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ARTICLE

# Facile Synthesis of Novel 3-Methoxy/ Phthalimido-N,N-diethylphenylene Diamine Substituted β-Lactams

Mahmood S. Magtoof[1], Shiwani Berry[2], Shamsher S. Bari[2], Bimal K. Banik[3] and Aman Bhalla[2,✉]

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## ABSTRACT

A novel series of 3-methoxy/phthalimido-*N,N*-diethylphenylene diamine linked β-lactam derivatives have been synthesized *via* Staudinger cycloaddition reaction. Various imines (**3a-c**) were prepared quantitatively by refluxing aldehydes (**1a-c**) with easily procurable *N,N*-diethylphenylene diamine (**2**). These on reaction with 2-methoxy/phthalimido acetyl chloride in presence of the triethylamine provide corresponding *cis*- and *trans*-1-(4'-diethylamino)phenylazetidin-2-ones (**4**,**5**). These synthesized β-lactams (**4**,**5**) have been characterized by spectroscopic techniques *viz*. $^1$H NMR, IR and elemental analysis (CHN).

## KEYWORDS

β-Lactams, *N,N*-Diethylphenylene diamine, *trans*- and *cis*-Azetidin-2-ones, Cycloaddition.

## INTRODUCTION

β-Lactams constitute an interesting class of compounds that have attracted constantly a growing interest ever since the discovery of penicillin by Alexander Fleming in 1929 [1]. β-Lactam derivatives have acquired prominent place amongst heterocyclic compounds and with the appropriate substitution possess several diverse and interesting biological activities such as antibacterial [2], antifungal [3], antitubercular [4], anti-inflammatory [5] and antiviral [6]. The increasing number of multi-drug resistant microbial pathogens, because of exhaustive use of these antibiotics, is one of the greatest health threats that we face. In this regard, numerous structural modifications of β-lactams have been done in order to enhance their spectrum, potency and specificity [7]. Especially, extensive research in the field of 3-alkoxy-β-lactams has been well documented in the literature because they are found to possess apoptotic activity against human leukaemia, breast, prostate and head-neck cancer cells, thus exhibiting antitumour activity [8].

The synthesis of novel 4-amino-*N,N*-diethylaniline derivatives have also been receiving great attention because of the bright colours [9] and pharmaceutical properties [10]. Use of 4-amino-*N,N*-diethylaniline in detection of quinones [11] (**I, II**) and as a nucleophile (**III**) are reported recently [12] (Fig. 1).

***Author affiliations:***

[1]Chemistry Department, Science College, Thiqar University, Thiqar, Nashyria, Iraq
[2]Department of Chemistry and Centre of Advanced Studies in Chemistry, Panjab University, Chandigarh-160 014, India
[3]Community Health Systems of South Texas; 3135 South Sugar Road, Edinburg, Texas, 8539, USA

✉To whom correspondence to be addressed:

Fax: +91 172 2545074
Tel: +91 172 2534417/+919872659217
E-mail: amanbhalla@pu.ac.in

