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SYNTHESIS OF NOVEL HETEROCYCLIC SYSTEM 4H-IMIDAZO [2, 1-b] PYRIDO [2,3-e] [1, 3, 4] THIADIAZINE

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Abstract

Diazotization of 3-amino-2-chloro pyridine (**3**) in the presence of dithizone (**5**) gave 4-phenyl-2-phenylazo-4H-pyrido [3,2-e] [1,3,4] thiadiazine (**6**). Reaction of 2-chloro-3-nitropyridine (**2, G=H**) with (**5**) afforded 4-phenyl -2-phenylazo -4H-pyrido [2,3-e] [1,3,4] thiadiazine (**7**). Reduction of the latter with H_2 gas in the presence of Raney nickel gave the corresponding amino derivative (**12**). One pot condensation and cyclization of the latter with phenacyl bromide gave a novel heterocyclic system (**13**).

Introduction

The synthesis and reactions of 4H-1,3,4-benzothiadiazine [1-3], pyridothiadiazine [4], pyrimidothiadiazine [4] and 1,2,4-triazinothiadiazine [5, 6] have been of recent interest to a number of research groups including our own [6,7].

A direct synthesis of 7-nitro-2-phenyl-4H-pyrido [3, 2-e] [1,3,4] thiadiazine (**4**) has been reported from condensation of benzothiohydrazide (**1**) with 2-chloro-3, 5-dinitropyridine (**2, G=NO_2**) in refluxing dimethylformamide [4]. The use of bidentate nucleophile and a pyridine ring with two neighbouring leaving groups to synthesis pyridothiadiazines is classical [4].

Here we wish to report a new approach for the synthesis of pyridothiadiazine. The synthesis of a new heterocyclic system 4H-imidazo [2,1-b] pyrido [2,3-e] [1,3,4] thiadiazine is also described.

Keywords: Benzothiadiazine; Imidazopyridothiadiazine; Pyridothiadiazine

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Results and Discussion

3-Amino-2-chloropyridine (**3**) was diazotized by a mixture of hydrochloric acid and sodium nitrite at -5°C. To this reaction mixture, dithizone (**5**) in chloroform was added to afford N'-phenyl - N'-(2-chloropyrido) -N-phenylazo-thiobenzoyl hydrazine (**8**). Compound (**8**) was refluxed in a mixture of triethylamine and acetonitrile to afford (**6**).

Reaction of benzothiohydrazide as a bidentate nucleophile with 2-chloro-3-nitropyridine (**2, G=H**) has already been reported [4]. One pot condensation and cyclization of (**2, G=H**) with dithizone (**5**) was achieved in refluxing acetonitrile. The product was identified as 4-phenyl-2-phenylazo 4H-pyrido [2,3-e] [1,3,4] thiadiazine (**7**).

Reaction of (**2, G=H**) with methyl-3-phenyl dithiocarbazate (**9**) and benzyl-3-phenyl dithiocarbazate (**10**) in a mixture of Et_3N/DMF gave the corresponding pyridothiadiazine (**11**, R=CH_3 and CH_2Ph) respectively. In

In both cases, the products are thought to arise via a Smiles rearrangement involving an S→N transfer of the nitrophenyl moiety prior to ring closure by sulphur. Such a rearrangement has been reported previously [3, 8].

We then directed our attention to the synthesis of a novel tricyclic compound derived from 1,3,4-thiadiazine. Compound **7** was reduced with hydrogen using Raney nickel as a catalyst to afford **12**. ^{1}H NMR of this compound showed a signal due to NH_2 at δ 4.5. FT-IR of (**12**) clearly showed two peaks characteristic of the NH_2 group at 3200 and 3300 cm^{-1}.

