A New Heterocyclic System: Imidazo[2,1-*d*][1,5]benzothiazepine. Its Synthesis from 4-Amino-2,3-dihydro-1,5-benzothiazepine

Jasjit S. Walia*, Amrik S. Walia,‡ David C. Lankin,
Robert C. Petterson and Janak Singh†

Chemistry Department, Loyola University,
New Orleans, LA 70118

Received January 16, 1985

The synthesis of 4-amino-2,3-dihydro-1,5-benzothiazepine and its transformation to the new heterocycle Imidazo[2,1-*d*][1,5]benzothiazepine is described.

J. Heterocyclic Chem., **22**, 1117 (1985).

The discovery of Thiazesim, a 1,5-benzothiazepine derivative, as an antidepressant agent by Krapcho and Turk [1] has led to the synthesis of many related compounds. The antianginal drug Diltiazem is the result of such efforts. The 1,5-benzothiazepines are known to possess coronary vasodilating and antihypertensive effects [2-4].

Our work in this area has provided a new convenient synthesis of 4-amino-2,3-dihydro-1,5-benzothiazepine (**2**). We also describe here the easy transformation of **2** to a novel heterocyclic system, imidazo[2,1-*d*][1,5]benzothiazepine (**6**).

We have previously reported [5,6] a convenient one step synthesis of 3-(2-aminophenylthio)propanenitrile (**1**). An intramolecular nucleophilic attack by the amino group onto the nitrile function in **1** would be expected to afford 4-amino-2,3-dihydro-1,5-benzothiazepine (**2**). The cyclisation of aminonitrile **1** to benzothiazepine **2** was achieved in 76% yield with trifluoroacetic acid in refluxing toluene [7]. The structure of benzothiazepine **2** has been established by elemental analysis, H^1-nmr, ir and ms data as well as by its hydrolysis to the known lactam **3**. The identity of the lactam **3** was confirmed by comparison of its spectral data with that of the sample prepared by an independent synthesis [8].

Treatment of **2** with phenyacyl bromide in 95% ethanol solution containing sodium bicarbonate gave in 57% yield phenyl substituted imidazo[2,1-*d*][1,5]benzothiazepine (**6a**).

The mode of formation of **6a** is delineated in Scheme-I. The initial displacement of the bromine atom in phenacylbromide by the ring nitrogen atom of **2** (Path-A) would lead to the resonance stabilized amidinium ion intermediate **4**. Further loss of elements of hydrogen bromide and water from **4** would furnish the heterocycle **6a**. The formation of the isomeric structure **7** would not be favoured since it requires the intermediacy of ammonium ion **5** (Path-B), which is devoid of charge stabilization [9a,b].

The recent studies on the 2-aminopyridines by the time dependent H^1-nmr [9a] and the molecular orbital calculations [10] reveal that the ring nitrogen atom is involved in the initial attack during these reactions. It is well known [11-14] that the reaction of 2-aminopyridine with phenacylbromide gives 2-phenylimidazo[1,2-*a*]pyridine. No formation of isomeric products has been observed especially in the case of alkylation reactions with α-haloaromatic ketones. Analogous reaction pattern is recorded during the reactions of 2-aminothiazoles with α-bromoketones [15,16].

The structure of **6a** was fully characterized by a high resolution (400 MHz) H^1-nmr [17,18] and C^{13}-nmr spectra. The detailed analyses of the H^1-nmr and C^{13}-nmr are summarized in Tables I and II, respectively.

Table I

H^1-NMR (400 MHz) of 13-Phenylimidazo[2,1-*d*][1,5]benzothiazepine (**6a**)

Proton Number	Chemical Shift ppm	Splitting Pattern	Coupling constant J, Hz
2	3.08	t	8.0
3	3.50	t	8.0
7	7.74	dd	1.4, 8.0
8 [a]	7.32	ddd	1.4, 8.0, 8.0
9 [a]	7.48	ddd	1.4, 8.0, 8.0
10	7.41	dd	1.4, 8.0
14	7.42	s	
16,20	7.82	dd	1.4, 8.0
17,19	7.38	ddd	1.4, 8.0, 8.0
18	7.35	dddd	1.4, 1.4, 8.0, 8.0

[a] Chemical shift values may be interchanged.

