 

# Utilization of DMF–PhCOCl Adduct as an Acid Activator in a New and Convenient Method for Preparation of β-Lactams

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An efficient one-pot synthesis of β-lactams by the reaction of imines with acetic acid derivatives in the presence of DMF and benzoyl chloride adduct, a cheap reagent, has been described. Optimization of solvents, temperature, and molar ratio of reagent was also performed. Several types of β-lactams including monocyclic, spirocyclic, *N*-alkyl, 3-butadienyl, and 3-electron-withdrawing group have been synthesized by this method in good to excellent yields. All steps of the reaction proceed at room temperature.

For about 80 years, the β-lactam antibiotics such as penicillins, cephalosporins, carbapenems, and monobactams have served as a powerful line of defense against bacterial infections.[1] Of course, the appearance of new types of bacteria resistant to the more commonly used β-lactam antibiotics is a problem of worldwide importance and it gives further impetus to the synthesis of new β-lactams.[2] The new cholesterol absorption inhibitor, Ezetimibe, has a β-lactam skeleton.[3] Besides being antibacterial and cholesterol absorption inhibitor drugs, various other biological activities have been discovered to be associated with β-lactams.[4] Azetidin-2-ones (β-lactams) can be employed as useful intermediates in organic synthesis as a term coined by Ojima,[5] a β-lactam synthon method.[6] β-Lactams have also proven highly popular as side-chain equivalents for the synthesis of Taxol and Taxotere, as well as numerous analogues.[7]

Building of a β-lactam ring is a crucial step in the synthesis of new β-lactams and due to the importance of this structural framework, the development of new synthetic methods for the formation of the β-lactam ring continues to be a challenging area in organic chemistry.[8]

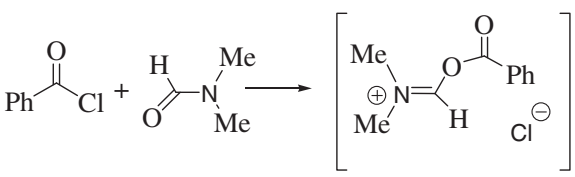
The Staudinger reaction (ketene–imine cycloaddition) is the most widely used and simple reaction for the synthesis of azetidin-2-ones which Professor Hermann Staudinger first reported in 1907.[9] After over 100 years, this general reaction yielding β-lactams remains one of the key methods for the synthesis of these strained heterocycles.[10] Most often, the ketene components used in the Staudinger reaction are usually produced in situ by the elimination of an acyl chloride in the presence of a base.[11] Other methods for ketene generation that are occasionally used are conceptually similar to the elimination of acyl chlorides but use different carboxy activating reagents. Activation of a carboxylic acid followed by treatment with triethylamine has been used to generate a ketene.[12] These methods are conventionally useful when the acid halides are not commercially available, difficult to prepare or when they are unstable. The high cost, unavailability, pollution, and low yields are disadvantages of some these acid activators. Furthermore in some cases, heating or cooling of the reaction is necessary.

DMF and benzoyl chloride adduct **1** has been used previously for the formylation of alcohols at room temperature.[13] According to above facts, in this paper the simple and efficient procedure for the preparation of β-lactams by the Staudinger reaction from imines and substituted carboxylic acids using DMF and benzoyl chloride adduct is described.

DMF and benzoyl chloride adduct **1** was generated in situ by reaction of *N*,*N*-dimethylformamide (DMF) and benzoyl chloride in dry $CH_2Cl_2$ at room temperature (Scheme 1).

Then the adduct **1** in dry $CH_2Cl_2$ was added to a solution of Schiff base **2a**, carboxylic acid **3a**, and triethylamine in dry $CH_2Cl_2$ at room temperature. After usual workup and crystallization from ethyl acetate, azetidin-2-one **4a** was obtained in 91%. This reaction is simple and clean because DMF and triethylammonium salt by-products were removed by simple aqueous work-up. Next the effect of solvents, temperature, and molar ratio of reagent were examined. According to Table 1, DMF or benzoyl chloride alone was inactive in the synthesis of azetidin-2-one **4a**. Among the solvents considered, dichloromethane showed the best result and cold media decreased the yield. As it is shown in the table, the highest yield of **4a** was obtained when 1.3 mmol of the adduct **1** and 1.3 mmol carboxylic acid **3a** react with 1.0 mmol of Schiff base **2a** in dry dichloromethane at room temperature (Entry 8).

On the basis of these successful results, the azetidin-2-ones **4a**–**4p** were synthesized by treatment of 1.0 mmol of imines **2**, 1.3 mmol of substituted acetic acids **3**, and 1.3 mmol of adduct **1** in the presence of triethylamine in dry dichloromethane at room temperature and they were purified by crystallization from EtOAc (Table 2). All products were characterized by their




**1**

**Scheme 1.**

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spectral data and elemental analyses. The *cis* stereochemistry was assigned by the comparison of the coupling constant H-3 and H-4 ($J_{3,4} > 4.0$ Hz).

Treatment of imine **5** derived from 4-methoxy-1-naphthylamine with various acetic acid derivatives in the presence of reagent **1** at room temperature gave *cis*-azetidin-2-ones **6a–6c** which were purified by crystallization from EtOAc (Scheme 2).

(Prop-2-enyloxy)acetic acid (**7**) was prepared from prop-2-enyl alcohol (allyl alcohol) and chloroacetic acid by a procedure described in the literature.[14] Reaction of (prop-2-enyloxy)-acetic acid (**7**) and corresponding imines in the presence of adduct **1** yielded the *cis*-azetidin-2-ones **8a–8c** in excellent yield (Scheme 3).

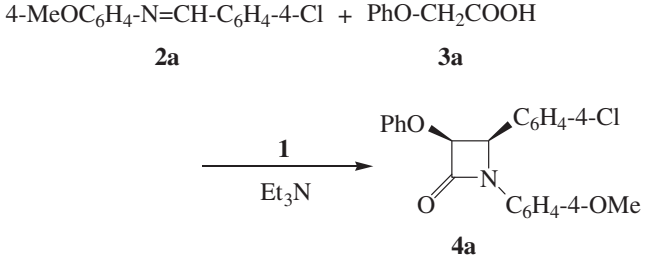
$\beta$-Lactams **9a–9c** were also easily obtained from sorbic acid (hexa-2,4-dienoic acid) by this method and purified by short column chromatography on silica gel (Scheme 4). The *trans* stereochemistry was deduced from H-3 and H-4 coupling constants ($J_{3,4} \leq 3.0$). [2 + 2] Cycloaddition reactions between butadienyl ketene (generated in situ) and corresponding imines gave the 3-butadienylazetidin-2-ones **9a–9c**. Previously Mahajan and co-workers were synthesized *trans*-dienyl-azetidin-2-one derivatives from sorbyl chloride and imines in the presence of triethylamine in $CH_2Cl_2$ and Diels–Alder reaction of these compounds has been investigated.[15]

Then to check the generality of this method, we synthesized azetidin-2-ones **10a–10f** from imines derived from aliphatic amines (Scheme 5). Azetidin-2-ones **10a–10f** were purified by crystallization from EtOAc. The good to excellent yields of products showed the versatility of this method in the synthesis of different $\beta$-lactams.

