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REGULAR ARTICLE

Crystalline salicylic acid as an efficient catalyst for ultrafast Paal–Knorr pyrrole synthesis under microwave induction

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Abstract. In this study, the viability of a wide range of crystalline aromatic and aliphatic carboxylic acids as organocatalysts has been investigated for solvent-free Paal–Knorr pyrrole synthesis under microwave activation. Among these potential catalysts, crystalline salicylic acid proved to be a remarkable catalyst because its efficiency remained high even under low microwave power irradiation or a shorter reaction time for the model reaction. The outstanding catalytic activity of salicylic acid allowed the Paal–Knorr cyclocondensation with a turnover frequency up to 1472 h^{-1} which is unique in the context of a metal-free homogeneous catalysis. The attractive feature of this organocatalyst is its assistance in ultrafast pyrrole synthesis with no risk of metal contamination.

Keywords. Salicylic acid and microwaves; Organocatalysis; Paal–Knorr reaction; 2,5-dimethylpyrrole.

1. Introduction

Heterocyclic scaffolds have found a great deal of attention not only in modern organic chemistry but also in medicinal chemistry and biochemistry.[1,2] Due to their large diversity, these heteroatomic organic motifs are ubiquitous in a wide range of natural products as well as pharmaceuticals.[3–8] Pyrrole core is an azaheterocyclic scaffold of significant interest in the synthesis of biologically active substances. These heterocycles have gained considerable attention in the pharmaceutical and agrochemical industry due to their biological profiles.[9–12] To date, various synthetic methodologies have already been implemented to access pyrrole derivatives.[13] Among diverse protocols, the straightforward synthesis of pyrrole ring from readily available primary amines, i.e., Paal–Knorr and Clauson-Kaas are typical methods for this purpose.[14] Paal–Knorr reaction consists of condensation of 1,4-dicarbonyls with primary amines affording pyrroles under acidic conditions.[15] Various catalysts have been employed for this reaction, namely Lewis acids,[16–18] solid acids,[19,20] supported ionic liquids,[21,22] functionalized magnetic nanoparticles,[22–27] deep eutectic solvents,[28–30] metal-organic frameworks,[31,32] and organocatalysts.[33–36] These catalysts have proved to be useful in the synthesis of pyrrole frameworks. However, from the industrial vantage point, metal contamination of sensible substrates during the reaction is a serious issue in the preparation of the final pharmaceutical product. Thus, more sustainable approaches using metal-free catalysts are needed to be considered for the Paal–Knorr reaction.

During the last two decades, research chemists have strived to achieve more sustainable catalytic processes. In this regard, the development of organocatalysts has attracted much attention.[37] The robustness, inexpensiveness, biodegradability and innocuousness of these small metal-free organic molecules make them a green tool for the synthesis of bioactive compounds.[38]

Salicylic acid and its derivatives are significant pharmacological agents and have made a valuable contribution to the development of medicinal drugs.[39–41] These scaffolds have proved to have an effect on physiological and pathological processes in plants.[42] With the advent of organocatalysis,[43] salicylic acid has also been employed as a catalyst for the synthesis of dihydropyridines and acridinediones,[44] hydrodeamination of aromatic amines,[45] oxidative para-acylation of unprotected anilines,[46] arylation of enol acetates,[47] synthesis of 2,3-dihydroquinazolin-

