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

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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 (Tozsera, 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 variousmethods 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 and halogenating agents such as $POCl_3$, $SOCl_2$ and $(COCl)_2$. Thionyl chloride ($SOCl_2$) has been used as solvent to convert acids into acid chlorides (Munch-Petersen, 1963). The reaction starts at once without warming but it is necessary to reflux for several hours to complete the reaction. A method has been reported whereby acid was first converted into the acid chloride using oxalyl chloride and a catalytic amount of dimethyl formamide (DMF) in dichloromethane, after 24 hours the excess oxalyl chloride was decomposed at low temperature by slow addition of excess DMF (Pal, 2011). Consequently, various methods have been developed to generate ketenes 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 (Bhalla, 2006), cyanuric chloride (Zarei, 2011), the Mukaiyama reagent (Matsui, 1998), methoxymethylene-*N*,*N*-dimethyliminiumsalt (Zarei, 2010), the Vilsmeier reagent (DMF and $SOCl_2$ or $(COCl)_2$) (Zarei, 2009), and $POCl_3$ (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 thionylcholride (or oxalyl chloride) was added dropwise to a mixture of Schiff bases **1a-d** and substituted acetic acids **2a-c** in dry CH_2Cl_2 in the presence of triethylamine at room temperature for

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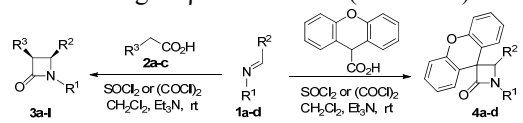
8-10 hours to give β-lactams **3a-l** (Scheme 1).



Scheme 1. Synthesis of β-lactams **3a–l** and **4a-d**

Among the tested solvents considered for the synthesis of β-lactam **3a** by thionyl chloride (or oxalyl chloride) in dry solvents at room temperature, dichloromethane showed to be the best one (Table 1). The yields were also better at room temperature than 0 ºC.

Table 1. Solvent and temperature optimization in the synthesis of **3a**

Entry	Solvent	Temp	Yield (%)	
			$SOCl_2$	$(COCl)_2$
1	CH_2Cl_2	rt	91	93
		0 ºC	79	78
2	$CHCl_3$	rt	83	81
		0 ºC	80	79
3	THF	rt	63	60
		0 ºC	61	53
4	Toluene	rt	72	75
		0 ºC	68	70
5	DMF	rt	50	51
		0 ºC	52	48
6	Acetonitrile	rt	55	52
		0 ºC	53	50

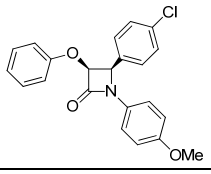
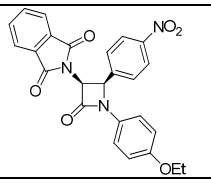
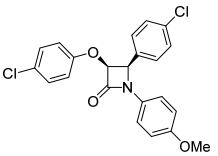
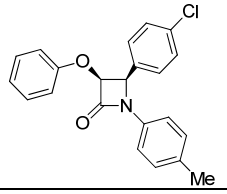
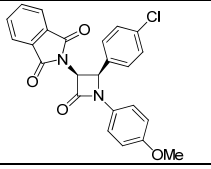
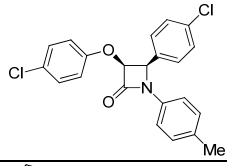
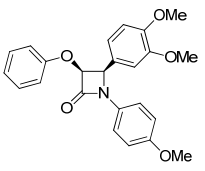
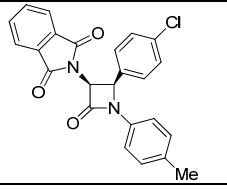
The molar optimization of thionyl chloride (or oxalyl chloride), carboxylic acid, imine and triethylamine for the synthesis of **3a** is shown in Table 2 of which 1.5 mmol of thionyl chloride (or oxalyl chloride), 5 mmol of triethylamine, 1.5 mmol of carboxylic acid and 1.0 mmol of imine proved to be the best molar ratios at room temperature.

