



Full paper/Mémoire

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

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ABSTRACT

The regiospecific 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.

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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

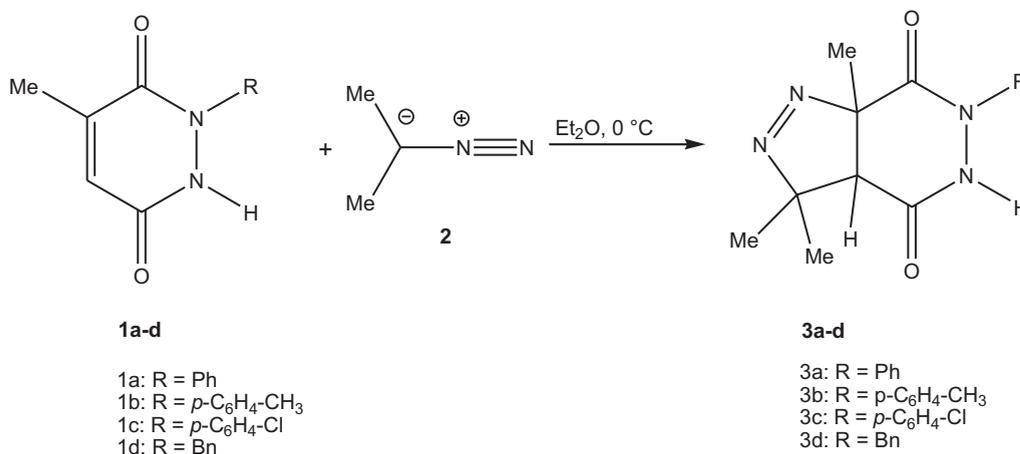
2.1. Synthesis of pyrazolines

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.



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	<i>p</i> -C ₆ H 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	<i>p</i> -C ₆ H 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 ₂ Ar), 93.41 (C-3), 96.91 (C-6a)

all adduct were deduced from their ¹³C-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*-dimethylcyclopropanes **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

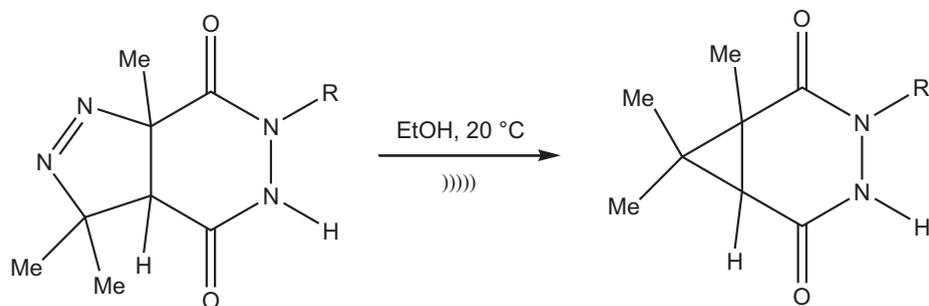
transfer [21] and allowing chemical reactions to occur. The creation of the so-called hot spots in the reaction mixture produces intense local temperatures and high pressures generated inside the cavitation bubble and at its interfaces when it collapses. In order to gauge the effect of different irradiation 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 were 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* relationship 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

Table 2
Synthesis of cyclopropanes under ultrasonication (25 °C, 30 kHz and 150 W).

**3a-d**

3a: R = Ph
3b: R = *p*-C₆H₄-CH₃
3c: R = *p*-C₆H₄-Cl
3d: R = Bn

4a-d

4a: R = Ph
4b: R = *p*-C₆H₄-CH₃
4c: R = *p*-C₆H₄-Cl
4d: R = Bn

Entry	R	Reaction time (min)		Yield (%)		M.P. (°C)
		Photolysis	Ultrasound	Photolysis	Ultrasound	
4a	Ph	45	15	35	95	112
4b	<i>p</i> -C ₆ H ₄ -CH ₃	40	20	45	90	143
4c	<i>p</i> -C ₆ H ₄ -Cl	35	15	40	85	127
4d	Bn	45	20	50	75	129

Table 3
Influence of the reaction intensity.

