Synthesis of N-(Azolyl)α-Ketohydrazidoyl Chlorides, Azolotriazole and Azolotriazine Derivatives

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Summary: 4-Nitro-3-phenyl-5-pyrazol-5-yl diazonium chloride (2) was coupled with different active methylene reagents such as malononitrile, benzoyl-acetonitrile, phenacylthiocyanate and ethyl α-chloroacetoacetate in ethanol solution to give the corresponding coupling products of pyrazolo [1,5-c]-as-triazines (3 and 4), pyrazol-5-ylhydrazone (5) and N-(pyrazol-5-yl)- α-ethoxycarbonylhydrazidoyl chloride (6) derivatives respectively. Also 2-amino-4-methyl-5-ethoxycarbonylthiazole (9) was diazotized to diazonium sulphate (10) and then coupled with acetoacetanilide, acetylacetone, 2-iminobutyronitrile, cyanoacetanilide, α-chloroacetylacetone and ethyl α-chloroacetoacetate to give thiazol-2-ylhydrazones (11 and 12), thiazolo [2,3-c]-as-triazines (13 and 14), N(thiazol-2-yl)-α-acetylhydrazidoyl chloride (15) and N-(Thiazol-2-yl)-α - ethoxycarbonylhydrazidoyl chloride (16) derivatives respectively. On the other hands, compounds (6) and (15) could be cyclized to pyrazolo [1,5-c]-1,2,4-triazole (7) and thiazolo [2,3-c]-1,2,4- triazole (18) via treatment with benzene/triethylamine solution. Also these compounds were reacted with potasium cyanide solution to give pyrazolo [1,5-c]-as-triazine (8) and thiazolo [2,3-c]-as-triazine (17) respectively.

Introduction

Arylhydrazones and heterocyclic hydrazones are versatile reagents and their chemistry has recently received considerable attention [1-6]. In continuation to this work, it seemed desirable to synthesise heterocyclic hydrazones in order to establish their chemical and biological activities [4-5]. Our previous attempts at preparing such compounds via coupling of diazotized 3-phenyl-5-aminopyrazole with active methylene compounds have led to either the formation of pyrazolo [1,5-c]-as-triazines or to the formation of acyclic hydrazones which spontaneously cyclized to pyrazolo [1,5-c]-as-triazines under the variety of reaction conditions [7-9]. The aim of the present work is to investigate the reactions of other diazotized amino-azoles, in addition to study the effect of introducing a nitro group into the pyrazole ring. Thus, diazotization of 5-amino-3-phenyl-4-nitropyrazole (1) by the action of nitrous acid, afforded 3-phenyl-4-nitropyrazol-5-yl diazonium chloride (2) which coupled with malononitrile and with benzoylacetonitrile to yield the corresponding pyrazolo [1,5-c]-as-triazine derivatives (3 and 4) respectively. These results are in contrast to previously reported observations [10], where the acyclic hydrazones were isolated. In this case the nitro group encourages the cyclization proceeds through withdrawing the electrons from the pyrazole ring i.e., the proton in position (1) becomes more acidic. The loss of this proton leaves behind a stabilized ion on the nitrogen at (1). The structure of compounds 3 and 4 were assigned on the basis of the elemental analysis and spectra data.

Also, diazonium chloride (2) could be coupled with phenacylthiocyanate to give the corresponding acyclic hydrazone (5). The formation of hydrazone (5) is assumed to be the usual coupling reaction in contrast to previous results [10].