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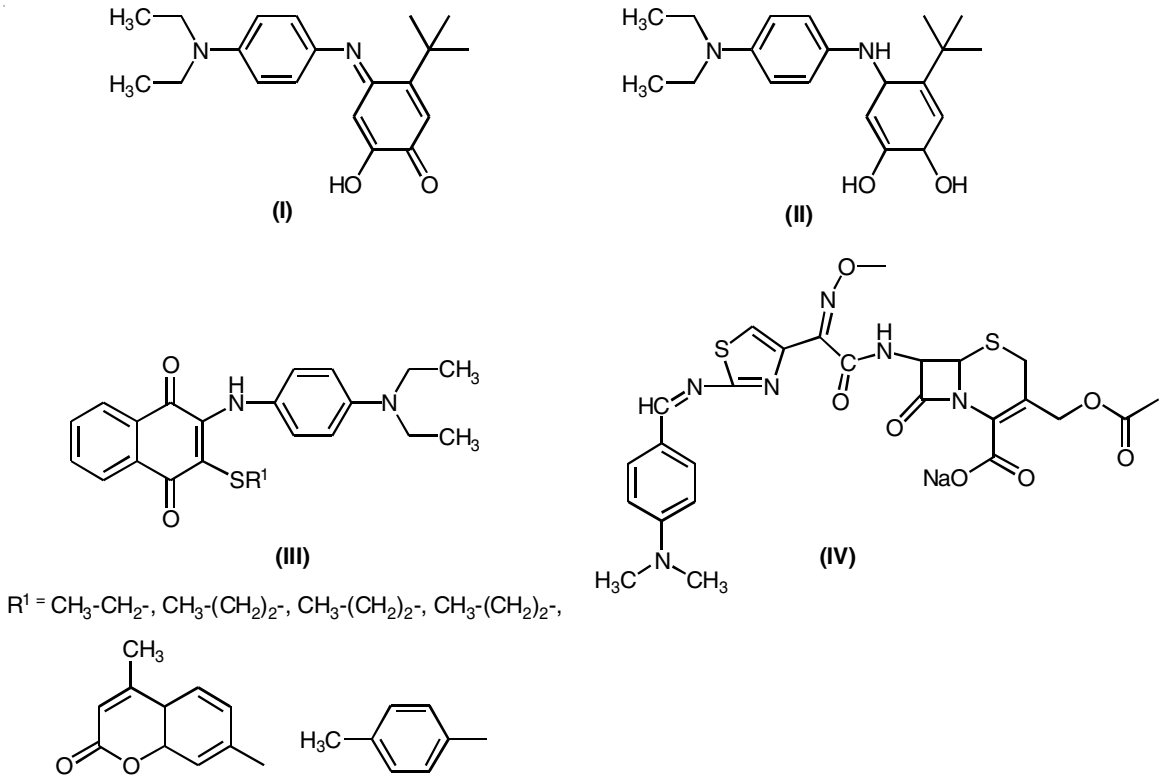



Fig. 1. Biologically active *N,N*-diethyl/methyl-amino/benzaldehyde-phenylene substituted molecules

Moreover, Abdulghani and Hussain [13] reported the synthesis of Schiff base derivatives of cefotaxime antibiotic (CFX) (**IV**) with isatin and 4-*N,N*-dimethyl-aminobenzaldehyde (Fig. 1).

In previous studies [14], we have demonstrated the synthesis of novel 3-thio/seleno-β-lactams and their Lewis acid mediated functionalization, (*Z*)- and (*E*)-3-allylidene-β-lactams, 3-keto-β-lactams, spirocyclic-β-lactams, stereoselective synthesis of *cis*- and *trans*-3-alkoxy-β-lactams, 4-pyrazolyl-β-lactams and bicyclic-β-lactams. Prompted by these studies and interest in the synthesis of novel β-lactam derivatives, it was envisaged to synthesize a series of novel 3-methoxy/phthalimido-β-lactam derivatives incorporating 4-amino-*N,N*-diethylaniline moiety into single framework *via* [2 + 2] cycloaddition reaction (**Scheme-I**).

