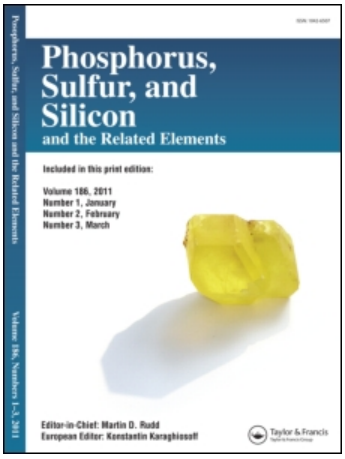


Phosphorus, Sulfur, and Silicon and the Related Elements
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713618290

An Efficient and Facile Synthesis of Novel Benzimid-(Thi) Azole Dicarboxaldehydes as a Versatile Precursors for new Ox-, Thi-and Diazepine Derivatives

Fawi M. Abd El Latif[a]
[a] Chemistry Department, Faculty of Science, South Valley University, Aswan, Egypt

To cite this Article Latif, Fawi M. Abd El(2000) 'An Efficient and Facile Synthesis of Novel Benzimid-(Thi) Azole Dicarboxaldehydes as a Versatile Precursors for new Ox-, Thi-and Diazepine Derivatives', Phosphorus, Sulfur, and Silicon and the Related Elements, 167: 1, 267 — 274
To link to this Article: DOI: 10.1080/10426500008082405
URL: http://dx.doi.org/10.1080/10426500008082405

Phosphorus, Sulfur and Silicon, 2000, Vol. 167, pp. 267-274
Reprints available directly from the publisher
Photocopying permitted by license only

AN EFFICIENT AND FACILE SYNTHESIS OF NOVEL BENZIMID-(THI) AZOLE DICARBOXALDEHYDES AS A VERSATILE PRECURSORS FOR NEW OX-, THI- AND DIAZEPINE DERIVATIVES

FAWI M. ABD EL LATIF*

Chemistry Department, Faculty of Science, South Valley University, Aswan, Egypt

(Received July 11, 2000; In final form September 14, 2000)

Novel 2-cyanomethylbenzimid-(thi)-azole-2,2-dicarboxaldehydes were prepared in quantitative yields and reacted easily with *o*-aminophenol derivatives to yield new multi-functionallized ox-, thi- and diazepine derivatives in one-pot reaction.

Keywords: 2-Cyanomethylbenzazole dicarboxaldehydes; ox-; thi-; diazepines; MS; NMR spectra

Heterocycles incorporating seven-membered ring have found wide applications in organic synthesis for their considerable pharmaceutical effects.[**1–4**] Ortho aminophenol derivatives are known to condense with *o*-haloesters or *o*-haloaldehydes to yield seven-membered rings[**5–8**].

Thus, 2-cyanomethylbenzimidazole **1a** and 2-cyanomethylbenzthiazole **1b** undergo an efficient Vilsmeier formylation ($POCl_3$ / DMF) to give the novel dicarboxaldehydes **3a,b** in 90, 85 % yields. The **MS** spectrum of **3a** showed m/z at 213 (M^+, 11), 212 (100), 211 (20), 182 (26), 170 (77), 143 (21), 118 (15). The **MS** of **3b** showed m/z at 230 (M^+, 20), 229 (M-1, 100), 198 (21), 187 (40), 160 (12), 134 (11). The **^{1}H NMR** spectra showed also an intense singlet peak at δ 8.9 ppm assigned for the two protons of aldehyde groups. Attempts to isolate the mono derivative **2** failed. The aldehydes **3** are very reactive and are considered as versatile precursors for a facile and mild heterocyclic synthesis. In continuation of our recent stud-

* Corresponding Author.

ies on the synthesis of new heterocycles, [9–12] we report herein the synthesis of new benzoxazepine, benzthiazepine, and benzdiazepine derivatives incorporating benzimidazole, and benzthiazolo moieties.

