Send Orders for Reprints to reprints@benthamscience.ae

44 *Letters in Organic Chemistry,* **2015,** *12,* **44-49**

An Easy and Convenient Synthesis of β-Lactams *via* a One-Pot Staudinger Reaction with 4-(4,6-Dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium Chloride Starting from Substituted Carboxylic Acids

Maaroof Zarei*

Department of Chemistry, College of Sciences, Hormozgan University, Bandar Abbas 71961, Iran

Received April 12, 2014: Revised August 27, 2014: Accepted October 20, 2014

Abstract: An easy and convenient direct synthesis of 2-azetidinones is described. The [2+2] cycloaddition reaction of imines and carboxylic acids using 4-(4,6-dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium chloride (DMTMM) has been employed to synthesize a variety of 2-azetidinones in high yields. The products were easily isolated because the by-products are highly soluble in water.

Keywords: β-Lactam, 2-Azetidinone, Staudinger reaction, DMTMM, Ketene, Imine.

INTRODUCTION

1,3,5-Triazine derivatives have been known for a long period of time. They have found widespread applications in the pharmaceutical, textile, plastic, and rubber industries, and are used as pesticides, dyestuffs, optical bleaches, explosives, and surface active agents [1].

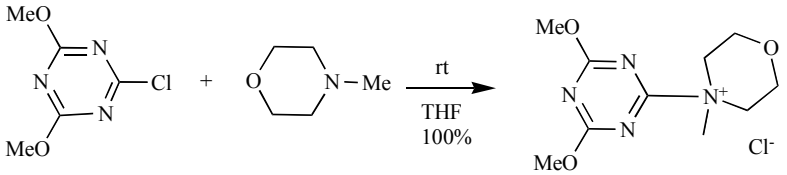
Treatment of 2-chloro-4,6-dimethoxy-1,3,5-triazine (CDMT) and *N*-methylmorpholine (NMM) in THF at room temperature afforded 4-(4,6-dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium chloride (DMTMM) as a white precipitate, which was found active for at least one month by storage in a well-capped bottle [2]. It is also commercially available. Unlike CDMT, DMTMM is not an irritating agent for eyes and nose [3].

Recently, DMTMM has been applied as a coupling agent, in amidation, esterification, glycosidation and phosphonylation methodology [4]. This coupling reagent is also useful for preparation of Weinreb amides [5], formyl amides [6] and 1,2,4-oxadiazole [7].

β-Lactams, 2-azetidinones, are very attractive heterocycles present as core structure in many biologically active compounds, particularly, in most widely used classes of antibiotics [8]. β-Lactams have been shown to possess a wide variety of pharmacological activities [9], for example, Ezetimibe is used clinically due to its cholesterol absorption inhibitor property [10]. In addition, the 2-azetidinone scaffold is a versatile intermediate in the preparation of many classes of compounds [11].

The Staudinger reaction (ketene-imine cycloaddition) is undoubtedly the most widely used route to 2-azetidinones where it can be used for synthesis of several types of 2-azetidinones [12]. Ketenes are commonly generated by reaction of acyl halides with tertiary amines [13]. Use of acid halide has some drawbacks such as commercial unavailability, handling and safety concerns. Because of the disadvantages, preparation of ketenes from carboxylic acids is very useful. This method includes treatment of the carboxylic acid with carboxylic acid activators to generate an activated intermediate, which then generates ketenes *in situ* by treatment with base [14]. However, harsh conditions, low yield, cost and difficulty in purification of product are some of the disadvantages.

In this paper, a method suitable for facile and efficient synthesis of β-lactams from carboxylic acids and DMTMM as the acid activator has been developed.



CDMT DMTMM

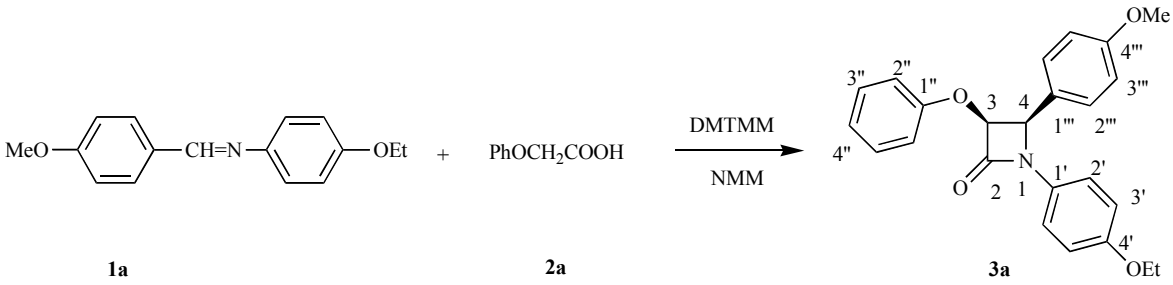
RESULTS AND DISCUSSION

Initially, equimolar amounts of aldehydes and amines were mixed and heated in ethanol 95% to give Schiff bases.