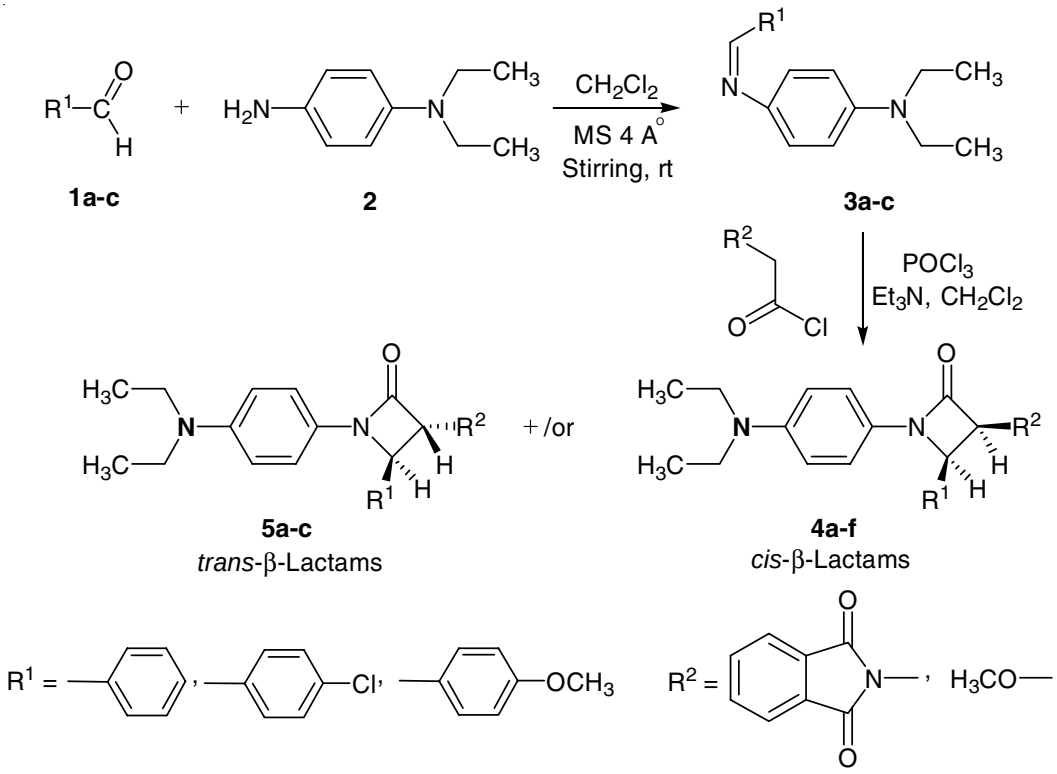
## EXPERIMENTAL

Melting points were determined with a Thomas-Hoover capillary melting point apparatus and are uncorrect. Infrared spectra (IR) were recorded using Perkin-Elmer Model 1430 spectrophotometer. The elemental analysis (C, H, N) were recorded on Flash 2000 Organic elemental analyzer. $^1$H NMR spectra were recorded using JEOL FT NMR System AL 300 (300 MHz) in the Department of Chemistry and Centre of Advance Studies in Chemistry. Thin layer chromatography (TLC) was performed using TLC grade silica gel 'G' (Acme Synthetic Chemicals). The spots were made visible by exposing plates to iodine vapours. Column chromatography was performed with silica gel (Acme Synthetic Chemicals, 60-120 mesh) and eluted with ethyl acetate: hexanes mixtures unless otherwise stated. All commercially available compounds or reagents were used without further purification. All the solvents used were of LR grade. Where necessary, the solvents were distilled and dried prior to use, when this seemed necessary by standard methods.

**Preparation of Schiff base (3a-c):** A solution of the appropriate aromatic aldehyde (1 mmol) and N,N-diethylphenylenediamine (1 mmol) in the presence of molecular sieves (4 Å) in dry methylene chloride (15 mL) was stirred at room temperature. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was filtered to remove the molecular sieves and the solvent was evaporated under vacuum to yield the imine, which was recrystallized from methylene chloride: hexane to afford a crystalline solid [15].

**Synthesis of 3-methoxy/phthalimido-2-one (4,5):** 2-Substituted acetyl chloride (0.55 mmol, 1.2 equiv.) in dry dichloromethane was added drop-wise to a solution of Schiff's base (0.46 mmol, 1 equiv.) and triethylamine (1.38 mmol, 3 equiv.) under nitrogen atmosphere, with constant stirring. The reaction mixture was stirred overnight at room temperature and the progress of the reaction was monitored by TLC. After completion of the reaction, the solvent was evaporated and the crude product was extracted with $CH_2Cl_2$. The organic layer was washed with water (3 × 10 mL), 1 N HCl (3 × 10 mL), 5 % $NaHCO_3$ (3 × 10 mL) and brine (3 × 10 mL), then dried ($Na_2SO_4$) and concentrated. The residue was purified by silica gel column chromatography with hexane/EtOAc (10:1) as eluant to afford pure products.

