*Send Orders for Reprints to reprints@benthamscience.net*

*Letters in Organic Chemistry,* **2013**, *10*, 645-650 

# A Simple and Highly Efficient Procedure for One-Pot Synthesis of 2-Azetidinones Using 3,5-Dinitrobenzoyl Chloride

Alireza Darvishi[a], Maaroof Zarei [b]* and Mohammad Reza Akhgar[a]

[a]*Department of Chemistry, Faculty of Science, Kerman Branch, Islamic Azad University, Kerman, Iran;* [b]*Department of Chemistry, College of Sciences, Hormozgan University, Bandar Abbas 71961, Iran*

***Received May 25, 2013: Revised July 09, 2013: Accepted July 12, 2013***

**Abstract:** One-pot synthesis of 2-azetidinones has efficiently been carried out in excellent yields by treatment of imines and substituted acetic acids with 3,5-dinitrobenzoyl chloride in the presence of triethylamine. The method is remarkably convenient and pure products were obtained by simple crystallization.

**Keywords:** β-Lactam, 2-Azetidinone, Staudinger reaction, 3,5-Dinitrobenzoyl chloride, Ketene, Imine.

## INTRODUCTION

2-Azetidinone (β-lactam) ring is present in several widely used families of antibiotics such as penicillins, cephalosporins, carbapenems, and other *β*-lactam antibiotics [1]. Ezetimibe is a new clinical drug which has 2-azetidinone ring and it is used as a cholesterol absorption inhibitor [2]. In addition, literature survey reveals that 2-azetidinones shown to possess other relevant biological activities [3]. Besides its fundamental importance in medicinal and pharmaceutical chemistry, the 2-azetidinone ring is a useful intermediate in organic synthesis (β-lactam synthon method) [4] and in the semi-synthesis of Taxol and Taxotere derivatives [5].

Because of these applications, synthesis of 2-azetidinones has received considerable attention over recent years and several methods have been reported for preparation of 2-azetidinones [6]. The most widely used and simple method for the synthesis of 2-azetidinones is the Staudinger reaction (ketene-imine cycloaddition) [7]. Generally, the ketene components are produced *in situ* by the reaction of an acyl chloride and a tertiary amine as a base [8]. Due to instability, commercial unavailability and difficulty in the preparation of acyl chloride, a variety of acid-activating agents have been used for *in situ* generation of ketenes from carboxylic acids in the modified Staudinger [2+2] cycloaddition [9]. Some of these acid activators have disadvantages such as unavailability, pollution, low or high temperature requirements tedious purification and low yields of products.

3,5-Dinitrobenzoyl chloride is a colored and active acyl chloride which is used for evaluation of biogenic amines in fish sauce [10], the recognition of chiral carboxylate anions [11], determination of residual amines used in bulk drug synthesis [12], derivatization of alcohols at dilute levels [13], determination of naphazoline in pharmaceuticals [14] and determination of putrescine and tyramine in fish [15].

*Address correspondence to these authors at the Department of Chemistry, Faculty of Science, Kerman Branch, Islamic Azad University, Kerman, Iran; and 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, mzarei@hormozgan.ac.ir

The objective of this work was to investigate the application of 3,5-dinitrobenzoyl chloride for the one-pot synthesis of 2-azetidinones from imines and carboxylic acids.

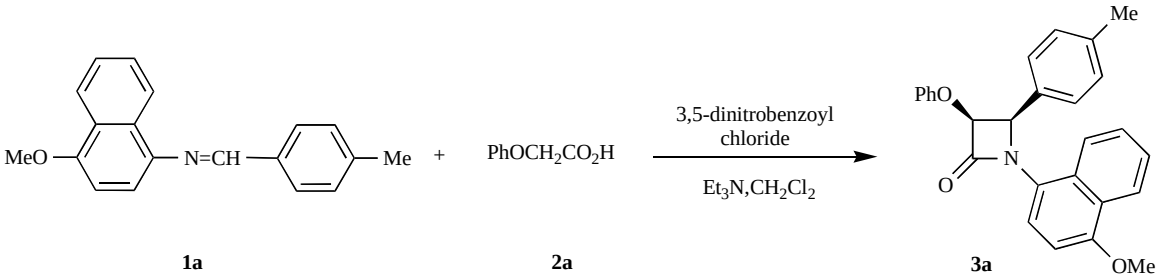
## RESULTS AND DISCUSSION

Imines were synthesized by reaction of corresponding amines and aldehydes in refluxing ethanol or by stirring overnight in the presence of anhydrous $Na_2SO_4$ in dry $CH_2Cl_2$. Reaction of imine **1a**, phenoxyacetic acid **2a** and 3,5-dinitrobenzoyl chloride in the presence of triethylamine in dry dichloromethane at room temperature gave pure *cis* β-lactam **3a** after purification by crystallization from 95% ethanol. Simple aqueous work-up removes the by-product of 3,5-dinitrobenzoyl chloride and any resulting salts. The stereochemistry of β-lactams were assigned by 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 [16]. The conditions were optimized using this reaction. The effect of solvent, temperature and quantity of reagent were investigated. In all reactions, 1.0 mmol of imine **1a** and three times the equivalents of phenoxyacetic acid **2a** with respect to the amount of 3,5-dinitrobenzoyl chloride were used. As it is shown in (Table **1**), dichloromethane gave the best results among the dry solvents tested. High decrease in the yield of β-lactam **3a** was observed when reaction was performed in cold media. The highest yield was obtained when 1.3 mmol phenoxyacetic acid and 1.3 mmol 3,5-dinitrobenzoyl chloride were reacted with 1.0 mmol of imine **1a** (Table **1**, entry 6). Therefore reactions of 1.0 mmol imine, 1.3 mmol acid and 1.3 mmol 3,5-dinitrobenzoyl chloride in the presence of triethylamine in dry dichloromethane at room temperature were used for next reactions.

