

## Reactions with 3-Amino-1,2,4-Triazole: Synthesis of Several New 1,2,4-Triazolo[5,1-a]pyrimidine Derivatives

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**Abstract**—Several new 1,2,4-triazolo[5,1-a]pyrimidine derivatives were synthesized via the reactions of 3-amino-1,2,4-triazole with active methylene nitriles and their ylidenes derivatives. The structures assigned for the reaction products were based on elemental analyses and spectral data.

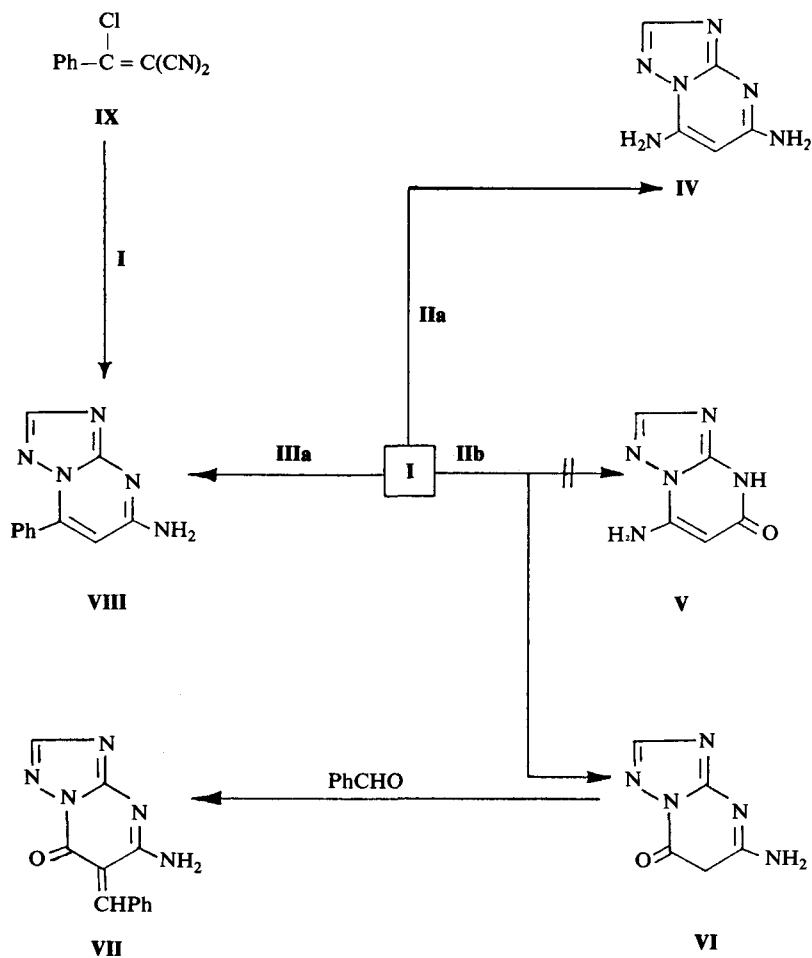
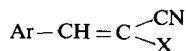
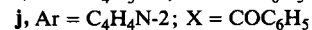
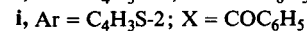
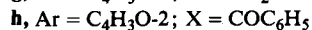
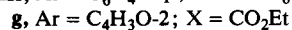
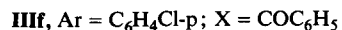
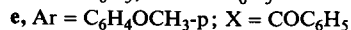
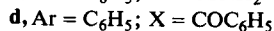
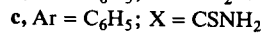
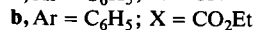
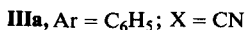
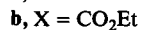
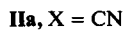
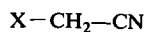
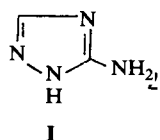
**Keywords**—1,2,4-triazolo[5,1-a]pyrimidine derivatives