**Detection method:** The solid products **4a-f** and **5e-g** were fully characterized by IR spectra using Perkin-Elmer Model 1430 spectrophotometer with potassium bromide (KBr) plates or Nujol with NaCl optics. $^1$H NMR spectra were recorded using JEOL FT NMR 300 MHz in $CDCl_3$ as a solvent and




**Scheme-I:** Synthesis of 3-methoxy/phthalimido substituted (4′-diethylamino)β-lactams (**4a-f** and **5d-f**)

chemical shift values were recorded in units δ (ppm) relative to tetramethylsilane ($Me_4Si$) as an internal standard.

**Data for the compounds are given below:**

***cis*-1-(4'-Diethylamino)phenyl-3-methoxy-4-phenyl-azetidine-2-one (4a):** Yield: 77 %; m.p.: 123-125 °C; IR ($CHCl_3$, $\nu_{max}$, $cm^{-1}$): 1749 (C=O); $^1H$ NMR (300 MHz, $CDCl_3$) δ: 1.1 (t, 6H, 2×$CH_3$), 3.1 (s, 3H, $OCH_3$), 3.2 (q, 4H, 2x$CH_2$), 4.6 (d, 1H, *J* = 4.8 Hz, $C_4$-H), 5.0 (d, 1H, *J* = 4.8 Hz, $C_3$-H), 7.0-7.7 (m, 9H, Ar).

***cis*-1-(4'-Diethylamino)phenyl-3-methoxy-4-(4'-chlorophenyl)azetidine-2-one (4b):** Yield: 67 %; m.p.: 120-121 °C; IR ($CHCl_3$, $\nu_{max}$, $cm^{-1}$): 1745 (C=O); $^1H$ NMR (300 MHz, $CDCl_3$) δ: 0.9 (t, 6H, 2x$CH_3$), 3.0 (s, 3H, $OCH_3$), 3.1 (q, 4H, 2x$CH_2$), 4.7 (d, 1H, *J* = 4.8 Hz, $C_4$-H), 5.0 (d, 1H, *J* = 4.8 Hz, $C_3$-H), 7.0-7.3 (m, 8H, Ar). Anal. calcd. (%) for $C_{20}H_{23}N_2O_2Cl$; C, 66.94; H, 6.41; N, 7.81. Found: C, 66.80; H, 6.38; N, 7.74.

***cis*-1-(4'-Diethylamino)phenyl-3-methoxy-4-(4'-methoxyphenyl)azetidine-2-one (4c):** Yield: 72 %; m.p.:121-123 °C; IR ($CHCl_3$, $\nu_{max}$, $cm^{-1}$): 1740 (C=O); $^1H$ NMR (300 MHz, $CDCl_3$) δ: 1.2 (t, 6H, 2×$CH_3$), 2.9 (s, 3H, $OCH_3$), 3.2 (q, 4H, 2×$CH_2$), 3.7 (s, 3H, $OCH_3$), 4.6 (d, 1H, *J* = 4.8 Hz, $C_4$-H), 5.0 (d, 1H, *J* = 4.8 Hz, $C_3$-H), 6.8-7.2 (m, 8H, Ar). Anal. calcd. (%) for $C_{21}H_{26}N_2O_3$; C, 71.18; H, 7.34; N, 7.90. Found: C, 71.05; H, 7.30; N, 7.83.

**1-(4'-Diethylamino)phenyl-3-phthalimido-4-phenyl azetidine-2-one (4d and 5d):** Yield: 77 %; m.p.: 144-146 °C; IR ($CHCl_3$, $\nu_{max}$, $cm^{-1}$): 1742 (C=O); $^1H$ NMR (300 MHz, $CDCl_3$) δ: 1.1 (bt, 6H, 2×$CH_3$), 3.3 (bq, 4H, 2×$CH_2$), 5.2 (d, 1H, *J* = 2.7 Hz, $C_4$-H *trans*), 5.3(d, 1H, *J* = 2.30 Hz, $C_3$-H *trans*), 5.4 (d, 1H, *J* = 5.4 Hz, $C_4$-H *cis*), 5.6 (d, 1H, *J* = 5.2 Hz, $C_3$-H *cis*), 6.5-7.6 (m, 13H, Ar).

