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One-pot synthesis of *trans*-β-lactams from ferrocenylketene generated by thermal wolff rearrangement

Mingshun Liu

College of Chemistry, Fuzhou University, Fuzhou, Fujian, P.R. China

Jian'an Wang

College of Chemistry, Fuzhou University, Fuzhou, Fujian, P.R. China

Xiaoxi Yuan

College of Chemistry, Fuzhou University, Fuzhou, Fujian, P.R. China

Rong Jiang

College of Chemistry, Fuzhou University, Fuzhou, Fujian, P.R. China

Nanyan Fu

College of Chemistry, Fuzhou University, Fuzhou, Fujian, P.R. China

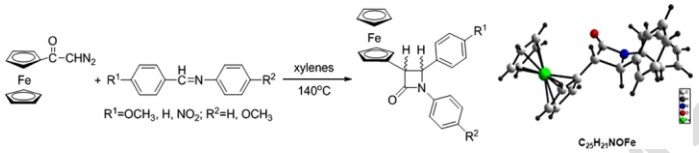
Address correspondence to Nanyan Fu. E-mail: nanyan_fu@fzu.edu.cn

Provide short biographical notes on all contributors here if the journal requires them.

ABSTRACT

A series of β-lactams containing the ferrocene moiety were synthesized *via* the Staudinger reaction between ferrocenylketene generated by the thermal Wolff rearrangement of the corresponding diazo ketone and various imines. The stereochemical outcome has been investigated and the *trans*-products were isolated as the main products, opposite to the reported results by Bonini and co-workers. The absolute configuration of (±)-*trans*-1,4-diphenyl-3-ferrocenylazetidin-2-one (**3c**) was determined by X-ray analysis. The stereoselectivity is discussed from the viewpoint of the reaction mechanism.

Graphical Abstract



KEYWORDS: ferrocenylketene, β-lactams, stereoselectivity, thermal Wolff rearrangement

Subject classification codes: include these here if the journal requires them

Introduction

The β-lactam antibiotic penicillin was discovered by Fleming in 1928.[1] Once the therapeutic value of this substance became known on the eve of World War II, a great effort was made not only to prepare this in large quantities, but also to elucidate the structure in order to obtain new generations of antibiotics by structural modification. Staudinger had reported in 1907 the reaction of diphenylketene and *N*-phenyl benzylidenenamine yielding 1,3,3,4-tetraphenylazetidin-2-one, marking not only the beginning of cycloaddition chemistry, but also that of the chemistry of β-lactams.[2] After more than one hundred years this versatile reaction yielding β-lactams is still one of the best choices for the synthesis of these strained

heterocycles.[3] For this reason, the reaction has been extensively investigated experimentally and theoretically during recent decades.[4] The accepted reaction mechanism[5] is a stepwise process, initiated by nucleophilic attack of an imine to a ketene, affording a zwitterionic intermediate, followed by a ring-closure process to give the final β-lactam product. The formation of such zwitterionic intermediates was first observed by Kagan and Luche in 1968.[6] Two new stereogenic centers at the C3 and C4 positions of the 2-azetidinone ring are generated during this process when a monosubstituted ketene and an acyclic imine are involved, so that the product may be *cis*-, *trans*-, or a mixture of *cis*- and *trans*-β-lactam derivatives, and the stereochemistry of β-lactams will strongly affect their biological activities. Usually the penicillin and cephalosporin antibiotics possess *cis*-β-lactam units,[7] whereas the cholesterol absorption inhibition activity is mainly associated with *trans*-β-lactam moieties.[8] Therefore the stereochemistry of the Staudinger reaction continues to attract considerable attention.[5]

Ferrocenyl as an aryl group in organic synthesis is useful when a bulky and stable three-dimensional metal-containing substituent with low toxicity is desired,[9] and ferrocenyl derivatives have recently found many applications in biological and medical systems.[10] Conjugates of ferrocene with antibiotics such as penicillins and cephalosporins have been reported.[11] Almost all of the ferrocenyl-penicillins and -cephalosporins exhibit antibiotic activity, some being highly active, while others proved to be potent β-lactamase inhibitors.[11d]

