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Syntheses of fused tetrahydro-β-carboline analogues through imide carbonyl activation using BBr_3: Evidence for the involvement of fused cyclic *N*-acyliminium ion intermediate

SELVARAJ MANGALARAJ, JAYARAMAN SELVAKUMAR, and CHINNASAMY RAMARAJ RAMANATHAN*

Department of Chemistry, Pondicherry University, Puducherry 605 014, India
e-mail: crrnath.che@pondiuni.edu.in

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Abstract. The fused cyclic *N*-acyliminium ion generated during the imide carbonyl activation reaction of phenethylphthalimide was confirmed by single crystal X-ray diffraction. The Lewis acid assisted imide carbonyl activation methodology was successfully extended to synthesize fused tetrahydro-β-carboline units from the corresponding *N*-indolylethylimides.

Keywords. Intramolecular cyclization; fused cyclic *N*-acyliminium ion; tetrahydro-β-carboline; BBr_3.

1. Introduction

Alkaloids possessing tetrahydro-β-carboline (THBC) framework exhibits a wide spectrum of biological activities.[1] Fused indole alkaloids such as pyrrolo-β-carbolines, indolo[*a*]quinolizine and isoindolo-β-carboline units were found in various alkaloids and therapeutic agents (figure 1).[1b]

These tetrahydro-β-carboline scaffolds are usually assembled through Bischler-Napieralski,[2] *N*-acyliminium ion,[3] RCM/isomerization/*N*-acyliminium ion cyclization,[4] Pictet-Spengler/Michael addition,[5] Pictet-Spengler/*N*-acyliminium ion cyclization,[6] radical coupling,[7] cascade gold catalysis,[8] aza Diels-Alder reaction,[9] dipolar cycloaddition[10] and intra-molecular Michael addition reaction.[11]

Due to the presence of structural diversity and complexity as well as the range of biological activity, the development of new synthetic methodology with a simple reagent or catalyst is always desirable for the fused tetrahydro-β-carboline skeleton. Our interest in the development of Lewis acid/Brønsted acid catalysis chemistry led us to develop the efficient protocol for the synthesis of tetrahydroisoquinoline, tetrahydro-β-carboline and related alkaloids as well as library of carbinols.[12] Previously, we have disclosed the first single step conversion of phenethylimides to corresponding tetrahydroisoquinoline scaffolds using boron tribromide and we have investigated the intermediate involved in this protocol using ^{1}H-NMR analysis.[12a] This study leads to the conclusion that the involvement of fused cyclic *N*-acyliminium ion as intermediate which are potential to accept various nucleophiles.[13] Though fused cyclic *N*-acyliminium ions were known for a decade in the literature, they have not been confirmed spectroscopically until recently.[14] Hence, we have initiated our effort to ascertain the structure of intermediate in Lewis acid assisted phenethylimide cyclization reaction and further extend the methodology to synthesize tetrahydro-β-carboline derivatives.

2. Experimental

2.1 *General Information*

Melting points reported in this work are uncorrected and were determined using EZ Melt, Stanford Research Systems, USA. Infrared spectra were recorded on Thermo Nicolet 6700 FT-IR Spectrophotometer using potassium bromide thin films and are reported in frequency of absorption (cm^{-1}). High resolution mass spectra (HRMS) were recorded on Q-TOF Micro mass spectrometer. ^{1}H and ^{13}C NMR were recorded on Brucker AVANCE 400 spectrometer. All the NMR spectra were recorded at room temperature in $CDCl_3$ or DMSO-d_6 using TMS as an internal standard. The chemical shifts are expressed in δ ppm down field from the signal of internal TMS. X-ray crystal data were collected on Oxford Diffraction Xcalibur diffractometer with Mo-Kα radiation ($\lambda = 0.71073$ Å). All the chemicals and reagents were purchased from Sigma Aldrich

*For correspondence

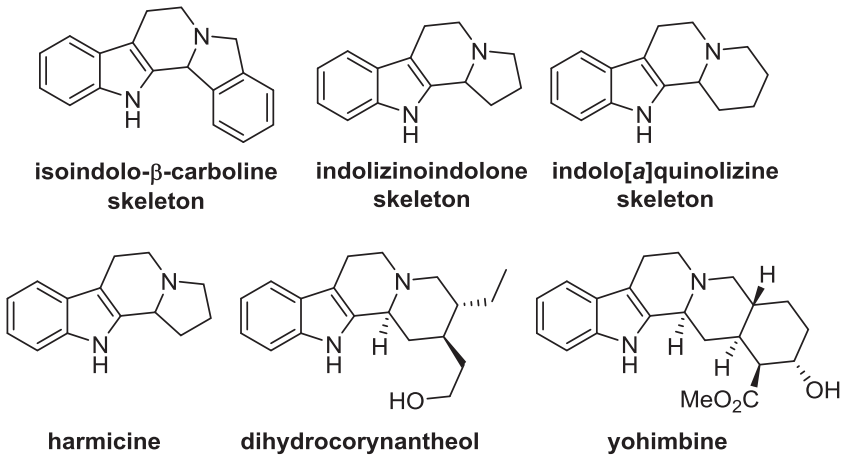


Figure 1. Condensed THBC - core containing alkaloids and drugs.

Chemicals and used without further purification. Column chromatography was performed using either silica gel 100–200 mesh (Merck, India) or neutral alumina (AVRA, India). TLC analyses were facilitated using $KMnO_4$ stain in addition to UV light with Merck 60 F254 pre-coated silica plates.

2.2 *General procedure for the preparation of indolylethylimide derivatives*[15]

Suspension of anhydride (18.725 mmol) in toluene in an oven dried round-bottom flask fitted with Dean-Stark set up was heated at reflux until complete dissolution of the anhydride and no additional water was removed. To this solution was added tryptamine (3.000 g, 18.725 mmol) and refluxing was continued until the water evolution was completed (12 h). Reaction mixture was concentrated under reduced pressure to give a residue which was purified through neutral alumina column chromatography using ethyl acetate:hexane as eluent (1:4).

