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2-AZABICYCLO[2.2.0]HEX-5-ENES AND 2-AZABICYCLO[2.2.0]HEXANES. A REVIEW

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Abstract – The synthesis and reactions of 2-azabicyclo[2.2.0]hex-5-enes and 2-azabicyclo[2.2.0]hexanes are reviewed.

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This paper is dedicated to Dr. Pierre Potier on the occasion of his 70th birthday.

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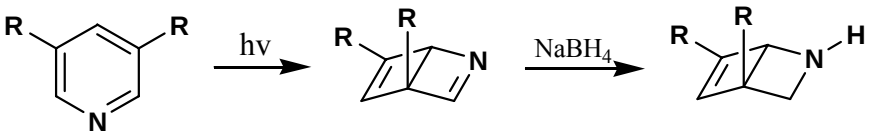
INTRODUCTION

The history of the 2-azabicyclo[2.2.0]hex-5-ene ring system begins with the 1970 report of Wilzbach that the parent 2-azabicyclo[2.2.0]hex-5-ene (**3a**) was synthesized (mg scale) by irradiation of pyridine (**1a**) at 2537 Å in aqueous sodium borohydride (Scheme 1). Photolysis of 3,5-lutidine (**1b**) under the same reaction conditions produced the corresponding 4,6-dimethyl-2-azabicyclo[2.2.0]hex-5-ene (**3b**). Under these conditions the initially formed Dewar pyridines (**2**) were reduced to **3a** and **3b** in unspecified yields.[1]



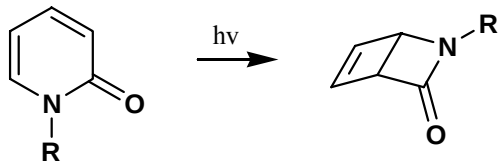
1a R = H
1b R = Me

2a R = H
2b R = Me

3a R = H
3b R = Me

Scheme 1

Soon after in 1972, Fowler reported a more general synthetic route to 2-azabicyclo[2.2.0]hex-5-enes based on electrocylic ring closure of *N*-alkoxycarbonyl-1,2-dihydropyridines.[2] Since then, alternative thermal (1985) and photochemical (1987) cycloaddition routes have been developed. This review will explore the scope and limitations of these synthetic methods and will discuss the synthetic utility of the 2-azabicyclo[2.2.0]hex-5-ene and 2-azabicyclo[2.2.0]hexane ring systems. This review will not discuss synthesis or reactions of 2-azabicyclo[2.2.0]hex-5-en-3-ones. A recent overview of the photochemical conversion of 2-pyridones (**4**) to bicyclo[2.2.0]hexane lactams (**5**) (Scheme 2) and their utility in the formation of monocyclic β-lactams has been reported elsewhere.[3]



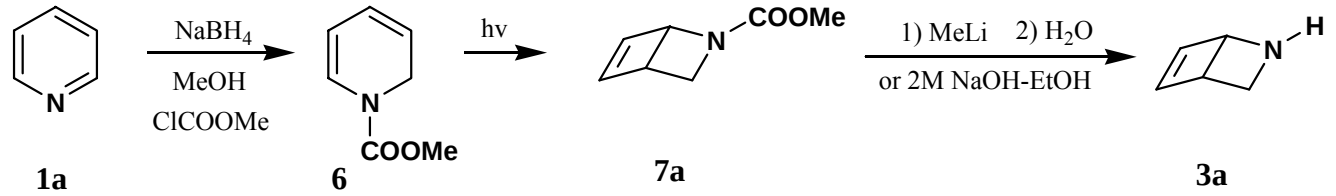
4 **5**

Scheme 2

I. SYNTHESIS OF 2-AZABICYCLO[2.2.0]HEX-5-ENES

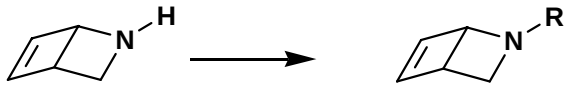
A. Synthesis of 2-azabicyclo[2.2.0]hex-5-enes *via* electrocylic ring closure.

Following Wilzbach's groundbreaking efforts (Scheme 1), Fowler and coworkers developed an improved synthetic route to the parent 2-azabicyclo[2.2.0]hex-5-ene (**3a**) from pyridine using an isolated *N*-acyl-1,2-dihydropyridine (**6**) as an intermediate (Scheme 3).[2,4] Irradiation of *N*-methoxycarbonyl-1,2-dihydropyridine (**6**) in acetone could be carried out on a multigram (40 g) scale to give *N*-methoxycarbonyl-2-azabicyclo[2.2.0]hex-5-ene (**7a**) in 50% yield. The presence of the carbamate functional group is necessary for successful ring closure. Reaction with methyllithium and subsequent hydrolysis of the carbamate (**7a**) gave the parent **3a**, although the yields were unspecified. Alternatively, hydrolysis of the carbamate could be accomplished by reaction of **7a** with 2M sodium hydroxide in refluxing ethanol for 24 hours.[5]



Scheme 3

The synthesis of a variety of *N*-substituted 2-azabicyclo[2.2.0]hex-5-enes was accomplished by reacting the appropriate alkylating reagent with **3a** and diisopropylamine. Compound (**3a**) was reacted as a tetrahydrofuran distillate from the hydrolysis of carbamate (**7a**); the yields reported below in Scheme 4 are overall from the carbamate (**7a**).[4]

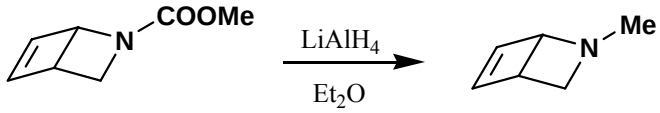


3a

7b R = $PhCH_2$- (49%)
7c R = $PhCH_2CH_2$- (25%)
7d R = $CH_2{=}CH(CH_2)_4$- (35%)
7e R = $MeO_2C(CH_2)_5$- (35%)
7f R = $CH_2{=}CHCH_2CO$- (34%)
7g R = $MeCOCH_2CH_2$- (33%)
7h R = *t*-BuOOC- (85%)

Scheme 4

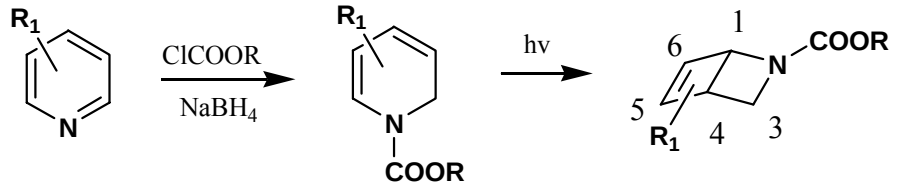
N-Methyl-2-azabicyclo[2.2.0]hex-5-ene (**7i**) was prepared by the $LiAlH_4$ reduction of the carbamate (**7a**); the isolated yield was 80%.[4]



7a **7i**

Scheme 5

Expanding on Fowler's methodology, the irradiation of substituted 1,2-dihydropyridines has provided a variety of *N*-alkoxycarbonyl-2-azabicyclo[2.2.0]hex-5-enes. *N*-Alkoxycarbonyl substituents are important because they stabilize both the dihydropyridine reactant and the resulting 2-azabicyclo[2.2.0]hex-5-ene, making both structures more resistant to air oxidation than simple *N*-alkyl derivatives. For example, amine (**7i**) has a half-life of 0.77 hours at 125 °C, while carbamate (**7a**) has a half-life of 1.13 hours at 157 °C.[4] The reaction of alkyl chloroformates with substituted pyridines (**8**) in the presence of sodium borohydride produced substituted 1,2-dihydropyridines (**9**), which in turn can be irradiated to produce *N*-alkoxycarbonyl-2-azabicyclo[2.2.0]hex-5-enes (**10**) with substituents at carbons 1, 4, 5, and 6 of the ring (Table 1).



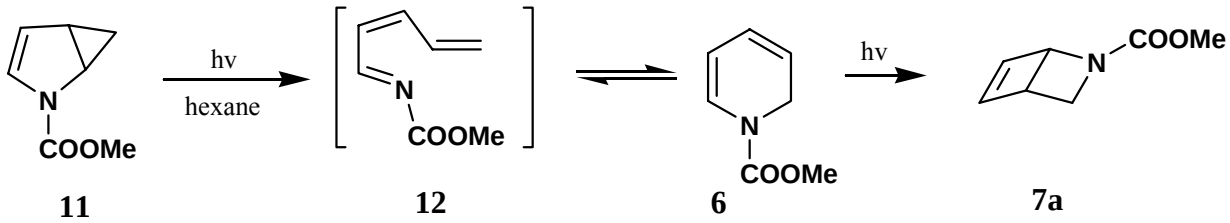
8 **9** **10**

Table 1: *N*-Alkoxycarbonyl-2-azabicyclo[2.2.0]hex-5-enes produced by irradiation of 1,2-dihydropyridines generated by sodium borohydride reduction of pyridine.

Entry	Pyridine		*N*-Alkoxycarbonyl-2-azabicyclo[2.2.0]hex-5-ene		Yield[a]	Ref.
1.	**8a**	R_1 = H	**10a**	R_1 = H, R = Et	52	6,7,8
2.	**8a**	R_1 = H	**10b**	R_1 = H, R = CH_2Ph	23	9
3.	**8b**	R_1 = 3-Me	**10c**	R_1 = 4-Me, R = Et	5	6,7
4.	**8c**	R_1 = 4-Me	**10d**	R_1 = 5-Me, R = Me	23	9
5.	**8c**	R_1 = 4-Me	**10e**	R_1 = 5-Me, R = Et	8	6,7
6.	**8c**	R_1 = 4-Me	**10f**	R_1 = 5-Me, R = CH_2Ph	26	9
7.	**8d**	R_1 = 3-Et	**10g**	R_1 = 4-Et, R = Me	NR	4
8.	**8e**	R_1 = 4-CH_2OH	**10h**	R_1 = 5-CH_2OH, R = Me	9	10
9.	**8f**	R_1 = 4-Ph	**10i**	R_1 = 5-Ph, R = Me	20	9
10.	**8g**	R_1 = 4-Br	**10j**	R_1 = 5-Br, R = CH_2Ph	23	11

a. Yield based on **8**.

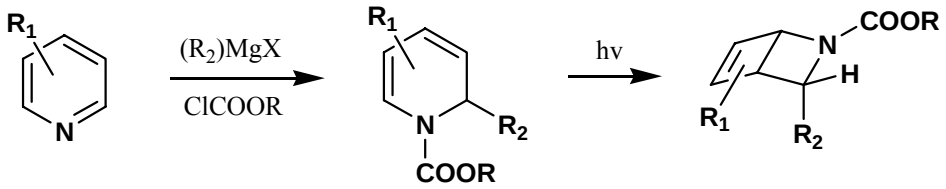
The synthesis of 2-azabicyclo[2.2.0]hex-5-ene (**7a**) was also accomplished by irradiation of 2-azabicyclo[3.1.0]hex-3-ene (**11**).[12] Irradiation of **11** produced 1,2-dihydropyridine (**6**) in 30 – 85% yield *via* the 1-azahexatriene intermediate (**12**); **12** was confirmed by direct observation when the photoirradiation was conducted in pentane at -40 °C. However, prolonged irradiation of **11** resulted in the formation of **7a** (yield unspecified), presumedly by photolytic ring closure of **6**.



