Research Article

An Ultrasound Mediated Green Synthesis of Benzimidazolylthiounsaturated nitriles Using Water as a Green Solvent

Sadhu Srinivas Rao, Chittireddy Venkata Ramana Reddy, and Pramod Kumar Dubey

Department of Chemistry, College of Engineering, Jawaharlal Nehru Technological University Hyderabad, Kukatpally, Hyderabad 500 085, India

Correspondence should be addressed to Sadhu Srinivas Rao; seenu604@gmail.com

Received 8 July 2014; Revised 27 September 2014; Accepted 20 October 2014; Published 9 November 2014

Academic Editor: Jonathan White

Copyright © 2014 Sadhu Srinivas Rao et al. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Reaction of 2-cyanothiomethylbenzimidazole **1** with an aromatic aldehydes in water under ultrasonic irradiation for 10–13 min gave the corresponding unsaturated nitriles **2a–h** which is an efficient and simple method under green conditions. The unsaturated nitrile derivatives were obtained in 86–98% yield with a short reaction time without any tedious workup procedures.

1. Introduction

The importance of heterocycles in many fields of science (including organic, inorganic, bioorganic, agricultural, industrial, pharmaceutical, and medicinal chemistry, as well as material science) can hardly be overstated and justifies a long-lasting effort to work out new synthetic protocols for their production [1]. Ultrasound enhances the reactivity of molecules towards many chemical reactions via the process of acoustic cavitation [2]. The assistance of US irradiation efficiently shortens the reaction times. Simple experimental procedure, very good yields, increased selectivity, and clean reaction of many US-induced organic transformations offer additional convenience in the field of synthetic organic chemistry [3–8]. Recently, US has been utilized to accelerate a wide number of synthetically useful organic reactions [9, 10]. In addition to the field of organic chemistry, sonochemistry has also been used in the preparation of micro- and nanomaterials (i.e., protein microspheres) [11].

The α,β -unsaturated nitriles play an important role in drug discovery programs. Various unsaturated nitrile derivatives are also reported to exhibit a wide spectrum of biological properties such as cardiogenic agents. Analogue possessing α,β -unsaturated nitriles at the 17- β position had high activity in natural products. In Digoxin, the unsaturated 17-lactone plays an important role in receptor binding. Saturation of

the lactone ring dramatically reduced the biological activity. In Digoxin, if the lactone group at 17th position is replaced with α,β -unsaturated nitriles ($-\text{C}=\text{C}-\text{CN}$ group), there is no loss in biological activity [12, 13] (see Figure 1).

Walker et al. reported [14] that condensation of 3-formyl-1H-indole-2-carboxylate with 3-nitrophenyl acetonitrile in piperidine using ethanol under reflux conditions for 70 h gave the corresponding α,β -unsaturated nitriles. Mukarram et al. reported [15] that the condensation of p-substituted benzaldehyde with active methylene compounds gave the corresponding unsaturated nitrile derivative, that is, entacapone, which is used for treatment of Parkinson's disease. Condensation of benzaldehyde with cyanoethyl acetate in ethanol at RT in the presence of a catalytic amount of Baker's yeast to give unsaturated nitriles was reported by Pratap et al. [16]. Al-Kadasi and Nazeruddin reported that the condensation of 4-hydroxycoumarin with aromatic aldehydes in water under ultrasound irradiations at ambient temperature gave excellent yield of the desired products in shorter reaction time [17]. Synthesis of 2-amino-4,6-diphenylnicotinonitriles via four-component reaction of malononitrile, aromatic aldehydes, acetophenone derivatives, and ammonium acetate in water under ultrasound irradiation is described by Safari et al. [18].

Based on the few literature citations given above herein we report an ultrasound mediated synthesis of

compound of an aromatic aldehyde leading to the formation of a C–C double bond following elimination of water as a byproduct (Scheme 1) (Table 1).