Entry	R	Reaction time and yield			
		100 W	150 W	200 W	250 W
4a	Ph	30 min/70%	15 min/95%	10 min/95%	10 min/95%
4b	<i>p</i> -C ₆ H ₄ -CH ₃	30 min/65%	20 min/90%	15 min/90%	15 min/90%
4c	<i>p</i> -C ₆ H ₄ -Cl	25 min/75%	15 min/85%	10 min/85%	10 min/85%
4d	Bn	25 min/60%	20 min/75%	10 min/75%	10 min/75%

conditions, the course of the thermal decomposition of pyrazolines into cyclopropanes still remains controversial. Indeed, the hitherto reported stereochemical results from thermal decomposition of 1-pyrazolines are quite divergent and strongly dependent on the nature of the substituents at the ring. Concerted [24] or diradical [25] mechanisms have been postulated to explain the most usual pyrolytic processes proceeding without stereoselectivity. Bearing in

mind the electron-withdrawing groups existing at the pyrazoline rings reported herein, our stereochemical results are consistent with the concerted thermal decomposition proposed by José et al. [26] of pyrazoline derivatives, which afford cyclopropanes by extrusion of nitrogen through a polar transition state, where the degree of bond breaking of the C(3a)-N bond is advanced over the bond breaking of the C(7)-N bond (Fig. 2).

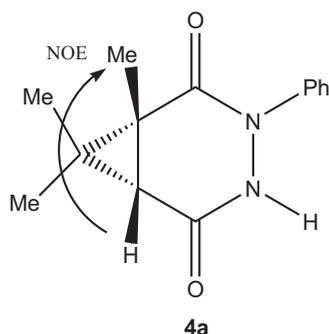


Fig. 1. NOE interaction between H-6 and the Me protons.

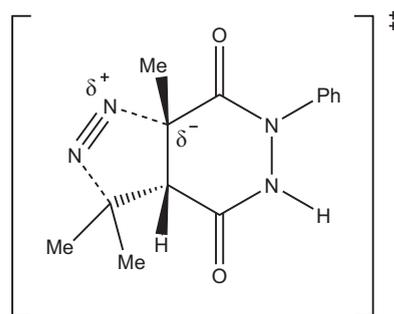


Fig. 2. Proposed transition states for the concerted nitrogen extrusion under ultrasonic conditions.

3. Conclusion

In this article, a new methodology to obtain functionalized bicycle-cyclopropanes under ultrasound irradiation has been used. The present procedure under ultrasound irradiation at room temperature significantly improved conventional methods, giving way to obvious advantages including simple operation, high yields, short reaction times and decreased toxicity.

4. Experimental

4.1. Apparatus and analysis

IR spectra were recorded on a Perkin-Elmer IR-197 spectrometer. NMR spectra were obtained on a Bruker AC 300 spectrometer operating at 300 MHz for ^1H and at 75.64 MHz for ^{13}C . Melting points were determined on a Buchi-510 capillary melting point apparatus. Coupling constants are given in Hz. Elemental analyses were performed on a PERKIN-ELMER 240B microanalyzer. Ultrasonication was performed in a GEX750-5 C ultrasonic processor equipped with a 3 mm wide and 140 mm long probe that was immersed directly into the reaction mixture. The operating frequency was 30–50 kHz and the output power was 0–750 W through manual adjustment. The temperature was controlled by a Buchi B-491 water bath at $25 \pm 1^\circ\text{C}$. All reagents were of commercial quality or purified by standard procedures.

4.2. General procedure for trapping of 2-diazopropane 2 with pyridazine-3,6-diones 1a–d

4.2.1. 1,3-dipolar cycloaddition of 2-diazopropane with pyridazine-3,6-diones 1a–d

To a solution of pyridazine-3,6-diones **1a–d** (1.0 mmol) in diethyl ether, cooled at 0°C , was added portionwise 2.6 M ethereal solution of 2-diazopropane. The reaction was kept at the same temperature during 1 h. the solvent was removed in a vacuum without heating to give brown oil, which was subjected to column chromatography (SiO_2 ; ethyl acetate/petroleum ether, 2:1) to afford compounds **3a–d**.

3,3,7a-trimethyl-6-phenyl-3a,5,6,7a-tetrahydro-3H-pyrazolo[3,4-d]pyridazine-4,7-dione **3a**

Anal. Calcd. For $\text{C}_{14}\text{H}_{16}\text{N}_4\text{O}_2$: C, 61.75; H, 5.92; N, 20.58%; Found: C, 62.00; H, 5.83; N, 20.50%; IR (KBr) $\nu_{\text{cm}^{-1}}$: 1640 (N=N); 1690 (C=O); 1700 (C=O); $^1\text{H-NMR}$ (300 MHz, CDCl_3) δ : 1.28 (s, 6H, CH_3), 1.75 (s, 3H, CH_3), 2.51 (s, 1H, 3a-H), 6.27 (s, 1H, NH), 6.55–7.20 (m, 5H, H_{arom}); $^{13}\text{C}\{^1\text{H}\}\text{NMR}$ (75 MHz, CDCl_3) δ : 19.16 (CH_3), 21.61 (CH_3), 27.59 (CH_3), 49.99 (C-3a), 93.47 (C-3), 97.21 (C-6a), 113.45–143.60 (C_{arom}), 169.67, 170.38 (C-4,C-7).

