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Facile and Eco-friendly Synthesis of 2-(2-Methoxyethyl sulfanyl)-1*H*-benzimidazoles and Their Antimicrobial Screening

DASARI VARAPRASAD, GANGULA MOHAN RAO, SUMANGALA RAO†,
AKULA KALYAN CHAKRAVARTHY and BARU VIJAYAKUMAR*
Department of Chemistry, C.K.M. College, Warangal-506 006, India
E-mail: svpdasari@yahoo.co.in

A simple and eco-friendly procedure for the preparation of 2-(2-methoxyethylsulfanyl)1*H*-benzimidazoles and their antimicrobial screening has been presented.

Key Words: 2-Mercapto-5/6 substituted-1*H*-benzimidazoles, 2-(2-Methoxyethyl mesylate, Antimicrobial screening.

INTRODUCTION

Substituted benzimidazoles have been shown to exhibit a diversified biological activities. Many compounds containing this heterocyclic nucleus are of either industrial or biological importance. Similarly, 2-mercapto-1*H*-benzimidazole and its derivates have also been reported to have potent biological activities. Such as antihelmintics[1,2] and antibacterial and antiviral as well as anticancer activities. These structures mimics like purine bases in deoxy ribonucleic acids and ribonucleic acids. In our ongoing research programme, we are interested in synthesizing 2-(2-methoxyethylsulfanyl)benzimidazole nucleosides as probable anticancer agents[3].

EXPERIMENTAL

Melting points are uncorrected and were recorded on a Perking-Elmer (AP1-2000) Seris instrument. The progress of the reaction was followed by TLC (pre-coated silica gel plates-Merck) and visualization was done using iodine/UV lamp and charring in ninhydrin solution. IR spectra were recorded on Jasco FTIR (400-7000) instrument. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ on a Varian-Gemini 200 MHz spectrometer using TMS as internal standard.

General experimental procedure: The compounds (**1a-h**) 5 g was dissolved in 10 % NaOH solution (50 mL) and the alkylating agent, 2-methoxyethyl mesylate (1.1 eq) was added and the mass was stirred at room temperature for 12 h. The progress of the reaction was monitored by TLC. In case of nitro benzimidazole the reaction mass was heated up to 40-45 ºC, for 4 h. After completion of the reaction

†Department of Microbiology, Padmavathi Degree College for Women, Warangal-506 006, India.

mass was neutralized (pH ≈ 7) with the acidic resin (IR 120). The resin was filtered off and washed with demineralized water. The aqueous filtrate was concentrated to 1/3 of the total volume and the product was extracted with dichloromethane (50 mL × 2), The solvent was evaporated and the obtained syrupy mass was titurated with hexane. A brown coloured solid separated out which was filtered and washed with ice-cold hexane. The solid obtained was 6.9 g (99 % yield), (**2a-h**).

Physical and spectral data of compounds

2-(2-Methoxy-ethylsulfanyl)-1*H*-benzimidazole (2a): 1*H*-benzimidazole-2-thiol (**1a**) (5 g) was alkylated with the invented eco-friendly methodology and obtained the required product was obtained as a brown (fine needles) solid of 6.9 g with 99 % yield, ^{1}H NMR ($CDCl_3$) δ 10.5 (s.1H), 7.5 (m.2H), 7.2 (m, 2H), 3.8 (m, 2H), 3.6 (s, 3H) 3.3 (t.2H), Mass: 209, ^{13}C NMR ($CDCl_3$): 35, 55, 75, 115, 123, 138, 142. m.f.: $C_{10}H_{12}N_2OS$, elemental analysis (%): Exp.: C: 57.3; H: 5.6; N: 13.0; S: 15.2, Theor.: C: 57.67; H: 5.81; N: 13.45; S: 15.40.

2-(2-Methoxy-ethylsulfanyl)-5-methoxy-1*H*-benzimidazole (2b): 5-methoxy 1*H*-benzimidazole-2-thiol (**1b**) 5 g, was alkylated with the same procedure methodology and obtained the product as a brown syrup (7 g) with 99 % yield, ^{1}H NMR ($CDCl_3$) δ 10.8 (s.1H), 7.6 (d.1H), 7.2 (s, 1H), 7.0 (d.1H) 3.9 (s, 3H), 3.7 (m.2H),3.4 (m.2H), 3.3 (s.3H) Mass: 239, ^{13}C NMR ($CDCl_3$): 36, 52, 56, 75, 102, 108, 117, 130, 139, 142, 157, m.f.: $C_{11}H_{14}N_2O_2S$, Elemental analysis (%): Exp.: C: 55.3; H: 6.10; N: 11.50; S: 13.26, Theor.: C: 55.44; H: 5.92; N: 11.76; S: 13.46.

