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A facile and efficient ultrasound-assisted stereospecific synthesis of novel bicyclo-cyclopropanes

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ABSTRACT

The regispecific synthesis of pyrazolines has been accomplished through the 1,3-dipolar cycloaddition of 2-diazopropane to pyridazine-3,6-dione derivatives. A convenient and inexpensive ultrasound-assisted preparation of bicyclo-cyclopropanes in a completely stereoselective manner in almost quantitative yields has been realized. The highly stereoselective extrusion of nitrogen suggests a concerted mechanism.

1. Introduction

Ultrasonic energy can clean or homogenize materials, accelerate both physical and chemical reactions [1]. The utilization of ultrasound energy in organic chemistry has been better known from the 1970s [2]. The use of ultrasound in chemical reactions in solution provides specific activation based on a physical phenomenon: acoustic cavitation [3]. Cavitation induces very high local temperatures and pressure inside bubbles (cavities), leading to a turbulent flow in the liquid and enhanced mass transfer [4]. Pyridazinone derivatives have been reported to possess a wide variety of biological activities like antidiabetic [5], anticancer [6] anti-AIDS, antihypertensive [7], antimicrobial [8], fungicida [9], herbicida [10], antifeedant [11], antiplatelet [12], analgesic, anti-inflammatory [13] and anticonvulsant activities [14]. The cyclopropane ring is a main structural part in many synthetic and natural compounds that exhibit a wide range of biological activities from enzyme inhibition to antibiotic, herbicidal, antitumor, and antiviral properties [15]. Cyclopropane derivatives have shown potent HIV antiviral activities as non-nucleoside reverse transcriptase inhibitors [16]. Due to diversity of cyclopropane containing compounds with biological activity, chemists have tried to find novel and facile methods for synthesis of these compounds [17]. In this article, we describe the results obtained for the regiospecific synthesis of pyrazolines by 1,3-dipolar cycloaddition of 2-diazopropane with pyridazine-3,6-dione derivatives. To the best of our knowledge, there are no literature examples for synthesis of cyclopropanes by ultrasonication. Herein, we wish to report a facile sonochemical synthesis of cyclopropanes in EtOH.

2. Results and discussion

2.1. Synthesis of pyrazolines

We have also investigated the cycloaddition reaction of several pyridazine-3,6-diones **1a–d** [18] with 2-diazopropane **2** [19]. The 1,3-dipolar cycloaddition of 2-diazopropane is, in each case, regiospecific. Unambiguous proofs for the obtained cycloadducts regiochemistry arised from their spectral data. However, regiochemical assignments of

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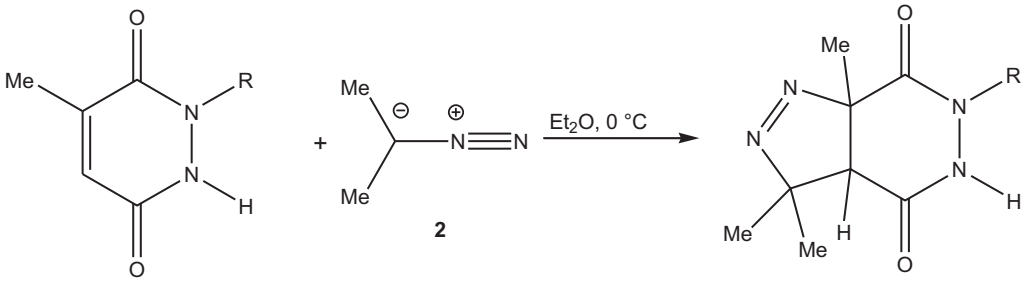
Table 1
Synthesis of pyrazolines via cycloaddition 1,3-dipolar.



