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A NEW [4 + 2] CYCLOADDITION STRATEGY FOR THE SYNTHESIS OF *N*-ACYL-7-AZABICYCLO[2.2.1]HEPTAN-2-ONES: A FORMAL SYNTHESIS OF (±)-EPIBATIDINE

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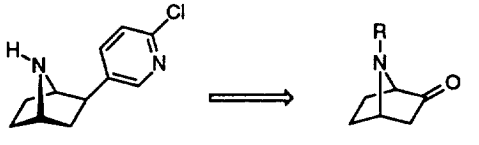
Abstract: *N*-Acyl-7-azabicyclo[2.2.1]heptan-2-one derivatives were prepared from *N*-acyl pyrroles *via* a [4 + 2] cycloaddition reaction with allenes. This represents a new synthetic approach for the synthesis of epibatidine and related analogs. © 1997 Elsevier Science Ltd.

In 1992 Daly *et al* isolated the alkaloid epibatidine (**1**) from the skin of the Ecuadorian poison dart frog, *Epipedobates tricolor*.[1] Epibatidine is the only known alkaloid containing the 7-azabicyclo[2.2.1]heptane structure to which is attached, in an *exo* orientation, a 5-(2-chloropyridyl) substituent. Epibatidine has been found to be 200–400 times more potent than morphine as an analgesic and appears to operate *via* a non-opioid mechanism since its effects are not blocked by the opiate receptor antagonist naloxone.[1] It has also been shown that epibatidine is an extremely potent agonist of the nicotinic acetyl choline receptor.[2] It has been found that both (+)- and (−)-epibatidine are equally potent analgesics, but this desirable activity is accompanied by high toxicity. This has generated interest in the preparation of analogs which may be selective nicotinic receptor analgesics with reduced toxicity.

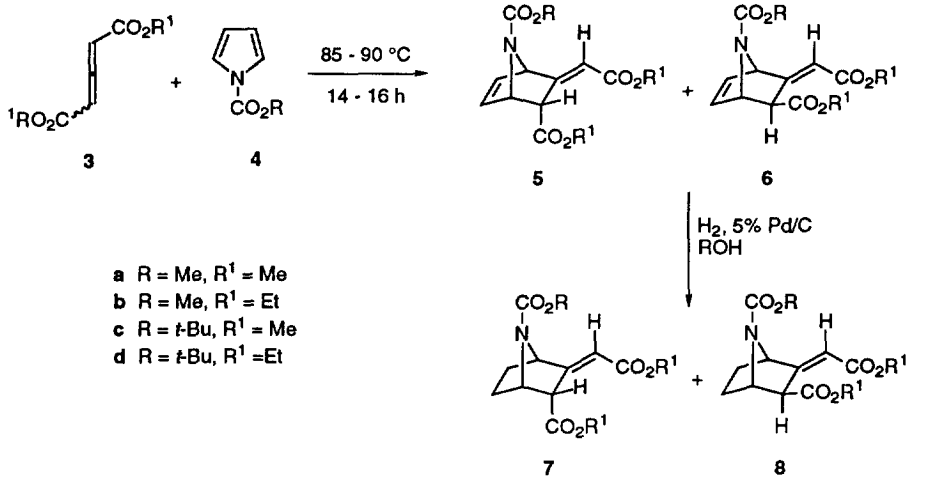
Due to its potent biological activity, uncommon structural features and its scarcity in nature, epibatidine (**1**) has attracted considerable attention from synthetic laboratories around the world.[3-4] Many different synthetic strategies have been developed for the preparation of this novel alkaloid, based primarily on different methods for the preparation of the 7-azabicyclo[2.2.1]heptane ring system.[3-5] In a number of syntheses of epibatidine (**1**), *N*-acyl-7-azabicyclo[2.2.1]heptan-2-ones (**2**) have been employed as key synthetic intermediates.[6-11] In addition, *N*-acyl-7-azabicyclo[2.2.1]heptan-2-ones have been envisaged as potential building blocks for the preparation of epibatidine analogs. Herein we wish to report a new strategy for the synthesis of *N*-acyl-7-azabicyclo[2.2.1]heptan-2-ones which utilizes a [4 + 2] cycloaddition reaction of *N*-acyl pyrroles with allenes.



