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Synthesis of cyanohydrin trimethylsilyl ethers of diacylferrocences

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The addition of trimethylsilyl cyanide (TMSCN) to diacylferrocenes [Fc $(COR)_2$] (R = Me, Et, Ph, *p*-ClC_6H_4, *m*-ClC_6H_4, *o*-ClC_6H_4, *p*-$MeOC_6H_4$, Fc = $C_5H_4FeC_5H_4$), catalysed by zinc iodide an acetonitrile provided the corresponding cyanohydrin trimethylsilyl ethers in moderate to high yields. Factors affecting the reaction and yields of adducts were investigated. In addition, the adduct of 1,1′-diacetylferrocene was structurally determined by X-ray crystallography.

Keywords: diacylferrocene, trimethylsilylcyanation, cyanohydrin trimethlysilyl ether

The development of practical technology for the preparation of cyanohydrins, α,β-unsaturated nitriles and β-aminoalcohols from readily-available carbonyl compounds is an important area in organic chemistry.[1] One straightforward method for synthesising such compounds makes use of cyanohydrin trimethylsilyl ethers, which are generally prepared by the addition of trimethylsilyl cyanide (TMSCN)[2] to carbonyl compounds in the presence of catalysts[3] commonly used in asymmetric synthesis.[4]

The synthesis of cyanohydrin trimethylsilyl ethers of monoacylferrocenes, as reported recently by our research group,[5] was catalysed by ZnI_2 and used CH_2Cl_2 as a solvent, but required a longer period of time. In this paper, we describe the cyanosilylation of diacylferrocenes via the addition of trimethylsilyl cyanide to various diacylferrocenes catalysed by ZnI_2 in CH_2Cl_2 or CH_3CN (Scheme 1),[6] with the finding that switching the solvent to CH_3CN leads to a reduction of the reaction time. Moreover, factors affecting the reaction and yields of adducts are discussed. The crystal structure of compound **3a** has been determined by single-crystal X-ray analysis.

Experimental

General

Melting points were obtained with an XT7-4 apparatus and are uncorrected. ^1H NMR spectra were recorded in $CDCl_3$ solutions on Bruker DRX-500 spectrometer with Me_4Si as internal standard. IR spectra were recorded on a NEXUS-670FT-IR spectrophotometer using KBr pellets. Elemental analyses were carried out on Perkin-Elemer-2400 analyser. X-ray analysis was performed on Bruker Smart CCD area detector. Silica gel (60H) plates and alkaline Al_2O_3 (100–200 mesh) were used for analytical TLC and for column chromatography, respectively. TMSCN and diacylferrocenes[7] were prepared according to literature methods. ZnI_2 and $BiCl_3$ were oven-dried at 120°C overnight. Dry CH_3CN and CH_2Cl_2 were distilled from P_2O_5. All other solvents and reagents were obtained from commercial sources and used without further purification.

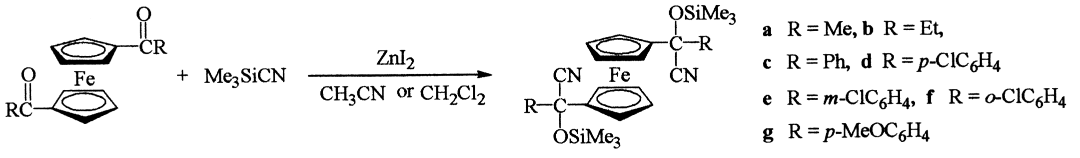
General procedure for the synthesis of **3a–3g**

Into a 100 ml 3-neck round-bottomed flask equipped with magnetic stirrer, reflux condenser and $CaCl_2$ drying tube was placed diacylferrocene (0.5 g, 1.1–0.76 mmol) in dry CH_2Cl_2 or CH_3CN and ZnI_2 (0.05–0.1 mmol). After stirring for 20 min, TMSCN (4.4–12.2 mmol) was added. The resulting solution was stirred under the conditions given in Table 1. The progress of the reaction was monitored by TLC. On completion, workup was as follows.

