Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron
Tetrahedron 63 (2007) 9359–9364

Reaction of β-lactam carbenes with alkyl isonitriles for a ready approach to 4-cyano and 4-carbamoyl substituted β-lactams

Lan-Qing Cheng and Ying Cheng*

Chemistry Department, Beijing Normal University, Beijing 100875, China

Received 6 May 2007; revised 27 June 2007; accepted 29 June 2007
Available online 10 July 2007

Abstract—The reaction of β-lactam carbenes with alkyl isonitriles was investigated. Two different types of products, 4-cyano- or 4-carbamoyl-β-lactams, were isolated, depending upon the nature of the alkyl group of the isonitriles. The cyano-β-lactams were derived by a N-to-C 1,3-rearrangement of the ketenimine intermediates, while the carbamoyl-β-lactams were the hydrolysis products of the intermediates. This work extends the application of β-lactam carbenes, and provides a very simple and efficient route to 4-cyano- or 4-carbamoyl-β-lactams, which are versatile synthetic intermediates and new chemical entities of potential biological activity.

1. Introduction

β-Lactam derivatives have attracted continued interests not only for their diverse and powerful antibiotic activity,[1] but also for their utility as versatile synthetic intermediates.[2] For example, some 4-carbamoyl- and 4-alkoxycarbonyl-β-lactams were found to be inhibitors of HIV-1 protease,[3] or human leukocyte elastase and porcine pancreatic elastase.[4] On the other hand, 4-cyano and 4-carbamoyl-β-lactams have been used as precursors of thienamycin and isopenam.[5] Over the past decades, many synthetic methods,[6] such as Kinugasa reaction of alkynes with nitrones,[7] Ugi three-component/four-center condensation of β-amino acids with aldehydes and isonitriles,[8] cyclization reactions of β-amino acids,[9] and reactions of chromium carbene complexes with imines,[10] have been developed for the construction of the β-lactam skeleton. However, the Staudinger reaction[11] still remains the most efficient route to β-lactams.

2-Azetidinone-4-ylidenes are β-lactam carbenes reported by Warkentin and co-workers in the 1990s.[12] The cyclopropanation reactivity toward both electron-rich and electron-deficient alkenes labeled β-lactam carbenes as ambiphilic carbenes.[13] We have been interested in the chemistry of nucleophilic and ambiphilic carbenes for some time.[14] Recently, our focus has been on the ambiphilic reactivity of β-lactam carbenes. We found that β-lactam carbenes could behave as good nucleophiles toward aryl isocyanates to produce spiro[azetidine-2-one-4,3′-indole-2′-one] derivatives.[14d] On the other hand, β-lactam carbenes acted as strong electrophiles toward aryl isonitriles to form high yields of 2-azetidinonylidene indoles, which rearranged almost quantitatively to δ-carbolin-2-one derivatives upon treatment with an acid.[14e] Our previous studies have indicated that the β-lactam carbenes are remarkable intermediates in synthesis of various β-lactam derivatives, as well as other novel heterocyclic compounds. To gain deeper insight into the unique reactivity of β-lactam carbenes and to further explore their synthetic applications, we undertook the current study to investigate the reaction of β-lactam carbenes with alkyl isonitriles. Interestingly, two different types of β-lactam derivatives, 4-cyano- or 4-carbamoyl-β-lactams, were isolated, depending upon the nature of the alkyl group of the isonitriles.

2. Results and discussion

We first studied the reaction between β-lactam carbenes and benzyl isonitriles. All β-lactam carbenes were 1-aryl-β-lactam-4-ylidenes **2** and were generated in situ by thermolysis of spiro[β-lactam-4,2′-oxadiazolines] **1** using Warkentin′s method.[12] According to our previous investigations,[14d,e] the optimal temperature for the generation of carbenes **2** was around 100–110 °C. Thus, the reaction of 1-bromophenyl-3,3-dimethyl-β-lactam-4-ylidene **2d** with benzyl isonitrile **3a** was initially examined in toluene at reflux to afford 4-benzyl-4-cyano-β-lactam **4d** in 40% yield. The reaction conditions were then optimized by varying the solvent [chosen to be unreactive toward carbenes and having a bp of about 100 °C] and the ratio of starting materials (Table 1). As indicated in Table 1, 1,4-dioxane was the best solvent among all that were studied such as toluene,

Keywords: β-Lactam carbene; 4-Cyano-β-lactam; 4-Carbamoyl-β-lactam; Ketenimine.
* Corresponding author. Tel.: +86 10 5880 5558; fax: +86 10 5880 2075; e-mail: ycheng2@bnu.edu.cn

0040–4020/$ - see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2007.06.111

Table 1. The optimization of reaction between 1-*p*-bromophenyl-3,3-dimethyl-β-lactam-4-ylidene **2d** and benzyl isonitrile **3a**

Entry	Starting materials	**1d**:**3a**	Solvent	Temp (°C)	Yield of **4d** (%)
1	**1d**, **3a**	1:1	Trichloroethane	110–120	46
2	**1d**, **3a**	1:1	Propionitrile	90–100	47
3	**1d**, **3a**	1:1	Toluene	110–120	40
4	**1d**, **3a**	1:1	1,4-Dioxane	100–110	52
5	**1d**, **3a**	1:1.5	1,4-Dioxane	100–110	57
6	**1d**, **3a**	1:2	1,4-Dioxane	100–110	53
7	**1d**, **3a**	1:2.5	1,4-Dioxane	100–110	56

Table 2. The reaction of β-lactam-4-ylidenes **2** with benzyl isonitriles **3** under optimal conditions

