β-Lactam Preparation via Staudinger Reaction with Activated Dimethylsulfoxide

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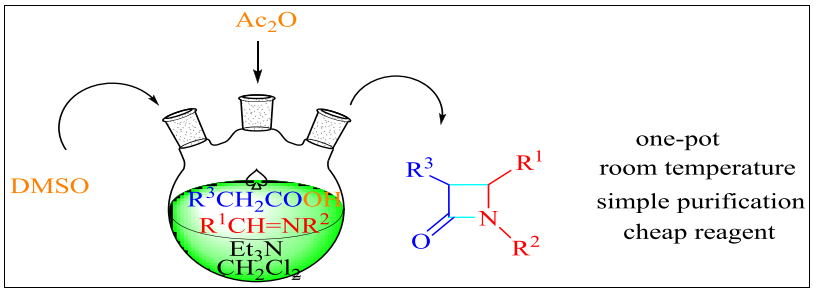

An efficient synthesis of β-lactams has been expediently accomplished. These β-lactams were synthesized by the Staudinger reaction of several substituted imines with various carboxylic acids using activated DMSO at ambient temperature. The imines and substituted acetic acids contain alkyl, aryl, hetero aryl, polycyclic, and 3-electron-withdrawing group underwent [2 + 2] ketene-imine cycloaddition reaction smoothly to obtain the desired β-lactams in good to excellent yields. This method is cheap, simple, convenient, and efficient, and the products are easily isolated.

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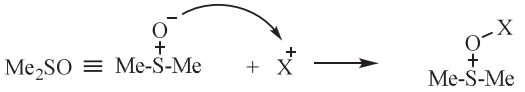
INTRODUCTION

Activated DMSO can be prepared by reaction of DMSO and a species of electrophile such as acetic anhydride, oxalyl chloride, dicyclohexylcarbodiimide, cyanuric chloride, and propylphosphonic anhydride which a sulfonium species containing a good-leaving group linked to the positive sulfur atom is formed [1]. This reagent has been used for the oxidation of alcohols [1], the synthesis of nitriles from aldoximes [2] and the synthesis of cross-linking of polysaccharides [3].



activated DMSO

The chemistry of β-lactams (2-azetidinones) has attracted considerable interest over the last few decades, mainly because of the important biological activity of this family of compounds; noteworthy is their widespread clinical application as antibacterial agents [4]. Ezetimibe (Zetia) has 2-azetidinone ring in its structure, the first in a new class of agents that inhibit cholesterol absorption in the intestine, and was approved by the FDA in October 2002 for the reduction of cholesterol levels in patients with hypercholesterolemia [5]. Other biological activity of 2-azetidinones is also well documented, and they have been found to be useful in a variety of biological applications [6]. Furthermore, the considerable variety of transformations related to the selective bond cleavage of the 2-azetidinone core has suggested an interesting use of the β-lactam skeleton as a synthon in organic synthesis [7] and in the semisynthesis of taxol derivatives [8].

Consequently, a great deal of work has been promoted for developing new and more efficient strategies for the synthesis of the 2-azetidinone ring [9]. Despite Staudinger reporting the reaction between ketenes and imines in 1907 [10], undoubtedly this reaction is the most widely used route, which can be used for the synthesis of several types of 2-azetidinones [11].

Ketenes are typically generated by the reaction of acyl halides with tertiary amines [12], but the preparation, isolation, and handling of acid chlorides is difficult, and they are unstable. Activation of carboxylic acids for the formation of amide or ester bonds is a key step in the synthesis of a large number of bioorganic molecules [13]. 2-Azetidinones can also be synthesized by the one-pot reaction of *in situ* activated carboxylic acids and imines [14]. Despite the generality and efficiency of number of the acid activator reagents, some limitations still remain. As a matter of fact, the high cost of the reagents, the need to low or high temperatures, low yield of products, harsh conditions, and chromatographic separations do not make these procedures appealing for large-scale preparations.

In recent communication [15], efficient use of DMSO and acetic anhydride as an acid activator in the synthesis of β-lactams by the Staudinger reaction was reported. In this paper, the versatility and utility of activated DMSO

for the activation of various carboxylic acids in β-lactam synthesis under simple and mild conditions are described.

RESULTS AND DISCUSSION

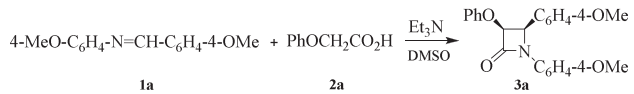
At first, the reaction of *N*-(4-Methoxybenzylidene)-4-methoxybenzenamine and phenoxyacetic acid in DMSO in the presence of triethylamine at room temperature was examined, but no reaction was observed after 13 h. Then several types of activated DMSO were used and progress of reaction was checked by TLC monitoring (Table 1). In all cases, TLC monitoring showed that a reaction took place to give β-lactam **3a** after purification by column chromatography (petroleum ether/EtOAc 7:3). According to the table, the highest yield of **3a** was obtained when DMSO/Ac_2O, DMSO/cyanuric chloride, DMSO/phosphonitrilic chloride, and DMSO/T3P were used as activated DMSO reagent, separately. Among of them, DMSO/Ac_2O is the best reagent because of safety, low cost, availability, and easiness of use.