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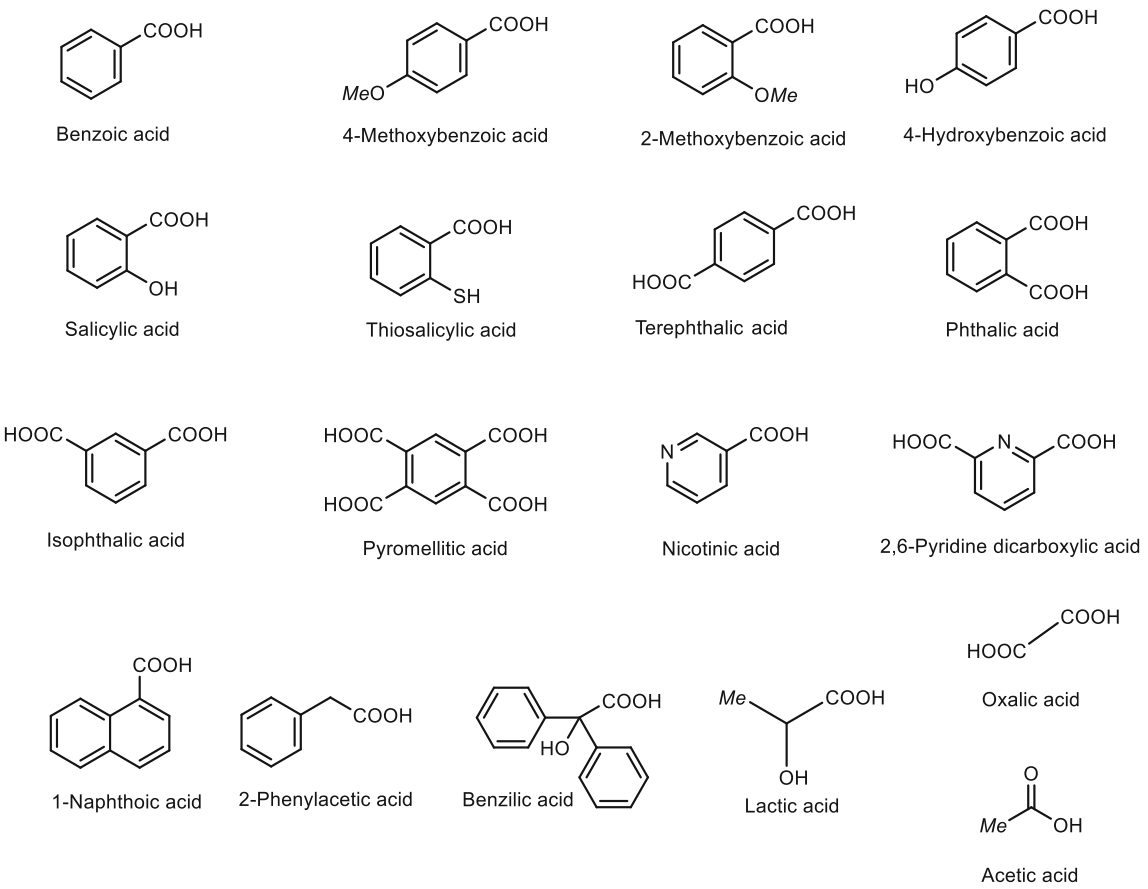


Scheme 1. Aromatic and aliphatic carboxylic acids used as potential organocatalysts for the synthesis of **1j**.

4(1H)-ones,[48] 3,4-dihydropyrimidin-2-(1*H*)-ones/thiones,[49] and 3-substituted-4-arylmethylideneisoxazol-5(4*H*)-ones.[50]

In our ongoing interest in the development of sustainable methodologies for the synthesis of 2,5-dimethylpyrrole derivatives,[16–18,33,35,36,51] we herein disclose our latest work on the Paal–Knorr pyrrole cyclocondensation by exploring the viability of salicylic acid as catalyst under microwave conditions.

2. Experimental

2.1 *Procedure for the preparation of 2,5-dimethylpyrroles*

A laboratory microwave oven MW 3100 (Landgraf Laborsysteme HLL GmbH, Langenhagen, Germany) equipped with a magnetic stirrer operating at 2450 MHz was used for syntheses of pyrrole derivatives.