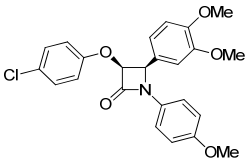
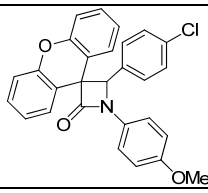
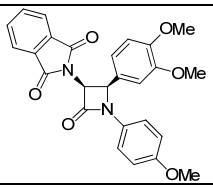
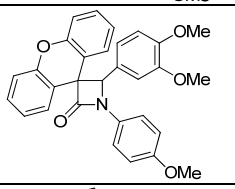
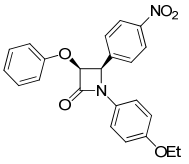
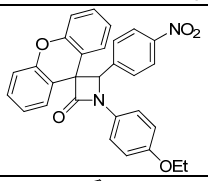
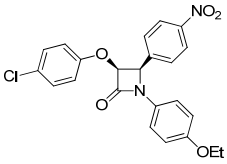
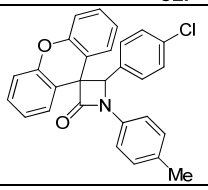
Table 2. Molar optimization of different reagent for the synthesis of **3a**

Entry	$SOCl_2$	$(COCl)_2$	Imine	Carboxylic acid	Base	Yield (%)
1	1	-	1	1	3	70
	-	1	1	1	3	68
2	1.3	-	1	1.3	4	85
	-	1.3	1	1.3	4	82
3	1.5	-	1	1.5	5	91
	-	1.5	1	1.5	5	93

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 $J_{3,4}$ = 4.3–5.9 Hz. Spiro-β-lactams **4a-d** were also prepared by the same method from 9*H*-xanthene-9-carboxylic, triethylamine, imines **1a-d** and thionyl cholride (or oxalyl chloride) at room temperature for 8-10 hours.

Table 3. Synthesis of β-lactams **3a-l** and **4a-d** with thionyl cholride or oxalyl chloride

β-Lactam	Structure	Yield (%)		β-Lactam	Structure	Yield (%)	
		$SOCl_2$	$(COCl)_2$			$SOCl_2$	$(COCl)_2$
3a		91	93	**3i**		88	85
3b		86	90	**3j**		90	91
3c		88	85	**3k**		87	89
3d		90	88	**3l**		86	83

3e		87	85	**4a**		90	87
3f		86	88	**4b**		91	89
3g		91	87	**4c**		87	85
3h		90	86	**4d**		85	83

[a] Isolated yield of pure products

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.[23] IR spectra were run on a Shimadzu FT-IR 8300 spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were recorded in DMSO-d_6 and $CDCl_3$ using a Bruker Avance DPX instrument (^{1}H NMR 250 MHz, ^{13}C 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

Thionylcholride or oxalyl chloride (1.5 mmol) was dissolved in CH_2Cl_2 (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 CH_2Cl_2 (20 mL) at room termrature and the mixture was stirred for 9 h at room temperature. The reaction mixture was washed successively with saturated $NaHCO_3$ (20 mL) and brine (10 mL). The organic layer was dried (Na_2SO_4), 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 ºC; IR (KBr) cm^{-1}: 1745 (CO, β-lactam); ^{1}H NMR (250 MHz, $CDCl_3$) δ 3.95 (OMe, s, 3H), 5.35 (H-4, d, 1H, *J* = 4.5 Hz), 5.55 (H-3, d, 1H, *J* = 4.5 Hz), 6.75-7.49 (ArH, m, 13H); ^{13}C NMR (62.9 MHz, $CDCl_3$) 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^+, ^{37}Cl], 379 [M^+, ^{35}Cl]. Anal. Calcd for $C_{22}H_{18}ClNO_3$: C, 69.57; H, 4.78; N, 3.69. Found: C, 69.51; H, 4.82; N, 3.64.

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 ($CDCl_3$) 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, 12H); ^{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); GC-MS m/z = 413 [M^+, ^{37}Cl], 415 [M^+, ^{35}Cl]; Anal. Calcd for: $C_{22}H_{17}Cl_2NO_3$: C, 63.78; H, 4.14; N, 3.38. Found: C, 63.73; H, 4.08; N, 3.25.

4(3,4dimethoxyphenyl)1(4methoxyphenyl)-3-phenoxyazetidin-2-one (3d): White solid (83%), mp 158-160 °C. IR (KBr) cm^{-1}: 1755 (CO, β-lactam); ^1H NMR ($CDCl_3$) δ 3.62, 3.72, 3.76 (3 OMe, 3 s, 9H), 5.44 (H-4, d, 1H, *J* = 5.8), 5.71 (H-3, d, 1H, *J* = 5.8), 6.68-7.37 (ArH, m, 12H); ^{13}C NMR ($CDCl_3$) δ 54.4, 54.7, 55.1 (OMe), 59.9 (C-4), 80.3 (C-3), 113.7-156.3 (aromatic carbons), 161.9 (CO, β-lactam); GC-MS m/z = 405 [M^+]; Anal. Calcd for $C_{24}H_{23}NO_5$: C, 71.10; H, 5.72; N, 3.45. Found: C, 71.23; H, 5.78; N, 3.51.

