Ultrasonics Sonochemistry 19 (2012) 475–478

Contents lists available at SciVerse ScienceDirect

Ultrasonics Sonochemistry

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

Efficient one-pot three-component synthesis of N-(4-arylthiazol-2-yl) hydrazones in water under ultrasound irradiation

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ARTICLE INFO

Article history:
Received 23 June 2011
Received in revised form 15 October 2011
Accepted 15 October 2011
Available online 10 November 2011

Keywords:
One-pot synthesis
Hydrazothiazole
Condensation
Ultrasound irradiation
Aqueous media

ABSTRACT

A highly efficient and facile one-pot three-component synthesis of N-(4-arylthiazol-2-yl) hydrazones was carried out in excellent yield without any catalyst in water under ultrasound irradiation.

1. Introduction

Schiff bases are well known for their pharmacological properties as anti-bacterial, anti-fungal, anti-cancer and anti-viral agents [1]. Similarly, thiazole derivatives possess activities such as anti-bacterial [2], anti-fungal [3], anti-inflammatory [4], anti-hypertensive [5], anti-HIV [6], anti-tumor [7], and anti-filarial [7c,d]. The potential possibility of hydrazothiazole derivatives for better therapeutic results has attracted extensive interest in last decade. Generally, N-(4-arylthiazol-2-yl) hydrazones are synthesised through two steps in conventional methods. Aromatic aldehydes or ketones react with thiosemicarbazide to yield thiosemicarbazones, which then react with ω-bromoacetophenone to obtain N-(4-arylthiazol-2-yl) hydrazones by the cyclization [8]. In spite of their potential utility, some of the reported two-step methods suffer from drawbacks such as long reaction time, use of organic solvents, and moderate yields. Compared with two-steps strategy, one-pot reaction provides useful products without isolation of any intermediate, and thus reduces time, saves both energy and raw materials [9]. Kamble et al. described the synthesis of 2-{2-[N-(2-hydroxybenzylidene)hydrazino]thiazol-4-yl}phenols by the one-pot condensation of α-halo ketones, thiosemicarbazide, and 2-hydroxybenzaldehyde in PEG-400 to give good results [10].

Organic reactions in aqueous media have currently attracted increasing interest because of environmental issues and the understanding of biochemical processes. Water offers many practical and economic advantages as a reaction solvent, including low cost, safe handing and environmental compatibility. Recently, many organic reactions in aqueous media have been described in the literatures [11]. On the other hand, a large number of organic reactions can be carried out in higher yield, shorter reaction time and milder conditions under ultrasonic irradiation than at classical conditions [12].

To the best of our knowledge, there is no report on one-pot three-component reaction in water for the synthesis of N-(4-arylthiazol-2-yl) hydrazones under ultrasound irradiation. Herein, we wish to report an efficient one-pot procedure for the synthesis of N-(4-arylthiazol-2-yl) hydrazones in water under ultrasound irradiation (Scheme 1).

2. Methods

2.1. Apparatus and analysis

Melting points were uncorrected. Sonication was performed in Tianjin AS 20500AT Ultrasonic Cleaner (with a frequency of 25 kHz and a nominal power 250 W). NMR spectra were measured on a Bruker AVANCE 600 (600 MHz) spectrometer using TMS as the

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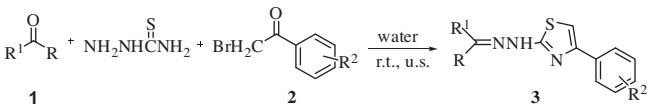
doi:10.1016/j.ultsonch.2011.10.017



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Scheme 1. One-pot three-component synthesis of N-(4-arylthiazol-2-yl) hydrazones under ultrasound irradiation.

internal standards and DMSO as a solvent. HRMS spectra were determined on a Bruker apex ultra 7.0 T Fourier transform mass spectrometer. IR spectra were recorded on a Rayleigh WQF-510 FTIR spectrometer. Elemental analyzes were taken with an Exeter Analytical CE-440 elemental analyzer.