In the case of CH_2Cl_2 as solvent, the colour of the reaction mixture changed from deep red to dark blue. After concentrating the solvent under reduced pressure, the residue was purified by alkaline Al_2O_3 column chromatography using petroleum ether (60–90°C) as eluent. Further purification was achieved by recrystallisation from petroleum ether.

Using CH_3CN as the solvent, the solid crude product that precipitated from solution was filtered under pressure, followed by recrystallisation to produce the desired pure product.

3a: Yellow crystals, m.p. 84–85°C. IR (KBr) ν 3108 (Fc, CH), 2236 (C≡N), 1254, 841 ($SiCH_3$) cm^{-1}; ^1H NMR ($CDCl_3$, 500MHz)



1 **2** **3**

Scheme 1

Table 1 Influence of substrates and reaction conditions on the addition

		Reaction conditions					
		Ratio (**1a–g:2**)	Solvent	Time/h	Temperature/°C	Inversion/%	Yield/%
1a		1:4	CH_2Cl_2	22	rt	60	72.8
1a		1:5	CH_3CN	4	rt	9*9	76.2
1b		1:5	CH_3CN	4	rt	99	77.1
1b		1:5	CH_2Cl_2	9	rt	75	47.8
1b		1:8	CH_2Cl_2	16	rt	80	49.4
1c		1:10	CH_3CN	4.5	rt	99	61.2
1c		1:15	CH_3CN	2	rt	99	69.8
1d	*p*-ClPh	1:10	CH_3CN	4	rt	99	71.4
1e	*m*-ClPh	1:10	CH_3CN	4	50	99	69.6
1e		1:15	CH_3CN	11	50	80	57.4
1f		1:15	CH_2Cl_2	24	reflux	65	47.3
1g		1:10	CH_3CN	5	rt	99	56.2
		1:10	CH_2Cl_2	9	rt	90	45.0

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δ 0.16 (s, 18H, $Si(CH_3)_3$), 1.94 (s, 6H, CH_3), 4.41, 4.57 (2s, br, 8H, ferroceneyl-H). Calc. for $C_{22}H_{32}FeN_2O_2Si_2$: C, 56.4; H, 6.9; N, 6.0. Anal. Found: C, 56.4; H, 7.3; N, 5.6%.

3b: Yellow crystals, m.p. 52–54°C. IR (KBr) ν 3102 (Fc, CH), 2234 (C≡N), 1253, 843 ($SiCH_3$) cm^{-1}; ^1H NMR ($CDCl_3$, 500MHz) δ 0.15 (s, 18H, $Si(CH_3)_3$), 1.08 (q, 6H, CH_2CH_3), 2.05–2.18 (m, 4H, CH_2CH_3), 4.31, 4.34, 4.36, 4.48, 4.50 (5s, 8H, ferroceneyl-H). Calc. for $C_{24}H_{36}FeN_2O_2Si_2$: C, 58.1; H, 7.3; N, 5.6. Anal. Found: C, 58.3; H, 7.4; N, 5.3%.

3c: Yellow crystals, m.p. 137–139°C. IR (KBr) ν 3081 (Fc, CH), 2230 (C≡N), 3063 (Ar, CH); 1253, 839 ($SiCH_3$) cm^{-1}; ^1H NMR ($CDCl_3$, 500MHz) δ 0.11 (s, 18H, $Si(CH_3)_3$), 7.35–7.71 (m, 10H, Ar), 4.37, 4.52, 4.65, 4.76, 5.01 (5s, 8H, ferroceneyl-H). Calc. for $C_{32}H_{36}FeN_2O_2Si_2$: C, 64.8; H, 6.1; N, 4.7. Anal. Found: C, 64.6; H, 6.4; N, 4.8%.

3d: Orange crystals, m.p. 144–146°C. IR (KBr) ν 3089 (Fc, CH), 2238 (C≡N), 3053 (Ar, CH); 1253, 845 ($SiCH_3$) cm^{-1}; ^1H NMR ($CDCl_3$, 500MHz) δ 0.16 (s, 18H, $Si(CH_3)_3$), 3.99, 4.16, 4.27, 4.35, 4.48, 4.56 (6s, 8H, ferroceneyl-H), 7.36, 7.51 (2d, *J* = 7.25Hz, 8H, Ar). Calc. for $C_{32}H_{34}Cl_2FeN_2O_2Si_2$: C, 58.1; H, 5.2; N, 4.2. Anal. Found: C, 58.0; H, 5.3; N, 4.3%.