Thus, the aldehydes **3a,b** reacted easily with the *o*-aminophenol derivatives **4a-d**, *o*-mercaptoaniline **4e**, and *o*-phenylenediamine **4f** in ethanolic piperidine at reflux temperature to yield the corresponding new multi-functionallized seven-membered rings **6a-l** in good yields. The reaction pathway is considered to proceed as shown in Scheme 1. The final products **6** would obtained *via* intramolecular nucleophilic attack on the cyano function of the intermediates **5a-f**. Compounds **6a-f** were unambiguously prepared in two steps. Stirring equimolar amounts of **3a** and **4a-f** in ethanol at room temperature yielded the corresponding Schiff bases **5a-f** in good yields. The Schiff bases **5** were subsequently cyclized into **6a-f** by refluxing in pyridine for 5 h. The structures of **5** and **6** are based on **IR, ^{1}H NMR, MS**, and analytical elemental data. Generally, the **IR** spectra of **5** showed an intense absorption at ν 2205 – 2215 cm^{-1} characteristic for the CN group. The **^{1}H NMR** spectra of **5a-d** revealed four singlet peaks at δ 3.3, 7.8, 8.9, and 11.3–11.5 ppm attributed to the NH, CH=N-, CHO, and OH groups respectively. However, the **^{1}H NMR** spectra of **6** showed that the peaks at δ 11.3–11.5 ppm disappeared as well as the absorption bands at 2205 – 2220 cm^{-1} of their **IR** spectra characteristic for the cyano group. The above spectroscopic data of **3, 5**, and **6** show that the CHO proton NMR spectral signal appeared at a higher field (δ 8.9 ppm). This high field shift may be a consequence of hydrogen bonding forming a five- or higher-membered ring chelate between the CHO as a polar group and both of the hydrogen atom of the NH and / or the nitrogen atom of benzimidazole, as shown in scheme 1. Although fused diazepinobenzazoles were reported [13], the present report is the first example of utilizing the novel benzimidazole and benzthiazole dicarboxaldehydes **3a,b** for the synthesis of new [1,5]benzazepinobenzazole derivatives and its new Schiff bases intermediates in an one-pot reaction.

EXPERIMENTAL

All melting points are uncorrected. **IR** spectra were recorded (KBr, ν = cm^{-1}) on a Shimadzu 408 and a Pye Unicam Spectrophotometer. **^{1}H NMR** spectra (DMSO-d_6, δ = ppm) were recorded on a Varian EM 390 90 MH_Z spectrometer. TMS was used as internal reference. Mass spectra

were recorded on a mass spectrometer MS 9 (AET) EI Mode. Elemental analysis were carried out at Microanalytical Center, Cairo University, Egypt.

2-Cyanomethylbenzazole-2,2-dicarboxaldehyde derivatives (3a,b)

A solution of 2-cyanomethylbenzimidazole **1a** (15.7 g, 0.1 mol) in 100 ml DMF was cooled to −10°C using an ice-acetone-salt bath. Phosphorus oxychloride (45.6 g, 0.3 mol) was added dropwise within 1h in such a rate as to keep the temperature below 10 °C, then the reaction mixture was heated on a water-bath for 2h. The mixture was poured onto ice-water (2L) and stirred overnight at room temperature. The solid product so formed was filtered, washed with water, dried and recrystallized from ethanol to give colourless crystals in 19.3 g, 90 % yield. Simialrly, 2-cyanomethylbenzthiazole **1b** was transformed into **3b** in 85% yield. The spectral, physical, and analytical data are listed in Table I.

General procedure for the synthesis of Schiff bases 5a-f

A mixture of **3a** (1 g, 0.01 mol), *o*-aminophenol **4a** (0.5 g, 0.01 mol) and 0.1 ml of piperidine was stirred in 40 ml of absolute ethanol at room temperature. A solid product was formed after 20 min and the mixture was stirred overnight. The formed product **5a** was filtered, washed with ethanol and recrystallized from dimethylformamide. The aldehyde **3a** reacted analogously with **4b-f** (0.01 mol of each) to give the corresponding Schiff bases **5b-f** (Table I).

3-Formyl-3-(benzazol-2-yl)-2-imino[1,5]benzoxazepines (6a-d, 6g-j), -benzthiazpines (6e, 6k) and 2-amino-3-(benzazol-2-yl)-3-formyl [1,5]benzdiazepines (6f, 6l) General procedure

A mixture of **3a** (1 g, 0.01 mol), *o*-aminophenol **4a** (0.5 g, 0.01 mol) and 0.1 ml of piperidine was refluxed in 40 ml of absolute ethanol for 5 h. The solution was concentrated under reduce pressure. The obtained residue was treated with methanol and the crude product **6a** was filtered, washed with methanol and recrystallized from ethanol. The aldehyde **3a** reacted analogously with **4b-f** (0.01 mol of each) to give the corresponding title compounds **6b-f**. Similarly, the aldehyde **3b** was reacted with **4a-f** (0.01 mol of each) under the same reaction conditions to give the corresponding benzthiazole products **6g-l**. The spectral, physical, and analytical data are listed in Table II.