In 2001, Bonini and co-workers reported a one-pot Staudinger reactions to synthesize ferrocene substituted β-lactams from ferrocenylacetic acid or the corresponding carbonyl chloride and imines.[12] Ferrocenyl ketene was generated by treatment of the acid with $PhOP(O)Cl_2$ and Et_3N or from the acyl chloride and Et_3N, and the unobserved intermediate was captured in[2+2]-cycloadditions with imines such as PhCH = NPh giving a *cis*-β-lactam.[12] The

first direct observation of ferrocenylketene was reported in 2005, and calculations showed that ferrocenylketene is destabilized by 1.6 kcal/mol relative to phenylketene by B3LYP isodesmic comparison to the corresponding alkenes.[13a] Ferrocenylketene was generated by Wolff rearrangement in CH_3CN and was directly observed by UV and IR spectroscopy as a short-lived and reactive intermediate in solution.[13]

However, it is not always convenient to generate short-lived ketenes by photochemical Wolff rearrangement when the imine has a strong absorption at 300‑350 nm bands or is not stable upon irradiation. Herein, we report a new way to generate ferrocenylketene from the corresponding diazo ketone by thermal Wolff rearrangement and the synthesis of ferrocenyl substituted β-lactams by reaction with imines. The stereochemical outcome of Staudinger reactions under these conditions is found to differ from those found previously for ferrocenylketene.[12]

Results and Discussion

As noted above there are two ways reported to generate ferrocenylketene, from ferrocenyl diazomethyl ketone by the photochemical Wolff rearrangement, in which the ketene was observed directly,[13] or from ferrocenylacetic acid by the acid activator $PhOP(O)Cl_2$ and Et_3N, or from the acetyl chloride and Et_3N,[12] where the ketene was not observed but the [2 + 2]-ketene-imine cycloaddition product was isolated. Because the reaction conditions, such as temperature,[14a] solvent,[14b] base,[14c] the chloride anion,[14d] and the metal[14d,e] may affect the stereochemical outcome, a clean ketene-imine reaction system should be applied to help understanding the influence of the reaction conditions on the stereoselectivity. The photochemical Wolff rearrangement is a clean way to generate ketenes, releasing only nitrogen

gas. However, it is not convenient to generate short-lived ketenes under irradiation when the imines or the β-lactam products have strong absorptions or are not stable during excitation. Thermal Wolff rearrangement is a more convenient choice. To the best of our knowledge, this is the first report of the thermal generation of ferrocenylketene from the corresponding diazo ketone.

Several reaction conditions were surveyed to generate ferrocenylketene leading to β-lactams, as shown in the **Table 1**. Compared with phenylketene, the formation of ferrocenylketene needs higher temperatures. Diazoacetylbenzene undergoes thermal Wolff rearrangement at 110^{o}C effectively, while thermal Wolff rearrangement of diazoacetylferrocene requires 140^{o}C. Higher temperature such as 170^{o}C in sealed tube has also been tested, and the results show that the thermal stability of ferrocenyl derivatives is not good and no desired product has been isolated. Because ferrocenylketene is highly reactive, adding diazoacetylferrocene, the precursor of the ketene, slowly to the reaction mixture at the desired temperature improves the yield of the [2 + 2]-cycloaddition product.

To investigate the stereochemical outcome of the [2 + 2]-cycloaddition of ferrocenylketene, the ketene was generated by the thermal Wolff rearrangement of diazoacetylferrocene in the presence of various imines under the optimized reaction conditions. The *cis*- or *trans*-stereochemistry of the products β-lactams was established on the basis of their ^{1}H NMR spectra. The coupling constant values for the signals corresponding to the C3 and C4 protons (5.6–6.4 Hz) for the *cis*-isomers and (2.0–2.8 Hz) for the *trans*-isomers are in agreement with the previously reported values.[15] Furthermore X-ray analysis of (±)-*trans*-1,4-diphenyl-3-ferrocenylazetidin-2-one (**3c**) confirmed the *trans*-configuration (**Figure 1**). In this way, the ratio of the *cis*/*trans* isomers were determined by ^{1}H NMR analysis of the product mixture, and then

both isomers were separated by column chromatography for yield calculation and structure characterization.

