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Tetrahedron Letters
Tetrahedron Letters 48 (2007) 8712–8714

The Vilsmeier reagent as an efficient acid activator for the synthesis of β-lactams

Aliasghar Jarrahpour* and Maaroof Zarei

Department of Chemistry, College of Sciences, Shiraz University, Shiraz 71454, Iran

Received 5 August 2007; revised 26 September 2007; accepted 3 October 2007
Available online 6 October 2007

Abstract—The Vilsmeier reagent (chloromethylenedimethylammonium chloride) has been used as an efficient and cheap acid activator for the one-step Staudinger reaction of substituted acetic acids and imines under mild conditions. This reaction is clean and the by-products are DMF and triethylamine hydrochloride which were removed by simple aqueous work-up.

Several natural and synthetic compounds, containing the β-lactam nucleus, are of clinical importance due to their high antibiotic activity[1] and the importance of β-lactams for the treatment of bacterial infections has been amply established.[2] Large efforts have been made on the synthesis and structural modification of the β-lactam nucleus to increase antimicrobial activity. However, the rapid emergence of bacterial strains resistant to most generally used members of this class of compounds requires a continuous effort for the design and synthesis of novel derivatives that are stable to β-lactamases and possess high potency and broad spectrum activity both in vitro and in vivo.[3] A number of naturally occurring monocyclic β-lactams such as nocardicins and monobactams have been shown to exhibit high antibacterial activity, suggesting that the biological activity is strictly correlated to the presence of a suitably functionalized 2-azetidinone ring[4] and that β-lactams do not require a conformationally constrained bicyclic structure to have antibacterial properties.[5] Some monocyclic β-lactams have been synthesized in our laboratory and have shown good antibacterial activities.[6]

In addition to their well-recognized properties as antibiotics, β-lactams have been recently shown to possess other relevant biological activities as inhibitors of prostate specific antigen,[7] thrombin,[8] human cytomegalovirus protein,[9] HIV-1 protease,[10] human leucocyte elastase[11] and cholesterol absorption.[12] Antifungal,[13] potential antimalarials[14] and anticancer[15] properties are also other new biological activities of these compounds. For natural products chemists, β-lactams hold a special attraction where these four membered, chiral heterocycles have been shown to be versatile synthons for a wide variety of natural products.[16]

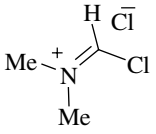
There are numerous methods available for the construction of the β-lactam ring. A widely used method is via the [2+2] cyclocondensation of ketenes to imines, a process known as the Staudinger reaction.[17] Generally, acid chlorides are used as precursor to ketenes.[18] However, the preparation, isolation and handling of acid chlorides are difficult and they are unstable. Therefore, various methods to generate ketenes from acid activating agents such as 1,1-carbonyldi-imidazole,[19] triphosgene,[20] ethyl chloroformate,[21] trifluoroacetic anhydride,[22] *p*-toluenesulfonyl chloride,[23] phosphorus derived reagents,[24] cyanuric chloride[25] and the Mukaiyama reagent[26] have been developed. Some of these reagents are expensive and toxic and in some cases the yield of products were low.

Chloromethylenedimethylammonium chloride (Vilsmeier reagent) **1** serves not only as a formylating agent,[27] but also as an activating reagent for carboxylic acids to give esters,[28] amides,[29] and acid chlorides[30] and for alcohols to give alkyl chlorides,[31] esters,[32] alkyl aryl sulfides[33] and imides.[34] Sharma and coworkers have used this reagent for the synthesis of β-lactams from β-amino acids.[35] It is easily prepared from *N*,*N*-dimethylformamide and a chlorinating reagent.[36]

Keywords: Vilsmeier reagent; β-Lactam; Staudinger reaction; Acid activator; Cycloaddition reaction.
* Corresponding author. Tel.: +98 711 228 4822; fax: +98 711 228 0926; e-mail addresses: jarrah@chem.susc.ac.ir; aliasghar6683@yahoo.com

0040-4039/$ - see front matter © 2007 Published by Elsevier Ltd.
doi:10.1016/j.tetlet.2007.10.012

Chloromethylenedimethylammonium chloride **1** was prepared from DMF and oxalyl chloride or thionyl chloride in dry dichloromethane. Treatment of imines **2** with various substituted acetic acids **3** and **1** in dry dichloromethane at 0 °C in the presence of triethylamine afforded β-lactams **4a**–**p**. After crystallization from ethyl acetate the pure β-lactams were obtained in high yields with complete cis-selectivity (Scheme 1, Table 1).[37]

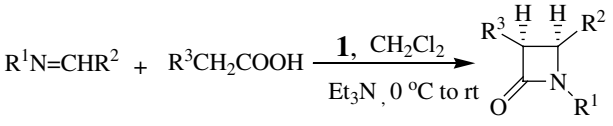


1

The cis stereochemistry of 2-azetidinones **4a**–**p** was deduced from the coupling constants of H-3 and H-4 which were calculated to be $J_{3,4} = 4.2$–5.8 Hz.

