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

Yogesh Kumar,[a] Bilash Kulia,[a] Prabhpreet Singh,[b] and Gaurav Bhargava*[a]

[a]*Department of Chemical Sciences, I. K. Gujral Punjab Technical University, Kapurthala, Punjab 144 603, India*
[b]*Department of Chemistry, Guru Nanak Dev University, Amritsar, Punjab 143 005, India*
E-mail: gaurav@ptu.ac.in

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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-arylaminopyrrolidine-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-isoquinoline[11] and octahydroindole[12] 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.[13-15] 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.[16] Aziridines are valuable intermediates in natural product synthesis as in the case of the (-)-mesembrine, (-)-platynesine, kainoids, sphingosines, epicapreomycidine, actinomycin, (±)-and feldamycin.[17,18] Members of this family exhibit potent activity against a variety of cancer cell lines, and were found to be particularly active against solid tumors.[19-21] In addition, aziridinopyrrolidines have shown interesting biological properties which makes them important synthetic targets.[22-25] However, the reported methods for preparation of aziridinopyrrolidines are cumbersome and have multistep reaction procedures.[17-21]

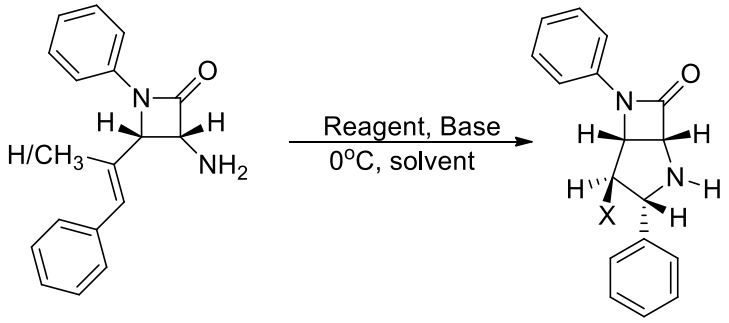
Recent publications from our laboratory have reported the synthesis and subsequent transformations of functionalized lactams for the synthesis of (2-oxo-4-styrylazetidin-3-yl)pyridine, butadienyl-4-iminomethylazetidin-2-ones, butenylidene-butadienyl-[2,2′-biazetidine]-4,4′-diones, 1,4-benzodiazepin-2-ones and dienyl thiazolidin-4-ones,[26-28] *etc*. 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.[29] 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.[30,31]

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.[32]

Results and Discussion

The starting materials 3-aminoazetidin-2-ones **1**, used in halocyclization reactions were prepared by reported methods.[33] 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*. I_2, Br_2, 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-*t*-butoxide. However, this resulted in deterioration of the products.



2a

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

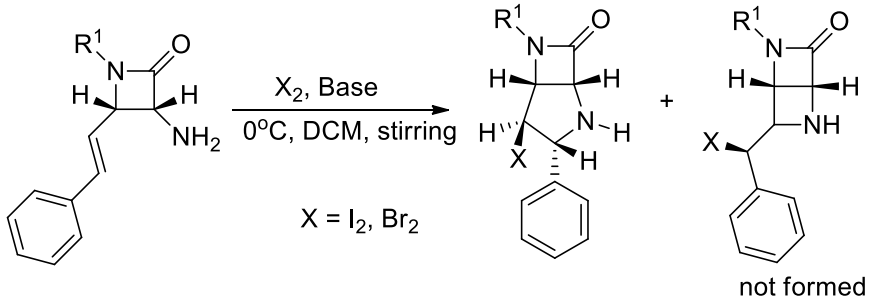
Table 1. Reaction of **1a** under different reaction conditions

S.No.	Reagent	Base	Solvent	Reaction Time[a]	Yield(%)[b]
1	NIS	K_2CO_3	DCM	30	40
2	I_2	K_2CO_3	DCM	90	90
3	Br_2	K_2CO_3	DCM	45	61
4	NBS	K_2CO_3	DCM	60	20
5	NCS	K_2CO_3	DCM	90	-
6	I_2	Na_2CO_3	DCM	90	80
7	Br_2	Na_2CO_3	DCM	90	45
8	I_2	*t*BuOK	DCM	90	-
9	I_2	NaH	DCM	90	-
10	I_2	K_2CO_3	DMF	80	55
11	I_2	K_2CO_3	THF	90	30

[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.* K_2CO_3 and Na_2CO_3 (Scheme 2). The reactions led to the formation of regio- and diastereo-isomerically pure 4-halo-3-aryl/akyl-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.



