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Synthesis of ferrocenoylphenylureas and the crystal structure of $FcCONHCONHC_6H_5$

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We replaced the benzoyl moiety by ferrocenoyl in benzoylphenylurea, and synthesized a series of new benzoylphenylureas containing a ferrocenyl moiety by the reaction of carbamylferrocene with phenylisocyanate in good yields. The title compounds were identified by IR, ^{1}H NMR spectroscopy, electron-impact mass spectrometry and elemental analyses. The crystal structure of 1-ferrocenoyl-3-phenylurea was determined. The bioactivities of the new compounds were also determined. Copyright © 2004 John Wiley & Sons, Ltd.

KEYWORDS: ferrocene; carbamylferrocene; benzoylphenylurea; bioactivity

INTRODUCTION

Since the discovery of a new insect stomach poison DU19111 in 1972,[1] a great number of benzoylphenylureas have been tested as potential insecticidal agents. The increasing importance of these compounds is connected with their mode of action, which affects only arthropod-specific biochemical processes.[2,3] Consequently, toxicity to vertebrates and environmental impact are very low and a high insecticidal selectivity is achieved. On the other hand, Okada *et al*.[4] reported antitumor activities of novel benzoylphenylurea derivatives, and one of them (coded HO-221) is presently under development for possible clinical use. HO-221 shows significant antitumor activities against various tumor models by oral administration, and is especially effective against solid tumor models.[5,6] Furthermore, HO-221 is free from cross-resistance to any known antitumor agents.[7] Its mode of action is reported to be the inhibition of DNA polymerase.[8]

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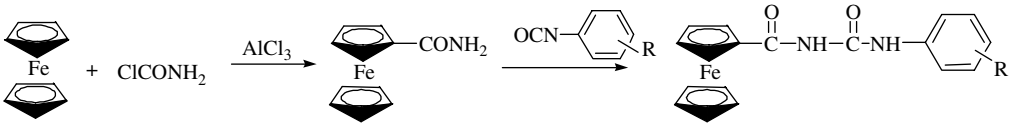
For many years, much interest has focused on ferrocenyl derivatives for their antitumor[9] and insecticidal activities.[10] Indeed, ferrocenyl groups have already been shown to replace phenyl moieties advantageously in biologically active compounds.[11,12] The substitution of a phenyl group by a ferrocenyl group in a bioactive compound was expected to induce great changes in molecular properties, such as the solubility and hydrophobicity.

Recently, our group has engaged in the incorporation of a ferrocene fragment into a molecule of organic compounds and obtained some biological compounds. For examples, *N*-*tert*-butyl-*N*′-ferrocenoyl-*N*-substituted benzoylhydrazines exhibit excellent larvicidal activities,[13,14] cyanoacrylates containing ferrocenyl moiety show good herbicidal activity[15] and 1-ferrocenecarboxysilatranes possess potential antibacterial activity.[16] In order to find new bioactive compounds, we present herein the synthesis, characterization, crystal structure and bioactivities of some ferrocenoyl-substituted phenylureas.

RESULTS AND DISCUSSION

Preparations

The reaction of ferrocene with carbamyl chloride in the presence of aluminum chloride affords carbamylferrocene in 72% yield, as shown in Scheme 1. Then, treatment of carbamylferrocene with phenylisocyanates in toluene under reflux results in ferrocenoyl-substituted phenylureas (**1**–**6**). All products



Scheme 1.

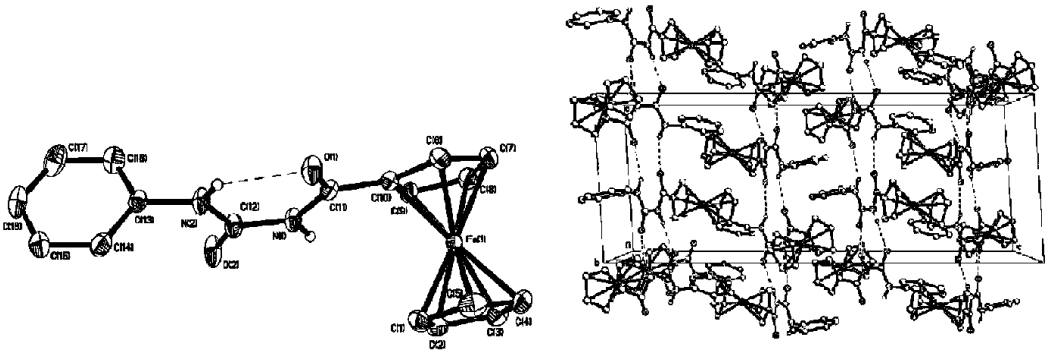


Figure 1. Molecular structure and cell structure of compound **1**.

1–**6** are coloured crystals and stable at room temperature and in air.

^{1}H NMR, IR and mass spectrometry

The title compounds **1**–**6** were characterized by ^{1}H NMR and elemental analyses. Compound **1** was also characterized by IR, electron-impact mass spectrometry (EI MS) and X-ray. The results are in accordance with the expected structures. Their ^{1}H NMR spectra are characteristic: the ferrocenyl substituent gives rise to a five-proton singlet for the nonsubsituted cyclopentadienyl ring and a double peak for the monosubstituted ring. The chemical shifts of two active hydrogen atoms are two singlet peaks in the downfield region at 8.29–11.36 ppm.