**1-(4'-Diethylamino)phenyl-3-phthalimido-4-(4'-chlorophenyl)azetidine-2-one (4e and 5e):** Yield: 69 %; m.p.: 119-121 °C; IR ($CHCl_3$, $\nu_{max}$, $cm^{-1}$): 1779 (C=O); $^1H$ NMR (300 MHz, $CDCl_3$) δ: 0.9 (t, 6H, 2x$CH_3$), 3.1 (q, 4H, 2x$CH_2$), 5.0 (d, 1H, *J* = 2.3 Hz, $C_4$-H *trans*), 5.2 (d, 1H, *J* = 1.59 Hz, $C_3$-H *trans*), 5.3 (d, 1H, *J* = 5.4 Hz, $C_4$-H *cis*), 5.7 (d, 1H, *J* = 5.6 Hz, $C_3$-H *cis*), 6.5-7.8 (m, 12H, Ar).

**1-(4'-Diethylamino)phenyl-3-phthalimido-4-(4'-methoxyphenyl)azetidine-2-one (4f** and **5f):** Yield: 72 %; m.p.: 141-142 °C IR ($CHCl_3$, $\nu_{max}$, $cm^{-1}$): 1778 (C=O), $^1H$ NMR (300 MHz, $CDCl_3$) δ: 1.3 (bt, 6H, 2×$CH_3$), 3.3 (bq, 4H, 2×$CH_2$), 3.6 (s, 3H, $OCH_3$), 3.7 (s, 3H, $OCH_3$), 5.1 (d, 1H, *J* = 3.7 Hz, $C_4$-H *trans*), 5.2 (d, 1H, *J* = 2.1 Hz, $C_3$-H *trans*), 5.3 (d, 1H, *J* = 5.1 Hz, $C_4$-H *cis*), 5.5 (d, 1H, *J* = 5.4 Hz, $C_3$-H *cis*), 6.5-7.8 (m, 12H, Ar).

## RESULTS AND DISCUSSION

Starting substrates N-(4'-diethylamino) substituted Schiff's bases (**3a-c**) were prepared by stirring equivalent amounts of an *N,N*-diethylphenylenediamine with substituted aldehyde using molecular sieves (4 Å) in dichloromethane. The synthesis of novel *cis*- and *trans*-1-(4'-diethylamino)-3-methoxy/phthalimido-β-lactams (**4**,**5**) has been achieved *via* Staudinger cycloaddition between the Schiff's bases (**3a-c**) and a ketene generated from 2-substituted acid chlorides (**Scheme-I**). Initially, 2-methoxyacetylchloride was treated with the solution of Schiff's base (**3a**) and triethylamine ($Et_3N$) in dry methylene chloride at 0 °C and reaction mixture was stirred overnight at room temperature. The progress of the reaction was monitored by thin-layer chromatography (TLC), it resulted in the exclusive formation of *cis*-3-methoxy-1-(4'-diethylamino)phenylazetidine-2-one (**4a**) in excellent yield (**Scheme-I**, Table-1, Entry 1).

The target product **4a** was purified by column chromatography on silica gel using ethyl acetate-hexane (1:10) as eluant and was identified as of *cis*-1-(4'-diethylamino)phenyl-3-methoxy-4-phenyl)azetidine-2-one on the basis of $^1$H NMR spectroscopy. Similar results were obtained with Schiff's bases (**3b-c**), which also furnished exclusive formation of *cis* β-lactams (**4b-c**).

Further, 2-phthalimidoacetyl chloride was subjected to cycloaddition with Schiff's base (**3a**) under similar reaction conditions. The progress of the reaction was monitored by thin-layer chromatography (TLC). After usual work up and column chromatography purification, the product was obtained with a $R_f$ (5 % ethylacetate–hexane) 0.78. Surprisingly, it was identified as a mixture of *cis*-β-lactam (**4d**) and *trans*-β-lactams (**5d**) (**Scheme-I**, Table-1, Entry 4) with $^1$H NMR spectroscopy. Further, to confirm these results the Schiff's bases (**3b-c**) were treated with 2-phthalimidoacetyl chloride which also furnished in separable mixture of *cis*-β-lactams (**4e-f**) and *trans*-β-lactams (**5e-f**) (**Scheme-I**, Table-1, Entries 5, 6).

