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Novel Synthesis of *Bis*-β-Lactams with Unusual 2,7-Phenanthrene and 9,10-Dihydrophenanthrene Derivatives

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ABSTRACT

Unusual and new *bis*-β-lactams substituted at the 2,7-position of the phenanthrene and 9,10-dihydrophenanthrne ring are prepared *via* Staudinger ketene-imine [2+2] cycloaddition reaction. This methodology is recognized as one of the most important and direct accesses route to β-lactams. The diastereoselectivity of cycloaddition processes is controlled by the structures of ketene and imine. The bulky group in the ketene and imine have a great influence on the stereochemical outcome of the β-lactam ring.

KEYWORDS

Bis β-lactams, Cycloaddition, Ketene, Unusual phenanthrene, Imine.

INTRODUCTION

In our earlier studies, we have demonstrated synthesis and biological evaluation of numerous β-lactams as anticancer agents. The current investigation has identified a novel *bis* β-lactam that has a 2,7-disubstituted phenanthrene ring at the nitrogen. This method has two distinctive features *i.e.*, indirect functionalization of the phenanthrene ring in two unusual positions at C_2 and C_7 centers using 9,10-dihydrophenanthrene as starting materials and preparation of novel *bis* β-lactams having sterically constraint polycyclic aromatic ring.

RESULTS AND DISCUSSION

We previously demonstrated bismuth nitrate-induced nitration of several aromatic compounds [1-5]. Reaction of 9,10-dihydrophenanthrene (**1**) with bismuth nitrate pentahydrate impregnated with clay produced a single 2,7-dinitro derivative (**2**) quantitatively under the influence of microwave irradiation. The dinitro product **2** was then attempted to transform to the corresponding diamino derivative (**3**) under the standard catalytic hydrogenation reaction over Pd/C in anhydrous ethanol at room temperature. Surprisingly an unusual aromatic compound corresponding to 2,7-dinitrophenanthrene derivative (**4**) was obtained as the minor product (**Scheme-I**, Table-1).

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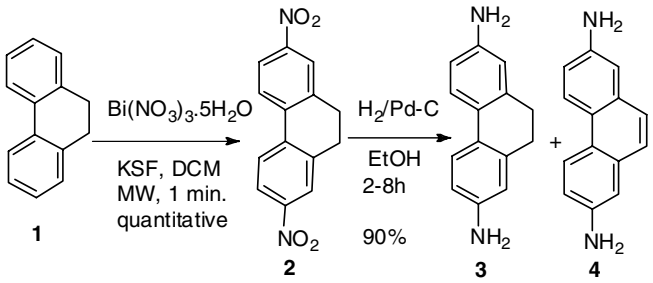


Scheme-I

TABLE-1
SYNTHESIS OF PHENANTHRENE AND 9,10-DIHYDROPHENANTHRENE-2,7-DIAMINE **3** AND **4**

Entry	Time (h)	Catalyst loading	Compound **3**[a] (%)	Compound **4**[a] (%)
1	2	5-10 mol %	80	20
2	3	5-10 mol %	70	30
3	5	10-15 mol %	30	70
4	8	10-15 mol %	10	90

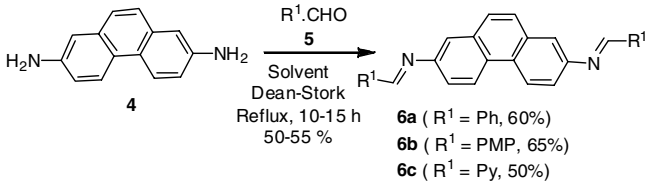
[a]Isolated yield after chromatography.

The formation of compound **4** was due to a catalytic oxidative dehydrogenation or aromatization reaction. This fascinating result deserved special attention based on our current study toward *bis* β-lactams. Our goal was to improve the yield of **4** by changing catalyst loading and the reaction conditions.

An increase in the catalyst amount to 10-20 mol % resulted in a substantial improvement in the yield of compound **4**. Moreover, it was the exclusive product with excess of catalyst and longer reaction time. The usual diamine **3** was obtained under controlled hydrogenation conditions with low catalyst loading and short reaction time.

This reaction is highly interesting because phenanthrene on electrophilic nitration furnish 9 or 10-nitro phenanthrene as the main product. Drastic reaction conditions may produce 9,10-dinitrophenanthrene and along with other oxidized products. There is no way to perform an electrophilic nitration at the C_2 position (mono-substitution) or C_2 and C_7 positions (di-substitution) because these are not the electron deficient centers in phenanthrene nucleus. Therefore, an indirect method as described above is devised for the preparation of unusual phenanthrene derivatives. However nitration of 9,10-dihydrophenanthrene produces 2,7-dinitro derivatives because of the symmetry present in the molecule. Since it is well known that Pd/C can be used to force a partially aromatic system to a fully aromatic compound, the reduction of the two nitro groups were performed with Pd/C under hydrogen atmosphere for a longer period of time. The observation was simultaneous reduction of the nitro groups as well as aromatization of the central ring. We envisage that the main driving force toward unusual diamino phenanthrene is high stability of the resulting aromatic system.