2.2. General procedure for the condensation of N-(4-arylthiazol-2-yl) hydrazones

Aromatic aldehydes or ketones (**1**, 0.5 mmol), thiosemicarbazide (0.5 mmol), substituted phenacyl bromide (**2**, 0.5 mmol) and water (8 mL) were mixed in a 25 mL round-bottomed flask. The reaction mixture was either stirred, or irradiated in the water bath of an ultrasonic cleaner, at room temperature for the period (the reaction was monitored by TLC, silica gel; petroleum ether:ethyl acetate = 3:1 V/V) as indicated in Table 2. After completion of the reaction, the reaction mixture was filtered, and the precipitate was washed with EtOH, affording the crude product, which was purified by column chromatography on basic alumina column (200–300 mesh) eluted with petroleum ether (b.p. 60–90 °C) or a mixture of petroleum ether and ethyl acetate (10:1 V/V). The authenticity of the products (**3a–3l**) was established by their ^{1}H NMR, ^{13}C NMR, IR, HRMS data or elemental analyzes.

*2.2.1. Compound **3a***

2-(2-Benzylidenehydrazinyl)-4-phenyl-1,3-thiazole, solid, m.p. 174–175 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ (ppm): 12.18 (s, 1H, NH), 8.05 (s, 1H, N=CH), 7.87 (d, J = 7.2 Hz, 2H, ArH), 7.67 (d, J = 7.2 Hz, 2H, ArH), 7.37–7.47 (m, 5H, ArH), 7.33 (s, 1H, thiazole H), 7.31 (t, J = 7.2 Hz, 1H, ArH); ^{13}C NMR (150 MHz, DMSO-d_6) δ (ppm): 168.7, 141.6, 135.1, 134.8, 129.7, 129.3, 129.1, 128.0, 126.7, 125.9, 104.1; IR (KBr, ν, cm^{-1}): 3394, 3305, 3151, 1560, 1535; Anal. Calcd for $C_{16}H_{13}N_3S$: C 68.79, H 4.69, N 15.04%; Found: C 68.72, H 4.64, N 14.88%.

*2.2.2. Compound **3b***

2-[2-(4-Methoxybenzylidene)hydrazinyl]-4-phenyl-1,3-thiazole, solid, m.p. 169–170 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ (ppm): 12.01 (s, 1H, NH), 8.00 (s, 1H, N=CH), 7.86 (d, J = 7.8 Hz, 2H, ArH), 7.61 (d, J = 9.0 Hz, 2H, ArH), 7.41 (t, J = 7.8 Hz, 2H, ArH), 7.27–7.32 (m, 2H, ArH + thiazole H), 7.00 (d, J = 9.0 Hz, 2H, ArH), 3.80 (s, 3H, CH_3); ^{13}C NMR (150 MHz, DMSO-d_6) δ (ppm): 168.3, 160.2, 150.6, 141.3, 134.7, 128.5, 127.8, 127.4, 127.0, 125.5, 114.3, 103.3, 55.2; IR (KBr, ν, cm^{-1}): 3290, 3112, 2962, 2846, 1612, 1565, 1511; Anal. Calcd for $C_{17}H_{15}N_3OS$: C 66.00, H 4.89, N 13.58%; Found: C 65.73, H 4.84, N 13.68%.

*2.2.3. Compound **3c***

2-{[2-(4-Phenyl-1,3-thiazol-2-yl)hydrazinylidene]methyl}phenol, solid, mp 195–196 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ (ppm): 12.15 (s, 1H, NH), 10.13 (s, 1H, OH), 8.33 (s, 1H, N=CH), 7.86 (d, J = 7.2 Hz, 2H, ArH), 7.62–7.65 (m, 1H, ArH), 7.41 (t, J = 7.8 Hz, 2H, ArH), 7.29–7.33 (m, 2H, ArH + thiazole H), 7.21–7.25 (m, 1H, ArH), 6.87–6.93 (m, 2H, ArH); ^{13}C NMR (150 MHz, DMSO-d_6) δ (ppm): 168.4, 156.4, 151.3, 139.9, 135.2, 130.0, 129.1, 128.1, 127.0, 126.0, 120.0, 116.6, 114.3, 103.9; IR (KBr, ν, cm^{-1}): 3317, 3052, 1618, 1538; Anal. Calcd for $C_{16}H_{13}N_3OS$: C 65.06, H 4.44, N 14.23%; Found: C 65.40, H 4.32, N 14.35%.

