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Research Article

Sustainable Synthesis of *N*-Alkyl-Pyrrolecarboxylic and Pyrrolepyrazinones Derivatives from Biosourced 3-Hydroxy-2-pyrones and Amines

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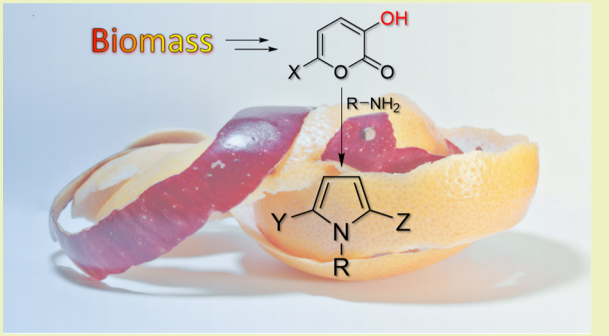
ABSTRACT: Pyrroles are important compounds present in biological systems, used for drug synthesis and in material chemistry. A typical strategy for the pyrrolic ring formation is centered on the Paal−Knorr reaction, where 1,4-dicarbonyl compounds react with amines giving N-substituted pyrrole derivatives. Often, the main problem of this approach is the availability of the appropriate carbonyl compounds. Here, we report a sustainable synthesis of N-substituted pyrrole carboxylic acid derivatives by the reaction of primary amines and 3-hydroxy-2-pyrones. These last compounds can easily be prepared using renewable sources and show the property to be masked 1,4-dicarbonyl compounds that are able to react efficiently with amines to form substituted pyrrolic rings. The reactions can be performed under sustainable conditions without solvents at 50−75 °C or in basic water−methanol solutions at room temperature, obtaining symmetric and asymmetric pyrroles from good to high yields. Moreover, dihydropyrrolepyrazinone derivatives can easily be prepared in high yields by the reaction of 3-hydroxy-2-pyrones and ethylenediamine.



KEYWORDS: *green chemistry, 2-pyrones, biomass, pyrroles, Paal−Knorr*

INTRODUCTION

The pyrrole ring is an extremely important heterocyclic structure that is found in natural, pharmaceutical molecules and in polymer materials.[1] For these reasons, the synthesis of pyrroles is a research area of great interest, and many strategies for this preparation were therefore envisaged.[2−4] One of the most important methods of pyrrole synthesis is the Paal−Knorr (P−K) condensation between 1,4-diketones and primary amines, which is often catalyzed by Brønsted or Lewis acids.[5−7] A limitation of this approach is the availability of substituted diketones, and for this reason, specific synthetic strategies are required for their preparation.[8]

Among the pyrrole-fused derivatives, dihydropyrrolepyrazinones are one of the most interesting classes of molecules as their moiety is present in many drugs.[9−12]

In the last years, a continuous challenge for the synthesis of chemicals from natural sources or, even better, from waste has been developed in order to lower the impact of petroleum derivatives. In this context, lignocellulose biomass is an important source of carbohydrates, and their manipulation allows the preparation of many platform molecules, which can be exploited in the synthesis of *N*-heterocycles.[13] Direct amination of C6 monosaccharides led to pyrrole 2-carbaldehydes in the presence of acids.[13,14] Biobased alcohols and diols can be used in the metal-catalyzed synthesis of substituted pyrroles.[13] More recently, the reaction of furans with aromatic amines was reported to afford *N*-arylpyrroles in good yields in the presence of acid zeolites[13] or Lewis acid catalyst Hf-SBA-15;[15] 5-hydroxymethylfurfural was used to prepare, in the presence of an iridium-based catalyst, the corresponding diketone, which in turn afforded very efficiently 2-hydroxymethyl pyrroles,[16] while a decarbonylation−amination reaction was performed to directly convert furfural to unsubstituted pyrrole over a Pd-based catalyst.[17]

Another important class of biomass-based derivatives is represented by aldaric acids, which are obtained by oxidation of monosaccharides,[18] and that have already been proven to be useful precursors of adipic acid and furandicarboxylic acid.[19] To the best of our knowledge, pyrroles can be prepared from

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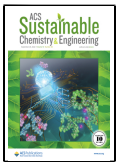

