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Synthesis of Highly Functionalized 7-Azabicyclo[2.2.1]heptadienes

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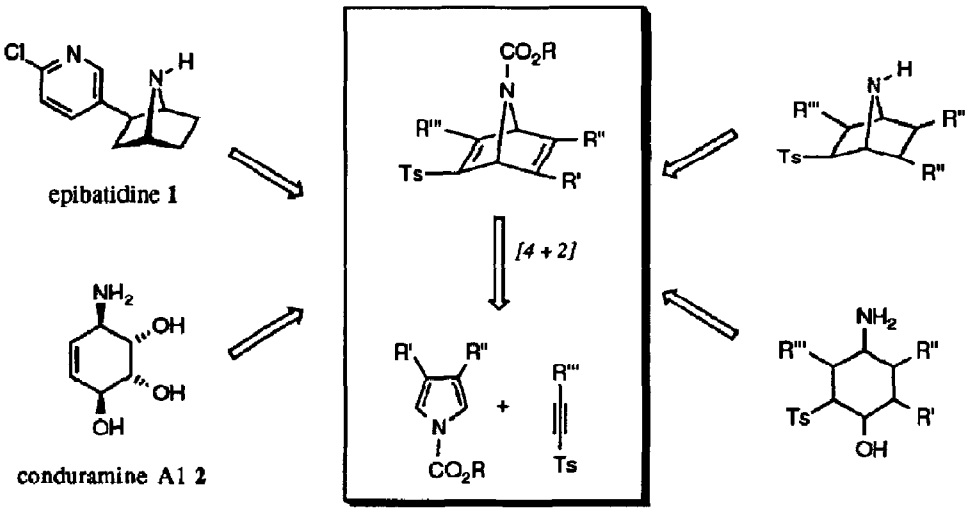
Abstract: Highly functionalized 7-azabicyclo[2.2.1]heptadiene derivatives have been synthesized *via* a [4 + 2] cycloaddition reaction between *N*-acyl-3,4-disubstituted pyrroles and ethynyl *p*-tolyl sulfone **5**.

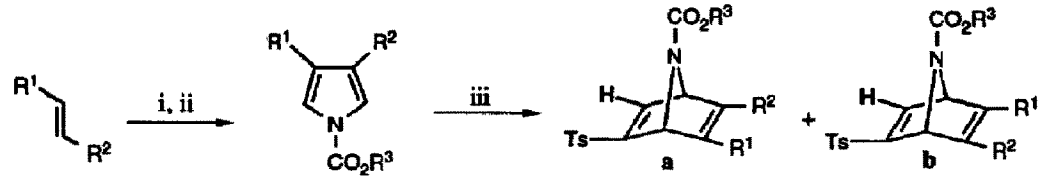
The [4 + 2] cycloaddition reaction of *N*-acylpyrrole substrates and an electron deficient acetylene has proven to be a useful method for the one-step construction of 7-azabicyclo[2.2.1]heptadiene ring systems.[1,2] Recent applications of this method have resulted in the preparation of a variety of 7-azabicyclo[2.2.1]heptadiene ring systems[3,4] and have led to syntheses of the potent non-opioid analgesic alkaloid epibatidine (**1**)[5,6] and the glycosidase inhibitory conduramine alkaloids (**2**).[7] The [4 + 2] cycloaddition reaction of *N*-acylpyrroles has also been shown to proceed with electron-deficient alkenes at high pressure to afford 7-azabicyclo[2.2.1]heptene ring systems.[1,8,9]



As part of an ongoing program of research in our laboratory aimed at the synthesis of epibatidine-related alkaloids it was of interest to further develop the existing [4 + 2] cycloaddition strategy for the synthesis of more highly functionalized 7-azabicyclo[2.2.1]heptadiene ring systems. The availability of highly functionalized 7-azabicyclo[2.2.1]heptadiene derivatives will undoubtedly prove useful for the preparation of complex epibatidine alkaloids and aminocyclitols.