The DMF and benzoyl chloride adduct **1** was also successfully employed for the synthesis of C-3 spiro-$\beta$-lactams. Treatment of xanthene-9-carboxylic acid with various imines in the presence of the adduct **1** and triethylamine afforded pure spiro-$\beta$-lactams **11a–11c** after crystallization from EtOAc (Scheme 6).

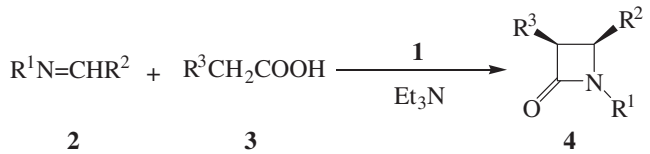
Although the [2 + 2] cycloaddition reaction of ketene–imine using $\alpha$-electron-withdrawing substituted carboxylic acids generally fails for the synthesis of azetidin-2-ones, this method was successfully extended to the synthesis of 3-azido and 3-acetyl-$\beta$-lactams. *cis*-3-Azido-$\beta$-lactams **12a–12c** and *trans*-3-acetyl-$\beta$-lactams **13a–13c** were synthesized from azidoacetic acid,[16] acetoacetic acid,[17] and corresponding imines using

**Table 1.** Reaction Condition in the Synthesis of Azetidin-2-one **4a**

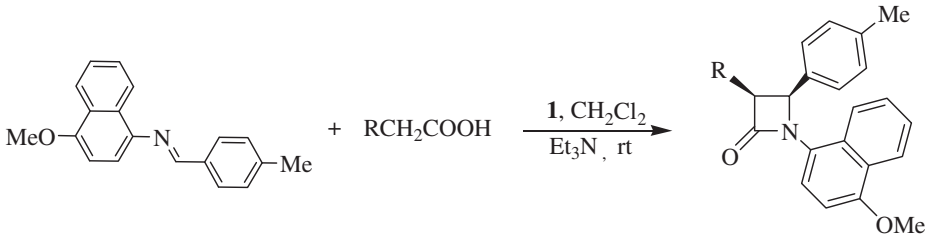



| Entry | Reagent | Solvent | Temp | Quantity of reagent /mmol | Yield /% |
|---|---|---|---|---|---|
| 1 | DMF | $CH_2Cl_2$ | rt | 1.5 | — |
| 2 | PhCOCl | $CH_2Cl_2$ | rt | 1.5 | — |
| 3 | **1** | $CH_2Cl_2$ | rt | 1.5 | 91 |
| 4 | **1** | DMF | rt | 1.5 | 63 |
| 5 | **1** | THF | rt | 1.5 | 76 |
| 6 | **1** | Toluene | rt | 1.5 | 48 |
| 7 | **1** | $CH_2Cl_2$ | 0 °C | 1.5 | 72 |
| 8 | **1** | $CH_2Cl_2$ | rt | 1.3 | 93 |
| 9 | **1** | $CH_2Cl_2$ | rt | 1.0 | 79 |

**Table 2.** Synthesis of Azetidin-2-ones **4a–4p** by Adduct **1**




| Entry | $R^1$ | $R^2$ | $R^3$ | Product | Isolated yield/% |
|---|---|---|---|---|---|
| 1 | 4-$MeOC_6H_4$ | 4-$ClC_6H_4$ | PhO | **4a** | 93 |
| 2 | 4-$MeOC_6H_4$ | 4-$MeOC_6H_4$ | PhO | **4b** | 89 |
| 3 | 4-$EtOC_6H_4$ | 4-$NO_2C_6H_4$ | PhO | **4c** | 90 |
| 4 | 4-$EtOC_6H_4$ | CH=CHPh | PhO | **4d** | 89 |
| 5 | 4-$MeOC_6H_4$ | 4-$MeC_6H_4$ | PhO | **4e** | 91 |
| 6 | 4-$EtOC_6H_4$ | CH=CHPh | PhthN | **4f** | 87 |
| 7 | 4-$EtOC_6H_4$ | 4-$NO_2C_6H_4$ | PhthN | **4g** | 85 |
| 8 | 4-$MeOC_6H_4$ | 4-$ClC_6H_4$ | PhthN | **4h** | 89 |
| 9 | 4-$MeOC_6H_4$ | 4-$MeC_6H_4$ | PhthN | **4i** | 83 |
| 10 | 4-$EtOC_6H_4$ | 4-$ClC_6H_4$ | 2-NaphthO | **4j** | 91 |
| 11 | $C_6H_5$ | 4-$NO_2C_6H_4$ | 2-NaphthO | **4k** | 90 |
| 12 | 4-$MeOC_6H_4$ | 4-$MeOC_6H_4$ | 2-NaphthO | **4l** | 88 |
| 13 | 4-$EtOC_6H_4$ | 4-$MeC_6H_4$ | MeO | **4m** | 86 |
| 14 | $C_6H_5$ | 4-$NO_2C_6H_4$ | MeO | **4n** | 92 |
| 15 | 4-$MeOC_6H_4$ | 4-$NO_2C_6H_4$ | 2,4-$Cl_2C_6H_3O$ | **4o** | 94 |
| 16 | 4-$EtOC_6H_4$ | 4-$MeOC_6H_4$ | 2,4-$Cl_2C_6H_3O$ | **4p** | 91 |