3,3,7a-trimethyl-6-(4-methylphenyl)-3a,5,6,7a-tetrahydro-3H-pyrazolo[3,4-d]pyridazine-4,7-dione **3b**

Anal. Calcd. For $\text{C}_{15}\text{H}_{18}\text{N}_4\text{O}_2$: C, 62.92; H, 6.34; N, 19.57%; Found: C, 62.87; H, 6.24; N, 19.45%; IR (KBr) $\nu_{\text{cm}^{-1}}$: 1645 (N=N); 1695 (C=O); 1700 (C=O); $^1\text{H-NMR}$ (300 MHz, CDCl_3) δ : 1.25 (s, 6H, CH_3), 1.25 (s, 6H, CH_3), 1.72 (s, 3H, CH_3), 2.31 (s, 3H, CH_3), 2.49 (s, 1H, 3a-H), 6.29 (s, 1H, NH), 6.85 and 7.08 (d, 4H, H_{arom} , $J=8.1\text{ Hz}$);

$^{13}\text{C}\{^1\text{H}\}\text{NMR}$ (75 MHz, CDCl_3) δ : 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), 128.9–136.9 (C_{arom}), 169.63, 170.21 (C-4,C-7).

6-(4-chlorophenyl)-3,3,7a-trimethyl-3a,5,6,7a-tetrahydro-3H-pyrazolo[3,4-d]pyridazine-4,7-dione **3c**

Anal. Calcd. For $\text{C}_{14}\text{H}_{15}\text{ClN}_4\text{O}_2$: C, 54.82; H, 4.93; N, 18.26%; Found: C, 54.73; H, 4.97; N, 18.38%; IR (KBr) $\nu_{\text{cm}^{-1}}$: 1640 (N=N); 1690 (C=O); 1705 (C=O); $^1\text{H-NMR}$ (300 MHz, CDCl_3) δ : 1.22 (s, 6H, CH_3), 1.64 (s, 3H, CH_3), 2.47 (s, 1H, 3a-H), 6.34 (s, 1H, NH), 6.69 and 7.13 (d, 2H, H_{arom} , $J=8.4\text{ Hz}$); $^{13}\text{C}\{^1\text{H}\}\text{NMR}$ (75 MHz, CDCl_3) δ : 19.17 (CH_3), 21.52 (CH_3), 27.34 (CH_3), 50.02 (C-3a), 93.43 (C-3), 97.01 (C-6a), 118.13–153.51 (C_{arom}), 168.97, 171.08 (C-4,C-7).

6-benzyl-3,3,7a-trimethyl-3,3a,5,6-tetrahydro-7aH-pyrazolo[3,4-d]pyridazine-4,7-dione **3d**

Anal. Calcd. For $\text{C}_{15}\text{H}_{18}\text{N}_4\text{O}_2$: C, 62.92; H, 6.34; N, 19.57%; Found: C, 62.98; H, 6.26; N, 19.61%; IR (KBr) $\nu_{\text{cm}^{-1}}$: 1640 (N=N); 1690 (C=O); 1700 (C=O); $^1\text{H-NMR}$ (300 MHz, CDCl_3) δ : 1.21 (s, 6H, CH_3), 1.62 (s, 3H, CH_3), 2.48 (s, 1H, 3a-H), 5.12 (s, 2H, CH_2Ar), 6.39 (s, 1H, NH), 7.26–7.35 (m, 5H, H_{arom}); $^{13}\text{C}\{^1\text{H}\}\text{NMR}$ (75 MHz, CDCl_3) δ : 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), 117.12–141.51 (C_{arom}), 167.99, 170.88 (C-4,C-7).