*Address correspondence to this author at the Department of Chemistry, College of Sciences, Hormozgan University, Bandar Abbas 71961, Iran; Tel: +98 761 766 0063; Fax: +98 761 667 0714;
E-mails: maaroof1357@yahoo.com, and mzarei@hormozgan.ac.ir

1875-6255/15 $58.00+.00

Table 1. Reaction condition in the synthesis of 2-azetidinone 3a.



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

Entry	Solvent	Temp	mmol DMTMM	Isolated Yield (%)
1	CH_2Cl_2	rt	1.0	67
2	Toluene	rt	1.0	30
3	THF	rt	1.0	56
4	DMF	rt	1.0	51
5	$CHCl_3$	rt	1.0	63
6	CH_2Cl_2	0 °C	1.0	42
7	CH_2Cl_2	40 °C	1.0	58
8	CH_2Cl_2	rt	1.3	80
9	CH_2Cl_2	rt	1.5	89

The β-lactam **3a** was synthesized by the [2+2] ketene-imine cycloaddition of 1.0 mmol (4-methoxybenzylidene)-4-ethoxyaniline **1a** and 1.0 mmol phenoxyacetic acid **2a** using 1.0 mmol DMTMM in dry CH_2Cl_2 in the presence of NMM. For optimizing the experimental conditions, this reaction was considered as a model reaction. Several dry solvents such as CH_2Cl_2, toluene, THF, DMF and $CHCl_3$ were tested as media (Table **1**). It was noticed that the best yield was found with CH_2Cl_2 (Table **1**, Entry 1). Also, the effect of temperature on the reaction was studied. When the reaction was performed at 0 °C (Table **1**, Entry 6), decrease of yield was observed and increase in temperature to 40 °C, was not better than room temperature (Table **1**, Entry 7). For optimization of the amount of the reagent, equimolar amount of phenoxyacetic acid relative to DMTMM was used. According to Table **1**, the highest yield was obtained when 1.5 mmol phenoxyacetic acid and 1.5 mmol DMTMM were reacted with 1.0 mmol of imine **1a** (Table **1**, entry 9).

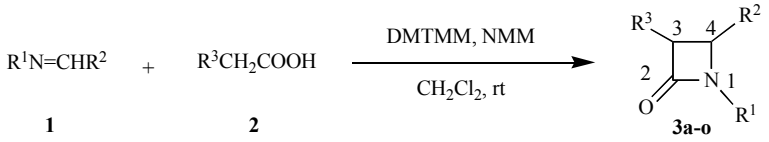
After aqueous workup and crystallization from EtOAc, a pure white solid was obtained. Full characterization of this compound was accomplished by spectroscopic methods (IR, ^{1}H-, and ^{13}C-NMR, and elemental analysis). The IR spectrum of this compound revealed C=O signal of β-lactam ring (1747 cm^{-1}) and no C=N signal. In ^{1}H-NMR spectrum, two doublet peaks at 5.21 and 5.41 ppm were observed, which can be attributed to the H-4 and H-3 of β-lactam ring, respectively. The *cis* stereochemistry of β-lactam **3a** was deduced from the coupling constant of H-3 and H-4, which was calculated to be 4.7 Hz. Moreover, the ^{13}C-NMR spectrum definitely showed the lactam CO at 162.6, C-3 at 81.2 and C-4 at 63.7 ppm. Elemental analysis also supported the formation of **3a**.

Using optimized reaction conditions, a series of substituted 2-azetidinones were prepared. The 2-azetidinones **3a-o** were synthesized by treatment of 1.0 mmol of imines **1**, 1.5 mmol of carboxylic acids **2** and 1.5 mmol of DMTMM in the presence of NMM in dry dichloromethane at room temperature (Scheme **1**, Table **2**).

To explore the scope and generality of this method, it was extended to various substituted contain 3-electron-withdrawing (Table **2**, Entry 12,13) and spirocyclic (Table **2**, Entry 14,15) ketenes. Also, the reaction proceeded efficiently with aliphatic substituted imines (Table **2**, Entry 5,6). After simple aqueous workup, 2-azetidinones **3a-k** and **3n-o** were purified by crystallization from EtOAc and 2-azetidinones **3l-m** by short column chromatography on silica gel. Spectral data and elemental analyses were used for characterization of all products. Their stereochemistry was assigned by the comparison of the coupling constant H-3 and H-4 ($J_{3,4}$> 4.0 Hz) for the *cis* stereoisomer and ($J_{3,4}\leq$ 3.0 Hz) for the *trans* stereoisomer [15].