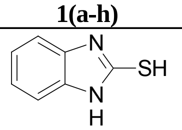
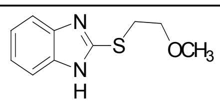
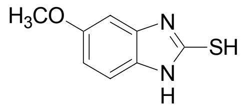
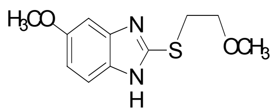
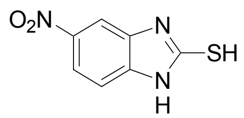
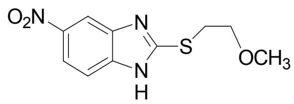
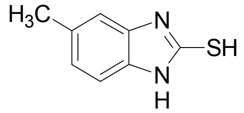
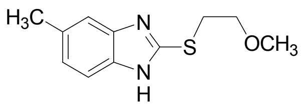
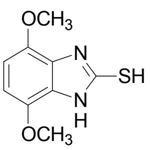
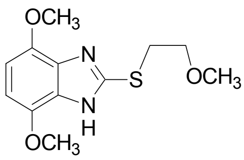
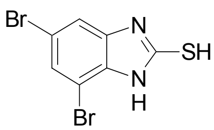
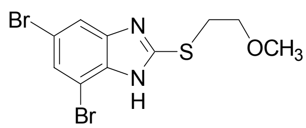
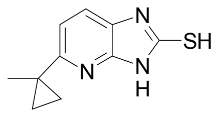
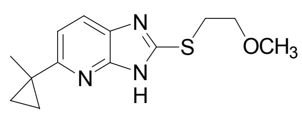
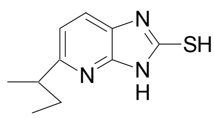
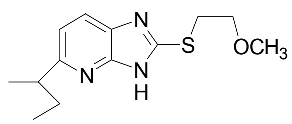
2-(2-Methoxy-ethylsulfanyl)-5-nitro-1*H*-benzimidazole (2c): 5-Nitro 1*H*-benzimidazole-2-thiol (**1c**) 5 g, was alkylated with the same procedure methodology and obtained the product as a yellow solid (7 g) with 99 % yield, ^{1}H NMR ($CDCl_3$): δ 10.8 (s.1H), 8.3 (d.1H), 8.0 (d, 1H), 7.5 (d.1H) 3.6 (m, 2H), 3.4 (m.2H), 3.2 (s.3H), Mass: 2254, ^{13}C NMR ($CDCl_3$): 35, 53, 75, 110, 117, 118, 139, 142, 144, m.f.: $C_{10}H_{11}N_3O_3S$, Elemental analysis (%): Exp.: C: 47.3; H: 4.28; N: 16.08; S: 12.3, Theor.: C: 47.47; H: 4.38; N: 16.59; S: 12.66.

2-(2-Methoxy-ethylsulfanyl)-5-methyl-1*H*-benzimidazole (2d): 5-Methyl 1*H*-benzimidazole-2-thiol (**1d**) 5 g was alkylated with the same procedure methodology and obtained the product as a yellow solid (6.8 g) with 99 % yield, ^{1}H NMR ($CDCl_3$) δ 10.5 (s.1H), 8.3 (s.1H), 8.0 (d, 1H), 7.5 (d.1H), 3.6 (m, 2H), 3.4 (m.2H), 3.2 (s.3H), 2.8 (s.3H), Mass: 222, ^{13}C NMR ($CDCl_3$) :21, 36, 54, 74, 115, 117, 124, 132, 134, 138, 142, m.f.: $C_{11}H_{14}N_2OS$, Elemental analysis: Exp.: C: 59.3; H: 6.05; N: 12.30; S:14.3, Theor.: C: 59.43; H: 6.35; N: 12.60; S: 14.42.

2-(2-Methoxy-ethylsulfanyl)-4,7-dimethoxy-1*H*-benzimidazole (2e): 4,7-Dimethoxy 1*H*-benzimidazole-2-thiol (**1e**) 5 g, was alkylated with the procedure described above methodology and obtained the product as a yellow solid (7 g) with 99 % yield, ^{1}H NMR ($CDCl_3$) δ 10.8 (s.1H), 7.8 (m.1H), 3.8 (m, 2H), 3.6 (m.2H), 3.4 (s.6H), 3.3 (s.3H), Mass: 269, ^{13}C NMR ($CDCl_3$): 35, 54, 56, 76, 110, 125, 142, m.f.: $C_{12}H_{16}N_2O_3S$, Elemental analysis (%): Exp.: C: 53.5; H: 5.5; N: 10.2; S:11.5, Theor.: C: 53.71; H: 6.01; N: 10.44; S: 11.95.