The electron donating power of the ferrocenyl group as measured by σ values[16] and carbocation forming reactions[17] is similar to that of methoxy, and much greater than that of 4-methoxyphenyl. Ferrocenyl ketene generated by photochemical Wolff rearrangement in CH_3CN has a rate constant for reaction with *n*-$BuNH_2$ less than that for the phenyl ketene by only a factor of 5.[3a] Rate constants of thermal ring closure of diferrocenylbisketene, diphenylbisketene and dimethoxybisketene have been reported, and show that the reactivity of the ferrocenyl substituted bisketene is quite similar to the phenyl substituted bisketene, and much lower than that of the bismethoxy substituted ketene.[13a],[18] These results reflect the tendency of aryl groups to stabilize ketenes, while methoxy destabilizes ketenes and stabilizes the elcctron deficient cyclobutenedione ring.

For comparison we also studied the [2 + 2]-cycloadditions of *p*-methoxyphenylketene, as well as some other substituted phenylketenes, under similar conditions as the controlled reactions. The results are shown in **Table 2**.

As shown in **Table 2** (Entries 1‑5), *trans*-products are isolated as the main products of the Staudinger reaction between ferrocenylketene and various substituted imines. With the increase of the electronic withdrawing ability of the substituent on the imines the *cis*/*trans* products ratio increased from only *trans* to 0.64:1. Similar trends were observed in the Staudinger reaction of substituted phenylketenes. However, the steric and electronic effect of the ketene substituent on the stereoselectivity is not strong, as shown comparing entries 3, 9, 17 and 21 (0.16:1, 0.10:1, 0.08:1, 0.10:1 respectively). Most interestingly, the *trans*-products are favored

in all the cases that we studied using thermal Wolff rearrangement, which is opposite to the reported results by Bonini and co-workers,[12] noted above for synthesis of β-lactams by using ferrocenylacetic acid with $PhOP(O)Cl_2$ activation, or the corresponding carbonyl chloride in the presence of triethylamine and imines with conventional heating (30 – 70°C) or microwave irradiation. Thus we find that the stereoselectivity of the Staudinger reaction of ferrocenylketene can be controlled by the reaction conditions, and in particular by the temperature.

Now it is widely accepted that the Staudinger reaction is a two-step process instead of a concerted [2 + 2]-cycloaddition.[5] On the basis of systematic studies of the uncatalyzed formation of β-lactams, Xu and co-workers[5a,b] proposed the stepwise mechanism of the Staudinger reaction involving mono-substituted ketenes. The reaction starts with nucleophilic attack of the imine to a ketene, giving a zwitterionic intermediate. The zwitterionic intermediate undergoes either conrotatory electrocyclic ring closure to produce a *cis*-β-lactam product, or it undergoes isomerization of the imine moiety to form a sterically more favorable intermediate, which produces the final *trans*-β-lactam product *via* contoratory electrocyclic ring closure. It was proposed that the diastereoselectivity is results from competition between direct ring closure and isomerization of the imine moiety in the zwitterionic intermediate. Since the electron withdrawing substituent on the imine could accelerate the direct ring-closure process the ratio of the *cis*-product could increase. Our experimental results support this explanation quite well.

It was reported previously[5a,b] that for reaction of PhSCH = C = O generated by thermal Wolff rearrangement with $4\text{-}RC_6H_4CH = N(i\text{-}Pr)$ that there is a correlation of log (*cis*/*trans*) with σ constants with a slope ρ of 1.62. Similarly in our study, a good linear correlation of log (*cis*/*trans*) with σ parameters for the aryl substituents with a slope ρ = 0.84 (r^2 = 0.99) is observed (entries 7, 9, 10, 11 and 13, **Figure 2**). The increase of *cis*/*trans* ratio with electron-

withdrawing aryl substituents on C of imines we observe is also consistent with the acceleration of the direct ring closure of intermediate to *cis*-β-lactam.

