First Synthesis of Novel Pentaheterocyclic Ring System of 1,2,4-Triazolo[2",3":6',1']pyrimido[4',5':2,3]pyrido[1,2-*a*]benzimidazole

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Reaction of 1-amino-3-arylpyrido[1,2-*a*]benzimidazole-2,4-dicarbonitrile (**1**) with dimethylformamide-dimethylacetal (DMF-DMA) gave 1-[*N*,*N*-(dimethylaminomethylene)amino]-3-arylpyrido[1,2-*a*]benzimidazole-2,4-dicarbonitrile (**2**). Compounds (**1**) reacted with triethylorthoformate yielding 1-[*N*-(ethoxymethylene)amino]-3-arylpyrido[1,2-*a*]benzimidazole-2,4-dicarbonitrile (**3**). 3-Amino-4-imino-5-aryl-6-cyanopyrimido[5',4':5,6]pyrido[1,2-*a*] benzimidazole (**4**) was synthesized *via* condensation of either (**2**) or (**3**) with hydrazine hydrate. Reactions of (**4**) with acetic anhydride, ethyl chloroformate or aryl isothiocyanate yielded the respective derivative of the new ring system namely 1,2,4-triazolo[2",3":6',1']pyrimido[4',5':2,3]pyrido[1,2-*a*]benzimidazole (**5-7**).

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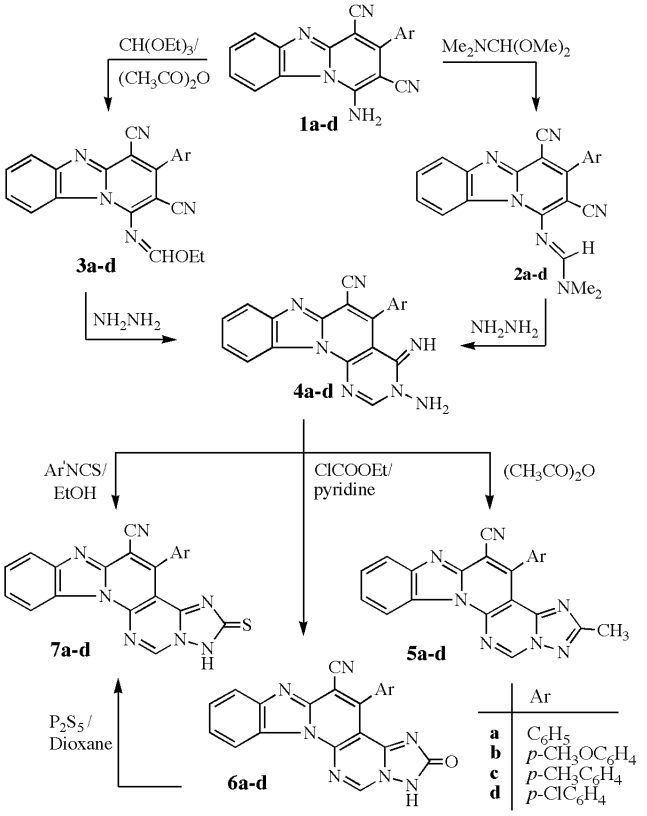
Introduction.

In continuation of our previous work in the synthesis of a variety of heterocycles from the readily available inexpensive starting materials [1-5], I report herein the utility of pyrido[1,2-*a*]benzimidazole derivatives (**1a-d**) as building blocks for the synthesis of new ring system namely 1,2,4- triazolo[2",3":6',1']pyrimido[4',5':2,3]pyrido[1,2-*a*]-benzimidazole of potential biological activity. The chemistry of pyrido[1,2-*a*]benzimidazole is now receiving considerable interest [6,7]. Also, utility of heterocyclic enaminonitriles is now receiving considerable interest [8]. However, to my knowledge, no trial has ever been made to utilize pyrimido[5',4':5,6]pyrido[1,2-*a*]benzimidazole as precursor for 1,2,4-triazolo[2",3":6',1']pyrimido[4',5':2,3]-pyrido[1,2-*a*]benzimidazole.