All these newly synthesized monocyclic *cis*- and *trans*-3-methoxy/phthalimido-1-(4'-diethylamino) phenyl-β-lactams (**4**, **5**) were purified by column chromatography on silica gel using ethyl acetate-hexane (1:10) as the eluant and their structures were established on the basis of various spectroscopic techniques *viz.,* FTIR, $^1$H NMR and elemental analysis (CHN). The spatial juxtaposition of the C3-H and C4-H was assigned *cis* and *trans* in products **4**, **5** on the basis of coupling constant values ($J$ = 4.1-5.6 Hz and $J$ = 2.1-3.7 Hz C3-H and C4-H), respectively in the $^1$H NMR spectra [14].

The plausible mechanism included above is in accordance with our earlier publication of stereoselective synthesis of *cis*- and *trans*-3-alkoxy-β-lactams [14]. Mechanistically, it starts with the formation of an active ester intermediate **V** by the reaction of 2-methoxy/phthalimido acetyl chloride and $Et_3N$. The Staudinger reaction occurs *via* stepwise manner which first involves the attack of imine **VI** to ketene **V**. This affords zwitterionic intermediate **VII** which upon direct ring closure afforded *cis*-β-lactams. Whereas, intermediate **VII** undergoes isomerization to form intermediate **VIII** which upon conrotatory cyclization yields *trans*-β-lactams. The possible mechanism of cycloaddition reaction to form target compounds is illustrated in **Scheme-II**.

## Conclusion

In conclusion, a successful attempt has been made towards the synthesis of novel monocyclic 3-methoxy/phthalimido-β-lactams derived from *N,N*-(4'-diethylamino)-substituted imines. The structures and stereochemistry of all the novel compounds were established on the basis of various spectroscopic techniques and elemental analysis (CHN). Further, conjugation of these novel β-lactams with other heterocyclic moieties to afford functionalized β-lactam heterocycles is underway in laboratory.

