Synthesis of 1-Benzoyl-3-aryl-4-hydroxy-4-phenylimidazolidin-2-thiones

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1-Benzoyl-3-aryl-4-hydroxy-4-phenylimidazolidin-2-thiones can be synthesized readily from the cyclization of 1-benzoyl-3-arylthioureas with bromine-acetophenone in the presence of excess triethylamine.

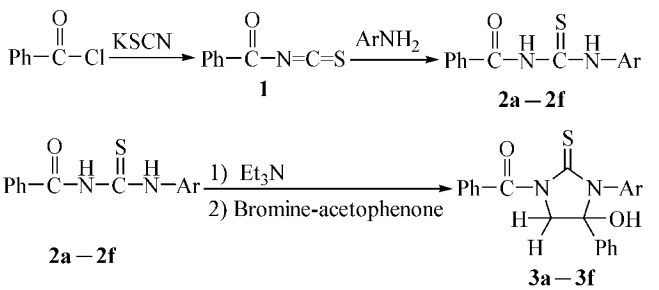
Keywords imidazolidin-2-thione, 1-benzoyl-3-arylthiourea, cyclic reaction

Introduction

Imidazole-2-thione derivatives have received attention because of their bioactivities and application to pharmaceutical synthesis.[1,2] In general, their synthetic methods are focused on the reaction of isothiocyanates with the corresponding amino compounds, such as aminoacetal.[1,3-5] In contrast, the synthesis of hydroxyimidazolidin-2-thiones is less explored.[6,7] In course of our investigation of imidazole derivatives, the preparation of 1,5-disubstituted-2,4-imidazolidinediones and 1,5-disubstituted-2-thioxo-4-imidazolidinones by the reaction of α-ketohemithioacetal with ureas and thioureas has been reported.[8] In this paper, we describe a novel synthesis of 1-benzoyl-3-aryl-4-hydroxy-4-phenylimidazolidin-2-thiones **(3)** by the reaction of 1-benzoyl-3-arylthioureas **(2)** with bromine-acetophenone in the presence of excess triethylamine. The structures of **3** were characterized by IR, NMR, MS and elemental analyses. The present methodology has the advantage of mild conditions, good yields and easy manipulation.

Results and discussion

Benzoyl chloride reacted with KNCS to give benzoylisothiocyanate **(1)**, which is very reactive and can be used for the next reaction directly, followed by the addition of aniline to the solution of **1** to afford 1-benzoyl-3-phenylthiourea **(2a)**. **2a** can react with bromine-acetophenone in dichloromethane but slowly, when triethylamine was added, the rate of reaction increased obviously. After normal treatment of the mixture, a pure product **3a** can be obtained. Its ^{1}H NMR spectrum showed that there are a characteristic AB coupling system [(3.57, d, J = 12.8 Hz, 1H), (3.79, d, J = 12.8 Hz, 1H), CH_2] and a singlet at 7.70 (s, 1H, OH, exchanged with D_2O). The ^{13}C NMR showed that there are 4 particular peaks at 43.77 (CH_2), 93.45 (C—OH), 172.00 (C = O) and 174.98 (C = S) other than aryl carbons. In its IR spectrum there existed an OH absorption band at 3215 cm^{-1}. The elemental analysis is agreed with formula $C_{22}H_{18}N_2O_2S$, and a particular ion $M^+ - H_2O$ [m/z 356 (100)] appeared in MS. These spectral data support the structure of **3a** being 1-benzoyl-3-phenyl-4-hydroxy-4-phenylimidazolidin-2-thione. With the optimized reaction condition and structural analysis in hand, the reaction was extended to other 1-benzoyl-3-arylthioureas **(2b—2f)**, and the corresponding products 1-benzoyl-3-aryl-4-hydroxy-4-phenylimidazolidin-2-thiones **3b—3f** were obtained.