In continuation of this work we report here a novel synthesis of some pyrazolo [1,5-c]-1,2,4-triazoles and pyrazolo[1,5-c]-as-triazines. Thus, coupling of diazonium chloride (2) with ethyl α-chloroacetoacetate has afforded the corresponding hydrazidoyl chlorides (6). The formation of (6) is assumed to proceed via coupling with the active hydrogen of methylene group followed by acyl group cleavage. The hydrazidoyl chloride structure (6) was suggested on the basis of the elemental analysis and spectral data. Compound (6) was cyclized into the pyrazolo [1,5-c]-1,2,4-triazole derivative (7) upon treatment with triethylamine/benzene solution. In order to explore the synthetic poten-

tialities of compound 6 as intermediate for the preparation of pyrazolo [1,5-c]-as-triazines, the reaction of (6) with a variety of reagents was performed. Thus, treatment of (6) with potassium cyanide in ethanolic aqueous medium has afforded the pyrazolo[1,5-c]-as-triazine derivative (8). Attempts to isolate acyclic product from this reaction were unsuccessful. The structure of compound (8) was established on the basis of the elemental analysis and spectral data (cf. chart 1).

In continuation to this work, 2-amino-5-ethoxycarbonyl-4-methylthiazole (9) could be diazotized in presence of sulphuric acid. The diazonium sulphate (10) could be successfully coupled with variety of active hydrogen reagents. It has been found that (10) reacts with β-diketo compounds such as acetoacetanilide and acetylacetone to yield the corresponding hydrazone (11 and 12) respectively. Also compound (10) reacts with activated nitrile compounds such as 3-