According to the above results, 2-azetidinones **3a-p** were synthesized by treatment of 1.0 mmol of corresponding Schiff basis **1**, 1.3 mmol of acetic acid derivative **2** and 1.3 mmol 3,5-dinitrobenzoyl chloride in the presence of triethylamine in dry $CH_2Cl_2$ at room temperature (Scheme **1**, Table **2**). Purification of β-lactams **3a-p** were performed by simple

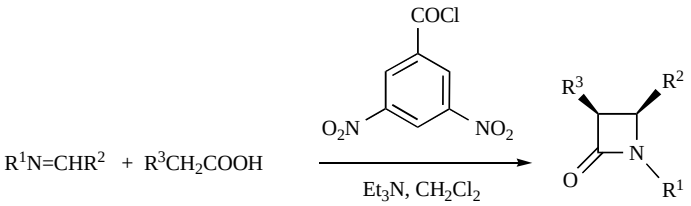
**1875-6255/13 $58.00+.00** 

**Table 1. Optimization of the Reaction Conditions for the Synthesis of β-lactam 3a**




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

| Entry | Solvent | Temp. | 3,5-dinitrobenzoyl Chloride (Equiv) | Yield % |
|---|---|---|---|---|
| 1 | DMF | rt | 1.0 | 46 |
| 2 | THF | rt | 1.0 | 51 |
| 3 | $CH_2Cl_2$ | rt | 1.0 | 77 |
| 4 | toluene | rt | 1.0 | 65 |
| 5 | $CH_2Cl_2$ | 0 °C | 1.0 | 33 |
| 6 | $CH_2Cl_2$ | rt | 1.3 | 90 |
| 7 | $CH_2Cl_2$ | rt | 1.5 | 88 |




**1** **2** **3a-p**

**Scheme 1.** Synthesis of 2-azetidinones **3a-p**.

**Table 2. Synthesis of 2-azetidinones 3a-p using 3,5-dinitrobenzoyl Chloride**

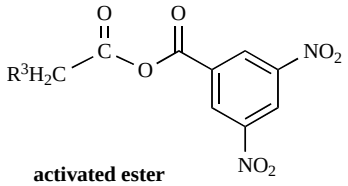
| Entry | $R^1$ | $R^2$ | $R^3$ | Product | Isolated Yield (%) |
|---|---|---|---|---|---|
| 1 | 4-MeONaphth-1-yl | 4-$MeC_6H_4$ | PhO | **3a** | 90 |
| 2 | 4-$EtC_6H_4$ | 4-$ClC_6H_4$ | 4-$ClC_6H_4O$ | **3b** | 86 |
| 3 | 4-$EtC_6H_4$ | 4-$ClC_6H_4$ | PhthN | **3c** | 92 |
| 4 | 4-$EtC_6H_4$ | 4-$ClC_6H_4$ | PhO | **3d** | 93 |
| 5 | 4-$EtC_6H_4$ | 4-$(Me_2N)C_6H_4$ | 4-$ClC_6H_4O$ | **3e** | 88 |
| 6 | 4-$EtC_6H_4$ | 4-$(Me_2N)C_6H_4$ | PhthN | **3f** | 91 |
| 7 | 4-$EtC_6H_4$ | 4-$(Me_2N)C_6H_4$ | PhO | **3g** | 90 |
| 8 | 4-$EtC_6H_4$ | 4-$(Me_2CH)C_6H_4$ | 4-$ClC_6H_4O$ | **3h** | 82 |
| 9 | 4-$EtC_6H_4$ | 4-$(Me_2CH)C_6H_4$ | PhthN | **3i** | 91 |
| 10 | 4-$EtC_6H_4$ | 4-$(Me_2CH)C_6H_4$ | PhO | **3j** | 86 |
| 11 | 4-$MeOC_6H_4$ | 4-$(Me_2N)C_6H_4$ | 4-$ClC_6H_4O$ | **3k** | 90 |

**Table 2. Contd…..**

| Entry | $R^1$ | $R^2$ | $R^3$ | Product | Isolated Yield (%) |
|---|---|---|---|---|---|
| 12 | 4-$MeOC_6H_4$ | 4-$(Me_2N)C_6H_4$ | PhthN | **3l** | 88 |
| 13 | 4-$MeOC_6H_4$ | 4-$(Me_2N)C_6H_4$ | PhO | **3m** | 82 |
| 14 | 4-$MeOC_6H_4$ | 4-$(Me_2CH)C_6H_4$ | 4-$ClC_6H_4O$ | **3n** | 84 |
| 15 | 4-$MeOC_6H_4$ | 4-$(Me_2CH)C_6H_4$ | PhthN | **3o** | 83 |
| 16 | 4-$MeOC_6H_4$ | 4-$(Me_2CH)C_6H_4$ | PhO | **3p** | 87 |

crystallization from 95% ethanol. All products were characterized by spectroscopic data and elemental analyses.

The mechanism of [2+2] cycloaddition of the imine and ketene has been previously investigated. It is actually a two-step process. In the first step, nitrogen atom of the imine, the nucleophile, attacks the lowest unoccupied molecular orbital (LUMO) of the ketene carbonyl group giving rise to a zwitterionic intermediate and a subsequent the second step, a four-electron conrotatory ring closure of the zwitterionic intermediate produced the β-lactam. This intermediate was detected and characterized by IR spectroscopy. Many different experimental factors, such as reaction temperature, solvent, electronic effects, and the steric hindrance of the ketene and imine substituents may affect the stereochemistry of β-lactams in the Staudinger reaction [17]. Then, it is assumed that the reaction proceeds *via* a [2+2] cycloaddition of the imine and ketene by formation of an activated ester [18]. This activated ester generates, *in situ*, the corresponding ketene in the presence of triethylamine.




