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Rapid synthesis of pyrroles using trichloroacetic acid under solvent-free conditions at room temperature

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ABSTRACT

A novel approach to explore the use of trichloroacetic acid for the synthesis of pyrroles has been described through the Paal-Knorr reaction of 2,5-hexandione with various amines at room temperature under solvent-free conditions.

KEYWORDS

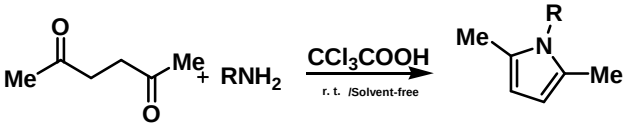
Pyrroles;
Paal-Knorr reaction;
Trichloroacetic acid;
Solvent-free synthesis.

INTRODUCTION

Naturally occurring substituted pyrroles, as well as synthetic derivatives thereof, exhibit wide ranges of biological activities, making them attractive compounds for organic chemists[1-2]. Different substituted pyrroles show variable biological activities such antiflammatory, antibacterial, antiviral and anticancer agents[3-5]. Various methods such as 1,3-dipolar cycloaddition reactions[6], aza-Wittig reactions[7], classical Hantzsch method[8], annulations reactions[9], and other multistep operations[10] are available for the construction of pyrroles. Despite these new developments, the Paal-Knorr reaction remains one of the most convenient methods which consists the cyclocondensation of primary amines with 1,4-dicarbonyl compounds to produce *N*-substituted pyrroles. In this context, several catalysts have been utilized to promote this condensation[11-21].

Although these methods are suitable for certain synthetic applications, many of these procedures are associated with several limitations such as expensive reagents, tedious workup, harsh reaction conditions and use of toxic solvents. Thus, the development of an alternate milder and clean procedure is still in demand for contemporary chemical synthesis of pyrroles.

As part of our program aimed at developing new selective greener methodologies for the preparation of pharmaceutically important scaffolds[22-24], we undertook improvement toward an efficient and versatile for the synthesis of pyrroles through the condensation of 2,5-hexandione and amines using trichloroacetic acid under solvent-free conditions at room temperature (Scheme 1).



Scheme 1 : Synthesis of pyrroles

RESULTS AND DISCUSSION

Trichloroacetic acid has been considered as an efficient, inexpensive and readily available solid reagent and it has been reported by our group for the synthesis of dihydropyrano [2,3-c] pyrazoles[22], benzo-xanthenes[23], coumarins and dihydroquinazolinones[24].

To optimize of the reaction conditions, aniline was chosen as the model for the reaction with 2,5-

hexandione. After carrying out the reaction at different conditions, by exploring the effect of varying the temperature and amount of reactants revealed that the best results are obtained with two equivalents of 2,5-hexandione and one equivalent of aniline using 5 mol% trichloroacetic acid at room temperature under solvent-free conditions. These conditions, afforded the corresponding product in 94% yield after 5 min. In the absence of trichloroacetic acid, only 20% yield of the product was obtained after 12 h at room temperature with recovery of starting material.

To show the generality of this method, the optimized system was used for the synthesis of other pyrrole derivatives. The results of several representative examples are summarized in TABLE 1, which clearly indicates the generality and scope of the reaction. Various functionalities present in the aniline, such as halogen, methoxy, carboxy, methyl, and nitro groups were tolerated (see TABLE 1). The substitution group on the phenyl ring did not make any difference in the Paal–Knorr reaction. Moreover, the reaction can also proceed with aliphatic amines (TABLE 1, entries 10, 12). In all these cases, the corresponding pyrroles were obtained in good yields after 5 min at room temperature.

Under further observation, it is observed that the reaction of diamines with 2,5-hexandione afforded bipyrrole compounds in good yield without any solvent at room temperature (TABLE 1, entry 11,12).

All the pyrrole products are known compounds and their structure was deduced from their IR and NMR spectroscopies data and their melting points, which agreed with reported values[11-21].

To show the merit of the present work in comparison with results reported recently in the literature, synthesis of N-phenyl-2,5-dimethylpyrrole was considered as a representative example (TABLE 2). As indicated in TABLE 2, our present method is better or comparable with others in terms of yield, reaction rate or conditions.