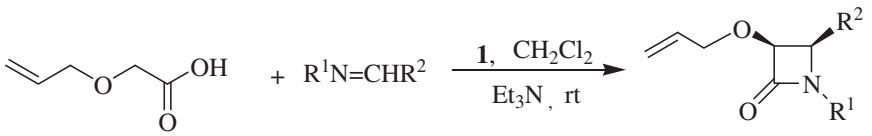

**5**

**6a,** R = PhO 92%

**6b,** R = MeO 84%

**6c,** R = PhthN 87%

**Scheme 2.**



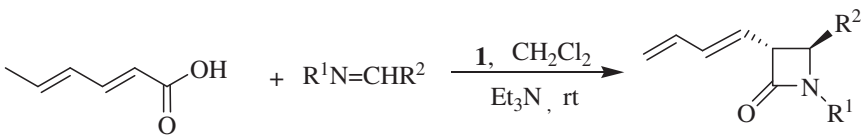

**7**

**8a,** $R^1 = C_6H_5$ ; $R^2 = 4\text{-}NO_2C_6H_4$ 88%

**8b,** $R^1 = 4\text{-}MeOC_6H_4$ ; $R^2 = 4\text{-}ClC_6H_4$ 85%

**8c,** $R^1 = 4\text{-}EtOC_6H_4$ ; $R^2 = 4\text{-}MeC_6H_4$ 89%

**Scheme 3.**



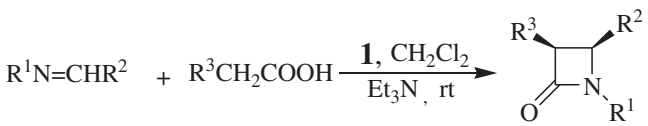

**sorbic acid**

**9a,** $R^1 = 4\text{-}MeOC_6H_4$ ; $R^2 = 4\text{-}ClC_6H_4$ 67%

**9b,** $R^1 = 4\text{-}EtOC_6H_4$ ; $R^2 = 4\text{-}NO_2C_6H_4$ 61%

**9c,** $R^1 = 4\text{-}MeOC_6H_4$ ; $R^2 = 4\text{-}MeC_6H_4$ 62%

**Scheme 4.**




**10a,** $R^1 = 4\text{-}MeOC_6H_4CH_2$ ; $R^2 = 4\text{-}NO_2C_6H_4$ ; $R^3 = PhO$ 92%

**10b,** $R^1 = 4\text{-}MeOC_6H_4CH_2$ ; $R^2 = 4\text{-}NO_2C_6H_4$ ; $R^3 = PhthN$ 85%

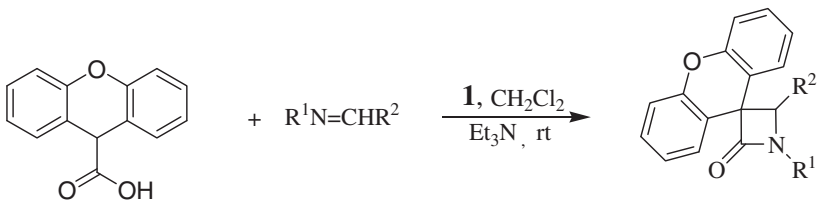
**10c,** $R^1 = C_6H_5CH_2$ ; $R^2 = 4\text{-}NO_2C_6H_4$ ; $R^3 = PhO$ 88%

