REACTION OF DIKETENE WITH 3-AMINO-5,6-DISUBSTITUTED-1,2,4-TRIAZINE DERIVATIVES [1]

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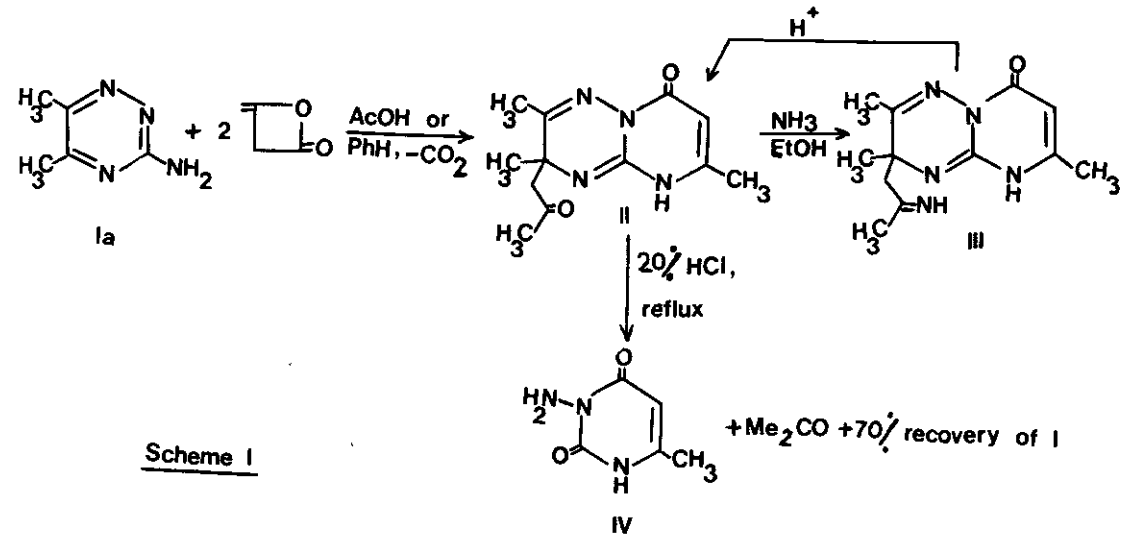
Abstract- Reaction of diketene with 3-amino-5,6-dimethyl-1,2,4-triazine (Ia) in acetic acid or benzene medium afforded 3-acetonyl-2,3,6-trimethyl-3H-pyrimido-[1,2-b]-1,2,4-triazin-8(5H)-one (II). On the other hand, reaction of diketene with 3-amino-5,6-diphenyl-1,2,4-triazine (Ib) gave rise to 3-acetoacetylamino-5,6-diphenyl-1,2,4-triazine (V) and 3-(3-acetyl-4-hydroxy-6-methylpyridin-2-one-1-yl)-5,6-diphenyl-1,2,4-triazine (VI), respectively. The reaction mechanism is discussed.