1a, R^1 = -C_6H_5
1b, R^1 = *p*-CH_3-C_6H_4
1c, R^1 = *p*-Cl-C_6H_4
1d, R^1= *p*-OMe-C_6H_4
1e, R^1 = *p*-F-C_6H_4
1f, R^1 = Cyclohexyl
1g, R^1 = Benzyl

2a, R^1 = -C_6H_5 X= I
2b, R^1 = *p*-CH_3-C_6H_4, X= I
2c, R^1 = *p*-Cl-C_6H_4, X= I
2d, R^1 = *p*-OMe-C_6H_4, X= I
2e, R^1 = *p*-F-C_6H_4, X= I
2f, R^1 = Cyclohexyl, X= I
2g, R^1 = Benzyl, X = I
2h, R^1 = -C_6H_5, X= Br
2i, R^1 = *p*-CH_3-C_6H_4 , X= Br
2j, R^1= *p*-Cl-C_6H_4, X=Br
2k, R^1= *p*-OMe-C_6H_4, X= Br
2l, R^1 = *p*-F-C_6H_4, X= Br
2m, R^1 = Benzyl, X = I

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**.

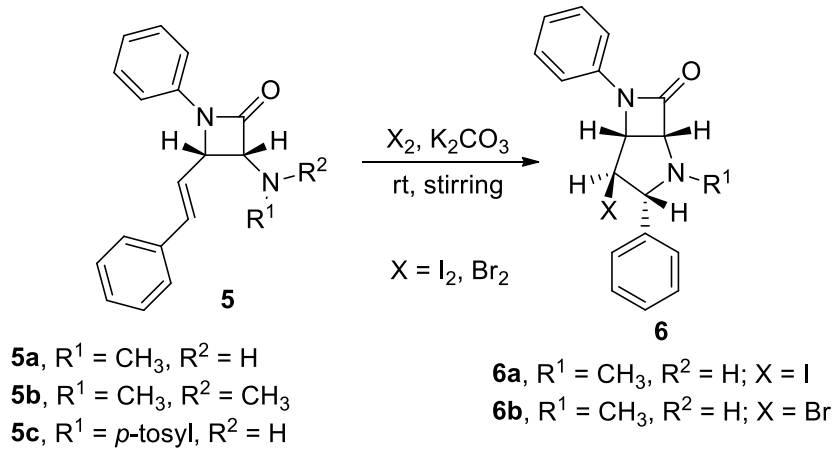
We next studied the effect of substituents of the participating nitrogen of 3-aminoazetidin-2-ones in these haloamination reactions (Scheme 3). Two substituents (i) electron withdrawing (tosyl), (ii) electron donating (methyl) were studied in these haloamination reactions. We have also explored the effect 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.

Table 2. Synthesis of 4-halo-3-aryl/alkyl-6-aryl-2,6-diazabicyclo[3.2.0]heptan-7-ones **2** by halocyclization reactions

S.No.	R^1	X[c]	Base	Product	Reaction Time[a]	Yield (%)[b]
1	C_6H_5	I	K_2CO_3	**2a**	90	90
2	*p*-CH_3-C_6H_4	I	K_2CO_3	**2b**	90	82
3	*p*-Cl-C_6H_4	I	K_2CO_3	**2c**	90	65
4	*p*-CH_3O-C_6H_4	I	K_2CO_3	**2d**	90	66
5	*p*-F-C_6H_4	I	K_2CO_3	**2e**	90	62
6	cyclohexyl	I	K_2CO_3	**2f**	90	75
7	Benzyl	I	K_2CO_3	**2g**	90	60
8	C_6H_5	Br	K_2CO_3	**2h**	45	61
9	*p*-CH_3-C_6H_4	Br	K_2CO_3	**2i**	45	55
10	*p*-Cl-C_6H_4	Br	K_2CO_3	**2j**	45	50
11	*p*-CH_3O-C_6H_4	Br	K_2CO_3	**2k**	45	55
12	*p*-F-C_6H_4	Br	K_2CO_3	**2l**	45	60
13	Benzyl	Br	K_2CO_3	**2m**	45	45
14	C_6H_5	I	Na_2CO_3	**2a**	90	80
15	*p*-CH_3-C_6H_4	I	Na_2CO_3	**2b**	90	75

[a] Reaction time in minutes. [b] Isolated yield after purification. [c]1.2 equivalent.

The reaction of *N,N*-disubstituted as well as mono N^5-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**

S. No.	R^1	R^2	X	Product	Reaction Time [a]	Yield(%)[b]
1	CH_3	H	I	**6a**	90	75
2	CH_3	H	Br	**6b**	50	40
3	CH_3	CH_3	I	**6c**	90	0
4	*p*-tosyl	H	I	**6d**	90	0

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

The diastereomerically pure, functionalized novel 4-halo-3-aryl/alkyl-6-aryl-2,6-diaza-bicyclo[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 $C_{18}H_{17}IN_2O$ 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 H_1 proton of the ring, an unresolved doublet of doublet at δ 4.94 having *J* 3.6Hz corresponding to H_5 of the lactam ring, a multiplet at δ 5.02 corresponding to H_3 & H_4 protons. The ^{13}C 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.[29] The 4-iodo-3,6-diphenyl-2,6-diazabicyclo[3.2.0]heptan-7-one (**2a**) has shown the *anti* stereochemistry between H^5 of azetidin-2-one and H^4 of the pyrrole ring (Figure 1).