4.2.2. General procedure for the irradiation of the pyrazolines 3a–d

4.2.2.1. *Photolysis irradiation of pyrazolines 3a–d*. All irradiation were carried out using similar conditions. Irradiation of an ethereal solution of the pyrazolines through pyrex with a high pressure mercury arc lamp (Philips HPK 125 W) at 0 – 5°C led to exclusive formation of *gem*-dimethylcyclopropanes. The derivative was dissolved in ether (pretreated by stirring with solid $[\text{NaCO}_3]$, filtering and flushing with argon) and irradiation at 5°C for a total of 1 h or until the starting material was consumed (TLC). After this period, the solvent was removed in a vacuum without heating to give brown oil, which was subjected to rapid silica filtration. The recovered solid was subjected to a recrystallization treatment from dichloromethane/light petroleum.

4.2.2.2. *Ultrasound irradiation of pyrazolines 3a–d*. The appropriate pyrazolines **3a–d** (1 mmol) was dissolved in ethanol (5 mL). The reaction was irradiated in the water bath of the ultrasonic cleaner at 25°C . The specific period employed is listed in Table 1. The solvent was evaporated under reduced pressure. The further purification was accomplished by column chromatography on silica (200–300 mesh, eluted with petroleum ether or a mixture of petroleum ether and diethyl ether).

1,7,7-trimethyl-3-phenyl-3,4-diazabicyclo[4.1.0]heptane-2,5-dione **4a**

Anal. Calcd. For $\text{C}_{14}\text{H}_{16}\text{N}_2\text{O}_2$: C, 68.83; H, 6.60; N, 11.47%; Found: C, 68.80; H, 6.55; N, 11.41%; IR (KBr) $\nu_{\text{cm}^{-1}}$: 1700 (C=O); 1710 (C=O); $^1\text{H-NMR}$ (300 MHz, CDCl_3) δ : 1.24 (s, 3H, CH_3), 1.28 (s, 3H, CH_3), 1.55 (s, 3H, CH_3), 2.16 (s, 1H, 6-H), 6.76–7.26 (m, 6H, H_{arom} , NH); $^{13}\text{C}\{^1\text{H}\}\text{NMR}$ (75 MHz, CDCl_3) δ : 10.31 (CH_3), 17.31 (CH_3), 22.91 (CH_3), 34.96 (C-7), 35.51 (C-6), 38.05 (C-1), 113.78–145.63 (C_{arom}), 172.48, 175.41 (C-2, C-5).

1,7,7-trimethyl-3-(4-methylphenyl)-3,4-diazabicyclo[4.1.0]heptane-2,5-dione **4b**

Anal. Calcd. For $C_{15}H_{18}N_2O_2$: C, 69.74; H, 7.02; N, 10.84%; Found: C, 69.69; H, 7.05; N, 10.76%; IR (KBr) $\nu_{cm^{-1}}$: 1710 (C=O); 1705 (C=O); 1H -NMR (300 MHz, $CDCl_3$) δ : 1.22 (s, 3H, CH_3), 1.27 (s, 3H, CH_3), 1.59 (s, 3H, CH_3), 2.14 (s, 1H, 6-H), 2.30 (s, 3H, CH_3), 6.39 (s, 1H, NH), 6.85 and 7.08 (d, 4H, H_{arom} , $J = 8.1$ Hz); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ : 10.31 (CH_3), 17.31 (CH_3), 21.13 (CH_3), 22.87 (CH_3), 34.93 (C-7), 35.49 (C-6), 38.13 (C-1), 128.9–136.9 (C_{arom}), 171.88, 174.62 (C-2, C-5).

3-(4-chlorophenyl)-1,7,7-trimethyl-3,4-diazabicyclo[4.1.0]heptane-2,5-dione **4c**

Anal. Calcd. For $C_{14}H_{15}ClN_2O_2$: C, 60.33; H, 5.42; N, 10.05%; Found: C, 60.41; H, 5.39; N, 9.98%; IR (KBr) $\nu_{cm^{-1}}$: 1690 (C=O); 1700 (C=O); 1H -NMR (300 MHz, $CDCl_3$) δ : 1.25 (s, 3H, CH_3), 1.29 (s, 3H, CH_3), 1.55 (s, 3H, CH_3), 2.19 (s, 1H, 6-H), 6.57 (s, 1H, NH), 6.71 and 7.19 (d, 2H, H_{arom} , $J = 8.4$ Hz) $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ : 11.01 (CH_3), 18.07 (CH_3), 22.90 (CH_3), 34.89 (C-7), 35.66 (C-6), 38.01 (C-1), 117.21–152.43 (C_{arom}), 171.36, 173.22 (C-2, C-5).