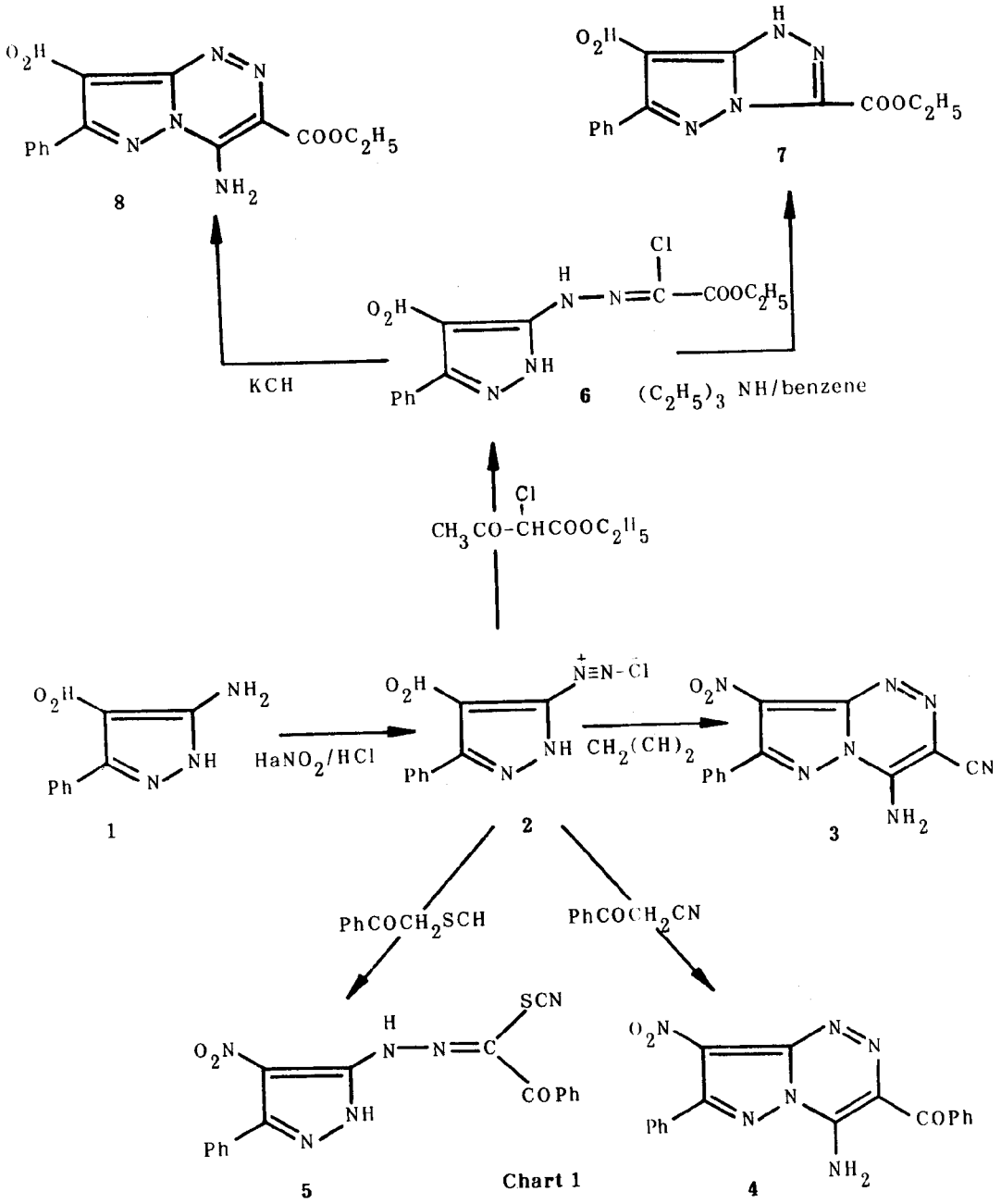

Chart 1

aminobutyronitrile and cyanoacetanilide to yield the respective thiazolo [2,3-c]-as-triazine derivatives (13 and 14) respectively. It has been shown that coupling reactions with β-diketo-compounds lead to the acyclic hydrazones (11) and (12), whereas β-keto-nitrile derivatives produce the cyclic products (13) and (14). The attempts to separate the acyclic hydrazones were unsuccessful. In clarification for the direct production of the cyclic compounds, it is assumed that the tautomeric structures (A) of the acyclic intermediate hydrazones help the cyclization process. The structures were suggested on the basis of the analytical and spectral data.

As an extention of our work an investigation of the coupling reaction of (10) with α-acetylacetore and ethyl α-chloroacetoacetate was undertaken. It has been found that, compound (10) reacts with α- chloroacetylacetone and ethyl α-chloroacetoacetate to yield the hydrazidoyl chloride derivatives (15 and 16) respectively. The synthetic potentialities of compounds (15) and (16) as intermediates for the preparation of thiazolo[2,3-a]-as-triazine and thiazolo[2,3a]-1,2,4-triazole derivatives, via reaction of (15) and (16) with different reagent have been investigated. Thus treatment of (15) with potassium cyanide in aqueous ethanolic solution has afforded the thiazolo [2,3-a]-as-triazine derivative (17), the reaction proceeding via a nucleophilic substitution reaction followed by the cyclization. Also it has been shown that cyclization of (15) in triethylamine/dry benzene solution yielded the corresponding thiazolo [2,3-a]-1,2,4- triazole derivative (18). It is clear that, the cyclization of (15) in a basic medium takes place via elimination of hydrogen chloride. The structures of compounds (17) and (18) were assigned on the basis of the analytical and spectral data (cf. chart 2).

Experimental

All melting points are uncorrected. IR spectra were recorded (KBr) on a Pye Unicam sp-1100 spectrophotometer. Elemental analysis has been carried out by the Microanalytical data unit at Cairo University.

Diazoltization of 5-Amino-3-phenyl-4-nitropyrazole (1):

A suspension of 5-Amino-3-phenyl-4-nitropyrazole (0.01 mole) in conc. Hydrochloric acid (4 ml) was heated at 100°C for 3 minutes and then cooled to 0°C. A solution of sodium nitrite (0.01 mole) in water (3 ml) was added dropwise with continuous stirring for 15 minutes to give the diazonium salt (2).

Coupling of diazotized (1) with different coupling reagents:

A suspension of diazotized (1) (0.01 mole, prepared as described before), was gradually added to a cold solution (0-5°C) of each of malononitrile, benzoylacetonitrile and phenacylthiocyanate (0.01 mole) in ethanol (20 ml) containing anhydrous sodium acetate (0.015 mole) with continous stirring for 30 minutes. The resulting reaction product was filtered off, washed with water and crystallized from the proper solvent to give the coupling products (3,4) and (5) respectively (cf. Tables 1-2).