11 **12** **6** **7a**

Scheme 6

Preparation of 3-*endo*-substituted *N*-alkoxycarbonyl-2-azabicyclo[2.2.0]hex-5-enes (**14**) is accomplished by irradiation of 2-substituted 1,2-dihydropyridines (**13**). For example, selective 1,2-addition of phenylmagnesium bromide at C2 of pyridine (**8a**) in the presence of methyl chloroformate provides 1,2-dihydropyridine (**13a**), which upon irradiation in CH_2Cl_2 affords 3-*endo*-phenyl-2-azabicyclohexene (**14a**) by a torquoselective disrotary ring closure.[9,13,14] Structures formed by this method are shown in Table 2. Because the 1,2-dihydropyridines (**13**) are typically unstable to chromatography, the residues formed upon alkyl chloroformate trapping of the addition products of organomagnesium reagents to pyridines were irradiated directly to the ring closure products (**14**). The substituent R_2 at C3 of the photoproducts (**14**) has been shown to be *endo*-oriented, when applicable, based on the large coupling between H4 and H3x in the ^{1}H NMR spectra.[13~15]



8 **13** **14**

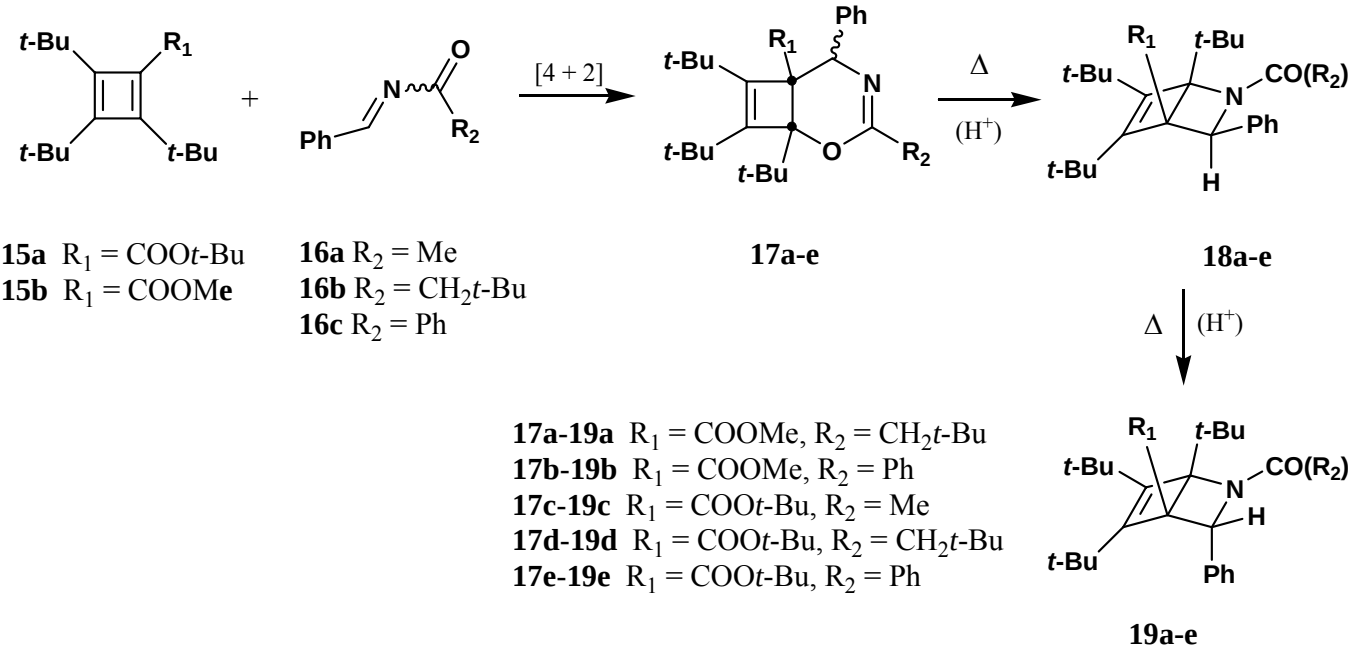
Table 2: Synthesis of 3-substituted-*N*-alkoxycarbonyl-2-azabicyclo[2.2.0]hex-5-enes produced by irradiation of 1,2-dihydropyridines.

Entry	Pyridine	*N*-Alkoxycarbonyl-2-azabicyclo[2.2.0]hex-5-ene	Yield[a]	Ref.
1.	**8a** R_1 = H	**14a** R_1 = H, R_2 = Me, R = Et	21	6,7
2.	**8a** R_1 = H	**14b** R_1 = H, R_2 = CH_2OH, R = Me	20	10,16
3.	**8a** R_1 = H	**14c** R_1 = H, R_2 = Ph, R = Me	20	9
4.	**8a** R_1 = H	**14d** R_1 = H, R_2 = Ph, R = Et	15	6,7
5.	**8a** R_1 = H	**14e** R_1 = H, R_2 = Ph, R = CH_2Ph	15	9
6.	**8c** R_1 = 4-Me	**14f** R_1 = 5-Me, R_2 = Ph, R = CH_2Ph	18	6,7
7.	**8c** R_1 = 3-Me	**14g** R_1 = 4-Me, R_2 = Me, R = Et	13	9
8.	**8h** R_1 = 4,5-di Me	**14h** R_1 = 5,6-di Me, R_2 = Ph, R = CH_2Ph	24	9

a. Yield based on 8.

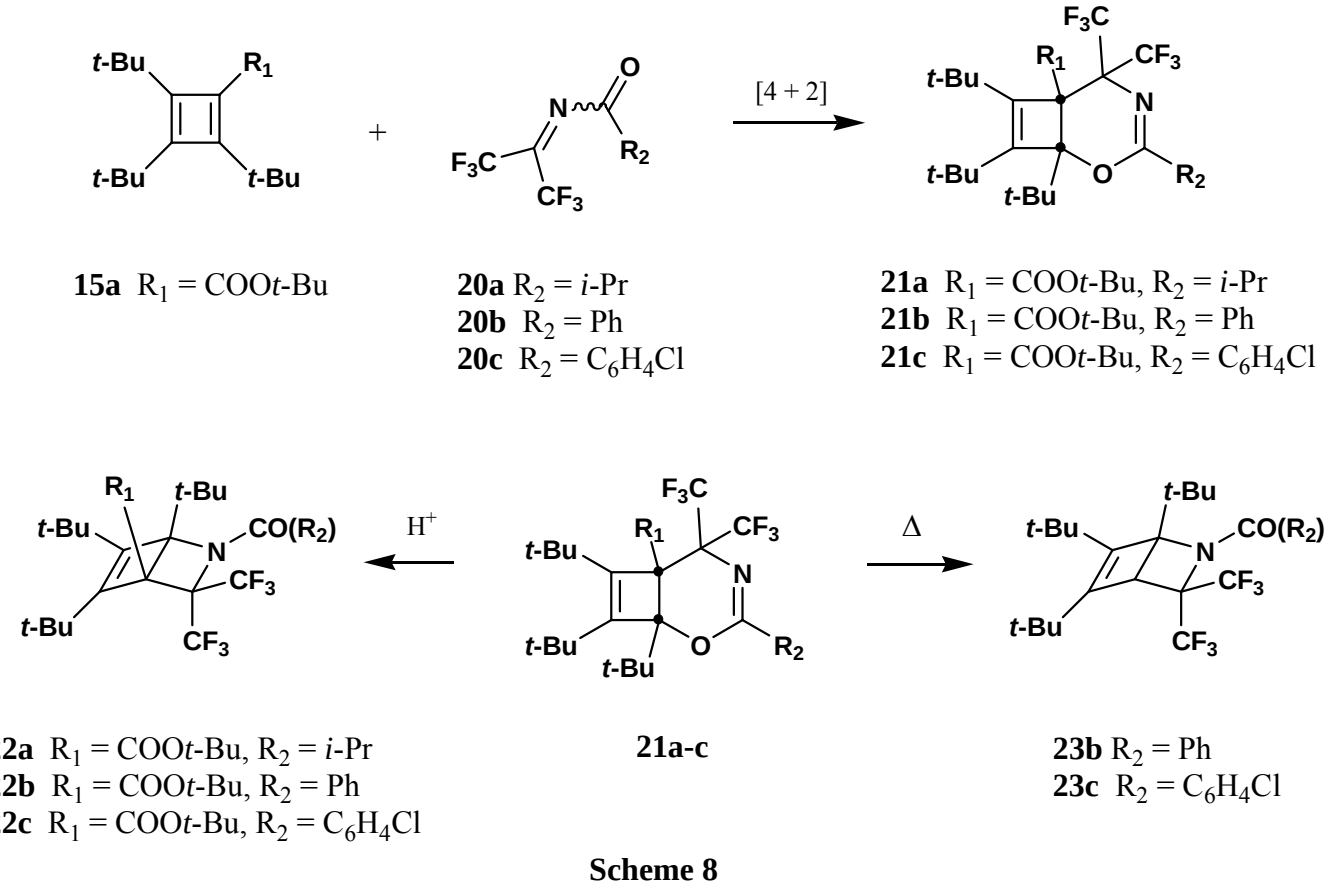
B. Synthesis of 2-azabicyclo[2.2.0]hex-5-enes *via* thermal [4+2] cycloaddition.

The preparation of 3-phenyl- and 3,3-di(trifluoromethyl)-2-azabicyclo[2.2.0]hex-5-enes by cycloadditions of *N*-acylimines and cyclobutadienes has been reported.[17,18] As shown in Scheme 7, 3-phenyl-2-azabicyclo[2.2.0]hex-5-enes (**18** and **19**) result from either thermal or acidic isomerization of the corresponding oxaazabicyclo[4.2.0]hexenes (**17**) that are formed from a thermal [4+2] cycloaddition of **15** and **16**. Isolated yields of **17a-e** range from 51 – 70%. *Exo* by-products (**18c)** and (**18d**) were also observed in yields of 7% and 10-24%, respectively. Isomerization of either **17** or **18** produced the thermodynamically more stable *endo* isomer (**19**) in yields ranging from 20% to quantitative.



Scheme 7

Cycloaddition reactions of **15a** and **20a-c** produced 2-azabicyclo[2.2.0]hex-5-enes (**21a**) (64%), (**21b**) (89%), and (**21c**) (59%); these reactions are portrayed in Scheme 8. Acid isomerization of **21a** and **21c** yielded **22a** (90%) and **22c** (26%); equilibrium conversions between **21b**/**22b** and **21c**/**22c** could be followed by ^{1}H NMR. Thermolysis of **21b** and **21c** at 165 ^{o}C yielded **23b** (58%) and **23c** (38%), respectively.[18]

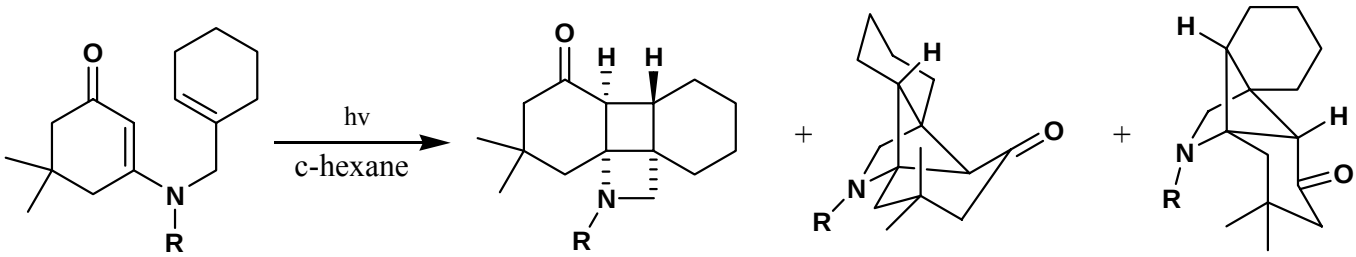


Scheme 8

II. SYNTHESIS OF 2-AZABICYCLO[2.2.0]HEXANES.

A. Synthesis of 2-azabicyclo[2.2.0]hexanes *via* photochemical [2+2] cycloaddition.

Swindell,[19] reinvestigating previous work by Schell,[20] reported that irradiation of vinylogous imides (**24**) through pyrex optics resulted in the formation of 2-azabicyclo[2.2.0]hexanes (**25a**) and (**25b**) as minor photoproducts. The other products have the 2-azabicyclo[2.1.1]hexane skeleton. The structures of products (**25a**) and (**27a**) were determined by X-Ray analysis.



24a R = COMe
24b R = CHO
24c R = $COOCH_2CCl_3$

25a 2 %
25b 14 %
25c -

26a 61 %
26b 60 %
26c 71 %

27a 7 %
27b 9%
27c -

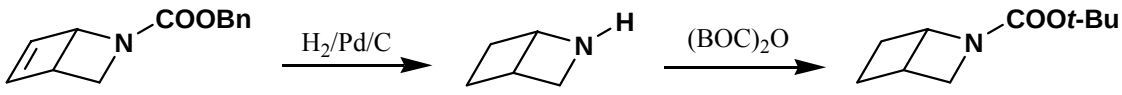
Scheme 9

B. Synthesis of 2-azabicyclo[2.2.0]hexanes *via* additions to the 5,6-alkene of 2-azabicyclo[2.2.0]hex-5-enes.

The olefinic linkage of 2-azabicyclo[2.2.0]hexanes can be functionalized by a variety of methods. In the following sections the regiochemical and stereochemical outcomes of various functionalization methods will be discussed.