3e: Orange crystals, m.p. 136–138°C. IR (KBr) ν 3104 (Fc, CH), 2241 (C≡N), 3058 (Ar, CH); 1254, 845 ($SiCH_3$) cm^{-1}; ^1H NMR ($CDCl_3$, 500MHz) δ 0.17 (s, 18H, $Si(CH_3)_3$), 4.04, 4.20, 4.30, 4.37, 4.50, 4.57 (6s, 8H, ferroceneyl-H), 7.32–7.54 (m, 8H, Ar). Calc. for $C_{32}H_{34}Cl_2FeN_2O_2Si_2$: C, 58.1; H, 5.2; N, 4.2. Anal. Found: C, 57.6; H, 5.2; N, 4.4%.

3f: Orange crystals, m.p. 134–136°C. IR (KBr) ν 3097 (Fc, CH), 2234 (C≡N), 3061 (Ar, CH); 1254, 846 ($SiCH_3$) cm^{-1}; ^1H NMR ($CDCl_3$, 500MHz) δ 0.19 (s, 18H, $Si(CH_3)_3$), 4.46, 4.70 (2s, br, 8H, ferroceneyl-H), 7.32, 7.39, 7.78 (3s, 8H, Ar). Calc. for $C_{32}H_{34}Cl_2FeN_2O_2Si_2$: C, 58.1; H, 5.2; N, 4.2. Anal. Found: C, 57.9; H, 5.1; N, 3.9%.

3g: Orange crystals, m.p. 140–142°C. IR (KBr) ν 3100 (Fc, CH), 2241 (C≡N), 3053 (Ar, CH); 1251, 844 ($SiCH_3$) cm^{-1}; ^1H NMR ($CDCl_3$, 500MHz) δ 0.14 (s, 18H, $Si(CH_3)_3$), 3.83 (s, 6H, OCH_3), 4.05, 4.26, 4.36, 4.58 (4s, 8H, ferroceneyl-H), 6.88, 7.49 (2d, *J* = 8.75Hz, 8H, Ar), Calc. for $C_{34}H_{40}FeN_2O_4Si_2$: C, 62.6; H, 6.1; N, 4.3. Anal. Found: C, 62.5; H, 6.5; N, 4.0%.

Single crystal X-ray diffraction analysis of 3a

Single crystal X-ray diffraction measurement of compound **3a** was carried out with a Bruker Smart 1000 CCD area detector at 293 (2) K. The determination of unit-cell parameters and data collection were performed with Mo Kα radiation (λ = 0.71073 A). The structure was solved by direct method and refined by full-matrix least-squares on F^2 with SHELXL-97. All non-hydrogen atoms were refined with anisotropic displacement parameters. Crystal data and experiment details for structure analysis are summarised in Table 2.

Table 2 Crystal data and structural refinement for compounds **3a** and **3g**

Compound	**3a**
Empirical formula	$C_{22}H_{32}FeN_2O_2Si_2$
Formula weight	468.53
Crystal system,	Orthorhombic,
Space group	Pna2(1)
a(Å)	20.715(9)
b(Å)	6.440(3)
c(Å)	18.411(8)
α(°)	90
β(°)	90
γ(°)	90
Z	4
V($Å^3$)	2456.0(19)
Calculated density (Mg/m_3)	1.267
Absorption coefficient (mm^{-1})	0.731
F(000)	992
θ range for data collection (°)	1.97–25.00
Limiting indices	–20≤h≤24, –7≤k≤4, –21≤l≤18
Reflections collected/unique	9746/3949 [R(int) = 0.0416]
Max. and min. transmission	1.000000 and 0.772322
Data/restraints/parameters	3949/1/263
Goodness-of-fit on F^2	1.067
Final R indices [*I*>2sigma(I)] R_1, wR_2	0.0485, 0.0866
R indices (all data) R_1, wR_2	0.0695, 0.0943
Largest diff. peak and hole (e. $Å^{-3}$)	0.361, −0.277

Results and discussion

Factors affecting the reaction

To increase the yield and shorten the reaction time in the TMSCN addition to carbonyl compounds, we investigated the influence of suitable solvent, temperature and the ratio of reactants. Furthermore, we also discussed the steric and electronic effects.