Preparation of 4-nitro-3-phenylpyrazol-5-yl hydrazidoyl chloride (6):

A solution of the ethyl α-chloroacetoacetate (0.01 mole) in ethanol (100 ml) was treated with a solution of anhydrous sodium acetate (3.5 gm) in water (10 ml). The reaction mixture was transferred to an ice-bath (0-5°C). To this solution was added a solution of diazotized (1) (0.1 mole), prepared as previously described, dropwise over 30 minutes, the reaction mixture was stirred for an additional 2 hrs and the solid product, so formed, was collected by filtration and recystallized from ethanol to give the hydrazidoyl chloride (6) (cf. Tables 1-2).

Diazotization of 2-Amino-4-(ethoxycarbonyl)-5-methylthiazole (9):

Compound 2-Amino-4-ethoxycarbonyl-5-methylthiazole (0.01 mole) was transferred to dry beaker then cooled to 0°C. To this solid was added conc. sulphuric acid (1.5 ml) drop by drop with continous stirring, then added followed addition of ice (5 gm), followed by solution of sodium nitrite (10 ml, 0.01 mole) dropwise over 15 minutes with continous stirring to give the diazonium sulphate (10).

Coupling of diazotized (9) with different active methylene reagents:

A suspension of diazotized (9) (0.01 mole), prepared as described previously, was gradually added to a cold solution (0-5°C) of each of

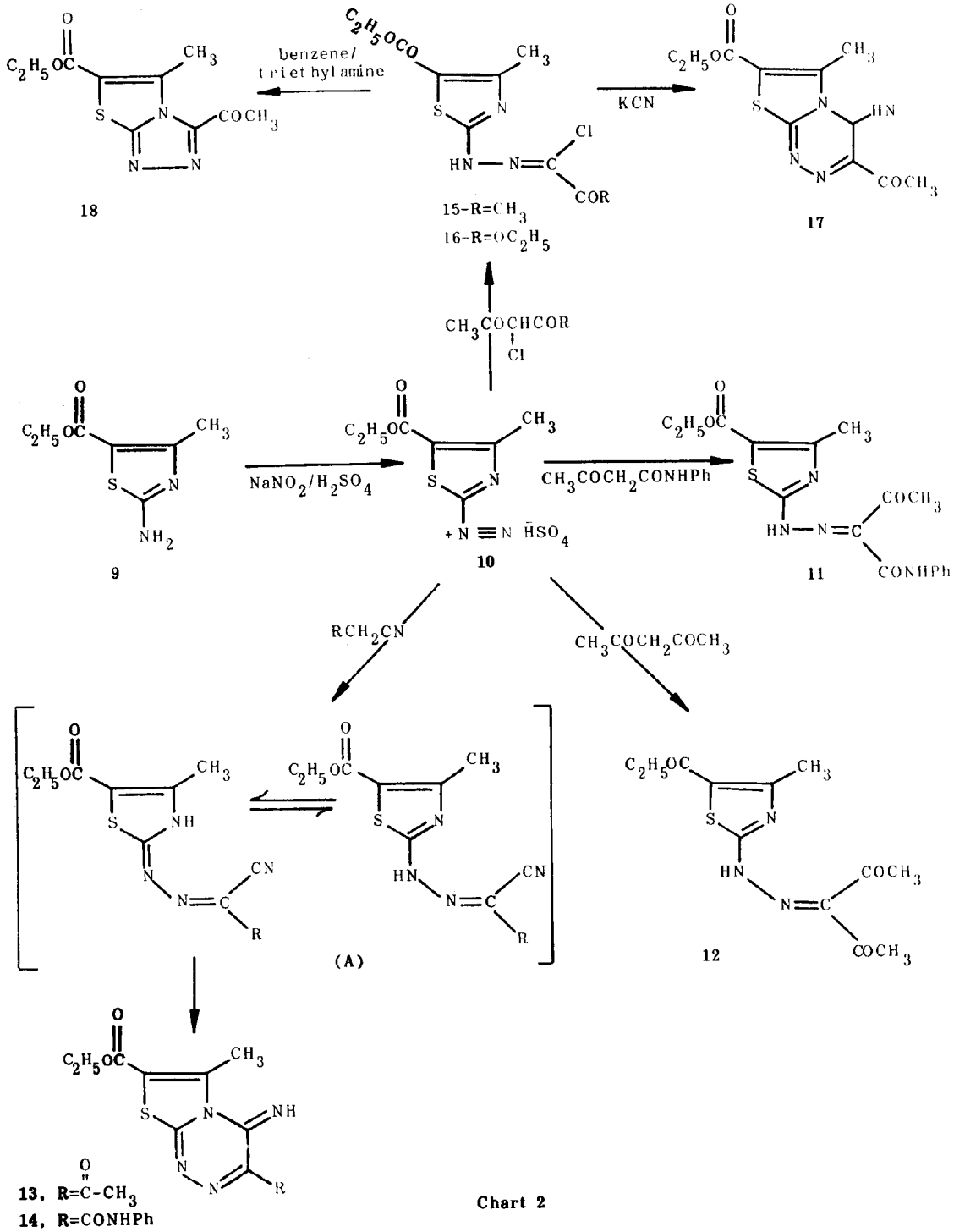
benzene/
triethylamine
KCN
NaNO2/H2SO4
CH3COCH2CONHPh
RCH2CN
CH3COCH2COCH3
CH3COCHCOR
Cl
18
15-R=CH3
16-R=OC2H5
17
9
10
11
12
(A)
13, R=C-CH3
14, R=CONHPh

