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Triethanolamine as an inexpensive and efficient catalyst for the green synthesis of novel 1*H*-pyrazolo[1,2-*a*]pyridazine-5,8-diones under ultrasound irradiation in water and their antibacterial activity†

Ahmad Khoraamabadi-zad,*[a] Mohammad Azadmanesh,[a] Roya Karamian,[b] Mostafa Asadbegy[b] and Maryam Akbari[b]

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Triethanolamine was found to be an efficient catalyst for the synthesis of new 1*H*-pyrazolo[1,2-*a*]pyridazine-5,8-diones by a one-pot reaction of maleic hydrazide, with aromatic aldehydes and malononitrile in H_2O under ultrasonic irradiation. The advantages of this method are the use of an inexpensive and readily available catalyst, easy workup, improved yields, and the use of H_2O as a green solvent. To assess their antibacterial activity, all the synthesized compounds were dissolved in DMSO and subjected to biological evaluation using the disc diffusion method against 3 Gram positive and 3 Gram negative bacteria.

The chemical applications of ultrasound, "Sonochemistry", have become an exciting new field of research which has been increasingly used in organic synthesis in recent years. This is because a large number of organic reactions can be carried out in higher yields, shorter reaction times and milder conditions under ultrasonic irradiation.[1–3] This may be due to the fact that the ultrasound (20–100 kHz, >10 W cm^{-2}) uses the energy to create cavitations, which involve the formation, growth, and implosive collapse of microscopic bubbles in a liquid. These bubbles are generated when the "negative" pressure during the rarefaction phase of the sound wave is sufficiently large to disrupt the liquid. The implosive collapse of the bubbles can locally produce extreme temperatures and pressures (5000 °C, 20 MPa) for very short times, because of compression of the gas phase inside the cavity. These hotspots may lead to irreversible changes such as the formation of excited states, bond breakage, and the generation of radicals.[4] Ultrasonication can also accelerate many multi-component reactions (MCRs) as well as condensation of maleic hydrazide with Knoevenagel condensation product.

Multi-component reactions (MCRs) have been known for over 150 years.[5] They play an important role in combinatorial chemistry because of their ability to synthesize small drug-like molecules with several degrees of structural diversity.[6,7] An MCR is a reaction in which three or more different starting materials react to form a product, where most, if not all of the atoms are incorporated in the final product. This reaction tool allows heterocyclic compounds to be synthesized in a few steps and usually in a one-pot operation.[8]

Nitrogen-containing heterocyclic compounds are widespread in nature, and their applications to biologically active pharmaceuticals, agrochemicals, and functional materials are becoming more and more important.[9] For example, pyrazole derivatives exhibit important biological properties such as anti-inflammatory,[10] antifungal,[11] anticancer,[12] antiviral,[13] antitumor,[14] anticoagulant[15] and antibacterial activities.[16] The development of new efficient methods to synthesize *N*-heterocycles with structural diversity is therefore one major interest of modern synthetic organic chemists.[17,18] Among a large variety of nitrogen-containing heterocyclic compounds those containing bridgehead hydrazine have received considerable attention because of their pharmacological properties and clinical applications.[19–21] The special importance of heterocycles in synthesis and medicinal chemistry, and the key role of pyrazole moiety in numerous biologically active compounds,[13,22] prompted us to synthesize a series of 1*H*-pyrazolo[1,2-*a*]pyridazine-5,8-dione derivatives by the three-component reaction of maleic hydrazide, malononitrile and aromatic benzaldehydes (Scheme 1) followed by subjection of these novel heterocycles to biological evaluation.

