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Synthesis of Pyrrolo[3, 4-d]Pyrimidine Thiono Derivatives via Aza Wittig Reaction

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Abstract

New pyrolo [3,4-d] pyrimidine derivatives were obtained from the aza-Wittig reactions of iminophosphorane with phenylisocyanates via of amino compounds with triphenylphosphine, hexachloroethane and triethyl-amine produced iminophosphorane.

Keywords: amino compound,isocyanate, pyrrole, pyrimidine, aza-Wittig reaction, synthesis

1. Introduction

The aza-Wittig reactions of iminophosphoranes have received increased attention in view of their utility in the synthesis of nitrogen heterocyclic compounds (Palacios et al., 2006, 2007; Lopez et al., 2007; Lertpibulpanya et al., 2006; Marsden et al., 2008; Haraguchi et al., 2004; Cushman et al., 2004; Depecker et al., 2004; Wnuk et al., 2004). The reaction is useful in the synthesis of acyclic imines and heterocumulenes and in the intramolecular formation of carbon-nitrogen double bonds in heterocyclic synthesis. Stability, basicity, and nucleophilicity of iminophosphoranes are mainly determined by the substitutes at the nitrogen atom. Carbonyl groups of aldehydes, ketones, acid halides, and heterocumulenes are generally reactive (Daboun et al., 1983). Recently we have been interested in the synthesis of new pyrrolo [3,4-d] pyrimidine derivatives via aza-Wittig reaction by pyrimidines nuclei with phenylisocyanate (He et al., 2013, 2014). Pyrimidine derivatives play an important role in several biological and pharmacological active substances such as antibacterial and antitumor agents as well as agrochemical and veterinary products (Wright et al., 1977; Taylor et al., 1992; Traxler et al., 1997; Vicentini et al., 1989; Molina et al., 1994). The nucleophilicity at the nitrogen is a factor of essential mechanistic importance in the use of these iminophosphoranes as aza-Wittig reagents. Iminophosphoranes are important reagents in synthetic organic chemistry, especially in the synthesis of naturally occurring products, compounds with biological and pharmacological activity (Ramazani et al., 2008). Organophosphorus compounds have been extensively employed in organic synthesis as useful reagents, as well as legends, in a number of transition metal catalysts (Kaska, 1983; Ramazani et al., 2006; Stolzenberg et al., 2005).

2. Experimental

2.1 Synthesis of 6-Amino-4-Hydroxy-2-Thiouracil Sodium Salt Derivatives (1a-f)

To a solution of 4.6 mg (0.2 Mol) of metallic sodium in 75 ml of absolute ethanol was added 7.6 gm (0.1 Mol) of powdered thiourea and arylidenocyano-ethyl-acetate (cinnamonitrile) ylidenocyanoethylacetate. The reaction mixture was heated under reflux (0.1 mol) for two hours, then filtered while hot. The sodium salt of 6-amino-4-hydroxy-2-thiouracil thus obtained was washed alcohol and dried.

2.2 Synthesis of 6-Amino-4-Hydroxy-2-Thiouracil Derivatives (2a-f)

To a cold solution sodium salt of 6-amino-4-hydroxy-2-thiouracil derivatives (1a-f) in ice-water was added dilute HCl until the mixture was neutralized, whereby crystalline products separated out, and crystallized from the appropriate solvent (ethanol) to give 6-amino-4-hydroxy-2-thiouracil derivatives (2a-f). The results are listed in Table 1.

2.3 Synthesis of 4-Hydroxy-6-Aminotriphenylphosphorane-2-Thiouracil (3a-f)

To a mixture of 6-amino-4-hydroxy-2-thiouracil derivatives 2a-f (1.56, 1.71, 2.22, 2.332.62, 8 mmol), triphenylphosphine (3.14 g, 12 mmol) and hexachloroethan (2.84 g, 12 mmol) in dry acetonitrile (40 ml) was

