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Debasish Bandyopadhyay
The University of Texas Rio Grande Valley, debasish.bandyopadhyay@utrgv.edu

Elvira Rhodes

Bimal K. Banik

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A green, chemoselective, and practical approach toward *N*-(2-azetidinonyl) 2,5-disubstituted pyrroles†

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Debasish Bandyopadhyay, Elvira Rhodes‡ and Bimal K. Banik*

Pyrrole and 2-azetidinone are two essential heterocyclic scaffolds, which are being broadly used in medicinal chemistry and drug discovery field. A green and practical method to synthesize novel *N*-(2-azetidinonyl) 2,5-disubstituted pyrroles, which are comprised of both pyrrole and 2-azetidinone moieties, has been developed. The classical Paal–Knorr reaction is one of the simplest and most economical methods for the synthesis of biologically important and pharmacologically useful pyrrole derivatives. The present procedure for the synthesis of *N*-(2-azetidinonyl) 2,5-disubstituted pyrroles (1,2,5-trisubstituted pyrroles) has been accomplished by reacting 3-amino β-lactams and 2,5-hexanedione in the presence of bismuth nitrate pentahydrate as an ecofriendly catalyst using microwave irradiation under solvent free condition. A comparison has also been made between the efficiency of microwave-assisted condition and the classical method (stirring at room temperature). The present method is equally effective for *N*-polyaromatic substituted β-lactams and optically pure β-lactams with chemically sensitive functionalities. The structure and stereochemistry of the products have been confirmed by extensive spectroscopic and X-ray crystallographic analyses. The present procedure for synthesizing *N*-(2-azetidinonyl) 2,5-disubstituted pyrroles may find application in the development of potent pharmacologically active molecules.

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Introduction

Nitrogen heterocycles are pervasive in drug development research, among which pyrrole and 2-azetidinone (β-lactam) are two most important pharmacophores, often found in synthetic and natural drugs.[1] They possess a central place among various classes of pharmacophores due to their diverse and interesting medicinal properties. However, more than 70 years of extensive, and sometimes unnecessary, use of β-lactams has enabled bacteria to develop a broad range of resistance mechanisms. The development of multidrug resistance has reduced the effectiveness of β-lactams as antimicrobial drugs.[2] The main reason for β-lactam resistance is the production of β-lactamase; consequently, the development of β-lactamase inhibitors has been one of the main strategies in drug development. Nonetheless, the versatility of the β-lactam core structure, combined with the innovation of medicinal chemists, has repeatedly led to the development of new generations of β-lactam antibiotics that are capable of overcoming the problems caused by mounting bacterial resistance. Other than anti-infective properties β-lactam derivatives have also demonstrated a wide range pharmacological activity which includes antidiabetic, anti-inflammatory, antiparkinsonian, anti-HIV as well as anticancer.[1–6]

On the other hand, pyrrole-derived alkaloids along with lamellarins are a large family of marine alkaloids with novel structures and promising bioactivities.[7] A variety of naturally occurring 3,4- or 2,5- di- or 1,2,5-trisubstituted pyrroles have been isolated from ascidians, mollusks, sponges and cucumbers. Many of these highly complex pyrroles have been found to exhibit bioactivity.[8,9] The pharmacological activity of 1-(2-hydroxy-3-dimethylaminopropyl)-2,5-dimethylpyrrole was also reported.[10] Based upon these encouraging results, the synthesis of novel *N*-(2-azetidinonyl)-2,5-disubstituted pyrroles was undertaken. We report herein the green synthesis of a variety of 1,2,5-trisubstituted pyrroles having 2-azetidinone scaffold on pyrrole nitrogen. These structurally unique molecules may reveal potential application in future drug discovery research.

Results and discussion

The continuing drive for practically simple and efficient organic transformations has resulted in the development of many novel concepts and methodologies. Of particular importance is the field of environmentally benign reactions. Over the past decade, protection of the environment and waste prevention has been increasingly emphasized by researchers

Department of Chemistry, The University of Texas-Pan American, 1201 West University Drive, Edinburg, Texas 78539, USA. E-mail: banik@utpa.edu; Fax: +1(956)3845006; Tel: +1(956)6658741

† Electronic supplementary information (ESI) available: The ^{1}H-, ^{13}C-NMR and IR spectra of the compounds (**4a–f**), (**4a′**, **b′**) and (**6a**, **b**) can be found online. CCDC 932934 932935 933213. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c3ra42266f

‡ Undergraduate research student

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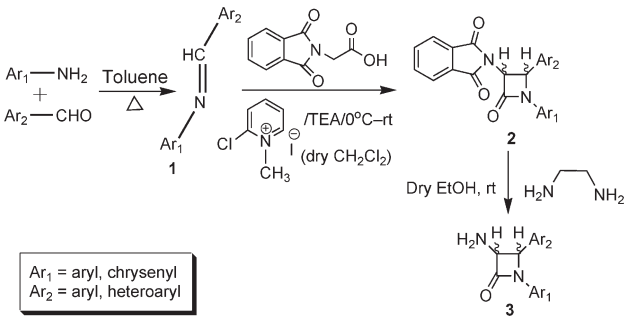
from both academia and industry.[11] For this reason the elimination or reduction of volatile solvents in organic synthesis is an important goal. These types of processes can contribute significantly in green chemistry. In this context development of solvent-free synthetic methods or the replacement of hazardous solvents with environmentally benign solvents has become an important and popular research topic in recent years.[12,13]

Our laboratory has been performing the microwave-induced reactions for many years. We have successfully developed several new reaction methodologies using microwave irradiation technique. Some recent examples include stereoselective synthesis of β-lactams,[14–16] synthesis of pyrroles,[17–20] aza-Michael addition,[21] and synthesis of quinoxalines[22]. On the other hand organo-bismuth chemistry[23–26] is considered as a promising field of research in synthetic organic chemistry. Bismuth nitrate pentahydrate, a solid salt is commercially available from a number of companies around the world, very economical and nontoxic compared to other Lewis acids. We have demonstrated the catalytic activity of trivalent bismuth nitrate pentahydrate in a number of examples. These investigations resulted in various novel methods that include nitration of aromatic systems,[27–29] Michael reaction,[30] protection of carbonyl compounds,[31] deprotection of oximes and hydrazones,[32] Paal–Knorr synthesis of pyrroles,[33] hydrolysis of amide,[34] electrophilic substitution of indoles,[35,36] synthesis of α-aminophosphonates,[37] and Hantzsch 1,4-dihydropyridines[38]. Our success in the bismuth nitrate-induced reaction has revealed that this reagent acts as a Lewis acid type of activator. It has been conceived by our group that *N*-(2-azetidinonyl) 2,5-dimethyl pyrroles can be easily prepared using bismuth nitrate as the catalyst. Moreover, it has been found that this reagent is compatible in the presence of acid-sensitive functionalities like primary amine and four-membered cyclic amide (β-lactam moiety). This idea has been extended in this paper to react 2,5-hexanedione with 3-amino substituted 2-azetidinones in the presence of catalytic amount of bismuth nitrate under solvent-free condition.

