Reversion of Paal–Knorr Synthesis: A New Strategy for Ring-Opening and N-Substituent Change in 1*H*-Pyrroles

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Abstract: 1*H*-Pyrroles were converted into 1,4-dicarbonyl compounds, and then into 1*H*-pyrroles with a different N-substituent by heating at 110 °C under nitrogen in 0.3 M sodium citrate buffer, pH 3, and in the presence of alkyl or aryl amines. The new pyrroles were obtained in low to very high yields depending upon the pH, the reaction time, the initial pyrrole and amine involved, and the proportion between both reagents.

Key words: amines, cyclizations, pyrroles, ring-closure reactions, ring-opening reactions

Paal–Knorr reaction is a simple, robust route to pyrroles that still remains as one of the most attractive methods for the synthesis of these heterocyclic structural motifs.[1] This classic cyclization reaction of 1,4-dicarbonyl compounds with amines is believed to take place through imine formation followed by cyclization and aromatization. In addition, similar compounds having two oxygenated functions, such as lipid oxidation products 4,5-epoxy-2-alkenals[2] and 4-hydroxy-2-alkenals,[3] have also been shown to produce pyrroles by analogous mechanisms in both model and biological systems. All these reactions are favored by formation of the aromatic ring and, when starting from 1,4-dicarbonyl compounds, pyrroles are produced almost quantitatively.[4] The aromatic stabilization in the pyrrole ring is determined by the nitrogen atom which provides two electrons for the π-system.[5] If these two electrons are removed from the system, the pyrrole ring will not be stabilized and the recovering of the corresponding 1,4-dicarbonyl compound might be eventually produced. The objective of this study was to investigate the reversion of Paal–Knorr reaction produced when 1-alkyl or aryl-1*H*-pyrroles were heated in acidic media and in the presence, or not, of alkyl- or aryl amines.

The heating of pyrroles in acid media produces the breakage and/or polymerization of the pyrrole ring. However, when this heating was carried out under controlled pH and temperature conditions[6] the identification of reaction products could be carried out. Figure 1 (A) shows the total ion chromatogram of GCMS analysis obtained for 2,5-dimethyl-1*H*-pyrrole after overnight heating in 0.3 M sodium citrate buffer, pH 3. This heating produced the disappearance of the initial pyrrole and the formation of 2,5-hexanedione, which was identified according to its retention index and mass spectrum. When the heating was carried out in the presence of an amine, the corresponding N-substituted 1*H*-pyrrole was identified as the major reaction product (Figure 1, B).

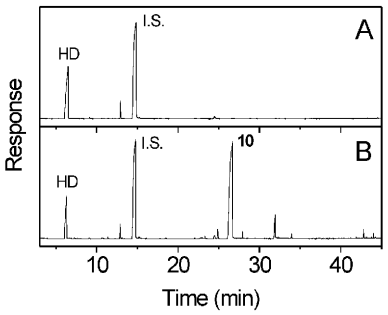

Figure 1 Total ion chromatograms of GCMS analysis for the reaction mixtures of (A) 2,5-dimethyl-1*H*-pyrrole, and (B) 2,5-dimethyl-1*H*-pyrrole and 4-methoxyphenylamine, after overnight heating at 110 °C in sodium citrate buffer pH 3.0. 2,5-Hexanedione (HD) and 1-(4-methoxyphenyl)-2,5-dimethyl-1*H*-pyrrole (**10**) were the major reaction products. The internal standard (2-pentylpyridine) is marked I.S.

The reaction yield depended on the reaction pH, the reaction time, the initial pyrrole and amine involved, and the proportion between both reagents. Figure 2 shows the effect of pH on the pyrrole formation in the reaction of both 1,2,5-trimethyl-1*H*-pyrrole and 2,5-dimethyl-1*H*-pyrrole with two representative aromatic and aliphatic amines. The maximum reaction yields were always obtained for reactions carried out at pH 3. A lower pH slightly decreased reaction yields. On the other hand, initial pyrroles were mostly stable at pH >5. In addition, aromatic amines always produced higher yields than aliphatic amines, and pyrroles were produced in a higher extent when starting from 2,5-dimethyl-1*H*-pyrrole than when starting from 1,2,5-trimethyl-1*H*-pyrrole (or when starting from 1*H*-pyrrole than from 1-methyl-1*H*-pyrrole, data not shown).

