Chemistry of Heterocyclic Compounds, Vol. 38, No. 5, 2002

SYNTHESIS OF 2-AMINO- AND 2-HYDRAZINO-SUBSTITUTED 5-NITRO-4,6-DIPHENYLPYRIMIDINES

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Nitrogen-containing derivatives of 5-nitro-4,6-diphenylpyrimidine have been synthesized by the reaction of 2-chloro-5-nitro-4,6-diphenylpyrimidine with amines or of 2-hydrazino-5-nitro-4,6-diphenylpyrimidine with carbonyl or β-dicarbonyl compounds. Their structures were confirmed by data of IR spectroscopy and mass spectrometry.

Keywords: aminopyrimidines, hydrazinopyrimidines, nitropyrimidines, chloropyrimidines, nucleophilic substitution, mass spectrometry.

Interest in substituted 5-nitropyrimidine is caused first of all by the fact that many of its derivatives possess a broad spectrum of biological activity. 4-Amino-, 4-alkylamino-, and phenylhydrazino-substituted 5-nitropyrimidines display marked antimicrobial, insecticidal, and growth-regulating properties [1]. Certain 4-amino-6-guanidino-5-nitropyrimidines have been patented as diuretics [2]. A powerful cytostatic effect is apparent in 4-amino substituted 6-dibromomethyl-2-methoxy-5-nitropyrimidines in relation to leukemia and carcinoma cells, however their use as antitumor agents is limited by high toxicity [3]. The less toxic 2-amino-6-benzyloxy-5-nitropyrimidines [4] and 2,4-diamino-6-aryl-5-nitropyrimidines [5] possess marked antitumor activity. It has been shown that the presence of a nitro group in the heterocycle increases the pharmacophoric properties of the molecule. 2-Arylamino-5-nitropyrimidines also possess anti-inflammatory properties [6].

Sterically hindered 5-nitropyrimidines, having aryl groups in the positions neighboring the nitro group have been little studied [7]. To make apparent the biological activity of 2-amino or 2-hydrazino derivatives of 5-nitro-4,6-diphenyl-pyrimidine we obtained compounds **2** and **4-6** from the currently available 2-chloro-5-nitro-4,6-diphenylpyrimidine (**1**) [7]. The presence in compound **1** of an electron-accepting nitro group ensures a more ready substitution of the chlorine atom by aromatic amines.

With substituted amines this reaction was carried out under conditions of either basic or acidic catalysis depending on the amine used (for compounds **2a-e**) or by fusing the initial chloropyrimidine **1** with the arylamine (for compounds **2f-h**) (Scheme 1).

The synthesis of 2-hydrazino-5-nitro-4,6-diphenylpyrimidine (**3**) was effected by nucleophilic substitution of the chlorine atom in compound **1** [7], enabling various derivatives at the hydrazine group to be obtained, including heterocycles, which are of interest as potentially biologically active compounds. There are data known on the biological activity of hydrazinopyrimidine derivatives [8,9]. Substituted 5-nitro-2-(R-1-pyrazolyl)-4,6-diphenylpyrimidines **4a,b** were obtained by us by reacting compound **3** with acetylacetone and

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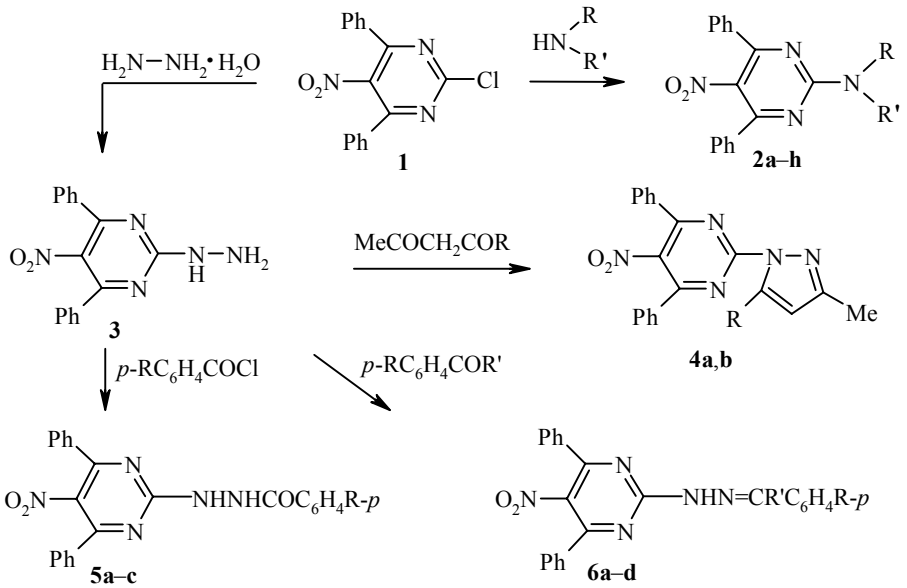
 0009-3122/02/3805-0564$27.00

