An efficient and clean synthesis of 1-aroyl-3-aryl-4-substituted imidazole-2-thiones in water

Xi-Cun Wang*, Fang Wang, Zheng-Jun Quan, Man-Gang Wang and Zheng Li

Gansu Key Laboratory of Polymer Materials, College of Chemistry and Chemical Engineering, Northwest Normal University, Lanzhou, Gansu 730070, P. R. China

Treatment 1-aryl-3-aroyl/benzofuroyl thioureas with α-bromo substituted carbonyl compounds in water affording 1-aroyl/benzofuroyl-3-aryl-4-substituted imidazole-2-thiones in excellent yields within short time.

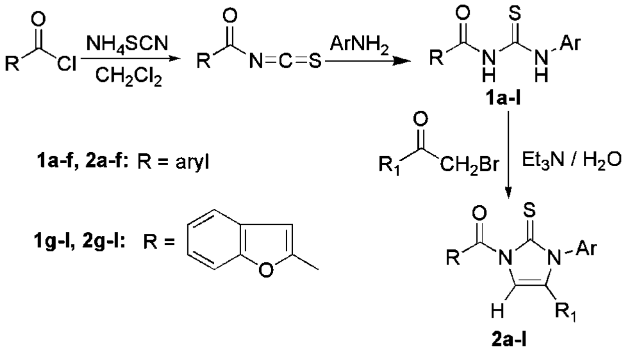
Keywords: 1-aroyl/benzofuroyl-3-aryl-4-substituted imidazole-2-thiones, synthesis in water, 1-aryl-3-aroyl/benzofuroyl thioureas, α-bromo substituted carbonyl compounds

The use of water as a medium in organic reaction has received considerable attention due to its several advantages, such as it is the cheapest solvent available on earth, non-hazardous to the environment, non-toxic and isolation of the organic products can be performed by simple phase separation.[1-4] Also there are beneficial effects of aqueous solvents on rates and selectivity of important organic transformations, *e.g.* Diels–Alder reaction, Aldol reaction and Michael addition.[5-6]

Imidazole-2-thione and its derivatives have received attention because of their bioactivities and application for pharmaceutical synthesis.[7,8] There are many methods reported in the literature for the preparation of imidazole-2-thione derivatives. Marckwald established the first synthetic route to 1-substituted imidazole-2-thione by reaction of isothiocyanate with aminoacetal in 1889.[9,10] Lawson prepared imidazole-2-thione and its derivatives from KSCN and the corresponding amino acid ester hydrochloride.[11,12] Fuentes described the reaction of D-fructosamines with different chiral imidazolidine-2-thione *N*-nucleosides.[13] In recently, Zeng described the synthesis of imidazole-2-thiones in acetone or dichloromethane under the atmosphere of nitrogen, and giving the aimed products with acceptable yields.[14] However, these reactions have with some drawbacks: extended reaction period at elevated temperature or strong condition, *e.g.* nitrogen atmosphere, particularly the use of some harmful organic solvent.

In this paper, we described an efficient and clean method for the preparation of imidazole-2-thiones by cyclisation reaction of 1-aryl-3-aroyl/benzofuroyl thioureas and α-bromo substituted carbonyl compounds in the presence of triethylamine (Et_3N) in aqueous media (Scheme 1).

As described in Scheme 1, treatment 1-phenyl-3-benzoyl thiourea (**1a**) with one equivalent of α-bromoacetone and triethylamine in aqueous media, afforded 1-benzoyl-3-phenyl-4- methylimidazole-2-thione (**2a**) in 95% yield within 15 min.



Scheme 1

To establish the generality, **1a** was treated with α-bromoacetophenone and α-bromoacetaldehyde, respectively, in water for 15 min. Compound **2d** was obtained with α-bromoacetophenone in good yield with high purity. However, with α-bromoacetaldehyde, no desired product was obtained. With these results, we synthesised compounds **2a–l** with moieties of aroyl/benzofuroyl. The results are listed in Table 1.

