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SYNTHESIS OF SUBSTITUTED 2-AMINO-5,6-DIHYDROPYRIMIDIN-4-ONES USING AN AZA-WITTIG REACTION

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An aza-Wittig reaction has been used for the first time in the synthesis of substituted 2-amino-5,6-dihydropyrimidin-4-ones via condensation of triphenyliminophosphoranes with aromatic heterocumulenes (arylisocyanates and thiocyanates).

Keywords: 2-amino-5,6-dihydropyrimidin-4-ones, N-arylcarbodiimides, heterocumulenes, triphenyliminophosphoranes, aza-Wittig reaction.

Over the last ten years the aza-Wittig reaction has gained a greater significance in the design of different heterocyclic systems [1]. A special role is attached to pyrimidine derivatives amongst six-membered nitrogen heterocyclic compounds as they occupy one of the leading positions amongst biologically active materials both natural and of synthetic derivation. Several methods are known for the annelation of an aromatic pyrimidine ring to various heterocycles using an aza-Wittig reaction. This is true, for example, in the condensation of heterocyclic 2-triphenylphosphoranylideneamino esters with isocyanates to give an annelated 2-alkoxy-4-pyrimidinone fragment [2-4]. However, information regarding the synthesis of 5,6-dihydropyrimidine derivatives using iminophosphoranes are absent in the literature as are other reliable methods for the synthesis of such structures although similar structures can attract interest as analogs of the reduced forms of nucleic base components.

We have developed a convenient preparative method for the synthesis of 3-substituted 2-alkylamino-5,6-dihydropyrimidin-4-ones **7** based on the cyclocondensation of [2-(N-R^1-carbamoyl)ethyl]-triphenyliminophosphoranes **5** with the heterocumulenes **6** (isocyanates and isothiocyanates) with a simultaneous participation of the amide group (see Scheme 1).

The acylation of different amines **2a-e** by β-bromopropionyl chloride (**1**) gave high yields of the amides **3a-e** (from 50-90% depending on the structure of the amine). As we have shown, the nucleophilic substitution of a bromine atom by azide ion in DMSO has to be carried out at a temperature not exceeding 40°C because of the thermal instability of the azides **4** formed. Best of all the Staudinger [5] reaction converting the azides **4** to iminophosphoranes **5** using triphenylphosphine is carried out in ether or methylene chloride at room temperature with cooling at the first stage and avoiding large amounts since the reaction sometimes occurs very vigorously.

The cyclocondensation of the iminophosphoranes **5** with heterocumulenes **6** (isocyanates and isothiocyanates) occurs in stages. Initially the components are stirred in dichloroethane solution at room temperature to form the carbodiimides and then the reaction mixture is refluxed for several hours. The dihydropyrimidinones **7** are generally purified by column chromatography and separated as the hydrochlorides or bases. According to mass spectrometric data the main side products are the unsymmetrical ureas **8** which are

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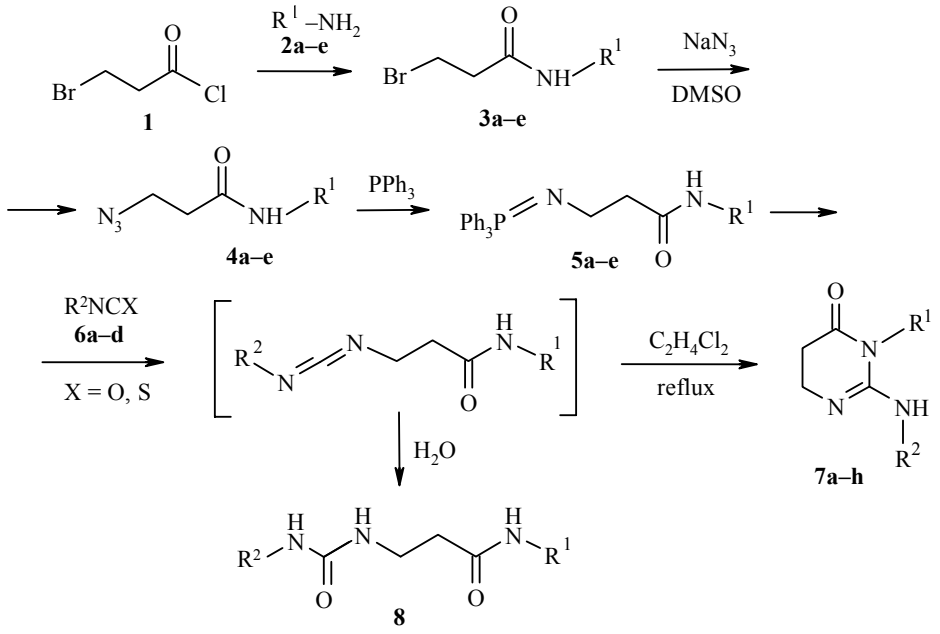