In another note, the anticancer activity of the marketed drugs often results in a number of undesired side effects as well as multidrug resistance (MDR). Therefore, it has become essential to develop new anticancer agents with less side effects, minimum toxicity, superior pharmacological properties, and improved overall activity against diverse classes of tumors. As a part of our ongoing research, we have been engaged for the synthesis of new anticancer agents with special emphasis on β-lactam anticancer for the past several years.[39–45] We have also developed new methodologies for the synthesis of anticancer pyrroles.[33,39] During the course of investigation on Paal–Knorr synthesis of pyrroles, we envisage that 1,2,5-trisubstituted pyrroles, where position 1 (nitrogen) is substituted by β-lactam moiety can be synthesized by reacting 3-amino β-lactams and 2, 5-hexanedione as the staring materials in the presence of an acidic catalyst following Paal–Knorr method.[46,47] The 3-amino β-lactams are easily



Scheme 1 Synthesis of 3-amino 2-azetidinones.

prepared from 3-phthalimido β-lactams which are synthesized through Staudinger cycloaddition[48] reaction of imines and acid chloride (equivalent) following Scheme 1.

Reaction of *C*,*N*-diaryl imines **1** with *N*-phthaloylglycine in the presence of triethylamine and 2-chloro-*N*-methylpyridinium iodide was performed at 0 °C–room temperature and a mixture of (±)-*cis* and (±)-*trans* β-lactams was isolated. However, polyaromatic imines **1** derived from 6-chrysenyl amine produced exclusively (±)-*trans* β-lactams. High temperature reaction also gave an identical result in comparable yield. The reaction proceeded well with diverse imines that have different types of aromatic groups (Scheme 1) in good to excellent yield of the products. At the beginning of our approach, to synthesize *N*-(2-azetidinonyl) 2,5-dimethyl pyrroles from 3-amino substituted β-lactams the reaction between 1 mmol of (±)-*trans*-3-amino-1,4-diphenylazetidin-2-one (**3a**) with 1.1 mmol of 2,5-hexanedione was used as a model study. Our initial study started with screening of catalyst loading to obtain optimal reaction conditions for the synthesis of *N*-(2-azetidinonyl) 2,5-disubstituted pyrroles. A number of bismuth salts *e.g.* bismuth chloride, bismuth bromide bismuth iodide, bismuth triflate, bismuth subnitrate, and bismuth nitrate pentahydrate were screened using 1 mmol of **3a** with 1.1 mmol of 2,5-hexanedione as the substrates under automated CEM microwave irradiation (260 Watts, 80 °C, 20–45 psi, 1 min). The results are shown in

Table 1 Microwave-assisted (260 Watts, 80 °C, 20–45 psi) synthesis of *N*-(2-azetidinonyl) 2,5-disubstituted pyrrole from 1 mmol of (±)-*trans*-3-amino-1,4-diphenylazetidin-2-one with 1.1 mmol of 2,5-hexanedione using bismuth-salts as catalyst (10 mol%) under solventless condition (1 min): catalyst optimization

Entry	Bi-salt (10 mol %)	Yield (%)[a]
1	$BiCl_3$	56
2	$BiBr_3$	51
3	BiI_3	40
4	$Bi(OTf)_3$	57
5	$Bi_5O(OH)_9(NO_3)_3$	36
6	$Bi(NO_3)_3{\cdot}5H_2O$	91
7	No catalyst	16

[a] isolated yield.

Table 2 Microwave-assisted (260 Watts, 80 °C, 20–45 psi) synthesis of *N*-(2-azetidinonyl) 2,5-disubstituted pyrrole from 1 mmol of (±)-*trans*-3-amino-1,4-diphenylazetidin-2-one with 1.1 mmol of 2,5-hexanedione using bismuth nitrate pentahydrate as catalyst under solventless condition (1 min): optimization of the amount of the catalyst

Entry	$Bi(NO_3)_3 \cdot 5H_2O$ (mol%)	Yield (%)[a]
1	30	73
2	25	71
3	20	83
4	15	87
5	10	91
6	5	96
7	2	63
8	1	39

[a] isolated yield.

Table 3 Microwave-assisted (260 Watts, 80 °C, 20–45 psi) synthesis of *N*-(2-azetidinonyl) 2,5-disubstituted pyrrole from 1 mmol of (±)-*trans*-3-amino-1,4-diphenylazetidin-2-one with 1.1 mmol of 2,5-hexanedione using bismuth nitrate pentahydrate as catalyst (5 mol%) for 1 min: solvent optimization

Entry	Solvent (1 mL)	Yield (%)[a]
1	Toluene	32
2	Dichloromethane	27
3	Tetrahydrofuran	78
4	Methanol	80
5	Ethanol	77
6	Dimethylsulfoxide	72
7	Water	81
8	Neat	96

[a] isolated yield.

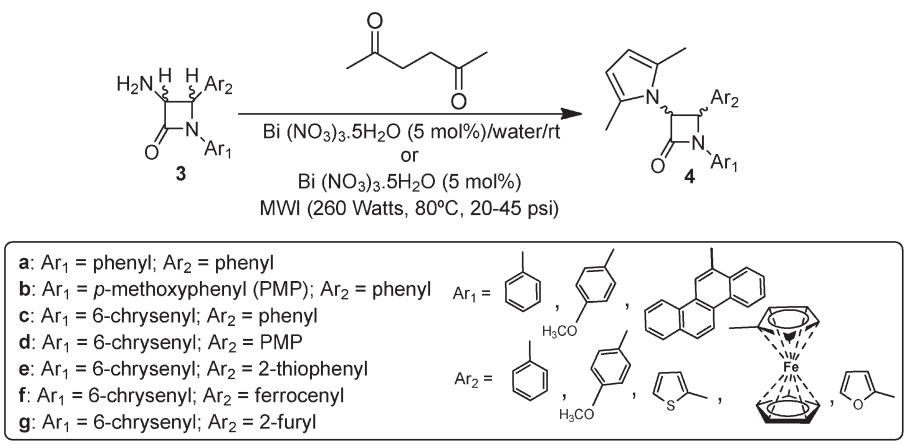
Table 1. It has also been discovered that the reaction gives products with extreme rapidity under microwave irradiation.

Bismuth nitrate pentahydrate was found to be the best catalyst among other bismuth salts under this condition (Entry 6, Table 1). Without using any catalyst (only microwave irradiation) 16% yield of the product was isolated after five minutes irradiation (Entry 7, Table 1). The same probe was used to optimize the amount of the catalyst bismuth nitrate pentahydrate (Table 2). The results show that 5 mol% bismuth nitrate pentahydrate was required to complete the reaction within a minute (Entry 6, Table 2).

