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Title: Stereoselective Synthesis of 7-(E)-Arylidene-2-chloro-6-azabicyclo[3.2.1]octanes via Aluminum Chloride Promoted Cyclization/Chlorination of Six-Membered Ring 3-Enynamides

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COMMUNICATION

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Stereoselective Synthesis of 7-(*E*)-Arylidene-2-chloro-6-aza-bicyclo[3.2.1]octanes via Aluminum Chloride Promoted Cyclization/Chlorination of Six-Membered Ring 3-Enynamides

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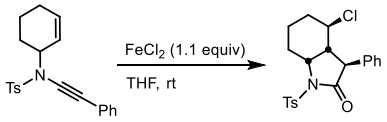
Abstract: An efficient stereoselective synthesis of 7-(*E*)-arylidene-2-chloro-6-azabicyclo[3.2.1]octanes is described. The aluminum chloride promoted cyclization/chlorination of six-membered ring 3-enynamides enables a straight forward approach to the 6-azabicyclo[3.2.1]octane nucleus incorporated in many biologically active compounds. Acid treatment of the resultant chlorinated arylideneazabicycles furnishes 3-alkanoyl-4-chlorocyclohexanamines in excellent yields and high stereoselectivity.

Keywords: amides; amines; cyclization; diastereoselectivity; halogenation; Lewis acids

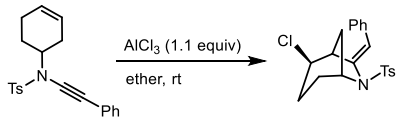
The 6-azabicyclo[3.2.1]octane is an important moiety found in a variety of biologically active compounds such as peduncularine,[1] actinobolamine,[2] and appears as a subunit in numerous alkaloids such as securinine,[3] D-normorphinans,[4] C-norbenzomorphans,[5] sarain A,[6] hetisine,[7] and other bridged aza-derivatives.[8] Due to the availability of functionalized 6-azabicyclo[3.2.1]octane building blocks that can be further elaborated into more complex bridged polycyclic systems or pharmaceuticals,[9] a number of synthetic strategies have been developed.[10] The known methods included the semipinacol rearrangement of *cis*-fused *β*-lactam diols,[11] the decarbonylative radical cyclization of · *α*-amino selenoester-tethered electron-deficient alkenes,[12] the rearrangement of 2-azabicyclo[2.2.2]octanes[13a,b] and 8-azabicyclo[4.2.1]nonanes,[13c] the samarium iodide-promoted intramolecular reductive coupling reaction of ketonitriles,[14] the tandem Horner-Emmons olefination-conjugated addition of 3-acetamidocyclohexanone,[15] and the [3 + 2] annulation of allylic silanes and chlorosulfonyl isocyanate.[1c] Recently, we disclosed a simple and mild entry into chlorinated fused bicyclic lactams via an $FeCl_2$-promoted cyclization/chlorination of simple six-membered ring 2-enynamides (Scheme 1, eq 1).[16] Here, we report a straight forward approach to the chlorinated 6-azabicyclo[3.2.1]octane system from readily accessible six-membered ring 3-enynamides[17] and inexpensive $AlCl_3$ (Scheme 1, eq 2).

Previous study: $FeCl_2$-promoted cyclization/chlorination of cyclic 2-enynamides[16]



(1)

This work: $AlCl_3$-promoted cyclization/chlorination of cyclic 3-enynamides



(2)

Scheme 1. Reaction of Lewis acids with cyclic enynamides

The requisite model substrate six-membered ring 3-enynamide **1a** is synthesized starting from commercially available 1,4-cyclohexanediol (see the Supporting Information for details). Initially, we focused on the screening of various Lewis acids for the cyclization of **1a**. Since $FeCl_2$ or $FeCl_3$ were capable of promoting the transformation of six-membered ring 2-enynamides into fused bicyclic lactams (Scheme 1, eq 1), **1a** was treated with 1.1 equiv of $FeCl_2$ or $FeCl_3$ in tetrahydrofuran (THF) at rt. However, both reactions led to an unidentified mixture of products (Table 1, entries 1 and 2). Gratifyingly, when **1a** was reacted with $FeCl_3$ in dichloromethane (DCM) at rt for 10 min, affording the chlorinated bridged azabicyclic compound **2a** as the only stereoisomer in 38% isolated yield together with a small amount of hydration product **3a**