Entry	**1**:R^1, X	**3a–c**:Y	Yield of **4** (%)
1	**1a**:Me, H	**3a**:H	**4a** (59)
2	**1b**:Me, Me	**3a**:H	**4b** (60)
3	**1c**:Me, OMe	**3a**:H	**4c** (57)
4	**1d**:Me, Br	**3a**:H	**4d** (57)
5	**1d**:Me, Br	**3b**:OMe	**4e** (56)
6	**1d**:Me, Br	**3c**:F	**4f** (58)
7	**1e**:Ph, Me	**3b**:OMe	**4g** (67)
8	**1f**:Ph, Br	**3b**:OMe	**4h** (60)

1,1,2-trichloroethane, and propionitrile. Increasing the ratio of **3a** over **1d** from 1:1 to 1:1.5 slightly improved the yield of product, but a large excess of isonitrile did not further improve the chemical yield. The scope of the reaction was investigated under optimal conditions by using carbenes **2** and benzyl isonitriles **3a–c** bearing different substituents (Scheme 1 and Table 2). In all cases studied, such as employing carbenes bearing a small methyl or a large phenyl group on the lactam ring, carbenes and isonitriles substituted by an electron-donating or an electron-withdrawing group on the phenyl rings, the reaction proceeded smoothly to produce 4-cyano-β-lactams **4** in 56–67% yields.

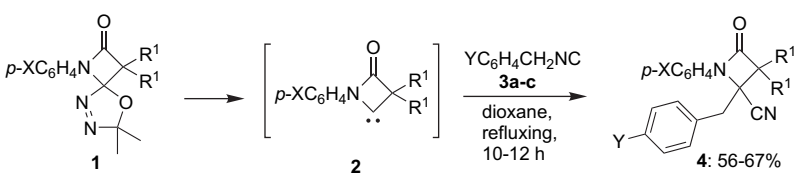
The structures of all products were elucidated based on spectroscopic data and microanalysis. The NMR spectra, mass data, and elemental analyses indicated compound **4** being the 1+1 adduct of carbene and isonitrile. To identify the products beyond doubt, the structure of **4d** was determined unambiguously by single crystal X-ray diffraction analysis.[15]

The formation of 4-benzyl-4-cyano-β-lactam **4** can be best explained by the C–C coupling reaction of the carbene with isonitrile to form a ketenimine intermediate **5**, followed by a N-to-C 1,3-benzyl migration of **5** to furnish the rearrangement of a ketenimine to a nitrile (Scheme 2). A few examples of 1,3-rearrangement of ketenimines to nitriles were reported in the literature.[16] The rearrangement of *N*-(benzyl)diphenylketenimines to nitrile was proposed via a caged radical pair mechanism.[16a]

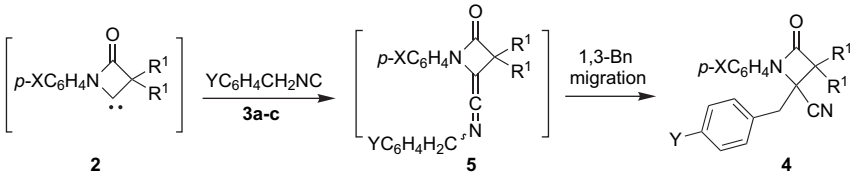
In order to clarify the reaction mechanism in terms of intermolecular or intramolecular rearrangement under our conditions, the reaction between carbene **2d** and (*S*)-1-phenylethylisonitrile **3d** was examined. From this reaction, two diasteroisomers **4i-I** and **4i-II** were isolated in 19 and 20% yields, respectively, by chromatography (Scheme 3). Chiral HPLC analysis indicated that both **4i-I** and **4i-II** are a mixture of two enantiomers in the ratio of 63:37 and 72:28, respectively. The major enantiomer of **4i-I** or **4i-II** was isolated through recrystallization of the mixture of two enantiomers. The single crystal X-ray diffraction analysis demonstrated that the major enantiomer of **4i-I** has (4*S*,1′*S*) absolute configuration, while the major enantiomer of **4i-II** is the (4*R*,1′*S*)-isomer (Fig. 1).[15] The existence of (*R*,*R*)- and (*S*,*R*)-isomers clearly indicated that the N-to-C 1,3-benzyl migration of a ketenimine to a nitrile could be an intermolecular rearrangement. Both of the major enantiomers of the two diasteroisomers showed retention of the absolute configuration of the migration group, which was in agreement with the caged radical pair mechanism.

In order to examine the scope of this reaction, other isonitriles including *n*-, *iso*-, and *tert*-alkyl substituted isonitriles were employed in the reaction with carbenes. The reaction of carbenes **2** with *n*-hexyl, cyclohexyl, or *tert*-butyl isonitrile was carried out under similar conditions to that for the benzyl isonitriles. However, a different type of product, a 4-alkylcarbamoyl-β-lactam **6**, was isolated in 52–77% yield (Table 3). The carbamoyl-β-lactams **6** were most probably derived from hydrolysis of the ketenimine intermediates **5**, possibly during the chromatographic work-up (Scheme 4). To validate our hypothesis, the reaction of **1c** with **3e** was monitored by IR spectroscopy, which showed the disappearance of the isonitrile (ν_{NC}=2146 cm^{-1}) and the formation of a ketenimine ($\nu_{C=C=N}$=2040 cm^{-1}), and no 4-carbamoyl-β-lactam **6a** (ν_{NH}=3260, ν_{CONH}=1650 cm^{-1}) was observed in the reaction mixture after 11 h of reaction. This result indicated that the 4-carbamoyl-β-lactams were indeed formed during the work-up process. The different outcomes from the reaction of β-lactam carbenes with benzyl and alkyl isonitriles can be explained by the different stabilities and steric effects of alkyl radicals. Since the benzyl radical is more stable than *n*- and *iso*-alkyl radicals, the fragmentation of *N*-(benzyl)ketenimines to benzyl radicals is easier than the ketenimines bearing *n*- and *iso*-alkyl groups. The *tert*-butyl and benzyl radicals have similar stability, suggesting that steric factors inhibit the migration of the former.

