Highly chemo- and diastereo-selective synthesis of 2,6-diazabicyclo[3.2.0]heptan-7-ones, pyrrolidines and perhydroazirino[2,3-c]pyrroles

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Abstract
The manuscript describes a simple, convenient and metal-free diastereoselective synthesis of 4-halo-3-aryl/alkyl-6-aryl-2,6-diazabicyclo[3.2.0]heptan-7-ones via intramolecular endo-trig haloamination of 3-aminoazetidin-2-ones and its facile transformations to previously unknown methyl 4-halo-3-arylamino pyrrolidine-2-carboxylates and N-deprotected diazabicyclo[3.1.0]-hexane-2-carboxylic acids in good yields. The synthesis of such heterocyclic system is important in terms of the usefulness as organic synthon as well as their diverse pharmacological profiles.

Keywords: Diazabicyclo[3.2.0]heptanones, pyrrolidines, aziridinopyrrolidines, β-lactams, endo-trig haloamination

Introduction

Over the past decades, β–lactams have emerged as a useful synthon in organic chemistry.1,2 Numerous researchers have explored the synthesis of a variety of novel heterocyclic systems via β–lactam synthon methodology.3 Ojima and his co-workers have described the crucial role of β–lactam synthon methodology in the synthesis of paclitaxel, docetaxel and new-generation taxoids viz. C-2- and C-3′-modified taxoids, etc.4-6 Alcaide et al. have utilized a variety of lactams as organic synthons for the construction of various alkaloid skeletons.7,8 Mahajan et al. have explored the β–lactam synthon approach towards the diastereoselective synthesis of functionalized octahydroisoquinolones,9 pyrroloxazine,10 tetra/octahydro-isoquinoline11 and octahydroindole12 ring systems. Literature survey clearly reveals that β–lactams are important synthons for the synthesis of a variety of useful aza-heterocyclic systems.4-12 Functionalized proline esters, the five-membered azaheterocyclic systems, are important organocatalysts as well as having vital roles in
biological systems. The perhydroazirino[2,3-c]pyrrole family of natural products has been of interest to the scientific community since their isolation over 50 years ago. Aziridines are valuable intermediates in natural product synthesis as in the case of the (-)-mesembrine, (-)-platynesine, kainoids, sphingosines, epicapreomycinide, actinomycin, (+)- and feldamycin. Members of this family exhibit potent activity against a variety of cancer cell lines, and were found to be particularly active against solid tumors. In addition, aziridinopyrrolidines have shown interesting biological properties which makes them important synthetic targets. However, the reported methods for preparation of aziridinopyrrolidines are cumbersome and have multistep reaction procedures.

Recent publications from our laboratory have reported the synthesis and subsequent transformations of functionalized lactams for the synthesis of (2-oxo-4-styrylazetidin-3-yl)pyridine, butadienyl-4-iminomethylazetidin-2-ones, butenylidene-butadienyl-[2,2'-biazetidine]-4,4'-diones, 1,4-benzodialezipin-2-ones and dienyl thiazolidin-4-ones. As a part of our ongoing interest in the synthesis of heterocyclic systems, we have reported earlier the metal free diastereoselective synthesis of diazabicyclo[3.2.0]heptan-7-ones and their transformations to functionalized proline esters. The reactions were highly diastereo- and chemo-selective and resulted in the formation of diazabicyclo[3.2.0]heptan-7-ones via an endo-trig haloamination reaction. The synthesis of such bicyclic system is important as earlier reports by different workers have revealed their usefulness as type C β-lactamase inhibitors.

The current manuscript summarizes an account of (a) study on halocyclizations of a variety of 3-aminoazetidin-2-ones using different haloaminating reagents; (b) a study on mechanistic insight for haloamination reaction using different substituents at nitrogen position; (c) synthetic transformations of diazabicyclo[3.2.0]heptan-7-ones derivatives; (d) lactam mediated synthesis of functionalized proline esters and (e) synthesis of previously unexplored aziridinopyrrolidines. The synthesis of such azaheterocyclic systems especially 4,6-diaryl-3,6-diazabicyclo[3.1.0]hexane-2-carboxylic acids are an important in view of their biological properties. Moreover, the earlier effort for the synthesis of N-deprotected 4,6-diaryl-3,6-diazabicyclo[3.1.0]hexane-2-carboxylic acids was unsuccessful.

Results and Discussion

The starting materials 3-aminoazetidin-2-ones 1, used in halocyclization reactions were prepared by reported methods. These variably substituted 3-aminoazetidin-2-ones 1 were initially investigated for intramolecular ring closure haloamination reactions using different combinations of halogenating reagents and bases in different solvents. The reaction led to the formation of pure 4-halo-3-aryl/alkyl-6-aryl-2,6-diazabicyclo[3.2.0]heptan-7-ones 2a-m (Scheme 1, Table 1). However, the yield of halocyclized products varied with the type of solvent, base and halogen used in the reactions. The reactions were, initially optimized with different halogenation reagents viz. I₂, Br₂, NIS, NBS and NCS. The best yield (90%) was achieved using iodine and potassium.
carbonate as base (Table 1; Entry 2). The halocyclization using NIS and NBS resulted in the formation of 4-halo-3-aryl/alkyl-6-aryl-2,6-diazabicyclo[3.2.0]heptan-7-ones in considerably lower yields. The use of sodium carbonate as base in halocyclization reactions of 1 using iodine and bromine resulted in slightly lower yields of the products (Table 1, entries 6-7). When NCS was used as a haloaminating reagent the reactions did not result in the desired product; the starting material remaining intact. The halocyclization was also tested using strong bases i.e. sodium hydride and potassium-1-hydroxide. However, this resulted in deterioration of the products.

Scheme 1. Halocyclization of 3-aminoazetidin-2-ones 1a.

Table 1. Reaction of 1a under different reaction conditions

<table>
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<tr>
<th>S.No.</th>
<th>Reagent</th>
<th>Base</th>
<th>Solvent</th>
<th>Reaction Time</th>
<th>Yield(%)</th>
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<td>2</td>
<td>I₂</td>
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<td>DCM</td>
<td>90</td>
<td>90</td>
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<tr>
<td>3</td>
<td>Br₂</td>
<td>K₂CO₃</td>
<td>DCM</td>
<td>45</td>
<td>61</td>
</tr>
<tr>
<td>4</td>
<td>NBS</td>
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<td>DCM</td>
<td>60</td>
<td>20</td>
</tr>
<tr>
<td>5</td>
<td>NCS</td>
<td>K₂CO₃</td>
<td>DCM</td>
<td>90</td>
<td>-</td>
</tr>
<tr>
<td>6</td>
<td>I₂</td>
<td>Na₂CO₃</td>
<td>DCM</td>
<td>90</td>
<td>80</td>
</tr>
<tr>
<td>7</td>
<td>Br₂</td>
<td>Na₂CO₃</td>
<td>DCM</td>
<td>90</td>
<td>45</td>
</tr>
<tr>
<td>8</td>
<td>I₂</td>
<td>tBuOK</td>
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<td>-</td>
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<tr>
<td>9</td>
<td>I₂</td>
<td>NaH</td>
<td>DCM</td>
<td>90</td>
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</tr>
<tr>
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<td>I₂</td>
<td>K₂CO₃</td>
<td>DMF</td>
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<td>55</td>
</tr>
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<td>K₂CO₃</td>
<td>THF</td>
<td>90</td>
<td>30</td>
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</tbody>
</table>

*a Reaction time in minutes. b Isolated yield after purification. DCM = dichloromethane

We also studied the effect of a substituent at the alpha position of styryl of 3-aminoazetidin-2-ones in these haloamination reactions. The reactions did not give any haloaminations even at high temperature or using harsh reaction conditions, probably due to the steric hindrance at the alpha position of styryl of 3-aminoazetidin-2-ones.
After optimization of the reaction conditions, diversely substituted 3-aminoazetidin-2-ones 1 were explored in haloaminating reaction with iodine/bromine in the presence of different bases viz. K₂CO₃ and Na₂CO₃ (Scheme 2). The reactions led to the formation of regio- and diastereoisomerically pure 4-halo-3-aryl/alkyl-6-aryl-2,6-diazabicyclo[3.2.0]heptan-7-ones 2 in good yields (Table-2; Entries 1-15). There was not much difference in the reactivity as well as yield of the products with changing substituents at the N-1 position of the lactam (Table 2). However the yield of the products in case of bromocyclization is comparatively low (Table 2, Entries 8-13). This is probably due to participation of bromine in side reactions due to its strong acidity.