Pyrimidines and their fused derivatives are used as fungicides<sup>1)</sup>, as excellent control for rice blast<sup>2)</sup>, and their outstanding systemic activity<sup>3)</sup> by root application against certain powdery mildews, such as those of cucumber, melon and some ornamentals<sup>4)</sup>. Moreover, many of pyrimidine derivatives are highly active as seed dressings against barely powery mildew, a major disease of barely in Europe<sup>5)</sup>. The above biological activities stimulated our interest for synthesis of several fused derivatives of this ring system. The reactions of 3-amino-1,2,4-triazole **I** with active methylene nitriles **IIa,b** and with the ylidene derivatives **IIIa-j** seemed to be a logic route for the synthesis of the desired derivatives. Thus, it has been found that **I** reacted with malononitrile **IIa** by fusion of the reactants at 170 °C in the presence of a catalytic amount of piperidine to yield a product of molecular formula C<sub>3</sub>H<sub>6</sub>N<sub>6</sub>, resulting from the addition of one molecule of **I** to one molecule of **IIa**. Structure **IV** was thus assigned for the reactions product based on elemental analysis and IR spectrum which revealed absorption bands for two amino groups and the absence of any band attributable to the presence of CN group. Similarly **I** reacted with ethyl cyanoacetate **IIb** to yield a product which could be formulated as **V** or **VI**. Structure **V** was readily ruled out based on the fact that the reaction product reacted with benzaldehyde to furnish the benzylidene derivative **VII**.

The behaviour of **I** towards several cinnamionitrile and acrylonitrile derivatives **IIIa-j** was also investigated. Thus, **I** reacted with **IIIa** to yield a product of molecular formula C<sub>12</sub>H<sub>8</sub>N<sub>6</sub>, resulting from the addition of one molecule of **I** to one molecule of

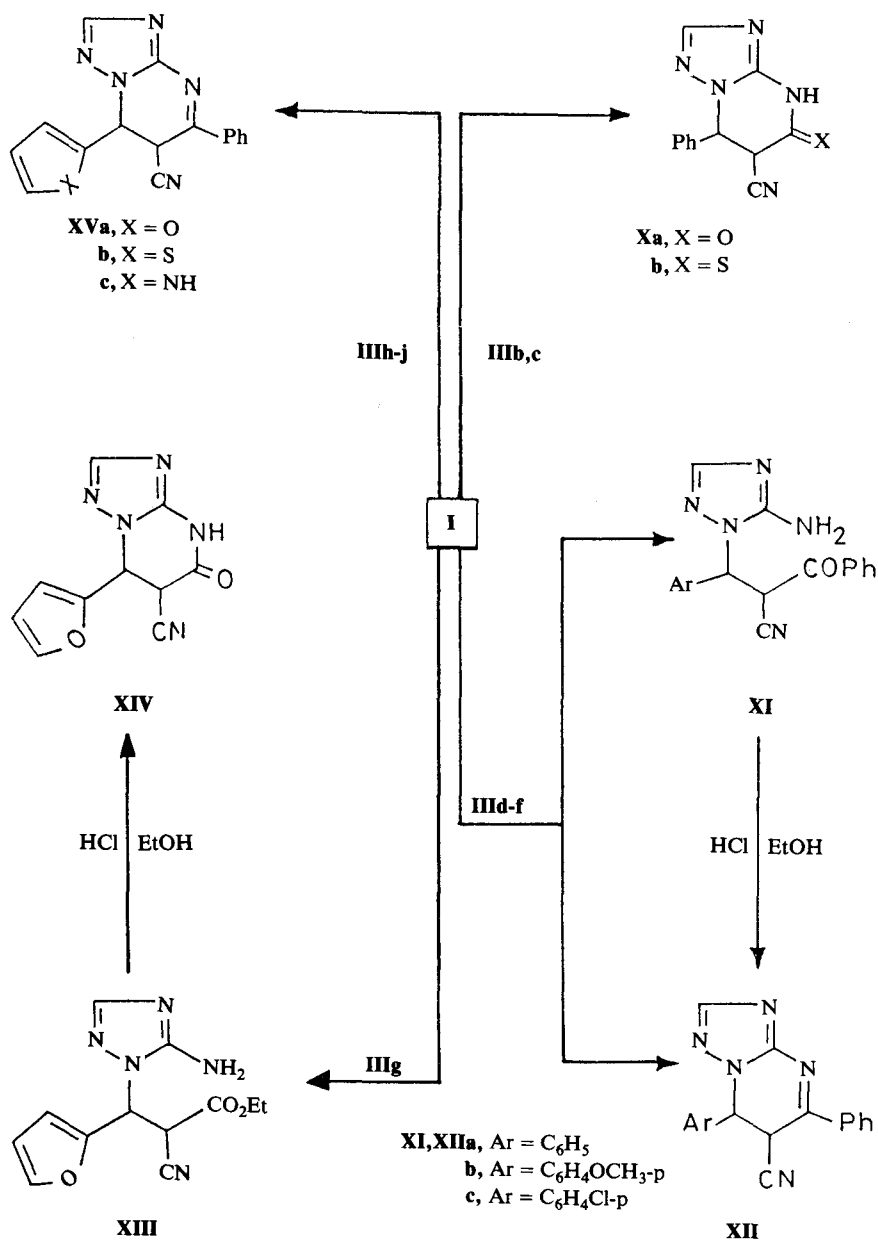
**IIIa** followed by dehydrocyanation. Structure **VIII** was assigned for the reaction product on the basis of elemental analysis and spectral data. Further proof of structure **VIII** was achieved via its synthesis by the reaction of **I** with the chloro-derivatives **IX** under the same experimental conditions. Similarly the ylidenes **IIIb,c** reacted with **I** to yield the 1,2,4-triazolo[5,1-a]pyrimidine derivatives **Xa,b**, respectively in good yields. Structure **Xa,b** was assigned based on both elemental analyses and spectral data.

