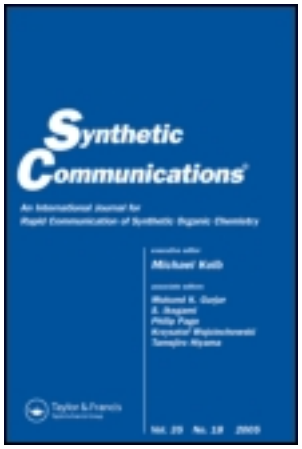

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SYNTHESIS OF β-LACTAMS FROM ACIDS AND IMINES USING THIOCARBONYLDIIMIDAZOLE

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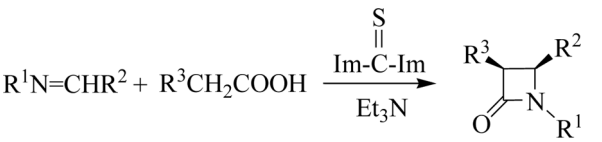
GRAPHICAL ABSTRACT



Abstract *Thiocarbonyldiimidazole has been found to be an efficient acid activator for the synthesis of β-lactams by ketene-imine cycloaddition at room temperature. The experimental procedure is simple and results in excellent yields of the products. All products were characterized by spectral data and elemental analyses.*

Keywords 2-Azetidinones; ketene; β-lactams; Staudinger reaction; thiocarbonyldiimidazole

INTRODUCTION

β-Lactam antibiotics have occupied a central role in the fight against pathogenic bacteria and the subsequent rise in quality of life for the world population as a whole.[1] However, the extensive use of common β-lactam antibiotics such as penicillins and cephalosporins in medicine has resulted in an increasing number of resistant strains of bacteria through mutation and β-lactamase gene transfer.[2] The medicinal application of β-lactams as cholesterol absorption inhibitor has been reported.[3] In addition, there are many important nonantibiotic uses of β-lactam (2-azetidinone)[4] such as human cytomegalovirus (HCMV) inhibitor,[5] human leukocyte elastase (HLE) inhibitor,[6] thrombin inhibitor,[7] porcine pancreatic elastase (PPE) inhibitor,[8] HIV-1 protease inhibitor,[9] cysteine protease inhibitor,[10] anticancer drugs,[11] antifungals,[12] potential antimalarials,[13] anti-influenzavirus agents,[14] antihyperglycemic compounds,[15] central nervous system (CNS) agents,[16] combatants of neurological diseases,[17] and antiproliferative drugs.[18]

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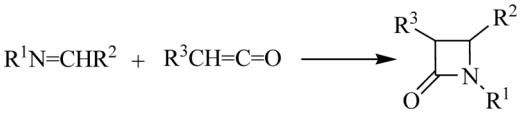


Scheme 1. The cycloaddition reaction of ketenes with imines.

These biological activities, combined with the use of β-lactams as starting materials to prepare several organic and medicinal compounds,[19] provide motivation to explore new methodologies for the synthesis of substances based on the β-lactam core.

Many synthetic methods were developed for the formation of the β-lactam ring.[20] The Staudinger reaction,[21] reactions of ketenes with imines (Scheme 1), is probably the most important synthetic tool to access β-lactams, and this reaction is still one of the best means for the synthesis of β-lactams.[22]

The most common method for the in situ production of ketene derivatives is the simple reaction of an acyl chloride with a tertiary amine as a base.[23] Because of instability and difficulty in the preparation of acyl chloride, the use of some activator of carboxylic acids for in situ generation of the ketene has been reported.[24] Thiocarbonyldiimidazole has been used previously for several organic transformations.[25]

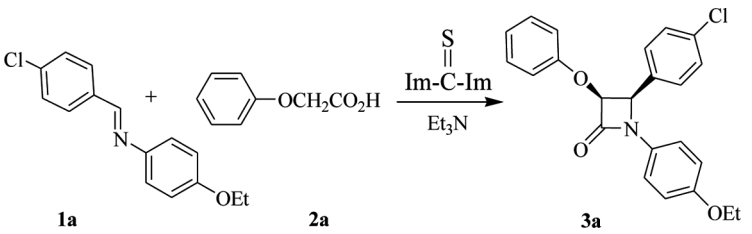
In this article we document the successful achievement of this goal and the synthesis of β-lactams by the Staudinger reaction from imines and substituted carboxylic acids using thiocarbonyldiimidazole as a simple and efficient method.