**10d,** $R^1 = C_6H_5CH_2$ ; $R^2 = 4\text{-}NO_2C_6H_4$ ; $R^3 = PhthN$ 86%

**10e,** $R^1 = Me$ ; $R^2 = 4\text{-}NO_2C_6H_4$ ; $R^3 = PhO$ 80%

**10f,** $R^1 = Me$ ; $R^2 = 4\text{-}MeC_6H_4$ ; $R^3 = PhthN$ 77%

**Scheme 5.**



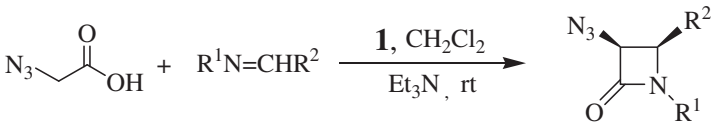

**xanthene-9-carboxylic acid**

**11a,** $R^1 = C_6H_5$ ; $R^2 = 4\text{-}NO_2C_6H_4$ 82%

**11b,** $R^1 = 4\text{-}EtOC_6H_4$ ; $R^2 = 4\text{-}NO_2C_6H_4$ 87%

**11c,** $R^1 = 4\text{-}MeOC_6H_4$ ; $R^2 = 4\text{-}MeOC_6H_4$ 85%

**Scheme 6.**

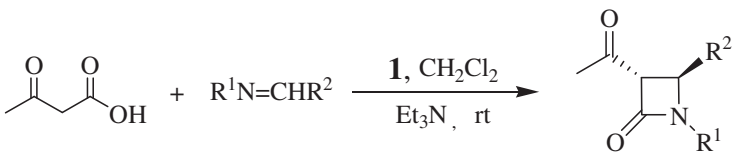



**azidoacetic acid**

**12a,** $R^1 = 4\text{-}EtOC_6H_4$ ; $R^2 = 4\text{-}MeC_6H_4$ 69%

**12b,** $R^1 = 4\text{-}MeOC_6H_4$ ; $R^2 = 4\text{-}ClC_6H_4$ 68%

**12c,** $R^1 = C_6H_5$ ; $R^2 = C_6H_5$ 60%




**acetoacetic acid**

**13a,** $R^1 = 4\text{-}MeOC_6H_4$ ; $R^2 = 4\text{-}MeOC_6H_4$ 59%

**13b,** $R^1 = 4\text{-}EtOC_6H_4$ ; $R^2 = 4\text{-}NO_2C_6H_4$ 62%

**13c,** $R^1 = C_6H_5$ ; $R^2 = C_6H_5$ 52%

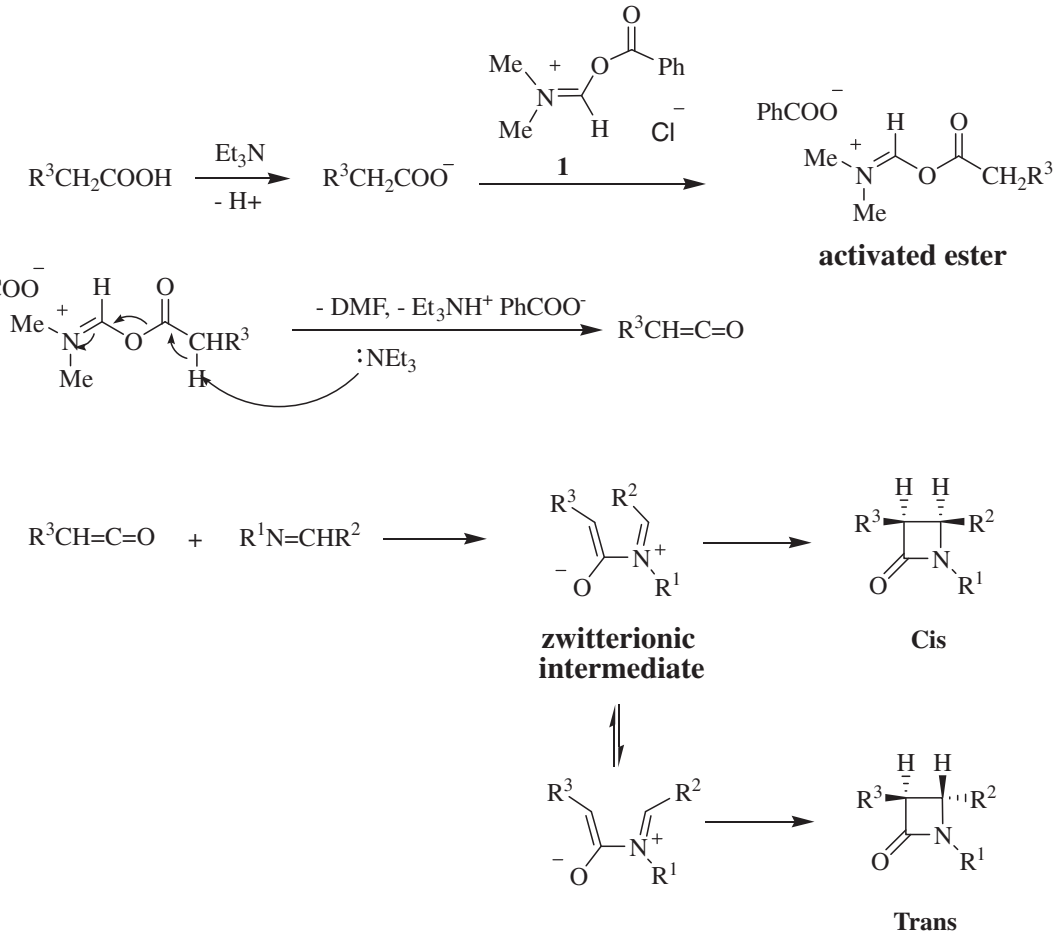
**Scheme 7.**

the adduct **1** in the presence of $Et_3N$ at room temperature, respectively (Scheme 7).

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 $\beta$-lactams in the Staudinger reaction. 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 ring closure of the zwitterionic intermediate producing the $\beta$-lactam. This intermediate was detected and characterized by IR spectroscopy. When the direct ring closure of the zwitterionic intermediate is fast enough, the final $\beta$-lactam product is *cis*, while when the direct ring closure is not so fast, the isomerization of the imine moiety in the zwitterionic intermediate occurs to form a sterically more favorable intermediate, which produces the final *trans*-$\beta$-lactam product. The relative (*cis*/*trans*) stereoselectivity is generated as a result of the competition between the direct ring closure and the isomerization of the imine moiety in the zwitterionic intermediate.[18] According to the above, it is suggested that the reaction proceeds via formation of an activated ester (Scheme 8) of which the same mechanism has been already reported.[12c,12t]

## Conclusion

In summary, DMF and benzoyl chloride adduct is a highly reactive acid activator which provides a convenient route to azetidin-2-ones from imines and a variety of carboxylic acids with good to excellent yields and good purity. The present methods offer several advantages in terms of simplicity, applicability, mildness, high yields, and availability of the reagents. Compared to other acid activators, it has been found to be superior in terms of its cost and safety, making them industrially viable. Also, this method, unlike some other methods, needs no heating or cooling of the reaction in the preparation of reagent and in the cycloaddition steps.




**Scheme 8.**

## Experimental

**General.** All required chemicals were purchased from Merck, Fluka, and 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 on a Bruker spectrophotometer ($^1$H NMR 300 MHz, $^{13}$C NMR 75 MHz) using tetramethylsilane as an internal standard and coupling constants are 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. Column chromatography was performed on silica gel 60 (Merck, 70–230 mesh). Spectral data for **4a**–**4j**, **4m**, **4o**, **10c**, **10f**, **11b**, **11c**, **12b**, and **12c** have been previously reported.[12c–12e,12j]

**General Procedure for the Synthesis of Azetidin-2-ones Using DMF and Benzoyl Chloride Adduct.** To a stirred solution of benzoyl chloride (0.15 mL, 0.18 g, 1.3 mmol) in dry dichloromethane (5 mL) was added dry dimethylformamide (0.1 mL, 0.1 g, 1.3 mmol) at room temperature and stirred for 5 min. Then this suspension mixture was added to a solution of the substituted acetic acid (1.3 mmol), corresponding Schiff base (1.0 mmol), and dry triethylamine (4.0 mmol) in 15 mL dry solvents ($CH_2Cl_2$, DMF, THF, and toluene) at room temperature and the mixture was stirred overnight. In the case of DMF and THF, water was added and extraction by $CH_2Cl_2$ was performed. Then the organic solution was washed successively with saturated $NaHCO_3$ (20 mL) and brine (20 mL). The organic layer was dried ($Na_2SO_4$), filtered and the solvent was removed under reduced pressure to give the crude products. β-Lactams **4a**–**4p**, **6a**–**6c**, **8a**–**8c**, **10a**–**10f**, and **11a**–**11c** were purified by crystallization from ethyl acetate and β-lactams **9a**–**9c**, **12a**–**12c**, and **13a**–**13c** by short column chromatography (hexane/EtOAc 9:1).

**3-(Naphthalen-2-yloxy)-4-(4-nitrophenyl)-1-phenylazetidin-2-one (4k):** Light-yellow solid. Mp: 189–191 °C; IR (KBr) cm$^{-1}$: 1356, 1529 ($NO_2$), 1749 (CO, β-lactam); $^1$H NMR (300 MHz, $CDCl_3$): δ 5.43 (H-4, d, 1H, $J = 5.1$ Hz), 5.63 (H-3, d, 1H, $J = 5.1$ Hz), 6.90–8.18 (ArH, m, 16H); $^{13}$C NMR (75 MHz, $CDCl_3$): δ 62.4 (C-4), 82.7 (C-3), 110.4, 115.7, 116.9, 118.2, 119.0, 123.5, 124.2, 126.6, 127.3, 128.9, 129.1, 129.9, 133.6, 134.4, 143.8, 146.5, 152.9, 157.1 (aromatic carbons), 162.4 (CO, β-lactam); Anal. Calcd for $C_{25}H_{18}N_2O_4$: C, 73.16; H, 4.42; N, 6.83%. Found: C, 73.24; H, 4.55; N, 6.77%.