It is very convenient to conduct the reaction with bismuth nitrate because of its stability in the presence of moisture and oxygen. The presence of small amounts of catalyst (5 mol%) is necessary for the success of the reaction. The reaction was then performed in various solvents as well as in neat condition under an identical microwave power using bismuth nitrate pentahydrate (5 mol%) as the catalyst to identify the best solvent/condition (Table 3). From these studies, it was confirmed that bismuth nitrate pentahydrate is the best catalyst, among all other Lewis acids investigated for this reaction, under neat condition (Entry 8, Table 3).

After determining the optimized condition we carried out a series of reaction (Scheme 2) using 3-amino β-lactams (1 mmol) with 2,5-hexanedione (1.1 mmol) in the presence of bismuth nitrate pentahydrate (5 mol%) under microwave irradiation (260 Watts, 80 °C, 20–45 psi). The 3-amino substituted β-lactams were synthesized following the procedure developed in our laboratory.[49,50]

The reaction proceeded equally well irrespective of the nature of substituent present in the β-lactam ring without any change of stereochemistry. A series of diversely *C*,*N*-disubstituted 3-amino β-lactams yielded the corresponding *N*-(2-azetidinoyl)-2,5-dimethyl pyrroles following Scheme 2. Upon extraction of the reaction mixture excellent yield of the corresponding pyrroles were obtained (Table 4). The model reaction was also conducted following classical condition, stirring a mixture of (±)-*trans*-3-amino-1,4-diphenylazetidin-2-one (1 mmol), 2,5-hexanedione (1.1 mmol) and bismuth nitrate (5 mol%) at room temperature, under solventless condition. The reaction yielded only 48% corresponding pyrrole even after 36 h. Next, the model reaction was conducted following the same classical condition in presence



Scheme 2 Stereoselective synthesis of *N*-(2-azetidinoyl)-2,5-dimethyl pyrroles.

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Table 4 Bismuth nitrate-induced synthesis of *N*-(2-azetidinonyl) 2,5-dimethyl pyrroles from 3-amino substituted β-lactams under solventless condition

Entry	Substrate (3-amino β-lactam)	Product [*N*-(2-azetidinonyl)-2, 5-dimethyl pyrrole]	Condition A: Stirring at room temperature		Condition B: MWI (260 Watts, 80 °C, 20–45 psi)	
			Time (h)	Yield (%)[a]	Time (min)	Yield (%)[a]
1	**3a**	**4a**	16	58	1	90
2[b]	**3a′**	**4a′**	16	61	1	96
3	**3b**	**4b**	16	66	1	98
4[b]	**3b′**	**4b′**	16	59	1	92
5	**3c**	**4c**	24	49	5	91
6	**3d**	**4d**	24	52	5	87
7	**3e**	**4e**	24	57	4	94
8	**3f**	**4f**	24	47	3	88
9	**3g**	**4g**	24	44	5	87
10	**5a**	**6a**	16	67	1	89
11	**5b**	**6b**	16	64	1	94

[a] isolated yield. [b] *cis* stereochemistry.

of 0.5 mL water which yields the corresponding pyrrole in 61% yield after 16 h. The same set of reactions (Table 4) were performed under classical condition by stirring a mixture of 3-amino β-lactam (1 mmol), 2,5-hexanedione (1.1 mmol) and bismuth nitrate (5 mol%) at room temperature in water (0.5 mL) and the results are summarized in Table 4.

The formation of a mixture of isomeric products in case of monoaryl imines had cast doubt about the analysis of the product distributions of earlier studies.[51,52] The present study confirmed the formation of two isomeric *cis* and *trans* products. Previous studies on the same reaction reported the formation of *trans* isomer only with imines that have monoaromatic groups at the C- and N-terminus. It appears that the electron withdrawing aromatic groups at the C- and N-terminus of the imine is responsible for the formation of the *trans* isomer. The effect of electron withdrawing property is highly significant when chrysenyl group is present at the N-terminus of the imine. In case of *N*-chrysenyl imines only the *trans* isomer was isolated as the sole product. The formation of *trans* isomer in case of *N*-chrysenyl imines and *N*-monoaryl imines can be rationalized through an isomerization of the enolate as described earlier.[42–44] Polyaromatic group (in this example, chrysenyl) on the nitrogen stabilizes the iminium ion greatly. The electron withdrawing property of monocyclic aromatic groups at the N-site of the imine is not sufficient to have a complete isomerization of the enolate and therefore, a mixture of *cis*- and *trans*-isomers is formed. The stereochemistries of the corresponding *cis* and *trans* *N*-(2-azetidinonyl) 2,5-dimethyl pyrroles (**4b** and **4b′**) have been confirmed by X-ray crystallographic analysis (Fig. 1 and 2).[53,54]

As mentioned earlier, the *trans* *N*-(2-azetidinonyl) 2,5-dimethyl pyrrole was isolated as the sole product for *N*-chrysenyl imine **1**, retaining the stereochemistry of the corresponding phthalimido β-lactams. No change in stereo-

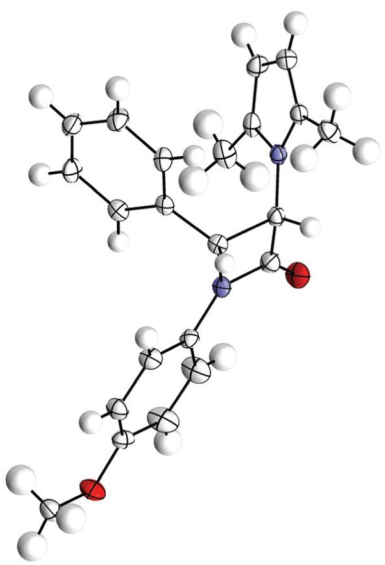


Fig. 1 X-ray crystallographic (ORTEP) structure of (**4b**). Thermal ellipsoids are shown with 50% probability.

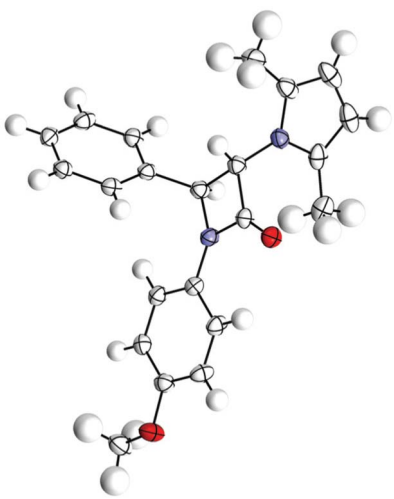


Fig. 2 X-ray crystallographic (ORTEP) structure of (**4b′**). Thermal ellipsoids are shown with 50% probability.