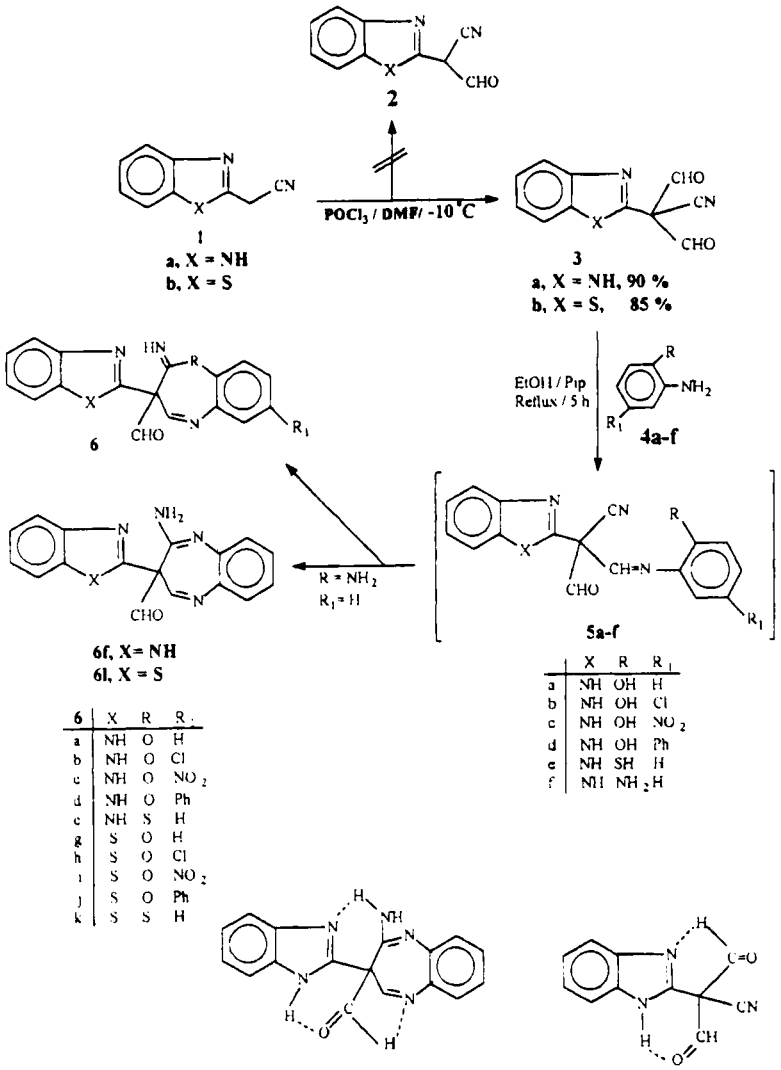
TABLE I The physical, analytical, and spectral data of compounds 3 and 5

Comp No.	*Mp °C Solvent of Recryst.*	*Yield %*	*Mol. Formula (M. Wt)*	*Analysis (%) Calcd./ Found*			*Spectra data*	
							^1H NMR (DMSO-d6)	*MS [M^+]*
				C	*H*	*N*	*δ ppm*	*m/z*
3a	230–31	90	$C_{11}H_7N_3O_2$	61.97	3.31	19.71	3.5 (s, 1H, NH), 7.1–7.8 (m, 4H, ArH),	213 (11)
	EtOH		(213.20)	61.84	3.15	19.58	8.9 (s, 2H, CHO)	
3b	160–61	85	$C_{11}H_6N_2O_2S$	57.38	2.63	12.17	7.1–7.8 (m, 4H, ArH), 9.1 (s, 2H, CHO)	229 (100)
	EtOH		(230.24)	57.23	2.51	12.02		
5a	250–52	75	$C_{17}H_{12}N_4O_2$	67.10	3.97	18.41	3.4 (s, 1H, NH), 7.1–7.8 (m, 9H, ArH+	304 (70)
	DMF		(304.31)	67.25	3.81	18.25	CH=N), 7.9 (s, 1H, CHO), 11.3 (s, 1H, OH)	
5b	252–53	80	$C_{17}H_{11}ClN_4O_2$	60.28	3.27	16.54	3.4 (s, 1H, NH), 7.1–7.8 (m, 8H, ArH +	340 (42)
	MeOH		(338.75)	60.12	3.15	16.40	CH58.45 3.17 20.05 =N), 7.9 (s, 1H, CHO), 11.5 (s, 1H, OH)	
5c	240–42	60	$C_{17}H_{11}N_5O_4$	58.45	3.17	20.05	3.3 (s, 1H, NH), 7.1–7.9 (m, 8H, ArH+	350 (65)
	DMF		(349.31)	58.31	3.02	20.21	CH=N), 8.1 (s, 1H, CHO), 11.4 (s, 1H, OH)	
5d	180–82	55	$C_{23}H_{16}N_4O_2$	72.62	4.24	14.73	3.4 (s, 1H, NH), 7.1–7.8 (m, 13H, ArH+	380 (80)
	DMF		(380.41)	72.48	4.11	14.58	CH=N), 7.9 (s, 1H, CHO), 11.4 (s, 1H, OH)	
5e	250–52	82	$C_{17}H_{12}N_4OS$	63.73	3.78	17.49	2.4 (s, 1H, SH), 3.2 (s, 1H, NH), 7.1–7.8	320 (100)
	EtOH		(320.37)	63.61	3.64	17.35	(m, 9H, ArH+ CH=N), 7.9 (s, 1H, CHO)	
5f	247–48	75	$C_{17}H_{13}N_5O$	67.32	4.32	23.09	3.1 (s, 1H, NH), 5.2 (s, 2H, NH_2),	303 (25)
	DMF		(303.33)	67.18	4.19	23.24	7.1–7.8 (m, 9H, ArH+ CH=N), 7.9 (s, 1H, CHO)	