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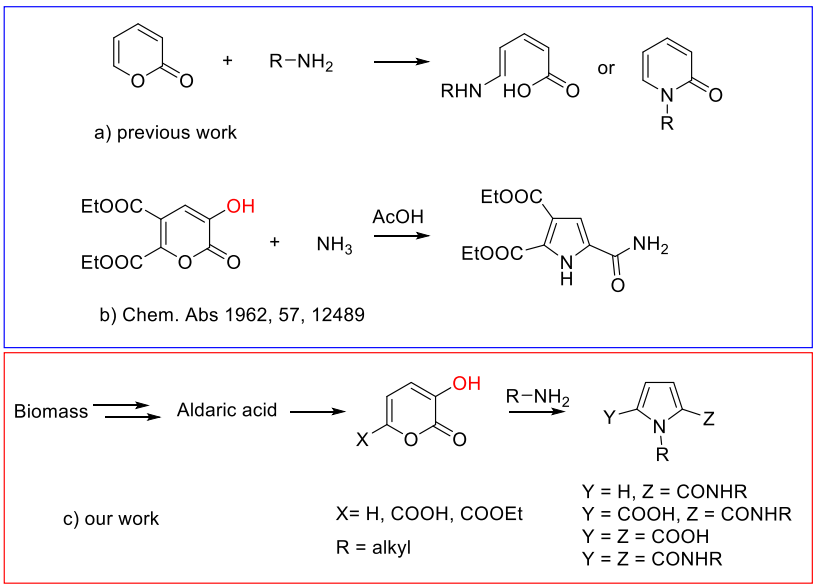
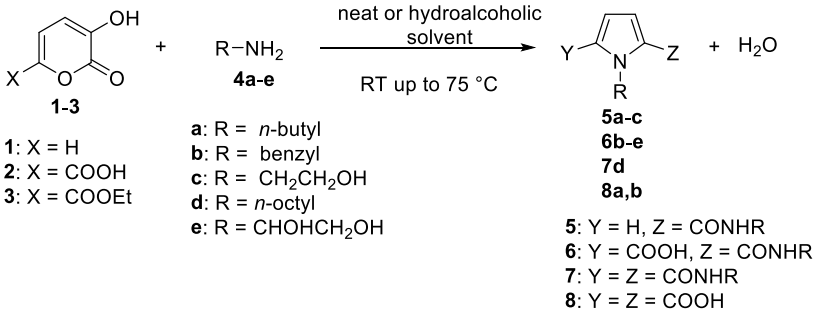


Figure 1. (a,b) Prior art and (c) novel approach proposed here.

Scheme 1. Reactions of Pyrones 1−3 with Amines 4a−e



galactaric acid, but the high temperature required by the process results in a double decarboxylation and only pyrrole or unsubstituted *N*-alkylpyrroles can be obtained with low yields.[20−22]

Recently, we reported a highly efficient synthesis of 3-hydroxy-2-pyrones from biosourced aldaric acids.[23] 2-Pyrones[24,25] are valuable synthons, mainly used in Diels−Alder reactions to give bicyclolactones that in turn can provide important dienes or aromatic compounds. The presence of the hydroxyl group at position 3 in the pyrone ring was revealed to be crucial in order to easily obtain aromatic carboxylic derivatives.[26]

The reaction of 2-pyrones with amines as nucleophiles is usually reported to lead to open-chain derivatives or to pyridones[27,28] (Figure 1a), but if a hydroxyl group is present at position 3 of the ring, this molecule becomes a masked 1,4-dicarbonyl derivative and therefore a good candidate for a P−K synthesis of pyrroles. As far as we know, only one example of this reactivity was reported for a 3-hydroxy-2-pyrone derivative toward ammonia, aniline, and 1,2-diaminobenzene in acetic acid to obtain the corresponding pyrrole derivative (Figure 1b).[29] Surprisingly, this reaction was not extended to other pyrones or to other amines.

We now report that the reaction of biosourced 3-hydroxy-2-pyrones **1−3** with alkyl primary amine can afford pyrroles in high yields under neat conditions without the use of promoters or in a KOH water/methanol solution (Figure 1c).

EXPERIMENTAL SECTION

A Bruker AV 400 MHz instrument was used to record ^{1}H NMR spectra (400 MHz) and ^{13}C NMR (100.6 MHz). ^{1}H and ^{13}C chemical shifts (δ) are given in ppm relative to the residual proton of the solvent. MS analyses were performed with an Esquire 3000 plus ion-trap mass spectrometer equipped with an ESI source. Melting points were determined with a Büchi 535 instrument and are uncorrected. Chromatographic separations were performed using Merck Kieselgel 60 silica gel. Before use, *n*-butylamine **4a** was distilled; amines **4b−d** and **4g** were distilled under reduced pressure. All other reagents and solvents were purchased from Aldrich and used without any further purification. Pyrones **1−3** were prepared from mucic acid by the procedures recently reported.[23,26,30] All the specific experimental procedures are reported in detail in the Supporting Information.

RESULTS AND DISCUSSION

The main reactions investigated in this work between pyrones **1−3** and amines **4a−e** are represented in the following general Scheme 1 while in Table 1 and 2 the results achieved are collected.