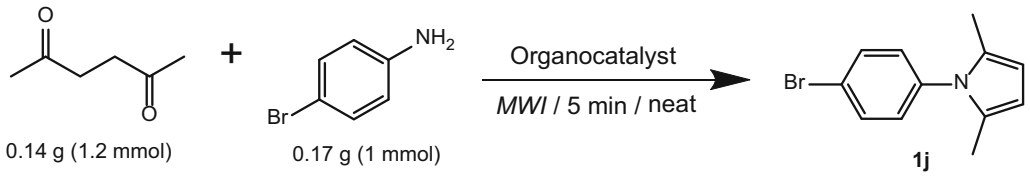
In a typical reaction, primary amine (1.0 mmol), hexane-2,5-dione (1.2 mmol) and salicylic acid (0.02 g, 0.15 mmol) were taken in an open vessel and irradiated for an appropriate time and monitored by GC. Water (20 mL) was added to the reaction mixture and stirred for 10 min. The mixture was then extracted by ethyl acetate (2 × 5 mL) and the organic layer was separated and dried over Na_2SO_4. The solvent was then evaporated under reduced pressure to obtain the corresponding product. In those cases where the reaction did not proceed to the completeness, the crude product was passed through a short column of neutral alumina [eluted with ethyl acetate/petroleum ether (3:7)] to give the pure pyrrole **1**.

2.2 *Selected spectroscopic data*

N-(4'-Acetylphenyl)-2,5-dimethylpyrrole (**1p**)[52] *[CAS Registry No. 83935-45-9]* M.p. 110–111 °C. ^{1}H NMR (500 MHz, DMSO-d_6): δ = 8.10 (d, 2H), 7.44 (d, 2H), 5.85 (s, 2H), 2.64 (s, 3H), 2.01 (s, 6H). ^{13}C NMR (125 MHz, DMSO-d_6): δ = 197.2, 142.4, 135.7, 129.3, 128.1, 127.6, 106.7, 12.9. MS (EI): *m/z (rel. intensity%)* = 213 (M^+, 100), 198 (7), 170 (30), 154 (21).

N-(4'-Carboxyphenyl)-2,5-dimethylpyrrole (**1r**)[53] *[CAS Registry No. 15898-26-78]* M.p. = 204–205 °C. ^{1}H NMR (500 MHz, DMSO-d_6): δ = 13.05 (s, COOH, 1H), 8.05 (d,

Table 1. Screening common carboxylic acids as organocatalyst on the synthesis of **1j** under microwave heating.[a]



Entry	Catalyst (0.15 mmol)	pK_a	Conversion (%)[b]
1	Benzoic acid	4.19	69
2	4-Methoxybenzoic acid	4.37	72
3	2-Methoxybenzoic acid		87
4	4-Hydroxybenzoic acid	4.48	72
5	Salicylic acid	2.97	100
6	Thiosalicylic acid	4.05	93
7	Terephthalic acid	3.51	40
8	Phthalic acid	2.89	84
9	Isophthalic acid	3.54	44
10	Pyromellitic acid	1.87	76
11	Nicotinic acid	4.75	67
12	2,6-Pyridine dicarboxylic acid	2.16	47
13	1-Naphthoic acid	3.70	68
14	2-Phenylacetic acid	4.28	76
15	Benzilic acid	3.04	96
16	Lactic acid	3.80	95
17	Oxalic acid dihydrate	1.27	53
18	Acetic acid *glacial*	4.76	71
19	–		10

[a]MWI: Microwave irradiation (420 W). [b]Gas chromatography assay (%).

