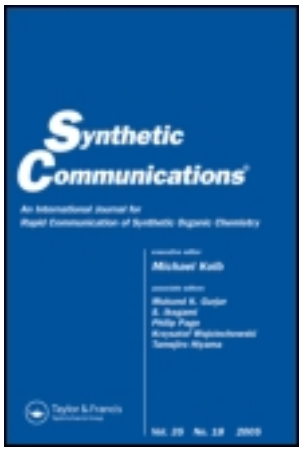

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REACTION OF ISATOIC ANHYDRIDE WITH BIFUNCTIONAL REAGENTS: SYNTHESIS OF SOME NEW QUINAZOLONE FUSED HETEROCYCLES, 2-SUBSTITUTED ANILINOHETEROCYCLIC DERIVATIVES AND OTHER RELATED COMPOUNDS

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REACTION OF ISATOIC ANHYDRIDE WITH BIFUNCTIONAL REAGENTS: SYNTHESIS OF SOME NEW QUINAZOLONE FUSED HETEROCYCLES, 2-SUBSTITUTED ANILINOHETEROCYCLIC DERIVATIVES AND OTHER RELATED COMPOUNDS

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ABSTRACT

A new synthesis of quinazolone fused heterocycles (**2**, **5**, **8**), anilinoheterocycles (**4**, **7**, **10**, **12**, **14**) and substituted 2-amino-quinoline (**15**, **16**) based on the reaction of isatoic anhydride (**1**) with different active bifunctional compounds in presence

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of glacial acetic acid and freshly fused sodium acetate is described. Structures of the newly prepared compounds are established by chemical and spectral data.

During the past 30 years several groups have described the use of 2H-3,1-benzoxazine-2,4(1H)-dione (isatoic anhydride) for the synthesis of quinazolinedione,[1] 4-quinazolinones[2] and benzodiazepine-5-ones.[3] It has been reported also that the reaction of isatoic anhydride with aromatic primary amines with ortho substituents to yield largely the abnormal products.[4] In the last few years we have reported several syntheses of quinazoline derivatives as a part of a program to develop new simple routes for the synthesis of functionally substituted heterocycles of anticipated biological activity that can be used as potential biodegradable agrochemicals.[5–7] In the present work we explore the synthetic potential of isatoic anhydride (**1**) to obtain some novel quinazolone fused heterocycles, anilinoheterocycles and substituted quinoline derivatives via the reaction with different bifunctional reagents containing reactive hydrogen atoms. No details regarding the synthesis of such compounds in the literature survey. The synthesized compounds possess latent functional subsituents and appear promising for utility in further chemical transformation and also biological studies. Thus, compound **1** reacts with *o*-phenylenediamine in refluxing acetic acid catalyzed by freshly fused sodium acetate to afford two products, benzoimidazolo[2,3-b]-quinazoline-6-one (**2**) and benzimidazole derivative (**4**) in 85% and 15% yield, respectively.

In a similar manner, it was found that, 1 reacts with 2,3-diaminopyridine to afford pyridoimidazolo[2,3-b]-quinazoline-6-one (**5**), and 2-(*o*-aminophenyl)-pyridoimidazole (**7**) in 70% and 30% yield respectively. The structure of **5**, **7** could be established for the reaction product based on IR, ^{1}H NMR and mass spectra. Moreover, it has been found that compound 1 reacts with 2-amino-3-hydroxypyridine in glacial acetic acid in the presence of freshly fused sodium acetate to give a single product, pyridooxazolo[2,3-b]quinazolin-6-one (**8**) in 85% yield.

Structure **8** was established on the basis of spectral data, which the mass spectra showed M^+ at 236 and the base peak of $M+2$ (238). On the other hand, **1** reacts with aminothiophenol in presence of glacial acetic acid containing a catalytic amounts of freshly fused sodium acetate to give a single product with molecular formula $C_{13}H_{10}N_2S$ ($M^+ = 226$). The product was assigned as 2-(*o*-aminophenyl)benzothiazole structure (**10**), based on spectral data. This result is in complete agreement with the previously reported work[8] of reaction of isatoic anhydride with mercaptans.