[a]*Faculty of Chemistry, Bu-Ali Sina University, Hamedan 6517838695, Iran. E-mail: khoram@gmail.com; Fax: +98-81-38380709; Tel: +98-81-38282807*

[b]*Department of Biology, Faculty of Science, Bu-Ali Sina University, Hamedan 651754161, Iran*

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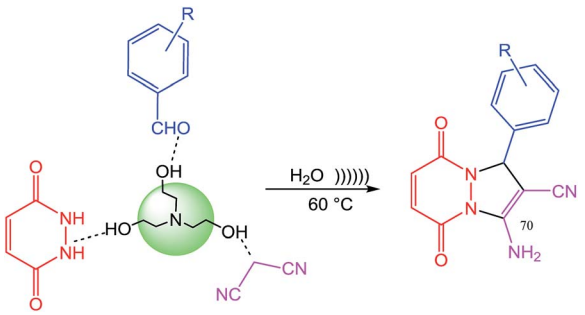


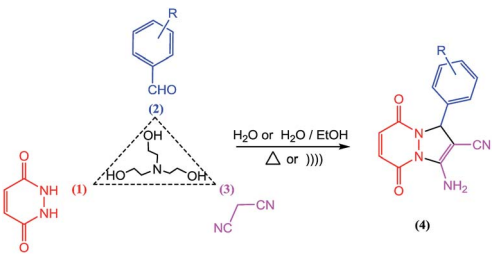
Scheme 1 Synthesis of 1*H*-pyrazolo[1,2-*a*]pyridazine-5,8-diones.

Antibacterial activity

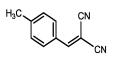
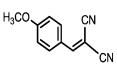
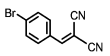
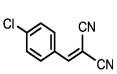
All 1*H*-pyrazolo[1,2-*a*]pyridazine-5,8-dione derivatives were separately dissolved to a final concentration of 1 mg mL^{-1} and sterilized by filtration using 0.45 μm Millipore. DMSO solutions were then tested by disc diffusion method against a panel of microorganisms including 3 Gram positive bacteria, namely *Bacillus cereus* (PTCC 1247), *Bacillus thuringiensis* (BT) and *Staphylococcus aureus* (Wild) and also 3 Gram negative bacteria, namely *Escherichia coli* (Wild), *Serratia marcescens* (PTCC 1111), and *Shigella boydii* (ATCC 9905).[23] All tests were carried out using 10 mL of suspension containing 1.5×10^8 bacteria per mL and spread on nutrient agar medium. Negative controls were prepared by using pure DMSO. Gentamicin (10 μg), penicillin (10 IU) and cephalexin (30 μg) antibiotic discs were used as positive reference standards.

As it is well known, *Staphylococcus aureus* and *Bacillus* species, especially *Bacillus cereus*, are food poisoning agents.[24] Since DMSO was used as a solvent, it was also screened against all bacteria in this study and no activity was found. Generally antibacterial activity of a compound is attributed mainly to its major components. However, today it is known that the synergistic or antagonistic effect of one component in minor percentage in a mixture has to be considered.[25,26] The results showed that, all the tested compounds displayed significant activities against *Bacillus cereus* and *Bacillus thuringiensis*, while, only compounds **4d** and **4e** (Table 2) were active against *Shigella*

Table 1 Synthesis of 1*H*-pyrazolo[1,2-*a*]pyridazine-5,8-diones using maleic hydrazide, aromatic aldehydes, malononitrile and 1–2 drops of triethanolamine as a catalyst in conventional and ultrasonic method



R= **a:** C_6H_5; **b:** 2,4-$Cl_2C_6H_3$; **c:** 2-ClC_6H_4; **d:** 2,6-$Cl_2C_6H_3$; **e:** 2-BrC_6H_4; **f:** 3-$NO_2C_6H_4$; **g:** 2-$CH_3OC_6H_4$; **h:** 3-ClC_6H_4

			Conventional method[b]		Ultrasonic method[c]	
Entry	R	Product	Time (min)	Yield (%)[a]	Time (min)	Yield (%)[a]
1	H	**4a**	400	15	90	40
2	2,4-DiCl	**4b**	210	60	35	70
3	2-Cl	**4c**	180	65	26	73
4	2,6-DiCl	**4d**	150	65	20	70
5	2-Br	**4e**	120	73	15	80
6	3-NO_2	**4f**	240	40	70	55
7	2-OCH_3	**4g**	200	65	50	75
8	3-Cl	**4h**	260	45	65	55
9	4-CH_3		6	88	2	95
10	4-OCH_3		7	85	3	90
11	4-Br		3	89	<1	90
12	4-Cl		5	87	1	92

[a] Isolated yields. [b] Method A. [c] Method B.

