

Ultrasonic-Assisted Simple, Mild and Efficient One-Pot Four-Component Synthesis of Highly Functionalized Pyrroles

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Abstract

The one-pot four-component reaction between isocyanide (1), dialkyl acetylene dicarboxylates (2) and five-membered cyclic imides such as succinimide or maleimide (3) was done to study the synthesis of highly functionalized pyrroles in attendance of ultrasound (sono-synthesis) and loss of ultrasound conditions (conventional method). The reaction speed was remarkably catalyzed with the aid of ultrasound irradiation. Moreover, this approach prepares multiple other benefits such as operational ease, higher yields and energy performance.

Keywords: *Ultrasound irradiation; Multicomponent reaction; Synthesis; Isocyanide; Highly congested pyrroles*

Introduction

Pyrrole is one of the most significant modest heterocycles, which is detected in a wide span of drug molecules and natural products, and is also of increasing connection in materials science. It was first separated from the bone pyrolysis products in 1857, and recognized as biologically relative when it was detected as a structural segment of chlorophyll and heme [1]. The present significance of pyrrole can be briefed in the parts that are described below. (a) The pyrrole nucleus is prevalent in nature, and, as formerly noted, is the key structural segment of chlorophyll and heme, two pigments necessary for life. Pyrrole sections are solely eminent in marine natural products, containing dimeric frames [2] and the axially chiral marinopyrroles [3]. (b) One important trait of natural and unnatural products including polypyrrole constructive segments is that they are almost interned in coordination and molecular diagnosis phenomena such as carrying of protons and chloride through phospholipid membranes [4]. (c) Pyrrole substructures are available in a great numeral of bioactive compositions containing HIV fusion inhibitors [5] and antitubercular compounds [6,7] among the others. (d) Pyrrole derivatives are various synthetic intermediates, and can be suited into many other heterocyclic structures [8]. (e) Pyrrole derivatives are solely significant in materials science such as semiconductors deduced from hexa (*N*-pirrolyl) benzene [9] glucose sensors based on polypyrrole-latex materials [10] and polypyrrole materials for the discovery and distinction of fugacious organic compounds [11], diagnosis, etc. [1,12].

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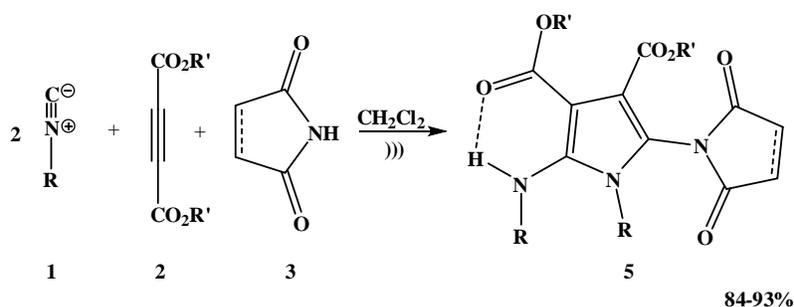
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Multicomponent reactions (MCRs) are usually described as reactions which more than two initial materials react to produce a product. Usually, there are three various feasible classification designs of MCRs relevant to reaction mechanism, components included, or inherent variability [13]. The expansion of novel MCRs is an attractive research matter in applied regions of medicinal, organic, and pharmaceutical chemistry [14]. MCRs have absorbed significant concern owing to their special synthetic proficiency. Hundreds of MCRs have lately been explained.

These reactions play an essential role in the synthesis of natural and unnatural products through their significance of pharmacological and therapeutic uses. Isocyanide-based multicomponent reactions (IMCRs) are especially as they are more diverse than other MCRs [15]. The large potential of isocyanides for the expansion of multicomponent reactions stands in the variety of bond forming procedures existing, functional group endurance, and the high levels of chemo-, regio-, and stereoselectivity often perceived. Furthermore, there are almost no limitations on the nature of the electrophiles and nucleophiles in IMCRs. MCRs including isocyanides have appeared as noteworthy tools for the synthesis of structurally versatile chemical libraries of drug-like heterocyclic compounds [16-19].