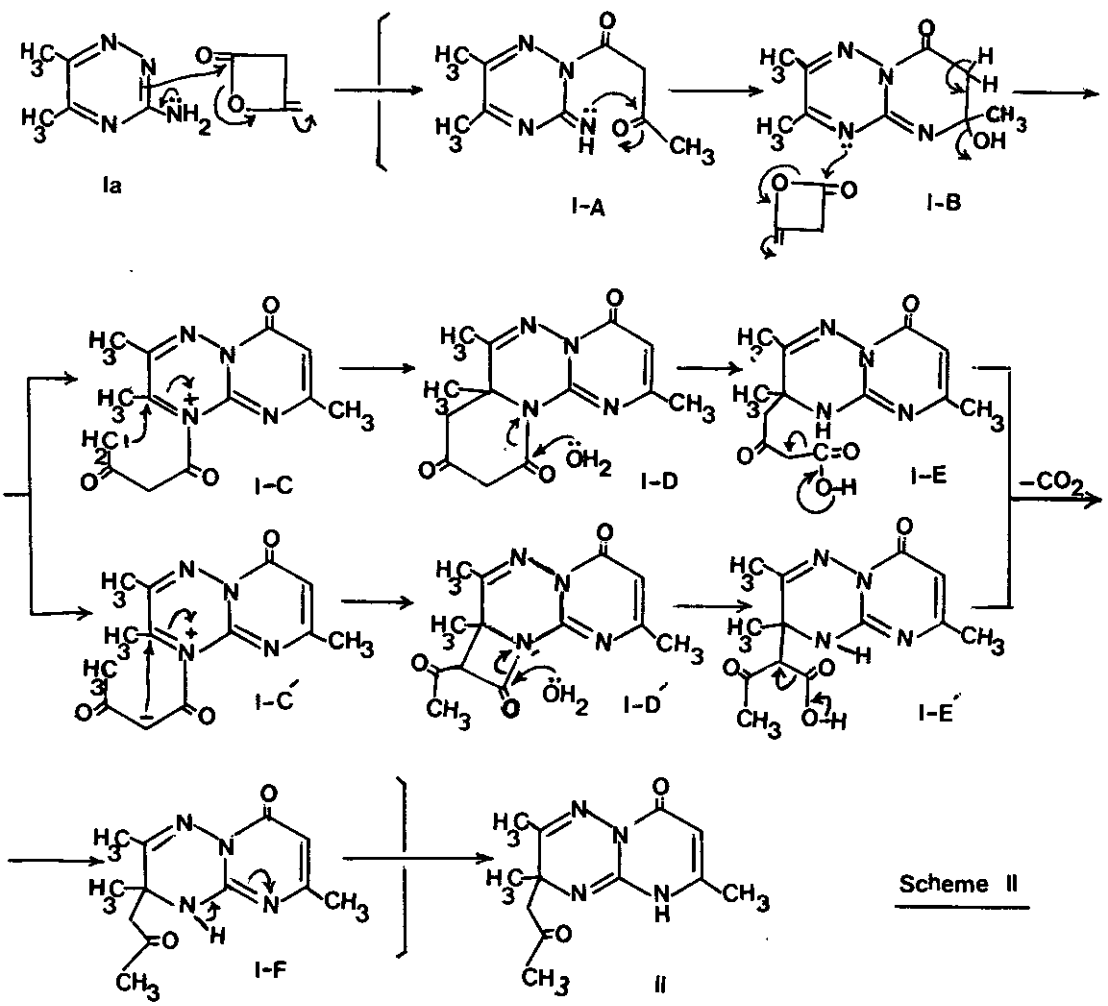
Reaction of diketene with 2-amino derivatives of N-heterocycles, such as 2-aminopyridine and 2-aminobenzoxazole, have been reported to give the corresponding N-acetoacetyl derivatives or cyclic compounds, respectively. In these reactions, diketene was considered to act as an acetoacetylating agent, which on further cyclization, the desired compounds were obtained [2,3]. In this paper we wish to report a new type of the reactivity of diketene toward 3-amino-1,2,4-triazine derivatives, substituted at 5 and 6 positions. When diketene was allowed to react with 3-amino-5,6-dimethyl-1,2,4-triazine (Ia) in acetic acid or benzene under reflux,the reaction proceeded with rapid evolution of carbon dioxide. After ceasing the evolution of carbon dioxide, the reaction product was purified by recrystallization from acetone. On the basis of elemental analysis and spectral data, the structure of the product was assigned as 3-acetonyl-2,3,6-trimethyl-3H-pyrimido[1,2-b]-1,2,4-triazin-8(5H)-one (II). Compound II showed a good stability toward hydrogenation and mild acid hydrolysis. Acid hydrolysis of this compound with 20% hydrochloric acid for 18 h resulted in the recovery of 70% of starting material. From the remaining aqueous solution, the uracil derivative III and acetone were identified. Identification of these compounds was an approval for the structure of compound II . Ammonolysis of compound II resulted in the formation of the imino derivative (IV), which on acid hydrolysis turned to compound II. Basic hydrolysis of compound II resulted in the ring rupturing (Scheme I).

As shown in scheme I, this reaction proceeded through involvement of two moles of diketene and one mole of amino derivative, followed by decarboxylation. The reaction mechanism is suggested as shown in Scheme II.