As illustrated in Scheme 1, the *N*-acyl-3,4-disubstituted pyrroles **4** were prepared by a simple two-step procedure. Treatment of the corresponding alkene with TosMIC according to the method of van Leusen *et al.* furnished the 3,4-disubstituted pyrroles.[10] Subsequent acylation of the pyrrole nitrogen atom was achieved in a straightforward fashion with the appropriate acylating reagent [$ClCO_2Me$, $(t\text{-}BuO)_2CO$, $ClCO_2Bn$] to furnish the *N*-acyl pyrroles **4** in high yield (80 - 95%). In general, it was found that potassium hydride was a superior base for the deprotonation/acylation reaction to that of alkyl lithium reagents (*n*-BuLi, *t*-BuLi, LDA) which led to incomplete reactions and low yields of the corresponding *N*-acyl pyrroles.[11]

Scheme 1

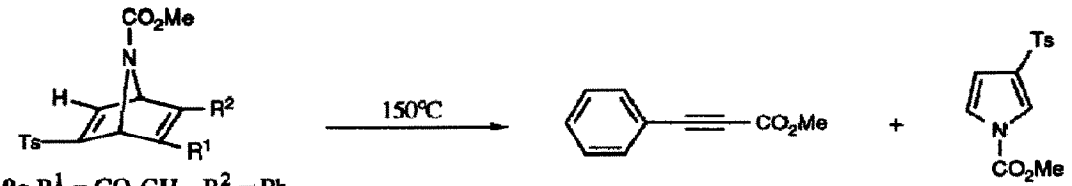


4 **6 - 12**

Reagents and Conditions: i) TosMIC, NaH, Et_2O, DMSO. ii) KH, THF, 0°C then $ClCO_2R^3$. iii) TsC≡CH (**5**), 85-110°C.

The [4 + 2] cycloaddition reaction between *N*-acylpyrroles **4** and the readily available ethynyl *p*-tolyl sulfone **5**[12] proceeded easily and in high yield to furnish the substituted 7-azabicyclo[2.2.1]heptadienes **6-12** (Table). In a typical reaction the *N*-acylpyrrole **4** (5 mmol) and **5** (10 mmol) were combined and heated neat at the prescribed temperature (Table) for 24 h. In the case of compounds **9**, **10** and **12**, a mixture of regioisomers (**a** and **b**) were obtained which could be separated by chromatography. Control of the reaction temperature was found to be critical to obtain high yields of the 7-azabicyclo[2.2.1]heptadiene derivatives. At temperatures above 140°C thermal decomposition of the 7-azabicyclo[2.2.1]heptadienes through a retro [4 + 2] cycloaddition reaction pathway was found to be a competing irreversible process.[13] As illustrated in Scheme 2, when **10** was heated at 150°C overnight, conversion into methyl phenylpropiolate **13** and *N*-carbomethoxy-3-*p*-toluenesulfonylpyrrole **14** was found to be quantitative.

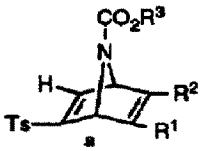
Scheme 2

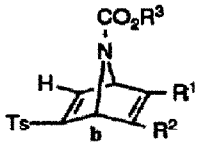


10a $R^1 = CO_2CH_3$, $R^2 = Ph$
10b $R^1 = Ph$, $R^2 = CO_2CH_3$

13 **14**

Table. *N*-Acyl-2-*p*-toluenesulfonyl-7-azabicyclo[2.2.1]heptadienes **6** - **12**.





Product[a]	R^1	R^2	R^3	Reaction Temp. (°C)	% Yield[b]	a:b[c]
6	H	H	Me	85	85	
7	H	H	*t*-Bu	85	86	
8	H	H	Bn	85	76	
9	CO_2Me	Me	Me	85	86	2:3
10	CO_2Me	Ph	Me	110	90	1:1
11	CO_2Me	CO_2Me	Me	85	81	
12	COMe	Ph	Me	85	87	1:1

[a]All new compounds were fully characterized by IR, NMR and elemental analysis.
[b]Isolated yields after chromatography (SiO_2). [c]Ratios determined by NMR.

