Research Article

Synthesis of N-Alkyl-2-thiomethyl Benzimidazoles: A Green Approach

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A green approach for the synthesis of N-alkyl-2-thiomethyl benzimidazoles **2** ($R=CH_3$, C_2H_5 , CH_2Ph) under different conditions has been developed from N-alkyl-2-chloromethyl benzimidazole (i.e., CH_3 , C_2H_5 , CH_2Ph) **1** by reaction with thiourea by physical grinding, or by using green solvents like ethanol and PEG-600, or by using microwave irradiation technique.

1. Introduction

Benzimidazoles are very useful intermediates/subunits for the development of molecules of pharmaceutical or biological interest [1, 2]. Benzimidazoles are an important class of bioactive molecules in the field of drugs and pharmaceuticals [3–7].

N-Methyl-o-phenylenediamine on treatment with thioacetic acid in HCl under reflux gave N-methyl-2-thiomethyl benzimidazole that was reported [8] by Casella et al. Rall et al. described [9] that N-methyl o-Phenylenediamine with S-benzyl thioacetic acid in aq. HCl under reflux gave N-benzyl-2-benzylthio methylbenzimidazole. Kato et al. reported [10] that 2-((methylthio)methyl)-1H-benzimidazole was prepared on treatment of S-methylthio acetic acid with o-phenylenediamine in aq. HCl under reflux for 16 hr. Reaction of S-methylthio methylbenzimidazole on treatment with methyl iodide in presence of sodium methoxide gave N-methyl-S-methylthio methylbenzimidazole that was reported by Haugwitz et al. [11]. Zubenko et al. reported [12] that N-methyl-2-chloromethyl benzimidazole was reacted with thiomethane in ethanol in NaOMe and gave N-methyl-2-methylthio methylbenzimidazole. Rao et al. [13] reported that N-alkyl-2-chlorobenzimidazole was treated with thiourea green conditions and gave N-alkyl-2-thiomethyl benzimidazole in good yields. In continuation of our earlier studies [14], we now wish to report a green syntheses of N-alkyl-2-thiomethylbenzimidazoles.

2. Results and Discussion

Reaction of **1a–c**, that is, N-alkyl-2-chloromethyl benzimidazole [8] ($R=CH_3$, C_2H_5 , or $PhCH_2$), independently, each with thiourea by a simple physical grinding of the reaction mixture in a mortar with a pestle, under solvent-free conditions, for 10–15 min at RT, followed by simple processing, gave respectively (1-methyl-1H-benzimidazol-2-yl)methanethiol (**2a**, i.e., **2**, $R=CH_3$), (1-ethyl-1H-benzimidazol-2-yl)methanethiol (**2b**, i.e., **2**, $R=C_2H_5$), and (1-benzyl-1H-benzimidazol-2-yl)methanethiol (**2c**, i.e., **2**, $R=CH_2Ph$) in excellent yields, matching the products identically with the ones reported [8] by the literature in all respects (m.p., m.m.p., and co-TLC) (Scheme 1).

The reaction of **1a**, **1b**, and **1c**, independently, each with thiourea in ethanol under reflux for 3 hr, followed by simple processing, gave respectively **2a** (i.e., **2**, $R=CH_3$), **2b** (i.e., **2**, $R=CH_2CH_3$), and **2c** (i.e., **2**, $R=CH_2Ph$) identical with the same products obtained above (Scheme 1).

The reaction was also carried out in PEG-600 as the green solvent. Thus, heating a mixture of **1a**, **1b**, and **1c**, independently, each with thiourea in PEG-600 for 3 hr without the use of any added base, followed by simple processing, gave, respectively, **2a** (i.e., **2**, $R=CH_3$), **2b** (i.e., **2**, $R=CH_2CH_3$), and **2c** (i.e., **2**, $R=CH_2Ph$) identical with the same products obtained above (Scheme 1).

Compounds **2a–c** could also be prepared by an alternative, green method. Thus, **1a**, **1b**, and **1c**, independently,

SCHEME 1: **2a**, R=CH₃; **2b**, R=C₂H₅; **2c**, R=CH₂Ph.

each with thiourea under microwave irradiation conditions for 2 min and subsequent processing, gave respectively **2a** (i.e., **2**, R=CH₃), **2b** (i.e., **2**, R=CH₂CH₃), and **2c** (i.e., **2**, R=CH₂Ph) identical with the products obtained above (Scheme 1).

Thus, the above four methods have different yields with one suffering from relatively poor yields. Among in ethanol and PEG-600, ethanol gives more yields whereas PEG-600 gives lower yields. Due to high molecular weight and viscous nature of PEG-600 (135 cp at 25°C), it may lower reaction rates, reduce product yields, and cause the reaction to be mass-transfer limited. Because of this, three of the four methodologies result in the preparation of the compounds giving high yields whereas PEG-600 gives lower yields. Among these four methodologies, the microwave irradiation is superior to that of three methods because microwave dielectric heating is more energy efficient than classical conductive heat transfer methods.

3. Experimental Section

Melting points were determined in open capillaries in sulfuric acid bath and are uncorrected. IR spectra were recorded with Jasco FT-IR 5300. ¹H NMR and ¹³C NMR were recorded in CDCl₃/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 vapors or UV lamp. Experiments under microwave irradiation were carried out by using the commercially available CEM Discover Microwave Reactor.