RESULTS AND DISCUSSION

The starting materials, Schiff bases **1a–d**, were synthesized from corresponding aldehydes and amines by condensation in ethanol at reflux. In a model study, the solution of *N*-(4-chlorobenzylidene)-4-ethoxyaniline **1a** and phenoxyacetic acid in dry dimethylformamide (DMF) was treated with thiocarbonyldiimidazole and dry triethylamine at room temperature. After extraction by chloroform, the usual workup, and crystallization from 95% EtOH, β-lactam **3a** was obtained as a white solid with 44% yield. This successful result encouraged us to investigate the optimum condition reactions. Then the effects of solvents, temperature of reaction, and quantity of reagent in the synthesis of **3a** were considered. According to Table 1, among the dry solvents examined, CH_2Cl_2 showed the best results. Also the workup in CH_2Cl_2 does not need extraction by chloroform. We found that the yields decreased at 0 °C. The molar optimization of reagent showed 1.5 mmol of thiocarbonyldiimidazole was needed to complete the reaction [thin-layer chromatographic (TLC) monitoring of the disappearance of the imine] in CH_2Cl_2 at room temperature. The indicated *cis* stereochemistry of the product was judged from the coupling constants of H-3 and H-4 of the β-lactam ring in ^{1}H NMR ($J > 4.0$).

Based on the successful results, 2-azetidinones **3a–l** were synthesized by treatment of 1.0 mmol of Schiff bases, 1.5 mmol of acetic acid derivatives, and 1.5 mmol

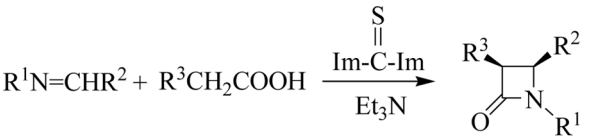
Table 1. Optimization of reaction condition in the synthesis of **3a**



1a **2a** **3a**

Entry	Solvent	Temperature (°C)	Thiocarbonyldiimidazole (mmol)	Yield (%)
1	DMF	rt	1.5	44
2	THF	rt	1.5	58
3	CH_2Cl_2	rt	1.5	94
4	Toluene	rt	1.5	47
5	CH_2Cl_2	0	1.5	70
6	CH_2Cl_2	rt	1.3	81
7	CH_2Cl_2	rt	1.1	55

thiocarbonyldiimidazole in the presence of triethylamine in dry CH_2Cl_2 at room temperature (Scheme 2, Table 2). β-Lactams **3a–l** were purified by recrystallization from EtOH. All products were characterized by spectral data and elemental analyses.



1 **2** **3**

Scheme 2. Synthesis of 2-azetidinones **3a–l** using thiocarbonyldiimidazole.

Table 2. Synthesis of 2-azetidinones **3a–l**

Product	R^1	R^2	R^3	Yield (%)
3a	4-$EtOC_6H_4$	4-ClC_6H_4	PhO	91
3b	4-$EtOC_6H_4$	4-ClC_6H_4	PhthN	87
3c	4-$MeOC_6H_4$	4-ClC_6H_4	MeO	85
3d	4-$EtOC_6H_4$	4-MeC_6H_4	PhO	90
3e	4-$EtOC_6H_4$	4-MeC_6H_4	PhthN	83
3f	4-$EtOC_6H_4$	4-MeC_6H_4	MeO	88
3g	4-$MeOC_6H_4$	4-$NO_2C_6H_4$	PhO	93
3h	4-$MeOC_6H_4$	4-$NO_2C_6H_4$	PhthN	87
3i	4-$MeOC_6H_4$	4-$NO_2C_6H_4$	MeO	91
3j	C_6H_5	C=C-C_6H_5	PhO	94
3k	C_6H_5	C=C-C_6H_5	PhthN	82
3l	C_6H_5	C=C-C_6H_5	MeO	92

CONCLUSION

In conclusion, we have developed a convenient and efficient method for the synthesis of 2-azetidinones; purification of products was performed with simple aqueous workup and recrystallization from EtOH. All β-lactams have *cis* stereochemistry, and the yields of products were good to excellent.

