Pergamon

Tetrahedron Letters, Vol. 36, No. 51, pp. 9261-9264, 1995
Elsevier Science Ltd
Printed in Great Britain
0040-4039/95 $9.50+0.00

0040-4039(95)02019-5

First Synthesis of 2-Aminopyrrole and Simple 1-Substituted-2-Aminopyrroles. Observation of Fast Proton Exchange at C-5.

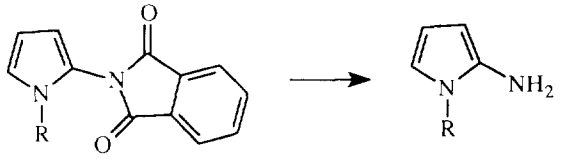
Michael De Rosa*, Roy P. Issac and Gregory Houghton

Department of Chemistry, The Pennsylvania State University Delaware County Campus
25 Yearsley Mill Road, Media, PA 19063, USA.

Abstract: *N*-(1-substituent-1*H*-pyrrol-2-yl)phthalimides can be used to prepare the previously unknown 2-aminopyrrole and 1-substituted 2-aminopyrroles which undergo fast proton exchange at C-5 in acetic acid at 25 °C.

To date neither 2-aminopyrrole, nor 1-substituted-2-aminopyrroles without further substitution on the ring, have been prepared.[1] All reported examples contain an electron-withdrawing group or a phenyl ring needed to stabilize the electron rich 2-aminopyrrole nucleus. As a result all previous studies on the properties of 2-aminopyrroles have been restricted to substituted derivatives. We report in this communication a simple method for the preparation of the unstable 2-aminopyrrole and simple 1-substituted-2-aminopyrroles in solution. Recently we reported that the reaction of *N*-chlorophthalimide with a 1-substituted pyrrole gave an *N*-(1-substituent-1*H*-pyrrol-2-yl)phthalimide (**1**).[2] Cleavage of this product should give the corresponding 2-aminopyrrole (**3**).[3] A mild one-pot method has been reported[4] in which the phthalimide derivative is partially reduced with $NaBH_4$/2-propanol to the *o*-hydroxymethyl benzamide which in turn is lactonized with aqueous acetic acid to give a primary amine and phthalide. A modified form of this procedure was used in this study.

The phthalimide derivatives **1a-d** were prepared from their respective pyrroles.[2]

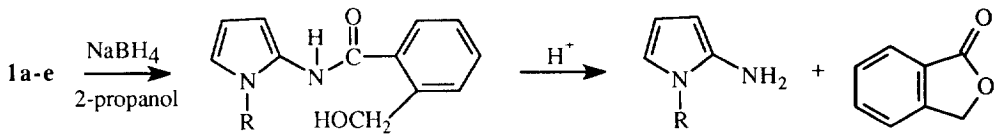


1a (R=CH_3)
1b (R=*t*-C_4H_9)
1c (R=CH_2CH_3)
1d (R=C_6H_5)
1e (R=H)

3a-e

Reaction conditions were worked out using *N*-(1-*t*-butyl-1*H*-pyrrol-2-yl)phthalimide (**1b**) as a model compound. Pyrrole **1b** was partially reduced with $NaBH_4$ and the *o*-hydroxymethyl benzamide **2b** was isolated and characterized.

Subsequent heating of **2b** in glacial acetic acid for 40 min at 80 °C gave a mixture whose 300 MHz ^{1}H nmr spectrum showed it to be composed of 2-amino-1-*t*-butylpyrrole (**3b**) and phthalide (**4**). The ^{1}H nmr spectrum had a two proton signal at 4.69 ppm that disappeared along with that of the pyrrole hydrogens when the reaction was carried out in CD_3COOD. This signal was assigned to the NH_2 group of **3b** and can be compared to that of the amino protons in more highly substituted 1-substituted-2-aminopyrroles that fall in the range of 3.6-5.1 ppm.[5] Phthalide (**4**) assignments were confirmed by taking the ^{1}H nmr spectrum of an authentic sample of **4** in acetic acid. Similarly the *o*-hydroxymethyl benzamide derivatives of 1-methyl-, 1-ethyl- and 1-phenylpyrrole were isolated and converted to their respective 2-aminopyrroles with glacial acetic acid.



