

A new and convenient synthesis of 2-arylbenzimidazoles through reaction of benzoylthiocyanates with *ortho*-phenylenediamines

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Dedicated to Prof. Richard R. Schmidt on the occasion of his 78th birthday

Abstract

This paper describes the reaction of benzoylthiocyanates with *ortho*-phenylenediamines forming the corresponding bithioureas which undergo cyclization with elimination of thiocyanic acid on refluxing in pyridine leading to the formation of 2-arylbenzimidazoles. The products have been characterized on the basis of satisfactory analytical and spectral (IR, NMR, MS) data, and the mechanism of their formation is proposed.

Keywords: Benzimidazoles, phenylenediamines, bithioureas, cyclodehydration

Introduction

Benzimidazoles constitute a well-known class of five-membered azaheterocycles possessing different types of biological activity.¹ These compounds are reported to have anthelmintic,² anticancer,³ antihypertensive⁴ and antiulcer activities.⁵ The conventional method for the synthesis of 2-arylbenzimidazoles involves reaction of *ortho*-phenylenediamines with aromatic acids, nitrile, imidates or *ortho*-esters under strongly acidic condition at very high temperature.⁶ Recently, the reaction of *ortho*-phenylenediamine with acid chlorides in the presence of KF/Al₂O₃ as a catalyst has been reported to afford 2-arylbenzimidazoles.⁷ Alternatively, the reactions of *ortho*-phenylenediamines with aromatic aldehydes in the presence of several oxidizing agents and catalysts such as MnO₂,⁸ PbOAc₄,⁹ NaHSO₃,¹⁰ DDQ,¹¹ thiamine hydrochloride,¹² FeCl₃/Al₂O₃,¹³ HMTA-Br₂,¹⁴ an ionic liquid [Pmim]BF₄,¹⁵ etc. have been employed for the synthesis of 2-arylbenzimidazoles. A three-component reaction of 2-bromo/iodoaniline, aldehydes and sodium azide in the presence of CuCl-TMEDA has been reported to afford 2-arylbenzimidazoles.¹⁶ Recently, non-conventional techniques such as microwave irradiation¹⁷ and ultrasonic irradiation¹⁸ have been employed to achieve easy

synthesis of 2-arylbenzimidazoles. For example, Joshi and coworkers have reported the synthesis of 2-arylbenzimidazoles by tetrabutylammonium fluoride mediated reaction of phenylene-1,2-diamines with aromatic aldehydes in aqueous medium under the influence of ultrasonic irradiation.¹⁸ Niknam and Fatehi-Raviz reacted phenylene-1,2-diamines with aromatic carboxylic acids in the presence of methylsulfonic acid over neutral alumina by microwave irradiation.¹⁹

The reactions of benzoylisothiocyanates are of interest to organic chemists from synthetic and mechanistic point of view.²⁰ The reactions of these heterocumulenes often depend on the structure of the isothiocyanates.²¹ In the present paper, we report 2:1 molar reactions of benzoylisothiocyanates with 1,2-phenylenediamines resulting into formation of corresponding bithioureas which undergo cyclization to 2-arylbenzimidazoles by refluxing in pyridine. There is a report on formation of 2-*N*-(acyl)aminobenzimidazoles by the reactions of benzoylisothiocyanates with 1,2-phenylenediamines.²²

Results and Discussion

A 1:2 molar reaction of 1,2-phenylenediamines **1** with benzoylisothiocyanates **2** in benzene afforded the corresponding *N,N'*-bis(benzoylthiocarbamoyl)-1,2-phenylenediamines **3** in almost quantitative yields. The products were characterized on the basis of their analytical and spectral data (Table 1) with reported values. The IR spectra of the products showed a broad band at 3330-3280 cm⁻¹ corresponding to the N-H linkage, a strong band at 1675±5 cm⁻¹ corresponding to an amide carbonyl absorption, and a strong absorption band around 1150 cm⁻¹ corresponding to the C=S bond.

