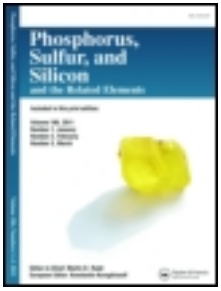

Phosphorus, Sulfur, and Silicon and the Related Elements

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HETEROCYCLIC SYNTHESES WITH THIOLES AND NITRILES: SYNTHESIS OF SOME NEW PYRIMIDO[4′,5′:4,5] THIAZOLO[3,2-a], THIAZOLO[3,2-a] AND TRIAZOLO[3,2-a]-BENZIMIDAZOLE DERIVATIVES

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HETEROCYCLIC SYNTHESES WITH THIOLES AND NITRILES: SYNTHESIS OF SOME NEW PYRIMIDO[4',5':4,5] THIAZOLO[3,2-*a*], THIAZOLO[3,2-*a*] AND TRIAZOLO[3,2-*a*]-BENZIMIDAZOLE DERIVATIVES

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Treatment of 6-benzoylbenzimidazole-2-thiol (**1**) and 3-amino-6-benzoylthiazolo[3,2-*a*]-benzimidazole-2-carbonitrile (**3**) with various reagents under different conditions is reported to afford cyclized and uncyclized compounds of potential pharmacological interest.

Keywords: 4-chloroacetylantipyrine; 2-bromodimedone; hydrazonyl chloride

Thiazolo[3,2-*a*]benzimidazole derivatives exhibit antibacterial activity[1] and act as hypoglycemic agents.[2] Their biological properties include antitumor,[3] antiviral,[4] antitubercular,[5] and anticonvulsant activity.[6] They have also been employed as fungicidal,[7] insecticide,[8] photographic sensitizer[9] and as chromophoric units in cyanine dyes.[10]

The versatile benefits and connection with previous efforts directed towards the facile synthesis of heterocyclic ring system,[11–13] and interest in the reaction of benzimidazole derivatives prompted us to investigate the reaction of 6-benzoyl-2-thiolobenzimidazole (**1**) with bromomalononitrile. This reaction yielded compound **2**, which was refluxed with anhydrous sodium acetate in ethanol to afford 3-amino-6-benzoylthiazolo[3,2-*a*]benzimidazole-2-carbonitrile (**3**). Its structure was confirmed by elemental analysis and spectral data. IR showed absorption bands at ν 3395,

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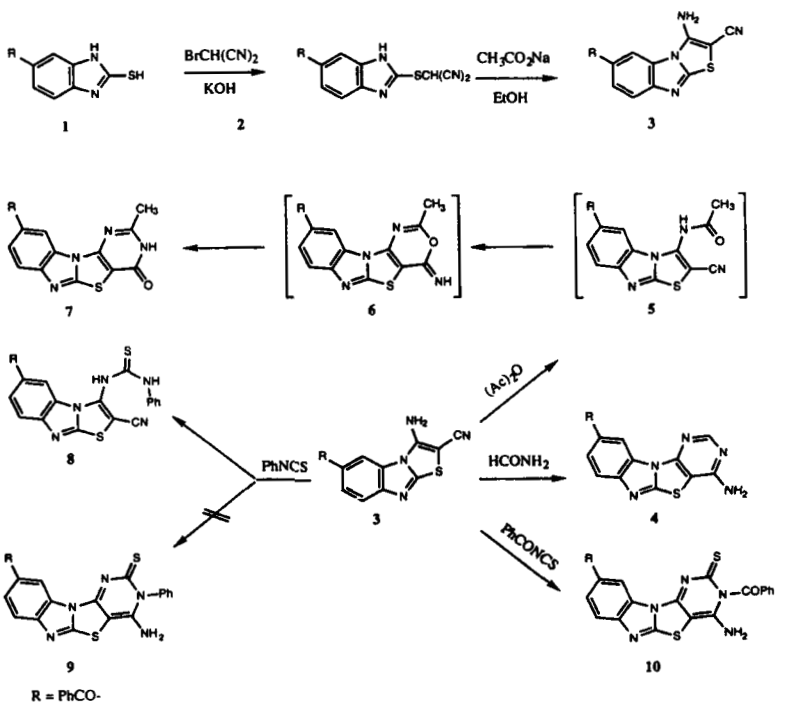
3259 cm^{-1} characteristic for (NH_2), a sharp cyano absorption band at ν 2200 and at ν 1654 cm^{-1} due to (CO) vibration. The ^{1}H-NMR spectrum revealed a multiplet at δ 7.33–8.21 attributed to NH_2 and the aromatic protons. Mass spectra revealed the molecular ion peak m/z = 318 (48%) compatible with the molecular formula $C_{17}H_{10}N_4OS$.