3. Experimental

3.1. General Considerations. All chemicals were purchased from commercial suppliers and used further without purification. IR Spectra were recorded with Jasca FT-IR 5300. ^1H NMR and ^{13}C NMR were recorded in $\text{CDCl}_3/\text{DMSO}$ using Varian 400-MHz instrument. Mass spectra were recorded on an Agilent LC-MS instrument giving only M^+ values in Q + 1 mode. Thin-layer chromatography (TLC) analyses were carried out on glass plates coated with silica gel GF-254 and visualization was achieved using iodine vapours or UV lamp. Ultrasound for sonication is generated with the help of ultrasonic instrument. The specifications, operating parameters, and the details of the set-up are as follows. Make: China; operating frequency: 36 ± 3 kHz; rated output power: 700 W; tank size: 240 mm $\times$ 135 mm $\times$ 100 mm.

3.2. Synthesis of 2a-h from 1 Using Sonochemical Method. To a mixture of **1** (10 mM), aromatic aldehyde (10 mM) in water (20 mL) was added under sonication, by keeping all sonication parameters constant till the completion of the reaction. The reaction progress was monitored by TLC; after

TABLE 1: Synthesis of **2a–h** from **1** using sonication.

S. number	Substrate	Ar-CHO	Reagent	Time (min)	Product	M.P. (°C)	Yield
a	1	-C ₆ H ₅	H ₂ O	10	2a	192–94	98
b	1	-C ₆ H ₄ -NO ₂ -p	H ₂ O	10	2b	248–50	93
c	1	-C ₆ H ₄ -NO ₂ -m	H ₂ O	11	2c	229–31	88
d	1	-C ₆ H ₄ -CH ₃ -p	H ₂ O	10	2d	240–42	87
e	1	-C ₆ H ₄ -CH ₃ -o	H ₂ O	11	2e	226–28	89
f	1	-C ₆ H ₄ -OH-p	H ₂ O	10	2f	238–40	85
g	1	-C ₆ H ₄ -OH-o	H ₂ O	13	2g	256–58	87
h	1	-C ₆ H ₄ -(OCH ₃)-p -(OCH ₃)-m	H ₂ O	12	2h	210–12	91

10–13 min, the reaction was found to be completed. The mixture was filtered and dried. The obtained crude product was recrystallized using ethyl acetate as solvent to obtain **2a–h**. The reaction time was confirmed by repeating the procedure for three more times.

3.3. Spectrometric Characterization of the Synthesized Compounds

3.3.1. 2-((1H-Benzimidazol-2-yl)thio)-3-phenylacrylonitrile (2a). IR (KBr): 3400–2800 cm⁻¹ (br, m, -NH-); ¹H-NMR (400 MHz, DMSO-d₆/TMS): δ 8.20 (s, 1H), 8.10 (d, *J* = 4.6 Hz, 2H), 7.66–7.33 (m, *J* = 6.6 Hz, 3H), 7.65–7.34 (m, *J* = 6.4 Hz, 4H), 7.38–7.27 (m, 2H), 10.6 (s, 1H, -NH-), ¹³C NMR: δ 140.5, 138.5, 135.0, 132.5, 128.3, 122.9, 115.5, 111.5 ppm;

MS (CI): *m/z* 278 [M⁺⁺ + 1]. Anal. Calcd. for C₁₆H₁₁N₃S: C, 69.29; H, 4.00; N, 15.15; S, 11.56. Found: C, 69.26; H, 3.96; N, 15.17; S, 11.59.

3.3.2. 2-((1H-Benzimidazol-2-yl)thio)-3-(4-nitrophenyl)acrylonitrile (2b). IR (KBr): 3400–2800 cm⁻¹ (br, m, -NH-); ¹H-NMR (400 MHz, DMSO-d₆/TMS): δ 8.16 (s, 1H), 8.02 (d, *J* = 4.4 Hz, 2H), 7.62–7.31 (m, *J* = 6.5 Hz, 2H), 7.61–7.44 (m, *J* = 6.5 Hz, 4H), 10.5 (s, 1H, -NH-), ¹³C NMR: δ 141.3, 137.5, 134.0, 131.5, 127.3, 121.9, 116.5, 110.5 ppm; MS (CI): *m/z* 323 [M⁺⁺ + 1]. Anal. Calcd. for C₁₆H₁₀N₄O₂S: C, 59.62; H, 3.13; N, 17.38; O, 9.93; S, 9.95. Found: C, 59.64; H, 3.16; N, 17.36; O, 9.95; S, 9.97.