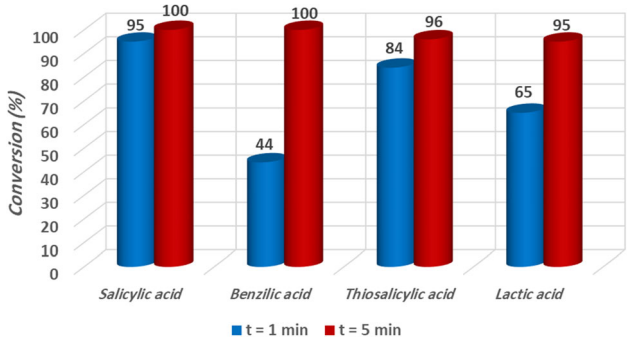


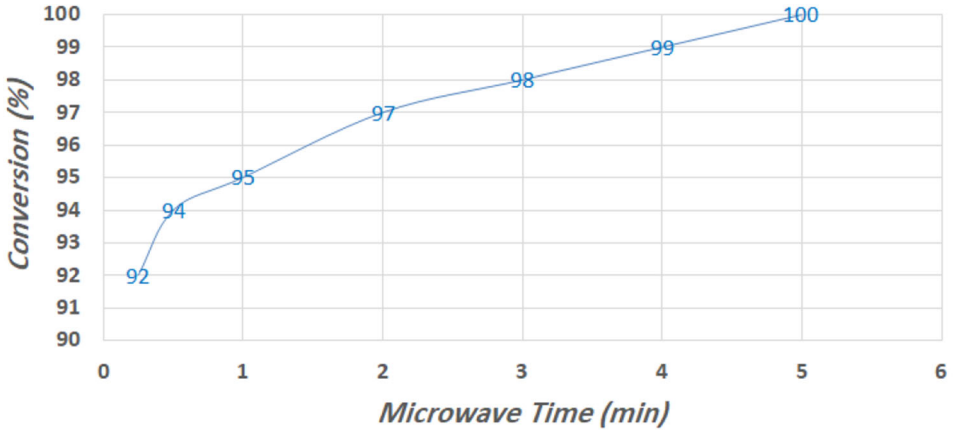
Figure 1. Effect of microwave time on 4 best catalysts (15 mol%).

J = 10 Hz, 2H), 7.40 (d, *J* = 10 Hz, 2H), 5.84 (s, 2H), 2.00 (s, 6H). ^{13}C NMR (125 MHz, DMSO-d_6): δ = 166.8, 142.2, 130.3, 128.1, 127.6, 106.6, 12.9. MS (EI): *m/z (rel. intensity %)* = 216 (11), 215 (90). 214 (M^+, 100), 170 (14), 154 (17).

3. Results and Discussion

Microwave-assisted organic synthesis (MAOS) has revolutionized the industry of pharmaceuticals and contributed effectively to the sustainable generation of bioactive heterocycles.[3] Acceleration of the reaction rate, minimization of byproduct, improved yields, reduction of reaction time as well as energy consumption in organic transformations are the attractive features of this eco-friendly tool.[54] In this regard, we started our investigation by screening various aromatic and aliphatic carboxylic acids (Scheme 1) as crystalline catalyst (0.15 mmol) in the condensation of hexane-2,5-dione (1.2 mmol) with 4-bromoaniline (1 mmol) under microwave conditions within 5 min (Table 1).

Low to moderate yield of product (40-72%) was obtained in the presence of a catalytic amount of benzoic acid, 4-methoxybenzoic acid, 4-hydroxybenzoic acid, terephthalic and isophthalic acid, nicotinic and 2,6-pyridine dicarboxylic acid, 1-naphthoic acid, oxalic and acetic acid (Table 1, entries 1, 2, 4, 7, 9, 11–13, 17, 18). 2-Methoxybenzoic acid, phthalic acid, pyromellitic acid and 2-phenylacetic acid gave good conversion (76-87%) of **1j** (Table 1, entries 3, 8, 10, 14). However, it was salicylic acid, thiosalicylic, benzilic and lactic acid which proved to be remarkable catalysts in the reaction affording the desired product in excellent yield (Table 1, entries 5, 6, 15, 16).



Microwave Time (min)	0.25	0.5	1	2	3	4	5
Conversion (%)	92	94	95	97	98	99	100
TOF (h-1)	1472	752	380	194	131	99	80

Figure 2. Effect of microwave time on salicylic acid (15 mol%) as catalyst.