Reaction of 3-amino-5,6-diphenyl-1,2,4-triazine (Ib) with diketene did not proceed in the same

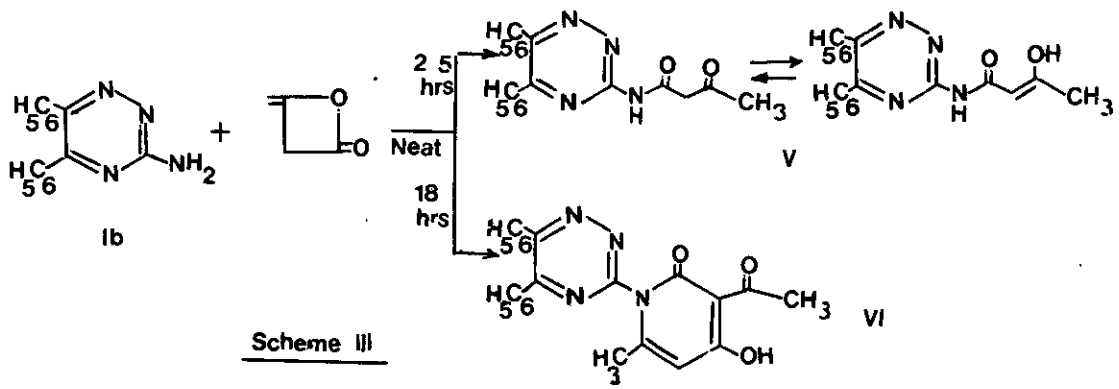


Scheme I



Scheme II

condition as above. The reaction was tried in neat condition at room temperature for 2.5 and 18 h . The reaction product (V), of the first run, was purified by recrystallization from benzene, and the product(VI),from the second run, was purified from acetone. On the basis of elemental analyses and spectral data, the structure of compounds V and VI were assigned as 3-acetoacetylamino-5,6-diphenyl-1,2,4-triazine (V) and 3-(3-acetyl-4-hydroxy-6-methyl-2-oxo-1H-pyridin-1-yl)-5,6-diphenyl-1,2,4-triazine (VI), respectively (Scheme III).



Scheme III

EXPERIMENTAL

Melting points were determined on a Kofler hot stage microscope and are uncorrected. The NMR spectra were obtained from a Varian T-60 spectrometer, and chemical shifts (δ) are in ppm relative to tetramethylsilane as an internal standard. IR spectra were obtained from a Unicam SP 1000 infrared spectrometer. Mass spectra were determined on a Varian Model Mat CH5 instrument.

Reaction of diketene with 3-amino-5,6-dimethyl-1,2,4-triazine (Ia). (a)- A mixture of compound (Ia) (1 g, 0.008 mol) and diketene (1.35 g, 0.016 mol) in benzene (10 ml) was refluxed for 1 h . The reaction proceeded with evolution of carbon dioxide. After cooling, the crystals obtained were filtered, and purified by recrystallization from acetone to give 0.48 g (24%) of II as colorless prisms, mp 225°C decomp. . Anal. calcd. for $C_{12}H_{16}N_4O_2$ (II): C, 58.05 ; H, 6.50 ; N, 22.57. Found : C, 57.93 ; H, 6.44 ; N, 22.62. IR ($CHCl_3$)cm^{-1} : 3400, 2900, 1700 (shoulder), 1680. NMR ($CDCl_3$) ppm : 1.53 (3H, s), 2.09 (3H, s), 2.20 (6H, s,2 methyl group), 5.22-5.75 (1H, b, exchanged with D_2O), 5.80 (1H, s). Mass: m/e M^+ : 248.

(b)- A mixture of Ia (2 g, 0.016 mol) and diketene (2.7 g, 0.032 mol) in glacial acetic acid (10 ml) was heated at 85-95° C for 1.5 h.The solvent was evaporated in vacuo, and the residue was dissolved in chloroform and submitted to silicagel column chromatography, using chloroform as an eluent. The first fraction was collected, and after condensing in vacuo, the crystals obtained were purified by recrystallization from acetone to give colorless prisms (1.2 g, 30%), mp 225° C (decomposed).The physical and spectral properties of the product was identical in every respect with that of compound II, obtained from the first run.