1. Hydrogenation.

Treatment of *N*-benzyloxycarbonyl-2-azabicyclo[2.2.0]hex-5-ene (**10b**) with H_2 resulted in the reduction of the double bond and removal of the *N*-benzoxycarbonyl group to provide the parent 2-azabicyclo[2.2.0]hex-5-ane (**28**) *in situ*. Subsequent reaction with di-*tert*-butyldicarbonate produced *N*-*tert*-butoxycarbonyl-2-azabicyclo[2.2.0]hex-5-ane (**29**) in 72% yield based on **10b**.[21]

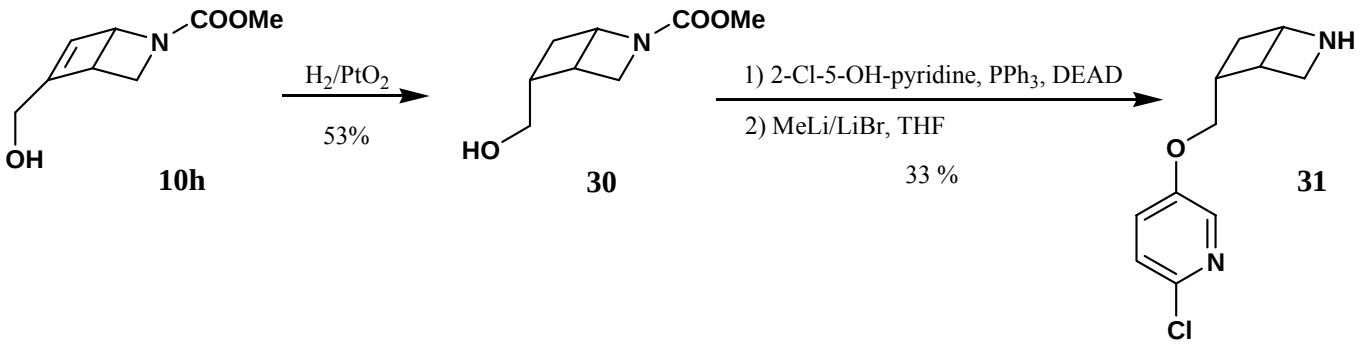


10b **28** **29**

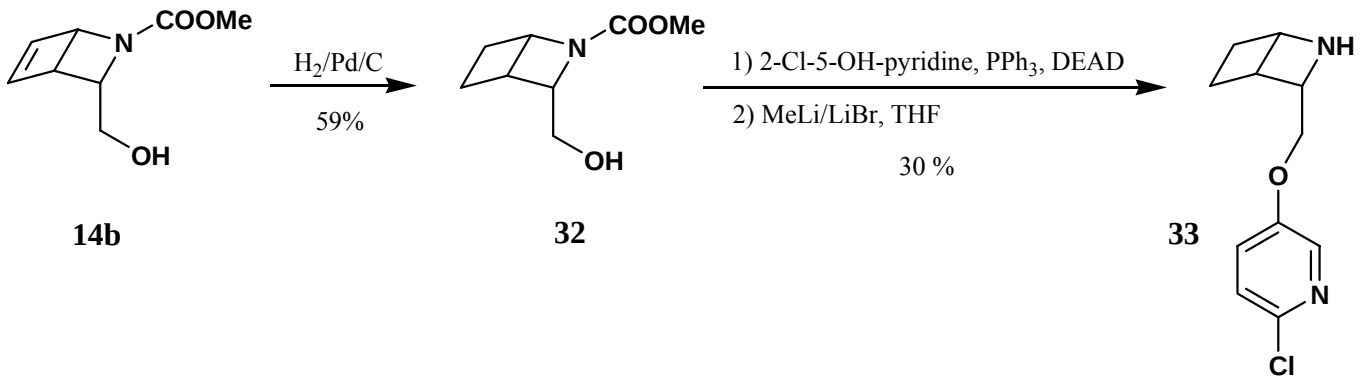
Scheme 10

Hydrogenation of *N*-alkoxycarbonyl-2-azabicyclo[2.2.0]hex-5-enes (**10h**) (Scheme 11) and (**14b**) (Scheme 12) likewise resulted in the reduction of the double bond.[10] Hydrogenation of **10h** selectively occurred from the *exo* face to afford 5-*endo*-hydroxymethyl-2-azabicyclo[2.2.0]hexane (**30**). Mitsunobu coupling of the hydroxyl groups of **30** and **32** with 2-chloro-5-hydroxypyridine gave the 5-*endo*-pyridoxymethyl analogues, and the removal of the *N*-methoxycarbonyl group with methyl-lithium/lithium bromide produced the free amines (**31**) and (**33**) respectively. Amines (**31**) and (**33**)

were evaluated for binding to nicotinic receptors, but both were found to be less effective as nicotine agonists than epibatidine or ABT-594.[10]



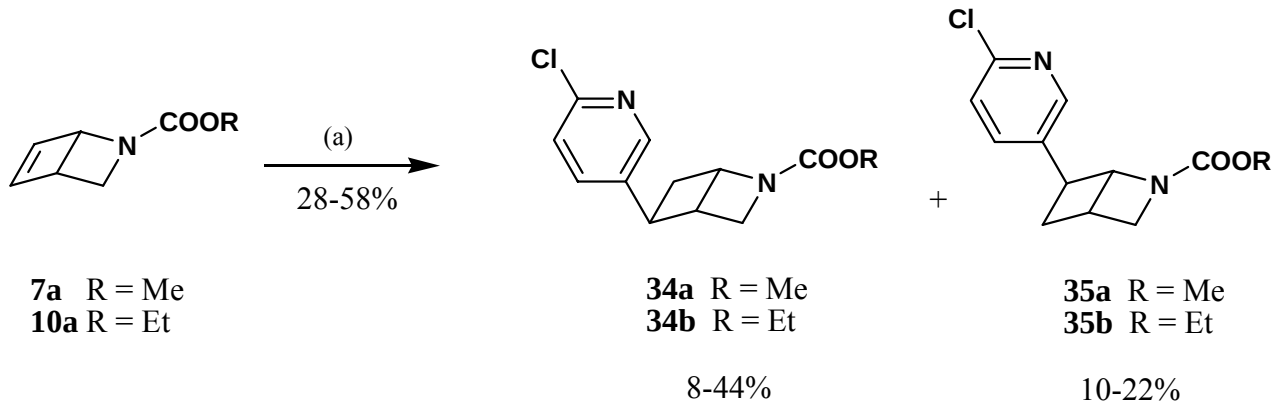
Scheme 11



Scheme 12

2. Reductive arylation.

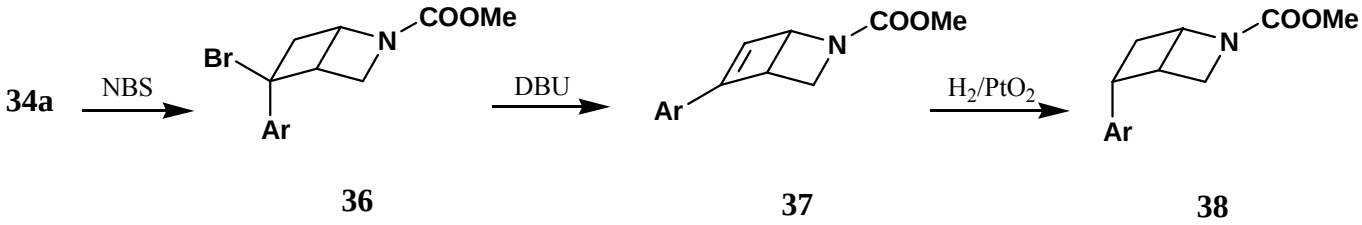
The double bonds of 2-azabicyclo[2.2.0]hex-5-enes (**7a**) and also (**10a**) have been reductively arylated using 3-iodo-6-chloropyridine in the presence of $Pd(OAc)_2$, $P(Ph)_3$, piperidine, DMF, and formic acid to afford a mixture of 5-*exo*- and 6-*exo*-aryl isomers (**34** and **35**, respectively).[22] The ratio of regioisomers (**34**) and (**35**) was temperature dependent and varied somewhat from trial to trial.



(a) $Pd(OAc)_2$, HCOOH, piperidine, Ph_3P, DMF, 60-65 °C, 3-I-6-Cl-pyridine

Scheme 13

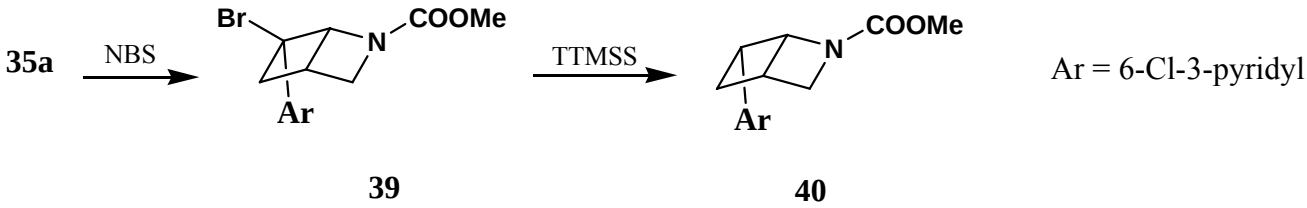
Compound (**34a**) could be epimerized in several steps. NBS bromination gave bromide (**36**), and subsequent DBU elimination of HBr gave alkene (**37**). Selective catalytic reduction from the *exo* face of **37** with H_2/PtO_2 produced 5-*endo*-aryl isomer (**38**) in an overall 20% yield (Scheme 14).



Ar = 6-Cl-3-pyridyl

Scheme 14

Regioisomer (**35a**) was alternatively epimerized. NBS bromination gave bromide (**39**), which was reduced stereoselectively with $(Me_3Si)_3SiH$/AIBN/toluene to give structure (**40**) (22% yield). This method of epimerization was employed because compound (**39**) did not undergo elimination of HBr without decomposition (Scheme 15).



Ar = 6-Cl-3-pyridyl

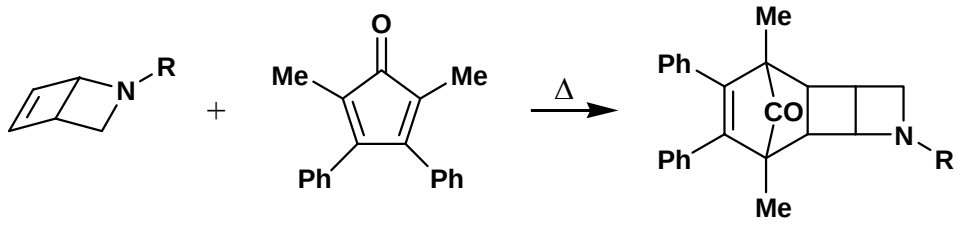
Scheme 15

The *N*-methoxycarbonyl group of compounds (**35a**, **38**, and **40**) was cleaved by reaction with methyl-lithium/lithium bromide ether solution in dry THF to give the corresponding free amine (see Schemes 11 and 12); yields are 44, 85, and 63 %, respectively. These free amines were evaluated for binding to nicotinic receptors, and results corroborated the finding that a bridged ring is crucial for analgesic activity of epibatidine analogues.[22]

3. Cycloaddition reactions.

a. [4+2] Cycloaddition reactions.

Warrener reported the reaction of 2-azabicyclo[2.2.0]hex-5-enes (**7a**) and (**7i**) with 2,5-dimethyl-3,4-diphenylcyclopenta-2,4-dienone (**41**) in refluxing benzene to yield cycloadducts (**42a**) and (**42i**) (Scheme 16); no yields or stereochemistry were reported.[23] Irradiation of the cycloadducts (dilute solution, $CHCl_3$, -20 ^oC, quartz, dry N_2) resulted in decarbonylation to dienes (**43a**) and (**43i**), which further fragmented to yield 1,4-dimethyl-2,3-diphenylbenzene (**44)** and the corresponding Δ^2-azetines (**45a**) and (**45i**) (Scheme 17); no yield was reported for **45a**.

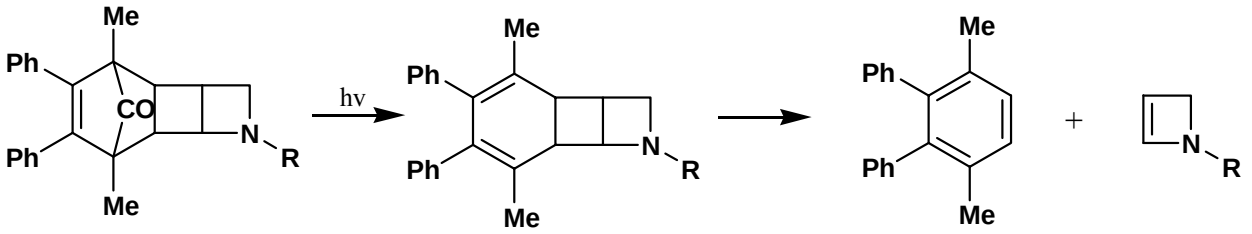


7a R = COOMe
7i R = Me

41

42a R = COOMe
42i R = Me

Scheme 16



42a R = COOMe
42i R = Me

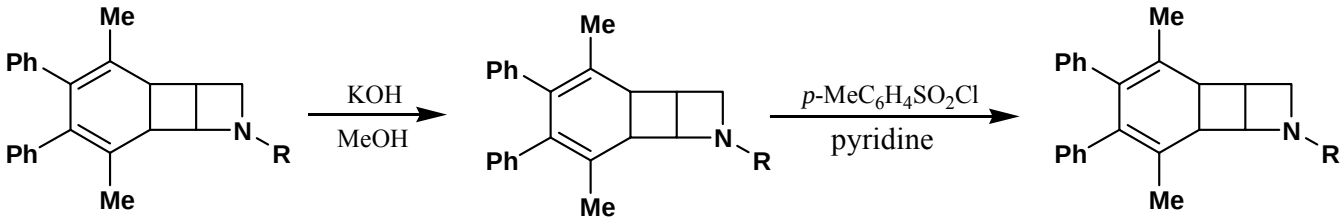
43a R = COOMe
43i R = Me

44

45a R = COOMe
45i R = Me (33 %)

Scheme 17

Hydrolysis of cycloadduct (**43a**) produced the parent **43b**, which was subsequently converted to the *N*-tosyl derivative (**43c**) by reaction with toluenesulfonyl chloride in pyridine (no yields reported).