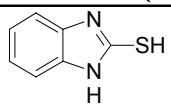
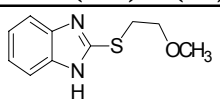
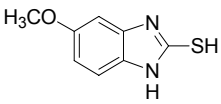
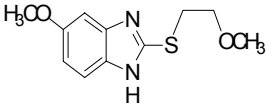
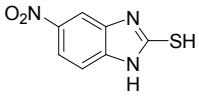
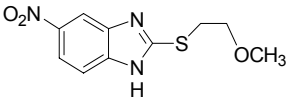
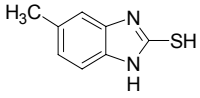
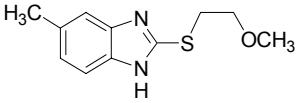
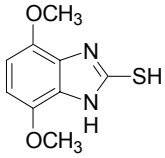
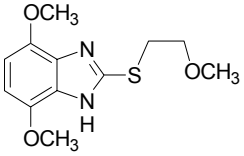
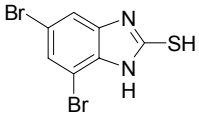
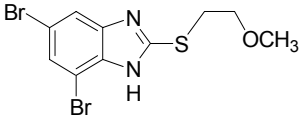
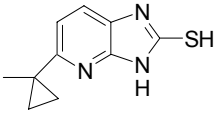
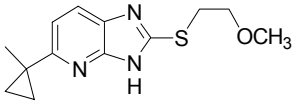
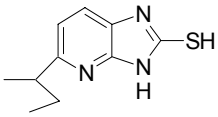
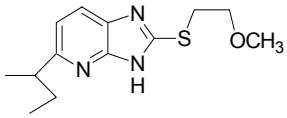
2-(2-Methoxy-ethylsulfanyl)-4,6-dibromo-1*H*-benzimidazole (2f): 4,6-Dibromo 1*H*-benzimidazole-2-thiol (**1f**) 5 g was alkylated with the procedure described above methodology and obtained the product as a yellow solid (7.2 g) with 99 % yield, ^{1}H NMR ($CDCl_3$) δ 10.9 (s.1H), 7.8 (s.1H), 7.7 (s, 1H), 3.8 (m.2H), 3.6 (m.2H), 3.3 (s.3H), Mass: 364, ^{13}C NMR ($CDCl_3$): 35, 54, 75, 112, 118, 140, m.f.: $C_{10}H_{10}N_2O_3SBr_2$, Elemental analysis (%): Exp.: C: 32.5; H: 2.8; N: 7.4; S: 8.5, Br: 43.5; Theor.: C: 32.81; H: 2.75; N: 7.65; S: 8.76; Br: 43.65.

TABLE-1
PRODUCTS OBTAINED IN TWO CASES LIKE CONVENTIONAL HEATING ON A WATER BATH AND MICROWAVE REACTION

2-Mercapto benzimidazole **1(a-h)**	Reagents and base	Product **2(a-h)**	Remarks
	MOE-Ms 0.5 % NaOH sol		99 %
	MOE-Ms 0.5 % NaOH sol		99 %
	MOE-Ms 0.5 % NaOH sol		99 %
	MOE-Ms 0.5 % NaOH sol		99 %
	MOE-Ms 0.5 % NaOH sol		99 %
	MOE-Ms 0.5 % NaOH sol		99 %
	MOE-Ms 0.5 % NaOH sol		99 %
	MOE-Ms 0.5 % NaOH sol		99 %

MOE-MS = Methoxyethyl mesylate.

TABLE-2
S-ALKYLATION'S WITH ALKYL HALIDES

Benzimidazole **1(a-h)**	Reagent/base	Product **(2a-h)** + **3(a-h)**	% of product
	MOE-Br NaOH/ACN		80:20 C.C
	MOE-Br DMSO-KOH		80:20 C.C
	MOE-Br KOH/EtOH Reflux-3hrs		90:10 C.C
	MOE-Br Powdered KOH MW reaction		80:20 C.C
	MOE-Br K_2CO_3/EtOH Reflux		90:10 C.C
	MOE-Br $NaHCO_3$/EtOH Reflux		80:20 C.C
	MOE-Br,K_2CO_3 EtOH, MW		90:10 C.C
	MOE-Br,KOH Acetone,MW		90:10 C.C

