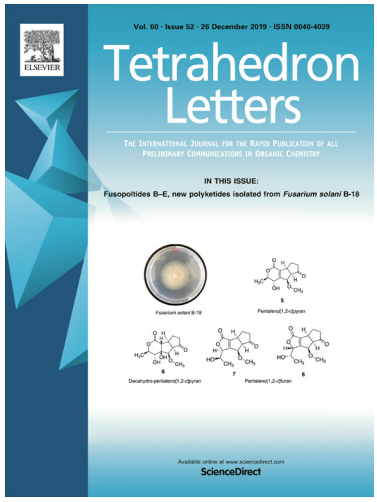
Journal Pre-proofs



N-Phenyl Substituent Controlled Diastereoselective Synthesis of β-Lactam-isatin Conjugates

Lalitha Gummidi, Nagaraju Kerru, Paul Awolade, Collins U. Ibeji, Rajshekhar Karpoormath, Parvesh Singh

PII: S0040-4039(20)30010-1
DOI: https://doi.org/10.1016/j.tetlet.2020.151601
Reference: TETL 151601

To appear in: *Tetrahedron Letters*

Received Date: 16 November 2019
Revised Date: 24 December 2019
Accepted Date: 7 January 2020

Please cite this article as: Gummidi, L., Kerru, N., Awolade, P., Ibeji, C.U., Karpoormath, R., Singh, P., *N*-Phenyl Substituent Controlled Diastereoselective Synthesis of β-Lactam-isatin Conjugates, *Tetrahedron Letters* (2020), doi: https://doi.org/10.1016/j.tetlet.2020.151601

N-Phenyl Substituent Controlled Diastereoselective Synthesis of *β*-Lactam-isatin Conjugates

Lalitha Gummidi[a], Nagaraju Kerru[a], Paul Awolade[a], Collins U. Ibeji[b], Rajshekhar Karpoormath[c], Parvesh Singh[a,*]

[a]School of Chemistry, Physics, University of KwaZulu-Natal, P/Bag X54001, Westville, Durban, South Africa

[b]Department of Pure and Industrial Chemistry, Faculty of Physical Sciences, University of Nigeria, Nsukka 410001, Enugu State, Nigeria

[c]Discipline of Pharmaceutical Sciences, College of Health Sciences, University of KwaZulu-Natal (UKZN), Westville, Durban 4001, South Africa

*Corresponding author. School of Chemistry & Physics, University of KwaZulu-Natal, Durban 4000, South Africa.

Graphical abstract

ga1

Highlights

- Diastereoselective synthesis of novel *β*-lactam-isatin molecular hybrids.
- Staudinger [2+2] cycloaddition reaction to afford *β*-lactams.

- Exploration of *N*-phenyl substitution effect for synthesis of *β*-lactams.
- *N*-phenyl electron-donating groups favoured *cis*-isomer.
- DFT studies also supports the *cis* and *trans* isomer formation.

Abstract

Unprecedented diastereoselective synthesis of novel *β*-lactam-isatin conjugates *via* a Staudinger [2+2] cycloaddition is described. The electronic nature of substituents on the imine *N*-phenyl moiety induced high levels of stereocontrol and plausibly controlled the competition between direct ring closure (conrotatory) and isomerization of the azabutadiene intermediate. The presence of electron-donating groups (OCH_3 and CH_3) at the *para*-position of the imine *N*-phenyl moiety increases the electron density of the imine nitrogen atom. This in turn increases direct conrotatory ring closure favoring the *cis*-isomer. On the other hand, electron-withdrawing groups (NO_2 and CF_3) at the *para*-position gave the thermodynamically more stable *trans*-isomer as the major products by promoting isomerization of the azadiene zwitterionic intermediate presumably due to a decrease in the electron density on the imine nitrogen atom. A varied diastereoselective behavior was observed for *meta*-position substituents, where OCH_3, CH_3 and NO_2 groups favored the *cis*-isomer, hence indicating the additional role of steric hindrance in the observed

diastereoselectivity. Additionally, the transition states of these reactions computed at the density functional theory (DFT) level were in accordance with the experimental results.

Keywords

[2+2]Cycloaddition

Substituents effect

Diastereoselectivity

DFT

Introduction

The serendipitous isolation of Penicillin from *Penicillium notatum* and cephalosporin from *Cephalosporium acremonium*, began an ever-increasing interest in the *β*-lactam (2-azetidinone) ring as potent antibiotics. Consequently, the *β*-lactam nucleus has been a coveted target in organic synthesis and medicinal chemistry.[1–3] It has also been used as building blocks and key intermediates for the synthesis of several heterocycles with biological significance such as the anticancer drugs Taxol and Taxotere.[4,5] The efficient synthetic protocols used to access the *β*-lactam scaffold include the Staudinger, Gilman-

Speeter and Kinugasa reactions.[6] Amidst these synthetic strategies, the Staudinger [2+2] cycloaddition of ketenes to imines is the most widely employed due to its simplicity and readily accessible substrates.[7–9] The synthetic strategy is further used for constructing spirocyclic, bicyclic and tricyclic *β*-lactams.[10] Moreover, transition metal catalysts have also been reported to give the *β*-lactam ring.[11,12]

