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Note

Simple route to ferrocenyl(alkyl)imidazoles

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Abstract

A suitable method for the synthesis of ferrocenyl(alkyl)imidazoles is proposed. The treatment of α-ferrocenylcarbinols with *N*,*N*′-carbonyldiimidazole affords the title compounds, are in more than 80% yields.

Keywords: Ferrocene derivatives of azoles; α-Ferrocenylalkylation; Imidazole; *N*,*N*′-Carbonyldiimidazole

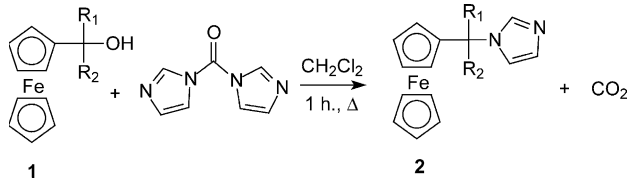
1. Results and discussion

The acid-catalyzed ferrocenylalkylation reaction using α-ferrocenylcarbinols in aqueous-organic is one of the most convenient methods for introducing ferrocenylalkyl groups into various nucleophilic substrates [1]. The ferrocenyl(alkyl)azoles FcCH(R)Az and the salts of azoles $[(FcCHR)_2Az]^+BF_4^-$ were synthesized (Fc, ferrocenyl; AzH, pyrazoles, polyfluoro benzimidazoles, triazoles, benzotriazoles) [2–4] in this way. Some of these compounds were found to exhibit antitumor activity [5,6]. The ferrocene derivatives of benzimidazoles are also of interest as ligands in metal complexes for catalysis [7].

However, under acidic conditions ferrocenylalkylation of imidazole was not realized because of the protonation of his N-basic center (basic pK_a 7.00). At the same time imidazole is actually one of the most significant heterocycles in biology. Therefore, it was important to synthesize its ferrocene derivatives in order to study potential ferrocene containing drugs.

Earlier the ferrocenyl(ethyl)imidazole $FcCH(CH_3)Im$ was obtained from the reaction between ferrocenyl(ethyl)benzotriazole $FcCH(CH_3)BTr$ and imidazole in methanol under acidic conditions (CH_3COOH or HCl) in lowish yields (30%) [8]. Using trimethylferrocenyl(methyl)ammonium iodide $FcCH_2NMe_3I$ as a ferrocenylalkylating agent in water at 100 °C we obtained a mixture of mono- and bis-ferrocenylmethyl derivatives of imidazole, (yields 30 and 15%, respectively) [9]. Other ferrocenyl(alkyl)ammonium salts are unstable and their synthesis is difficult [10]. Therefore, the homologues FcCH(R)Im (R = Me, Et and so on) were not prepared.

In the present work we propose a new method for the introducing of imidazolyl groups into ferrocenylalkyl compounds by the ferrocenylalkylation reaction of *N*,*N*′-carbonyldiimidazole. The mixture of equimolar amounts of ferrocenylcarbinols and *N*,*N*′-carbonyldiimidazole in methylene dichloride was boiled for 1 h. 1N-Ferrocenyl(alkyl)imidazoles were synthesized in high yields. We are planning to investigate these compounds as biologically active components.



1 2

a R_1 = H, R_2 = H, yeld 80%
b R_1 = H, R_2 = CH_3, 85%
c R_1 = H, R_2 = C_3H_7, 78%
d R_1 = H, R_2 = Ph, 82%
e R_1 = CH_3, R_2 = CH_3, 80%

It is important to note, that this simple procedure allows us to realize the ferrocenylalkylation reaction of *N*,*N*′-carbonyldiimidazole selectively. Actually 1N-ferrocenyl(alkyl)imidazole was the only product formed.

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2. Experimental

^{1}H-NMR spectra were obtained on 'Bruker-200-WP'. Mass spectra were measured on 'Kratos MS-890' spectrometer (ionizing strain 70 eV), IR spectra were recorded on IR-20 spectrometer (Karl Zeiss).

Dichloromethane was dried over $CaCl_2$. *N*,*N*′-Carbonyldiimidazole (CDI) was purchased from Lancaster and used without purification. Ferrocenylmetanol **1a** was obtained from trimethylferrocenylmethylammonium iodide [11], carbinols **1b**, **c**, **d** were received by acylation of ferrocene by corresponding acid chlorides [12] with the subsequent reduction by lithium aluminium hydride in diethyl ether [3,13], 2-ferrocenyl-2-hydroxypropane **1e**—by reaction of ferrocene with acetone in sulfuric acid [14].