The reaction yield also depended on the reaction time. Thus, the more stable initial pyrrole (having either the less basic or the less volatile amine), the longer reaction time needed to achieve the equilibrium. Figure 3 shows the time-course of formation of 1-(4-methoxyphenyl)-2,5-dimethyl-1*H*-pyrrole (**10**) when starting from 2,5-dimethyl-1*H*-pyrrole or from 1-benzyl-2,5-dimethyl-1*H*-pyrrole (**4**), and the time-course of formation of **4** when starting from 2,5-dimethyl-1*H*-pyrrole or from **10**. When ammonia was produced, the reaction proceeded very rapidly and

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the product was obtained within a few hours. Thus, **10** and **4** were produced in less than 16 hours when starting from 2,5-dimethyl-1*H*-pyrrole. On the other hand, when the produced amine was not volatile, the reaction proceeded much more slowly, and an equilibrium between the initial and the produced pyrrole was observed. This equilibrium was always shifted to the pyrrole with the less basic amine. Thus, **10** was recovered in a higher extent than **4** in both the reaction of **10** with benzylamine and the reaction of **4** with 4-methoxyphenylamine.

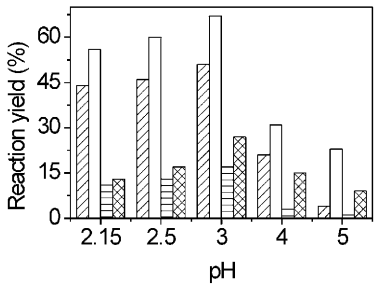


Figure 2 Effect of pH on the formation of 1-(4-methoxyphenyl)-2,5-dimethyl-1*H*-pyrrole (**10**) by reaction of 1,2,5-trimethyl-1*H*-pyrrole and 2,5-dimethyl-1*H*-pyrrole with 4-methoxyphenylamine (striped and open bars, respectively), and on the formation of 1-benzyl-2,5-dimethyl-1*H*-pyrrole (**4**) by reaction of 1,2,5-trimethyl-1*H*-pyrrole and 2,5-dimethyl-1*H*-pyrrole with benzylamine (horizontally striped and cross-hashed bars, respectively).

Both the employed amine and the initial pyrrole also determined the yield of the reaction. Table 1 shows the yields of the different pyrroles prepared in this study. These compounds were prepared from two different pyrroles (1*H*-pyrrole and 2,5-dimethyl-1*H*-pyrrole) and several aliphatic and aromatic amines at two pyrrole/amine ratios. Yields were higher when starting from 2,5-dimethyl-1*H*-pyrrole than when starting from 1*H*-pyrrole, therefore suggesting that the higher stability of the intermediate dicarbonyl compound produced, the higher reaction yield. In addition to pH and initial reactants, steric effects also influenced the reaction yield, and aromatic N-substituted pyrroles with free α-positions were usually produced in higher extents than those aromatic N-substituted pyrroles with one or two methyls at the α-positions of the phenyl ring (the exception was compound **12**, which was produced in the highest extent at 1:1 pyrrole/amine ratio). Furthermore, an increase in the concentration of the amine increased the yield of the reaction. In fact, when 2,5-dimethyl-1*H*-pyrrole was employed as the starting pyrrole and the reaction was carried out with an excess of *p*-toluidine or 4-methoxyphenylamine, for example, the produced pyrroles (**8** or **10**, respectively) were recovered quantitatively. All these data suggest that the reaction is

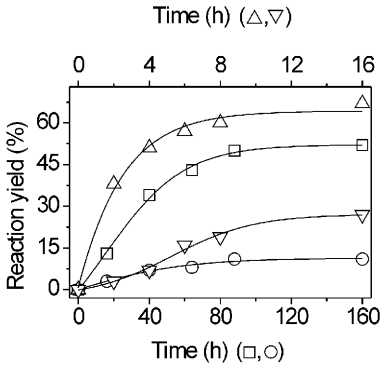
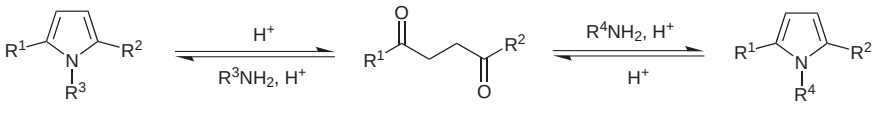


Figure 3 Time-courses of formation of 1-(4-methoxyphenyl)-2,5-dimethyl-1*H*-pyrrole (**10**) by reaction of 2,5-dimethyl-1*H*-pyrrole and 1-benzyl-2,5-dimethyl-1*H*-pyrrole (**4**) with 4-methoxyphenylamine (Δ and □, respectively), and on the formation of 1-benzyl-2,5-dimethyl-1*H*-pyrrole (**4**) by reaction of 2,5-dimethyl-1*H*-pyrrole and 1-(4-methoxyphenyl)-2,5-dimethyl-1*H*-pyrrole (**10**) with benzylamine (∇ and ○, respectively).

an equilibrium that may be shifted depending on the concentration and stability of reagents and products (Scheme 1).

