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Ultrasonic-assisted Synthetic Improvement of Fluorinated Five- and Six-membered Triazolotriazine and Triazinophthalazine Heterocycles

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In this investigation a simple synthetic method for the synthesis of trifluoromethyl-1H-benzo[e][1,2,4]triazolo[1,2-a][1,2,4]triazine-1,3(2H)-diones and (trifluoromethyl)benzo [5,6][1,2,4]triazino[1,2-b]phthalazine-8,13-diones has been developed using urazole or phthalazine and aceteimidoyl chloride derivatives at room temperature under ultrasound irradiations. In the comparison to the conventional method the ultrasound irradiation increased the yield and the reactions times decreased considerably.

Keywords: Ultrasound irradiation, Trifluoroacetimidoyl chloride, Urazole, Phthalazine

INTRODUCTION

Ultrasonic-assisted chemical synthesis as a modern and environmentally synthetic pathway is an advantage tools that is being attracted more and more to accelerate organic reactions [1]. Thus, a large groups of organic synthesis can be carried out under ultrasonic irradiation in short reaction times, mild conditions and high yields [2-4] and it is considered as a processing aid in terms of energy conservation and waste minimization [5]. Ultrasound irradiation, is an effective and safe technique for reagent activation in the synthesis of heterocyclic compounds, which results to the several important advantage such as shorter reaction times and higher yields. This method has been considered as a clean and useful technique in organic synthesis compared to conventional methods, and the procedure is, generally, more comfortable [6].

Ultrasound-assisted organic synthesis is a green methodology which is used for a large number of organic synthetic pathways and has significant advantages such as high efficiency, low waste, low energy requirements and short reaction time. Sonochemistry (in the region of 20 kHz to 1 MHz) has various applications because of its high energy and the ability to disperse reagent in small particles and accelerate reactions.

Urazoles are attractive heterocyclic compounds and have potential pharmaceutical applications and valuable utilities in the area of protein modification chemistry because of the simplicity of chemical synthesis and ease of optimization of reaction conditions [7-9]. Also compounds contain phthalazine skeleton show a continuous range of effects, from being positive allosteric modulators that enhance inhibition exhibiting anxiolytic, anticonvulsant, sedative-hypnotic and myorelaxant activities [10]. Also phethalazine derivatives are important 1,2-N,N-binucleophiles for synthesis of indazolophthalazinetrione heterocycles *via* three-component coupling reactions [11, 12].

In addition to, trifluoromethylated heterocyclic compounds are one the most attractive groups of organofluoro compounds. Trifluoromethyl group is a subject of current attractive in both organic synthesis and biochemistry [13-16]. In continuation of our research program focused on the synthesis and the reactivity study of fluoromethylated derivatives prepared from acetimidoyl chloride derivatives [17-21], in this study in order to decreasing of reaction time and improving yield we have developed the new methodology for the synthesis of (trifluoromethyl)-1H-benzo[e][1,2,4]triazolo[1,2-a][1,2,4] triazine-1,3(2H)-diones and (trifluoromethyl)benzo[5,6][1,

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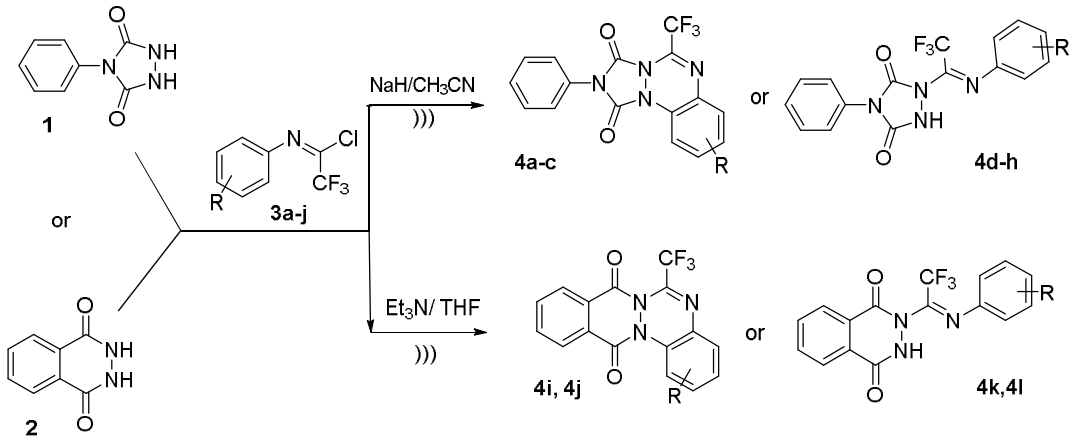


Scheme 1. Reactions of imidoyl chloride derivatives with urazole and phthalazine under ultrasound irradiation

2,4]triazino [1,2-b]phthalazine-8,13-diones under ultrasound irradiation (Scheme 1).