2.2a *2-(2-(1H-Indol-3-yl)ethyl)isoindoline-1,3-dione (**3a**)*: 4.250 g, yellow solid, 78%, yield; M.p. 166–167°C (*Lit.*[15] 166–168°C); IR (KBr, cm^{-1}): 3383, 3044, 2942, 2858, 1767, 1703, 1233; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.05 (br s, 1H), 7.83 (dd, J = 5.4, 3.0 Hz, 2H), 7.74 (dt, J = 8.0, 0.8 Hz, 1H), 7.70 (dd, J = 5.4, 3.0 Hz, 2H), 7.34 (dt, J = 7.6, 0.8 Hz, 1H), 7.19 (td, J = 7.6, 1.2 Hz, 1H), 7.13 (td, J = 8.0, 1.2 Hz, 1H), 7.08 (d, J = 2.4 Hz, 1H), 4.04–3.99 (m, 2H), 3.19–3.15 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): 168.51, 136.37, 134.00, 132.34, 127.55, 123.31, 122.27, 122.14, 119.66, 119.01, 112.59, 111.24, 38.66, 24.60.

2.2b *1-(2-(1H-Indol-3-yl)ethyl)pyrrolidine-2,5-dione (**3b**)*: 3.211 g, tan solid, 71% yield; M.p. 166–167°C (*Lit.*[16] 163–166°C); IR (KBr, cm^{-1}): 3265, 3052, 2925, 1764, 1694, 1401, 1339; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.04 (br s, 1H), 7.66 (d, J = 8.0 Hz, 1H), 7.34 (d, J = 8.0 Hz, 1H), 7.19 (t, J = 7.6 Hz, 1H), 7.13 (t, J = 7.6 Hz, 1H), 7.08 (d, J = 1.9 Hz, 1H), 3.83 (t, J = 7.6 Hz, 2H), 3.06 (t, J = 7.6 Hz, 2H), 2.61 (s, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): 177.38, 136.29, 127.64, 122.27, 122.23, 119.67, 118.77, 112.41, 111.30, 39.65, 28.29, 23.45.

2.2c *1-(2-(1H-Indol-3-yl)ethyl)piperdine-2,6-dione (**3d**)*: [6e]3.215 g, tan solid, 67% yield; M.p. 174–175°C, IR (KBr, cm^{-1}): 3333, 2971, 2958, 1718, 1665, 1456, 1354; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.02 (br s, 1H), 7.77 (d, J = 7.6 Hz, 1H), 7.34 (d, J = 8.0 Hz, 1H), 7.20–7.12 (m, 2H), 7.06 (d, J = 1.7 Hz, 1H), 4.07 (t, J = 8.0 Hz, 2H), 2.98 (t, J = 8.0 Hz, 2H), 2.61 (t, J = 6.4 Hz, 4H), 1.87 (p, J = 6.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): 172.67, 136.27, 127.78, 122.25, 122.13, 119.56, 119.25, 113.06, 111.17, 40.45, 32.99, 23.84, 17.26.

2.2d *2-(2-(1H-Indol-3-yl)ethyl)hexahydro-1H-isoindole-1,3(2H)-dione (**3e**)*: 3.496 g, pale orange solid, 63% yield; M.p. 145–146°C; IR (KBr, cm^{-1}): 3364, 2944, 2860, 1766, 1694, 1401, 1341; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.02 (br s, 1H), 7.69 (d, J = 7.6 Hz, 1H), 7.34 (d, J = 8.0 Hz, 1H), 7.18 (t, J = 7.2 Hz, 1H), 7.15–7.11 (m, 1H), 7.07 (d, J = 1.8 Hz, 1H), 3.82 (t, J = 7.6 Hz, 2H), 3.07 (t, J = 7.6 Hz, 2H), 2.78–2.72 (m, 2H), 1.79–1.77 (m, 2H), 1.64–1.61 (m, 2H), 1.42–1.31 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): 179.98, 136.25, 127.63, 122.28, 122.13, 119.55, 118.93, 112.17, 111.21, 39.73, 39.12, 23.69, 23.37, 21.62.

2.3 *General procedure for the preparation of substituted indolyl-ethylimide derivatives*[17,12d]

A mixture of hydrazine hydrochloride (1 mmol) and masked aldehyde (1 mmol) in 100 mL of 4% H_2SO_4 was heated at reflux for 12 h. The reaction mixture was cooled to room temperature and treated with aqueous $NaHCO_3$. The tryptamine product was extracted with CH_2Cl_2 (4 x 50 mL). The combined organic layer was dried over anhydrous Na_2SO_4, filtered and the solvent was evaporated under reduced pressure. The residue was purified through neutral alumina column chromatography using ethyl acetate:hexane (1:4) as eluent to give indolyl imides **3c, 3f–k** as solid.

2.3a *1-(2-(5,7-Dimethyl-1H-indol-3-yl)ethyl)pyrrolidine-2,5-dione (**3c**)*: [12d] 148 mg, pale yellow solid, 55% yield; M.p. 192–193°C; IR (KBr, cm^{-1}): 3348, 3125, 2860, 1769, 1691, 1405, 1264; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.84 (br s, 1H), 7.28 (s, 1H), 7.05 (d, J = 2.2 Hz, 1H), 6.83 (s, 1H), 3.83–3.79 (m, 2H), 3.03–3.00 (m, 2H), 2.62 (s, 4H), 2.43 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) : 177.26, 134.09, 128.98, 127.27, 124.42, 121.95, 119.97, 115.88, 112.25, 39.58, 28.15, 23.47, 21.45, 16.51.

2.3b *2-(2-(7-Methyl-1H-indol-3-yl)ethyl)hexahydro-1H-isoindole-1,3(2H)-dione (**3f**)*: 164 mg, orange solid, 53% yield; M.p. 190–191°C; FT-IR (KBr, cm^{-1}): 3373, 2943, 2856, 1765, 1699, 1444, 1399, 1340; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.94 (br, s, 1H), 7.54 (d, J = 7.6 Hz, 1H), 7.09–7.08 (m, 1H), 7.07–7.04 (m, 1H), 7.00–6.98 (m, 1H), 3.83-3.80 (m, 2H), 3.07–3.03 (m, 2H), 2.79–2.73 (m, 2H), 2.47 (s, 3H), 1.84–1.77 (m, 2H), 1.67–1.61 (m, 2H), 1.46–1.39 (m, 2H), 1.37–1.29 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 179.97, 135.87, 127.20, 122.77, 121.95, 120.35, 119.89, 116.77, 112.87, 39.79, 39.17, 23.77, 23.60, 21.70, 16.71. HRMS (ESI): $[M+H]^+$ Found 311.1752 and calculated 311.1681 for $C_{19}H_{23}N_2O_2$.