Our synthetic strategy towards polycyclic aromatic β-lactam involved the ketene-imine cycloaddition reaction. Therefore the resulting 2,7-diaminophenenthrene **4** was treated with diverse aldehyde to prepare corresponding diimine (Schiff base) **6a-c** with moderate to good yields under refluxing toluene with a dean stark apparatus (**Scheme-II**, Table-2).



Scheme-II

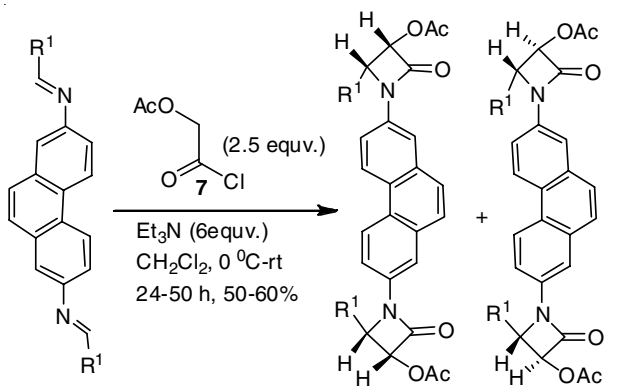
TABLE-2
SYNTHESIS OF 2,7-DIIMINE PHENANTHRENE (SCHIFF BASE) **6a-c**

Entry	R^1	Solvent	Time[a] (h)	Immine	Yield[b] (%)
1	Ph	Toluene	20	6a	50
2	PMP	Benzene	15	6b	55
3	2-Py	Xylene	20	6c	50

[a]Reflux up to boiling point.
[b]After crystallization with different combination of solvent(s).

All diimine were purified by crystallization of the crude mixture with different solvent combination at low temperature. Probably all the Schiff bases are very labile on silica gel bed. In most of the cases it turned in to the amine *via* reversible reaction over silica gel bed. After successful synthesis of various imine corresponding to unusual 2-7-phenanthrene nucleus, we perform Staudinger ketene-imine [2+2] cycloaddition reaction towards our goal. Herein to study the feasibility of the cycloaddition reaction for the synthesis of *bis*-β-lactam, the reaction of **6a** with acetoxy acetyl chloride was selected as model. Treatment of imine **6a** with 1.3 equiv of acetoxyacetyl chloride (**7**) in dichloromethane in presence of triethylamine at 0 °C was conducted.

To our surprise the reaction went smoothly and afforded the corresponding racemic *cis* and *trans* β-lactam **8a** and **9a** in good yield with 6:4 diastereomeric ratio. The *cis* and *trans* stereochemistry of the β-lactam ring at C_3 and C_4 position was established from the ^{1}H NMR data of the crude reaction mixture. A high coupling constant of J = 4.92 and 5.1 Hz at C_3 and C_4 positions corresponds to *cis* β-lactam and the low coupling constant value J = 1.6 and 1.7 Hz is for *trans* β-lactam (**Scheme-III**, Table-3). The *cis* and *trans* diastereoisomers **8a** and **9a** were separated by flash column chromatography.



Scheme-III

TABLE-3
SYNTHESIS OF 3-ACETOXY *BIS*-β-LACTAM TATHERED WITH UNUSUAL 2,7-PHENANTHRENE RING **8a-c** AND **9a-c**

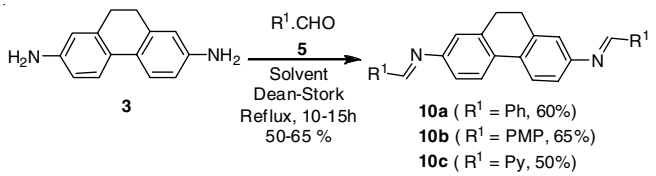
Entry	R^1	Time (h)	Compound	Yield[a] (%)	Diastero-selectivity[b]
1	Ph	30	**8a+9a**	60:40	6:4
2	PMP	24	**8b+9b**	70:30	7:3
3	Py	48	**8c+9c**	75:25	7.5:2.5

[a]Isolated yield after column chromatography, inseparable mixture.
[b]Determined by means of ^{1}H NMR analysis of crude reaction mixture.

