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A Total Synthesis of (±)-Epibatidine

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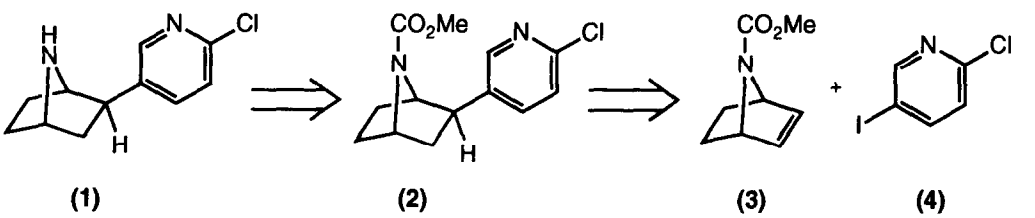
Abstract: *A total synthesis of the potent non-opiate analgesic alkaloid epibatidine is described, in which the key step is a reductive palladium-catalysed Heck-type coupling. The synthesis is concise (two steps from known compounds), highly convergent, and completely stereoselective for the desired exo-isomer.*

Epibatidine (**1**) is an alkaloid which has recently been isolated from the Ecuadoran poison frog *Epipedobates tricolor*.[1] Its structure is unusual among alkaloids in containing a chloropyridine, and it appears to be unique in possessing the 7-azabicyclo[2.2.1]heptane ring system. Our attention was attracted to this compound both by its unusual structure, and by its biological activity, since it shows hot-plate analgesic activity at 1/200th of the dose of morphine, and is similarly many times more active in the Straub-tail reaction.

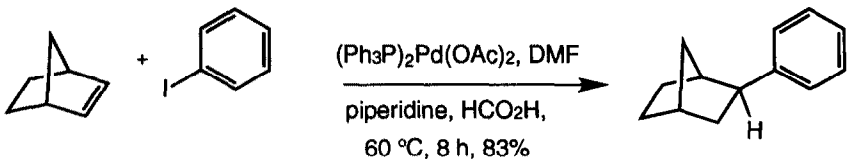
In this Letter, we report a total synthesis of racemic epibatidine. During the course of this work, three other syntheses of epibatidine have appeared.[2,3,4] Our approach differs from these, and the retrosynthetic analysis is shown in Scheme 1. The key disconnection is a reductive palladium-catalysed Heck-type coupling between two known compounds, the N-protected azabicyclo[2.2.1]-heptene (**3**) and 2-chloro-5-iodopyridine (**4**).



(1) **(2)** **(3)** **(4)**

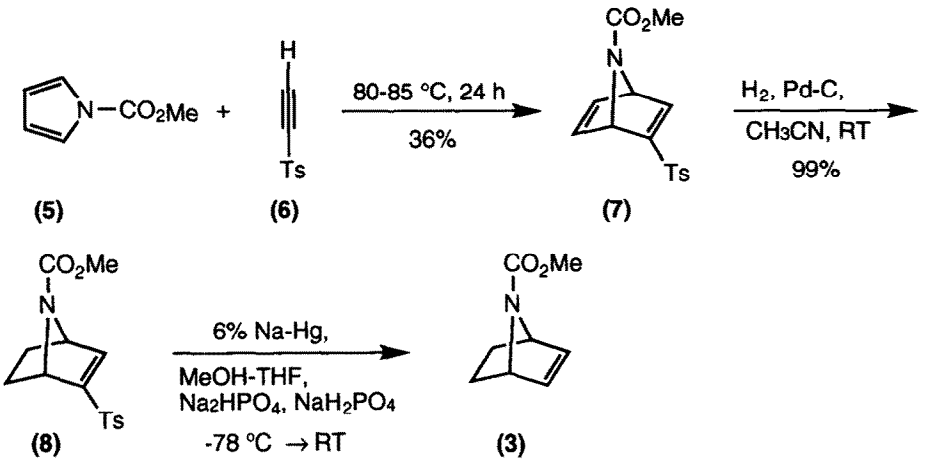
Scheme 1

It was expected that the coupling would be stereoselective for the desired *exo*-isomer of (**2**), on the basis of the known reductive coupling between iodobenzene and norbornene (Scheme 2).[5,6] However, to our knowledge, this type of reductive coupling has not been reported for halopyridines, nor for any heterobicycloalkenes.