1 **2a** R = BOC
2b R = Ts

Based on a previous report which demonstrated that allenic esters readily undergo a [4 + 2] cycloaddition reaction with *N*-acyl pyrroles,[12] this approach was investigated as a potential route for the synthesis of **1** and related analogs. As illustrated in Scheme 1, the *N*-acyl pyrroles **4** (1.8 equivalents) were heated with the allenic esters **3**[13] neat for 14–16 h to furnish the Diels–Alder adducts **5** and **6** in consistently good yields (65 -75%). Only two of the possible four isomers were obtained where the exo-isomer **6** was present in slight excess (**5**:**6**, 2:3).. Although the two isomers could not be easily separated and independently characterized at this point, the structure and relative stereochemistry of each isomer was assigned by NMR and X-ray crystallographic analysis of advanced intermediates. Moreover, the relative stereochemical assignments of **5** and **6** were consistent with structures elegantly established by Agosta from the corresponding reaction of *N*-acyl pyrroles with allenic acids.[14]

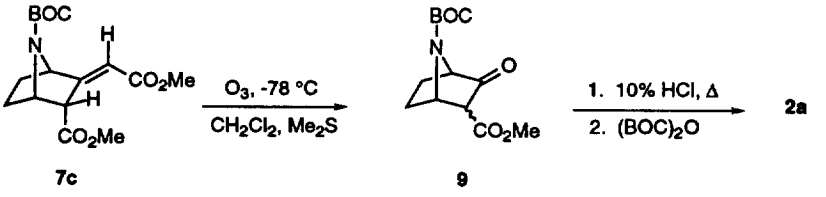
Scheme 1



The mixture of cycloaddition adducts **5** and **6** were regioselectively hydrogenated over 5% palladium on carbon to give the alkylidenes **7** and **8** in quantitative yield (98%, Scheme 1). The stereoisomers **7** and **8** were readily separated by chromatography and carried on independently. The structure of each stereoisomer was established by NMR and the structure of **7c** was unequivocally confirmed by X-ray crystallographic analysis of the corresponding *N*-deacylated hydrochloride salt.[15]

The *endo* isomer **7c** was then subjected to ozonolysis (Scheme 2). This provided the required 7-(*t*-butoxycarbonyl)-3-methoxycarbonyl-7-azabicyclo[2.2.1]heptan-2-one (**9**) in as mixture of isomers (70%, α:β, 1.4:1). The β-keto ester **9** has recently been converted into epibatidine (**1**) by simple transformations performed in these laboratories.[10] Hydrolysis, decarboxylation and re-acylation of **9** furnished the 7-(*t*-butoxycarbonyl)-7-azabicyclo[2.2.1]heptan-2-one (**2a**) which has been used as a key intermediate in several syntheses of epibatidine (**1**).[6,8-11]