*2.2.4. Compound **3d***

2-[2-(2-Chlorobenzylidene)hydrazinyl]-4-phenyl-1,3-thiazole, solid, mp 174–175 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ (ppm): 12.40 (s, 1H, NH), 8.40 (s, 1H, N=CH), 7.93 (dd, J = 7.8 Hz, 1.8 Hz, 1H, ArH), 7.84–7.88(m, 2H, ArH), 7.51 (dd, J = 7.8 Hz, 1.2 Hz, 1H, ArH), 7.38–7.44 (m, 4H, ArH), 7.36 (s, 1H, thiazole H), 7.31 (t, J = 7.2 Hz, 1H, ArH); ^{13}C NMR (150 MHz, DMSO-d_6) δ (ppm): 168.4, 138.7, 132.6, 132.0, 131.7, 131.1, 130.4, 130.2, 129.1, 128.1, 127.9, 126.7, 126.0, 104.6; IR (KBr, ν, cm^{-1}): 3415, 3249, 3151, 1573; Anal. Calcd for $C_{16}H_{12}ClN_3S$: C 61.24, H 3.85, N 13.39%; Found: C 61.54, H 3.77, N 13.71%.

*2.2.5. Compound **3e***

2-[2-(3-Chlorobenzylidene)hydrazinyl]-4-phenyl-1,3-thiazole, solid, mp 163–164 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ (ppm): 12.36 (s, 1H, NH), 8.03 (s, 1H, N=CH), 7.89–7.84 (m, 2H, ArH), 7.71 (s, 1H, ArH), 7.64–7.61(m, 1H, ArH), 7.48–7.39 (m, 4H, ArH), 7.36 (s, 1H, thiazole H), 7.31 (dt, J = 7.2 Hz, 1.2 Hz, 1H, ArH); ^{13}C NMR (150 MHz, DMSO-d_6) δ (ppm): 168.5, 151.0, 140.0, 137.1, 135.0, 134.1, 131.2, 129.3, 129.1, 128.1, 126.0, 125.9, 125.4, 104.4; IR (KBr, ν, cm^{-1}): 3415, 3155, 3072, 1581; Anal. Calcd for $C_{16}H_{12}ClN_3S$: C 61.24, H 3.85, N 13.39%; Found: C 61.25, H 4.00, N 13.11%.

*2.2.6. Compound **3f***

2-[2-(4-Chlorobenzylidene)hydrazinyl]-4-phenyl-1,3-thiazole, solid, mp 178–179 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ (ppm): 12.07 (s, 1H, NH), 8.03 (s, 1H, N=CH), 7.85 (d, J = 7.2 Hz, 2H, ArH), 7.66 (d, J = 8.4 Hz, 2H, ArH), 7.48 (d, J = 7.8 Hz, 2H, ArH), 7.40 (t, J = 7.8 Hz, 2H, ArH), 7.34–7.27 (m, 2H, ArH + thiazole H); ^{13}C NMR (150 MHz, DMSO-d_6) δ (ppm): 168.6, 151.0, 140.4, 135.1, 134.1, 133.8, 129.4, 129.1, 128.3, 128.0, 126.0, 104.2; IR (KBr, ν, cm^{-1}): 3434, 3286, 3160, 1581, 1502; Anal. Calcd for $C_{16}H_{12}ClN_3S$: C 61.24, H 3.85, N 13.39%; Found: C 61.00, H 3.76, N 13.87%.