Scheme 2. Intramolecular endo-trig-halocyclization of 1 for the synthesis of 4-halo-3-aryl/alkyl-6-aryl-2,6-diazabicyclo[3.2.0]heptan-7-ones 2.

We next studied the effect of substituents of the participating nitrogen of 3-aminoazetidin-2-ones in these haloamination reactions (Scheme 3). Two substituents (i) electron withdrawing (tosyl), (ii) electron donating (methyl) were studied in these haloamination reactions. We have also explored the effect of N,N-dimethyl substitution for these haloamination reactions. The reaction of N-mono methylated 3-aminoazetidin-2-ones underwent halocyclization in good to fair yield (Table 3; Entries 1-2). However, the reaction of N-tosylated 3-aminoazetidin-2-ones did not give any useful product even at high temperature or using harsh reaction conditions.

![Scheme 2](image-url)
Table 2. Synthesis of 4-halo-3-aryl/alkyl-6-aryl-2,6-diazabicyclo[3.2.0]heptan-7-ones 2 by halocyclization reactions

<table>
<thead>
<tr>
<th>S.No.</th>
<th>R¹</th>
<th>X°</th>
<th>Base</th>
<th>Product</th>
<th>Reaction Time¹</th>
<th>Yield (%)²</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>C₆H₅</td>
<td>I</td>
<td>K₂CO₃</td>
<td>2a</td>
<td>90</td>
<td>90</td>
</tr>
<tr>
<td>2</td>
<td>p-CH₃C₆H₄</td>
<td>I</td>
<td>K₂CO₃</td>
<td>2b</td>
<td>90</td>
<td>82</td>
</tr>
<tr>
<td>3</td>
<td>p-Cl-C₆H₄</td>
<td>I</td>
<td>K₂CO₃</td>
<td>2c</td>
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<td>I</td>
<td>K₂CO₃</td>
<td>2d</td>
<td>90</td>
<td>66</td>
</tr>
<tr>
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<td>p-F-C₆H₄</td>
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<td>K₂CO₃</td>
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<td>90</td>
<td>62</td>
</tr>
<tr>
<td>6</td>
<td>cyclohexyl</td>
<td>I</td>
<td>K₂CO₃</td>
<td>2f</td>
<td>90</td>
<td>75</td>
</tr>
<tr>
<td>7</td>
<td>Benzyl</td>
<td>I</td>
<td>K₂CO₃</td>
<td>2g</td>
<td>90</td>
<td>60</td>
</tr>
<tr>
<td>8</td>
<td>C₆H₅</td>
<td>Br</td>
<td>K₂CO₃</td>
<td>2h</td>
<td>45</td>
<td>61</td>
</tr>
<tr>
<td>9</td>
<td>p-CH₃C₆H₄</td>
<td>Br</td>
<td>K₂CO₃</td>
<td>2i</td>
<td>45</td>
<td>55</td>
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<tr>
<td>10</td>
<td>p-Cl-C₆H₄</td>
<td>Br</td>
<td>K₂CO₃</td>
<td>2j</td>
<td>45</td>
<td>50</td>
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<td>p-CH₃O-C₆H₄</td>
<td>Br</td>
<td>K₂CO₃</td>
<td>2k</td>
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<td>55</td>
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<td>12</td>
<td>p-F-C₆H₄</td>
<td>Br</td>
<td>K₂CO₃</td>
<td>2l</td>
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<tr>
<td>13</td>
<td>Benzyl</td>
<td>Br</td>
<td>K₂CO₃</td>
<td>2m</td>
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<td>45</td>
</tr>
<tr>
<td>14</td>
<td>C₆H₅</td>
<td>I</td>
<td>Na₂CO₃</td>
<td>2a</td>
<td>90</td>
<td>80</td>
</tr>
<tr>
<td>15</td>
<td>p-CH₃C₆H₄</td>
<td>I</td>
<td>Na₂CO₃</td>
<td>2b</td>
<td>90</td>
<td>75</td>
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</tbody>
</table>

¹ Reaction time in minutes. ² Isolated yield after purification. ³ 1.2 equivalent.

The reaction of N,N-disubstituted as well as mono N⁵-tosylatedazetidin-2-one did not provide any desired product and only led to the recovery of the starting material, even after several hours of stirring at different temperatures using even higher amounts of iodine/bromine or using different bases, such as potassium carbonate, sodium carbonate, sodium hydride and potassium-t-butoxide. From these experimental observations, it may be concluded that the endo-trig haloamination reaction was not observed in the presence of an electron withdrawing group at the N-position and that the reaction is facilitated by the presence of an electron donating group. However, the reaction of 5b and 5c was not observed due to the more steric crowding for endo-trig haloamination reaction.
Scheme 3. 4-Halo-2-methyl-3,6-diphenyl-2,6-diazabicyclo[3.2.0]heptan-7-ones 6.

Table 3. 4-Halo-2-methyl-3,6-diphenyl-2,6-diazabicyclo[3.2.0]heptan-7-ones 6

<table>
<thead>
<tr>
<th>S. No.</th>
<th>R¹</th>
<th>R²</th>
<th>X</th>
<th>Product</th>
<th>Reaction Time a</th>
<th>Yield(%) b</th>
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<tr>
<td>1</td>
<td>CH₃</td>
<td>H</td>
<td>I</td>
<td>6a</td>
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<td>75</td>
</tr>
<tr>
<td>2</td>
<td>CH₃</td>
<td>H</td>
<td>Br</td>
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<td>CH₃</td>
<td>I</td>
<td>6c</td>
<td>90</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>p-tosyl</td>
<td>H</td>
<td>I</td>
<td>6d</td>
<td>90</td>
<td>0</td>
</tr>
</tbody>
</table>

a Reaction time in minutes.     b Isolated yield after purification.

The diastereomerically pure, functionalized novel 4-halo-3-aryl/alkyl-6-aryl-2,6-diazabicyclo[3.2.0]heptan-7-ones 2, thus obtained were characterized on the basis of analytical and spectral evidence. The compound, 4-iodo-3,6-diphenyl-2,6-diazabicyclo[3.2.0]heptan-7-one 2a for example, analyzed for C₁₈H₁₇IN₂O showed a molecular ion peak at m/z 391 (M+1) in its mass spectrum. Its IR spectrum showed strong absorption peaks at 1755 cm⁻¹ corresponding to the carbonyl group of a azetidin-2-one. The ¹H NMR (300 MHz) spectrum showed a characteristic doublet at δ 4.91 having J 3.6 Hz corresponding to H₁ proton of the ring, an unresolved doublet of doublet at δ 4.94 having J 3.6Hz corresponding to H₅ of the lactam ring, a multiplet at δ 5.02 corresponding to H₃ & H₄ protons. The ¹³C NMR have shown the presence of one carbonyl carbon at δ 164.2 and four aliphatic carbons at δ 30.7, 67.2, 71.80, and δ 74.7 corresponding to C-4, C-5, C-1 and C-3 respectively. The relative stereochemistry of the different ring protons has been established with the help of earlier report. The 4-iodo-3,6-diphenyl-2,6-diazabicyclo[3.2.0]heptan-7-one (2a) has shown the anti stereochemistry between H⁵ of azetidin-2-one and H⁴ of the pyrrole ring (Figure 1).
A proposed mechanism for the formation of azabicyclo[3.2.0]heptanes involves the initial coordination of halogen to the double bond at C-4 position of $\beta$-lactam leading to formation of a halonium ion. This is followed by a nucleophilic attack of nitrogen attached to C-3 position of lactam ring to the C-6 position of halonium ion (Scheme-4) thereby yielding corresponding diazabicyclo[3.2.0]heptanes 2 in good yields.

Scheme 4. A plausible mechanism depicting the formation of 4- halo-3-phenyl-6-aryl-2,6-diazabicyclo[3.2.0]heptan-7-ones
The 4-halo-3-aryl/alkyl-6-aryl-2,6-diazabicyclo[3.2.0]heptan-7-ones 2 were explored for the synthesis of pyrrolidine esters by amidolytic ring hydrolysis of N\textsuperscript{6}-C\textsuperscript{7} bond using different bases viz. sodium alkoxide. The reaction resulted in the formation of 4-halo-5-phenyl-3-arylamino-pyrrolidine-2-carboxylic acid methyl esters 7 in excellent yields (90%; Scheme-5, Table 4).