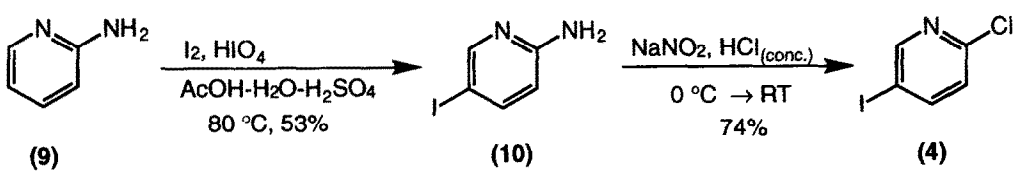
Scheme 2

The known N-methoxycarbonyl 7-azabicyclo[2.2.1]-heptene (**3**) was synthesised following the route of Altenbach *et al.*,[7] which is shown in Scheme 3. The key step is a Diels-Alder reaction between N-methoxycarbonylpyrrole (**5**)[8,9] and *para*-toluenesulphonylacetylene (**6**)[10] to give the N-protected heterobicyclic compound (**7**). Selective catalytic hydrogenation of (**7**) reduced only the less-substituted alkene to give (**8**). Finally, the *para*-toluenesulphonyl group was reductively cleaved using 6% sodium amalgam in methanol-THF, yielding the N-protected 7-azabicyclo[2.2.1]-heptene (**3**) required for the coupling step.



Scheme 3

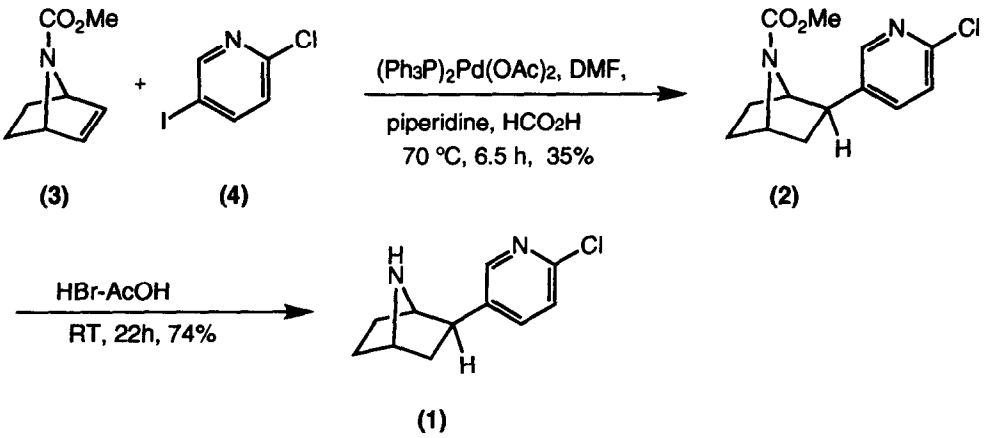
The 2-chloro-5-iodopyridine (**4**), required as the other component for the coupling, was prepared in two steps from 2-aminopyridine (**9**) as shown in Scheme 4. Direct iodination of 2-aminopyridine in the presence of periodic acid gave 2-amino-5-iodopyridine (**10**).[11] Diazonium salt formation in concentrated hydrochloric acid then afforded 2-chloro-5-iodopyridine (**4**).[12]



Scheme 4

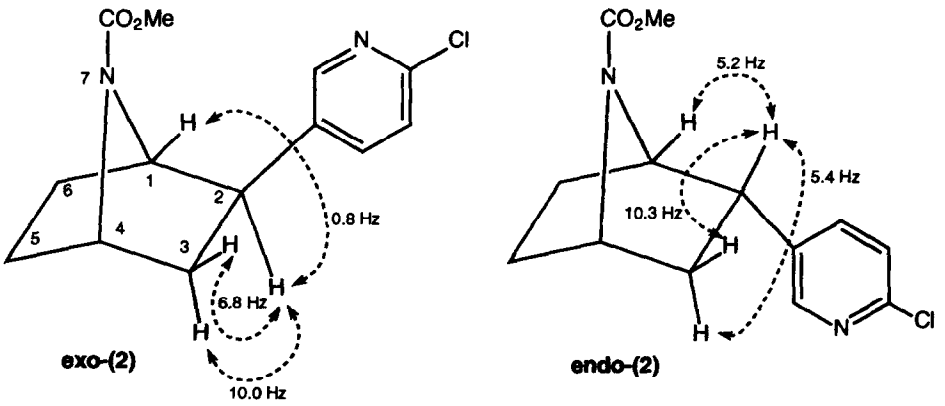
The crucial reductive coupling reaction is shown in Scheme 5. A 2.5-fold excess of the readily available iodopyridine (**4**) was used over the more precious N-protected 7-azabicyclo[2.2.1]-heptene (**3**), as precedented by the reaction between iodobenzene and norbornene[5] (Scheme 2). Compounds (**3**) and (**4**) were heated