Chart 2

Table 1: List of New Compounds

Compd. No.	M.p. °C	Yield %	Solvent for Recrystal	M.Formula and (M. Weight)	Found / Calcd. C	H	Analysis % N	Cl	S
3	>260	65	EtOH	$C_{12}H_7N_7O_2$	51.0	2.3	34.6	...	...
				(281)	51.2	2.5	34.9	...	...
4	226	70	EtOH	$C_{18}H_{12}N_6O_3$	60.1	3.1	23.0	...	...
				(360)	60.0	3.3	23.3	...	...
5	115	50	EtOH	$C_{18}H_{12}N_6O_3S$	62.6	3.4	24.2	...	9.1
				(344)	62.8	3.5	24.4	...	9.3
6	158	55	EtOH	$C_{13}H_{12}N_5O_4Cl$	46.0	3.4	20.7	10.4	...
				(337.5)	46.2	3.5	20.7	10.5	...
7	>260	75	Ben./Pet.	$C_{13}H_{11}N_5O_4$	51.6	3.6	23.1	...	...
				(301)	51.8	3.6	23.2	...	...
8	186	62	EtOH	$C_{14}H_{12}N_6O_4$	51.1	3.5	25.4	...	...
				(328)	51.2	3.6	25.6	...	...
11	143	65	EtOH	$C_{17}H_{18}N_4O_4S$	54.2	4.7	14.6	...	8.4
				(374)	54.5	4.8	14.9	...	8.5
12	110	60	EtOH	$C_{12}H_{15}N_3O_4S$	48.2	4.9	14.0	...	10.6
				(297)	48.5	5.0	14.1	...	10.8
13	230	70	EtOH	$C_{11}H_{13}N_5O_2S$	47.1	4.5	24.8	...	11.3
				(279)	47.3	4.6	25.1	...	11.5
14	>260	66	EtOH	$C_{16}H_{15}N_5O_3S$	53.7	4.1	16.5	...	8.8
				(357)	53.8	4.2	16.7	...	8.9
15	145	67	EtOH	$C_{10}H_{12}N_3O_3ClS$	41.3	3.9	14.3	12.1	11.1
				(289.5)	41.4	4.1	14.5	12.2	11.0
16	150	63	EtOH	$C_{11}H_{14}N_3O_4ClS$	41.1	4.2	13.0	10.9	9.8
				(319.5)	41.3	4.4	13.1	11.1	10.0
				(280)	47.1	4.3	20.0	...	11.4
18	>260	65	Ben./ pet.	$C_{10}H_{11}N_3O_3S$ (253)	47.3	4.1	16.7	...	12.5
					47.4	4.3	16.6	...	12.6