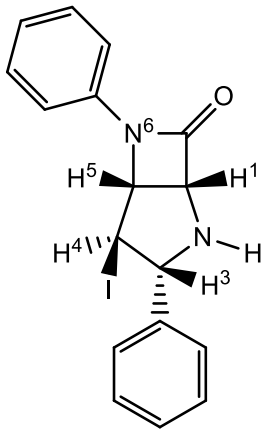
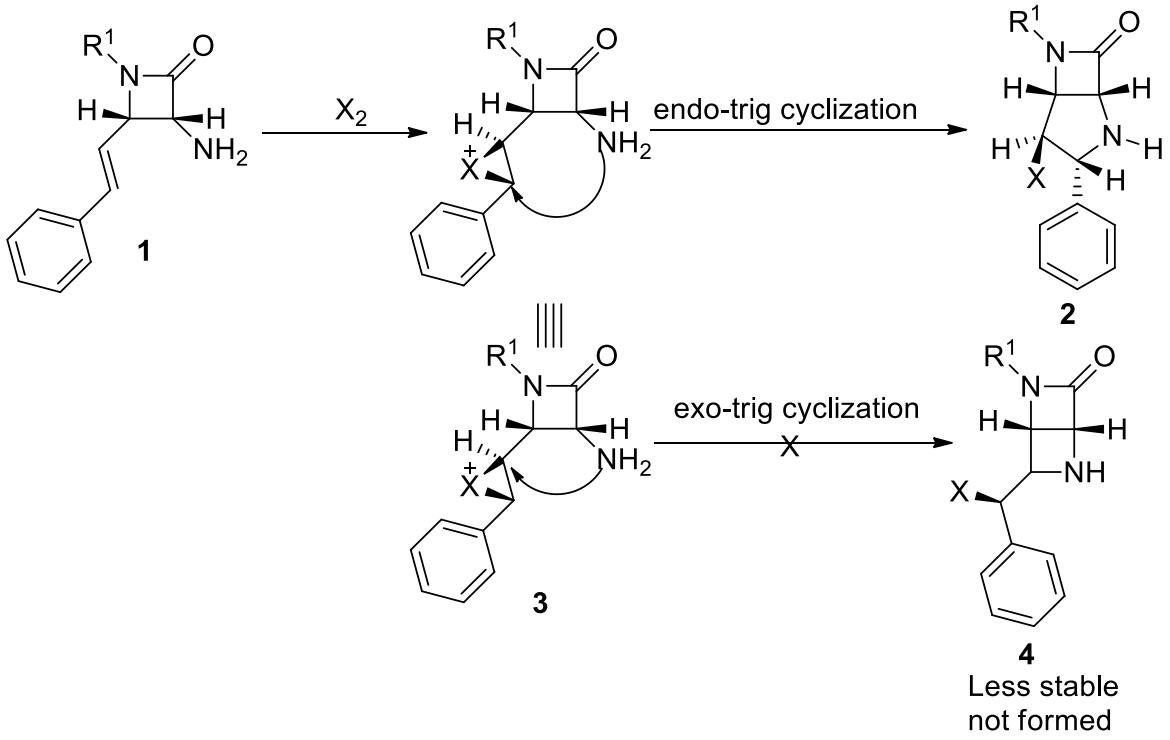


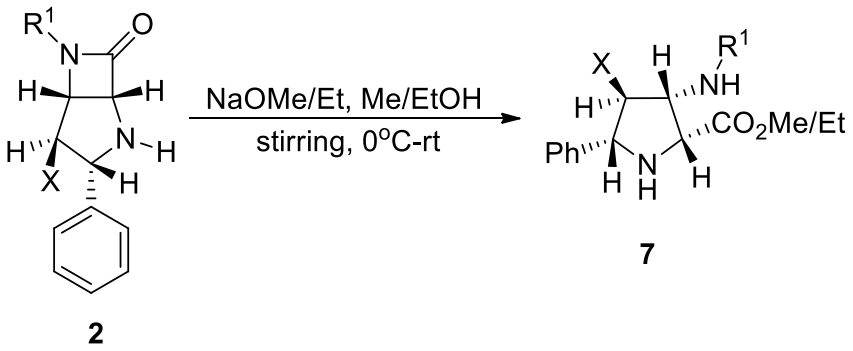
Figure 1. 4-Iodo-3,6-diphenyl-2,6-diazabicyclo[3.2.0]heptan-7-one **2a**.

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 *β*–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-diaza-bicyclo[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^6-C^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).



2 **7**

Scheme 5. Synthesis of alkyl 4-iodo-5-aryl-3-(arylamino)pyrrolidine-2-carboxylates **7**.

