H C^4-H, 7.43 - 7.56 (m 9H, Aromatic) Mass-spectrum m/z (rel:intensities %) 328 (100 M^+) 311 (21, MOH^+), 251 (6, M-Ph^+), 219 (26 X^*), 217 (56, M-$ClC_6H_4^+$), 203 (18), 185 (21, Y^*), 139 (21, ClC_6H_4-$^+$-C = O), 111 (18, $ClC_6H_4^+$), 105 (19, Ph^+ C = O), 77 (41, Ph^+). $C_{18}H_{17}N_2O_2Cl$ (328.85) Cale: C 65.74, H 5.21, N 8.52, Cl 20.80. Obs: C 65.60, H 5.26, N 8.26, Cl 10.85.

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