**activated ester**

## EXPERIMENTAL

### General Procedures

All required chemicals were purchased from Merck, Fluka or Acros chemical companies. The melting points were determined on a Buchi 535 apparatus and are uncorrected. IR spectra were measured on a galaxy series FT-IR 5000 spectrometer. NMR spectra were recorded in $CDCl_3$ using a Bruker spectrophotometer ($^1$H NMR 250 MHz, $^{13}$C NMR 62.9 MHz) 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. Thin-layer chromatography was carried out on silica gel 254 analytical sheets obtained from Fluka. Spectral data for **3a** has been previously reported [19].

### General Procedure for the Synthesis of Imines

A mixture of amine (10.0 mmol) and aldehyde (10.0 mmol) was refluxed in ethanol for 3-4 hours. After cooling of the solution, the precipitate was filtered and washed with ethanol to give pure imine. Except **1d**, other imines have been reported previously [18c,20].

#### *4-Ethyl-N-(4-isopropylbenzylidene)aniline (1d)*

Light-yellow oil. IR (KBr) $cm^{-1}$: 1625 (C=N, imine); Anal. Calcd for $C_{18}H_{21}N$: C, 86.01; H, 8.42; N, 5.57; Found: C, 86.13; H, 8.56; N, 5.65.

### General Procedure for the Synthesis of 2-azetidinones 3a-p

A 3,5-dinitrobenzoyl chloride (1.3 mmol) was added to a solution of the substituted acetic acid (1.3 mmol), the imine (1.0 mmol) and $Et_3N$ (4.0 mmol) in dry $CH_2Cl_2$ (12 mL) at room temperature and the mixture was stirred overnight. The mixture was washed successively with saturated $NaHCO_3$ (12 mL) and brine (12 mL). The organic layer was dried ($Na_2SO_4$), filtered and the solvent was removed under reduced pressure to give the crude products. 2-azetidinones **3a-p** were purified by crystallization from 95% ethanol.

#### *3-(4-Chlorophenoxy)-4-(4-chlorophenyl)-1-(4-ethylphenyl)azetidin-2-one (3b)*

White solid. mp: 159-161 $^o$C IR (KBr) $cm^{-1}$: 1750 (CO, β-lactam); $^1$H NMR ($CDCl_3$) δ 1.27 (Me, t, 3H, *J* = 7.0), 2.59 ($CH_2$, q, 2H, *J* = 7.0), 5.43 (H-4, d, 1H, *J* = 4.9), 5.56 (H-3, d, 1H, *J* = 4.9), 6.78-7.33 (ArH, m, 12H); $^{13}$C NMR ($CDCl_3$) δ 14.7 (Me), 33.6 ($CH_2$), 62.8 (C-4), 80.9 (C-3), 115.9-156.9 (aromatic carbons), 161.7 (CO, β-lactam); Anal. Calcd for $C_{23}H_{19}Cl_2NO_2$: C, 67.00; H, 4.64; N, 3.40; Found: C, 67.11; H, 4.74; N, 3.34**.**

#### *2-(2-(4-Chlorophenyl)-1-(4-ethylphenyl)-4-oxoazetidin-3-yl)isoindoline-1,3-dione (3c)*

White solid. mp: 175-177 $^o$C IR (KBr) $cm^{-1}$:1735, 1775 (CO, phth), 1786 (CO, β-lactam); $^1$H NMR ($CDCl_3$) δ 1.33 (Me, t, 3H, *J* =7.0 ), 2.57 ($CH_2$, q, 2H, *J* = 7.0), 5.23 (H-4, d, 1H, *J* =5.0 ), 5.33 (H-3, d, 1H, *J* = 5.0), 6.78-7.33 (ArH, m, 12H); $^{13}$C NMR ($CDCl_3$) δ 14.6 (Me), 34.8 ($CH_2$), 62.3 (C-4), 63.8 (C-3), 116.1-156.2 (aromatic carbons), 161.5 (CO, phth ), 166.3 (CO, β-lactam); Anal. Calcd for $C_{25}H_{19}ClN_2O_3$: C, 69.69; H, 4.44; N, 6.50; Found: C, 69.77; H, 4.57; N, 6.44.

#### *4-(4-Chlorophenyl)-1-(4-ethylphenyl)-3-phenoxyazetidin-2-one (3d)*

White solid. mp: 182-184 $^o$C IR (KBr) $cm^{-1}$: 1739 (CO, β-lactam); $^1$H NMR ($CDCl_3$) δ 1.31 (Me, t, 3H, *J* = 7.0), 2.83 ($CH_2$, q, 2H, *J* =7.0), 5.24 (H-4, d, 1H, *J* = 4.8), 5.45 (H-3, d,

1H, *J* = 4.8), 6.68-7.23 (ArH, m, 13H); $^{13}$C NMR ($CDCl_3$) δ 14.6 (Me), 33.2 ($CH_2$), 63.8 (C-4), 82.0 (C-3), 115.0-156.8 (aromatic carbons), 163.7 (CO, β-lactam); Anal. Calcd for $C_{23}H_{20}ClNO_2$: C, 73.11; H, 5.33; N, 3.71; Found: C, 73.03; H, 5.45; N, 3.78.