Pyrroles **5−8** were isolated through procedures similar to the one used for reactions reported in Table 1 and 2 (except for pyrrole **8b** that was obtained from hydrolysis of the corresponding ammonium salt **8′b**) and characterized. Pyrroles **6** and **8** were obtained by hydrolysis, during work up, of the corresponding ammonium salts **6′** and **8′** formed during the reaction. Ammonium salts of *N*-hydroxyethyl and *N*-octyl

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Table 1. Reactions of Pyrones 1−3 with Amines 4a−e under Neat Conditions after 24 h[a]

entry	pyrone	amines **4a−e**	molar ratio[b]	*T* (°C)	pyrrole (anal. yield)
1	1	*n*-butylamine (**4a**)	6	65	**5a** (72%)
2	1	benzylamine (**4b**)	6	65	**5b** (33%)
3	1	ethanolamine (**4c**)	6	65	**5c** (96%)
4	2	*n*-butylamine (**4a**)	12	65	
5	2	*n*-octylamine (**4d**)	12	65	**6d** (74%)[c]
6	2	*n*-octylamine (**4d**)[d]	12	65	**6d** (59%, 72%[e])
7	2	benzylamine (**4c**)	12	90	**6b** (30%)
8	2	benzylamine (**4c**)[d]	13	65	**6b** (64%)
9	2	ethanolamine (**4c**)	6	65	**6c** (94%)
10	2	iso serinol (**4e**)	6	65	**6e** (87%)
11	2	ethanolamine (**4c**)	6	50	**6c** (95%)
12	2	iso serinol (**4e**)	6	50	**6e** (95%)
13	3	*n*-octylamine (**4d**)	13	75	**7d** (83%)

[a]Conversion of pyrones >95% except for entry 4 (16%); analytical yields were determined by ^{1}H NMR using an internal standard (see Supporting Information) and were not optimized. Pyrroles **6** were present in the mixture as the corresponding ammonium salt **6′**. [b]Molar ratio amine/pyrone. [c]Analytical yield is given after 46 h. [d]Water was added to the mixture (9 or 10 M ratio water/pyrone). [e]Analytical yield is given after 48 h.

Table 2. Reactions of Pyrone 2 with Amines 4a−b in Aqueous Solution at r.t. after 24 h[a]

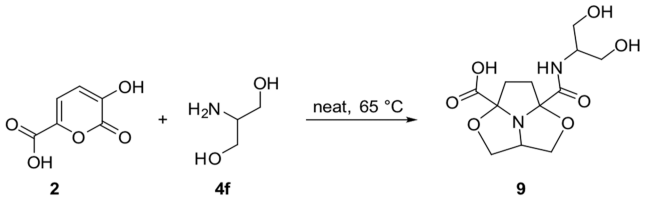
entry	amines **4a−e**	molar ratio[b]	conditions	pyrrole (anal. yield)
1	*n*-butylamine (**4a**)	3	D_2O/KOH	**8a** (51%)
2	benzylamine (**4b**)	3.5	water/KOH	**8b** (18%)[b]
3	benzylamine (**4b**)	3	D_2O/CD_3OD/KOH	**8b** (60%)[c]

[a]Conversion of pyrones >95%; analytical yields were determined by ^{1}H NMR using an internal standard (see Supporting Information) and were not optimized; pyrroles **8** were present in the mixture as the corresponding ammonium salt **8′**. [b]Analytical yield is given after 18 h. [c]Analytical yield is given after 16 h.

pyrrole derivatives, respectively, **6′c** and **6′d** were also isolated. The purification processes were not optimized.

The reactivity of the three pyrroles studied **1−3** as well as that of the amines **4** tested is quite different, but the reaction is versatile and quite general so as to allow the preparation of several symmetric and asymmetric pyrroles variably substituted also on the pyrrole ring.

Scheme 3. Reaction of Pyrone 2 with Serinol (4f)



3-Hydroxy-2-pyrone (**1**) is the most reactive species. It can easily be obtained from decarboxylation of the pyrone **2**,[30] a process that, as we will see, can also take place during the reactions with the amines studied.

In order to obtain asymmetric 1,2-disubstituted pyrroles, pyrone **1** was tested with three primary aliphatic amines: *n*-butylamine (**4a**), an amine with an aromatic group such as benzylamine (**4b**), and an amine with a hydroxyl group such as ethanolamine (**4c**). In all cases, the reactions were performed in neat conditions at 65 °C.

The reactivities observed were quite different: in the first case, the pyrrole **5a** was formed in 72% yield (Table 1, entry 1) while the reaction with benzylamine (**4b**) gave lower yields on the corresponding pyrrole **5b** (33%) despite the complete conversion of the pyrone **1** (Table 1, entry 2).