Nevertheless, stereoselectivity remains the focus of the Staudinger [2+2] cycloaddition reaction, as the biological activity of the resulting ring is dictated by its stereo-structure.[13,14] For example, the *β*-lactam antibiotics penicillin and cephalosporin possess *cis*-structures while trinems and thienamycins possess *trans*-structures.[14] Additionally, stereoselective construction of the *β*-lactam ring has been attempted, either by using chiral catalysts, asymmetric substrates or chiral auxiliaries.[15–17]

For diastereoselectivity, the electronic effects of substituents on the ketene and imine substrates are key factors affecting the stereo-outcomes. Electron-donating groups (EDGs) on the ketene and electron-withdrawing groups (EWGs) on the imine favor direct ring closure, giving the *cis*-product, while EWGs and EDGs on the ketene and imine, respectively, lower the rate of direct ring closure favoring the *trans*-product.[18]

Furthermore, molecular hybridization, a versatile and emerging tool for constructing bioactive molecules with the improved ability of being recognized by multiple receptors has

been employed in the synthesis of new *β*-lactam conjugates.[19] For instance, β-lactam grafted spiro-oxindole hybrids exhibited potent antimicrobial activity,[20] and purine-lactam hybrids exhibited good antiviral activity.[21] Similarly, *β*-lactam-isatin-triazole conjugates displayed promising *in vitro* protozoal activity against *Trichomonas vaginalis*.[22]

In continuation of our search for new molecular scaffolds with improved pharmacological profiles *via* the molecular hybridization approach,]23] we herein report the synthesis of novel *β*-lactam-isatin molecular conjugates *via* a Staudinger [2+2] cycloaddition protocol using inexpensive and *in-situ* generated ketenes. Subsequently, we examined the corresponding substitution effects on the *N*-phenyl imine diastereoselectivity (Scheme 1sch1). Density functional theory (DFT) calculations were also employed to substantiate the experimental results.

Results and Discussion

We commenced our study by investigating the optimum reaction conditions for the synthesis of *β*-lactam-isatin conjugates. We specifically focused on the selection of a suitable solvent and a base and their subsequent effect on reaction times and yields (Table 1tbl1). In all reactions, 1 mmol of imine **1a**, two equivalents of 2-(2,3-dioxoindolin-1-yl) acetic acid **2** and two equivalents of *p*-toluenesulfonyl chloride (*p*-TsCl) were used as a model reaction at 0 °C under a nitrogen atmosphere. It should be noted that the ketene used for all reactions was generated *in situ* from 2-(2,3-dioxoindolin-1-yl)acetic acid using *p*-

TsCl as an activating agent in triethylamine. Initially, we investigated the most suitable solvent for the reaction using triethylamine as a base and various solvents (DMF, CH_2Cl_2, EtOH, *t*-BuOH, THF, $CHCl_3$, MeCN and 1,4-dioxane). Among the tested solvents, CH_2Cl_2 was found to be superior in terms of conversion *(*Table 2 tbl2*). Furthermore, the model reaction was explored with different bases (*Table 1*, entries 9-16). The* use of Et_3N, DIPEA, pyridine and DBU gave the *β*-lactam adduct **3a** in moderate to good yields. On the other hand, no conversion was observed with NaOH, CS_2CO_3, NaH, *t*-BuOK and K_3PO_4. Hence, the non-nucleophilic Et_3N proved to be the most effective base.

With the optimized conditions in hand, we next turned our focus to study the effect of substituents on the *N*-aryl imine moiety on the diastereoselectivity in the Staudinger [2+2] cycloaddition reaction. A variety of imines bearing electron-donating and electron-withdrawing groups at *para*- and *meta*-positions of the *N*-phenyl ring were examined keeping the isatin-ketene fixed (Scheme 1). All the reactions gave a mixture of *cis*- and *trans*-*β*-lactams, as deduced from ^{1}H-NMR spectroscopy of the crude product, and the results are summarized in Table 2. The stereochemistry of *β*-lactams **3a-q** and **4a-q** were established based on the coupling constants (*J*) between the C9-H and C11-H protons of the *β*-lactam ring, where *J* = 2.0-2.8 Hz represents the *trans*-isomer while *J* = 5-6 Hz represents the *cis*-isomer.[24] Fascinatingly, the *cis/trans* ratio of the *β*-lactams varied with the electronic nature of the *N*-phenyl imine substituents.[25] In parallel, we assume that a steric interaction between the *N*-substituents and the carbonyl group could also exist, hence,

decreasing the isomerization.[26] The steric interaction is similar to the Thorpe-Ingold effect,[27] and results in the two π-systems (C=C and C=N π-bonds) being close to each other (Fig. 1 fig1), favoring direct ring closure and preferring the *cis*-*β*-lactams. Our argument is supported by the predominance of the major *cis*-diastereomer in the case of imines with 3-CH_3, 3-OCH_3, 3,4,5-OCH_3 and 3-NO_2 substituents (Table 2, entries 14-17) where the steric hindrance of these groups presumably superseded their mesomeric effect, and hence accelerate the direct ring closure. The unsubstituted (H), electron-donating (4-OCH_3, 4-CH_3) and halogens (4-Cl, 4-Br, 4-I and 4-F) substituents on the *N*-aryl imine moieties also favored the *cis*-isomer (Table 2, entries 1-7) due to an increase in the electron density on the imine nitrogen atom through resonance effect (ESI, Fig. S60).