Results and Discussion.

My initial attention was directed toward synthesis of such new ring system namely 1,2,4-triazolo[2",3":6',1']pyrimido-[4',5':2,3]pyrido[1,2-*a*]benzimidazole **5-7** (Scheme 1). For this purpose 1-amino-3-arylpyrido[1,2-*a*]benzimidazole-2,4-dicarbonitriles **1a-d** each was treated with dimethylformamide-dimethylacetal (DMF-DMA) in dioxane under reflux. The reaction furnished the corresponding 1-[*N*,*N*-(dimethylaminomethylene)amino]-3-arylpyrido[1,2-*a*]benzimidazole-2,4-dicarbonitrile **2a-d** in good yields, respectively. The assignment of structure **2a-d** is compatible with its spectral data. For example, the ^{1}H-NMR spectra of **2a** revealed the presence of singlet signals in the region δ 3.3-3.4 ppm assignable to the two methyl groups. Treatment of **1a-d** with triethylorthoformate in acetic anhydride at reflux yielded the respective 1-[*N*-(ethoxymethylene)amino]-3-arylpyrido[1,2-*a*]benzimidazole-2,4-dicarbonitrile **3a-d** respectively in good yield. The structures of the latter derivatives were confirmed by their analytical and spectroscopic analyses (Table 1, 2). For example, the IR spectra of **3a-d** showed the absence of NH_2 bands. Instead, they revealed the presence of three bands at ν 2230 (CN), 1640 (N=CHOEt) and 1620 (ring C=N) cm^{-1}. Their ^{1}H NMR spectra showed, in each case, the following signals: a triplet at δ 1.5 (3H, J=7Hz, OCH_2CH_3), a quartet at δ 4.4 (2H, J=7Hz, OCH_2CH_3) and singlet signal at δ 8.5 (1H, N=*CH*). By condensation of **2a-d** with NH_2NH_2 in ethanol at room temperature afforded 3-amino-4-imino-5-aryl-6-cyanopyrimido[5',4':5,6]pyrido[1,2-*a*]benzimidazoles **4a-d**, respectively. The assigned structure **4** for the latter products followed their elemental and spectral data (IR, ^{1}H NMR) (see Table 2) and their alternative synthesis. Thus treatment of 1-[*N*-(ethoxymethylene)amino]-3-arylpyrido[1,2-*a*]benzimidazole-2,4-dicarbonitrile **3a-d** with hydrazine hydrate in

Scheme 1



ethanol at room temperature (Scheme 1) gave products identical with compounds **4** in all respects (mp., mixed mp.).

By refluxing each of **4a-d** with acetic anhydride resulted in cyclization to afford the corresponding 14-aryl-13-cyano-2-methyl-1,2,4-triazolo[2",3":6',1']pyrimido-[4',5':2,3]pyrido[1,2-*a*]benzimidazoles **5a-d** (Scheme 1). The formation of the triazole ring involving both amino and imino groups was evidenced by the absence of absorption bands due to these groups in the IR spectrum of **5a-d**. Also, the ^{1}H NMR spectrum of **5a** revealed the following signals at δ 2.5 (s, 3H, CH_3), 7.5-8.4 (m, 9H, ArH) and 10.1 (s, 1H, pyrimidine-CH) ppm. In the mass spectrum of