***3-(4-Chlorophenoxy)-4-(4-(dimethylamino)phenyl)-1-(4-ethylphenyl)azetidin-2-one (3e)***

White solid. mp: 150-152 °C IR (KBr) cm$^{-1}$: 1750 (CO, β-lactam); $^1$H NMR ($CDCl_3$) δ 1.36 (Me, t, 3H, *J* =7.0 ), 2.35 ($CH_2$, q, 2H, *J* =7.0 ), 2.99 (2Me, s, 6H), 5.32 (H-4, d, 1H, *J* = 4.9), 5.45 (H-3, d, 1H, *J* = 4.9), 6.77-7.33 (ArH, m, 12H); $^{13}$C NMR ($CDCl_3$) δ 14.8 (Me), 32.3 ($CH_2$), 41.3 (Me-N), 63.7 (C-4), 81.7 (C-3), 113.9-160.1 (aromatic carbons), 161.7 (CO, β-lactam); Anal. Calcd for $C_{25}H_{25}ClN_2O_2$: C, 71.33; H, 5.99; N, 6.66; Found: C, 71.41; H, 6.12; N, 6.72.

***2-(2-(4-(Dimethylamino)phenyl)-1-(4-ethylphenyl)-4-oxoazetidin-3-yl)isoindoline-1,3-dione (3f)***

White solid. mp: 153-155 °C IR (KBr) cm$^{-1}$:1735, 1775 (CO, phth), 1790 (CO, β-lactam); $^1$H NMR ($CDCl_3$) δ 1.35 (Me, t, 3H, *J* = 6.9 ), 2.44 ($CH_2$, q, 2H, *J* = 6.9), 2.91 (2Me, s, 6H), 5.35 (H-4, d, 1H, *J* =5.0), 5.43 (H-3, d, 1H, *J* =5.0), 6.59-7.85 (ArH, m, 12H); $^{13}$C NMR ($CDCl_3$) δ 14.3 (Me), 32.7 ($CH_2$), 40.7 (Me-N), 62.3 (C-4), 63.1 (C-3), 114.4-155.3 (aromatic carbons), 161.1 (CO, phth), 166.3 (CO, β-lactam); Anal. Calcd for $C_{27}H_{25}N_3O_3$: C, 73.78; H, 5.73; N, 9.56; Found: C, 73.88; H, 5.87; N, 9.49.

***4-(4-(Dimethylamino)phenyl)-1-(4-ethylphenyl)-3-phenoxyazetidin-2-one (3g)***

White solid. mp: 177-179 °C IR (KBr) cm$^{-1}$: 1744 (CO, β-lactam); $^1$H NMR ($CDCl_3$) δ 1.32 (Me, t, 3H, *J* = 7.0), 2.56 ($CH_2$, q, 2H, *J* = 7.0), 2.90 (2Me, s, 6H), 5.28 (H-4, d, 1H, *J* =4.8), 5.47 (H-3, d, 1H, *J* =4.8), 6.74-7.30 (ArH, m, 13H); $^{13}$C NMR ($CDCl_3$) δ 14.8 (Me), 32.2 ($CH_2$), 40.4 (Me-N), 63.8 (C-4), 81.4 (C-3), 114.3-157.1 (aromatic carbons), 162.1 (CO, β-lactam); Anal. Calcd for $C_{25}H_{26}N_2O_2$: C, 77.69; H, 6.78; N, 7.25; Found: C, 77.76; H, 6.90; N, 7.33.

***3-(4-Chlorophenoxy)-1-(4-ethylphenyl)-4-(4-isopropylphenyl)azetidin-2-one (3h)***

White solid. mp: 111-113 °C IR (KBr) cm$^{-1}$: 1759 (CO, β-lactam); $^1$H NMR ($CDCl_3$) δ 1.29 (2Me, d, 6H, *J* = 6.9 ), 1.37(Me, t, 3H, *J* = 7.0), 3.17 ($CH_2$, q, 2H, *J* = 7.0 ), 3.46 (CH, sept, 1H, *J* = 6.9), 5.35 (H-4, d, 1H, *J* =5.0 ), 5.48 (H-3, d, 1H, *J* =5.0), 6.78-7.33 (ArH, m, 12H); $^{13}$C NMR ($CDCl_3$) δ 14.8 (Me), 25.1 (Me), 34.7 ($CH_2$), 37.9 (CH), 63.7 (C-4), 81.7 (C-3), 115.1-156.2 (aromatic carbons), 161.5 (CO, β-lactam); Anal. Calcd for $C_{26}H_{26}ClNO_2$: C, 74.36; H, 6.24; N, 3.34; Found: C, 74.30; H, 6.34; N, 3.25.

***2-(1-(4-Ethylphenyl)-2-(4-isopropylphenyl)-4-oxoazetidin-3-yl)isoindoline-1,3-dione (3i)***

White solid. mp: 224-226 °C IR (KBr) cm$^{-1}$: 1735, 1770 (CO, phth), 1778 (CO, β-lactam); $^1$H NMR ($CDCl_3$) δ 1.17 (2Me, d, 6H, *J* = 7.0), 1.31 (Me, t, 3H, *J* = 6.8), 2.74 ($CH_2$, q, 2H, *J* =6.8), 3.00 (CH, sept, 1H, *J* = 7.0) 5.37 (H-4, d, 1H, *J* =4.7), 5.76 (H-3, d, 1H, *J* =4.7), 6.90-8.37 (ArH, m, 12H); $^{13}$C NMR ($CDCl_3$) δ 14.8 (Me), 24.2 (Me), 33.0 ($CH_2$), 37.7 (CH), 61.04 (C-4), 63.7 (C-3), 114.9-160.6 (aromatic carbons), 167.3 (CO, β-lactam); Anal. Calcd for $C_{28}H_{26}N_2O_3$: C, 76.69; H, 5.98; N, 6.39; Found: C, 76.81; H, 6.09; N, 6.31.