2.3c *2-(2-(5,7-Dimethyl-1H-indol-3-yl)ethyl)hexahydro-1H-isoindole-1,3(2H)-dione (**3g**)*: 182 mg, pale orange solid, 56% yield; M.p. 130–131°C; FT-IR (KBr, cm^{-1}): 3357, 2929, 2857, 1769, 1699, 1403, 1261; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.84 (br s, 1H), 7.32 (s, 1H), 7.04 (d, J = 2.3 Hz, 1H), 6.83 (s, 1H), 3.82-3.78 (m, 2H), 3.04-3.00 (m, 2H), 2.78–2.76 (m, 2H), 2.43 (s, 6H), 1.84–1.78 (m, 2H), 1.68-1.62 (m, 2H), 1.45–1.32 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 179.97, 134.23, 129.15, 127.48, 124.57, 122.09, 120.01, 116.31, 112.43, 39.82, 39.25, 23.78, 23.62, 21.71, 21.59, 16.65. HRMS (ESI): $[M+H]^+$ Found 325.1910 and calculated 325.1838 for $C_{20}H_{24}N_2O_2$.

2.3d *2-(2-(5-Fluoro-1H-indol-3-yl)ethyl)hexahydro-1H-isoindole-1,3(2H)-dione (**3h**)*: 264 mg, colourless solid, 84% yield; M.p. 156–157°C; FT-IR (KBr, cm^{-1}): 3367, 2943, 2860, 1766, 1693, 1489, 1406, 1265, 1164, 800; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.05 (br s, 1H), 7.31 (dd, J = 9.6, 2.4 Hz, 1H), 7.24 (t, J = 4.4 Hz, 1H), 7.11 (d, J = 2.4 Hz, 1H), 6.92 (td, J = 8.8, 2.4 Hz, 1H), 3.81-3.78 (m, 2H), 3.01 (td, J = 7.6, 0.4 Hz, 2H), 2.78-2.75 (m, 2H), 1.81-1.76 (m, 2H), 1.64-1.60 (m, 2H), 1.43-1.37 (m, 2H), 1.35-1.25 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 179.93, 158.00 (d, J = 234.0 Hz, 1C), 132.73, 128.14 (d, J = 9.0 Hz, 1C), 124.05, 112.61 (d, J = 4.0 Hz, 1C), 111.84 (d, J = 9.0 Hz, 1C), 110.66 (d, J = 27.0 Hz, 1C), 103.95 (d, J = 23.0 Hz, 1C), 39.79, 38.95, 23.75, 23.31, 21.68. HRMS (ESI): $[M+H]^+$ Found 315.1496 and calculated 315.1431 for $C_{18}H_{20}FN_2O_2$.

2.3e *2-(2-(5-Chloro-1H-indol-3-yl)ethyl)hexahydro-1H-isoindole-1,3(2H)-dione (**3i**)*: 258 mg, pale yellow solid, 78% yield; M.p. 150–151°C; FT-IR (KBr, cm^{-1}): 3363, 2947, 2864, 1764, 1687, 1406, 1348; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.06 (br s, 1H), 7.61 (d, J = 2.0 Hz, 1H), 7.25 (d, J = 8.4 Hz, 1H), 7.14 (dd, J = 8.4, 2.0 Hz, 2H), 7.10–7.00 (m, 1H), 3.79 (t, J = 7.6 Hz, 2H), 3.02 (td, J = 7.6, 0.8 Hz, 2H), 2.79–2.73 (m, 2H), 1.83-1.76 (m, 2H), 1.64–1.61 (m, 2H), 1.45–1.36 (m, 2H), 1.35–1.25 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 179.94, 134.56, 128.86, 125.48, 123.65, 122.59, 118.49, 112.30, 112.25, 39.77, 39.05, 23.73, 23.19, 21.67. HRMS (ESI): $[M+H]^+$ Found 331.1203 and calculated 331.1135 for $C_{18}H_{20}ClN_2O_2$.

2.3f *2-(2-(5-Bromo-1H-indol-3-yl)ethyl)hexahydro-1H-isoindole-1,3(2H)-dione (**3j**)*: 255 mg, pale yellow solid, 68% yield; M.p. 147–148°C; FT-IR (KBr, cm^{-1}): 3336, 2934, 2858, 1773, 1691, 1344, 603; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.08 (br s, 1H), 7.76 (d, J = 1.6 Hz, 1H), 7.24 (d, J = 1.6 Hz, 1H), 7.22–7.19 (m, 1H), 7.07 (d, J = 2.4 Hz, 1H), 3.79 (t, J = 3.6 Hz, 2H), 3.04–3.00 (m, 2H), 2.79–2.72 (m, 2H), 1.81–1.76 (m, 2H), 1.64–1.60 (m, 2H), 1.45–1.38 (m, 2H), 1.35–1.29 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 179.94, 134.84, 129.53, 125.13, 123.49, 121.58, 112.98, 112.69, 112.25, 39.77, 39.07, 23.73, 23.17, 21.66. HRMS (ESI): $[M+H]^+$ Found 375.0691 and calculated 375.0630 for $C_{18}H_{20}BrN_2O_2$.

2.3g *2-(2-(7-Fluoro-1H-indol-3-yl)ethyl)hexahydro-1H-isoindole-1,3(2H)-dione (**3k**)*: 192 mg, pale yellow solid, 61% yield; M.p. 192–193°C; FT-IR (KBr, cm^{-1}): 3352, 2947, 2860, 1769, 1704, 1432, 1341, 782; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.22 (br, s, 1H), 7.44 (d, J = 7.6 Hz, 1H), 7.10 (d, J = 2.4 Hz, 1H), 7.03 (td, J = 8.0, 4.8 Hz, 1H), 6.89 (dd, J = 11.2, 8.0 Hz, 1H), 3.83–3.79 (m, 2H), 3.07–3.04 (m, 2H), 2.79–2.73 (m, 2H), 1.81–1.77 (m, 2H), 1.63–1.61 (m, 2H), 1.45–1.36 (m, 2H), 1.35–1.29 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 179.96, 149.69 (d, J = 242.0 Hz, 1C), 131.43 (d, J = 5.0 Hz, 1C), 124.59 (d, J = 14.0 Hz, 1C), 122.97, 119.91 (d, J = 6.0 Hz, 1C), 114.81 (d, J = 3.0 Hz, 1C), 113.22 (d, J = 2.0 Hz, 1C), 107.06 (d, J = 16.0 Hz, 1C), 39.78, 38.98, 23.75, 23.40, 21.68. HRMS (ESI): $[M+H]^+$ Found 315.1496 and calculated 315.1435 for $C_{18}H_{20}FN_2O_2$.

