Synthesis of Some New Pyrazoloquinazolinone and Quinazolinone Derivatives

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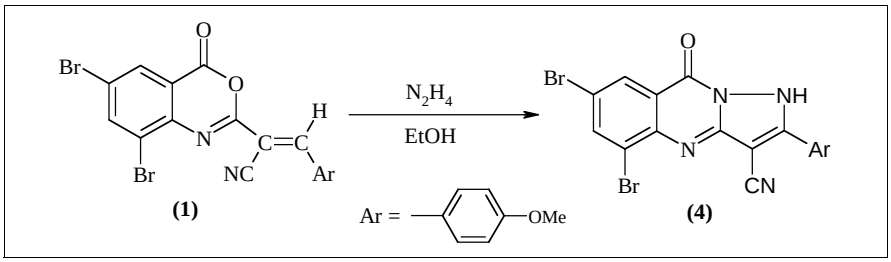

The benzoxazinone derivative 2-(6,8-dibromo-4-oxo-4*H*-benzo[*d*]-1,3-oxazin-2-yl)-3-(4-methoxyphenyl)acrylonitrile (**1**) has been used as a starting material for preparation of the hitherto unknown pyrazoloquinazolinone and quinazolinone derivatives. Under different conditions the benzoxazinone (**1**) was reacted with hydrazine hydrate to provide the pyrazolocarbonitrile derivative (**2**) and the azine derivative (**3**) and/or the pyrazoloquinazoline derivative (**4**). When (**4**) was conducted to react either with EAA (ethyl acetoacetate) or Ac_2O/AcOH (acetic anhydride/acetic acid) mixture or phthalic anhydride/acetic acid mixture, the pyrazoloquinazoline carbonitrile (**5**), pyrazolo-quinazoline acetic acid (**6**) or the pyrazoloquinazolinone derivative (**7**) were formed respectively. When (**1**) was reacted with phenylhydrazine, a mixture of the quinazolinone derivative (**8**) and the hydrazone derivative (**9**) were obtained. The benzoxazinone derivative (**1**) was found also to react with benzylamine in ethanol or without solvent to give the quinazolinone derivative (**10**) or the quinazolindione (**11**) respectively. Fusion of (**1**) with ammonium acetate yielded the quinazolinone (**12**), which was methylated to give (**13**) and thiated to the thioxyquinazoline derivative (**14**), while reaction of (**1**) with formamide gave the *N*-formylquinazoline derivative (**15**).