In the Table 2, optimization of temperature, solvent and molar of reagent was performed. In all cases DMSO/Ac_2O was applied as a reagent. It was observed that dichloromethane was the best solvent for this reaction with the highest yield. Furthermore, yield at room temperature was higher than at 0°C. According to Table 1, the highest yield of **3a** was obtained when 1.5 mmol of DMSO/Ac_2O and 1.5 mmol phenoxyacetic acid react with 1.0 mmol of Schiff base **1a** in dry dichloromethane at room temperature (entry 9).

Next, the ability of DMSO and Ac_2O to activate various acetic acid derivatives was investigated for the synthesis of a range of 2-azetidinones (Scheme 1, Table 3). As can be seen from the table, this method was applied for the conversion of a range of carboxylic acids and imines into the corresponding β-lactams in good to excellent yields. 2-Azetidinones **3m–n** which contain aliphatic substituents can also be synthesized by this method. The lower stability of alkyl-substituted imines compared with aryl-substituted imines led to lower yields of 2-azetidinones **3m–n**. Especially, 2-azetidinone **3n** was obtained in a poorer yield

Table 1

Comparison of activated DMSO reagents for the synthesis of β-lactam **3a**



1a 2a 3a

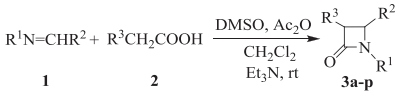
Entry	Reagent	Temperature	Mol of reagent	Yield (%)
1	DMSO	RT	–	–
2	DMSO/Ac_2O	RT	1.0	61
3	DMSO/$(COCl)_2$	RT	1.0	41
4	DMSO/DCC	RT	1.0	28
5	DMSO/$MeSO_2Cl$	RT	1.0	35
6	DMSO/cyanuric chloride	RT	1.0	51
7	DMSO/phosphonitrilic chloride	RT	1.0	55
8	DMSO/P_4O_{10}	RT	1.0	43
9	DMSO/$(CF_3SO_2)_2O$	RT	1.0	29
10	DMSO/T3P	RT	1.0	56

Table 2

Optimization of the reaction conditions for the synthesis of β-lactam **3a**

Entry	Reagent (mmol)	Solvent	Temperature	Yield (%)
1	DMSO (-)	DMSO	RT	–
2	Ac_2O (1.0)	DMSO	RT	43
3	Ac_2O (1.0)	CH_2Cl_2	RT	–
4	DMSO/Ac_2O (1.0)	CH_2Cl_2	RT	61
5	DMSO/Ac_2O (1.0)	CH_3CN	RT	29
6	DMSO/Ac_2O (1.0)	THF	RT	37
7	DMSO/Ac_2O (1.0)	toluene	RT	45
8	DMSO/Ac_2O (1.3)	CH_2Cl_2	RT	83
9	DMSO/Ac_2O (1.5)	CH_2Cl_2	RT	91
10	DMSO/Ac_2O (2.0)	CH_2Cl_2	RT	89
11	DMSO/Ac_2O (1.5)	CH_2Cl_2	0 °C	85

Scheme 1



because of the lower stability of the imine derived from the aliphatic amine and an aldehyde. The heteroaromatic-substituted 2-azetidinone **3o** was also prepared in good yield using activated DMSO. β-Lactams **3a–p** were purified by crystallization from EtOAc after simple aqueous workup, exception β-lactam **3n** by column chromatography on silica gel. This reaction is very simple and clean because the byproducts of the reaction are highly water soluble and can be easily removed by aqueous workup.

The structure of the products was confirmed by ^{1}H-NMR, ^{13}C-NMR, IR, and elemental analyses. Particularly, the ^{1}H-NMR spectra of the 2-azetidinone derivatives show a characteristic shift of the 2-azetidinone ring protons at about 4.5 and 5.5 ppm. Furthermore, the comparison of the coupling constant H-3 and H-4 (2-azetidinone ring protons) were ascertained stereochemistry of 2-azetidinones [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] [16].

Dibenz(b,f)1,4-oxazapine **4** as a cyclic imines can be prepared from *o*-aminophenol and *o*-chlorobenzaldehyde which it is a strong irritant to the eyes and skin [17]. Treatment of this cyclic imine with various substituted acetic acids in the presence of DMSO and Ac_2O at room temperature gave *trans* β-lactams **5a–c** which were purified by crystallization from EtOAc (Scheme 2).