However, the *para*-positioning of electron-withdrawing groups (4-NO_2 and 4-CF_3) reversed the diastereoselectivity thus favoring the thermodynamically more stable *trans*-*β*-lactam as the major product (Table 2, entries 8 and 9). This could be due to the decreased electron density on the imine nitrogen atom (*via* resonance) thus decreasing direct conrotatory ring closure and initiating isomerization which gives the *trans*-isomer (ESI, Fig. S61). Similar behavior is observed with halogenated (*i.e.* Cl and Br) and alkyl halogenated (CF_3) groups at the *meta*-position on *N*-aryl imine moieties that affords *trans*-selectivity (Table 2, entries 10-13) presumably due to the mesomeric (-) effect of the substituents.

Based on the obtained results, it is conceivable that the electron-donating groups on the *N*-phenyl imine, irrespective of their position (*para* and *meta*), accelerate direct ring closure,

thus resulting in the increase of *cis*-selectivity due to an increase in the electron density on the imine nitrogen atom *via* resonance effects in the *cis*-transition state. Whereas, the *para* positioning of electron-withdrawing groups on the *N*-phenyl imine results in *trans*-selectivity due to the decrease in the electron density on the imine nitrogen atom thereby accelerating its isomerization.

A plausible mechanism for the formation of *β*-lactam-isatin hybrids is represented in Scheme 2 sch2. The reaction can proceed through less steric hindered *exo* attack of the ketene, which leads to the formation of azadiene zwitterionic intermediate (ZW1) followed by direct conrotatory ring closure to give *cis*-*β*-lactam derivatives.[28] Otherwise, isomerization of the iminium moiety delivers the thermodynamically more stable intermediate (ZW2), which consequently undergoes ring closure to give the *trans*-*β*-lactams.

The structure of *cis*-*β*-lactam (*9S 11R*) was confirmed by single-crystal X-ray analysis (Fig. 2 fig2). Evidently, H-9 and H-11 are oriented on the same side of the plane in the 4-membered *β*-lactam ring with respect to the two stereogenic centers.

Computational Methods

To gain an insight into the diastereoselectivity of the isatin-lactam conjugates, density functional theory calculations were performed on the stepwise-reaction mechanism for the [2+2] cycloaddition reaction. The modelled reactions used for these studies had 4-NO_2, 3-NO_2, 4-OCH_3 and 3-OCH_3 groups attached to the imine phenyl ring. The M06/6-31+G(d,p) level of theory was initially used to obtain the optimized structures (see ESI for details). The results obtained from the DFT calculations revealed that the ring closure step is the rate-determining step for the formation of either the *cis* or *trans* product. Transition state-TS1 (Fig. 3 and 4 fig3,fig4) for both the methoxy and nitro substituents on the phenyl ring

differ by an average of 2.5 kcal/mol (Table 3 tbl3). Comparing the transition state energies (Fig. 3 and Table 3) showed that the lower transition state (TS) activation free energies of 4-OCH_3, 3-OCH_3 and 3-NO_2 favored the *cis*-*β*-lactam conformation (TS2) compared to the higher activation energies of their *trans*-*β*-lactam conformations. This implies that the rate-determining step involving the direct ring closure for 4-OCH_3, 3-OCH_3 and 3-NO_2 is faster leading to the *cis*-isomer. On the other hand, the lower ΔG value of *trans* 4-NO_2 (TS3) (18.69 kcal/mol) revealed that the *trans* conformation is favored compared to the *cis*-form with a higher energy barrier of 26.50 kcal/mol. Furthermore, to verify the reliability of the results obtained using the 6-31+G(d,p) basis set, augcc-pVDZ basis set was applied. The free energies calculated using the M06/augcc-pVDZ levels are consistent with those from the M06/6-31+G(d,p) level.

In addition, the imine bond distances of the transition states (TS) were computed for two substituents (4-OCH_3 and 4-NO_2) and are shown in the ESI (Table S1). These results revealed that the imine bond distances were shorter for the TS that gives *cis* products and thus supports the direct ring closure of intermediates. Whereas, the same bond distance in the transition states for *trans* products were longer thus favoring isomerization. We further determined the force constant, which is an indication of the bond strength at the DFT level.[29] Again, the force constant values were found to be higher for transition states that led to *cis*-*β*-lactams.

Commented [A1]: Page: 9
This label is not available in the Reference label. Kindly check the reference.