However, in past report, the existence of some drawbacks such as long reaction times, harsh conditions, high temperature have been mentioned [22]. due to the potential pharmaceutical applications and valuable utilities of (trifluoromethyl)-1H-benzotriazolotriazine-diones and (trifluoromethyl)benzotriazinophthalazine diones in the area of protein modification chemistry we decided to synthesis of the these heterocycles under ultrasound irradiation. Clean reactions, excellent yields and short reaction times are some remarkable features of this method.

EXPERIMENTAL

Apparatus

A multiwave ultrasonic generator (Bandlin Sonopuls Gerate-Typ: UW 3200, Germany) equipped with a converter/transducer and titanium oscillator (horn), 12.5 mm in diameter, operating at 45 kHz with a maximum power output of 780 W, was used for the ultrasonic irradiation. The ultrasonic generator automatically adjusted the power level. Melting points were determined on a Melt-Tem II melting point apparatus and are uncorrected. Mass spectra were recorded on an Agillent, 6410 QQQ, LC mass spectrometer (direct injection). Element analyses (CHN) were performed with a EUROVECTOR EuroEA3000 CHNSO analyzer. NMR spectra were recorded on a Bruker model DRX-400 or 300 AVANCE spectrometer (400 MHz) with TMS as internal standard. IR spectra were obtained on a Thermo scientific, Nicolet is10 FT-IR spectrometer.

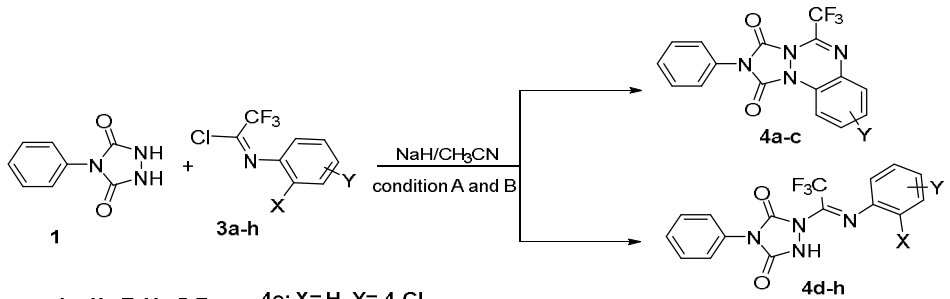
General procedure for the synthesis of 4a-h compounds. To a solution of the urazole 1 (1 mmol), sodium hydride (2 mmol) in dry acetonitrile (5 ml) was added a solution of aceteimidoyl chloride derivative 3 (1 mmol) in dry acetonitrile (5 ml). The reaction mixture was irradiated with ultrasound for 45-60 min. After completion of the reaction, as indicated by TLC, the solvent was evaporated at reduced pressure; a precipitate formed was washed with n-hexane and was recrystallized from 95% ethanol for compounds 4a-c or was purified by plate chromatography on silica gel (n-Hexane/ethyl acetate 6:2) for compounds 4d-h.

General procedure for the synthesis of 4i-4l compounds. To a solution of the 2,3-dihydrophthalazine-1, 4-dione 2 (1 mmol), Et_3N (3 mmol) and THF (5 ml) was added a solution of aceteimidoyle chloride derivatives 3 (1 mmol) in THF (5 ml). This reaction mixture was sonicated. The progress of the reaction was monitored by TLC. After completion of the reaction, the solvent was evaporated under reduced pressure and the resulting crude product was purified by plate chromatography on silica gel using hexane-ethyl acetate (6:2), producing the desired products 4i-l, in 80-95% yield.

