Heterocyclic Letters
Vol. 5 | No.3 |431-442| May-July| 2015
ISSN : (print) 2231–3087 / (online) 2230-9632
CODEN: HLEEAI
http://heteroletters.org

ONE-POT SYNTHESIS OF ISOQUINUCLIDINE DERIVATIVES THROUGH MULTICOMPONENT AZA-DIELS-ALDER REACTIONS PROMOTED BY NIOBIUM PENTAETHOXIDE

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ABSTRACT
The bicyclic isoquinuclidine system can be found in many natural products and has several pharmacological properties. In this paper is described an one-pot sysnthesis of Isoquinuclidine derivatives through multicomponent aza-Diels-Alder reactions between aniline derivatives, benzaldehyde and 2-cyclohexenone, promoted by niobium pentaethoxide under mild conditions, affording the expected products in high yields.

KEYWORDS: Isoquinuclidine derivatives, Niobium pentaethoxide, multicomponent reaction, aza-Diels-Alder, Lewis acid.

INTRODUCTION
The bicyclic system of isoquinuclidines (2-aza-biclyclo[2.2.2]octanes) can be found in many natural products and have several pharmacological properties, such as cholinergic agonist activity, anesthetics, glycosidase inhibitors, hypoglycemic agents, antimalarial and antileishmanial agents, expectorants and others[i,ii]. Among these compounds we can mention the alkaloids ibogaine (**1**), mearsine (**2**) and cannivonine (**3**) (figure 1), which are isolated, respectively, from *Tabernantheiboga*, *Vacciniumoxycoccus* and *Peripentadeniamearsii*[i-vii].

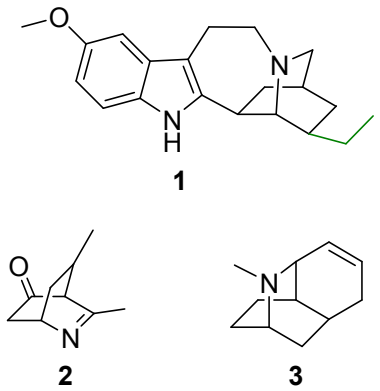
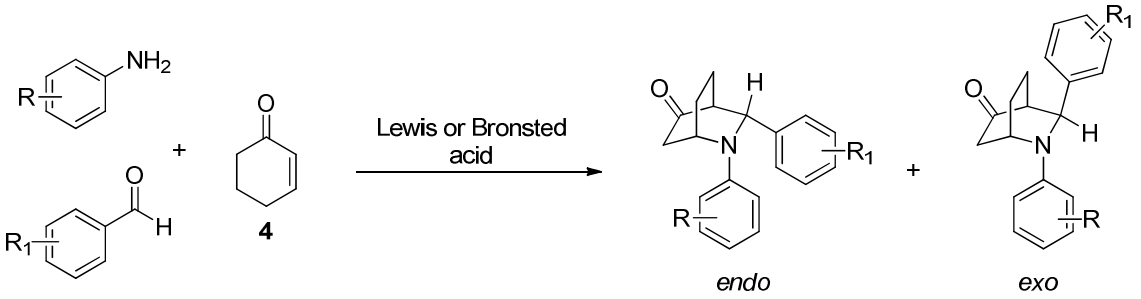


Figure 1: Structures of natural isoquinuclidine derivatives.

The isoquinuclidine derivatives are important synthetic intermediates in the organic synthesis[viii-xii] and could be prepared by multicomponent aza-Diels-Alder reaction between aniline and benzaldehyde derivatives and 2-cyclohexenone (**4**) catalyzed by several Lewis or Bronsted acids, such as: $BiCl_3$, $InCl_3$,TPP,(*S*)-proline, Binol derivatives, α-zirconium phosphate and others[xiii-xxiii] (Scheme 1), in which, usually, a pair of diastereoisomers with *endo* and *exo* stereochemistry is formed with different ratios between these isomers, depending on the reaction conditions used.The multicomponent reaction (MCR) proceeds initially by the formation *in situ* of Schiff base, resulting from the condensation reaction between the aniline derivative and benzaldehyde derivative. The formation of *endo* and *exo* adducts of isoquinuclidine derivatives occurs through the aza-Diels-Alder reaction between Schiff base (dienophile) and the enolate of 2-cyclohexenone (**4**) (diene)[xiii-xxiii].



Scheme 1: Multicomponent aza-Diels-Alder reaction for the synthesis of isoquinuclidine derivatives.

The multicomponent aza-Diels-Alder reaction is known as a powerful method for the synthesis of nitrogen heterocyclic compounds, through a process in which three or more substances react in the same reaction "*pot*"affording the products in one operation, incorporating the characteristics of each reactant used and with great structural complexity[xxiv,xxv]. The MCRs also have additional advantages, such as being selective and having atom economy, playing a very important role in modern synthetic methodology[xxvi,xxvii]. The use of catalysts (metallic, acid or enzymatic) in the development of MCRs has also been the subject of study in several research groups[xxviii-xxxv]. The catalysts can favor the occurrence of reactions that do not occur in its absence, reducing reaction times, improving reactions yields and varying the ratio of the products formed.

The niobium(V)ethoxide is a colorless liquid which is soluble in most organic solvents. In the presence of water, it readily degrades into niobic oxide (Nb_2O_5) and ethanol. $Nb(OEt)_5$ is used as a precursor of thin films of niobium pentoxide, with large importance in the fields of optoelectronic devices, metallurgy, batteries, implants and other various applications[xxxvi-xl]. However, more recently several research groups reported the use of $Nb(OEt)_5$ as catalyst in organic synthesis. Some applications are: cyclotrimerization of isocyanates, amination of allylic alcohols, opening of epoxides, Diels-Alder reactions and oxidations[xli-xlvii].