***1-(4-Ethylphenyl)-4-(4-isopropylphenyl)-3-phenoxyazetidin-2-one (3j)***

White solid. Yield: (0.40 g, 86%), mp: 166-168 °C IR (KBr) cm$^{-1}$: 1755 (CO, β-lactam); $^1$H NMR ($CDCl_3$) δ 1.06 (2Me, d, 6H, *J* = 7.0), 1.10 (Me, t, 3H, *J* = 7.0), 2.56 ($CH_2$, q, 2H, *J* =7.0), 2.73 (CH, sept, 1H, *J* = 7.0), 5.25 (H-4,d, 1H, *J* = 4.8), 5.45 (H-3, d, 1H, *J* =4.8), 6.52-7.28 (ArH, m, 13H); $^{13}$C NMR ($CDCl_3$) δ 12.5 (Me), 23.5 (Me), 34.2 ($CH_2$), 38.4 (CH), 61.3 (C-4), 81.0 (C-3), 112.0-156.9 (aromatic carbons), 161.7 (CO, β-lactam); Anal. Calcd for $C_{26}H_{27}NO_2$: C, 81.01; H, 7.06; N, 3.63; Found: C, 81.13; H, 7.16; N, 3.71.

***3-(4-Chlorophenoxy)-4-(4-(dimethylamino)phenyl)-1-(4-methoxyphenyl)azetidin-2-one (3k)***

White solid. mp: 209-211 °C IR (KBr) cm$^{-1}$: 1734 (CO, β-lactam); $^1$H NMR ($CDCl_3$) δ 2.84 (2Me, s, 6H), 3.82 (MeO, s, 3H), 5.20 (H-4, d, 1H, *J* = 4.7), 5.41 (H-3, d, 1H, *J* =4.7 ), 6.68-7.23 (ArH, m, 12H); $^{13}$C NMR ($CDCl_3$) δ 41.8 (Me), 55.2 (Me), 63.6 (C-4), 81.2 (C-3), 113.8-159.8 (aromatic carbons), 162.6 (CO, β-lactam); Anal. Calcd for $C_{24}H_{23}Cl\,N_2O_3$: C, 68.16; H, 5.48; N, 6.62; Found: C, 68.08; H, 5.60; N, 6.66.

***2-(2-(4-(Dimethylamino)phenyl)-1-(4-methoxyphenyl)-4-oxoazetidin-3-yl)isoindoline-1,3-dione(3l)***

White solid. mp: 209-211 °C IR (KBr) cm$^{-1}$:1724, 1772 (CO, phth), 1785 (CO, β-lactam); $^1$H NMR ($CDCl_3$) δ 2.58 (2Me, s, 6H), 3.72 (MeO, s, 3H), 5.37 (H-4, d, 1H, *J* =5.5), 5.61 (H-3, d, 1H, *J* =5.5), 6.78-7.78 (ArH, m, 12H); $^{13}$C NMR ($CDCl_3$) δ 41.78 (Me), 55.5 (Me), 58.8 (C-4), 60.3 (C-3), 114.5-156.5 (aromatic carbons), 160.1 (CO, Phth), 166.7 (CO, β-lactam); Anal. Calcd for $C_{26}H_{23}N_3O_4$: C, 70.73; H, 5.25; N, 9.52; Found: C, C, 70.78; H, 5.32; N, 9.48.

***4-(4-(Dimethylamino)phenyl)-1-(4-methoxyphenyl)-3-phenoxyazetidin-2-one (3m)***

White solid. mp: 222-224 °C IR (KBr) cm$^{-1}$: 1731 (CO, β-lactam); $^1$H NMR ($CDCl_3$) δ 2.86 (2Me, s, 6H), 3.73 (MeO, s, 3H), 5.27 (H-4, d, 1H, *J* = 4.7), 5.48 (H-3, d, 1H, *J* =4.7), 6.59-7.31 (ArH, m, 13H); $^{13}$C NMR ($CDCl_3$) δ 40.7 (Me), 55.2 (Me), 61.7 (C-4), 81.1 (C-3), 112.8-159.7 (aromatic carbons), 162.2 (CO, β-lactam); Anal. Calcd for $C_{24}H_{24}N_2O_3$: C, 74.21; H, 6.23; N, 7.21; Found: C, 74.33; H, 6.37; N, 7.30.

***3-(4-Chlorophenoxy)-4-(4-isopropylphenyl)-1-(4-methoxyphenyl)azetidin-2-one (3n)***

White solid. mp: 169-171 °C IR (KBr) cm$^{-1}$: 1731 (CO, β-lactam); $^1$H NMR ($CDCl_3$) δ 1.27 (2Me, d, 6H, *J* =7.0), 2.79 (CH, sept, 1H, *J* = 7.0), 3.9 (Me, s, 3H), 5.45 (H-4,d, 1H, *J* =4.8 ), 5.62 (H-3, d, 1H, *J* =4.8 ), 6.80-7.90 (ArH, m, 12H); $^{13}$C NMR ($CDCl_3$) δ 23.8 (Me), 36.8 (CH), 56.2 (Me), 61.6 (C-4), 81.3 (C-3), 115.6-160.5 (aromatic carbons), 166.2 (CO, β-lactam); Anal. Calcd for $C_{25}H_{24}ClNO_3$: C, 71.17; H, 5.73; N, 3.32; Found: C, 71.09; H, 5.85; N, 3.26.