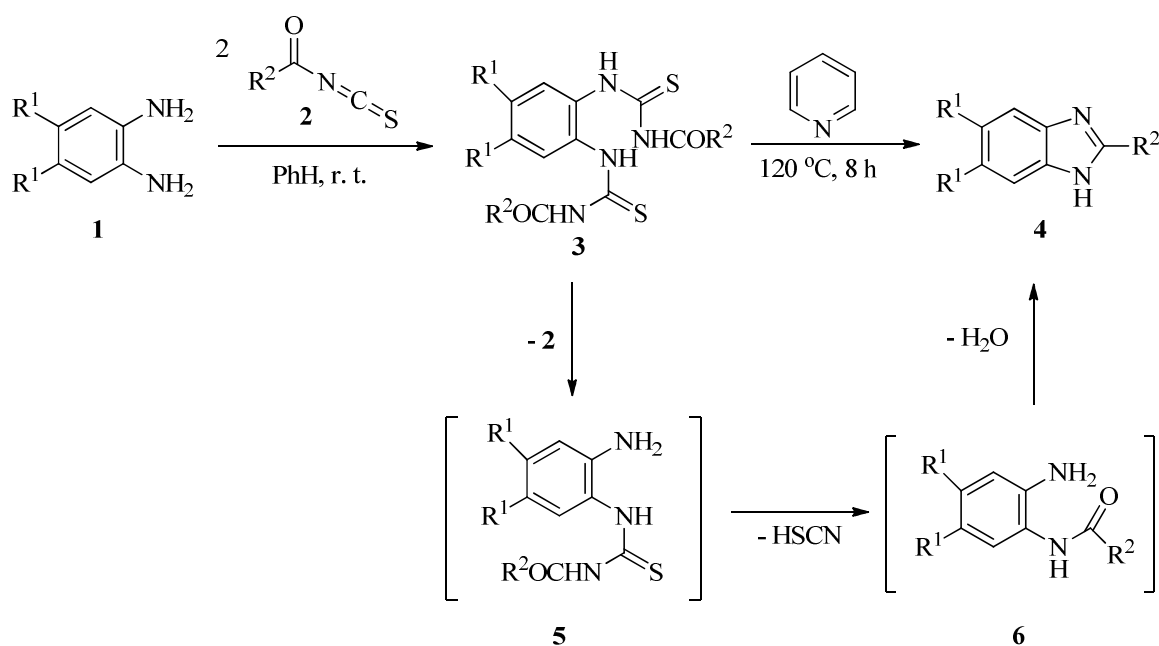
The products **3a-h**, after characterization, were dissolved in pyridine and heated at 120 °C for 15 hours. After distilling off the pyridine and cooling, a solid product was obtained which was washed with water, dried and recrystallized with ethanol. The solid products have been characterized as 2-arylbenzimidazoles **4a-h** on the basis of their analytical and spectral data, and undepressed mixed mp with authentic samples.²³

The IR spectra of the products **4** showed no absorption in the carbonyl region indicating the removal of both the carbonyl groups in the product. The IR spectra showed a broad band around 3350 cm⁻¹. Similarly, the ¹³C spectra did not show any downfield signal corresponding to the carbonyl carbons. Instead, a low-field signal at around δ 152 was observed in all products that has been assigned to azomethine carbon. The ¹H NMR spectra exhibited a downfield signal corresponding to one proton. This signal was D₂O exchangeable; so assigned to NH proton. These significant spectral features of the products led us to characterize these products as 2-arylbenzimidazoles. Finally, the authentic samples of **4a** and **4b** were prepared according to a reported method for comparing the mp and spectral data. The comparison of spectral data and undepressed mixed mp with the authentic sample confirmed the products as 2-arylbenzimidazoles.

Table 1. Analytical IR spectral data of *N,N'*-bis(benzoylthiocarbamoyl)-1,2-phenylenediamines

No.	R ¹	R ²	m. p. (°C)	Yield (%)	Mol. Formula [*]	IR (KBr, cm ⁻¹)
3a	H	Ph	179-180	95	C ₂₂ H ₁₈ N ₄ O ₂ S ₂	3330, 1674, 1147
3b	H	4-MeOPh	165-167	98	C ₂₄ H ₂₂ N ₄ O ₄ S ₂	3320, 1680, 1145
3c	H	4-ClPh	190-192	90	C ₂₂ H ₁₆ Cl ₂ N ₄ O ₂ S ₂	3310, 1674, 1147
3d	H	3-MePh	159-160	95	C ₂₄ H ₂₂ N ₄ O ₂ S ₂	3330, 1674, 1147
3e	Me	Ph	185-187	92	C ₂₄ H ₂₂ N ₄ O ₂ S ₂	3320, 1680, 1148
3f	Me	3-MePh	200-201	96	C ₂₆ H ₂₆ N ₄ O ₂ S ₂	3330, 1675, 1147
3g	Me	4-MeOPh	169-171	95	C ₂₆ H ₂₆ N ₄ O ₄ S ₂	3320, 1678, 1145
3h	Me	4-ClPh	199-200	90	C ₂₄ H ₂₀ Cl ₂ N ₄ O ₂ S ₂	3320, 1680, 1145

* All compounds gave analysis for C, H, and N in the range of ± 0.4 .