3-benzyl-1,7,7-trimethyl-3,4-diazabicyclo[4.1.0]heptane-2,5-dione **4d**

Anal. Calcd. For $C_{15}H_{18}N_2O_2$: C, 69.74; H, 7.02; N, 10.84%; Found: C, 69.61; H, 7.00; N, 10.73%; IR (KBr) $\nu_{cm^{-1}}$: 1690 (C=O), 1705 (C=O); 1H -NMR (300 MHz, $CDCl_3$) δ : 1.25 (s, 3H, CH_3), 1.28 (s, 3H, CH_3), 1.52 (s, 3H, CH_3), 2.17 (s, 1H, 6-H), 5.11 (s, 2H, CH_2Ar), 6.76 (s, 1H, NH), 7.24–7.31 (m, 5H, H_{arom}); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ : 11.09 (CH_3), 18.06 (CH_3), 22.87 (CH_3), 34.83 (C-7), 35.56 (C-6), 38.04 (C-1), 50.62 (CH_2Ar), 116.19–142.41 (C_{arom}), 172.01, 172.29 (C-2, C-5).

References

- [1] (a) P.R. Gogate, *Chemical engineering and processing: process intensification* 47 (2008) 15; (b) S. Mika, P.T. Duong, S.R. Amaty, *Ultrasound technology in green chemistry*, Springer; 1st Edn. 2011; (c) T.J. Mason, D. Peters, *Practical sonochemistry*, second ed., Ellis Horwood, London, 2002; (d) J.L. Luche, *Synthetic organic sonochemistry*, Plenum Press, New York, 1998.
- [2] M.A. Margulis, *High. Energ. Chem.* 38 (2004) 135.
- [3] (a) Y. Hua, Y. Zou, H. Wub, D. Shi, *Ultrason. Sonochem.* 19 (2012) 264; (b) G. Shukla, R.K. Verma, G.K. Verma, M.S. Singh, *Tetrahedron Lett.* 52 (2011) 7195; (c) Z. Shobeiri, M. Pourayoubi, A. Heydari, T.M. Percino, M.A.L. Ramírez, *C. R. Chimie* 14 (2011) 597.
- [4] (a) H. Wang, Y. Zou, X. Zhao, D. Shi, *Ultrason. Sonochem.* 18 (2011) 1048; (b) E. Ruiz, H. Rodriguez, J. Coro, V. Niebla, A. Rodriguez, R.M. Alvarez, H.N. Armas, M. Suarez, N. Martin, *Ultrason. Sonochem.* 19 (2012) 221.
- [5] A.A. Siddiqui, M.S. Wani, *Indian J. Chem.* 43B (2004) 1574.
- [6] (a) W. Malinka, A. Redzicka, O. Lozach, *Fármaco* 59 (2004) 457; (b) P.G. Maria, V. Claudia, G. Carla, G. Nicoletta, B. Alessandro, D.P. Vittorio, *J. Med. Chem.* 46 (2003) 1055.
- [7] (a) S. Demirayak, A.C. Karaburun, R. Beis, *Eur. J. Med. Chem.* 39 (2004) 1089; (b) A.C. Karaburun, I. Kayagil, K. Erol, B. Sirmagul, S. Demirayak, *Arch. Pharm. Res.* 27 (2004) 13.
- [8] M. Sonmez, I. Borber, E. Akbas, *Eur. J. Med. Chem.* 41 (2006) 101.
- [9] X.J. Zou, L.H. Lai, G.Y. Jin, Z.X. Zhany, *J. Agric. Food. Chem.* 50 (2002) 3757.
- [10] H. Xu, X.M. Zou, Y.Q. Zhu, B. Liu, H.L. Tao, X.H. Hu, H.B. Sang, F.Z. Hu, Y.H. Wang, *Z. Yang, Pest. Manag. Sci.* 62 (2006) 522.
- [11] S. Cao, N. Wei, C. Zhao, L. Li, Q. Huang, X. Qian, *J. Agric. Food. Chem.* 53 (2005) 3120.
- [12] (a) S.C. Cherng, W.H. Huang, C.Y. Shiau, A.R. Lee, T.C. Chou, *Eur. J. Pharmacol.* 532 (2006) 32; (b) E. Stelo, M. Fraiz, M. Yamez, Y. Terrades, R. Laguna, E. Cano, F. Rayina, *Bioorg. Med. Chem.* 10 (2002) 2873.
