Thionyl chloride (or oxalyl chloride) as an efficient acid activator for one-pot synthesis of β-lactams

E. Ebrahimi and A. Jarrahpour*

Department of Chemistry, College of Sciences, Shiraz University, Shiraz 71454, Iran
E-mails: jarrah@susc.ac.ir & aliasghar6683@yahoo.com

Abstract

Thionyl chloride (or oxalyl chloride) has been used as an efficient and cheap acid activator for one-pot synthesis of β-lactams in good to excellent yields by reaction between imines and acids in the presence of triethylamine at room temperature.

Keywords: Thionyl chloride; Oxalyl chloride; β-Lactam; Staudinger reaction; acid activator; Cycloaddition reaction

1. Introduction

Several natural and synthetic β-lactam compounds are of clinical importance because of their high antibiotic activity (Singh, 2004). In addition to their well-recognized antibiotic activity, β-lactams have been shown other biological activities as inhibitors of prostate specific antigen (Adlington, 1997), thrombin (Sutton, 2004), human cytomegalovirus protein (Gonzalez-Muniz, 2004), HIV-1 protease (Tozsara, 2005), human leukocyte elastase (Marchand-Brynaert, 2004) and cholesterol absorption (Bai, 2007), antifungal (Desai, 2006), potential antimalarials (Jarrahpour, 2011) and anticancer (Banik, 2005) properties.

There are numerous methods available for the construction of the β-lactam ring. [2+2] Cycloaddition of ketenes to imines (Staudinger reaction) is perhaps the most widely used (Staudinger, 1907). Several numbers of various methods have been introduced for the preparation of ketenes (Tidwell, 2006), the reaction of acyl halides with tertiary amines is the most commonly used (Jarrahpour, 2007). However, in a number of cases, the use of acyl halides produces poor results. For example, when ketenes of acyl halides contain strong electron withdrawing groups, the resulted low yields of the corresponding β-lactams are obtained (Motoyoshiya, 1988). Sometimes, the acid halides are not commercially available and they are prepared from carboxylic acids using acid activating agents such as 1,1-carbonyldi-imidazole (Nahmany, 2006), triphosgene (Deshmukh, 2002), ethyl chloroformate (Bose, 1979), trifluoroacetic anhydride (Bose, 1973), p-toluenesulfonyl chloride (Jarrahpour, 2010), phosphorus derived reagents (Bhalia, 2006), cyanuric chloride (Zarei, 2011), the Mukaiyama reagent (Matsui, 1998), methoxymethylene-N,N-dimethyliminiumsalt (Zarei, 2009), and POCl₃ (Bari, 2010).

2. Results and discussion

It is noticeable that the preparation, isolation and handling of acid chlorides are difficult and they are unstable. Therefore, thionyl chloride (or oxalyl chloride) has been used as acid activator to prepare ketenes in situ. Therefore, in this paper, we report the utility of thionyl chloride (or oxalyl chloride) as acid activator to prepare ketenes in situ in the one-pot synthesis of β-lactams. A solution of 1.5 mmol of thionyl chloride (or oxalyl chloride) was added dropwise to a mixture of Schiff bases 1a-d and substituted acetic acids 2a-c in dry CH₂Cl₂ in the presence of triethylamine at room temperature for
The molar optimization of thionyl chloride (or oxalyl chloride), carboxylic acid, imine and triethylamine for the synthesis of 3a is shown in Table 2 of which 1.5 mmol of thionyl chloride (or oxalyl chloride), 5 mmol of triethylamine, 1.5 mmol of carboxylic acid and 1.0 mmol of imine proved to be the best molar ratios at room temperature.

Table 2. Molar optimization of different reagent for the synthesis of 3a

<table>
<thead>
<tr>
<th>Entry</th>
<th>SOCl₂</th>
<th>(COCl)₂</th>
<th>Imine</th>
<th>Carboxylic acid</th>
<th>Base</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>-</td>
<td>1</td>
<td>1</td>
<td>3</td>
<td>70</td>
</tr>
<tr>
<td>2</td>
<td>1.3</td>
<td>1</td>
<td>1</td>
<td>1.3</td>
<td>4</td>
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<tr>
<td>3</td>
<td>1.5</td>
<td>1</td>
<td>1.5</td>
<td>5</td>
<td>93</td>
<td></td>
</tr>
</tbody>
</table>