Based upon the successful synthesis of our *bis*-β-lactam, we performed similar experiments to prepare the corresponding β-lactams **8b-c** and **9b-c**. The imines **6b** and **6c** was used successfully to furnish the desired products in good to excellent yields. The complete observations of the results are delineated in (**Scheme-III**, Table-3). All the products were purified through flash column chromatography and were characterized through NMR analysis. The data of *bis*-β-lactams are consistent with compounds **8a** and **9a.** This promising results prompted us to investigate β-lactam synthesis with other diimines.

In this context the *bis*-β-lactam **12 a-c** corresponding to the 2,7-damino-9,10-dihydrophenanthrene **3** to generalized the scope of methodology were studied.

We performed the similar reaction for the synthesis of imine **9a-c** by condensing the diverse aromatic and heterocyclic aldehydes under refluxing condition. The results are shown in (**Scheme-IV**, Table-4).



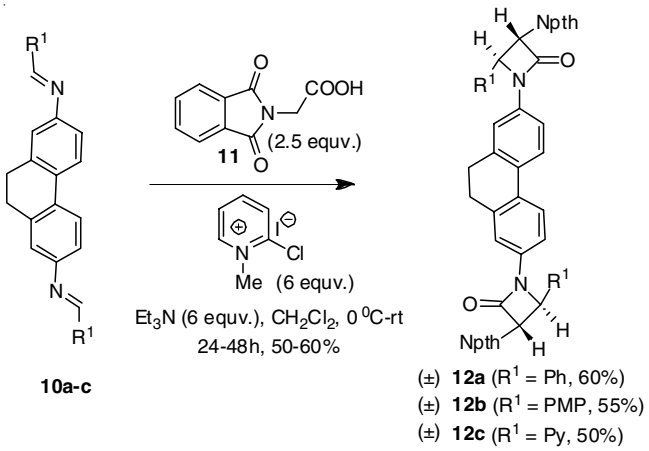
Scheme-IV

TABLE-4

Entry	R^1	Solvent	Time[a] (h)	Compound	Yield[b] (%)
1	Ph	Toluene	20	**10a**	60
2	PMP	Benzene	15	**10b**	65
3	2-Py	Xylene	20	**10c**	50

[a]Reflux up to boiling point.
[b]After crystallization with different combination of solvent(s).

The imine **10a-c** was then treated with N-phthalimido glycine **11** in presence of triethylamine and 2-chloro-1- methyl pyridinium iodide as an acid activator. The reaction underwent smoothly to furnish the exclusively *trans* β-lactam **12a-c** with high degree of stereochemical control in good yield (**Scheme-V**, Table-5). The stereochemistry of the *trans* β-lactam is established from the coupling constants at the C_3 and C_4 positions of the lactams ring. The low coupling constant J = 2.3 and 2.4 Hz is assigned for the *trans* isomer. Therefore, the ring aromaticity of the imine and the structure of the ketene have detrimental roles in controlling the stereochemical outcome in Staudinger ketene-imine [2+2] cyclo addition reaction of the β-lactam synthesis [6-12]. The current outcome of the relative stereochemistry of Staudinger reaction of the β-lactam synthesis is one of the major challenges.



Scheme-V

TABLE-5
SYNTHESIS OF N-PHTHALIMIDO *BIS*-β-LACTAM TATHERED WITH 9,10-DIHYDROPHENANTHRENE RING **12a-c**

Entry	R^1	Time (h)	Compound	Yield[a] (%)	Stereochemistry[b] (C_3-C_4)
1	Ph	30	**12a**	50	β-α *trans*
2	PMP	24	**12b**	60	β-α *trans*
3	Py	48	**12c**	50	β-α *trans*

[a]Isolated yield after column chromatography.
[b]Determined by means of ^{1}H NMR analysis.

We assume that the bulky group in N-phthalimido ketene allows the approach of the diimine selectively from one of the faces of the ketene in the transition state of the cycloaddition reaction [13].

The electron withdrawing group in cyclic N-phthalimido ketene blocks the direct ring closure the transition state leading to the formation of *trans* β-lactam [14,15]. In addition to the ketene, the constraint ring of polyaromatic compound has also the crucial role in the stereochemical outcome of reaction.

Conclusion

Synthesis of *bis* β-lactam substituted at unusual position of the phenanthrene ring is successfully achieved. Based upon our earlier results on anticancer β-lactams, these new compounds may prove to be useful. Further, the availability of 2,7-diamino-phenanthrene opens up the possibility of preparing new structures that were not possible before by existing literature methods. The cyclic ketene inbuilt electron withdrawing group successfully delivered the *trans* products exclusively.

The acyclic ketene counterpart of the reaction led the mixture of *cis* and *trans* β-lactams. It assume that the planar structure and weak electron withdrawing group allow both the concerted and stepwise ring closure leading the mixture of *cis/trans* compounds. The investigative study on the stereochemical outcome and unique motif with unusual phenanthrene nucleus is the main fascination of this work.

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