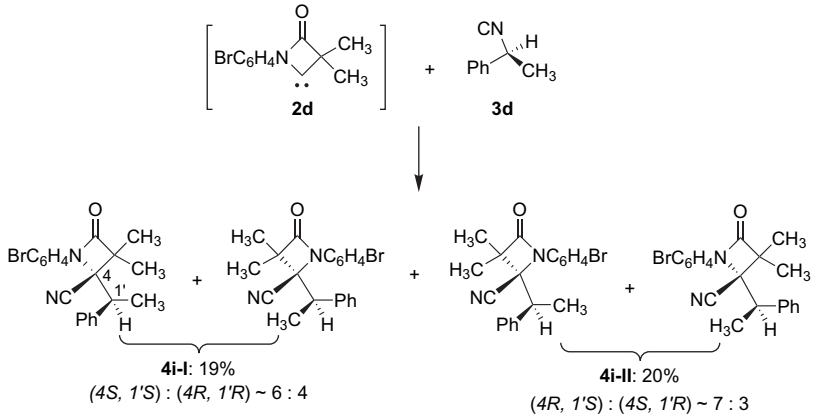
In summary, we have shown that the reaction of β-lactams with alkyl isonitriles could either afford 4-cyano- or 4-carbamoyl-β-lactam dependent upon the nature of the alkyl group of isonitriles. The 4-cyano-β-lactams were derived by N-to-C 1,3-rearrangement of the ketenimine intermediates, while the 4-carbamoyl-β-lactams were the hydrolysis products of



Scheme 1.



Scheme 2.



Scheme 3.

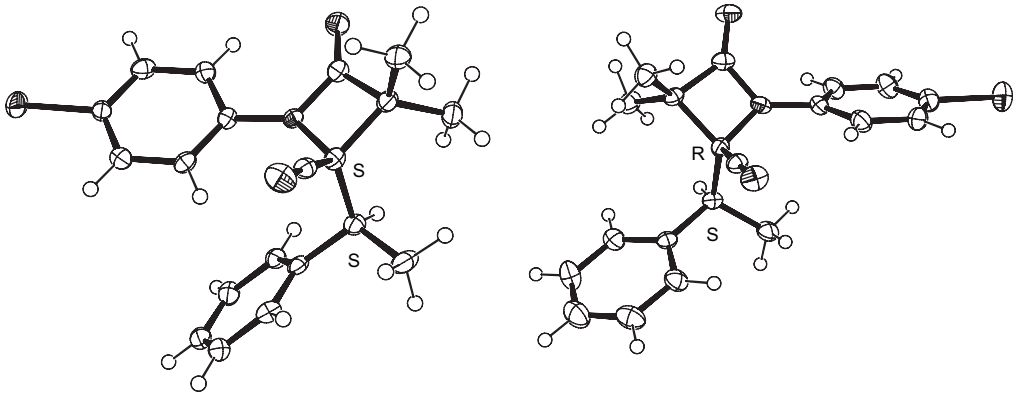
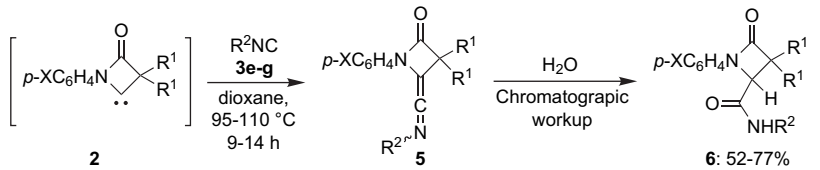


Figure 1.

Table 3. The reaction of β-lactam-4-ylidenes **2** with alkyl isonitriles **3** in 1,4-dioxane

Entry	**1**:R^1, X	**3e–g**:R^2	**1**:**3**	Temp (°C)	Time (h)	Yield of **6** (%)
1	**1c**:Me, OMe	**3e**:*n*-Hexyl	1:2	100–110	9	**6a** (64)
2	**1e**:Ph, Me	**3e**:*n*-Hexyl	1:2	100–110	9	**6b** (68)
3	**1g**:Ph, Cl	**3e**:*n*-Hexyl	1:2	100–110	9	**6c** (60)
4	**1e**:Ph, Me	**3f**:Cyclohexyl	1:2	100–110	9	**6d** (77)
5	**1f**:Ph, Br	**3f**:Cyclohexyl	1:2	100–110	9	**6e** (71)
6	**1c**:Me, OMe	**3g**:*t*-Bu	1:3[a]	90–95[a]	14	**6f** (52)

[a] The reaction was carried out under a slightly lower temperature than the boiling point of the solvent with a large excess of isonitrile, because *tert*-butyl isonitrile has lower boiling point.



Scheme 4.

the ketenimines. This work further extends the application of β-lactam carbenes, and provides a very simple and efficient route to 4-cyano- or 4-carbamoyl-β-lactams, which are versatile synthetic intermediates and new chemical entities of potential biological activity.

3. Experimental section

3.1. General

Melting points are uncorrected. ^{1}H NMR (500 MHz) and ^{13}C NMR (125 MHz) were recorded in $CDCl_3$ on a Bruker Avance 500 spectrometer. The solvent 1,4-dioxane was distilled from sodium benzophenone ketyl.