2a (74%)
2b (93%)
2c (97%)
2d (97%)
2e (77%)

3a-e **4**

Pyrrole did not react with *N*-chlorophthalimide to give the corresponding phthalimide derivative.[2] It has been reported that the trimethylsilyl group, in 1-trimethylsilylpyrrole, can be removed in boiling water or refluxing ethanol.[6] 1-Trimethylsilylpyrrole[6] was reacted with *N*-chlorophthalimide and desilylated pyrrole **1e** was obtained in 29 % percent yield after aqueous workup. Reduction with $NaBH_4$ gave the *o*-hydroxymethyl benzamide **2e**. Heating **2e** in glacial acetic acid for 40 min at 80 °C yielded a mixture whose ^{1}H nmr spectrum showed it to be composed of the previously unknown 2-aminopyrrole (**3e**) and phthalide (**4**). The NH_2 protons of 2-aminopyrrole (**3e**) appeared at 4.48 ppm.[7]

It was found that 2-amino-1-*t*-butylpyrrole (**3b**) decomposed upon attempted separation from **4** by column chromatography or tlc. An attempt was made to remove the phthalide (**4**) by hydrolysis with 40 % aqueous sodium hydroxide. Surprisingly 2-amino-1-*t*-butylpyrrole (**3b**) was *water soluble* and was extracted into the aqueous phase. It could then salted out of the aqueous solution and obtained, in solution, in either chloroform or deuteriochloroform. Figure 1 illustrates the 300 MHz ^{1}H nmr of **3b** in deuteriochloroform. In a similar fashion the 1-methyl and 1-ethyl derivatives were obtained. The ^{1}H nmr spectrum of 2-amino-1-phenylpyrrole (**3d**) indicated that it could also be obtained in this manner but was accompanied by significant decomposition of the product. The parent 2-aminopyrrole (**3e**) was miscible in water and it was not possible to salt it out of an aqueous solution. Only 2-amino-1-*t*-butylpyrrole (**3b**) could be isolated solvent free; but it decomposed rapidly in the absence of a solvent.

No coupling between the protons at C-3/C-4 and C-5 of the pyrrole ring was observed in the ^{1}H nmr spectra of the 2-aminopyrroles **3a-e** in the acetic acid reaction mixture. The absence of coupling was attributed to a fast proton exchange at C-5 that decoupled that proton from the protons at C-3 and C-4 of the pyrrole

ring. When an equal volume of glacial acetic acid was added to a solution of 2-amino-1-*t*-butylpyrrole (**3b**), the same splitting pattern was observed as in pure glacial acetic acid. This confirmed that fast proton exchange

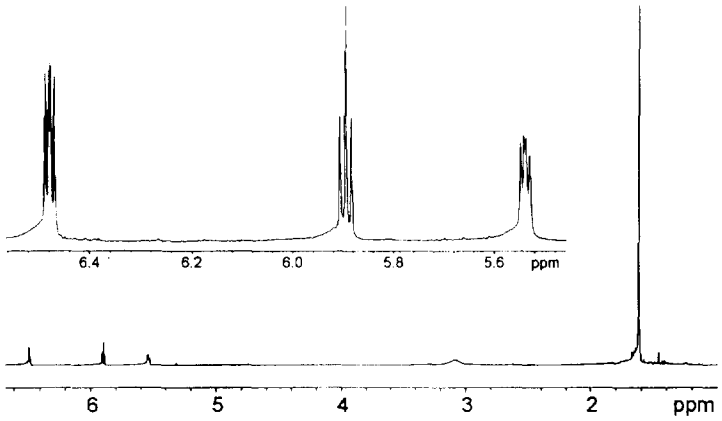


Figure 1: 300 MHz spectrum of 2-amino-1-*t*-butylpyrrole (**3b**) in $CDCl_3$.

occurred in the presence of acetic acid. Interestingly in the ^1H nmr spectrum of 1-*t*-butylpyrrole, taken in glacial acetic acid, the ring protons appeared as apparent triplets. Electron-donating (methyl) substituents at C-2 are known to increase the rate of hydrogen exchange at C-5.[8]

Previous studies have reported that 2-aminopyrroles, containing electron-withdrawing substituents on the ring, are protonated at C-5 by trifluoroacetic acid (TFA).[9] In contrast the ^1H nmr spectrum of 2-amino-1-*t*-butylpyrrole (**3b**) in a 1:1 v/v solution of $CHCl_3$/TFA showed only fast proton exchange at C-5.

In previous studies proton exchange has been studied by isotope exchange.[8] Unsubstituted 2-aminopyrroles appear to be the first pyrrole system reported where proton exchange at C-5 is sufficiently fast on the nmr time scale to observe its effects (decoupling) directly by ^1H nmr under such mild conditions (CH_3COOH and 25 °C).

Acknowledgment: This work was funded through grants CHE 9007784 and CHE 9420655 from the National Science Foundation. High field ^1H nmr spectra were courtesy of Prof. Mark Timken, Widener University.

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(*Received in USA* 14 *March* 1995; *revised* 6 *September* 1995; *accepted* 18 *October* 1995)