2.4 *General procedure for BBr_3 mediated cyclization followed by $NaBH_4$/ MeOH reduction*

A 50 mL two-neck round-bottom flask was charged with **3a–k** (0.2 mmol, 1 equiv), 4Å molecular sieves (50 mg), anhydrous CH_2Cl_2 (10 mL) and a stir bar. The flask was capped with a rubber septum and maintained in nitrogen atmosphere. Boron tribromide (1 mL, 5 equiv or 2 mL, 10 equiv) was added and stirred at room temperature for given time. To this reaction mixture was added $NaBH_4$ (5 equiv), methanol (3 mL) and stirred for 30 min under nitrogen atmosphere. Then the reaction mixture was quenched with aqueous $NaHCO_3$. Organic layer was separated and aqueous layer was extracted with ethyl acetate (3 × 50 mL). The combined organic layer was washed with aqueous $NaHCO_3$, dried over anhydrous Na_2SO_4 and filtered. The solvent was removed under reduced pressure. The crude mixture was purified through neutral alumina column chromatography using ethyl acetate:hexane (4:1) as eluent. For the substrate **3a** $NaBH_4$/TFA was used as a reducing mixture.

2.4a *7,8,13,13b-Tetrahydro-5H-benzo[1,2]indolizino[8,7-b]indol-5-one (**4a**)*: 38 mg, 69% yield, pale yellow solid; M.p. 215–216°C (*Lit.*[16] 212–214°C); IR (KBr, cm^{-1}): 3225, 2932, 2841, 1670, 1461; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.33 (s, 1H), 7.91 (d, J = 7.6 Hz, 1H), 7.81 (dd, J = 7.6, 1.0 Hz, 1H), 7.62 (td, J = 7.6, 1.0 Hz, 1H), 7.52–7.47 (m, 2H), 7.37 (d, J = 8.1 Hz, 1H), 7.22 – 7.16 (m, 1H), 7.11 (td, J = 7.6, 1.0 Hz, 1H), 5.83 (s, 1H), 4.87 (ddd, J = 13.0, 6.0, 0.7 Hz, 1H), 3.41 (ddd, J = 13.0, 11.0, 5.1 Hz, 1H), 2.98 (dddd, J = 13.8, 11.0, 6.1, 2.5 Hz, 1H), 2.92 – 2.84 (m, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$): 168.15, 142.88, 136.55, 132.56, 132.02, 128.90, 126.79, 124.51, 122.63, 122.10, 120.09, 118.69, 111.07, 109.52, 57.02, 38.18, 21.66.

2.4b *5,6,11,11b-Tetrahydro-1H-indolizino[8,7-b]indol-3(2H)-one (**4b**)*: 38 mg, 84% yield, off white solid; M.p. 251–252°C (*Lit.*[18] 250°C); IR (KBr, cm^{-1}): 3253, 2978, 2848, 1664, 1454, 1311; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.02 (br s, 1H), 7.50 (d, J = 8.0 Hz, 1H), 7.34 (dt, J = 8.0, 0.8 Hz, 1H), 7.23–7.16 (m, 1H), 7.16–7.09 (m, 1H), 4.94 (td, J = 6.9, 2.0 Hz, 1H), 4.54 (ddd, J = 12.9, 5.2, 1.8 Hz, 1H), 3.04 (dddd, J = 12.9, 10.4, 6.0, 1.0 Hz, 1H), 2.89–2.82 (m, 2H), 2.63–2.5 (m, 3H), 2.01–1.89 (m, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$): 176.36, 136.41, 133.30, 126.96, 122.41, 120.05, 118.60, 111.12, 108.49, 54.41, 37.75, 31.78, 25.85, 21.18.

2.4c *8,10-Dimethyl-5,6,11,11b-tetrahydro-1H-indolizino[8,7-b]indol-3(2H)-one (**4c**)*: 42 mg, 82% yield, pale blue solid. M.p. 252–253°C; IR (KBr, cm^{-1}): 3263, 2916, 2851, 1665, 1436, 1366, 1267; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.72 (br, s, 1H), 7.13 (s, 1H), 6.84 (s, 1H), 4.95–4.92 (m, 1H), 4.54–4.50 (m, 1H), 3.02 (td, J = 11.2, 6.0 Hz, 1H), 2.84 (dd, J = 15.6, 5.6 Hz, 1H), 2.80–2.75 (m, 1H), 2.67–2.48 (m, 3H), 2.45 (s, 3H), 2.42 (s, 3H), 2.02-1.91 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): 173.33, 134.20, 133.13, 129.67, 126.79, 124.78, 119.93, 116.00, 108.67, 54.49, 37.78, 31.81, 25.99, 21.51, 21.29, 16.77; HRMS (ESI) : $[M+H]^+$ Found 255.1509; Calculated 255.1497; for $C_{16}H_{19}N_2O$.

2.4d *1,2,3,6,7,12b-Hexahydroindolo[2,3-a]quinolizin-4(12H)-one (**4d**)*: 30 mg, 62% yield, off white solid; M.p.: 239–240°C, (*Lit.*[19] 240–241°C); IR (KBr, cm^{-1}): 3265, 3052, 1596, 1434, 1262; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.85 (s, 1H), 7.51 (d, J = 7.6 Hz, 1H), 7.34 (d, J = 8.0 Hz, 1H), 7.21–7.16 (m, 1H), 7.15–7.09 (m, 1H), 5.20–5.13 (m, 1H), 4.84–4.75 (m, 1H), 2.90–2.72 (m, 3H), 2.61–2.57 (m, 1H), 2.41 (m, 2H), 1.96–1.95 (m, 1H), 1.88–1.73 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): 169.24, 136.23, 133.32, 126.90, 122.15, 119.83, 118.41, 110.94, 109.59, 54.40, 40.16, 32.44, 29.07, 21.01, 19.40.