RESULTS AND DISCUSSION

Our researches were focused on the synthesis of

Table 1. Synthesis of Trifluoromethyl-1H-benzo[e][1,2,4]triazolo[1,2-a][1,2,4]triazine-1,3(2H)-diones Under Ultrasound Irradiation 4a-c and Compounds 4d-h[a]



4a: X= F, Y= 5-F
4b: X= F, Y= 4-F
4c: X=F, Y= H
4d: X= Br, Y= H
4e: X= H, Y= 4-Cl
4f: X=H, Y= 3-CF_3
4g: X= H, Y= 4-CH_3
4h: X= CH_3, Y=4-CH_3

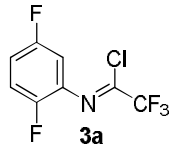
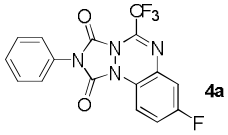
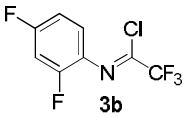
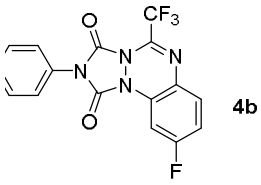
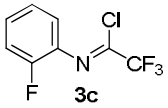
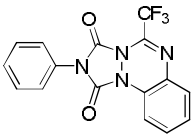
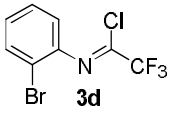
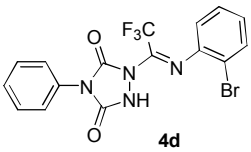
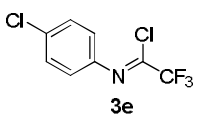
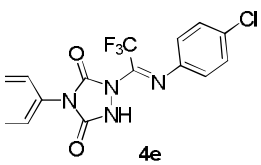
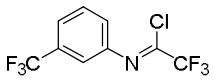
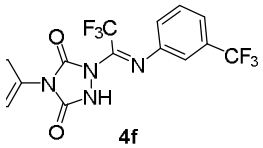
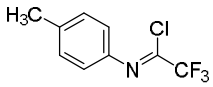
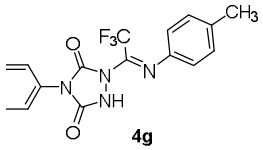
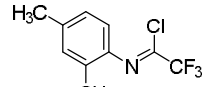
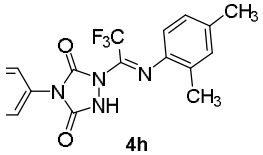
Entry	acetimidoyl chloride derivatives	Products	Condition A Reflux [20]		Condition B Ultrasonic	
			Time (h)	Yield (%)	Time (min)	Yield (%)
1	 **3a**	 **4a**	8	92	45	95
2	 **3b**	 **4b**	8	92	45	95
3	 **3c**	 **4c**	9	88	45	92
4	 **3d**	 **4d**	12	78	60	85
5	 **3e**	 **4e**	12	80	60	87

Table 1. Continued

6	 **3f**	 **4f**	12	85	60	90
7	 **3g**	 **4g**	14	80	60	87
8	 **3h**	 **4h**	13	80	60	87

[a]Reactions conditions: urazole (1 mmol), sodium hydride (2 mmol) in dry acetonitrile (5 ml), aceteimidoyl chloride derivative (1 mmol) in dry acetonitrile (5 ml).

trifluoromethylated heterocyclics under a convenient and easy methods [17-22]. In our studies to find a new method for carried out reactions in clean conditions for a shorter time and higher yields, the effect of ultrasound irradiation in accelerating the reactions drew our attention. Ultrasound irradiation has been established as a significant technique in synthetic organic chemistry, because it has been applied as an efficient energy and heating source for organic reactions [23,24].

After finding suitable conditions for the synthesis of (trifluoromethyl)-1H benzo[e][1,2,4]triazolo[1,2-a][1,2,4] triazine-1,3(2H)-diones and (trifluoromethyl)benzo[5,6][1, 2,4]triazino[1,2-b]phthalazine-8,13-diones in the previous work [20], we have developed reaction under ultrasound irradiation. This method was examined by the reaction of urazole and several acetimidoyle chlorides [25-27] 3a-h in the presence of NaH in CH_3CN solvent under ultrasound irradiation and at the reflux conditions (Table 1).