![Scheme 5. Synthesis of alkyl 4-iodo-5-aryl-3-(arylamino)pyrrolidine-2-carboxylates 7.](image)

**Table 4. Alkyl 4-iodo-5-aryl-3-(arylamino)pyrrolidine-2-carboxylates 7**

<table>
<thead>
<tr>
<th>S.No.</th>
<th>R\textsuperscript{1}</th>
<th>X</th>
<th>Base</th>
<th>Solvent</th>
<th>Product\textsuperscript{a}</th>
<th>Yield (%)\textsuperscript{b}</th>
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<td>CH\textsubscript{3}OH</td>
<td>7a</td>
<td>85</td>
</tr>
<tr>
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<td>NaOCH\textsubscript{3}</td>
<td>CH\textsubscript{3}OH</td>
<td>7c</td>
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<td>CH\textsubscript{3}OH</td>
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</tr>
<tr>
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<td>I</td>
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<td>C\textsubscript{2}H\textsubscript{5}OH</td>
<td>7l</td>
<td>81</td>
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\textsuperscript{a}Isolated yields after purification. \textsuperscript{b}Reaction time 90 minutes

The diastereomerically pure, functionalized alkyl 4-iodo-5-aryl-3-(arylamino)pyrrolidine-2-carboxylates (7) thus obtained were characterized on the basis of analytical and spectral evidence. The compound, methyl 4-iodo-5-phenyl-3-(phenylamino)pyrrolidine-2-carboxylate 7a for example, analyzed for C\textsubscript{18}H\textsubscript{19}IN\textsubscript{2}O\textsubscript{2} showed a (M+1) molecular ion peak at m/z 423 in its mass spectrum (Figure 2). The \textsuperscript{1}H NMR (300 MHz) spectrum showed a characteristic doublet (J 7.5 Hz) at δ 4.70 corresponding to H\textsubscript{2} of the ring, a broad singlet at δ 4.46 corresponding to H\textsubscript{3} and H\textsubscript{4} of the ring, a doublet at δ 4.11 having J 7.2 Hz assigned to H\textsubscript{5}. The \textsuperscript{13}C NMR have shown the presence
of one carbonyl carbon at δ 172.1 and four aliphatic carbons at δ 71.0, 66.0, 61.7 & 29.3 corresponding to C-5, C-2, C-4 and C-3 respectively.

Figure 2. Methyl 4-iodo-5-phenyl-3-(phenylamino)pyrrolidine-2-carboxylate 7a.

4-Halo-5-phenyl-3-aryliminopyrrolidine-2-carboxylic acid alkyl esters 7 were also explored for the synthesis of 3,6-diazabicyclo[3.1.0]hexane-2-carboxylic acids 8 by intramolecular nucleophilic substitution reaction (90%; Scheme-6). The intramolecular nucleophilic substitution reactions were studied at different temperature using different solvents to provide N-deprotected 4,6-diaryl-3,6-diazabicyclo[3.1.0]hexane-2-carboxylic acids 8 in good yields (Table-5, Entries 1-16) at 50°C. We have also studied the one pot formation of 8 by the treatment of 2 with sodium alkoxide in corresponding alcohol at 50 °C. From these observations, it may be concluded that there was initial formation of 7 at 50 °C which underwent intramolecular nucleophilic substitution reaction to yield 8a-d.

Scheme 6. Synthesis of 4,6-diaryl-3,6-diazabicyclo[3.1.0] hexane-2-carboxylic acids 8

The diastereomerically pure, functionalized novel 4,6-diaryl-3,6-diazabicyclo[3.1.0] hexane-2-carboxylic acids 8 thus obtained were characterized on the basis of analytical and spectral evidence. (Figure 3) The compound, methyl 4,6-diphenyl-3,6-diazabicyclo[3.1.0]hexane-2-carboxylic acid (C17H16N2O2) 8a for example, showed a molecular ion peak at m/z (M+1) 281 in its mass spectrum. The 1H NMR (300MHz) spectrum showed a characteristic doublet (J 1.8 Hz) at δ 4.10 corresponding to H2 of the ring, a doublet (J 1.8 Hz) at δ 3.68 corresponding to H5 of the ring, two doublet of doublet at δ 3.23 & 3.08 having J 4.5, 2.1 Hz assigned to H3 and H4 respectively. The 13C NMR have shown the presence of one carbonyl carbon at δ 173.8 and four aliphatic carbons at δ 64.3, 63.6, 49.7, 49.0 corresponding to C-5, C-2, C-3 and C-4 respectively.
Table 5. 4,6-diaryl-3,6-diazabicyclo[3.1.0] hexane-2-carboxylic acids 8

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<td>8d</td>
<td>82</td>
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</table>

^a Isolated yields after purification

Figure 3. 4,6-Diphenyl-3,6-diazabicyclo[3.1.0]hexane-2-carboxylic acid 8a.

A plausible mechanism involves the initial formation of 4-halo-5-phenyl-3-arylamino-pyrrolidine-2-carboxylate ester 7 as an intermediate in the transformation of 4-halo-3-phenyl-6-aryl-2,6-diazabicyclo[3.2.0]heptan-7-one (2) into 4,6-diaryl-3,6-diazabicyclo[3.1.0]hexane-2-carboxylic acid (8) (Scheme-7). The intramolecular nucleophilic attack of nitrogen in intermediate 9 to the adjacent halogenated carbon of pyrrole ring thereby yielding corresponding diazabicyclo-[3.1.0]hexane-2-carboxylic acid in good yields.
Conclusions

We have developed a simple, convenient and metal free diastereoselective method for the functionally decorated 4-halo-3,6-diaryl-2,6-diazabicyclo[3.2.0]heptan-7-ones via intramolecular endo-trig haloamination of 3-aminoazetidin-2-ones in good to excellent yield and competitive exo-trig haloamination was not observed. These diazabicyclo[3.2.0]heptan-7-ones served as novel β-lactam synths for the synthesis of highly functionalized proline esters. The one pot amidolytic ring opening of diazabicyclo[3.2.0]heptan-7-ones with sodium alkoxide also provided an easy access to previously unknown N-deprotected diazabicyclo[3.1.0]hexane-2-carboxylic acids in good yields.

Experimental Section

General. Oxygen- and moisture-sensitive reactions were carried out under nitrogen atmosphere. Solvents were purified and dried by standard methods prior to use. All commercially available reagents and solvents (purchased from Aldrich, Merck, Spectrochem, Acros) were used without further purification unless otherwise noted. Analytical thin layer chromatography (TLC) was
General Papers

General procedure for synthesis of compound 4-halo-3,6-diaryl-2,6-diaza-bicyclo[3.2.0]heptan-7-one 2. To a solution of compounds 1 (0.1 g, 1 equiv) in DCM (10 mL) was added bromine/iodine (1.2 equiv). The reaction was stirred for 10 minutes. This was followed by addition of K₂CO₃ at 0 °C. The solution was stirred at 0 °C for 1–2 h. The progress of the reaction was monitored with the help of tlc. After completion of the reaction, reaction mixture was diluted with DCM and washed with Na₂S₂O₃/water solution followed by brine solution. The dichloromethane solution was dried over anhydrous Na₂SO₄ and solvent was evaporated. Crude residue was purified by flash column chromatography using silica gel (100:200 mesh) in EtOAc/cyclohexane (2:8) as an elutent system to get compounds 2.

4-Iodo-3,6-diphenyl-2,6-diazabicyclo[3.2.0]heptan-7-one (2a). Yield: 90%; White solid, mp 118–119 °C; δ₁ H NMR (300 MHz, CDCl₃) 7.36 (d, J 7.2 Hz, 2H), 7.10–7.19 (m 5H), 6.97–7.04 (t, J 7.5 Hz, 1H), 6.90 (d, J 7.5 Hz, 2H), 5.02 (d, J 3.9 Hz, 2H), 4.94 (bs, 1H), 4.91 (d, J 3.6 Hz, 1H). δ C NMR (75 MHz, CDCl₃) δ 164.2, 139.6, 136.1, 129.0, 128.2, 127.2, 125.3, 116.8, 74.7, 71.8, 67.8, 30.7. MS (El) m/z 391 (M+1)+, vₘₐₓ (KBr)/cm⁻¹ 1755, HRMS calculated for C₁₇H₁₅IN₂O (M+H)+ 391.0307, found 391.0314.