2-5 a $R^1 = CH_2Ph$, **b** $R^1 = CH_2$-2-thienyl, **c** $R^1 = CH_2$-2-furyl, **d** $R^1 = c\text{-}C_5H_9$, **e** $R^1 = Ph$;
6a $R^2 = p\text{-}FC_6H_4$, **b** $R^2 = p\text{-}MeO_2CC_6H_4$, **c** $R^2 = Ph$, **d** $R^2 = p\text{-}MeOC_6H_4$,
7a $R^1 = CH_2Ph$, $R^2 = p\text{-}FC_6H_4$; **b** $R^1 = CH_2Ph$, $R^2 = p\text{-}MeO_2CC_6H_4$; **c** $R^1 = CH_2Ph$, $R^2 = Ph$; **d** $R^1 = CH_2$-2-thienyl, $R^2 = Ph$; **e** $R^1 = CH_2$-2-thienyl, $R^2 = p\text{-}MeOC_6H_4$;
f $R^1 = CH_2$-2-furyl, $R^2 = Ph$; **g** $R^1 = c\text{-}C_5H_9$, $R^2 = Ph$; **h** $R^1 = Ph$, $R^2 = p\text{-}MeO_2CC_6H_4$

the hydrolysis products of the carbodiimides. It should be noted the formation of the dihydropyrimidinones **7** occurs principally with the use of aromatic heterocumulenes. For aliphatic cumulenes the main reaction products are the ureas **8**, evidently due to hydrolysis of the unstable intermediate aliphatic carbodiimides.

EXPERIMENTAL

^{1}H NMR spectra were recorded on Bruker MSL-300 (300 MHz) and Varian Mercury-400 (400 MHz) instruments with DMSO-d_6 and with TMS as internal standard. Monitoring of the purity of the compounds obtained was carried out by TLC on Sorbfil plates in the system hexane–ethyl acetate. Mass-spectra (LC-Mass) were obtained on a Thermo Finnigan (USA) Surveyor MSQ instrument using a Waters Xterra MS C18 (3.5 nm, 2.1 × 30 mm) column.

β-Bromopropionic Acid N-R^1-Amides 3a-e (General Method). β-bromopropionyl chloride **1** (41 g, 0.23 mol) was added dropwise, slowly over 1 h to a mixture of the amine **2** (0.2 mol) in methylene chloride (150 ml) and KOH (15 g, 0.25 mol, as a 20% aqueous solution) at -5°C. After stirring for a further 1 h at 0°C the product was gradually raised to room temperature. The reaction mixture was diluted with methylene chloride (100 ml). The organic layer was successively washed with water (2 × 50 ml), aqueous HCl solution (3%, 2 × 100 ml), saturated sodium carbonate solution (2 × 50 ml), and water (100 ml), dried over Na_2SO_4, evaporated in vacuo to a volume of 5-80 ml, and then diluted with an equal volume of hexane. The precipitate formed was filtered off, washed with a mixture of hexane and methylene chloride (1:1), and dried in air. The amides **3** were used in the following syntheses without additional purification.

β-Bromopropionic Acid N-Benzylamide (3a), yield 34.5 g (72%).

β-Bromopropionic Acid N-(2-Thienyl)methylamide (3b), yield 34.2 g (69%).

β-Bromopropionic Acid N-(2-Furyl)methylamide (3c), yield 36.2 g (77%).

β-**Bromopropionic Acid N-Cyclopentylamide (3d)**, yield 37.0 g (84%).

β-**Bromopropionic Acid N-Phenylamide (3e)**, yield 33.2 g (73%).

β-**Azidopropionic Acid N-Substituted Amides 4a-e (General Method).** Sodium azide (15 g, 0.25 mol) was added portionwise, slowly (30 min) with vigorous stirring to a solution of the corresponding amide **3** (0.1 mol) in DMSO (150 ml) at 40°C. The reaction mixture was stirred at this temperature to the completion of the reaction (monitoring by TLC using the system ethyl acetate–hexane (1:3)). At the completion of the reaction the mixture was poured into iced water (400 ml) and extracted with ether (3 × 100 ml) and the extract was dried (Na_2SO_4) and evaporated in a gentle vacuum (about 0.5 atm.). The azides **4** formed were not subjected to prolonged storage and were used in subsequent syntheses without additional purification.