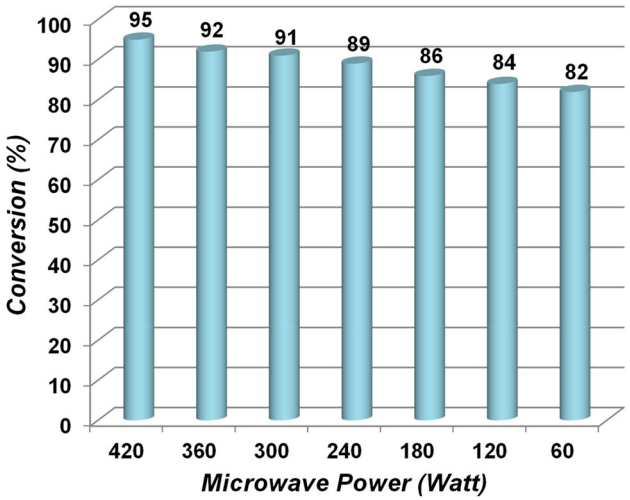


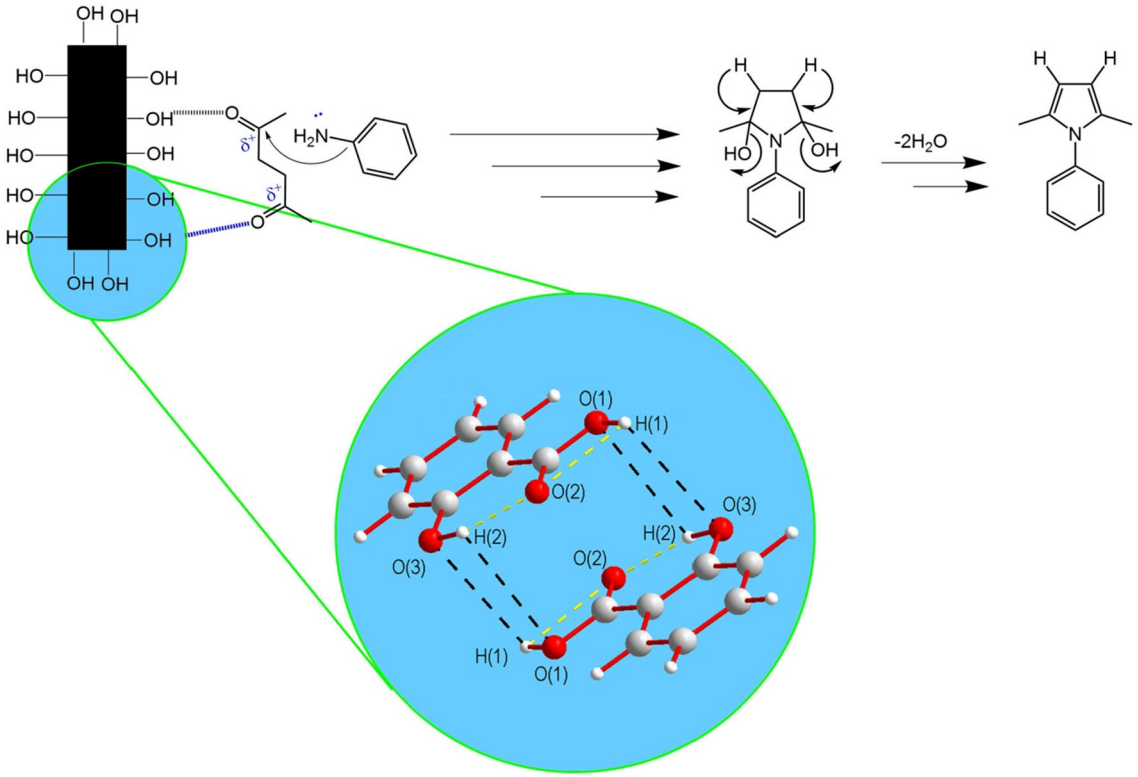
Figure 3. Effect of microwave power on salicylic acid (15 mol%) as catalyst within 1 min.

