Tr. J. of Chemistry
20 (1996) , 228 – 233.

Synthesis of Optically Active Camphorsulphonylbenzimidazoles

Mashooda HASAN, Humaira MASOOD, Naeema KHAN, M. ZIA-UL-HAQ
Department of Chemistry, Quaid-i-Azam University,
Islamabad-PAKISTAN

Received 26.10.1995

The preparation of optically active camphorsulphonylbenzimidazole (**1**), a mixture of regioisomeric 5-nitro- (**2A**) and 6-nitro-(**2B**) camphorsulphonylbenzimidazoles, 5-nitro-(**3A**) and 6-nitro-(**3B**) 2-methyl camphorsulphonylbenzimidazoles is described. In this study the structure of the purified camphorsulphonylbenzimidazoles **1, 2B, 3A** and **3B** was confirmed by their mass and ^{1}H NMR spectral analysis. The specific rotation of each pure compound is also reported.

Introduction

The importance of sulphonamides as drugs cannot be ignored. A number of sulphonamides have been synthesized to keep pace with the growing needs of the phamaceutical industry. For these reasons camphorsulphonyl derivatives are of special interest. The synthesis of DL-camphor-10-sulphonanilide has been studied by Cremlyn et al[1] and the same research group has also synthesized camphorimide[2]. New 2-, 3-, 4-pyridyl-, 2-picolyl-, 2- thiazolyl-, cyclopentyl-, cyclohexyl-, d-10-camphorsulphonamide derivatives have been prepared via the reaction of camphorsulphonyl chloride with the appropriate amine[3]. It is expected that they will exert an antibacterial effect and may find an application in plastic products. Different benzimidazolesulphonamides have also been found useful as pesticides[4–7], fungicides, herbicides and as intermediates for dyes, diuretics, antibacterial and hypoglycemic agents. Consequently, we synthesized optically active sulphonamides having camphor as well as benzimidazole moieties in their structure. Such compounds can then be tested for their biological activity by interested research groups. The present work describes the synthesis of optically active camphorsulphonylbenzimidazole (**1**), regioisomeric 5- and 6-nitro-camphorsulphonylbenzimidazoles (**2A** and **2B**) and 5- and 6- nitro-, 2- methylbenzimidazoles (**3A** and **3B**). These compounds were prepared by using the standard method for sulphonamide preparation.

Results and Discussion

Compound **1** was synthesized by the reaction of benzimidazole with camphorsulphonyl chloride in dry acetone in the presence of triethylamine. The regioisomeric mixtures **2** and **3** were prepared by the reaction of 5-nitrobenzimidazole and 2-methyl, 5-nitrobenzimidazole separately with camphorsulphonyl chloride under

identical conditions. (Scheme 1). Optically active camphorsulphonamide prepared[8] from (+) camphor-10-sulphonic acid was used in each experiment. Compound **1** was purified by thin layer chromatography on silica-gel using ethyl acetate as the solvent and subsequent recrystallization from methanol. The regioisomeric mixture **2** which was obtained in the reaction described above showed two spots in thin layer chromatography on silica-gel plate with ethyl acetate as solvent. The regioisomer having lower R_f value was numbered as **2B** and the one having higher R_f as **2A**. The mixture was subjected to fractional crystallization from methanol, but separation of regioisomers could not be achieved. The mixture was then chromatographed on silicagel column with n-hexane-ethyl acetate gradient. Earlier fractions gave a mixture of **2A** and **2B** which could not be separated in spite of repeated column chromatography. Pure **2B** was obtained from later fractions which could be recrystallized from methanol in the form of colourless crystals. The crude regioisomeric mixture **3** also showed two distinct spots besides some impurities when subjected to thin layer chromatography on silica-gel in ethyl acetate. Impurities were removed through recrystallization from methanol. Separation of regioisomers **3A** and **3B** could be achieved through fractional crystallization from methanol, where **3B** crystallized out in preference and the mother liquid was richer in **3A**. Repeated recrystallization of the first crop of crystals yielded colourless crystals of **3B** and the mother liquid on further purification through recrystallization gave colourless shining crystals of 3A.