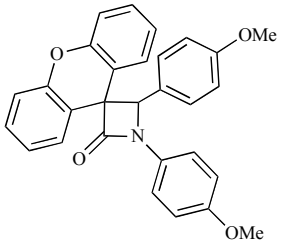
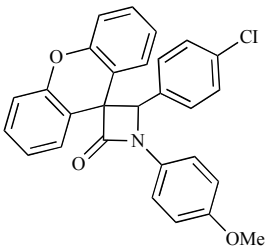
This reaction is easy and clean because the by-product of the reaction with DMTMM (2-hydroxy-4,6-dimethoxy-1,3,5-triazine, HO-MDT) and resulting salts are water soluble and then they are easily removed by simple aqueous workup.

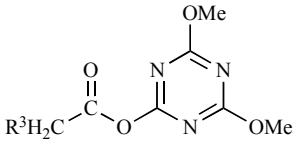
A plausible mechanism for the formation of β-lactams by this method is proposed *via* an activated ester, according to a reported mechanism for the Staudinger reaction [16].



Scheme 1.

Table 2. Synthesis of 2-azetidinones 3a-o using DMTMM.

Entry	R^1	R^2	R^3	*cis/trans*	Product	Isolated Yield (%)
1	4-$EtOC_6H_4$	4-$MeOC_6H_4$	PhO	*cis*	**3a**	89
2	4-MeC_6H_4	2-Naphthyl	PhO	*cis*	**3b**	91
3	4-$MeOC_6H_4$	CH=CHPh	PhO	*cis*	**3c**	94
4	4-MeONaphthyl	4-MeC_6H_4	MeO	*cis*	**3d**	86
5	$PhCH_2$	4-$NO_2C_6H_4$	MeO	*cis*	**3e**	88
6	4-$MeOC_6H_4CH_2$	4-$(Me_2N)C_6H_4$	2,4-$Cl_2C_6H_3O$	*cis*	**3f**	93
7	4-EtC_6H_4	4-$(Me_2N)C_6H_4$	4-ClC_6H_3O	*cis*	**3g**	88
8	4-$EtOC_6H_4$	4-$(Me_2CH)C_6H_4$	2-NaphthO	*cis*	**3h**	85
9	C_6H_5	4-$NO_2C_6H_4$	PhS	*cis*	**3i**	86
10	4-$EtOC_6H_4$	4-ClC_6H_4	PhthN	*trans*	**3j**	81
11	4-MeC_6H_4	2-Naphthyl	PhthN	*trans*	**3k**	84
12	4-$MeOC_6H_4$	4-ClC_6H_4	4-$MeC_6H_4SO_2$	*trans*	**3l**	52
13	4-$MeOC_6H_4$	4-$MeOC_6H_4$	N_3	*cis*	**3m**	69
14				-	**3n**	79
15				-	**3o**	73



activated ester

EXPERIMENTAL

General

Chemical materials were purchased from Acros and Merck in high purity. Melting points were determined in open capillaries using a Buchi 535 apparatus apparatus and are uncorrected. FTIR spectra were recorded on a galaxy series FT-IR 5000 spectrometer in spectroscopic grade KBr pellets for all the powders. ^1H (300 MHz) and ^{13}C NMR (75 MHz) spectra were recorded in deuterated chloroform on a Bruker spectrometer. Chemical shifts are reported in ppm (δ) relative to TMS and coupling constants (*J*) are reported in Hz. Microanalyses were performed by the Elemental Analyzer (Elemental, Vario EL III). The purity determination of the products and reaction monitoring were accomplished by TLC on silica gel 254 analytical sheets obtained from Fluka.

Silica gel 60 (Merck, 70-230 mesh) was used for column chromatography. Spectroscopic data for **3a, 3c-d, 3g-h, 3j,** and **3n** have been previously reported [14k, 16b, 17].

General Procedure for the Synthesis of 2-azetidinones

To a stirred solution of CDMT (1.5 mmol) in dry CH_2Cl_2 (15 mL), *N*-methylmorpholine (NMM) (6.0 mmol) was added dropwise and allowed to stir for 10 min. To the white suspension containing DMTMM salt, the Schiff base (1.0 mmol) and the carboxylic acid (1.5 mmol) were added and the mixture was stirred overnight. The mixture was washed successively with saturated $NaHCO_3$ (15 mL) and brine (15 mL), dried with Na_2SO_4 and concentrated *in vacuo*. 2-Azetidinones **3a-k, 3n-o** were purified by crystallization from EtOAc and 2-azetidinones **3l-m** by short column chromatography on silica gel.

