A novel ferrocenylalkylating reagent. Ferrocenylalkylation of imidazole and its derivatives

V. V. Gumenyuk, Zh. V. Zhilina, Yu. S. Nekrasov, V. N. Babin, and Yu. A. Belousov*

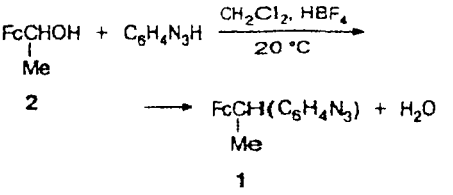
A. N. Nesmeyanov Institute of Organoelement Compounds, Russian Academy of Sciences, 28 ul. Vavilova, 117813 Moscow, Russian Federation.
Fax: 007 (095) 135 5085. E-mail: yusnekr@ineos.ac.ru

Reactions of α-(1-benzotriazolyl)ethylferrocene (**1**) with 1,2,4-triazole, imidazole, benzimidazole, and adenine have been studied in the MeOH—HCl, MeOH, and AcOH systems. Compound **1** is a novel ferrocenylalkylating reagent which, unlike α-hydroxyalkylferrocenes, is capable of alkylating imidazole, benzimidazole (even in the absence of an acid catalyst), and adenine (regioselectively at the N(3) position). The antitumor activity discovered for ferrocenylalkylazoles of the type **1** may be attributed to the ability of such compounds to ferrocenylalkylate nucleic bases.

Key words: α-(1-benzotriazolyl)ethylferrocene, ferrocenylalkylazoles; benzotriazole, imidazole, benzimidazole, adenine, ferrocenylalkylation.

Reaction of ferrocenylalkylation using α-hydroxyalkylferrocenes in aqueous-organic media catalyzed by fluoroboric acid is one of the most convenient methods of introduction of ferrocenylalkyl group into various nucleophilic substrates. In particular, mono- and binuclear ferrocenylalkylazoles exhibiting antitumor activity, as well as ferrocenylalkyl DNA derivatives, were synthesized by this method.[1,2] At the same time, attempts at direct ferrocenylalkylation of imidazole (ImH) under these conditions have failed. Replacement of α-hydroxyalkylferrocenes by an alternative alkylating agent, the $[FcCH(Me)NMe_3]^+I^-$ salt, also does not give any satisfactory results.[3,4] Ferrocenylalkylation of benzimidazole (BimH) and adenine (AdH) proceeds with difficulty to give the products in low yields.[5,6] Under conditions of acid catalysis this fact is explained, probably, by the comparatively high basicity of imidazoles. Sometimes the influence of this factor can be decreased by increasing the temperature and using either an acid excess, or modified nucleophiles.[3] The goal of this work is to search for novel ferrocenylalkylating agents which are capable of alkylating highly basic azoles without acid catalysis.

It is well known[7] that some aralkylbenzotriazoles make it possible to introduce an aralkyl moiety into various molecules. Therefore, it was quite reasonable to use for the same purpose organometallic analogs, ferrocenylalkylbenzotriazoles, which we synthesized earlier.[1] In particular, α-(1-benzotriazolyl)ethylferrocene (**1**) is stable in the air, very soluble in most organic solvents, and can be rapidly (for 5 min) prepared from the corresponding α-hydroxyethylferrocene (**2**) in quantitative yield by reaction with benzotriazole in methylene chloride in the presence of aqueous HBF_4.



2 → **1**

Product **1** is easily crystallized from ether and can be used without additional purification.

When compound **1** is used as the ferrocenylalkylating agent in the reaction with 1,2,4-triazole (*s*-TrH), α-(1-triazolyl)ethylferrocene (**3**) is formed under the same conditions of the two-phase system (see Table 1). However, we failed to carry out this reaction with imidazole and adenine under similar conditions. Only α-ferrocenylethyl derivative of benzimidazole **4** was obtained in small yield; the yield of **4** increased, to a certain extent, when the reaction temperature increased (see Table 1 and Experimental).

At the same time imidazole and adenine react with compound **1** under more drastic conditions. The syntheses of α-(imidazolyl)ethylferrocene (**5**) and α-(3-adenyl)ethylferrocene **6** are carried out in glacial acetic acid (or concentrated HCl in methanol) under reflux for 1.5—3 h.

The crucial result is the ferrocenylalkylation of benzimidazole without acid catalyst (although in a low yield, 7—8%). The reaction was carried out by refluxing a benzimidazole solution with compound **1** in methanol.