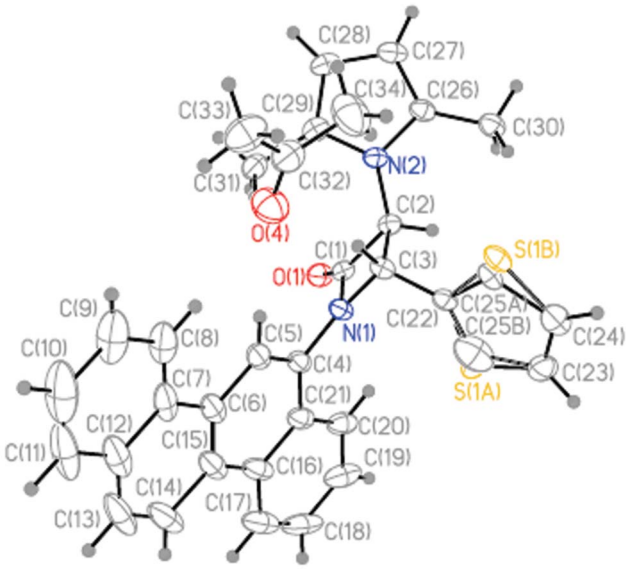
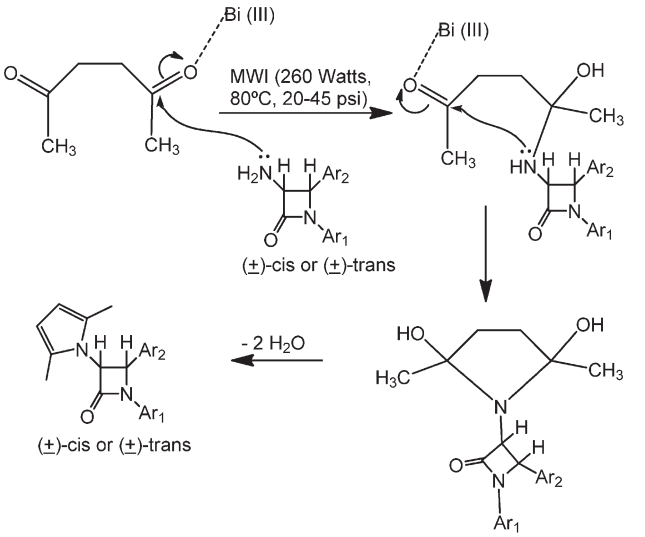
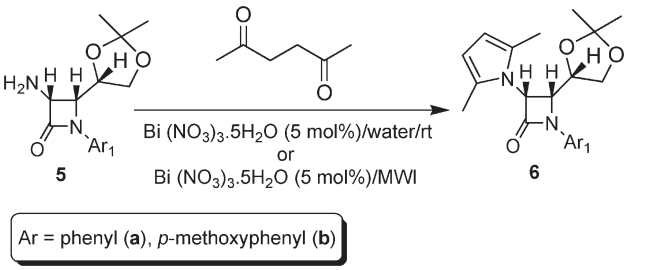


Fig. 3 X-ray crystallographic (ORTEP) structure of (**4e**) acetone solvate. Thermal ellipsoids are shown with 50% probability.



Scheme 3 Plausible mechanism for the synthesis of *N*-(2-azetidinonyl) 2,5-dimethyl pyrroles.



Scheme 4 Synthesis of optically pure *N*-(2-azetidinoyl)-2,5-dimethyl pyrroles.

chemistry was observed in this reaction. The *trans* stereochemistry of one the polyaromatic imine derived *trans* *N*-(2-azetidinonyl) 2,5-dimethyl pyrrole (**4e**) has been confirmed by X-ray crystallographic analysis (Fig. 3).[55] The sulfur atom of the thiophenyl moiety (S1A–B) and the carbon atom (C25A–B) are disordered. Both the sulfur atom and the carbon atom occupy 50% of the time flipping back and forth from each position. Probably because of extremely high rate of flipping the subsequent flippomers are not visible individually in NMR time scale and only one set of values was observed.[56] This observation is highly interesting because this is the first example of a molecule, having β-lactam core, exists in flippomer forms.

The mechanism of the reaction has not been studied in detail. A plausible mechanistic pathway involves the nucleophilic attack of the electron pair on nitrogen attached to C-3 of the 2-azetidinone ring system to one of the carbonyl groups of 2,5-hexanedione under the influence of bismuth nitrate pentahydrate. The process is highly accelerated under microwave irradiation. A second nucleophilic attack to the other carbonyl group and subsequent dehydration-aromatization yields *N*-(2-azetidinonyl) 2,5-dimethyl pyrrole as the sole product (Scheme 3). This reaction suggests the capability of bismuth nitrate to serve as a Lewis activator.

The effectiveness of our newly developed methodology was further tested for the synthesis of optically pure *N*-(2-azetidinoyl)-2,5-dimethyl pyrroles. To achieved this goal, 3-Phthalimido substituted 2-azetidinones were synthesized from optically pure 2,2-dimethyl-1,3-dioxolane-4-carboxaldehyde following a published method.[57] The 3-phthalimido substituted β-lactams were deprotected by ethylene diamine as reported from our laboratory.[50] The corresponding 3-amino substituted β-lactams (**5**) produced 3-pyrrole substituted β-lactams (**6**) upon treatment with 2,5-hexanedione in the presence of 5 mol% of bismuth nitrate pentahydrate at room temperature as well as under microwave-induced procedure (Scheme 4) as discussed herein. Synthetic method for the preparation of optically pure *N*-(2-azetidinoyl)-2,5-dimethyl pyrroles is still unknown despite gigantic development in this field in the past several decades. Because of the mild conditions of the experiments, it is gratifying to note that no deprotection of the acid-sensitive ketal group to diol and subsequent oxidation, rearrangement and lactonization was occurred in the synthesis of pyrroles (**6**) (Scheme 4). The bismuth nitrate-catalyzed pyrrole formation reaction of 3-amino β-lactams as described herein is very simple and can be used with remarkable success.

Conclusion

Among the wide variety of heterocycles, which have been explored for developing pharmaceutically significant molecules, 2-azetidinones and pyrroles are noteworthy. The discovery, development and identification of pharmacologi-

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cally active compounds has gained immense importance in the present era. Because of the interest of β-lactams and pyrroles in organic and medicinal chemistry, research in this field continues to produce new and appealing innovations. The discovery and development of commercially viable orally active β-lactam antibiotics and inhibitors of Class A and C β-lactamases remain as significant challenges for medicinal chemists. The production, under environmentally benign conditions, of more efficient and cost-effective medicines is one of most exciting dreams of industrial medicinal chemistry. The present economical method satisfies most of the principles of green chemistry and the unique structures of the *N*-(2-azetidinoyl)-2,5-dimethyl pyrroles reported in this paper may provide important new leads for the discovery of drugs for many dreadful diseases with novel mechanisms of action.