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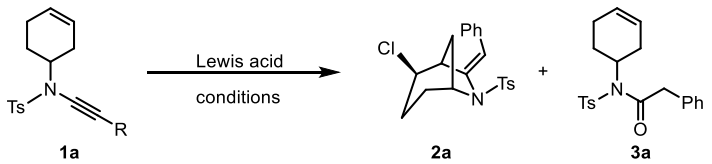
Table 1. Optimization of reaction conditions[a)]



1a 2a 3a

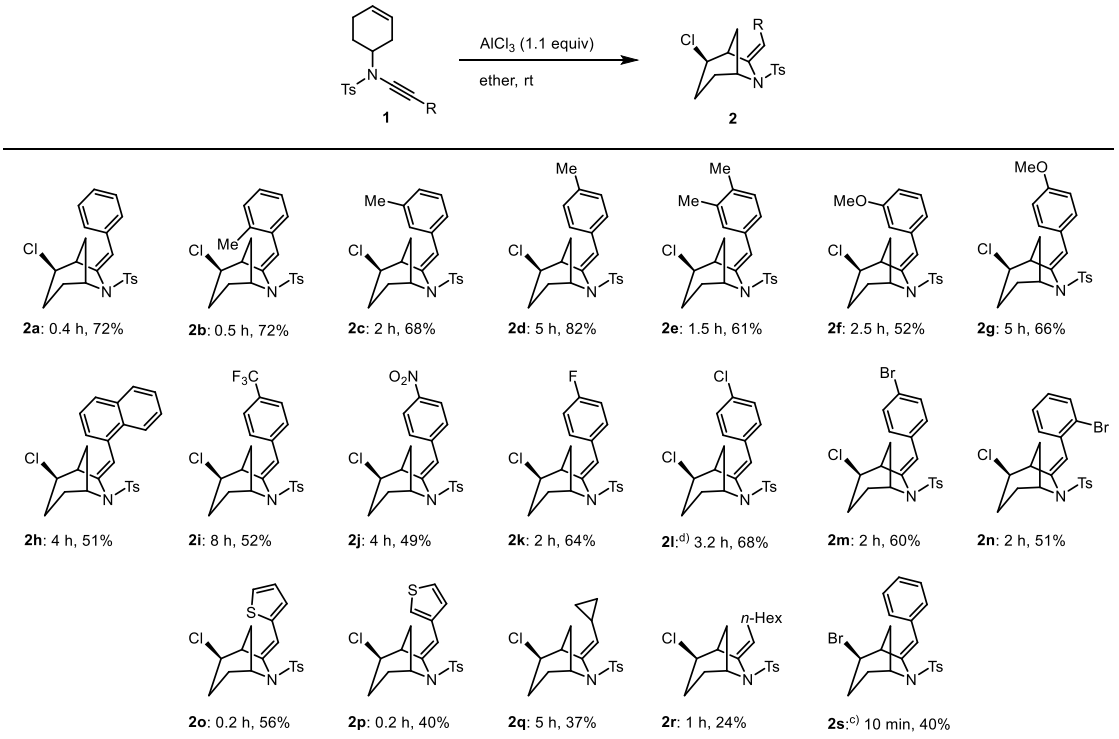
entry	MCl_n	solvent	[M]	*T* (°C)	time	yield (%)[b)]	
						2a	**3a**
1	$FeCl_2$	THF	0.1	rt	1 d	-	-
2	$FeCl_3$	THF	0.1	rt	4 min	-	-
3	$FeCl_3$	DCM	0.1	rt	10 min	38[c)]	5[c)]
4	$InCl_3$	DCM	0.1	rt	2.5 h	34	10
5	$TiCl_4$	DCM	0.1	rt	2.4 h	17	6
6	$AlCl_3$	DCM	0.1	rt	5 h	47	13
7	$ZnCl_2$	DCM	0.1	rt	5 h	N.R.	-
8	$CuCl_2$	DCM	0.1	rt	1 d	N.R.	-
9	$AlCl_3$	ether	0.1	rt	25 min	62[c)]	11[c)]
10	$AlCl_3$	toluene	0.1	rt	25 min	21	12
11	$AlCl_3$	DCE	0.1	rt	2 d	33	6
12	$AlCl_3$	THF	0.1	rt	1 h	-	-
13	$AlCl_3$	ether	0.1	0	3 h	51[c)]	12[c)]
14	$AlCl_3$	ether	0.1	35	20 min	62	17
15	$AlCl_3$	ether	0.01	rt	5 h	60[c)]	22[c)]
16	$AlCl_3$	ether	0.25	rt	25 min	72[c)]	11[c)]
17[d)]	$AlCl_3$	ether	0.25	rt	35 min	55	4