3-Electron-withdrawing β-lactams **6a–c** were easily obtained from azidoacetic acid and various imines in the presence of triethylamine by this method as *cis* stereoisomer after short column chromatography on silica gel (Scheme 3).

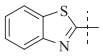
Activated DMSO was successfully applied for the synthesis of C-3 spiro-2-azetidinones **8a–f** by the cycloaddition reaction of xanthene-9-carboxylic acid **7** with Schiff bases in the presence of triethylamine (Scheme 4).

The synthesis of 2-azetidinone **3a** was also performed in the presence of other acid activators for comparison (Table 4). It is noteworthy that 2-azetidinone **3a** was obtained in high yields when activated DMSO or the Mukaiyama reagent were used as the acid activator at room temperature. The cost of the Mukaiyama reagent and its byproduct are disadvantages of this reagent.

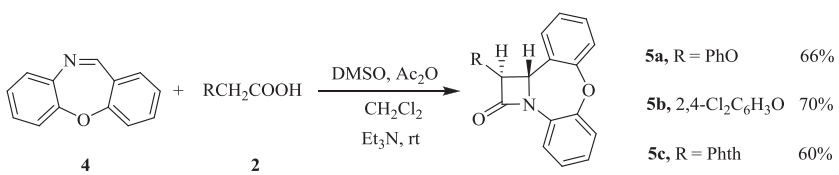
Mechanism for the formation of 2-azetidinones by this method is proposed via an activated ester (Scheme 5).

Table 3

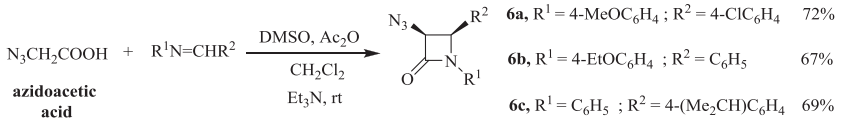
Synthesis of 2-azetidinones **3a–p** using activated DMSO

Entry	R^1	R^2	R^3	*cis*/*trans*	Product	Isolated yield (%)
1	4-$MeOC_6H_4$	4-$MeOC_6H_4$	PhO	*cis*	**3a**	91
2	4-$MeOC_6H_4$	4-ClC_6H_4	PhO	*cis*	**3b**	93
3	4-MeONaphthyl	4-$MeOC_6H_4$	PhO	*cis*	**3c**	91
4	4-MeONaphthyl	4-ClC_6H_4	PhO	*cis*	**3d**	89
5		4-$MeOC_6H_4$	PhO	*cis*	**3e**	86
6	4-$MeOC_6H_4$	4-$MeOC_6H_4$	PhthN	*trans*	**3f**	88
7	4-$MeOC_6H_4$	4-ClC_6H_4	PhthN	*trans*	**3g**	84
8	4-MeONaphthyl	4-ClC_6H_4	PhthN	*trans*	**3h**	85
9		4-$MeOC_6H_4$	PhthN	*trans*	**3i**	83
10	4-$EtOC_6H_4$	CH=CHPh	PhthN	*cis*	**3j**	86
11	C_6H_5	4-$NO_2C_6H_4$	MeO	*cis*	**3k**	92
12	4-MeONaphthyl	4-$MeOC_6H_4$	PhO	*cis*	**3l**	78
13	Me	4-$NO_2C_6H_4$	PhO	*cis*	**3m**	78
14	Me	$C_6H_5CH_2$	MeO	*cis*	**3n**	65
15	4-$MeOC_6H_4$	2-furyl	PhO	*cis*	**3o**	87
16	4-$EtOC_6H_4$	4-ClC_6H_4	2-naphthO	*cis*	**3p**	88