This procedure offered the advantages of no pollution by using water as solvent, simple operation, and the obtained products were pure in short reaction time compared with the results obtained by the reported method.[14]

In conclusion we have shown an efficient and clean method for the preparation of 1-aroyl/benzofuroyl-3-aryl-4-substituted imidazole-2-thiones with high yields in the presence of triethyl-

Table 1 Synthesis of compounds **2a–2l** in water

Compd.	R	Ar	R_1	M.p./ °C (Lit.)[14]	Yield/%	
					a	b
2a	C_6H_5	C_6H_5	CH_3	158–159(157–159)	95	75
2b	C_6H_5	$4\text{-}ClC_6H_4$	CH_3	211–212(209–211)	93	82
2c	C_6H_5	$4\text{-}CH_3C_6H_4$	CH_3	216–217(215–217)	90	78
2d	C_6H_5	C_6H_5	C_6H_5	206–207(208–210)	80	85
2e	C_6H_5	$4\text{-}ClC_6H_4$	C_6H_5	214–215(215–217)	80	83
2f	C_6H_5	$4\text{-}BrC_6H_4$	C_6H_5	235–236(233–235)	82	87
2g	2-benzofuran	C_6H_5	CH_3	188–189	80	77
2h	2-benzofuran	$4\text{-}ClC_6H_4$	CH_3	218–219	92	80
2i	2-benzofuran	$2\text{-}ClC_6H_4$	CH_3	208–209	75	78
2j	2-benzofuran	$3\text{-}BrC_6H_4$	CH_3	189–190	88	82
2k	2-benzofuran	$4\text{-}CH_3C_6H_4$	C_6H_5	233–234	83	79
2l	2-benzofuran	$4\text{-}BrC_6H_4$	C_6H_5	256–258	75	71

[a] Synthesis in water.
[b] Preparation according to literature method.[14]

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* Correspondent. E-mail: wangxicun@nwnu.edu.cn

amine under mild reaction conditions, and an easy work up procedure. Finally, as the synthesis of 1-aroyl/benzofuroyl-3-aryl-4-substituted imidazole-2-thiones is carried out in water it can be considered as an environmentally friendly reaction.

Experimental

1-Aryl-3-aroylthioureas[15] and 1-aryl-3-(2-benzofuroyl) thioureas[16] were prepared according to literature procedures.

Synthesis of 1-benzoyl/(2-benzofuroyl)-3-aryl-4-substituted imidazole-2-thiones **2a–l**. *General procedure*: α-bromo substituted carbonyl compound (1 mmol) was added to a suspension of 1-aryl-3-benzoyl/(2-benzofuroyl) thiourea (**1**) (1 mmol) and triethylamine (1 mmol) in 6 mL H_2O. Then the mixture was heated under refluxing for 15 min. After the reaction was completed, crude product was obtained by filtering and recrystallisation from EtOH-H_2O (4:1) to give the pure product **2**. The results are shown in Table 1.

The products **2a–2f** gave m.p.s and spectral data consistent with the published data.[14]

2g: Yield: 80%, m.p. 188–189 °C. IR (KBr): 3093, 1605, 1557, 1469, 1369, 1257, 1227 cm^{-1}. ^{1}H NMR (DMSO-d_6, 400 Hz): δ = 8.10–8.06 (m, 2H, ArH), 7.75–7.67 (m, 4H, ArH), 7.65–7.61 (m, 1H, ArH), 7.46–7.39 (m, 2H, ArH), 7.32–7.25 (m, 1H, ArH), 6.86–6.85 (d, 1H, *J* = 1.2 Hz, =CH), 2.06 (d, 3H, *J* = 6 Hz, CH_3). ^{13}C NMR (DMSO-d_6, 100 Hz): δ = 174.7, 167.4, 154.9, 152.2, 137.3, 134.8, 130.0, 129.9, 129.6, 127.5, 126.9, 123.6, 122.9, 111.9, 111.2, 104.9, 15.5. Anal. Calcd for $C_{19}H_{14}N_2O_2S$: C, 68.25; H, 4.22; N, 8.38. Found: C, 68.34; H, 4.13; N, 8.33.

2h: Yield: 92%, m.p. 218–219 °C. IR (KBr): 3103, 1604, 1557, 1469, 1369, 1257, 1227 cm^{-1}. ^{1}H NMR (DMSO-d_6, 400 Hz): δ = 8.12–8.08 (m, 2H, ArH), 7.75–7.65 (m, 3H, ArH), 7.60–7.53 (m, 1H, ArH), 7.44–7.24 (m, 2H, ArH), 7.17–7.14 (m, 1H, ArH), 6.92 (d, 1H, *J* = 1.2 Hz, =CH), 2.03 (d, 3H, *J* = 6 Hz, CH_3). ^{13}C NMR (DMSO-d_6, 100 Hz): δ = 175.5, 167.4, 154.9, 152.2, 136.6, 135.8, 135.1, 133.9, 130.0, 127.5, 126.9, 123.6, 122.9, 111.9, 111.2, 104.8, 15.5. Anal. Calcd for $C_{19}H_{13}ClN_2O_2S$: C, 61.87; H, 3.55; N, 7.60. Found: C, 61.80; H, 3.61; N, 7.53.

