A Concise Route to Novel 1-Aryl and 1-Pyridyl-2-Azabicyclo[2.1.1]hexanes

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Abstract: A number of novel 1-aryl and 1-pyridyl-2-azabicyclo[2.1.1]hexane derivatives were prepared by an intramolecular [2+2] photocycloaddition in the presence of acetophenone as the sensitizer. Substitution of the azabicyclo[2.1.1]hexane ring was accomplished by appropriate choice of the heteroaryl ketone and allylamine starting materials. Several aryl **9a-e, g** and pyridyl analogs **9h-l** were prepared by this method. The structures of **9a** and **9i** were verified by X-ray crystallography. Several of the photoproducts **9** were converted into the corresponding N-Me and N-H 2,4-methanonicotine analogs **4** by reduction or hydrolysis of the *N*-carboethoxy group.

Key words: intramolecular, [2+2], photocycloaddition, ene-carbamate, azabicyclohexane

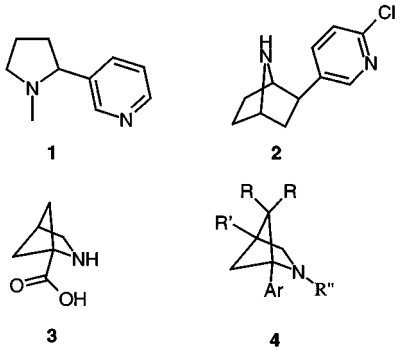
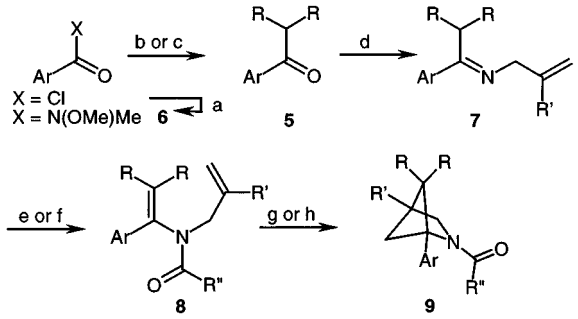


Figure 1



Conditions: (a) HN(OMe)Me·HCl, Et_3N, CH_2Cl_2; (b) MeMgCl, THF; (c) i-PrMgCl, THF; (d) allylamine, c-hexane, 3 Å sieves; (e) diethyl pyrocarbonate, toluene, 110 °C; (f) AcCl, toluene,N,N-diethylaniline, 0-25° C; (g) benzene, 2% acetophenone, hv; (h) acetone, hv.

Scheme 1

A common strategy often utilized to find more potent, more selective and less toxic biologically active molecules relies on the synthesis of ring constrained analogs. These conformationally restricted analogs, where the key pharmacophoric elements are held rigidly with respect to each other, often provide information about important ligand-receptor interactions. The natural products nicotine (**1**) and epibatidine (**2**) display potent biological activity in mammals and invertebrate pests by modulation of the nicotinic acetylcholine receptor (nAChR).[1] However, **1** and **2** are highly toxic and lack receptor selectivity. For these reasons, it was of interest to investigate a novel class of rigid nicotine analogs based on the 2-azabicyclohexane ring system. A key method for construction of bicyclo[2.1.1]hexanes utilizes an intramolecular photochemical [2+2] cycloaddition.[2,3] The work of Hammond and Liu demonstrated that photocycloaddition of 1,5-hexadienes in the presence of a sensitizer leads to exclusive formation of bicyclo[2.1.1]hexanes.[4] This methodology was exploited by Clardy[5a,b] and Pirrung[5c] for the synthesis of 2,4-methanoproline (**3**) and Liu in the synthesis of 1-phenylbicyclo[2.1.1]hexane.[4c] It was recognized that an extension of the Clardy/Pirrung/Liu methodology would not only provide a concise entry into 1-heteroaryl-2-azabicyclohexanes **4** but also allow for the exploration of substituted azabicyclic analogs by the appropriate choice of the starting materials.[6,7]

The target azabicyclohexanes **4** were prepared in a few steps starting from a substituted acetophenone or a heteroaryl ketone **5**. The ketones **5** were prepared by addition of a Grignard reagent to the Weinreb amide **6**. The imines **7** were prepared by combination of a ketone **5** with 1.5 equivalents of allylamine in cyclohexane in the presence of 3 Å molecular sieves.[8] In some cases a co-solvent such as benzene or ether was added to enhance the solubility of the ketone. The imines **7** could be purified by distillation under reduced pressure, however, the crude imines were sufficiently pure for further use. The E/Z configuration of imines **7** ranged from 97:3-95:5 (R = H) to 93:7-78:22 (R = Me), with purities of > 95% as determined by NMR spectroscopy. Yields of **7** ranged from 77-97%.