43a R = COOMe

43b R = H

43c R = *p*-$MeC_6H_4SO_2$

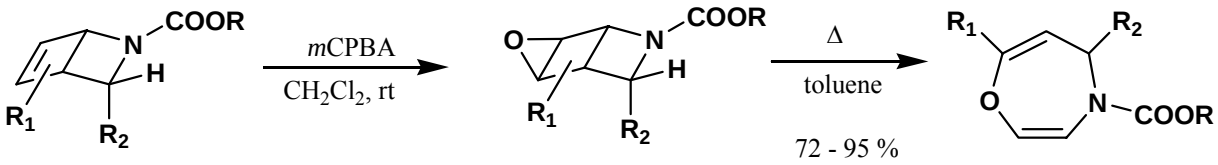
Scheme 18

Irradiation of either **43b** or **43c** does not produce the corresponding Δ^2-azetines (**45**); no product information was provided.[23]

b. [2+1] Cycloaddition reactions.

Tsuchiya and coworkers have reported a series of [2+1] cycloaddition reactions of *N*-alkoxycarbonyl-2-azabicyclo[2.2.0]hex-5-enes (**7a**, **10**, and **14**) to generate *N*-alkoxycarbonyl-3-azatricyclo[4.1.0.0^{2,5}]heptanes (**46**).[13,14] 3-Aza-oxatricyclo[4.1.0.0^{2,5}]heptanes were produced by a general procedure of adding a methylene chloride solution of *m*-chloroperbenzoic acid to the

2-azabicyclo[2.2.0]hex-5-enes at room temperature (Table 3). Oxirane compounds (**46)** in toluene were refluxed for 5–10 hours to give 4,5-dihydro-1,4-oxazepines (**47**) in yields that ranged from 72–95 %.[14]

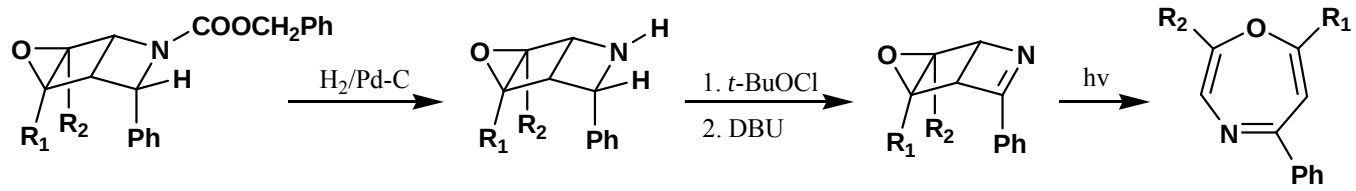


7a,10,14 **46a-h** **47a-h**

Table 3: *N*-Alkoxycarbonyl-3-azatricyclo[4.1.0.0^{2,5}]heptanes produced by reaction of *m*CPBA with *N*-alkoxycarbonyl-2-azabicyclo[2.2.0]hex-5-enes.

Entry	*N*-alkoxycarbonyl-2-aza-bicyclo[2.2.0]hex-5-ene	*N*-alkoxycarbonyl-3-Aza-oxatricyclo[4.1.0.0^{2,5}]heptanes	Yield	Ref
1.	**7a** $R_1 = R_2 = H$, R = Me	**46a**	89	14
2.	**10b** $R_1 = R_2 = H$, R = CH_2Ph	**46b**	86	14
3.	**10d** R_1 = 5-Me, R_2 = H, R = Me	**46c**	75	14
4.	**10f** R_1 = 5-Me, R_2 = H, R = CH_2Ph	**46d**	67	14
5.	**10i** R_1 = 5-Ph, R_2 = H, R = Me	**46e**	89	14
6.	**14e** R_1 = H, R_2 = Ph, R = CH_2Ph	**46f**	85	14
7.	**14f** R_1 = 5-Me, R_2 = Ph, R = CH_2Ph	**46g**	80	14
8.	**14h** R_1 = 5,6-di Me, R_2 = Ph, R = CH_2Ph	**46h**	73	13

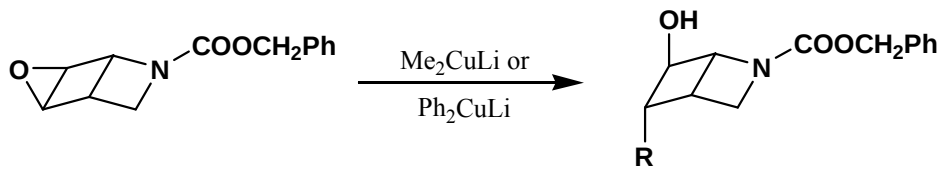
Fully unsaturated 1,4-oxazepines (**50**) were synthesized after the *N*-benzyloxycarbonyl functional group of the oxiranes (**46**) was removed via a two-step dehydrogenation procedure.[13] The parent oxiranes (**48**) were treated with *t*-butyl hypochlorite, and then DBU at 0°C to yield 7-oxa-3-azatricyclo[4.1.0.0^{2,5}]hept-3-enes (**49**), which were subsequently photolyzed in acetonitrile at 0 ^{o}C to yield **50**.



46d $R_1 = R_2 = H$ **48d** (46 %) **49d** (67 %) **50f** (91 %)
46e R_1 = Me, R_2 = H **48e** (58 %) **49e** (80 %) **50g** (96 %)
46f $R_1 = R_2$ = Me **48f** (73 %) **49f** (73 %) **50h** (93 %)

Scheme 19

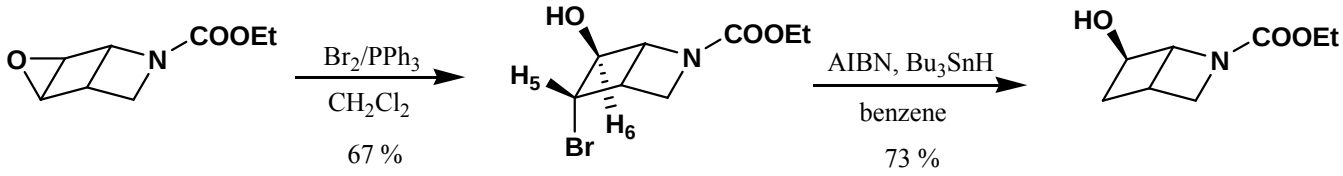
Oxirane (**46b**) undergoes regioselective epoxide ring opening reactions at C5 with lithium dimethylcopper or lithium diphenylcopper to afford the 6-*exo*-alcohols (**51**) (Scheme 20).[24]



46b **51a** R = Me
51b R = Ph

Scheme 20

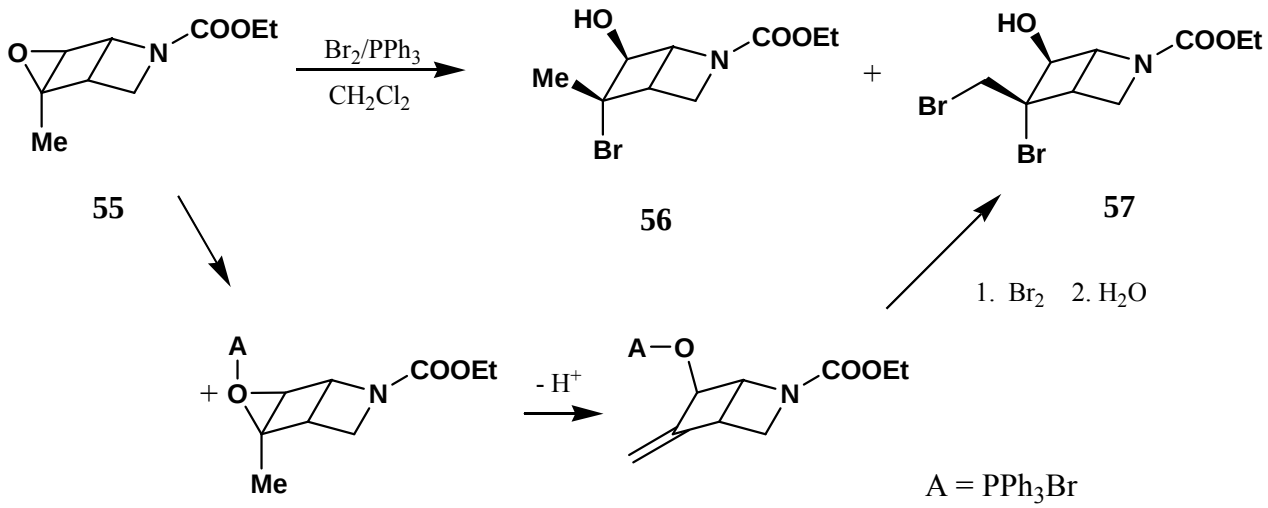
Addition of epoxide (**52**) to a methylene chloride solution of bromine/triphenylphosphine resulted in regioselective ring opening to afford a bromohydrin, assigned as 5-*endo*-bromo-6-*exo*-hydroxyl-2-azabicyclo[2.2.0]hexane (**53**).[6] Bromohydrin (**53**) undergoes reductive debromination upon reaction with tributyltin hydride in refluxing benzene to yield the *exo*-substituted 2-azabicyclo[2.2.0]hexanol (**54**).[6]



52 **53** **54**

Scheme 21

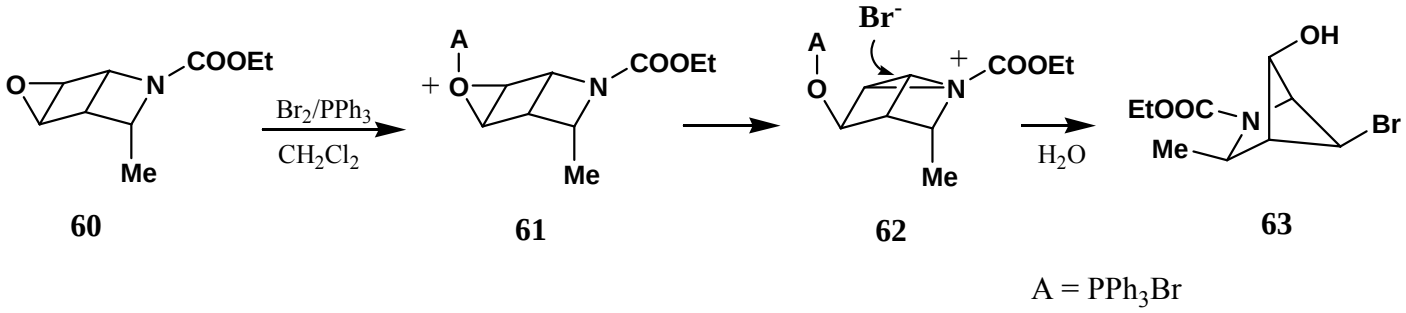
The 5-*endo*-methyl epoxide (**55**) afforded a mixture of bromohydrin (**56**) (20 %) and dibromoalcohol (**57**) (14 %).[6] The source of the dibromo alcohol (**57**) is proposed to be bromination of olefin (**59**) which is formed by deprotonation of cationic intermediate (**58**) (Scheme 22).



55 **56** **57** **58** **59**

Scheme 22

The 3-*endo*-methyl epoxide (**60**) afforded solely the rearranged bromohydrin (**63**).[6] It is proposed that the *endo* methyl group blocks nucleophilic attack from this face in intermediate (**61**), and carbamate nitrogen participation facilitates formation of the rearranged product (see Section IIIA and IIIB below).



