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Naturally occurring organic acids for organocatalytic synthesis of pyrroles via Paal–Knorr reaction

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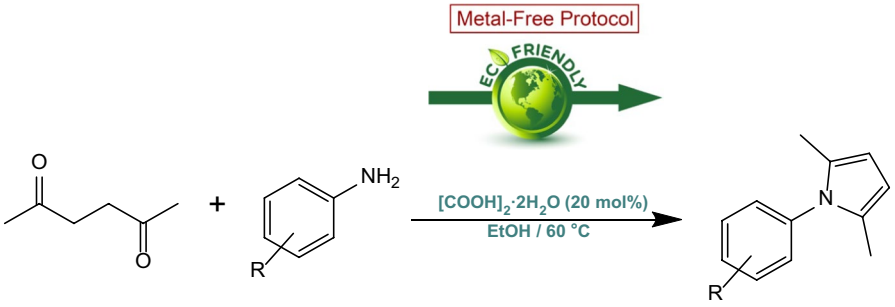
Abstract

In this study, common naturally occurring organic acids, namely oxalic, malonic, succinic, tartaric and citric acid (as safe, inexpensive, and biodegradable organocatalysts), have been employed for Paal–Knorr pyrrole synthesis. The organocatalyzed reaction proved to be effective in ethanol at 60 °C. However, the reaction rate is mainly dominated by the nature and position of functional groups on the aromatic ring of substrate. This metal-free procedure tolerates a series of functional groups and should be considered as an asset to the pharmaceutical industry since no metal contamination could take place during the synthesis of pyrrole scaffolds.

Graphic abstract



Keywords Organocatalysis · Paal–knorr reaction · 2,5-dimethylpyrrole · Metal-free protocol

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Introduction

Since 2000, organocatalysts have made a valuable contribution to develop eco-friendly synthetic protocols in organic reactions [1, 2]. These small organic molecules are usually robust, inexpensive, safe, stable to air and moisture and biodegradable without having any detrimental effect on the environment [3, 4]. Due to these interesting characteristics, metal-free organocatalyzed reactions have gained a great deal of interest for synthesizing bioactive compounds, since no metal contamination (with regard to the pharmaceutically relevant product) is expected [5, 6].

Azaheterocyclic frameworks are present in a variety of biologically active substances (including natural products and synthetic molecules) [7]. Due to their high structural diversity, these privileged structures have contributed actively to the pharmaceutical research and drug synthesis [8]. Pyrrole moieties represent an important class of azaheterocycles and are widely used as intermediates in the synthesis of a variety of pharmacophores [9–11]. These moieties are of increasing interest in pharmaceutical industry owing to their appearance in various natural products and their utility in medicinal chemistry [12–15]. Among various straightforward methods to construct the pyrrole scaffold, Paal–Knorr cyclocondensation of 1,4-dicarbonyls with primary amines has gained tremendous popularity among synthetic chemists [16–19]. In general, this reaction is catalyzed by Lewis acids [20] or heterogeneous solid supports endowed with acidic sites [21, 22]. However, despite a plethora of methodologies reported in the literature for the Paal–Knorr synthesis of pyrroles, the use of organocatalysts remains scarce [23–25].

Naturally occurring organic acids constitute a class of inexpensive organocatalysts containing usually two or three carboxylic functionalities. In general, aliphatic dicarboxylic and tricarboxylic organic acids exhibit better catalytic activity than monocarboxylic ones presumably due to their lower pK_a values. These acids have proved to be effective for catalyzing various organic reactions, e.g., citric acid for the synthesis of pyrrolidinones [26], pyrano[2,3-e]pyrimidin-amines [27], quinolines, spiro[4H-pyran-oxindoles] and xanthenes [28], itaconic acid for the synthesis of 4H-isoxazol-5-ones [29], malic acid for synthesis of quinolones via Friedländer reaction [30] and bisindolylmethanes [31], oxalic acid for synthesis of 1-(benzothiazolylamino) methyl-2-naphthols [32], 2,3-dihydroquinazolin-4(1H)-ones [33], 1,8-dioxodecahydroacridines [34] and 3-aminoisoxazolmethyl-naphthols [35], succinic acid for the synthesis of α-amino phosphonates [36], and tartaric acid for the Beckmann rearrangement of ketoximes [37] and synthesis of dihydropyrrol-2-ones [38].

