Ultrasonics Sonochemistry 18 (2011) 704–707

Contents lists available at ScienceDirect

Ultrasonics Sonochemistry

journal homepage: www.elsevier.com/locate/ultsonch

Ultrasound-promoted synthesis of 3-trichloromethyl-5-alkyl(aryl)-1,2,4-oxadiazoles

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ARTICLE INFO

Article history:
Received 12 April 2010
Received in revised form 16 August 2010
Accepted 30 September 2010
Available online 14 October 2010

Keywords:
1,2,4-Oxadiazoles
Heterocycles
Ultrasonic irradiation

ABSTRACT

The alternative synthesis of 12 1,2,4-oxadiazoles using ultrasound irradiation from trichloroacetoamidoxime and acyl chlorides is reported. Seven of them are novel compounds. The 3-trichloromethyl-5alkyl(aryl)-1,2,4-oxadiazoles have been synthesised in better yields and shorter reaction times compared to the conventional method. This protocol can be applicable for preparation of 1,2,4-oxadiazoles containing aryl or alkyl groups attached at their C-5 side-chain.

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1. Introduction

1,2,4-Oxadiazoles are well-known heterocyclic compounds that have been given much attention in pharmacological evaluations [1]. This heterocycle has been utilized as ester or amide bioisosters [2], and it is being examined as having a role in certain drug systems, including the potent S_1P_1 agonist, hemetabotropic glutamate subtype (mGlu5) receptor, muscarinic receptor for the treatment of Alzheimer's disease [3]. Several papers described the use of 1,2,4-oxdiazole in peptide mimetic synthesis, including the design of amino acyl-Gly dipeptidomimetics, signal transduction inhibitors, or cell adhesion inhibitors [3–9]. Recent publications have also shown their applicability in the field of luminescent liquid crystals, materials for optical devices, and charge-transporters for organic light-emitting diodes (OLEDs) [10–13].

The most common protocol for the synthesis of 1,2,4-oxadiazoles involves O-acylation of amidoximes followed by intramolecular condensation with water elimination [9]. The commonly used acylating agents are acyl chlorides [9,15], anhydrides, esters [2,13], and trichloroalkanes and carboxylic acid (with coupling agents like DCC, DIC or EDC) [14]. However, these reactions required long reactions times, high temperatures, produce by-products and, in general, have difficult purifications [16,17]. Ultrasound irradiation, an efficient and innocuous technique for reagent activation in the synthesis of organic compounds, and in particular heterocyclic compounds, has been applied with success, and generates products in good to excellent yields [18–20].

Ultrasound-promoted synthesis has attracted much attention during the past few decades. One advantage of using cavitation as an energy source to promote organic reactions includes shorter reaction times [19]. During the rarefaction cycle in the cavitation process, the molecules of the liquid are separated, generating bubbles that subsequently collapse in the compression cycle. These rapid and violent implosions generate short-lived regions with temperatures of roughly 5000 °C, pressures of about 1000 atm and heating and cooling rates above 10 billion °C per second. Such localized hot spots can be thought as micro reactors in which the energy of sound is transformed into a useful chemical form [19–21]. This procedure has been considered as a clean and useful protocol in organic synthesis compared with traditional methods, and the procedure is, in general, more convenient [19].

In previously work we synthesised 3-trichloromethyl-5-alkyl-1,2,4-oxadiazoles in good yields using toluene reflux for 20 h [9]. In this context we decided to explore the efficient, simple and fast synthesis of their corresponding heterocycles using ultrasound irradiation.

2. Results

The precursor trichloroacetoamidoxime **1** was synthesised in excellent yields (90%) by reaction of trichloroacetonitrile with hydroxylamine hydrochloride in water at 25 for 3 h [9].

In order to optimize the reaction conditions, a small solvent screen was studied (Table 1). In these experiments, we have

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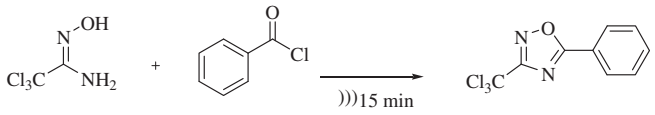
doi:10.1016/j.ultsonch.2010.09.016

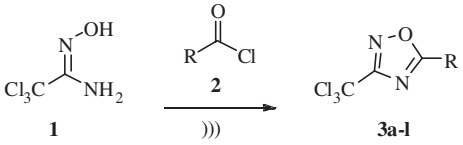
Table 1
Optimization for the synthesis of 3-trichloromethyl-5-phenyl-1,2,4-oxadiazoles **3a**.

Entry	Solvent	Time (min)	Yield (%)
1	Toluene	15	76
2	Hexane	15	90
3	THF	15	95
4	Ethyl acetate	15	92
5	1,2-Dichloroetane	15	93



1 **2a** **3a**

Scheme 1.