Selection of solvent

We investigated the influence of different solvents on the reaction through the comparison of parallel experiments with different combinations, and obtained the results shown in Table 1. Apparently, there is a shorter reaction time and higher yield of the adducts in ZnI_2–CH_3CN than in ZnI_2–CH_2Cl_2. So we chose the ZnI_2–CH_3CN group as our catalyst system.

The use of a particular solvent can affect the Gibbs energy of reagents and transition state of a reaction.[8] Since a solvent may affect the rates of two competing reaction in different ways, a change in solvent may strongly modify the composition of a product mixture formed from competing reaction paths. In our reaction, we tested for a change in solvent polarity and found that the highly polar solvent CH_3CN was more suitable for catalyst ZnI_2 in the cyanosilylation of diacylferrocene. The solvent effect also offered some theoretical justification for a reasonable reaction mechanism.

TMSCN/substrate ratio and temperature

In order to conduct the reaction smoothly, TMSCN has to be in excess (Table 1). We also found that an excessive amount of TMSCN not only led to a higher yield of the target product but also shortened the reaction time for the same substrate. For instance, changing the ratio of TMSCN from 10:1 to 15:1 resulted in increasing the yield for **3c** from 61.2 to 69.8% (invested >99%). At the same time, the reaction time was shortened from 4.5h to 2h. In addition, the substrates of large steric hindrance need more TMSCN than those of less steric hindrance. Only **1e** and **1f** with large hindrance need a higher reaction temperature, and the other compounds with less steric hindrance were performed at room temperature.

Influence of steric and electronic effect

It is important to point out that the steric and electronic effects are the main influence factors in the addition of carbonyl. The bigger the volume of the substrate, the more steric hindrance near the carbonyl group appears, and the addition of carbonyl is more difficult. As is shown in Table 1, the reaction activity and yield are high when the substrate bears a less bulky group as in **1a** (R = CH_3) and **1g** (R = CH_2CH_3). With the steric hindrance increasing in the sequence **1f** > **1e** > **1d**, the reaction rate decreases in the same sequence. For example, treatment of **1d** at room temperature for 4h gave **3d** in 71.4% yield. But when **1f** was treated at 50°C for 11h, product **3f** was obtained only in 57.4% yield in the same solvent. Compound **1e** also needs a raise in the reaction temperature. Obviously, the higher steric hindrance of an acyl residue, the more difficult is the addition reaction.

The electronic effect is more significant than steric hindrance for three compounds **1c**, **1d** and **1g**, which have alike structures but different electronic effects. Compound **1d** has an electron withdrawing group (*p*-Cl) and **1c** without substrate, while **1g** bears an electron donating group (*p*-MeO). An electron donating group decreases the electrophilicity of the C=O carbon atom and deactivates the addition reaction, while on the contrary, an electron withdrawing group increases the electrophilicity of the C=O carbon atom and facilitates the reaction. These expectation are confirmed by the experiment (see Table 1).

X-ray structure analysis of 3a

To firmly establish the structures of the new compounds **3a–g**, X-ray crystallographic analysis of compound **3a** was carried out. Selected bond distances and angles are given in Table 3. The molecular structure is shown in Fig 1. The substituting groups of ferrocene lie on its two sides due to the steric hindrance. The bond angles of N(2)–C(18)–C(17) and N(1)–C(7)–C(6) both close to 180°, shows sp hybridisation for the C≡N carbon atoms. Moreover, because of the influence of neighbouring Csp^2 and Csp atoms, the bond distances of C(1)–C(6), C(6)–C(7), C(12)–C(17) and C(17)–C(18) (See Table 3) are shorter than those of normal bond distance of C–C(1.54Å).