Table 1

Chemical and Physical Properties of Prepared Compounds **2 – 7**

Comp.	Yield %	Mp °C solvent	Molecular Formula	Analysis (%) Calcd./ Found C	H	N	Mass Spectra m/z (%)
2a	85	282	$C_{22}H_{16}N_6$	72.51	4.43	23.07	364 (M^+, 100), 322 (16), 182 (10.4)
		DMF	(364.4)	72.60	4.31	23.22	
2b	82	261	$C_{23}H_{18}N_6O$	70.03	4.60	21.31	395 (M+1, 27), 394 (M^+, 100), 352 (13),
		DMF	(394.42)	70.00	4.85	21.08	307 (10), 197 (13)
2c	80	293	$C_{23}H_{18}N_6$	73.00	4.79	22.21	379 (M+1, 26), 378 (M^+, 100), 336 (12),
		DMF	(378.42)	72.83	4.95	22.52	334 (16), 189 (11), 84 (18)
2d	83	320	$C_{22}H_{15}ClN_6$	66.25	3.79	21.07	400 (M+2, 34), 399 (M+1, 28), 398
		DMF	(398.84)	66.02	3.64	21.21	(M^+, 100), 358 (14), 199 (10)
3a	80	390	$C_{22}H_{15}N_5O$	72.31	4.14	19.17	365 (M^+, 30), 309 (100), 141 (20),
		DMF	(365.38)	72.60	4.25	19.40	151 (25), 77 (18)
3b	78	280	$C_{23}H_{17}N_5O_2$	69.86	4.33	17.71	395 (M^+, 80), 339 (100), 269 (60), 65 (32)
		AcOH	(395.41)	70.10	4.14	17.90	
3c	79	243	$C_{23}H_{17}N_5O$	72.81	4.52	18.46	379 (M^+, 100), 323 (98), 322 (34),
		AcOH	(379.41)	72.63	4.71	18.21	140 (12), 102 (12), 65 (77)
3d	77	250	$C_{22}H_{14}ClN_5O$	66.08	3.53	17.52	401 (M+2, 22), 400 (M+1, 25), 399
		AcOH	(399.82)	66.30	3.33	17.50	(M^+, 86), 343 (100), 308 (21),
							157 (13), 102 (30), 63 (28)
4a	82	295	$C_{20}H_{13}N_7$	68.37	3.73	27.91	351 (74), 333 (M^+, 100), 167 (23),
		Dioxane	(351.35)	68.51	3.80	28.21	102 (18), 77 (20), 51 (27)
4b	81	292	$C_{21}H_{15}N_7O$	66.13	3.96	25.71	381 (M^+, 100), 363 (69), 183 (14), 161 (20)
		Dioxane	(381.38)	66.09	4.11	25.52	
4c	84	275	$C_{21}H_{15}N_7$	69.03	4.14	26.83	365 (M^+, 69), 347 (100), 174 (27),
		Dioxane	(365.38)	69.30	4.06	27.00	140 (12), 102 (16), 65 (17)
4d	80	290	$C_{20}H_{12}ClN_7$	62.23	3.14	25.41	387 (M+2, 33), 386 (M+1, 28), 385
		Dioxane	(385.80)	62.35	3.40	25.13	(M^+, 100), 367 (69), 334 (28)
							333 (35), 167 (16), 75 (18)
5a	73	367	$C_{22}H_{13}N_7$	70.39	3.49	26.12	375 (M^+, 100), 333 (30), 153 (11),
		DMF	(375.37)	70.21	3.60	26.08	306 (10), 167 (10), 51 (9)
5b	72	330	$C_{23}H_{15}N_7O$	68.14	3.73	24.19	405 (M^+, 100), 347 (17), 335 (10), 321 (10)
		DMF	(405.39)	68.30	3.92	24.01	
5c	75	365	$C_{23}H_{15}N_7$	70.94	3.88	25.18	389 (M^+, 100), 375 (14), 347 (38),
		DMF	(389.39)	70.73	3.92	25.35	174 (13), 161 (13)
5d	74	390	$C_{22}H_{12}ClN_7$	64.47	2.95	23.92	411 (M+2, 20), 410 (M+1, 40),
		DMF	(409.82)	64.66	3.03	24.15	409 (M^+, 100), 102 (25), 63 (15)
6a	78	380	$C_{21}H_{11}N_7O$	66.84	2.94	25.98	377 (M^+, 16), 361 (100), 333 (42),
		DMF	(377.35)	66.95	2.70	25.79	306 (10) 181 (12)
6b	77	355	$C_{22}H_{13}N_7O_2$	64.86	3.22	24.07	407 (M^+, 100), 406 (61), 363 (12),
		AcOH	(407.37)	65.01	3.42	24.00	321 (23), 161 (11)
6c	80	415	$C_{22}H_{13}N_7O$	67.51	3.35	25.05	391 (M^+, 81), 349 (100), 321 (16),
		DMF	(391.37)	67.23	3.61	25.20	102 (10), 77 (12)
6d	76	420	$C_{21}H_{10}ClN_7O$	61.25	2.45	23.81	413 (M+2, 46), 411 (M^+, 100), 167 (27),
		DMF	(411.79)	61.43	2.26	24.01	102 (20), 50 (21)
7a	82	410	$C_{21}H_{11}N_7S$	64.11	2.82	24.92	394 (M+1, 29), 393 (M^+, 100), 335 (90),
		DMF	(393.41)	64.31	3.01	24.79	333 (17), 167 (28), 51 (16)
7b	85	348	$C_{22}H_{13}N_7SO$	62.40	3.09	23.16	423 (M^+, 24), 286 (91), 269 (100), 134
		DMF	(423.43)	62.61	3.21	23.35	(32), 51 (24)
7c	83	350	$C_{22}H_{13}N_7S$	64.85	3.22	24.07	408 (M+1, 27), 407 (M^+, 100), 349 (74),
		DMF	(407.43)	65.03	3.05	24.23	174 (39), 161 (30), 102 (16), 51 (14)
7d	80	390	$C_{21}H_{10}N_7ClS$	58.94	2.36	22.92	429 (M+2, 40), 428 (M+1, 33), 427 (M^+,
		DMF	(427.86)	58.83	2.53	22.71	86), 369 (25), 368 (38), 334 (100), 167
							(33), 166 (15), 102 (17), 50 (16)