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

S.No.	R^1	X	Base	Solvent	Product[a]	Yield (%)[b]
1	C_6H_5	I	$NaOCH_3$	CH_3OH	**7a**	85
2	*p*-$CH_3C_6H_4$	I	$NaOCH_3$	CH_3OH	**7b**	88
3	*p*-ClC_6H_4	I	$NaOCH_3$	CH_3OH	**7c**	75
4	*p*-$CH_3OC_6H_4$	I	$NaOCH_3$	CH_3OH	**7d**	79
5	C_6H_5	Br	$NaOCH_3$	CH_3OH	**7e**	87
6	*p*-$CH_3C_6H_4$	Br	$NaOCH_3$	CH_3OH	**7f**	90
7	*p*-ClC_6H_4	Br	$NaOCH_3$	CH_3OH	**7g**	80
8	*p*-$CH_3OC_6H_4$	Br	$NaOCH_3$	CH_3OH	**7h**	82
9	C_6H_5	I	$NaOC_2H_5$	C_2H_5OH	**7i**	86
10	*p*-$CH_3C_6H_4$	I	$NaOC_2H_5$	C_2H_5OH	**7j**	82
11	C_6H_5	Br	$NaOC_2H_5$	C_2H_5OH	**7k**	73
12	*p*-$CH_3C_6H_4$	Br	$NaOC_2H_5$	C_2H_5OH	**7l**	81

[a]Isolated yields after purification. [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 $C_{18}H_{19}IN_2O_2$ showed a (M+1) molecular ion peak at *m/z* 423 in its mass spectrum (Figure 2). The ^{1}H NMR (300 MHz) spectrum showed a characteristic doublet (*J* 7.5 Hz) at δ 4.70 corresponding to H_2 of the ring, a broad singlet at δ 4.46 corresponding to H_3 and H_4 of the ring, a doublet at δ 4.11 having *J* 7.2 Hz assigned to H_5. The ^{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.

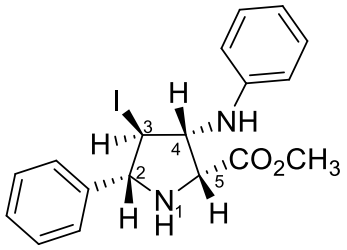
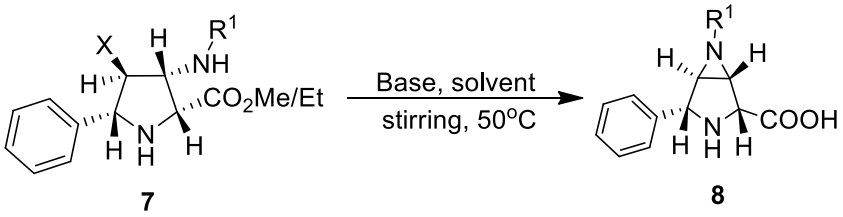


Figure 2. Methyl 4-iodo-5-phenyl-3-(phenylamino)pyrrolidine-2-carboxylate **7a**.

4-Halo-5-phenyl-3-arylaminopyrrolidine-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 ($C_{17}H_{16}N_2O_2$) **8a** for example, showed a molecular ion peak at *m/z* (M+1) 281 in its mass spectrum. The ^{1}H NMR (300MHz) spectrum showed a characteristic doublet (*J* 1.8 Hz) at δ 4.10 corresponding to H_2 of the ring, a doublet (*J* 1.8 Hz) at δ 3.68 corresponding to H_5 of the ring, two doublet of doublet at δ 3.23 & 3.08 having *J* 4.5, 2.1 Hz assigned to H_3 and H_4 respectively. The ^{13}C 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**

S.No	R^1	X	Base	Solvent	Product	Yield (%)[a]
1	C_6H_5	I	$NaOCH_3$	CH_3OH	**8a**	90
2	*p*-$CH_3C_6H_4$	I	$NaOCH_3$	CH_3OH	**8b**	88
3	*p*-ClC_6H_4	I	$NaOCH_3$	CH_3OH	**8c**	82
4	*p*-$CH_3OC_6H_4$	I	$NaOCH_3$	CH_3OH	**8d**	85
5	C_6H_5	Br	$NaOCH_3$	CH_3OH	**8a**	87
6	*p*-$CH_3C_6H_4$	Br	$NaOCH_3$	CH_3OH	**8b**	79
7	*p*-ClC_6H_4	Br	$NaOCH_3$	CH_3OH	**8c**	82
8	*p*-$CH_3OC_6H_4$	Br	$NaOCH_3$	CH_3OH	**8d**	80
9	C_6H_5	I	$NaOC_2H_5$	C_2H_5OH	**8a**	84
10	*p*-$CH_3C_6H_4$	I	$NaOC_2H_5$	C_2H_5OH	**8b**	78
11	*p*-ClC_6H_4	I	$NaOC_2H_5$	C_2H_5OH	**8c**	81
12	*p*-$CH_3OC_6H_4$	I	$NaOC_2H_5$	C_2H_5OH	**8d**	76
13	C_6H_5	Br	$NaOC_2H_5$	C_2H_5OH	**8a**	85
14	*p*-$CH_3C_6H_4$	Br	$NaOC_2H_5$	C_2H_5OH	**8b**	78
15	*p*-ClC_6H_4	Br	$NaOC_2H_5$	C_2H_5OH	**8c**	79
16	*p*-$CH_3OC_6H_4$	Br	$NaOC_2H_5$	C_2H_5OH	**8d**	82