In order to predict the stereochemical outcome of β-lactam formation, an empirical classification of the stereochemical preference of different ketenes was devised by Georg and co-workers, grouped as "Bose-Evans ketenes" with strong electron-donating substituents (such as *O*-alkyl, *O*-aryl, and *N*-alkylaryl) and having a distinct preference for *cis*-β-lactams formation, "Sheehan ketenes" with medium sized substituents producing complex stereochemical outcomes, and "Moore ketenes" with moderately electron-donating substituents (such as *S*-alkyl, *S*-aryl, alkyl, and aryl) and favoring the *trans*-β-lactams formation.[19] Our experimental results fit this rule quite well since ferrocenylketene, as well as other substituted phenylketenes belong to "Moore ketenes". However, as found by Xu and co-workers,[5b] and in our study the ketene reactivity is temperature dependent, and thus the Georg classification varies according to temperature. The *trans* selectivity often increases with temperature, and this explains the opposite results obtained by Bonini and us.

Conclusion

In conclusion, thermal Wolff rearrangement was applied to generate ferrocenylketene at 140^{o}C and the Staudinger reaction with various imines was carried out *in situ* with the formation of β-lactams containing the ferrocenyl moiety. *trans*-Products were favored under this reaction condition. Electron withdrawing groups on the imine increase the *cis*/*trans* products ratio. Compared to the results reported by Bonini, the product stereochemistry changes from *cis* to *trans* at higher temperature of the thermal Wolff rearrangement. This provides a way to control the stereoselectivity of the Staudinger reaction of ferrocenylketene.

Experimental

General procedures

Infrared spectra were recorded on a Perkin–Elmer 2000 series Fourier Transform IR spectrometer. Melting points were determined with an Electrothermal X-4 series digital mp apparatus without corrections. The NMR spectra were recorded on Bruker Avance 400 MHz/500 MHz or Varian Inova 500 MHz spectrometer; chemical shifts are reported in ppm in δ-values against tetramethylsilane (TMS) as an internal standard and the coupling constants in Hertz. Low and high resolution mass spectra were determined using an Applied Biosystems (Sciex) QStar or API300LC/MS/MS spectrometer. Elemental analyses were carried out using a Vario Micro elemental analyzer.

General procedure for synthesis of α-diazo ketones 1a-1d

The carbonyl chloride (5 mmol) in ether (5 mL) was added dropwise to a stirred pre-cooled solution of freshly prepared diazomethane (20 mmol) in ether (40 mL), and then the mixture was stirred on an ice-water bath overnight. The solvent was evaporated under reduced pressure. Purification of the residue by column chromatography on neutral alumina or silica gel (elution with petroleum ether/ethyl acetate = 4:1 v/v) gave the diazo ketone.

*2-Diazo-1-ferrocenylethanone (**1a**)* 0.79 g, 62% yield; red solid; mp 77–78ºC; IR (KBr): 3086, 2925, 2107, 1597, 1455, 1379, 1347, 1249, 1152, 1107, 1064, 1026, 1004, 918, 826, 814, 743, 525, 500 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.23 (s, 5H), 4.46 (t, *J* = 2.0 Hz, 2H), 4.69 (t, *J* = 2.0 Hz, 2H), 5.50 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 53.35, 68.42, 70.04, 71.69, 79.30,

189.32. Elem. Anal. Calcd for $C_{12}H_{10}FeN_2O$: C, 56.73; H, 3.97; N, 11.03. Found: C, 56.55; H, 3.82; N, 11.13.[13a]

General procedure for synthesis of imines 2a-2i

A mixture of amine (2 mmol) and aromatic aldehyde (2 mmol) was dissolved in anhydrous EtOH (10 mL) at room temperature, and left to stir on an ice-water bath. The precipitate formed was collected by filtration, and the filtrate was washed with cold anhydrous EtOH. The product was recrystallized from anhydrous EtOH,[20] with yields of 77–92%.