*2.2.7. Compound **3g***

5-Methoxy-2-{[2-(4-phenyl-1,3-thiazol-2-yl)hydrazinylidene]methyl}phenol, solid, mp 181–182 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ (ppm): 12.17 (s, 1H, NH), 9.51 (s, 1H, OH), 8.36 (s, 1H, N=CH), 7.86 (d, J = 7.8 Hz, 2H, ArH), 7.45–7.38 (m, 2H, ArH), 7.34–7.28 (m, 2H, ArH + thiazole H), 7.26 (d, J = 7.8 Hz, 1H, ArH), 6.97 (d, J = 8.4 Hz, 1H, ArH), 6.97 (td, J = 7.8 Hz, 1.2 Hz, 1H, ArH), 3.83 (s, 3H, CH_3); ^{13}C NMR (150 MHz, DMSO-d_6) δ (ppm): 168.4, 148.5, 145.9, 140.0, 135.1, 129.1, 128.0, 126.0, 121.0, 119.7, 118.4, 113.0, 103.8, 56,3; IR (KBr, ν, cm^{-1}): 3459, 3342, 3162, 3031, 1621, 1596, 1540; Anal. Calcd for $C_{17}H_{15}N_3O_2S$: C 62.75, H 4.65, N 12.91%; Found: C 62.32, H 4.67, N 12.56%.

*2.2.8. Compound **3h***

N,N-Dimethyl-4-{[2-(4-phenyl-1,3-thiazol-2-yl)hydrazinylidene]methyl}aniline, solid, mp 183–184 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ (ppm): 11.79 (s, 1H, NH), 7.92 (s, 1H, N=CH), 7.87–7.82 (m, 2H, ArH), 7.47 (d, J = 9.0 Hz, 1H, ArH), 7.40 (t, J = 7.8 Hz, 2H, ArH), 7.29 (t, J = 7.2 Hz, 1H, ArH), 7.23 (s, 1H, thiazole H), 6.74 (d, J = 8.4 Hz, 2H, ArH), 2.95 (s, 6H, 2CH_3); ^{13}C NMR (150 MHz, DMSO-d_6) δ (ppm): 168.9, 151.5, 150.9, 142.9, 140.0, 135.3, 129.1, 128.0, 126.0, 122.3, 112.4, 103.4, 40.3; IR (KBr, ν, cm^{-1}): 3372, 3290, 3104, 2798, 1606, 1565, 1523; Anal. Calcd for $C_{18}H_{18}N_4S$: C 67.05, H 5.63, N 17.38%; Found: C 66.82, H 5.55, N 17.10%.

*2.2.9. Compound **3i***

2-(2-Cyclopentylidenehydrazinyl)-4-phenyl-1,3-thiazole, solid, mp 156–157 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ (ppm): 10.55 (s, 1H, NH), 7.86–7.82 (m, 2H, ArH), 7.36 (dd, J = 10.6 Hz, 4.9 Hz, 2H, ArH), 7.30–7.26 (m, 1H, ArH), 7.22 (s, 1H, thiazole H), 2.36 (dd, J = 11.2 Hz, 7.0 Hz, 4H, 2CH_2), 1.82–1.75 (m, 2H, CH_2), 1.73–1.66 (m, 2H, CH_2); ^{13}C NMR (150 MHz, DMSO-d_6) δ (ppm): 170.2, 162.1, 151.0, 135.4, 129.0, 127.8, 126.0, 103.6, 33.3, 29.1, 25.1; IR (KBr, ν, cm^{-1}): 3145, 2917, 2856, 1560; HRMS: m/z Calcd for $C_{14}H_{15}N_3NaS$: $[M+Na]^+$, 280.0879; Found: 280.0895.

*2.2.10. Compound **3j***

2-(2-Cyclohexylidenehydrazinyl)-4-phenyl-1,3-thiazole, solid, mp 148–149 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ (ppm): 10.79 (s, 1H, NH), 7.86–7.82 (m, 2H, ArH), 7.39 (dd, J = 10.7 Hz, 4.8 Hz, 2H, ArH), 7.28 (t, J = 7.8 Hz, 1H, ArH), 7.21 (s, 1H, thiazole H), 2.44 (t, J = 5.8 Hz, 2H, CH_2), 2.23–2.27 (m, 2H, CH_2), 1.56–1.66 (m, 6H, 3CH_2); ^{13}C NMR (150 MHz, DMSO-d_6) δ (ppm): 170.6, 155.6, 135.5, 129.0, 127.8, 126.0, 103.6, 35.2, 27.6, 27.3, 26.0, 25.6; IR (KBr, ν, cm^{-1}): 3062, 2948, 1558; HRMS: m/z Calcd for $C_{15}H_{18}N_3S$: $[M+H]^+$, 272.1216; Found: 272.1216.