Scheme 23

3,7-Diazatricyclo[4.1.0.0^{2,5}]heptanes (**65)** are produced by the addition of ethoxycarbonylnitrene (**64**) generated from *N*-ethoxycarbonyl-*p*-nitrobenzenesulfamide (by treatment with triethylbenzylammonium bromide and sodium bicarbonate) to a methylene chloride solution of the 2-azabicyclo[2.2.0]hex-5-enes at room temperature (Table 4). Aziridine compounds (**65**) were heated in refluxing xylene solutions for 6–10 hours to produce 4,5-dihydro-1,4-diazepines (**66**) in yields that ranged from 57–89%.[9]

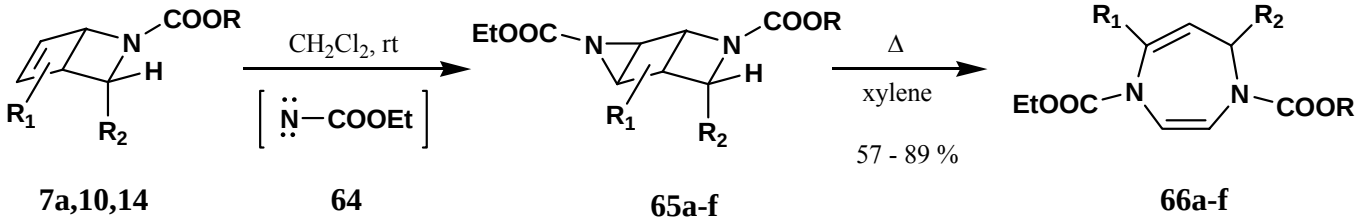
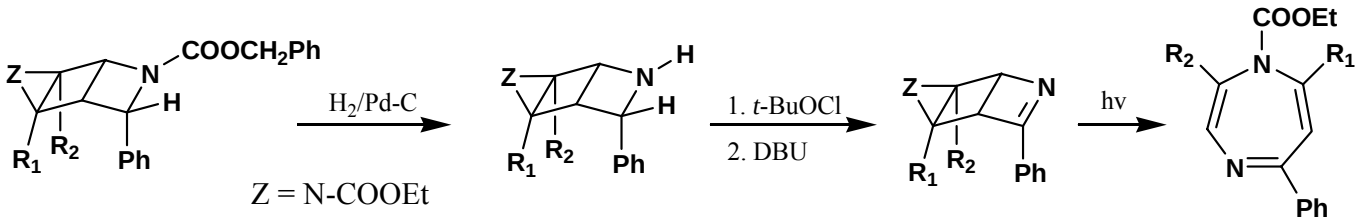


Table 4: 3,7-Diazatricyclo[4.1.0.0^{2,5}]heptanes.[a]

Entry	*N*-Alkoxycarbonyl-2-aza-bicyclo[2.2.0]hex-5-ene		3,7-Diazatricyclo-[4.1.0.0^{2,5}]heptanes	Yield	Ref.
1.	**7a**	$R_1 = R_2 = H$, R = Me	**65a**	42	9
2.	**10b**	$R_1 = R_2 = H$, R = CH_2Ph	**65b**	33	9
3.	**10f**	R_1 = 5-Me, $R_2 = H$, R = CH_2Ph	**65c**	30	9
4.	**14e**	$R_1 = H$, R_2 = Ph, R = CH_2Ph	**65d**	26	9
5.	**14f**	R_1 = 5-Me, R_2 = Ph, R = CH_2Ph	**65e**	28	9
6.	**14h**	R_1 = 5,6-di Me, R_2 = Ph, R = CH_2Ph	**65f**	24	13

a. Produced by reaction of *N*-ethoxycarbonyl-*p*-nitrobenzenesulfamide, triethylbenzylammonium bromide, and sodium bicarbonate with *N*-alkoxycarbonyl-2-azabicyclo[2.2.0]hex-5-enes.

Fully unsaturated 1,4-diazepines (**69f-g**) were synthesized by the same method as described previously for fully unsaturated 1,4-oxazepines (**50**) (see above).[13] Cleavage of the *N*-carbonylbenzyloxy group (**65** to **67**) was successfully accomplished without cleavage of the azetidine benzylic amino bond in compounds (**67d-f**) (Scheme 24).



65d $R_1 = R_2 = H$
65e $R_1 = Me$, $R_2 = H$
65f $R_1 = R_2 = Me$

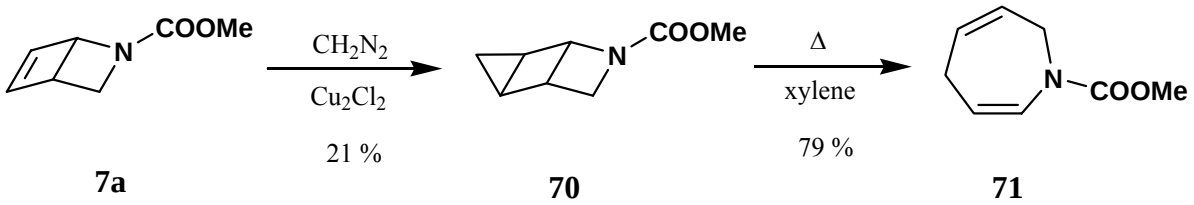
67d (64 %)
67e (76 %)
67f (83 %)

68d (82 %)
68e (86 %)
68f (81 %)

69f (84 %)
69g (65 %)
69h (72 %)

Scheme 24

Treatment of carbamate (**7a**) with diazomethane in the presence of copper(I) chloride gave the 7-methylene compound (**70**) in 21% yield.[9] On heating in refluxing xylene, compound (**70**) produced the 2,5-dihydroazepine (**71**) in 79% yield (Scheme 25).

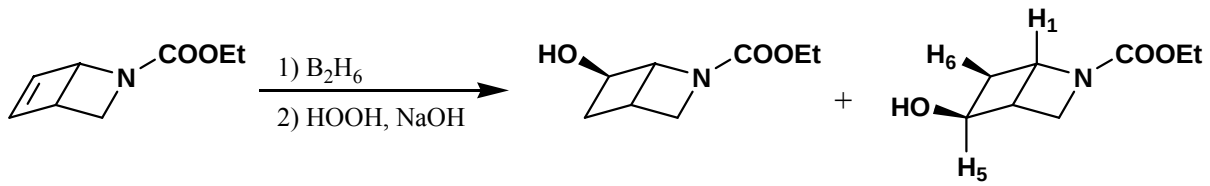


7a **70** **71**

Scheme 25

4. Oxidative hydroboration.

The addition of borane in THF to alkene (**10a**) followed by 30% hydrogen peroxide in sodium hydroxide afforded low yields of a mixture of 6-*exo*-alcohol (**54**) (9%) and 5-*exo*-alcohol (**72**) (5%).[6] The 6-*exo*-alcohol was independently prepared from epoxide (**52**) (see above). The structure of the 5-*exo*-alcohol (**72**) was partially based upon the coupling of the *exo* proton H6 with $H5_{endo}$ (J = 5.1 Hz).



10a **54** **72**

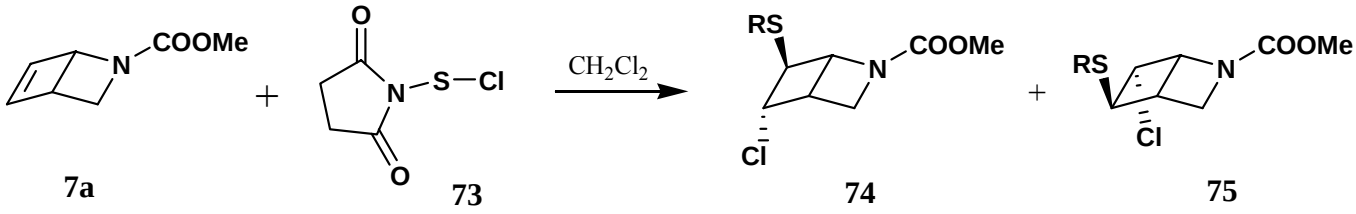
Scheme 26

5. Halogen and pseudohalogen additions.

a. Addition of succinimide-*N*-sulfenyl chloride

Tsuchiya reported the reaction of succinimide-*N*-sulfenyl chloride (**73**) with the alkene of (**7a**) in methylene chloride to give a 6:1 mixture of regioisomers (**74**) and (**75**) (Scheme 27).[9] The major isomer was originally assigned as structure (**75**); however, the stereochemical assignments have been reversed on the basis of 400 MHz ^{1}H NMR spectroscopic evidence (50 ^{o}C). There was an absence of

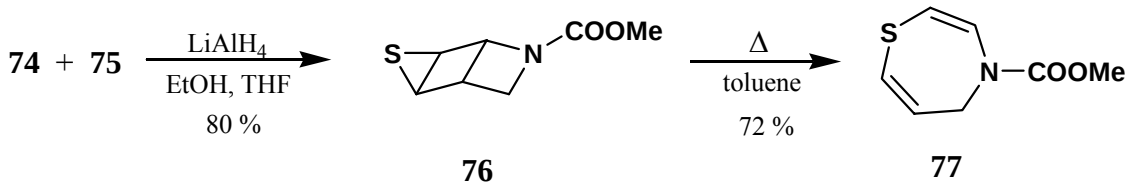
major coupling between H6 and H1 in the major isomer, but coupling (J = 6.5 Hz) in the minor isomer.[9,25] Both regioisomers were reduced with lithium aluminum hydride at -75 °C to afford the 7-thia compound (**76**) in 80% yield; compound (**76**) was subsequently refluxed in toluene for 6 hours to yield the 4-methoxycarbonyl- 4,5-dihydro-1,4-thiazepine (**77**) in 72% yield.[9]



7a **73** **74** **75**

R = -*N*-succinimido

Scheme 27

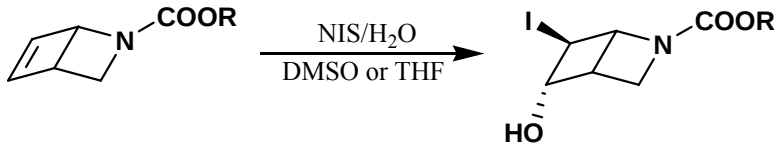


76 **77**

Scheme 28

b. Addition of IX (X = OH, OAc, F)

The reaction of I^+ electrophiles with 2-azabicyclo[2.2.0]hex-5-enes was recently reported by Krow.[8,26] Reaction of *N*-iodosuccinimide (NIS) with alkene (**10a**) in aqueous DMSO afforded only 5-*endo*-hydroxy-6-*exo*-iodo-2-azabicyclo[2.2.0]hexane (**78a**). Similarly, reaction of NIS and alkene (**10b**) in aqueous THF yielded only the iodo alcohol (**76b**).

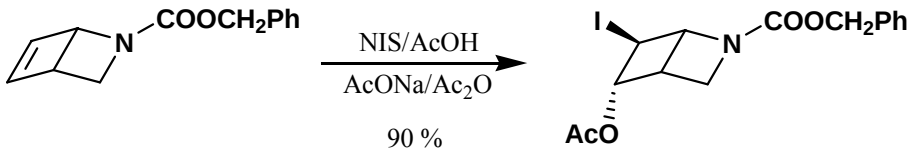


10a R = Et
10b R = CH_2Ph

78a R = Et (97 %)
78b R = CH_2Ph (91 %)

Scheme 29

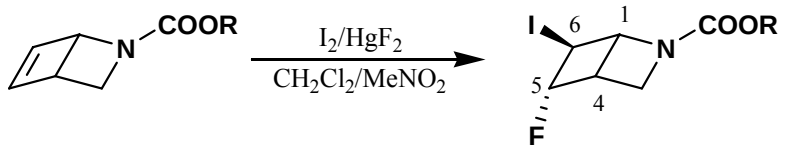
Iodo acetate (**79**) was the only product isolated from the reaction of alkene (**10b**) and NIS in buffered acetic acid (Equation 22).[26]



10b **79**

Scheme 30

In the aprotic solvent system 8:5 nitromethane:methylene chloride, iodine in the presence of mercuric fluoride reacted with alkenes (**10**) to afford 6-*exo*-iodo-5-*endo*-fluoro addition products (**80**).[26] The structures were readily assigned on the basis of the absence of coupling between $H6_n$ and H1, which places the iodo group exo, and the large coupling (J = 6.8 Hz) between $H5_x$ and H4, which places the fluoro group endo.



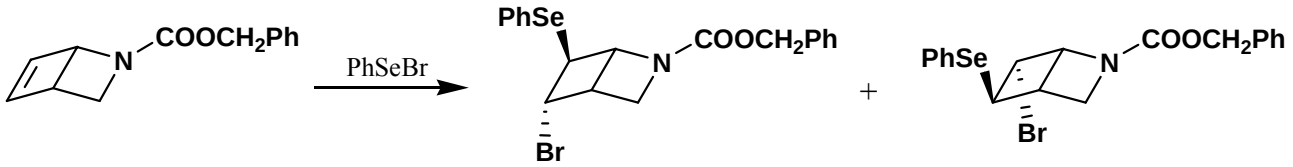
10a R = Et
10b R = CH_2Ph

80a R = Et (72 %)
80b R = CH_2Ph (68 %)

Scheme 31

c. Addition of PhSeBr

Reaction of alkene (**10b**) and phenylselenyl bromide in aprotic methylene chloride gives a 7:1 mixture of selenides (**81**) and (**82**); the total yield is 83%.[26] The same reaction performed in the more polar solvent system 8:5 nitromethane:methylene chloride alters the ratio of the regioisomers (**81**) and (**82**) to 3:1 with a combined yield of 90%.