a) Reactions were conducted employing 0.25 mmol (1.0 equiv) of **1a** with Lewis acid (1.1 equiv) in the indicated solvent under nitrogen.
b) NMR yield unless otherwise indicated.
c) Isolated yield from column chromatography over silica gel.
d) 2.2 equiv of $AlCl_3$ was employed.

(Table 1, entry 3). In this transformation, $FeCl_3$ acts as a Lewis acid and the chloride source. The relative stereochemistry of **2a** was determined by NMR spectroscopic measurements and was compared to those of the azabicyclic analog **2l**[18] (vide infra), which was confirmed by single-crystal X-ray analysis. To increase the yield of **2a**, other chloride-containing Lewis acids were examined in DCM. Cyclization of **1a** with $InCl_3$ (34%, entry 4), $TiCl_4$ (17%, entry 5), and $AlCl_3$ (47%, entry 6) gave **2a** in moderate yields while only the starting material was recovered with $ZnCl_2$ (entry 7) and $CuCl_2$ (entry 8). Since the best result in this series was obtained with 1.1 equiv of $AlCl_3$, the effect of solvent, reaction temperature, concentration, and $AlCl_3$ loading were further evaluated. Performing the reaction with $AlCl_3$ in ether (0.1 M concentration) at rt for 25 min gave a better result (62%, entry 9) than those carried out in toluene (21%, entry 10), dichloroethane (DCE) (33%, entry 11), and THF (0%, entry 12). Conducting the reaction at 0 °C for 3 h in ether decreased the yield of **2a** (51%, entry 13). Running the reaction in ether at reflux for 20 min did not improve the yield of **2a** (62%, entry 14). When **1a** was reacted with $AlCl_3$ at a lower concentration (0.01 M) in ether at rt for 5 h, **2a** was isolated in 60% yield (entry 15). With a higher concentration (0.25 M) in ether, the cyclization was complete in 25 min to deliver **2a** in 72% yield (Table 1, entry 16). Moreover, increasing the loading of $AlCl_3$ to 2.2 equiv did not improve the yield of **2a** (55%, entry 17). Therefore, we identified 1.1 equiv of $AlCl_3$ in ether (0.25 M) at rt under nitrogen as the optimal reaction conditions for the formation of **2a** from **1a** (Table 1, entry 16).

As shown in Table 2, the optimal conditions allowed efficient cyclization/chlorination for substrates bearing methyl, methoxy, or naphthyl substituents on the phenyl ring of the alkynyl fragment, generating the corresponding chlorinated azabicycles in moderate to good yields (**2b**, 72%; **2c**, 68%; **2d**, 82%; **2e**, 61%; **2f**, 52%; **2g**, 66%; **2h**, 51%). Electron-deficient substituents including trifluoromethyl-, nitro-, fluoro-, chloro-, and bromo-substituent at the *para*- or *ortho*-position of the phenyl ring were also reactive, affording the desired chlorinated azabicycles **2i**–**n** in comparable results ranging from 49 to 68% yields. Among them, the structure of azabicycle **2l** was confirmed by X-ray diffraction analysis.[18] In addition, substrates **1o** and **1p** bearing a thienyl moiety at the alkyne were also tolerated and generated the corresponding thienyl-containing azabicycles **2o** (56%) and **2p**