As part of our research work on synthetic methodologies using niobium compounds in a variety of reactions[xlviii-lvi], in this work we described an efficient method for the synthesis of isoquinuclidine derivatives by a multicomponent aza-Diels-Alder reaction between aniline derivatives, benzaldehyde and 2-cyclohexenone, in the presence of $Nb(OEt)_5$.

RESULTS AND DISCUSSION

We have initially optimized the synthesis of the Isoquinuclidine derivatives using the reaction among 2-cyclohexenone (**4**), aniline (**5a**) and benzaldehyde (**6**) as a model. Initial tests were performed using different concentrations of$Nb(OEt)_5$, at different reaction times. On the basis of preliminary tests, the reaction time was fixed at four days and it was used 1.0 equivalent of

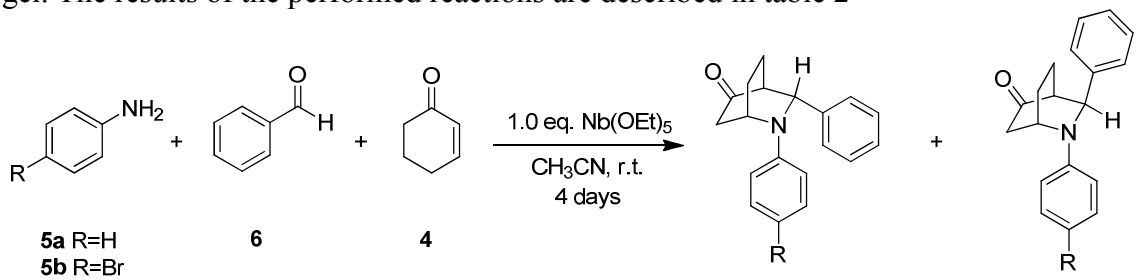
$Nb(OEt)_5$ for each mmol of aniline derivative utilized (table 1, entry 5). The use of low concentrations of niobium pentaethoxide promotes the formation of adducts of interest but in small amounts, not allowing their isolation (Table 1, entries 2 and 3).

Table 1: Optimization of MCR between aniline (**5a**), benzaldehyde (**6**) and 2-cyclohexenone (**4**).

Entry	Aniline	$Nb(OEt)_5$ (equiv.)	Time (days)	Yields (%)
1	**5a**	0.0	7	NR*
2	**5a**	0.25	7	Trace
3	**5a**	0.5	7	Trace
4	**5a**	1.0	5	77
5	**5a**	1.0	4	80
6	**5a**	1.0	3	65

* It was only observed the formation of intermediate (Schiff base)

After optimization of the reaction conditions, other anilines derivatives (**5b–h**) were examined in the presence of $Nb(OEt)_5$. The Isoquinuclidine derivatives were obtained by multicomponent aza-Diels-Alder reactions between aniline derivatives (**5a-h**) (1.0 mmol), benzaldehyde (**6**) (1.0 mmol) and 2-cyclohexenone (**4**) (1.0 mmol) in the presence of $Nb(OEt)_5$ (1.0 mmol), at room temperature, using CH_3CN (3.0 mL), as solvent and after four days. (Scheme 2) The obtained products were purified by column chromatography on silica gel. The results of the performed reactions are described in table 2



5a R=H
5b R=Br
5c R=F
5d R=Cl
5e R=I
5f R=OMe
5g R=Me
5h R=Et

6 **4** **7 (a-h)** **8 (a-h)**

Scheme 2: Synthesis of isoquinuclidine derivatives in the presence of $Nb(OEt)_5$.

Table 2: Synthesis of isoquinuclidine derivatives promoted by $Nb(OEt)_5$.

Entry	Aniline	R	Yields[a] (%)	Ratio[b] 7:8
1	**5a**	H	80	60:40
2	**5b**	Br	86	50:50
3	**5c**	F	94	51:49
4	**5d**	Cl	78	52:48
5	**5e**	I	86	50:50
6	**5f**	OMe	74	57:43
7	**5g**	Me	93	61:39
8	**5h**	Et	95	59:41

[a] Isolated yield
[b] The products ratios were determined by ^1H NMR analysis of the crude product

Analyzing the results shown in table 2, it is possible to conclude that the $Nb(OEt)_5$ is a good promoter for the multicomponent reaction between aniline derivatives, benzaldehyde and 2-cyclohexenone, leading to isoquinuclidine derivatives in high yields, under mild reaction conditions (room temperature) in the presence of acetonitrile. The products were obtained in moderate ratios of *endo***7** and *exo* **8** diastereoisomers.

All products were isolated and characterized by spectroscopic and spectrometric methods (^{1}H NMR, ^{13}C NMR, IR and mass spectra). The relative stereochemistry of *endo* and *exo* adducts was determined by enhance nuclear Overhauser effect between the bridge methylene hydrogens (H-7) and hydrogen H-3, whose signal in ^{1}H-NMR is easily identifiable (Figure 2 and Table 3).