3.2. General procedure for the reaction of β-lactam carbenes with alkyl isonitriles

Under nitrogen atmosphere, a mixture of spiro[β-lactam-4,2′-oxadiazoline] **1**[12] (1 mmol) and isonitrile **3** (1.5 mmol for benzyl isonitriles **3a–d**, or 2–3 mmol for alkyl isonitriles **3e–g**) was refluxed in 1,4-dioxane (30 mL) for 9–14 h (note: the temperature was kept around 90–95 °C in the reaction with *tert*-butyl isonitrile). After removal of the solvent, the residue was chromatographed on a silica gel column eluting with a mixture of petroleum ether (60–90 °C) and ethyl acetate to give 4-cyano-β-lactams **4** (petroleum ether/ethyl acetate from 15:1 to 10:1) or 4-carbamoyl-β-lactams **6** (petroleum ether/ethyl acetate from 5:1 to 2:1), respectively, from the reaction with benzyl isonitriles or alkyl isonitriles.

3.2.1. 4-Benzyl-4-cyano-3,3-dimethyl-1-phenyl-β-lactam 4a. Colorless crystals, 59%; mp 90–91 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ=7.39 (d, J=8.3 Hz, 2H), 7.28–7.31 (m, 7H), 7.15 (t, J=7.0 Hz, 1H), 3.59 (d, J=14.9 Hz, 1H), 3.27 (d, J=14.9 Hz, 1H), 1.67 (s, 3H), 1.51 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ=169.1, 135.7, 133.3, 130.0, 129.2, 128.8, 127.9, 125.3, 118.8, 117.8, 63.0, 59.3, 39.3, 21.9, 18.1; IR ν (cm^{-1}) 1759, 1596; MS (EI) m/z (%): 91 (100), 171 (77), 290 (M^+, 23%). Anal. Calcd for $C_{19}H_{18}N_2O$: C 78.59, H 6.25, N 9.65. Found: C 78.66, H 6.10, N 9.78.

3.2.2. 4-Benzyl-4-cyano-3,3-dimethyl-1-(*p*-methylphenyl)-β-lactam 4b. White solid, 60%; mp 106–107 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ=7.28–7.31 (m, 7H), 7.10 (d, J=8.2 Hz, 2H), 3.58 (d, J=14.9 Hz, 1H), 3.25 (d, J=14.9 Hz, 1H), 2.33 (s, 3H), 1.66 (s, 3H), 1.50 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ=168.9, 135.2, 133.3, 133.0, 129.9, 129.7, 128.7, 127.8, 119.0, 117.9, 63.1, 59.2, 39.2, 21.9, 21.0, 18.2; IR ν (cm^{-1}) 1767, 1514; MS (EI) m/z (%): 91 (100), 185 (40), 304 (M^+, 15%). Anal. Calcd for $C_{20}H_{20}N_2O$: C 78.92, H 6.62, N 9.20. Found: C 78.84, H 6.77, N 9.16.

3.2.3. 4-Benzyl-4-cyano-3,3-dimethyl-1-(*p*-methoxyphenyl)-β-lactam 4c. Colorless crystals, 57%; mp 111–112 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ=7.28–7.32 (m, 7H), 6.82 (d, J=9.0 Hz, 2H), 3.81 (s, 3H), 3.50 (d, J=14.9 Hz, 1H), 3.25 (d, J=14.8 Hz, 1H), 1.67 (s, 3H), 1.50 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ=168.9, 157.4, 133.3, 129.9, 128.7, 128.6, 127.8, 121.2, 118.0, 114.5, 63.4, 59.2, 55.5, 39.4, 21.8, 18.1; IR ν (cm^{-1}) 1763, 1511; MS (EI) m/z (%): 91 (70), 149 (88), 202 (100), 320 (M^+, 75%)/321 (M+1, 50). Anal. Calcd for $C_{20}H_{20}N_2O_2$: C 74.98, H 6.29, N 8.74. Found C 74.98, H 6.17, N 8.43.

3.2.4. 4-Benzyl-4-cyano-3,3-dimethyl-1-(*p*-bromophenyl)-β-lactam 4d. Colorless crystals, 57%; mp 125–126 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ=7.36 (d, J=8.7 Hz, 2H), 7.28–7.33 (m, 5H), 7.19 (d, J=8.7 Hz, 2H), 3.50 (d, J=14.8 Hz, 1H), 3.27 (d, J=14.8 Hz, 1H), 1.68 (s, 3H), 1.51 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ=169.0, 134.8, 133.0, 132.1, 130.0, 128.9, 128.1, 120.1, 118.1, 117.4, 63.2, 59.6, 39.7, 21.9, 18.0; IR ν (cm^{-1}) 1774, 1490; MS (EI) m/z (%): 90 (100), 368 (M^+, 5%)/370 (6). Anal. Calcd for $C_{19}H_{17}BrN_2O$: C 61.80, H 4.64, N 7.59. Found: C 61.74, H 4.91, N 7.61.

3.2.5. 1-(*p*-Bromophenyl)-4-cyano-3,3-dimethyl-4-(*p*-methoxybenzyl)-β-lactam 4e. Colorless crystals, 56%; mp 114–115 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ=7.37 (d, J=8.9 Hz, 2H), 7.20 (d, J=7.0 Hz, 2H), 7.19 (d, J=6.8 Hz, 2H), 6.83 (d, J=8.6 Hz, 2H), 3.83 (s, 3H), 3.43 (d, J=14.8 Hz, 1H), 3.22 (d, J=14.8 Hz, 1H), 1.66 (s, 3H), 1.51 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ=169.1, 159.4, 134.8, 132.1, 131.2, 124.8, 120.2, 118.1, 117.5, 114.2, 63.5, 59.5, 55.3, 38.9, 22.0, 18.0; IR ν (cm^{-1}) 1759, 1611, 1586, 1515, 1488; MS (EI) m/z (%): 121 (100), 398 (M^+, 4%)/400 (3). Anal. Calcd for $C_{20}H_{19}BrN_2O_2$: C 60.16, H 4.80, N 7.02. Found: C 60.16, H 4.80, N 7.02.