Conclusion

We have employed the Staudinger ketene-imine [2+2] cycloaddition methodology for the diastereoselective synthesis of 17 novel isatin-*β*-lactams hybrids. The electronic nature of substituents at the *para*-position of the *N*-phenyl imine induced high levels of stereocontrol. For instance, strong electron-donating groups promoted *cis*-selectivity *via* increasing the electron density on the imine nitrogen atom thus facilitating direct ring closure of the azabutadiene intermediate. Whereas, strong electron-withdrawing groups at the same position reversed the diastereoselectivity presumably by facilitating isomerization of the intermediate. However, at the *meta* position**,** both electronic and steric factors played a role in controlling the diastereoselectivity of these reactions. Additionally, the DFT-predicted transition states and bond distances further supported the experimental outcome.

Acknowledgments

Lalitha Gummidi (GL) gratefully thank the National Research Foundation (NRF) of South Africa for their financial support (NRF-TWAS-UID: 110887) and University of KwaZulu-Natal. Further thanks go to the Centre for High Computing Performance (CHPC) in Cape Town (South Africa) for access and use of computational resources.

Declaration of Interest Statement

The authors declare no conflict of interest, financial or otherwise.

References

Commented [A2]: AUTHOR: Please note that as the reference [1] supplied more than once, the repletion has been removed from the list. Please check, and amend accordingly.

Anushree, K.; Iwao, O. *Tetrahedron,* **2012**, *68*, 10640-10664.

[1] K. Anushree O. Iwao Tetrahedron 68 2012 10640 10664

Nikhilesh, A.; Archana, Y. J.; Tushar, A. P.; Shradha, S.; Yeramwar, S. S. H.; Jaya, D.; Chamanlal, J. S.; Kishor, S. J. *Eur. J. Med. Chem.* **2014**, *74*, 619-656.

[2] A. Nikhilesh Y.J. Archana A.P. Tushar S. Shradha S.S.H. Yeramwar D. Jaya J.S. Chamanlal S.J. Kishor Eur. J. Med. Chem. 74 2014 619 656

(a) Ojima, I.; Zuniga, E. S.; Seitz, J. D. *Top. Heterocycl. Chem.* **2012**, *30*, 1-64; (b) Fernandez, I.; Sierra, M. A. *Top. Heterocycl. Chem.* **2012**, *30*, 65-84; (c) Mandal, B.; Basu, B. *Top. Heterocycl. Chem.* **2012**, *30*, 85-110. (d) Tidwell, T. T. *Top. Heterocycl. Chem.* **2012**, *30*, 111-145. (e) Turos, E. *Top. Heterocycl. Chem.* **2012**, *30*, 147-181. (f) Banik, I.; Banik, B. K. *Top. Heterocycl. Chem.* **2012**, *30*, 183-222.

[3]

(a) I. Ojima E.S. Zuniga J.D. Seitz Top. Heterocycl. Chem. 30 2012 1 64

(b) I. Fernandez M.A. Sierra Top. Heterocycl. Chem. 30 2012 65 84

(c) B. Mandal B. Basu Top. Heterocycl. Chem. 30 2012 85 110

(d) T.T. Tidwell Top. Heterocycl. Chem. 30 2012 111 145

(e) E. Turos Top. Heterocycl. Chem. 30 2012 147 181

(f) I. Banik B.K. Banik Top. Heterocycl. Chem. 30 2012 183 222

(a) Maaroof, Z.; Masoud, M. *Tetrahedron* **2011**, *67*, 5832-5840; (b) Vishu, M.; Parvesh, S.; Neha, M.; Vipan, K. *Synlett* **2014**, *25*, 1124-1126; (b) Aman, B.; Garima, M.; Shamsher, S. B.; Anu, K.; Shiwani, B.; Geeta, H. *Tetrahedron Lett.* **2017**, *58*, 1160-1165; (c) Aman, B.; Shamsher, S. B.; Sunil, V.; Jitender, B.; Kiran, S.; Dipika, N. *Tetrahedron Lett.* **2016**, *57*, 4763-4766; (d) Amandeep, S.; Shalinia, H. K.; Palak, S.; Amit, A.; Vipan, K. *Synlett* **2017**, *28*, 2642-2646; (e) Pardeep, S.; Shaveta, S.; Raghu, R.; Vipan, K.; Mohinder, P. M.; Shereen, N.; Livia, V.; Jiri, G.; Phillip, J. R.; Tzu, S. F.; Kelly, C. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 4561-4563; (f)

Raghu, R.; Vaishali, S.; Melissa, J. H.; Neal, P.; Dominique, H.; Lisa, A. W.; Kirkwood, M. L.; Vipan, K. *Med. Chem. Res.* **2014**, *23*, 3671-3680.