These β-lactams 3a–l and 4a-d were purified by recrystallization from EtOAc (Table 3). All of the obtained β-lactams were the cis ones. The cis stereochemistry of 2-azetidinones 3a–l were deduced from the coupling constants of H-3 and H-4 of the ring which were calculated to be J₃,₄ = 4.3–5.9 Hz. Spiro-β-lactams 4a-d were also prepared by the same method from 9H-xanthene-9-carboxylic, triethylamine, imines 1a-d and thionyl chlroide (or oxalyl chloride) at room temperature for 8-10 hours.
3. CONCLUSION

In this article, it has been shown that thionyl chloride (or oxalyl chloride) has been used as an efficient and cheap acid activator for one-pot synthesis of β-lactams. The [2+2] cycloaddition reaction between imines and ketenes which are produced in situ from carboxylic acids using thionyl chloride (or oxalyl chloride) in the presence of triethylamine at room temperature afforded the desired 2-azetidinones. Other advantages of this method are short reaction times and excellent yields.

4. Experimental Section

4.1. General

All needed chemicals were purchased from Merck, Fluka and Acros chemical companies. All reagents and solvents were dried prior to use according to standard methods. IR spectra were run on a Shimadzu FT-IR 8300 spectrophotometer. 1H NMR and 13C NMR spectra were recorded in DMSO-d6 and CDCl3 using a Bruker Avance DPX instrument (1H NMR 250 MHz, 13C NMR 62.9 MHz). Chemical shifts (δ) were reported in parts per million (ppm) downfield from TMS. All of the coupling constants (J) are in hertz. The mass spectra were recorded on a Shimadzu GC-MS QP 1000 EX instrument. Elemental analyses were run on a Thermo Finnigan Flash EA-1112 series. Melting points were determined in open capillaries with Buchi 510 melting point apparatus. Thin-layer chromatography was carried out on silica gel F254 analytical sheets obtained from Fluka.

4.2. Typical procedure for synthesis of 3a

Thionylchloride or oxalyl chloride (1.5 mmol) was dissolved in CH2Cl2 (10 mL) and added drop wise to mixture of a solution of phenoxyacetic acid (1.5 mmol), N (4chlorobenzylidene)4methoxybenzenamine (1 mmol) and triethylamine (5 mmol) in dry CH2Cl2 (20 mL) at room termpature and the mixture was stirred for 9 h at room temperature. The reaction mixture was washed successively with saturated NaHCO3 (20 mL) and brine (10 mL). The organic layer was dried (Na2SO4), filtered and the solvent removed to give the crude product 3a, which was then purified by recrystallization from ethyl acetate to give pure β-lactam 3a as white solid.

5. Selected experimental data

4-(4-Chlorophenyl)-1-(4methoxyphenyl)-3-phenoxyazetidin-2-one (3a): Yield: 91%, mp: 180–182 °C; IR (KBr) cm⁻¹: 1745 (CO, β-lactam); 1H NMR (250 MHz, CDCl3) δ 3.95 (OMe, s, 3H), 6.75-7.49 (ArH, m, 13H); 13C NMR (62.9 MHz, CDCl3) δ 56.4 (OMe), 60.8 (C-4), 82.6 (C-3), 113.5, 115.7, 117.8, 119.4, 125.6, 129.5, 131.8, 136.1, 138.7, 145.5, 150.2, 158.3 (aromatic...
carbons), 161.8 (CO, β-lactam); GC–MS m/z=381 [M⁺, 35Cl], 379 [M⁺, 37Cl]. Anal. Caled for C₂₂H₁₇Cl₂NO₃: C, 63.78; H, 4.14; N, 3.38. Found: C, 69.51; H, 4.82; N, 6.90.

3-(4-Chlorophenoxy)-4-(4-chlorophenyl)-1-(4-methoxyphenyl)azetidin-2-one (3b): White solid (86%), mp: 181-183 °C IR (KBr) cm⁻¹: 1744 (CO, β-lactam); 1H NMR (CDCl₃) δ 8.01 (Me, t, 3H, J = 7.0 Hz), 7.96 (OCH₂, q, 2H, J = 7.0 Hz), 5.47 (H-4, d, 1H, J = 4.7 Hz), 5.63 (H-3, d, 1H, J = 4.8 Hz), 6.77-7.49 (ArH, m, 12H); 13C NMR (CDCl₃) δ 161.4 (CO), 129.4, 129.5, 140.3, 148.2, 155.1, 156.3 (aromatic carbons), 161.8 (CO, β-lactam); GC–MS m/z = 413 [M⁺, 37Cl], 415 [M⁺, 35Cl]; Anal. Caled for C₂₅H₁₉N₃O₆: C, 65.64; H, 4.19; N, 9.19. Found: C, 65.71; H, 4.24; N, 9.11.

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References


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