Scheme 2



Scheme 3



Scheme 4

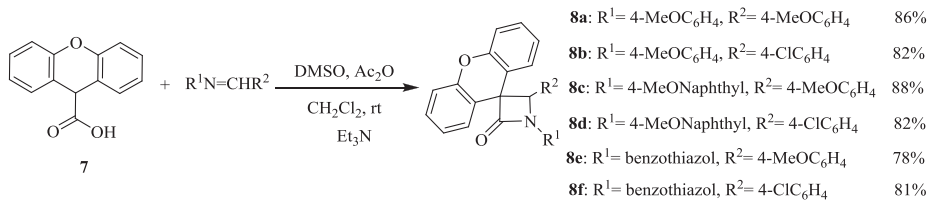


Table 4

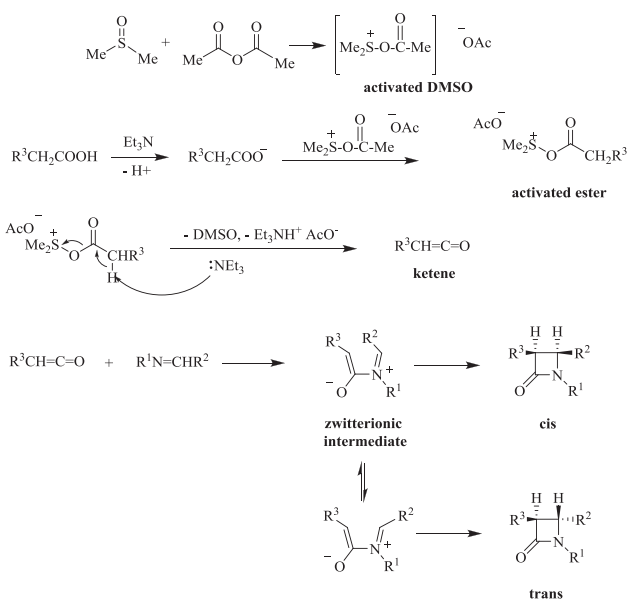
Comparison of acid activators for the synthesis of 2-azetidinone **4a**

Entry	Acid activator	Temperature	Yield (%)
1	DMSO/Ac_2O	RT	91
2	$POCl_3$	RT	62
3	Me_2S/Br_2	RT	67
4	cyanuric chloride	RT	44
5	cyanuric chloride	0°C	71
6	Mukaiyama reagent	RT	83

Activated DMSO can activate carboxylic acids to give an activated ester and then generate a ketene *in situ* in the presence of Et_3N. Finally, the ketene reacts with an imine to produce the β-lactam, according to the reported mechanism for the Staudinger reaction [18]. Many different experimental factors, such as reaction temperature, solvent, electronic effect, and the steric hindrance of the ketene and imine substituents may affect on stereochemistry of β-lactams in the Staudinger reaction.

In summary, a simple and convenient one-pot methodology to synthesize a variety of 2-azetidinones from readily available Schiff bases and carboxylic acids using DMSO and acetic anhydride has been extended. Monocyclic, spirocyclic, polycyclic, *N*-alkyl, and 3-electron-withdrawing group 2-azetidinones are obtained in good to excellent yields by this method. This reaction is easy and clean and the byproducts were removed by simple aqueous workup.

Scheme 5



EXPERIMENTAL

All required chemicals were purchased from Merck (Merck, KGaA, Darmstadt, Germany), Fluka (Sigma-Aldrich, St. Louis, MO) or Acros (Thermo Fisher Scientific, Geel, Belgium) chemical companies. The melting points were determined on a Buchi 535 apparatus (BÜCHI Labortechnik AG, Flawil, Switzerland) and are uncorrected. IR spectra were measured on a Galaxy Series FT-IR 5000 spectrometer (Mattson Instruments, Madison, WI). NMR spectra were recorded in $CDCl_3$ using a Bruker spectrophotometer (^{1}H-NMR 250 MHz, ^{13}C-NMR 62.9 MHz; Bruker Corporation, Billerica, MA) using tetramethylsilane as an internal standard, and coupling constants were given in cycles per second (Hz). Elemental analyses were run on a Vario EL III elemental analyzer (Hanau, Germany). Thin-layer chromatography was carried out on Silica gel 254 analytical sheets obtained from Fluka. Column chromatography was performed on silica gel 60 (Merck, 70–230 mesh). Spectral data for **3a–b**, **3g**, **3j–m**, **3o–p**, **5a**, **6a–b**, and **8a–b** have been previously reported [18b,c,19].

General procedure. Ac_2O (1.5 mmol) was added to a solution of the substituted acetic acid (1.5 mmol), the

Schiff base (1.0 mmol), DMSO (1.5 mmol), an Et_3N (5.0 mmol) in dry CH_2Cl_2 (10 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 EtOAc or by short column chromatography (petroleum ether/EtOAc) as a mentioned in the text.

1-(4-Methoxynaphthalen-1-yl)-4-(4-methoxyphenyl)-3-phenoxyazetidin-2-one (3c). White solid. mp: 169–171°C IR (KBr) cm^{-1}: 1751 (CO, β-lactam); ^{1}H-NMR ($CDCl_3$) δ 3.32, 3.48 (2OMe, 2s, 6H), 5.66 (H-4, d, 1H, J = 4.6), 5.82 (H-3, d, 1H, J = 4.6), 6.69–7.95 (ArH, m, 15H); ^{13}C-NMR ($CDCl_3$) δ 52.7, 55.5 (2OMe), 62.7 (C-4), 81.3 (C-3), 114.6–156.2 (aromatic carbons), 162.2 (CO, β-lactam); *Anal.* Calcd for $C_{27}H_{23}NO_4$: C, 76.22; H, 5.45; N, 3.29; Found: C, 76.30; H, 5.59; N, 3.36.