2-(2-Methoxy-ethylsulfanyl)-5-(1-methyl-cyclopropyl)-3*H*-imidazo[4, 5-b]-pyridine (2 g): 5-(1-Methyl-cyclopropyl)-3*H*-imidazo[4, 5-b]pyridine-2-thiol **(1 g)** 5 g, was alkylated with the same methodology and obtained the required product as a yellow solid (7 g) with 99 % yield ^{1}H NMR ($CDCl_3$-200 MHz): 8.3 (s, 1H), 8.09 (d, 2H), 7.6 (d, 2H), 3.6 (m, 2H), 3.4 (m, 2H), 3.2 (s, 3H), Mass (m/z): 254 (M^+) HPLC: 99 %, Column: HypersilGold, 150 mm × 4.6 mm, 5u(SHCL05H003); mobile phase: acetonitrile: 50 Mm NH_4OAc Buffer (Gradient); UV: 254 nm.

5-*sec*-Butyl-2-(2-methoxy-ethylsulfanyl)-3*H*-imidzo[4,5-b]pyridine (2 h): 5-*sec*-Butyl-3*H*-imidzo[4,5-b]pyridine (1 h) 5 g, was alkylated adopting the above procedure and obtained the required product as a yellow solid (7 g) with 99 % yield ^{1}H NMR ($CDCl_3$-200 MHz): 8.3 (s, 1H), 8.09 (d, 2H), 7.6 (d, 2H), 3.6 (m, 2H), 3.4

(m, 2H), 3.2 (s, 3H), Mass (m/z): 254 (M^+) HPLC: 99 %, Column: HypersilGold, 150mm × 4.6 mm, 5u (SHCL05H003); mobile phase: acetonitrile: 50 Mm NH_4OAc buffer (Gradient); UV: 254 nm.

Antimicrobial activity of compounds 2a-2h: Test discs (6 mm in diameter) impregnated with 10 mg of the appropriate sample were used to test both antibacterial and antifungal activities at pH 6.9-8, respectively. Discs were applied on the surface of plates containing each 10 mL of antibiotic medium, inoculated with 10^6 CFU/mL of the microorganisms. The following strains were used to test the activities (*Porteus vulgaris, Pseudomonas aeroginosa, Escherichia coli, Salmonella typhi, Klebsiella pneumoniate, Staphylococcus citreus, Staphylococcus aureus, Candida albicans*). The growth inhibition was tested after 24 h incubation at ambient temperature. All the results are shown in the Table-3.

TABLE-3
GROWTH INHIBITION ACTIVITY OF 2-(2-METHOXYETHYLSUFANYL)-SUBSTITUTED-1*H*-BENZIMIDAZOLES (**2a-h**)

	Antimicrobial activity of drugs (Activity tested with standard antibacterial and fungal drugs)										
Bacteria/fungus/ virus	Erythro mycin	Strepto mycin	Chloro phenicol	**2a**	**2b**	**2c**	**2d**	**2e**	**2f**	**2g**	**2h**
Porteus vulgaris	++	++	++	-	++	-	+	-	-	++	-
Psuedomonas aeroginosa	++	++	++	+	+	+	+	++	+	++	+
Escherichia coli	++	++	--	-	++	+	++	++	+	++	+
Salmonella typhi	++	+	+	-	+++	+	+	+	+	++	+
Klebsiella pneumoniate	++	++	++	-	+	+	-	++	+	+++	++
Staphylococcus citreus	++	++	++	-	+	-	-	+	+	++	++
Staphylococcus aureus	++	++	++	++	+++	-	+	+	+	-	++
Candida albicans	------	------	-------	+	++	++	++	++	++	++	++

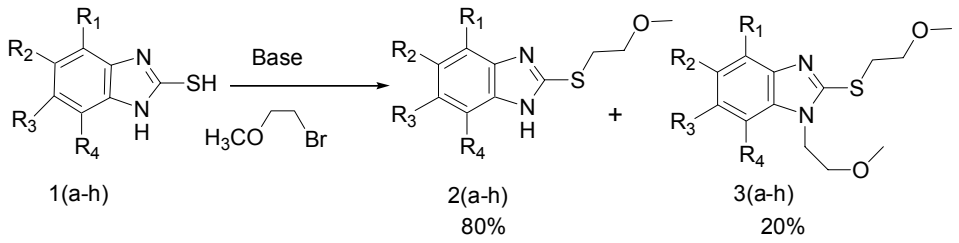
Note: Sample10 mg in 10 mL at pH = 6.5-7.9;
Presence or absence of inhibition zone is shown as '+' or '-',
(+ = 5 nm, ++ = 10 mm, +++ = 12 mm, ++++ = 15 mm, '-' = No inhibition).