Experimental

General

Melting points were determined in a Fisher Scientific electrochemical Mel-Temp* manual melting point apparatus (Model 1001) equipped with a 300 °C thermometer. FT-IR spectra were recorded on a Bruker Alpha modular Platinum-ATR FT-IR spectrometer with OPUS software, using the samples directly (neat) without making pallets. ^{1}H-NMR (600 MHz) and ^{13}C-NMR (150 MHz) spectra were obtained at room temperature with Bruker superconducting Ultrashield™ Plus 600 MHz NMR spectrometer with central field 14.09 Tesla, coil inductance 89.1 Henry and magnetic energy 1127.2 kJ using $CDCl_3$ as solvent. Elemental analyses (C, H, N) were conducted using the Perkin-Elmer 2400 series II elemental analyzer, their results were found to be in good agreement (±0.2%) with the calculated values for C, H, N. Bismuth nitrate pentahydrate (reagent grade) 98% (Cat # 248592-500G, Batch # MKBC6772) purchased from Sigma-Aldrich Corporation was used. All other chemicals were purchased from Sigma-Aldrich Corporation (analytical grade). Throughout the project solvents were purchased from Fisher-Scientific. Deionized water was used for the preparation of all aqueous solutions.

General procedure for the synthesis of *N*-(2-azetidinonyl)-2,5-dimethyl pyrrole from 3-amino substituted β-lactam

The substrate (3-amino substituted β-lactam, 1.0 mmol), 2,5-hexanedione (1.1 mmol) and bismuth nitrate pentahydrate (5 mol%, 24 mg) were mixed together in a microwave vial with a magnetic stir bar. The mixture was irradiated in an automated microwave (CEM Corporation) and the progress of the reaction was monitored by TLC. After completion of the reaction (Table 4) dichloromethane (7 mL) was added to the reaction mixture and the organic layer was washed with saturated sodium bicarbonate solution, brine and water successively. It was dried over anhydrous sodium sulfate and the solvent was removed under reduced pressure. The crude mass was purified through a small silica gel column using ethyl acetate/hexanes as eluent. The spectral and analytical data are as follow:

(±)-*Trans*-3-(2,5-dimethyl-1*H*-pyrrol-1-yl)-1,4-diphenylazetidin-2-one (**4a**): Yellowish crystals (90%, 284 mg, dichloromethane/hexanes); mp 149–150 °C; IR (neat) 2966 (Ar CH), 1751 (lactam CO), 1598 and 1499 (Ar C=C), 1370 (CH_3), 1228 (C—N), 768 and 745 (*mono*-substituted benzene) cm^{-1}; ^{1}H-NMR (600 MHz, $CDCl_3$) δ 2.13 (6H, s, pyrroyl C(2,5) CH_3), 5.07 (1H, d, J = 2.34 Hz, C(4)H), 5.19 (1H, d, J = 2.46 Hz, C(3)H), 5.84 (2H, s, pyrroyl C(3,4)H), 7.13–7.44 (10H, m, phenyl H); ^{13}C-NMR (150 MHz, $CDCl_3$) δ 12.98, 64.02, 70.15, 107.48, 117.50, 124.70, 125.72, 128.60, 129.00, 129.36, 129.41, 135.99, 137.04, 163.63. Anal. Calcd for $C_{21}H_{20}N_2O$: C, C, 79.72; H, 6.37; N, 8.85. Found: C, 79.87; H, 6.29; N, 8.88.

(±)-*Trans*-3-(2,5-dimethyl-1*H*-pyrrol-1-yl)-1-(4-methoxyphenyl)-4-phenylazetidin-2-one (**4b**): white crystals (98%, 339 mg, dichloromethane/hexanes); mp 164–165 °C; IR (neat) 2926 (Ar CH), 1759 (lactam CO), 1548 and 1508 (Ar C=C), 1381 (CH_3), 1292, 1239 (C—N), 838 (*para*-substituted benzene) cm^{-1}; ^{1}H-NMR (600 MHz, $CDCl_3$) δ 2.02 (6H, s, pyrroyl C(2,5) CH_3), 3.67 (3H, s, OCH_3), 4.91 (1H, d, J = 2.10 Hz, C(4)H), 5.05 (1H, d, J = 2.28 Hz, C(3)H), 5.72 (2H, s, pyrroyl C(3,4)H), 6.74 (2H, d, J = 6.84 Hz, C(2,6) *p*-methoxyphenyl H), 7.18–7.31 (7H, m, C(3,5) *p*-methoxyphenyl and phenyl H); ^{13}C-NMR (150 MHz, $CDCl_3$) δ 12.96, 55.47, 64.11, 70.12, 107.41, 114.55, 118.85, 125.77, 128.59, 128.96, 129.42, 130.52, 136.05, 156.63, 162.98. Anal. Calcd for $C_{22}H_{22}N_2O_2$: C, 76.28; H, 6.40; N, 8.09. Found: C, 76.22; H, 6.37; N, 8.02.

(±)-*Trans*-1-(chrysen-6-yl)-3-(2,5-dimethyl-1*H*-pyrrol-1-yl)-4-phenylazetidin-2-one (**4c**): yellow crystals (91%, 424 mg, dichloromethane/diethyl ether/hexanes); mp 111–113 °C; IR (neat) 2959 (Ar CH), 1767 (lactam CO), 1593 (Ar C=C), 1386 (CH_3), 1303, 1239 (C—N), 820, 756, 699 (*meta*-substituted benzene) cm^{-1}; ^{1}H-NMR (600 MHz, $CDCl_3$) δ 2.19 (6H, s, pyrroyl C(2,5) CH_3), 5.37 (1H, d, J = 2.58 Hz, C(4)H), 5.60 (1H, d, J = 2.58 Hz, C(3)H), 5.81 (2H, s, pyrroyl C(3,4)H), 7.15–7.26 (5H, m, phenyl H), 7.54–7.62 (2H, m, chrysenyl H), 7.70–7.71 (2H, m, chrysenyl H), 7.88–7.90 (2H, m, chrysenyl H), 8.40–8.42 (1H, m, chrysenyl H), 8.43 (1H, s, chrysenyl C(5)H), 8.48 (1H, d, J = 8.34 Hz, chrysenyl H), 8.57 (1H, d, J = 9.12 Hz, chrysenyl H), 8.72–8.74 (1H, m, chrysenyl H); ^{13}C-NMR (150 MHz, $CDCl_3$) δ 13.31, 65.70, 68.43, 107.65, 114.02, 120.92, 122.81, 123.67, 124.55, 125.97, 126.79, 126.84, 126.90, 126.95, 127.54, 127.56, 127.76, 128.66, 128.71, 128.99, 129.30, 129.99, 131.41, 131.68, 132.28, 135.85, 164.95. Anal. Calcd for $C_{33}H_{26}N_2O$: C, 84.95; H, 5.62; N, 6.00. Found: C, 84.83; H, 5.51; N, 5.93.