The reaction of compound **3** with boiling formamide gave 9-benzoylpyrimido[4',5':4,5]thiazolo[3,2-*a*]benzimidazole-4-amine (**4**). Its structure is based on elemental analysis and spectral data. Compound **3** was refluxed with acetic anhydride to afford compound **7**, [14] *via N*-acetylation to yield **5** which apparently cyclized into **6** which then in turn rearranged to **7**. The IR spectrum of compound **7** showed absorption bands at 3349, 2926, 1669 and 1654 cm^{-1} assignable to NH, CH_3, 2CO group respectively. The ^{1}H-NMR spectrum revealed a singlet at δ 2.85 corresponding to (3 H) of CH_3 besides a multiplet at δ 7.40–8.80 ppm, (9 H) attributed to the aromatic and NH protons.

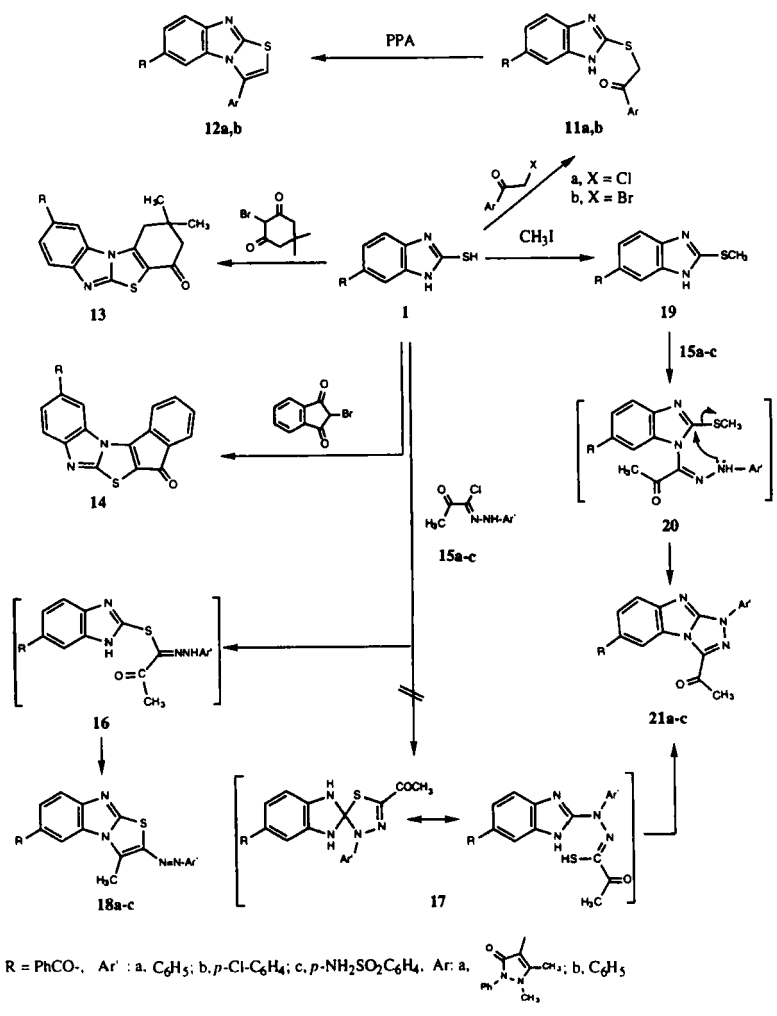


SCHEME 1

Compound **3** reacted with phenyl isothiocyanate to afford a product whose IR spectrum showed a cyano absorption band at ν 2198 cm^{-1}. The anticipated structure of **9** was therefore excluded and **8** was assigned as being a thiourea derivative. The reaction of **3** with benzoyl isothiocyanate led to the cyclized product **10**. The IR spectrum of **10** did not show any absorption bands that can be attributed to the presence of the cyano group. The cyclization in the second case may be enhanced by the presence of a carbonyl group and may be inhibited in the first case due to stereochemical aspects.