Earlier we reported[8] that alkylation of adenine with α-hydroxyethylferrocene **2** in a $H_2O—CH_2Cl_2$ system in the presence of fluoroboric acid proceeds ambiguously to form a mixture of mono- and binuclear products.[8] In

Translated from *Izvestiya Akademii Nauk. Seriya Khimicheskaya*, No. 1, pp. 172—174, January, 1997.

1066-5285/97/4601-0168 $18.00

Table 1. Conditions for the synthesis of α-(*N*-azolyl)ethylferrocenes FcCH(Me)Az

Ferrocenyl-alkylating agent (FA)	Heterocycle (AzH)	Acid (Cat)	FA : AzH : Cat	Reaction conditions		Reaction product (yield (%))
				T/°C	*t*/min	
1	*s*-TrH	HBF_4	1 : 1 : 1	20	5	**3** (42)
1	ImH	HCl	1 : 2 : 2	Refluxing	180	**5** (30)
1	ImH	AcOH	1 : 1	The same	75	**5** (20)
1	BimH	HBF_4	1 : 1 : 1	20	10	**4** (5)
1	BimH	HBF_4	1 : 1 : 1	40	15	**4** (20)
1	BimH	AcOH	1 : 1	Refluxing	75	**4** (25)
1	BimH	—	1 : 1	The same	90	**4** (7)
1	AdH	HCl	1 : 2 : 2	The same	180	**6** (12)
2	AdH	HBF_4	1 : 1 : 1	20	10	**7** (20) + + **8** (5)

particular, 3-ferrocenylethyl derivative of adenine **7** was isolated in the form of hydrotetrafluoroborate in small yield (~20%). Biferrocenylethyl adenine derivative **8** was obtained in lower yield. The novel ferrocenylalkylating agent **1** makes it possible to carry out selective ferrocenylethylation of adenine at the 3* position (see Table 1 and Experimental).

Therefore, the results obtained indicate that α-(1-benzotriazolyl)ethylferrocene is a novel ferrocenylalkylating reagent and, unlike α-hydroxyethylferrocene, it is capable of alkylating imidazole, benzimidazole (even without a catalyst), and adenine (regioselectively at the position N(3)). These data suggest that the antitumor activity discovered in ferrocenylalkylazoles of the **1** type may be attributed, to a certain extent, to their ability to ferrocenylalkylate nucleic acid bases.[2]

Experimental

^{1}H NMR spectra were recorded on a Bruker-200-WP (200 MHz) instrument with $SiMe_4$ used as the external standard. Mass spectra were obtained on a Kratos MS-890 mass spectrometer (70 eV).

α-[1-(1,2,4-Triazolyl)]ethylferrocene (3). Compound **1** (0.166 g, 0.5 mmol) was added to a suspension of 1,2,4-triazole (0.03 g, 0.5 mmol) in 4 mL of freshly distilled CH_2Cl_2 with stirring; to the resulting mixture 0.2 mL of 38% HBF_4 was then added with stirring. Five minutes later the mixture was treated with 10 mL of Et_2O and 10 mL of H_2O. The organic fraction was separated and washed with water to neutral pH value, and the solvent was removed in air. The residue was dissolved in CH_2Cl_2 and chromatographed on a column packed with Al_2O_3 (CH_2Cl_2 as the eluent). After removal of the solvent the residue was dried *in vacuo* to give compound **3** (0.06 g) in the form of a dark yellow viscous oil. ^{1}H NMR (acetone-d_6), δ: 8.28, 7.75 (both s, 1 H each, heterocycle); 5.45 (m, 1 H, CH); 4.18 (s, 5 H, Cp unsubstituted); 3.80—4.40 (group of signals, Cp substituted); 1.7 (d, 3 H, CH_3). MS, *m/z*: 281 $[M]^+$.

α-(1-Benzimidazolyl)ethylferrocene (4). *A.* Compound **1** (0.17 g, 0.5 mmol) was added to a suspension of benzimidazole (0.059 g, 0.5 mmol) in 3 mL of freshly distilled CH_2Cl_2 with stirring; to the resulting mixture 0.2 mL of 38% HBF_4 was then added, and the mixture stirred for 10 min; α-(1-benzimidazolyl)ethylferrocene was isolated by a procedure similar to that described above (CH_2Cl_2—MeOH (6 : 1) as the eluent). Compound **4** (0.0083 g) was obtained in the form of an orange oil. ^{1}H NMR (acetone-d_6), δ: 8.01 (s, 1 H, C(2)H of heterocycle); 7.63, 7.22 (both m, 2 H each, C_6H_4 of heterocycle); 5.78 (q, 1 H, CH); 4.54—3.91 (group of signals, 9 H, Cp); 1.98 (d, 3 H, CH_3). MS, *m/z*: 330 $[M]^+$.