(±)-*Trans*-1-(chrysen-6-yl)-3-(2,5-dimethyl-1*H*-pyrrol-1-yl)-4-(4-methoxyphenyl)azetidin-2-one (**4d**): yellowish red amorphous solid (87%, 431 mg, dichloromethane/diethyl ether/hexanes); mp 142 °C; IR (neat) 2951 (Ar CH), 1758 (lactam CO), 1611, 1592, 1516, (Ar C=C), 1388 (CH_3), 1301, 1244, 1173 (C—N), 822 (*para*-substituted benzene), 754 (*meta*-substituted benzene) cm^{-1}; ^{1}H-NMR (600 MHz, $CDCl_3$) δ 2.20 (6H, s, pyrroyl C(2,5) CH_3), 3.59 (3H, s, OCH_3), 5.36 (1H, d, J = 2.64 Hz, C(4)H), 5.54 (1H, d, J = 2.64 Hz, C(3)H), 5.80 (2H, s, pyrroyl C(3,4)H), 6.70 (2H, d, J = 8.88 Hz, *para*-methoxyphenyl C(2,6)H), 7.28 (2H, d, J = 8.82 Hz, *para*-methoxyphenyl C(3,5)H), 7.55–7.90 (6H, m, chrysenyl H), 8.38–8.40 (1H, m, chrysenyl H), 8.42 (1H, s, chrysenyl C(5) H), 8.49 (1H, d, J = 8.28 Hz, chrysenyl H), 8.56 (1H, d, J = 9.06 Hz, chrysenyl H), 8.71–8.73 (1H, m, chrysenyl H); ^{13}C-NMR (150 MHz, $CDCl_3$) δ 13.32,

55.19, 65.55, 68.47, 107.54, 114.29, 114.70, 120.92, 122.83, 123.66, 124.49, 126.77, 126.89, 126.90, 127.42, 127.48, 127.55, 127.58, 127.72, 128.66, 128.70, 160.07, 165.09. Anal. Calcd for $C_{34}H_{28}N_2O_2$: C, 82.23; H, 5.68; N, 5.64. Found: C, 82.07; H, 5.62; N, 5.56.

(±)-*Trans*-1-(chrysen-6-yl)-3-(2,5-dimethyl-1*H*-pyrrol-1-yl)-4-(thiophen-2-yl)azetidin-2-one (**4e**): Light yellow (almost colorless) crystal (94%, 443 mg, dichloromethane/diethyl ether/hexanes); mp 231 °C; IR (neat) 3102, 2970 (Ar CH), 1765 (lactam CO), 1510, 1588 (Ar C=C), 1388 (CH_3), 1301, 1237 (C—N), 822, 757, 701 (*meta*-substituted benzene) cm^{-1}; ^{1}H-NMR (600 MHz, $CDCl_3$) δ 2.26 (6H, s, pyrroyl C(2,5) CH_3), 5.56 (1H, d, J = 2.52 Hz, C(4)H), 5.82 (2H, s, pyrroyl C(3,4)H), 5.84 (1H, d, J = 2.52 Hz, C(3)H), 6.77 (1H, dd, J = 4.98 Hz and 3.60 Hz, thiophenyl C(3)H), 7.04 (1H, dd, J = 4.50 Hz and 0.84 Hz, thiophenyl C(4)H), 7.11 (1H, dd, J = 5.94 Hz and 0.96 Hz, thiophenyl C(5)H), 7.57–7.92 (4H, m, chrysenyl H), 8.29–8.30 (2H, m, chrysenyl H), 8.47 (1H, s, chrysenyl C(5) H), 8.52–8.73 (4H, m, chrysenyl H); ^{13}C-NMR (150 MHz, $CDCl_3$) δ 13.32, 62.19, 69.31, 107.73, 115.36, 120.92, 122.84, 123.65, 124.31, 126.36, 126.82, 126.97, 126.98, 127.11, 127.29, 127.42, 127.53, 127.82, 127.96, 128.71, 128.73, 130.06, 130.73, 131.62, 132.27, 139.06, 164.73. Anal. Calcd for $C_{31}H_{24}N_2OS$: C, 78.78; H, 5.12; N, 5.93. Found: C, 78.89; H, 5.02; N, 5.87.

(±)-*Trans*-1-(chrysen-6-yl)-3-(2,5-dimethyl-1*H*-pyrrol-1-yl)-4-(ferrocenyl)azetidin-2-one (**4f**): Orange crystal (88%, 505 mg, dichloromethane/diethyl ether); mp 244–246 °C; IR (neat) 2953, 2926 (Ar CH), 1728 (lactam CO), 1597, 1574 (Ar C=C), 1381 (CH_3), 1273 (C—N), 822, 738, 699 (*meta*-substituted benzene) cm^{-1}; ^{1}H-NMR (600 MHz, $CDCl_3$) δ 2.39 (6H, s, pyrroyl C(2,5) CH_3), 3.68 (5H, s, ferrocenyl C(1′, 2′, 3′, 4′, 5′)H, 3.99 (1H, m, ferrocenyl H), 4.01 (1H, m, ferrocenyl H), 4.06 (1H, m, ferrocenyl H), 4.08 (1H, m, ferrocenyl H), 5.38 (1H, d, J = 2.58 Hz, C(4)H), 5.49 (1H, d, J = 2.58 Hz, C(3)H), 5.84 (2H, s, pyrroyl C(3,4)H), 7.58–7.96 (6H, m, chrysenyl H), 8.22 (1H, m, chrysenyl H), 8.57 (1H, s, chrysenyl H), 8.59–8.78 (3H, m, chrysenyl H); ^{13}C-NMR (150 MHz, $CDCl_3$) δ 13.50, 63.52, 65.97, 66.95, 67.04, 68.67, 68.71, 68.76, 68.88, 83.62, 107.77, 116.61, 120.99, 122.81, 123.79, 124.27, 126.87, 127.05, 127.09, 127.53, 127.57, 127.88, 127.98, 128.08, 128.56, 128.80, 130.09, 131.25, 131.63, 132.35, 165.56. Anal. Calcd for $C_{37}H_{30}FeN_2O$: C, 77.35; H, 5.26; N, 4.88. Found: C, 78.23; H, 5.17; N, 4.79.