Scheme 1



2 a R + R' = $(CH_2CH_2)_2O$, **b** R + R' = $(CH_2CH_2)_2NPh$; **c**–**h** R = H; **c** R' = CH_2Ph, **d** R' = Ph, **e** R' = C_6H_4Me-*p*, **f** R' = C_6H_4COOH-*o*, **g** R' = C_6H_4COOMe-*o*, **h** R' = C_6H_4COOEt-*p*; **4 a** R = Me, **b** R = OH; **5 a** R = H, **b** R = Cl, **c** R = NO_2; **6 a** R = H, R' = Me, **b** R = R' = Me, **c** R = OMe, R' = CH_2CH_2Ph, **d** R = R' = H

acetoacetic ester. 2-(Aroylhydrazino)-5-nitro-4,6-diphenyl-pyrimidines **5a-c** and (5-nitro-4,6-diphenyl-2-pyrimidinyl)hydrazones **6a-d** were also obtained by the acylation of compound **3** or reaction of it with carbonyl compounds.

Intense bands were present in the IR spectra of the compounds obtained for the stretching vibrations of the nitro group. The antisymmetrical vibrations (ν_{as}) of the nitro group in them were displayed at higher frequencies than for nitroaromatic compounds (Table 2). This is linked with the presence in the molecule of two phenyl groups in positions *ortho* to the nitro group causing it to move out of the plane of the heterocycle [10]. An analogous displacement of the bands of this vibration was observed previously for 3-nitro-2,4,6-triphenylpyridine (ν_{as} at 1540 cm^{-1}) [11] and 2-nitro-1,3,5-triphenylbenzene (ν_{as} at 1531 cm^{-1}) [12], in which the nitro group is moved from the plane of the aromatic ring by 64° [13]. In addition, the position of the band for the antisymmetrical vibrations of the nitro group in the obtained pyrimidines depends on the donor properties of the substituent at position 2 of the heterocycle [10]. For alkylamines **2a-c** it was at 1544.6±1.3, for arylamines **2d-h** 1532.9±4.1, for aroylhydrazines **5a-c** 1531.2±6.3, and for hydrazones **6a-c** 1537.3±1.1 cm^{-1}.

The band for the symmetric stretching vibrations (ν_s) of the nitro group in 2-nitro-1,3,5-triphenylbenzene was noted at 1367 cm^{-1} [12], but in 3-nitro-2,4,6-triphenylpyridine it was at 1363 cm^{-1} [11]. Correspondingly for the compounds obtained in the present work the values of ν_s lie in the ranges: 1354.8±1.6 (compounds **2a,b**), 1341.9±3.6 (compounds **2d-h**), 1349.7±1.0 (compounds **5a-c**), and 1334.3±0.7 cm^{-1} (compounds **6a-c**). Two bands were observed in the IR spectrum of hydrazone **6d** in the region of the stretching vibrations of the nitro group at 1546.0 and 1525.9 (ν_{as}), 1349.4 and 1329.0 cm^{-1} (ν_s) possibly due to the presence of two forms of the hydrazone.

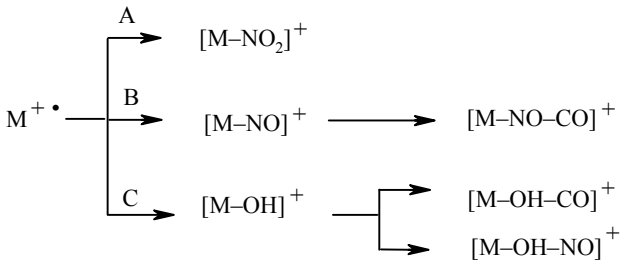
The peaks of the molecular ions in the mass spectra of the compounds obtained had high intensity except for hydrazone **6d** (Table 2). It is known that there are three directions A, B, C for the dissociative ionization of nitrobenzenes and nitroheterocycles. The direction of ionization depends on the substituent and type of substitution, but mainly proceeds along direction A [14,15].

