Monatsh Chem (2013) 144:405–409
DOI 10.1007/s00706-012-0841-2

ORIGINAL PAPER

Squaric acid catalyzed simple synthesis of N-substituted pyrroles in green reaction media

**Najmadin Azizi · Anahita Davoudpour ·
Farshid Eskandari · Ehlham Batebi**

Received: 6 November 2011 / Accepted: 15 August 2012 / Published online: 22 September 2012

Abstract An operationally simple and efficient protocol for squaric acid catalyzed synthesis of N-substituted pyrroles via the reaction of 2,5-dimethoxytetrahydrofuran and 2,5-hexandione with aryl amines in green reaction media (water, deep eutectic solvent, and polyethylene glycol) under ultrasound irradiation or thermal conditions in good to excellent yields has been developed.

Keywords Aromatic amine · Green chemistry · Pyrrole · Squaric acid · Novel organocatalyst

Introduction

Developments of eco-friendly methodologies which are environmentally clean, waste-free, high purity, and prevent pollution have received much attention in recent years. To reach this goal, the use of green reaction media, reagents, and catalysts should be investigated. By applying alternative reaction conditions, more efficient processes and new catalysts can be discovered allowing the preparation of innovative materials. Water, a unique solvent in organic synthesis, is not only abundant, inexpensive and environmentally benign, but also shows novel reactivity and selectivity for simple synthesis of organic compounds such as pharmaceutical products, agrochemicals, fine chemicals, and synthetic intermediates [1–3].

On the other hand, organocatalysts have several advantages. They are usually robust, inexpensive, readily available, and non-toxic. Because of their inertness toward moisture and oxygen, demanding reaction conditions, for example inert atmosphere, low temperatures, absolute solvents, etc., are, in many instances, not required. Because of the absence of transition metals, organocatalytic methods seem to be especially attractive for the preparation of drug-like compounds [4, 5].

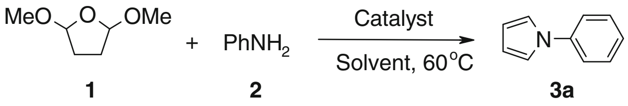
Pyrrole containing heterocycles are an important class of compounds displaying remarkable pharmacological properties such as antibacterial, antiviral, anti-inflammatory, antitumoral, and antioxidant activities [6]. Furthermore, they are useful intermediates in the synthesis of natural products [7] and are also widely used in material science [8]. Consequently, an enormous number of procedures have been developed for the construction of pyrroles in the literature [9–12]. Despite these new developments, the Paal–Knorr reaction [13] remains one of the most attractive methods for the synthesis of N-substituted pyrroles [14–26]. In an attempt to design a green, pronounced procedure to synthesize *N*-arylpyrrole derivatives in green reaction media, many methods in green solvents such as ionic liquid, water, and solventless conditions have been used to synthesize pyrrole derivatives in different reaction conditions (Table 1).

Results and discussion

In our continuing effort to utilize green solvents as environmentally attractive media in organic synthesis [27–29], herein we developed a novel organocatalyst (squaric acid) [30] for an efficient preparation of *N*-arylpyrroles from the reaction of aromatic amines with 2,5-dimethoxytetrahydrofuran (**1**) and 2,5-hexandione (**4**) in green reaction media: water, deep eutectic solvent (DES), and polyethylene glycol (PEG).

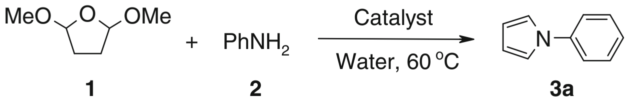
N. Azizi (✉) · A. Davoudpour · F. Eskandari · E. Batebi
Chemistry and Chemical Engineering Research Center of Iran,
P.O. Box 14335-186, Tehran, Iran
e-mail: azizi@ccerci.ac.ir

Table 1 Comparison of the catalytic efficiency of various green methods reported in the literature