(±)-*Trans*-1-(chrysen-6-yl)-3-(2,5-dimethyl-1*H*-pyrrol-1-yl)-4-(furan-2-yl)azetidin-2-one (**4g**): Yellow crystal (87%, 396 mg, dichloromethane/diethyl ether/hexanes); mp 135–137 °C; IR: 2912 (Ar CH), 1753 (lactam CO), 1581, 1560 (Ar C=C), 1377 (CH_3), 1310 (C–N), 782 (*meta*-substituted benzene) cm^{-1}; ^{1}H-NMR δ (ppm): ^{1}H-NMR (600 MHz, $CDCl_3$) δ 2.30 (6H, s, pyrroyl C(2,5) CH_3), 5.47 (1H, d, J = 2.46 Hz, C(4)H), 5.65 (1H, d, J = 2.46 Hz, C(3)H), 5.91 (2H, s, pyrroyl C(3,4)H), 6.77 (2H, m, furyl H), 7.35–8.59 (12H, m, Ar–H); ^{13}C-NMR δ (ppm): 13.45, 65.63, 68.55, 107.65, 114.41, 114.77, 122.98, 123.77, 124.56, 126.86,127.00, 127.55, 127.81, 128.78, 129.07, 129.38, 129.97, 135.98, 141.05, 160.14, 165.23. Anal. Calcd for $C_{31}H_{24}N_2O_2$: C, 81.56; H, 5.30; N, 6.14. Experimental: C, 81.58; H, 5.29; N, 6.08.

(±)-*Cis*-3-(2,5-dimethyl-1*H*-pyrrol-1-yl)-1,4-diphenylazetidin-2-one (**4a′**): Deep brown amorphous solid (96%, 303 mg, dichloromethane/hexanes); mp 136–137 °C; IR (neat) 2958 (Ar CH), 1720 (lactam CO), 1603 and 1460 (Ar C=C), 1384 (CH_3), 1278 (C—N), 742 and 697 (*mono*-substituted benzene) cm^{-1}; ^{1}H-NMR (600 MHz, $CDCl_3$) δ 2.09 (6H, s, pyrroyl C(2,5) CH_3), 5.21 (1H, d, J = 5.49 Hz, C(4)H), 5.32 (1H, d, J = 5.49 Hz, C(3)H), 7.03 (2H, m, pyrroyl C(3,4)H), 7.27–7.81 (10H, m, phenyl H); ^{13}C-NMR (150 MHz, $CDCl_3$) δ 14.12, 61.27, 68.18, 107.99, 117.65, 124.52, 125.95, 126.16, 128.81, 129.03, 129.14, 129.17, 135.84, 137.16, 162.05. Anal. Calcd for $C_{21}H_{20}N_2O$: C, 79.72; H, 6.37; N, 8.85. Found: C, 79.69; H, 6.31; N, 8.89.

(±)-*Cis*-3-(2,5-dimethyl-1*H*-pyrrol-1-yl)-1-(4-methoxyphenyl)-4-phenylazetidin-2-one (**4b′**): white crystals (92%, 318 mg, dichloromethane/hexanes); mp 147–148 °C; IR (neat) 2922 (Ar CH), 1739 (lactam CO), 1546 and 1512 (Ar C=C), 1396 (CH_3), 1239 and 1173 (C—N), 819 (*para*-substituted benzene) cm^{-1}; ^{1}H-NMR (600 MHz, $CDCl_3$) δ 2.11 (6H, br s, pyrroyl C(2,5) CH_3), 3.72 (3H, s, OCH_3), 5.34 (1H, d, J = 5.58 Hz, C(4)H), 5.67 (1H, d, J = 5.58 Hz, C(3)H), 6.80 (2H, d, J = 9.06 Hz, C(2,6) *p*-methoxyphenyl H), 6.95 (2H, d, J = 7.02 Hz, pyrroyl C(3,4)H), 7.09–7.37 (7H, m, C(3,5) *p*-methoxyphenyl and phenyl H); ^{13}C-NMR (150 MHz, $CDCl_3$) δ 13.64, 55.54, 61.43, 64.83, 107.04, 114.54, 118.59, 126.57, 128.09, 128.28, 131.40, 132.66, 136.46, 156.64, 162.37. Anal. Calcd for $C_{22}H_{22}N_2O_2$: C, 76.28; H, 6.40; N, 8.09. Found: C, 76.31; H, 6.33; N, 8.00.

(3*R*,4*R*)-4-((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)-3-(2,5-dimethyl-1*H*-pyrrol-1-yl)-1-phenylazetidin-2-one (**6a**): Yellow amorphous solid (89%, 302 mg, dichloromethane/hexanes); mp 122–124 °C; IR (neat) 2958, 2930 (Ar CH), 1759 (lactam CO), 1602 and 1495 (Ar C=C), 1370 (CH_3), 1291, 1212 (C—N), 712 and 699 (*mono*-substituted benzene) cm^{-1}; ^{1}H-NMR (600 MHz, $CDCl_3$) δ 1.39 (3H, s, dioxolane CH_3), 1.39 (3H, s, dioxolane CH_3), 2.12 (3H, s, pyrroyl CH_3), 2.31 (3H, s, pyrroyl CH_3), 2.91 (1H, dd, J = 7.53 Hz and 2.46 Hz, dioxolane C(5)H), 3.16 (1H, dd, J = 8.30 Hz and 0.54 Hz, dioxolane C(5)H), 4.30 (1H, dd, J = 5.70 Hz and 3.12 Hz, C(4)H), 5.42 (1H, d, J = 5.70 Hz, C(3)H), 5.74 (1H, ddd, J = 14.46 Hz, 3.33 Hz and 0.60 Hz, dioxolane C(4)H), 7.09–7.74 (7H, m, Ar H); ^{13}C-NMR (150 MHz, $CDCl_3$) δ 14.05, 14.39, 25.54, 26.57, 62.95, 65.78, 68.18, 76.34, 107.77, 109.15, 118.22, 124.86, 130.88, 132.48, 137.82, 163.15. Anal. Calcd for $C_{20}H_{24}N_2O_3$: C, 70.56; H, 7.11; N, 8.23. Found: C, 70.48; H, 6.99; N, 8.16.

(3*R*,4*R*)-4-((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)-3-(2,5-dimethyl-1*H*-pyrrol-1-yl)-1-(4-methoxyphenyl)azetidin-2-one (**6b**): Pale yellow amorphous solid (94%, 347 mg, dichloromethane/hexanes); mp 130–132 °C; IR (neat) 2967 (Ar CH), 1753 (lactam CO), 1572 and 1516 (Ar C=C), 1398 (CH_3), 1291, 1254 (C—N), 832 (*para*-substituted benzene) cm^{-1}; ^{1}H-NMR (600 MHz, $CDCl_3$) δ 1.26 (3H, s, dioxolane CH_3), 1.35 (3H, s, dioxolane CH_3), 2.18 (3H, s, pyrroyl CH_3), 2.38 (3H, s, pyrroyl CH_3), 2.98 (1H, dd, J = 7.71 Hz and 2.46 Hz, dioxolane C(5)H), 3.23 (1H, t, J = 8.58 Hz, dioxolane C(5)H), 3.81 (3H, s, OCH_3), 3.86 (1H, dd, J = 8.34 Hz and 2.40 Hz, C(4)H), 5.49 (1H, d, J = 5.58 Hz, C(3)H), 5.77 (2H, s, pyrroyl H), 5.84 (1H, dd, J = 14.79 Hz, 2.82 Hz, dioxolane C(4)H), 6.90 (2H, d, J = 9.06 Hz, C(2,6) *p*-methoxyphenyl H), 7.85 (2H, d, J = 8.92 Hz, C(3,5) *p*-methoxyphenyl H); ^{13}C-NMR (150 MHz, $CDCl_3$) δ 14.03, 14.31, 25.55, 26.55, 55.47, 63.05, 65.75, 68.13, 76.30, 105.81, 107.67, 114.09, 119.63, 123.41, 134.18, 156.72, 162.57. Anal. Calcd for $C_{21}H_{26}N_2O_4$: C, 68.09; H, 7.07; N, 7.56. Found: C, 67.96; H, 7.00; N, 7.47.