[a] Isolated yields after purification

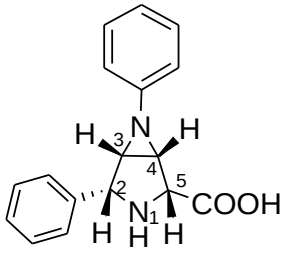
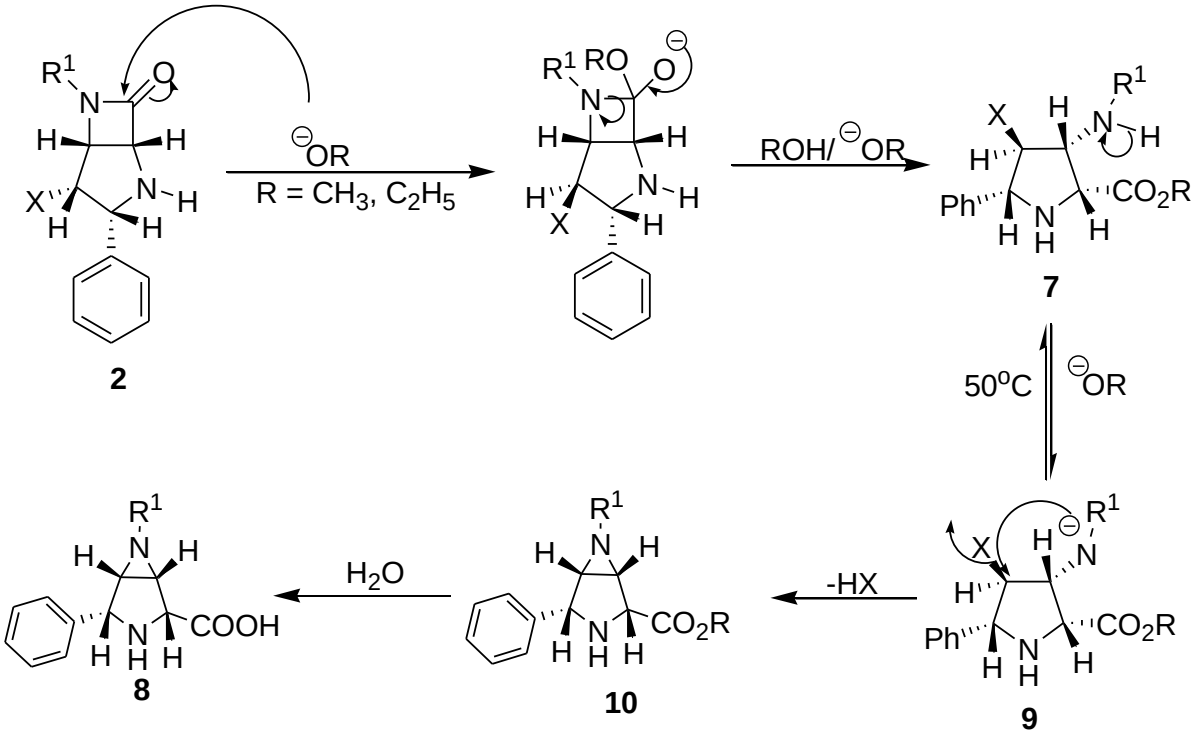


Figure 3. 4,6-Diphenyl-3,6-diazabicyclo[3.1.0]hexane-2-carboxylic acid **8a**.

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.



Scheme 7. Plausible mechanism depicting the formation of 4,6-diaryl-3,6-diazabicyclo[3.1.0]-hexane-2-carboxylic acids **8**.

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 synthons for the synthesis of highly functionalized proline esters. The one pot amidiolytic 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

conducted on Merck Kieselgel 60 F254. Compounds were visualized with both short- and long-wavelength UV light. Column chromatography was performed on silica gel (100-200 mesh). Melting points were determined in capillary tubes using a Mel-Temp apparatus and are not corrected. Infrared spectra were obtained as films on KBr salt plates except where otherwise specified, using a Perkin Elmer FT-IR spectrometer. ^{1}H NMR spectra were obtained with $CDCl_3$ at 300 & 500 MHz, using Bruker spectrometers (residual chloroform referenced to 7.26 ppm) or DMSO-d_6 (residual DMSO referenced to 2.50 ppm and residual water in DMSO-d_6 appearing at 3.33 ppm). Chemical shift values are expressed as parts per million downfield from TMS and *J* values are in hertz. Splitting patterns are indicated as s: singlet, d: doublet, t: triplet, m: multiplet, dd: double doublet, ddd: doublet of a doublet of a doublet, and br: broad peak. ^{13}C NMR spectra were recorded with $CDCl_3$ at 75 MHz, using Bruker spectrometers (residual chloroform referenced to 77.0 ppm) or DMSO-d_6 (residual DMSO referenced to 39.5 ppm). Infrared spectra were recorded on a Perkin Elmer FT-IR spectrometer. HRMS were recorded on Bruker high resolution spectrometer (Bruker microTOF QII).

