Synthesis of β-lactams *via* Staudinger reaction using *N*-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline as a carboxylic acid activator

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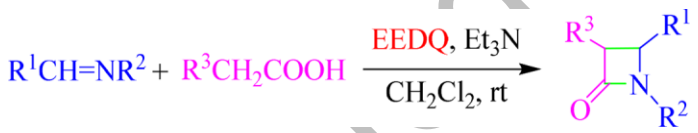
Abstract

N-Ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline (EEDQ) has been used as an efficient and convenient reagent for the one-pot synthesis of β-lactams by [2+2] ketene-imine cycloaddition (Staudinger reaction). Clean, simplicity of method and good to excellent yield of products are some advantages of this method.

GRAPHICAL ABSTRACT



KEYWORDS: β-Lactam, 2-Azetidinone, Staudinger reaction, EEDQ, Ketene, Imine

INTRODUCTION

2-Azetidinones, generally referred as β-lactams, show a unique ring system, with interesting chemistry and great biological activities.[1] The 2-azetidinone ring system is the key of antibacterial activity in β-lactam antibiotics which have been widely used as chemotherapeutic agents for treating microbial diseases.[2,3] Antibiotic resistance is a

growing problem of modern medicine and some patients die annually from infection due to antibiotic resistance.[4] In addition, β-lactams possess many other pharmacological activities such as human cytomegalovirus protease inhibitors, LHRH antagonists, cholesterol absorption inhibitors, anticancer agents, antihyperglycemic, antimalarial, anti-HIV, anti-inflammatory and analgesic activities.[5] Furthermore, the considerable variety of transformations related to the selective bond cleavage (enhanced by the ring strain) of the 2-azetidinone core has suggested a systematic use of the β-lactam skeleton as a synthon in organic synthesis.[6,7] Then many synthetic methods have been developed for the formation of the β-lactam ring.[8,9] The Staudinger reaction[10] is most common method which applied for the synthesis of β-lactams.[11–13]

A number of methods for generation of ketenes have been reported,[14–16] but reaction of acyl chlorides with triethylamine is the most approach.[17–18] However, sometimes application of acyl chlorides gave inadequate results and low yield of products. Also stability of acyl chlorides is low and preparation, isolation, and handling of acid chlorides are difficult. Recently some coupling reagents as carboxylic acid activator have been used in the Staudinger reaction such as Vilsmeier reagent,[19] cyanuric fluoride,[20] 1,1-carbonyldiimidazole,[21] 2-fluoro-1-methylpyridinium *p*-toluenesulfonate,[22] propylphosphonic anhydride (T3P),[23] phosphonitrilic chloride[24] and diphosphorustetraiodide.[25] But some of them is expensive, need to control of temperatures and painful chromatographic separations of products. *N*-Ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline (EEDQ) is a highly specific reagent for activation of carboxyl groups in the coupling of amino acids in high yield and without racemization.[26]

Also applications of EEDQ for conversion of carboxylic acids to esters[27] and amides[28] have been reported.

To the best of our knowledge, 2-ethoxy-l-(ethoxycarbonyl)-l,2-dihydroquinoline (EEDQ) has not been used as a reagent for the synthesis of β-lactams ring. In this paper, we wish to report that EEDQ can be successfully utilized as a convenient reagent for the synthesis of β-lactams ring from imines and substituted acetic acids.

RESULTS AND DISCUSSION

Initially, a mixture of equimolar aldehydes and amines in ethanol was refluxed for 3 hours. After cooling, resulting precipitate were separated by filtration, and then were washed with cold ethanol to give pure corresponding Schiff bases (Scheme 1). Reaction of phenoxyacetic acid, *N*-(4-methoxyphenyl)-1-phenylmethanimine with EEDQ in the presence of triethylamine in dry dichloromethane gave β-lactam **5a** after crystallization from ethanol. Among the dry solvents, the best yield was obtained using dichloromethane. When cold media or refluxing dichloromethane was used, decrease of yield was observed. According to table 1, the highest yield was obtained when 1.3 mmol phenoxyacetic acid and 1.3 mmol EEDQ were reacted with 1.0 mmol of imine in dry dichloromethane at room temperature (Table 1, Entry 8).