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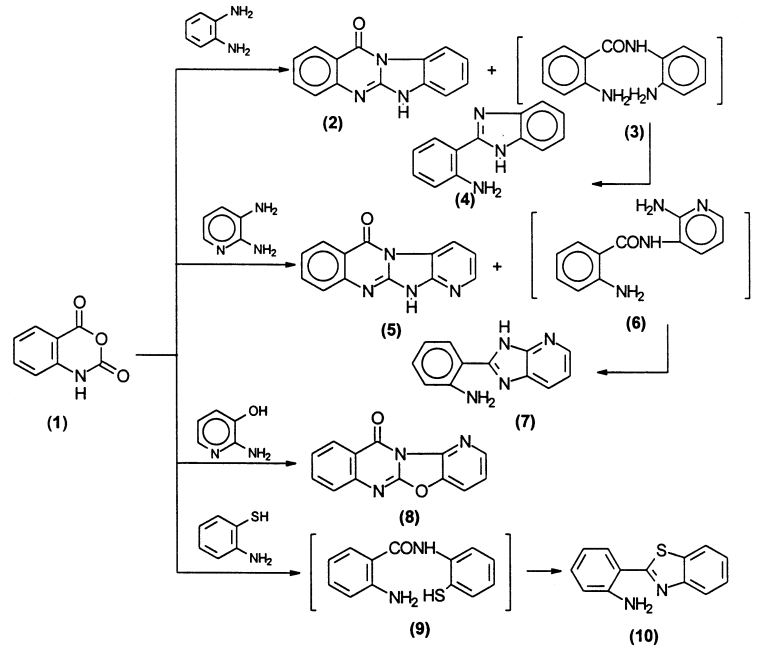

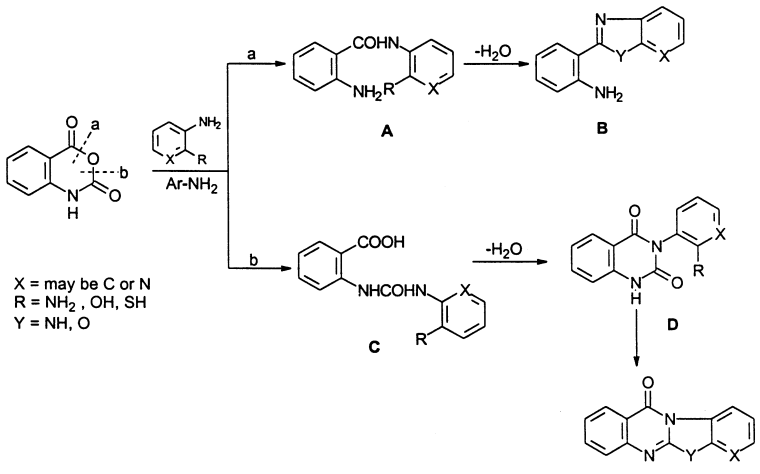

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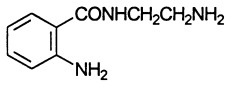
The formation of the reaction products **2–10** can be assumed according to the following proposed reaction mechanism.

The condensation of isatoic anhydride (**1**) with *o*-substituted primary aromatic amines has been found to yield the corresponding substituted anthranilamides (A), earlier believed to be the sole normal products of this reaction[4] and, concurrently, the corresponding *ω*-substituted *o*-uramidobenzoic acid (C), the latter, may undergo cyclization to form the 3-substituted benzoylene ureas (D) which followed by intramolecular cyclization to give the corresponding quinazolone derivatives. All these primary amines yielded both substituted anthranilamides and substituted uramidobenzoic acids. Ring closure of the latter to 3-substituted benzoylene ureas, by action of acetic acid/sodium acetate, occurred when R was amino and hydroxyl groups, but was not observed to occur when R was a thiol group. The obstruction to cyclization is probably steric, but is not satisfactorily rationalized from the evidence at hand. The structures of R affected also the proportions of A and C formed in the initial reactions, as well as the ease of cyclization of C to D.