Purified compounds were subjected to melting point, specific rotation, mass- and ^{1}H NMR spectral determinations. Percentage yields, physical properties, specific rotation and mass spectral fragments of these compounds are listed in Table 1. The mass spectral fragmentation pattern of all these compounds shows the molecular ion peak as well as the characteristic peaks for benzimidazole and camphor moiety in each case. Regioisomers exhibit similar fragmentation.

Table 1. Physical Properties Percentage Yield and Mass Spectral Fragmentation Pattern of purified Compounds

Comp. No.	Melting Point (MeOH)	R_f (Ethylacetate)	Percentage Yield	Mass Spectral Fragmentation Pattern low resolution m/z	$[\alpha]D^{22}$ Acetone. $1 \times 10^{-4}M$)
1	143°	0.76	28	331.8(33%),268.1,215,152 151,123,111,110,109(100%) 108,104,103,95,91,90,81,69, 65,64,63,35	-1.56°
2A	Impure	0.83	25	377(2%),332,215,152,151,131, 123,110,109(100%), 108,104,	
2B	209°	0.79		103,91,90,95,81,69,65,64, 63,55,	+15.36°
3A	153°	0.78	23	390.9(6%),332,268,215(100%) 152,151,133,123,110,109,108, 104,103,95,91,83,81,69,67, 65,64,63,55	-67.7°
3B	172°	0.64			-2.0°

Final confirmation of the structure was done with the help of ^{1}H NMR spectroscopy. Structure of the synthesized compounds and type of protons present in each of them are shown in Figure 1. Table 2 shows

the chemical shifts, peak pattern and coupling constants of the compounds. All chemical shifts characteristic of aromatic and aliphatic regions in these compounds with their expected peak pattern are visible and have been assigned to all protons. Assignment of structure to regioisomers **3A** and **3B** has also been achieved on the basis of ^{1}H NMR data. The slow moving isomer **3B** has an aromatic proton at the lowest field at 8.70 ppm with meta and para coupling (J=2.2 and 0.5 Hz) which means that this proton is H_d which is in the vicinity of NO_2 and $-SO_2-$ groups. In **3A** the proton having meta and para coupling (H_a) appears at a relatively higher field at 8.56 ppm being in the neighbourhood of only a NO_2 group. Therefore compound **3A** is 2-methyl, 5-nitro and compound **3B** is 2-methyl, 6-nitro-p-toluenesulphonylbenzimidazole (Figure 1). Similar work on regioisomeric p-toluenesulphonyl benzimidazoles[9] has also shown that the slow moving regioisomers are 6- nitro-p-toluenesulphonyl benzimidazoles. In addition, ^{1}H NMR data of **2B** are analogous to **3B** where H_d appears at the lowest field and H_a at the highest field among the three aromatic protons. Thus **2B** has been ascribed the structure shown in Figure 1: 6-nitro-p- toluenesulphonyl benzimidazole.

Table 2. ^{1}H NMR Chemical Shifts (ppm), Peak Pattern and Coupling Constants (Hz) of the Pure Camphorsulphonylbenzimidazoles **1, 2B, 3A** and **3B**

Comp. No.	H_a (1H)	H_b (1H)	H_d (1H)	H_f (1H)	H_e (1H)	H_g-H_i (7H)	H_k (3H)	H_l (3H)	H_m
	7.82	7.43	7.90	3.76	3.22	1.44-2.50	1.11	0.83	0.26
	ddd	m	ddd	d	d	m	s	s	s
1	J_{ab} = 6.6	(H_c also)	J_{cd}=6.6					(1H)	
	J_{ad}=1.3			$J_{e,f}$=14.6					
	J_{ad}=0.6	(Total 2H)	J_{bd}=1.3						
			J_{ad}=0.6						
	6.73	7.99	8.01	2.9	2.95	1.46-2.61	1.03	0.97	7.7
	dd	dd	dd	d	d	m	s	s	s
2B	J_{ab}=8.7	J_{ab}=8.5	J_{bd}=2.6						(1H)
	J_{ad}=v.v.small	J_{bd}=2.5	J_{ad}=negligible	$J_{e,f}$=14.5					
	7.56	8.29	8.03	3.20	3.72	1.48-5.52	1.16	0.87	2.9
	dd	dd	dd	d	d	m	s	s	s
3A	J_{ab}=2.2	J_{bd}=9.0	J_{bd}=9.0						(3H)
	J_{ad}=negligible			$J_{e,f}$=14.49					
		J_{ab}=2.2	J_{ad}=0.45						
	7.64	8.14	8.70	3.25	3.65	1.7-2.41	1.04	0.75	2.8
	dd	dd	dd	d	d	m	s	s	s
3B	J_{ab}=8.8	J_{ab}=8.8	J_{bd}=2.2						(3H)
	J_{ad}=0.44	J_{bd}=2.2	J_{ad}=0.5	$J_{e,f}$=14.6					