**1,4-Bis(4-methoxyphenyl)-3-(naphthalen-2-yloxy)-azetidin-2-one (4l):** Light-yellow solid. Mp: 173–175 °C; IR (KBr) cm$^{-1}$: 1745 (CO, β-lactam); $^1$H NMR (300 MHz, $CDCl_3$): δ 3.68, 3.74 (2OMe, s, 6H), 5.48 (H-4, d, 1H, $J =$ 4.9 Hz), 5.60 (H-3, d, 1H, $J = 4.9$ Hz), 6.82–7.89 (ArH, m,

15H); $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 55.1, 55.8 (OMe), 63.5 (C-4), 81.5 (C-3), 108.6, 111.3, 115.9, 117.4, 117.7, 121.9, 123.5, 124.2, 125.0, 129.1, 129.7, 130.4, 131.8, 136.2, 145.7, 150.8, 154.0, 156.2 (aromatic carbons), 161.6 (CO, $\beta$-lactam); Anal. Calcd for $C_{27}H_{23}NO_4$: C, 76.22; H, 5.45; N, 3.29%. Found: C, 76.16; H, 5.57; N, 3.32%.

**3-Methoxy-4-(4-nitrophenyl)-1-phenylazetidin-2-one (4n):** White solid. Mp: 124–126 °C; IR (KBr) cm$^{-1}$: 1347, 1539 ($NO_2$), 1746 (CO, $\beta$-lactam); $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 3.31 (OMe, s, 3H), 4.81 (H-4, d, 1H, $J$ = 4.5 Hz), 5.10 (H-3, d, 1H, $J$ = 4.5 Hz), 6.71–7.93 (ArH, m, 9H); $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 56.6 (OMe), 64.0 (C-4), 84.7 (C-3), 118.3, 119.1, 123.5, 127.9, 128.6, 133.1, 136.9, 156.8 (aromatic carbons), 164.1 (CO, $\beta$-lactam); Anal. Calcd for $C_{16}H_{14}N_2O_4$: C, 64.42; H, 4.73; N, 9.39%. Found: C, 64.49; H, 4.84; N, 9.45%.

**3-(2,4-Dichlorophenoxy)-1-(4-ethoxyphenyl)-4-(4-methoxyphenyl)azetidin-2-one (4p):** White crystalline solid. Mp: 155–157 °C; IR (KBr) cm$^{-1}$: 1748 (CO, $\beta$-lactam); $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 1.31 (Me, t, 3H, $J$ = 6.9 Hz), 3.59 (OMe, s, 3H), 3.99 ($OCH_2$, q, 2H, $J$ = 6.9 Hz), 5.40 (H-4, d, 1H, $J$ = 4.4 Hz), 5.52 (H-3, d, 1H, $J$ = 4.4 Hz), 6.71–7.54 (ArH, m, 11H); $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 14.6 (Me), 55.5 (OMe), 61.1 ($OCH_2$), 63.4 (C-4), 83.2 (C-3), 113.6, 117.3, 118.0, 126.8, 127.1, 127.5, 129.3, 129.7, 130.1, 130.7, 132.4, 138.1, 150.8, 155.9 (aromatic carbons), 161.2 (CO, $\beta$-lactam); Anal. Calcd for $C_{24}H_{21}Cl_2NO_4$: C, 62.89; H, 4.62; N, 3.06%. Found: C, 62.81; H, 4.76; N, 3.11%.

**1-(4-Methoxynaphthalen-1-yl)-3-phenoxy-4-*p*-tolylazetidin-2-one (6a):** White solid. Mp: 182–184 °C; IR (KBr) cm$^{-1}$: 1751 (CO, $\beta$-lactam); $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 2.44 (Me, s, 3H), 3.62 (OMe, s, 3H), 5.27 (H-4, d, 1H, $J$ = 4.8 Hz), 5.57 (H-3, d, 1H, $J$ = 4.8 Hz), 6.75–8.03 (ArH, m, 15H); $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 22.5 (Me), 55.6 (OMe), 61.4 (C-4), 83.3 (C-3), 107.4, 109.7, 111.0, 112.8, 113.3, 115.9, 117.4, 118.5, 119.1, 122.4, 130.8, 131.5, 132.2, 137.9, 147.4, 150.8, 152.7, 157.5 (aromatic carbons), 163.4 (CO, $\beta$-lactam); Anal. Calcd for $C_{27}H_{23}NO_3$: C, 79.20; H, 5.66; N, 3.42%. Found: C, 79.31; H, 5.80; N, 3.49%.

**3-Methoxy-1-(4-methoxynaphthalen-1-yl)-4-*p*-tolylazetidin-2-one (6b):** White solid. Mp: 135–137 °C; IR (KBr) cm$^{-1}$: 1745 (CO, $\beta$-lactam); $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 2.48 (Me, s, 3H), 3.29, 3.62 (2OMe, s, 6H), 4.84 (H-4, d, 1H, $J$ = 4.5 Hz), 5.26 (H-3, d, 1H, $J$ = 4.6 Hz), 6.72–7.85 (ArH, m, 10H); $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 23.7 (Me), 56.3, 57.1 (OMe), 63.7 (C-4), 82.8 (C-3), 108.8, 110.6, 112.3, 112.8, 118.0, 119.1, 123.9, 124.5, 131.9, 133.4, 136.2, 143.9, 151.6, 154.6 (aromatic carbons), 162.1 (CO, $\beta$-lactam); Anal. Calcd for $C_{22}H_{21}NO_3$: C, 76.06; H, 6.09; N, 4.03%. Found: C, 76.14; H, 6.17; N, 3.95%.

**2-[1-(4-Methoxynaphthalen-1-yl)-2-oxo-4-*p*-tolylazetidin-3-yl]isoindoline-1,3-dione (6c):** White solid. Mp: 201–203 °C; IR (KBr) cm$^{-1}$: 1738, 1776 (CO, phth), 1781 (CO, $\beta$-lactam); $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 2.44 (Me, s, 3H), 3.58 (OMe, s, 3H), 5.26 (H-4, d, 1H, $J$ = 4.7 Hz), 5.39 (H-3, d, 1H, $J$ = 4.7 Hz), 6.77–7.94 (ArH, m, 14H); $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 24.2 (Me), 56.7 (OMe), 61.2 (C-4), 64.2 (C-3), 106.4, 109.2, 111.4, 113.1, 113.6, 113.9, 120.3, 122.4, 122.9, 123.5, 124.1, 127.9, 132.3, 134.6, 139.7, 140.3, 149.4, 153.7 (aromatic carbons), 160.9 (CO, phth), 163.5 (CO, $\beta$-lactam); Anal. Calcd for $C_{29}H_{22}N_2O_4$: C, 75.31; H, 4.79; N, 6.06%. Found: C, 75.40; H, 4.93; N, 6.13%.