A number of methods are known for conversion of imines **7** into ene-amides or ene-carbamates **8** by treatment with acyl chlorides, chloroformates or anhydrides, usually in the presence of a base.[9] The carbamate moiety appeared attractive since it could be cleaved to give a secondary amine or it could be reduced with $LiAlH_4$ to provide an *N*-methylated product. A survey of carbamoylating reagents (EtO_2CCl, $(tBOC)_2O$, $(EtO_2C)_2O$), solvents (1,2-dichloro-

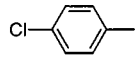
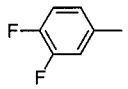
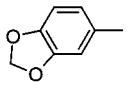
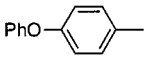
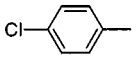
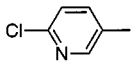
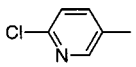
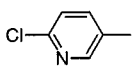
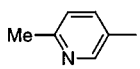
ethane, toluene, cyclohexane) and conditions (0 °C - reflux, presence of base) revealed that the preferred reaction conditions consisted of heating a toluene solution of imine **7** with a slight excess of diethyl pyrocarbonate under reflux for 24-48 hours until judged complete (TLC/NMR). Yields ranged from 90-100%. Several of the ene-carbamates **8** were found to be somewhat unstable to silica gel chromatography. The crude ene-carbamates **8a-f** were sufficiently pure (90-95%, NMR) to be used directly in the photolysis step. In contrast, ene-amide **8g** was prepared in 94% yield by reaction of a toluene solution of imine **7** with acetyl chloride in the presence of N,*N*-diethylaniline[9c] and purified by silica gel chromatography without incident.

All of the photocycloaddition reactions were carried out on preparative scale (0.010-0.038mol). Typically, solutions of the ene-carbamates **8** in benzene were subjected to photolysis with a 450W Hanovia lamp in the presence of acetophenone as the photosensitizer.[10] The initial investigation was conducted on **8a** resulting in a 52% yield of the cycloaddition product **9a** (Table 1).[11] The ^{1}H and ^{13}C NMR data for **9a** was consistent for the 2-azabicyclo[2.1.1]hexane ring system. The structure of **9a** was also verified by X-ray crystallography. Several other aryl analogs **9b-e** were prepared under similar conditions in isolated, purified yields of 50-66%. However, hindered ene-carbamate **8f** was resistant to photocycloaddition under these conditions returning only unreacted starting material. One example of a photocycloaddition with an ene-amide was performed. Ene-amide **8g** was subjected to photolysis under the described conditions only to provide a significant amount of polymeric material. In contrast, photolysis in acetone provided **9g** in 63% yield.

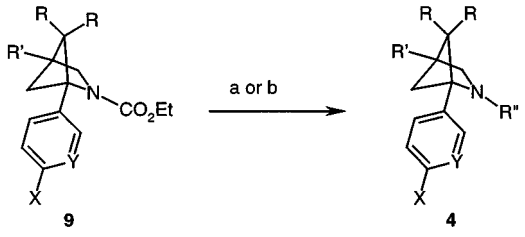
The synthesis of the 1-pyridyl-2-azabicyclohexanes **9** proved to be somewhat more difficult. In general, the pyridyl ene-carbamates **8h-l** usually required some purification. Chromatography of **8h**, **8k**, and **8l** on silica gel provided the ene-carbamates in 21-80% yield but also led to recovery of a significant amount of the corresponding ketone **5**. The pyridyl analogs **9h**, **9k** and **9l** were prepared from purified ene-carbamates in 32-68% yield. However, 6-chloropyridyl analogs **9i** and **9j**, containing substitution on the azabicyclohexane moiety, were prepared from crude ene-carbamates.[12] For these compounds the reaction products were also accompanied by significant amounts of polymeric material that had to be periodically removed from the outside of the immersion well during the course of the reaction. These factors partially account for the lower yields of **9i** and **9j** (Table 1).

The 2,4-methanonicotine analogs **4a,b,e,f** were prepared by reduction of the 2-azabicyclohexanes **9a,b,e,f** with $LiAlH_4$ in THF.[13] Alternatively, the carbamate moiety of **9a,e** could be cleaved with aqueous base in methanol to give the secondary amines **4c,d** (Scheme 2). In general, the 2,4-methanonicotines **4** were obtained and characterized as oils after purification by chromatography. They could also be converted into stable, crystalline borane complexes by treatment with borane in THF at 0 °C.[14]

Table 1 Photochemical [2+2] Cycloaddition of 8

product	Ar	R	R'	R"	time (h)	Yield[a] (%)
9a		H	H	OEt	48	52[b, 11]
9b		H	H	OEt	72	50[b]
9c		Me	H	OEt	168	55[b]
9d		H	H	OEt	39	53[b]
9e		H	H	OEt	72	66[b]
9f		Me	Me	OEt	108	0
9g		H	H	Me	41	63[c]
9h		H	H	OEt	16	68[d]
9i		H	Me	OEt	90	35[e]
9j		Me	H	OEt	180	21[e]
9k		H	H	OEt	72	32[f]
9l		H	H	OEt	106	47[d]

[a]unoptimized: chromatographically homogenous material. [b]based on crude starting ene-carbamate. [c]based on purified starting ene-amide; reaction was conducted in acetone. [d]based on purified enecarbamate. [e]based on crude-starting ene-carbamate. [f]purified ene-carbamate contained 3-acetylpyridine.