Table 3 Selected bond distances (Å) and angles (°) of **3a**

Fe(1)–C(2)	2.033(5)	Fe(1)–C(14)	2.051(6)	Si(2)–O(2)	1.666(5)	O(2)–C(17)	1.421(7)
Fe(1)–C(5)	2.035(6)	Fe(1)–C(4)	2.052(5)	Si(2)–C(22)	1.837(9)	C(1)–C(6)	1.521(7)
Fe(1)–C(1)	2.036(5)	Fe(1)–C(15)	2.055(5)	Si(2)–C(20)	1.858(7)	C(6)–C(6)	1.478(8)
Fe(1)–C(16)	2.036(7)	Si(1)–O(1)	1.667(5)	Si(2)–C(21)	1.889(9)	C(6)–C(8)	1.532(7)
Fe(1)–C(12)	2.045(5)	Si(1)–C(9)	1.820(10)	N(1)–C(7)	1.143(7)	C(12)–C(17)	1.513(7)
Fe(1)–C(13)	2.045(5)	Si(1)–C(10)	1.849(6)	N(2)–C(18)	1.139(7)	C(17)–C(18)	1.511(8)
Fe(1)–C(3)	2.047(6)	Si(1)–C(11)	1.876(8)	O(1)–C(6)	1.440(7)	C(17)–C(19)	1.528(7)
C(2)–Fe(1)–C(1)	40.70(19)	O(1)–Si(1)–C(9)	109.1(4)	C(22)–Si(2)–C(21)	110.1(5)	N(1)–C(7)–C(6)	1.786(7)
C(5)–Fe(1)–C(1)	41.1(2)	O(1)–Si(1)–C(10)	112.0(3)	C(20)–Si(2)–C(21)	110.3(4)	O(2)–C(17)–C(18)	104.4(4)
C(16)–Fe(1)–C(12)	40.6(2)	C(9)–Si(1)–C(10)	110.7(3)	C(6)–O(1)–Si(1)	132.0(3)	O(2)–C(17)–C(12)	112.1(4)
C(12)–Fe(1)–C(13)	40.83(19)	O(1)–Si(1)–C(11)	104.2(3)	C(17)–O(2)–Si(2)	132.3(3)	C(18)–C(17)–C(12)	107.8(4)
C(2)–Fe(1)–C(3)	41.00(19)	C(9)–Si(1)–C(11)	110.3(4)	O(1)–C(6)–C(7)	104.4(4)	O(2)–C(17)–C(19)	111.5(4)
C(13)–Fe(1)–C(14)	40.29(18)	C(10)–Si(1)–C(11)	110.4(3)	O(1)–C(6)–C(1)	112.4(5)	C(18)–C(17)–C(19)	107.1(5)
C(5)–Fe(1)–C(4)	40.8(2)	O(2)–Si(2)–C(22)	102.3(3)	C(7)–C(6)–C(1)	108.9(4)	C(12)–C(17)–C(19)	113.4(4)
C(3)–Fe(1)–C(4)	39.8(3)	O(2)–Si(2)–C(20)	112.1(3)	O(1)–C(6)–C(8)	109.0(4)	N(2)–C(18)–C(17)	178.6(7)
C(16)–Fe(1)–C(15)	40.3(3)	C(22)–Si(2)–C(20)	110.6(3)	C(7)–C(6)–C(8)	108.8(5)		
C(14)–Fe(1)–C(15)	40.2(2)	O(2)–Si(2)–C(21)	111.2(4)	C(1)–C(6)–C(8)	112.9(4)		

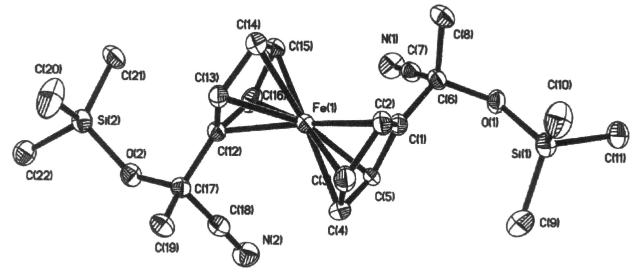

Fig.1 X-ray structure of **3a**.

Supplementary data

Full details of data collection and structure refinements have been deposited with the Cambridge Crystallographic Data Centre, CCDC No. 227070 for compound **3a**. Copies of this information may be obtained free of charge from The Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (www.ccdc.cam.ac.uk/conts/retrieving.html; fax: +44 1223 336033; e-mail: deposit@ccdc.cam.ac.uk)

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