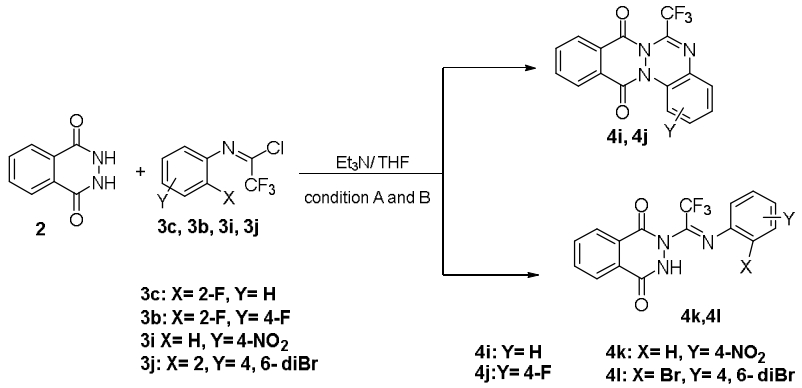
Also for developing this synthetic methodology, we examined the reaction of phthalazine and some aceteimidoyl chloride derivatives in the presence of Et_3N in THF under ultrasonic irradiation at ambient temperature (Table 2). As shown in Tables 1 and 2, in the event that the reactions were carried out under conventional method, the times is longer and the reaction yields is lower. While when the same reactions were performed in the influence of ultrasonic conditions gave higher yields in shorter reaction times. Generally, the similar effect was seen in all reactions and it was apparent that ultrasound irradiation can accelerate the reaction significantly to reduce the times with high yields. We found that ultrasonic irradiation was very effective and useful in our work, because the products could be synthesized in short time with excellent yields.

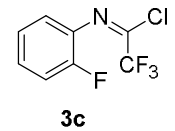
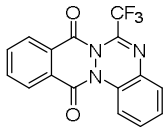
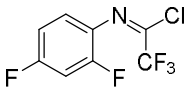
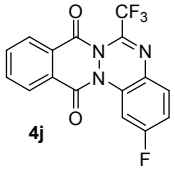
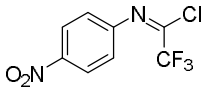
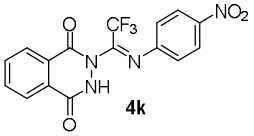
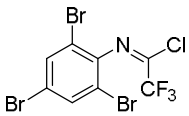
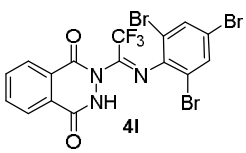
Based on the results of this study, it seems that the ultrasound irradiation improves the reaction time and yield in clean conditions. For more examination of the influence of ultrasound irradiation in this transformation, comparison of the reaction by two methods, reflux conditions and ultrasound irradiation at ambient temperature was preformed (Tables 1 and 2). Using ultrasound irradiation in comparison with reflux conditions is better in both yield and especially in the reaction times. The high yield transformations were carried out without any significant amounts of undesirable byproducts. All the products were characterized by NMR, IR and elemental analyses [20].

CONCLUSIONS

It the result we presented an easy and simple procedure for the synthesis of (trifluoromethyl)-1H-benzo

Table 2. Synthesis of (Trifluoromethyl)benzo[5,6][1,2,4] triazino[1,2-b]phthalazine-8,13-diones Under Ultrasound Irradiation 4i, 4j and Compounds 4k,4l[a]



Entry	Aceteimidoyl chloride derivatives	Products	Condition A Reflux [20]		Condition B Ultrasonic	
			Time (h)	Yield (%)	Time (min)	Yield (%)
1	 3c	 4i	10	88	50	92
2	 3b	 4j	9	90	50	95
3	 3i	 4k	12	76	60	80
4	 3j	 4l	12	80	60	85

[a]Reaction conditions: 2,3-dihydrophthalazine-1,4-dione (1 mmol), Et_3N (3 mmol) and THF (5 ml) was added a solution of aceteimidoyle chloride derivatives (1 mmol) in THF (5 ml).

[e][1,2,4]triazolo[1,2-a][1,2,4]triazine-1,3(2H)-diones and (trifluoromethyl) benzo[5,6][1,2,4]triazino[1,2-b]phthalazine-8,13-diones derivatives using ultrasound irradiation. Besides using a small amount of solvents, shorter reaction times, clean reaction and excellent yield are other advantage of this method.

ACKNOWLEDGMENTS

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