Ar: **a**, C_6H_5; **b**, 4-ClC_6H_4; **c**, 4-BrC_6H_4; **d**, 4-IC_6H_4; **e**, 2-Cl-4-FC_6H_3; **f**, 4-$CH_3C_6H_4$

According to the structures of **3**, we can propose a mechanism for the reaction of 1-benzoyl-3-arylthioureas **(1)** with Br_2/acetophenone in the presence of excess triethylamine. Triethylamine attacks the 1-H of 1-benzoyl-3-arylthioureas **(1)** in the first step due to the acidity of 1-H. Bromoacetophenone **(5)** is produced *in situ* by bromination of acetophenone, and the carbon of the bromomethyl group of **5**, is attacked by the 1-nitrogen atom of **4** to form intermediate **6**, followed by intramolecular attack of the carbonyl by the 3-nitrogen and hydrogen transfer to

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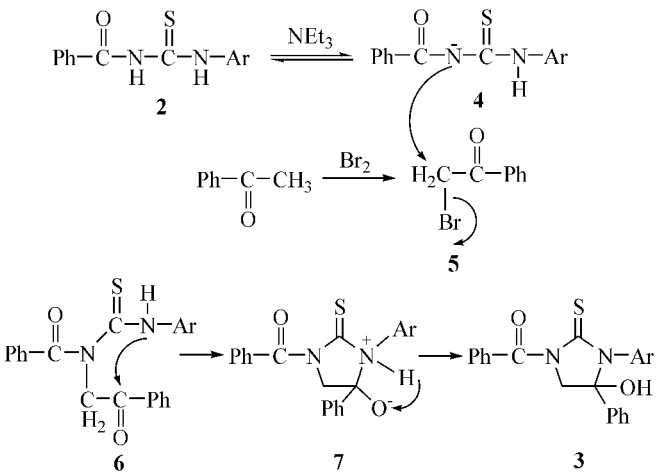
give **3**.



In conclusion, 1-benzoyl-3-aryl-4-hydroxy-4-phenylimidazolidin-2-thiones (**3a—3f**) can be synthesized readily from the cyclization of 1-benzoyl-3-arylthioreas (**2a—2f**) with bromine-acetophenone in the presence of excess triethylamine. The present methodology has the advantage of mild conditions, good yields and easy manipulation.

Experimental

Melting points were determined with an Electrothermal Eng. Ltd. Digital Melting Point apparatus and were uncorrected. The elemental analyses of C, H and N were performed on a Carlo Erba 1110 elemental analyzer. The infrared spectra were recorded on a Mattson Alpha-Centauri FT-IR spectrometer. The ^1H and ^{13}C NMR spectra were recorded on an INOVA-400 MHz NMR spectrometer in DMSO-d_6 using TMS as an internal standard. The mass spectra were determined with a Micromass TOF-HRMS spectrometer.

Synthesis of 1-*benzoyl*-3-*arylthioureas* (**2a—2f**)

Benzoyl chloride (2.5 g, 0.018 mol) was added dropwise into a solution of potassium thiocyanate (2.1 g, 0.022 mol) in acetone (50 mL). The mixture was stirred under reflux for 30 min, then cooled to room temperature, the inorganic salt formed was filtered off to yield benzoylisothiocyanate (**1**). Then, the arylamine (0.018 mol) was added into the solution of **1**, and the mixture was refluxed for 2 h, then cooled to room temperature. After removing acetone, cold water was added into the residue with stirring, the solid was collected by filtration and recrystallized from 95 % ethanol to afford pure 1-benzoyl-3-arylthioureas (**2a—2f**).

2a Yield 79%, m.p. 142—143 ℃; ^1H NMR ($CDCl_3$, 400 MHz) δ: 12.60 (s, 1H, NH), 9.11 (s, 1H, NH), 7.20—8.00 (m, 10H, ArH); IR (KBr) ν: 3275, 1674, 1145 cm^{-1}; MS (70 eV) *m/z* (%): 256 (M^+, 45). Anal. calcd for $C_{14}H_{12}N_2OS$: C 65.60, H 4.72, N 10.93; found C 65.39, H 4.70, N 10.88.

2b Yield 82%, m.p. 135—137 ℃; ^1H NMR ($CDCl_3$, 400 MHz) δ: 12.62 (s, 1H, NH), 9.14 (s, 1H, NH), 7.30—8.00 (m, 9H, ArH); IR (KBr) ν: 3398, 1678, 1157 cm^{-1}; MS (70 eV) *m/z* (%): 290 (M^+, 19). Anal. calcd for $C_{14}H_{11}N_2OSCl$: C 57.83, H 3.81, N 9.63; found C 57.67, H 3.80, N 9.60.