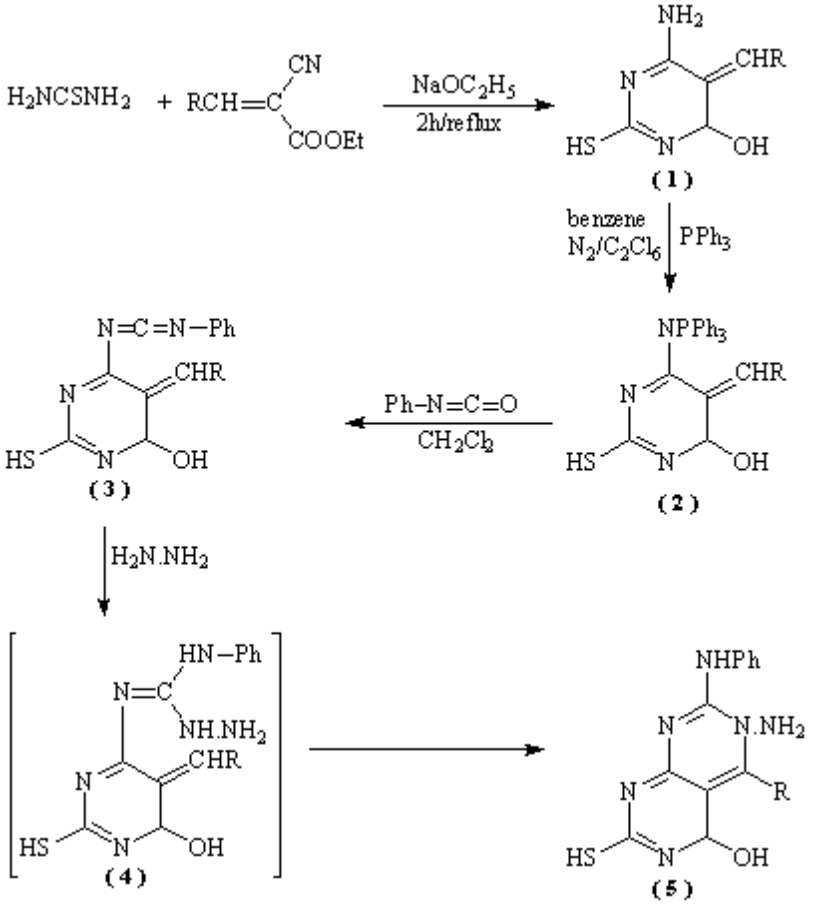
Table 1. Characterization of compounds (1-5) a-f

Comp. No.	M.P. °C	Colour	Yield %	Cryst.	M.F (M. Wt.)	Analysis % calced (found) C	H	N	S	M.S.
1a	>300	Yellow	40	Ethanol	$C_5H_6N_3OSNa$ (179.17)	33.52 (33.50)	3.38 (3.38)	23.45 (23.48)	17.89 (17.85)	179
1b	>300	Pale yellow	50	Ethanol	$C_6H_9N_3OSNa$ (194.20)	37.11 (37.12)	4.67 (4.66)	21.64 (21.70)	16.51 (16.56)	194
1c	>300	Brown	80	Ethanol	$C_9H_8N_3O_2SNa$ (245.23)	44.08 (44.10)	3.29 (3.30)	17.13 (17.15)	13.07 (13.12)	245
1d	>300	White	70	Ethanol	$C_{11}H_{11}N_3OSNa$ (256.27)	51.55 (51.56)	4.33 (4.32)	16.40 (16.44)	12.51 (12.50)	256
1f	>300	Yellow	85	Ethanol	$C_{12}H_{12}N_3O_2SNa$ (285.29)	50.52 (50.48)	4.24 (4.22)	14.73 (14.75)	11.24 (11.30)	285
2a	218-220	Yellow	40	Ethanol	$C_5H_6N_3OS$ (156.18)	38.45 (38.45)	3.87 (3.88)	26.90 (26.86)	20.53 (20.48)	156
2b	200-202	Pale yellow	50	Ethanol	$C_6H_9N_3OS$ (171.21)	42.09 (42.12)	5.30 (5.30)	24.54 (24.50)	18.72 (18.75)	171
2c	244-246	White	80	Ethanol	$C_9H_8N_3O_2S$ (222.24)	48.64 (48.66)	3.63 (3.62)	18.91 (18.94)	14.43 (14.48)	222
2d	187-189	Yellow	70	Ethanol	$C_{11}H_{11}N_3OS$ (233.28)	56.63 (56.60)	4.75 (4.76)	18.01 (18.05)	13.74 (13.70)	233
2f	>300	Yellow	90	Ethanol	$C_{12}H_{12}N_3O_2S$ (262.30)	54.95 (54.90)	4.61 (4.60)	16.02 (16.06)	12.22 (12.28)	262
3a	123-125	Pale yellow	20	Ethanol	$C_{23}H_{20}N_3OSP$ (417.46)	66.17 (66.20)	4.83 (4.80)	10.07 (10.12)	7.68 (7.64)	417
3b	144-146	White	40	Ethanol	$C_{23}H_{22}N_3OSP$ (419.48)	65.86 (65.84)	5.29 (5.30)	10.02 (10.06)	7.64 (7.70)	419
3c	133-135	Brownish yellow	50	Ethanol	$C_{27}H_{22}N_3OSP$ (467.52)	69.36 (69.35)	4.74 (4.74)	8.99 (9.00)	6.86 (6.90)	467
3d	168-170	White	40	Ethanol	$C_{29}H_{23}N_3OSP$ (492.55)	70.42 (70.40)	4.71 (4.70)	8.53 (8.50)	6.51 (6.46)	492
3f	283-285	White	60	Ethanol	$C_{24}H_{22}N_3OSP$ (431.49)	66.81 (66.78)	5.14 (5.10)	9.74 (9.78)	7.43 (7.40)	431
4a	114-116	Pale yellow	60	Ethanol	$C_{12}H_{10}N_4OS$ (258.29)	55.80 (55.80)	3.90 (3.90)	21.69 (21.70)	12.41 (12.40)	258
4b	162-164	Pale yellow	20	Ethanol	$C_{13}H_{12}N_4OS$ (272.32)	57.34 (57.34)	4.44 (4.44)	20.57 (20.50)	11.77 (11.70)	272
4c	154-156	Pale yellow	45	Ethanol	$C_{16}H_{11}N_4O_2S$ (323.34)	59.43 (59.45)	3.43 (3.40)	17.33 (17.35)	9.91 (9.90)	324
4d	149-151	White	20	Ethanol	$C_{18}H_{14}N_4OS$ (334.39)	64.65 (64.68)	4.22 (4.20)	16.75 (16.70)	9.59 (9.65)	334
4f	259-261	Pale yellow	35	Ethanol	$C_{19}H_{16}N_4O_2S$ (364.42)	62.62 (62.60)	4.43 (4.44)	15.37 (15.40)	8.80 (8.86)	364