In contrast to the behaviour of **IIa-c** toward **I**, the benzoylacrylonitrile derivatives **IIIb-f** reacted base catalysed with **I** to yield a separable mixture of the Michael adducts **XIa-c** and the as-triazolo[5,1-a]pyrimidines **XIIa-c**, in each case, respectively. Structure **XIa-c** and **XIIa-c** were based on both elemental analyses and spectral data. From the stereochemical point of view the cyano and benzoyl groups in compound **XI** must be arranged in a manner so that cyclization takes place via elimination of water from the NH<sub>2</sub> and CO groups rather than cyclization via addition to the cyano function. This assumption finds support by the fact that the band related to the CN group in **XII** is so obvious. Moreover, no absorption band related to the presence of the CPh group was detected in the IR spectrum of **XII** (see Experimental). An unequivocal support of structure **XIIa-c** was achieved via their synthesis by the action of ethanolic hydrochloric acid on **XIa-c** respectively. On the other hand, **IIIg** reacted with **I** to give the corresponding Michael adduct **XIII** only. **XIII** could be converted into the corresponding a-triazolo[5,1-a]pyrimidine derivative **XIV** by boil-



ing in ethanol-hydrochloric acid solution. Again, the stereochemistry of **XIII** was investigated. The CN and the COOEt groups must be located in the way that permits cyclization of **XIII** to **XIV** via ethanol elimination. If it is the other way round the cyano function should have been involved in the cyclization reaction, a fact which finds no confirmation owing to the appearance of the absorption band related to the presence of the CN group in

the IR spectrum of **XIV**. Moreover, cyclization via loss of ethanol finds support by the fact that the <sup>1</sup>H-NMR spectrum of **XIV** did not reveal any bands related to the COOEt group. Moreover, the heterocyclic ylidene derivatives **IIIa-j** behaved similarly toward **I** to give the as-triazolodihydropyrimidine derivatives **XVa-c** respectively in excellent yields. The structure of **XVa-c** was established on elemental analyses and spectroscopic backgrounds.