2.4e *2,3,4,4a,7,8,13b,13c-Octahydro-1H-benzo[1,2]indolizino[8,7-b]indol-5(13H)-one (**4e**)*: 41 mg, 73% yield, pale yellow solid. M.p. 248–249°C; IR (KBr, cm^{-1}): 3294, 2928, 2846, 1668, 1429, 1346, 1273; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.00 (br s, 1H), 7.51 (d, J = 7.6 Hz, 1H), 7.34 (d, J = 8.0 Hz, 1H), 7.18

(td, J = 6.8, 1.2 Hz, 1H), 7.15-7.11 (m, 1H), 4.86 (d, J = 5.2 Hz, 1H), 4.54 (dd, J = 12.8, 5.2 Hz, 1H), 3.01-2.75 (m, 4H), 2.69–2.62 (m, 1H), 2.34–2.31 (m, 1H), 1.58–1.46 (m, 3H), 1.29–1.25 (m, 1H), 1.17–1.01 (m, 2H), 0.83–0.73 (m, 1H); ^{13}C-NMR (100 MHz, DMSO-d_6): 172.46, 136.25, 131.13, 126.44, 120.88, 118.46, 117.69, 111.00, 107.78, 55.59, 41.90, 37.03, 36.64, 23.42, 23.29, 22.58, 22.46, 20.80; HRMS (ESI) (m/z) : $[M+H]^+$ Found 281.1652; Calculated 281.1654; for $C_{18}H_{21}N_2O$.

2.4f *12-Methyl-2,3,4,4a,7,8,13b,13c-octahydro-1H-benzo[1,2]indolizino[8,7-b]indol-5(13H)-one (**4f**)*: 50 mg, 86% yield, pale yellow solid; M.p. 220–221°C; FT-IR (KBr, cm^{-1}): 3287, 2928, 2852, 1673, 1434, 1302, 1271; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.96 (s, 1H), 7.36 (d, J = 8.0 Hz, 1H), 7.07-7.03 (m, 1H), 7.00 (d, J = 7.2 Hz, 1H), 4.88 (d, J = 4.9 Hz, 1H), 4.54 (dd, J = 12.8, 4.8 Hz, 1H), 3.01–2.92 (m, 1H), 2.90–2.75 (m, 3H), 2.71–2.64 (m, 1H), 2.50 (s, 3H), 2.34–2.30 (m, 1H), 1.57–1.46 (m, 4H), 1.31–1.00 (m, 2H), 0.83–0.73 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.77, 135.93, 129.76, 126.41, 122.80, 120.06, 120.00, 116.02, 110.80, 56.42, 43.00, 38.12, 37.35, 29.69, 23.71, 23.04, 22.63, 21.21, 16.72; HRMS-ESI (m/z): $[M+H]^+$ Found 295.1809 and calculated 295.1810 for $C_{19}H_{23}N_2O$.

2.4g *10,12-Dimethyl-2,3,4,4a,7,8,13b,13c-octahydro-1H-benzo[1,2]indolizino[8,7-b]indol-5(13H)-one (**4g**)*: 50 mg, 81% yield, pale yellow solid; M.p. 236–237°C; FT-IR (KBr, cm^{-1}): 3251, 2937, 2846, 1668, 1430, 1365, 1269; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.68 (s, 1H), 7.15 (s, 1H), 6.84 (s, 1H), 4.86 (d, J = 4.8 Hz, 1H), 4.55–4.45 (m, 1H), 2.99–2.91 (m, 1H), 2.83–2.74 (m, 3H), 2.69–2.61 (m, 1H), 2.45 (s, 3H), 2.42 (s, 3H), 2.33-2.30 (m, 1H), 1.54–1.45 (m, 3H), 1.27–1.23 (m, 1H), 1.16–1.01 (m, 2H), 0.82–0.72 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.85, 134.35, 130.07, 129.53, 126.81, 124.61, 119.86, 115.83, 110.51, 56.56, 43.14, 38.32, 37.48, 23.86, 23.80, 23.20, 22.78, 21.48, 21.36, 16.80; HRMS-ESI (m/z): $[M+H]^+$ Found 309.1967 and calculated 309.1967 for $C_{20}H_{25}N_2O$.

2.4h *10-Fluoro-2,3,4,4a,7,8,13b,13c-octahydro-1H-benzo[1,2]indolizino[8,7-b]indol-5(13H)-one (**4h**)*: 45 mg, 76% yield, pale yellow; M.p. 263–264°C; FT-IR (KBr, cm^{-1}): 3281, 2942, 2846, 1673, 1450, 1426, 1320, 1251, 1225, 847; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.88 (s, 1H), 7.34-7.25 (m, 1H), 7.14 (dd, J = 9.0, 2.4 Hz, 1H), 6.92 (td, J = 9.0, 2.4 Hz, 1H), 4.85 (d, J = 4.8 Hz, 1H), 4.54 (ddd, J = 12.8, 5.6, 1.2 Hz, 1H), 3.00–2.93 (m, 1H), 2.81–2.74 (m, 3H), 2.67–2.60 (m, 1H), 2.32 (d, J = 14.4 Hz, 1H), 1.54–1.45 (m, 3H), 1.27–1.23 (m, 1H), 1.27–1.04 (m, 2H), 0.82–0.72 (m, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 172.65, 156.87 (d, J = 230.0 Hz, 1C), 133.44, 132.94, 126.76 (d, J = 10.0 Hz, 1C), 111.90 (d, J = 10.0 Hz, 1C), 108.79 (d, J = 26.0 Hz, 1C), 108.28 (d, J = 5.0 Hz, 1C), 102.73 (d, J = 23.0 Hz, 1C), 55.68, 41.98, 37.06, 36.67, 23.49, 23.33, 22.61, 22.50, 20.82; HRMS-ESI (m/z): $[M+H]^+$ Found 299.1599 and calculated 299.1560 for $C_{18}H_{20}FN_2O$.