Table II

C^{13}-NMR of 13-Phenylimidazo[2,1-*d*][1,5]benzothiazepine (**6a**)

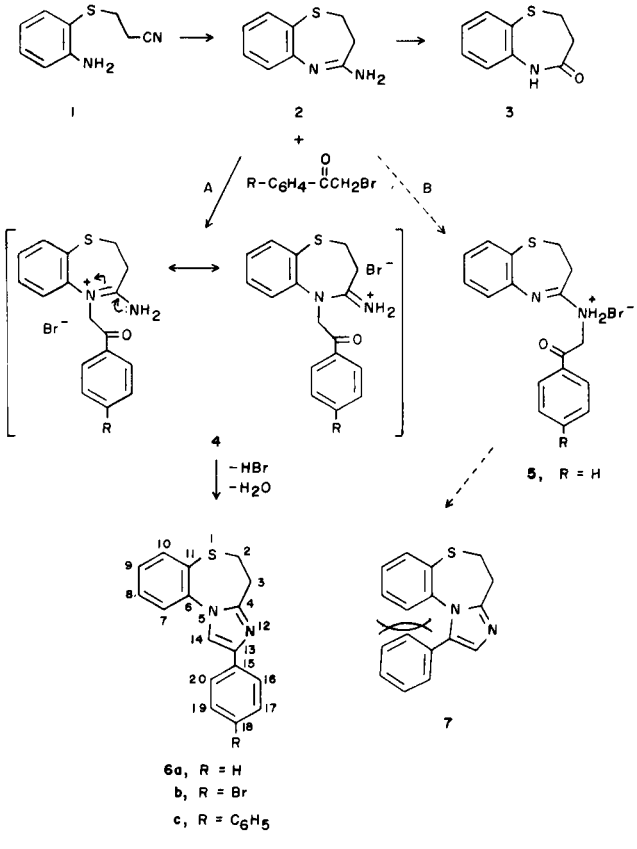
Carbon	Chemical Shift ppm	Carbon Atom	Chemical Shift (ppm)
2	26.52	11	127.18
3	38.27	13	140.84 [a]
4	141.18 [a]	14	123.52
6	147.29	15	133.56
7	114.89	16,20	124.70
8	135.79	17,19	128.32
9	127.72	18	126.67
10	129.72		

[a] The chemical shift values may be interchanged.

The aromatic proton in **6a** at position 7 is observed at δ 7.74 as a doublet of a doublet (J's = 1.4 and 8.0 Hz). Inspection of molecular models show that in the isomeric structure **7a** the phenyl ring at C-14 will be forced out of plane of the imidazole ring, because of sever steric interaction with the fused benzene ring. In that situation, the proton at C-7 should experience a pronounced anisotropic shielding effect. No such effect is observed.

In the C^{13}-nmr, as expected for an unencumbered phenyl substituted imidazole **6a**, the *ortho* carbon atoms (16, 20) and *meta* carbon atoms (17, 19) appear as singlets at 124.70 and 128.32 ppm respectively. The relatively pronounced chemical shift difference (δ *ortho* - δ *meta* = 3.62 ppm) is attributed to the shielding of the *ortho* carbons caused by interannular conjugation effect of the imidazole ring nitrogen [19].

Scheme I



The *para*-bromo and *para*-phenyl substituted imidazo-[2,1-*d*][1,5]benzothiazepines **6b** and **6c** respectively were likewise obtained from the reaction of aminoimine **2** with α,*p*-dibromoacetophenone and α-bromo-*p*-phenylacetophenone.