At the first glance, it can be seen that these catalysts had a vicinal -OH (or -SH) functional group to the -COOH one. Thus, it was assumed that hydrogen bonding between the -OH and the carboxylate ion tends to stabilize the conjugated carboxylate base and hence better hydrogen-bonding donating ability was observed for the acid-catalyzed synthesis of pyrroles *via* Paal-Knorr reaction. Besides, salicylic acid having an OH in *ortho* gave by far a higher conversion of **1j** compared to its *para* analogue (4-hydroxybenzoic acid) (Table 1, entries 4, 5) to confirm the stabilization of COOH by H-bonding resulting in the superior catalytic activity of salicylic acid, i.e. *ortho*-HO-C_6H_4(-COOH) >> *para*-HO-C_6H_4(COOH). The same trend was observed by other benzoic acid derivatives (Table 1, entries 2, 3) and (Table 1, entries 7–9), e.g. *ortho*-MeO-C_6H_4(COOH) > *para*-MeO-C_6H_4(COOH) as well as *ortho*-$C_6H_4(COOH)_2$ >> *para*-C_6H_4(-$COOH)_2$ ≈ *meta*-$C_6H_4(COOH)_2$.

To find out the effect of catalyst, the reactions in the presence of four best catalysts were carried out under microwave irradiation within 1 min. The obtained results revealed the superiority of salicylic acid over benzylic, lactic and thiosalicylic acid, as shown in Figure 1. Therefore, we concluded that the reaction progress is mainly related to the intrinsic crystal structure of the catalyst. Thereafter, we decided to examine the reaction progress in shorter reaction times. As demonstrated in Figure 2, a 92% conversion of **1j** took place even after 15 s of irradiation, offering a turnover frequency of 1472 h^{-1} which is remarkable especially in the context of a metal-free homogeneous catalysis.

These findings encouraged us to use low power microwave irradiation to highlight the catalyst effect (Figure 3). We, therefore, examined the reactions between 60-420 W in 1 min and found the prominence of catalyst on the reaction progress (because of high conversions) even in lower microwave powers.

In general, the reaction rate remained high when low power of microwave and short reaction time was applied. In order to find why salicylic acid proved to be an outstanding catalyst for the model reaction, pK_a values were first compared. As shown in Table 1, there is no direct relationship between pK_a of the carboxylic acids with the yield of the reaction. For instance, within 5 min microwave irradiation, oxalic acid (pK_a = 1.27), pyromellitic acid (pK_a = 1.87), and



Scheme 2. Plausible mechanism for salicylic acid-catalyzed Paal–Knorr pyrrole cyclocondensation.

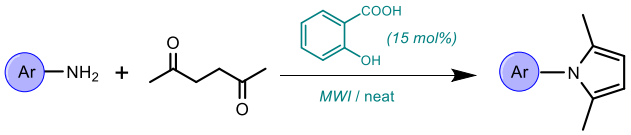
salicylic acid (pK_a = 2.97) afforded the product **1j** in 53, 76, and 100 % yields, respectively (Table 1, entries 5, 10, 17) to show pK_a plays a minor role in the reaction. On the other hand, when salicylic acid was dissolved in ethyl acetate (2 mL) and used for the reaction (420 W, 5 min), a significant decrease in the yield of **1j** was observed (72%) to prove the crystalline nature of salicylic acid plays a critical role on the reaction rate. Thus, the mechanism of the reaction was proposed based on the intrinsic crystal structure of catalyst as shown in Scheme 2. Indeed, in the crystalline form of salicylic acid, there are various intermolecular and intramolecular hydrogen bonds[55] which differentiate it from other benzoic acid derivatives. Therefore, the ultrafast catalyzed reaction is due to its several acidic hydrogens,[56] which play a vital role in activating the substrates (Scheme 2). In other words, salicylic acid possesses a three-dimensional structure in its solid state[56] containing multiple hydrogen bondings to promote proton transfer (acid) catalysis.