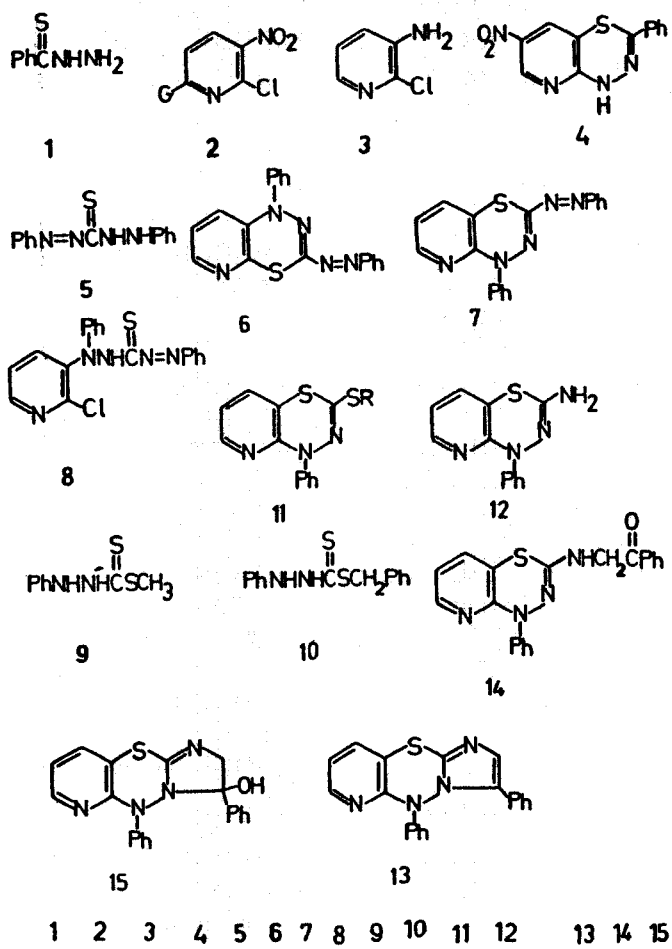
One pot condensation and cyclization of (**12**) occurred when it was reacted with phenacyl bromide. The product was identified as 3,5-diphenyl-4H-imidazo [2, 1-b] pyrido [2,3-e][1,3,4] thiadiazine (**13**) which is a novel heterocyclic system and is reported for the first time. Although we could not isolate the intermediate, it is now generally accepted that in most cases in heterocyclic compounds imino tautomers are present only in amounts too small to be detected [9]. Therefore, it is assumed that an amino group first attacks bromomethyl moiety to give intermediate (**14**). Cyclization involves the attack of nitrogen on carbonyl groups along with the subsequent dehydration and aromatization of another intermediate (**15**) to give (**13**). These patterns of condensation and cyclization have only recently been observed[10].

Experimental Section

The melting points are uncorrected and were obtained by a Kofler Huzbank Rechart type 7841 melting point apparatus. IR spectra were obtained on a 4300 Shimadzu spectrometer. The ^{1}H NMR spectra were recorded on a Varian 60 spectrometer, unless otherwise stated, using TMS as internal reference, and mass spectra were scanned on a Varian Mat CH-7 instrument at 70 eV.

1-N'-Phenyl 1-N' (2-chloro-3-pyridyl) 4-N-phenyl thiohydrocarbazide (8)

Compound **3** (1.28 g, 0.01 mol) was dissolved in conc. HCl (6 ml). To this solution sodium nitrite (0.69 g, 0.01 mol) in water (2 ml) was added at -5°C. The reaction mixture was stirred for 30 mins at 0°C. A solution of compound **5** (2.56 g, 0.01 mol) in chloroform (20 ml) was added to the above mixture. After 1 h, a solution of 10% sodium hydroxide (5 ml) was added. The solid was crystallized from acetone to afford the title compound



(40%), m.p. 197-198°C, IR (KBr disk): ν 3250, 1600, 1510, 805 cm^{-1}; ^1H NMR ($CDCl_3$): δ 6.8-8.1 (m, 13H, Ph, pyridines' protons), 9.3 (bs, 1H, NH); MS: m/z 367 (M^+).

4-Phenyl-2-phenylazo-4H-pyrido [3,2-e] 1, 3, 4-thiadiazine (6)

Compound **8** (0.64 g, 0.005 mol) was refluxed in a mixture of acetonitrile (20 ml) and triethylamine (4 ml) for 5 h. The reaction mixture was cooled down to room temperature, the precipitated solid was filtered off and washed with water to afford 0.37 g (65%) of the title compound, m.p. 148-150°C. MS: m/z 331 (M^+). UV ($CHCl_3$) λ max= 325 nm.