3.3.3. 2-((1H-Benzimidazol-2-yl)thio)-3-(3-nitrophenyl)acrylonitrile (2c). IR (KBr): 3400–2800 cm⁻¹ (br, m, -NH-); ¹H-NMR (400 MHz, DMSO-d₆/TMS): δ 8.21 (s, 1H), 8.16

(d, $J = 4.4$ Hz, 2H), 7.98–7.35 (m, $J = 6.4$ Hz, 2H), 7.60–7.43 (m, $J = 6.5$ Hz, 4H), 10.6 (s, 1H, –NH–), ^{13}C NMR: δ 141.2, 138.5, 134.2, 131.7, 127.5, 120.9, 117.5, 111.5 ppm; MS (CI): m/z 323 [$\text{M}^{++} + 1$]. Anal. Calcd. for $\text{C}_{16}\text{H}_{10}\text{N}_4\text{OS}$: C, 59.62; H, 3.13; N, 17.38; O, 9.93; S, 9.95. Found: C, 59.64; H, 3.16; N, 17.36; O, 9.95; S, 9.97.

3.3.4. 2-((1H-Benzimidazol-2-yl)thio)-3-(*o*-tolyl)acrylonitrile (**2d**). IR (KBr): 3400–2800 cm^{-1} (br, m, –NH–); ^1H -NMR (400 MHz, $\text{DMSO}-d_6/\text{TMS}$): δ 8.15 (s, 1H), 8.22 (d, $J = 4.2$ Hz, 2H), 7.85–7.63 (m, $J = 6.4$ Hz, 2H), 7.62–7.45 (m, $J = 6.3$ Hz, 4H), 12.2 (s, 1H, –NH–), 3.86 (s, 3H), ^{13}C NMR: δ 140.2, 136.5, 133.2, 130.7, 127.4, 120.7, 117.4, 111.3 ppm; MS (CI): m/z 292 [$\text{M}^{++} + 1$]. Anal. Calcd. for $\text{C}_{17}\text{H}_{13}\text{N}_3\text{S}$: C, 70.08; H, 4.50; N, 14.42; S, 11.00. Found: C, 70.11; H, 4.53; N, 14.45; S, 11.04.

3.3.5. 2-((1H-Benzimidazol-2-yl)thio)-3-(*p*-tolyl)acrylonitrile (**2e**). IR (KBr): 3400–2800 cm^{-1} (br, m, –NH–); ^1H -NMR (400 MHz, $\text{DMSO}-d_6/\text{TMS}$): δ 8.23 (s, 1H), 8.25 (d, $J = 4.1$ Hz, 2H), 7.75–7.53 (m, $J = 6.3$ Hz, 2H), 7.65–7.42 (m, $J = 6.2$ Hz, 4H), 12.2 (s, 1H, –NH–), 3.72 (s, 3H), ^{13}C NMR: δ 140.4, 136.7, 133.5, 131.7, 126.4, 120.7, 116.4, 110.3 ppm; MS (CI): m/z 292 [$\text{M}^{++} + 1$]. Anal. Calcd. for $\text{C}_{17}\text{H}_{13}\text{N}_3\text{S}$: C, 70.08; H, 4.50; N, 14.42; S, 11.00. Found: C, 70.11; H, 4.53; N, 14.45; S, 11.04.

3.3.6. 2-((1H-Benzimidazol-2-yl)thio)-3-(4-hydroxyphenyl)acrylonitrile (**2f**). IR (KBr): 3400–2800 cm^{-1} (br, m, –NH–); ^1H -NMR (400 MHz, $\text{DMSO}-d_6/\text{TMS}$): δ 8.20 (s, 1H), 8.28 (d, $J = 4.0$ Hz, 2H), 7.78–7.59 (m, $J = 6.0$ Hz, 2H), 7.60–7.48 (m, $J = 6.0$ Hz, 4H), 10.0 (s, 1H, –NH–, D_2O exchangeable), 12.5 (s, 1H, –OH, D_2O exchangeable) ^{13}C NMR: δ 140.6, 136.9, 133.7, 132.7, 124.4, 121.7, 115.4, 111.3 ppm; MS (CI): m/z 294 [$\text{M}^{++} + 1$]. Anal. Calcd. for $\text{C}_{16}\text{H}_{11}\text{N}_3\text{OS}$: C, 65.51; H, 3.78; N, 14.32; O, 5.45; S, 10.93. Found: C, 65.55; H, 3.76; N, 14.34; O, 5.46; S, 10.95.