together at 70 °C for 6.5 hours in solution in DMF containing piperidine, formic acid, and 8 mol% of the palladium catalyst formed *in situ* from palladium (II) acetate and triphenylphosphine. The desired reductively-coupled product (2) was formed in a moderate 35% yield after chromatography; however this yield has not yet been optimised. We were delighted to find that (2) was formed completely stereoselectively as the desired *exo*-isomer, and none of the corresponding *endo*-product could be isolated.



Scheme 5

The assignment of the stereochemistry of (2) was made on the basis of the lack of a coupling between H-1 and H-2 in the ^{1}H nmr spectrum[13] , implying a dihedral angle close to 90°,which is only consistent with the *exo*-isomer. Molecular modelling studies on both the *exo*- and *endo*-isomers of (2) using the program MacroModel[14] showed that the only conformational flexibility was that the CO_2Me and chloropyridine groups each had two alternative rotational positions, 180° apart. Thus the rigidity of the ring system allowed prediction of ^{1}H nmr coupling constants, using the Nmr submode within MacroModel, and these are shown in Scheme 6. This lack of coupling was also observed in the spectrum of the closely-related compound N-acetylepibatidine during the original structural elucidation,[1] and it is also seen in the spectrum of epibatidine itself.



Observed for 2-H:
δ 2.89 (1 H, dd, *J* 9.1, 5.0 Hz)

Scheme 6

Finally, deprotection of **(2)** was achieved by stirring in hydrogen bromide solution in acetic acid,[3] at room temperature for 22 hours, to give racemic epibatidine **(1)** in quantitative crude yield (74% after chromatography). This material had an identical ^{1}H nmr spectrum[15] to those published in two of the previous syntheses,[2,3] and its infrared and mass spectra matched those in the original structural elucidation.[1]

In summary, we have developed a synthesis of racemic epibatidine which is concise (only two steps from known compounds), stereoselective for the desired *exo*-isomer, and highly convergent. Since the key coupling reaction does not occur until the penultimate step of the synthesis, this route should be well suited to the production of analogues for biological testing, by variation of either the pyridine or azabicyclo[2.2.1]-heptene ring systems. Also, since both **(3)** and **(4)** are achiral, this synthesis could in principle be extended to incorporate an asymmetric coupling reaction, by using chiral phosphine ligands on the palladium catalyst.

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13. ^{1}H nmr data for **(2)** (200 MHz, $CDCl_3$): δ 8.22 (1 H, d, *J* 2.5 Hz), 7.60 (1 H, dd, *J* 8.2, 2.5 Hz), 7.23 (1 H, d, *J* 8.2 Hz), 4.44 (1 H, br t), 4.20 (1 H, br s), 3.67 (3 H, s), 2.89 (1 H, dd, *J* 9.1, 5.0 Hz), 2.03 (1 H, dd, *J* 12.0, 8.5 Hz), 1.9-1.7 (3 H, m), 1.65-1.5 (2 H, m).
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15. ^{1}H nmr data for **(1)** (200 MHz, $CDCl_3$): δ 8.27 (1 H, d, *J* 2.6 Hz), 7.76 (1 H, dd, *J* 8.4, 2.5 Hz), 7.24 (1 H, d, *J* 8.4 Hz), 3.84 (1 H, t, *J* 3.5 Hz), 3.60 (1 H, br s), 2.79 (1 H, dd, *J* 8.8, 5.3 Hz), 1.94 (1 H, dd, *J* 12.2, 9.1 Hz), 1.72-1.50 (5 H, m).

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