## EXPERIMENTAL

All melting points are not corrected. The IR spectra in KBr disks were recorded on a Pye-Unicam SP<sub>3</sub>-300 Spectrophotometer. The <sup>1</sup>H-NMR spectra were recorded in CDCl<sub>3</sub> or (CD<sub>3</sub>)<sub>2</sub>SO on a Varian EM-360 spectrometer (90 MHz), with TMS as an internal reference. The elemental analyses were carried out by the Microanalytical Centre at Cairo University, Egypt.

### General procedure for the reactions of I with IIa,b and IIIa-i:

A solution of I (0.01 mole) in ethanol (30 ml) was treated with each of IIa,b or IIIa-i (0.01 mole) in the presence of a catalytic amount of piperidine (0.5 ml) and the whole was heated under reflux from 3-4 hours. The solid products obtained either when the reaction mixtures were still boiling or after cooling were filtered off and crystallized from the proper solvents to give IV, VI, VIII, Xa,b, XIa-c, XIIa-c,

Table I. List of the newly synthesized compounds

Compound*	Colour	Yield (%)	M.p. (°C)	Molecular formula	Elemental analysis (%)							
					Calcd.				Found			
					C	H	N	S or Cl	C	H	N	S or Cl
IV	Orange	36	>300	C <sub>5</sub> H <sub>6</sub> N <sub>6</sub>	40.00	4.00	47.61	—	40.4	4.2	48.0	—
VI	Pale yellow	90	>360	C <sub>5</sub> H <sub>5</sub> N <sub>5</sub> O	39.73	3.30	46.35	—	40.0	3.2	46.6	—
VII	Yellow	65	240	C <sub>12</sub> H <sub>9</sub> N <sub>5</sub> O	60.25	3.76	29.28	—	60.5	3.9	29.5	—
VIII	Pale yellow	70	265	C <sub>12</sub> H <sub>8</sub> N <sub>6</sub>	61.01	3.38	35.59	—	61.2	3.5	35.2	—
Xa	Yellow	75	285	C <sub>12</sub> H <sub>9</sub> N <sub>5</sub> O	60.25	3.76	29.28	—	60.4	3.8	29.6	—
Xb	Yellow	78	>300	C <sub>12</sub> H <sub>9</sub> N <sub>5</sub> S	56.47	3.52	27.45	12.50	56.7	3.7	27.4	12.8
XIa	colourless	35	215	C <sub>18</sub> H <sub>15</sub> N <sub>5</sub> O	68.13	4.73	22.08	—	68.3	4.8	22.2	—
XIb	Pale yellow	30	220	C <sub>19</sub> H <sub>17</sub> N <sub>5</sub> O	68.88	5.13	21.14	—	68.9	5.4	21.4	—
XIc	Pale yellow	40	230	C <sub>18</sub> H <sub>14</sub> N <sub>5</sub> ClO	61.45	3.98	19.9	10.09	61.5	3.8	20.1	10.2
XIIa	Yellow	55	260	C <sub>18</sub> H <sub>13</sub> N <sub>5</sub>	72.24	4.34	23.41	—	72.4	4.4	23.6	—
XIIb	Pale yellow	60	265	C <sub>19</sub> H <sub>15</sub> N <sub>5</sub> O	69.30	4.55	21.27	—	69.6	4.6	21.4	—
XIIc	colourless	50	270	C <sub>18</sub> H <sub>12</sub> N <sub>5</sub> Cl	64.76	3.59	20.98	10.64	65.0	3.7	21.1	10.7
XIII	Brown	70	230	C <sub>12</sub> H <sub>13</sub> N <sub>5</sub> O <sub>3</sub>	52.36	4.72	25.45	—	52.5	4.9	25.7	—
XIV	Brown	70	320	C <sub>10</sub> H <sub>6</sub> N <sub>5</sub> O <sub>2</sub>	60.60	3.03	35.35	—	60.8	3.1	35.5	—
XVa	Dark brown	85	>300	C <sub>16</sub> H <sub>11</sub> N <sub>5</sub> O	66.43	3.80	24.22	—	66.6	3.7	24.6	—
XVb	Brown	90	195	C <sub>16</sub> H <sub>11</sub> N <sub>5</sub> S	62.95	3.60	22.95	—	62.8	3.7	23.0	—
XVc	Dark brown	92	>320	C <sub>16</sub> H <sub>12</sub> N <sub>6</sub>	66.66	4.16	29.16	—	66.8	4.4	29.2	—