3.3.7. 2-((1H-Benzimidazol-2-yl)thio)-3-(2-hydroxyphenyl)acrylonitrile (**2g**). IR (KBr): 3400–2800 cm^{-1} (br, m, –NH–); ^1H -NMR (400 MHz, $\text{DMSO}-d_6/\text{TMS}$): δ 8.16 (s, 1H), 8.22 (d, $J = 4.3$ Hz, 2H), 7.72–7.56 (m, $J = 6.2$ Hz, 3H), 7.58–7.28 (m, $J = 6.0$ Hz, 4H), 10.2 (s, 1H, –NH–, D_2O exchangeable); 12.3 (s, 1H, –OH, D_2O exchangeable); ^{13}C NMR: δ 141.6, 135.9, 132.7, 131.7, 123.4, 120.7, 114.4, 110.3 ppm; MS (CI): m/z 294 [$\text{M}^{++} + 1$]. Anal. Calcd. for $\text{C}_{16}\text{H}_{11}\text{N}_3\text{OS}$: C, 65.51; H, 3.78; N, 14.32; O, 5.45; S, 10.93. Found: C, 65.55; H, 3.76; N, 14.34; O, 5.46; S, 10.95.

3.3.8. 2-((1H-Benzimidazol-2-yl)thio)-3-(3,4-dimethoxyphenyl)acrylonitrile (**2h**). IR (KBr): 3400–2800 cm^{-1} (br, m, –NH–); ^1H -NMR (400 MHz, $\text{DMSO}-d_6/\text{TMS}$): δ 8.52 (s, 1H), 7.78 (d, $J = 4.1$ Hz, 2H), 7.77–6.92 (m, $J = 6.2$ Hz, 2H), 7.56–6.94 (m, $J = 6.0$ Hz, 4H), 10.5 (s, 1H, –NH–), 3.26 (s, 3H), 2.89 (s, 3H), ^{13}C NMR: δ 141.4, 135.5, 130.7, 130.2, 123.2, 119.7, 114.4, 109.3 ppm; MS (CI): m/z 338 [$\text{M}^{++} + 1$]. Anal. Calcd. for $\text{C}_{16}\text{H}_{11}\text{N}_3\text{OS}$: C, 64.08; H, 4.48;

N, 12.45; O, 9.48; S, 9.50. Found: C, 64.10; H, 4.46; N, 12.47; O, 9.45; S, 9.52.

4. Conclusion

In summary, we have developed a simple, atom economical, highly efficient, environmentally benign procedure for the synthesis of benzimidazolylacrylonitriles using simple ultrasonochemical method using water as a green solvent. Further, the reaction was successful without decrease in product yield. The advantages of the present procedure are the generally good yields, mild and environmentally benign inexpensive bench top chemicals, or solvents and operational simplicity.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