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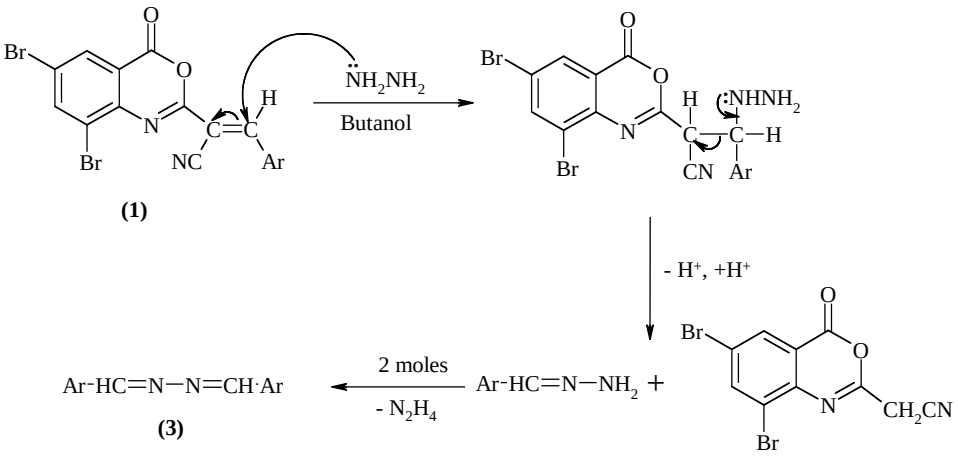
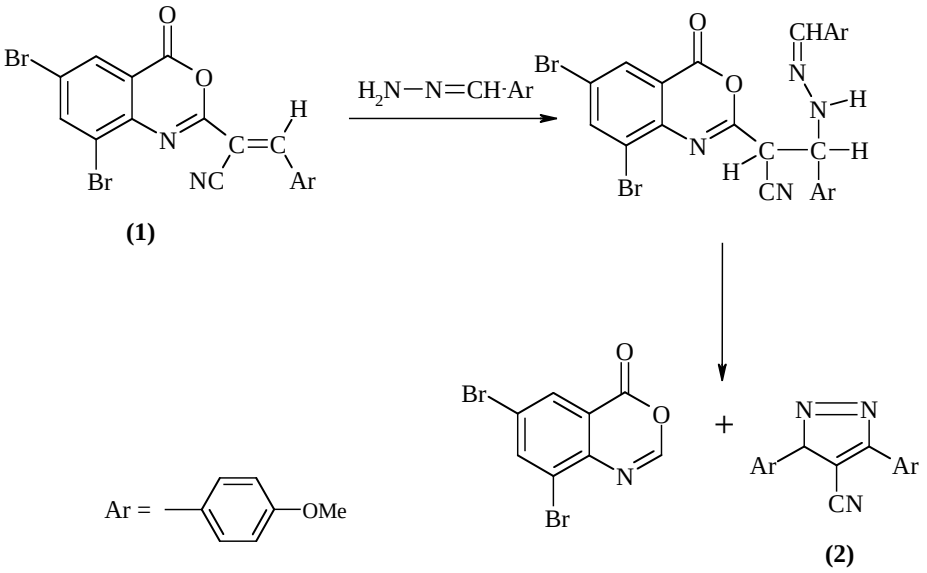
The pronounced biological and pharmacological activities as anticonvalsant [1,2], antihistaminic [3,4], antihypertensive [5-8] of these classes of compounds have stimulated the authors to synthesize these compounds. Hydrazinolysis of [9] 2-(6,8-dibromo-4-oxo-4*H*-benzo[*d*]-1,3-oxazin-2-yl)-3-(4-methoxyphenyl)acrylonitrile (**1**) with hydrazine hydrate in 1-butanol provided a mixture of 3,5-bis-(4-methoxyphenyl)-1*H*-pyrazole-4-carbonitrile (**2**) and [10] *N*,*N*-bis-(4-methoxybenzylidene)hydrazine (**3**). The following mechanism below summarizes their formation.

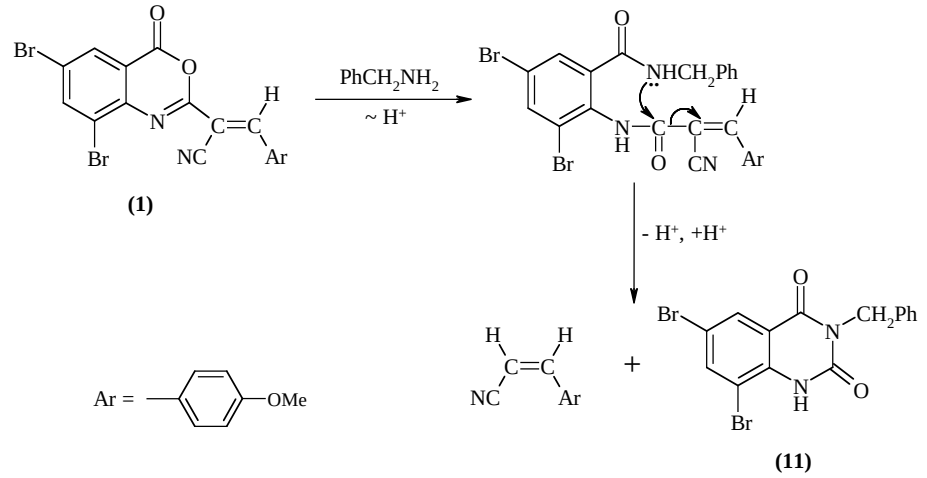
However, when the reaction was carried out in ethanol, 5,7-dibromo-2-(4-methoxyphenyl)-9-oxo-1,9-dihydropyrazolo[5,1-*b*]quinazolin-3-carbonitrile (**4**) was obtained in fairly good yield. The structure of (**4**) was further supported by the following chemical proofs. Reaction of (**4**) with EAA (ethyl acetoacetate) yielded 5,7-dibromo-2-(4-methoxyphenyl)-9-oxo-1-(1,3-dioxobutyryl)-1,9-dihydro-





pyrazolo[5,1-*b*]quinazolin-3-carbonitrile (**5**). The pyrazoloquinazoline derivative (**4**) was reacted with Ac_2O/AcOH mixture to give 5,7-dibromo-3-cyano-2-(4-methoxyphenyl)-9-oxo-1,2,3,9-tetrahydropyrazolo[5,1-*b*]quinazolin-2-acetic acid (**6**). On the other hand (**4**) was conducted to react with phthalic anhydride/AcOH to give 3-acetyl-5,7-dibromo-2-(4-methoxyphenyl)-3*H*-pyrazolo[5,1-*b*]quinazolin-9-one (**7**).