[4]

(a) Z. Maaroof M. Masoud Tetrahedron 67 2011 5832 5840

(b) M. Vishu S. Parvesh M. Neha K. Vipan Synlett 25 2014 1124 1126

(b) B. Aman M. Garima S.B. Shamsher K. Anu B. Shiwani H. Geeta Tetrahedron Lett. 58 2017 1160 1165

(c) B. Aman S.B. Shamsher V. Sunil B. Jitender S. Kiran N. Dipika Tetrahedron Lett. 57 2016 4763 4766

(d) S. Amandeep H.K. Shalinia S. Palak A. Amit K. Vipan Synlett 28 2017 2642 2646

(e) S. Pardeep S. Shaveta R. Raghu K. Vipan P.M. Mohinder N. Shereen V. Livia G. Jiri J.R. Phillip S.F. Tzu C. Kelly Bioorg. Med. Chem. Lett. 21 2011 4561 4563

(f) R. Raghu S. Vaishali J.H. Melissa P. Neal H. Dominique A.W. Lisa M.L.

Kirkwood K. Vipan Med. Chem. Res. 23 2014 3671 3680

(a) Ojima, I. *Acc. Chem. Res.* **1995**, *28*, 383-389; (b) Hodge, M.; Chen, O. H.;

Bane, S.; Sharma, S.; Loew, M.; Banerjee, A.; Alcaraz, A. A.; Snyder, J. P.;

Kingston, D. G. I. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 2884-2887.

[5]

(a) I. Ojima Acc. Chem. Res. 28 1995 383 389

(b) M. Hodge O.H. Chen S. Bane S. Sharma M. Loew A. Banerjee A.A. Alcaraz J.P.

Snyder D.G.I. Kingston Bioorg. Med. Chem. Lett. 19 2009 2884 2887

Luigino-Troisi, C. G.; Emanuela, P. *Top. Heterocycl. Chem.* **2010**, *22*, 101-209.

[6] C.G. Luigino-Troisi P. Emanuela Top. Heterocycl. Chem. 22 2010 101 209

(a) Gedey, S.; Van der Eycken, J.; Fulop, F. *Lett. Org. Chem.* **2004**, *1*, 215-220; (b)

Zarei, M. *Monatsh. Chem*. **2013**, *144*, 1021-1025; (c) Aranda, M. T.; Perez-Faginas, P.; Gonzalez-Muniz, R. Curr. Org. *Synth*. **2009**, *6*, 325-341; (d) Fu, N.; Tidwell, T. T. *Tetrahedron*, **2008**, *64*, 10465-10496.

[7]

(a) S. Gedey J. Van der Eycken F. Fulop Lett. Org. Chem. 1 2004 215 220

(b) M. Zarei Monatsh. Chem. 144 2013 1021 1025

(c) M.T. Aranda P. Perez-Faginas R. Gonzalez-Muniz Curr. Org. Synth. 6 2009 325 341

(d) N. Fu T.T. Tidwell Tetrahedron 64 2008 10465 10496

Claudio, P.; Jesus, M. A.; Inaki, G.; Mikel, O. *Eur. J. Org. Chem*. **1999**, *12*, 3223-3235.

[8] P. Claudio M.A. Jesus G. Inaki O. Mikel Eur. J. Org. Chem. 12 1999 3223 3235

(a) Zhongyan, H.; Chen, W.; Etsuko, T.; Yuji, S.; Norio, S. *Org. Lett*. **2015**, *17*,

5610-5613; (b) Cooper, R. D. G.; Daugherty, B. W.; Boyd, D. B. Pure & App. Chem. **1987**, *59*, 485-492; (c) Taggi, A. E.; Hafez, A. M. Wack, H.; Young, B.; Drury, W. J.; Lectka, T. *J. Am. Chem. Soc.* **2000**, *122,* 7831-7832; (d) Hodous, B. L.; Fu, G. C. *J. Am. Chem. Soc.* **2002**, *124*, 1578-1579; (e)Taggi, A. E.; Hafez, A. M. Wack, H.; Young, B.; Dana, F.; Lectka, T. *J. Am. Chem. Soc.* **2002**, *124,* 6626-6635; (f) Palomo, C.; Aizpurua, J. M.; Mielgo, A.; Linden, A. *J. Org. Chem.* **1996**, *61,* 9186-9195.

[9]

(a) H. Zhongyan W. Chen T. Etsuko S. Yuji S. Norio Org. Lett. 17 2015 5610 5613

(b) R.D.G. Cooper B.W. Daugherty D.B. Boyd Pure & App. Chem. 59 1987 485 492

(c) A.E. Taggi A.M. Hafez H. Wack B. Young W.J. Drury T. Lectka J. Am. Chem. Soc. 122 2000 7831 7832

(d) B.L. Hodous G.C. Fu J. Am. Chem. Soc. 124 2002 1578 1579

(e) A.E. Taggi A.M. Hafez H. Wack B. Young F. Dana T. Lectka J. Am. Chem. Soc. 124 2002 6626 6635

(f) C. Palomo J.M. Aizpurua A. Mielgo A. Linden J. Org. Chem. 61 1996 9186 9195

(a) Aman, B.; Paloth, V.; Shamsher, S. B. *Eur. J. Org. Chem.* **2006**, *2006*, 4943-4950; (b) Aman, B.; Shamsher, S. B.; Jitender, B.; Sadhika, K.; Sanjay, M. *Tetrahedron Lett.* **2016**, *57*, 2822-2828; (c) Bari, S. S.; Aman, B.; Reshma, G. H. *Tetrahedron Lett.* **2013**, *54*, 483-486. (d) Dinesh, R. G.; Amol, R. J.; Santosh, V. L.; Nilesh, M. K.; Rohini, R. J.; Ramesh, A. J.; Mamoru, K. *Tetrahedron Lett.* **2014**, *55*, 5998-6000; (e) Lal, D. S. Y.; Vijai, K. R. *Tetrahedron Lett.* **2008**, *49*, 5553-5556; (f) Han-Ming, Z.; Zhong-Hua, G.; Song, Y. *Org. Lett.* **2014**, *11*, 3079-3081.