4-Phenyl-2-phenylazo-4H-pyrido [2,3-e] 1,3,4 thiadiazine (7)

Compound (**2, G=H**), (1.58 g, 0.01 mol) and 5 (2.56g, 0.01 mol) were refluxed in a mixture of acetonitrile (40 ml) and triethylamine (10 ml) for 2 h. The reaction mixture was cooled down to room temperature. The precipitated solid was filtered off, washed with water and crystallized from EtOH to give 2.5 g (75%) of the title compound, m. p. 164-165°C, ^1H NMR δ ($CDCl_3$), 6.4, 7.4 (m, 10H), 7.7 (m, 3H), MS: m/z M^+ 331. UV ($CHCl_3$), λ max = 322 nm.

2-Amino-4-phenyl-4H-pyrido[2,3-e]1,3,4-thiadiazine (12)

Compound **7** (1 g, 0.003 mol) was dissolved in MeOH. To this solution, Raney nickel (0.2 g) was added. This mixture was placed in an hydrogenation apparatus under pressure of hydrogen gas (3 atm. and temperature of 50°C for 6 h). The reaction mixture was filtered off. The filtrate was evaporated and the residue was crystallized from benzene-pet ether (b. p. 80-100) to afford the title compound, 0.37 g (50%), m.p. 200-202°C; FTIR ν (KBr disk); 3300, 3190, 1610, 1558 cm^{-1}; ^1H NMR, δ (80 MHZ), 4.5 (bs, 2H, NH_2 exchangeable with D_2O), 6.7-7.6 (m, 8H, aromatic), M.S: m/z M^+242. MS=m/z 242 (M^+).

3,5-Diphenyl-imidizo [2,1-b] pyrido [2,3-e] 1,3,4-thiadiazine (13)

Compound **12** (0.2 g, 0.0082 mol) and phenacyl bromide (0.163 g, 0.0082 mol) was refluxed in EtOH for 24 h. To this solution, water (1ml) was added. The solid which was precipitated was filtered off, dried and crystallized from benzene-pet ether (b.p. 80-100) to give 0.13 g (45%) of **13**; m.p. 230-233°C, FTIR, ν (KBr disk), 3100, 1580, 01510 cm^{-1}; ^1H NMR, δ (80 MHZ, CD_3OD), 6.8-7.9 (m). MS: m/z 342 (M^+).

2-Methylmercapto-4-phenyl-4H pyrido [2,3-e] 1,3,4 - thiadiazine (11, R=Me)

Compound (**2, G=H**), (1.58 g, 0.01 mol), and methyl-3-phenyldithiocarbazate (**9**) (1.98 g, 0.01 mol) were dissolved in a mixture of DMF (10 ml) and triethylamine (2 ml). The reaction mixture was refluxed for 12 h. To this solution, water (1ml) was added. The residue was directly subjected to column chromatography using $CHCl_3$ as eluent to afford the title compound, 1.5 g (55%), m.p. 140°C; FTIR ν (KBr disk), 1598, 1512, 1500 cm^{-1}; ^1H NMR δ ($CDCl_3$), 2.6 (s, 3H, SMe), 7.3-7.7 (m, 7H), 8.3 (m, 1H), MS: m/z M^+ 273.

2-Benzylmercapto-4-phenyl-4H-pyrido [2,3-e] 1,3,4 - thiadiazine (11, R=Bn)

Compound (**2, G=H**), (0.1589 g, 0.001 mol), and benzyl-3-phenyldithiocarbazate (**10**) (0.274 g, 0.001 mol) were dissolved in DMF (5 ml) and triethylamine (2 ml).

The reaction mixture was refluxed for 14 h. To this solution, water (1 ml) was added. The precipitated solid was filtered off and directly subjected to column chromatography using $CHCl_3$ as eluent to afford the title compound (45%), 185°C FTIR, U (KBr disk), 1580, 1500 cm^{-1}, ^1H NMR δ ($CDCl_3$), 4.5 (s, 2H, CH_2), 7.3-7.7 (d, 10H), 8.1 (m, 3H).

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