2.4i *10-Chloro-2,3,4,4a,7,8,13b,13c-octahydro-1H-benzo[1,2]indolizino[8,7-b]indol-5(13H)-one (**4i**)*: 47 mg, 74% yield, brown solid; M.p. 250–251°C; FT-IR (KBr, cm^{-1}): 3254, 2932, 2848, 1668, 1428, 1268, 671; ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.24 (br s, 1H), 7.45 (d, J = 2.0 Hz, 1H), 7.33 (dd, J = 8.4, 0.4 Hz, 1H), 7.04 (dd, J = 8.8, 2.4 Hz, 1H), 4.86 (d, J = 4.4Hz, 1H), 4.27 (dd, J = 12.8, 5.6 Hz, 1H), 2.90 (td, J = 12.8, 4.4 Hz, 1H), 2.80 (dd, J = 15.2, 4.4 Hz, 1H), 2.72–2.65 (m, 2H), 2.61–2.53 (m, 1H), 2.08–2.04 (m, 1H), 1.48–1.40 (m, 3H), 1.17–1.11 (m, 1H), 1.07–0.97 (m, 1H), 0.93–0.85 (m, 1H), 0.59–0.49 (m, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 172.40, 134.67, 133.13, 127.59, 123.17, 120.69, 117.07, 112.44, 107.84, 55.48, 41.84, 36.94, 36.48, 23.37, 23.24, 22.51, 22.40, 20.63; HRMS-ESI (m/z): $[M+H]^+$ Found 315.1263 and calculated 315.1264 for $C_{18}H_{20}ClN_2O$.

2.4j *10-Bromo-2,3,4,4a,7,8,13b,13c-octahydro-1H-benzo[1,2]indolizino[8,7-b]indol-5(13H)-one (**4j**)*: 55 mg, 77% yield, yellow solid; M.p. 253–254°C; FT-IR (KBr, cm^{-1}): 3249, 2929, 2847, 1668, 1429, 1310, 1228, 796; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.60 (s, 1H), 7.62 (d, J = 2.0 Hz, 1H), 7.261–7.19 (m, 2H), 4.84 (d, J = 4.8 Hz, 1H), 4.55 (dd, J = 4.8, 9.2 Hz, 1H), 3.00–2.93 (m, 1H), 2.86–2.72 (m, 3H), 2.70–2.65 (m, 1H), 2.32–2.29 (m, 1H), 1.54–1.46 (m, 3H), 1.28–1.25 (m, 1H), 1.11–1.00 (m, 2H), 0.80–0.70 (m, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 172.44, 134.93, 132.97, 128.30, 123.27, 120.11, 112.97, 111.09, 107.78, 55.47, 41.86, 36.96, 36.50, 23.39, 23.26, 22.53, 22.42, 20.63; HRMS-ESI (m/z): $[M+H]^+$ Found 359.0760 and calculated 359.0759 for $C_{18}H_{20}BrN_2O$.

2.4k *12-Fluoro-2,3,4,4a,7,8,13b,13c-octahydro-1H-benzo[1,2]indolizino[8,7-b]indol-5(13H)-one (**4k**)*: 43 mg, 72% yield, pale yellow solid; M.p. 280–281°C; FT-IR (KBr, cm^{-1}): 3260, 2939, 2845, 1668, 1427, 1347,

1222, 732; ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.47 (br, s, 1H), 7.23 (d, $J = 7.6$Hz, 1H), 6.97–6.93 (m, 1H), 6.92–6.87 (m, 1H), 4.86 (d, $J = 3.2$ Hz, 1H), 4.29 (dd, $J = 12.4$, 5.6 Hz, 1H), 2.91 (td, $J = 12.4$, 4.0 Hz, 1H), 2.82 (dd, $J = 15.2$, 4.0 Hz, 1H), 2.78–2.73 (m, 2H), 2.64–2.56 (m, 1H), 2.08–2.05 (m, 1H), 1.47–1.43 (m, 3H), 1.18–1.15 (m, 1H), 1.08–0.98 (m, 1H), 0.93–0.83 (m, 1H), 0.60–0.50 (m, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 172.49, 149.27 (d, $J = 289.0$ Hz, 1C), 132.50, 130.43, 123.72 (d, $J = 12.0$ Hz, 1C), 118.90, 113.99, 108.97, 105.96 (d, $J = 17.0$ Hz, 1C), 55.58, 41.83, 36.92, 36.50, 23.41, 23.28, 22.55, 22.44, 20.91; HRMS-ESI (m/z): $[M+Na]^+$ Found 321.1378 and calculated 321.1379 for $C_{18}H_{19}FN_2ONa$.

3. Results and Discussion

3.1 *Structural characterization of the intermediate*

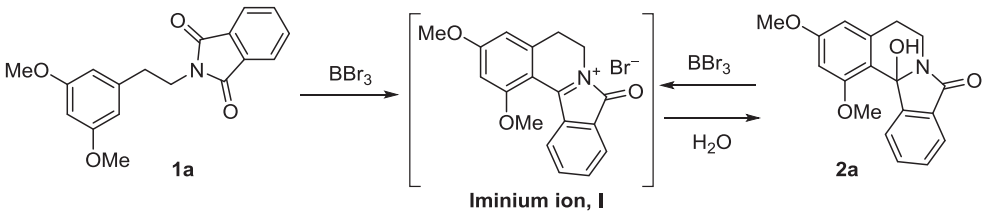
The reaction of appropriately substituted phenethylphthalimide **1a** in presence of BBr_3 successfully delivered a dark red coloured cyclic compound which after quenching with water furnished the isoindoloisoquinolinone derivative **2a**. The observation of dark red coloured reaction mixture in this reaction indicates the formation of highly conjugated system as an intermediate.[20] This was conveniently proved by analyzing the ^{1}H NMR of the mixture of imide **1a** and BBr_3 as well as the mixture of cyclized compound **2a** and BBr_3 which were found super imposable with each other. Hence, we speculated that the involvement of fused cyclic *N*-acyliminium ion **I** as an intermediate. The ^{1}H NMR study showed that the cyclized product **2a** and starting material **1a** on treatment with BBr_3 afforded the same compound, the fused cyclic *N*-acyliminium ion **I**, which on quenching with water furnished the hydroxy lactam **2a**. To further ascertain and prove the ^{1}H NMR spectroscopic evidence for the involvement of fused cyclic *N*-acyliminium ion, we have initiated our effort to get the single crystal suitable for structural analysis (scheme 1).