EXPERIMENTAL

All required chemicals were purchased from Merck and Acros chemical companies. The melting points were determined on a Buchi 535 apparatus and are uncorrected. Infrared (IR) spectra were measured on a Shimadzu Fourier transform (FT)–IR 8300 spectrophotometer. NMR spectra were recorded on a Bruker spectrophotometer (^{1}H NMR 250 MHz, ^{13}C NMR 62.9 MHz) using tetramethylsilane as an internal standard, and coupling constants are given in cycles per second (Hz). Elemental analyses were run on a Vario EL III elemental analyzer. TLC was carried out on silica-gel 254 analytical sheets obtained from Merck. The data for Schiff bases previously have been reported in the literature.[24a,b,26] Phthaloylglycine was prepared by a reported method.[27]

General Procedure for the Synthesis of 2-Azetidinones 3a–l Using Thiocarbonyldiimidazole

Thiocarbonyldiimidazole (0.27 g, 1.5 mmol) was added to a solution of the substituted acetic acid (1.5 mmol), corresponding Schiff base (1.0 mmol) and dry triethylamine (0.51 g, 0.70 mL, 5.0 mmol) in 15 mL dry solvents [CH_2Cl_2, DMF, tetrahydrofuran (THF), and toluene] at room temperature, and the mixture was stirred overnight. In the cases of DMF and THF, water was added, and extraction by 2×10 mL $CHCl_3$ was performed. Then the organic solution was washed successively with saturated $NaHCO_3$ (20 mL) and brine (20 mL). The organic layer was dried (Na_2SO_4) and filtered, and the solvent was removed under reduced pressure to give the crude products. β-Lactams **3a–l** were purified by recrystallization from EtOH.

1-(4-Methoxyphenyl)-4-(4-nitrophenyl)-3-phenoxyazetidin-2-one (3g)

White solid (93%), mp: 195–197 °C; IR (KBr) cm^{-1}: 1744 (CO, β-lactam); ^{1}H NMR ($CDCl_3$) δ 3.81 (OMe, s, 3H), 5.32 (H-4, d, 1H, $J = 4.6$), 5.53 (H-3, d, 1H, $J = 4.6$), 6.77–7.49 (ArH, m, 13H); ^{13}C NMR ($CDCl_3$) δ 56.3 (OMe), 60.9 (C-4), 82.7 (C-3), 113.4–160.1 (aromatic carbons), 161.7 (CO, β-lactam). Anal. calcd. for $C_{22}H_{18}N_2O_5$: C, 67.69; H, 4.65; N, 7.18. Found: C, 67.61; H, 4.75; N, 7.14.

2-(1-(4-Methoxyphenyl)-2-(4-nitrophenyl)-4-oxoazetidin-3-yl)isoindoline-1,3-dione (3h)

Light-yellow solid (87%), mp: 170–172 °C. IR (KBr) cm^{-1}: 1736, 1773 (CO, phth), 1784 (CO, β-lactam); ^{1}H NMR (DMSO-d_6) δ 3.81 (OMe, s, 3H), 5.37 (H-4,

d, 1H, $J = 4.8$), 5.76 (H-3, d, 1H, $J = 4.8$), 6.90–8.37 (ArH, m, 12H); ^{13}C NMR (DMSO-d_6) δ 58.3 (OMe), 60.7 (C-4), 63.2 (C-3), 113.4-157.5 (aromatic carbons), 162.3 (CO, phth), 165.4 (CO, β-lactam). Anal. calcd. for $C_{24}H_{17}N_3O_6$: C, 65.01; H, 3.86; N, 9.48. Found: C, 64.93; H, 3.94; N, 9.42.