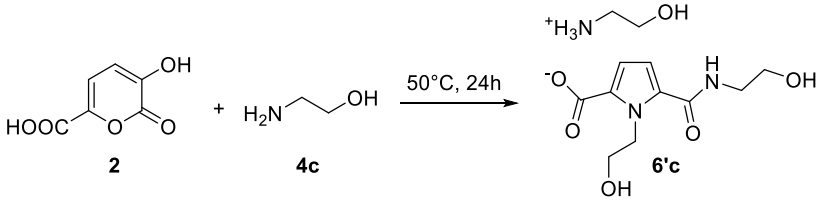
An amine structurally similar to benzylamine, but with a bigger steric hindrance on the nitrogen atom such as cyclohexylamine, was also tested under the same reaction conditions. As expected, poor reactivity toward pyrone **1** (not reported in the table) was observed as in this case, the reactant was only partially converted. The corresponding pyrrole was tentatively detected in the crude by ^{1}H NMR analysis in very low yields (Supporting Information, Figure S39) and not isolated.

Conversely, the reaction of **1** with ethanolamine (**4c**) gave pyrrole **5c** in almost quantitative yield (Table 1, entry 3).

In order to obtain *N*-substituted 2,5-pyrroledicarboxylic derivatives, the procedure described above was then extended to pyrone **2**. Again, the reactivity of the following aliphatic primary amines was tested: two linear amines such as *n*-butylamine (**4a**) and *n*-octylamine (**4d**), an amine with an aromatic group such as benzylamine (**4b**) and two amines bearing hydroxyl groups such as ethanolamine (**4c**) and 3-amino-1,2-propanediol (iso serinol, **4e**).

Different from the results obtained for pyrone **1**, the reaction of pyrone **2** with *n*-butylamine (**4a**), although in a larger excess (12:1 M ratio) with respect to the one used for pyrone **1**, did not give the corresponding pyrrole (Table 1, entry 4). The ^{1}H NMR analysis of the crude revealed a poor conversion (16%) and the presence of small amount of pyrone **1** together with traces of unidentified products, showing that a partial

Scheme 2. Gram-Scale Reaction of Pyrone 2 with Amine 4c



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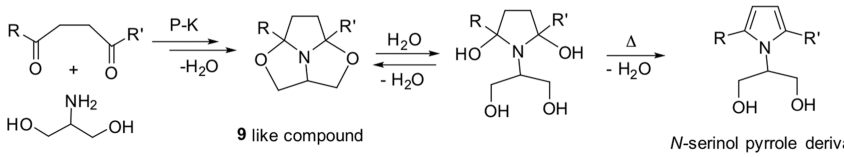
Scheme 4. Synthesis of *N*-Serinol Pyrrole Derivatives



Scheme 5. Reactions of Pyrones 1−2 with Amine 4g

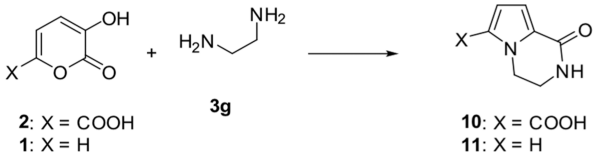


Table 3. Reactions of Pyrones 1−2 with Amine 4g[a]

entry	pyrone	molar[b] ratio	solvent	*T* (°C)	*t* (h)	pyrone conv.	product (anal. yield)
1	2	7	Neat	65	24	100	**10** (97%)
2	2	3	H_2O	55	24	95	**10** (72%)
3	1	6	Neat	65	54	100	**11** (15%)
4	1	2.2	H_2O	70	16	100	**11** (50%)
5	1	1.5	MeOH	reflux	5	100	**11** (80%)

[a]Analytical yields were determined by ^{1}H NMR using an internal standard (see Supporting Information) and were not optimized. Compounds **10**−**11** were present in the mixtures as the corresponding ammonium salt. [b]Molar ratio amine/pyrone.

decarboxylation of **2** occurred, while no pyrrole derivatives were possibly detected (Supporting Information, Figure S40). Decarboxylation of pyrone **2** induced by an organic base, was already observed[26] while the lack of reactivity of **2** toward *n*-butylamine was attributed to the scarce solubility of the corresponding pyrone ammonium salt into the reaction medium.

In order to favor the solubility of the pyrone ammonium salt in *n*-butylamine (**4a**), a small amount of water was added in the reaction media. In this case, ^{1}H NMR analysis of the crude showed the formation of a very complex mixture including pyrone **one** and its corresponding pyrrole **5a** together with at least two other pyrroles (Supporting Information, Figure S41). Although some ^{1}H NMR signals could be tentatively assigned to the expected pyrrole from **2**, the reaction was not further investigated as all the products occurred in low yields.

We then tested the reactivity of pyrone **2** toward a more lipophilic amine such as *n*-octylamine (**4d**), hoping for a better solubility of the corresponding ammonium salt of **2** in the reaction medium. The mixture was initially not homogeneous but turned into a fluid solution after 36−46 h, and as expected, amine **4d** reacted more efficiently than *n*-butylamine (**4a**) with pyrone **2**. The ^{1}H NMR spectrum of the crude showed the formation, after 46 h, of the corresponding pyrrole **6d** in good yield (74%, Table 1, entry 5) and small amount (7%) of a product, tentatively assigned to corresponding decarboxylated pyrrole.