Taking into account the importance of organocatalysis as a green approach for chemical transformations [39–42] and our ongoing interest in the development of practical methodologies for the synthesis of 2,5-dimethylpyrrole derivatives [20, 23, 25, 43–45], we herein disclose our latest work on the Paal–Knorr pyrrole cyclocondensation by investigating on a range of common naturally occurring organic acids (Fig. 1) as eco-friendly catalysts.

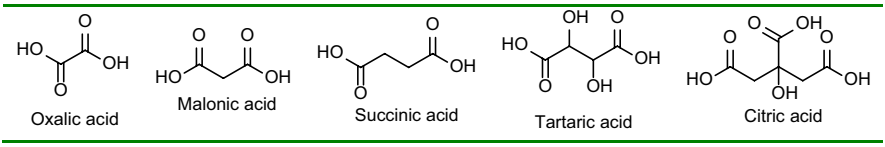


Fig. 1 Naturally occurring organic acids used as organocatalysts in this study

Experimental

General procedure for the preparation of 2,5-dimethylpyrroles

In a typical reaction, primary aromatic amine (1 mmol), hexane-2,5-dione (1.2 mmol) and a naturally occurring organic acid (0.2 mmol) were dissolved in ethanol (2 mL) and stirred at 60 °C for an appropriate reaction time. After completion of the reaction (monitored by GC), water (2 × 10 mL) was added to the reaction mixture in order to remove the catalyst. The obtained solution was extracted by ethyl acetate (2 × 5 mL), and the organic layer was separated and dried over Na_2SO_4. The separated organic phase was evaporated under reduced pressure to give the corresponding pyrrole. In cases where the reaction did not proceed to completeness, crude product was purified by recrystallization (in ethanol) or by column chromatography [ethyl acetate/petroleum ether (3:7)] to give the pure product **1**. All products **1a–r** are known compounds, and their structures were confirmed by melting point and/or identified by comparison of their GC and GC/MS with those of authentic samples reported in our previous papers.

N-Phenyl-2,5-dimethylpyrrole **(1a):** m.p. 50–51 °C [20, 23, 25, 43–45]

N-(4′-Methylphenyl)-2,5-dimethylpyrrole **(1b):** m.p. 44–45 °C [20, 23, 25, 44, 45]

N-(3′-Methylphenyl)-2,5-dimethylpyrrole **(1c):** oil [20, 23, 25, 44, 45]

N-(2′-Methylphenyl)-2,5-dimethylpyrrole **(1d):** oil [20, 23, 25, 44, 45]

N-(2′,4′-Dimethylphenyl)-2,5-dimethylpyrrole **(1e):** m.p. 87–88 °C [46]

N-(2′,5′-Dimethylphenyl)-2,5-dimethylpyrrole **(1f):** oil [20, 23, 25, 43–45]

N-(4′-Bromophenyl)-2,5-dimethylpyrrole **(1g)**: m.p. 75–76 °C [20, 23, 25, 43–45]

N-(4′-Chlorophenyl)-2,5-dimethylpyrrole **(1h)**: m.p. 55–57 °C [20, 25, 43, 45]

N-(3′-Chlorophenyl)-2,5-dimethylpyrrole **(1i)**: m.p. 51–52 °C [20, 23]

N-(3′,4′-Dichlorophenyl)-2,5-dimethylpyrrole **(1j)**: m.p. 100–101 °C [20, 23, 25, 43–45]

N-(2′,5′-Dichlorophenyl)-2,5-dimethylpyrrole **(1k)**: m.p. 139–140 °C [20]

N-(4′-Carboxyphenyl)-2,5-dimethylpyrrole **(1l)**: m.p. 204–205 °C [47]

N-(4′-Acetylphenyl)-2,5-dimethylpyrrole **(1m)**: m.p. 110–111 °C [47]

N-(3′-Acetylphenyl)-2,5-dimethylpyrrole **(1n)**: m.p. 69–70 °C [48]

N-(4′-nitrophenyl)-2,5-dimethylpyrrole **(1o)**: m.p. 146–147 °C [20, 23, 25, 43–45]