2i: Yield: 75%, m.p. 208–209 °C. IR (KBr): 3093, 1607, 1547, 1467, 1372, 1263, 1227 cm^{-1}. ^{1}H NMR (DMSO-d_6, 400 Hz): δ = 8.11–8.07 (m, 2H, ArH), 7.77–7.69 (m, 3H, ArH), 7.65–7.63 (m, 1H, ArH), 7.46–7.36 (m, 2H, ArH), 7.10–7.05 (m, 1H, ArH), 6.86–6.85 (d, 1H, *J* = 1.3 Hz, =CH), 2.02 (d, 3H, *J* = 6 Hz, CH_3). ^{13}C NMR (DMSO-d_6, 100 Hz): δ = 175.5, 167.4, 154.9, 152.2, 139.2, 137.6, 134.6, 133.8, 133.3, 131.6, 130.2, 127.5, 126.6, 123.5, 122.6, 111.9, 111.7, 104.5, 15.0. Anal. Calcd for $C_{19}H_{13}ClN_2O_2S$: C, 61.87; H, 3.55; N, 7.60. Found: C, 61.81; H, 3.62; N, 7.52.

2j: Yield: 88%, m.p. 189–190 °C. IR (KBr): 3104, 1605, 1557, 1469, 1369, 1256, 1227 cm^{-1}. ^{1}H NMR (DMSO-d_6, 400 Hz): δ = 8.12–8.08 (m, 2H, ArH), 7.75–7.65 (m, 3H, ArH), 7.63–7.55 (m, 1H, ArH), 7.41–7.24 (m, 2H, ArH), 7.17–7.13 (m, 1H, ArH), 6.92 (d, 1H, *J* = 1.2 Hz, =CH), 2.03 (d, 3H, *J* = 6 Hz, CH_3). ^{13}C NMR (DMSO-d_6, 100 Hz): δ = 174.9, 167.4, 154.9, 152.2, 137.0, 136.7, 134.2, 133.2, 130.6, 127.8, 127.1, 125.9, 125.4, 123.0, 122.4, 111.7, 111.2, 105.3, 15.5. Anal. Calcd for $C_{19}H_{13}BrN_2O_2S$: C, 55.22; H, 3.17; N, 6.78. Found: C, 55.15; H, 3.23; N, 6.73.

2k: Yield: 83%, m.p. 233–234 °C. IR (KBr): 3070, 1605, 1554, 1461, 1374, 1257, 1233 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 Hz): δ = 8.05 (d, 2H, *J* = 7.6 Hz, ArH), 7.64–7.11 (m, 12H, ArH), 6.78 (s, 1H, =CH), 2.35 (s, 3H, CH_3). ^{13}C NMR ($CDCl_3$, 100 Hz): δ = 174.6, 169.9, 155.6, 152.5, 139.1, 138.3, 134.7, 130.3, 129.5, 129.2, 129.0, 128.5, 127.3, 126.8, 123.6, 122.9, 111.3, 108.3, 105.3, 20.9. Anal. Calcd for $C_{25}H_{18}N_2O_2S$: C, 73.15; H, 4.42; N, 6.82. Found: C, 73.19; H, 4.39; N, 6.85.

2l: Yield: 75%, m.p 256–258 °C. IR (KBr): 3070, 1608, 1557, 1461, 1374, 1260, 1233 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 Hz): δ = 8.06 (d, 2H, *J* = 7.6 Hz, ArH), 7.95–7.25 (m, 12H, ArH), 6.73 (s, 1H, =CH). ^{13}C NMR ($CDCl_3$, 100 Hz): δ = 174.6, 169.8, 155.8, 152.5, 139.2, 138.0, 134.4, 130.7, 129.6, 129.3, 129.0, 128.4, 127.3, 126.1, 123.6. 122.2, 111.3, 108.4, 105.1. Anal. Calcd for $C_{24}H_{15}BrN_2O_2S$: C, 60.64; H, 3.18; N, 5.89. Found: C, 60.69; H, 3.13; N, 5.85.

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