1-(4-Methoxynaphthalen-1-yl)-4-(4-chlorophenyl)-3-phenoxyazetidin-2-one (3d). White solid. mp: 161–163°C IR (KBr) cm^{-1}: 1749 (CO, *β*-lactam); ^{1}H-NMR ($CDCl_3$) *δ* 3.56 (OMe, s, 3H), 5.18 (H-4, d,1H, J = 4.5 Hz), 5.36 (H-3, d, 1H, J = 4.5 Hz), 6.80–7.37 (ArH, m, 15H); ^{13}C-NMR ($CDCl_3$) *δ* 56.3 (OMe), 62.8 (C-4), 82.4 (C-3), 114.1–159.5 (aromatic carbons), 162.9 (CO, *β*-lactam); *Anal.* Calcd for $C_{26}H_{20}ClNO_3$: C, 72.64; H, 4.69; N, 3.26. Found: C, 72.74; H, 4.81; N, 3.19.

1-(Benzo[d]thiazol-2-yl)-4-(4-methoxyphenyl)-3-phenoxyazetidin-2-one (3e). Light-yellow solid. mp: 159–161°C IR (KBr) cm^{-1}: 1636 (C=N), 1751 (CO, β-lactam); ^{1}H-NMR ($CDCl_3$) *δ* 3.68 (OMe, s, 3H), 4.59 (H-4, d, 1H, J = 4.8), 5.45 (H-3, d, 1H, J = 4.8), 6.88–7.97 (ArH, m, 13H); ^{13}C-NMR ($CDCl_3$) *δ* 55.5 (OMe), 62.0 (C-3), 81.6 (C-4), 111.9–152.4 (aromatic carbons), 161.7 (C=N), 163.3 (CO, β-lactam); *Anal.* Calcd for $C_{23}H_{18}N_2O_3S$: C, 68.64; H, 4.51; N, 6.96. Found: C, 68.71; H, 4.64; N, 7.02.

2-(1,2-Bis(4-methoxyphenyl)-4-oxoazetidin-3-yl)isoindoline-1,3-dione (3f). White solid. mp: 196–198°C IR (KBr) cm^{-1}: 1724, 1759 (CO, phth), 1775 (CO, β-lactam); ^{1}H-NMR ($CDCl_3$) δ 3.57, 3.68 (2OMe, 2s, 6H), 5.43 (H-4, d, 1H, J = 2.2), 5.81 (H-3, d, 1H, J = 2.2), 6.77–8.14 (ArH, m, 12H); ^{13}C-NMR ($CDCl_3$) δ 55.5, 56.7 (2 OMe), 61.7 (C-4), 63.7 (C-3), 115.2–155.2 (aromatic carbons), 160.9 (CO, phth), 162.6 (CO, β-lactam); *Anal.* Calcd for $C_{25}H_{20}N_2O_5$: C, 70.08; H, 4.71; N, 6.54. Found: C, 70.00; H, 4.81; N, 6.49.

2-(2-(4-Chlorophenyl)-1-(4-methoxynaphthalen-1-yl)-4-oxoazetidin-3-yl)isoindoline-1,3-dione (3h). White solid. mp: 180–182°C IR (KBr) cm^{-1}: 1735, 1767 (CO, phth), 1776 (CO, β-lactam); ^{1}H-NMR ($CDCl_3$) δ 3.87 (OMe, s, 3H), 5.49 (H-4, d, 1H, J = 2.3), 5.85 (H-3, d, 1H, J = 2.3), 6.73–8.45 (ArH, m, 14H); ^{13}C-NMR ($CDCl_3$) δ 56.3 (OMe), 63.8 (C-4), 64.5 (C-3), 115.3–156.3 (aromatic carbons), 161.8 (CO, phth), 164.8 (CO, β-lactam); *Anal.* Calcd for $C_{28}H_{19}ClN_2O_4$: C, 69.64; H, 3.97; N, 5.80. Found: C, 69.75; H, 4.11; N, 5.86.

2-(1-(Benzo[d]thiazol-2-yl)-2-(4-methoxyphenyl)-4-oxoazetidin-3-yl)isoindoline-1,3-dione (3i). Pale yellowish solid. mp: 168–170°C IR (KBr) cm^{-1}: 1626 (C=N), 1738, 1766 (CO, phth), 1778 (CO, β-lactam); ^{1}H-NMR ($CDCl_3$) δ 3.68 (OMe, s, 3H), 5.44 (H-4, d, 1H, J = 2.3), 5.82 (H-3, d, 1H, J = 2.3), 6.76–8.15 (ArH, m, 12H); ^{13}C-NMR ($CDCl_3$) δ 53.5 (OMe), 62.4 (C-4), 66.2 (C-3), 108.7–156.2 (aromatic carbons), 160.6 (C=N), 161.8 (CO, phth), 164.0 (CO, β-lactam); *Anal.* Calcd for $C_{25}H_{17}N_3O_4S$: C, 65.92; H, 3.76; N, 9.23. Found: C, 70.01; H, 3.87; N, 9.27.