Entry	Catalyst/mol %	Solvent	Temp./°C	Time/h	Yield/%	Ref.
1	$Bi(NO_3)_3$ (0.05)	Neat	90	0.08	100	[26]
2	I_2 (5)	Neat (MW)	60	0.08	98	[10]
3	–	Water (MW)	150	0.5	96	[23]
4	$FeCl_3$ (2)	Water	60	1	95	[22]
5	–	Water	140	0.33	88	[17]
6	Ferrite nanoparticle	Water	140	0.33	88	[18]
7	$Bi(NO_3)_3$ (5)	Water	82	24	87	[21]
8	–	Neat	120	3.5	90	[6]
9	$Sc(OTf)_3$	Neat	RT	0.5	93	[15]
10	–	Ionic liquid	RT	3	96	[21]
11	Squaric acid (0.5)	Water	60	3	95	This work
12	Squaric acid (0.5)	DES	60	3	75	This work
13	Squaric acid (0.5)	PEG	60	3	92	This work

Table 2 Screening of different catalysts



Entry	Catalyst (1 mol %)	Yield/%	Entry	Catalyst (1 mol %)	Yield/%
1	–	0	11	CF_3SO_3H	85
2	$B(OH)_3$	30	12	HBF_4	86
3	$SiCl_4$	60	13	$AlCl_3$	88
4	TCA[e]	60	14	$H_3PMo_{12}O_{40}$	80
5	$RuCl_3 \cdot 7H_2O$	65	15	H_2SO_4	95
6	Proline	65 (0)[a]	16	HCl	88
7	ZnI_2	72	17	Squaric acid (0.5)	95 (70)[a]
8	$ZrCl_4$	80	18	Squaric acid (0.5)	0[b]
9	$HClO_4$	83	19	Squaric acid (0.5)	92[c]
10	PTSA	83	20	Squaric acid (0.5)	75[d]

Reaction conditions: amine (1.01 mmol), 2,5-dimethoxytetrahydrofuran (1 mmol), 2 cm^3 water

[a] Reaction in the presence of ultrasound

[b] Reaction under solvent free condition

[c] Reaction in polyethylene glycol

[d] Reaction in choline chloride—urea deep eutectic solvent

[e] Trichloroisocyanuric acid

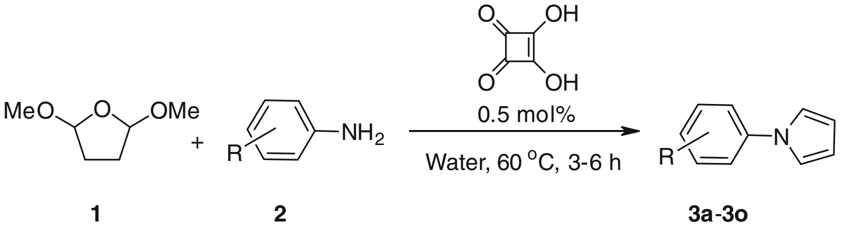
Initial experimentation was focussed on the catalytic activity-screening study of reaction conditions. Thus, 2,5-dimethoxytetrahydrofuran was treated with aniline with various catalysts at various temperatures. The results of this extensive catalyst screening and optimization of several reaction conditions are shown in Table 2. It was found that both the yields and the rates of the reactions were improved when various catalysts were used under these conditions. After a survey of different reaction conditions, the reaction was best carried out by using one equivalent of aniline and one equivalent of 2,5-dimethoxytetrahydrofuran in the presence of sulfuric acid (1 mol %) and squaric acid (0.5 mol %) in 2 cm^3 water at 60 °C to afford *N*-phenylpyrrole in a 95 % yield; however, we exclusively used squaric acid since squaric acid is green, reusable, and more environmentally friendly than sulfuric acid.

We also investigated the effects of common organic solvents, and the influence of different solvent effects on the rate and the course on these reactions under an optimized reaction condition. In cyclohexane, acetonitrile, THF, and solvent free conditions the reaction did not take place and the starting materials were recovered; low yields of the product were observed in dichloromethane (30 %) and ethanol (50 %). Furthermore, the same reaction in green solvents such as deep eutectic solvent and polyethylene glycol gave excellent yields of products in the presence of squaric acid (Table 2).