B. Compound **4** was obtained from 0.059 g of benzimidazole and 0.17 g of compound **1** at 40 °C using the aforementioned procedure.

C. A mixture of benzimidazole (0.083 g, 0.7 mmol), compound **1** (0.23 g, 0.7 mmol), and 2 mL of glacial acetic acid was refluxed for 75 min under argon and then neutralized with 7 mL of a 50% KOH solution in water. After treatment with Et_2O (2×10 mL) and a Et_2O—CH_2Cl_2 mixture (3 : 1), the organic fraction was separated and the solvent was removed. The residue was chromatographed on a column packed with Al_2O_3 (CH_2Cl_2—MeOH (6 : 1) as the eluent). After removal of the solvent the residue of compound **4** was dried. MS, *m/z*: 330 $[M]^+$.

D. A solution of benzimidazole (0.18 g, 1 mmol) in 2 mL of MeOH was added to a solution of compound **1** (0.331 g, 1 mmol) in 6 mL of MeOH. The resulting mixture was refluxed for 1.5 h under argon and chilled; the solvent was then removed, and the residue was chromatographed on a column packed with Al_2O_3 (CH_2Cl_2 as the eluent). After removal of the solvent, the residue was dried to give 0.026 g of compound **4**. MS, *m/z*: 330 $[M]^+$.

α-(1-Imidazolyl)ethylferrocene (5). *A.* Reaction of imidazole (0.048 g, 0.7 mmol), compound **1** (23 g, 0.7 mol), and 2 mL of glacial acetic acid was carried under argon using procedure *C* (see synthesis of compound **4**), a CH_2Cl_2—MeOH mixture (4 : 1) as the eluent. After removal of the solvent and drying the residue, compound **5** (0.04 g) was obtained in the form of a dark-yellow oily material. ^{1}H NMR (acetone-d_6), δ : 7.45, 7.07, 6.83 (all s, 1 H each, heterocycle); 5.35 (m, 1 H, CH); 4.24—4.69 (group of signals, 9 H, Cp); 1.79 (d, 3 H, CH_3). MS, *m/z*: 280 $[M]^+$.

B. Compound **1** (0.331 g, 1 mmol) was dissolved with heating in 6 mL of MeOH, and a solution of imidazole

* Characterization of this compound as 3-adenine derivative based on its ^{1}H NMR spectra (by the value $|\Delta\delta|$ between the signals of the purine protons C(2)H and C(8)H by analogy with alkyl and aralkyl isomers of adenine[9,10]).

(0.136 g, 2 mmol) in 6 mL of H_2O and 0.18 mL of conc. HCl were added. The resulting mixture was refluxed for 2.5 h, neutralized with a 10% solution of alkali (10 mL), and treated with Et_2O (3×20 mL). The organic layer was separated, the solvent was evaporated on air and the residue was chromatographed on a column packed with Al_2O_3 (MeOH as the eluent). After drying, compound **5** was obtained (0.085 g). MS, m/z: 280 $[M]^+$.

α-(3-Adenyl)ethylferrocene (6). Compound **6** ((0.021 g) was synthesized from compound **1** (0.166 g, 0.5 mmol) in 3 mL of MeOH, adenine (0.135 g, 1 mmol) in 6 mL of H_2O, and 0.18 mL of conc. HCl by a procedure similar to the previous one (see the synthesis of compound **5**, procedure ***B***). Compound **6** was obtained in the form of a yellow solid, m.p. 180—182 °C (decomp.). MS, m/z: 347 $[M]^+$. ^1H NMR (C_6D_6), δ: 8.79, 7.50 (both s, 1 H each, adenine); 5.67 (m, 1 H, CH); 3.92 (s, 5 H, Cp unsubstituted); 4.08—4.44 (group of signals, Cp substituted); 1.54 (d, 3 H, CH_3). ^1H NMR (CD_3CN), δ: 8.22, 7.88 (both s, 1 H each, adenine); 5.70 (m, 1 H, CH); 4.18 (s, 5 H, Cp unsubstituted); 4.08—4.44 (group of signals, Cp substituted); 1.95 (d, CH_3) (this signal and that of CD_3CN overlap).