1-(4-Ethoxyphenyl)-4-(4-methoxyphenyl)-3-phenoxy-azetidin-2-one (3a) [17b]

White crystalline solid. M.p. 166-168 °C (lit. 168-170 °C) [17b]. IR (KBr) cm^{-1}: 1752 (CO, β-lactam); ^1H NMR ($CDCl_3$) δ 1.28 (t, 3H, *J* = 7.0, Me), 3.61 (s, 3H, OMe), 3.93 (q, 2H, *J* = 7.0, OCH_2), 5.19 (d, 1H, *J* = 4.6, C4H), 5.45 (d, 1H, *J* = 4.6, C3H), 6.61-7.21 (m, 13H, ArH).

4-(Naphthalen-2-yl)-3-phenoxy-1-p-tolylazetidin-2-one (3b)

White solid. M.p. 186-188 °C IR (KBr) cm^{-1}: 1744 (CO, β-lactam); ^1H NMR ($CDCl_3$) δ 2.51 (s, 3H, Me), 5.28 (d, 1H, *J* =4.7, C4H), 5.47 (d, 1H, *J* =4.7, C3H), 6.74-7.30 (m, 16H, ArH); ^{13}C NMR ($CDCl_3$) δ 24.7 (Me), 63.7 (C4), 81.4 (C3), 114.3 (C2'), 119.2 (C2"), 122.4 (C3'), 124.8 (C4"), 126.0 (C5'"), 126.4 (C6'"), 126.7 (C4'"), 128.2 (C7'"), 128.4 (C9'"), 128.5 (C2'"), 129.1 (C10'"), 129.4 (C4'), 129.9 (C3"), 130.3 (C3'"), 131.4 (C8'"), 134.7 (C1'"), 144.6 (C1'), 157.1 (C1"), 162.3 (CO, β-lactam); Anal. Calcd for $C_{26}H_{21}NO_2$: C, 82.30; H, 5.58; N, 3.69; Found: C, 82.36; H, 5.65; N, 3.65.

1-(4-Methoxyphenyl)-3-phenoxy-4-styrylazetidin-2-one (3c) [17c]

White solid; m.p. 181–183 °C (lit. 182-184 °C) [17c]. IR (KBr) cm^{-1}: 1749 (CO, β-lactam); ^1H NMR ($CDCl_3$) δ 3.58 (s, 3H, OMe), 5.17 (dd, 1H, *J* = 5.0, 8.6, C4H), 5.66 (d, 1H, *J* = 5.0, C3H), 6.25 (dd, *J* = 8.6, 16.0, C5H), 6.76 (d, 1H, *J* = 16.0, C6H), 6.88-7.93 (m, 14H, ArH).

3-Methoxy-1-(4-methoxynaphthalen-1-yl)-4-p-tolyl-azetidin-2-one (3d) [17a]

White solid. M.p. 135-137 °C (lit. 135-137 °C) [17a]. IR (KBr) cm^{-1}: 1746 (CO, β-lactam); ^1H NMR ($CDCl_3$) δ 2.49 (s, 3H, Me), 3.38, 3.60 (2s, 6H, 2OMe), 4.85 (d, 1H, *J* = 4.5, C4H), 5.24 (d, 1H, *J* = 4.6, C3H), 6.75-7.81 (m, 10H, ArH).

1-Benzyl-3-methoxy-4-(4-nitrophenyl)azetidin-2-one (3e)

White solid. M.p. 60-62 °C IR (KBr) cm^{-1}: 1747 (CO, β-lactam). ^1H NMR ($CDCl_3$) δ 3.38 (s, 3H, OMe), 3.88, 4.75 (2d, 2H, *J* = 14.9, CH_2-benzyl), 4.94 (d, 1H, *J* = 4.7, C4H), 5.41 (d, 1H, *J* = 4.7, C3H), 6.82-7.95 (m, 9H, ArH); ^{13}C NMR ($CDCl_3$) δ 45.2 (CH_2), 55.8 (OMe), 61.5 (C3), 81.4 (C4), 112.9 (C2"), 117.3 (C3"), 121.9 (C4'), 125.0 (C2'), 130.1 (C3'), 134.6 (C1'), 141.8 (C1"), 154.0 (C4"), 163.1 (CO, β-lactam). Anal. Calcd for $C_{17}H_{16}N_2O_4$: C, 65.38; H, 5.16; N, 8.97. Found: C, 65.46; H, 5.29; N, 9.03.