The present studies provide a convenient method for the synthesis of a 1,5-benzothiazepine incorporating cyclic amidine functionality, and its further transformation to the new heterocyclic imidazo[2,1-*d*][1,5]benzothiazepines.

EXPERIMENTAL

Spectra were determined as follows: ir, Perkin Elmer 337; pmr, Jeol GX400 and Varian A-60A or Em-360 with tetramethylsilane as an internal standard; mass spectra, Hitashi-Perkin Elmer RMU-6A operating at 70 eV. Elemental analyses were performed by Chemalytics, Inc., Tempe, Arizona. Melting points were measured on a Thomas-Hoover apparatus and are uncorrected. Analysis by thin layer chromatography (tlc) involved the use of Eastman Kodak precoated silica gel sheets, with fluorescent indicator as the adsorbent, development with chloroform, and visualization with iodine vapor and/or ultraviolet light. "Vaseline" is a high viscosity petroleum jelly, which has an ir spectrum very much like Nujol.

4-Amino-2,3-dihydro-1,5-benzothiazepine (**2**).

To a solution of 3-(2-aminophenylthio)propanenitrile (**1**) [5,6] (20.0 g, 0.112 mole) in 1.5 liters of refluxing thiophene-free toluene was added 20 ml of trifluoroacetic acid. The course of the reaction was monitored by tlc and refluxing was discontinued after three days when the starting material was no longer present in the reaction mixture. The solution was allowed to cool to room temperature after which it was neutralized with saturated sodium bicarbonate solution. The resulting precipitate was collected and air-dried to give 15.3 g (77% yield) of crude **2**. Recrystallization from toluene gave analytically pure **2**, mp 175-177°; ir (KBr) 3410 m, 3290 m (NH_2), 1645 s (C=N), 755 s cm^{-1} (1,2-disubstituted aromatic ring); pmr (deuteriochloroform): δ 2.23 (2H, t, J = 7.0 Hz, CH_2S-), 3.28 (2H, t, J = 7.0 Hz, -CH_2C=N), 3.55 (2H, br s, NH_2), 7.10-6.53 (3H, m, aromatic), 7.25 (1H, dd, J = 7.0 Hz, J = 1.5 Hz, aromatic); ms: m/e M^+ 178.

Anal. Calcd. for $C_9H_{10}N_2S$: C, 60.64; H, 5.61. Found: C, 60.98; H, 5.68.

Reactions of 4-Amino-2,3-dihydro-1,5-benzothiazepine (**2**).

(a) With Phenacyl bromide.

A solution of 4-amino-2,3-dihydro-1,5-benzothiazepine (**2**) (1.79 g, 0.01 mole), phenacyl bromide (2.07 g, 0.01 mol), and 3.0 g of sodium bicarbonate in 50 ml of 95% ethanol was stirred for 0.75 hour at ambient temperature (23-24°) and then refluxed for an additional 1.5 hours. The ethanol was evaporated and the residue dissolved in acetone. The inorganic salts were filtered and the acetone was concentrated to about 50-75 ml. Pentane was added until the solution became cloudy after which it was refrigerated (5°). The crystals which were formed were collected and dried, affording 1.57 g (57% yield) of **6a**, mp 116-117.5°. Recrystallization from acetone afforded pure **6a**, mp 119-120°; ir (Vaseline mull): 1601 m, 1530 m, 1268 m, 1170 m, 988 m, 850 w-m, 782 m, 768 m-s, 755 m, 690 m-s cm^{-1} (monosubstituted and 1,2-disubstituted aromatic ring); ms: m/e M^+ 278.

Anal. Calcd. for $C_{17}H_{14}N_2S$: C, 73.37; H, 5.07; N, 10.07; S, 11.50. Found: C, 73.27; H, 4.92; N, 9.77; S, 11.56.

(b) With α,*p*-Dibromoacetophenone.