N-(3′-nitrophenyl)-2,5-dimethylpyrrole **(1p)**: m.p. 84–85 °C [20, 23, 25, 43–45]

N-(2′-Cyanophenyl)-2,5-dimethylpyrrole **(1r)**: m.p. 85–86 °C [20]

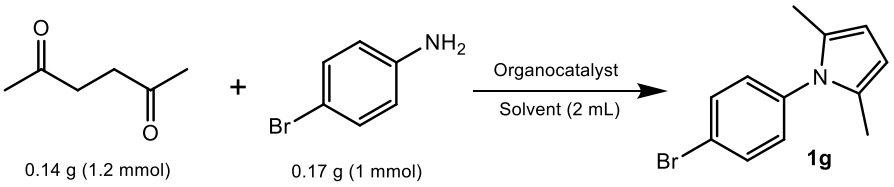
N-Benzyl-2,5-dimethylpyrrole **(1s)**: m.p. 44–45 °C [20, 43, 44]

N-Hexyl-2,5-dimethylpyrrole **(1t)**: oil [20]

Results and discussion

Among various naturally occurring organic acids used in this study, oxalic acid remains the strongest organic acid having the lowest pK_a value ($pK_a = 1.27$) mainly because its C_2 structure contains two carboxylic groups joined directly together. Consequently, initial screening reactions between hexane-2,5-dione (1.2 mmol) and 4-bromoaniline were made in the presence of oxalic acid as the most acidic organocatalyst (Table 1). The first organocatalyzed model reaction was carried out using microwave heating under solvent-free conditions. While the uncatalyzed reaction afforded poor yield of **1g** (Table 1, entry 1), the same reaction in the presence of

Table 1 Optimization of the reaction conditions for the synthesis of **1g**



Entry	Catalyst	Solvent	Conditions	Time	Conversion (%)[a]
1	–	–	MWI[b]	15 min	28
2	Oxalic acid dihydrate (1 mmol)	–	MWI	15 min	44
3	Oxalic acid dihydrate (0.5 mmol)	–	MWI	15 min	50
4	Oxalic acid dihydrate (0.2 mmol)	–	MWI	15 min	100
5	Oxalic acid dihydrate (0.2 mmol)	–	MWI	10 min	72
6	Oxalic acid dihydrate (0.2 mmol)	–	25 °C	60 min	40
7	Oxalic acid dihydrate (0.2 mmol)	Hexane	25 °C	60 min	63
8	Oxalic acid dihydrate (0.2 mmol)	Ethanol	25 °C	60 min	79
9	Oxalic acid dihydrate (0.2 mmol)	–	60 °C	60 min	84
10	Oxalic acid dihydrate (0.2 mmol)	Hexane	60 °C	60 min	79
11	Oxalic acid dihydrate (0.2 mmol)	Water	60 °C	60 min	38
12	Oxalic acid dihydrate (0.2 mmol)	Ethanol	60 °C	60 min	100
13	–	Ethanol	60 °C	60 min	10
14	Oxalic acid dihydrate (0.2 mmol)	Ethanol	60 °C	30 min	100
15	Oxalic acid dihydrate (0.2 mmol)	Ethanol	60 °C	15 min	95
16	Oxalic acid dihydrate (0.1 mmol)	Ethanol	60 °C	15 min	93
17	Oxalic acid dihydrate (0.5 mmol)	Ethanol	60 °C	15 min	95

[a]Gas Chromatography assay (%).

[b]Microwave irradiation (420 W).

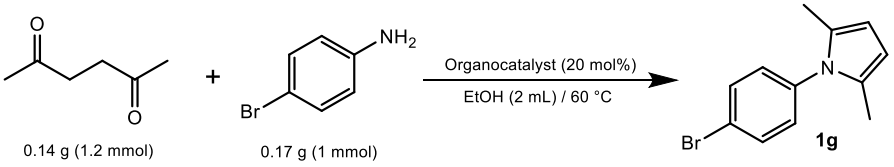
oxalic acid improved the reaction yield (Table 1, entries 2–5). Various amounts of catalyst were investigated to reveal that 20 mol% of catalyst was the optimum amount for the quantitative conversion of **1g** (Table 1, entry 4).