2c Yield 81%, m.p. 143—144 ℃; ^1H NMR ($CDCl_3$, 400 MHz) δ: 12.61 (s, 1H, NH), 9.12 (s, 1H, NH), 7.30—8.00 (m, 9H, ArH); IR (KBr) ν: 3375, 1677, 1150 cm^{-1}; MS (70 eV) *m/z* (%): 334 (M^+, 15). Anal. calcd for $C_{14}H_{11}N_2OSBr$: C 50.16, H 3.31, N 8.36; found C 50.04, H 3.30, N 8.38.

2d Yield 84%, m.p. 154—156 ℃; ^1H NMR ($CDCl_3$, 400 MHz) δ: 12.62 (s, 1H, NH), 9.11 (s, 1H, NH), 7.40—8.00 (m, 9H, ArH); IR (KBr) ν: 3360, 1666, 1149 cm^{-1}; MS (70 eV) *m/z* (%): 382 (M^+, 15). Anal. calcd for $C_{14}H_{11}N_2OSI$: C 43.99, H 2.90, N 7.33; found C 43.90, H 2.91, N 7.32.

2e Yield 85%, m.p. 132—134 ℃; ^1H NMR ($CDCl_3$, 400 MHz) δ: 12.58 (s, 1H, NH), 9.14 (s, 1H, NH), 7.10—8.00 (m, 8H, ArH); IR (KBr) ν: 3244, 1670, 1157 cm^{-1}; MS (70 eV) *m/z* (%): 308 (M^+, 10). Anal. calcd for $C_{14}H_{10}N_2OSClF$: C 54.46, H 3.26, N 9.07; found C 54.35, H 3.24, N 9.03.

2f Yield 80%, m.p. 157—159 ℃; ^1H NMR ($CDCl_3$, 400 MHz) δ: 12.49 (s, 1H, NH), 9.13 (s, 1H, NH), 7.20—8.00 (m, 9H, ArH), 2.37 (s, 3H, CH_3); IR (KBr) ν: 3256, 1674, 1149 cm^{-1}; MS (70 eV) *m/z* (%): 270 (M^+, 53). Anal. calcd for $C_{15}H_{14}N_2OS$: C 66.64, H 5.22, N 10.36; found C 66.45, H 5.20, N 10.32.

Synthesis of 1-*benzoyl*-3-*aryl*-4-*hydroxy*-4-*phenylimidazolidin*-2-*thiones* (**3a—3f**)

Triethylamine (4 mL, 28.8 mmol) was added to a solution of 1-benzoyl-3-arylthioureas (**2**) (3.9 mmol) in dichloromethane (60 mL) with stirring, then, a solution of bromine (6.0 mmol), acetophenone (6.0 mmol) in dichloromethane (10 mL) was added dropwise with stirring under nitrogen atmosphere at room temperature. After the reaction was complete (TLC), the mixture was washed with water twice, then, the dichloromethane was evaporated, the residue was washed with water and ethyl acetate/petroleum ether (1 : 10, *V* : *V*) to afford crude product, which can be purified by the recrystallization from 95% ethanol to yield pure crystals **3a—3f**.

3a Yield 82%, m.p. 162—164 ℃; ^1H NMR (DMSO-d_6, 400 MHz) δ: [(3.57, d, J = 12.8 Hz, 1H), (3.79, d, J = 12.8 Hz, 1H), CH_2], 7.30—7.60 (m, 13H, ArH), 7.70 (s, 1H, OH), 7.84—7.87 (m, 2H, ArH); ^{13}C NMR (DMSO-d_6) δ: 43.77, 93.45, 126.54, 126.96, 127.90, 128.08, 128.45, 128.89, 132.00, 136.24, 138.63, 141.16, 172.00, 174.98; IR (KBr) ν: 3215, 1594, 1015 cm^{-1}; MS (70 eV) *m/z* (%): 356 [$M^+ - H_2O$ (100)]. Anal. calcd for $C_{22}H_{18}$-

N_2O_2S: C 70.57, H 4.84, N 7.48; found C 70.40, H 4.82, N, 7.45.