5a the molecular ion peak at m/z 375 (Table 1) was observed. These data along with the elemental analysis data are consistent with molecular formula $C_{22}H_{13}N_7$.

Similarly, reaction of **4a-d** with ethyl chloroformate, yielded the corresponding 1,2,4-triazolo[2",3":6',1']-pyrimido[4',5':2,3]pyrido[1,2-*a*]benzimidazol-2(1*H*)ones **6a-d** (Scheme 1). The IR spectrum of the product **6a** showed characteristic bands at 3355, 2229 and 1697 assignable to the NH, nitrile and amidecarbonyl group respectively. It's ^{1}H NMR spectrum showed a multiplet signal at δ 7.2-9 (ArH), a singlet at δ 9.1 (pyrimidine-CH) and a singlet at δ 9.3 (NH) ppm (see Table 2) .

Next, the reaction of **4a-d** with phenyl isothiocyanate was studied in ethanol under reflux and it was found that in each case a single product was obtained. On the basis of their elemental analyses and the spectral data (IR, ^{1}H NMR, MS), the products isolated were assigned the structure **7a-d**. Repetition of the reaction between **4a-d** using *p*-methyl phenyl isothiocyanate gave also the same product **7a-d** which were identical in all respects (mp., mixed mp., spectra) with that obtained by using phenyl isothiocyanate. The presence of sulphur in compounds **7a-d** confirms that the reaction proceeds *via* elimination of the arylamine moiety (Scheme 1). The assigned structures **7a-d** were also substantiated by their alternative synthesis by refluxing **6a-d** with phosphorus pentasulfide in dry dioxane. The products afforded were identical in all respects (mp., mixed mp., spectra) with **7a-d** obtained by using aryl isothiocyanate with **4a-d** (Scheme 1). Both IR and ^{1}H NMR spectral data of the isolated products 14-aryl-13-cyano-2-thioxo-1,2,4-triazolo-[2",3":6',1']pyrimido[4',5':2,3]pyrido[1,2-*a*]benzimidazole **7a-d** (Table 2) are compatible with their assigned structures.