Ultrasound can speed up chemical reactions to purvey increased yields, reduced reaction times and improved selectivity, hence ultrasound irradiation has been considered as an effective technique in organic synthesis over the last two decades [20-26]. Usually, ultrasound acts by the event of cavitation; which includes the development, oscillation, and collapse of bubbles under the operation of an acoustic field. There are three several theories concerning cavitation: the hotspot, the plasma and electrical the plasma theory; and the most general one is the hot spot theory. It has been empirical shown that, the cavitation collapse makes harsh situations inward the medium for pressures up to 1800 atmosphere pressure a sorely short time and temperatures of 2000 K to 5000 K. Inward the collapsing cavity have been generated below sonic conditions [26,27]. The collapse generates a couple of strong physical results out of the bubble such as-shear forces, jets and shock waves. These effects can afford chemical, physical and biological changes effectively. Therefore, ultrasound has discovered applications in life sciences, synthetic chemistry, and materials science as well as in medicinal chemistry [28].

As part of our current studies on the chemistry of isocyanides [29-35] and in continuation of our research program to understanding the effect of ultrasound irradiation on isocyanide-based multicomponent reactions [36], here, we report an effective approach for the making of highly functionalized pyrroles through one-pot four-component reaction of isocyanide (1), dialkyl acetylene dicarboxylates (2) and five-membered cyclic imides such as succinimide or maleimide (3) to produce the desired products 5 in good yields (up to 93%) (SCHEME 1).



SCHEME 1. One-pot four-component synthesis of highly congested pyrrole derivatives 5 under ultrasound irradiation.

Results and Discussion

At the beginning of this work, we studied a diversity of ultrasound conditions with the sample reaction including cyclohexyl isocyanide (1a) (0.220 g, 2 mmol), dimethyl acetylene dicarboxylate (2a) and (0.142 g, 1.0 mmol) and succinimide (3a) (0.099 g, 1.0 mmol) in CH₂Cl₂ (15 mL) under ultrasonic irradiation to give the pyrrole product (5a). In order to consider the efficacy of ultrasound wave's frequency, the reaction was carried out in 5, 10, and 15 kHz respectively. When the frequency was 10 kHz, the yield of 5a (84%) (TABLE 1 entry 2) was better than that with 5 kHz within 90 min (52%, TABLE 1, entry 1). With enhance of ultrasound waves frequency from 10 to 15 kHz (TABLE 1, entries 2, 3), the reaction yield did not change a significant value (84% in the similar time). The consequences are shown that there is an optimum ultrasound wave's frequency for efficient synthesis of 5a in the 10 kHz.

TABLE 1. The synthesis of 5a under ultrasound irradiation in various frequencies.