Hence, the $CDCl_3$ solutions of **1a**+BBr_3 and **2a**+BBr_3 in two NMR tubes were left aside for slow evaporation of the solvent hoping to get a single crystal of the intermediate. Fortunately, the $CDCl_3$ solution of **2a**+BBr_3 furnished the cubic orange red colour crystals suitable for crystal structure analysis. The presence of fused cyclic *N*-acyliminium ion as an intermediate along with counter anion Br_3^- was obtained by X-ray crystallographic analysis (figure 2). Since, the mixture **2a**+BBr_3 had been stored for long period of time, the decomposition of excess BBr_3 might have produced Br_2. The reaction of Br_2 with Br^- might have generated Br_3^- as counter anion along with the fused cyclic *N*-acyliminium ion.

3.2 *Synthesis of fused tetrahydro-β-carboline derivatives*

The successful intramolecular electrophilic substitution between aryl nucleophile and activated carbonyl electrophile leads to the condensed heterocyclic lactams from phenethylimides as well as indolyl ethyl imides.[12] This encouraged us to extend the Lewis acid BBr_3 assisted intramolecular cyclization methodology to other nucleophiles such as heteroarenes, which are, eventually useful precursor to synthesize fused heteroarene polycyclic lactams. Indole, a heteroarene motif present in various physiologically active molecules possesses the tendency to react with electrophiles very fast due to its electron rich nature.[21] Hence, to increase the scope of this cyclization methodology, the indole nucleophile was chosen to replace the phenyl nucleophile. To explore the reactivity of indole moiety under this cyclization condition (using BBr_3) various substituted and unsubstituted indolylethylimides imides are prepared. The unsubstituted indolylethylimides are prepared by simple condensation reaction of tryptamine with corresponding anhydrides (figure 3).[12d]

The required substituted indolylethylimides are conveniently prepared in four simple steps adopting the methodology developed in this laboratory.[12d,17] This involves the condensation of anhydride with 4-aminobutanol followed by Swern oxidation of primary alcohol to aldehyde. The aldehyde was protected *in situ* using 1,3-propanediol in presence of catalytic amount



Scheme 1. Generation of fused cyclic *N*-acyliminium ion.

of *p*-toluenesulphonic acid. Finally, the imide derivatives of tryptamine were successfully arrived at through the Fischer indole synthesis protocol from protected aldehyde and substituted phenylhydrazine hydrochloride in good yields (table 1). Imide **4c** is prepared by following our earlier reported procedure from succinic anhydride and dimethylpheneylhydrazine hydrochloride (table 1).[12d]

Indolylethylphthalimide similar to phenethylphthalimide is expected to deliver fused cyclic *N*-acyliminium ion under established cyclization condition with BBr_3. Accordingly, the phthalimide derivative of tryptamine **3a** was treated with BBr_3 in dichloromethane at 0°C to room temperature and that delivered the fused cyclic *N*-acyl iminium ion. *In situ* reduction of iminium ion intermediate, instead of quenching with water, using $NaBH_4$/TFA mixture was carried out to avoid the formation of hydroxyl lactam. This cyclization and reduction sequence successfully furnished the condensed pentacyclic tetrahydro-β-carboline **4a** in 69% yield. Success of this experiment prompted us to examine the other substituted indolylethylimide derivatives. As expected all the imides under one-pot cyclization and reduction sequence delivered the cyclized products in good yields. For complete conversion of imides to fused cyclic iminium ion, the unsubstituted and methyl substituted indolylethylimides required 12 h at room temperature in presence of BBr_3 (5 equiv) (table 2). On the other hand, substituted indolylethylimides **4e–4k** required 24 h

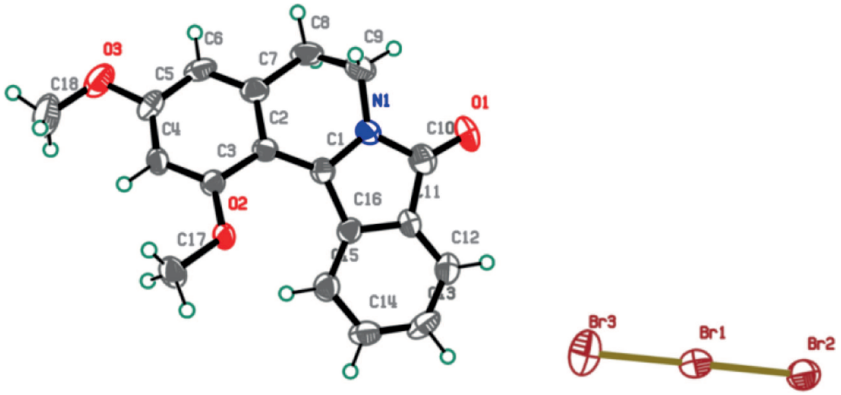


Figure 2. ORTEP diagram of the fused cyclic *N*-acyliminium ion with 50% probability level.

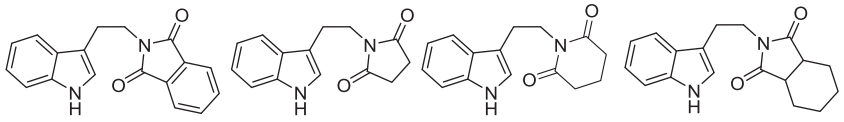


Figure 3. Unsubstitued indolylethylimides prepared to synthesize THBC's.

Table 1. Preparation of substituted 2-(3-indolyl)ethylimides.