1-(4-Methoxybenzyl)-3-(2,4-dichlorophenoxy)-4-(4-(dimethylamino)phenyl)azetidin-2-one (3f)

White solid. M.p. 102-104 °C. IR (KBr) cm^{-1}: 1754 (CO, β-lactam); ^1H NMR ($CDCl_3$) δ 2.90 (s, 6H, 2Me), 3.55 (s, 3H, OMe), 3.84, 4.81 (2d, 2H, *J* = 14.6, CH_2-benzyl), 4.86 (d, 1H, *J* = 4.9, C4H), 5.58 (d, 1H, *J* = 4.9, C3H), 6.84-7.81 (m, 11H, ArH); ^{13}C NMR ($CDCl_3$) δ 40.2 (Me-N), 44.8 (CH_2), 55.0 (OMe), 64.6 (C3), 81.9 (C4), 111.4 (C3"), 115.9 (C3'), 120.3 (C2'"), 122.5 (C2"), 127.4 (C1"), 128.1 (C6'"), 129.9 (C4'"), 130.3 (C5'"), 133.4 (C2'), 138.6 (C3'"), 140.0 (C1'), 144.2 (C4"), 151.1 (C1'"), 157.4 (C4'), 164.2 (CO, β-lactam); Anal. Calcd for $C_{25}H_{24}Cl_2N_2O_3$: C, 63.70; H, 5.13; N, 5.94. Found: C, 63.79; H, 5.25; N, 5.87.

4-(4-(Dimethylamino)phenyl)-1-(4-ethylphenyl)-3-phenoxyazetidin-2-one (3g) [14k]

White solid. M.p. 178-180 °C (lit. 177-179 °C). IR (KBr) cm^{-1}: 1746 (CO, β-lactam); ^1H NMR ($CDCl_3$) δ 1.35 (t, 3H, *J* = 7.0, Me), 2.54 (q, 2H, *J* = 7.0, CH_2), 2.89 (s, 6H, 2Me), 5.30 (d, 1H, *J* =4.6, C4H), 5.46 (d, 1H, *J* =4.6, C3H), 6.77-7.36 (m, 13H, ArH).

1-(4-Ethoxyphenyl)-4-(4-isopropylphenyl)-3-(naphthalen-2-yloxy)azetidin-2-one (3h) [17c]

White solid. M.p. 185-187 °C (lit. 182-184 °C). IR (KBr) cm^{-1}: 1742 (CO, β-lactam); ^1H NMR ($CDCl_3$) δ 1.25 (d, 6H, *J* = 7.0, 2Me), 1.35 (t, 3H, *J* = 7.0, Me), 2.68 (septet, 1H, CH), 4.00 (q, 2H, *J* = 7.0, OCH_2), 5.34 (d, 1H, *J* = 4.7, C4H), 5.50 (d, 1H, *J* = 4.7, C3H), 6.78-7.80 (m, 15H, ArH).

4-(4-Nitrophenyl)-1-phenyl-3-(phenylthio)azetidin-2-one (3i)

White solid. M.p. 153-155 °C. IR (KBr) cm^{-1}: 1750 (CO, β-lactam). ^1H NMR ($CDCl_3$) δ 4.36 (d, 1H, *J* = 4.4, C4H), 4.89 (d, 1H, *J* = 4.4, C3H), 6.74-8.07 (m, 14H, ArH); ^{13}C NMR ($CDCl_3$) δ 59.4 (C3), 62.3 (C4), 109.5 (C2'), 118.3 (C3'"), 126.0 (C3"), 128.8 (C4'), 129.3 (C1"), 132.7 (C2'"), 135.1 (C4"), 136.0 (C3'), 139.9 (C2"), 142.5 (C1'), 145.2 (C1'"), 157.1 (C4'"), 161.7 (CO, β-lactam); Anal. Calcd for $C_{21}H_{16}N_2O_3S$: C, 67.00; H, 4.28; N, 7.44. Found: C, 66.90; H, 4.40; N, 7.39.

2-(2-(4-Chlorophenyl)-1-(4-ethoxyphenyl)-4-oxoazetidin-3-yl)isoindoline-1,3-dione (3j) [16b]

White solid. M.p. 186-188 °C (lit. 185-187 °C) [16b]. IR (KBr) cm^{-1}: 1727, 1757 (CO, phth), 1784 (CO, β-lactam). ^1H NMR ($CDCl_3$) δ 1.35 (t, 3H, *J* = 6.9, Me), 3.98 (q, 2H, *J* = 6.9, OCH_2), 5.21 (d, 1H, *J* = 4.6, C4H), 5.35 (d, 1H, *J* = 4.6, C3H), 6.74-7.77 (m, 12H, ArH).

2-(2-(Naphthalen-2-yl)-4-oxo-1-p-tolylazetidin-3-yl)isoindoline-1,3-dione (3k)

White solid. M.p. 240-242 °C IR (KBr) cm^{-1}: 1735, 1775 (CO, phth), 1791 (CO, β-lactam); ^1H NMR ($CDCl_3$) δ 2.43 (s, 3H, Me), 5.36 (d, 1H, *J* =2.5, C4H), 5.43 (d, 1H, *J* =2.5,

C3H), 6.58-7.83 (m, 15H, ArH); ^{13}C NMR ($CDCl_3$) δ 24.3 (Me), 62.3 (C4), 63.2 (C3), 113.8 (C2'), 114.4 (C2'''), 114.7 (C10'''), 117.3 (C2''), 120.8 (C5'''), 121.9 (C6'''), 122.3 (C4'''), 124.0 (C7'''), 126.6 (C9'''), 129.3 (C4'), 132.7 (C1'''), 135.5 (C3'), 136.2 (C1''), 138.1 (C3''), 142.7 (C8'''), 146.4 (C3'''), 155.5 (C1'), 161.2 (CO, phth), 166.2 (CO, β-lactam); Anal. Calcd for $C_{28}H_{20}N_2O_3$: C, 77.76; H, 4.66; N, 6.48; Found: C, 77.85; H, 4.79; N, 6.55.