Entry	Frequency (kHz)	Time (min)	Yield (%)
1	5	90	52
2	10	90	84
3	15	90	84

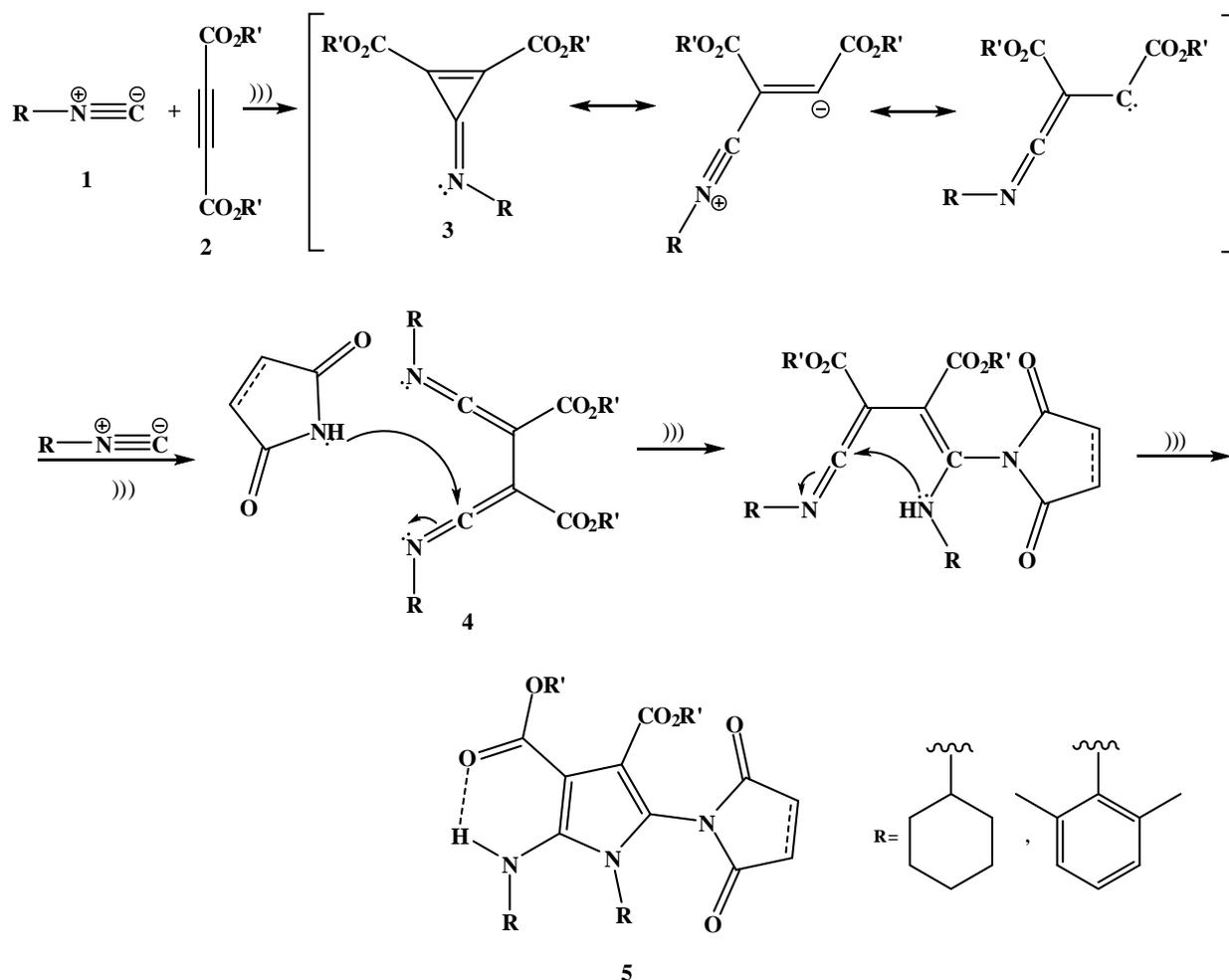
After detection, more effective frequency (10 kHz), to define the role of ultrasound, this approach was tested by the reaction of different initial materials (isocyanide (1), dialkyl acetylene dicarboxylates (2) and five-membered cyclic imides such as succinimide or maleimide (3)) in ultrasonic irradiation (TABLE 2). As is known, the affection of ultrasound on the reaction is that it can significantly shorten the reaction time and increase the yields compared with classical conditions. The equal result was also attended in our experiments. The yields of obtaining pyrroles 5 are explained in TABLE 2. All compounds 5a-f were characterized by their melting points and FT-IR spectra and compared with those reported in the literature.

TABLE 2. Comparison of the times and yields of the reactions with or without sonication for the synthesis of highly congested pyrrole derivatives.

Product	R	R'	Imide	Mp (°C) Found Reported		With sonication ^a		Without sonication ^b	
						Yield ^c (%)	Time(min)	Yield (%)	Time(h)
5 ^a	Cyclohexyl	Me	Succinimide	211-213	212-214	84	90	72	48
5 ^b	Cyclohexyl	Me	Maleimide	215-217	217-219	88	85	78	48
5 ^c	Cyclohexyl	Et	Succinimide	155-157	155-157	89	85	76	48
5 ^d	Cyclohexyl	Et	Maleimide	144-146	145-147	88	90	75	48
5 ^e	2,6-Dimethylphenyl	Me	Succinimide	255-257	255-257	93	80	84	48
5 ^f	2,6-Dimethylphenyl	Me	Maleimide	233-236	232-235	91	80	81	48

^a Reaction condition: Reaction of succinimide or maleimide (1), dialkyl acetylene dicarboxylates (2) and isocyanide (3) in CH_2Cl_2 under ultrasound irradiation. ^b Reaction condition: Reaction of succinimide or maleimide (1), dialkyl acetylene dicarboxylates (2) and isocyanide (3) in CH_2Cl_2 under reflux condition. ^c Yields of isolated products

However, we have not performed experimentally the mechanism of the reaction, an acceptable reaction sequence that accounts for the constitution of (5) is described in SCHEME 2. On the basis of the well-established chemistry of isocyanides [37,38], it is possible that the initial step is the formation of a reactive 1:1 intermediate from isocyanide (1) and dialkyl acetylene dicarboxylate (2) which is followed by further reaction with the isocyanide to generate the bis-ketenimine intermediate (4). The bis-ketenimine intermediate may then react with cyclic imide. Cyclization under the reaction conditions produces (5).