1-(4-Ethoxyphenyl)-4-(4-nitrophenyl)-3-phenoxyazetidin-2-one (**3g**) : Yield 91%; Mp: 180-182°C; IR (KBr, cm^{-1}): 1753 (CO β-lactam); 1350, 1527 (NO_2), ^1H-NMR ($CDCl_3$) δ (ppm): 1.37 (Me, t, 3H, *J* = 7.0 Hz),3.96 (OCH_2, q, 2H, *J* = 7.0 Hz), 5.47 (H-4, d, 1H, *J* = 4.7 Hz), 5.63 (H-3, d, 1H, *J* = 4.72 Hz), 6.76–8.17 (ArH, m, 13H); 13C-NMR δ (ppm): 14.7 (Me), 61.1(OCH_2), 63.7 (C-4), 81.2 (C-3), 115.1, 115.4,118.7, 122.6,123.5, 129.0, 129.4, 129.7, 140.5, 148.1, 156.2, 156.4 (aromatic carbon), 161.8 (CO β-lactam); GC-MS m/z = 404 [M^+]; Analysis calculated for $C_{23}H_{20}N_2O_5$: C, 68.31; H, 4.98; N, 6.93.Found: C, 68.33; H, 4.97; N, 6.90%.

3-(4-Chlorophenoxy)-1-(4ethoxyphenyl)-4-(4-nitrophenyl)azetidin-2-one (**3h**) : Yield 90%; Mp: 180-182°C; IR (KBr, cm^{-1}): 1743 (CO β-lactam); 1342, 1522 (NO_2), ^1H-NMR ($CDCl_3$) δ (ppm): 1.34 (Me, t, 3H, *J* = 7.0 Hz), 3.92 (OCH_2, q, 2H, *J* = 7.0 Hz), 5.46 (H-4, d ,1H, *J* = 4.7 Hz), 5.56 (H-3, d, 1H, *J* = 4.7 Hz), 6.72–8.18 (ArH, m, 12H); ^{13}C-NMR δ (ppm): 14.7 (Me), 60.8 (OCH_2), 63.7 (C-4), 81.3 (C-3),115.1, 116.8, 118.7, 123.7, 127.7, 128.9, 129.4, 129.5, 140.3, 148.2, 155.1, 156.3 (aromatic carbon), 161.4 (CO β-lactam); GC-MS m/z = 438 [M^+]; Analysis calculated for $C_{23}H_{19}ClN_2O_5$: C, 62.95; H, 4.36; N, 6.38. Found: C, 62.93; H, 4.39; N, 6.37%.

2-(1-(4-Ethoxyphenyl)-2-(4-nitrophenyl)-4-oxoazetidin-3-yl)isoindol-ine-1,3-dione (3i): Light-yellow crystalline solid (91%), mp: 179-181 °C IR ($CHCl_3$) cm^{-1}: 1337, 1521 (NO_2), 1736, 1773 (CO, Phth), 1784 (CO, β-lactam); ^1H NMR (DMSO-d_6) δ 1.26 (Me, t, 3H, *J* = 7.0), 3.87 (OCH_2, q, 2H, *J* = 7.0 Hz), 5.37 (H-4, d, 1H, *J* = 4.8), 5.76 (H-3, d, 1H, *J* = 4.8 Hz), 6.90-8.37 (ArH, m, 12H); ^{13}C NMR (DMSO-d_6) δ 14.5 (Me), 58.3 (OCH_2), 60.7 (C-4), 63.2 (C-3), 113.4-157.5 (aromatic carbons), 162.3 (CO, phth), 165.4 (CO, β-lactam); GC-MS m/z = 457 [M^+]; Anal. Calcd for $C_{25}H_{19}N_3O_6$: C, 65.64; H, 4.19; N, 9.19. Found: C, 65.71; H, 4.24; N, 9.11.

1(4Ethoxyphenyl)2(4nitrophenyl)spiro[azetidine-3,9'-xanthen]-4-one (4c): Light-yellow crystalline solid (79%), mp: 186-188 °C IR ($CHCl_3$) cm^{-1}: 1343, 1529 (NO_2), 1757 (CO, β-lactam); ^1H NMR ($CDCl_3$) δ 1.38 (Me, t, 3H, *J* = 7.0), 4.05 (OCH_2, q, 2H, *J* = 7.0), 5.12 (H-4, s, 1H), 6.87-7.89 (ArH, m, 16H); ^{13}C NMR ($CDCl_3$) δ 14.8 (Me), 63.8 (OCH_2), 64.5 (C-4), 73.4 (C-3), 115.3-156.3 (aromatic carbons), 164.8 (CO, β-lactam); GC-MS m/z = 478 [M^+]; Anal. Calcd for $C_{29}H_{22}N_2O_5$: C, 72.79; H, 4.63; N, 5.85. Found: C, 72.84; H, 4.73; N, 5.78.

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