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53 All reflection intensities were measured at 110(2) K using a KM4/Xcalibur (detector: Sapphire3) with enhance graphite-monochromated Mo-Kα radiation (λ = 0.71073 Å) under the program CrysAlisPro (Version 1.171.36.20, Agilent Technologies, 2012). The program CrysAlisPro (Version 1.171.36.20, Agilent Technologies, 2012) was used to refine the cell dimensions. Data reduction was done using the program CrysAlisPro (Version 1.171.36.20, Agilent Technologies, 2012). The structure was solved with the program SHELXS-97 (Sheldrick, 2008) and was refined on F^2 with SHELXL-97 (Sheldrick, 2008). Analytical numeric absorption corrections based on a multifaceted crystal model were applied using CrysAlisPro (Version 1.171.36.20, Agilent Technologies, 2012). The temperature of the data collection was controlled using the system Cryojet (manufactured by Oxford Instruments). The H atoms were placed at calculated positions using the instruction AFIX 13, AFIX 43 or AFIX 137 with isotropic displacement parameters having values 1.2 or 1.5 times *U*eq of the attached C atoms. Fw = 346.42, colorless lath, 0.34 × 0.14 × 0.08 mm^3, orthorhombic, *P*bcn (no. 60), a = 31.2908(12), b = 9.2585(3), c = 12.6610(5) Å, V = 3668.0(2) Å ^{3}, Z = 8, D_c = 1.255 g cm^{-3}, μ = 0.081 mm^{-1}, abs. corr. range: 0.990–0.998. 8916 Reflections were measured up to a resolution of $(\sin\theta/\lambda)_{max}$ = 0.57 Å^{-1}. 2867 Reflections were unique (R_{int} = 0.0505), of which 2068 were observed [$I > 2\sigma(I)$]. 238 Parameters were refined. $R1/wR2$ [$I > 2\sigma(I)$]: 0.0434/0.0870. $R1/wR2$ [all refl.]: 0.0730/0.0960. S = 1.015. Residual electron density found between −0.18 and 0.17 e Å^{-3}. Crystallographic data for (±)-*Cis*-3-(2,5-dimethyl-1*H*-pyrrol-1-yl)-1-(4-methoxyphenyl)-4-phenylazetidin-2-one have been deposited as DBTX-312 (Cis) with the Cambridge Crystallographic Data Centre as CCDC 932934. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 IEZ, UK (fax: +44 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk).

54 All reflection intensities were measured at 100(2) K using a SuperNova diffractometer (equipped with Atlas detector) with Cu-Kα radiation (mirror optics, λ = 1.54178 Å) under the program CrysAlisPro (Version 1.171.36.24 Agilent Technologies, 2012). The program CrysAlisPro (Version 1.171.36.24 Agilent Technologies, 2012) was used to refine the cell dimensions. Data reduction was done using the program CrysAlisPro (Version 1.171.36.24 Agilent Technologies, 2012). The structure was solved with the program SHELXS-97 (Sheldrick, 2008) and was refined on F^2 with SHELXL-97 (Sheldrick, 2008). Analytical numeric absorption corrections based on a multifaceted crystal model were applied using CrysAlisPro (Version 1.171.36.24 Agilent Technologies, 2012). The temperature of the data collection was controlled using the system Cryojet (manufactured by Oxford Instruments). The H atoms were placed at calculated positions using the instructions AFIX 13, AFIX 43 or AFIX 137 with isotropic displacement parameters having values 1.2 or 1.5 times *U*eq of the attached C atoms. Fw = 346.42, very thin colorless lath, 0.49 × 0.17 × 0.03 mm^3, monoclinic, $P2_1/n$ (no. 14), a = 9.5368(2), b = 11.2841(3), c = 16.5037(5) Å, β = 90.689(2)°, V = 1775.90(8) Å^3, Z = 4, D_c = 1.296 g cm^{-3}, μ = 0.664 mm^{-1}, abs. corr. range: 0.830–0.981. 18253 Reflections were measured up to a resolution of $(\sin\theta/\lambda)_{max}$ = 0.59 Å^{-1}. 3194 Reflections were unique (R_{int} = 0.0284), of which 3004 were observed [$I > 2\sigma(I)$]. 238 Parameters were refined. $R1/wR2$ [$I > 2\sigma(I)$]: 0.0392/0.0941. $R1/wR2$ [all refl.]: 0.0415/0.0957. S = 1.067. Residual electron density found between −0.20 and 0.21 e Å^{-3}. Crystallographic data for (±)-*Trans*-3-(2,5-dimethyl-1*H*-pyrrol-1-yl)-1-(4-methoxyphenyl)-4-phenylazetidin-2-one (**4a**) have been deposited as DBTX-312 (Trans) with the Cambridge Crystallographic Data Centre as CCDC 932935. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 IEZ, UK (fax: +44 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk).

55 X-ray crystallographic data were recorded with an automatic single crystal X-ray diffractometer consists of a 3 kw X-ray generator, Saturn 724 CCD detector, AFC12K goniometer, and X-stream 2000 (for nitrogen generation). The compound crystallizes in the $P2_1/n$ space group with only one molecule in the asymmetric unit, situated on a general position. All non-hydrogen atoms were refined anisotropically. Hydrogen atoms were placed on calculated positions and were refined with U_{iso}(H) = 1.2–1.5 U_{eq} (C). The title compound (20 mg) was added to 10 mL of acetone then methylene chloride was added drop wise until the compound dissolved. Suitable X-ray quality crystals were formed from slow evaporation of the solvent. An X-ray quality colorless platelet crystal (crystal system: monoclinic) was selected for structural analysis. In regards to the thiophene ring, there is only one sulfur atom but this sulfur atom flips back and forth between two positions hence there is one sulfur atom located 50% of the time at each position. Crystallographic data for (±) *Trans-N*-(chrysen-6-yl)-3-(2,5-dimethyl-1*H*-pyrrol-1-yl)-4-(thiophen-2-yl)azetidin-2-one acetone solvate have been deposited as tcdptaa with the Cambridge Crystallographic Data Centre as CCDC 933213. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 IEZ, UK (fax: +44 1223 336033 or e-mail:deposit@ccdc.cam.ac.uk).

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