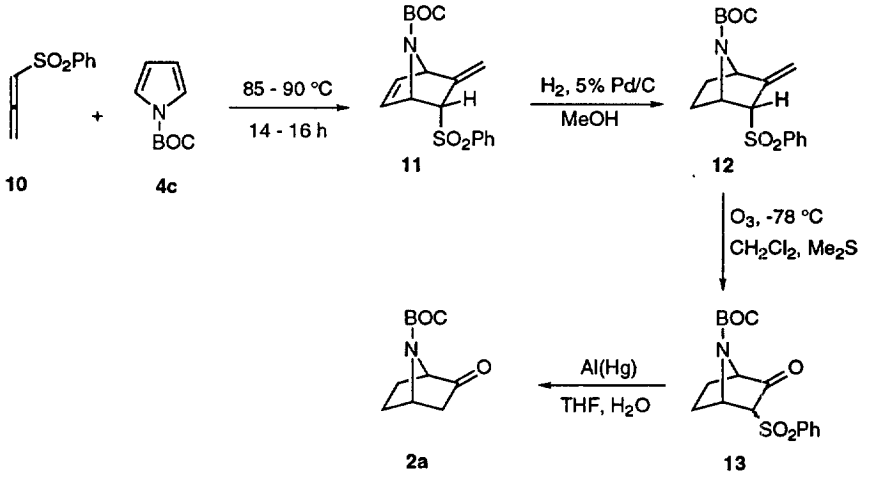
Scheme 2



It was quite surprising that all of the *exo*-isomers **8a-d** were not reactive toward ozonolysis. In addition, alternative methods of oxidation (OsO_4, $NaIO_4$ or $KMnO_4$) were also not effective. Moreover, attempts to epimerize isomers **8a** and **8c** into **7a** and **7c**, respectively, were unsuccessful.

As an alternative to the ester sequence, the *N*-acyl pyrroles were reacted with 1-(benzenesulfonyl)-1,2-propadiene (**10**)[16] to give the cycloadduct **11** as the sole product in 45% yield (Scheme 3). Subsequent hydrogenation of **11** over 5% palladium on carbon proceeded regioselectively to reduce the 5,6-carbon-carbon double bond and furnished **12** in 90% yield. Ozonolysis of **12** gave the β-keto sulfone **13** in 78% yield (*exo*:*endo*, 2.5:1). The benzenesulfonyl group was then reductively cleaved using Al(Hg)[17] to give **2a** in 60% yield. This approach with the allenic sulfone **10** proved to be more efficient and high yielding than the ester sequence and provided **2a** in 19% overall yield (four steps).

Scheme 3



In summary, the [4 + 2] cycloaddition reaction between *N*-acyl pyrroles and electron deficient allenes is an excellent method to prepare 7-azabicyclo[2.2.1]heptenes. These compounds can then be readily converted into *N*-acyl 7-azabicyclo[2.2.1]heptan-2-ones which have been shown to be useful precursors for the synthesis of epibatidine and more importantly should prove to be useful for the preparation of epibatidine analogs.

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15. All compounds gave satisfactory spectral and microanalytical data. **5c**: ^{1}H NMR ($CDCl_3$, 300 MHz at 50°C) δ 6.39 (dd, J = 5.7, 2.4 Hz, 1H), 6.29 (dd, J = 5.7, 1.8 Hz, 1H), 6.03 (d, J = 15 Hz, 1H), 4.95 (br s, 2H), 3.98 (t, J = 2.4 Hz, 1H), 3.65 (s, 3H), 3.63 (s, 3H), 1.39 (s, 9H). **7c**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.84 (d, J = 2.7 Hz, 1H), 4.50 (d, J = 5.1 Hz, 1H), 4.46 (t, J = 4.8 Hz, 1H), 3.88 (t, J = 2.7 Hz, 1H), 3.65 (s, 3H), 3.59 (s, 3H), 1.96 (m, 1H), 1.62 - 1.59 (m, 3H), 1.37 (s, 9H). **12**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.89 (d, J =7.5 Hz, 2H), 7.67–7.54 (m, 3H), 6.40 (d, J = 2.4 Hz), 6.33 (d, J = 2.5 Hz), 5.35 (s, 1H), 5.32 (s, 1H), 4.82 (s, 1H), 4.67 (s, 1H), 4.28 (t, J = 1.8, 3.6 Hz, 1H), 1.38 (s, 9H). **13**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.96–7.84 (m, 2H), 7.84–7.49 (m, 3H), 4.91 (s, 0.7H), 4.83 (t, J = 4.2 Hz, 0.3H), 4.29 (d, J = 6 Hz, 0.3H), 4.21 (s, 0.7H), 4.03 (d, J = 5.1 Hz, 0.3H), 3.6 (s, 0.7H), 1.98–1.86 (m, 2H), 1.63–1.48 (m, 2H), 1.38 (s, 9H).
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