References

- [1] T. Eicher, *The Chemistry of Heterocycles: Structure, Reactions, Syntheses, and Applications*, vol. 2, Wiley-VCH, Weinheim, Germany, 2003.
- [2] J. P. Lorimer, *Applied Sonochemistry: Uses of Power Ultrasound in Chemistry and Processing*, vol. 1, Wiley-VCH, Weinheim, Germany, 2002.
- [3] L. Song, S. Zhang, X. Wu, and Q. Wei, "Synthesis of porous and trigonal TiO_2 nanoflake, its high activity for sonocatalytic degradation of rhodamine B and kinetic analysis," *Ultrasonics Sonochemistry*, vol. 19, no. 6, pp. 1169–1173, 2012.
- [4] R. Ghahremanzadeh, F. Fereshtehnejad, P. Mirzaei, and A. Bazgir, "Ultrasound-assisted synthesis of 2,2'-(2-oxindoline-3,3'-diyl)bis(1H-indene-1,3(2H)-dione) derivatives," *Ultrasonics Sonochemistry*, vol. 18, no. 1, pp. 415–418, 2011.
- [5] E. Kowsari and M. Mallakmohammadi, "Ultrasound promoted synthesis of quinolines using basic ionic liquids in aqueous media as a green procedure," *Ultrasonics Sonochemistry*, vol. 18, no. 1, pp. 447–454, 2011.
- [6] J.-Y. He, H.-X. Xin, H. Yan, X.-Q. Song, and R.-G. Zhong, "Convenient ultrasound-mediated synthesis of 1,4-diazabutadienes under solvent-free conditions," *Ultrasonics Sonochemistry*, vol. 18, no. 1, pp. 466–469, 2011.
- [7] J.-T. Li, Y. Yin, and M.-X. Sun, "An efficient one-pot synthesis of 2,3-epoxyl-1,3-diaryl-1-propanone directly from acetophenones and aromatic aldehydes under ultrasound irradiation," *Ultrasonics Sonochemistry*, vol. 17, no. 2, pp. 363–366, 2010.
- [8] A. Bazgir, S. Ahadi, R. Ghahremanzadeh, H. R. Khavasi, and P. Mirzaei, "Ultrasound-assisted one-pot, three-component synthesis of spiro[indoline-3,4'-pyrazolo[3,4-b]pyridine]-2,6'-(1'H)-diones in water," *Ultrasonics Sonochemistry*, vol. 17, no. 2, pp. 447–452, 2010.
- [9] K. S. Suslick, "Sonochemistry," *Science*, vol. 247, no. 4949, pp. 1439–1445, 1990.
- [10] H. Fillion and J. L. Luche, *Synthetic Organic Sonochemistry*, Plenum Press, New York, NY, USA, 1998.
- [11] A. Gedanken, "Using sonochemistry for the fabrication of nanomaterials," *Ultrasonics Sonochemistry*, vol. 11, no. 2, pp. 47–55, 2004.

- [12] C. H. Heathcock, R. C. D. Brown, and T. C. Norman, "Synthesis of Petrosins C and D," *The Journal of Organic Chemistry*, vol. 63, no. 15, pp. 5013–5030, 1998.
- [13] X. Wang, A. Guram, E. Bunel, G.-Q. Cao, J. R. Allen, and M. M. Faul, "Palladium-catalyzed one-pot synthesis of 2-alkyl-2-arylcyanoacetates," *Journal of Organic Chemistry*, vol. 73, no. 4, pp. 1643–1645, 2008.
- [14] S. D. Walker, C. J. Borths, E. Divirgilio et al., "Development of a scalable synthesis of a GPR40 receptor agonist," *Organic Process Research and Development*, vol. 15, no. 3, pp. 570–580, 2011.
- [15] S. J. Mukarram, R. Khan, and R. Yadav, "Efficient method for the manufacture of (E)—Entacapone polymorphic form A," United States Patent No.: 0004935, 2007.
- [16] U. R. Pratap, D. V. Jawale, R. A. Waghmare, D. L. Lingampalle, and R. A. Mane, "Synthesis of 5-arylidene-2,4-thiazolidinediones by Knoevenagel condensation catalyzed by baker's yeast," *New Journal of Chemistry*, vol. 35, no. 1, pp. 49–51, 2011.
- [17] A. M. A. Al-Kadasi and G. M. Nazeruddin, "Ultrasound assisted catalyst-free one-pot synthesis of bis-coumarins in neat water," *International Journal of Chemical Sciences*, vol. 10, no. 1, pp. 324–330, 2012.
- [18] J. Safari, S. H. Banitaba, and S. D. Khalili, "Ultrasound-promoted an efficient method for one-pot synthesis of 2-amino-4,6-diphenylnicotinonitriles in water: a rapid procedure without catalyst," *Ultrasonics Sonochemistry*, vol. 19, no. 5, pp. 1061–1069, 2012.
- [19] V. R. Reddy, P. K. Dubey, and S. S. Rao, "Synthesis of α -benzylthiobenzimidazole acetonitriles and their chemoselective reduction of the double bond with NaBH_4 ," *Journal of Heterocyclic Chemistry*. In press.