[10]

(a) B. Aman V. Paloth S.B. Shamsher Eur. J. Org. Chem. 2006 2006 4943 4950

(b) B. Aman S.B. Shamsher B. Jitender K. Sadhika M. Sanjay Tetrahedron Lett. 57 2016 2822 2828

(c) S.S. Bari B. Aman G.H. Reshma Tetrahedron Lett. 54 2013 483 486

(d) R.G. Dinesh R.J. Amol V.L. Santosh M.K. Nilesh R.J. Rohini A.J. Ramesh K. Mamoru Tetrahedron Lett. 55 2014 5998 6000

(e) D.S.Y. Lal K.R. Vijai Tetrahedron Lett. 49 2008 5553 5556

(f) Z. Han-Ming G. Zhong-Hua Y. Song Org. Lett. 11 2014 3079 3081

Robert, T. *Org. Biomol. Chem.* **2013**, *11*, 5976-5988; (b) Cody, R. P.; Thomas, L. *Chem. Rev.* **2014**, *114*, 7930-7953; (c) Xuejun, Z.; Richard, P. H.; Hongyan, L.; Yu, Z.; Whitney, L. J. Ruth, F. *Org. Lett.* **2008**, *10*, 3477-3479; (d) Eva, H.; Julio, P.; Victor, R.; Daniel, M.; Pablo, C.; Isabel, M. M.; Tomas, L. S.; Santiago, G. G. *J. Am. Chem. Soc.* **2003**, *125*, 3706-3707.

[11] Robert, T. *Org. Biomol. Chem.* **2013**, *11*, 5976-5988; (b) Cody, R. P.; Thomas, L. *Chem. Rev.* **2014**, *114*, 7930-7953; (c) Xuejun, Z.; Richard, P. H.; Hongyan, L.;

Yu, Z.; Whitney, L. J. Ruth, F. *Org. Lett.* **2008**, *10*, 3477-3479; (d) Eva, H.; Julio, P.; Victor, R.; Daniel, M.; Pablo, C.; Isabel, M. M.; Tomas, L. S.; Santiago, G. G. *J. Am. Chem. Soc.* **2003**, *125*, 3706-3707.

Insu, K.; Sang, W. R.; Dong, G. L.; Chulbom, L. *Org. Lett.* **2014**, *16*, 2482-2485.

[12] K. Insu W.R. Sang G.L. Dong L. Chulbom Org. Lett. 16 2014 2482 2485

Cossilo, F. P.; Arrieta, A.; Sierra, M. A. *Acc. Chem. Res.* **2008**, *41*, 925-936.

[13] F.P. Cossilo A. Arrieta M.A. Sierra Acc. Chem. Res. 41 2008 925 936

Xu, J. *ARKIVOC*, **2009**, *ix*, 21-44.

[14] J. Xu ARKIVOC ix 2009 21 44

Aleksandar, R. T.; Vanya, B. K.; Ranko, P. B.; Nikolay, G. V. *Tetrahedron*, **2009**, *65*, 10339-10347.

[15] R.T. Aleksandar B.K. Vanya P.B. Ranko G.V. Nikolay Tetrahedron 65 2009 10339 10347

Cody, R. P.; Thomas, L. *Chem. Rev.* **2014**, *114*, 7930-7953.

[16] R.P. Cody L. Thomas Chem. Rev. 114 2014 7930 7953

(a) Lei, J.; Yong, L.; Jiaxi, X. *J. Am. Chem. Soc.* **2006**, *128*, 6060-6069; (b) Zhanhui, Y.; Jiaxi, X. *Tetrahedron*, **2015**, *71*, 2844-2852.

[17]

(a) J. Lei L. Yong X. Jiaxi J. Am. Chem. Soc. 128 2006 6060 6069

(b) Y. Zhanhui X. Jiaxi Tetrahedron 71 2015 2844 2852

(a) Viegas, J. C.; Danuello, A.; Silva, B. V.; Barreiro, E. J.; Fraga, C. A. M. *Curr. Med. Chem.* **2007**, *14*, 1829-1852; (b) Parvesh, S.; Bukola, J.; Nagaraju, K.; Oluwakemi, E.; Ajay, B. *Curr. Med. Chem.* **2017**, *24*, 4180-4212; (c) Carmen, L.; Alicja, K.; Taira, K.; Yasuo, K. *J. Med. Chem.* **2004**, *47*, 6973-6982; (d) Daniel, A. E.; Robert, S. M.; O-Brien, T. *J. Med. Chem.* **2004**, *47*, 3463-3482.