Conditions: (a) $LiAlH_4$/THF; (b) NaOH/aq. MeOH.

Scheme 2

Analysis of the crystal structure data from compounds **9a**, **9i** and **4c** (borane complex), as well as measurement of inter-nitrogen distance in molecular models of **4b**,[15] suggest that the azabicyclohexanes **4** fulfill the classical pharmacophore models for nicotinic agonists.[16,17]

Table 2 2,4-Methanonicotine analogs 4

product	X	Y	R	R'	R"	Yield (%)
4a	Cl	CH	H	H	Me	77
4b	Cl	N	H	H	Me	50
4c	Cl	CH	H	H	H	62
4d	Me	N	H	H	H	78
4e	Cl	N	H	Me	Me	72
4f	Cl	N	Me	H	Me	69

In summary, a concise synthesis of 1-aryl and 1-pyridyl-2-azabicyclo[2.1.1]hexanes using a photosensitized [2+2] cycloaddition was demonstrated on preparative scale. The substitution on the azabicyclic ring was varied by proper choice of the ketone and allylamine starting materials. The carbamates **9** were converted into novel 2,4-methanonicotine analogs **4**.

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References and Notes

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(10) **Typical procedure for 9a**: A solution of crude imine **7a** (6.4 g, 33.0 mmol) and diethyl pyrocarbonate (7.3 mL, 49.5 mmol) in about 80 mL toluene was heated under reflux. After 24 h, additional diethyl pyrocarbonate (2.0 mL, 13.6 mmol) was added and the mixture was heated under reflux for an additional 12 h. The solvent was removed in vacuo. The residue was dissolved in toluene and concentrated (twice) to provide the crude ene-carbamate **8a**. A portion of the crude ene-carbamate (6.0 g, 22.6 mmol) was dissolved in 300 mL benzene (spectrophotometric grade) containing acetophenone (0.6 mL, 2% v/v) and degassed with nitrogen for at least 30 minutes. Irradiation was performed at room temperature with a medium pressure 450 W Hanovia Hg lamp in a water-cooled Pyrex immersion apparatus. After 48 h, the solvent was removed in vacuo and the residue was purified by chromatography on silica gel with 20% ethyl acetate/hexane as eluent to afford 3.1 g (52%) of **9a** as a white solid. mp 75.5-77 °C (ether/hexanes); ^{1}H NMR (300 MHz): δ=7.29 (d, 2H, J = 8.5, aryl), 7.21 (d, 2H, J = 8.5, aryl), 3.90 (q, 2H, J = 7.2, CH_2O), 3.60 (s, 2H, CH_2N), 2.88-2.84 (m, 1H, $CH_{bridgehead}$), 2.09-2.04 (m, 2H, 2 x CH), 1.92 (dd, 2H, J = 4.5, 1.8, 2 x CH), 0.97 (t, 3H, J = 7.2, CH_3); ^{13}C NMR (75.4 MHz): δ=157.02 (C = O), 137.51, 132.80, 127.82 and 127.78 (CH aryl), 73.26 (1-C), 60.32 (CH_2O), 52.67 (CH_2N), 43.75 (CH_2), 34.33 ($HC_{bridgehead}$), 14.09 (CH_3); MS (APCI+) 268.0 (MH^+, ^{37}Cl, 40); 266.0 (MH^+, ^{35}Cl, 100)**;** IR: υ=1687.4 cm^{-1} (C = O); Anal. Calcd for $C_{14}H_{16}ClNO_2$ (265.74): C, 63.28; H, 6.07; N, 5.27. Found: C, 63.29, H, 6.03, N, 5.14.

(11) Significant improvement in isolated yield of **9a** (87%) was obtained when distilled ene-carbamate **8a** was used.

(12) The estimated purity of ene-carbamates **8i** and **8j** was only 78% and 70%, respectively, by NMR spectroscopy.

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(15) Inter-nitrogen distance for compound **4b** ranges from 4.32-4.99 Å based on rotation of the bond connecting the pyridine to the azabicyclic ring.

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(17) Compound **4b** was shown to activate acetylcholine receptors in embryonic cockroach neuronal cells. This response to application of **4b** was blocked by the nAChR antagonist mecamylamine. Thus, **4b** appears to be a nAChR agonist.

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