TABLE 1. Characteristics of the Compounds Synthesized

Compound	Empirical formula	Found / Calculated		mp, °C*[2]	Yield, %
		N, %	M*		
2a	$C_{20}H_{18}N_4O_3$	15.23 / 15.46	362.13780 / 362.13788	182-183	96
2b	$C_{26}H_{23}N_5O_2$	16.06 / 16.00	437.18452 / 437.18516	157-158	84
2c	$C_{23}H_{18}N_4O_2$	14.76 / 14.65	382.14258 / 382.14297	119-122	95
2d	$C_{22}H_{16}N_4O_2$	14.96 / 15.21	368.12713 / 368.12732	154-156	92
2e	$C_{23}H_{18}N_4O_2$	14.60 / 14.65	382.14220 / 382.14297	144-146	78
2f	$C_{23}H_{16}N_4O_4$	13.70 / 13.59	412.11620 / 412.11715	295-298	74
2g	$C_{24}H_{18}N_4O_4$	13.00 / 13.14	426.13288 / 426.13279	200-202	80
2h	$C_{25}H_{20}N_4O_4$	12.72 / 12.51	440.14841 / 440.14844	249-251	85
4a	$C_{21}H_{17}N_5O_2$	19.27 / 18.86	371.13894 / 371.13822	248-250	96
4b	$C_{20}H_{15}N_5O_3$	18.51 / 18.76	373.11769 / 373.11748	231-234	60
5a	$C_{23}H_{17}N_5O_3$	16.60 / 17.02	411.13167 / 411.13313	257-260	92
5b	$C_{23}H_{16}ClN_5O_3$	15.74 / 15.71	445.09468 / 445.09416	248-250	93
5c	$C_{23}H_{16}N_6O_5$	18.34 / 18.41	456.11892 / 456.11821	256-259	80
6a	$C_{24}H_{19}N_5O_2$	17.15 / 17.11	409.15380 / 409.15386	163-167	94
6b	$C_{25}H_{21}N_5O_2$	16.70 / 16.54	423.16854 / 423.16951	171-174	96
6c	$C_{32}H_{27}N_5O_3$	13.12 / 13.23	529.21045 / 529.16443	162-164	96
6d	$C_{23}H_{17}N_5O_2$	17.69 / 17.71	395.13858 / 395.13822	191-193	98

* Data of high resolution mass spectra.

*[2] Compounds were recrystallized as follows: **2a,c-e, 6b** from ethanol, **6a,d** from methanol, **2b,f-h, 4a,b, 5a-c, 6c** from an ethanol–dioxan mixture.



It has been shown that in 5-nitropyrimidines the $[M\text{-}NO_2]^+$ ion is completely absent in certain cases, such as 2,4-diamino-6-methyl-5-nitropyrimidine [15] and 2-dimethylamino-5-nitropyrimidine [16]. In other cases all three routes of decomposition exist, for example for 2-methoxy-5-nitro-4,6-diphenylpyrimidine [16] the ions detected were $[M\text{-}NO_2]^+$ 17%, $[M\text{-}NO]^+$ 25%, and $[M\text{-}OH]^+$, $[M\text{-}OH\text{-}CO]^+$, and $[M\text{-}OH\text{-}NO]^+$ 3.5, 7.7, and 1.5% respectively.