EXPERIMENTAL

All melting points were determined on a Stuart melting point apparatus and are uncorrected. Elemental analyses were carried out at the microanalytical center, University of Cairo, Giza, Egypt. Infrared spectra (KBr) were recorded on a Pye Unicam SP-300 infrared spectrophotometer. ^{1}H NMR spectra were determined on a Varian Gemini 200 spectrometer (200 MHz) in deuterated DMSO with TMS as an internal standard. Mass spectra were recorded on a GCMS-QP 1000-Ex, Schimadzu, Japan. The starting 1-amino-3-arylpyrido[1,2-*a*]benzimidazole-2,4-dicarbonitrile **1a-d** [9] was prepared as previously described. The physical constants with the spectral data of new synthesized compounds are listed in Tables 1 and 2.

1-[*N*,*N*-(dimethylaminomethylene)amino]-3-arylpyrido[1,2-*a*]-benzimidazole-2,4-dicarbonitrile (**2a-d**).

A mixture of **1a-d** (5 mmoles) and dimethylformamide-dimethylacetal (DMF-DMA) (0.71 g, 6 mmoles) was refluxed for 4 h in dioxane (40 mL). After cooling, the solid that precipitated was collected and crystallized from the proper solvent (Table 1) to give products **2a-d**.

Table 2

Spectral Data of **2– 7** IR (ν/cm^{-1}) ^{1}H NMR (δ/ppm)