TABLE II The physical, analytical, and spectral data of compounds 6

Comp No.	*Mp°C Solvent of Recryst.*	*Yield %*	*Mol. Formula (M. Wt)*	*Analysis (%) Calcd./ Found*			*Spectra data*	
							^{1}H NMR (DMSO-d6) δ ppm	*MS [M$^+$]*
				C	*H*	*N*	*δ ppm*	*m/z*
6a	145–47	70	$C_{17}H_{12}N_4O_2$	67.10	18.41	18.41	3.4 (s, 1H, NH), 3.5 (s, 1H, NH), 7.1–7.8	304 (80)
	EtOH		(304.31)	67.28	3.86	18.28	(m, 9H, ArH+ CH=N-azep), 8.8 (s, 1H, CHO)	
6b	140–42	65	$C_{17}H_{11}ClN_4O_2$	60.29	3.27	16.54	3.4 (s, 1H, NH), 3.6 (s, 1H, NH), 7.1–7.8	340 (42)
	MeOH		(338.75)	60.16	3.13	16.44	(m, 8H, ArH+ CH=N-azep), 8.9 (s, 1H, CHO)	
6c	290–92	55	$C_{17}H_{11}N_5O_4$	58.46	3.17	20.05	3.3 (s, 1H, NH), 3.5 (s, 1H, NH), 7.1–7.8	350 (65)
	EtOH		(349.31)	58.35	3.06	20.24	(m, 8H, ArH+ CH=N-azep), 8.8 (s, 1H, CHO)	
6d	150–52	50	$C_{23}H_{16}N_4O_2$	72.63	4.24	14.73	3.4 (s, 1H, NH), 3.5 (s, 1H, NH), 7.1–7.8	380 (80)
	MeOH		(380.41)	72.45	4.09	14.56	(m, 13H, ArH+ CH=N-azep), 8.9 (s, 1H, CHO)	
6e	83–84	75	$C_{17}H_{12}N_4OS$	63.74	3.78	17.49	3.2 (s, 1H, NH), 3.5 (s, 1H, NH), 7.1–7.8	320 (100)
	MeOH		(320.37)	63.60	3.62	17.34	(m, 9H, ArH+ CH=N-azep), 8.9 (s, 1H, CHO)	
6f	210–12	60	$C_{17}H_{13}N_5O$	67.33	4.32	23.09	3.1 (s, 1H, NH), 6.5 (s, 2H, NH_2), 7.1–7.8	303 (100)
	MeOH		(303.33)	67.21	4.20	23.22	(m, 9H, ArH+ CH=N-azep), 8.8 (s, 1H, CHO)	
6g	135–37	70	$C_{17}H_{11}N_5O_2S$	63.54	3.54	13.08	3.5 (s, 1H, NH), 7.1–7.8 (m, 9H, ArH+	321 (80)