The reaction of isatoic anhydride with ethylene diamine in the presence of acetic acid and freshly fused sodium acetate occurs readily to afford two products. The anthranilamide derivative (**11**) 2-imidazolylaniline derivative (**12**). Similarly, 1 reacts with ethanolamine to afford two products, one of them has the molecular formula $C_9H_{12}N_2O_2$ (35%, $M^+ = 180$) **13** and the other products $C_9H_{10}N_2O$ (65%, $M^+ = 162$) **14**.

Both structures (**13**) and (**14**) were established on their spectral data (cf. experimental). Compounds **12** and **14** were assumed to be formed via the direct intramolecular cyclization of its corresponding isolable anthranilamide **11** and **13** respectively. The formation of **11** and **13** derivatives are in complete agreement with the previously reported work.[9]



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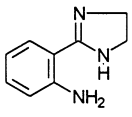

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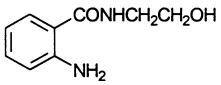

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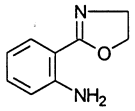
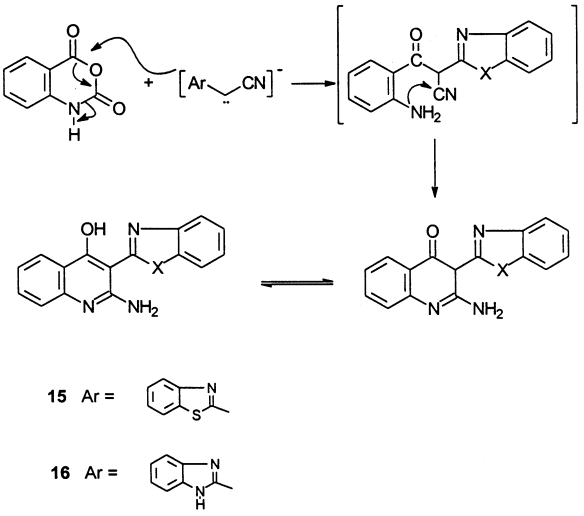


14

Isatoic anhydride is capable of reacting with active methylene compounds, as shown by its reaction with 2-cyanomethylbenzothiazole and 2-cyanomethylbenzoimidazole to produce 3-(benzothiazol-2-yl)-2-amino-4-hydroxyquinoline (**15**) and 3-(benzimidazol-2-yl)-2-amino-4-hydroxyquinoline (**16**) respectively.



15 Ar =

16 Ar =

The mechanism proposed for the reaction by route (a) is the attack of the nuceophilic group on the No. 4 carbon atom of the anhydride ring. The sodium acetate appears to act as a catalyst by ionizing the activated nitriles, followed by cyclization reaction to give the isolable reaction products. Mass spectral measurements and analytical data are in complete agreement with structures **15** and **16**.

The results presented have thus opened a direct and efficient routes to access to the otherwise not readily obtainable quinazolone fused heterocycles and *o*-anilinoheterocycles.

EXPERIMENTAL

All melting points are uncorrected. FTIR spectra (KBr) were recorded on a Nicolet Magna Model 550 IR spectrophotometer. ^{1}H-NMR spectra in $CDCl_3$ were determined on a Brucker WP Spectrometer at 200 MHz with

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TMS as internal standard. Mass spectra were recorded at 70 eV with a varian MAT 311 instrument. Elemental analyses (C.H) agree satisfactorily with the calculated values.

Reaction of 1 with *o*-Phenylenediamine

A mixture of isatoic anhydride (1) (1 g, 0.006 mol), *o*-phenylenediamine (0.86 g, 0.008 mol) and freshly fused sodium acetate (0.3 g) in glacial acetic acid (30 mL) was refluxed for 2 h, during which time yellowish crystals separated from the solution. The reaction mixture was then cooled to room temperature, the crystals were collected by filtration then fractionally recrystallized using dilute acetic acid to obtain (85%) of compound (**2**) and (15%) of compound (**4**) (cf. Table 1, 2).