	IR ν/cm^{-1}	^{1}H NMR (d_6-DMSO) (δ/ppm)
2a	2210 (CN)	3.34 (s, 3H, Me), 3.37 (s, 3H, Me), 7.4-8.7 (m, 10H, Ar and olefinic-H)
2b	2214 (CN)	3.33 (s, 3H, Me), 3.36 (s, 3H, Me), 3.88 (s, 3H, OMe), 7.14-8.7 (m, 9H, Ar and olefinic-H)
2c	2214 (CN)	2.5 (s, 3H, Me), 3.33 (s, 3H, Me), 3.36 (s, 3H, Me), 7.2-8.6 (m, 9H, Ar and olefinic-H)
2d	2214 (CN)	3.33 (s, 3H, Me), 3.37 (s, 3H, Me), 7.3-8.7 (m, 9H, Ar and olefinic-H)
3a	2214 (CN), 1643 (N=CHOEt), 1612 (ring C=N)	1.5 (t, 3H, Me), 4.6 (q, 2H, CH_2), 7.4-8.7 (m, 10H, Ar and olefinic-H)
3b	2221 (CN), 1643 (N=CHOEt), 1612 (ring C=N)	1.5 (t, 3H, Me), 3.9 (s, 3H, OMe), 4.2 (q, 2H, CH_2), 7.2-8.8 (m, 9H, Ar and olefinic-H)
3c	2214 (CN), 1640 (N=CHOEt), 1612 (ring C=N)	1.5 (t, 3H, Me), 2.4 (s, 3H, Me), 4.5 (q, 2H, CH_2), 7.3-8.7 (m, 9H, Ar and olefinic-H)
3d	2214 (CN), 1643 (N=CHOEt), 1612 (ring C=N)	1.5 (t, 3H, Me), 4.5 (q, 2H, CH_2), 7.3-8.7 (m, 9H, Ar and olefinic-H)
4a	2221 (CN), 3340, 3301, 3055 (NH, NH_2)	3.5 (s, 2H, NH_2), 6.4 (s, 1H, NH), 7.1-8.6 (m, 9H, pyrimid-H), 9.0 (s, 1H, pyrimid-H)
4b	2229(CN), 3448, 3294, 3209 (NH, NH_2)	3.5 (s, 2H, NH_2), 3.9 (s, 3H, OMe), 6.4 (s, 1H, NH), 7.1-8.5 (m, 8H, Ar), 9.1 (s, 1H, pyrimid-H)
4c	2229(CN), 3448, 3294, 3047 (NH, NH_2)	2.4 (s, 3H, Me), 3.5 (s, 2H, NH_2), 7.3-8.5 (m, 9H, Ar and NH), 9.0 (s, 1H, pyrimid-H)
4d	2220 (CN), 3440, 3300, 3060 (NH, NH_2)	3.4 (s, 2H, NH_2), 6.3 (s, 1H, NH), 7.0-8.5 (m, 8H, Ar), 9.0 (s, 1H, pyrimid-H)
5a	2207 (CN)	2.5 (s, 3H, Me), 7.5-8.4 (m, 9H, Ar), 10.1 (s, 1H, pyrimid-H)
5b	2221 (CN)	2.5 (s, 3H, Me), 3.9 (s, 3H, OMe), 7.1-8.5 (m, 8H, Ar), 10.0 (s, 1H, pyrimid-H)
5c	2220 (CN)	2.4 (s, 3H, Me), 2.6 (s, 3H, Me), 7.3- 8.6 (m, 8H, Ar), 10.0 (s, 1H, pyrimid-H)
5d	2229 (CN)	2.5 (s, 3H, Me), 7.1-8.4 (m, 8H, Ar), 10.1 (s, 1H, pyrimid-H)
6a	1697 (CO), 2229 (CN), 3355 (NH)	7.2-9.0 (m, 9H, Ar), 9.1 (s, 1H, pyrimid-H), 9.3 (s, 1H, NH)
6b	1697 (CO), 2229 (CN), 3394 (NH)	3.8 (s, 3H, OMe), 7.1-8.9 (m, 8H, Ar), 9.1 (s, 1H, pyrimid-H), 9.5 (s, 1H, NH)
6c	1690 (CO), 2229 (CN), 3402 (NH)	2.3 (s, 3H, Me), 7.3-8.0 (m, 8H, Ar), 8.9 (s, 1H, pyrimid-H), 9.3 (s, 1H, NH)
6d	1697 (CO), 2229 (CN), 3400 (NH)	7.4-8.9 (m, 8H, Ar), 9.0 (s, 1H, pyrimid-H), 9.3 (s, 1H, NH)
7a	2221 (CN)	7.2-8.1 (m, 9H, Ar), 9.1 (s, 1H, pyrimid-H), 10.1 (s, 1H, NH)
7b	2221 (CN)	3.8 (s, 3H, OMe), 7.3-8.3 (m, 8H, Ar), 9.0 (s, 1H, pyrimid-H), 10.0 (s, 1H, NH)
7c	2221 (CN)	2.4 (s, 3H, Me), 7.1-8.2 (m, 8H, Ar), 9.4 (s, 1H, pyrimid-H), 10.1 (s, 1H, NH)
7d	2221 (CN)	7.0-8.3 (m, 8H, Ar), 9.1 (s, 1H, pyrimid-H), 10.1 (s, 1H, NH)

1-[*N*-(ethoxymethylene)amino]-3-arylpyrido[1,2-*a*] benzimidazole-2,4-dicarbonitrile (**3a-d**).

To a solution of compound **1a-d** (50 mmoles) in acetic anhydride (30 mL), triethyl orthoformate (5.8 g, 50 mmoles) was added. The mixture was refluxed for 5 h; the excess acetic anhydride was distilled off under reduced pressure. The crude product, obtained by cooling, was crystallized from the proper solvent (Table 1) to give **3a-d**.

3-Amino-4-imino-5-aryl-6-cyanopyrimido[5',4':5,6]pyrido[1,2-*a*]-benzimidazole (**4a-d**).

Method A.

A mixture of compound **2a-d** (50 mmoles) and hydrazine hydrate (d=1.029) (5 mL) was stirred for 8 h in ethanol (20 mL) at room temperature. The solid that separated was collected by filtration and crystallized from dioxane to give products **4a-d**.