4-Benzyl-3-methoxy-1-methylazetidin-2-one (3n). Colorless oil. IR (neat) cm^{-1}: 1755 (CO, β-lactam); ^{1}H-NMR ($CDCl_3$) δ 2.33 (CH_2-benzyl, dd, 1H, J = 5.0, 14.7), 2.84 (CH_2 − benzyl, dd, 1H, J = 5.0, 14.7), 2.91 (N − Me, s, 3H), 3.58 (OMe, s, 3H), 4.37 (H-4, m, 1H), 5.25 (H-3, d, 1H, J = 5.0), 7.11–7.58 (ArH, m, 5H); ^{13}C-NMR ($CDCl_3$) δ 30.1 (N − Me), 33.9 (CH_2), 55.7 (OMe), 60.9 (C-3), 81.7 (C-4), 119.5–148.8 (aromatic carbons), 162.5 (CO, β-lactam). *Anal.* Calcd for $C_{12}H_{15}NO_2$: C, 70.22; H, 7.37; N, 6.82. Found: C, 70.31; H, 7.49; N, 6.87.

1-(2,4-Dichlorophenoxy)-1,12b-dihydro-2H-azeto[1,2-d]dibenzo[b,f][1,4]oxazepin-2-one (5b). White solid. mp: 149–151°C IR (KBr) cm^{-1}: 1750 (CO, β-lactam); ^{1}H-NMR ($CDCl_3$) δ 5.44 (H-4, d, 1H, J = 2.1), 5.69 (H-3, d, 1H, J = 2.1), 7.19–7.92 (ArH, m, 11H); ^{13}C-NMR ($CDCl_3$) δ 63.5 (C-4), 81.8 (C-3), 113.1–157.9 (aromatic carbons), 162.8 (CO, β-lactam); *Anal.* Calcd for $C_{21}H_{13}Cl_2NO_3$: C, 63.34; H, 3.29; N, 3.52. Found: C, 63.49; H, 3.42; N, 3.59.

2-(2-Oxo-1,12b-dihydro-2H-azeto[1,2-d]dibenzo-[b,f][1,4]oxazepin-1-yl)isoindoline-1,3-dione (5c). Pale yellowish solid. mp: 188–200°C IR (KBr) cm^{-1}: 1726, 1753 (CO, phth), 1783 (CO, β-lactam);^{1}H-NMR ($CDCl_3$) δ 5.31 (H-4, d, 1H, J = 2.4), 5.52 (H-3, d, 1H, J = 2.4), 7.00–7.98 (ArH, m, 12H); ^{13}C-NMR ($CDCl_3$) δ 61.3 (C-4), 64.8 (C-3), 115.5–157.0 (aromatic carbons), 161.9 (CO, phth), 164.2 (CO, β-lactam); *Anal.* Calcd for $C_{23}H_{14}N_2O_4$: C, 72.25; H, 3.69; N, 7.33. Found: C, 72.36; H, 3.78; N, 7.38.

3-Azido-4-(4-isopropylphenyl)-1-phenylazetidin-2-one (6c). Light-yellow solid. mp: 91–93°C IR (KBr) cm^{-1}: 2118 (N_3), 1754 (CO, β-lactam);^{1}H-NMR ($CDCl_3$) δ 1.18 (2Me, d, 6H, J = 6.7), 2.69 (CH, sept, 1H, J = 6.7), 5.09 (H-4, d, 1H, J = 4.9), 5.40 (H-3, d, 1H, J = 4.9), 6.81–7.76 (ArH, m, 9H); ^{13}C-NMR ($CDCl_3$) δ 24.6 (Me), 34.2 (CH), 63.1 (C-4), 68.5 (C-3), 111.3–151.7 (aromatic carbons), 162.7 (CO, β-lactam); *Anal.* Calcd for $C_{18}H_{18}N_4O$: C, 70.57; H, 5.92; N, 18.29. Found: C, 70.64; H, 6.04; N, 18.21.

1-(4-Methoxynaphthalen-1-yl)-2-(4-methoxyphenyl)spiro[azetidine-3,9′-xanthen]-4-one (8c). White solid. mp: 171–173°C IR (KBr) cm^{-1}: 1747 (CO, β-lactam); ^{1}H-NMR ($CDCl_3$) δ 3.69, 3.71 (2 OMe, 2s, 6H), 4.94 (H-4, s, 1H), 6.94–7.70 (ArH, m, 18H); ^{13}C-NMR ($CDCl_3$) δ 53.6, 56.0 (2OMe), 61/5 (C-4), 72.8 (C-3), 108.7–154.3 (aromatic carbons), 165.4 (CO, β-lactam); *Anal.* Calcd for

$C_{33}H_{25}NO_4$: C, 79.34; H, 5.04; N, 2.80. Found: C, 79.27; H, 5.13; N, 2.83.

