The first synthesis of 3-phenothiazine-β-lactams is herein reported. Thirteen new derivatives of β-lactams were synthesized using various Schiff bases and (phenothiazin-10-yl)acetic acid, which in turn was prepared starting from phenothiazine. The sole product of the Staudinger ketene–imine [2 + 2] cycloaddition reaction is the trans-β-lactam. All the synthesized compounds were characterized by elemental analyses and spectral (IR, 1H-NMR, and 13C-NMR) data.

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INTRODUCTION

The emergence of drug-resistant bacteria and fungi presents a major problem in the medical field, and then the need for the development of novel types of antimicrobial agents is urgent [1]. Phenothiazine 1 and its derivatives are relatively inexpensive, widely available, and nontoxic compounds, which have widespread application in medicinal chemistry such as anti-inflammatory, antimalarial, antipsychotic, antimicrobial, antitubercular, antitumor, antihistaminic, and analgesic properties [2]. Some drugs like promazine, chlorpromazine, and triflupromazine contain phenothiazine moiety in their structures.

The chemistry of β-lactams or 2-azetidinones continues to be an emerging field in the organic and pharmaceutical chemistry [3]. These compounds are present in antibacterial (penicillins, cephalosporins, and carbapenems) and cholesterol absorption inhibitor (ezetimibe) drugs [4]. Also, they show various other biological activities such as human cytomegalovirus inhibitor, human leukocyte elastase inhibitor, thrombin inhibitor, porcine pancreatic elastase inhibitor, human immunodeficiency virus 1 protease inhibitor, cysteine protease inhibitor, anticancer, antifungal, potential antimalarials, anti-influenza virus, antihyperglycemic, central nervous system active agents, combatant of neurological diseases, antiproliferative, antitubercular, antioxidant, and insecticidal [5].

Apart from their pharmacological activities, β-lactams have been attracting considerable interest in organic synthesis as versatile synthetic intermediates, a methodology known as the “β-lactam synthon method” [6]. [2 + 2] Ketene–imine cycloaddition (Staudinger reaction) is the most common convergent route to the formation of the β-lactam ring [7]. Ketenes can be generated in situ by treatment of acid chlorides [8] with a base or by treatment of carboxylic acids with an appropriate activator and base [9].

Chloromethylenedimethylammonium chloride (Vilsmeier reagent) 2 has been mostly used as an acid activator for the synthesis of esters [10], amides [11], β-sultams [12], diacylhydrazines [13], 1,3,4-oxadiazoles [14], and β-lactams [15].

In this paper, we wish to report the synthesis of new β-lactams incorporated with phenothiazine at 3-position by [2 + 2] ketene–imine cycloaddition reaction in the presence of Vilsmeier reagent.

RESULTS AND DISCUSSION

The starting material, (phenothiazin-10-yl)acetic acid 4, was prepared from phenothiazine 1 as depicted in Scheme 1. Phenothiazine 1 was reacted with ethyl chloroacetate to afford ethyl phenothiazine acetate 3 in 93% yield. The ester 3 was converted into (phenothiazin-10-yl)acetic acid 4 by treating with potassium hydroxide solution and then acidification of the mixture. Purification of compound 4 was performed by crystallization from 95% ethanol.
(Phenothiazin-10-yl)acetic acid 4 was activated with Vilsmeier reagent 2 in the presence of triethylamine to the generation of ketene in situ. β-Lactams 6a–m were synthesized by [2 + 2] ketene–imine cycloaddition (Staudinger reaction). Treatment of Schiff bases 5 with (phenothiazin-10-yl)acetic acid 4 and the Vilsmeier reagent 2 in dry dichloromethane at room temperature (RT) in the presence of triethylamine afforded crude β-lactam 6a–m (Scheme 2 and Table 1). After simple aqueous workup and purification by crystallization from 95% ethanol, pure trans-β-lactams 6a–m were obtained in high yields. Unlike simple monocyclic β-lactams, all new β-lactams 6a–m were highly colored (violet). Indication of stereochemistry of the β-lactams was deduced from the coupling constant of H-3 and H-4, which were calculated to be $J = 2.2–3.0$ Hz for the trans stereoisomer. Cis and trans stereoisomer of β-lactams was determined by calculation of the coupling constant of H-3 and H-4 ($J_{3,4} > 4.0$ Hz for cis and $J_{3,4} \leq 3.0$ Hz for the trans stereoisomer) [16].

Products formation was confirmed by IR, $^1$H-NMR, and $^{13}$C-NMR and elemental analysis. IR spectra of β-lactams 6a–m showed sharp peaks at 1742–1759 cm$^{-1}$ because of β-lactam carbonyl group. Their $^1$H-NMR spectra showed well-separated doublet of doublet for H-3 protons at 4.45–5.15 ppm and 4.65–5.51 ($J = 2.2–3.0$ Hz), respectively. $^{13}$C-NMR spectra of products 6a–m showed a characteristic peak at 160.8–164.2 ppm for the β-lactam carbonyl group.

Mechanism for the Staudinger reaction [17] has been previously reported that the reaction performed via formation of an activated ester. Temperature, solvent, electronic effects, and the steric hindrance of the ketene and imine substituents affect the stereochemistry of β-lactams in the Staudinger reaction. Ketene derived from (phenothiazin-10-yl)acetic acid 4 has steric hindrance and then lead to trans isomer.