[18]

(a) J.C. Viegas A. Danuello B.V. Silva E.J. Barreiro C.A.M. Fraga Curr. Med. Chem. 14 2007 1829 1852

(b) S. Parvesh J. Bukola K. Nagaraju E. Oluwakemi B. Ajay Curr. Med. Chem. 24 2017 4180 4212

(c) L. Carmen K. Alicja K. Taira K. Yasuo J. Med. Chem. 47 2004 6973 6982

(d) A.E. Daniel S.M. Robert O-Brien, T J. Med. Chem. 47 2004 3463 3482

Natarajan, A.; Govindasami, P.; Raghavachary, R.; Subban, K.; Johnpaul, M. *Eur. J. Med. Chem.* **2011**, *46*, 600-607.

[19] A. Natarajan P. Govindasami R. Raghavachary K. Subban M. Johnpaul Eur. J. Med. Chem. 46 2011 600 607

Matthias, D.; Karen, M.; Rob, D. V.; Tim, H. M. J.; Gery, D.; Norbert, D. K. *J. Med. Chem.* **2012**, *55*, 5637-5641.

[20] D. Matthias M. Karen D.V. Rob H.M.J. Tim D. Gery D.K. Norbert J. Med. Chem. 55 2012 5637 5641

Raghu, R.; Pardeep, S.; Nathan, T. H.; Ryan, M. F.; Neal, P.; Kirkwood, M. L.; Vipan, K. *Eur. J. Med. Chem.* **2013**, *63*, 897-906.

[21] R. Raghu S. Pardeep T.H. Nathan M.F. Ryan P. Neal M.L. Kirkwood K. Vipan Eur. J. Med. Chem. 63 2013 897 906

Kerru, N.; Venkata, H. S. S. B.; Ravada, K.; Suresh, M.; Parvesh, S.; Sreekantha, B. J. *Lett. Drug Des. Discov.* **2018**, *15*, 118-126; (b) Parvesh, S.; Nomandla, N.; Ramgopal, M.; Nagaraju, K.; Neha, M.; Oluwakemi, E.; Md-Shahidul, I. *Lett. Drug Des. Discov.* **2018**, *15*, 127-135; (c) Kerru, N.; Gummidi, L.; Parvesh, S.; Chunduri, V. R. *Heterocycl. Commun.* **2017**, *23*, 365-368.

[22] Kerru, N.; Venkata, H. S. S. B.; Ravada, K.; Suresh, M.; Parvesh, S.; Sreekantha, B. J. *Lett. Drug Des. Discov.* **2018**, *15*, 118-126; (b) Parvesh, S.; Nomandla, N.; Ramgopal, M.; Nagaraju, K.; Neha, M.; Oluwakemi, E.; Md-Shahidul, I. *Lett. Drug Des. Discov.* **2018**, *15*, 127-135; (c) Kerru, N.; Gummidi, L.; Parvesh, S.; Chunduri, V. R. *Heterocycl. Commun.* **2017**, *23*, 365-368.

Bhalla, A.; Venugopalan, P.; Bari, S. S. *Tetrahedron*, **2006**, *62*, 8291-8302.

[23] A. Bhalla P. Venugopalan S.S. Bari Tetrahedron 62 2006 8291 8302

(a) Lei, J.; Yong, L.; Jiaxi, X. *J. Am. Chem. Soc.* **2006**, *128*, 6060-6069; (b) Zhanhui, Y.; Jiaxi, X. *Tetrahedron*, **2015**, *71*, 2844-2852.

[24]

(a) J. Lei L. Yong X. Jiaxi J. Am. Chem. Soc. 128 2006 6060 6069

(b) Y. Zhanhui X. Jiaxi Tetrahedron 71 2015 2844 2852

(a) Bonan, L.; Yikai, W.; Da-Ming, D.; Jiaxi, X. *J. Org. Chem.* **2007**, *72*, 990-997; (b) Yikai, W.; Yong, L.; Lei, J.; Da-Ming, D.; Jiaxi, X. *J. Org. Chem.* **2006**, *71*, 6983-6990.

[25]

(a) L. Bonan W. Yikai D. Da-Ming X. Jiaxi J. Org. Chem. 72 2007 990 997

(b) W. Yikai L. Yong J. Lei D. Da-Ming X. Jiaxi J. Org. Chem. 71 2006 6983 6990

(a) Luh, T. Y.; Hu, Z. *Dalton Trans.* **2010**, *39*, 9185-9192; (b) Jung, M. E.; Piizzi, G. *Chem. Rev.* **2005**, *105*, 1735-1766.

[26]

(a) T.Y. Luh Z. Hu Dalton Trans. 39 2010 9185 9192

(b) M.E. Jung G. Piizzi Chem. Rev. 105 2005 1735 1766

(a) Hou, S.; Li, X.; Xu, *J. Sci. China. Chem.* **2013**, *56*, 370-379; (b) Luis, R.D.; Mar, R.; Jose, A. *RSC Adv.* **2015**, *5*, 37119-37129.