3.2.6. 1-(*p*-Bromophenyl)-4-cyano-3,3-dimethyl-4-(*p*-fluorobenzyl)-β-lactam 4f. Pale yellow crystals, 58%; mp 109–110 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ=7.38 (d, J=8.9 Hz, 2H), 7.25 (dd, J=8.6, 5.3 Hz, 2H), 7.19 (d, J=8.8 Hz, 2H), 7.00 (t, J=8.6 Hz, 2H), 3.46 (d, J=14.8 Hz, 1H), 3.25 (d, J=14.8 Hz, 1H), 1.67 (s, 3H), 1.51 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ=168.9, 163.5, 161.5, 134.7, 132.2, 131.8, 131.7, 128.8, 120.2, 118.3, 117.3, 115.9, 115.7, 63.2, 59.7, 39.1, 22.0, 17.9; IR ν (cm^{-1}) 1765, 1601, 1593, 1510, 1489; MS (EI) m/z (%): 109 (100), 155 (55), 169 (60), 249 (30), 386 (M^+, 10%)/388 (10). Anal. Calcd for $C_{19}H_{16}BrFN_2O$: C 58.93, H 4.16, N 7.23. Found: C 58.91, H 4.21, N 7.27.

3.2.7. 4-Cyano-3,3-diphenyl-1-(*p*-methylphenyl)-4-(*p*-methoxybenzyl)-β-lactam 4g. Colorless crystals, 67%; mp 170–171 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ=7.55 (d, J=7.7 Hz, 2H), 7.38–7.43 (m, 10H), 7.21 (d, J=7.7 Hz, 2H), 6.70 (d, J=8.5 Hz, 2H), 6.66 (d, J=7.6 Hz, 2H), 3.80 (s, 3H), 3.38 (d, J=14.3 Hz, 1H), 3.22 (d, J=14.3 Hz, 1H), 2.38 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ=165.8, 159.3, 136.1, 134.9, 134.8, 132.5, 131.7, 130.5, 130.0, 128.94, 128.87, 128.8, 128.6, 128.5, 124.0, 120.0, 118.3, 113.8, 75.4, 66.6, 55.3, 38.3, 21.1; IR ν (cm^{-1}) 1758, 1613, 1514; MS (MALDI-TOF): 459 (M+1), 481 (M+Na^+). Anal. Calcd for $C_{31}H_{26}N_2O_2$: C 81.20, H 5.72, N 6.11. Found: C 81.39, H 5.40, N 6.12.

3.2.8. 4-Cyano-3,3-diphenyl-1-(*p*-bromophenyl)-4-(*p*-methoxybenzyl)-β-lactam 4h. Colorless crystals, 60%; mp 180–181 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ=7.47 (s, 4H), 7.45 (d, J=5.2 Hz, 4H), 7.36–7.42 (m, 6H), 6.73 (d, J=8.8 Hz, 2H), 6.69 (d, J=8.6 Hz, 2H), 3.80 (s, 3H), 3.27 (d, J=14.4 Hz, 1H), 3.23 (d, J=14.4 Hz, 1H); ^{13}C NMR

(125 MHz, $CDCl_3$): δ=165.8, 159.4, 134.8, 134.5, 134.4, 132.9, 132.4, 131.7, 130.2, 129.7, 129.1, 128.9, 128.69, 128.66, 123.8, 121.5, 121.0, 118.9, 117.9, 113.9, 75.8, 66.5, 55.3, 39.4; IR ν (cm^{-1}) 1760, 1612, 1515, 1489; MS (MALDI-TOF): 523 (M+1), 545 ($M+Na^+$). Anal. Calcd for $C_{30}H_{23}BrN_2O_2$: C 68.84, H 4.43, N 5.35. Found: C 68.81, H 4.36, N 5.14.

The mixture of (4*S*,1′*S*) and (4*R*,1′*R*) 1-(*p*-bromophenyl)-4-cyano-3,3-dimethyl-4-(1-phenylethyl)-β-lactam **4i-I** [(4*S*,1′*S*)/(4*R*,1′*R*)=63:37] was obtained in 19% yield. Optical pure (*S*,*S*)-**4i-I** was isolated from recrystallization of the mixture of two enantiomers with a solution of dichloromethane, ethyl acetate, and *n*-hexane (2:1:9).

3.2.9. (*S*,*S*)-1-(*p*-Bromophenyl)-4-cyano-3,3-dimethyl-4-(1-phenylethyl)-β-lactam 4i-I. White crystals, mp 151–152 °C, $[\alpha]_D^{25}$ −90.1 (*c* 0.53 g/100 mL, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$): δ=7.24 (d, *J*=6.0 Hz, 2H), 7.19 (t, *J*=7.3 Hz, 1H), 7.10 (t, *J*=7.4 Hz, 2H), 7.05 (d, *J*=8.9 Hz, 2H), 6.76 (d, *J*=8.9 Hz, 2H), 3.39 (q, *J*=7.0 Hz, 1H), 1.70 (s, 3H), 1.66 (s, 3H), 1.57 (d, *J*=7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ=169.6, 138.6, 134.8, 131.3, 129.0, 128.7, 128.3, 120.9, 117.7, 116.9, 68.6, 59.7, 44.2, 22.2, 17.8, 17.0; IR ν (cm^{-1}) 1771, 1490; MS (EI) *m*/*z* (%): 105 (100), 382 (1%, M^+)/384 (1). Anal. Calcd for $C_{20}H_{19}BrN_2O$: C 62.67, H 5.00, N 7.31. Found C 62.50, H 5.33, N 7.24.