Performing the same reaction in the presence of water (9 or 10 M ratio water/pyrone), the yield of pyrrole **6d** did not substantially change (Table 1, entry 6) although the mixture became homogeneous after few minutes. It has to be noted that under these conditions, the reagent **2** was fully converted after 24 h giving **6d** in 59% yield, but during the following 24 h, an additional 13% of this product was further formed clearly due to the evolution of reaction intermediates.

The reaction of pyrone **2** with benzylamine (**4b**) was than tested under similar conditions (large excess of amine, 12:1 M ratio, 65 °C). Unfortunately, the target pyrrole was not formed, and unreacted pyrone was found (80%) probably, again, because of the poor solubility of the pyrone salt. By increasing the temperature to 90 °C, the mixture becomes homogenous, and under these conditions, the reaction take place affording, after 24 h, pyrrole **6b** in 30% yield (Table 1, entry 7). The ^{1}H NMR analysis of the crude revealed that pyrrole **5b** was also formed in 21% yield (Supporting Information, Figure S42). Although a decarboxylation of pyrrole **6b** cannot be excluded, pyrrole **5b** was probably formed as a result of the partial in situ

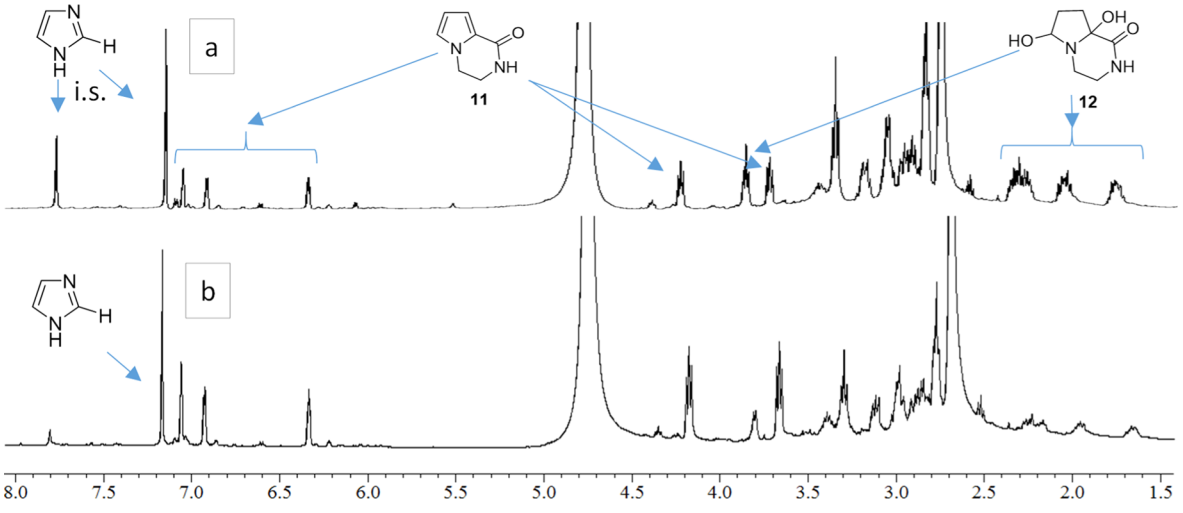


Figure 2. (a) ^{1}H NMR (D_2O) of the fresh solution of crude after 54 h at 65 °C and (b) ^{1}H NMR of the solution in D_2O after 17 h at 65 °C.