added dropwise of tiethylamine (2.42 g, 24 mmol) at room temperature. After for 6h, the solvent was removed under reduced pressure and the residue was recrystallized from EtOH to give iminophosphorane (3a-f).

2.4 Synthesis of Pyrrolo [3,4-D] Pyrimidine Derivatives (5a-f)

With a mixture of iminophosphorane derivatives (3a-f) (4.17, 4.19, 4.92, 4.92, 4.31 respectively). (10 mmol) in dry methylene dichloride (25 ml) was added phenyl isocyanate (10 mmol) under nitrogen at room temperature. After the reaction mixture was standing 8-10 hours at 0-5 °C, the solvent was removed off under reduce pressure and ether (petroleum ether (1: 2, 20 ml) was added to precipitate triphenylphosphine oxide. Filtered, the solvent was removed to give carbodiimide derivatives, which were directly cyclized to pyrrolo [3,4-d] pyrimide derivatives (4a-f).



Where (1, 2, 3, 4) a-f: a, R = H; b, R = CH_3-; c, R = C_6H_5-; d, R=p-CH_3 O-C_6H_4 ; f, R=C_4H_3O.

3. Results and Discussion

The 6-amino-5-alkyl or/aryl-4-hydroxy-2-mercapto pyrimidine derivatives 1a-f was obtained by cyclization of alkylidine or/arylidine with thiourea under basic condition. The structure of compounds 1a-f were confirmed by elemental analysis (c.f. Table 1), and IR spectrum (γ KBr) showed general absorption bands at 3500 cm-1 (OH), and at 3370-3350 cm-1 (NH2). The 1H NMR spectrum (DMSO)[10] of compounds 1a-f showed signals. 1a: at 9.0 ppm(s, 1H, OH), 8.7 ppm(s, 1H, SH), at 8.5 ppm(s, 1H, Hpyrimidine), 6 ppm(s, 2H, CH2), at 5.2 ppm(br, 2H, NH2). 1b: at 9.0 ppm(s, 1H, OH), at 8.7 ppm(s, 1H, SH), at 8.5 ppm(s, 1H, Hpyrimidine), at 6 ppm(s, 1H, CH), at 5.2 ppm(br, 2H, NH2), at 2.3 ppm(s, 3H, CH3). 1c: at 9.0 ppm(s, 1H, OH), at 8.7 ppm(s, 1H, SH), at 8.5 ppm(s, 1H, Hpyrimidine), at 6 ppm(s, 2H, CH2), at 5.2 ppm(br, 2H, NH2), 1b: at 9.0 ppm(s, 1H, OH), at 8.7 ppm(s, 1H, SH), at 8.5 ppm(s, 1H, Hpyrimidine), at 8.3-7 ppm(m, 5H, Ar-H+), at 6 ppm(s, 1H, CH), at 5.2 ppm(br, 2H, NH2). Thinopyrimidine derivatives 1a-f were converted to iminophosphorane 2a-f via reaction with triphenylphosphine, hexachloroethane and triethylamine (Scheme). The structure of compounds 2a-f were