Comp No.	*Mp°C Solvent of Recryst.*	*Yield %*	*Mol. Formula (M. Wt)*	*Analysis (%) Calcd./ Found*			*Spectra data*	
							^{1}H NMR (DMSO-d6) δ ppm	*MS [M$^+$]*
				C	*H*	*N*	*δ ppm*	*m/z*
	EtOH		(321.35)	63.41	3.44	13.22	CH=N-azep), 8.8 (s, 1H, CHO)	
6h	122–23	75	$C_{17}H_{10}ClN_3O_2S$	57.39	2.83	11.81	3.6 (s, 1H, NH), 7.1–7.8 (m, 8H, ArH+	357 (20)
	MeOH		(355.80)	57.23	2.67	11.64	CH=N-azep), 8.9 (s, 1H, CHO)	
6i	295–97	50	$C_{17}H_{10}N_4O_4S$	60.71	2.97	16.66	3.4 (s, 1H, NH), 7.2–7.8 (m, 8H, ArH+	336 (30)
	DMF		(336.35)	60.56	2.82	16.53	CH=N-azep), 8.8 (s, 1H, CHO)	
6j	240–42	60	$C_{23}H_{15}N_3O_2S$	69.51	63.80	10.57	3.6 (s, 1H, NH), 7.1–7.8 (m, 13H,	397 (35)
	MeOH		(397.45)	69.37	3.65	10.41	ArH+ CH=N-azep), 8.9 (s, 1H, CHO)	
6k	137–39	75	$C_{17}H_{11}N_3OS_2$	60.51	3.29	12.45	3.5 (s, 1H, NH), 7.1–7.8 (m, 9H, ArH+	337 (80)
	EtOH		(337.42)	60.37	3.13	12.31	CH=N-azep), 8.9 (s, 1H, CHO)	
6l	150–52	65	$C_{17}H_{12}N_4OS_2$	63.73	3.78	14.49	-----	320 (45)
	EtOH		(320.37)	63.61	3.62	14.34		



6	X	R	R1
a	NH	O	H
b	NH	O	Cl
c	NH	O	NO_2
d	NH	O	Ph
e	NH	S	H
g	S	O	H
h	S	O	Cl
i	S	O	NO_2
j	S	O	Ph
k	S	S	H

	X	R	R1
a	NH	OH	H
b	NH	OH	Cl
c	NH	OH	NO_2
d	NH	OH	Ph
e	NH	SH	H
f	NH	NH_2	H

SCHEME 1

References

[1] R. Latticll, L. Rudolf, B. Wilhelm, M. Josef, and E. Granzer, *Ger. Offen*, **2**, 707, 269, *Chem. Abstr.*, **90**, 103949d, (1979).
[2] G. Heinisch and B. B. Matuszczak, *J. Heterocyclic Chem.*, **34**, 1421, (1997).
[3] I. Ito and T. Ueda, *Chem. Pharm. Bull.*, **18 (10)**, 1994, (1970); I. Ito, T. Ueda, and N. Oda, *Chem. Pharm. Bull.*, **18 (10)**, 2058, (1970); I. Ito and T. Ueda, *Chem. Pharm. Bull.*, **23 (8)**, 1646, (1975).
[4] H. Won-Hun, C. Young, L. Tae-Gyun, J. Yun-HO, and Y. Hoon, *Arch. Pharmacal Res*, **18 (5)**, 366, (1995).
[5] M. H. Rao, A. P. R. Reddy, and V. Veeranagaiah, *Synthesis*, 446, (1992).
[6] P. C. Gogoi and J. C. S. Kataky, *Heterocycles*, **32 (2)**, 237, (1991).
[7] F. M. Abd El Latif, *J. Heteroatom Chem.*, **6**, 575, (1995).
[8] F. M. Abd El Latif, *J. Heterocyclic Chem.*, in press.
[9] M. A. Z. Badr, S. A. Mahgoub, O.S. Mustafa, A. A. Gies, and F. M. Abd El Latif, *Phosphorus Sulfur and Silicon*, **73**, 26, (1992).
[10] M. A. Barsy, F. M. Abd El Latif, S. M. Ahmed, and M. A. El-Maghraby, *Phosphorus Sulfur and Silicon*, in press.
[11] M. H. Elnagdi, M. A. Barsy, F.M. Abd El Latif, and K. U. Sadek, *J. Chem. Res. (S)*, 26, (1998).
[12] M. A. Raslan, F.M. Abd El Latif, H. H. Otto, and K. U. Sadek, *Org. Prep. Proc. Int.*, **32 (3)**, (2000) in press.
[13] C. Omar, E. El Mokhtar, and Z. Rachid, Z., *Tetrahedron Lett.*, **31 (38)**, 5467, (1990).