Table 2. Substrate scope of cyclization/chlorination of six-membered ring 3-enynamides[a), b)]



a) Reactions were performed employing $AlCl_3$ (1.1 equiv) and **1a** (0.25 mmol) in 1.0 mL of ether at rt under nitrogen.

b) A small amount of the hydration product was isolated in each case.

c) Compound **2s** was obtained from **1a** and $InBr_3$ (1.1 equiv) in DCM (0.1 M) at rt for 10 min.

d) The structure was confirmed by X-ray diffraction analysis.[18]

(40%)
in moderate yields. When alkylynamides, such as cyclopropylynamide **1q** and *n*-hexylynamide **1r**, were subjected to the reaction conditions, the desired chlorinated azabicycles **2q** (37%) and **2r** (24%) were isolated in low yields. While attempting to synthesize the brominated azabicyclic analog **2s** with $AlBr_3$ failed, the reaction of $InBr_3$ with **1a** successfully delivered the brominated azabicycle **2s** in 40% isolated yield (DCM, rt, 10 min) (Table 2).

Scheme 2 shows a postulated reaction pathway for the diastereoselective formation of the chloro-substituted azabicycle **2a** from the six-membered ring 3-enynamide **1a**. Activation of the

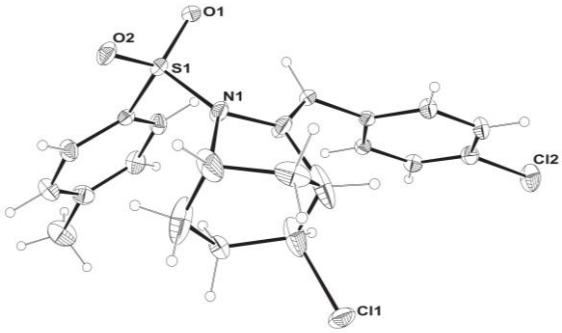
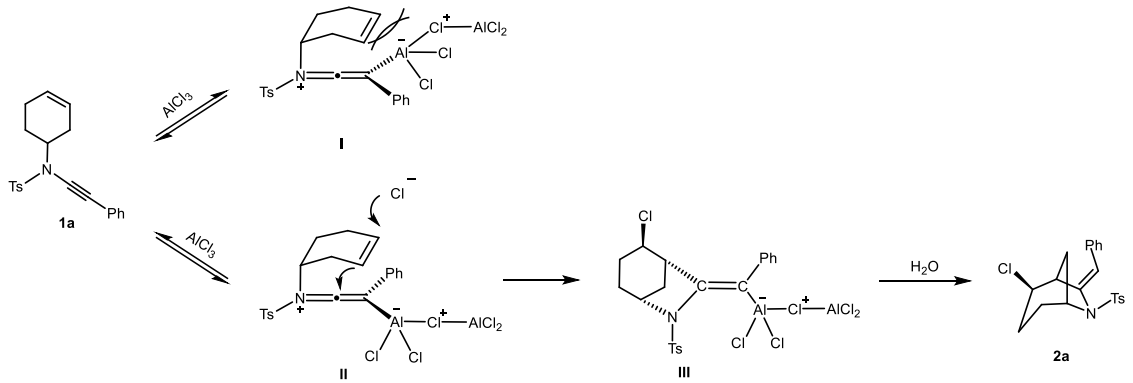
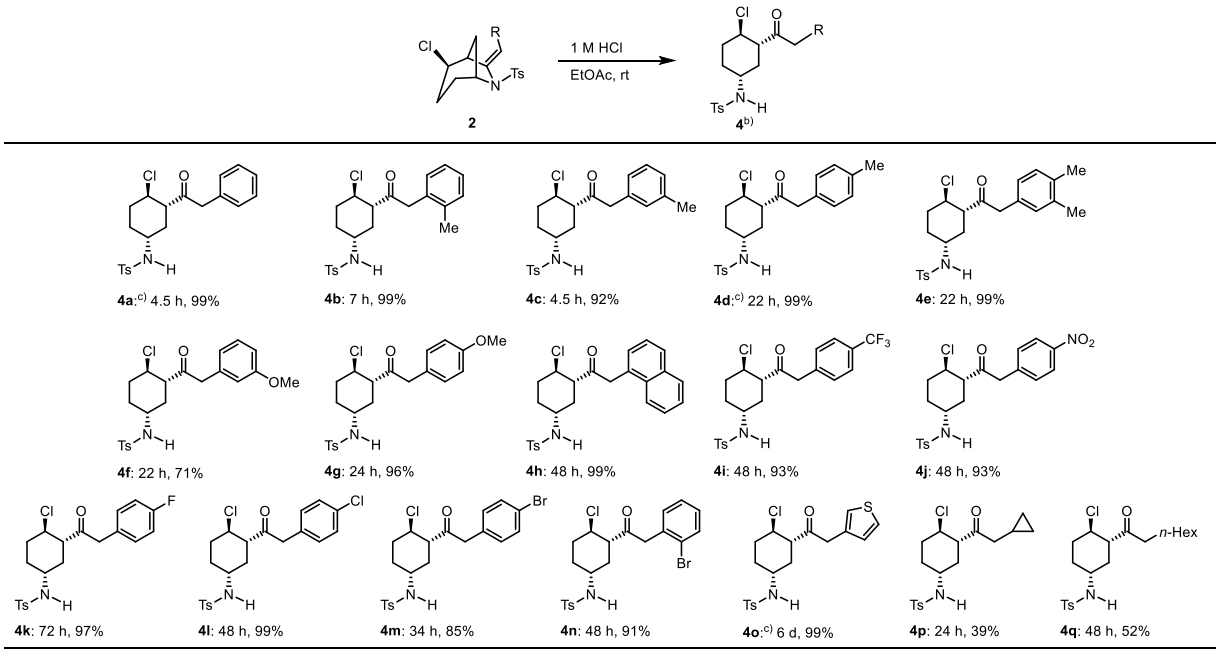


Figure 1. ORTEP drawing for compound **2l**.[18]



Scheme 2. Proposed mechanism for the $AlCl_3$-promoted cyclization/chlorination of **1a**

Table 3. Substrate scope for the formation of 3-alkanoyl-4-cholrocyclohexanamines **4**[a)]