confirmed by elemental analysis (c.f. Table 1), and IR spectrum (KBr), general absorption band at 3500 cm^{-1} (OH). The 1H NMR spectrum (DMSO)[10] of compounds 2a-f showed signals, 2a: at 9.0 ppm(s, 1H, OH), at 8.7 ppm(s, 1H, SH), at 8.5 ppm(s, 1H, Hpyrimidine), 6 ppm(s, 2H, CH2), at 5.2 ppm(br, 2H, NH2), 2b: at 9.0 ppm(s, 1H, OH), at 8.7 ppm(s, 1H, SH), at 8.5 ppm(s, 1H, Hpyrimidine), at 6 ppm(s, 1H, CH), at 5.2 ppm(br, 2H, NH2), at 2.3 ppm(s, 3H, CH3), 2c: at 9.0 ppm(s, 1H, OH), at 8.7 ppm(s, 1H, SH), at 8.5 ppm(s, 1H, Hpyrimidine), 6 ppm(s, 2H, CH2), at 5.2 ppm(br, 2H, NH2), at 8.3-7(m, 10H, Ar-H+). Iminophosphorane 2a-f reacted with aromatic isocyanates to give carbodiimides 3a-f (Scheme 1). The structure of compounds 3a-f were confirmed by elemental analysis (c.f. Table 1), and IR spectrum (KBr), general absorption band at 3500 cm^{-1} (OH). The 1H NMR spectrum (DMSO)[10] of compounds 3a-f showed signals, 3a: at 9.0 ppm(s, 1H, OH), at 8.7 ppm(s, 1H, SH), at 8.5 ppm(s, 1H, Hpyrimidine), 6 ppm(s, 2H, CH2), at 5.2 ppm(br, 2H, NH2), 3b: at 9.0 ppm(s, 1H, OH), at at 8.7 ppm(s, 1H, SH), at 8.5 ppm(s, 1H, Hpyrimidine), at 6 ppm(s, 1H, CH), at 5.2 ppm(br, 2H, NH2), at 2.3 ppm(s, 3H, CH3), 3c: at 9.0 ppm(s, 1H, OH), at 8.7 ppm(s, 1H, SH), at 8.3-7(m, 10H, Ar-H+), at 8.5 ppm(s, 1H, Hpyrimidine), 6 ppm(s, 2H, CH2), at 5.2 ppm(br, 2H, NH2) . The carbodiimides 3a-f reacted with hydrazine to give the guanidine derivatives intermediate 4 via nucleophilic addition, which cyclizes to give compounds 5a-f (Scheme 1). The structure of compounds 5a-f were confirmed by elemental analysis (c.f. Table 1), and IR spectrum (KBr), general absorption band at 3500 cm^{-1} (OH), and 3370-3350 cm^{-1} (NH2, NH). The 1H NMR spectrum (DMSO)[10] of compounds 5a-f showed signals, 5a: at 9.5(s, 1H, NH), at 9.0 ppm(s, 1H, OH), at 8.7 ppm(s, 1H, SH) 8.5 ppm(s, 1H, Hpyrimidine), at 6 ppm(s, 2H, CH2), at 5.2 ppm(br, 2H, NH2), 5b : at 9.0 ppm(s, 1H, OH), at 8.7 ppm(s, 1H, SH), at 8.5 ppm(s, 1H, Hpyrimidine), at 6 ppm(s, 1H, CH), at 5.2 ppm(br, 2H, NH2), at 2.3 ppm(s, 3H, CH3), 5c: at 9.0 ppm(s, 1H, OH), 8.7 ppm(s, 1H, SH), at 8.3-7 ppm(m, 10H, Ar-H+), at 8.5 ppm(s, 1H, Hpyrimidine), at 6 ppm(s, 2H, CH2), at 5.8 ppm(br, 2H, NH2).

In conclusion, we have developed an efficient synthesis pyrimidinopyrimidine thione derivatives via aza-Wittig reactions. This method utilizes easily accessible starting materials and allows mild reaction conditions, straightforward product isolation and good yields.

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