X-Ray crystal data and structure refinement. CCDC 972460 contains the supplementary crystallographic data. C₁₇H₁₅I₁N₂O₁, V = 2958.9(2) Å³ Mr = 390.21, Z = 8, orthorhombic, a = 9.8710(5) Å, m = 2.165 mm⁻¹, b = 16.0822(8) Å, T = 100(2) K, c = 18.6387(8) Å, a = 90, b = 90 g = 90; b = 104.719(2), Tₘᵢₙ = 0.655, Tₘₐₓ = 0.677, Rₑₙₙ = 0.0252, 3047 measured reflections, wR(F2) = 0.0759, S = 1.155

4-Iodo-3-phenyl-6-(p-tolyl)-2,6-diazabicyclo[3.2.0]heptan-7-one (2b). Yield: 82%; White solid, mp 129–131 °C; δ₁ H NMR (300 MHz, CDCl₃) 7.37 (dd, J 6.9, 0.9 Hz, 2H), 7.11–7.21 (m, 3H), 6.96 (d, J 8.1 Hz, 1H), 6.78 (dd, J 6.6, 1.8 Hz, 2H), 5.01 (d, J 3.6 Hz, 2H), 4.91 (bs, 2H), 2.24 (s, 3H). δ C NMR (75 MHz, CDCl₃) δ 163.9, 139.7, 134.2, 133.6,
129.5, 128.2, 127.1, 125.4, 116.8, 74.8, 71.8, 67.8, 30.8, 20.9. MS (EI) m/z 405 (M+1)\(^+\), \(v_{\text{max}}\) (KBr)/cm\(^{-1}\) 1755, HRMS calculated for C\(_{18}\)H\(_{17}\)N\(_2\)O (M+H\(^+\)) 405.0464, found 405.0488.

6-(4-Chlorophenyl)-4-iodo-3-phenyl-2,6-diazabicyclo[3.2.0]heptan-7-one (2c). Yield: 65%; Pale yellow solid, mp 143–144; \(\delta_{\text{H}}\) \(^1\)H NMR (300 MHz, CDCl\(_3\)) 7.35 (dd, J 8.1, 1.2 Hz, 2H), 7.10–7.20 (m, 5H), 6.83 (d, J 6.6 Hz, 2H), 5.01 (d, J 3.6 Hz, 2H); \(\delta_{\text{C}}\) NMR (75 MHz, CDCl\(_3\)) \(\delta\) 164.1, 139.5, 134.6, 129.1, 128.9, 128.3, 127.2, 125.3, 118.0, 74.5, 72.2, 67.9, 30.3. MS (EI) m/z 425 (M+1), \(v_{\text{max}}\) (KBr)/cm\(^{-1}\) 1755, HRMS calculated for C\(_{17}\)H\(_{16}\)Cl\(_2\)N\(_2\)O (M+H\(^+\)) 424.9918, found 424.9915.

4-Iodo-6-(4-methoxyphenyl)-3-phenyl-2,6-diazabicyclo[3.2.0]heptan-7-one (2d). Yield: 66%; White solid, mp 137–139; \(\delta_{\text{H}}\) \(^1\)H NMR (300 MHz, CDCl\(_3\)) 7.37 (d, J 7.2 Hz, 2H), 7.10–7.19 (m, 5H), 6.80 (dd, J 6.6, 1.8 Hz, 2H), 5.01 (d, J 3.6 Hz, 2H); \(\delta_{\text{C}}\) NMR (75 MHz, CDCl\(_3\)) \(\delta\) 163.9, 139.7, 134.2, 133.7, 129.5, 128.2, 127.1, 125.3, 116.8, 74.8, 71.7, 67.8, 55.9, 30.8. MS (EI) m/z 421 (M+1), \(v_{\text{max}}\) (KBr)/cm\(^{-1}\) 1750, HRMS calculated (M+H\(^+\)) 409.0213, found 409.0207, Anal. Calc. for C\(_{17}\)H\(_{16}\)O\(_2\)N: C, 50.02; H, 3.46; N, 6.86; found: C, 50.06; H, 3.51; N, 6.81.

6-(4-Fluorophenyl)-4-iodo-3-phenyl-2,6-diazabicyclo[3.2.0]heptan-7-one (2e). Yield: 62%; Pale yellow solid, mp 124–127; \(\delta_{\text{H}}\) \(^1\)H NMR (300 MHz, CDCl\(_3\)) 7.34–7.37 (m, 2H, ArH), 7.10–7.26 (m, 5H, ArH), 6.82–6.85 (m, 2H, ArH), 5.00 (d, J 3.6 Hz, 2H); \(\delta_{\text{C}}\) NMR (75 MHz, CDCl\(_3\)) \(\delta\) 164.5, 128.8, 128.7, 126.7, 123.6, 74.7, 71.8, 67.9, 52.7, 31.8, 30.6, 29.7, 25.0. MS (EI) m/z 397 (M+1), \(v_{\text{max}}\) (KBr)/cm\(^{-1}\) 1755, HRMS calculated (M+H\(^+\)) 397.0777, found 397.0773, Anal. Calc. for C\(_{17}\)H\(_{16}\)F\(_2\)N\(_2\)O: C, 51.53; H, 5.34; N, 7.07; found: C, 51.60; H, 5.39; N, 7.04.

6-Cyclohexyl-4-iodo-3-phenyl-2,6-diazabicyclo[3.2.0]heptan-7-one (2f). Yield: 75%; Pale yellow solid, mp 110–111; \(\delta_{\text{H}}\) \(^1\)H NMR (500 MHz, CDCl\(_3\)) 7.18–7.39 (m, 5H, ArH), 5.07 (d, J 4.0 Hz, 2H, H\(_3\) & H\(_4\)), 5.02 (s, 1H, H\(_1\)) 5.00 (d, J 3.5 Hz, 1H, H\(_5\)), 3.57–3.62 (m, 1H, cyclohexyl-H), 0.85–1.95 (m, 10H, cyclohexyl-H), \(\delta_{\text{C}}\) NMR (75 MHz, CDCl\(_3\)) \(\delta\) 164.5, 128.8, 128.7, 126.7, 123.6, 74.7, 71.8, 67.9, 52.7, 31.8, 30.6, 29.7, 25.0. MS (EI) m/z 509 (M+1), \(v_{\text{max}}\) (KBr)/cm\(^{-1}\) 1755, HRMS calculated (M+H\(^+\)) 509.1755, found 509.1753, Anal. Calc. for C\(_{17}\)H\(_{21}\)N\(_2\)O: C, 51.53; H, 5.34; N, 7.07; found: C, 51.60; H, 5.39; N, 7.04.

6-Benzyl-4-iodo-3-phenyl-2,6-diazabicyclo[3.2.0]heptan-7-one (2g). Yield: 60%; Yellow solid, mp 125–126; \(\delta_{\text{H}}\) \(^1\)H NMR (500 MHz, CDCl\(_3\)) 7.21–7.36 (m, 10H, ArH), 5.04 (d, J 3.5 Hz, 2H, H\(_3\) & H\(_4\)), 4.94 (s, 1H, H\(_1\)) 4.92 (d, J 3.5 Hz, 1H, H\(_5\)), 4.09–4.14 (m, 2H, CH\(_2\)), \(\delta_{\text{C}}\) NMR (75 MHz, CDCl\(_3\)) \(\delta\) 170.1, 143.4, 128.8, 128.7, 128.5, 127.9, 127.2, 126.6, 123.5, 74.4, 70.3, 65.8, 47.2, 29.7. MS (EI) m/z 511 (M+1), \(v_{\text{max}}\) (KBr)/cm\(^{-1}\) 1752, HRMS calculated (M+H\(^+\)) 511.1752, found 511.1753, Anal. Calc. for C\(_{18}\)H\(_{17}\)N\(_2\)O: C, 53.48; H, 4.24; N, 6.93; found: C, 53.52; H, 4.29; N, 6.89.

4-Bromo-3,6-diphenyl-2,6-diazabicyclo[3.2.0]heptan-7-one (2h). Yield: 61%; Brown solid, mp 131–132; \(\delta_{\text{H}}\) \(^1\)H NMR (300 MHz, CDCl\(_3\)) 7.38 (m, 2H, ArH), 7.10–7.22 (m, 5H, ArH), 6.97–7.04 (m, 1H, ArH), 6.93 (m, 2H, ArH), 5.02 (bs, 1H, H\(_3\)), 4.92 (d, J 3.6 Hz, 1H, H\(_4\)), 4.91 (bs, 1H, H\(_5\)), 4.83 (d, J 3.6 Hz, 1H, H\(_5\)), \(\delta_{\text{C}}\) NMR (75 MHz, CDCl\(_3\)) \(\delta\) 164.1, 139.0, 136.1, 129, 128.2, 127.2, 125.4, 124.5, 116.7, 73.1, 71.7, 66.1, 52.7. MS (EI) m/z 343
(M+1)\(^+\), Anal. Calc. for C\(_{17}\)H\(_15\)BrN\(_2\)O: C, 59.49; H, 4.41; N, 8.16; found: C, 59.41; H, 4.38; N, 8.20.