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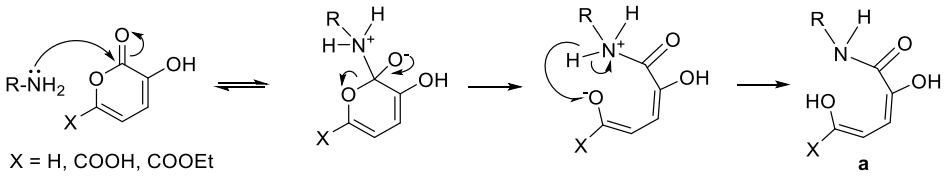
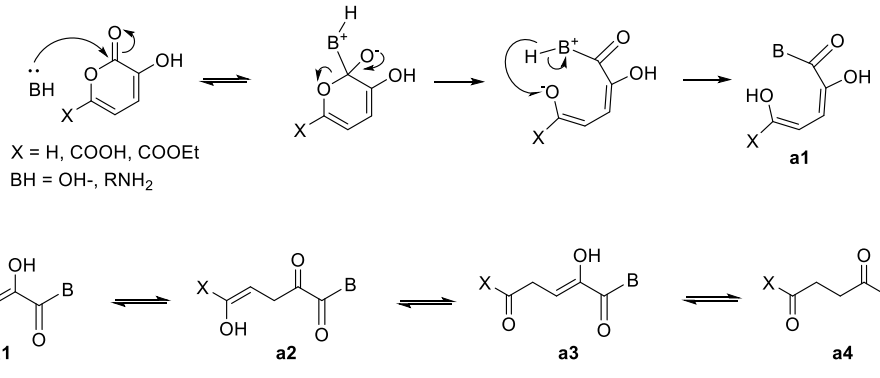
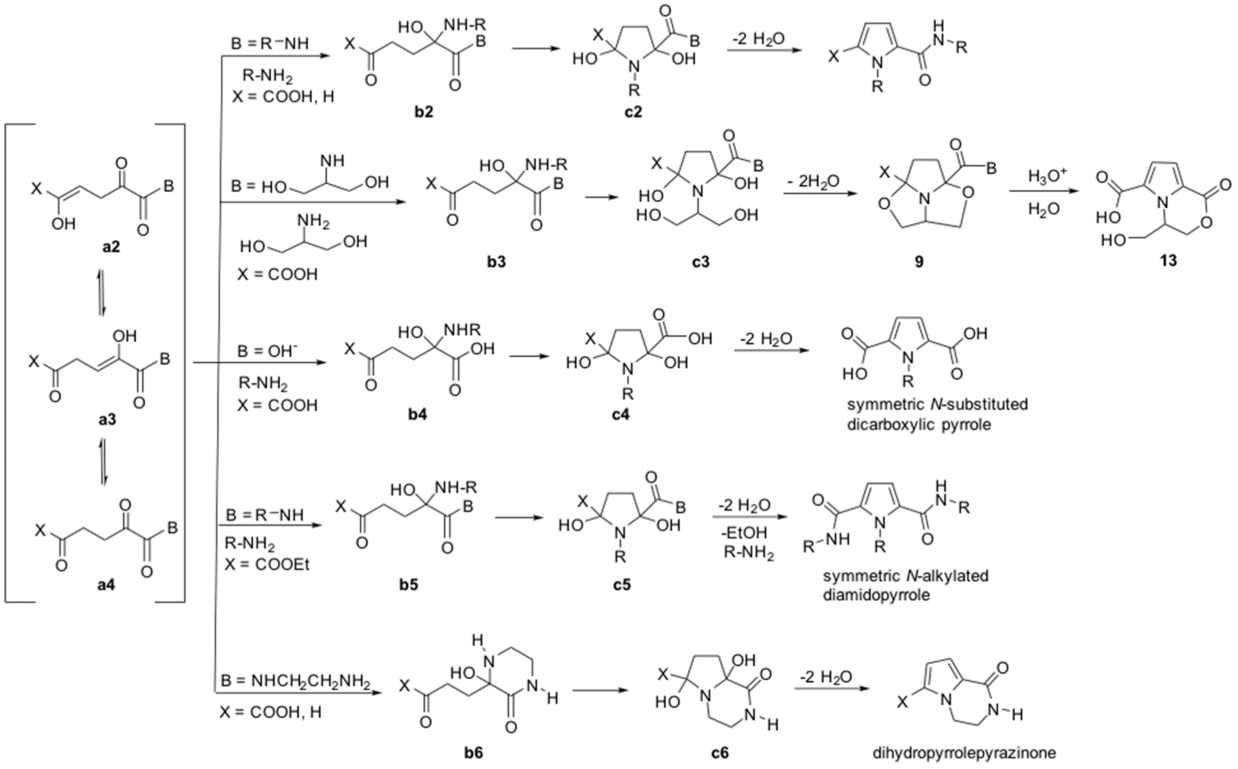
Scheme 6. Ring-Opening of Pyrone Using Primary Amine



Scheme 7. Ring-Opening of Pyrone Using a Nucleophile



Scheme 8. Pyrrole Formation from 3-Hydroxy-2-pyrones



decarboxylation of pyrone **2** to pyrone **1**, which in turn, reacting with the amine **4b**, produced pyrrole **5b**.

To minimize the decarboxylation reaction, the temperature was then lowered trying to make the mixture homogeneous by adding water in a 9:1 M ratio with respect to the pyrone. Under these conditions, even if the mixture remained heterogeneous, the reaction of **2** and **4b** occurred also at 65 °C and the yield in the desired pyrone **6b** increased to 64% (Table 1, entry 8); in this case, a lower amount of **5b** was formed (15%).

Pyrone **2** was found to be even less reactive than pyrone **1** toward cyclohexylamine. The ^{1}H NMR analysis of the reaction performed at 65 °C, after 24 h, showed only unconverted pyrone **2** (not reported in the table, Supporting Information, Figure S43).