a) All reactions were conducted by treatment of **2** with 5 molar equiv of 0.1 M $HCl_{(aq)}$ in EtOAc at rt.
b) Isolated yields.
c) The structure was confirmed by X-ray diffraction analysis.[18]

possible diastereomeric keteniminium ions **I** and **II**. However, intermediate **I** should be less favored due to a steric hindrance imposed by the bulky tetrahedral aluminum species on the cyclohexene ring. With a less congested planar phenyl ring at the α-face of the cyclohexene, intermediate **II** could undergo a highly stereoselective aza-Prins-type cyclization,[19] providing the kinetically favored chlorinated azabicyclo[3.2.1]octane intermediate **III**. Protonation of **III** upon aqueous workup resulted in the formation of **2a**.

The resultant chlorinated azabicycles could be transformed stereoselectively into 3-alkanoyl-4-chlorocyclohexanamines which are found in many pharmaceutically active compounds.[20] Thus, treatment of **2a** with 5 molar equiv of 1.0 M $HCl_{(aq)}$ in EtOAc at rt for 4.5 h afforded 3-alkanoyl-4-chlorocyclohexanamine **4a** in a quantitative yield with excellent stereoselectivity (Table 3). While various aryl-substituted chlorinated azabicycles **2** were converted quantitatively into the corresponding 3-alkanoyl-4-chlorocyclohexanamines **4a**–**o**, alkyl-substituted azabicycles **2q** and **2r** delivered low yields of the desired 3-alkanoyl-4-chlorocyclohexanamines **4p** (39%) and **4q** (52%).