The mixture of (4*R*,1′*S*) and (4*S*,1′*R*) 1-(*p*-bromophenyl)-4-cyano-3,3-dimethyl-4-(1-phenylethyl)-β-lactam **4i-II** [(4*R*,1′*S*):(4*S*,1′*R*)=72:28] was obtained in 20% yield. Racemic product **4i-II** was isolated first from recrystallization of the mixture of two enantiomers with a solution of dichloromethane, ethyl acetate, and *n*-hexane (2:1:9). After removal of the racemic **4i-II**, the mother liquid was concentrated to precipitate the optical pure (4*R*,1′*S*)-**4i-II**.

3.2.10. (4*R*,1′*S*)-1-(*p*-Bromophenyl)-4-cyano-3,3-dimethyl-4-(1-phenylethyl)-β-lactam 4i-II. Colorless crystals, mp 108–109 °C, $[\alpha]_D^{25}$ +64.3 (*c* 0.58 g/100 mL, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$): δ=7.58 (d, *J*=7.5 Hz, 2H), 7.53 (d, *J*=8.7 Hz, 2H), 7.42 (d, *J*=7.6 Hz, 2H), 7.38 (t, *J*=7.6 Hz, 2H), 7.32 (t, *J*=7.1 Hz, 1H), 3.42 (q, *J*=6.9 Hz, 1H), 1.56 (s, 3H), 1.46 (d, *J*=6.9 Hz, 3H), 1.14 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ=170.4, 140.5, 134.6, 132.6, 129.0, 127.7, 127.5, 124.2, 120.4, 118.6, 67.9, 60.0, 45.6, 22.0, 21.9, 19.0; IR ν (cm^{-1}) 1769, 1491; MS (EI) *m*/*z* (%): 115 (75), 128 (77), 143 (100), 170 (62), 382 (1%, M^+). Anal. Calcd for $C_{20}H_{19}BrN_2O$: C 62.67, H 5.00, N 7.31. Found C 62.62, H 5.08, N 7.22.

3.2.11. 3,3-Dimethyl-4-(*n*-hexylcarbamoyl)-1-(*p*-methoxyphenyl)-β-lactam 6a. White solid, 64%; mp 123–124 °C; ^1H NMR (500 MHz, $CDCl_3$): δ=7.33 (d, *J*=8.9 Hz, 2H), 6.91 (d, *J*=8.9 Hz, 2H), 5.88 (br s, 1H), 4.19 (s, 1H), 3.82 (s, 3H), 3.29 (q, *J*=6.3 Hz, 2H), 1.53 (s, 3H), 1.43–1.47 (m, 2H), 1.31 (s, 3H), 1.23 (br s, 6H), 0.87 (t, *J*=6.9 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ=170.7, 167.5, 156.6, 130.8, 117.9, 114.7, 64.8, 55.5, 55.1, 39.3, 31.3, 29.4, 26.4, 22.8, 22.5, 17.2, 13.9; IR ν (cm^{-1}) 3260, 1744, 1650; MS (MALDI-TOF): 333 (M+1), 355 ($M+Na^+$), 371 ($M+K^+$). Anal. Calcd for $C_{19}H_{28}N_2O_3$: C 68.65, H 8.49, N 8.43. Found: C 68.48, H 8.27, N 8.40.

3.2.12. 4-(*n*-Hexylcarbamoyl)-3,3-diphenyl-1-(*p*-methylphenyl)-β-lactam 6b. White solid, 68%; mp 181–182 °C; ^1H NMR (500 MHz, $CDCl_3$): δ=7.73 (d, *J*=7.4 Hz, 2H), 7.50 (d, *J*=7.3 Hz, 2H), 7.37–7.41 (m, 4H), 7.30–7.33 (m, 3H), 7.26 (t, *J*=7.2 Hz, 1H), 7.18 (d, *J*=8.3 Hz, 2H), 5.66 (t, *J*=5.8 Hz, 1H), 5.21 (s, 1H), 2.92–2.97 (m, 1H), 2.78–2.83 (m, 1H), 2.34 (s, 3H), 1.16–1.20 (m, 2H), 1.05–1.09 (m, 2H), 0.88–0.91 (m, 4H), 0.84 (t, *J*=7.3 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ=166.63, 166.59, 139.3, 137.2, 134.8, 134.6, 129.9, 128.8, 128.5, 127.9, 127.7, 127.5, 127.4, 116.7, 70.9, 65.2, 39.3, 31.3, 28.8, 26.3, 22.4, 20.9, 13.9; IR ν (cm^{-1}) 3252, 1753, 1655; MS (MALDI-TOF): 463 ($M+Na^+$), 479 ($M+K^+$). Anal. Calcd for $C_{29}H_{32}N_2O_2$: C 79.06, H 7.32, N 6.36. Found: 79.21, H 7.79, N 6.31.