*2.2.11. Compound **3k***

4-(4-Chlorophenyl)-2-[2-(1-*p*-tolylethylidene)hydrazinyl]-1,3-thiazole, solid, mp 240–241 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ (ppm): 11.22 (s, 1H, NH), 7.89 (d, J = 8.5 Hz, 2H, ArH), 7.68 (d, J = 8.1 Hz, 2H, ArH), 7.47 (d, J = 8.5 Hz, 2H, ArH), 7.37 (s, 1H, thiazole H), 7.22 (d, J = 8.2 Hz, 2H, ArH), 2.33 (s, 3H, CH_3), 2.31 (s, 3H, CH_3); ^{13}C NMR (150 MHz, DMSO-d_6) δ (ppm): 170.5, 147.2, 138.7, 135.6, 134.1, 132.4, 129.5, 129.3, 127.7, 127.0, 126.1, 105.3, 21.3, 14.5; IR (KBr, ν, cm^{-1}): 3332, 1697, 1683, 1670, 1560, 1510; HRMS: m/z Calcd for $C_{18}H_{17}ClN_3S$: $[M+H]^+$, 342.0826; Found: 342.0829.

*2.2.12. Compound **3l***

2-(2-Cyclohexylidenehydrazinyl)-4-*p*-tolyl-1,3-thiazole, solid, mp 132–133 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ (ppm): 10.84 (s, 1H, NH), 7.71 (d, J = 8.1 Hz, 2H, ArH), 7.22 (d, J = 8.0 Hz, 2H, ArH), 7.18 (s, 1H, thiazole H), 2.39 (t, J = 6.9 Hz, 4H, 2CH_2), 2.32 (s, 3H, CH_3), 1.80–1.69 (m, 6H, 3CH_2); ^{13}C NMR (150 MHz, DMSO-d_6) δ (ppm): 170.6, 155.6, 135.5, 129.0, 127.8, 126.0, 103.6, 35.2, 27.6, 27.3, 26.0, 25.6; IR (KBr, ν, cm^{-1}): 3062, 2948, 1558; HRMS: m/z Calcd for $C_{15}H_{18}N_3S$: $[M+H]^+$, 272.1216; Found: 272.1216.

Table 1
The effect of solvents on reaction of benzaldehyde, thiosemicarbazide and phenacyl bromide under ultrasound irradiation.[a]

Entry	Solvent	Time (min)	Yield (%)
1	EtOH	50	63
2	2-Propanol	50	65
3	CH_3CN	50	45
4	CH_2Cl_2	50	56
5	H_2O	50	90

[a] *Reaction condition:* benzaldehyde, 0.5 mmol; thiosemicarbazide, 0.5 mmol; phenyacyl bromide, 0.5 mmol; solvent: 8 mL; reaction temperature: 25 °C.

Table 2
The effect of reaction temperature on the yield of **3a** under ultrasound irradiation.

Entry	Temperature (°C)	Time (min)	Yield (%)
1	25	50	90
2	35	40	82
3	45	40	78

3. Results and discussion

In order to verify the effect of solvents on the condensation under ultrasound, the condensation of benzaldehyde (**1a**), thiosemicarbazide and phenacyl bromide to form **3a** in different solvents was accomplished at room temperature under ultrasound irradiation. The results are summarized in Table 1. As shown, the reaction in water completed in 50 min with yield of 90%, water was more effective than organic solvents.

The effect of temperature on the yield of **3a** was also observed. As shown in Table 2, the condensation of benzaldehyde (**1a**), thiosemicarbazide and phenacyl bromide was carried out in 90% yield within 50 min at 25 °C in water under ultrasound (Table 2, entry 1). So the reaction temperature was chosen at 25 °C.