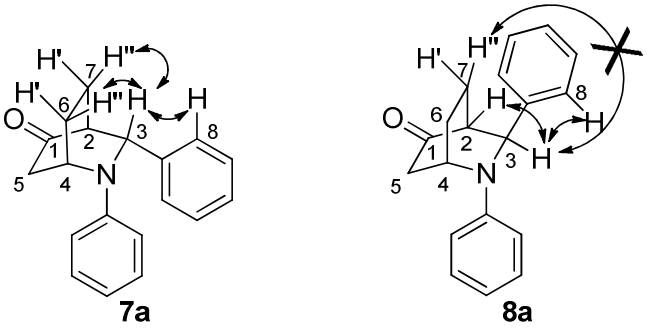


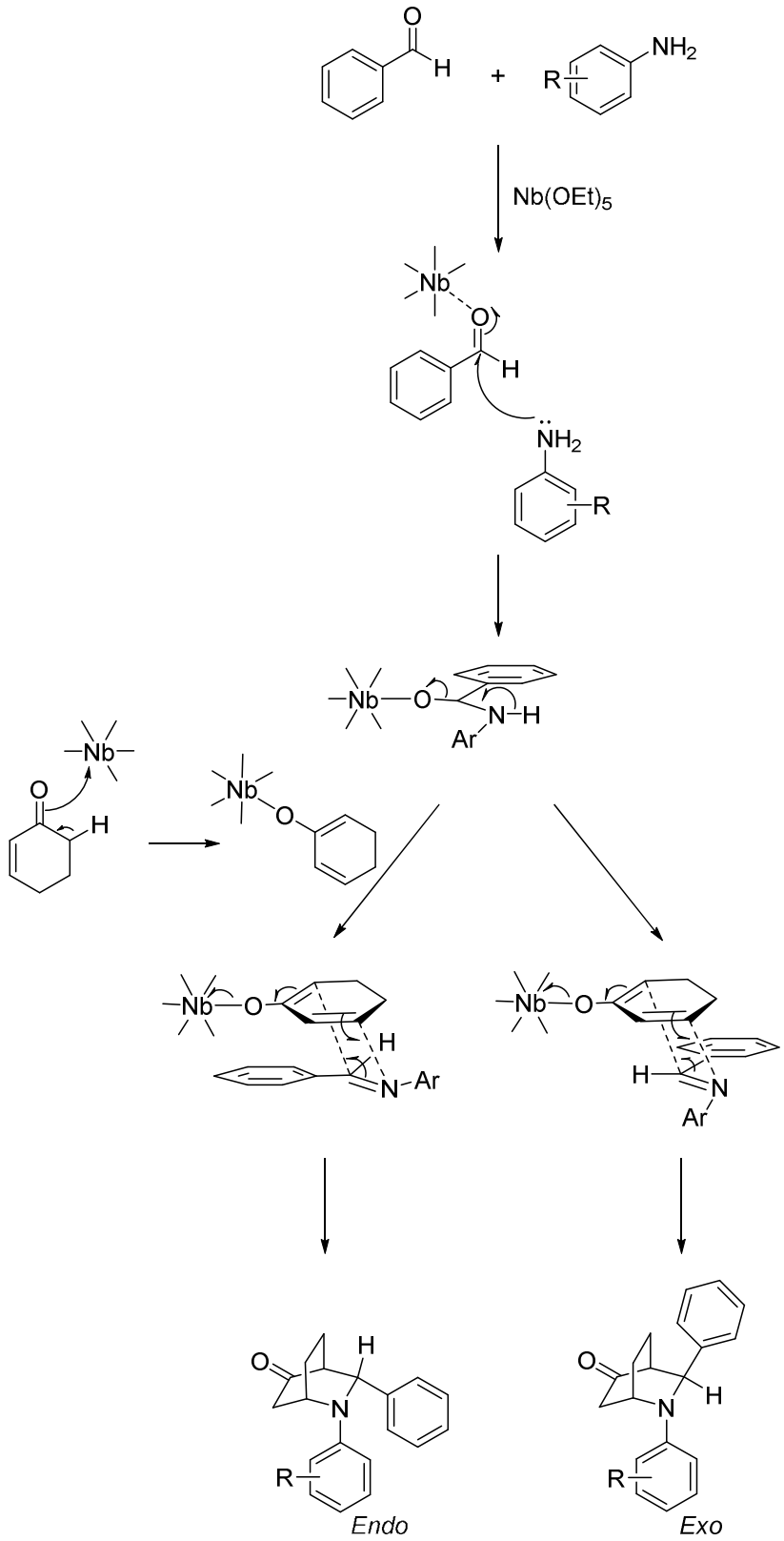
Figure 2: Observed NOE interactions in compound **7a** and **8a**.

Table 3: Observed NOE interactions in NOEDiff^{1}H NMR experiments[a]

Compound	Irradiated signal	Observed (%)
7a	H-3	H-7''(3%); H-6''(1%); H-2(7%); H-8(6%)
	H-4	H-8(8%); H-5'(3%); H-5''(2%); H-6'(3%); H-6''(2%)
8a	H-3	H-2(5%); H-8(5%)
	H-4	H-8(9%); H-5'(3%); H-5''(3%); H-6'(2%); H-6''(2%)

[a] in $CDCl_3$ solution

The multicomponent reaction proceeds initially by the formation in situ of Schiff base, resulting from the condensation reaction between the aniline derivative and benzaldehyde, the $Nb(OEt)_5$ complex with the oxygen of benzaldehyde due to niobium atom be highly oxophilic[lvii-lix]. The formation of endo and exo adducts of isoquinuclidine derivatives occurs through the reaction of aza-Diels-Alder between Schiff base (dienophile) and the enolate of 2-cyclohexenone (diene). The enolate is formed due to a strong coordination of niobium pentaethoxide with enone. (Scheme 3)



Scheme 3: Proposed reaction mechanism of MCR for the synthesis of isoquinuclidine derivatives with $Nb(OEt)_5$.

In the table 4, is presented a brief comparison between the data obtained with the reported in the literature[xiii-xxiii].