3b Yield 82%, m.p. 168—170 ℃; ^{1}H NMR (DMSO-d_6, 400 MHz) δ: [(3.55, d, J = 12.8 Hz, 1H), (3.75, d, J = 12.8 Hz, 1H), CH_2], 7.20—7.75 (m, 12H, ArH), 7.90 (s, 1H, OH), 8.00—8.10 (m, 2H, ArH); IR (KBr) ν: 3215, 1594, 1016 cm^{-1}; MS (70 eV) m/z (%): 390 [$M^+ - H_2O$ (65)]. Anal. calcd for $C_{22}H_{17}ClN_2O_2S$: C 64.62, H 4.19, N 6.85; found C 64.50, H 4.17, N 6.88.

3c Yield 89%, m.p. 159—161 ℃; ^{1}H NMR (DMSO-d_6, 400 MHz) δ: [(3.56, d, J = 12.8 Hz, 1H), (3.76, d, J = 12.8 Hz, 1H), CH_2], 7.20—7.65 (m, 12H, ArH), 7.88 (s, 1H, OH), 7.98—8.07 (m, 2H, ArH); IR (KBr) ν: 3217, 1594, 1015 cm^{-1}; MS (70 eV) m/z (%): 434 [$M^+ - H_2O$ (48)]. Anal. calcd for $C_{22}H_{17}BrN_2O_2S$: C 58.29, H 3.78, N 6.18; found C 58.10, H 3.75, N 6.14.

3d Yield 90%, m.p. 164—166 ℃; ^{1}H NMR (DMSO-d_6, 400 MHz) δ: [(3.55, d, J = 12.6 Hz, 1H), (3.76, d, J = 12.6 Hz, 1H), CH_2], 7.10—7.70 (m, 12H, ArH), 7.84 (s, 1H, OH), 7.85—7.90 (m, 2H, ArH); ^{13}C NMR (DMSO-d_6) δ: 43.93, 92.97, 93.49, 126.62, 128.02, 128.15, 128.25, 128.96, 130.49, 132.20, 136.09, 136.85, 138.54, 140.95, 172.11, 175.10; IR (KBr) ν: 3226, 1597, 1010 cm^{-1}; MS (70 eV) m/z (%): 482 [$M^+ - H_2O$ (85)]. Anal. calcd for $C_{22}H_{17}IN_2O_2S$: C 52.81, H 3.42, N 5.60; found C 52.65, H 3.40, N 5.62.

3e Yield 87%, m.p. 162—164 ℃; ^{1}H NMR (DMSO-d_6, 400 MHz) δ: [(3.55, d, J = 12.6 Hz, 1H), (3.77, d, J = 12.6 Hz, 1H), CH_2], 7.25—7.80 (m, 11H, ArH), 7.91 (s, 1H, OH), 8.02—8.11 (m, 2H, ArH); IR (KBr) ν: 3214, 1596, 1015 cm^{-1}; MS (70 eV) m/z (%): 408 [$M^+ - H_2O$ (92)]. Anal. calcd for $C_{22}H_{16}ClFN_2O_2S$: C 61.90, H 3.78, N 6.56; found C 61.78, H 3.76, N 6.53.

3f Yield 86%, m.p. 155—157 ℃; ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 2.23 (s, 3H, CH_3), [(3.54, d, J = 12.8 Hz, 1H), (3.77, d, J = 12.8 Hz, 1H), CH_2], 7.00—7.60 (m, 12H, ArH), 7.65 (s, 1H, OH), 7.85—7.90 (m, 2H, ArH); ^{13}C NMR (DMSO-d_6) δ: 20.54, 43.69, 93.45, 126.50, 127.84, 127.94, 128.07, 128.18, 128.45, 128.89, 131.96, 136.02, 136.06, 136.28, 141.29, 171.95, 175.03; IR (KBr) ν: 3231, 1596, 1016 cm^{-1}; MS (70 eV) m/z (%): 370 [$M^+ - H_2O$ (100)]. Anal. calcd for $C_{23}H_{20}N_2O_2S$: C 71.11, H 5.19, N 7.21; found C 71.02, H 5.18, N 7.20.

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