**3-(Allyloxy)-4-(4-nitrophenyl)-1-phenylazetidin-2-one (8a):** White solid. Mp: 62–64 °C; IR (KBr) cm$^{-1}$: 1347, 1533 ($NO_2$), 1752 (CO, $\beta$-lactam); $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 4.53–4.58 ($CH_2O$, m, 2H), 5.11–5.24 (vinylic H, m, 2H), 5.36 (H-4, d, 1H, $J$ = 4.4 Hz), 5.57 (H-3, d, 1H, $J$ = 4.4 Hz), 5.88–5.96 (vinylic H, m, 1H), 6.85–8.09 (ArH, m, 9H); $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 56.9 ($OCH_2$), 62.7 (C-4), 83.2 (C-3), 110.2, 112.8, 119.5, 123.2, 123.8, 128.8, 129.4, 135.9, 146.0, 151.7 (C=C, aromatic carbons), 164.2 (CO, $\beta$-lactam); Anal. Calcd for $C_{18}H_{16}N_2O_4$: C, 66.66; H, 4.97; N, 8.64%. Found: C, 66.73; H, 5.11; N, 8.57%.

**3-(Allyloxy)-4-(4-chlorophenyl)-1-(4-methoxyphenyl)-azetidin-2-one (8b):** White solid. Mp: 71–73 °C; IR (KBr) cm$^{-1}$: 1754 (CO, $\beta$-lactam); $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 3.67 (OMe, s, 3H), 4.47–4.54 ($CH_2O$, m, 2H), 5.17–5.27 (vinylic H, m, 2H), 5.33 (H-4, d, 1H, $J$ = 4.7 Hz), 5.52 (H-3, d, 1H, $J$ = 4.7 Hz), 5.82–5.94 (vinylic H, m, 1H), 6.79–7.72 (ArH, m, 8H); $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 55.7 (OMe), 56.4 ($OCH_2$), 63.5 (C-4), 82.3 (C-3), 108.8, 111.5, 116.1, 122.8, 123.2, 126.5, 127.0, 138.4, 142.9, 157.4 (C=C, aromatic carbons), 163.7 (CO, $\beta$-lactam); Anal. Calcd for $C_{19}H_{18}ClNO_3$: C, 66.38; H, 5.28; N, 4.07%. Found: C, 66.44; H, 5.39; N, 4.13%.

**3-(Allyloxy)-1-(4-ethoxyphenyl)-4-*p*-tolylazetidin-2-one (8c):** White solid. Mp: 68–70 °C; IR (KBr) cm$^{-1}$: 1751 (CO, $\beta$-lactam); $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 1.38 (Me, t, 3H, $J$ = 7.0 Hz), 2.30 (Me, s, 3H), 3.91 ($OCH_2$, q, 2H, $J$ = 7.0 Hz), 4.49–4.55 ($CH_2$O-allyl, m, 2H), 5.14–5.25 (vinylic H, m, 2H), 5.38 (H-4, d, 1H, $J$ = 4.5 Hz), 5.59 (H-3, d, 1H, $J$ = 4.5 Hz), 5.85–5.96 (vinylic H, m, 1H), 6.84–7.65 (ArH, m, 8H); $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 14.2, 22.1 (Me), 56.9 ($CH_2$O-allyl), 60.6 ($OCH_2$), 62.7 (C-4), 83.5 (C-3), 109.3, 110.1, 118.7, 121.9, 122.4, 124.8, 128.5, 133.0, 147.1, 154.3 (C=C, aromatic carbons), 163.9 (CO, $\beta$-lactam); Anal. Calcd for $C_{21}H_{23}NO_3$: C, 74.75; H, 6.87; N, 4.15%. Found: C, 74.67; H, 6.99; N, 4.08%.

**3-(Buta-1,3-dienyl)-4-(4-chlorophenyl)-1-(4-methoxyphenyl)azetidin-2-one (9a):** White solid. Mp: 96–98 °C; IR (KBr) cm$^{-1}$: 1743 (CO, $\beta$-lactam); $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 3.65 (OMe, s, 3H), 3.73 (H-3, dd, 1H, $J$ = 2.5, 8.3 Hz), 4.69 (H-4, d, 1H, $J$ = 2.5 Hz), 5.17–5.24 (vinylic H, m, 2H), 5.84 (vinylic H, dd, 1H, $J$ = 8.3, 15.9 Hz), 5.97 (vinylic H, dd, 1H, $J$ = 10.6, 15.9 Hz), 6.12 (vinylic H, m, 1H), 6.81–7.43 (ArH, m, 8H); $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 55.7 (OMe), 61.0 (C-3), 63.5 (C-4), 112.6, 113.3, 117.5, 123.1, 123.6, 124.0, 127.4, 128.4, 135.3, 138.1, 140.9, 153.4 (C=C, aromatic carbons), 164.2 (CO, $\beta$-lactam); Anal. Calcd for $C_{20}H_{18}ClNO_2$: C, 70.69; H, 5.34; N, 4.12%. Found: C, 70.75; H, 5.49; N, 4.17%.

**3-(Buta-1,3-dienyl)-1-(4-ethoxyphenyl)-4-(4-nitrophenyl)-azetidin-2-one (9b):** White solid. Mp: 93–95 °C; IR (KBr) cm$^{-1}$: 1341, 1535 ($NO_2$), 1745 (CO, $\beta$-lactam); $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 1.26 (Me, t, 3H, $J$ = 7.0 Hz), 3.77 (H-3, dd, 1H, $J$ = 2.4, 8.1 Hz), 3.95 ($OCH_2$, q, 2H, $J$ = 7.0 Hz), 4.72 (H-4, d, 1H, $J$ = 2.4 Hz), 5.22–5.30 (vinylic H, m, 2H), 5.80 (vinylic H, dd, 1H, $J$ = 8.1, 16.0 Hz), 6.04 (vinylic H, dd, 1H, $J$ = 10.2, 16.0 Hz), 6.18 (vinylic H, m, 1H), 6.75–8.11 (ArH, m, 8H); $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 15.1 (Me),

60.9 ($OCH_2$), 61.5 (C-3), 63.2 (C-4), 110.7, 115.9, 116.3, 124.8, 125.5, 126.2, 128.1, 128.3, 132.9, 135.7, 150.3, 156.8 (C=C, aromatic carbons), 163.6 (CO, β-lactam); Anal. Calcd for $C_{21}H_{20}N_2O_4$: C, 69.22; H, 5.53; N, 7.69%. Found: C, 69.15; H, 5.67; N, 7.62%.