Preparation of β-lactams 3

General procedure

A flamed-dried three-neck flask was charged with a solution of imine (0.20 mmol) in 10 mL of dry xylenes (or toluene). The flask was immersed in an oil bath and heated to desired temperature. A solution of diazo ketone (0.26 mmol) in 5 mL of dry xylenes was then added dropwise through dropping funnel. After the addition, the resulting solution was stirred for another 12 h at the same temperature. After removal of the solvent, the residue was purified by flash chromatography to remove highly polar impurities. The product mixture was submitted to ^{1}H NMR analysis to determine the *cis*/*trans* ratio. Column chromatography of the crude mixture on neutral alumina or silica gel afforded the corresponding *cis*- and *trans*-β-lactam products.[5a]

(±)-trans-1-Phenyl-4-(4-methoxyphenyl)-3-ferrocenylazetidin-2-one ***(3a)*** The reaction mixture was chromatographed on a neutral alumina using 10:1 petroleum ether/EtOAc (v/v) to afford the indicated compound as a yellow solid: 61 mg, 70% yield; mp 163^{o}C; IR (KBr): 2959, 2920, 2832, 1742, 1615, 1598, 1512, 1500, 1463, 1383, 1371, 1307, 1244, 1177, 1154, 1108,

1038, 1002, 826, 814, 753, 692, 487 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.81 (s, 3H), 3.94 (d, *J* = 2.8 Hz, 1H), 4.19 (s, 8H), 4.27 (s, 1H), 4.84 (d, *J* = 2.8 Hz, 1H), 6.92 (d, *J* = 8.8 Hz, 2H), 7.04 (t, *J* = 7.2 Hz, 1H), 7.24‑7.28 (m, 2H), 7.32–7.36 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 55.5, 60.5, 62.9, 67.1, 67.6, 68.3, 68.5, 69.1, 81.9, 114.8, 117.3, 124.0, 127.4, 129.3, 129.9, 137.9, 160.0, 165.7; EI-MS: *m/z* 437.1 (M^+); HRMS (EI): Calcd for $C_{26}H_{23}FeNO_2$ (M^+): 437.1078, Found: 437.1074. Anal. Calcd for $C_{26}H_{23}FeNO_2$: C, 71.41; H, 5.30; N, 3.20. Found: C, 71.63; H, 5.24; N, 3.11.

X-ray crystallographic investigations

The diffraction data were measured on a Rigaku Saturn 724 CCD diffractometer with Mo Ka radiation (0.778) by ω scan mode at 293(2) K. All data were corrected by semi-empirical method using SADABS program. The program SAINT14 was used for integration of the diffraction profiles. The structure was solved by the direct methods using SHELXS program of the SHELXL-97 package and refined with SHELXL. The final refinement was performed by full matrix least-squares methods with anisotropic thermal parameters for all non-hydrogen atoms on F2. The hydrogen atoms were placed in the geometrically calculated positions. All hydrogen atoms were included in the final refinement in the riding model approximation with displacement parameters derived from the parent atoms to which they were bonded.

X-ray crystallography data for **3c**: $C_{25}H_{21}FeNO$, Mr = 407.28, yellow block crystal, orthorhombic, space group Pca2 (1), T = 293(2) K, a = 9.865 (2), b = 20.857 (4), c = 9.4829 (19) Å, α = β = γ = 90.00 °, V = 1951.1 (7) $Å^3$, Z = 4, μ(Mo-Kα) = 0.778 mm^{-1}, 15791 reflections collected, 4343 unique (R_{int} = 0.0487), R1 = 0.0844 (I > 2σI), wR2 = 0.2148 for all data.[21]

Supporting information

Full synthetic details (**1**, **2**, and **3**), their FT-IR, ^{1}H NMR, ^{13}C NMR and MS spectral data (**1** and **3**), and copies of FT-IR, ^{1}H NMR, ^{13}C NMR and MS spectra of **1** and **3** have been included in supplementary data. Supplementary data associated with this article can be found through the supplementary content section of this article's web page.

Acknowledgements

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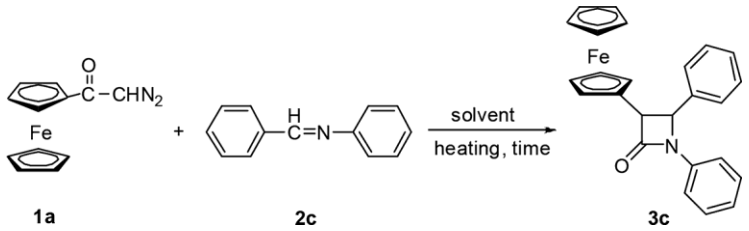
[21] Further crystallographic data have been deposited with the Cambridge Crystallographic Data Centre. Copies of the data (CCDC 735635) can be obtained free of charge from CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (Tel: +44 1223 762910; fax:+44 1223 336 033; e-mail: deposit@ccdc.cam.ac.uk, http://www.ccdc.cam.ac.uk/deposit).