We also did the experiment for synthesis of 2-benzylidenhydrazo-4-phenylthiazole using two-steps method by stirring alone without ultrasound. The benzaldehyde reacted with thiosemicarbazide in water at room temperature to form benzaldehyde thiosemicarbazone, which then reacted with phenacyl bromide to give the corresponding 2-benzylidenhydrazo-4-phenylthiazole (**3a**), the invert yield and reaction time for reaction to give **3a** were 54.6% and 130 min, respectively. Under ultrasound, one-pot reaction in water at room temperature was completed within 50 min to obtain **3a** in 90% yield. It is apparent that one-pot reaction under ultrasound was more efficient than the classical two-steps approach.

Encouraged by this result, we extended the reaction to other aromatic aldehydes or ketones and substituted phenacyl bromide under ultrasound irradiation or conventional stirring respectively. The results are summarized in Table 3. As shown in Table 3, the aromatic aldehyde with electron-rich functionality as well as electron-poor functionality condensed with thiosemicarbazide and phenacyl bromide to afford the corresponding N-(4-arylthiazol-2-yl) hydrazones

Table 3
Reaction of aromatic aldehydes or ketones, thiosemicarbazide and phenacyl bromide with and without ultrasound irradiation.

Entry	R/R^1	R^2	**3**	Conventional stirring		Ultrasonic irradiation	
				Time (min)	Yield (%)	Time (min)	Yield (%)
1	C_6H_5/H	H	**3a**	90	80	50	90
2	4-$CH_3OC_6H_5$/H	H	**3b**	180	76	60	95
3	2-OHC_6H_5/H	H	**3c**	240	82	100	90
4	2-ClC_6H_5/H	H	**3d**	240	78	70	89
5	3-ClC_6H_5/H	H	**3e**	240	89	120	89
6	4-ClC_6H_5/H	H	**3f**	180	72	100	88
7	2-OH,4-$CH_3OC_6H_5$/H	H	**3g**	180	92	70	92
8	4-$N(CH_3)_2C_6H_5$/H	H	**3h**	210	65	100	86
9	$(CH_2)_4$	H	**3i**	180	60	90	88
10	$(CH_2)_5$	H	**3j**	180	80	80	89
11	4-$CH_3C_6H_5$/CH_3	4-Cl	**3k**	240	62	120	92
12	$(CH_2)_5$	4-CH_3	**3l**	240	87	100	93

in excellent yields (89–95%). Furthermore, substituted phenacyl bromide smoothly reacted with thiosemicarbazide and aromatic aldehyde or ketones affording the corresponding products **3k**, **3l** in excellent yields of 92%, 93% (Table 2, entries 11 and 12). Compared with conventional stirring, the reaction under ultrasound irradiation was completed in shorter time to give the title compounds in higher yields. According to the two-step method in the literature [8a], the total yield of compound **3a**, **3c** and **3h** was 64.2%, 83.4% and 55.8%, respectively. Whereas, the present procedure gave **3a**, **3c** and **3h** in 90%, 90% and 86% yield (Table 2, entries 1, 3 and 8), respectively.

Compared with the one-pot reaction in PEG-400 [10], the advantage of the present procedure is the use of water instead of PEG-400, the reaction temperature is also reduced from 40 to 25 °C. However, the disadvantages include the longer reaction time and a little lower yield.

It can be observed that almost all reactions were complete in 1–2 h in water under ultrasound irradiation without any added catalyst or organic solvents at r.t. The reaction time was shorter and the yield was higher under ultrasound than under conventional stirring.

Cavitation is the origin of sonochemistry. In the heterogeneous reactions involving immiscible liquid, the reaction between these species can only occur in the interfacial region between the liquids. Sonication can be used to produce very fine emulsions and enhances mass transfer from immiscible liquids. This is possible because cavitational collapse at or near the interface disrupts it and implies jets of one liquid into the other to form the emulsion [12a,b]. These can cause the reaction to take place rapidly.

4. Conclusion

In conclusion, we have described a simple and highly efficient protocol for the synthesis of N-(4-arylthiazol-2-yl) hydrazones in water as reaction medium at room temperature. Ultrasound irradiation can greatly accelerate the reaction. This process avoids the use of organic solvents and catalyst. Furthermore, the procedure offers several advantages including improved yields, simple experimental procedure, cleaner reactions, and low cost, which makes it a useful and attractive strategy in view of economic and environmental advantages.

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