Treatment of (**1**) with ethanolic solution of phenylhydrazine gave a mixture of 6,8-dibromo-4-oxo-3-phenylamino-3,4-dihydroquinazolin-2-yl) acetonitrile (**8**) and *p*-anisaldehyde phenylhydrazone (**9**). In contrast to Ismail [11] and our previous results [7,9] aminolysis of benzoxazinone (**1**) with primary amines depends not only on the type of amine but also on the conditions, beside the nature of group in position-2, since in ethanolic solution, benzylamine reacted with (**1**) to give the quinazolinone derivative (**10**), while in excess of benzylamine, the dione derivative (**11**) was obtained according to the following mechanism:



Fusion of (**1**) with ammonium acetate gave the quinazolinone derivative (**12**), whose structure was confirmed by the following chemical proofs: Methylation of (**12**) with dimethylsulphate furnished 2-(6,8-dibromo-3-methyl-4-oxo-3,4-dihydroquinazolin-2-yl)-3-(4-methoxyphenyl)acrylonitrile (**13**). Thiation of (**12**) with P_2S_5 gave 2-(6,8-dibromo-4-thioxo-3,4-dihydroquinazolin-2-yl)-3-(4-methoxyphenyl)acrylonitrile (**14**). Formylation of (**1**) with excess formamide, yielded the N-formylquinazolinone derivative (**15**).