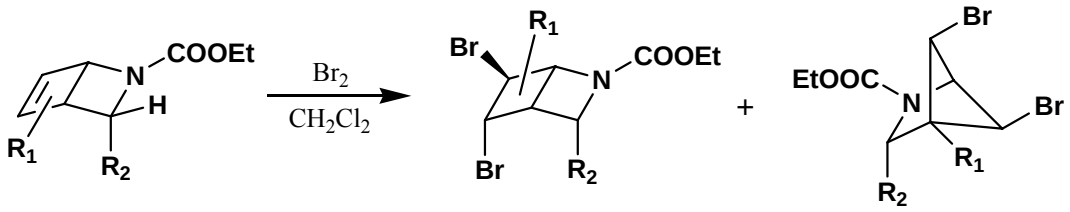
10b **81** **82**

Scheme 32

III. ADDITION/REARRANGEMENT REACTIONS OF 2-AZABICYCLO[2.2.0]HEX-5-ENES

A. Addition of bromine

Addition of bromine to 2-azabicyclo[2.2.0]hex-5-enes provides 6-*exo*-5-*endo*-dibromo addition products (**83**) in addition to the rearranged 5-*anti*-6-*anti*-dibromo-2-azabicyclo[2.1.1]hexanes (**84**) (Table 5).[6,8] The unrearranged dibromides (**83**) are thought to result from an Ad_E2 mechanism shown in Scheme 33. The bromonium ion (**85**) is formed by selective coordination at the *exo* face; subsequent *anti* addition of bromide at C5, the position remote from nitrogen, accounts for the observed stereochemistry. The rearrangement products (**84**) are proposed to result from the conversion of bromonium ion (**85**) to the aziridinium ion (**86**) *via* neighboring-group participation by the nitrogen. Regioselective attack at C_1 by bromide would account for the formation of the rearranged azabicyclohexanes (**84**). It is interesting to note that *endo* methyl- or phenyl-substitution at C3 on 2-azabicyclo[2.2.0]hex-5-enes (**14a**,**d**,**e**) resulted in exclusive formation of the rearranged dibromides. It is hypothesized that the *endo* C3 substituents on bromonium ion (**85**) retard the approach of the bromide nucleophile at C5.

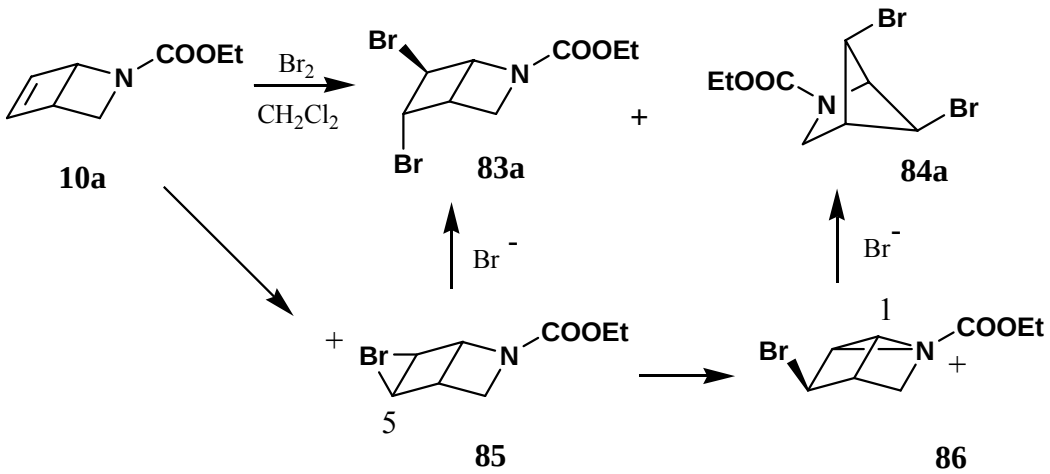


10, 14 **83** **84**

Table 5 – Products formed during reaction of *N*-ethoxycarbonyl-2-azabicyclo[2.2.0]hex-5-enes with bromine.[6,a]

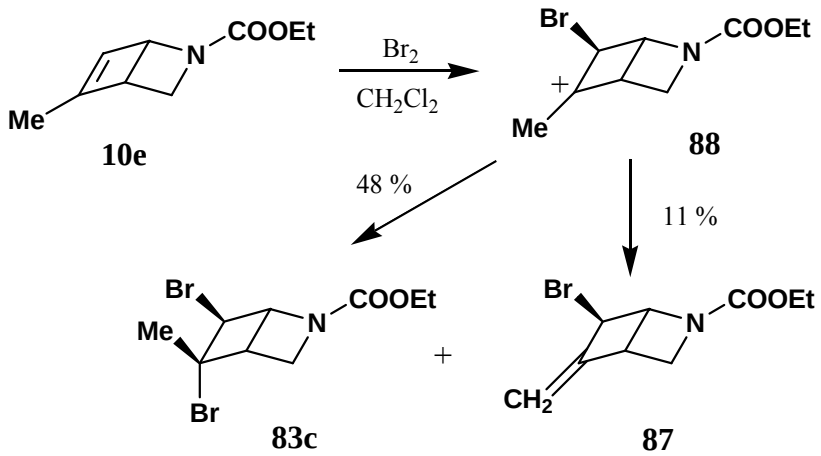
Entry	2-Azabicyclo[2.2.0]hex-5-ene	Products	Yield (ratio)
1.	**10a** R_1 = H, R_2 = H	**83a**, **84a** (R_1 = H, R_2 = H)	61–78 (55:45)
2.	**10c** R_1 = 4-Me, R_2 = H	**83b** R_1 = 4-Me, R_2 = H,	
		84b R_1 = Me, R_2 = H	73 (27:73)
3.	**10e** R_1 = 5-Me, R_2 = H	**83c** R_1 = 5-Me, R_2 = H	48
4.	**14a** R_1 = H, R_2 = Me	**84d** R_1 = H, R_2 = Me	99
5.	**14d** R_1 = H, R_2 = Ph	**84e** R_1 = H, R_2 = Ph	80
6.	**14e** R_1 = 4-Me, R_2 = Me	**84f** R_1 = Me, R_2 = Me	89

a. See also Scheme 39.



Scheme 33

Addition of bromine to the 5-methyl-2-azabicyclo[2.2.0]hex-5-ene (**10e**) takes a different course; a mixture of unrearranged dibromide (**83c**) and bromoalkene (**87**) is formed (Scheme 34). This difference is believed to result from the formation of the tertiary carbocation (**88**), from which both observed products can be reasonably derived.[6]



Scheme 34

B. Addition of BrOH

Reaction of hypobromous acid with 2-azabicyclo[2.2.0]hex-5-enes affords mixtures of unrearranged (**89**) and rearranged (**90**) bromohydrins.[7,8] Bromonium ion (**85**) is again the suspected intermediate in a mechanism similar to the one discussed above for the formation of dibromide compounds (**83**) and (**82**) (see Table 6 below).

The 5-methyl-2-azabicyclo[2.2.0]hex-5-ene (**10e)** again affords a by-product attributed to the formation of carbocation (**88**). In addition to the *trans*-bromohydrin (**89c**), a dibromo alcohol identified as **90** with the aid of NOE experiments is produced in a yield of 19%. Compound (**92**) is believed to result from the reaction of hypobromous acid with olefin (**87**). Formation of the primary alcohol by attack of water is at the less substituted primary carbon of the bromonium ion (**91**), ostensibly for steric reasons (Scheme 35).

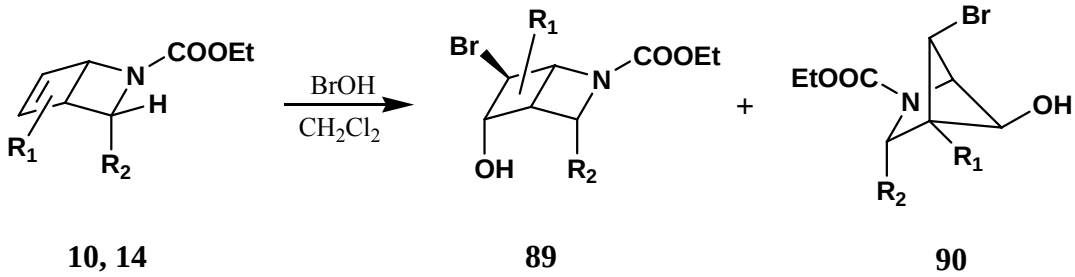
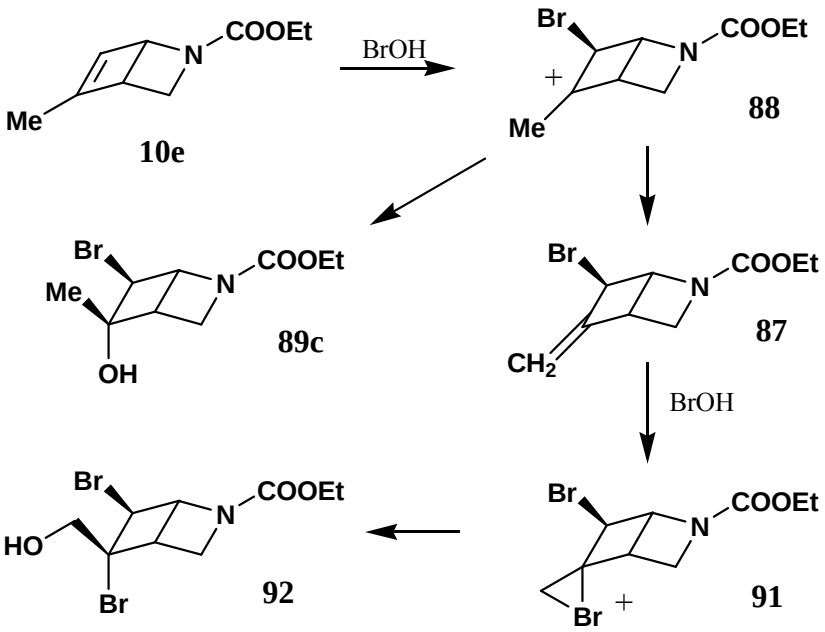


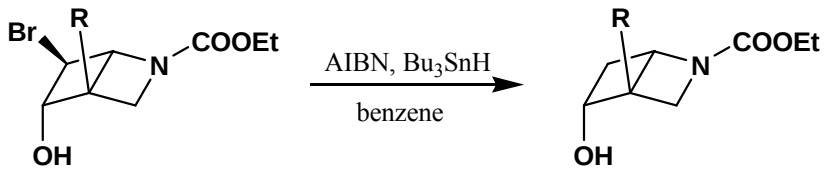
Table 6 – Products formed during reaction of *N*-ethoxycarbonyl-2-azabicyclo[2.2.0]hex-5-enes with hypobromous acid.[7]

Entry	2-Azabicyclo[2.2.0]hex-5-ene	Products	Yield (ratio)
1.	**10a** R_1 = H, R_2 = H	**89a**, **90a** (R_1 = H, R_2 = H)	70–80 (7:3)
2.	**10c** R_1 = 4-Me, R_2 = H	**89b** R_1 = 4-Me, R_2 = H,	
		90b R_1 = Me, R_2 = H	54 (2:8)
3.	**10e** R_1 = 5-Me, R_2 = H	**89c** R_1 = 5-Me, R_2 = H	76
4.	**14a** R_1 = H, R_2 = Me	**90d** R_1 = H, R_2 = Me	85
5.	**14d** R_1 = H, R_2 = Ph	**90e** R_1 = H, R_2 = Ph	60
6.	**14e** R_1 = 4-Me, R_2 = Me	**90f** R_1 = Me, R_2 = Me	47



Scheme 35

Unrearranged bromohydrins (**89a**) and (**89b**) undergo reductive debromination upon reaction with tributyltin hydride in refluxing benzene to yield the 5-*endo*-substituted 2-azabicyclo[2.2.0]hexanols (**93a**) and (**93b**), respectively.[6]

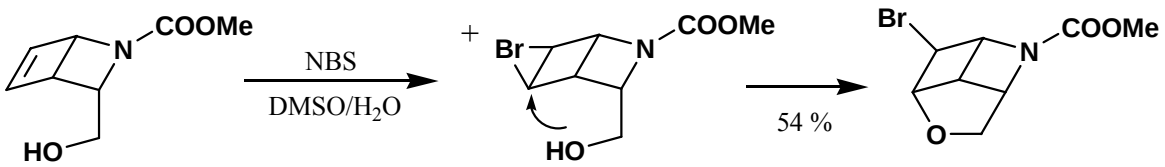


89a R = H
89b R = Me

93a R = H (73 %)
93b R = Me (53 %)

Scheme 36

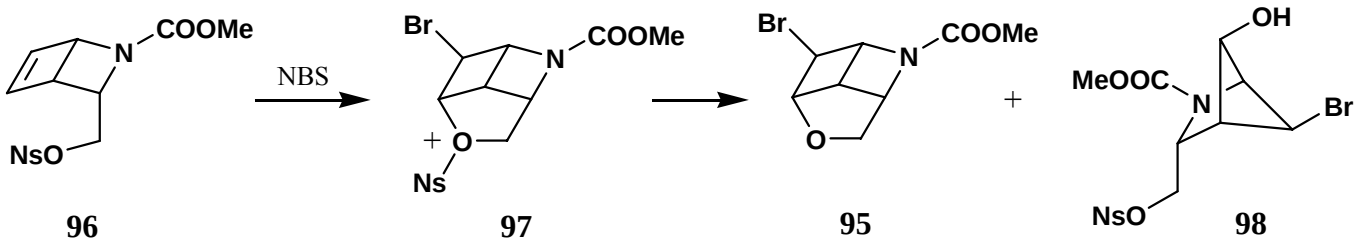
If a neighboring nucleophilic oxygen atom is present as in 3-hydroxymethyl-2-azabicyclo[2.2.0]hex-5-ene (**14b**), the initially formed bromonium ion (**94**) is usually captured by intramolecular attack to give the azatricycle (**95**).[16] Protection of the oxygen of **14b** with a bulky and relatively acid-stable TBDMS group resulted in longer reaction times with NBS (69 hours versus 19 hours for **14b**), but again only tricycle (**93**) was isolated in 50% yield.[16]



14b **94** **95**

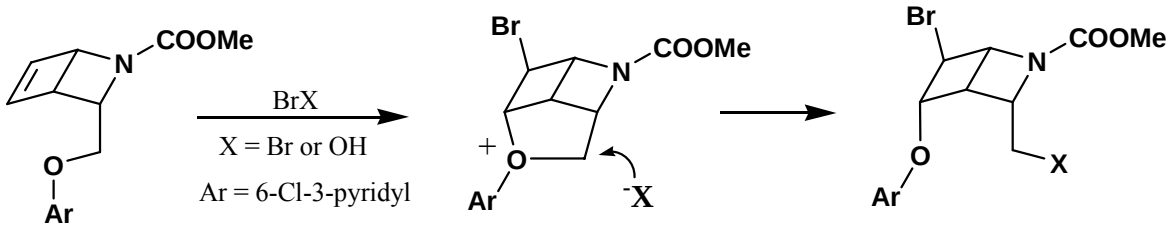
Scheme 37

The reaction of nosylate (**96**) with NBS affords a mixture of tricycle (**95**) and rearranged bicycle (**98**) *via* intermediate (**97**) with a positive charge adjacent to the nosyl group (Scheme 38).[16] Yields varied according to the solvent employed. In 2:1 DMSO:H_2O, the reaction afforded 9% tricycle (**95**) and 16% rearranged bicycle (**98**); in 2:1 THF:H_2O, the reaction afforded 19% tricycle (**95**) and 69% bicycle (**98**).