**3-(Buta-1,3-dienyl)-1-(4-methoxyphenyl)-4-*p*-tolylazetidin-2-one (9c):** White solid. Mp: 93–95 °C; IR (KBr) $cm^{-1}$: 1748 (CO, β-lactam); $^1H$ NMR (300 MHz, $CDCl_3$): δ 2.37 (Me, s, 3H), 3.59 (OMe, s, 3H), 3.82 (H-3, dd, 1H, $J = 2.4$, 8.3 Hz), 4.74 (H-4, d, 1H, $J = 2.4$ Hz), 5.20–5.27 (vinylic H, m, 2H), 5.86 (vinylic H, dd, 1H, $J = 8.3$, 15.9 Hz), 6.00 (vinylic H, dd, 1H, $J = 10.1$, 15.9 Hz), 6.23 (vinylic H, m, 1H), 6.86–7.55 (ArH, m, 8H); $^{13}C$ NMR (75 MHz, $CDCl_3$): δ 21.9 (Me), 56.0 (OMe), 62.4 (C-3), 63.7 (C-4), 109.5, 113.3, 118.2, 122.2, 123.0, 125.7, 127.5, 128.8, 134.1, 135.0, 142.6, 155.1 (C=C, aromatic carbons), 164.5 (CO, β-lactam); Anal. Calcd for $C_{21}H_{21}NO_2$: C, 78.97; H, 6.63; N, 4.39%. Found: C, 80.10; H, 6.77; N, 4.42%.

**1-(4-Methoxybenzyl)-4-(4-nitrophenyl)-3-phenoxyazetidin-2-one (10a):** Light-yellow crystalline solid. Mp: 94–96 °C; IR (KBr) $cm^{-1}$: 1335, 1538 ($NO_2$), 1748 (CO, β-lactam); $^1H$ NMR (300 MHz, $CDCl_3$): δ 3.78 (OMe, s, 3H), 3.96, 4.80 ($CH_2$-benzyl, 2d, 2H, $J = 14.7$ Hz), 4.86 (H-4, d, 1H, $J = 4.5$ Hz), 5.46 (H-3, d, 1H, $J = 4.5$ Hz), 6.68–8.11 (ArH, m, 13H). $^{13}C$ NMR (75 MHz, $CDCl_3$): δ 44.3 ($CH_2$), 55.3 (OMe), 60.5 (C-3), 82.0 (C-4), 114.1, 115.2, 122.1, 123.3, 126.1, 128.9, 129.1, 129.4, 140.8, 147.9, 156.4, 159.5 (aromatic carbons), 164.9 (CO, β-lactam); Anal. Calcd for $C_{23}H_{20}N_2O_5$: C, 68.31; H, 4.98; N, 6.93%. Found: C, 68.24; H, 5.08; N, 6.98%.

**2-[1-(4-Methoxybenzyl)-2-(4-nitrophenyl)-4-oxoazetidin-3-yl]isoindoline-1,3-dione (10b):** White solid. Mp: 124–126 °C; IR (KBr) $cm^{-1}$: 1337, 1530 ($NO_2$), 1735, 1772 (CO, phth), 1788 (CO, β-lactam); $^1H$ NMR (300 MHz, $CDCl_3$): δ 3.70 (OMe, s, 3H), 3.89, 4.84 ($CH_2$-benzyl, 2d, 2H, $J =$ 14.5 Hz), 5.22 (H-4, d, 1H, $J = 4.6$ Hz), 5.64 (H-3, d, 1H, $J = 4.6$ Hz), 6.81–8.25 (ArH, m, 12H). $^{13}C$ NMR (75 MHz, $CDCl_3$): δ 45.1 ($CH_2$), 55.7 (OMe), 60.2 (C-4), 62.7 (C-3), 110.7, 114.5, 115.4, 127.7, 128.2, 128.5, 129.9, 144.6, 146.2, 148.5, 158.8 (aromatic carbons), 161.1 (CO, phth), 163.6 (CO, β-lactam); Anal. Calcd for $C_{25}H_{19}N_3O_6$: C, 65.64; H, 4.19; N, 9.19%. Found: C, 65.72; H, 4.31; N, 9.27%.

**2-[1-Benzyl-2-(4-nitrophenyl)-4-oxoazetidin-3-yl]isoindoline-1,3-dione (10d):** White crystalline solid. Mp: 137–139 °C; IR (KBr) $cm^{-1}$: 1341, 1537 ($NO_2$), 1732, 1774 (CO, phth), 1784 (CO, β-lactam); $^1H$ NMR (300 MHz, $CDCl_3$): δ 3.93, 4.81 ($CH_2$-benzyl, 2d, 2H, $J = 14.7$ Hz), 5.25 (H-4, d, 1H, $J = 5.0$ Hz), 5.56 (H-3, d, 1H, $J = 5.0$ Hz), 6.84–8.17 (ArH, m, 13H). $^{13}C$ NMR (75 MHz, $CDCl_3$): δ 44.6 ($CH_2$), 61.7 (C-4), 64.3 (C-3), 113.6, 119.1, 121.5, 127.1, 128.0, 128.2, 128.9, 141.5, 143.8, 146.3, 154.9 (aromatic carbons), 160.6 (CO, phth), 162.8 (CO, β-lactam); Anal. Calcd for $C_{24}H_{17}N_3O_5$: C, 67.44; H, 4.01; N, 9.83%. Found: C, 67.54; H, 4.14; N, 9.75%.