Table 2 Antibacterial activity of 1*H*-pyrazolo[1,2-*a*]pyridazine-5,8-diones derivatives[a]

Inhibition zone (mm)							
Compound*	Concentration	B.c (+)	S.a (+)	B.t (+)	E.c (−)	S.b (−)	S.m (−)
4b	1 (mg mL^{-1})	15 ± 0.43[a]	NA	19 ± 0.14[a]	9 ± 0.34[a]	11 ± 0.41[a]	11 ± 0.26[a]
	0.1 (mg mL^{-1})	13 ± 0.33[b]	NA	16 ± 0.16[b]	7 ± 0.16[b]	9 ± 0.18[b]	9 ± 0.55[b]
	0.01 (mg mL^{-1})	11 ± 0.28[c]	NA	11 ± 0.14[c]	NA	NA	NA
4c	1 (mg mL^{-1})	10 ± 0.28[a]	NA	11 ± 0.33[a]	NA	9 ± 0.21[a]	13 ± 0.25[a]
	0.01 (mg mL^{-1})	8 ± 0.12[b]	NA	8 ± 0.36[b]	NA	7 ± 0.16[b]	11 ± 0.22[b]
	0.01 (mg mL^{-1})	NA	NA	7 ± 0.00[c]	NA	NA	8 ± 0.12[c]
4d	1 (mg mL^{-1})	16 ± 0.26[a]	11 ± 0.21[a]	24 ± 0.48[a]	7 ± 0.00	NA	8 ± 0.17[a]
	0.01 (mg mL^{-1})	14 ± 0.11[b]	9 ± 0.33[b]	16 ± 0.54[b]	NA	NA	7 ± 0.10[b]
	0.01 (mg mL^{-1})	10 ± 0.47[c]	8 ± 0.56[c]	14 ± 0.36[c]	NA	NA	NA
4e	1 (mg mL^{-1})	15 ± 0.11[a]	21 ± 0.17[a]	10 ± 0.23[a]	10 ± 0.53[a]	7 ± 0.55	13 ± 0.46[a]
	0.01 (mg mL^{-1})	12 ± 0.47[b]	18 ± 0.16[b]	8 ± 0.44[b]	9 ± 0.24[b]	NA	10 ± 0.12[b]
	0.01 (mg mL^{-1})	8 ± 0.13[c]	14 ± 0.14[c]	NA	NA	NA	7 ± 0.38[c]
4g	1 (mg mL^{-1})	15 ± 0.26[a]	NA	10 ± 0.17[a]	8 ± 0.34[a]	8 ± 0.46[a]	9 ± 0.17[a]
	0.1 (mg mL^{-1})	12 ± 0.13[b]	NA	7 ± 0.00[b]	7 ± 0.14[b]	NA	7 ± 0.00[b]
	0.01 (mg mL^{-1})	8 ± 0.16[c]	NA	NA	NA	NA	NA
4f	1 (mg mL^{-1})	17 ± 0.13[a]	NA	12 ± 0.23[a]	9 ± 0.17[a]	7 ± 0.54	14 ± 0.56[a]
	0.1 (mg mL^{-1})	15 ± 0.21[b]	NA	10 ± 0.44[b]	8 ± 0.00[b]	NA	11 ± 0.16[b]
	0.01 (mg mL^{-1})	11 ± 0.15[c]	NA	7 ± 0.00[c]	NA	NA	9 ± 0.18[c]
4h	1 (mg mL^{-1})	10 ± 0.37[a]	NA	8 ± 0.19	9 ± 0.18[b]	7 ± 0.33	7 ± 0.33
	0.1 (mg mL^{-1})	8 ± 0.10[b]	NA	NA	NA	NA	NA
	0.01 (mg mL^{-1})	NA	NA	NA	NA	NA	NA
Positive control	Gentamaicin 10 μg	25 ± 0.18	35 ± 0.24	26 ± 0.17	NA	26 ± 0.17	18 ± 0.46
	Penicillin 10 IU	NA	NA	NA	NA	NA	NA
	Cephalexin 30 μg	22 ± 24	NA	20 ± 0.12	NA	20 ± 0.34	16 ± 0.15
Negative control	DMSO	NA	NA	NA	NA	NA	NA