Interaction of adenine with α-hydroxyethylferrocene (2). α-Hydroxyethylferrocene (0.23 g, 1 mmol) was added to a suspension of 0.135 g (1 mmol) of adenine in 2 mL of freshly distilled anhydrous CH_2Cl_2 under argon with vigorous stirring. Fluoroboric acid (38%) (0.4 mL) was then added, and the reaction mixture was stirred for additional 5 min and treated with 10 mL of Et_2O and 10 mL of H_2O. The organic layer was washed with water to pH 5—6; after removal of the solvent, was chromatographed on a column packed with Al_2O_3 (CH_2Cl_2 as the eluent). **6,9-Di(ethylferrocenyl)adenine (8)** was obtained in the form of a light-yellow solid, m.p. 72—75 °C (from ether). MS, m/z: 559 $[M]^+$. ^1H NMR (acetone-d_6), δ: 8.25, 8.66 (both s, 2 H, C(2)H, C(8)H); 7.0 (d, 1 H, N—H); 6.1 (q, 1 H, CH); 5.73 (br, 1 H, CH); 4.52, 4.56 (both s, 10 H, Cp unsubstituted); 4.45—5.0 (group of signals, Cp substituted); 2.35, 1.77 (both d, 3 H each, CH_3). **α-(3-Adenyl)ethylferrocene hydrotetrafluoroborate (7)** was eluted with an acetone—water mixture (1 : 1). After removal of the solvent product **7** was obtained in the form of a yellow solid. Found (%): C, 47.21; H, 4.19; N, 16.00. $C_{17}H_{18}BF_4FeN_5$. Calculated (%): C, 46.90; H, 4.14; N, 16.09. ^1H NMR (acetone-d_6), δ: 8.6, 8.32 (both s, 1 H each, C(8)H, C(2)H); 6.93 (br, 2 H, NH_2); 6.1 (m, 1 H, CH); 4.68—4.89 (group of signals, 9 H, Cp); 2.63 (d, 3 H, CH_3). The water layer was neutralized with an aqueous solution of NH_4OH and treated with EtOH. The organic layer was separated. After removal of the solvent the residue was dried over $CaCl_2$ in a desiccator to afford a yellow solid — **α-(3-adenyl)ethyl)ferrocene (6)**, m.p. 181—183 °C (decomp.). ^1H NMR (C_6D_6), δ: 8.82, 7.55 (both s, 1 H each, adenine); 5.69 (m, 1 H, CH); 3.99 (s, 5 H, Cp unsubstituted); 3.6—4.0 (group of signals, Cp substituted); 1.55 (d, 3 H, CH_3).

References

1. N. S. Kochetkova, V. I. Boev, L. V. Popova, and V. N. Babin, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1985, 1397 [*Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 1985, **34**, 1278 (Engl. Transl.)].
2. V. N. Babin, P. M. Raevskii, K. G. Shchitkov, L. V. Snegur, and Yu. S. Nekrasov, *Zh. Ross. Khim. Obshch. im. D. I. Mendeleeva*, 1995, **39**, 19 [*Mendeleev. Chem. J.*, 1995, **39**, 17 (Engl. Transl.)].
3. V. I. Boev, D. Sci. (Chem.) Thes., Lipetsk State Ped. Inst., Lipetsk, 1993.
4. L. V. Snegur, Ph. D. (Chem.) Thes., INEOS RAN, Moscow, 1993.
5. V. I. Boev, P. M. Betankourt, L. V. Popova, and V. N. Babin, *Zh. Obshch. Khim.*, 1991, **61**, 1651 [*J. Gen. Chem. USSR*, 1991, **61** (Engl. Transl.)].
6. Shi-Chow Chen, *J. Organomet. Chem.*, 1980, **202**, 183.
7. A. R. Katritzky and X. Lan, *Chem. Soc. Rev.*, 1994, **23**, 363.
8. V. V. Gumenyuk, Zh. V. Zhilina, L. V. Snegur, and V. N. Babin, *Tez. VI Vseross. konf. po metalloorganicheskoi khimii* [*VI All-Russian Conf. on Organometallic Chem., Abstrs.*], Nizhnii Novgorod, 1995, Part 2, 373 (in Russian).
9. L. B. Townsend, R. K. Robins, R. N. Loeppky, and N. J. Leonard, *J. Am. Chem. Soc.*, 1964, **86**, 5320.
10. A. E. Beasley and M. Rasmussen, *Aust. J. Chem.*, 1981, **34**, 1107.

Received July 5, 1996;
in revised form October 30, 1996