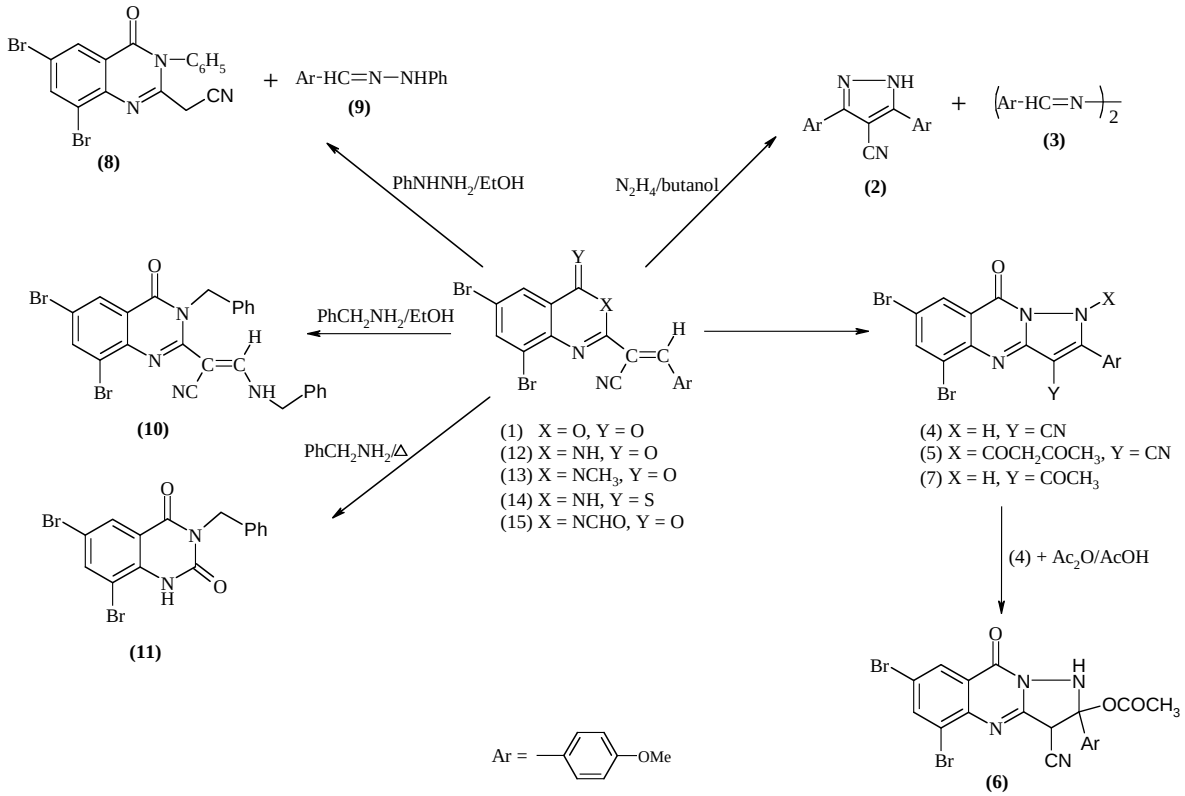


Table 1

Characterization Data of Prepared Compounds

Compd No.	M P ℃ (colour)	Yield % (solvent)	Mol. For. (M.Wt)	Analysis (Required/found)		
				C	H	N
2	287-90	50	$C_{18}H_{15}N_3O_2$	70.80	4.91	4.20
	(Brown)	E	(305.34)	71.25	4.60	4.30
3	178-80	40	$C_{16}H_{16}N_2O_2$	–	–	–
	(Pale yellow)	E	(268.32)			
4	257-60	45	$C_{18}H_{10}Br_2N_4O_2$	45.60	2.12	11.81
	(Brown)	D	(474.11)	45.80	2.23	11.65
5	235-37	50	$C_{22}H_{14}Br_2N_4O_4$	47.33	2.52	10.03
	(Brown)	T	(558.19)	47.50	2.32	10.25
6	348-50	55	$C_{20}H_{14}Br_2N_4O_4$	44.98	2.64	10.49
	(Yellow)	B	(534)	45.20	2.25	10.62
7	350-52	40	$C_{19}H_{13}Br_2N_3O_3$	46.46	2.66	8.55
	(Colorless)	T/E	(491.17)	46.75	2.55	8.30
8	151-54	45	$C_{16}H_{10}Br_2N_4O$	44.27	2.32	12.85
	(Orange)	B	(434.09)	44.60	2.22	12.62
9	120-22	40	$C_{14}H_{14}N_2O$	74.31	6.23	12.37
	(Yellowish white)	B	(226.28)	74.50	6.22	12.21
10	218-20	55	$C_{25}H_{18}Br_2N_4O$	54.66	3.12	10.20
	(Colorless)	P	(549.25)	53.72	3.48	9.98
11	255-57	65	$C_{15}H_{10}Br_2N_2O_2$	43.93	2.45	6.80
	(Colorless)	P	(410.07)	44.90	2.38	6.42
12	340-43	90	$C_{18}H_{11}Br_2N_3O_2$	46.85	2.38	9.11
	(Yellow)	D	(461.13)	46.94	2.32	9.13
13	270-73	75	$C_{19}H_{13}Br_2N_3O_2$	48.03	2.75	8.84
	(Yellow)	E	(475.13)	48.51	2.57	8.68
14	> 360	75	$C_{18}H_{11}Br_2N_3OS$	45.30	2.32	8.81
	(Green)	D	(477.18)	45.92	2.12	8.25
15	240-43	80	$C_{19}H_{11}Br_2N_3O_3$	46.65	2.26	8.59
	(Green)	B	(489.13)	46.91	2.10	8.33

B: Benzene: D: Dioxane: E : Ethanol: P: Petroleum ether (80-100 ℃): T: Toluene.