[a] a, b and c show that the SD values are different for different concentrations ($P < 0.05$). NA: not active. *: see Table 1.

boydii. When comparing the antibacterial activity of the tested samples to those of reference antibiotics, the inhibitory potency of some of the tested compounds were found to be good. Although all the above bacteria were resistant to Penicillin, the antibacterial effects of some tested samples were higher than those of Penicillin on these bacteria. The above results indicate that the synthesized compounds may be used in treatment of diseases caused by tested bacteria.

Data obtained from antibacterial assays are the averages of triplicate analyses and recorded as means ± standard deviation. Analysis of variance was performed by Excel and SPSS procedures using Student's *t*-test, and p value < 0.05 was regarded as significant. Results of antibacterial assessment are presented in Table 2.

Conclusions

In this work, novel 1*H*-pyrazolo[1,2-*a*]pyridazine-5,8-diones have been synthesized in the presence of a catalytic amount of triethanolamine, which is itself a relatively benign compound used as an emulsifier and surfactant in many industrial products such as liquid laundry detergents, dishwashing liquids, general cleaners, hand cleaners, printing inks *etc.* The advantages of this procedure are green reaction conditions, good yields, short reaction times and the availability of the catalyst (see Table 1 for comparison of yields and reaction times of conventional and sonication procedures). Notably, triethanolamine catalyzes both the Knoevenagel condensation of malononitrile with substituted benzaldehydes and also the reaction of the condensation product with maleic hydrazide.[27,28] As is seen in Table 1, for entries 9–12, the reaction stops at the Knoevenagel condensation product. A closer inspection reveals that such products are stabilized through conjugation of the phenyl ring with the double bond moiety. The percentages and reaction times of other entries of Table 1 prove that the presence of substituents at 3 and especially at 2 positions of the phenyl ring prevents the above said conjugation and hence makes the reaction to proceed.

In addition, the results of biological assessment clearly demonstrate that all the 1*H*-pyrazolo[1,2-*a*]pyridazine-5,8-diones exhibit antibacterial properties which may be helpful in developing new therapeutic agents and preventing the progress of various diseases. Future research should envision studies on modification of these compounds to increase their antibacterial activity (see Table 2).