The IR spectra of compound **1** has been recorded in the range 400–4000 cm^{-1}. The characteristic bands of the ferrocenyl group in the IR spectra of compound **1** appear at 1151 and 1029 cm^{-1}. The strong absorption at 1670 cm^{-1} is the asymmetric vibration of C═O. The symmetric vibration of C═O is a medium peak at 1373 cm^{-1}. The MS spectra show that the molecular ion peak of compound **1** is $m/z = 348$ and the base peak is $m/z = 229$.

Crystal structure

An orange needle crystal of compound **1** was recrystallized from acetonitrile. Figure 1 shows the molecular and cell structures of compound **1** and gives the atom-numbering scheme. Selected bond distances and angles of the compound are listed in Table 1. From the crystal structure we find that the urea bridge forms a stable six-membered ring by an intermolecular hydrogen bond. This structure is similar to the uridine ring, which is in accord with the reported structure.[18]

Table 1. Selected bond lengths and angles of compound **1**

Bond lengths (Å)		Bond Angles (°)	
O(1)–C(11)	1.221(3)	C(11)–N(1)–C(12)	128.9(3)
O(2)–C(12)	1.224(3)	C(11)–N(1)–H(1B)	115.6
N(1)–C(11)	1.368(4)	C(12)–N(1)–H(1B)	115.6
N(1)–C(12)	1.399(4)	C(12)–N(2)–C(13)	118.9(3)
N(2)–C(12)	1.331(4)	C(12)–N(2)–H(2B)	120.6
N(2)–C(13)	1.434(4)	C(13)–N(2)–H(2B)	120.6
C(10)–C(11)	1.481(4)	O(1)–C(11)–N(1)	122.1(3)
		O(1)–C(11)–C(10)	122.0(3)
		N(1)–C(11)–C(10)	115.9(3)
		O(2)–C(12)–N(2)	122.8(3)
		O(2)–C(12)–N(1)	118.7(3)
		N(2)–C(12)–N(1)	118.6(3)

Biological evaluation

The antitumor activities of compounds **4** and **5** were determined *in vitro* against KB cells at 5 ppm using reported methods.[19] For example, the inhibition was 5.72% for compound **4** at 5 ppm. The data indicate that the compound possesses potential antitumor activities. We also determined the insecticidal activities of compounds **1**–**6** against Oriental armyworm [*Mythimna* (= *Pseudaletia*) *separata* (Walker)] by foliar application at 500 ppm using reported methods.[13,14] Only compounds **4** and **5** exhibit potential inhibiting activities. For example, the relative inhibition were 10% for the two compounds at 500 ppm.

EXPERIMENTAL

Instruments

The title compounds were synthesized under a nitrogen atmosphere. Proton NMR spectra were obtained at 200 MHz using a Bruker AC-P200 spectrometer in $CDCl_3$ solution with tetramethylsilane as internal standard. Chemical shift values δ are given in parts per million. IR spectra were recorded on a Bruker Equinox 55 spectrometer in KBr discs. Elemental analyses were determined on a Yanaca CHN Corder MT-3 elemental analyzer. MS was undertaken with a VG ZAB-HS spectrometer using the EI method. Melting points were taken on a Thomas–Hoover melting-point apparatus and were uncorrected.

Synthesis

Solvents were dried by standard methods and distilled prior to use. Carbamyl chloride was synthesized by the literature method.[20] Carbamylferrocene was synthesized according to a reported procedure.[17] Phenylisocyanates were obtained by the reaction of phenylamines with triphosgene.[21]

Synthesis of title compounds

A solution of carbamylferrocene (1 mmol) and substituted phenylisocyanate (1.1 mmol) in 20 ml of toluene was boiled for 5 h. After cooling, the resulting precipitate was collected and washed with benzene. The precipitate was purified by vacuum column chromatography on silica gel using chloroform as eluent. Finally, the products **1**–**6** were obtained in excellent yields.

*3-Ferrocenoyl-1-phenylurea (**1**)*

Yellow solid, m.p. 209–210 °C, yield 85.3%. ^{1}H NMR ($CDCl_3$): δ 4.26 (5H, s), 4.52 (2H, d), 5.00 (2H, d), 7.14 (1H, t), 7.36 (2H, d), 7.62 (2H, d), 9.06 (1H, s), 10.93 (1H, s). Anal. Found: C, 62.23; H, 4.57; N, 8.10. Calc. for $C_{18}H_{16}FeN_2O_2$: C, 62.09; H, 4.63; N, 8.05%. IR (KBr): 3445, 3261, 3126, 1670, 1523, 1489, 1443, 1373, 1284, 1199, 1151, 1029, 816, 772, 704. EI MS (%): m/z 348.0 (M+, 16), 229.0 (100), 211.0 (20), 119.0 (58), 91.0 (34).