RESULTS AND DISCUSSION

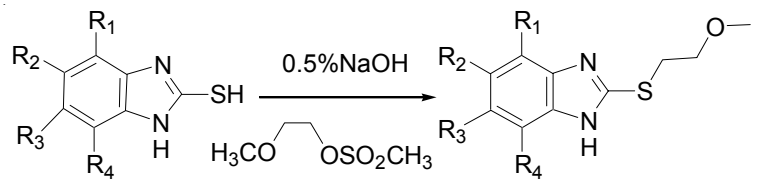
The literature revealed that 2-(2-methoxy ethylsulfanyl)-1*H*-benzimidazoles can be prepared by the reaction of 2-mercaptobenzimidazole with alkyl halides in the presence of a strong base like sodium in ethanol (EtONa)[4-6]. Although the use of strong bases like sodium hydroxide gives good yields of the S-alkylated products, the disadvantages lies in the formation of competing side products like N-alkylated ones in 1:1 ratio. The use of strong bases gave good yields along with side products; we worked to get a single S-alkylated product using a modified alkylating reagent called methoxy ethyl mesylate.

Recently, an alternative approach has been reported for the synthesis of S-alkylated compounds in CsF-celite condition[7]. Other methods reported are dibenzyl carbonate in the presence of DABCO or DBU for the benzylations and alkylations[8].

However, the availability of substituted dibenzyl carbonates limits this method to use phase catalyst conditions. From the literature it is evidenced that though there are some methods available for the preparation of these title compounds, yet there is no simple and efficient method for the synthesis of these important heterocyclic without the use of either expensive reagents or strong bases along with phase transfer conditions. In this paper, we wish to report a simple but efficient methodology for the synthesis of 2-(2-methoxyethylsulfanyl)-1*H*-benzimidazole in excellent yields (98-99) without using column chromatography.



General schemes



R_1=R_2=R_3=R_4=H, R_1=R_3=R_4=H; R_2=NO_2, OCH_3, CH_3, CF_3, R_1=R_4=OCH_3, R_1=R_3=Br

Scheme with newly developed protocol

2-Mercaptobenzimidazole (**1a-h**) on heating with methoxyethyl mesylate (1.1 eq) in 0.5 % sodium hydroxide solution at 50-60 ºC for about 3 h, gave the corresponding product in 99 % yield. All the products were identified with the spectral data and elemental analysis data.

Conclusion

A convenient and useful method for the synthesis of 2-alkyl thio benzimidazole in excellent yields is reported. The advantage of this methodology is the use of very mild conditions which can tolerate various functional groups that can be used for further synthetic manipulations; commercial availability of large number of substituted benzimidazole or easy methods of their preparation makes this reaction a more attractive choice. All the compounds were tested for antibacterial and antifungal actvities screening.

REFERENCES

1. B.V. Kumar, H.G.S. Rathore and V.M. Reddy, *Indian J. Chem.*, **21B**, 1126 (1982); B.V. Kumar and V.M. Reddy, *Indian J. Chem.*, **24B**, 1098, 1298 (1985).
2. P.N. Preston and G. Tennant, Condensed Benzimidazoles, Vol. 1 (1981).
3. P.N. Preston, Commercial Applications of Benizimidazoles, Vol. 2 (1981).
4. V.K. Ramanatham, V.S.R.S.K. Kotha and R.G. Kotarkonda, *J. Heterocycl. Chem.*, **42**, 153 (2005).
5. A.O. Fitton and R.K. Smalley, University of Stafford, Lances England, Practical Heterocyclic Chemistry (1968).
6. J.S. Rao, D.S. Iyengar, U.T. Bhalerao and S. Nagabhushan, *Indian J. Chem.*, **26B**, 788 (1987).
7. K.V. Klimesova, K. Waisser, J. Kaustova, H.M. Dahse and U. Mollmann, *Bioorg. Med. Chem. Lett.*, **12**, 3275 (2002).
8. D. Varaprasad, Y.S. Sanghvi and AK. Chakravarthy, *Org. Process Res. Dev.*, **11**, 468 (2007).

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UNIVERSITY OF GRONINGEN, THE NETHERLANDS

Contact:
Royal Society of Chemistry, Thomas Graham House,
Science Park, Milton Road, Cambridge CB4 0WF, UK
Tel: +44 (0) 1223 432254 / 432380; Fax: +44 (0) 1223 423623
Email: RSC Conferences Email: RSC Conferences