\*All compounds are crystallized from DMF except compounds VII, VIII, X and XIII from ethanol.

XIII and XVa-c respectively (cf. Tables I and II).

The same reaction products could also be obtained by heating a solid mixture of the reactants in the presence of 2-3 drops of piperidine.

The same procedure is applicable for the reaction of I with IX to give VIII via another route.

#### Reactions with 3-amino-1,2,4-triazole

*Hydrolysis of XIa-c into XIIa-c and XIII into XIV: General procedures:*

A solution of each of XIa-c or XIII (1 gm) in ethanol (20 ml) was treated with conc. HCl (5 ml) and the reaction mixture was heated under reflux for 2 hours. The solid product obtained after cooling were filtered off, washed with water and the crystallized from the proper solvents to give XIIa-c and XIV respectively. (cf. Tables I and II).

#### Formation of the ylidene VII:

A solution of VI (0.01 mole) in absolute ethanol (20 ml) was treated with benzaldehyde (0.01 mole)

in the presence of 2-3 drops of triethylamine and the reaction mixture was heated under reflux for 2-3 hours. The solid product obtained after cooling was filtered off and crystallized from ethanol to give the ylidene derivative VII (Table I and II).

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Table II. Spectroscopic data of products listed in Table I

Compound	IR [cm <sup>-1</sup> ]	<sup>1</sup> H-NMR [ values]
IV	3350, 3300, 3250(NH <sub>2</sub> ); 1640(C = N) and 1600(C = C).	6.3(s, 1H, triazole H-5); 5.4(s, br, 4H, two-NH <sub>2</sub> ) and 7.1(s, 1H, aromatic).
VI	3300, 3220(NH <sub>2</sub> ); 1690(CO) and 1640(C = N).	2.5(s, 2H, CH <sub>2</sub> ); 6.3(s, 1H, triazole H-5) and 5.1(s, br, 2H, NH <sub>2</sub> ).
VII	3300, 3270(NH <sub>2</sub> ); 1680(CO); 1630(C = N) and 1600(C = C).	5.3(s, br, 2H, NH <sub>2</sub> ); 6.2(s, 1H, triazole H-5); 6.4(s, 1H, vinyl) and 7.1-7.5(s, 5H, Ar'H).
VIII	3370, 3280(NH <sub>2</sub> ); 2200(CN); 1640(C = N) and 1600(C = C).	5.2(s, br, 2H, NH <sub>2</sub> ); 6.3(s, 1H, triazole H-5) and 7.1-7.5(m, 5H, Ar'H).
Xa	3350(NH), 2220(CN); 1680(CO); 1640(C = N) and 1600(C = C)	2.8(d, 1H, CH); 3.0(d, 1H, CH); 6.3(s, 1H, triazole H-5) and 7.3-7.5(m, 6H, Ar'H and NH).