A solution of 4-amino-2,3-dihydro-1,5-benzothiazepine (**2**), (1.78 g, 0.01 mole) α,*p*-dibromoacetophenone (2.78 g, 0.01 mole) and 3.5 g of sodium bicarbonate in 100 ml of 95% ethanol was stirred for one hour at room temperature and then heated to reflux for an additional 3.5 hours. After filtration and evaporation of the ethanol, the residue was leached with acetone, which was concentrated. Crystallization at 5° gave **6b** (59% yield), mp 149-151°. Recrystallization from acetone provided analytically pure **6b**, mp 150-151°; ir (Vaseline): 1600 w, 1555 m, 1530 m, 1460 m-s, 1272 m, 1175 m-s, 1005 m, 945 m, 828 m-s, 755 and 735 m-s; pmr (deuteriochloroform): δ 3.05 (2H, m, -CH_2-S-), 3.50 (2H, m, -CH_2-C=N-), 8.15-7.00 (14H, m, aromatic protons).

Anal. Calcd. for $C_{17}H_{13}BrN_2S$: C, 57.42; H, 3.64; N, 7.84; S, 8.96; Br, 22.40. Found: C, 57.29; H, 3.62; N, 7.66; S, 9.10; Br, 22.37.

(c) With α-Bromo-4-phenylacetophenone.

A solution of 4-amino-2,3-dihydro-1,5-benzothiazepine (**2**) (0.89 g, 0.005 mole), α-bromo-*p*-phenylacetophenone (1.38 g, 0.005 mole), and 3.0

g of sodium bicarbonate in 70 ml of 95% ethanol was stirred for one hour at room temperature and then refluxed for an additional two hours. The ethanol was evaporated and the residue dissolved in acetone. The insoluble inorganic salts were filtered and the solution, after concentrating was cooled, yielding colorless fine crystals (64%), mp 169-171°C. Recrystallization from acetone provided pure **6c**, mp 169-170°C; ir (Vaseline): 1550 and 1525 w, 1455 m-s, 1400 m, 1260 m, 1165 m, 1075 w-m, 850 m-s, 690 m; pmr (deuteriochloroform): δ 3.05 (2H, m, $-CH_2-S-$), 3.50 (2H, m, $-CH_2-C=N-$), 8.0-7.0 (14H, m, aromatic protons).

Anal. Calcd. for $C_{23}H_{18}N_2S$: C, 77.95; H, 5.12; N, 7.90; S, 9.03. Found: C, 78.18; H, 5.21; N, 7.76; S, 8.78.

2,3-Dihydro-1,5-benzothiazepine-4(5*H*)-one (**3**).

A solution of 4-amino-2,3-dihydro-1,5-benzothiazepine (**2**) (0.89 g, 0.005 mole) in 50 ml of ethanol and 3.0 g of sodium bicarbonate in 20 ml of water was stirred for a few minutes, 100 ml of ethanol was added and the solution was heated to reflux for 20 hours. The ethanol was evaporated and acetone added. After filtration and cooling, colorless crystals of lactam **3** separated; yield 55%, mp 208-211°. Recrystallization provided analytically pure **3**, mp 211-211.5°, (Lit mp 215-216°) [8]; m/e M^+ 179; pmr (deuteriochloroform): δ 2.6 (t, 2H, CH_2, J = 3.6 Hz), 3.45 (t, 2H, CH_2, J = 3.5 Hz), 8.4-6.9 (m, 5H, 4H aromatic and 1NH proton); ir (Vaseline) 3100, 3210 (NH), 1675 s (CONH), 755 s cm^{-1} (1,2-disubstituted aromatic ring).

Anal. Calcd. for C_9H_9NSO: C, 60.33; H, 5.06; N, 7.82; S, 17.87. Found: C, 59.93, H, 4.91; N, 7.96; S, 17.22.

Acknowledgements:

We are grateful to the Edward G. Schlieder Educational Foundation for support of this study. We thank Dr. M. A. Porubcan of the Squibb Institute for Medical Research for H^1-nmr (400 MHz) and C^{13}-nmr spectra.

