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# Ultrasound promoted synthesis of 5-hydroxy-5-trihalomethyl-4,5-dihydroisoxazoles and β-enamino trihalomethyl ketones in water

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**Abstract**

A convenient method for the preparation of 5-hydroxy-5-trihalo-4,5-dihydroisoxazoles and β-enamino trihalomethyl ketones, from the reaction of 1,1,1-trihalo-4-alkoxy-3-alken-2-ones with hydroxylamine and anilines, respectively, using water as solvent and under ultrasound irradiation is reported.


*Keywords:* Enones; Isoxazoles; Enaminones; Water; Ultrasound

## 1. Introduction

Isoxazoles and enaminones derivatives, containing trihalomethyl groups are useful intermediates in organic synthesis [1], e.g., isoxazoles have been used for the synthesis of fungicides [1a,2] and enaminones as versatile synthetic intermediates in the preparation of antimalarial trifluoromethyl quinolines [3,4]. β-Enamino trihalomethyl ketones are commonly prepared from β-alkoxy trihalomethyl ketones [5] or acetylenes [3]. The synthesis of isoxazoles through route [3 + 2] uses, in general, 1,3-diketones derivatives as the CCC block, and the hydroxylamine as the NO block [6]. In the course of our extensive investigations of synthesis of heterocycles, we have developed a general synthesis of a large number of 1,1,1-trihalo-4-alkoxy-3-alken-2-ones [7,8], important halogen-containing building blocks, and demonstrated their usefulness in heterocyclic preparations, e.g. isoxazoles [8,9], pyrazolines [7d,8,10,11], pyrazoles [8,11,12], pyrazolium chlorides [13], pyrrolidinones [14], pyrimidines and pyrimidinones [15], pyridines [16], thiazines [17], diazepines [18], thiazolo pyrimidinones [19] and selenazoles [20] has been described.

Spiegler and Götz [1a] reported the first work which showed the synthesis of 5-hydroxy-5-trichloromethyl-4,5-dihydroisoxazoles from the reaction of 4-ethoxy-1,1,1-trichloro-3-buten-2-one with hydroxylamine hydrochloride, in water at room temperature, with a reaction time of 24 h. However, this reaction was an isolated result using only one substrate and did not demonstrate the real scope of the reaction. Since 1991 the scope of this reaction has been extended in our laboratory with the publication of a series of papers about the synthesis of 5-hydroxy-5-trichloromethyl-4,5-dihydroisoxazoles using *conventional methods*, where, the general procedure involves the reaction of 4-alkoxy-1,1,1-trihalo-3-alken-2-ones with a saturated aqueous solution of hydroxylamine hydrochloride, in a mixture of water and pyridine at 35–70 °C, with a range of reaction times

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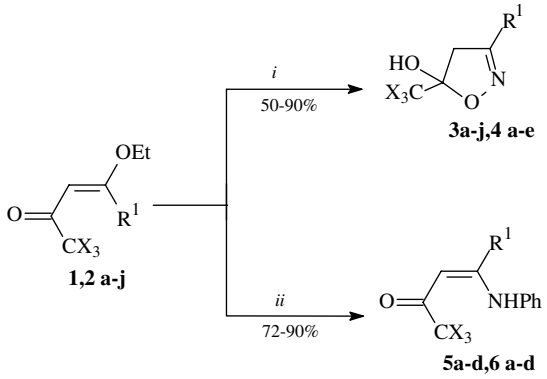
between 8 and 16 h [7a,8,10]. In our research program there is an interest to improve the methodologies for the construction of heterocyclic systems containing trihalomethyl groups, thus, we are investigating alternative methods for the preparation these compounds.

The chemical applications of ultrasound, 'sonochemistry', have become an exciting field of research during the last years. Scientists know that the chemical effects of ultrasound are diverse and include substantial improvements in both stoichiometric and catalytic chemical reactions. In some cases, ultrasonic irradiation can increase reactivities by nearly a millionfold. Thus, ultrasound has been utilized to accelerate a number of synthetically useful reactions [21,22]. Many of the observed effects are due to cavitations [21]. The formation, growth and collapse of bubbles in an irradiated liquid with consequent high local temperatures and pressures. To understand the cavitations phenomena remember that the compression of a gas generates heat. On a macroscopic scale, one can feel this when pumping a bicycle tire; the mechanical energy of pumping is converted into heat as the tire is pressurized. The compression of cavities when they implode in irradiated liquids is so rapid than little heat can escape from the cavity during collapse. The surrounding liquid, however, is still cold and will quickly quench the heated cavity. Thus, one generates a short-lived, localized hot spot in an otherwise cold liquid. Such a hot spot is the source of homogeneous sonochemistry; it has a temperature of roughly 5000 °C, a pressure of about 1000 atmospheres, a lifetime considerably less than a microsecond, and heating and cooling rates above 10 billion °C per second. Thus, cavitation serves as a means of concentrating the diffuse energy of sound into a chemically useful form [23].

The use of sonochemical methods in organic synthesis are increasingly interested in the last years, as demonstrated in Suzuki cross-coupling in ionic liquid [24], organometallic reactions, metal-catalyzed hydrogenation, phase transfer, generation of free radicals, polymer synthesis and reactions in aqueous solution [25]. The use of ultrasound in heterocycles system is not very much explored. Soufiaoui et al. reported the synthesis of the isoxazolines, with addition of the catalyst $Ca(OCl_2)$ or NaOCl [26]. In recent paper Ji-Tai Li et al., reported a Biginelli reaction-type to synthesize the 3,4-dihydropyrimidin-2-ones catalyzed by $NH_2SO_3H$ and sonocation [27]. On the other hand, organic reactions in aqueous media, is a chemical processes that has undergone 20 years. Breslow in 1980 [28], demonstrated that Diels-Alder reactions can give high *endo*/*exo* selectivity. Since then, many other reactions were studied in this medium, e.g. hetero Diels-Alder, Barbier-Grinard, Reformatsky, the Claisen rearrangement, reduction, and oxidation reactions [29]. Furthermore, the transformations of organic compounds in superheated water at elevated pressures, including in heterocyclic systems, pyridines, pyrroles, thiophenes and heterocycles with




| X | |
|---|---|
| F | **1,3,5** |
| Cl | **2,4,6** |

| **1 – 6** | **a** | **b** | **c** | **d** | **e** | **f** | **g** | **h** | **i** | **j** |
|---|---|---|---|---|---|---|---|---|---|---|
| $R^1$ | H | Me | Et | *n*-Pr | *iso*-Bu | *tert*-Bu | *n*-Pentyl | *iso*-Pentyl | *n*-Hex 1 | Ph |

*Reagents and Conditions:* y

*i* = $NH_2OH \cdot HCl$ and Py, $H_2O$, ultrasound, 30 min, 45°C

*ii* = $NH_2Ph$, $H_2O$, ultrasound 15-20 min, 45°C

Scheme 1.