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 K_2CO_3 at 0 ºC. The solution was stirred at 0 ºC 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 $Na_2S_2O_3$/water solution followed by brine solution. The dichloromethane solution was dried over anhydrous Na_2SO_4 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 ºC; δ_H ^{1}H NMR (300 MHz, $CDCl_3$) 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, $CDCl_3$) δ 164.2, 139.6, 136.1, 129.0, 128.2, 127.2, 125.3, 124.4, 116.8, 74.7, 71.8, 67.8, 30.7. MS (EI) *m/z* 391 $(M+1)^+$, ν_{max} (KBr)/cm^{-1} 1755, HRMS calculated for $C_{17}H_{15}IN_2O$ $(M+H)^+$ 391.0307, found 391.0314.

X-Ray crystal data and structure refinement. CCDC 972460 contains the supplementary crystallographic data. $C_{17}H_{15}I_1N_2O_1$, V = 2958.9(2) Å^3 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), T_{min} = 0.655, T_{max} = 0.677, R_{int} = 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 ºC; δ_H ^{1}H NMR (300 MHz, $CDCl_3$) 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, $CDCl_3$) 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 $(M+1)^+$, ν_{max} (KBr)/cm^{-1} 1755, HRMS calculated for $C_{18}H_{17}IN_2O$ $(M+H)^+$ 405.0464, found 405.0488..

6-(4-Chlorophenyl)-4-iodo-3-phenyl-2,6-diazabicycle[3.2.0]heptan-7-one (2c). Yield: 65%; Pale yellow solid, mp 143–144; δ_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), 4.92 (bs, 2H). δ_C NMR (75 MHz, $CDCl_3$) δ 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 $(M+1)^+$, ν_{max} (KBr)/cm^{-1} 1755, HRMS calculated for $C_{17}H_{14}ClIN_2O$ $(M+H)^+$ 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; δ_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), 4.91 (bs, 2H), 3.21 (s, 3H). δ_C NMR (75 MHz, $CDCl_3$) δ 164.0, 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 $(M+1)^+$, ν_{max} (KBr)/cm^{-1} 1755, HRMS calculated for $C_{18}H_{17}IN_2O_2$ $(M+H)^+$ 421.0413, found 421.0411.

6-(4-Fluorophenyl)-4-iodo-3-phenyl-2,6-diazabicycle[3.2.0]heptan-7-one (2e). Yield: 62%; Pale yellow solid, mp 124–127; δ_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, H_3 & H_4), 4.92 (m, 2H, H_1 & H_5). δ_C NMR (75 MHz, $CDCl_3$) δ 163.9, 139.7, 134.2, 133.7, 129.6, 128.3, 128.0, 127.2, 125.4, 116.9, 74.8, 71.8, 67.9, 30.8. MS (EI) *m/z* 409 $(M+1)^+$, ν_{max} (KBr)/cm^{-1} 1750, HRMS calculated $(M+H)^+$ 409.0213, found 409.0207, Anal. Calc. for $C_{17}H_{14}FIN_2O$: C, 50.02; H, 3.46; N, 6.86; found: C, 50.06; H, 3.51; N, 6.81.

6-Cyclohexyl-4-iodo-3-phenyl-2,6-diazabicyclo[3.2.0]heptan-7-one (2f). Yield: 75%; Pale yellow solid, mp 110–111; δ_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), δ_C NMR (75 MHz, $CDCl_3$) δ 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 $(M+1)^+$, ν_{max} (KBr)/cm^{-1} 1755, HRMS calculated $(M+H)^+$ 397.0777, found 397.0773, Anal. Calc. for $C_{17}H_{21}IN_2O$: 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; δ_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). δ_C NMR (75 MHz, $CDCl_3$) δ 170.1, 143.4, 128.8, 128.7, 128.5, 127.9, 127.2, 126.6, 123.5, 74.4, 70.3, 65.8, 47.26, 29.7. MS (EI) *m/z* 405 $(M+1)^+$, ν_{max} (KBr)/cm^{-1} 1752, HRMS calculated $(M+H)^+$ 405.0464, found 405.0462, Anal. Calc. for $C_{18}H_{17}IN_2O$: 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; δ_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_1), 4.83 (d, *J* 3.6 Hz, 1H, H_5). δ_C NMR 75 MHz, $CDCl_3$) δ 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 $C_{17}H_{15}BrN_2O$: 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; δ_H ^{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_5), 2.24 (s, 3H, CH_3). δ_C NMR (75 MHz, $CDCl_3$) δ 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 $C_{18}H_{17}BrN_2O$: 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, δ_H ^{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). δ_C NMR (75 MHz, $CDCl_3$) δ 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 $C_{17}H_{14}BrClN_2O$: 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, δ_H ^{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). δ_C NMR (75 MHz, $CDCl_3$) δ 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 $C_{18}H_{17}BrN_2O_2$: 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, δ_H ^{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). δ_C NMR (75 MHz, $CDCl_3$) δ 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 $C_{17}H_{14}FBrN_2O$: 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, δ_H ^{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_5), 4.10-4.15 (m, 2H, CH_2). δ_C NMR (75 MHz, $CDCl_3$) δ 169.1, 143.4, 128.8, 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 $C_{18}H_{17}IN_2O$: 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_2CO_3 at 0 ^oC. The solution was stirred at 0 ^oC. 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 $Na_2S_2O_3$/water solution followed by brine solution. The dichloromethane solution was dried over anhydrous Na_2SO_4 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 **6**.