The structures of the 7-azabicyclo[2.2.1]heptadienes were determined by ^1H NMR.[14] From these studies it was discovered that the chemical shifts of the bridgehead protons (*H1* and *H4*) of **6** had been previously incorrectly assigned in the literature.[2] From 2D COSY experiments it was determined that the bridgehead proton adjacent to the *p*-toluenesulfonyl group, *H1*, actually exhibits a chemical shift at δ 5.23 ppm, while the more downfield chemical shift was found to correspond to *H4* (δ 5.45 ppm). The observation that *H1* was shielded relative to *H4* was consistent throughout this series of compounds. The shielding effect can best be explained in terms of an orientation in solution of the *p*-toluenesulfonyl group in which *H1* lies in close proximity to the shielding region of the aryl sulfonyl group. Conversely, the ester group of derivatives **9** - **11** was found to have a deshielding effect on the chemical shift of the neighboring bridgehead protons.[15]

In summary, the [4 + 2] cycloaddition reaction between *N*-acylpyrroles and ethynyl *p*-tolyl sulfone **5** is a facile method for the preparation of a variety of highly functionalized 7-azabicyclo[2.2.1]heptadienes. Conversion of the 7-azabicyclo[2.2.1]heptadiene derivatives into epibatidine-related compounds is currently under investigation.

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14. The *N*-acyl groups and the bridgehead protons of the 7-azabicyclo[2.2.1]heptadienes **6 - 12** exhibited a broadened ^{1}H NMR signal (300 MHz) at room temperature characteristic of a mixture of *N*-acyl rotomers which coalesced at elevated temperatures (C_6D_6; 60°C). (A similar observation was reported in ref. 4.)
15. Selected ^{1}H NMR data (300 MHz, $CDCl_3$): (**6**) δ 7.76 (d, J = 8.0 Hz, 2H, *o-Ph*), 7.63 (s, 1H, *H3*), 7.38 (d, J = 8.0 Hz, 2H, *m-Ph*), 6.98 (s,1H, *H6*), 6.93 (s, 1H, *H5*), 5.45 (s, 1H, *H4*), 5.23 (s, 1H, *H1*), 3.45 (br s, 3H, OCH_3), 2.46 (s, 3H, CH_3). (**9a**) δ 7.77 (d, J = 7.9 Hz, 2H, *o-Ph*), 7.70 (s, 1H, *H3*), 7.36 (d, J = 8.0 Hz, 2H, *m-Ph*), 5.50 (s, 1H, *H1*), 5.22 (s, 1H, *H4*), 3.64 (s, 3H, OCH_3), 3.49 (br s, 3H, OCH_3), 2.45 (s, 3H, CH_3), 2.26 (s, 3H, CH_3). (**9b**) δ 7.79 (d, J = 8.3 Hz, 2H, *o-Ph*), 7.74 (s, 1H, *H3*), 7.38 (d, J = 8.2 Hz, 2H, *m-Ph*), 5.59 (s, 1H, *H4*), 5.11 (s, 1H, *H1*), 3.75 (s, 3H, OCH_3), 3.45 (br s, 3H, OCH_3), 2.45 (s, 3H, CH_3), 2.21 (s, 3H, CH_3). (**11**) δ 7.77 (s, 1H, *H3*), 7.76 (d, J = 8.0 Hz, 2H, *o-Ph*), 7.36 (d, J = 8.0 Hz, 2H, *m-Ph*), 5.62 (s, 2H, *H4,H1*), 3.84 (s, 3H, OCH_3), 3.70 (s, 3H, OCH_3), 3.56 (br s, 3H, OCH_3), 2.45 (s, 3H, CH_3).

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