The reactivity of pyrone **2** at 65 °C was then investigated with two β-aminoalcohols such as ethanolamine (**4c**) and iso serinol (**4e**). The reaction of pyrone **2** with ethanolamine (**4c**) afforded the target pyrrole **6c** in very good yield (94%, Table 1, entry 9), and only 1% decarboxylated pyrrole **5c** was detected

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in the spectrum of the crude. The reaction of **2** with **4e** gave also very good yield (87%, Table 1, entry 10) in the corresponding pyrrole **6e**. Both reactions resulted in an almost complete conversion to the target pyrroles even at lower temperature (Table 1, entries 11−12).

Moreover, symmetric *N*-alkylated 2,5-diamidopyrrole derivatives can be easily synthetized following the same protocol by reaction of alkyl esters of pyrone **2** with amines. For example, pyrone ethyl ester **3** reacted with *n*-octylamine **4d**, giving pyrrole **7d** in 83% yield (Table 1, entry 13).

Finally, with the aim of highlighting the scalability of our process, as example, a gram-scale reaction between pyrone **2** (2.0 g) and ethanolamine **4c** was performed under the same reaction conditions used for the reaction in Table 1, entry 11 (Scheme 2). 65% ethanolamine was recovered by distillation, and the ammonium salt of *N*-hydroxyethyl pyrrole derivative **6′c** was obtained in 64% yield as precipitate by adding ethanol to the crude.

The reactions investigated showed that primary alkylamines with the nitrogen atoms on secondary carbon atoms, like cyclohexylamine or 3-amino-1-butanol (results not reported) or anyway sterically hindered amines, such as benzylamine, provided modest or low yields of the corresponding pyrrole derivatives. Conversely, *β*-aminoalcohols, such as ethanolamine or iso serinol, were very reactive toward pyrones, providing pyrroles in high yields (Table 1).

For this reason, we decided to investigate the reactivity of a *β*-aminoalcohol with the nitrogen atom on a secondary carbon atom such as 2-amino-1,3-propanediol (serinol, **4f**). Performing the reaction under the typical conditions used (neat, 65 °C, 24 h), pyrone **2** (conversion 91%) gave in 24 h as the main product the tricyclic compound **9** (51%, analytical yield) (Scheme 3) while low amounts of pyrroles were tentatively detected by ^{1}H NMR analysis (Supporting Information, Figure S44). Even by prolonging the reaction times (65 °C for 48 h), compound **9** was detected as the main product (62%) together with a mixture of pyrroles. The reaction performed at higher temperature (90 °C for 24 h) gave anyway 36% of **9** together with a complex mixture of at least three pyrroles including the corresponding decarboxylated pyrrole (Supporting Information, Figure S45).

Tricyclic compound **9** was isolated and characterized, and its structure was assigned by comparison with similar molecules.[31]

This compound is the typical intermediate in the synthesis of *N*-serinol pyrrole derivatives from 1,4 diketones[32,33] and serinol (P−K like reaction), which evolves to the corresponding pyrrole by hydrolysis of the oxazolidine rings and subsequent dehydration (Scheme 4).

Therefore, in order to favor the ring-opening of **9** by hydrolysis, the reaction was performed in water at 90 °C for 18 h, but again, **9** was the main product (45%) together with 15% pyrrole. Only by adding aqueous HCl to the mixture, the tricyclic compound **9** almost totally disappeared, and the yield of the pyrrole increased to 26% (Supporting Information, Figure S46).

Considering the assumed reaction mechanism, (see the next section) we investigated the reaction of pyrone **2** with amines, exploiting the possibility to open the ring of the pyrone by the nucleophile OH^-.

In this case, the reaction with amines, after acidification, allows the direct preparation of symmetric N-substituted pyrroles 2,5-dicarboxylic acid. Pyrone **2** reacted in the presence of aqueous KOH with *n*-butylamine or benzylamine, at room temperature, leading respectively to *N*-alkyl pyrroles dicarboxylic acid **8a** and **8b** (Table 2, entries 1−2). In the last case, the mixture in aqueous medium was not homogeneous and poor amount of pyrrole **8b** was formed (Table 2, entry 2). The reaction was then performed using methanol as co-solvent to obtain a homogeneous reaction mixture. The reaction was monitored during time, and it was found that it reached 60% yield of pyrrole **8b** (Table 2, entry 3) within 16 h; during the following hours, the yield substantially did not change (Supporting Information, Table S1 and Figure S38). It has to be underlined that pyrrole **8b** is not probably formed by hydrolysis of the corresponding amide. In fact, in a test experiment, pyrrole **6b** was refluxed in water at the same molar ratio between KOH and pyrrole used to prepare **8b**, but surprisingly, only 11% of **6b** underwent hydrolysis after 5 days (Supporting Information, Figure S47).