3-(Methylamino)-1-phenyl-4-((*E*)-styryl)azetidin-2-one (5a). White solid, δ_H ^{1}H NMR (500 MHz, $CDCl_3$) 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, H_6), 6.53 (dd, *J* 16.0, 8.0 Hz, 1H, H_5), 4.86 (t, *J* 6.5 Hz, 1H, H_3), 4.46 (d, *J* 5.5 Hz, 1H, H_3), 2.90 (s, 3H, NCH_3). δ_C NMR (75 MHz, $CDCl_3$) 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 $C_{18}H_{18}N_2O$: 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 ^{1}H NMR (500 MHz, $CDCl_3$) 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, H_6), 6.30 (dd, *J* 15.5, 9.0 Hz, 1H, H_5), 4.88 (t, *J* 6.5 Hz, 1H, H_3), 4.45 (d, *J* 6.0 Hz, 1H, H_3), 2.92 (s, 6H, $N(CH_3)_2$). δ_C NMR (75 MHz, $CDCl_3$) 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 $C_{19}H_{20}N_2O$: 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 ^{1}H NMR (500 MHz, $CDCl_3$) 7.74-7.77 (m, 2H, ArH), 7.06-7.31 (m, 12H, ArH), 6.45 (d, *J* 15.5 Hz, 1H, H_6), 5.93 (dd, *J* 16.0, 9.0 Hz, 1H, H_5), 5.06 (t, *J* 6.5 Hz, 1H, H_3), 4.78 (d, *J* 6.5 Hz, 1H, H_3), 2.71 (s, 3H, CH_3). δ_C NMR (75 MHz, $CDCl_3$) 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 $C_{24}H_{22}N_2O_3S$: 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 ^{1}H NMR (500 MHz, $CDCl_3$) 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, H_3 & H_4), 4.95 (s, 1H, H_1), 4.92 (d, *J* 3.0 Hz, 1H, H_5), 2.40 (s, 3H, CH_3). δ_C NMR (75 MHz, $CDCl_3$) 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 $C_{18}H_{17}IN_2O$: 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 ^{1}H NMR (500 MHz, $CDCl_3$) 7.43-7.49 (m, 4H, ArH), 7.28-7.37 (m, 5H, ArH), 7.10 (m, 1H, ArH), 5.00 (s, *1*H, H_3), 4.81-4.89 (m, 2H, H_1 & H_4), 4.82 (d, *J* 3.5 Hz, 1H, H_5), 2.44 (s, 3H, CH_3). δ_C NMR (75 MHz, $CDCl_3$) 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 $C_{18}H_{17}BrN_2O$: 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 ^oC 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_2SO_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_H ^1H 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_2), 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_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 $C_{18}H_{19}IN_2O_2$: 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_H ^1H 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), 4.06-4.10 (m, 1H, H_5), 3.66 (s, 3H, $COOCH_3$), 2.23 (s, 3H, CH_3). δ_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 $C_{19}H_{21}IN_2O_2$: 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_H ^1H 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_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 $C_{18}H_{18}ClIN_2O_2$: 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_H ^1H 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_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 $C_{19}H_{21}IN_2O_3$: 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; δ_H ^{1}H NMR (300 MHz, $CDCl_3$) 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 (d, *J* 6.0 Hz, 1H, H_2), 4.48 (d, *J* 6 Hz, 1H, H_5), 4.40 (bs, 1H, H_3), 4.07 (dd, *J* 3.9, 2.1 Hz, 1H, H_4), 3.68 (s, 3H, $COOCH_3$). δ_C NMR (75 MHz, $CDCl_3$) δ 171.6, 145.6, 139.4, 129.4, 128.8, 126.9, 118.7, 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 $C_{18}H_{19}BrN_2O_2$: 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-(p-tolylamino)pyrrolidine-2-carboxylate (7f). Yield: 90%; White solid; δ_H ^{1}H NMR (300 MHz, $CDCl_3$) 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, H_2), 4.47 (d, *J* 5.7 Hz, 1H, H_5), 4.36 (bs, 1H, H_3), 4.06 (dd, *J* 6, 3.6 Hz, 1H, H_4), 3.68 (s, 3H, $COOCH_3$), 2.22 (s, 3H, CH_3). δ_C NMR (75 MHz, $CDCl_3$) δ 171.8, 143.3, 139.9, 129.8, 128.8, 128.2, 128.0, 126.8, 114.1, 70.0, 64.9, 61.9,56, 52.2, 29.7, 20.4. MS (EI) *m/z* 389 $(M+1)^+$, HRMS calculated $(M+H)^+$ 389.0865, found 389.0852, Anal. Calc. for $C_{19}H_{21}BrN_2O_2$: C, 58.62; H, 5.44; N, 7.20; found: C, 58.60; H, 5.41; N, 7.28.