Compound **1** underwent cyclocondensation when refluxed with 4-chloroacetylantipyrine[15] and phenacyl bromide in absolute ethanol to yield the ketones **11a, b** which on treatment with PPA, underwent a cyclodehydration, to give a single compound (TLC) in each case, 7-benzoyl-1,3-thiazolo[3,2-*a*]benzimidazole derivatives **12a, b**. Structures **11** and **12** were established based on elemental analyses and spectroscopic studies. Thus, the mass spectrum of **12a** revealed a molecular ion peak m/z = 464 (16%) corresponding to the molecular formula $C_{27}H_{20}N_4O_2S$. Its ^{1}H-NMR spectrum showed a singlet at δ 2.31 and 3.43 for the antipyrine CH_3 and NCH_3, respectively and a multiplet at δ 6.8–7.84 attributed to the SCH protons and the aromatic protons. Similarly, compound **1** reacted with 2-bromodimedone[16] in absolute ethanol to afford 4-benzoyl-7,9-dihydro-8,8-dimethylbenzo[3′,2′:4,5]thiazolo[3,2-*a*]benzimidazole-10(H)- one (**13**) in a yield of 60%. Also, compound **1** reacted with indan-1,3-dione in the presence of *N*-bromosuccinimide to furnish compound **14** in a yield of 55%. Analytical and spectral data are consistent with structure **13** and **14** (Scheme 2, Tables I and II).

When compound **1** reacted with the hydrazonyl chloride derivatives **15a-c**[17] in ethanolic sodium ethoxide solution products identified as 2-arylazo-7-benzoyl-1-methyl-1,3-thiazolo[3,2-*a*]benzimidazole **18a-c** or 1-acetyl-3H-3-aryl-7-benzoyl-1,2,4-triazolo-[4,3,*a*]benzimidazole **21a-c** were formed. Structure **21** resulted *via* elimination of H_2S from the corresponding compound **17** which was obtained by a 1,3-dipolar cycloaddition of nitrilimine to the double bond of the imidazole ring. The formation of compound **18** is explained by a stepwise reaction involving substitution to give the acyclic hydrazone **16**. Cyclization of the latter is completed by elimination of water. The structures **18a-c** were deduced from their ele-



SCHEME 2

mental analysis and spectral evidence. The IR spectrum of these compounds showed the absences of a NH absorption band and its mass spectra revealed the molecular ion peak compatible with the assigned structure. The ^{1}H-NMR spectrum revealed besides the expected signals the absence of a singlet corresponding to the NH group (Table II).

TABLE I Physical and analytical data of the newly compounds

Comp No.	*MP°C Solvent*	*Yield %*	*MF M.wt.*	*Analysis% (Calcd./Found)*			
				C	*H*	*N*	*S*
1	260	80	$C_{14}H_{10}N_2O_4S$	66.12	3.96	11.01	12.60
	EtOH		(254.312)	66.20	3.90	11.30	12.80
2	172	65	$C_{17}H_{10}N_4OS$	64.14	3.16	17.59	10.07
	EtOH		(318.34)	64.20	3.20	17.60	10.07
3	245	80	$C_{17}H_{10}N_4OS$	64.14	3.16	17.59	10.07
	DMF		(318.34)	64.20	3.20	17.60	10.80
4	> 300	71	$C_{18}H_{11}N_5OS$	62.59	3.20	20.27	9.28
	EtOH		(345.378)	62.80	3.30	20.20	10.00
7	> 300	48	$C_{19}H_{12}N_4O_2S$	63.32	3.35	15.54	8.89
	AcOH		(360.39)	63.60	3.40	15.90	8.80
8	219	75	$C_{24}H_{15}N_5OS_2$	63.55	3.31	15.44	14.12
	EtOH		(453.548)	63.40	3.30	15.90	14.50
10	308	78	$C_{25}H_{15}N_5O_2S_2$	62.35	3.13	14.45	13.31
	EtOH		(481.546)	62.60	3.10	14.70	13.70
11a	221	72	$C_{27}H_{22}N_4O_3S$	67.20	4.59	11.61	6.64
	EtOH		(482.558)	67.30	4.80	11.20	6.80
11b	195	76	$C_{22}H_{16}N_2O_2S$	70.94	4.33	7.52	8.60
	EtOH		(372.44)	70.50	4.30	7.50	8.70
12a	292	40	$C_{27}H_{20}N_4O_2S$	69.80	4.33	12.06	6.90
	EtOH/H_2O		(464.547)	69.30	4.40	12.10	6.40
12b	263	76	$C_{22}H_{14}N_2OS$	74.55	3.98	7.90	9.04
	EtOH		(354.425)	74.50	4.00	8.10	9.10
13	206	68	$C_{22}H_{18}N_2O_2S$	70.54	4.84	7.47	8.56
	EtOH		(374.59)	70.70	4.80	7.50	8.50
14	> 300	70	$C_{23}H_{12}N_2O_2S$	72.61	3.17	7.36	8.42
	DMF		(380.42)	73.00	3.10	7.40	8.30
18a	(190–5)	63	$C_{23}H_{16}N_4OS$	69.67	4.06	14.13	8.08