Acknowledgements

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27 Preparation of maleic hydrazide, Hydrazine hydrate (1.2 mmol, 98%) was added drop-wise to an ice-cold solution of maleic anhydride (1.0 mmol) in 10 mL acetic acid and the reaction mixture was refluxed for 4 h. A solid was obtained after cooling the reaction mixture to room temperature. This crude product was filtered and washed with 50% ethanol to give maleic hydrazide. (Yield: 75%; Mp: >300 °C)., General procedure for the synthesis of 1*H*-pyrazolo [1,2-*a*]pyridazine-5,8-diones, Conventional method, Maleic hydrazide (3.0 mmol), aromatic aldehyde (3.0 mmol), malononitrile (3.0 mmol) and 1–2 drops of triethanolamine (0.3 mmol, 10 mol%) were stirred and refluxed in 10 mL ethanol–H_2O (30 : 70). The progress of the reaction was monitored by TLC. After completion of the reaction, the mixture was poured into the cold water (50 mL), the yellow precipitate filtered, washed several times with 1 M sodium bicarbonate solution, water and finally with hot 50% ethanol then filtered and dried, Ultrasonic method, Maleic hydrazide (3.0 mmol), aromatic aldehyde (3.0 mmol), malononitrile (3.0 mmol) and 1–2 drops of triethanolamine (0.3 mmol, 10 mol%) were added to 5 mL H_2O and the reaction vessel was placed in ultrasonic bath at 60 °C. The progress of the reaction was monitored by TLC. After completion of the reaction, the mixture was poured in cold water (50 mL), the precipitated solid was filtered, washed several times with 1 M sodium bicarbonate solution, water and finally with hot 50% ethanol then filtered and dried. The experimental results are summarized in Table 1. All the new compounds were characterized by their spectral data (NMR, IR, Mass spectra). For more details see ESI†
28 ***3-Amino-5,8-dioxo-1-phenyl-5,8-dihydro-1H-pyrazolo[1,2-a]-pyridazine-2-carbonitrile (4a)***, m.p.: 291–294 °C (dec.) ^{1}H NMR (400 MHz, DMSO-d_6) δ(ppm) 5.97 (s, 1H), 7.03 (s, 2H), 7.34 (m, 5H), 7.98 (s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ(ppm) 63.19, 64.90, 117.28, 128.31, 129.99, 130.19, 136.75, 137.41, 139.15, 151.82, 154.64, 157.69; IR (KBr, cm^{-1}): 3388, 3328, 3236, 2196, 1666, 1645, 1559, 1437, 1370, 1287, 1173, 852, 699, 489; MS, *m*/*z* (%): 266 (M^+)., ***3-Amino-1-(2,4-dichlorophenyl)-5,8-dioxo-5,8-dihydro-1H-pyrazolo[1,2-a]pyridazine-2-carbonitrile (4b)***, m.p.: 273–275 °C (dec.) ^{1}H NMR (400 MHz, DMSO-d_6) δ(ppm) 6.28 (s, 1H), 7.01–7.10 (dd, 2H), 7.42 (d, 1H), 7.58 (d, 1H), 7.63 (s, 1H), 8.07 (s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ(ppm) 60.53, 61.77, 117.21, 129.65, 130.79, 133.89, 135.36, 136.79, 137.04, 152.50, 154.27, 157.68; IR (KBr, cm^{-1}): 3375, 3252, 3183, 3063, 2197, 1666, 1589, 1562, 1476, 1436, 1374, 1285, 1257, 1147, 1123, 1048, 992, 850, 815, 655, 581,487; MS, *m*/*z* (%): 334 (M^+)., ***3-Amino-1-(2-chlorophenyl)-5,8-dioxo-5,8-dihydro-1H-pyrazolo[1,2-a]pyridazine-2-carbonitrile (4c)***, m.p.: 271–273 °C (dec.); ^{1}H NMR (400 MHz, DMSO-d_6) δ(ppm) 6.31 (s, 1H), 7.03 (d, 1H), 7.09 (d, 1H), 7.35 (s, 2H) , 7.47 (d, 2H), 8.04 (s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ(ppm) 62.83, 64.52, 117.00, 129.46, 131.54, 131.67, 132.82, 136.94, 137.16, 152.40, 154.52, 157.71, 158.09; IR (KBr, cm^{-1}): 3384, 3265, 3185, 3062, 2202, 1698, 1677, 1644, 1586, 1562, 1476, 1436, 1371, 1336, 1288, 1255, 1123, 1048,