**1-Methyl-4-(4-nitrophenyl)-3-phenoxyazetidin-2-one (10e):** White solid. Mp: 91–93 °C; IR (KBr) $cm^{-1}$: 1333, 1531 ($NO_2$), 1750 (CO, β-lactam). $^1H$ NMR (300 MHz, $CDCl_3$): δ 2.91 (Me–N, s, 3H), 5.14 (H-4, d, 1H, $J = 4.5$ Hz), 5.49 (H-3, d, 1H, $J = 4.5$ Hz), 6.73–8.06 (ArH, m, 9H). $^{13}C$ NMR (75 MHz, $CDCl_3$): δ 29.0 (Me–N), 62.4 (C-4), 82.7 (C-3), 112.7, 122.4, 129.1, 130.8, 134.6, 137.7, 151.8, 155.3 (aromatic carbons), 163.4 (CO, β-lactam). Anal. Calcd for $C_{16}H_{14}N_2O_4$: C, 64.42; H, 4.73; N, 9.39%. Found: C, 64.51; H, 4.88; N, 9.46%.

**2-(4-Nitrophenyl)-1-phenylspiro[azetidine-3,9′-xanthen]-4-one (11a):** Light-yellow solid. Mp: 195–197 °C; IR (KBr) $cm^{-1}$: 1339, 1536 ($NO_2$), 1753 (CO, β-lactam); $^1H$ NMR (300 MHz, $CDCl_3$): δ 5.24 (H-4, s, 1H), 6.74–8.05 (ArH, m, 17H); $^{13}C$ NMR (75 MHz, $CDCl_3$): δ 62.8 (C-4), 74.1 (C-3), 113.6, 115.1, 119.5, 122.7, 123.1, 125.4, 129.0, 129.7, 133.9, 143.8, 148.2, 150.3, 154.0, 157.5 (aromatic carbons), 164.2 (CO, β-lactam); Anal. Calcd for $C_{27}H_{18}N_2O_4$: C, 74.64; H, 4.18; N, 6.45%. Found: C, 74.72; H, 4.28; N, 6.39%.

**3-Azido-1-(4-ethoxyphenyl)-4-*p*-tolylazetidin-2-one (12a):** Pale-yellow solid. Mp: 93–95 °C; IR ($CHCl_3$) $cm^{-1}$: 2121 ($N_3$), 1745 (CO, β-lactam). $^1H$ NMR (300 MHz, $CDCl_3$): δ 1.33 (Me, t, 3H, $J = 6.9$ Hz), 2.36 (Me, s, 3H), 3.98 ($OCH_2$, q, 2H, $J = 6.9$ Hz), 5.09 (H-4, d, 1H, $J = 5.1$ Hz), 5.47 (H-3, d, 1H, $J = 5.1$ Hz), 6.84–7.57 (ArH, m, 8H). $^{13}C$ NMR (75 MHz, $CDCl_3$): δ 14.1, 22.5 (Me), 60.7 ($OCH_2$), 62.2 (C-3), 65.4 (C-4), 110.3, 115.9, 121.4, 126.7, 127.3, 142.1, 144.9, 154.6 (aromatic carbons), 163.4 (CO, β-lactam). Anal. Calcd for $C_{18}H_{18}N_4O_2$: C, 67.07; H, 5.63; N, 17.38%. Found: C, 67.15; H, 5.75; N, 17.43%.

**3-Acetyl-1,4-bis(4-methoxyphenyl)azetidin-2-one (13a):** White solid. Mp: 71–73 °C; IR (KBr) $cm^{-1}$: 1711 (CO, ketone), 1756 (CO, β-lactam); $^1H$ NMR (300 MHz, $CDCl_3$): δ 2.37 (Me, s, 3H), 3.71, 3.75 (2OMe, s, 6H), 3.92 (H-3, d, 1H, $J = 2.4$ Hz), 4.89 (H-4, d, 1H, $J = 2.4$ Hz), 6.78–7.50 (ArH, m, 8H); $^{13}C$ NMR (75 MHz, $CDCl_3$): δ 29.7 (Me), 55.3, 55.6 (OMe), 60.9 (C-3), 67.3 (C-4), 113.5, 118.1, 125.1, 125.8, 127.0, 144.5, 153.7, 156.3 (aromatic carbons), 161.8 (CO, β-lactam), 196.3 (CO, ketone); Anal. Calcd for $C_{19}H_{19}NO_4$: C, 70.14; H, 5.89; N, 4.31%. Found: C, 70.07; H, 5.96; N, 4.34%.

**3-Acetyl-1-(4-ethoxyphenyl)-4-(4-nitrophenyl)azetidin-2-one (13b):** White solid. Mp: 66–68 °C; IR (KBr) $cm^{-1}$: 1341, 1530 ($NO_2$), 1709 (CO, ketone), 1753 (CO, β-lactam); $^1H$ NMR (300 MHz, $CDCl_3$): δ 1.38 (Me, t, 3H, $J = 7.0$ Hz), 2.31 (MeCO, s, 3H), 3.94 (H-3, d, 1H, $J = 2.5$ Hz), 4.04 ($OCH_2$, q, 2H, $J = 7.0$ Hz), 4.74 (H-4, d, 1H, $J = 2.5$ Hz), 6.86–8.09 (ArH, m, 8H); $^{13}C$ NMR (75 MHz, $CDCl_3$): δ 15.1, 29.0 (Me), 60.5 ($OCH_2$), 61.8 (C-3), 66.9 (C-4), 115.4, 117.9, 122.3, 124.6, 129.2, 143.8, 148.3, 154.5 (aromatic carbons), 162.4 (CO, β-lactam), 198.1 (CO, ketone); Anal. Calcd for $C_{19}H_{18}N_2O_5$: C, 64.40; H, 5.12; N, 7.91%. Found: C, 64.48; H, 5.23; N, 7.97%.

**3-Acetyl-1,4-diphenylazetidin-2-one (13c):** White solid. Mp: 77–79 °C; IR (KBr) $cm^{-1}$: 1712 (CO, ketone), 1752 (CO, β-lactam); $^1H$ NMR (300 MHz, $CDCl_3$): δ 2.35 (Me, s, 3H), 3.97 (H-3, d, 1H, $J = 2.5$ Hz), 4.82 (H-4, d, 1H, $J = 2.5$ Hz), 6.94–7.43 (ArH, m, 10H); $^{13}C$ NMR (75 MHz, $CDCl_3$): δ 28.8 (Me), 61.3 (C-3), 67.2 (C-4), 117.2, 119.5, 122.0, 122.7, 123.6, 124.1, 133.9, 140.4 (aromatic carbons), 163.1 (CO, β-lactam), 198.6 (CO, ketone); Anal. Calcd for $C_{17}H_{15}NO_2$: C, 76.96; H, 5.70; N, 5.28%. Found: C, 80.05; H, 5.81; N, 5.24%.

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