Method B.

Equimolecular quantities of **3a-d** and hydrazine hydrate (50 mmoles each) in ethanol (20 mL) were stirred for 30 min and then left at room temperature for 24 h. The solid that separated was collected by filtration and crystallized from dioxane to give products identical in all respects with compounds **4a-d** which obtained by Method A.

14-Aryl-13-cyano-2-methyl-1,2,4-triazolo[2",3":6',1']pyrimido-[4',5':2,3]pyrido[1,2-*a*]benzimidazole (**5a-d**).

A solution of **4a-d** (5 mmoles) in acetic anhydride (20 mL) were refluxed for 3 h and cooled. The solid that formed were collected and crystallized from a suitable solvent (Table 1) to give **5a-d**.

14-Aryl-13-cyano-1,2,4-triazolo[2",3":6',1']pyrimido[4',5':2,3]-pyrido[1,2-*a*]benzimidazol-2(1*H*)one (**6a-d**).

To a solution of compound **4a-d** (5 mmoles) in pyridine (20 mL), ethyl chloroformate (0.5 mL, 5 mmoles) was added. The mixture was stirred for 6 h at room temperature. The solid that formed were collected and crystallized from the proper solvent (Table 1) to give **6a-d**.

14-Aryl-13-cyano-2-thioxo-1,2,4-triazolo[2",3":6',1']pyrimido-[4',5':2,3]pyrido[1,2-*a*]benzimidazole (**7a-d**).

Method A.

A mixture of compound **4a-d** (5 mmoles) and phenyl isothiocyante (0.6, 5 mmoles) in ethanol (20 mL) was refluxed for 3 h and then cooled. The solid that precipitated was collected and crystallized from the proper solvent (Table 1) to give **7a-d**.

Method B.

As method A except using *p*-methylphenyl isothiocyante instead of phenyl isothiocyanate. The compounds prepared are identical with **7a-d** which were obtained by method A.

Method C.

A mixture of compound **6a-d** and phosphorus pentasulfide (5 mmoles each) in dry dioxane (20 mL) was refluxed for 2 h in an oil bath (115-120 °C) and then cooled. The solid that precipitated was collected and crystallized from suitable solvent to give **7a-d** (Table 1).

REFERENCES AND NOTES

[1] H. M. Hassaneen, A. S. Shawali, M. S. Algharib and N. M. Elwan, *Arch. Pharm. Res*., **16**, 75 (1993).

[2] N. M. Elwan, A. A. Fahmy, T. A. Abdallah and H. M. Hassaneen, *Sulfur Lett*., **18**, 9 (1994).

[3] N. M. Elwan, H. A. Abdelhadi, T. A. Abdallah and H. M. Hassaneen, *Tetrahedron*, **52**, 3451 (1996).

[4] E. M. Awad, N. M. Elwan, H. M. Hassaneen, A. Linden and H. Heimgartner, *Helv. Chim. Acta*., **84**, 1172 (2001).

[5] E. M. Awad, N. M. Elwan, H. M. Hassaneen, A. Linden and H. Heimgartner, *Helv. Chim. Acta*., **85**, 320 (2002).

[6] M. Dupuy, F. Pinguet, O. Chavignon, J. C. Teulade, J. P. Chapat and Y. Blache, *Heterocycl. Commun.,* **7**, 23 (2001).

[7] B. Rachwal, P. Alaugh and K. Shaw, USA Patent 159, 362, 23 (1998); *Chem. Abstr*., **132**, 194375p (2000).

[8] K. M. AL-Zaydi, M. A. AL-Shiekh and E. A. Hafez, *J. Chem. Res. S*., **1**, 13 (2000).

[9] K. Bogdarowcz-Szwed and A. Czarny, *Jour. Fuer Prakt Chemie*, **335**, 279 (1993).