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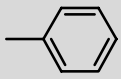
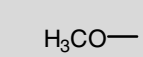
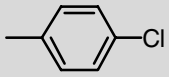
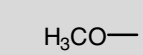
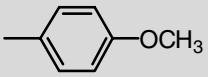
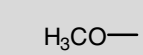
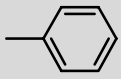
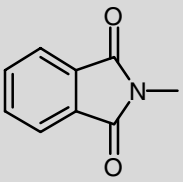
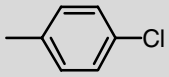
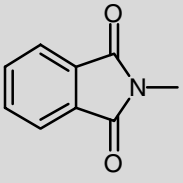
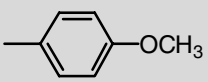
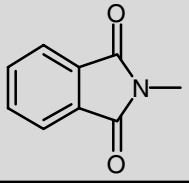
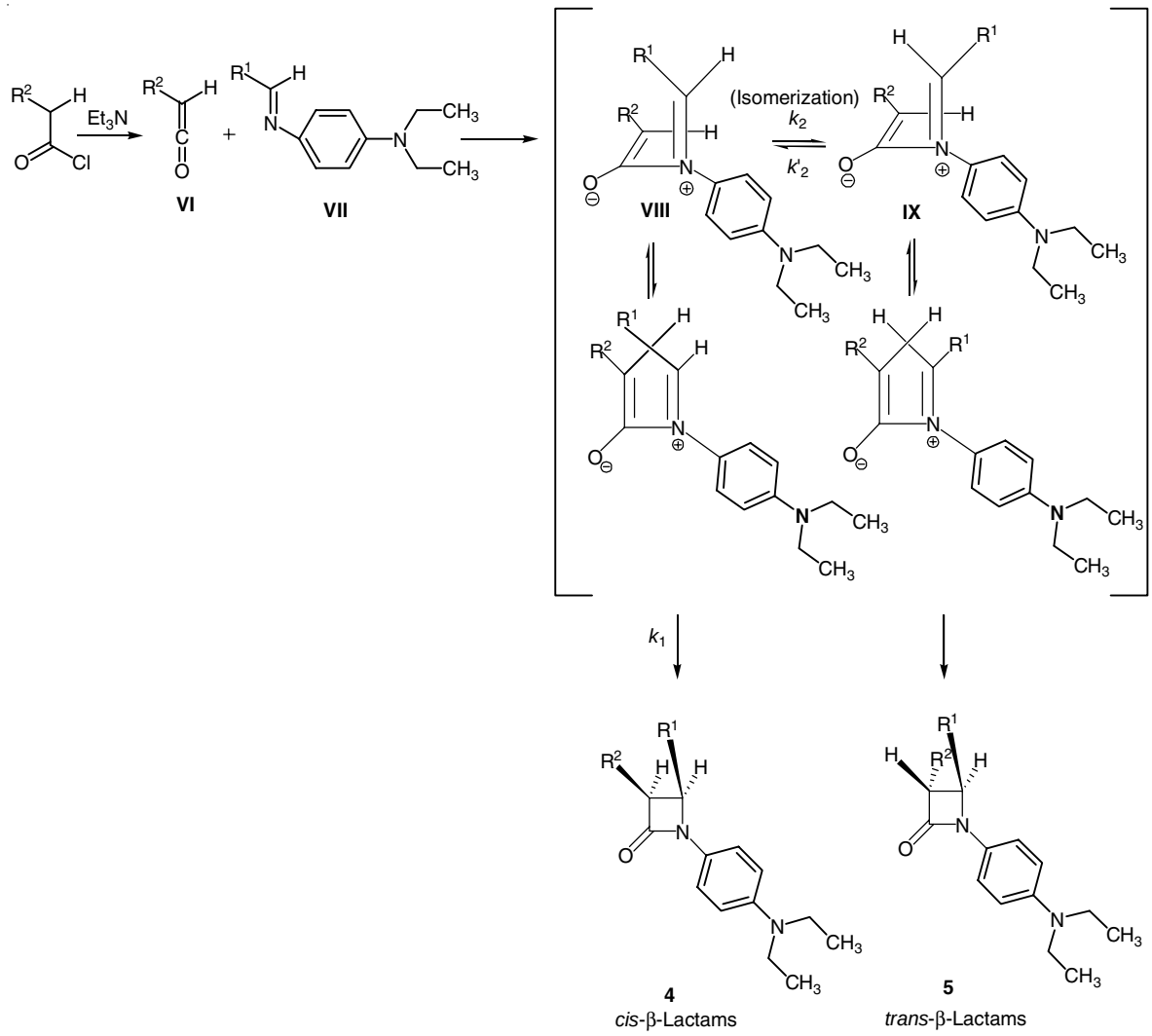
TABLE-1
3-METHOXY/PHTHALIMIDO-1-(4'-DIETHYLAMINO)PHENYL-β-LACTAMS

| Entry | Substituents | | *cis*-β-Lactams (**4**) | *trans*-β-Lactams (**5**) | m.p. (°C) | Yield (%) |
|---|---|---|---|---|---|---|
| | $R^1$ | $R^2$ | | | | |
| 1 |  |  | **4a** | – | 123-125 | 77 |
| 2 |  |  | **4b** | – | 120-121 | 67 |
| 3 |  |  | **4c** | – | 121-123 | 72 |
| 4 |  |  | **4d** | **5d** | 144-146 | 77 |
| 5 |  |  | **4e** | **5e** | 119-121 | 69 |
| 6 |  |  | **4f** | **5f** | 141-142 | 72 |




**Scheme-II:** Plausible mechanism for synthesis of 3-methoxy/phthalimido-1-(4'-diethylamino)phenyl β-lactams (**4**, **5**)

CS-037/2010 dated 28-10-2010, FIST-II/PURSE-II (DST) and UGC-CAS, Punjab University, Chandigarh, India. The authors gratefully acknowledge the financial support for this work from the Indian Council of Cultural Relations, New Delhi, Government of India, under ICCR (Indo-Iraqi, CEP Scheme), TF/OCF grant and Department of Science and Technology (DST), New Delhi, Government of India, project no. SR/FTP/CS-135/2006 dated 13-03-2007. S.B. acknowledge the financial support from University Grants Commission (UGC) vide sanction No. F1-17.1/2011-12/RGNF-ST-HIM-9284/(SA-III/web site) dated 06-06-2012.

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