1022, 992, 848, 753, 702, 611, 560, 487; MS, *m*/*z* (%): 300 (M^+)., ***3-amino-1-(2,6-dichlorophenyl)-5,8-dioxo-5,8-dihydro-1H-pyrazolo[1,2-a]pyridazine-2-carbonitrile (4d)***, m.p.: 274–276 °C (dec.); ^{1}H NMR (400 MHz, DMSO-d_6) δ(ppm) 6.75 (s, 1H), 7.06 (d, 1H), 7.12 (d, 1H), 7.39 (t, 1H), 7.45 (d, 1H,), 7.56 (d, 1H), 8.17 (s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ(ppm) 58.18, 61.20, 116.61, 130.76, 130.92, 132.08, 132.53, 134.05, 136.79, 136.88, 153.18, 154.25, 157.62; IR (KBr, cm^{-1}): 3381, 3261, 2193, 1696, 1671, 1645, 1561, 1438, 1370, 1288, 1256, 1121, 840, 782, 559, 485; MS, *m*/*z* (%): 334 (M^+)., ***3-Amino-1-(2-bromophenyl)-5,8-dioxo-5,8-dihydro-1H-pyrazolo[1,2-a]pyridazine-2-carbonitrile (4e)***, m.p.: 287–289 °C (dec.); ^{1}H NMR (400 MHz, DMSO-d_6) δ(ppm) 6.30 (s, 1H), 7.03 (d, 1H), 7.09 (d, 1H), 7.26–7.48 (m, 3H), 7.61 (d, 1H), 8.04 (s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ(ppm)58.39, 61.90, 117.08, 129.41, 130.54, 131.97, 135.82, 136.94, 137.26, 154.40, 157.22, 158.71, 158.90; IR (KBr, cm^{-1}): 3381, 3310, 3263, 3184, 2199, 1697, 1673, 1649, 1585, 1562, 1470, 1436, 1367, 1288, 1144, 1020, 991, 849, 749, 487; MS, *m*/*z* (%): 346 (M^+ + 2), 344 (M^+)., ***3-Amino-1-(3-nitrophenyl)-5,8-dioxo-5,8-dihydro-1H-pyrazolo-[1,2-a]pyridazine-2-carbonitrile(4f)***, m.p.: 269–271 °C (dec.); ^{1}H NMR (400 MHz, DMSO-d_6) δ(ppm) 6.22 (s, 1H), 7.01 (d, 1H), 7.07 (d, 1H), 7.68 (d, 1H), 7.92 (d, 1H, J=7.4 Hz), 8.09 (s, 1H), 8.18 (d, 1H), 8.34 (s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ(ppm) 62.03, 93.97, 117.26, 123.47, 125.08, 131.85, 135.32, 137.11, 141.48, 149.55, 152.28, 154.86, 157.78; IR (KBr, cm^{-1}): 3383, 3262, 3182, 3071, 2199, 1674, 1645, 1584, 1544, 1436, 1353, 1289, 1153, 994, 849, 731, 688, 594, 570, 488; MS, *m*/*z* (%): 311 (M^+)., ***3-Amino-1-(2-methoxyphenyl)-5,8-dioxo-5,8-dihydro-1H-pyrazolo[1,2-a]pyridazine-2-carbonitrile (4g)***, m.p.: 258–260 °C (dec.); ^{1}H NMR (400 MHz, DMSO-d_6) δ(ppm) 3.73 (s,3H), 6.17 (s, 1H), 6.92 (d, 1H), 7.00–7.08 (m, 3H), 7.22 (d, 1H), 7.28 (t, 1H), 7.92 (s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ(ppm) 57.41, 61.35, 62.24, 113.26, 122.26, 126.35, 129.18, 131.15, 136.57, 137.32, 152.23, 154.30, 157.68, 158.06; IR (KBr, cm^{-1}): 3371, 3245, 3181, 3062, 2197, 1686, 1669, 1644, 1588, 1563, 1492, 1442, 1373, 1344, 1291, 1247, 1027, 993, 850, 758, 749, 559, 489; MS, *m*/*z* (%): 296 (M^+)., ***3-Amino-1-(3-chlorophenyl)-5,8-dioxo-5,8-dihydro-1H-pyrazolo[1,2-a]pyridazine-2-carbonitrile (4h)***, m.p.: 278–280 °C (dec.); ^{1}H NMR (400 MHz, DMSO-d_6) δ(ppm) 6.31 (s, 1H), 7.03 (d, 1H), 7.09 (d, 1H), 7.35 (s, 2H), 7.44–7.50 (m, 2H), 8.04 (s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ(ppm) 58.43, 60.93, 117.86, 123.75, 124.68, 131.67, 134.79, 136.94, 141.58, 149.55, 152.22, 155.16, 157.71; IR (KBr, cm^{-1}): 3384, 3265, 3062, 2202, 1689, 1676, 1645, 1437, 1288, 849, 753, 561; MS, *m*/*z* (%): 300 (M^+).