3.1. Preparation of **2** from **1**

3.1.1. Physical Grinding Method. A mixture of **1a-c** (10 mM) and thiourea (0.76 g, 10 mM) was ground for about 10–15 min in a mortar with a pestle at RT to obtain a homogeneous mixture. The completion of the reaction was monitored by TLC on silica gel-G plates using authentic samples of the

starting material and the target compounds as references. The mixture was then treated with ice-cold water (≈30–40 mL). The separated solid was filtered, washed with water (2 × 10 mL), and dried to obtain crude **2a-c**. Yields are shown in Table 1. Recrystallization of the crude product from ethyl acetate gave pure **2a-c**. IR, ¹H NMR, and LC-MS spectra for the compounds **2a-c** were found to be in agreement with the structures assigned to them.

3.1.2. In Ethanol. A mixture of **1a-c** (10 mM) and thiourea (0.76 g, 10 mM) in ethanol was refluxed on water bath for 3 hr. The progress of the reaction was monitored on TLC for the disappearance of **1**. After the completion of the reaction (≈3 hr), the excess ethanol was rotary evaporated and the residue poured into ice-cold water (30 mL). The separated solid was filtered, washed with water (2 × 10 mL), and dried. For yields, please see Table 1. The crude products were purified by recrystallization from ethyl acetate to obtain pure **2a-c**, identical with the same products obtained above.

3.1.3. In PEG-600. A mixture of **1a-c** (10 mM), thiourea (0.76 g, 10 mM), and PEG-600 (20 mL) was heated on a steam-bath at 100°C for 3 hr. At the end of this period, the mixture was cooled to RT and poured into ice-cold water (≈50 mL). The separated solid was filtered, washed with water (2 × 10 mL), and dried. Yields are shown in Table 1. The crude product was purified by recrystallization from ethyl acetate to obtain pure **2a-c**, identical with the same products obtained above.

3.1.4. Under Microwave Condition. A mixture of **1a-c** (10 mM) and thiourea (0.76 g, 10 mM) was taken in a 10 mL CEM-reaction tube sealed by rubber stopper and subjected to microwave irradiation for 2 min at 130°C in a commercial microwave reactor. After that, the tube was cooled and the completion of reaction was checked by TLC. Then, the reaction mixture was poured into ice-cold water (50 mL). The separated solid was filtered, washed with water (2 × 10 mL), and dried. Yields are shown in Table 1. The crude products

TABLE I: Preparation of **2a–c** from **1** under different green conditions.

S. number	SM	Reagent	Product	Methods													
				Physical grinding			Ethanol		Green solvents			PEG-600		Microwave irradiation			
				Time (Min)	Temp	Yield* (%)	Time (Min)	Temp	Yield* (%)	Time (Min)	Temp (°C)	Yield* (%)	Time (Min)	Temp	Yield* (%)		
1.	1	DMS	2a	10–15	RT	79	180	Reflux	81	180	100	2	RT/450 W	61	2	RT/450 W	82
		DES	2b	10–15	RT	77	180	Reflux	79	180	100	2	RT/450 W	58	2	RT/450 W	81
		PhCH ₂ Cl	2c	10–15	RT	75	180	Reflux	74	180	100	2	RT/450 W	54	2	RT/450 W	78

*Yield refers to recrystallized products.

were purified by recrystallization from ethyl acetate to obtain pure **2a–c**, identical with the same products obtained above.

3.2. Characterization Data

(1-Methyl-1H-benzimidazol-2-yl)methanethiol, **2a**. M.P. 141–45°C (Lit.⁽⁷⁾ m.p. 139–43°C); IR (KBr): 2418–2396 cm^{−1} (–SH); ¹H NMR (400 MHz, DMSO-d₆/TMS): δ 3.66 (s, 3H, –NCH₃), 9.24 (s, 1H, –SH), and 7.35–8.47 (complex, m, and 4H aryl protons); ¹³C NMR: δ 172.2, 138.8, 132.5, 125.4, 118.4, and 25.9 ppm; MS (CI): m/z 179 [M⁺⁺+1].

(1-Ethyl-1H-benzimidazol-2-yl)methanethiol, **2b**. M.P. 118–22°C (Lit.⁽⁷⁾ m.p. 120–24°C); IR (KBr): 2485–2312 cm^{−1} (–SH); ¹H NMR (400 MHz, DMSO-d₆/TMS): δ 2.75 (q, 2H, and –NCH₂ of ethyl), 2.45 (t, 3H, and –CH₃ of ethyl), 8.98 (s, 1H, and –SH), and 7.29–8.45 (complex, m, and 4H aryl protons); ¹³C NMR: δ 170.6, 136.5, 130.2, 124.3, 116.4, 26.9, and 22.8 ppm; MS (CI): m/z 193 [M⁺⁺+1].

(1-Benzyl-1H-benzimidazol-2-yl)methanethiol, **2c**. M.P. 134–38°C (Lit.⁽⁷⁾ m.p. 136–39°C); IR (KBr): 2229–2258 cm^{−1} (–SH); ¹H NMR (400 MHz, DMSO-d₆/TMS): δ 3.60 (s, 2H, and –NCH₂ of benzyl), 8.63 (s, 1H, and –SH), and 7.28–8.48 (complex, m, 9H, and 5 aromatic benzyl + 4H aryl protons); ¹³C NMR: δ 170.4, 137.8, 135.3, 134.5, 126.4, 123.4, 118.4, and 44.9 ppm; MS (CI): m/z 255 [M⁺⁺+1].

4. Conclusion

In conclusion, we have developed simple and green synthesis of N-alkyl-2-thiomethyl benzimidazole under different conditions.

Conflict of Interests

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

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