Reaction of 1 with 2,3-Diaminopyridine

A mixture of (**1**) (1.63 g, 0.01 mol), 2,3-diaminopyridine (3.27 g, 0.03 mol) and freshly fused sodium acetate (0.5 g) in glacial acetic acid (50 mL) was refluxed for 4 h, during which time yellowish solid material separated from the solution. The reaction mixture was then cooled to room temperature, the crystals were collected by filtration then fractionally

Table 1. Characterization Data of the Newly Prepared Compounds

Compound no.	M.P. (°C)	Yield %	Molecular formula	Analysis, Found (Calcd) %	
				C	H
2	120	85	$C_{14}H_9N_3O$	71.3 (71.5)	3.8 (3.8)
4	210	15	$C_{13}H_{11}N_3$	74.5 (74.6)	5.3 (5.3)
5	215	60	$C_{13}H_8N_4O$	66.0 (66.1)	3.4 (3.4)
7	165	35	$C_{12}H_{10}N_4$	68.5 (68.6)	4.6 (4.8)
8	200	85	$C_{14}H_8N_2O_2$	71.1 (71.2)	3.5 (3.4)
10	140	80	$C_{13}H_{10}N_2S$	69.2 (69.0)	4.3 (4.9)
11	240	80	$C_9H_{13}N_3O$	60.1 (60.3)	7.2 (7.3)
12	220	20	$C_9H_{11}N_3$	66.1 (66.6)	6.8 (6.8)
13	55	60	$C_9H_{12}N_2O_2$	59.7 (60.0)	6.7 (6.6)
14	90	40	$C_9H_{10}N_2O$	66.5 (66.6)	6.1 (6.2)
15	> 300	70	$C_{16}H_{11}N_3OS$	65.3 (65.5)	3.7 (3.8)
16	> 300	60	$C_{16}H_{12}N_4O$	69.1 (69.5)	4.3 (4.3)

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Table 2. Spectroscopic Data of the Newly Prepared Compounds

Compound no.	IR (cm^{-1}) (Selected bands)	^1H NMR (ppm)	Mass spectra (Base peak)
2	3300 (NH), 1650 (-CON)	6.3–7.4 (m, 8H, Ar-H), 8.3 (s, 1H, NH)	236 (M + 1)
4	3350–3400 (NH_2), 3300 (NH)	6.4 (s, 2H, NH_2), 6.5–7.7 (m, 8H, Ar-H), 8.25 (s, 1H, NH)	209 (M^+)
5	3292 (NH), 1630 (-CON)	6.4–8.2 (m, 7H, Ar-H), 8.4 (s, 1H, NH)	236 (M^+)
7	3300–3400 (NH_2), 3260 (NH)	6.2 (s, 2H, NH_2), 6.3–8.2 (m, 7H, Ar-H), 8.2 (s, 1H, NH)	210 (M^+)
8	1647 (-CON)	6.3–7.5 (m, 8H, Ar-H)	238 (M + 2)
10	3350–3400 (NH_2), 1600 (C=N)	6.3 (s, 2H, NH_2), 6.4–7.5 (m, 8H, Ar-H)	226 (M^+)
11	3330–3400 (NH_2), 1630 (-CON)	3.25 (t, 2H, CH_2), 3.45 (t, 2H, CH_2), 4.7 (bs, 2H, NH_2), 6.4 (s, 2H, NH_2), 6.4–7.5 (m, 4H, Ar-H), 8.3 (s, 1H, NH)	179 (M^+)
12	3350–3400 (NH_2), 3300 (NH), 1600 (C=N)	3.2 (t, 2H, CH_2), 3.35 (t, 2H, CH_2), 6.4 (s, 2H, NH_2), 6.45–7.5 (m, 4H, Ar-H), 8.2 (s, 1H, NH)	161 (M − 1)
13	3350–3400 (NH_2), 3350 (OH), 3300 (NH), 1650 (-CON)	1.8 (s, 1H, OH), 3.2 (t, 2H, CH_2), 3.35 (t, 2H, CH_2), 6.3 (s, 2H, NH_2), 6.4–7.5 (m, 4H, Ar-H), 8.3 (s, 1H, NH)	180 (M^+)
14	3350–3400 (NH_2), 1600 (C=N)	3.2 (t, 2H, CH_2), 3.4 (t, 2H, CH_2), 6.3 (s, 2H, NH_2), 6.4–7.5 (m, 4H, Ar-H)	162 (M^+)
15	3360–3400 (NH_2), 3350 (OH)	6.2 (s, 2H, NH_2), 6.35–8.0 (m, 8H, Ar-H), 8.3 (s, 1H, OH)	294 (M + 1)
16	3350–3400 (NH_2), 3350 (OH), 3300 (NH).	6.25 (s, 2H, NH_2), 6.3–8.1 (m, 8H, Ar-H), 8.3 (s, 1H, OH), 8.45 (s, 1H, NH).	276 (M^+)