REFERENCES AND NOTES

‡ University of Alabama in Birmingham, VA Hospital, Birmingham, Alabama 35294.

† Squibb Institute for Medical Research, E3113, P.O. Box 4000, Princeton, NJ 08540.

[1] J. Krapcho and C. F. Turk, *J. Med. Chem.*, **9**, 191 (1966).

[2] H. Kugita, H. Inoue, M. Ikezaki, M. Konda and S. Takeo, *Chem. Pharm. Bull.*, **19**, 595 (1971).

[3] T. Meshi, J. Sugihara and Y. Sato, *Chem. Pharm. Bull.*, **19**, 1546 (1971).

[4] T. Nagao, H. Narita, M. Sato, H. Nakajima and A. Kiyomoto, *Clin. and Exper. Hyper. Theor.* and *Pract.*, **A4**, 285 (1982) and references therein.

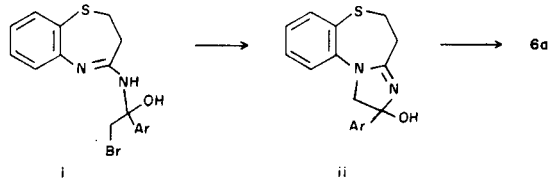
[5] D. C. Lankin, R. C. Petterson and R. A. Velazquez, *J. Org. Chem.*, **39**, 2801 (1974).

[6] N. M. Bikales, U. S. Patent 3,211,718 (1965); *Chem. Abstr.*, **64**, p845f (1966).

[7] Attempted cyclization of **1** with strong mineral acid (*e.g.* hydrochloric acid) led to the products arising from retro Michael reaction and polymerization.

[8] W. H. Mills and J. B. Whitworth, *J. Chem. Soc.*, 2738 (1927).

[9a] For mechanistic studies, refer to E. S. Hand and W. W. Pandler, *Tetrahedron*, **38**, 49 (1982). [b] An alternative pathway involving the reversibly generated unstable alpha-bromo carbinolamine intermediate (i) would also give rise to **6a** *via* (ii). The halogen in (i) is however much less reactive (compared to that in phenacylhalide) and thus cyclization would be expected to be less facile. This route is therefore considered less likely, but a small contribution toward the product formation cannot be completely overruled.



[10] J. Fossey, A. Loupy and H. Strzelecks, *Tetrahedron*, **37**, 1935 (1981).

[11] H. L. Blewitt in "Special Topics in Heterocyclic Chemistry", A. Weissberger and E. C. Taylor, eds, John Wiley and Sons, New York, 1977, p 177.

[12] I. A. Kaye, C. L. Parris and W. J. Burlant, *J. Am. Chem. Soc.*, **75**, 746 (1953).

[13] P. L. Julian, E. W. Meyer, A. Magrini and W. Cole, *J. Am. Chem. Soc.*, **67**, 1203 (1945).

[14] A. J. Elliott, H. Guzik and J. R. Soler, *J. Heterocyclic Chem.*, **19**, 1437 (1982). For a similar reaction of 2-amino-4-picoline with diketene, *etc.*, see: H. L. Yale, B. Toeplitz, J. Z. Gougoutas and M. Puar, *J. Heterocyclic Chem.*, **10**, 123 (1973).

[15] V. P. Arya, *Indian J. Chem.*, **10**, 598 (1972).

[16] S. Kano, *J. Pharm. Soc. Japan*, **92**, 51 (1972).

[17] For H^1-nmr of thiazepines, see: P. W. W. Hunter and G. A. Webb, *Tetrahedron*, **29**, 147 (1973).

[18] G. Toth, A. Szollosy, A. Levai and H. Duddeck, *Org. Magn. Reson.*, **20**, 133 (1982).

[19] M. Begtrup, *Acta Chem. Scand.*, **27**, 3101 (1973).