Experimental

All solvents were distilled and dried where necessary before use, according to conventional procedures. Fractions were monitored by thin-layer chromatography using precoated silica- gel glass plates 0.2 mm., Art 5554 HF_{254} (E. Merck). Preparative thin-layer chromatography was carried out on 20x20 cm. glass plates coated with a 1 mm. thick layer of Kiesselgel HF_{254}. Kiesselgel 60(70-230 mesh ASTM) was used for column chromatography. Melting points were recorded on Gallenkamp melting point apparatus and are uncorrected. ^{1}H NMR spectra were scanned on a Brucker AM-400 spectrometer operating at 400.1 MHz. Chemical shifts are given in δ scale (ppm), s=singlet, d=doublet, q=quartet, ddd=doublet of doublet of

doublet, m=multiplet. Mass spectra were recorded on MAT 1125 mass spectrometer. Optical rotations were measured on a JASCO 20-A polarimeter with c=1x10^{-4} molar solution in acetone.

Benzimidazole was prepared by the usual procedure, i.e. refluxing equimolar quantities of o-phenylenediamine and formic acid in 4N hydrochloric acid. 5-Nitrobenzimidazole was prepared using 1,2-diamino, 4-nitrobenzene and formic acid in a 1:2 molar ratio. 2-Methyl, 5-nitrobenzimidazole was also prepared using a 1:2 molar ratio of 1,2-diamino, 4-nitrobenzene and acetic acid to obtain high yield.

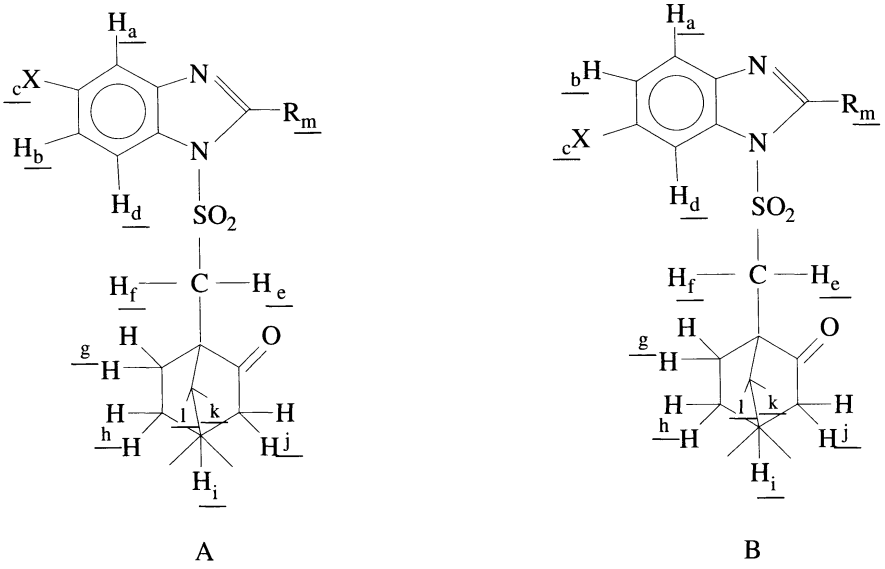


Figure 1. Structure and Type of Protons in the Synthesized Compounds

Camphor-10-sulphonyl chloride

(+) Camphor-1-sulphonic acid (59 g, 0.23 mole) and phosphorous pentachloride (52 g, 0.23 mole) were mixed together in a three enecked 500 ml round bottom flask equipped with efficient gas traps and a mechanical stirrer. The flask was immersed in an ice-water mixture. When the mixture liquified, the stirrer was applied slowly at first due to the formation of lumps. When the vigorous reaction subsided, the cooling bath was removed and stirring continued until the chloride was completely dissolved (6 hours). The mixture was allowed to stand for 4 hours and then it was poured into a 500 ml beaker containing crushed ice. This mixture was immediately poured into a second beaker containing crushed ice. The process was repeated several times until all evidence of the reaction disappeared. The product was collected on a suction filter, washed several times with cold water and dried. Yield 25.0g (40 %), m.p. 65° C.