1 **3a-l**

R = Ph, MePh, 4-nitroPh, 2-fluorPh, 2-MeOPh, 3-bromoPh, 2-iodoPh, Me, Et, $ClCH_2$, Cl_2CH CCl_3

Scheme 2.

observed that the reaction between trichloroacetoamidoxime **1** with benzoyl chloride **2a** under ultrasonic irradiation was solvent dependent (Scheme 1, Table 1). Although the reaction time was shorter than in the literature, the procedure could be improved, and thus other solvent were tested. We found that the ethyl acetate was the appropriated solvent for these reactions. Though the reaction in THF showed goods yields (95%), the reaction require two steps for extraction of the final product. Thus, ethyl acetate was the better solvent for the reaction, since the solvent of reaction was the same as used in the extraction in the latter case.

The important points of this reaction process include the easier work-up, shorter reaction time, and higher yields than the conventional method.

The 5-alkyl(aryl)-3-trichloromethyl-1,2,4-oxadiazoles **3a-l** were synthesised by treatment of trichloroacetamidoxime **1** with acyl chlorides **2a-l** for 15 min under ultrasonic irradiation using ethyl acetate as solvent (Scheme 2). The heterocycles **3a-l** were obtained in good yields without purification (84–98%). The scope and generality of this process is illustrated by a series of twelve compounds and the results are presented in Table 2. The compounds **2a-j** were synthesised by conventional method according to the literature [9]. The products were identified using both analytical and spectral data (^1H and ^{13}C NMR) and all compounds are in full agreement with the proposed structure.

3. Conclusions

In conclusion, we have described the simple and rapid preparation of 1,2,4-oxadiazoles under ultrasound irradiation. The final products were obtained in short times and excellent yields (84–98%), better than through the use of the conventional process (60–90%), which required significantly longer reaction times.

3.1. General methods

All solvents and reagents were obtained from Aldrich and used without further purification. The NMR spectra were recorded on a Bruker DPX 400 (^1H at 400.13 MHz and for ^{13}C at 100.63 MHz) spectrometer, 5 mm sample tubs, 298 K, digital resolution of ± 0.01 ppm, 0.5 M in $CDCl_3$, containing TMS as internal standard. Mass spectra were obtained using an HP 6890 GC connected to an HP 5973 MSD and interfaced by a Pentium PC. The GC was equipped with a split-splitless injector, auto sampler, cross-linked HP-5 capillary column (30 m, 0.32 mm of internal diameter), and helium was used as the carrier gas.

3.2. Synthesis of 3-trichloromethyl-5-alkyl(aryl)-1,2,4-oxadiazoles

To a solution of the trichloroacetoamidoxime **1** (0.003 mol) in ethyl acetate was added of acyl chloride **2a-l** (0.0036 mol). The reaction mixtures were irradiated with an ultrasound probe for 15 min (the reaction was monitored by TLC). After that time, the organic layer was washed twice in water, twice in Na_2CO_3 solution, and one in water. The organic layer was dried and the solvent was removed under reduced pressure. Finally, the 5-alkyl(aryl)-3-trichloromethyl-1,2,4-oxadiazoles were obtained in good yields without any further purification.

3.3. Products data

3.3.1. 3-Trichloromethyl-5-phenyl-1,2,4-oxadiazole 3a

$C_9H_5Cl_3N_2O$; 263; mp 72 °C**;** yield (90%); ^1H NMR (400 MHz; $CDCl_3$): δ (ppm) 8.20 and 7.26 (m, 5H, Ph); MS CG–MS (EI 70 eV): *m/z* (%) 262(9)[M^{+1}], 264 (9), 229(63), 228(9.5), 227(100), 126(22), 124(33), 105(25), 103(35), 77(74), 76(21), 50(21), 51(43).

3.3.2. 3-Trichloromethyl-5-[4-methylphenyl]-1,2,4-oxadiazoles 3b

$C_{10}H_7Cl_3N_2O$; 275; mp 163; yield (93%); ^1H NMR (400 MHz; $CDCl_3$): δ (ppm) 8.12–7.82 (m, 4H, aryl), 2.42 (s, 3H, CH3); MS CG–MS (EI 70 eV): *m/z* (%) 275 [M^{+1}] (1), 272(20), 271(71), 269(100),126(6), 119(20), 117(26), 108(15), 91(10).

3.3.3. 3-Trichloromethyl-5-[4-nitrophenyl]-1,2,4-oxadiazole 3c

$C_9H_4Cl_3N_3O_3$; 306; mp 110; yield (94%); ^1H NMR (400 MHz; $CDCl_3$): δ (ppm) 8.95–8.46 (m, 4H, aryl); ^{13}C NMR (100 MHz; $CDCl_3$): δ (ppm) 177.1 (C5), 169.7 (C3), 148.3–125.2 (aryl), 99.9 (CCl_3); MS CG–MS (EI, 70 eV): *m/z* (%) 306 [M^+], 307(10), 273(66), 272(12), 271(100), 126(29), 124(44), 120(7), 118 (7), 117(6).