In conclusion, a novel approach to explore the use of trichloroacetic acid for the synthesis of pyrroles has been described through the Paal-Knorr reaction at room temperature under solvent-free conditions. This method offers several advantages including high yields, short reaction times, solvent-free condition, mild reaction conditions at room temperature and the use of cheap and easily accessible catalyst.

TABLE 1 : Synthesis of pyrroles using trichloroacetic acid as a catalyst at room temperature

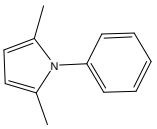
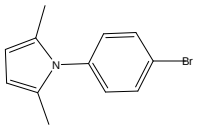
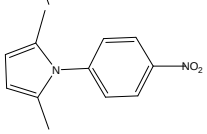
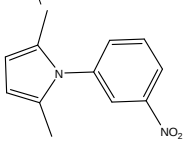
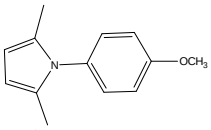
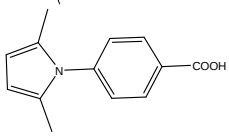
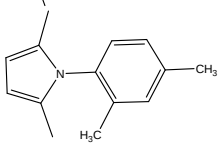
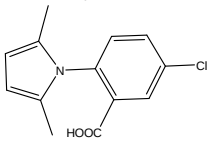
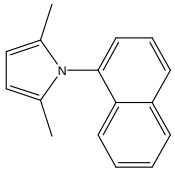
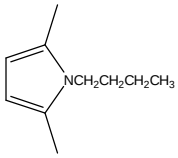
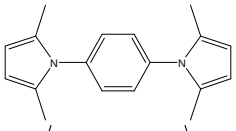
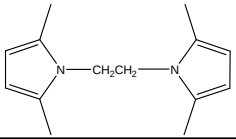
Entry	Amine	Product	Yield (%)	Reference
1	$C_6H_5NH_2$		94	19
2	4-$BrC_6H_4NH_2$		93	18
3	4-$NO_2C_6H_4NH_2$		90	19
4	3-$NO_2C_6H_4NH_2$		91	21
5	4-$OCH_3C_6H_4NH_2$		94	17
6	4-$COOHC_6H_4NH_2$		85	17
7	2,4-$(CH_3)_2C_6H_3NH_2$		82	14
8	2-CO_2H-4-Cl $C_6H_3NH_2$		88	20
9	1-naphthyl amine		80	16
10	n-butyl amine		91	15
11	1,4-phenylene diamine		93	16
12	Ethylene diamine		90	17

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TABLE 2 : Comparison of some recent procedures for the synthesis of 2,5-Dimethy-1-phenyl-1H-pyrrole

Entry	Catalyst	Conditions	Time (min)	Yield (%)	Ref.
1	$Sc(OTf)_3$ (1 mol %)	Solvent-free, 30 °C	25	93	11
2	$InCl_3$ (5 mol%)	Solvent-free, r.t.	30	90	13
3	$ZrCl_4$ (15 mol%)	ultrasonic irradiation, 40 °C	7	98	14
4	sulfamic acid (5 mol%)	solvent-free, r. t.	30	92	15
5	N,N'-diiodo-N,N'-1,2-ethanediylbis(p-toluenesulphonamide) (0.15 mmol)	CH_3CN, r. t.	20	96	16
6	silica sulfuric acid (0.15g)	solvent-free, r. t.	15	90	17
7	uranyl nitrate hexahydrate (10 mol%)	ultrasonic irradiation, methanol, reflux	30	94	18
8	Xanthan sulfuric acid (0.10 g)	solvent-free, r. t.	15	90	19
9	$PS/GaCl_3$(10 mol%)	CH_3CN, Reflux	20	92	20
10	BiCl3/SiO2 (0.30 g)	n-hexane, r.t.	60	98	21
11	Trichloroacetic acid (5 mol%)	solvent-free, r. t.	5	94	This work

EXPERIMENTAL

General procedure for the synthesis of pyrroles

A mixture of 2,5-hexanedione (2 mmol), amine (1 mmol), and trichloroacetic acid (5 mol%) was stirred at room temperature under solvent-free conditions for 5 min. The progress of reactions was monitored by TLC (ethyl acetate/n-hexane). After completion of the reaction, water (5 mL) was added and the mixture was stirred for 10 min in order to solve the catalyst. The obtained solid was collected by filtration to give, in many cases, the pure pyrroles.

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