Scheme 38

The oxygen atom attached to the 6-chloro-3-pyridyl group of olefin (**99**) exhibits neighboring group participation as well; however, in this case the nucleophile X^- (bromide or hydroxide) exclusively displaces the cationic pyridoxy group from the primary carbon by S_N2 substitution. The result is formation of bicycle (**101**).[16]



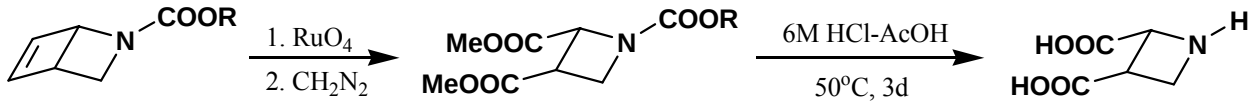
99 **100** **101a** X = OH (67 %)
101b X = Br (52 %)

Scheme 39

IV. CLEAVAGE REACTIONS OF 2-AZABICYCLO[2.2.0]HEX-5-ENES

A. Olefin cleavage of 2-azabicyclo[2.2.0]hex-5-ene.

Arakawa reported the conversion of *N*-alkoxycarbonyl-2-azabicyclo[2.2.0]hex-5-enes (**7a**) and (**7h**) to the corresponding azetidine-*cis*-2,3-diesters (**102a**) and (**102b**) by oxidation with ruthenium tetroxide followed by reaction with diazomethane (Scheme 40).[5] Acidic hydrolysis of diester (**102b**) resulted in the formation of amino acid (**103**) in 85% yield. Acidic hydrolysis of diester (**102a**) afforded a complicated mixture of products which did not include amino acid (**103**).



7a R = Me
7h R = *t*-Bu

102a R = Me (58 %)
102b R = *t*-Bu (67 %)

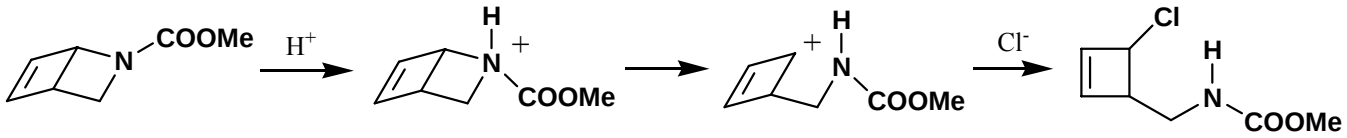
103 (85 % from **102b**)

Scheme 40

B. Allylic cleavage of 2-azabicyclo[2.2.0]hex-5-ene.

1. Cleavage with HCl

Fowler and coworkers reported that reaction of *N*-methoxycarbonyl-2-azabicyclo[2.2.0]hex-5-ene (**7a**) with HCl in benzene yielded olefin (**106**); yield of the olefin was not indicated.[4] Ring cleavage is probably initiated by protonation of the nitrogen (Scheme 41).

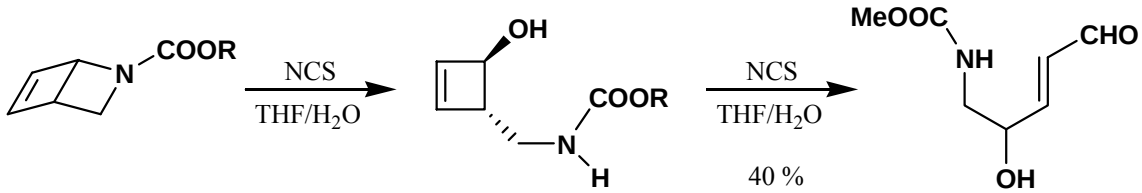


7a **104** **105** **106**

Scheme 41

2. Cleavage with chloronium ion.

Reaction of *N*-chlorosuccinimide (NCS) in aqueous THF with 2-azabicyclo[2.2.0]hex-5-enes (**7a**) and (**10b**) results in cleavage of the C1-N bond to afford cyclobuten-3-ols (**107**).[27] When the alkene (**7a**) is reacted with an excess of NCS in THF/water and heat is applied, ring-opened hydroxyl aldehyde (**108**) is obtained.



7a R = Me
10b R = CH_2Ph

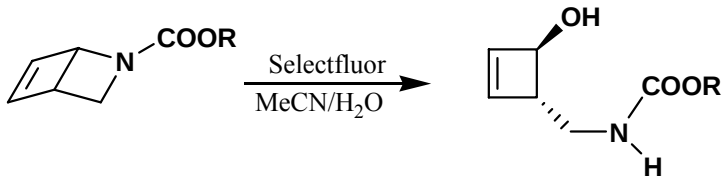
107a R = Me (76 %)
107b R = CH_2Ph (13 %)

108

Scheme 42

3. Cleavage with Selectfluor.

The reagent Selectfluor or F-TEDA-BF_4 (1-fluoro-4-chloromethyl-1,4-diazoniabicyclo[2.2.0]octane bis(tetrafluoroborate)), a source of positive fluorine, reacts with 2-azabicyclo[2.2.0]hex-5-enes (**7a**) and (**10b**) in aqueous acetonitrile to afford the cyclobuten-3-ol (**109**) (Scheme 43).[27] Ring cleavage at the C1-N bond is proposed to be facilitated by addition of the fluoronium electrophile to the nitrogen rather than the olefin. The reaction mechanism is believed to be the same for the reaction with chloronium ion (see above).



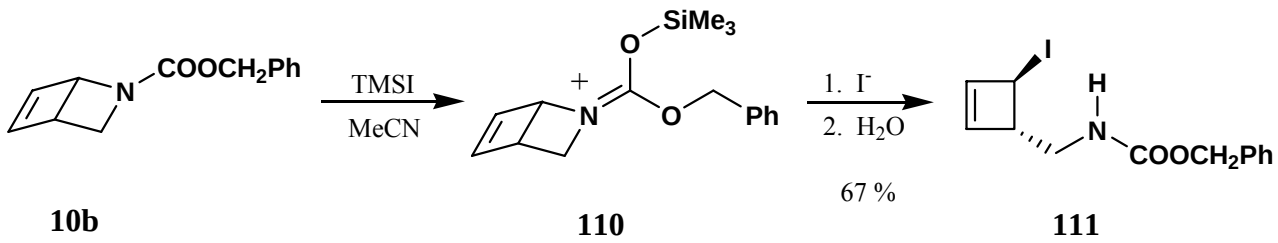
7a R = Me
10b R = CH_2Ph

109a R = Me (76 %)
109b R = CH_2Ph (74 %)

Scheme 43

4. Cleavage with trimethylsilyl iodide

Trimethylsilyl iodide (TMSI) was reacted with *N*-benzyloxycarbonyl-2-azabicyclo[2.2.0]hex-5-ene (**10b**) in acetonitrile at ambient temperature for 24 hours to yield olefin (**111**).[21] It was proposed that the oxygen atom of the carbamate group undergoes silylation to yield the cation (**110**), which activates the 2-azabicyclo[2.2.0]hex-5-ene toward ring cleavage.



Scheme 44

5. Cleavage and regiospecific two-atom insertions with chlorosulfonyl isocyanate.

Chlorosulfonyl isocyanate (CSI) was reacted with *N*-alkoxycarbonyl-2-azabicyclo[2.2.0]hex-5-enes (**10**) in methylene chloride either at -30 ^{o}C (*N*-ethoxy substituted) or at ambient temperature (*N*-benzyloxycarbonyl substituted), and the initial products were reacted with thiophenol or sodium sulfite to remove the chlorosulfonyl group.[11] Insertion products (**110**) were isolated; a product (**111**) also was afforded in a reaction of **10a**. The results are shown in Table 7.

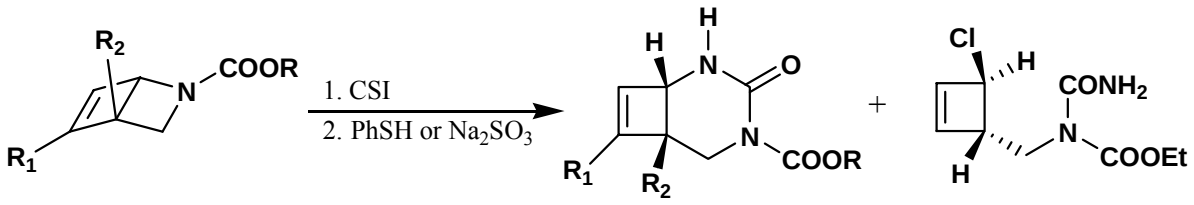
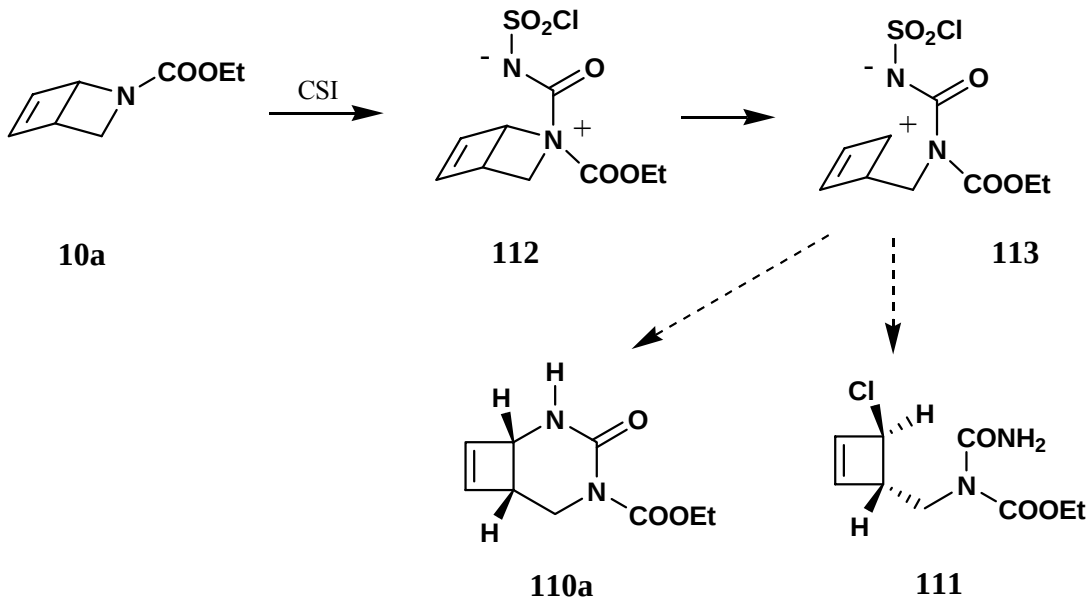


Table 7: Products formed in the reaction of CSI with 2-azabicyclo[2.2.0]hex-5-enes (**10**).[11]