The reaction mechanism always implied the ring-opening, producing the dicarbonyl compound and the amine as a preliminary step to the formation of the new pyrrole ring. Thus, when the reaction was carried out between 1-benzyl-2,5-dimethyl-1*H*-pyrrole-^{15}N and 4-methoxyphenylamine, the formation of **10** and benzylamine-^{15}N was produced. 1-(4-Methoxyphenyl)-2,5-dimethyl-1*H*-pyrrole-^{15}N was not detected even at trace levels. For analogous reasons cyclic amines, such as pyrrolidine or piperidine, did not reacted under the same conditions. Nevertheless, although the 1,4-dicarbonyl derivative was always detected by GCMS, the free dicarbonyl derivative might not be an essential intermediate in the pyrrole exchange. Thus, the incoming amine could also react directly with a protonated pyrrole or with the carbonyl derivative formed by hydrolysis of one of the enamine moieties.

The above results indicate that 1*H*-pyrroles can be converted into 1,4-dicarbonyl compounds and, lately, into new 1*H*-pyrroles with a different N-substituent. This reaction, which may be related to the previously described conversion of a furan into a pyrrole,[7] suggests that pyrroles might be considered as protected 1,4-dicarbonyl compounds. In addition, the change of the N-substituent may have a special interest in the analysis of pyrroles in natural products where these compounds are easily decomposed under the experimental conditions usually employed for the isolation and hydrolysis of natural



Scheme 1 Ring-opening and cyclization of 1*H*-pyrroles.

Table 1 Yields of Isolated Pyrroles Prepared in this Study[a]

Compound	R^1	R^2	R^5	Yield (%) (1:1)[b]	Yield (%) (1:2)[b]
1	$CH_3(CH_2)_3$	H	H	1	3
2	$CH_3(CH_2)_3$	Me	Me	2	5
3	$PhCH_2$	H	H	1	3
4	$PhCH_2$	Me	Me	24	34
5	2-MeC_6H_4	H	H	4	5
6	2-MeC_6H_4	Me	Me	52	55
7	4-MeC_6H_4	H	H	3	5
8	4-MeC_6H_4	Me	Me	53	99
9	4-$MeOC_6H_4$	H	H	2	5
10	4-$MeOC_6H_4$	Me	Me	66	98
11	2-Me-4-$MeOC_6H_3$	H	H	2	4
12	2-Me-4-$MeOC_6H_3$	Me	Me	81	99
13	2-Me-6-MeC_6H_3	H	H	1	3
14	2-Me-6-MeC_6H_3	Me	Me	42	65

[a] R^1, R^2, and R^5 are the substituents at positions 1, 2, and 5, respectively, of the pyrrole ring. Pyrroles with $R^2 = R^5 = H$ were obtained from 1*H*-pyrrole. Pyrroles with $R^2 = R^5 = CH_3$ were obtained from 2,5-dimethyl-1*H*-pyrrole. Reaction scheme is given in Scheme 1.
[b] Pyrrole/amine ratio.

macromolecules. Furthermore, during in vitro and in vivo of both Maillard reaction and lipid oxidation, different pyrrole motifs are produced by reaction of carbohydrates and oxidized lipids with the terminal amino groups of proteins.[8] These protein-bound pyrroles are believed to inhibit protease action[9] and to produce a change of protein charge that has been related, for example, to macrophage receptor recognition of oxidatively damaged low density lipoproteins as a primary or secondary event in atherogenesis.[10] The analysis of bound pyrroles is difficult because they are usually destroyed during the acid hydrolysis of proteins and there is not a certainty of their structures.[11] The new reaction described in this study can be employed to develop new analytical procedures for the characterization and determination of these products.

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(6) Reactions were carried out by heating at 110 °C under an inert atmosphere, the pyrrole (0.1 mmol) in 3 mL of 0.3 M sodium citrate buffer (pH 3), and in the presence, or not, of the amine (0.1 mmol). The pyrroles produced were extracted three times with $CHCl_3$–MeOH (3:2) and purified by TLC. Identity of purified compounds was confirmed by ^1H NMR, ^{13}C NMR and MS.

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