Comp No.	MP°C Solvent	Yield %	MF M.wt.	Analysis% (Calcd./Found)			
				C	H	N	S
	EtOH		(396.47)	69.60	4.10	14.20	8.20
18b	240	52	$C_{23}H_{15}N_4OSCl$	64.10	3.50	13.00	7.44
	EtOH		(430.96)	64.00	3.50	13.10	7.80
18c	245	42	$C_{23}H_{17}N_5O_3S_2$	58.09	3.60	14.72	13.48
	EtOH		(475.55)	58.10	3.60	14.70	13.49
21a	235	68	$C_{23}H_{16}N_4O_2$	72.62	4.24	14.72	
	DMF		(380.40)	72.80	4.30	14.90	
21b	200	62	$C_{23}H_{15}N_4O_2Cl$	66.58	3.64	13.56	
	EtOH		(414.89)	66.60	3.70	13.60	
21c	291	42	$C_{23}H_{17}N_5O_4S$	60.12	3.72	15.24	6.97
	EtOH/DMF		(459.48)	60.30	3.80	15.40	6.60

On the other hand, 6-benzoyl-2-methylsulfonylbenzimidazole (**19**) reacted with hydrazonyl chloride in absolute ethanol in the presence of TEA to afford **21a-c**. These latter products resulted *via* elimination of methanthiole from the corresponding acyclic adduct **20**. The structures of **21a-c** were inferred from their elemental analyses and spectral data. Thus, their ^{1}H-NMR spectra revealed besides the expected signals, no signals due to either (SCH_3) or (NH) protons (Tables I and II).

EXPERIMENTAL

Melting points were recorded on a Gallenkamp melting point apparatus and are uncorrected. IR spectra were recorded as KBr pellets with a FTIR-8201 PC spectrophotometer (Shimadzu). ^{1}H NMR spectra were obtained on a Varian Gemini 200 MHz spectrometer in DMSO-d_6 or $CDCl_3$ as solvent and TMS as an internal reference. Mass spectra were performed on a Shimadzu GCMS-QP 1000 Ex at 70 ev. Microanalysis were performed by the Microanalytical center University of Cairo. 4-Chloroacetylantipyrine[15] and hydrazonyl chloride derivatives **15a-c**[17] were prepared according to reported procedures.