After optimization of reaction condition, β-lactams **5a-i** were synthesized by this method (Scheme 2, Table 2). Also, spiro-β-lactams **5j-m** were prepared using EEDQ from xanthene-9-carboxylic acid or fluorene-9-carboxylic acid. The progress of all reactions

was followed by TLC monitoring. After simple aqueous work-up, all products were purified by crystallization from ethanol. β-Lactams **5a-m** were characterized by spectral data. The reaction was performed in mild reaction condition with good to excellent yield of products.

The stereochemistry of β-lactams **5a-i** were determined by the comparison of the coupling constant H-3 and H-4 ($J_{3,4}$> 4.0 Hz) for the *cis* stereoisomer and ($J_{3,4}$≤ 3.0 Hz) for the *trans* stereoisomer.[29]

Temperature, solvent, electronic effects, and the steric hindrance of the ketene and imine substituents affect the stereochemistry of β-lactams in the Staudinger reaction. 3-Phthalimido-β-lactams **5c**, **5g** and **5i** were obtained as *trans* stereoisomer because ketenes derived from phthalimidoacetic acid have more steric hindrance than aryloxyketenes.

Proposed mechanism according to a reported mechanism for the Staudinger reaction[30-31] and for carboxylic acid activation using EEDQ,[32] was represented in scheme 3 *via* formation of a mixed anhydride which *in situ* generated of ketene.

CONCLUSIONS

In summary, we have developed a simple synthesis of monocyclic and spiro- β-lactams by one-pot [2+2] ketene-imine cycloaddition of imines and substituted acetic acids using *N*-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline (EEDQ). Due to the mild reaction

condition, good yields, and easily accessible starting material, we think that this new synthetic approach has the potential in the synthesis of various β-lactams.

EXPERIMENTAL

Melting points were measured by the capillary tube method with an opti-melt MPA100 apparatus. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker Spectrospin Advance 400 spectrometer using TMS as an internal standard and $CDCl_3$ as a solvent. Chemical shifts were reported in ppm (δ) and coupling constants (*J*) were reported in Hz. IR spectra were recorded from KBr disk on the Shimadzu FT IR-8400S. Elemental analyses were run on a Thermo Finnigan Flash EA–1112. Commercial aluminum-backed plates of silica gel 60 F_{254} was used to monitor the progress of reactions by thin layer chromatography (TLC).

General Procedure For The Synthesis Of 2-Azetidinones (5a-M)

EEDQ (1.3 mmol) was added to a solution of the substituted acetic acid (1.3 mmol), the Schiff base (1.0 mmol) and Et_3N (5.0 mmol) in dry CH_2Cl_2 (15 mL) at room temperature, and the mixture was stirred overnight. The mixture was washed successively with saturated $NaHCO_3$ (15 mL) and brine (15 mL). The organic layer was dried (Na_2SO_4), filtered and the solvent was removed under reduced pressure. The crude residue was purified by crystallization from 95% EtOH.

4-(2,4-Dichlorophenyl)-1-(4-Methoxyphenyl)-3-Phenoxyazetidin-2-One (5b)

White solid. m.p. 132-135 ^{o}C, IR (KBr) cm^{-1}: 1755 (CO, β-lactam), ^{1}H NMR ($CDCl_3$) δ: 3.69 (s, 3H, OMe) , 5.52 (d, 1H, *J*=4.9, H-4), 5.71 (d, 1H, *J*=4.9, H-3), 6.75-7.29 (m, 12H, ArH); ^{13}C NMR ($CDCl_3$) δ: 54.4 (OMe), 57.0 (C-4),80.3 (C-3), 113.5, 114.8, 117.6, 121.5, 124.8, 126.3,127.7,128.2, 128.7, 128.9, 133.2, 133.9, 155.7, 155.9 (aromatic carbons), 161.3 (CO, β-lactam), Anal. Calcd for $C_{22}H_{17}Cl_2NO_3$: C, 63.78; H, 4.14; N, 3.38. Found: C, 63.87; H, 4.28; N, 3.43.