**Scheme 1**

The formation of products **3** has been explained by usual nucleophilic attack of amines **1** on carbon atom of the isothiocyanate linkage in substrates **2** (Scheme 1). On refluxing in pyridine, the removal of one aroylisothiocyanate moiety may lead to the formation of *N*-(benzoylthiocarbamoyl)-1,2-phenylenediamines **5**. The formation of *N*-(benzoylthiocarbamoyl)-1,2-phenylenediamines **5** from the reaction of amines **1** with isothiocyanates **2** has been reported previously by refluxing in acetonitrile.²² The intermediate product **5** may lead to the formation of 2-arylbenzimidazoles **4** by dethiocyanation to intermediate product **6** and concomitant cyclodehydration. It is worth mentioning that when intermediate products **5** were refluxed in acetonitrile in the presence of DCC, cyclization took place with desulfurization resulting into formation of 2-*N*-(acyl)aminobenzimidazole indicating the sensitivity of reaction towards

solvents and cyclodehydrating agents used in the reaction.²² The present study demonstrates benzoylthiocyanates as excellent alternatives to aldehydes and carboxylic acids used in other methods for preparation of 2-arylbenzimidazoles as no catalyst is employed in this case.

Conclusions

In summary, the paper reports a new and convenient entry to a biologically important heterocyclic compounds, 2-arylbenzimidazoles and demonstrates the dependence of the outcome of the decomposition of *N,N'*-bis(benzoylthiocarbamoyl)-1,2-phenylenediamines on solvent. This reaction, to the best of our knowledge, is first report on the formation of 2-arylbenzimidazoles from these substrates.

Experimental Section

General. Melting points have been recorded on a Stuart Scientific melting point apparatus and are uncorrected. The IR spectra were recorded on a Perkin-Elmer-781 IR spectrophotometer using KBr disc of the sample. The ¹H and ¹³C NMR spectra were recorded in a DMSO-*d*₆ solution at 300 MHz and 75.4 MHz, respectively, on a Bruker™ 300 MHz spectrometer. The mass spectra were recorded on a Finnigan LCQ Deca mass spectrometer by electrospray ionization. The 1,2-phenylenediamines were procured from Aldrich Chemicals and benzoylthiocyanates were prepared by reactions of acid chlorides with potassium thiocyanate according to reported methods.²⁴

General procedure for the preparation of *N,N'*-bis(benzoylthiocarbamoyl)-1,2-phenylenediamines (3a-h). Benzoyl isothiocyanates (10 mmol) were added to a solution of 1,2-phenylenediamines (5 mmols) in 6 mL of benzene under vigorous stirring. After complete addition of isothiocyanate, the reaction mixture was cooled in an ice bath to get the solid product in almost quantitative yield. The products were used as such in next step for cyclization reaction.

General procedure for the cyclization of *N,N'*-bis(benzoylthiocarbamoyl)-1,2-phenylenediamines (3a-h). The product from the last step (2 mmol of each) was refluxed in 6 mL of pyridine on an oil bath for 8 h. After completion of the reaction, pyridine was distilled off and the reaction mixture was allowed to attain the room temperature. A solid product was formed in the flask that was recrystallized with ethanol to get pure products that have been characterized as 2-arylbenzimidazoles on the basis of following analytical and spectral data.

2-Phenyl-1*H*-benzimidazole (4a). Yield: 75%; mp 288-290 °C (lit., 290-292 °C),¹⁵ IR (KBr, cm⁻¹): 3350, 2995, 1630, 1590; ¹H NMR (DMSO-*d*₆): δH 12.52 (bs, 1H, NH), 7.88 (d, *J* 7.8 Hz, 2H, arom.), 7.45-7.35 (m, 5H, Arom.), 7.26-7.12 (m, 2H, arom.); ¹³C NMR (DMSO-*d*₆): δC

151.5, 144.0, 135.5, 130.2, 129.4, 128.3, 126.8, 122.0, 121.5, 119.5, 111.8; MS (ESI): m/z 194 (M^+)

2-(4-Methoxyphenyl)-1H-benzimidazole (4b). Yield: 88%; mp 224-226 °C (lit., 226 °C), IR (KBr, cm^{-1}): 3340, 2910, 1635, 1600; ^1H NMR (DMSO- d_6): δ H 12.09 (bs, 1H, NH), 7.85 (d, J 7.6 Hz, 2H, arom.), 7.71-7.68 (m, 2H, arom.), 7.52-7.46 (m, 2H, arom.), 7.21 (d, J 8.0 Hz, 2H, arom.), 3.92 (s, 3H, OCH_3); ^{13}C NMR (DMSO- d_6): δ C 161.0, 151.2, 144.5, 134.5, 128.8, 123.0, 122.1, 121.8, 119.2, 115.0, 112.5, 56.5; MS (ESI): m/z 224 (M^+).