Table 2

^{1}H-NMR and MS Data of Prepared Compounds

Compd No.	^{1}H-NMR (δ in ppm)	MS (m/z %)	IR cm^{-1}		
			$\nu_{NH,OH}$	$\nu_{C=N}$	$\nu_{C=O}$
2	8.22 (broad, NH), 8.10 (d, 4H), 7.18 (d, 4H) and 3.8 (s, 3H)	$[M-2]^{+\cdot}$ (303, 8%), 287 (100%), 259 (16%), 231 (19%) and 215 (15%)	3380, 3181	2199	-
3	8.65 (s, 2H), 7.85 (d, 4H), 7.08 (d, 4H) and 3.84 (s, 6H)	$[M^{+\cdot}]$ (268, 100%), 240 (23%), 162 (10%), 161 (94.5%) and 134 (30%)	-	-	-
4	8.24 (d, 1H), 8.01 (d, 1H), 8.25 (d, 2H), 7.13 (d, 2H), 7.8 (broad, 1H) and 3.85 (s, 3H)	$[M^{+\cdot}]$ (474, 100%), 444 (7%) and 431 (38%)	3303	2199	-
5	-	$[M]^{+\cdot}$ (558, 27%), 557 (30%), 514 (24%), 394 (27%) and 234 (4%)	3422	2206	1683
6	8.29-8.33 (deformed, d, 2H), 7.97-8.01 (deformed, d, 2H), 7.12-7.17 (deformed, 2H), 3.86 (s, 3H), 1.93 (s, 3H) and 1.21 (s, 1H)	$[M-3]^{+\cdot}$ (531, 1.5%), 474 (100%), 473 (11%), 459 (3%) and 444 (4%)	3425	2232	1728
7	—	$[M]^{+\cdot}$ (491, 19%), 490 (37%) and 104 (100%)	3260	-	1723, 1699
8	—	$[M]^{+\cdot}$ (434, 8%), 395 (5%), 135 (97%) and 92 (78%)	3430	2209	1685
9	–	$[M]^{+\cdot}$ (226, 100%), 211 (6%), 195 (1.5%) and 90 (8%)	3313	-	-
10	8.6-8.2 (broad, 3H), 7.85 (deformed 2H), 7.6-7.2 (broad, 9H) and 4.1 (s, 4H)	$[M+2]^{+\cdot}$ (551, 0.5%), 158 (17%), 106 (100%) and 91 (87%)	3274	2207	1681
11	10.88 (broad, 1H), 8.05 (d, 1H), 8.2 (d, 1H), 7.3 (m, 5H) and 5.1 (s, 2H)	$[M]^{+\cdot}$ (410, 27%), 393 (8%), 303 (6%), 142 (2%) and 91 (100%)	3355	-	1718, 1661
12	11.8 (hump, 1H), 8.44 & 8.18 (broad 2H), 8.36 (s, 1H), 8.04-8.01 (d, 2H), 7.2 & 7.17 (d, 2H) and 3.8 (s, 3H)	$[M+2]^{+\cdot}$ (463, 5%), 461 (60%), 460 (100%), 380 (12%) and 277 (26%)	3240	2229	1679
13	—	$[M+2]^{+\cdot}$ (477, 17%), 476 (24%), 475 (23%), 460 (100%), 445 (12%) and 353 (6%)	-	2218	1659
14	—	$[M+1]^{+\cdot}$ (478, 13%), 477 (16%), 445 (9%), 444 (17%), 380 (22%), 301 (13%), 184 (19%) and 170 (25%)	3320	2229	-
15	9.04 (s, 1H), 8.35 & 8.18 (deformed 2H), 8.25 (s, 1H), 7.2 & 7.24 (d, 2H), 6.85 & 6.65 (d, 2H) and 3.75 (s, 3H)	$[M]^{+\cdot}$ (489, 70%), 473 (100%), 448 (22%) and 396 (18%)	-	2206	1710, 1687

EXPERIMENTAL

Melting points were measured on an electrothermal melting point apparatus and are uncorrected. Elemental analyses were carried out at the Micro-Analytical unit, Cairo University, Giza. Infrared spectra were measured on a Unicam SP-1200 spectrometer using KBr wafer technique. ^{1}H NMR spectra were measured in DMSO-d_6 on a Varian plus instrument (300 MHz). The mass spectra were determined using HP model MS-5988 at electron energy 70 eV.

3,5-Bis-(4-methoxyphenyl)-1*H*-pyrazole-4-carbonitrile (**2**) and [10] *N*,*N*-Bis(4-methoxybenzylidene)hydrazine (**3**).

A mixture of benzoxazinone (**1**) (0.01 mol) and hydrazine hydrate (0.01 mol) in 1-butanol (30 mL) was refluxed for 6 h. The solid that formed after concentration of the solvent was collected and crystallized to give (**2**) and (**3**) which were identified by mp and mixed mp with authentic sample.

5,7-Dibromo-2-(4-methoxyphenyl)-9-oxo-1,9-dihydropyrazolo-[5,1-*b*]quinazoline-3-carbonitrile (**4**).