Table 4: Comparison of the results obtained.

Aniline	Lewis acid	Catalyst ratio (%)	Solvent	Time (hours)	Products ratio(%) *Endo(7):Exo(8)*	Yield (%)
5 a	**$Nb(OEt)_5$**	**100**	**CH_3CN**	**96**	**60 / 40**	**80**
	$BiCl_3$	20	MeCN	14	69 / 31	72
	$InCl_3$	20	CH_3CN	24	69 / 31	65
5 b	**$Nb(OEt)_5$**	**100**	**CH_3CN**	**96**	**50 / 50**	**86**
	TPP	40	CH_3CN	24	62 / 38	70
	α-Zr	20	H_2O	24	79 / 21	91
5 c	**$Nb(OEt)_5$**	**100**	**CH_3CN**	**96**	**51 / 49**	**94**
	α-Zr	20	H_2O	24	76 / 24	89
5 d	**$Nb(OEt)_5$**	**100**	**CH_3CN**	**96**	**52 / 48**	**78**
	TPP	40	CH_3CN	24	58 / 42	64
	α-Zr	20	H_2O	24	80 / 20	87
5 f	**$Nb(OEt)_5$**	**100**	**CH_3CN**	**96**	**57 / 43**	**74**
	$InCl_3$	20	CH_3CN	24	68 / 32	60
	TPP	40	CH_3CN	24	59 / 41	55
5 g	**$Nb(OEt)_5$**	**100**	**CH_3CN**	**96**	**61 / 39**	**93**
	$InCl_3$	20	CH_3CN	24	73 / 27	62
	TPP	40	CH_3CN	24	64 / 36	57
	α-Zr	20	H_2O	27	85 / 15	83

Analyzing the table 4, we can conclude that the $Nb(OEt)_5$ gives a better yield if compared to the majority of others catalyst, however, the reaction time were longer than the others results founded in the literature.

In conclusion, a concise multicomponent aza-Diels-Alder reaction catalyzed by niobium pentaethoxide was described for the synthesis of isoquinuclidine derivatives. The method reported here is simple and efficient, affording the expected products in high yields, under mild reaction conditions, and in good reaction times.

EXPERIMENTAL

All reactions were performed under an atmosphere of N_2. Acetonitrile was distilled from calcium hydride. All commercially available reagents were used without further purification. Thin-layer chromatography was performed on 0.2 mm Merck 60F254 silica gel aluminum sheets and the spots were visualized by treatment with vaniline/methanol/water/sulfuric acid mixture. ACROS 80-230 silica gel 60 was employed for column chromatography. A Perkin–Elmer RX-FTIR System was used to record IR spectra (neat or film). NMR spectra were recorded on a Bruker AVANCE DRX 400 spectrometer (5 mm dual probe) operating at 400.13 MHz (^1H) or 100.61 MHz (^{13}C). The ^1H-NMR spectra were acquired with a spectral width of 8.3 kHz and 32 k data points and 16 or 32 scans. For ^{13}C-NMR spectra a spectral width of 23.98 kHz was used with 32 k data points and 3072 or 4096 scans. Measurements were carried out in $CDCl_3$, using tetramethylsilane as internal reference for ^1H and $CDCl_3$ as an internal reference for ^{13}C. MS analyses were recorded on a GCMS-QP2010 Plus (Shimadzu) and ESI-HRMS analyses were recorded a micrOTOF (Bruker).

General Procedure for the Multicomponent aza-Diels-Alder reaction between aniline derivatives, benzaldehyde and 2-cyclohexenone with $Nb(OEt)_5$:
A solution of benzaldehyde (**6**) (1.0 mmol), 2-cyclohexenone (**4**) (1.0 mmol) and the respective aniline (**5a-h**) (1.0 mmol) in anhyd CH_3CN (3.0 mL) was added to a solution of niobium pentaethoxide (1.0 mmol) in anhyd CH_3CN (2.0 mL), at room temperature under nitrogen atmosphere. After completion of the addition, stirring was continued at the same temperature for 4 days. The reaction mixture was quenched by the addition of H_2O (3.0 mL). The mixture was extracted with EtOAc (10.0 mL). The organic layer was separated and washed with sat. $NaHCO_3$ solution (3 × 10.0 mL), brine (2 × 10.0 mL), and then dried over $MgSO_4$. The solvent was removed under reduced pressure and the products were purified by column chromatography through silica gel using in most cases a mixture of hexane and EtOAc (9:1 respectively) as eluent.

3-*Endo*-phenyl-2-phenyl-2-azabicyclo[2.2.2]octan-5-one (7a). Yield 0.1330 g (48%). White solid.Mp 158 – 161 ºC.^{1}H NMR spectrum, δ, ppm (*J*, Hz): 7.29 – 7.12 (m, 7H); 6.71 (t, 1H, *J*=7.3); 6.64 (d, 2H, *J*= 8.1); 4.63 (d, 1H, *J*=2.8); 4.53 (m, 1H); 2.79 – 2.70 (m, 2H); 2.44 (dd, 1H, J_1=19.0 e J_2=2.5); 2.26 (m, 1H); 2.16 – 2.00 (m, 2H); 1.71 (m, 1H).^{13}C NMR spectrum, δ, ppm: 211.8 (C=O); 148.1 (C); 141.7 (C); 129.3 (2CH); 129.0 (2CH); 127.6 (CH); 125.6 (2CH); 117.7 (CH); 113.3 (2CH); 65.9 (CH); 52.2 (CH); 48.5 (CH); 45.9 (CH_2); 22.7 (CH_2); 22.6 (CH_2). IR ν_{max}: 1723; 1595; 1501; 748; 693 cm^{-1}.MS: *m/z* = 277 $(M)^+$; 248; 234; 180; 158; 131; 104; 77.