4-(4-Chlorophenyl)-1-(4-methoxyphenyl)-3-tosylazetidin-2-one (3l)

White solid. M.p. 166-168 °C. IR (KBr) cm^{-1}: 1151, 1327 (SO_2), 1746 (CO, β-lactam). ^{1}H NMR ($CDCl_3$) δ 2.11 (s, 3H, Me), 3.54 (s, 3H, OMe), 4.51 (d, 1H, *J* = 2.4, C4H), 5.49 (d, 1H, *J* = 2.4, C3H), 6.88-7.80 (m, 12H, ArH); ^{13}C NMR ($CDCl_3$) δ 23.7 (Me), 56.3 (OMe), 61.5 (C4), 82.8 (C3), 114.1 (C3'), 115.9 (C2'), 119.5 (C2'''), 120.3 (C3'''), 122.0 (C2''), 124.3 (C3''), 128.0 (C1'), 131.7 (C4'''), 134.1 (C1''), 140.6 (C1'''), 145.4 (C4''), 155.6 (C4'), 163.0 (CO, β-lactam); Anal. Calcd for $C_{23}H_{20}ClNO_4S$: C, 62.51; H, 4.56; N, 3.17. Found: C, 62.63; H, 4.71; N, 3.24.

3-Azido-1,4-bis(4-methoxyphenyl)azetidin-2-one (3m)

Pale-yellow solid. M.p. 89-91 °C IR (KBr) cm^{-1}: 1745 (CO, β-lactam), 2129 (N_3). ^{1}H NMR ($CDCl_3$) δ 3.66, 3.71 (2s, 6H, 2OMe), 5.10 (d, 1H, *J* = 5.0, C4H), 5.22 (d, 1H, *J* = 5.0, C3H), 6.81-7.49 (m, 8H, ArH); ^{13}C NMR ($CDCl_3$) δ 56.1, 57.4 (2OMe), 60.7 (C3), 68.4 (C4), 112.9 (C3''), 114.7 (C3'), 121.3 (C2''), 125.5 (C2'), 126.2 (C1''), 139.4 (C1'), 141.8 (C4''), 155.1 (C4'), 162.6 (CO, β-lactam). Anal. Calcd for $C_{17}H_{16}N_4O_3$: C, 62.95; H, 4.97; N, 17.27. Found: C, 63.06; H, 5.09; N, 17.34.

1,2-Bis(4-methoxyphenyl)spiro[azetidine-3,9'-xanthen]-4-one (3n) [17b]

White solid. M.p. 162-164 °C (lit. 161-163 °C) [17b]. IR (KBr) cm^{-1}: 1753 (CO, β-lactam); ^{1}H NMR ($CDCl_3$) δ 3.58, 3.69 (2s, 6H, 2OMe), 5.09 (s, 1H, C4H), 6.71-7.82 (m, 16H, ArH).

2-(4-Chlorophenyl)-1-(4-methylphenyl)spiro-[azetidine-3,9'-xanthen]-4-one (3o)

White solid. M.p. 228-230 °C IR (KBr) cm^{-1}: 1753 (CO, β-lactam); ^{1}H NMR ($CDCl_3$) δ 2.27 (s, 3H, Me), 5.36 (s, 1H, C4H), 6.70-8.11 (m, 16H, ArH); ^{13}C NMR ($CDCl_3$) δ 24.1 (Me), 61.9 (C-4), 73.5 (C-3), 108.3 (C2'), 111.2 (C5''), 117.5 (C3''), 121.0 (C1''), 121.9 (C4''), 127.4 (C2''), 129.9 (C3'''), 130.7 (C3'), 135.3 (C2'''), 141.3 (C4'), 147.8 (C4'''), 151.3 (C1'''), 153.7 (C1'), 154.6 (C6''), 163.4 (CO, β-lactam); Anal. Calcd for $C_{28}H_{20}ClNO_2$: C, 76.80; H, 4.60; N, 3.20. Found: C, 76.72; H, 4.71; N, 3.27.

CONCLUSION

In summary, a novel and efficient method for the direct synthesis of β-lactams from carboxylic acids and imines using DMTMM has been developed. This method offers several advantages over the previously reported methods such as good to excellent yields of the products, simple workup, and straightforward synthesis of β-lactams *via* available starting materials. The reagents for the preparation of DMTMM are cheap and economically beneficial.