A mixture of (**1**) (0.01 mol) and hydrazine hydrate (0.01 mol) in ethanol (30 mL) was refluxed for 5 h. The solid that formed while heating was collected and crystallized to give (**4**).

5,7-Dibromo-2-(4-methoxyphenyl)-9-oxo-1-(1,3-dioxobutyryl)-1,9-dihydropyrazolo[5,1-*b*]quinazoline-3-carbonitrile (**5**).

A mixture of (**4**) (0.01 mol) and ethyl acetoacetate (0.01 mol) in ethanol (50 mL) was refluxed for 3 h. The solid that formed after concentration of the solvent was collected and crystallized to give (**5**).

5,7-Dibromo-3-cyano-2-(4-methoxyphenyl)-9-oxo-1,2,3,9-tetra-hydropyrazolo[5,1-*b*]quinazolin-2-acetic acid (**6**).

A mixture of (**4**) (0.01 mol) and acetic anhydride (5 mL) in acetic acid (30 mL) was refluxed for 3 h. The solid that formed after concentration of the solvent was collected and crystallized to give (**6**).

3-Acetyl-5,7-dibromo-2-(4-methoxyphenyl)-3*H*-pyrazolo[5,1-*b*]-quinazolin-9-one (**7**).

A mixture of (**4**) (0.01 mol) and phthalic anhydride (0.01 mol) in acetic acid (30 mL) was refluxed for 3 h. The solid that formed after concentration of the solvent was collected and crystallized to give (**7**).

(6,8-Dibromo-4-oxo-3-phenylamino-3,4-dihydroquinazolin-2-yl)acetonitrile (**8**) and *p*-Anisaldehyde phenyl hydrazone (**9**).

A mixture of (**1**) (0.01 mol) and phenyl hydrazine (0.01 mol) in ethanol (30 mL) was refluxed for 3 h. The solid that formed

after concentration of the solvent was collected and crystallized to give (**8**) and (**9**).

2-(3-Benzyl-6,8-dibromo-4-oxo-3,4-dihydroquinazolin-2-yl)-3-(benzylamino)acrylonitrile (**10**).

A mixture of (**1**) (0.01 mol) and benzyl amine (0.01 mol) in ethanol (50 mL) was refluxed for 5 h. The solid that formed after concentration of the solvent was collected and crystallized to give (**10**).

3-Benzyl-6,8-dibromo-1*H*-quinazoline-2,4-dione (**11**).

A mixture of (**1**) (0.01 mol) and benzylamine (20 mL) was refluxed for 3 h. After cooling, the reaction mixture was poured onto ice cold HCl, the solid that formed was collected and crystallized to give (**11**).

2-(6,8-Dibromo-4-oxo-3,4-dihydroquinazolin-2-yl)-3-(4-methoxy-phenyl)acrylonitrile (**12**).

A mixture of (**1**) (0.01 mol) and ammonium acetate (0.04 mol) was heated in oil bath at 180-190 ℃ for 3 h. The residue was triturated with warm water, then collected and crystallized to give (**12**).

2-(6,8-Dibromo-3-methyl-4-oxo-3,4-dihydroquinazolin-2-yl)-3-(4-methoxy phenyl)acrylonitrile (**13**).

A mixture of (**12**) (0.01 mol) and dimethylsulphate (0.01 mol) in sodium hydroxide (50 mL) was refluxed for 5 h. After cooling, the reaction mixture was poured in ice cold hydrochloric acid, the solid formed was collected and crystallized to give (**13**).

2-(6,8-Dibromo-4-thioxo-3,4-dihydroquinazolin-2-yl)-3-(4-methoxyphenyl)acrylonitrile (**14**).

A mixture of (**12**) (0.01 mol) and phosphorous pentasulphide (0.02 mol) was heated in a sand bath at 250 ℃ for 5 h. The solid that formed after cooling was triturated with boiling water, collected and crystallized to give (**14**).

2-(6,8-Dibromo-3-formyl-4-oxo-3,4-dihydroquinazolin-2-yl)-3-(4-methoxy phenyl) acrylonitrile (**15**).

A mixture of (**1**) (0.01 mol) and formamide (30 mL) was refluxed for 3 h. After cooling, the reaction mixture was poured into water, and the solid that formed was collected and crystallized to give (**15**).

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