SUPPLEMENTAL MATERIAL

Supplemental data for this article can be accessed on the publisher's website.

ACKNOWLEDGEMENTS

Financial support from Payame noor University Research Council is gratefully acknowledged.

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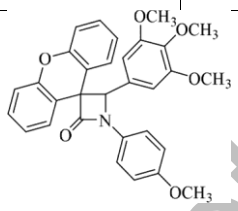
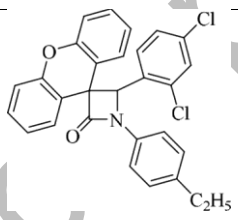
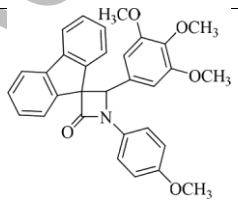
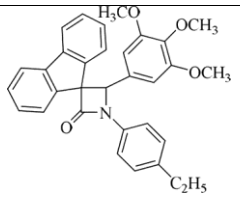
Table 1. Reaction condition in the synthesis of β-lactams

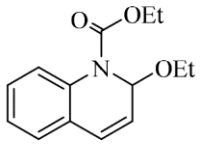
Entry	Solvent	Temp	mmol EEDQ	Yield (%)
1	CH_2Cl_2	rt	1.0	69
2	THF	rt	1.0	23
3	Toluene	rt	1.0	52
4	DMF	rt	1.0	47
5	$CHCl_3$	rt	1.0	60
6	CH_2Cl_2	0 ^oC	1.0	48
7	CH_2Cl_2	40 ^oC	1.0	53
	CH_2Cl_2	rt	1.3	88
	CH_2Cl_2	rt	1.5	87

Table 2. Synthesis of β-lactams **5a-m** using EEDQ

Entry	R^1	R^2	R^3	*cis/trans*	Product	Yield (%)
1	4-$MeOC_6H_4$	Ph	PhO	*cis*	**5a**	88
	4-$MeOC_6H_4$	2,4-$Cl_2C_6H_3$	PhO	*cis*	**5b**	96
	4-$MeOC_6H_4$	2,4-$Cl_2C_6H_3$	PhthN	*trans*	**5c**	71
	4-$MeOC_6H_4$	3,4,5-$(MeO)_3C_6H_2$	2,4-$Cl_2C_6H_2O$	*cis*	**5d**	93
	4-EtC_6H_4	2,4-$Cl_2C_6H_3$	PhO	*cis*	**5e**	83
	4-EtC_6H_4	2,4-$Cl_2C_6H_3$	2,4-$Cl_2C_6H_2O$	*cis*	**5f**	91
	4-EtC_6H_4	2,4-$Cl_2C_6H_3$	PhthN	*trans*	**5g**	89
	4-EtC_6H_4	3,4,5-$(MeO)_3C_6H_2$	PhO	*cis*	**5h**	83
	4-EtC_6H_4	3,4,5-$(MeO)_3C_6H_2$	PhthN	*trans*	**5i**	88
				-	**5j**	80
11				-	**5k**	84
12				-	**5l**	48

13		-	**5m**	53

Scheme 1. Preparation of Schiff bases.



***N*-Ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline (EEDQ)**

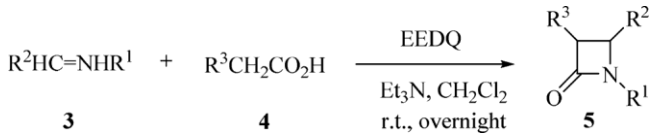
R^1-NH_2 + R^2-CHO $\xrightarrow[\text{reflux , 3 h}]{\text{EtOH}}$ R^1-N=CH-R^2

1 **2** **3**

R^1= 4-$MeOC_6H_4$, 4-EtC_6H_4

R^2= 2,4-$Cl_2C_6H_3$, 3,4,5-$(MeO)_3C_6H_2$

Scheme 2. Preparation of β-lactams.



3 4 5

Scheme 3. Proposed mechanism.