CONFLICT OF INTEREST

The author confirms that this article content has no conflict of interest.

ACKNOWLEDGEMENTS

The author gratefully acknowledges Hormozgan University Research Council for the financial support of this study.

REFERENCES

[1] Blotny, G. Recent applications of 2,4,6-trichloro-1,3,5-triazine and its derivatives in organic synthesis. *Tetrahedron*, **2006**, *62*, 9507.

[2] (a) Kunishima, M.; Kawachi, C.; Iwasaki, F.; Terao, K.; Tani, S. Synthesis and characterization of 4-(4,6-dimethoxy-1,3,5-triazin-2.yl)-4-methylmorpholinium chloride. *Tetrahedron Lett.*, **1999**, *40*, 5327; (b) Zivanovic, A. 4-(4,6-Dimethoxy-1,3,5-triazin-2.yl)-4-methylmorpholinium chloride. *Synlett*, **2012**, *23*, 2426.

[3] Kunishima, M.; Kawachi, C.; Morita, J.; Terao, K.; Iwasaki, F.; Tani, S. 4-(4,6-Dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholiniumchloride: An efficient condensing agent leading to the formation of amides and esters. *Tetrahedron*, **1999**, *55*, 13159.

[4] Al-Warhi, T. I.; AL-Hazimi, H. M. A.; El-Faham, A.; Albericio, F. Synthesis of 2-(4,6-dimethoxy-1,3,5-triazin-2-yloxyimino) derivatives: Application in solution peptide synthesis. *Molecules*, **2010**, *15*, 9403 and references cited therein.

[5] De Luca, L.; Giacomelli, G.; Taddei, M. An easy and convenient synthesis of Weinreb amides and hydroxamates. *J. Org. Chem.*, **2001**, *66*, 2534.

[6] De Luca, L.; Giacomelli, G.; Porcheddu, A.; Salaris, M. A new, simple procedure for the synthesis of formyl amides. *Synlett*, **2004**, 2570.2

[7] Ramu, T.; Prasanthi, S.; Mangarao, N.; Basha, G. M.; Srinuvasarao, R.; Siddaiah, V. A simple and straightforward protocol to 3,5-disubstituted 1,2,4-oxadiazoles from carboxylic acids. *Chem. Lett.*, **2013**, *42*, 722.

[8] Long, A. T. E.; Turos, E. *N*-Thiolated β-lactams. *Curr. Med. Chem.-Anti-Infective Agents*, **2002**, *1*, 251.

[9] Mehta, P. D.; Sengar, N. P. S.; Pathak, A. K. 2-Azetidinone: A new profile of various pharmacological activities. *Eur. J. Med. Chem.*, **2010**, *45*, 5541.

[10] Li, S.; Liu, G.; Jia, J.; Li, X.; Yu, C. Liquid chromatography–negative ion electrospray tandem mass spectrometry method for the quantification of ezetimibe in human plasma. *J. Pharm. Biomed. Anal.*, **2006**, *40*, 987.

[11] (a) Alcaide, B.; Almendros, P.; Aragoncillo, C. β-Lactams: Versatile building blocks for the stereoselective synthesis of non-β-lactam products. *Chem. Rev.*, **2007**, *107*, 4437; (b) Palomo, C.; Oiarbide, M. in *Topics in Heterocyclic Chemistry*; Banik, B. K. (Ed.); Springer-Verlag; Berlin; **2010**; Vol. 22, pp 211-259; (c) Suffness, M. *Taxol Science and Applications*, CRC Press, Boca Raton, Florida, USA, **1995**.

[12] (a) Cossio, F. P.; Arrieta, A.; Sierra, M. A. The mechanism of the ketene-imine (Staudinger) reaction in its centennial: still an unsolved problem? *Acc. Chem. Res.*, **2008**, *41*, 925; (b) Jarrahpour, A.; Zarei, M. Synthesis of novel *N*-(4-ethoxyphenyl) azetidin-2-ones and their oxidative *N*-deprotection by ceric ammonium nitrate. *Molecules*, **2007**, *12*, 2364; (c) Jarrahpour, A.; Zarei, M. Synthesis of novel *N*-sulfonyl monocyclic β-lactams as potential antibacterial agents. *Molecules*, **2006**, *11*, 49; (d) Pheko, T.; Singh, G. S. Reaction of 2-diazo-1,2-diphenylethanone with 2-[(arylimino)methyl] phenols. *Lett. Org. Chem.* **2006**, *3*, 212.