1a-d

1a: R = Ph
1b: R = *p*-C_6H_4-CH_3
1c: R = *p*-C_6H_4-Cl
1d: R = Bn

3a-d

3a: R = Ph
3b: R = p-C_6H_4-CH_3
3c: R = *p*-C_6H_4-Cl
3d: R = Bn

Entry	R	Yield (%)	^{13}C NMR ($CDCl_3$) δ
3a	Ph	75	19.16 (CH_3), 21.61 (CH_3), 27.59 (CH_3), 49.99 (C-3a), 93.47 (C-3), 97.21 (C-6a)
3b	*p*-C_6H_4-CH_3	80	19.12 (CH_3), 21.13 (CH_3), 21.51 (CH_3), 27.55 (CH_3), 49.96 (C-3a), 93.45 (C-3), 97.17 (C-6a).
3c	*p*-C_6H_4-Cl	65	19.17 (CH_3), 21.52 (CH_3), 27.34 (CH_3), 50.02 (C-3a), 93.43 (C-3), 97.01 (C-6a)
3d	Bn	85	19.20 (CH_3), 21.51 (CH_3), 27.31 (CH_3), 50.01 (C-3a), 50.72 (CH_2Ar), 93.41 (C-3), 96.91 (C-6a)

all adduct were deduced from their ^{13}C-NMR spectra. Particularly the chemical shifts of C-6a (97.01–97.21 ppm) are in excellent agreement with those usually obtained when this quaternary carbon is attached to an oxygen atom (Table 1) [20].

2.2. Formation of cyclopropanes

The photolysis of an ethereal solution of the pyrazolines **3a–d** through pyrex with a high pressure mercury arc lamp at 0–5 °C led to exclusive formation of bicyclo-cyclopropanes **4a–d**.

As shown in Table 2, pyrazoline derivatives **3a–d** were sonicated in EtOH in an ultrasonic cleaning bath afforded *gem*-dimeylcyclopropanes **4a–d**.

The results were summarized in Table 2. Firstly, it can easily be seen that the irradiation of pyrazolines was carried out in good yield in ethanol under ultrasound irradiation (30 kHz, 150 W) within 15 min. The results show that the method to obtain bicyclo-cyclopropanes **4a–d** under ultrasonic irradiation from pyrazoline derivatives **3a–d** offers several significant advantages including faster reaction rates, higher purity, and higher yields. In comparison with conventional methods, the main advantage of ultrasound application is the significant decrease in the reaction times and milder experimental conditions. Thus, while the conventional method requires 35–45 min, ultrasonic irradiation affords the respective products in only 15–20 min (Table 2). These results support the idea that the energy provided by ultrasound significantly accelerates these reactions. The difference in yields and reaction times may be a consequence of the specific effects of ultrasound, in particular, cavitation, a physical process that creates, enlarges, and implodes gaseous and vaporous cavities in an irradiated liquid, thus enhancing the mass transfer [21] and allowing chemical reactions to occur. The creation of the so-called hot spots in the reaction mixture produces intense local temperatures and high pressures generated inside the cavitation bubble and at its interfaces when it collapses. In order to gauge the effect of different irradiation frequencies, the model reaction was performed under three different frequencies of 30, 40 and 50 kHz. The cyclopropane **4a** yield for these frequencies was 95, 80 and 65% respectively. It seems that the lower frequency of ultrasound irradiation can improve the yield of cyclopropane derivatives.

Secondly, using the formation of 1,7,7-trimethyl-3-phenyl-3,4-diazabicyclo[4.1.0]heptane-2,5-dione **4a** as a standard reaction, pyrazolines was sonicated under various sets of conditions in order to obtain optimal irradiation power conditions at a constant room temperature of 25 ± 1 °C and constant frequency 30 kHz (Table 3). By increasing the irradiation power from 100 to 200 W, the reaction time of **4a** decreased from 30 to 10 min and the yield increased from 70 to 95%. The reaction time and yield of **4a** did not change from 200 to 250 W, therefore, 200 W of ultrasonic irradiation was sufficient to push the reaction forward. The best yield for **4a** was obtained by ultrasonic irradiation for 10 min at room temperature and 200 W.

Under stationary irradiations, pyrazolines **3a–d** afforded the corresponding cyclopropanes **4a–d** with total stereospecificity [22]. The stereochemistry of this ultrasonic product was determined from a NOESY spectrum. The *cis* relation ship existing between the Me groups and the proton H-6 in compounds **4a** could be deduced from observation of an NOE effect between H-6 and the methyl protons (Fig. 1).

Whereas a diradical mechanistic pathway has been proposed by several groups [23] to explain the highly stereoselective evolution of pyrazolines under photolytic