4-Bromo-3-phenyl-6-(p-tolyl)-2,6-diazabicyclo[3.2.0]heptan-7-one (2i). Yield: 55%; Brown solid; \(\delta\)\(^1\)H NMR (300 MHz, CDCl\(_3\)) 7.39 (m, 2H, ArH), 7.10-7.23 (m, 3H, ArH), 6.97 (m, 2H, ArH), 6.80 (m, 2H, ArH), 5.02 (s, 1H, H\(_3\)), 4.91 (d, J 3.6 Hz, 1H, H\(_4\)), 4.90 (bs, 1H, H\(_1\)), 4.81 (d, J 3.6 Hz, 1H, H\(_3\)), 2.24 (s, 3H, CH\(_3\)). \(\delta\)\(_C\) NMR (75 MHz, CDCl\(_3\)) \(\delta\) 163.8, 139.0, 134.2, 133.6, 129.5, 128.2, 127.2, 125.4, 116.8, 73.1, 71.6, 66.2, 52.7, 20.9. MS (EI) \(m/z\) 357 (M+1)\(^+\), Anal. Calc. for C\(_{18}\)H\(_{17}\)BrN\(_2\)O: C, 60.52; H, 4.80; N, 7.84; found: C, 60.49; H, 4.75; N, 7.87.

4-Bromo-6-(4-chlorophenyl)-3-phenyl-2,6-diazabicyclo[3.2.0]heptan-7-one (2j). Yield: 50%; Light brown solid; \(\delta\)\(^1\)H NMR (300 MHz, CDCl\(_3\)) 7.30-7.40 (m, 3H, ArH), 7.16-7.22 (m, 2H), 7.13 (m, 2H, ArH), 6.86 (m, 2H, ArH), 5.02 (s, 1H, H\(_3\)), 4.93 (d, J 3.6 Hz, 1H, H\(_4\)), 4.89 (s, 1H, H\(_1\)), 4.81 (d, J 3.6 Hz, 1H, H\(_5\)). \(\delta\)\(_C\) NMR (75 MHz, CDCl\(_3\)) \(\delta\) 163.5, 134.5, 129.6, 129.1, 128.8, 128.3, 127.5, 125.5, 117.9, 73.0, 71.5, 66.0, 51.6. MS (EI) \(m/z\) 377 (M+1)\(^+\), Anal. Calc. for C\(_{17}\)H\(_{14}\)BrClN\(_2\): C, 54.06; H, 3.74; N, 7.42; found: C, 54.03; H, 3.68; N, 7.45.

4-Bromo-6-(4-methoxyphenyl)-3-phenyl-2,6-diazabicyclo[3.2.0]heptan-7-one (2k). Yield: 55%; Brown solid; \(\delta\)\(^1\)H NMR (300 MHz, CDCl\(_3\)) 7.37-7.51 (m, 4H, ArH), 7.10-7.18 (m, 2H, ArH), 7.06 (m, 2H, ArH), 6.86 (m, 2H, ArH), 5.01 (s, 1H, H\(_3\)), 4.92 (d, J 3.6 Hz, 1H, H\(_4\)), 4.91 (s, 1H, H\(_1\)), 4.83 (d, J 3.6 Hz, 1H, H\(_5\)), 3.18 (s, 3H, OCH\(_3\)). \(\delta\)\(_C\) NMR (75 MHz, CDCl\(_3\)) \(\delta\) 164.0, 134.3, 129.7, 129.2, 128.8, 128.3, 127.5, 125.4, 116.8, 73.1, 71.6, 66.2, 57.8, 52.7. MS (EI) \(m/z\) 373 (M+1)\(^+\), Anal. Calc. for C\(_{18}\)H\(_{17}\)BrN\(_2\)O: C, 57.92; H, 4.59; N, 7.51; found: C, 57.91; H, 4.55; N, 7.57.

4-Bromo-6-(4-fluorophenyl)-3-phenyl-2,6-diazabicyclo[3.2.0]heptan-7-one (2l). Yield: 60%; Brown solid; \(\delta\)\(^1\)H NMR (300 MHz, CDCl\(_3\)) 7.02-7.29 (m, 7H, ArH), 6.78-6.81 (m, 2H, ArH), 4.76-4.96 (m, 2H, H\(_3\) & H\(_4\)), 4.66 (t, J 3.3 Hz, 1H, H\(_5\)), 4.66 (s, 1H, H\(_1\)). \(\delta\)\(_C\) NMR (75 MHz, CDCl\(_3\)) \(\delta\) 163.5, 134.5, 129.6, 129.1, 128.8, 128.3, 127.5, 125.5, 117.9, 73.0, 71.5, 66.0, 51.6. MS (EI) \(m/z\) 361 (M+1)\(^+\), Anal. Calc. for C\(_{17}\)H\(_{15}\)FBrN\(_2\)O: C, 56.53; H, 3.91; N, 7.76; found: C, 56.55; H, 3.96; N, 7.73.

6-Benzyl-4-bromo-3-phenyl-2,6-diazabicyclo[3.2.0]heptan-7-one (2m). Yield: 45%; Yellow solid; \(\delta\)\(^1\)H NMR (500 MHz, CDCl\(_3\)) 7.23-7.37 (m, 10H, ArH), 5.01 (s, 1H, H\(_3\)), 4.93 (d, J 3.5 Hz, 1H, H\(_4\)), 4.81 (s, 1H, H\(_1\)), 4.68 (d, J 3.5 Hz, 1H, H\(_3\)), 4.10-4.15 (m, 2H, CH\(_2\)). \(\delta\)\(_C\) NMR (75 MHz, CDCl\(_3\)) \(\delta\) 169.1, 143.4, 128.7, 128.7, 128.6, 127.8, 127.2, 126.7, 123.5, 73.0, 69.9, 65.8, 50.6, 47.2. MS (EI) \(m/z\) 357 (M+1)\(^+\), Anal. Calc. for C\(_{18}\)H\(_{17}\)IN\(_2\)O: C, 60.52; H, 4.80; N, 7.84; found: C, 60.54; H, 4.85; N, 7.80.

General procedure for synthesis of 4-halo-2-alkyl-3,6-diaryl-2,6-diazabicyclo[3.2.0]heptan-7-ones (6). To a solution of compounds 5 (0.1 g, 1 equiv) in DCM (10 mL) was added bromine/iodine (1.2 equiv). The reaction was stirred for 10 minutes. This was followed by addition of K\(_2\)CO\(_3\) at 0 °C. The solution was stirred at 0 °C. The progress of the reaction
was monitored with the help of tlc. After completion of the reaction, reaction mixture was
diluted with DCM and washed with Na₂S₂O₅/water solution followed by brine solution.
The dichloromethane solution was dried over anhydrous Na₂SO₄ and solvent was
evaporated. Crude residue was purified by flash column chromatography using silica gel
(100:200 mesh) in EtOAc/cyclohexane (2:8) as an eluent system to get compounds 6.

3-(Methylamino)-1-phenyl-4-((E)-styryl)azetidin-2-one (5a). White solid, δ_H 1H NMR
(500 MHz, CDCl₃) 7.48 (m, 2H, ArH), 7.43-7.45 (m, 2H, ArH), 7.28-7.38 (m, 5H, ArH),
7.10 (m, 1H, ArH), 6.85 (d, J 16.5 Hz, 1H, H₆), 6.53 (dd, J 16.0, 8.0 Hz, 1H, H₅), 4.86 (t, J
6.5 Hz, 1H, H₃), 4.46 (d, J 5.5 Hz, 1H, H₃), 2.90 (s, 3H, NCH₃). δ_C NMR (75 MHz, CDCl₃)
δ 165.9, 138.3, 136.0, 135.3, 129.1, 128.3, 128.1, 126.6, 124.3, 116.7, 57.5, 56.1, 32.4. MS
(EI) m/z 279 (M+1)⁺, Anal. Calc. for C₁₈H₁₈N₂O: C, 77.67; H, 6.52; N, 10.06; found: C, 77.71; H, 6.54; N, 10.02.