Methyl 4-bromo-3-((4-chlorophenyl)amino)-5-phenylpyrrolidine-2-carboxylate (7g). Yield: 80%; Brown solid; δ_H ^{1}H NMR (500 MHz, $CDCl_3$) 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, H_2), 4.46 (d, *J* 5.5 Hz, 1H, H_5), 4.37 (bs, 1H, H_3), 4.08 (dd, *J* 6.0 & 3.0 Hz, 1H, H_4), 3.65 (s, 3H, $COOCH_3$). δ_C NMR (75 MHz, $CDCl_3$) 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 $C_{18}H_{18}BrClN_2O_2$: C, 52.77; H, 4.43; N, 6.84; found: C, 52.73; H, 4.39; N, 6.87.

Methyl 4-bromo-3-((4-methoxyphenyl)amino)-5-phenylpyrrolidine-2-carboxylate (7h). Yield: 82%; Brown solid; δ_H ^{1}H NMR (500 MHz, $CDCl_3$) 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, H_2), 4.46 (d, *J* 5.5 Hz, 1H, H_5), 4.34 (bs, 1H, H_3), 4.09 (dd, *J* 6.5 & 3.5 Hz, 1H, H_4), 3.69 (s, 3H, OCH_3), 3.52 (s, 3H, $COOCH_3$). δ_C NMR (75 MHz, $CDCl_3$) 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 $C_{19}H_{21}BrN_2O_3$: C, 56.31; H, 5.22; N, 6.91; found: C, 56.29; H, 5.17; N, 6.96.

Ethyl 4-iodo-5-phenyl-3-(phenylamino)pyrrolidine-2-carboxylate (7i). Yield: 86%; White solid; δ_H ^{1}H NMR (500 MHz, $CDCl_3$) 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, H_2), 4.46 (m, 2H, H_3 & H_4), 4.17 (m, 2H, CH_2), 4.08 (d, *J* 7.0 Hz, 1H, H_5), 1.27 (t, *J* 7.5 Hz, 3H, CH_2CH_3). δ_C NMR (75 MHz, $CDCl_3$) 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 $C_{19}H_{21}IN_2O_2$: C, 52.31; H, 4.85; N, 6.42; found: C, 52.27; H, 4.79; N, 6.47.

Ethyl 4-iodo-5-phenyl-3-(p-tolylamino)pyrrolidine-2-carboxylate (7j). Yield: 82%; White solid; δ_H ^{1}H 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). δ_C NMR (75 MHz, $CDCl_3$) δ 171.4, 143.5, 139.4, 129.4, 128.7, 128.1, 126.3, 120.8, 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 $C_{20}H_{23}IN_2O_2$: 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 ^{1}H 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_5), 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). δ_C 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 $C_{19}H_{21}BrN_2O_2$: 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 ^{1}H 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_5), 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). δ_C 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 $C_{20}H_{23}BrN_2O_2$: 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 ^{o}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 elutent 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 ^{1}H 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,

H_2), 3.68 (d, *J* 1.8 Hz, 1H, H_5), 3.23 (dd, *J* 4.5, 2.1 Hz, 1H, H_3), 3.08 (dd, *J* 4.5, 2.1 Hz, 1H, H_4). δ_C NMR (75 MHz, $DMSOD_6$) 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 $C_{17}H_{16}N_2O_2$: 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; δ_H ^{1}H 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, H_2), 3.65 (d, *J* 2.0 Hz, 1H, H_5), 3.19 (dd, *J* 4.0, 2.0 Hz, 1H, H_3), 3.08 (dd, *J* 4.5, 2.0 Hz, 1H, H_4), 2.27 (s, 3H, CH_3). δ_C NMR (75 MHz, DMSO-D_6) 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 $C_{18}H_{18}N_2O_2$: 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; δ_H ^{1}H 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, H_2), 3.64 (d, *J* 2.0 Hz, 1H, H_5), 3.20 (dd, *J* 4.5, 2.0 Hz, 1H, H_3), 3.08 (m, 1H, H_4). δ_C NMR (75 MHz, DMSO-D_6) 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 $C_{17}H_{15}ClN_2O_2$: 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; δ_H ^{1}H 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, H_2), 3.66 (d, *J* 1.5 Hz, 1H, H_5), 3.23 (dd, *J* 4.5, 2.0 Hz, 1H, H_3), 3.19 (s, 3H, OCH_3) 3.07 (dd, *J* 4.5 & 2.0 Hz, 1H, H_4). δ_C NMR (75 MHz, DMSO-D_6) 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 $C_{18}H_{18}N_2O_3$: C, 69.66; H, 5.85; N, 9.03; found: C, 69.63; H, 5.78; N, 9.08.

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