### *2-(2-(4-Isopropylphenyl)-1-(4-methoxyphenyl)-4-oxoazetidin-3-yl)isoindoline-1,3-dione (3o)*

White solid. mp: 261-263 °C IR (KBr) $cm^{-1}$: 1735, 1775 (CO, phth), 1785 (CO, β-lactam); $^1$H NMR ($CDCl_3$) δ 1.17 (2Me, d, 6H, *J* = 6.9), 2.73 (CH, sept, 1H, *J* = 6.9), 3.74 (MeO, s, 3H), 5.26 (H-4, d, 1H, *J* = 5.1), 5.36 (H-3, d, 1H, *J* = 5.1), 6.86-7.82 (ArH, m, 12H); $^{13}$C NMR ($CDCl_3$) δ 24.1 (Me), 35.2 (CH), 55.3 (OMe), 60.8 (C-4), 62.8 (C-3), 114.8-160.1 (aromatic carbons), 162.2 (CO, phth), 166.8 (CO, β-lactam); Anal. Calcd for $C_{27}H_{24}N_2O_4$: C, 73.62; H, 5.49; N, 6.36; Found: C, 73.69; H, 5.59; N, 6.28.

### *4-(4-Isopropylphenyl)-1-(4-methoxyphenyl)-3-phenoxyazetidin-2-one (3p)*

White solid. mp: 254-256 °C IR (KBr) $cm^{-1}$: 1740 (CO, β-lactam); $^1$H NMR (250 MHz, $CDCl_3$) δ 1.34 (2Me, d, 6H, *J* =7.0), 2.82 (CH, sept, 1H, *J* = 7.0), 3.62 (MeO, s, 3H), 5.29 (H-4, d, 1H, *J* =4.6 ), 5.56 (H-3, d, 1H, *J* =4.6), 6.69-7.69 (ArH, m, 13H); $^{13}$C NMR ($CDCl_3$) δ 24.5 (Me), 37.2 (CH), 55.1 (Me), 63.7 (C-4), 81.1 (C-3), 113.9-159.9 (aromatic carbons), 162.5 (CO, β-lactam); Anal. Calcd for $C_{25}H_{25}NO_3$: C, 77.49; H, 6.50; N, 3.61; Found: C, 77.60; H, 6.64; N, 3.68.

## CONCLUSION

In conclusion, 3,5-dinitrobenzoyl chloride is an efficient reagent for the one-pot synthesis 2-azetidinones (β-lactams) from imines and carboxylic acids under mild conditions. Simple aqueous work-up removes the by-product of 3,5-dinitrobenzoyl chloride and any resulting salts. Pure products were obtained by crystallization from 95% ethanol with excellent yields. This method is remarkably simple and convenient for the synthesis of 2-azetidinones.

## CONFLICT OF INTEREST

The author(s) confirm that this article content has no conflict of interest.

## ACKNOWLEDGEMENTS

Support for this work by the Kerman Branch of Islamic Azad University, is gratefully acknowledged.

## REFERENCES

[1] (a) Ceric, H.; Sindler-Kulyk, M.; Kovacevic, M.; Peric, M.; Zivkovic, A. Azetidinone-isothiazolidinones: Stereoselective synthesis and antibacterial evaluation of new monocyclic beta-lactams. *Bioorg. Med. Chem.* **2010**, *18*, 3053–3058; (b) Morin, R. B.; Gorman, M. *Chemistry and Biology of β-Lactam Antibiotics*; Academic: New York, NY, 1982; (c) Long, T. E.; Turos, E. *N*-Thiolated β–lactams. *Curr. Med. Chem. Anti-Infective Agents* **2002**, *1*, 251-268; (d) Hwu, J. R.; Ethiraj, S. K.; Hakimelahi, G. H. Biological activity of some monocyclic- and bicyclic β-lactams with specified functional groups. *Mini-Rev. Med. Chem.* **2003**, *3*, 305-313.

[2] (a) Xu, X.; Fu, R.; Chen, J.; Chen, S.; Bai, S. Ezetimibe analogs with a reorganized azetidinone ring: Design, synthesis, and evaluation of cholesterol absorption inhibitions. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 101-104; (b) Burnett, D. A. β-Lactam cholesterol absorption inhibitors. *Curr. Med. Chem.* **2004**, *11*, 1873-1887.

[3] (a) O'Boyle, N. M.; Greene, L. M.; Keely, N. O.; Wang, S.; Cotter, T. S.; Zisterer, D. M.; Meegan, M. J. Synthesis and biochemical activities of antiproliferative amino acid and phosphate derivatives of microtubule-disrupting β-lactam combretastatins. *Eur. J. Med. Chem.* **2013**, *62*, 705-721; (b) Jarrahpour, A.; Ebrahimi, E.; Khalifeh, K.; Sharghi, H.; Sahraei, M.; Sinou, V.; Latour, C.; Brunel, J. M. Synthesis of novel β-lactams bearing an anthraquinone moiety, and evaluation of their antimalarial activities. *Tetrahedron* **2012**, *68*, 4740-4744. For review see: (c) 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*, 5541-5560; (d) Veinberg, G.; Vorona, M.; Shestakova, I.; Kanepe, I.; Lukevics, E. Design of β-lactams with mechanism based nonantibacterial activities. *Curr. Med. Chem.* **2003**, *10*, 1741-1757.

[4] (a) Kiss, L.; Forro, E.; Fulop, F. Selective syntheses of novel highly functionalized β-aminocyclohexanecarboxylic acids. *Tetrahedron* **2012**, *68*, 4438-4443. For a review, see: (b) Alcaide, B.; Almendros, P.; Aragoncillo, C. β-Lactams: versatile building blocks for the stereoselective synthesis of non-β-lactam products. *Chem. Rev.* **2007**, *107*, 4437-4492; (c) Alcaide, B.; Almendros, P. β-Lactams as versatile synthetic intermediates for the preparation of heterocycles of biological interest. *Curr. Med. Chem.* **2004**, *11*, 1921-1949; (d) Deshmukh, A. R. A. S.; Bhawal, B. M.; Krishnaswamy, D.; Govande, V. V.; Shinkre, B. A.; Jayanthi, A. Azetidin-2-ones, synthon for biologically important compounds. *Curr. Med. Chem.* **2004**, *11*, 1889-1920; (e) Ojima, I.; Delaloge, F. Asymmetric synthesis of building-blocks for peptides and peptidomimetics by means of the β-lactam synthon method. *Chem. Soc. Rev.* **1997**, *26*, 377-386; (f) Palomo, C.; Oiarbide, M. in *Topics in Heterocyclic Chemistry*; Banik, B. K. (Ed.); Springer-Verlag; Berlin; **2010**; Vol. 22, pp 211-259.