2-(4-Chlorophenyl)-1-(4-methoxynaphthalen-1-yl)spiro[azetidine-3,9′-xanthen]-4-one (8d). White solid. mp: 161–163°C IR (KBr) cm^{-1}: 1756 (CO, β-lactam); ^{1}H-NMR ($CDCl_3$) δ 3.61 (OMe, s, 3H), 5.42 (H-4, s, 1H), 6.86–7.62 (ArH, m, 16H); ^{13}C-NMR ($CDCl_3$) δ 56.0 (OMe), 66.8 (C-4), 73.7 (C-3), 116.5–152.1 (aromatic carbons), 164.1 (CO, β-lactam); *Anal.* Calcd for $C_{32}H_{22}ClNO_3$: C, 76.26; H, 4.40; N, 2.78. Found: C, 76.18; H, 4.49; N, 2.74.

1-(Benzo[d]thiazol-2-yl)-2-(4-methoxyphenyl)spiro[azetidine-3,9′-xanthen]-4-one (8e). Pale yellowish solid. mp: 151–153°C IR (KBr) cm^{-1}: 1637 (C=N), 1755 (CO, β-lactam); ^{1}H-NMR ($CDCl_3$) δ 3.68 (OMe, s, 3H), 5.29 (H-4, s, 1H), 6.82–7.99 (ArH, m, 16H). ^{13}C-NMR ($CDCl_3$) δ 56.2 (OMe), 62.2 (C-4), 71.8 (C-3), 108.9–154.9 (aromatic carbons), 161.8 (C=N), 166.0 (CO, β-lactam); *Anal.* Calcd for $C_{29}H_{20}N_2O_3S$: C, 73.09; H, 4.23; N, 5.88. Found: C, 73.17; H, 4.33; N, 5.83.

1-(Benzo[d]thiazol-2-yl)-2-(4-chlorophenyl)spiro[azetidine-3,9′-xanthen]-4-one (8f). Pale yellowish solid. mp: 155–157°C IR (KBr) cm^{-1}: 1632 (C=N), 1744 (CO, β-lactam); ^{1}H-NMR δ 5.14 (H-4, s, 1H), 6.78–7.96 (ArH, m, 16H); ^{13}C-NMR δ 62.4 (C-4), 71.2 (C-3), 108.7–154.2 (aromatic carbons), 161.5 (C=N), 164.0 (CO, β-lactam); *Anal.* Calcd for $C_{28}H_{17}ClN_2O_2S$: C, 69.92; H, 3.56; N, 5.82. Found: C, 70.01; H, 3.69; N, 5.87.

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REFERENCES AND NOTES

[1] Tidwell, T. T. Synthesis 1990, 22, 857.

[2] Song, Y.; Shen, D.; Zhang, Q.; Chen, B.; Xu, G. Tetrahedron Lett 2014, 55, 639.

[3] Petronijevic, Z.; Maluckov, B.; Smelcerovic, A. Tetrahedron Lett 2013, 54, 3210.

[4] (a) Pérez-Ruiz, R.; Sáez, J. A.; Domingo, L. R.; Jiménez, M. C.; Miranda, M. A. Org Biomol Chem 2012, 10, 7928; (b) Hwu, J. R.; Ethiraj, S. K.; Hakimelahi, G. H. Mini-Rev Med Chem 2003, 3, 305.

[5] Earl, J.; Kirkpatrick, P. Nat Rev Drug Discov 2003, 2, 97.

[6] (a) Mehta, P. D.; Sengar, N. P. S.; Pathak, A. K. Eur J Med Chem 2010, 45, 5541; (b) Arya, N.; Jagdale, A. Y.; Patil, T. A.; Yeramwar, S. S.; Holikatti, S. S.; Dwivedi, J.; Shishoo, C. J.; Jain, K. S. Eur J Med Chem 2014, 74, 619.

[7] (a)Palomo, C.; Oiarbide, M. In Topics in Heterocyclic Chemistry; Banik, B. K., Ed.; Springer-Verlag; Berlin; 2010; Vol. 22, pp 211–259; (b) Alcaide, B.; Almendros, P. Chem Rec 2011, 11, 311; (c) Alcaide, B.; Almendros, P.; Aragoncillo, C. Chem Rev 2007, 107, 4437.

[8] Hodge, M.; Chen, O.-H.; Bane, S.; Sharma, S.; Loew, M.; Banerjee, A.; Alcaraz, A. A.; Snyder, J. P.; Kingston, D. G. I. Bioorg Med Chem Lett 2009, 19, 2884.

[9] For review see: (a) Alcaide, B.; Almendros, P. Progress in Heterocyclic Chemistry 2011, 22, 85–107; (b) Aranda, M. T.; Perez-Faginas, P.; Gonzalez-Muniz, R. Curr Org Synth 2009, 6, 325; (c) Fu, N.; Tidwell, T. T. Tetrahedron 2008, 64, 10465; (d) Xu, J. Tetrahedron 2012, 68, 10696; (e) Kamath, A.; Ojima, I. Tetrahedron 2012, 68, 10640.