Ammonolysis of compound II- A mixture of compound II (0.5 g, 0.002 mol) and 28% aqueous ammonia solution (15 ml) in ethanol (15 ml) was heated in a sealed tube at 80-85° C for 5 h . After cooling, the reaction mixture was condensed under reduced pressure, and the residue was dissolved in chloroform and submitted to alumina column chromatography, using petroleum ether and chloroform as eluents. The chloroform fraction was condensed under reduced pressure, and the solid obtained was purified by recrystallization from acetonitril to give colorless needles (0.2 g, 40%) , mp 190° C (decomposed). Anal. Calcd. for $C_{12}H_{17}N_5O$ (IV) : C, 58.28 ; H, 6.93; N, 28.32. Found : C, 58.21 ; H, 6.97 ; N, 27.95. IR (KBr) cm^{-1} : 3400, 3120 , 2900, 1670, 1640. NMR (DMSO-D_6) ppm : 1.21 (3H, s), 1.33 (3H, s), 1.80 (3H, s), 1.97 (3H, s), 2.74 (2H, s), 5.48 (1H, s), 7.16 (1H, s), 7.68 (1H, s, exchanged with D_2O). Mass m/e M^+ : 247 .

Acid hydrolysis of compound IV - A mixture of compound IV (0.1 g, 0.0004 mol) and 5% HCl (5 ml) was refluxed for 30 min . After cooling, the reaction mixture was extracted with chloroform . The chloroform layer was condensed under reduced pressure. The crystals obtained were purified by recrystallization from acetone to yield prisms (0.07 g, 70%) , mp 225° C (decomposed) . The properties of the product were identical in every respect with those of compound II.

Acid hydrolysis of compound II - A mixture of compound II (0.9 g, 0.018 mol) in 20% HCl (10 ml) was refluxed for 18 h . The reaction mixture was partly distilled. From the distilate acetone was identified through its 2,4-dinitrophenylhydrazone derivative. The remaining was cooled, extracted with chloroform (50 ml).The chloroform layer was dried over sodium sulfate, and condensed under reduced pressure to recover 0.63 g (70%) of the starting II. The aqueous layer was neutrallized with 20% NaOH, and extracted with chloroform (50ml). The extract was condensed under reduced pressure to give 0.13 g of colorless prisms of mp 275-277° C.The structure of this compound was assigned as 3-amino-6-methyluracil (III), which was physically and spectroscopically identical with the reference compound [4].

Reaction of 3-amino-5,6-diphenyl-1,2,4-triazine (Ib) with diketene - (a)- A mixture of compound Ib (0.5 g, 0.002 mol) and diketene (2.52 g, 0.03 mol) was stirred at room temperature for 2.5 h. . The excess of diketene was evaporated under reduced pressure. The oily residue was rubbed with petroleum ether to get yellow crystals, which were purified by recrystallization from benzene to yellow needles (0.45 g, 67%) , mp 148-149° C . Anal. calcd. for $C_{19}H_{16}N_4O_2$ (V) : C, 68.67, H, 4.81; N, 16.86. Found : C, 68.73; H, 4.69; N, 16.73. IR ($CHCl_3$) cm^{-1} : 3400, 3000, 1720, 1690, 1620. NMR ($CDCl_3$) ppm : 2.04 (=C(OH)Me, s), 2.26 ($-CO-Me$, s), 4.11 ($-CO-CH_2-CO-$, s), 6.38 ($-CO-\underline{CH}=C(OH)-$, s), 7.35 (10H, ring), 9.50 (1H, NH, bs), 13.75 (=C(OH) , s). Mass m/e M^+ : 332.

(b)- A mixture of compound Ib (0.5 g, 0.002 mol) and diketene (2.52 g, 0.03 mol) was stirred at room temperature for 18 h . The excess of diketene was removed under reduced pressure. The remaining oily residue was extracted with hot benzene (3 times, 20 ml). The extract was partially condensed, from which yellow needles were separated. The crystals obtained were purified by recrystallization from acetone to yellow needles (0.125g , 16%),. mp 222-223° C . Anal. calcd. for $C_{23}H_{18}N_4O_3$: C, 69.34; H, 4.52; N, 14.07. Found C, 69.51; H, 4.50; N, 13.95. IR ($CHCl_3$) cm^{-1} : 2970, 1715, 1700 (shoulder), 1660, 1615. NMR ($CDCl_3$) ppm : 2.13 (3H, s), 2.68 (3H, s), 6.02 (1H, s), 7.33-7.72 (10H, ring), 15.95 (1H, b). Mass m/e M^+ : 398.

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