3-*Exo*-phenyl-2-phenyl-2-azabicyclo[2.2.2]octan-5-one (8a).Yield0.0887 g (32%). Yellowsolid.Mp 138 – 141 ºC. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 7.43 – 7.28 (m, 7H); 6.73 (t, 1H, *J*= 7.3); 6.61 (d, 2H, *J*=8.1); 4.78 (d, 1H, *J*=2.8); 4.57 (m, 1H); 2.77 (dt, 1H, J_1=18.7 e *J*=3.3); 2.72 (dd, 1H, J_1=5.8 andJ_2=2.8); 2.43 (dd, 1H, J_1=18.7andJ_2=1.8); 2.28 (m, 1H); 1.93 (m, 1H); 1.77 – 1.62 (m, 2H).^{13}C NMR spectrum, δ, ppm: 213.7 (C=O); 148.2 (C); 140.0 (C); 129.3 (2CH); 128.8 (2CH); 127.4 (CH); 126.1 (2CH); 117.7 (CH); 113.1 (2CH); 62.4 (CH); 51.0 (CH); 48.1 (CH); 42.3(CH_2); 26.0 (CH_2); 16.3 (CH_2).IR ν_{max}: 1718; 1593; 1494; 1221; 746; 690 cm^{-1}.MS: *m/z* = 277 $(M)^+$; 248; 234; 200; 180; 158; 131; 104; 77.

3-*Endo*-phenyl-2(4-bromo-phenyl)-2-azabicyclo[2.2.2]octan-5-one (7b).Yield 0.1527 g (43%).White solid.Mp 119 – 121 ºC. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 7.35 – 7.20 (m, 7H); 6.55 – 6.51 (m, 2H); 4.61 (d, 1H, *J*=2.5); 4.50 (m, 1H); 2.82 – 2.72 (m, 2H); 2.48 (dd, 1H, J_1=18.9andJ_2=2.9); 2.25 (m, 1H); 2.10 (m, 1H); 1.80 – 1.72 (m, 2H).^{13}C NMR spectrum, δ, ppm: 211.2 (C=O); 147.0 (C); 141.0 (C) 132.0 (2CH); 129.1 (2CH); 127.8 (CH); 125.5 (2CH); 115.0 (2CH); 109.8 (C); 65.9 (CH); 52.1 (CH); 48.8 (CH); 45.7 (CH_2); 22.8 (CH_2); 22.5 (CH_2).IR ν_{max}: 1727; 1588; 1490; 700; 669 cm^{-1}.MS: *m/z* = 355 $(M)^+$; 357 (M+2); 328; 314; 260; 236; 131; 117; 103; 91; 77.

3-*Exo*-phenyl-2(4-bromo-phenyl)-2-azabicyclo[2.2.2]octan-5-one (8b).Yield0.1527 g (43%). White solid.Mp 159 – 162 ºC.^{1}H NMR spectrum,δ, ppm (*J*, Hz): 7.40 – 7.30 (m, 5H); 7.23 – 7.19 (m, 2H); 6.48 – 6.45 (m, 2H); 4.71 (d, 1H, *J*= 2.3); 4.49 (m, 1H); 2.74 – 2.68 (m, 2H); 2.48 (dd, 1H, J_1=18.7 andJ_2= 1.7); 2.25 (m, 1H); 1.91 (m, 1H); 1.75 – 1.68 (m, 2H).^{13}C NMR spectrum, δ, ppm: 213.2 (C=O); 147.1 (C); 139.3 (C) 132.0 (2CH); 129.0 (2CH); 127.6 (CH); 126.1 (2CH); 114.7 (2CH); 109.7 (C); 62.3 (CH); 50.9 (CH); 48.5 (CH); 42.3 (CH_2); 25.9 (CH_2); 16.2 (CH_2).IR ν_{max}: 1723; 1589; 1488; 803; 694 cm^{-1}.MS: *m/z* = 355 $(M)^+$; 357 (M+2); 328; 314; 260; 236; 117; 103; 91; 76.

3-*Endo*-phenyl-2(4-fluoro-phenyl)-2-azabicyclo[2.2.2]octan-5-one (7c).Yield0.1415 g (48%). White solid.Mp 136 – 137 ºC. ^{1}H NMR spectrum, δ,ppm (*J*, Hz): 7.27 – 7.15 (m, 5H); 6.84 – 6.76 (m, 2H); 6.53 – 6.48 (m, 2H); 4.52 (d, 1H, *J*=2.5); 4.38 (m. 1H); 2.73 – 2.68 (m, 2H); 2.40 (dd, 1H, J_1=18.7andJ_2=2.5); 2.19 (m, 1H); 2.12 – 1.98 (m, 2H); 1.68 (m, 1H).^{13}C NMR spectrum,δ, ppm (*J*, Hz): 211.6 (C=O); 155.8 (C-F, d,$^{1}J_{C-F}$=236.4); 144.6 (C, d, $^{4}J_{C-F}$= 1.5); 141.6 (C); 129.0 (2CH); 127.7 (CH); 125.6 (2CH); 115.7 (CH, d, $^{2}J_{C-F}$= 22.0); 114.3 (CH, d, $^{3}J_{C-F}$= 7.3); 114.2 (CH); 66.3 (CH); 52.2 (CH); 49.3 (CH); 46.0 (CH_2); 22.6 (CH_2); 22.5 (CH_2).IR ν_{max}: 1730; 1509; 1264; 731. 702 cm^{-1}.MS: *m/z* = 295 $(M)^+$; 252; 218; 198; 176; 131; 122; 103; 95; 77.