[10] Staudinger, H. Liebigs Ann Chem 1907, 356, 51.

[11] (a) Fodor, L.; Csomos, P.; Holczbauer, T.; Kalman, A.; Csampai, A.; Sohar, P. Tetrahedron Lett 2011, 52, 224; (b) Zarei, M.; Karimi-Jaberi, Z.; Movahedi, A. Synth Commun 2013, 43, 728; (c) Keri, R. S.; Hosamani, K. M.; Shingalapur, R. V.; Reddy, H. R. S. Eur J Med Chem 2009, 44, 5123; (d) Zarei, M.; Jarrahpour, A. Synlett 2011 2572; (e) Zarei, M.; Mohamadzadeh, M. Tetrahedron 2011, 67, 5832; (f) Jarrahpour, A.; Nazari, M. Iran J Sci Technol A 2015, 39, 259.

[12] (a) Tidwell, T. T. Ketenes II; John Wiley & Sons: New Jersey, 2006, pp 55–192; (b) Jarrahpour, A.; Zarei, M. Molecules 2006, 11, 49; (c) Pagadala, R.; Meshram, J. S.; Chopde, H. N.; Jetti, V.; Udayini, V. J. Heterocyclic Chem 2011, 48, 1067.

[13] (a) Unsworth, W. P.; Coulthard, G.; Kitsiou, C.; Taylor, R. J. K. J Org Chem 2014, 79, 1368; (b) Zarei, M. J Chem Res 2012, 36, 118; (c) Jarrahpour, A.; Ebrahimi, E.; Sinou, V.; Latour, C.; Brunel, J. M. Eur J Med Chem 2014, 87, 364.

[14] (a) Smith, S. R.; Douglas, J.; Prevet, H.; Shapland, P.; Slawin, A. M. Z.; Smith, A. D. J Org Chem 2014, 79, 1626; (b) Darvishi, A.; Zarei, M.; Akhgar, M. R. Lett Org Chem 2013, 10, 645; (c) Jarrahpour, A.; Zarei, M. Tetrahedron Lett 2009, 50, 1568; (d) Khademi Shiraz, A.; Zarei, M. Monatsh Chem 2015, 146, 941; (e) Nahmany, M.; Melman, A. J Org Chem 2006, 71, 5804; (f) Jarrahpour, A.; Zarei, M. Molecules 2007, 12, 2364; (g) Bose, A. K.; Kapur, J. C.; Sharma, S. D.; Manhas, M. S. Tetrahedron Lett 1973 2319; (h) Jarrahpour, A.; Zarei, M. Tetrahedron Lett 2007, 48, 8712; (i) Zarei, M. J Chem Res 2013, 37, 25; (j) Zarei, M.; Jarrahpour, A. Heterocycl Commun 2014, 20, 355; (k) Chopde, H. N.; Pagadala, R.; Meshram, J. S.; Jetti, V. JHeterocyclic Chem 2010, 47, 1361; (l) Zarei, M. Monatsh Chem 2013, 144, 1021; (m) Jarrahpour, A.; Motamedifar, M.; Zarei, M.; Mimouni, M. Phosphorus Sulfur Silicon 2010, 185, 287; (n) Zarei, M. Lett Org Chem 2015, 12, 44; (o) Coulthard, G.; Unsworth, W. P.; Taylor, R. J. K. Tetrahedron Lett 2015, 56, 3113; (p) Jarrahpour, A.; Ebrahimi, E.; Sinou, V.; Latour, C.; Brunel, J. M. Eur J Med Chem 2014, 87, 364.

[15] Zarei, M. Tetrahedron Lett 2014, 55, 5354.

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

[17] Gutch, P. K.; Acharya, J. Heterocycl Commun 2007, 13, 393.

[18] (a) Wang, Y.; Liang, Y.; Jiao, L.; Du, D.-M.; Xu, J. J Org Chem 2006, 71, 6983; (b) Jarrahpour, A.; Zarei, M. Tetrahedron 2010, 66, 5017; (c) Zarei, M. Bull Chem Soc Jpn 2012, 85, 360.

[19] (a) Zarei, M.; Jarrahpour, A.; Ebrahimi, E.; Aye, M.; Torabi Badrabady, S. A. Tetrahedron 2012, 68, 5505; (b) Jarrahpour, A.; Zarei, M. Phosphorus Sulfur Silicon 2009, 184, 1738; (c) Akkurt, M.; Karaca, S.; Jarrahpour, A.; Zarei, M.; Büyükgünör, O. Acta Crystallogr Sect E 2008, 64, 924; (d) Matsui, S.; Hashimoto, Y.; Saigo, K. Synthesis 1998 1161; (e) Jarrahpour, A.; Zarei, M. Tetrahedron 2009, 65, 2927; (f) Zarei, M. Tetrahedron 2013, 69, 6620; (g) Zarei, M. Monatsh Chem 2014, 145, 1495.