3-(Dimethylamino)-1-phenyl-4-((E)-styryl)azetidin-2-one (5b). White solid, δ_H 1H NMR
(500 MHz, CDCl₃) 7.46-7.51 (m, 4H, ArH), 7.28-7.40 (m, 5H, ArH), 7.07 (m, 1H, ArH),
6.75 (d, J 16.0 Hz, 1H, H₆), 6.30 (dd, J 15.5, 9.0 Hz, 1H, H₅), 4.88 (t, J 6.5 Hz, 1H, H₃),
4.45 (d, J 6.0 Hz, 1H, H₃), 2.92 (s, 6H, N(CH₃)₂). δ_C NMR (75 MHz, CDCl₃) δ 165.9, 138.7,
136.6, 135.6, 130.1, 128.7, 128.1, 126.6, 124.6, 124.3, 116.3, 57.5, 56.8, 38.3. MS (EI) m/z
293 (M+1)⁺, Anal. Calc. for C₁₉H₂₀N₂O: C, 78.05; H, 6.89; N, 9.58; found: C, 78.11; H, 6.93; N, 9.54.

4-Methyl-N-(2-oxo-1-phenyl-4-((E)-styryl)azetidin-3-yl)benzenesulfonamide (5c). White solid, δ_H 1H NMR (500 MHz, CDCl₃) 7.74-7.77 (m, 2H, ArH), 7.06-7.31 (m, 12H,
ArH), 6.45 (d, J 15.5 Hz, 1H, H₆), 5.93 (dd, J 16.0, 9.0 Hz, 1H, H₅), 5.06 (t, J 6.5 Hz, 1H,
H₃), 4.78 (d, J 6.5 Hz, 1H, H₃), 2.71 (s, 3H, CH₃). δ_C NMR (75 MHz, CDCl₃) δ 166.2,
139.4, 137.0, 136.3, 136.0, 135.3, 131.5, 130.1, 129.4, 128.7, 128.1, 126.6, 124.6, 124.3,
117.1, 57.5, 56.1, 16.2. MS (EI) m/z 419 (M+1)⁺, Anal. Calc. for C₂₄H₂₂N₂O₃S: C, 68.88;
H, 5.30; N, 6.69; found: C, 68.95; H, 5.33; N, 6.65.

4-Iodo-2-methyl-3,6-diphenyl-2,6-diazabicyclo[3.2.0]heptan-7-one (6a). Yield: 75%;
White solid, δ_H 1H NMR (500 MHz, CDCl₃) 7.43-7.45 (m, 2H, ArH), 7.28-7.38 (m, 5H,
ArH), 7.10 (m, 1H, ArH), 6.92 (m, 1H, ArH), 5.03 (d, J 4.0 Hz, 2H, H₃ & H₄), 4.95 (s, 1H,
H₁), 4.92 (d, J 3.0 Hz, 1H, H₃), 2.40 (s, 3H, CH₃). δ_C NMR (75 MHz, CDCl₃) δ 163.9,
139.4, 136.3, 129.4, 128.3, 127.4, 125.3, 124.6, 116.3, 74.7, 71.6, 67.5, 43.7, 30.7. MS (EI)
m/z 405 (M+1)⁺, HRMS calculated (M+H)+ 405.0464, found 405.0655, Anal. Calc. for
C₁₈H₁₇I₂N₂O: C, 53.48; H, 4.24; N, 6.93; found: C, 53.54; H, 4.30; N, 6.89.

4-Bromo-2-methyl-3,6-diphenyl-2,6-diazabicyclo[3.2.0]heptan-7-one (6b). Yield: 40%;
Brown solid; δ_H 1H NMR (500 MHz, CDCl₃) 7.43-7.49 (m, 4H, ArH), 7.28-7.37 (m, 5H,
ArH), 7.10 (m, 1H, ArH), 5.00 (s, JH, H₃), 4.81-4.89 (m, 2H, H₁ & H₄), 4.82 (d, J 3.5 Hz,
1H, H₃), 2.44 (s, 3H, CH₃). δ_C NMR (75 MHz, CDCl₃) δ 165.3, 138.0, 135.6, 129.1, 128.7,
128.4, 126.7, 124.3, 117.0, 73.8, 71.9, 66.2, 52.7, 45.8. (EI) m/z 357 (M+1)+. Anal. Calc. for C_{18}H_{17}BrN_{2}O: C, 60.52; H, 4.80; N, 7.84; found: C, 60.50; H, 4.71; N, 7.78.

**Typical procedure for the preparation of alkyl 4-iodo-5-aryl-3-(arylamino)pyrrolidine-2-carboxylates (7).** To a solution of compounds 2 (30mg, 1 eq) in methanol/ethanol (5 mL), NaOMe/NaOEt (3 eq) was added and the reaction mixture was stirred at 0°C for 1.5 h. The progress of the reaction was monitored with the help of TLC. After completion of the reaction, the mixture was quenched with ice and pH adjust to 6-7 extracted with ethyl acetate (3 times). The combined organic layers were washed with water and brine, dried over anhydrous Na_{2}SO_{4} and the solvent was evaporated to get compound (7) as a pure product as solid.

**Methyl 4-iodo-5-phenyl-3-(phenylamino)pyrrolidine-2-carboxylate (7a).** Yield: 85%; White solid; δ_{t}^{1}H NMR (500 MHz, CDCl_{3}) 7.52 (m, 2H, ArH), 7.31-7.39 (m, 3H, ArH), 7.19 (t, J 7.5 Hz, 2H, ArH), 6.76 (t, J 7.5 Hz, 1H, ArH), 6.63 (d, J 7.8 Hz, 2H, ArH), 4.70 (d, J 7.5 Hz, 1H, H), 4.46 (bs, 2H, H_{3} & H_{4}), 4.11 (d, J 7.2 Hz, 1H, H_{5}), 3.64 (s, 3H, COOCH_{3}). δ^{13}C NMR (75 MHz, CDCl_{3}) δ 172.1, 145.8, 139.3, 129.3, 128.9, 128.4, 127, 118.7, 113.9, 71.0, 66.0, 61.7, 52.3, 29.3. MS (EI) m/z 423 (M+1)+, HRMS calculated (M+H)+ 423.0569, found 423.0561, Anal. Calc. for C_{18}H_{19}I_{2}N_{2}O_{2}: C, 51.20; H, 4.54; N, 6.63; found: C, 51.12; H, 4.49; N, 6.69.

**Methyl 4-iodo-5-phenyl-3-(p-tolylamino)pyrrolidine-2-carboxylate (7b).** Yield: 88%; White solid; δ_{t}^{1}H NMR (300 MHz, CDCl_{3}) 7.51 (m, 2H, ArH), 7.31-7.38 (m, 3H, ArH), 6.99 (m, 2H, ArH), 6.53 (d, J 8.4 Hz, 2H, ArH), 4.69 (d, J 7.2 Hz, 1H, H_{2}), 4.43 (bs, 2H, H_{3} & H_{4}), 3.66 (s, 3H, COOCH_{3}), 2.23 (s, 3H, CH_{3}). δ^{13}C NMR (75 MHz, CDCl_{3}) δ 172.3, 143.5, 140.1, 129.6, 128.7, 128.2, 126.9, 120.3, 114.1, 71.3, 66.5, 61.8, 52.2, 33.9, 20.4. MS (EI) m/z 437 (M+1)+, HRMS calculated (M+H)+ 437.0726, found 437.0726, Anal. Calc. for C_{19}H_{21}I_{2}N_{2}O_{2}: C, 52.31; H, 4.85; N, 6.42; found: C, 52.29; H, 4.80; N, 6.44.

**Methyl 3-((4-chlorophenyl)amino)-4-iodo-5-phenylpyrrolidine-2-carboxylate (7c).** Yield: 75%; White solid; δ_{t}^{1}H NMR (500 MHz, CDCl_{3}) 7.43-7.45 (m, 2H, ArH), 7.28-7.39 (m, 3H, ArH), 7.12 (d, J 8.0 Hz, 2H, ArH), 6.81-6.89 (m, 2H, ArH), 4.69 (d, J 6.0 Hz, 1H, H_{2}), 4.48 (bs, 2H, H_{3} & H_{4}), 4.12 (d, J 7.0 Hz, 1H, H_{5}), 3.63 (s, 3H, CH_{3}). δ^{13}C NMR (75 MHz, CDCl_{3}) δ 171.4, 146.6, 139.4, 129.1, 128.5, 128.4, 127.1, 117.3, 114.2, 71.2, 65.8, 61.8, 52.6, 29.7. MS (EI) m/z 457 (M+1)+, HRMS calculated (M+H)+ 457.0180, found 457.0177, Anal. Calc. for C_{18}H_{18}Cl_{2}I_{2}N_{2}O_{2}: C, 47.34; H, 3.97; N, 6.13; found: C, 47.31; H, 3.92; N, 6.17.