Xb	3350(NH), 2220(CN); 1640(C = N) and 1600(C = C).	2.9(d, 1H, CN); 3.1(d, 1H, CH); 6.3(s, 1H, triazole H-5) and 7.2-7.8(m, 6H, Ar'H and NH).
XIa	3350, 3270(NH <sub>2</sub> ); 2220(CN); 1690(CO); 1640(C = N) and 1600(C = C)	2.8(d, 1H, CH); 3.3(d, 1H, CH); 5.3(s, br, 2H, NH <sub>2</sub> ); 6.4(s, 1H, triazole H-5) and 7.1-7.5(m, 10H, Ar'H).
XIb	3340, 3270(NH <sub>2</sub> ); 2210(CN); 1690(CO); 1640(C = N); and 1600(C = C).	2.8(d, 1H, CH); 3.2(d, 1H, CH); 3.5(s, 3H, CH <sub>3</sub> ); 5.3(s, br, 2H, NH <sub>2</sub> ); 6.5(s, 1H, triazole H-5) and 7.1-7.5(m, 9H, Ar'H).
XIc	3380, 3270(NH <sub>2</sub> ); 2220(CN); 1680(CO); 1630(C = N) and 1600(C = C).	2.7(d, 1H, CH); 3.0(d, 1H, CH); 5.2(s, br, 2H, NH <sub>2</sub> ); 5.4(s, 1H, triazole H-5) and 7.3-7.8(m, 9H, Ar'H).
XIIa	3350, 3270(NH <sub>2</sub> ); 2220(CN); 1640(C = N) and 1600(C = C).	2.8(d, 1H, CH); 3.1(d, 1H, CH); 6.3(s, 1H, triazole H-5) and 7.1-7.6(m, 10H, Ar'H).
XIIb	3350, 3280(NH <sub>2</sub> ); 2220(CN); 1630(C = N) and 1600(C = C).	2.8(d, 1H, CH); 3.0(d, 1H, CH); 3.4(s, 3H, CH <sub>3</sub> ); 6.4(s, 1H, triazole H-5) and 7.3-7.7(m, 9H, Ar'H).
XIIc	3370, 3280(NH <sub>2</sub> ); 2220(CN); 1640(C = N) and 1600(C = C).	2.7(d, 1H, CH); 3.1(d, 1H, CH); 6.4(s, 1H, triazole H-5) and 7.3-7.7(m, 9H, Ar'H).
XIII	3350, 3270(NH <sub>2</sub> ); 2220(CN); 1735(CO) and 1630(C = N).	1.3(t, 3H, CH <sub>3</sub> ); 2.8(d, 1H, CH); 3.0(d, 1H, CH); 4.2(q, 2H, CH <sub>2</sub> CH <sub>3</sub> ); 5.3(s, br, 2H, NH <sub>2</sub> ); 6.4(s, 1H, triazole H-5); 6.5(q, 1H, furan H-3); 6.8(q, 1H, furan H-4) and 7.4(dd, 1H, furan H-5).
XIV	3300(NH); 2220(CN); 1680(CO) and 1620(C = N)	2.8(d, 1H, CH); 3.0(d, 1H, CH); 6.4(s, 1H, triazole H-5); 6.5(q, 1H, furan H-3); 6.8(q, 1H, furan H-4); 7.4(dd, 1H, furan H-5) and 8.2(s, 1H, NH).
XVa	2220(CN) and 1640(C = N)	2.8(d, 1H, CH); 3.2(d, 1H, CH); 6.4(s, 1H, triazole H-5); 6.5(q, 1H, furan H-3); 6.8(q, 1H, furan H-4) and 7.3-8.0(m, 6H, Ar'H and furan H-5).
XVb	2200(CN) and 1640(C = N)	2.8(d, 1H, CH); 3.1(d, 1H, CH); 6.4(s, 1H, triazole H-5) and 6.9-8.2(m, 8H, Ar'H and thiophene H-5).
XVc	3370(NH); 2200(CN) and 1640(C = N).	2.8(d, 1H, CH); 3.0(d, H, CH); 6.1(d, 1H, pyrrole H-3); 6.3(s, 1H, pyrrole H-4); 6.4(s, 1H, triazole H-5); 6.6(d, 1H, pyrrole H-5) and 7.3-7.9(m, 6H, Ar'H and NH).