2-(4-Chlorophenyl)-1H-benzimidazole (4c). Yield: 68%; mp 291-293 °C (lit., 292-293 °C); IR (KBr, cm^{-1}): 3350, 2920, 1630, 1600; ^1H NMR (DMSO- d_6): δ H 12.20 (bs, 1H, NH), 8.10 (d, J 8.9 Hz, 2H), 7.45-7.30 (m, 4H, arom.), 7.15-6.95 (m, 2H, arom.); ^{13}C NMR (DMSO- d_6): δ C 150.5, 144.2, 135.5, 134.9, 130.9, 129.7, 128.8, 123.5, 122.2, 119.5, 111.5; MS (ESI): m/z 228 (M^+).

2-(3-Methylphenyl)-1H-benzimidazole (4d). Yield: 82%; mp 217-219 °C (lit., 217-219 °C); IR (KBr, cm^{-1}): 3360, 2950, 1635, 1590; ^1H NMR (DMSO- d_6): δ H 12.21 (bs, 1H, NH), 8.12 (d, J 8.1 Hz, 1H, arom.), 7.80 (s, 1H, arom.), 7.59 (d, J 8.0 Hz, 2H, arom.), 7.39-7.19 (M, 4H, arom.), 2.35 (s, 3H, CH_3); ^{13}C NMR (DMSO- d_6): δ C 151.9, 140.4, 135.5, 131.0, 123.0, 122.2, 119.4, 111.9, 20.9; MS (ESI): m/z 208 (M^+).

5,6-Dimethyl-2-phenyl-1H-benzimidazole (4e). Yield: 85%; mp 254-255 °C; IR (KBr, cm^{-1}): 3355, 2910, 1640, 1590; ^1H NMR (DMSO- d_6): δ H 12.24 (bs, 1H, NH), 8.28 (d, 8.9 Hz, 2H, arom.), 7.51-7.41 (m, 3H, arom.), 7.30 (s, 2H, arom.), 2.49 (s, 6H, two CH_3); MS (ESI): m/z 222 (M^+); Anal. Calcd. for $\text{C}_{15}\text{H}_{14}\text{N}_2$: C 81.05, H 6.35, N 12.60%. Found: C 80.85, H 6.48, N 12.34%

5,6-Dimethyl-2-(4-methoxyphenyl)-1H-benzimidazole (4f). Yield: 94%; mp 263-264 °C; IR (KBr, cm^{-1}): 3360, 2920, 1630, 1585; ^1H NMR (DMSO- d_6): δ H 12.00 (bs, 1H, NH), 7.95 (d, J 8.1 Hz, 2H, arom), 7.30 (s, 2H, arom), 6.98 (d, 7.9 Hz, 2H, arom), 4.13 (s, 3H, OCH_3), 2.55 (s, 6H, two CH_3); MS (ESI): m/z 252 (M^+); Anal. Calcd. for $\text{C}_{16}\text{H}_{16}\text{N}_2\text{O}$: C 76.16, H 6.39, N 11.10%. Found: C 76.32, H 6.28, N 11.26%.

5,6-Dimethyl-2-(4-chlorophenyl)-1H-benzimidazole (4g). Yield: 79%; mp 230-232 °C; IR (KBr, cm^{-1}): 3360, 2920, 1630, 1600; ^1H NMR (DMSO- d_6): δ H 12.24 (bs, 1H, NH), 8.28 (d, 8.9 Hz, 2H, arom.), 7.51-7.41 (m, 2H, arom.), 7.30 (s, 2H, arom.), 2.49 (s, 6H, two CH_3); MS (ESI): m/z 256 (M^+); Anal. Calcd. for $\text{C}_{15}\text{H}_{13}\text{ClN}_2$: C 70.18, H 5.10, N 10.91%. Found: $\text{C}_{15}\text{H}_{13}\text{ClN}_2$: C 70.28, H 4.98, N 10.78%.

5,6-Dimethyl-2-(3-methylphenyl)-1H-benzimidazole (4h). Yield: 87%; mp 240-241 °C; IR (KBr, cm^{-1}): 3370, 2970, 1640, 1585; ^1H NMR (DMSO- d_6): δ H 12.44 (bs, 1H, NH), 7.90 (d, J 7.9 Hz, 1H, arom.), 7.75 (s, 1H, arom.), 7.32 (s, 2H, arom.), 7.30 (m, 2H, arom.), 2.89 (s, 3H, CH_3), 2.44 (s, 6H, two CH_3); MS (ESI): m/z 236 (M^+); Anal. Calcd. for $\text{C}_{16}\text{H}_{16}\text{N}_2$: C 81.32, H 6.82, N 11.85%. Found: C 81.05, H 6.80, N 11.63%.

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