Camphor-10-sulphonylbenzimidazole (1)

Benzimidazole (2.0 g, 0.016 mole) was dissolved in dry acetone (100 ml). Dry ethylamine (2.3 ml) was added to this solution. Then a concentrated solution of camphor-10-sulphonyl chloride (4.5 g, 0.016 mole) in dry acetone was added and the mixture was stirred for two hours at room temperature. The solid formed

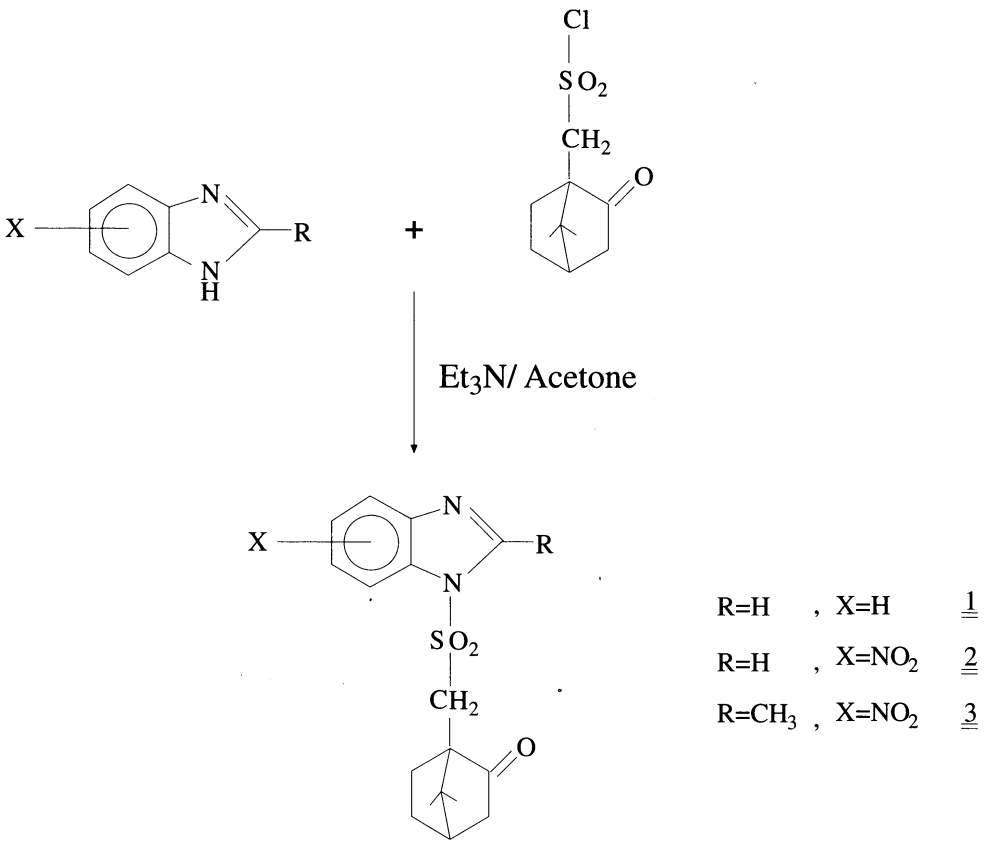
was filtered off and the solvent was removed from the clear solution under reduced pressure which gave a yellow solid. Purification of the product was carried out by preparative thin-layer chromatography using ethyl acetate as the solvent. The product (1.57 g) was recrystallized from methanol in the form of colourless shining crystals. Percentage yield, physical properties and mass spectral fragmentation pattern are given in Table 1, whereas Table 2 shows ^{1}H NMR data for **1**.