In the next step of our investigation, the same reaction was carried out under classical conditions. The optimized catalyst molar ratio (20 mol%) under hexane, water, ethanol and solvent-free conditions was investigated within 1 h. Upon solvent screening at room temperature, ethanol was found to be the most suitable solvent for the reaction (79%) (Table 1, entry 8). In order to simulate the results obtained by microwave heating, the same catalyzed reaction was performed at 60 °C within 1 h (Table 1, entries 9–12). Ethanol proved to be the best medium over water, hexane and neat conditions with its quantitative conversion and green nature. In order to evaluate the need of the catalyst, the uncatalyzed reaction was also performed in ethanol at 60 °C within 1 h. Poor yield of **1g** was obtained (10%) to show the necessity of catalyst for the reaction (Table 1, entries 13). Time decrease of the catalyzed reaction from 60 min to 30 min gave also the same quantitative conversion (Table 1, entries 12, 14). Besides, reducing the reaction time to 15 min did not lead to quantitative conversion even with an increase in the amount of catalyst (Table 1, entries 15–17).

In order to determine the effect of organocatalyst type on the reaction rate, a range of naturally occurring organic acids (Fig. 1) was also investigated in ethanol at 60 °C within 15, 30 and 60 min (Table 2). While oxalic, malonic, tartaric and citric acid gave excellent yield of **1g** within 30 min (Table 2, entries 2, 3, 5, 6), succinic acid needed twice that time (60 min) to catalyze the reaction and to produce the product in excellent yield (Table 2, entry 4).

These findings show a direct relationship between pK_{a1} and activity of catalysts to suggest the strength of acids play the main role in the reaction. As the solubility

Table 2 Screening various naturally occurring organic acids on the synthesis of **1g**

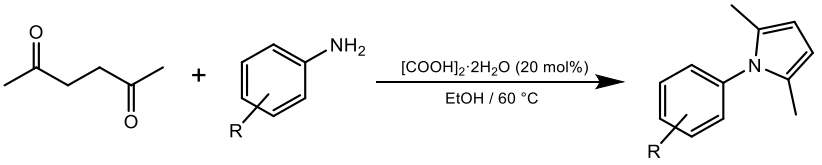


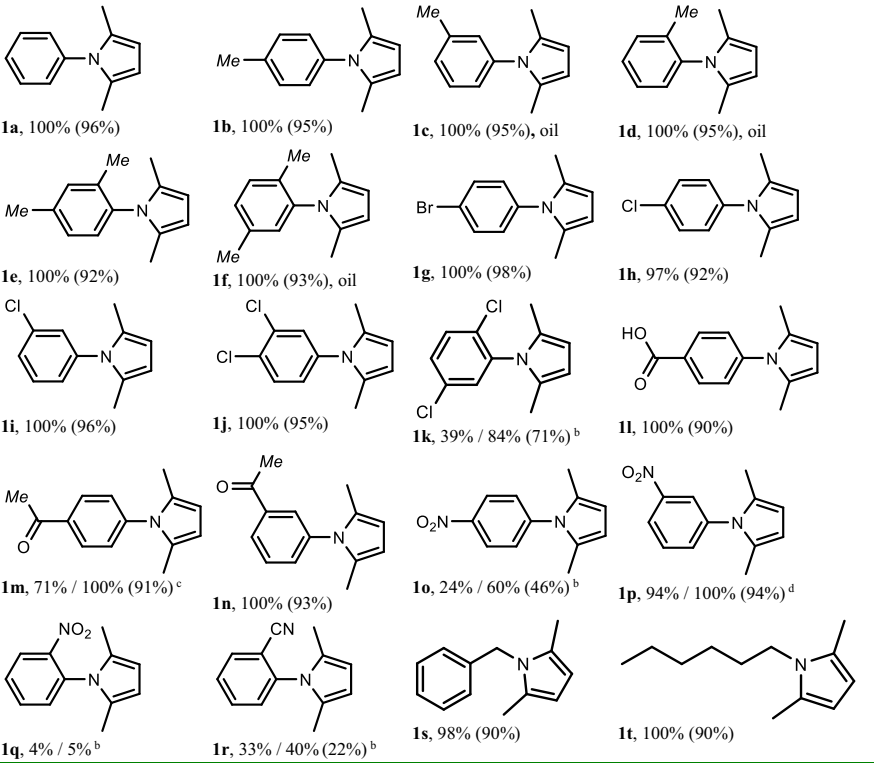
Entry	Organocatalyst	pK_{a1}	Conversion (%)		
			15 min	30 min	60 min
1	–				10
2	Oxalic acid dihydrate	1.27	95	100	100
3	Malonic acid	2.86	94	98	100
4	Succinic acid	4.16	63	78	93
5	L-(+)-Tartaric acid	3.00	92	98	100
6	Citric acid monohydrate	3.13	91	96	100