In conclusion, we have achieved variety of novel phenothiazin-substituted β-lactams using [2 + 2] cycloaddition reaction of a ketene with different imines (Staudinger reaction) in excellent yields. An aqueous workup and simple crystallization from 95% ethanol were sufficient to obtain pure products because Vilsmeier reagent produces water-soluble by-products.

All required chemicals were purchased from Merck (Merck KGaA, Darmstadt, Germany), Fluka (Sigma-Aldrich, St. Louis, MO), and Acros (Thermo Fisher Scientific, Geel, Belgium) chemical companies. The melting points were determined on an Electrothermal 9200 apparatus and are uncorrected. IR spectra were measured on a Galaxy series FT-IR 5000 spectrometer. NMR spectra were recorded in DMSO-$d_6$ using a Bruker spectrophotometer ($^1$H-NMR 300 MHz and $^{13}$C-NMR 75 MHz) with 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. (Chloromethylene)dimethylammonium chloride (Vilsmeier reagent) 2 was obtained as a white solid by a reported procedure [18]. Schiff bases 5 were prepared according to reported methods, and their spectral data have been previously reported [19].

### EXPERIMENTAL

The synthesis of ethyl phenothiazine acetate 3. This procedure was modified from the literature [1]. Phenothiazine (1.0 g, 5.0 mmol), potassium hydroxide (0.34 g, 6.0 mmol), and potassium iodide (0.1 g, 0.6 mmol) were combined in 15 mL dry DMSO. After 10 min of stirring at RT, ethyl chloroacetate (1.6 mL, 15.0 mmol) was added dropwise. The reaction mixture was heated at 80°C for 2 days. After cooling the reaction mixture, 45 mL water was added, and it was extracted with chloroform (2 × 40 mL). The combined organic layers were washed with water (40 mL), dried over sodium sulfate, filtered, and rotary evaporated to give...
### Table 1

Synthesis of β-lactams 6a–m containing phenothiazine moiety.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Schiff base</th>
<th>β-Lactam</th>
<th>Product</th>
<th>Isolated yield (%)</th>
</tr>
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<tr>
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<td>6d</td>
<td>91</td>
</tr>
<tr>
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<td>93</td>
</tr>
<tr>
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<tr>
<td>Entry</td>
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<td>β-Lactam</td>
<td>Product</td>
<td>Isolated yield (%)</td>
</tr>
<tr>
<td>-------</td>
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</tr>
<tr>
<td>7</td>
<td><img src="image" alt="Schiff base 7" /></td>
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</table>
crude product. The crude was purified by crystallization from 95% ethanol.

The synthesis of (phenothiazin-10-yl)acetic acid 4. This procedure was modified from the literature [1]. Ethyl phenothiazine acetate 3 (0.31 g, 1.1 mmol) was dissolved in EtOH (10 mL). The solution was warmed up to 70°C, and solution of KOH (0.18 g, 3.3 mmol) in 5 mL water was added. The reaction mixture was stirred for 90 min. After cooling, the mixture was acidified to pH = 3 by slow addition of 30% hydrochloric acid. The resulting solid was filtered and washed with cold water. The crude acid was crystallized from 95% ethanol to afford the pure product

General procedure for the synthesis of β-lactams 6a-m. The Vilsmeier reagent ((chloromethylene)dimethylammonium chloride) (1.5 mmol) was added to a solution of (phenothiazin-10-yl)acetic acid 4 (1.0 mmol), and triethylamine (5.0 mmol) in dry CH2Cl2 (20 mL) at RT, and the mixture was stirred overnight. The reaction mixture was washed successively with 30% hydrochloric acid. The resulting solid was filtered and washed with cold water. The crude acid was crystallized from 95% ethanol to afford the pure product.
1-(4-Methoxyphenyl)-3-(phenothiazin-10-yl)-1-phenylazetidin-2-one (6d). Violet solid, mp 158–160°C. IR (KBr) cm⁻¹: 3380, 1710, 1610, 1570, 1510, 1480, 1440, 1320, 1290, 1260, 1230, 1210, 1180, 1160, 1130, 1110, 1080, 1060, 1040, 1020, 990, 970, 950, 930, 910, 890, 870, 850, 830, 810, 790, 770, 750, 730, 710, 690, 670, 650, 630, 610, 590, 570, 550, 530, 510, 490, 470, 450, 430, 410, 390, 370, 350, 330, 310, 290, 270, 250, 230, 210, 190, 170, 150, 130, 110, 90, 70, 50, 30, 10, 0 cm⁻¹. 1H-NMR (300 MHz) δ 6.86–6.73 (ArH, m, 6H), 6.97–7.30 (ArH, m, 9H); 13C-NMR δ 56.7 (OMe), 59.9 (C-4), 66.1 (C-3) 106.2, 113.9, 118.7, 121.4, 122.6, 124.1, 127.1, 127.9, 128.2, 128.7, 129.4, 132.1, 144.5, 157.0 (aromatic carbons), 161.3 (CO, β-lactam); elemental Anal. Caled for C₂₉H₂₂N₂O₂:S: C, 71.44; H, 4.85; N, 6.17; S, 7.08.

REFERENCES AND NOTES

Month 2018

Synthesis of Novel β-Lactams from Phenothiazin-10-ylacetic Acid