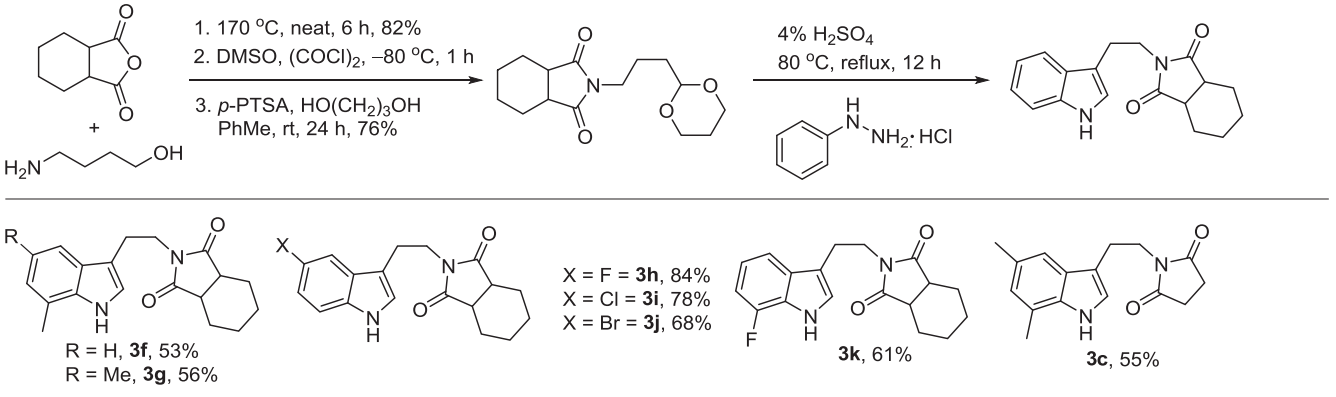
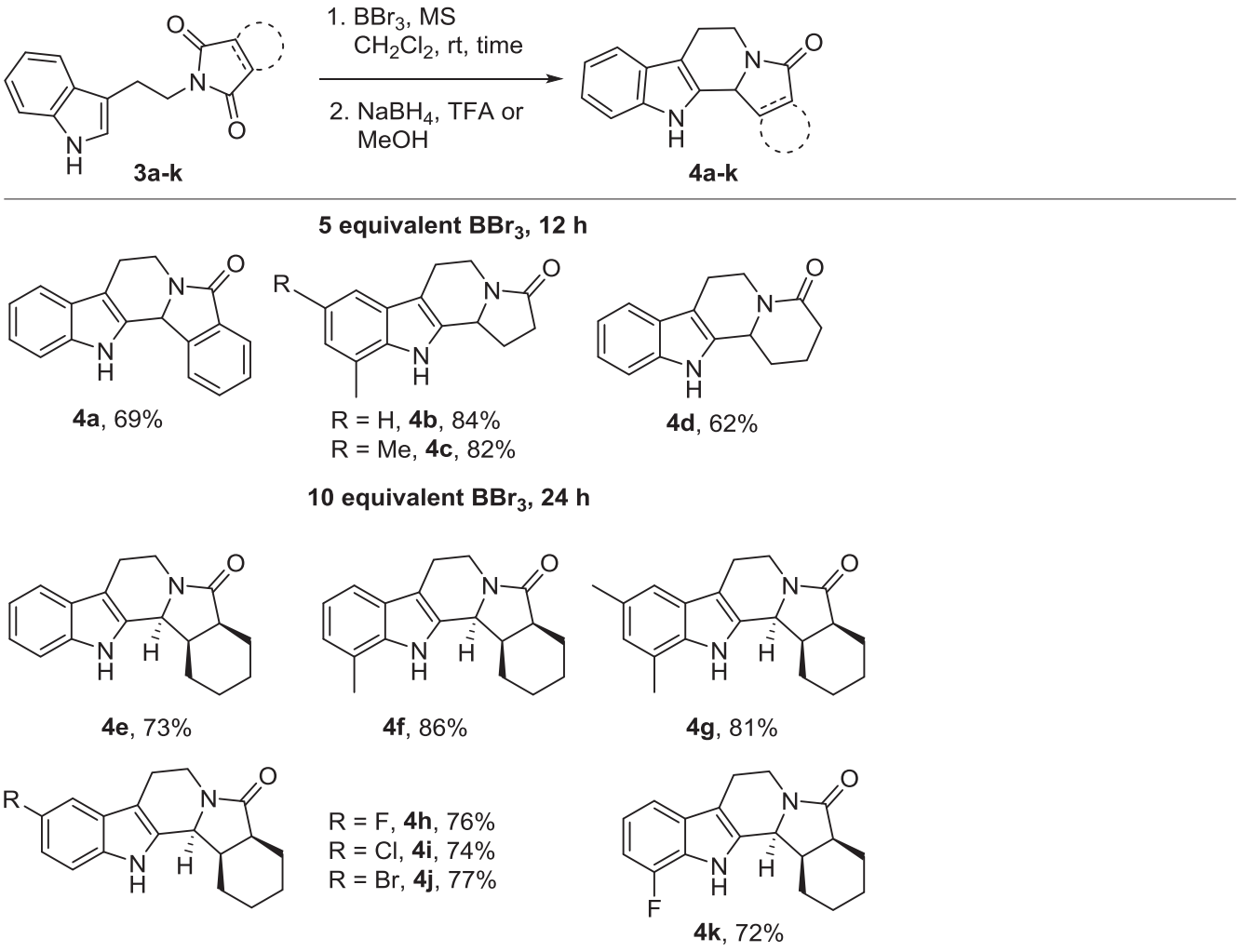


Table 2. Synthesis of fused THBC polycyclic lactams.



at room temperature in presence of BBr_3 (10 equiv) (table 2).

The inductively electron withdrawing groups such as fluoro, chloro and bromo substituents present in the indole moiety reduces the nucleophilicity of indole ring and that might have been the reason for increase in reaction time. Fused cyclic *N*-acyliminium ions generated from the imides **3e–k** underwent diastereoselective reduction using $NaBH_4$/MeOH and produced single diastereomer of the cyclized compounds **4e–k**. From ^{1}H NMR spectra of the cyclized molecules the relative orientation of the hydrogen attached with ring junction carbons are found to be *cis* orientated.[12d] Plenty of indole alkaloids contain fused polyalicyclic ring systems with THBC units. Hence, this methodology would be an easy protocol to synthesize diverse alicyclic units fused with THBC cores.

4. Conclusions

We have established a simple and convenient methodology for the synthesis of condensed THBC polycyclic lactamic skeletons from the corresponding easily accessible imides, through Lewis acid activation of imide carbonyl group. The formation of fused cyclic *N*-acyliminium ion in this cyclization reaction was supported by single crystal X-ray structural analysis.

Supplementary Information

CCDC details for the iminium ion (932118), ^{1}H and ^{13}C NMR spectra of the imides **3f-3k** and all cyclized compounds **4a–4k** are provided in Supporting information which is available at www.ias.ac.in/chemsci.

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