[27]

(a) S. Hou X. Li J. Xu Sci. China. Chem. 56 2013 370 379

(b) R.D. Luis R. Mar A. Jose RSC Adv. 5 2015 37119 37129

(a) Cremer, D.; Kraka, E. *Current Org. Chem.* **2010,** *14*, 1524-1560; (b) Ibeji, C. U.;

Lawal, M. M.; Tolufashe, G. F.; Govender, T.; Naicker, T.; Maguire, G. E.;

Honarparvar, B. *Chem. Phys. Chem. 2019*, *20*, 1126-1134.

[28]

(a) D. Cremer E. Kraka Current Org. Chem. 14 2010 1524 1560

(b) C.U. Ibeji M.M. Lawal G.F. Tolufashe T. Govender T. Naicker G.E. Maguire B.

Honarparvar Chem. Phys. Chem. 20 2019 1126 1134

Figure 1. *Cis*- and *trans*-*β*-lactams formation through conrotatory ring closure.

Figure 2. ORTEP diagram of the X-ray crystal structure of **3g** (CCDD Number: 1907796).

Figure 3. M06/6-31+G(d,p) Gibbs free energy profile (kcal mol^{-1}).

Figure 4. Optimized geometries of transition states for the [2+2] cycloaddition stepwise reaction mechanism of 4-methoxy and 4–nitro substituted *β*-lactam-isatin conjugates.

Scheme 1. Synthesis of isatin linked *β*-lactams 3a-q and 4a-q

Scheme 2. A plausible mechanism for the Staudinger [2+2] cycloaddition reaction.

Table 1. Effect of various solvents and bases for the synthesis of **3a**.[a]

fx2

Entry	Solvent	Base	Time (h)	*cis:trans*[b]	Yield **3a**[c] (%)
1	DMF	Et_3N	12	74:26	28
2	CH_2Cl_2	Et_3N	4	73:27	71
3	$CHCl_3$	Et_3N	4	82:18	31
4	EtOH	Et_3N	12	_	NR
5	*t*-BuOH	Et_3N	12	_	NR
6	THF	Et_3N	12	72:28	21
7	Acetonitrile	Et_3N	12	77:23	14
8	1,4-Dioxane	Et_3N	12	_	NR
9	CH_2Cl_2	DIPEA	4	69:31	14

10	CH_2Cl_2	Pyridine	4	76:24	32
11	CH_2Cl_2	CS_2CO_3	4	–	NR
12	CH_2Cl_2	NaOH	4	–	NR
13	CH_2Cl_2	NaH	4	–	NR
14	CH_2Cl_2	*t*-BuOK	4	–	NR
15	CH_2Cl_2	DBU	4	71:29	26
16	CH_2Cl_2	K_3PO_4	4	–	NR

[a] Reagents and conditions: imine (**1a**; 1 mmol), isatin acetic acid (**2**; 2 mmol), *p*-TsCl (2 mmol), base (4 mmol), solvent (15 mL)

[b] The major products are *cis*-isomers

[c] Isolated yield; (–): Not observed; NR: No Reaction.

Table 2. *Cis*- and *trans*-*β*-lactams **3a-q** and **4a-q**.

Entry	R	Yield[a] (%)	*cis:trans*[b]
1	H	71	3a:4a (73:27)
2	4-OCH_3	68	3b:4b (88:12)
3	4-CH_3	72	3c:4c (83:17)
4	4-Cl	69	3d:4d (79:21)
5	4-Br	73	3e:4e (83:17)
6	4-I	71	3f:4f (81:19)
7	4-F	78	3g:4g (93:7)
8	4-NO_2	66	3h:4h (14:86)
9	4-CF_3	76	3i:4i (16:84)
10	3-Cl	70	3j:4j (18:82)
11	3-Br	68	3k:4k (21:79)
12	3-CF_3	73	3l:4l (9:91)
13	3,4-di-Cl	72	3m:4m (13:87)
14	3-CH_3	64	3n:4n (77:23)
15	3-OCH_3	66	3o:4o (92:8)
16	3,4,5-OCH_3	63	3p:4p (83:17)
17	3-NO_2	74	3q:4q (79:21)

[a] Isolated yield after purification by column chromatography.

[b] Determined by ^{1}H NMR spectroscopy of the crude products.

Table 3. Calculated free energies (Δ*G* kcal/mol) by using M06 functional with different basis set.

	6-31+G(d,p)			augcc-pVDZ		
R	**TS1**	***cis***	***Tran***	**TS1**	***cis***	***Tran***

		TS-2	***s***		**TS-2**	***s***
			TS-3			**TS-3**
4-OCH_3	17.88	21.99	26.96	17.51	21.3	26.80
4-NO_2	18.01	26.96	19.00	16.26	26.50	18.69
3-OCH_3	15.04	18.01	25.96	14.92	17.88	25.66
3-NO_2	14.51	16.86	24.88	14.02	16.44	24.33

All energies are reported relative to REACT (kcal/mol)