**Methyl 4-iodo-3-((4-methoxyphenyl)amino)-5-phenylpyrrolidine-2-carboxylate (7d).** Yield: 79%; White solid; δ_{t}^{1}H NMR (500 MHz, CDCl_{3}) 7.32-7.38 (m, 4H, ArH), 7.10-7.25 (m, 3H, ArH), 6.83-6.87 (m, 2H, ArH), 4.69 (d, J 6.5 Hz, 1H, H_{2}), 4.49 (bs, 2H, H_{3} & H_{4}), 4.15 (d, J 7.5 Hz, 1H, H_{5}), 3.77 (s, 3H, OCH_{3}), 3.60 (s, 3H, COOCH_{3}). δ^{13}C NMR (75 MHz, CDCl_{3}) δ 169.0, 145.6, 137.7, 129.1, 128.7, 128.3, 127.0, 117.0, 113.6, 71.2, 66.5,
61.3, 55.8, 52.0, 29.6. MS (EI) m/z 453 (M+1)+, HRMS calculated (M+H) 453.0675, found 453.0669, Anal. Calc. for C_{19}H_{21}N_{2}O_{3}: C, 50.46; H, 4.68; N, 6.19; found: C, 50.39; H, 4.63; N, 6.21.

**Methyl 4-bromo-5-phenyl-3-(phenylamino)pyrrolidine-2-carboxylate (7e).** Yield: 87%; White solid; δ̂1H NMR (300 MHz, CDCl₃) 7.50 (m, 2H, ArH), 7.29-7.38 (m, 3H, ArH), 7.17 (t, J 6.6 Hz, 2H, ArH), 6.75 (t, J 7.5 Hz, 1H, ArH), 6.61 (d, J 7.8 Hz, 2H, ArH), 4.60 (J 6.0 Hz, 1H, H₂), 4.48 (J 6 Hz, 1H, H₃), 4.40 (bs, 1H, H₄), 4.07 (dd, J 3.9, 2.1 Hz, 1H, H₅), 3.68 (s, 3H, COOCH₃). δC NMR (75 MHz, CDCl₃) δ 171.6, 145.6, 139.4, 129.4, 128.8, 126.9, 113.9, 69.8, 64.5, 61.8, 56.3, 52.3, 33.8. MS (EI) m/z 375 (M+1)+, HRMS calculated (M+H)+ 375.0708, found 375.0704, Anal. Calc. for C_{18}H_{19}BrN_{2}O_{2}: C, 57.61; H, 5.10; N, 7.47; found: C, 57.59; H, 5.04; N, 7.50.

**Methyl 4-bromo-5-phenyl-3-(tolylamino)pyrrolidine-2-carboxylate (7f).** Yield: 90%; White solid; δ̂1H NMR (300 MHz, CDCl₃) 7.5 (m, 2H, ArH), 7.28-7.38 (m, 3H, ArH), 6.98 (d, J 7.8 Hz, 2H, ArH), 6.51 (d, J 7.8 Hz, 2H, ArH), 4.60 (d, J 5.7 Hz, 1H, H₂), 4.47 (d, J 5.7 Hz, 1H, H₃), 4.36 (bs, 1H, H₄), 4.06 (dd, J 6, 3.6 Hz, 1H, H₅), 3.68 (s, 3H, COOCH₃), 2.22 (s, 3H, CH₃). δC NMR (75 MHz, CDCl₃) δ 171.8, 143.3, 139.9, 129.8, 128.8, 128.2, 128.0, 126.8, 114.3, 70.0, 64.9, 61.9, 56.2, 29.7, 20.4. MS (EI) m/z 389 (M+1)+, HRMS calculated (M+H)+ 389.0865, found 389.0852, Anal. Calc. for C_{18}H_{19}BrN_{2}O_{2}: C, 58.62; H, 5.44; N, 7.20; found: C, 58.60; H, 5.41; N, 7.28.

**Methyl 4-bromo-3-(4-chlorophenylamino)-5-phenylpyrrolidine-2-carboxylate (7g).** Yield: 80%; Brown solid; δ̂1H NMR (500 MHz, CDCl₃) 7.42-7.45 (m, 2H, ArH), 7.28-7.38 (m, 3H, ArH), 7.11 (t, J 6.5 Hz, 2H, ArH), 6.81-6.87 (m, 2H, ArH), 4.62 (d, J 5.5 Hz, 1H, H₂), 4.46 (d, J 5.5 Hz, 1H, H₃), 4.37 (bs, 1H, H₄), 4.08 (dd, J 6.0 & 3.0 Hz, 1H, H₅), 3.65 (s, 3H, COOCH₃). δC NMR (75 MHz, CDCl₃) δ 169.7, 145.2, 139.0, 129.6, 129.1, 128.7, 125.1, 116.7, 114.3, 70.9, 64.7, 60.9, 56.1, 53.0. MS (EI) m/z 409(M+1)+, HRMS calculated (M+H)+ 409.0318, found 409.0313, Anal. Calc. for C_{18}H_{18}BrClN_{2}O_{2}: C, 52.77; H, 4.43; N, 6.84; found: C, 52.73; H, 4.39; N, 6.87.

**Methyl 4-bromo-3-(4-methoxyphenylamino)-5-phenylpyrrolidine-2-carboxylate (7h).** Yield: 82%; Brown solid; δ̂1H NMR (500 MHz, CDCl₃) 7.47-7.49 (m, 2H, ArH), 7.28-7.42 (m, 3H, ArH), 7.22-7.23 (m, 2H, ArH), 7.04-7.06 (m, 2H, ArH), 4.61 (d, J 6.0 Hz, 1H, H₂), 4.46 (d, J 5.5 Hz, 1H, H₃), 4.34 (bs, 1H, H₄), 4.09 (dd, J 6.5 & 3.5 Hz, 1H, H₅), 3.69 (s, 3H, OCH₃), 3.52 (s, 3H, COOCH₃). δC NMR (75 MHz, CDCl₃) δ 171.8, 146.0, 139.0, 129.1, 128.7, 128.1, 126.6, 118.4, 114.3, 70.9, 64.7, 61.3, 57.5, 56.1, 52.7. MS (EI) m/z 405 (M+1)+, HRMS calculated (M+H)+ 405.0814, found 405.0806, Anal. Calc. for C_{19}H_{21}BrN_{2}O_{3}: C, 56.31; H, 5.22; N, 6.91; found: C, 56.29; H, 5.17; N, 6.96.

**Ethyl 4-ido-5-phenyl-3-(phenylamino)pyrrolidine-2-carboxylate (7i).** Yield: 86%; White solid; δ̂1H NMR (500 MHz, CDCl₃) 7.28-40 (m, 5H, ArH), 7.06-7.12 (m, 2H, ArH), 6.76 (t, J 7.5 Hz, 1H, ArH), 6.62 (d, J 7.5 Hz, 2H, ArH), 4.70 (d, J 6.0 Hz, 1H, H₂), 4.46 (m, 2H, H₃ & H₄), 4.17 (m, 2H, CH₂), 4.08 (d, J 7.0 Hz, 1H, H₃), 1.27 (t, J 7.5 Hz, 3H, CH₂CH₃). δC NMR (75 MHz, CDCl₃) δ 170.7, 145.6, 139.4, 129.4, 128.7, 128.3, 127.0,
118.7, 113.6, 71.2, 66.1, 61.3, 60.3, 29.3, 14.5. MS (EI) m/z 437 (M+1)^+, HRMS calculated (M+H) 437.0726, found 437.0720, Anal. Calc. for C_{19}H_{21}N_{2}O_{2}: C, 52.31; H, 4.85; N, 6.42; found: C, 52.27; H, 4.79; N, 6.47.

**Ethyl 4-ido-5-phenyl-3-(p-tolylamino)pyrrolidine-2-carboxylate (7j).** Yield: 82%; White solid; δ_H 1H NMR (500 MHz, CDCl_3) 7.35-7.49 (m, 4H, ArH), 7.22-7.28 (m, 3H, ArH), 7.05 (d, J 8.5 Hz, 2H, ArH), 4.68 (d, J 7.0 Hz, 1H, H_2), 4.39-4.50 (m, 2H, H_3 & H_4), 4.10-4.18 (m, 3H, CH_2 & H_5), 2.27 (s, 3H, CH_3), 1.28 (t, J 7.5 Hz, 3H, CH_2CH_3). &^NMR (75 MHz, CDCl_3) δ 171.4, 143.5, 139.4, 129.4, 128.7, 128.1, 126.3, 114.3, 71.2, 66.5, 62.0, 60.3, 33.8, 20.7, 13.8. MS (EI) m/z 451 (M+1)^+, HRMS calculated (M+H)^+ 451.0882, found 451.0879, Anal. Calc. for C_{20}H_{23}N_{2}O_{2}: C, 53.34; H, 5.15; N, 6.22; found: C, 53.31; H, 5.10; N, 6.27.