TABLE II Spectral data of the newly compounds

Compd. No.	*IR (ν cm^{-1}) Selected Bands*	*^1H NMR (δ)*	*MS m/z (%)*
1	3410 (NH), 1654 (CO)		254 (100), 177 (60), 149 (30)
2	3421 (NH), 2191, 2142 (2 CN), 1654 (CO)		318 (48), 241 (46), 255 (100), 177 (95), 105 (68), 77 (79)
3	3395, 3359 (NH_2), 2200 (CN), 1654 (CO)	7.33–8.21 (m, 10H, Ar-H + NH_2)(	
4	3330–3280 (NH_2), 1666 (CO)	7.10–7.89 (m, 10 H, Ar-H + NH_2), 8.2 (s, 1H, N=CH-N-)	346 (17), 318 (42), 290 (13), 254 (35), 177 (100)
7	3349 (NH), 2926 (CH_3, 1669, 1954 (2CO)	2.85 (s, 3H, CH_3), 7.4–8.8 (m, 9H, Ar-H + N-H)	360 (18), 242 (40), 310 (10), 177 (85), 105 (100), 77 (50)
8	3400, 3250 (2NH), 2198 (CN), 1656 (CO)	6.56 (s, 1H, NH), 6.81 (s, 1H, NH), 7.01–8.10 (m, 13H, Ar-H)	
10	3392, 3139 (NH_2), 1715, 1656 (2CO)	6.92–7.90 (m, 13H, Ar-H + NH_2)	481 (13), 366 (2.6), 254 (100), 178 (8.5), 144(18.5)
11a	3392 (NH), 2986 (-CH-aliph), 1679 (CO), 1650 (CO)		483 (19), 482 (16.7), 255 (92), 215 (58), 177 (100)
11b	3330 (NH), 1690 (CO), 1653 (CO)		
12a	2980 (-CH-aliph), 1669, 1653 (2CO)	2.31 (s, 3H, CH_3), 3.43 (s, 3H, -N-CH_3), 6.8–7.84 (m, 14H, Ar-H + S-CH=)	464 (16), 414 (40), 254 (100), 228 (10), 177 (51)
12b	1654 (CO), 1630 (C=N)		

Compd. No.	*IR (ν cm^{-1}) Selected Bands*	*^1H NMR (δ)*	*MS m/z (%)*
13	2982 (-CH-aliph), 1675 (CO), 1653 (CO)	1.03 (s, 3H, CH_3), 1.09 (s, 3H, CH_3), 2.20 (s, 2H, CH_2), 2.40 (s, 2H, CH_2), 7.20–7.98 (m, 8H, Ar-H)	374 (8), 360 (100), 310 (35), 263 (54.5), 105 (27), 77 (37.5)
14	1670 (CO), 1650 (CO)		380 (9), 367 (26), 366 (100), 289 (44), 77 (25)
18a	1654 (CO), 1635 (C=N)		396 (11.7), 313 (77), 177 (100), 116 (14), 77 (25)
18b	1649 (CO), 1635 (C=N)		
18c	3230 (SO_2NH_2), 1654 (CO)	2.13 (s, 3H, CH_3), 7.4–8.2 (m, 4H, Ar-H+NH_2)	
21a	1698, 1654 (2CO), 1637 (C=N)	2.7 (s, 3H, CH_3), 7.2–8.1 (m, 13H, Ar-H)	
21b	1693, 1651 (2CO), 1630 (C=N)	2.79 (s, 3H, CH_3), 7.3--8.30 (m, 12H, Ar-H)	416 (20), 415 (15.7), 414 (58.5), 337 (100), 232 (18), 77 (50)
21c	1701, 1650 (2CO), 1630 C=N)		

(6-Benzoylbenzimidazol-2-ylsulphamyl)malononitrile (2)

To an aqueous solution of 6-benzoylbenzimidazol-2-thiol (1) (2.54 g, 0.01 mol) and KOH (0.56 g; 0.01 mol), an ethanolic solution of bromomalononitrile (1.45 g, 0.01 mol) was added dropwise with stirring for 2 h at room temperature. The resulting precipitate was collected by filtration and crystallized from ethanol.

3-Amino-6-benzoylthiazolo[3,2-*a*]benzimidazole-2-carbonitrile (3)

Compound **2** (3.18 g; 0.01 mol) was refluxed in absolute ethanol in the presence of anhydrous sodium acetate (1.64 g; 0.02 mol) for 5 h. The resulting precipitate was separated by filtration, washed several times with water and recrystallized from DMF.

9-Benzoylpyrimido[4′,5′:4,5]thiazolo[3,2-*a*]benzimidazole-4-amine (4)

Compound **3** (1.59 g; 0.005 mol) was refluxed in formamide (10 ml) at 150°C for 5 h. After cooling, the reaction mixture was poured onto cold water and the solid formed was collected and recrystallized from ethanol.

9-Benzoyl-2-methylpyrimido[4′,5′:4,5]thiazolo[3,2-*a*]benzimidazol-4(3H)-one (7)

Compound **3** (1.59g; 0.005 mol) was refluxed in a mixture of Ac_2O/AcOH (1:1) (15 ml) for 6 h, after cooling the obtained solid was collected and recrystallized from acetic acid.