3-*Exo*-phenyl-2(4-fluoro-phenyl)-2-azabicyclo[2.2.2]octan-5-one (8c).Yield0.1359 g (46%). White solid.Mp 130 – 133 ºC.^{1}H NMR spectrum,δ,ppm (*J*, Hz): 7.40 – 7.30 (m, 5H); 6.89 – 6.84 (m, 2H); 6.55 – 6.50 (m, 2H); 4.71 (d, 1H, *J*=2.0); 4.47 (m, 1H); 2.79 – 2.69 (m, 2H); 2.42 (dd, 1H, J_1=18.7 andJ_2=1.8); 2.28 (m, 1H); 1.91 (m, 1H); 1.78 – 1.62 (m, 2H).^{13}C NMR spectrum, δ, ppm (*J*, Hz): 213.6 (C=O); 155.7 (C-F, d,$^{1}J_{C-F}$= 236.4); 144.7 (C, d, $^{4}J_{C-F}$= 2.2); 139.9 (C); 128.9 (2CH); 127.5 (CH); 126.1 (2CH); 115.7 (CH, d, $^{2}J_{C-F}$= 22.7); 114.0 (CH, d, $^{3}J_{C-F}$= 7.3); 62.7 (CH); 51.0 (CH); 48.8 (CH); 42.0 (CH_2); 26.2 (CH_2); 16.2 (CH_2).IR ν_{max}: 1724; 1507; 1226; 747; 702 cm^{-1}.MS: *m/z* = 295 $(M)^+$; 252; 218; 198; 176; 122; 111; 95; 77.

3-*Endo*-phenyl-2(4-chloro-phenyl)-2-azabicyclo[2.2.2]octan-5-one (7d).Yield 0.1262 g (41%). Colorless solid.Mp 143 – 145 ºC.^{1}H NMRspectrum, δ,ppm (*J*, Hz): 7.32 – 7.22 (m, 5H); 7.12 – 7.08 (m, 2H); 6.63 – 6.55 (m, 2H); 4.61 (d, 1H, *J*=2.8); 4.49 (m, 1H); 2.81 – 2.74 (m, 2H); 2.47 (dd, 1H, J_1=18.9 andJ_2=2.8); 2.25 (m, 1H); 2.15 – 2.05 (m, 2H); 1.75 (m, 1H).^{13}C NMR spectrum, δ, ppm: 211,3 (C=O); 146.6 (C); 141.1 (C); 129.2 (2CH) 129.1 (2CH); 127.7 (CH); 125.5 (CH); 122.6 (C); 116.2 (CH); 114.5 (2CH); 65.9 (CH); 52.1 (CH); 48.9 (CH); 45.8 (CH_2); 22.7 (CH_2); 22.5 (CH_2).IR ν_{max}: 1729; 1494; 1264; 733; 701 cm^{-1}.MS: *m/z* = 311 $(M)^+$; 313 (M+2); 282; 268; 214; 192; 131; 117; 111; 91; 77.

3-*Exo*-phenyl-2(4-chloro-phenyl)-2-azabicyclo[2.2.2]octan-5-one (8d).Yield0.1164 g (33%). Colorlesssolid.Mp 138 – 141 ºC.^{1}H NMR spectrum,δ, ppm (*J*, Hz): 7.40 – 7.31 (m, 5H); 7.10 – 7.06 (m, 2H); 6.53 – 6.49 (m, 2H); 4.73 (d, 1H, *J*= 2.3); 4.49 (m, 1H); 2.75 – 2.69 (m, 2H); 2.42 (dd, 1H, J_1=18.7andJ_2=1.8); 2.25 (m, 1H); 1.91 (m, 1H); 1.76 – 1.64 (m, 2H).^{13}C NMR spectrum, δ, ppm: 213.3 (C=O); 146.7 (C); 139.4 (C) 129.1 (2CH); 129.0 (2CH); 127.6 (CH); 126.1 (2CH); 122.6 (C); 114.2 (2CH); 62.4 (CH); 50.9 (CH); 48.5 (CH); 42.3 (CH_2); 25.9 (CH_2); 16.2 (CH_2).IR ν_{max}: 1725; 1494; 1264; 734; 702 cm^{-1}.MS: *m/z* = 311 $(M)^+$; 313 (M+2); 268; 192; 128; 111; 97; 77.

3-*Endo*-phenyl-2(4-iodo-phenyl)-2-azabicyclo[2.2.2]octan-5-one (7e).Yield 0.1733 g (43%). Oilyliquid.^{1}H NMR spectrum,δ, ppm (*J*, Hz): 7.43 – 7.39 (m, 2H); 7.34 – 7.24 (m, 5H); 6.45 – 6.40 (m, 2H); 4.61 (d, 1H, *J*=2.8); 4.49 (m, 1H); 2.81 – 2.72 (m, 2H); 2.46 (dd, 1H, J_1=18.9 andJ_2=2.8); 2.23 (m, 1H); 2.17 – 2.02 (m, 2H); 1.75 (m, 1H).^{13}C NMR spectrum, δ, ppm: 211.2 (C=O); 147.6 (C); 140.9 (C) 137.8 (2CH); 129.1 (2CH); 127.8 (CH); 125.5 (2CH); 115.6 (2CH); 79.0 (C); 65.7 (CH); 52.1 (CH); 48.8 (CH); 45.7 (CH_2); 22.8 (CH_2); 22.5 (CH_2).IR ν_{max}: 1724; 1487; 1272; 799; 703; 500 cm^{-1}.Found, *m/z*: 404.0526 $[M+H]^+$.$C_{19}H_{18}INO$.Calculated, *m/z*: 404.0506.