**Ethyl 4-bromo-5-phenyl-3-(phenylamino)pyrrolidine-2-carboxylate (7k).** Yield: 73%; Brown solid; δ_H 1H NMR (500 MHz, CDCl_3) 7.50 (m, 2H, ArH), 7.32-7.48 (m, 5H, ArH), 7.23-7.28 (m, 2H, ArH), 7.02 (t, J 7.5 Hz, 1H, ArH), 4.61 (d, J 5.5 Hz, 1H, H_2), 4.46 (d, J 5.5 Hz, 1H, H_3), 4.39 (bs, 1H, H_3), 4.06-4.13 (m, 3H, CH_2 & H_4), 1.19 (t, J 7.5 Hz, 3H, CH_2CH_3). &^NMR (75 MHz, CDCl_3) δ 171.1, 145.2, 139.4, 129.4, 129.1, 127.8, 126.3, 118.7, 114.0, 69.9, 64.4, 61.6, 60.6, 56.9, 14.5. MS (EI) m/z 390 (M+1)^+, HRMS calculated (M+H)^+ 389.0865, found 389.0855, Anal. Calc. for C_{19}H_{21}BrN_{2}O_{2}: C, 58.62; H, 5.44; N, 7.20; found: C, 58.59; H, 5.36; N, 7.24.

**Ethyl 4-bromo-5-phenyl-3-(p-tolylamino)pyrrolidine-2-carboxylate (7l).** Yield: 81%; Brown solid; δ_H 1H NMR (500 MHz, CDCl_3) 7.28-7.49 (m, 5H, ArH), 7.22 (m, 2H, ArH), 7.05 (m, 2H, ArH), 4.59 (d, J 6.0 Hz, 1H, H_2), 4.47 (d, J 6.0 Hz, 1H, H_3), 4.36 (bs, 1H, H_3), 4.08-4.17 (m, 3H, CH_2 & H_4), 2.21 (s, 3H, CH_3), 1.28 (t, J 7.5 Hz, 3H, CH_2CH_3). &^NMR (75 MHz, CDCl_3) δ 170.1, 143.4, 139.8, 129.7, 129.4, 128.7, 128.1, 126.6, 114.3, 70.3, 64.7, 62.0, 60.6, 56.1, 29.7, 21.5, 13.7. MS (EI) m/z 404 (M+1)^+, HRMS calculated (M+H)^+ 403.1021, found 403.1014, Anal. Calc. for C_{20}H_{23}BrN_{2}O_{2}: C, 59.56; H, 5.75; N, 6.95; found: C, 59.51; H, 5.73; N, 6.98.

**Typical procedure for the preparation of 4,6-diaryl-3,6-diazabicyclo[3.1.0] hexane-2-carboxylic acids (8).** To a solution of compound 2 (30mg, 1 eq) in methanol/ethanol (5 mL), NaOMe/NaOEt (6.5 eq) was added and the reaction mixture was stirred at room temperature for 1 hr. Then the reaction mixture was heated up to 50 °C for 30 minutes. The progress of the reaction was monitored with the help of TLC. After completion of the reaction, the mixture was quenched with ice and pH adjust to 6-7. Now, the reaction mixture was concentrated under reduced pressure and purified via flash column chromatography using silica gel (100:200 mesh) in MeOH/DCM (1:9) as an eluent system to get compound 6 as a pure product.

**4,6-Diphenyl-3,6-diazabicyclo[3.1.0]hexane-2-carboxylic acid (8a).** Yield: 90%; Brown solid; δ_H 1H NMR (300 MHz, MeOD) 7.68 (dd, J 8.4 & 1.5 Hz, 2H, ArH), 7.31-7.42 (m, 3H, ArH), 7.12 (t, J 7.8 Hz, 2H, ArH), 6.58 (d, J 7.8 Hz, 3H, ArH), 4.10 (d, J 1.8 Hz, 1H,
H2), 3.68 (d, J 1.8 Hz, 1H, H3), 3.23 (dd, J 4.5, 2.1 Hz, 1H, H3), 3.08 (dd, J 4.5, 2.1 Hz, 1H, H4). δC NMR (75 MHz, DMSO-d6) δ 173.8, 154.1, 141.8, 129.07, 128.6, 127.8, 127.5, 121.7, 120.9, 64.3, 63.6, 49.7, 49.0. MS (EI) m/z 281 (M+1)+, HRMS calculated (M+H)+ 281.1290, found 281.1289, Anal. Calc. for C17H16N2O2: C, 72.84; H, 5.75; N, 9.99; found: C, 72.78; H, 5.71; N, 10.02.

4-Phenyl-6-(p-tolyl)-3,6-diazabicyclo[3.1.0]hexane-2-carboxylic acid (8b). Yield: 88%; Brown solid; δH 1H NMR (500 MHz, MeOD) 7.51 (m, 2H, ArH), 7.25-7.48 (m, 3H, ArH), 7.03 (m, 2H, ArH), 6.70 (d, J 7.5 Hz, 2H, ArH), 4.09 (d, J 2.0 Hz, 1H, H2), 3.65 (d, J 2.0 Hz, 1H, H3), 3.19 (dd, J 4.0, 2.0 Hz, 1H, H3), 3.08 (dd, J 4.5, 2.0 Hz, 1H, H4), 2.27 (s, 3H, CH3). δC NMR (75 MHz, DMSO-d6) δ 172.8, 154.5, 141.7, 129.1, 128.5, 127.5, 127.4, 121.8, 121.3, 64.3, 63.9, 49.8, 49.2, 21.4. MS (EI) m/z 295 (M+1)+, HRMS calculated (M+H)+ 295.1447, found 295.1440, Anal. Calc. for C18H18N2O2: C, 73.45; H, 6.16; N, 9.52; found: C, 73.38; H, 6.10; N, 9.54.

6-(4-Chlorophenyl)-4-phenyl-3,6-diazabicyclo[3.1.0]hexane-2-carboxylic acid (8c). Yield: 82%; Brown solid; δH 1H NMR (500 MHz, MeOD) 7.25-7.51 (m, 5H, ArH), 6.99-7.02 (m, 2H, ArH), 6.71-6.76 (m, 2H, ArH), 4.10 (d, J 2.0 Hz, 1H, H2), 3.64 (d, J 2.0 Hz, 1H, H3), 3.20 (dd, J 4.5, 2.0 Hz, 1H, H3), 3.08 (m, 1H, H4). δC NMR (75 MHz, DMSO-d6) δ 172.1, 154.5, 141.8, 129.4, 128.3, 127.4, 127.0, 121.5, 120.8, 64.4, 63.3, 48.9, 47.9. MS (EI) m/z 315 (M+1)+, HRMS calculated (M+H)+ 315.0900, found 315.0891, Anal. Calc. for C17H15ClN2O2: C, 64.87; H, 4.80; N, 8.90; found: C, 64.85; H, 4.85; N, 8.96.

6-(4-Methoxyphenyl)-4-phenyl-3,6-diazabicyclo[3.1.0]hexane-2-carboxylic acid (8d). Yield: 85%; Brown solid; δH 1H NMR (500 MHz, MeOD) 7.23-7.53 (m, 5H, ArH), 6.74-7.02 (m, 4H, ArH), 4.10 (d, J 1.5 Hz, 1H, H3), 3.66 (d, J 1.5 Hz, 1H, H3), 3.23 (dd, J 4.5, 2.0 Hz, 1H, H3), 3.19 (s, 3H, OCH3) 3.07 (dd, J 4.5 & 2.0 Hz, 1H, H4). δC NMR (75 MHz, DMSO-d6) δ 173.8, 154.2, 141.5, 129.8, 128.7, 127.7, 127.4, 121.9, 120.4, 64.4, 63.0, 55.8, 49.9, 48.9. MS (EI) m/z 311 (M+1)+, HRMS calculated (M+H)+ 311.1396, found 310.1388, Anal. Calc. for C18H18N2O3: C, 69.66; H, 5.85; N, 9.03; found: C, 69.63; H, 5.78; N, 9.08.

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