Table 1. [2 + 2]-Cycloaddition of diazoketone 1a and imine 2c under different reaction conditions

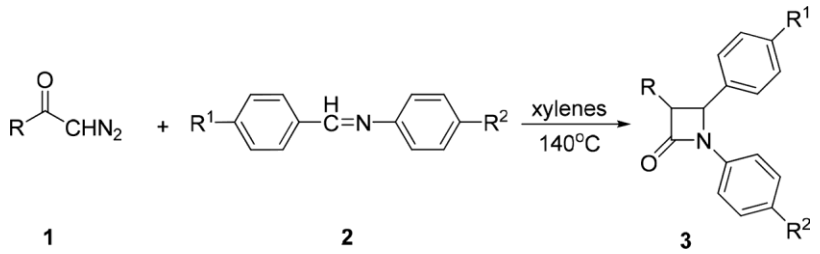


1a 2c 3c

Entry	Temp (^{o}C)	Time (h)	Solvent	Yield (%)[a]	*cis*/*trans*
1	80	2 h	Toluene	Trace	
2		12 h	Toluene	5	Only *trans*
3	110	2 h	Toluene	27	
4		12 h	Toluene	40	0.14:1
5	140	2 h	Xylenes	54	
6		12 h	Xylenes	74	0.16:1

Note: [a] The isolated yield of *trans*-**3c**.

Table 2. [2 + 2]-Cycloaddition of diazo ketones 1 and imines 2 with different substituents



1 2 3

Entry	**1**	**2**	R	R^1	R^2	**3**	*cis/trans*	Yield(%)[a]
1	a	a	Fc	CH_3O	H	a	Only *trans*	70
2		b		H	OCH_3	b	Only *trans*	82
3		c		H	H	c	0.16:1	74
4		d		O_2N	OCH_3	d	0.40:1	40
5		e		O_2N	H	e	0.64:1	50
6	b	f	*p*-CH_3O-Ph	$(CH_3)_2N$	H	f	Only *trans*	52
7		a		CH_3O	H	g	0.05:1	78
8		b		H	OCH_3	h	0.07:1	77
9		c		H	H	i	0.10:1	70
10		g		Cl	H	j	0.13:1	63
11		h		Br	H	k	0.15:1	74
12		d		O_2N	OCH_3	l	0.30:1	45
13		e		O_2N	H	m	0.40:1	46

14	c	i	Ph	CH_3O	OCH_3	n	0.02:1	76
15		a		CH_3O	H	o	0.03:1	71
16		b		H	OCH_3	p	0.02:1	77
17		c		H	H	q	0.08:1	83
18		d		O_2N	OCH_3	r	0.30:1	49
19		e		O_2N	H	s	0.25:1	37
20	d	a	*p*-O_2N-Ph	CH_3O	H	t	0.08:1	57
21		c		H	H	u	0.10:1	36
22		e		O_2N	H	v	0.25:1	43

Note: [a] The isolated yield of *trans*-**3**.

Figure 1. X-ray structure of (±)-*trans*-1,4-diphenyl-3-ferrocenylazetidin-2-one (**3c**).

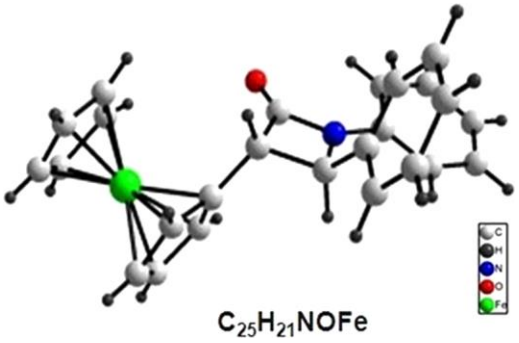


Figure 2. Correlation of log (*cis*/*trans*) with σ (entries 7, 9, 10, 11 and 13).