3-*Exo*-phenyl-2(4-iodo-phenyl)-2-azabicyclo[2.2.2]octan-5-one (8e).Yield 0.1733 g (43%). Oilyliquid.^{1}H NMR spectrum, δ, ppm (*J*, Hz): 7.42 – 7.37 (m, 5H); 7.35 – 7.28 (m, 2H); 6.39 – 6.35 (m, 2H); 4.72 (d, 1H, *J*=2.5); 4.49 (m, 1H); 2.74 – 2,67 (m, 2H); 2.42 (dd, 1H, J_1=18.7andJ_2=1.8); 2.25 (m, 1H); 1.91 (m, 1H); 1.75 – 1.63 (m, 2H).^{13}C NMR spectrum, δ, ppm: 213.1 (C=O); 147.6 (C); 139.2 (C) 138.0 (2CH); 129.0 (2CH); 127.6 (CH); 126.0 (2CH); 115.4 (2CH); 79.0 (C); 62.2 (CH); 51.0 (CH); 48.3 (CH); 42.4 (CH_2); 25.8 (CH_2); 16.2 (CH_2).IR ν_{max}: 1725; 1488; 1283; 798; 701; 497 cm^{-1}.Found, *m/z*: 404.0535 [M + H]$^{+}$.$C_{19}H_{18}INO$.Calculated, *m/z*: 404.0506.

3-*Endo*-phenyl-2-(4-methoxy-phenyl)-2-azabicyclo[2.2.2]octan-5-one (7f).Yield 0.1296 g (42%). Yellowsolid.Mp 103 – 105 ºC.^{1}H NMRspectrum,δ,ppm (*J*, Hz): 7.32 – 7.21 (m, 5H); 6.78 – 6.74 (m, 2H); 6.64 – 6.61 (m, 2H); 4.58 (d, 1H, *J*=2.5); 4.44 (m, 1H); 3.72 (s, 3H); 2.80 – 2.73 (m, 2H); 2.46 (dd, 1H, J_1 =18.7 andJ_2=2.5); 2.27 (m, 1H); 2.14 (m, 1H); 1.78 – 1.70 (m, 2H).^{13}C NMR spectrum, δ, ppm: 212.0 (C=O); 152.1 (C); 142.5 (C); 142.2 (C); 128.9 (2CH); 127.5 (CH); 125.7 (2CH); 114.8 (2CH); 114.6 (2CH); 66.2 (CH); 55.7 (CH_3); 52.3 (CH); 49.3 (CH); 46.1 (CH_2); 22.7 (CH_2); 22.3 (CH_2).IR ν_{max}: 1727; 1510; 1264; 731; 703 cm^{-1}.MS: *m/z* = 307 (M)$^{+}$; 292; 264; 230; 264; 188; 149; 131; 117; 103; 91; 77.

3-*Exo*-phenyl-2-(4-methoxy-phenyl)-2-azabicyclo[2.2.2]octan-5-one (8f).Yield 0.0977 g (32%). Yellowsolid.Mp 117 – 119 ºC. ^{1}H NMR spectrum,δ,ppm (*J*, Hz): 7.44 – 7.27 (m, 5H); 6.76 – 6.72 (m, 2H); 6.57 – 6.53 (m, 2H); 4.70 (d, 1H, *J*=2.0); 4.44 (m, 1H); 3.70 (s, 3H); 2.76 (dt, 1H, J_1= 18,7 andJ_2= 3.0); 2.66 (m, 1H); 2.38 (dd, 1H, J_1=18.7 andJ_2=1.8); 2.27 (m, 1H); 1.89 (m, 1H); 1.77 – 1.68 (m, 2H).^{13}C NMR spectrum, δ, ppm: 214.0 (C=O); 152.0 (C); 142.7 (C); 140.4 (C); 128.8 (2CH); 127.4 (CH); 126.3 (2CH); 114.9 (2CH); 114.3 (2CH); 66.7 (CH); 55.7 (CH_3); 51.1 (CH); 48.8 (CH); 42.0 (CH_2); 26.3 (CH_2); 16.3 (CH_2).IR ν_{max}: 1729; 1508; 1267; 729; 700 cm^{-1}.MS: *m/z* = 307 (M)$^{+}$; 264; 230; 211; 188; 149; 131; 117; 103; 91; 77.

3-*Endo*-phenyl-2(4-methyl-phenyl)-2-azabicyclo[2.2.2]octan-5-one (7g).Yield 0.1653 g (57%). Colorlesssolid.Mp 160 – 162 ºC. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 7.31 – 7.22 (m, 5H); 6,99 (d, 2H, *J*=8.3); 6.60 – 6.56 (m, 2H); 4.62 (d, 1H, *J*=2.5); 4.51 (m, 1H); 2.80 – 2.72 (m, 2H); 2.46 (dd, 1H, J_1=18.7andJ_2=2.5); 2.28 (m, 1H); 2.22 (s, 3H); 2.13 (m, 1H); 2.04 (m, 1H); 1.74 (m, 1H).^{13}C NMR spectrum, δ, ppm: 212.0 (C=O); 146.0 (C); 141.9 (C); 129.8 (2CH); 128.9 (2CH); 127.5 (CH); 127.0 (C); 125.6 (2CH); 113.4 (2CH); 65.9 (CH); 52.2 (CH); 48.7 (CH); 46.0 (CH_2); 22.7 (CH_2); 22.5 (CH_2); 20.2 (CH_3).IR ν_{max}: 1729; 1516; 1264; 732; 703 cm^{-1}.MS: *m/z* = 291 (M)$^{+}$; 248; 214; 194; 172; 131; 118; 103; 91; 77; 65.