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recrystallized using dilute acetic acid to give (60%) of compound (**5**), and (35%) of compound (**7**) (cf. Table 1, 2).

Reaction of 1 with 2-Amino-3-hydroxypyridine

A mixture of (1) (1 g, 0.006 mol), 2-amino-3-hydroxypyridine (0.88 g, 0.008 mol) and freshly fused sodium acetate (0.3 g) in glacial acetic acid (30 mL) was refluxed for 2 h, during which time yellowish crystals separated from the solution. The mixture was then cooled to room temperature, the crystals were collected by filtration then recrystallized from dilute ethanol to obtain compound (**8**).

Reaction of 1 with 2-Aminothiophenol

A mixture of (**1**) (1 g, 0.006 mol), 2-aminothiophenol (1.0 g, 0.008 mol) and freshly fused sodium acetate (0.4 g) in glacial acetic acid (40 mL) was refluxed for 3 h. The reaction mixture was cooled and the precipitate solid material filtered, dried, and crystallized from acetic acid to give compound **10** (cf. Table 1, 2).

Reaction of 1 with Ethylene Diamine

A mixture of (**1**) (1.63 g, 0.001 mol), ethylene diamine (1.8 g, 0.03 mol) and freshly fused sodium acetate (0.5 g) in glacial acetic acid (50 mL) was refluxed for 4 h. The reaction mixture was then cooled to room temperature, the crystals were collected by filteration then fractionally recrystallized using dilute acetic acid to give (80%) of compound (**11**) and (20%) of compound **12** (cf. Table 1, 2).

Reaction of 1 with Ethanolamine

A mixture of (**1**) (1.63 g, 0.01 mol), ethanolamine (1.83 g, 0.03 mol) and freshly fused sodium acetate (0.5 g) in presence of glacial acetic acid (50 mL) was refluxed for 4 h. The reaction mixture was then cooled to room temperature, the crystals were collected by filteration then fractionally recrystallized from dilute acetic acid to give (60%) of compound (**13**) and (40%) of compound (**14**) (cf. Table 1, 2).

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Reaction of 1 with 2-Cyanomethylbenzothiazole

A mixture of (**1**) (1 g, 0.006 mol) 2-cyanomethylbenzothiazole (1.04 g, 0.006 mol) and freshly fused sodium acetate (0.3 g) in presence of glacial acetic acid (30 mL) was refluxed for 2 h. The reaction mixture was then cooled to room temperature and the precipitated solid material filtered, dried and recrystallized from ethanol to give **15** (cf. Table 1, 2).

Reaction of 1 with 2-Cyanomethylbenzimidazole

A mixture of (**1**) (1 g, 0.006 mol), 2-cyanomethylbenzimidazole (0.94 g, 0.006 mol) and freshly fused sodium acetate (0.3 g) in presence of glacial acetic and (30 mL) was refluxed for 2 h. The reaction mixture was then cooled and the separated solid material was recrystallized from ethanol to give **16** (cf. Table 1, 2).

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