TABLE 2. Data of IR and Mass Spectra of the Compounds Synthesized

Compound	IR spectrum, ν_{NO_2}, cm^{-1}		Mass spectrum (I_{rel}, %)						
	ν_{as}	ν_s	M^+	$[M-NO_2]^+$	$[M-NO]^+$	$[M-NO-CO]^+$	$[M-OH]^+$	$[M-OH-CO]^+$	$[M-OH-NO]^+$
2a	1543.8	1353.5	100	14.2	(31.2)*	2.8	2.0	16.1	2.7
2b	1544.1	1356.4	58.4	1.7	—	—	—	0.5	—
2c	1545.9	1339.1	100	5.4	1.0	0.7	0.7	1.4	2.6
2d	1534.5	1344.7	100	19.3	3.1	2.2	0.9	5.4	7.9
2e	1536.8	1342.0	100	17.8	2.2	1.5	0.7	4.7	5.0
2f	1533.5	1341.0	63.3	1.9	—	—	1.2	(100)*	1.1
2g	1531.0	1338.3	55.2	0.9	0.8	(30.2)*	0.3	0.4	—
2h	1528.8	1343.5	100	6.1	0.9	1.4	0.4	(12.4)*	2.1
4a	1530.1	1353.0	100	19.0	0.7	0.5	—	5.0	4.6
4b	1532.9	1349.2	100	12.9	1.9	—	—	3.3	—
5a	1536.7	1350.1	20.1	—	0.6	—	—	—	—
5b	1531.9	1350.2	34.5	—	—	—	—	0.5	—
5c	1524.9	1348.7	100	1.1	0.4	—	—	5.3	—
6a	1536.3	1334.1	91.1	13.4	0.7	—	2.5	3.1	19.2
6b	1538.4	1335.3	100	10.9	0.7	0.2	2.7	2.8	12.2
6c	1537.2	1334.3	33.9	9.6	2.0	—	2.5	5.3	3.2
6d	1546.0	1349.4	12.7	—	—	—	—	—	1.0
	1525.9	1329.0							

* The ion probably also contains elements of fragmentation of the substituent at position 2 of the pyrimidine ring.

In the mass spectra of compounds **2**, **4**, and **6** the $[M-NO_2]^+$ ions were recorded with a large scatter (1-19%) of intensity (Table 2). Judging by the low intensity of the peaks of $[M-NO]^+$ and $[M-NO-CO]^+$ ions the elimination of NO from the molecular ions of 2-amino-substituted compounds is a minor process, i.e. nitro–nitrite isomerism as an intermediate step in the route B direction of dissociation [15] for these compounds is not characteristic, unlike the 2-methoxy-substituted compound. The relatively high intensity of these peaks in the mass spectra of compounds **2a,g** is probably linked with the special features of the fragmentation of substituents in position 2 of the pyrimidine ring (for **2a** $[M-CH_2O]^+$, for **2g** $[M-COOMe+H]^+$).

The intensity of the peaks for the $[M-OH]^+$ ions in compounds **2, 4**, and **6** was small (less than 2.5%) or they were generally not recorded, but the intensity of the peaks for the $[M-OH-CO]^+$ and $[M-OH-NO]^+$ ions was significant, i.e. dissociation was taking place according to route C. This is linked with the presence of a phenyl group in the position *ortho* to the nitro group, which makes possible fission of a hydroxyl group from the molecular ion [15].

Consequently routes A and C predominate on dissociative ionization of the 5-nitropyrimidines **2**, **4**, and **6**, although to a lesser extent than in the case of nitro aromatic compounds. In difference to compounds **2**, **4**, and **6** the main direction of ionization of aroylhydrazones **5** is linked with fission of the acyl residue. The synthesized compounds display weak fungicidal activity.

EXPERIMENTAL

The IR spectra of compounds **2** and **4-6** were taken in KBr disks on a Bruker Vertor 22 spectrophotometer, and the mass spectra on a FM 8200 instrument with direct insertion of sample into the ion source. A check on the progress of reactions and the homogeneity of the compounds obtained was effected by TLC (Silufol UV 254, chloroform).

Compounds **1** and **3** were obtained by the procedure of [7]. The characteristics of compounds synthesized for the first time are given in Tables 1 and 2.

2-Morpholino-5-nitro-4,6-diphenylpyrimidine (2a). A solution of chloropyrimidine **1** (2.5 g, 8 mmol) and morpholine (1.5 g, 17 mmol) in ethanol (25 ml) was boiled for 2 h. After cooling, the solid was filtered off, washed with water, and with ethanol. The morpholino derivative **2a** (2.7 g) was obtained.

5-Nitro-4,6-diphenyl-2-(4-phenylpiperazino)pyrimidine (2b). A solution of chloropyrimidine **1** (0.46 g, 1.5 mmol) and 4-phenylpiperazine (0.32 g, 2 mmol) in ethanol (6 ml) was boiled adding triethylamine (0.15 g, 1.5 mmol) for 2 h. After cooling, the solid was filtered off, washed with water, and with ethanol. The piperazino derivative **2b** (0.54 g) was obtained.

2-Benzylamino-5-nitro-4,6-diphenylpyrimidine (2c) was obtained analogously to compound **2a**.