3.3.4. 3-Trichloromethyl-5[2-fluorphenyl]-1,2,4-oxadiazole 3d

$C_9H_4Cl_3FN_2O$; 279; mp 53; yield (95%); ^1H NMR (400 MHz; $CDCl_3$): δ (ppm) 8.09–7.13 (m, 4H, aryl); ^{13}C NMR (100 MHz; $CDCl_3$): δ (ppm) 174.7 (C5), 170.5 (C3), 157.2–116.9 (aryl), 91.0 (CCl_3); MS CG–MS (EI 70 eV): *m/z* (%) 280 [M^{+1}] (11), 282(10), 249(11), 247(66), 246(11), 245(100), 126(27), 124(46), 123(23), 121(31).

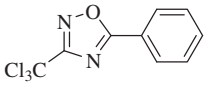
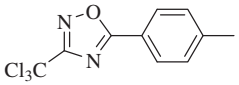
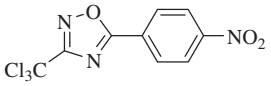
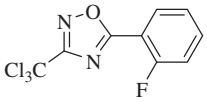
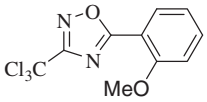
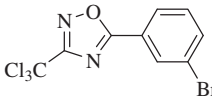
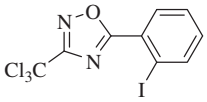
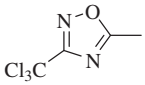
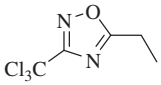
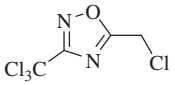
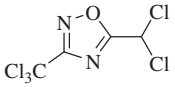
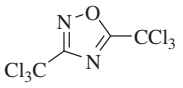
3.3.5. 3-Trichloromethyl-5-[2-metoxiphenyl]-1,2,4-oxadiazole 3e

$C_{10}H_7Cl_3N_2O_2$; 291; yield (84%); ^1H NMR (400 MHz; $CDCl_3$): δ (ppm) 9.25–8.34 (m, 4H, aryl), 4.63 (s, 3H, OCH_3); ^{13}C NMR (100 MHz; $CDCl_3$): δ (ppm) 177.2 (C5), 170.1 (C3), 158.4–110.9 (aryl), 85.4 (CCl_3); MS CG–MS (EI 70 eV): *m/z* (%) 291[M+] (7), 292(6), 133(100), 132(12), 126(10), 124(16), 121(38), 119(10), 105(19), 104(14), 77(32).

3.3.6. 3-Trichloromethyl-5-[3-bromophenyl]-1,2,4-oxadiazole 3f

$C_9H_4BrCl_3N_2O$; 339; mp 185; yield (96%); ^1H NMR (400 MHz; $CDCl_3$): δ (ppm) 8.36–7.46 (m, 4H, aryl); ^{13}C NMR (100 MHz; $CDCl_3$): δ (ppm) 170.7 (C5), 165.9 (C3), 136.1–121.8 (aryl), 91.2

Table 2
Synthesis of 3-trichloromethyl-5-alkyl(aryl)-1,2,4-oxadiazoles **3a-l** under ultrasound irradiation.

	Product	MF/WM	Conventional method		Ultrasound irradiation	
			Time (hour)	Yields (%)	Time (min)	Yields (%)
3a		$C_9H_5Cl_3N_2O$ (261,95)	20	70	15	92
3b		$C_{10}H_7Cl_3N_2O$ (275,96)	20	90	15	93
3c		$C_9H_4Cl_3N_3O_3$ (306,93)	20	64	15	94
3d		$C_9H_4Cl_3FN_2O$ (279,94)	20	78	15	95
3e		$C_{10}H_7Cl_3N_2O_2$ (291,96)	20	80	15	84
3f		$C_9H_4BrCl_3N_2O$ (339,86)	20	74	15	96
3g[a]		$C_9H_4Cl_3IN_2O$ (387,84)	20	85	15	98
3h[a]		$C_4H_3Cl_3N_2O$ (199,93)	20	61	15	86
3i[a]		$C_5H_5Cl_3N_2O$ (213,95)	20	60	15	90
3j[a]		$C_4H_2Cl_4N_2O$ (233,89)	20	80	15	89
3k[a]		$C_4HCl_5N_2O$ (267,85)	20	74	15	88
3l[a]		$C_4Cl_6N_2O$ (301,8)	20	90	15	90

[a] Ref. [9].

(CCl_3); MS CG–MS (EI 70 eV): *m/z* (%) 343[M+ 4] (11), 342(13), 341(22), 308(45), 306(100), 304(61), 156(23), 154(25), 126(34), 124(53).

3.3.7. 3-Trichloromethyl-5-[2-iodophenyl]-1,2,4-oxadiazole 3g

$C_9H_4ICl_3N_2O$; 387; mp 115; yield (98%); ^{1}H NMR (400 MHz; $CDCl_3$): δ (ppm) 9.31–8.39 (m, 4H, aryl); ^{13}C NMR (100 MHz; $CDCl_3$): δ (ppm) 170.4 (C5), 163.6 (C3), 94.1–140.5 (aryl), 91.1 (CCl_3); MS CG–MS (EI 70 eV): *m/z* (%) 387 [M+] (31), 388(34), 354(66), 353(100), 288(13), 126(24), 124(35), 77(4), 76(52).

Acknowledgment

The authors would like to thanks the CNPq (Project 476769/2004-3) and CAPES for financial support.

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