[5] (a) Hodge, M.; Chen, O.-H.; Bane, S.; Sharma, S.; Loew, M.; Banerjee, A.; Alcaraz, A. A.; Snyder, J. P.; Kingston, D. G. I. Synthesis and bioactivity of a side chain bridged paclitaxel: A test of the T-Taxol conformation. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 2884–2887; (b) Suffness, M. *Taxol Science and Applications*, CRC Press, Boca Raton, Florida, USA, 1995.

[6] (a) Gedey, S.; Van der Eycken, J.; Fülop, F. Synthesis of Alicyclic β-lactams *via* the Ugi Reaction on a Solid Support. *Lett. Org. Chem.* **2004**, *1*, 215-220; (b) Pheko, T.; Singh, G. S. Reaction of 2-diazo-1,2-diphenylethanone with 2-[(arylimino)methyl]phenols. *Lett. Org. Chem.* **2006**, *3*, 212-213; (c) Zarei, M. A convenient synthesis of 2-azetidinones via 2-fluoro-1-methylpyridinium *p*-toluenesulfonate. *Monatsh. Chem.* **2013**, *144*, 1021-1025; (d) Kinugasa, M.; Hashimoto, S. The reactions of copper(I) phenylacetylide with nitrones. *J. Chem. Soc., Chem. Commun.,* **1972**, 466-467; (e) Barański, A.; Jasiński, R. [2+3] Cycloaddition reactions of conjugated nitroalkenes to nitrones. *Wiad. Chem.* **2002**, *56*, 829; For review see: (f) Alcaide, B.; Almendros, P. *Progress in Heterocyclic Chemistry* **2011**, *22*, 85-107; (g) Aranda, M. T.; Perez-Faginas, P.; Gonzalez-Muniz, R. An update on the synthesis of β-lactams. *Curr. Org. Synth.* **2009**, *6*, 325-341; (h) Fu, N.; Tidwell, T. T. Preparation of β-lactams by [2+2] cycloaddition of ketenes and imines. *Tetrahedron* **2008**, 64, 10465-10496.

[7] (a) Staudinger, H. Zur kenntniss der ketene. Diphenylketen. *Liebigs Ann. Chem.* **1907**, *356*, 51–123. (b) Fodor, L.; Csomos, P.; Holczbauer, T.; Kalman, A.; Csampai, A.; Sohar, P. Expected and unexpected reactions of 1,3-benzothiazine derivatives, I. Ring transformation of β-lactam-condensed 1,3-benzothiazines into 4,5-dihydro-1,4-benzothiazepines and indolo-1,4-benzothiazepines. *Tetrahedron Lett.* **2011**, *52*, 224–227; (c) Zarei, M.; Karimi-Jaberi, Z.; Movahedi, A. Synthesis of β-lactams from acids and imines using thiocarbonyldiimidazole. *Synth. Commun.* **2013**, *43*, 728–734; (d) Jarrahpour, A.; Motamedifar, M.; Zarei, M.; Mimouni, M. Synthesis of new N-sulfonyl monocyclic β-lactams and the investigation of their antibacterial activities. *Phosphorus Sulfur Silicon* **2010**, *185*, 287–297; (e) Jarrahpour, A.; Zarei, M. Synthesis of novel *N*-sulfonyl monocyclic β-lactams as potential antibacterial agents. *Molecules* **2006**, *11*, 49–58; (f) 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*, 320-327; (g) Keri, R. S.; Hosamani, K. M.; Shingalapur, R. V.; Reddy, H. R. S. RETRACTED: 2-Azetidinone derivatives: design, synthesis, *in vitro* antimicrobial, cytotoxic activities and DNA cleavage study. *Eur. J. Med. Chem.* **2009**, *44*, 5123–5130; (h) Zarei, M.; Jarrahpour, A. A mild and efficient route to 2-azetidinones using the cyanuric chloride–DMF complex. *Synlett* **2011**, 2572–2576. (i) Cremonesi, G.; Croce, P. D.; Forni, A.; La Rosa, C. Stereoselective synthesis of

constrained norbornane-derived spiro-β-lactams. *Tetrahedron* **2013**, *69*, 1175-1182.

[8] Tidwell, T. T. *Ketenes II*. John Wiley & Sons, New Jersey, **2006**, pp 55-192.