3.2.13. 1-(*p*-Chlorophenyl)-3,3-diphenyl-4-(*n*-hexylcarbamoyl)-β-lactam 6c. White solid, 60%; mp 170–171 °C; ^1H NMR (500 MHz, $CDCl_3$): δ=7.72 (d, *J*=7.5 Hz, 2H), 7.48 (d, *J*=7.4 Hz, 2H), 7.39–7.44 (m, 4H), 7.36 (d, *J*=8.9 Hz, 2H), 7.32 (t, *J*=7.5 Hz, 3H), 7.27 (t, *J*=7.3 Hz, 1H), 5.61 (t, *J*=5.6 Hz, 1H), 5.21 (s, 1H), 2.90–2.96 (m, 1H), 2.80–2.85 (m, 1H), 1.17–1.20 (m, 2H), 1.16–1.22 (m, 2H), 1.06–1.11 (m, 2H), 0.89–0.94 (m, 4H), 0.85 (t, *J*=7.3 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ=166.7, 166.2, 139.0, 136.9, 135.6, 130.2, 129.5, 128.9, 128.6, 128.0, 127.9, 127.43, 127.36, 118.1, 71.3, 65.3, 39.4, 31.2, 28.8, 26.3, 22.4, 13.9; IR ν (cm^{-1}) 3218, 1755, 1650; MS (MALDI-TOF): 483 ($M+Na^+$), 499 ($M+K^+$). Anal. Calcd for $C_{28}H_{29}ClN_2O_2$: C 72.95, H 7.69, N 6.08. Found: 72.97, H 6.55, N 6.07.

3.2.14. 4-Cyclohexylcarbamoyl-3,3-diphenyl-1-(*p*-methylphenyl)-β-lactam 6d. White solid, 77%; mp 230–231 °C; ^1H NMR (500 MHz, $CDCl_3$): δ=7.73 (d, *J*=7.3 Hz, 2H), 7.49 (d, *J*=7.2 Hz, 2H), 7.37–7.41 (m, 4H), 7.29–7.31 (m, 3H), 7.26 (t, *J*=7.0 Hz, 1H), 7.17 (d, *J*=8.3 Hz, 2H), 5.48 (d, *J*=8.5 Hz, 1H), 5.18 (s, 1H), 3.44–3.50 (m, 1H), 2.34 (s, 3H), 1.59–1.64 (m, 2H), 1.49 (t, *J*=15.5 Hz, 2H), 1.40 (d, *J*=10.0 Hz, 1H), 1.21 (q, *J*=13.2 Hz, 1H), 1.10 (q, *J*=13.4 Hz, 1H), 0.91–0.97 (m, 2H), 0.83 (dq, *J*=12.0, 2.5 Hz, 1H), 0.37 (dq, *J*=11.4, 3.2 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ=166.6, 165.5, 139.3, 137.2, 134.8, 134.6, 129.9, 128.8, 128.6, 127.8, 127.7, 127.6, 127.5, 116.7, 70.9, 65.3, 47.8, 32.5, 31.8, 25.2, 24.53, 24.46, 20.9; IR ν (cm^{-1}) 3247, 1754, 1648; MS (MALDI-TOF): 461 ($M+Na^+$), 477 ($M+K^+$). Anal. Calcd for $C_{29}H_{30}N_2O_2$: C 79.42, H 6.89, N 6.39. Found: C 79.19, H 6.97, N 6.17.

3.2.15. 1-(*p*-Bromophenyl)-4-cyclohexylcarbamoyl-3,3-diphenyl-β-lactam 6e. White solid, 71%; mp 244–245 °C; ^1H NMR (500 MHz, $CDCl_3$): δ=7.71 (d, *J*=7.9 Hz, 2H), 7.50 (d, *J*=8.7 Hz, 2H), 7.46 (d, *J*=7.7 Hz, 2H), 7.41 (t, *J*=7.8 Hz, 2H), 7.37 (d, *J*=8.8 Hz, 2H), 7.31 (t, *J*=7.5 Hz, 2H), 7.27 (t, *J*=7.0 Hz, 1H), 5.40 (d, *J*=8.5 Hz, 1H), 5.18 (s, 1H), 3.44–3.51 (m, 1H), 1.60 (d, *J*=8.8 Hz, 2H), 1.50 (t, *J*=17.7 Hz, 2H), 1.40 (d, *J*=13.0 Hz, 1H), 1.21 (q, *J*=12.9 Hz, 1H), 1.11 (q, *J*=13.1 Hz, 1H), 0.93–0.98 (m, 2H), 0.83 (dq, *J*=14.2, 2.7 Hz, 1H), 0.37 (dq, *J*=11.6, 2.9 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ=166.8, 165.1, 139.0, 136.9, 136.1, 132.4, 128.9, 128.7, 128.0, 127.9, 127.5, 127.4, 118.3, 117.8, 71.3, 65.3, 47.9, 32.6, 31.8, 25.2, 24.54, 24.47; IR ν (cm^{-1}) 3233, 1755, 1649;

MS (MALDI-TOF): 525 ($M+Na^+$), 541 ($M+K^+$). Anal. Calcd for $C_{28}H_{27}BrN_2O_2$: C 66.80, H 5.41, N 5.56. Found: C 66.71, H 5.37, N 5.59.

3.2.16. 4-(*tert*-Butylcarbamoyl)-3,3-dimethyl-1-(*p*-methoxyphenyl)-β-lactam 6f. White solid, 52%; mp 134–135 °C; ^1H NMR (500 MHz, $CDCl_3$): δ=7.32 (d, J=8.9 Hz, 2H), 6.90 (d, J=8.9 Hz, 2H), 5.65 (s, 1H), 4.05 (s, 1H), 3.82 (s, 3H), 1.50 (s, 3H), 1.33 (s, 3H), 1.32 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$): δ=170.9, 166.8, 156.5, 130.7, 117.9, 114.6, 65.1, 55.5, 55.1, 51.9, 28.7, 22.8, 17.1; IR ν (cm^{-1}) 3299, 1742, 1656; MS (MALDI-TOF): 304 (M^+), 327 ($M+Na^+$), 343 ($M+K^+$). Anal. Calcd for $C_{17}H_{24}N_2O_3$: C 67.08, H 7.95, N 9.20. Found: C 66.97, H 7.96, N 9.02.