***N*-Phenyl-N′-(6-benzoyl-2-cyanothiazolo[3,2-*a*]benzimidazol-3-yl) thiourea (8)**

To a solution of **3** (1.59 g; 0.005 mol) in dry acetone (20 ml) was added phenyl isothiocyanate (0.68 g; 0.005 mol), and the reaction mixture was refluxed for 2 h. The resulting precipitate was filtered off and recrystallized from ethanol.

4-Amino-3,9-dibenzoylpyrimido[4′,5′:4,5]thiazolo[3,2-*a*] benzimidazol-2-thione (10)

To a solution of (0.82 g; 0.005 mol) of benzoyl isothiocyanate (prepared in situ from benzoyl chloride and ammonium thiocyanate) in dry acetone was added **3** (1.59 g; 0.005 mol) and the reaction mixture was refluxed for 2 h. On cooling, a solid product was separated, filtered off, and recrystallized from ethanol.

7-Benzoyl-1-(2′,3′-dimethyl-5′-oxo-1′-phenylpyrazol-4′-yl)thiazolo [3,2-*a*] benzimidazole (12a): ***Prepared by a two step reaction***

Step I

A mixture of compound **1** (1.27 g; 0.005 mol) and 4-chloroacetyl antipyrine (1.33 g; 0.005 mol) in ethanol (50 ml) was refluxed for 6 h. The reaction mixture was cooled and neutralized by Na_2CO_3 solution 5%. The obtained solid was collected and recrystallized from ethanol to give compound **11a**.

Step II

To polyphosphoric acid (10 ml) at room temperature, compound **11a** (2.4 g) was added. The reaction mixture was heated to 180°C and refluxed for 1 h. After the usual work up, the solid formed was separated, washed with water and recrystallized from ethanol/ H_2O to give **12a**.

7-Benzoyl-1-phenylthizolo[3,2-*a*]benzimidazole (12b)

It was prepared by the same manner as described in preparation of **12a** except that the phenacyl bromide was used instead of 4-chloroacetyl antipyrine.

4-Benzoyl-7,9-dihydro-8,8-dimethylbenzo[3′,2′:4,5]thiazolo[3,2-*a*] benzimidazole-11(H)-one (13)

A mixture of compound **1** (1.27 g; 0.005 mol) and 2-bromodimedone (1.09 g; 0.005 mol) in absolute ethanol (30 ml) was heated under reflux for 5 h. The reaction mixture was concentrated, cooled to room temperature

and neutralzied by a 5% aqueous Na_2CO_3 solution. The separated solid was recrystallized from ethanol and colorless needles were obtained.

4-Benzoylindeno[3′,2′:4,5]thiazolo[3,2-*a*]benzimidazole-11(H)-one (14)

A mixture of indan-1,3-dione (0.73 g; 0.005 mol), N-bromosuccinimide (1.78 g; 0.01 mol) in carbon tetrachloride (30 ml) was refluxed for about 2 h. The reaction mixture was filtered and the solvent distilled off. The residue was further refluxed with compound **1** (1.27 g; 0.005 mol) in absolute ethanol for 8 h. The solid which separated at the end of the refluxing period was filtered, dissolved in boiling water and neutralized with sodium carbonate solution to give a pale yellow precipitate which was filtered off and recrystallized from DMF.

7-Benzoylthiazolo[3,2-*a*]benzimidazole derivatives (18a-c): *General Procedure*

A mixture of compound **1** (1.27 g; 0.005 mol) and the appropriate hydrazonyl chloride **15a-c** (0.005 mol) in ethanol/ sodium ethoxide solution was refluxed for 6 h. The solvent was evaporated and the residue was triturated with methanol. The solid obtained was collected and crystallized from ethanol.

7-Benzoyltriazolo[4,3-*a*]benzimidazole derivatives (21a-c)

To a solution of 2-methylsulfonylbenzimidazole (1.34 g; 0.005 mol) and the appropriate hydrazonyl chloride **15a-c** (0.005 mol) in ethanol (30 ml) was added triethylamine (0.005 mol). The resulting solution was refluxed for 3 h. The solid formed was collected by filtration and crystallized from ethanol/ DMF. (see Table I, II).

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