of the organocatalysts in ethanol is higher, their activity is improved when compared with other solvents.

After obtaining the best reaction conditions, a range of primary aryl amines bearing electron-donating and electron-withdrawing substituents with different positions on the aromatic ring was investigated to confirm the generality of the present method (Table 3). Primary aromatic amine derivatives bearing electron-donating methyl groups and aniline itself were readily converted to their corresponding pyrroles quantitatively (**1a**–**1f**). Excellent yields of products **1g**–**1j** were also obtained with regard to haloaniline derivatives with an exception for **1k** (71%) demanding

Table 3 Organocatalyzed synthesis of N-substituted pyrrole derivatives[a]





[a]Reaction conditions: primary amine (1.0 mmol), hexane-2,5-dione (1.2 mmol), oxalic acid dihydrate (0.2 mmol), ethanol (2 mL), 60 °C, 30 min; product **1**, GC yield (isolated yield)

[b]The reaction was carried out for 150 min

[c]The reaction was carried out for 90 min

[d]The reaction was carried out for 60 min

extended reaction time (150 min) which may be explained mainly by the steric hindrance of Cl in *ortho* position. Interestingly, anilines with electron-withdrawing functionalities such as carboxylic and acetyl underwent Paal–Knorr cyclocondensation in excellent yield (**1l**–**1n**). Aliphatic amines such as benzylamine and *n*-hexylamine were also readily converted to their corresponding 2,5-dimethylpyrrole giving excellent yields of **1s** and **1t**. However, the trend of the reaction was best shown with nitro as an electron-withdrawing functional group on aniline where longer reaction time is required. While quantitative conversion was obtained for NO_2 in *meta* position within 60 min (**1p**), the *para* position gave a modest yield of **1o** (46%) and 2-nitroaniline as substrate gave trace amount of **1q** (even after 150 min) because of its electron-withdrawing nature as well as steric hindrance in *ortho* position. Similarly, the same phenomenon was observed in aniline bearing cyano group in *ortho* position, which resulted in poor yield of **1r** (22%). In general, a decreased product yield was noticed when a bulky group such as chloro, nitro and cyano was introduced into the *ortho* position of the substrate, (i.e., **1k**, **1q**, **1r**). Thus, it may be assumed that the organocatalyzed reaction is governed by electronic (**1m**, **1o**) as well as steric effects (**1k**, **1q**, **1r**) leading to a further decrease in the reaction rate.

Conclusions

In summary, a sustainable methodology has been developed by employing naturally occurring organic acids (oxalic, malonic, succinic, tartaric and citric acid) as green catalysts for Paal–Knorr pyrrole synthesis in ethanol. It was found the organocatalyzed reaction of 4-bromoaniline and hexane-2,5-dione proceeded excellently, affording the quantitative conversion of product **1g**. Nevertheless, the reaction rate was directly proportional to the acidic strength of the organocatalyst. Therefore, the reaction scope was extended to other aliphatic and aromatic primary amines by choosing oxalic acid as catalyst. The effect of various functional groups at different positions on the aromatic ring of substrate was examined. It was observed that steric and electronic effects are two factors dominating the reaction rate.

The eco-friendly aspects of this work consist in the use of a non-toxic, inexpensive and biodegradable catalyst in a green medium providing a clean reaction profile with simple purification. This metal-free method provides an alternative access to pharmaceutically relevant pyrrole scaffolds and may be considered as a valuable asset to fine chemical industry.

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