On the other hand, most of the chemical manufacturing industries and chemistry laboratories use electricity generated from coal for heating purposes and organic solvents which are responsible for environmental pollution. In view of this, attempts have been made to use alternate energy sources in organic synthesis and industry. In this context, ultrasound may offer green technology by improving product yields and selectivities, enhancing product recovery and minimizing the production of waste. In order to verify the effect of ultrasound irradiation, we have performed the reaction of aniline with 2,5-dimethoxytetrahydrofuran in the presence of squaric acid under ultrasound irradiation. The reaction can be completed.

With our optimized reaction conditions, the condensation of various commercial aromatic amines with 2,5-dimethoxytetrahydrofuran was examined to explore the scope and limitation of the reaction. As revealed in Table 3, a series of aromatic amines bearing either electron-donating or electron-withdrawing groups on the aromatic ring was investigated. Aryl amines with electron-rich groups reacted rapidly, while substitution of electron-withdrawing groups on the benzene ring did not decrease the reactivity. Steric and electronic effects of the aniline substituents did not make any difference on the yield and time of the reaction. Moreover, 2-nitroaniline, the substrate

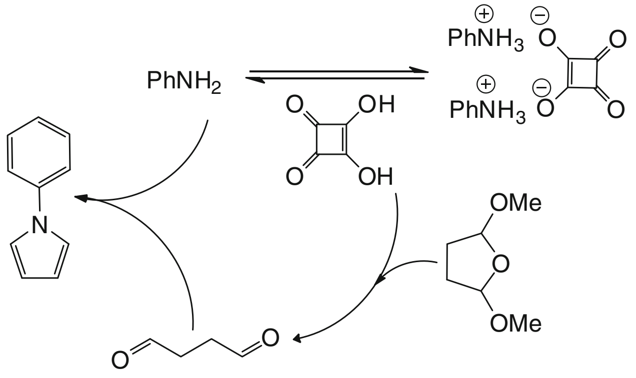
Table 3 Synthesis of *N*-arylpyrroles from 2,5-dimethoxytetrahydrofuran in water



Entry	Amine	Product	Yield/%	Ref.
1	$C_6H_5NH_2$	**3a**	95	[22]
2	4-$ClC_6H_4NH_2$	**3b**	97	[19]
3	4-$BrC_6H_4NH_2$	**3c**	90	[21]
4	4-$IC_6H_4NH_2$	**3d**	92	[22]
5	3,4-$Cl_2C_6H_3NH_2$	**3e**	90	[15]
6	2-$ClC_6H_4NH_2$	**3f**	95	[22]
7	2-$NO_2C_6H_4NH_2$	**3g**	90	[17]
8	4-$MeOC_6H_4NH_2$	**3h**	94	[21]
9	4-$MeC_6H_4NH_2$	**3i**	92	[21]
10	4-*i*-$PrC_6H_4NH_2$	**3j**	94	[19]
11	4-*n*-$BuC_6H_4NH_2$	**3k**	90	[25]
12	4-$NO_2C_6H_4NH_2$	**3l**	85	[22]
13	2-$MeC_6H_4NH_2$	**3m**	90	[22]
14	2,6-$Me_2C_6H_3NH_2$	**3n**	88	[14]
15	2,4,6-$Me_3C_6H_2NH_2$	**3o**	90	[16]

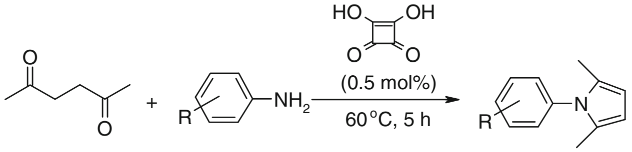
Reaction conditions: amine (1.1 mmol), 2,5-dimethoxytetrahydrofuran (1 mmol), squaric acid (0.5 mol %), 2 cm^3 water, 60 °C with a strong electron-withdrawing group, underwent smooth condensation providing excellent yield of the desired pyrrole derivative.