Acknowledgements

This work was supported by the National Natural Science Foundation of China for Distinguished Young Scholars (no. 20525207), Program for New Century Excellent Talents in University (no. NCET-04-0143) and the 'PCSIRT'.

References and notes

1. (a) Morin, R. B.; Gorman, M. *Chemistry and Biology of β-lactam antibiotics*; Academic: New York, NY, 1982; Vols. 1–3; (b) Dürckheimer, W.; Blumbach, J.; Lattrell, R.; Scheunemann, K. H. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 180–202; (c) Singh, G. S. *Mini-Rev. Med. Chem.* **2004**, *4*, 93–109; (d) Singh, G. S. *Mini-Rev. Med. Chem.* **2004**, *4*, 69–92.
2. (a) Ojima, I. *Acc. Chem. Res.* **1995**, *28*, 383–389; (b) Ojima, I.; Delaloge, F. *Chem. Soc. Rev.* **1997**, *26*, 377–386; (c) Alcaide, B.; Almendros, P. *Curr. Med. Chem.* **2004**, *11*, 1921–1949; (d) Deshmukh, A. R. A. S.; Bhawal, B. M.; Krishnaswamy, D.; Govande, V. V.; Shinkre, B. A.; Jayanthi, A. *Curr. Med. Chem.* **2004**, *11*, 1889–1920; (e) Zanobini, A.; Gensini, M.; Magull, J.; Vidovic, D.; Kozhushkov, S. I.; Brandi, A.; de Meijere, A. *Eur. J. Org. Chem.* **2004**, 4158–4166.
3. Sperka, T.; Pitlik, J.; Bagossi, P.; Toezser, J. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 3086–3090.
4. Gerard, S.; Galleni, M.; Dive, G.; Marchand-Brynaert, J.; Batiment, L. *Bioorg. Med. Chem.* **2004**, *12*, 129–138.
5. Hirai, K.; Iwano, Y.; Fujimoto, K. *Tetrahedron Lett.* **1982**, *23*, 4025–4026.
6. (a) Singh, G. S. *Tetrahedron* **2003**, *59*, 7631–7649; (b) Magriotis, P. A. *Angew. Chem., Int. Ed.* **2001**, *113*, 4507–4509; (c) Coates, C.; Kabir, J.; Turos, E. *Sci. Synth.* **2005**, *21*, 609–646.
7. Marco-Contelles, J. *Angew. Chem., Int. Ed.* **2004**, *43*, 2198–2200.
8. (a) Kehagia, K.; Ugi, I. *Tetrahedron* **1995**, *51*, 9523–9530; (b) Ugi, I. *Angew. Chem.* **1982**, *94*, 826–835; Ugi, I. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 810–819; (c) Kolb, J.; Beck, B.; Dömling, A. *Tetrahedron Lett.* **2002**, *43*, 6897–6901.
9. (a) Lee, J.-C.; Kim, G. T.; Shim, Y. K.; Kang, S. H. *Tetrahedron Lett.* **2001**, *42*, 4519; (b) Escalante, J.; Gonzalez-Tototzin, M. A.; Avina, J.; Munoz-Muniz, O.; Juaristi, E. *Tetrahedron* **2001**, *57*, 1883.
10. Hegedus, L. S.; McGuire, M. A.; Schultze, L. M.; Chen, Y.; Anderson, O. P. *J. Am. Chem. Soc.* **1984**, *106*, 2680–2687.
11. (a) Palomo, C.; Aizpurua, J. M.; Ganboa, I.; Oiarbide, M. *Eur. J. Org. Chem.* **1999**, 3223–3235; (b) Venturini, A.; Gonzalez, J. *Mini-Rev. Org. Chem.* **2006**, *3*, 185–194.
12. (a) Zoghbi, M.; Warkentin, J. *J. Org. Chem.* **1991**, *56*, 3214–3215; (b) Zoghbi, M.; Warkentin, J. *Can. J. Chem.* **1993**, *71*, 912–918.
13. (a) Zoghbi, M.; Warkentin, J. *Can. J. Chem.* **1992**, *70*, 2967–2971; (b) Zoghbi, M.; Horne, S. E.; Warkentin, J. *J. Org. Chem.* **1994**, *59*, 4090–4095.
14. (a) Cheng, Y.; Meth-Cohn, O. *Chem. Rev.* **2004**, *104*, 2507–2530; (b) Cheng, Y.; Yang, H.; Meth-Cohn, O. *Chem. Commun.* **2003**, 90–91; (c) Cheng, Y.; Zhu, Q.; Li, Q.-S.; Meth-Cohn, O. *J. Org. Chem.* **2005**, *70*, 4840–4846; (d) Cheng, Y.; Wang, B.; Cheng, L.-Q. *J. Org. Chem.* **2006**, *71*, 4418–4427; (e) Cheng, Y.; Cheng, L.-Q. *J. Org. Chem.* **2007**, *72*, 2625–2630.
15. CCDC 621182, 645831, and 645830 [**4d**, (*S*,*S*)-**4i-I** and (*R*,*S*)-**4i-II**] contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
16. (a) Lee, K.-W.; Horowitz, N.; Ware, J.; Singer, L. A. *J. Am. Chem. Soc.* **1977**, *99*, 2622–2627; (b) Alajarin, M.; Vidal, A.; Tovar, F. *Lett. Org. Chem.* **2004**, *1*, 340–342; (c) Shustov, G. V.; Kachanov, A. V.; Kostyanovsky, R. G. *Izv. Akad. Nauk, Ser. Khim.* **1992**, 2584–2591; (d) Aumann, R.; Heinen, H. *Chem. Ber.* **1988**, *121*, 1739–1743.