To evaluate the scope and limitations of this protocol, different substituted pyrroles were synthesized from a range of primary amine derivatives with hexane-2,5-dione. As depicted in Table 2, aniline and its methyl and methoxy derivatives were readily converted to their corresponding pyrroles quantitatively (**1a–1f**). Strong electron-withdrawing nitro substituted anilines had a negative influence on the reaction rate and even after extended reaction time, only the *meta*-NO_2 derivative gave a quantitative yield of **1h**. This is while a modest yield of **1g** (45%) was obtained from the *para*-NO_2 substrate and the *ortho* one had no activity. The same trend was observed for chloro and cyano at *ortho* position of aniline (**1n** and **1o**) which may be explained mainly by the electronic effect as well as steric hindrance of bulky groups in the *ortho* position of the substrate.

Excellent yields of products **1j-1m** were obtained with regard to all other haloaniline derivatives. Interestingly, anilines with other electron-withdrawing functionalities such as carboxylic and acetyl underwent Paal–Knorr cyclocondensation in excellent yield too (**1p–1r**). The same trend was also observed for aliphatic amines (**1s–1v**).

The turnover frequency (TOF) for this catalytic protocol, which is defined as a mole of converted substrate (primary amine) per mole of catalyst per hour, is listed in Table 2. In most cases, good to high values of TOF in the range of 37 to 133 h^{-1} were achieved. Very low TOF values (e.g. 8 h^{-1} for **1o**) is because of substrates with lesser reactivity as well as a steric hindrance.

Table 2. Access to pyrroles using a combination of salicylic acid (15 mol%) and microwave irradiation.



Entry	Ar	Time	Conversion (%)[a]	Yield (%)[b]	TOF (h^{-1})[c]
1a	4-Methoxyphenyl	3 min	100	95	133
1b	Phenyl	3 min	100	96	133
1c	4-Methylphenyl	3 min	100	95	133
1d	3-Methylphenyl	3 min	100	94	133
1e	2-Methylphenyl	4 min	100	95	100
1f	2,5-Dimethylphenyl	4 min	100	95	100
1g	4-Nitrophenyl	10 min	55	45	22
1h	3-Nitrophenyl	10 min	100	95	40
1i	2-Nitrophenyl	10 min	–	–	–
1j	4-Bromophenyl	5 min	100	98	80
1k	4-Chlorophenyl	3 min	100	95	133
1l	3-Chlorophenyl	3 min	98	90	131
1m	3,4-Dichlorophenyl	5 min	90	82	72
1n	2,5-Dichlorophenyl	10 min	17	7	7
1o	2-Cyano	10 min	21	10	8
1p	4-Acetylphenyl	10 min	92	85	37
1q	3-Acetylphenyl	10 min	100	93	40
1r	4-Carboxyphenyl	10 min	92	92	37
1s	*n*-Butyl	3 min	100	87	133
1t	*n*-Hexyl	3 min	100	96	133
1u	Cyclohexyl	5 min	95	77	76
1v	Benzyl	5 min	97	95	78

[a]Gas chromatography assay (%); [b]Yields refer to those of pure isolated products. [c]TOF: Turnover frequency = moles of a converted substrate (primary amine)/(moles of salicylic acid × reaction time in h).

4. Conclusions

The viability of a range of aromatic and aliphatic carboxylic acids as potential organocatalysts in the direct condensation of 4-bromoaniline and hexane-2,5-dione under solvent-free microwave irradiation was investigated. Among these organocatalysts, salicylic acid exhibited the highest catalytic activity. The remarkable effect of salicylic acid on the reaction was proved when both the reaction time was shortened and the microwave power was decreased. The highest turnover frequency (TOF) was found to be 1472 h^{-1} when a catalytic amount of salicylic acid was used in combination with 420 W microwave irradiation. Indeed, the reaction required only 15 seconds to achieve a high conversion (92%) of 4-bromoaniline to **1j**. The scope and generality of this protocol were explored with respect to various primary amines, showing that the nature of the functional group and its position on the aromatic ring of a substrate, are the main factors which dominate the reaction rate. The attractive features of this green protocol are clean reaction profile, metal-free homogeneous catalysis, accelerated reaction rate leading to pyrrole scaffolds with no risk of metal contamination.

Conflict of interest The authors declare no conflict of interest.

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