- [13] (a) V.K. Chintakunta, Y. Aketta, M.S. Yedula, P.K. Mamnoor, P. Mishra, S.R. Casturi, V.R. Rajagopalan, *Eur. J. Med. Chem.* 37 (2002) 339; (b) B.S. Fumiss, A.J. Hanaford, P.W.G. Smith, A.R. Tatchell, 5th Edn, *Vogel's textbook of practical organic chemistry*, 695, Longman Group Ltd, London, 1989, 1015 p.; (c) M. Gokce, G. Bakir, M.F. Sachin, E. Kupeli, E. Yesilada, *Arzneimittel-Forschung* 55 (2005) 318; (d) M. Sukurolu, E.B. Caliskan, S. Unlu, M.F. Sahin, E. Kupeli, E. Yasilada, E. Banogulu, *Arch. Pharm. Res.* 28 (2005) 509.
- [14] (a) A. Hallot, R. Brodin, J. Merlier, J. Brochard, J.P. Chambon, K. Bizierek, *J. Med. Chem.* 29 (1986) 369; (b) A. Perio, J.P. Chambon, R. Calassi, M. Heaulme, K. Bizierek, *J. Pharmacol. Exp. Ther.* 239 (1986) 542; (c) R. Sivkumar, N. Anbalagan, V. Gunasekaran, J.T. Leonard, *Biol. Pharm. Bull.* 26 (2003) 1407.
- [15] Q. Ke-Ming, W. Hai-Hong, W. Li-Ming, L. Yin, Y. Xian-Hui, W. Xiao-Ming, Z. Hai-Liang, *Bioorg. Med. Chem.* 20 (2012) 2010.
- [16] (a) Y. Baba, G. Saha, S. Nakao, C. Iwata, T. Tanaka, T. Ibuka, H. Ohishi, Y. Takemoto, *J. Org. Chem.* 66 (2001) 81; (b) L.A. Yanovskaya, V.A. Dombrovsky, A.K. Khusid, *Tsiklopropanis funkcionalnimi gruppami. Sintez i primeneniye. (Cyclopropanes with Functional Groups. Synthesis and Application)*, Nauka, Moscow, 1980.
- [17] D. Ellis, K.L. Kuhen, B. Wu, B. Anaclerio, K. Wolff, H. Yin, B. Bursulaya, J. Caldwell, D. Karanewsky, Y. He, *Bioorg. Med. Chem. Lett.* 16 (2006) 4246.
- [18] J.X. Araújo-Júnior, M. Schmitt, C. Antheaume, J.J. Bourguignon, *Tetrahedron Lett.* 48 (2007) 7817.
- [19] S.D. Andrews, A.C. Day, P. Raymond, M.C. Whiting, *Organic Syntheses* 6 (1988) 392.
- [20] S.R. Yong, A.T. Ung, S.G. Pyne, B.W. Skelton, A.H. White, *Tetrahedron* 63 (2007) 1191.
- [21] N. Ben Hamadi, M. Msaddek, *C. R. Chimie* 14 (2011) 891.
- [22] J. Li, X. Zhang, Z. Lin, J. Beilstein, *Org. Chem.* 3 (2007) 13.
- [23] J.M. Jiménez, J.L. Bourdelande, R.M. Ortuño, *Tetrahedron* 53 (1997) 3777.
- [24] (a) E. Muray, O. Illa, J.A. Castillo, A. Alvarez-Larena, J.L. Bourdelande, V. Branchadell, R.M. Ortuño, *J. Org. Chem.* 68 (2003) 4906, and references therein; (b) T. Karatsu, H. Itoh, T. Kikunaga, Y. Ebashi, H. Hotta, A. Kitamura, *J. Org. Chem.* 60 (1995) 8270; (c) D.H. White, P.B. Condit, R.G. Bergman, *J. Am. Chem. Soc.* 94 (1972) 1348.
- [25] (a) I. Tabushi, K. Takagi, M. Okano, R. Oda, *Tetrahedron* 23 (1967) 2621; (b) T.V. Van Auken, K.L. Rinehart Jr., *J. Am. Chem. Soc.* 84 (1962) 3736.
- [26] (a) A. Padwa, M. Meske, A. Rodriguez, *Heterocycles* 40 (1995) 191; (b) D.E. Reedich, R.S. Sheridan, *J. Am. Chem. Soc.* 110 (1988) 3697; (c) R.J. Crawford, G.L. Erickson, *J. Am. Chem. Soc.* 89 (1967) 3907; (d) R.J. Crawford, L.H. Ali, *J. Am. Chem. Soc.* 89 (1967) 3908.