3-*Exo*-phenyl-2(4-methyl-phenyl)-2-azabicyclo[2.2.2]octan-5-one (8g).Yield 0.1057 g (36%). Colorless solid.Mp 169 – 171 ºC.^{1}H NMR spectrum,δ, ppm (*J*, Hz): 7.42 – 7.27 (m. 5H); 6.96 (d, 2H. *J*=1.41); 6.51 (d, 2H, *J*=8.6); 4.74 (d, 1H, *J*=2.3); 4.51 (m, 1H); 2.75 (dt, 1H, J_1=18.8andJ_2=3.0); 2.69 (dd, 1H, J_1=5.6andJ_2=2.3); 2.39 (dd, 1H, J_1=18.8andJ_2=1.8); 2.25 (m, 1H); 2.20 (s, 3H); 1.89 (m, 1H); 1.75 – 1.62 (m, 2H).^{13}C NMR spectrum, δ, ppm: 213.9 (C=O); 146.0 (C); 140.2 (C); 129.9 (2CH); 128.8 (2CH); 127.4 (CH); 126.9 (C); 126.2 (2CH); 113.1 (2CH); 62.4 (CH); 51.0 (CH); 48.3 (CH); 42.1 (CH_2); 26.1 (CH_2); 20.2 (CH_2); 16.4 (CH_3).IR ν_{max}: 1724; 1517; 1264; 732; 703 cm^{-1}.MS: *m/z* = 291 (M)$^{+}$; 248; 214; 194; 172; 118; 91; 77; 65.

3-*Endo*-phenyl-2(4-ethyl-phenyl)-2-azabicyclo[2.2.2]octan-5-one (7h).Yield 0.1711 (56%) Oilyliquid. ^{1}H NMR spectrum,δ, ppm (*J*, Hz): 7.32 – 7.22 (m. 5H); 7.01 (d, 2H, *J*=8.8); 6.62

– 6,59 (m, 2H); 4.63 (d, 1H, *J*=2.8); 4,12 (m. 1H); 2.78 – 2.72 (m, 2H); 2.53 (q, 2H, J_1=15.2 andJ_2=7.6); 2.47 (dd, 1H, J_1=18.9 andJ_2=2.8); 2,28 (m, 1H); 2.13 (m, 1H); 1.73 (m, 1H); 1.26 (t, 1H, *J*=7.1); 1.17 (t, 3H, *J*=7.6).^{13}C NMR spectrum,δ, ppm: 212.0 (C=O); 146.1 (C); 142.0 (C); 133.5 (C); 128.9 (2CH); 128.6 (2CH); 127.5 (CH); 125.6 (2CH); 113.4 (2CH); 66.0 (CH); 52.3 (CH); 48.6 (CH); 46.0 (CH_2); 27.7 (CH_2); 22.7 (CH_2); 22.6 (CH_2); 15.7 (CH_3).IR ν_{max}: 1728; 1514; 1265; 731; 701 cm^{-1}.Found,*m/z*: 306.1860 $[M + H]^+$. $C_{21}H_{23}NO$.Calculated, *m/z*: 306.1852.

3-*Exo*-phenyl-2(4-ethyl-phenyl)-2-azabicyclo[2.2.2]octan-5-one (8h). Yield 0.1188 g (39%). Oily liquid.^{1}H NMR spectrum,δ, ppm (*J*, Hz): 7.42 – 7.25 (m, 5H); 6.99 (d, 2H, *J*=8.8 Hz); 6.54 (m, 2H); 4.74 (d, 1H, *J*=2.3); 4.52 (m, 1H); 2.76 (dt, 1H, J_1=18.7 and J_2=3.0); 2.68 (dd, 1H, J_1=5.8and J_2=2.8); 2.50 (q, 2H, J_1= 15.2 andJ_2=7.6); 2.39 (dd, 1H, J_1=18.7 andJ_2=1.8); 2.25 (m, 1H); 1.89 (m, 1H); 1.72 (m, 1H); 1.64 – 1.56 (m, 2H); 1.15 (t, 3H, *J*=7.6).^{13}C NMR spectrum, δ, ppm: 213.9 (C=O); 146.2 (C); 140.3 (C); 133.5 (C); 128.8 (2CH); 128.6 (2CH); 127.4 (CH); 126.2 (2CH); 113.1 (2CH); 62.5 (CH); 51.0 (CH); 48.2 (CH); 42.2 (CH_2); 27.7 (CH_2); 26.1 (CH_2); 16.4 (CH_2); 15.7 (CH_3).IR ν_{max}: 1728; 1514; 1265; 731; 702 cm^{-1}.Found,*m/z*: 306.1758 $[M +H]^+$. $C_{21}H_{23}NO$.Calculated, *m/z*: 306.1852.

ACKNOWLEDGEMENTS

The authorswouldliketo thank Fundação de Amparo à Pesquisa do Estado de São Paulo (FAPESP), Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq) and Coordenadoria de Aperfeiçoamento de Pessoal do Nível Superior (CAPES) for their financial support. We would also like special Thanks to A. E. M. Crotti, L. A. B. de Moraes and H. J. Dias to University of São Paulo in Ribeirão Preto by analyses of MS and B. M. de Souza and M. S. Palma to São Paulo State University in Rio Claro by analyses of HRMS.

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Received on June19, 2015.