2.1. General procedure

The mixture of equimolar amounts of ferrocenylcarbinol and *N*,*N*′-carbonyldiimidazole in anhydrous CH_2Cl_2 was refluxed for 1 h. The resulting mass was cooled, 50 ml ether was added and then flushed by 20% solution of phosphoric acid (2×50 ml). An aqueous phase was alkalized up to pH 5 and then extracted by CH_2Cl_2 (2×50 ml). An organic layer was dried over anhydrous sodium sulphate. Solvents were removed in vacuo. The resulting product was dried over $CaCl_2$.

2.2. Ferrocenyl(methyl)imidazole (**2a**)

Yield: 80%. Yellow crystals, m.p. 65 °C, MS *m*/*z* (relative intensity, %): 266 (100) $[M]^+$. IR (KBr, ν, cm^{-1}): 3150–2970, 1690–1520, 1450, 1220–1100, 1110–1000, 830, 491. ^{1}H-NMR ($CDCl_3$, δ, ppm): 4.15–4.12 (m, 9H, Fc); 4.83 (s, 2H, CH_2); 6.87 (s, 1H, CH); 6.98 (s, 1H, CH); 7.44 (s, 1H, CH).

2.3. Ferrocenyl(ethyl)imidazole (**2b**)

Yield: 85%. Red–orange crystals, m.p. 75–76 °C, MS *m*/*z* (%): 280 (38) $[M]^+$. IR (KBr, ν, cm^{-1}): 3118, 2992, 2940, 2868, 1671, 1510, 1415–1390, 1240, 1115, 1090, 1010, 923, 840, 754, 641. ^{1}H-NMR ($CDCl_3$, δ, ppm): 1.73–1.77 (d, $J = 6.9$, 3H, CH_3); 4.10–4.16 (m, 9H, Fc); 5.07–5.17 (q, 1H, CH); 6.86 (s, 1H, CH); 6.96 (s, 1H, CH); 7.44 (s, 1H, CH).

2.4. Ferrocenyl(butyl)imidazole (**2c**)

Yield: 78%. Dark brown oil, MS *m*/*z* (%): 308 (100) $[M]^+$. IR (KBr, ν, cm^{-1}): 3109, 2972, 2885, 1692, 1511, 1425, 1292, 1174, 1118, 1090, 1040–1020, 923, 835, 754. ^{1}H-NMR ($CDCl_3$, δ, ppm): 0.93 (m, 3H, CH_3); 1.15 (m, 2H, CH_2); 2.00 (m, 2H, CH_2); 4.05–4.15 (m, 9H, Fc); 4.92 (t, 1H, CH); 6.89 (s, 1H, CH); 7.01 (s, 1H, CH); 7.52 (s, 1H, CH).

2.5. Ferrocenyl(benzyl)imidazole (**2d**)

Yield: 82%. Yellow crystals, m.p. 91–92 °C, MS *m*/*z* (%): 342 (75) $[M]^+$. IR (KBr, ν, cm^{-1}): 3111, 2944, 2872, 1518, 1472, 1140, 1123, 1015, 927, 840, 740–710. ^{1}H-NMR ($CDCl_3$, δ, ppm): 4.10–4.25 (m, 9H, Fc); 6.15 (s, 1H, CH); 6.82 (s, 1H, CH); 7.05 (s, 1H, CH); 7.14–7.30 (m, 5H, Ph); 7.45 (s, 1H, CH).

2.6. Ferrocenyl(iso-propyl)imidazole (**2e**)

Yield: 80%. Yellow crystals, m.p. 104–105 °C, MS *m*/*z* (%): 294 (23) $[M]^+$. IR (KBr, ν, cm^{-1}): 3118, 3090, 3011, 1510, 1482, 1398, 1380, 1281, 1215, 1116, 1087, 1010, 910, 850, 830–815, 724, 510, 482. ^{1}H-NMR ($CDCl_3$, δ, ppm): 1.45 (s, 6H, CH_3), 4.10–4.19 (m, 9H, Fc); 6.89 (s, 1H, CH); 6.93 (s, 1H, CH); 7.38 (s, 1H, CH).

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