In summary, we have disclosed an efficient strategy to 2-chloro-7-arylidene-6-azabicyclo[3.2.1]octane framework by aluminum chloride promoted cyclization/chlorination of six-membered ring 3-enynamides. The reaction proceeds smoothly at rt and required only the inexpensive and environmentally-friendly $AlCl_3$, providing direct access to the chlorinated bridged azabicyclic compounds in a highly stereoselective manner. The bridged azabicycles can be transformed quantitatively and stereoselectively into 3-alkanoyl-4-chlorocyclohexanamines which may be of interest in pharmaceutical chemistry. Further studies on the use of Lewis acid for the synthesis of azaspirocycles from cyclic enynamides are currently underway.

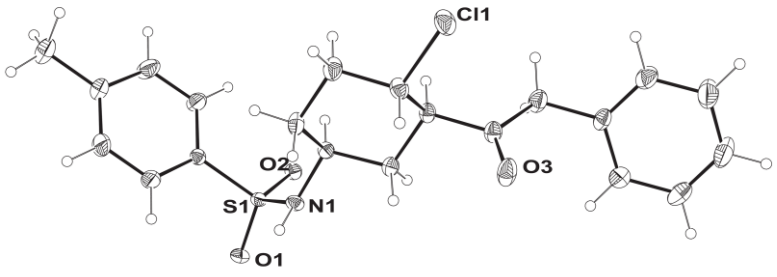


Figure 2. ORTEP drawing for compound **4a**.[18]

Experimental Section

Synthesis of (1*S,2*R**,5*R**)-7-((*E*)-Benzylidene)-2-chloro-6-tosyl-6-azabicyclo[3.2.1]octane (2a)**

To a dry and nitrogen-flushed two-neck-flask, equipped with a magnetic stirring bar and a septum were added dry $AlCl_3$ (0.0367 g, 0.28 mmol, 1.1 equiv), dry ether (1.0 mL, 0.25 M), and **1a** (0.0879 g, 0.25 mmol, 1.0 equiv). The reaction mixture was allowed to stir at room temperature until no trace of the starting material was detected on TLC. The resulting mixture was filtered through a pad of Celite/silica gel and concentrated under reduced pressure. Flash column chromatography of the resulting residue over silica gel with 1:30 ethyl acetate/hexanes gave the chlorinated azabicycle **2a** as a white solid; yield: 0.0681 g (0.18 mmol, 72%).

Synthesis of *N*-((1*R,3*S**,4*R**)-4-Chloro-3-(2-phenylacetyl)cyclohexyl)-4-methylbenzenesulfonamide (4a)**

To a solution of **2a** (0.0560 g, 0.14 mmol, 1.0 equiv) in EtOAc (5.6 mL, 0.025 M) was added hydrochloric acid (0.72 mL, 0.72 mmol, 1 M HCl). The reaction mixture was stirred at room temperature until no trace of the starting material was detected on TLC. The reaction mixture was added saturated $NaHCO_{3(aq)}$ until the *p*H value of the aqueous layer was above 10. The aqueous layer was extracted with EtOAc (30.0 mL × 3). The organic solution was washed with brine (30.0 mL × 3) and dried over anhydrous $MgSO_4$ and finally evaporated under reduced pressure to give the crude product. The crude mixture was purified *via* flash column chromatography over silica gel (EtOAc/hexanes 1:10) to give **4a** as a white solid; yield: 0.0576 g (0.14 mmol, 99%).

Supporting Information

Spectroscopic characterization and copies of $^1H/^{13}C$ NMR spectra of compounds **1a**–**r**, **2a**–**s**, **3a, 4a**–**q** and X-ray crystallographic information files for compounds, **2l**, **4a**, **4d** and **4o** are available as supporting information.

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