[13] (a) Rafai Far, A. Ketenes in polymer-assisted synthesis. *Angew. Chem. Int. Ed.*, **2003**, *42*, 2340; (b) Allen, A. D.; Tidwell, T. T. Ketenes and other cumulenes as reactive intermediates. *Chem. Rev.*, **2013**, *113*, 7287; (c) Zarei, M. One-step synthesis of β-lactams using cyanuric fluoride. *J. Chem. Res.*, **2013,** *37*, 25.

[14] (a) Zigheimat, F.; Islami, M. R.; Nourmohammadian, F. Cycloaddition reactions of *N*-benzotriazolylketene as a heteroarylketene: A practical approach to the synthesis of novel azetidinones. *Synlett*, **2014**, *25*, 229; (b) Zarei, M. A convenient synthesis of 2-azetidinones *via* 2-fluoro-1-methylpyridinium p-toluenesulfonate. *Monatsh. Chem.* **2013**, *144*, 1021; (c) Cremonesi, G.; Croce, P. D.; Forni, A.; La Rosa, C. Stereoselective synthesis of constrained norbornane-derived spiro-β-lactams. *Tetrahedron*, **2013**, *69*, 1175; (d) Jarrahpour, A.; Zarei, M. The Vilsmeier reagent as an efficient acid activator for the synthesis of β-lactams. *Tetrahedron Lett.*, **2007**, 48, 8712; (e) Zarei, M.; Jarrahpour, A. A mild and efficient route to 2-azetidinones using the cyanuric chloride–DMF complex. *Synlett* **2011**, 2572; (f) Nahmany, M.; Melman, A. Simple approach to β-lactam derivatives from *N*-acylimidazoles. *J. Org. Chem.*, **2006,** *71,* 5804; (g) Jarrahpour, A.; Zarei, M. DMF-dimethyl sulfate as a new reagent for the synthesis of β-lactams. *Tetrahedron Lett.*, **2009,** *50,* 1568; (h) Jarrahpour, A.; Fadavi, A.; Zarei, M. Synthesis of structurally diverse 2-azetidinones *via* Staudinger reaction on a solid support. *Bull. Chem. Soc. Jpn.,* **2011,** *84,* 320; (i) Zarei, M.; Karimi-Jaberi, Z.; Movahedi, A. Synthesis of β-lactams from acids and imines using thiocarbonyldiimidazole. *Synth. Commun.*, **2013**, *43,* 728; (j) Zarei, M. A facile and effective synthesis of 2-azetidinones *via* phosphonitrilic chloride. *Tetrahedron* **2013**, *69*, 6620; (k) Darvishi, A.; Zarei, M.; Akhgar, M. R. A simple and highly efficient procedure for one-pot synthesis of 2-azetidinones using 3,5-dinitrobenzoyl chloride. *Lett. Org. Chem.,* **2013**, *10*, 645*;* (l) Keri, R .S.; Hosamani, K. M.; Shingalapur, R. V.; Reddy, H. R. S. 2-Azetidinone derivatives: Design, synthesis, *in vitro* antimicrobial, cytotoxic activities and DNA cleavage study. *Eur. J. Med. Chem.*, **2009,** *44,* 5123. (m) Zarei, M.; Mohamadzadeh, M. 3-Thiolated 2-azetidinones: synthesis and *in vitro* antibacterial and antifungal activities. *Tetrahedron,* **2011**, *67,* 5832; (n) Smith, S. R.; Douglas, J.; Prevet, H.; Shapland, P.; Slawin, A. M. Z.; Smith, A. D. Isothiourea-catalyzed asymmetric synthesis of β-lactams and β-amino esters from arylacetic acid derivatives and *N*-sulfonylaldimines. *J. Org. Chem.*, **2014**, *79*, 1626.

[15] Georg, G. I. *The Organic Chemistry of β-Lactams*, Verlag Chemie: New York, **1993**.

[16] (a) Wang, Y.; Liang, Y.; Jiao, L.; Du, D.-M.; Xu, J. Do reaction conditions affect the stereoselectivity in the Staudinger reaction? *J. Org. Chem.,* **2006**, *71*, 6983; (b) Jarrahpour, A.; Zarei, M. Efficient one-pot synthesis of 2-azetidinones from acetic acid derivatives and imines using methoxymethylene-N,N-dimethyliminiumsalt. *Tetrahedron*, **2010**, *66*, 5017.

[17] (a) Zarei, M. Utilization of DMF-PhCOCl adduct as an acid activator in a new and convenient method for preparation of β-lactams. *Bull. Chem. Soc. Jpn.,* **2012**, *85*, 360; (b) Jarrahpour, A.; Zarei, M. The Vilsmeier reagent: a useful and versatile reagent for the synthesis of 2-azetidinones. *Tetrahedron*, **2009,** *65*, 2927; (c) Zarei, M. One-pot sequence synthesis of azetidin-2-one using diethyl chlorophosphate. *J. Chem. Res.*, **2012,** *36*, 118.