SCHEME 2. Proposed mechanism for the formation of highly congested pyrrole derivatives 5a-f under ultrasound irradiation.

The effect of ultrasound on yield was investigated. The pyrrole product (5a) (TABLE 2, entry 1) was obtained in 84% yield under sonication. It is apparent that the ultrasound can accelerate the nucleophilic attack of isocyanide and five-membered cyclic imides (SCHEME 2). The reason may be the phenomenon of cavitations produced by ultrasound. Cavitation was the

production of micro bubbles in a liquid when a large negative pressure was applied to it. In succeeding compression cycles can collapse violently with the release of large amounts of energy in and around these micro bubbles. The 'hot-spot' theory suggested that temperatures of up to 5000 K and pressures of several thousand atmospheres were produced during this collapse [39-41], which can cause reaction rapidly. Because cavitation induces very high local temperatures and pressure inside the bubbles (cavities), leading to a turbulent flow in the liquid and enhanced mass transfer [42-44]. It was the physical aspect of ultrasound which led starting materials to pervade faster in solvent and nucleophiles (isocyanide and imide) attack more efficiently to target species. Only taking advantage of ultrasound was the pyrrole derivative (5a) produced in good yield (84%) within a shorter time period (90 min).

All products described herein were previously prepared by classical methods [45]. As shown in TABLE 2 and SCHEME 1, the reaction of isocyanide (1), dialkyl acetylene dicarboxylates (2) and succinimide or maleimide (3), produces the pyrrole derivatives (5) in good yields (up to 93%). The ultrasound technique represented a better procedure in terms of the higher yield, milder reaction condition and easier workup. For example, compound (5a) was previously prepared in a moderate yield (72%), after standing 48 h in reflux conditions [46] whereas under ultra-sonication, (5a) was obtained in a 84% yield for 90 min (TABLE 2).

In Summary, under ultrasound irradiation; the reaction is fast and simple to execute and the products are isolated in good yields. The work-up is very simple. The reaction time is short (less than 90 min) and the products are obtained in good purity. To the best of our knowledge, this new approach provides the first example of an effective one-pot four-component method for the synthesis of highly congested pyrroles under ultrasound irradiation using isocyanides. This method, based on four-component free-catalyst reaction under ultrasonic irradiation, is the most simple and convenient and would be applicable for the synthesis of different types of highly functionalized pyrroles.

Experimental

Melting points were evaluated on an Electrothermal 9100 apparatus and are uncorrected. IR spectra were registered on a Jasco 6300 FTIR spectrometer. The chemicals used in this work were purchased from Merck (Germany) and Fluka (Switzerland) without further purification. TLC was used to follow the reactions. Sonication was performed in a Bandelin SONOPULS ultrasonic homogenizers (made in Germany) with 20 kHz processing frequency, a nominal power 250 W, uniform sonic waves.

Typical procedure for the synthesis of 1'-cyclohexyl-5-cyclohexylamino-2,5-dioxo-2,3,4,5-tetrahydro-1'H-[1,2']bipyrrolyl-3',4'-dicarboxylic acid dimethyl ester under ultrasound irradiation (5a)

The cyclohexyl isocyanide (0.220 g, 2.0 mmol) was added to a mixture of succinimide (0.099 g, 1.0 mmol) and dimethyl acetylene dicarboxylate (0.142 g, 1.0 mmol) in CH₂Cl₂ (15 mL) and the resulting mixture was sonicated for 90 min. The ultrasound wave's frequency in this experiment was kept on 10 kHz and the progress of the reaction was followed by TLC. After completion of the reaction as indicated by TLC, the solvent was removed under vacuum and the solid residue was washed with diethyl ether and crystallized from n-hexane-CH₂Cl₂ (4:1) to give cream crystals (84%). Mp 211°C to 213°C.

Conclusion

In conclusion, we have expanded a easy, one-pot four-component approach for the preparation of highly congested pyrrole derivatives in CH₂Cl₂ under ultrasound radiations. The method is simple, starts from simply available commercial starting materials, and prepares biologically interesting highly functionalized pyrroles in good yields.

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