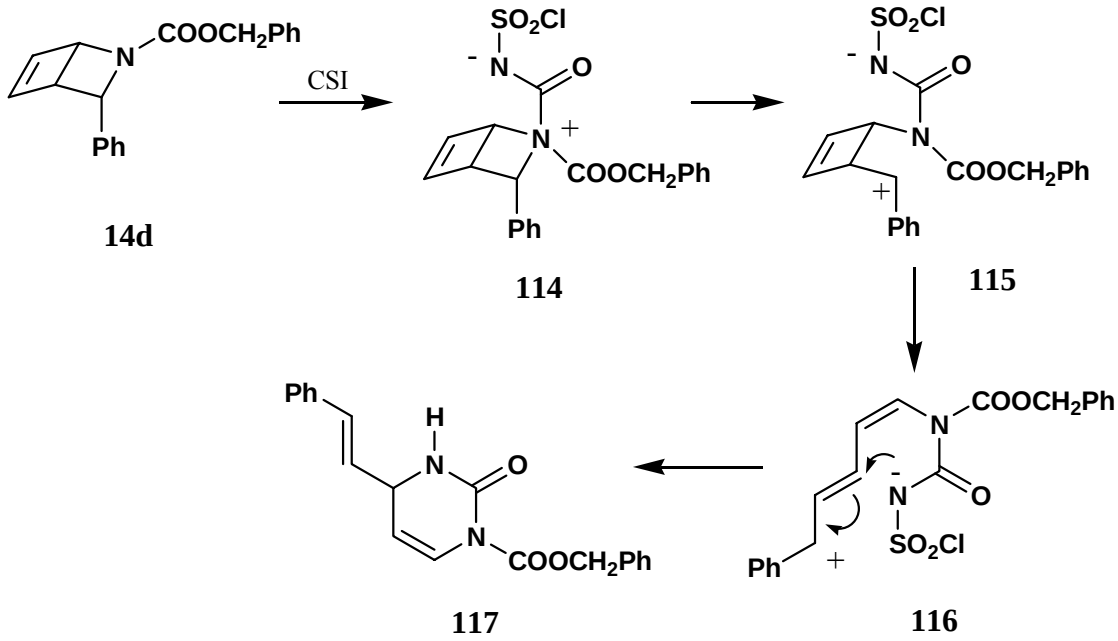
Entry	*N*-Alkoxycarbonyl-2-azabicyclo[2.2.0]hex-5-ene		product(s)	yield (ratio)
1.	**10a**	$R_1 = R_2 = H$, R = Et	**110a** + **111**	45 (45:55)
2.	**10b**	$R_1 = R_2 = H$, R = CH_2Ph	**110b**	62
3.	**10c**	$R_1 = H$, $R_2 = Me$, R = Et	**110c**	82
4.	**10e**	$R_1 = Me$, $R_2 = H$, R = Et	**110d**	32
5.	**10j**	$R_1 = Br$, $R_2 = H$, R = CH_2Ph	**110e**	75

An explanation for the molecular rearrangements leading to cyclobutenes (**110**) and (**111**) is shown in Scheme 45, using the parent azabicycle (**10a**) as an example. Addition of CSI to the nitrogen atom on the *exo* face affords the zwitterionic species (**112**), which may ring open to give the cyclobutenylallylic cation (**113**). Intramolecular ring closure of **113** provides azabicycle (**110a**) upon reductive workup. Alternatively, if chloride ion is present, intermediate (**113**) may be trapped to afford the chlorocyclobutene (**111**) upon reductive workup.



Scheme 45

Reaction of CSI and *N*-benzyloxycarbonyl-2-azabicyclo[2.2.0]hex-5-ene (**14d**) followed by reductive workup with sodium sulfite yielded the unusual product (**117**) in 70% yield.[11] It is postulated that the *endo* phenyl group at C3 in **14d** may stabilize positive charge at this position as well, leading to the rearrangement shown in Scheme 46.



Scheme 46

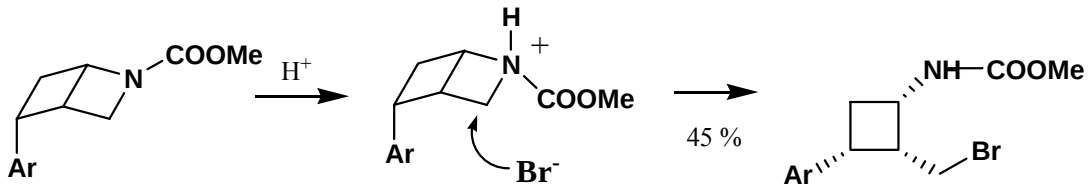
V. REACTIONS OF 2-AZABICYCLO[2.2.0]HEXANES

A. Azetidine ring cleavage.

1. Cleavage with HBr

Reaction of *N*-methoxycarbonyl-2-azabicyclo[2.2.0]hexane (**38**) with 30 wt % hydrogen bromide in

acetic acid at ambient temperature afforded cyclobutane (**119**).[21] In contrast to the cationic 2-azabicyclo[2.2.0]hex-5-ene intermediates discussed above, formation of an allylic cation intermediate is not possible with this saturated ring system. The ring is therefore believed to be cleaved by nucleophilic attack at the primary carbon, displacing the protonated carbamate nitrogen.



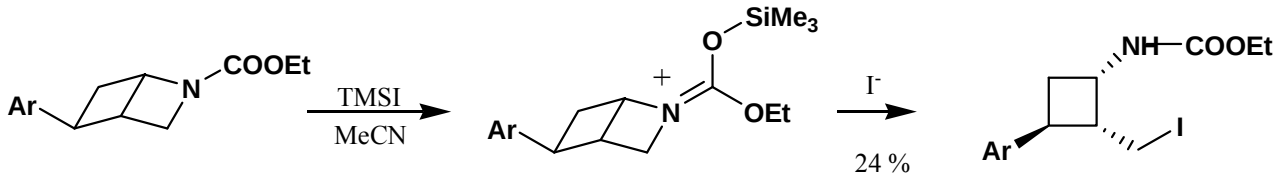
38 **118** **119**

Ar = 6-Cl-3-pyridyl

Scheme 47

2. Cleavage with trimethylsilyl iodide

Krow and coworkers reported the reaction of *N*-methoxycarbonyl-2-azabicyclo[2.2.0]hexane (**34b**) with trimethylsilyl iodide in acetonitrile which produces cyclobutane (**121**).[22] As shown above in Scheme 44, it was proposed that the oxygen atom of the carbamate group undergoes silylation to yield the cation (**120**). The ring is cleaved by nucleophilic attack at the primary carbon, displacing the charged carbamate nitrogen.



34b **120** **121**

Ar = 6-Cl-3-pyridyl

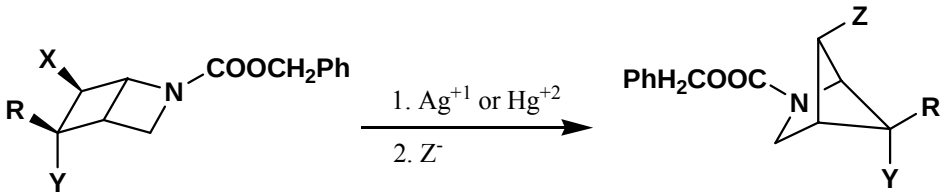
Scheme 48

B. Rearrangement of 6-*exo*-X isomers of *N*-carboalkoxy-2-azabicyclo[2.2.0]hexanes.

1. Rearrangement of 6-*exo*-halides

The stereoselective addition/rearrangement of 6-*exo*-iodo- and 6-*exo*-bromo-*N*-alkoxycarbonyl-2-azabicyclo[2.2.0]hexanes (**89a, 78b**, **80b**, **122a** and **122b**) mediated with silver(I) or mercury(II) salts to produce 5,6-difunctionalized-2-azabicyclo[2.2.1]hexanes (**123**) containing *syn*-hydroxy and *syn*-fluoro substituents has been recently reported by Krow.[24,26] Results as reported are shown in Table 8 below.

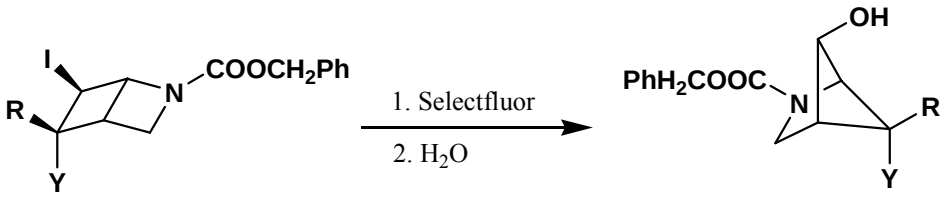
Selectfluor also effects the rearrangement of 6-*exo*-iodo-*N*-carboalkoxy-2-azabicyclo[2.2.0]hexanes (**78b, 80b**, **122a, 122b**, and **124**) to produce 5,6-difunctionalized 2-azabicyclo[2.2.1]hexanes (**125**).[24] The results are summarized in Table 9. The 6-*exo*-bromide (**89a**) that was rearranged with silver(I) fluoride (see Table 8) did not react with Selectfluor; and the 6-*exo*-phenylselenide (**81**) (see Scheme 32) was unreactive with Selectfluor as well.



78b,80b,89a,122 **123a-i**

Table 8: *N*-Benzyloxycarbonyl-5,6-difunctionalized-2-azabicyclo[2.2.1]hexanes produced by metal-catalyzed rearrangement of 6-*exo*-iodo(bromo)-*N*-benzyloxycarbonyl-2-azabicyclo[2.2.0]hexanes

Entry	Reactant	R	X	Y	reagents/temp/time	product	Y	Z	Yield	Ref
1	**89a**	H	Br	OH	AgF/$MeNO_2$/85 °C/12 h	**123a**	OH	F	20	26
2	**78b**	H	I	OH	AgF/$MeNO_2$/60 °C/24 h	**123a**	OH	F	58	26
3	**78b**	H	I	OH	HgF_2/$MeNO_2$/60 °C/24 h	**123a**	OH	F	65	26
4	**78b**	H	I	OH	AgOAc/AcOH/60 °C/36 h	**123b**	OH	OAc	60	26
5	**78b**	H	I	OH	$HgCl_2$/$MeNO_2$/60 °C/24 h	**123c**	OH	Cl	74	26
6	**80b**	H	I	F	AgF/$MeNO_2$/60 °C/24 h	**123d**	F	F	67	26
7	**80b**	H	I	F	dry HgF_2/$MeNO_2$/60 °C/24 h	**123d**	F	F	54	26
8	**80b**	H	I	F	moist HgF_2/$MeNO_2$/60 °C/24 h	**123e**	F	OH	60	26
9	**80b**	H	I	F	$Hg(OAc)_2$/AcOH/60 °C/24 h	**123f**	F	OAc	73	26
10	**80b**	H	I	F	$HgCl_2$/$MeNO_2$/60 °C/24 h	**123g**	F	Cl	63	26
11	**122a**	Me	I	F	moist HgF_2/$MeNO_2$/60 °C/16 h	**123h**	OH	F	53	24
12	**122b**	Me	I	OH	moist HgF_2 /$MeNO_2$/60 °C/16 h	**123i**	OH	OH	37	24



78b,80b,122, 124 **125a-e**

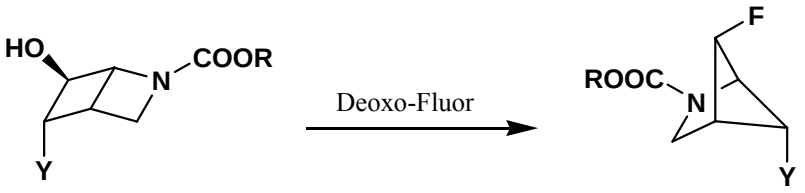
Table 9: *N*-Benzyloxycarbonyl-5,6-difunctionalized-2-azabicyclo[2.2.1]hexanes.[24,a]

Entry	Reactant	R	Y	temp/time	product	Y	Yield
1	**78b**	H	OH	25 °C/12 h	**125a**	OH	68
2	**80b**	H	F	25 °C/12 h	**125b**	F	84
3	**122a**	Me	F	60 °C/20 h	**125c**	F	71
4	**122b**	Me	OH	60 °C/20 h	**125d**	OH	62
5	**124**	H	Cl	25 °C/12 h	**125e**	Cl	75

a. Produced by Selectfluor-mediated rearrangement of 6-*exo*-iodo-*N*-benzyloxycarbonyl-2-azabicyclo-[2.2.0]hexanes in 1:1 MeCN/H_2O.

2. Rearrangement of 6-*exo*-alcohols.

Reaction of 6-*exo*-hydroxy-*N*-carboalkoxy-2-azabicyclo[2.2.0]hexanes (**51a**, **51b** and **53**) and Deoxo-Fluor [bis(2-methoxyethyl)aminosulfur trifluoride] afforded rearranged 5-*anti*-fluoro compounds (**126**) (Table 10).[24] The attempted synthesis of the rearranged 5-*anti*-fluoro (**126a**) *via* reaction of alcohol (**51a**) with Selectfluor was unsuccessful; no reaction was observed.



51,53 **126a-c**

Table 10: *N*-Alkoxycarbonyl-5,6-difunctionalized 2-azabicyclo[2.2.1]hexanes.[24,a]

Entry	Reactant	R	Y	reagents/temp/time	product	Yield
1	**51a**	CH_2Ph	Me	CH_2Cl_2/25 ^oC /2 h	**126a**	75
2	**51b**	CH_2Ph	Ph	CH_2Cl_2/25 ^oC/9 h	**126b**	77
3	**53**	Et	Br	CH_2Cl_2/reflux/12 h	**126c**	60

a. Produced by Deoxo-Fluor mediated rearrangement of 6-*exo*-hydroxy-2-azabicyclo[2.2.0]hexanes.

ACKNOWLEDGEMENTS

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