As natural extension of the reaction of pyrones with amines, the reactivity of pyrones **1** and **2** with ethylenediamine (**4g**) was tested. As expected, the reaction ran efficiently giving the corresponding dihydropyrrolepyrazinone derivatives (Scheme 5), thanks to, in this case, a double intramolecular cyclization process. In Table 3 are collected the achieved results.

Pyrone **2** reacted efficiently with ethylenediamine under neat conditions at 65 °C, affording the target pyrrole **10** in very high yield (Table 3, entry 1). Under these conditions, only traces of decarboxylated derivative **11**[11] were detected by ^{1}H NMR analysis of the crude. The reaction performed in water with a lower molar ratio amine/pyrone led to a lower pyrrole yield (Table 3, entry 2).

Switching to pyrone **1**, the reaction under neat conditions at 65 °C provided only a small amount of the corresponding expected dihydropyrrolepyrazinone **11**, although total conversion of **1** was observed (Table 3, entry 3). The ^{1}H NMR analysis of the crude (D_2O, imidazole as an internal standard) revealed the presence of signals compatible with a pyrrolidine derivative **12** (Figure 2a) as the main product. Heating the NMR sample tube containing the D_2O solution at 65 °C for 16 h, the pyrrolidine **12** (not isolated) evolved to pyrrole **11** as evidenced in Figure 2b.

Performing the reaction in water, a significant increase in the yield is obtained (Table 2, entry 4), but the best yield (85%) was achieved using methanol as solvent (Table 2, entry 5).

In the light of the results obtained and on the base of the chemistry known, some reaction mechanism considerations can be presented. As mentioned above, 3-hydroxy-2-pyrones can be considered masked 1,4-dicarbonyl derivatives. In fact, the reaction with appropriated nucleophiles leads to the pyrone ring-opening with formation of 1,4-dienol derivative **a** (Scheme 6).

In Scheme 6, as an example, the reaction steps between a primary amine and a generic 3-hydroxy-2-pyrone are reported.

More in general, depending on the pyrones and the nucleophile chosen, primary amines or hydroxide, the pyrone ring-opening leads to the formation of 1,4-dienol derivative **a1**, which is in tautomeric equilibrium with the corresponding monocarbonyl and dicarbonyl forms (**a2**−**a4**) (Scheme 7).

Monocarbonyl and dicarbonyl tautomeric forms **a2**−**a4** (Scheme 8) can react with the amine present following the typical P−K reaction steps, giving the corresponding pyrrole derivatives.

In Scheme 8 are reported the common intermediates generated in the reactions investigated here: the carbonyl forms **a2**−**a4** react with the chosen nucleophile to give the first

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common hemiaminal intermediate **b2**−**b6**. Then, these species evolve to give the corresponding 2,5-dihydroxypyrrolidine intermediates **c2**−**c6** that subsequently dehydrate to pyrroles.

Only when the reaction is performed with serinol (Scheme 8, second reaction), the process ends to the compound **9**, and only by acid hydrolysis, it is possible to convert **9** to the pyrrole **13**. Although in low yields, small amount of the *N*-serinol pyrrole derivative was isolated and tentatively assigned to structure **13** (Supporting Information).

As underlined above, *β*-aminoalcohols lead to higher yields in the corresponding pyrrole derivatives in comparison with the aliphatic ones tested (other examples not reported here confirm this trend).

The reason can not only be attributed to the good solubility of the pyrone ammonium salts in these media but also, considering the high selectivity of the reactions with *β*-aminoalcohols, a template catalysis effect[34] cannot be excluded due to the complex hydrogen bond network, which can be formed between the reactant, the intermediates, and these kinds of amines.

CONCLUSIONS

3-Hydroxy-2-pyrones are interesting compounds easily obtainable from renewable sources such as polysaccharides. Their potentiality as synthons has probably not yet been fully exploited, until now, due to their limited availability. In this paper, we investigated the reactions of three 3-hydroxy-2-pyrones with several amines, showing the versatility of this combination for the preparations of variably substituted pyrroles. The reaction is based on the particular properties of these pyrones to give 1,4-diketo derivatives after the ring-opening process, which can be triggered by a nucleophilic species. The dicarbonyl derivatives so formed, in the presence of amines, give the corresponding pyrroles through the P−K reaction. By playing with the appropriate reactant and reaction conditions, it is possible to reach from good to high yield of N-substituted and ring-substituted pyrroles. In several cases, the reactions can be performed under green conditions, which means in the absence of solvents or any other promoter. In some cases, low amounts of hydroalcoholic solvent can favor the reaction.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acssuschemeng.2c03661.

Detailed experimental procedures, ^{1}H NMR, ^{13}C NMR, MS and melting point of new compounds, copies of all ^{1}H NMR, ^{13}C NMR and selected ^{1}H NMR spectra of reaction mixtures (PDF)

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Notes

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ABBREVIATIONS

P−K, Paal−Knorr

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