[9] (a) Banik, B. K.; Banik, I.; Becker, F. F. Asymmetric synthesis of anticancer β-lactams via Staudinger reaction: Utilization of chiral ketene from carbohydrate. *Eur. J. Med. Chem.* **2010**, *45*, 846–848; (b) Zarei, M.; Mohamadzadeh, M. 3-Thiolated 2-azetidinones: synthesis and *in vitro* antibacterial and antifungal activities. *Tetrahedron* **2011**, *67*, 5832-5840. (c) Jarrahpour, A.; Zarei, M. DMF-dimethyl sulfate as a new reagent for the synthesis of β-lactams. *Tetrahedron Lett.* **2009**, *50*, 1568–1570; (d) Jarrahpour, A.; Zarei, M. The Vilsmeier reagent: a useful and versatile reagent for the synthesis of 2-azetidinones. *Tetrahedron* **2009**, *65*, 2927–2934; (e) Nahmany, M.; Melman, A. Simple approach to β-lactam derivatives from N-acylimidazoles. *J. Org. Chem.* **2006**, *71*, 5804-5806; (f) 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*, 2364-2379; (g) Bose, A. K.; Kapur, J. C.; S. D. Sharma, Manhas, M. S. Synthesis of β-lactams through the reaction of mixed anhydrides and imines. *Tetrahedron Lett.* **1973**, *14*, 2319-2320; (h) Jarrahpour, A.; Zarei, M. The Vilsmeier reagent as an efficient acid activator for the synthesis of β-lactams. *Tetrahedron Lett.* **2007**, *48*, 8712–8714; (i) Zarei, M. One-step synthesis of β-lactams using cyanuric fluoride. *J. Chem. Res.* **2013**, *37*, 25–27. (j) Matsui, S.; Hashimoto, Y.; Saigo, K. Application of erythro-2-Amino-1,2-diphenylethanol as a Highly Efficient Chiral Auxiliary. Highly Stereoselective Staudinger-Type β-Lactam Synthesis Using a 2-Chloro-1-methylpyridinium Salt as the Dehydrating Agent. *Synthesis* **1998**, 1161-1166; (k) Zarei, M. One-pot sequence synthesis of azetidin-2-one using diethyl chlorophosphate. *J. Chem. Res.* **2012**, *36*, 118-120; (l) Palomo, C.; Aizpurua, J. M.; Urchegui, R.; Iturburu, M.; de Retana, A. O.; Cuevas, C. A convenient method for .beta.-lactam formation from .beta.-amino acids using phenyl phosphorodichloridate reagent. *J. Org. Chem.* **1991**, *56*, 2244-2247; (m) Unsworth, W. P.; Kitsiou, C.; Taylor, R. J. K. Direct imine acylation: Rapid access to diverse heterocyclic scaffolds. *Org. Lett.* **2013**, *15*, 258-261.

[10] Chin-Chen, M. L.; Carda-Broch, S.; Peris-Vicente, J.; Rambla-Alegre, M.; Esteve-Romero, J.; Marco-Peiró, S. Evaluation of biogenic amines in fish sauce by derivatization with 3,5-dinitrobenzoyl chloride and micellar liquid chromatography. *J. Food Comp. Anal.* **2013**, *29*, 32–36.

[11] Hyun, M. H.; Kim, S. N.; Choi, H. J.; Sakthivel, P. Liquid chromatographic resolution of N-(3,5-dinitrobenzoyl)-α-amino acids on a new chiral stationary phase: the first liquid chromatographic utilization of a double-ureide pocket for the recognition of chiral carboxylate anions. *Bull. Korean Chem. Soc.* **2007**, *28*, 1980-1984.

[12] Morley, J.; Elrod Jr, L.; Linton, C.; Shaffer, D.; Krogh, S. Determination of residual amines used in bulk drug synthesis by pre-column derivatization with 3,5-dinitrobenzoyl chloride and high-performance liquid chromatography. *J. Chromatogr., A* **1997**, *766*, 77–78.

[13] Valdez, D.; Reier, J. C. A simplified procedure for the derivatization of alcohols at dilute levels in aqueous solutions with 3,5-dinitrobenzoyl chloride. *J. Chromatogr. Sci.* **1986**, *24*, 356-360.

[14] Tsunetoshi, K.; Koji, K. Color raction between imidazoline and 3,5-dinitrobenzoyl chloride, and determination of naphazoline in pharmaceuticals. *Chem. Pharm. Bull.* **1972**, *20*, 700-707.

[15] Chin-Chen, M.-L.; Bose, D.; Esteve-Romero, J.; Peris-Vicente, J.; Rambla-Alegre, M.; Carda-Broch, S. Determination of putrescine and tyramine in fish by micellar liquid chromatography with UV detection using direct injection. *Open Anal. Chem. J.* **2011**, *5*, 22-26.

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

[17] (a) Wright, S. W. in *Name Reactions for Carbocyclic Ring Formations*, ed. by J. J. Li, John Wiley & Sons, New Jersey, **2010**, p. 4569. (b) Yu, Z.-X.; Xu, J. New insights into the torquoselectivity of the Staudinger reaction. *J. Am. Chem. Soc.* **2009**, *131*, 1542-1549. (c) Cossío, 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*, 925-936.

[18] (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*, 6983-6990; (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*, 5017-5023; (c) 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*, 360-368.

[19] Zarei, M.; Jarrahpour, A.; Ebrahimi, E.; Aye, M.; Torabi Badrabady, S. A. On-column *N*-dearylation of 2-azetidinones by silica-supported ceric ammonium nitrate. *Tetrahedron* **2012**, *68*, 5505-5512.

[20] (a) Donthiri, R. R.; Patil, R. D.; Adimurthy, S. NaOH-catalyzed imine synthesis: aerobic oxidative coupling of alcohols and amines. *Eur. J. Org. Chem.* **2012**, *24*, 4457-4460. (b) Holík, M.; Běluša, J.; Břicháček, J. $^{1}$H-NMR study of a transfer of substituent effects in para-substituted benzylideneanilines and their conjugate acids. *Collect. Czech. Chem. Commun.* **1978**, *43*, 610-620. (c) Neuvonen, H.; Neuvonen, K.; Fueloep, F. Substituent cross-interaction effects on the electronic character of the C=N bridging group in substituted benzylidene anilines − models for molecular cores of mesogenic compounds. A $^{13}$C NMR study and comparison with theoretical results. *J. Org. Chem.* **2006**, *71*, 3141-3148. (d) Liu, H.; Dagousset, G.; Masson, G.; Retailleau, P.; Zhu, J. Chiral Brønsted Acid-Catalyzed Enantioselective Three-Component Povarov Reaction. *J. Am. Chem. Soc.* **2009**, *131*, 4598-4599.