acetoacetanilide, acetylacetone, 3-iminobutyronitrile and cyanoacetanilide (0.01 mole) in ethanol (20 ml) containing anhydrous sodium acetate (0.015 mole) with continous stirring for 3 hrs. The resulting reaction product was increased with dilution or with an added dilute solution of ammonia (15%), the product was collected by filtration and recrystallized from the appropriate solvent to give the coupled products (11, 12, 13) and (14) respectively (cf. Tables 1-2)/

Preparation of 4-ethoxycarbonyl-5-methylthiazol-2-yl hydrazidoyl chlorides (15 and 16):

A solution of α-choroacetylacetone or ethyl α-chloroacetoacetate (0.4 mole) in ethanol (100 ml) was treated with anhydrous sodium acetate (13.5 gm) and then cooled (0- 5°C). To this solution was added dropwise a solution of diazotized (9) (0.1 mole) (prepared as described before), over 30 minutes with continuous stirring for 2 hrs and the

Table 2: List of IR Data of Prepared Compounds

Compound No.	cm^{-1} (ν) max (selected band)
3	1605 (C=N), 2210(C=N), 3100-3200(NH_2).
4	1600(C=N), 1720(C=O), 3140-3300(NH_2).
5	1620(C=N), 1720(C=O), 2220(SCN), 3100-3300(NH).
6	1610(C=N), 1660(C=O), 2900-3200 (CH_3CH_2, NH).
7	1600(C=N), 1665(C=O), 2900-3150(CH_3CH_2,NH).
8	1605(C=N), 1660(3 C=O), 2900(CH_3), 3100-3300(NH).
11	1710, 1680, 1660(3 C=O), 2900(CH_3), 3100-3300(NH).
12	1710, 1690, 1660(3 C=O), 2900-3000(CH_3) 3100-3400(NH).
13	1660(C=O), 2900-3000(CH_3), 3100-3250(NH).
14	1685, 1660(2 C=O), 2900-3050(CH_3), 3150-3400(NH).
15	1700, 1665(2 C=O), 2900(CH_3), 3100-3300(NH)
16	1660(2C=O), 2900(CH_3), 3000-3200(NH)
17	1700, 1660(2C=O), 2900(CH_3), 3100-3300(NH).
18	1710, 1665(2 C=O), 2900-3050(CH_3).

solid product, so formed, was collected by filtration and recrystallized from ethanol to give the thiazolyl hydrazidoyl chloride derivatives (15) and (16) respectively (cf. Tables 1-2).

Cyclization of hydrazidoyl chloride derivatives (6 and 15):

A suspension of each of (6) or (15) (1 gm) in dry benzene (20 ml) was treated with triethylamine (1 ml). The reaction mixture was refluxed for 3 hrs. The solution was then removed *in vacuo*. The remaining solid product was washed with petroleum ether (60/80) and collected by filtration. The solid product was recrystallized from the proper solvent to give fused triazole derivatives (7 and 18) respectively (cf. Tables 1-2).

Reaction of hydrazidoyl chlorides (6) and (15) with potassium cyanide:

A solution of each of (6) or (15) (0.01 mole) in ethanol (20 ml) was treated with a solution of potassium cyanide (0.03 mole) in water (5 ml). The reaction mixture was triturated with water-ice. The solid products, so formed, were collected by filtration and recrystallized from the appropriate solvent to give fused triazines derivatives (8) and (17) respectively (cf. Tables 1-2).

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