In this method the ketenes are formed not from the acid chlorides but directly from the carboxylic acids. Thus, we found that the Staudinger reaction of imines with carboxylic acids using (chloromethylene)dimethylammonium chloride **1** as an activating agent proceeded smoothly under mild conditions. This reaction system is quite practical, since the starting carboxylic acids can be easily handled and stored.

This Letter describes the first example of the use of the Vilsmeier reagent in the synthesis of β-lactams from acids and imines. This method is very efficient, particularly for larger scale applications and especially as the side products are innocuous and no side reactions were observed under these reaction conditions. All the reactants could be mixed at the same time in this procedure and the generation of a ketene prior to addition of the imine was unnecessary.



2 **3** **4a-p**

Scheme 1.

Acknowledgement

The authors thank the Shiraz University Research Council for financial support (Grant No. 86-GR-SC-23).

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Table 1. Synthesis of β-lactams **4a**–**p** from imines **2** and acids **3**

Entry	R^1	R^2	R^3	Product[a]	Yield[b] (%)	Mp (°C)
1	4-$EtOC_6H_4$	4-$NO_2C_6H_4$	PhO	**4a**	93	180–182
2	4-$EtOC_6H_4$	4-ClC_6H_4	PhO	**4b**	87	164–166
3	4-$EtOC_6H_4$	4-$MeOC_6H_4$	PhO	**4c**	81	168–170
4	4-$MeOC_6H_4$	4-MeC_6H_4	PhO	**4d**	88	165–167
5	4-$MeOC_6H_4$	3,4-$DiMeOC_6H_3$	PhO	**4e**	83	186–188
6	4-$MeOC_6H_4$	4-ClC_6H_4	PhO	**4f**	86	181–183
7	4-$MeOC_6H_4$	C≡CPh	PhthN	**4g**	90	189–191
8	4-$EtOC_6H_4$	4-$NO_2C_6H_4$	PhthN	**4h**	91	190–192
9	4-$EtOC_6H_4$	4-$MeOC_6H_4$	PhthN	**4i**	82	199–201
10	4-$EtOC_6H_4$	4-MeC_6H_4	PhthN	**4j**	89	202–204
11	4-$MeOC_6H_4$	3,4-$DiMeOC_6H_3$	3-NO_2PhthN	**4k**	80	198–200
12	4-$EtOC_6H_4$	4-MeC_6H_4	MeO	**4l**	84	133–135
13	4-$EtOC_6H_4$	4-$NO_2C_6H_4$	2,4-$DiClC_6H_3O$	**4m**	94	160–162
14	4-$EtOC_6H_4$	4-ClC_6H_4	2,4-$DiClC_6H_3O$	**4n**	92	182–184
15	4-$EtOC_6H_4$	4-$NO_2C_6H_4$	2-NaphthO	**4o**	95	174–176
16	4-$EtOC_6H_4$	4-ClC_6H_4	2-NaphthO	**4p**	90	140–142

[a] All products were characterized by IR, ^{1}H NMR, ^{13}C NMR, mass and elemental analysis.
[b] Isolated yield of pure products.

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37. *Typical procedure*: Chloromethylenedimethylammonium chloride (1.5 mmol) was added to a solution of phenoxyacetic acid (1.5 mmol), (4-nitrobenzylidene)-4-ethoxyaniline (1 mmol) and triethylamine (6 mmol) in dry CH_2Cl_2 (20 ml) at 0 °C and the mixture was stirred for 8 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 was removed to give the crude product, which was purified by crystallization from ethyl acetate to give pure β-lactam **4a** in 93% yield. Mp: 180–182 °C IR (KBr) cm^{-1}: 1744 (CO, β-lactam); ^1H NMR (250 MHz, $CDCl_3$) δ 1.30 (Me, t, 3H, $J = 7.0$ Hz), 3.89 (OCH_2, q, 2H, $J = 6.95$ Hz), 5.39 (H-4, d, 1H, $J = 4.8$ Hz), 5.55 (H-3, d, 1H, $J = 4.8$ Hz), 6.68–8.08 (ArH, m, 13H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 14.74 (Me), 61.11 (OCH_2), 63.72 (C-4), 81.24 (C-3), 115.17–156.49 (aromatic carbons), 161.82 (CO, β-lactam); GC–MS $m/z = 404$ [M^+]; Anal. Calcd for $C_{23}H_{20}N_2O_5$: C, 68.31; H, 4.98; N, 6.93. Found: C, 68.28; H, 5.05; N, 6.88.