5-Nitro-4,6-diphenyl-2-phenylaminopyrimidine (2d). A mixture of chloropyrimidine **1** (0.46 g, 1.5 mmol), aniline (0.19 g, 2 mmol), and conc. HCl (0.2 ml) in ethanol (5 ml) was boiled for 11 h. After cooling the reaction mixture, 10% NH_4OH solution was added to give an alkaline reaction, the precipitate was filtered off, washed with water, and with ethanol. Compound **2d** (0.51 g) was obtained.

5-Nitro-4,6-diphenyl-2-(4-toluidino)pyrimidine (2e). A mixture of chloropyrimidine **1** (0.93 g, 3.0 mmol), *p*-toluidine (0.35 g, 3.2 mmol), and sodium acetate (0.25 g, 3.0 mmol) in ethanol (5 ml) was boiled for 13 h. After cooling, the solid was filtered off, washed with water, and with ethanol. Compound **2e** (0.9 g) was obtained.

2-[(2-Carboxyphenyl)amino]-5-nitro-4,6-diphenylpyrimidine (2f). A mixture of chloropyrimidine **1** (1.9 g, 6 mmol) and anthranilic acid (1.0 g, 7.5 mmol) was fused at 150-160°C for 1 h. The melt was rubbed with saturated aqueous sodium bicarbonate solution, the solid was filtered off, washed with water, and boiled with acetic acid (8 ml) for 5 min. After cooling, the solid was filtered off, and washed with ethanol. Compound **2f** (1.8 g) was obtained.

2-[(2-Methoxycarbonylphenyl)amino]-5-nitro-4,6-diphenylpyrimidine (2g). A mixture of chloropyrimidine **1** (1.2 g, 4.0 mmol) and methyl anthranilate (0.6 g, 4.0 mmol) was fused at 150-165°C for 2 h. The reaction mixture was boiled with dioxane (20 ml), the solid was filtered off, and washed with ethanol. Compound **2g** (1.3 g) was obtained.

2-[(4-Ethoxycarbonylphenyl)amino]-5-nitro-4,6-diphenylpyrimidine (2h) was obtained analogously to compound **2g**.

2-(3,5-Dimethyl-1-pyrazolyl)-5-nitro-4,6-diphenylpyrimidine (4a). A mixture of hydrazinopyrimidine **3** (1.5 g, 4.9 mmol) and acetylacetone (0.6 g, 6.0 mmol) in ethanol (7 ml) was boiled for 4 h. After cooling, the solid was filtered off, washed with ethanol, and compound **4a** (1.8 g) was obtained.

2-(5-Hydroxy-3-methyl-1-pyrazolyl)-5-nitro-4,6-diphenylpyrimidine (4b). A mixture of hydrazinopyrimidine **3** (1.5 g, 4.9 mmol) and acetoacetic ester (0.7 g, 5.5 mmol) in ethanol (15 ml) was boiled for 1 h, 10% NaOH solution (2.5 ml) was added, and boiling was continued for a further 2 h. Water (50 ml) was added to the reaction mixture, and the mixture was filtered. The filtrate was acidified with acetic acid. The precipitated solid was filtered off, and washed with water. Compound **4b** (1.1 g) was obtained.

2-[(4-Chlorobenzoyl)hydrazino]-5-nitro-4,6-diphenylpyrimidine (5b). A mixture of hydrazinopyrimidine **3** (0.45 g, 1.5 mmol), *p*-chlorobenzoyl chloride (0.32 g, 1.8 mmol), and triethylamine (0.18 g) was boiled for 8 h. The reaction mixture was evaporated, the solid was treated with sodium bicarbonate solution, filtered off, and washed with water. Compound **5b** (0.62 g) was obtained.

2-Benzoylhydrazino-5-nitro-4,6-diphenylpyrimidine (5a) and 5-Nitro-2-[(4-nitrobenzoyl)-hydrazino]-4,6-diphenylpyrimidine (5c) were obtained analogously to compound **5b**.

Acetophenone (5-Nitro-4,6-diphenyl-2-pyrimidinyl)hydrazone (6a). A mixture of hydrazinopyrimidine **3** (0.43 g, 1.4 mmol) and acetophenone (0.20 g, 1.7 mmol) in methanol (10 ml) was boiled for 3 h. The precipitated solid was filtered off, and washed with methanol. Hydrazone **6a** (0.54 g) was obtained.

Hydrazones **6b-d** were obtained analogously.

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