Camphor-10-sulphonyl 5(6)-nitro-benzimidazoles (2A and 2B)

Compound **2** (2.0 g, 0.012 mole) in dry acetone (200 ml), dry triethylamine (1.66 ml, 0.012 mole) and a concentrated solution of camphor- 10-sulphonyl chloride (3.60 g, 0.012 mole) in dry acetone were reacted in the same way as described for the preparation of **1**. After the main reaction the product exhibited two distinct spots (R_f=0.83 and 0.79) on thin layer chromatography in ethyl acetate besides some impurities. The isomer having lower R_f was designated as **2B** and that having higher R_f as **2A**.

Separation of 2B

The product was subjected to fractional crystallization from methanol, but separation of regioisomers could not be achieved. Then the recrystallized reaction mixture (1.28 g) was dissolved in minimum amount of ethyl acetate and was subjected to column chromatography on silica-gel in n-hexane-ethyl acetate gradient. The earlier fractions gave a mixture of **2A** and **2B** and the later fractions yielded pure **2B** (800 mg), which was recrystallized from methanol in the form of colourles crystals. Percentage yield, physical properties and mass spectral fragmentation pattern are shown in Table 1, whereas ^{1}H NMR data is given in Table 2.



Scheme 1. Synthesis of Camphorsulphonyl Benzimidazoles

Camphor-10-sulphonyl, 2-methyl 5(6)-nitrobenzimidazoles (3A and 3B)

The procedure described for the preparation of **2A** and **2B** was followed using 2-methyl 5-nitrobenzimidazole (8.4 g, 0.033 mole) and dry triethylamine (5.1 ml, 0.033 mole) and concentrated solution of camphor-10- sulphonyl chloride (5.50 g, 0.33 mole) in dry acetone. After the removal of the solvent, the crude product exhibited two distinct spots besides some impurities on a thin-layer chromatography in ethyl acetate. Recrystallization of the crude product from methanol yielded 4.69 g of light yellow crystals which showed two spots (R_f =0.78 and 0.64) on thin-layer chromatography in ethyl acetate.

Separation of 3A and 3B

The purified mixture of **3A** and **3B** (1.0 g) was dissolved in minimum amount of methanol and was allowed to stand. The first crop of crystals gave 20 mg pure **3B**.

The mother liquor was concentrated and the second crop of crystals obtained was subjected to two more recrystallizations. In this way 25 mg of **3A** was obtained in the form of colourless needles. Physical properties and mass spectral fragmentation pattern of **3A** and **3B** are shown in Table 1, whereas their ^{1}H NMR data are listed in Table 2.

Acknowledgement

M. H. is grateful to URF, Quaid-i-Azam University for the grant received for this work. Mass and ^{1}H NMR spectra of the synthesized compounds were measured in the H.E.J. Research Institute of Chemistry, University of Karachi, Karachi, Pakistan.

References

1. R. J. Cremlyn, L. Wu, C. R. Theocharis and W. Jones, **J. Chem. Soc. Pak.,** Vol. 9, No.2, 167 (1987).
2. R. Cremlyn and R. Nunes, **J. Chem Soc. Pak.,** Vol. 9, No. 4, 611 (1987).
3. S. A. K. Shubber, I. Kazandji, **J. Sci.,** 31(3), 529-38 (1990).
4. P. E. Wittreich, A. Folkers and M. Robinson, **C. A.** Vol. 58, 9087 g (1963 to Merck & Co. Inc.) US 3,056, 777 (CI 260-239.9) Oct. 2, 1962, appl. Dec. 19, 1960 3pp.
5. T. J. Newbold, A. Percival, (Fisons Pest Control Ltd.) **C. A.** Vol. 70, 96797 j U.S.3,430,259 (C1.260-309.2; C O7d, A oln) 25 Feb. 1969, Appl. 11 Jul. 1966 2pp.
6. F. I. Chimetron 439, 128 **C. A.** Vol. 65, 20135 d (1968).
7. Fisons Pest Control Ltd. Neph Appl. 6,610 554, **C. A.** Vol. 67, 73610s (1967).
8. P. D. Bartlett and L. H. Knox, **Org. Synth.,** 45, 14 (1965).
9. M. Hasan, N. Rashid, K. Akhtar, Osman Malik and H. Duddeck, **Revue Roumaine de Chimie,** 38(6), 711-718 (1993).