The role of the squaric acid as a catalyst is still not clear. Brønsted acidity is the main factor that influences the reactivity and selectivity of the process. We tentatively propose the mechanism of the present reaction to proceed in a manner similar to that described for the analogous Bronsted acid—catalyzed imine formation as outlined in Scheme 1. The reversible acid–base reaction of aniline with squaric acid gives the salt anilinium squarate. Furthermore, 2,5-dimethoxytetrahydrofuran is hydrolyzed in the presence of a catalytic amount of squaric acid to the 1,4-dicarbonyl compound in water as supported by ^{1}H NMR. Condensation of activated 1,4-dicarbonyl compound with aniline produces *N*-phenylpyrrole.



Scheme 1

Table 4 Preparation of pyrroles from 2,5-hexandione in water



4 **2** **5a-5i**

Entry	Amine	Product	Yield/%	Ref.
1	$C_6H_5NH_2$	**5a**	95	[15]
2	4-$MeC_6H_4NH_2$	**5b**	95	[15]
3	2-$MeC_6H_4NH_2$	**5c**	90	[16]
4	4-$MeOC_6H_4NH_2$	**5d**	90	[27]
5	4-$ClC_6H_4NH_2$	**5e**	85	[27]
6	2,4-$Cl_2C_6H_3NH_2$	**5f**	88	[15]
7	3,4-$Cl_2C_6H_3NH_2$	**5g**	90	[18]
8	4-$BrC_6H_4NH_2$	**5h**	85	[15]
9	2,6-$Me_2C_6H_3NH_2$	**5i**	40	[15]

Reaction conditions: aromatic amine (1.1 mmol), 2,5-hexandione (1 mmol), squaric acid (0.5 mol %), 2 cm^3 water, 60 °C

The scope and generality of the current methodology were further extended for condensation of 2,5-hexandione (**4**) with various amines under identical conditions, and several representative examples are summarized in Table 4. The reaction was clean and proceeded smoothly to give the corresponding substituted pyrroles in good to excellent yields. Aromatic amines with electron-donating groups as well as electron-withdrawing groups were found to be equally amenable to these conditions without remarkable difference in yields and reaction time between. However, a clear difference in the rate of the reaction as well as the yield of the product was apparent when hindered amines such as 2,6-dimethylaniline were used. The reaction between 2,6-dimethylaniline and 2,5-hexandione was remarkably slow, and the product was obtained in low yields. Furthermore, aliphatic amines such as benzylamine, cyclohexylamine, and pyrrolidine did not give acceptable yields of the product at this reaction condition, because of irreversible salt formation between aliphatic amines and squaric acid.

In summary, we have described a simple, highly efficient, and facile procedure for practical synthesis of substituted pyrroles from readily available starting materials.

Experimental

Reactions were monitored by TLC and GC. ^{1}H NMR spectra were recorded at 500 MHz and ^{13}C NMR spectra at 125 MHz, using $CDCl_3$ or DMSO-d_6 as solvent. Chemical shifts have been expressed in ppm downfield from TMS. Melting points were recorded on a Büchi 535 melting point apparatus. All starting materials and catalysts are commercially available and were purchased and used without further purification. Water and other solvents were distilled before used. Sonication was performed by a Hielscher ultrasonic device (Vial Tweeter at UIS250v); the best results were obtained when a continuously switched on irradiation was applied at 80 % of the maximum power output (amplitude).

General procedure

To a mixture of 0.1 cm^3 aniline (1.01 mmol) and 0.13 cm^3 2,5-dimethoxytetrahydrofuran (1 mmol) or 0.12 cm^3 2,5-hexandione (1 mmol) in 2 cm^3 water, 5 mg squaric acid (0.5 mol %) was added and stirred at 60 °C for 180–360 min. After the reaction was completed, in the cases of solid products, pure products were isolated by filtration and washing with hot water or ethanol. In few cases, an aqueous mixture was extracted with 10 cm^3 of diethyl ether or ethyl acetate and dried over anhydrous

Na_2SO_4, and the solvent was removed under reduced pressure to give the desired products after purification.

Acknowledgments The financial support of this work was provided by the Iran National Science Foundation (INSF) and is gratefully appreciated.

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