3-Methoxy-1-(4-methoxyphenyl)-4-(4-nitrophenyl)azetidin-2-one (3i)

Light-yellow crystalline solid (91%), mp: 133–135 °C. IR (KBr) cm^{-1}: 1750 (CO, β-lactam); ^{1}H NMR ($CDCl_3$) δ 3.28, 3.69 (2 OMe, 2 s, 6H), 4.88 (H-4, d, 1H, $J = 4.6$), 5.37 (H-3, d, 1H, $J = 4.6$), 6.72–7.64 (ArH, m, 8H); ^{13}C NMR ($CDCl_3$) δ 55.3, 57.5 (2 OMe), 64.1 (C-4), 82.6 (C-3), 115.7–159.3 (aromatic carbons), 161.8 (CO, β-lactam). Anal. calcd. for $C_{17}H_{16}N_2O_5$: C, 62.19; H, 4.91; N, 8.53. Found: C, 62.28; H, 5.04; N, 8.58.

3-Phenoxy-1-phenyl-4-styrylazetidin-2-one (3j)

White solid (94%), mp: 185–187 °C. IR (KBr) cm^{-1}:1749 (CO, β-lactam); ^{1}H NMR ($CDCl_3$) δ 4.90 (H-4, dd, 1H, $J = 4.9$, 8.5), 5.37 (H-3, d, 1H, $J = 4.9$), 6.23 (H-5, dd, $J = 8.5$, 16.0), 6.75 (H-6, d, 1H, $J = 16.0$), 6.87–7.38 (ArH, m, 14H); ^{13}C NMR ($CDCl_3$) δ 63.7 (C-4), 81.5 (C-3), 115.0-157.4 (C=C, aromatic carbons), 162.2 (CO, β-lactam). Anal. calcd. for $C_{23}H_{19}NO_2$: C, 80.92; H, 5.61; N, 4.10. Found: C, 80.84; H, 5.70; N, 4.12.

2-(2-Oxo-1-phenyl-4-styrylazetidin-3-yl)isoindoline-1,3-dione (3k)

White solid (82%), mp: 196–198 °C. IR (KBr) cm^{-1}: 1732, 1753 (CO, phth), 1779 (CO, β-lactam); ^{1}H NMR ($CDCl_3$) δ 5.13 (H-4, dd, 1H, $J = 5.4$, 8.8), 5.61 (H-3, d, 1H, $J = 5.4$), 6.29 (H-5, dd, $J = 8.8$, 15.9), 6.87 (H-6, d, 1H, $J = 15.9$), 7.04–7.86 (ArH, m, 13H); ^{13}C NMR ($CDCl_3$) δ 61.5 (C-4), 64.1 (C-3), 113.7–158.6 (C=C, aromatic carbons), 163.8 (CO, phth), 166.5 (CO, β-lactam). Anal. calcd. for $C_{25}H_{18}N_2O_3$: C, 76.13; H, 4.60; N, 7.10. Found: C, 76.20; H, 4.73; N, 7.16.

3-Methoxy-1-phenyl-4-styrylazetidin-2-one (3l)

White crystal solid (92%), mp: 101–03 °C. IR (KBr) cm^{-1}: 1748 (CO, β-lactam); ^{1}H NMR ($CDCl_3$) δ 3.28 (OMe, s, 3H), 5.03 (H-4, dd, 1H, $J = 5.5$, 8.5), 5.68 (H-3, d, 1H, $J = 5.5$), 6.32 (H-5, dd, $J = 8.5$, 16.0), 6.85 (H-6, d, 1H, $J = 16.0$), 7.19–7.82 (ArH, m, 10H); ^{13}C NMR ($CDCl_3$) δ 57.7 (OMe), 61.0 (C-4), 82.1 (C-3), 118.6–155.8 (C=C, aromatic carbons), 167.3 (CO, β-lactam); Anal. calcd. for $C_{18}H_{17}NO_2$: C, 77.40; H, 6.13; N, 5.01. Found: C, 77.49; H, 6.25; N, 4.95.

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