*3-Ferrocenoyl-1-(4-bromophenyl)urea (**2**)*

Red solid, m.p. 245–246 °C, yield 71.8%. ^{1}H NMR ($CDCl_3$): δ 4.27 (5H, s), 4.54 (2H, d), 4.86 (2H, d), 7.30 (2H, d), 7.53 (2H, d), 8.29 (1H, s), 10.84 (1H, s). Anal. Found: C, 50.73; H, 3.52; N, 6.45. Calc. for $C_{18}H_{15}BrFeN_2O_2$: C, 50.62; H, 3.54; N, 6.56%.

*3-Ferrocenoyl-1-(2-chlorophenyl)urea (**3**)*

Red solid, m.p. 210–212 °C, yield 91.5%. ^{1}H NMR ($CDCl_3$): δ 4.27 (5H, s), 4.54 (2H, d), 4.99 (2H, d), 7.10 (1H, t), 7.29 (1H, t), 7.40 (1H, d), 8.40 (1H, d), 8.87 (1H, s), 11.36 (1H, s). Anal. Found: C, 56.56; H, 3.94; N, 7.43. Calc. for $C_{18}H_{15}ClFeN_2O_2$: C, 56.50; H, 3.94; N, 7.32%.

*3-Ferrocenoyl-1-(4-trifluoromethoxyphenyl)urea (**4**)*

Yellow solid, m.p. 195–197 °C, yield 53.5%. ^{1}H NMR ($CDCl_3$): δ 4.37 (5H, s), 4.61 (2H, d), 4.99 (2H, d), 7.21 (2H, d), 7.61 (2H, d), 8.50 (1H, s), 10.95 (1H, s). Anal. Found: C, 52.95; H, 3.53; N, 6.57. Calc. for $C_{19}H_{15}F_3FeN_2O_3$: C, 52.80; H, 3.50; N, 6.48%.

*3-Ferrocenoyl-1-(3-nitrophenyl)urea (**5**)*

Red solid, m.p. 216–218 °C, yield 88.0%. ^{1}H NMR ($CDCl_3$): δ 4.42 (5H, s), 4.70 (2H, d), 5.09 (2H, d), 7.50 (1H, t), 7.74 (1H, t), 8.64 (1H, d), 8.80 (1H, s), 11.33 (1H, s). Anal. Found: C, 54.85; H, 3.88; N, 10.63. Calc. for $C_{18}H_{15}FeN_3O_4$: C, 54.99; H, 3.85; N, 10.69%.

*3-Ferrocenoyl-1-(4-chlorophenyl)urea (**6**)*

Yellow solid, m.p. 240–242 °C, yield 88.8%. ^{1}H NMR ($CDCl_3$): δ 4.30 (5H, s), 4.59 (2H, d), 4.87 (2H, d), 7.41 (2H, d), 7.67 (2H, d), 9.25 (1H, s), 10.20 (1H, s). Anal. Found: C, 56.42; H, 3.83; N, 7.49. Calc. for $C_{18}H_{15}ClFeN_2O_2$: C, 56.50; H, 3.95; N, 7.32%.

X-ray crystallography

A crystal of compound **1** was obtained from acetonitrile. Diffraction measurements of compound **1** were carried out on a Bruker SMART 1000CCD diffractometer operating at 50 kV and 20 mA using Mo Kα radiation ($\lambda = 0.710\,73$ Å). Data collection at 293 K and reduction were performed using the SMART and SAINT software.[22] A multiscan method was applied to the raw intensities.[23]. The crystal structure was

Table 2. Crystallographic data for compound **1**

Empirical formula	$C_{18}H_{16}FeN_2O_2$
Crystal system, space group	Monoclinic, $P2_1/c$
Unit cell dimensions	
a (Å)	10.185(3)
b (Å)	11.365(4)
c (Å)	26.798(8)
β (°)	93.804(6)
V(Å^3)	3095.1(16)
Z	8
D_{calc}(mg mm^{-3})	1.494
Absorption coefficient (mm^{-1})	0.985
F (0 0 0)	1440
Crystal size (mm^3)	0.24 × 0.20 × 0.16
θ range for data collection (°)	1.52 to 26.41
Limiting indices	$-11 <= h <= 12$, $-14 <= k <= 14$, $-33 <= l <= 14$
Reflections collected	17416
Independent reflections	6318 ($R_{int} = 0.0553$)
Completeness to $\theta = 25.33°$	99.5
GOF	1.008
Final R indices [$I > 2\sigma(I)$]	$R_1 = 0.0468$, $wR_2 = 0.0841$
R indices (all data)	$R_1 = 0.0905$, $wR_2 = 0.0972$

determined by direct methods and refined by full-matrix least squares using the SHELXTL-PC program package.[24] Non-hydrogen atoms were subjected to anisotropic refinement. All hydrogen atoms were generated geometrically (C–H lengths fixed at 0.96 Å), assigned appropriate isotropic thermal parameters, and included in structure factor calculations in the final stage of F^2 refinement. A summary of the crystal data is given in Table 2.

Acknowledgements

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