Iminophosphoranes 5a-e (General Method). The azidopropionic acid amide **4** (0.1 mol) and triphenylphosphine (26 g, 0.1 mol) in methylene chloride (100 ml) were mixed with a little cooling and then stirred at about 20°C to the completion of the reaction (TLC monitoring in chloroform). The reaction mixture was evaporated in vacuo and the residue was recrystallized from a suitable solvent. The substituted iminophosphoranes **5** can be stored for prolonged periods without marked decomposition.

2-(N-Benzylcarbamoyl)ethyltriphenyliminophosphorane (5a), yield 31.5 g (72%); mp 143-144°C (ethyl acetate–hexane). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.3 (2H, t, *J* = 7.5, CH_2CO); 3.2 (2H, m, CH_2N=P + H_2O signal); 4.3 (2H, m, $C_6H_5CH_2$); 7.2-7.6 (20H, m, arom.); 9.0 (1H, m, NHCO).

2-[N-(2-Thienyl)methylcarbamoyl]ethyltriphenyliminophosphorane (5b), yield 35.2 g (79%); mp 138-140°C (ethyl acetate–hexane). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.25 (2H, t, *J* = 7.5, CH_2CO); 3.25 (2H, m, CH_2N=P + H_2O signal); 4.4 (2H, m, 2-thienyl-CH_2); 6.9-7.6 (18H, m, arom.); 9.0 (1H, m, NHCO).

2-[N-(2-Furyl)methylcarbamoyl]ethyltriphenyliminophosphorane (5c), yield 27.7 g (65%); mp 131-132°C (ethyl acetate–hexane). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.25 (2H, t, *J* = 7.5, CH_2CO); 3.2 (2H, m, CH_2N=P + H_2O signal); 4.25 (2H, d, 2-furyl-CH_2); 6.2 (1H, s, 3H-furyl); 6.3 (1H, s, 4H-furyl); 7.4-7.6 (16H, m, arom.); 9.0 (1H, m, NHCO).

2-(N-Cyclopentyl)ethyltriphenyliminophosphorane (5d), yield 29.4 g (71%); mp 108-110°C (ethyl acetate–hexane). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.5-2.1 (8H, m, cyclopentyl); 2.3 (2H, t, *J* = 7.5, CH_2CO); 3.3 (2H, m, CH_2N=P + H_2O signal); 5.1 (1H, m, CH-cyclopentyl); 7.3-7.6 (15H, m, arom.); 8.85 (1H, m, NHCO).

2-(N-Phenylcarbamoyl)ethyltriphenyliminophosphorane (5e), yield 31.4 g (73%); mp 71-72°C (ether). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.35 (2H, t, *J* = 7.5, CH_2CO); 2.9 (2H, t, *J* = 7.5, CH_2N=P); 7.1-7.6 (20H, arom.); 10.7 (1H, m, NHCO).

2-N-R^2-N_3-R^1-5,6-Dihydropyrimidin-4-ones (7a-h) (General Method). The heterocumulene **6** (2.5 mmol) was added to a solution of the substituted iminophosphorane **5** (2 mmol) in dichloroethane (30-50 ml). The product was stirred for 1 h at 40-50°C and refluxed for 2-6 h (monitored by TLC using the system hexane-ethyl acetate (2:1)). At the end of the reaction the product was passed through a silica gel layer (KSK, 40/60 μ, 20 × 80 mm) using a 3:1 mixture of hexane and ethyl acetate as eluent and collecting 10 ml fractions. The fractions containing the dihydropyrimidone **7** (R_f 0.3-0.5) were combined and evaporated in vacuo and the residue was recrystallized from a suitable solvent or separated as the hydrochlorides using dioxane hydrochloride.

3-Benzyl-2-(*p*-fluorophenyl)amino-5,6-dihydropyrimidin-4-one Hydrochloride (7a), yield 0.368 g (55%); mp 223-224°C (2-propanol). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.9 (2H, t, *J* = 7.5, CH_2CO); 3.5 (2H, t, *J* = 7.5, CH_2N=C); 5.2 (2H, s, $C_6H_5CH_2$); 7.1 (2H, m, H-3 in F-C_6H_4); 7.3 (3H, m, 2-H in F-C_6H_4 + 1H in C_6H_5); 7.4 (4H, m, C_6H_5); 9.0 (1H, br. s, NH); 11.0 (1H, br. s, HCl). Mass spectrum, *m/z*: 298 [M+H]. Found, %: C 61.08, H 5.42, N 12.23. $C_{17}H_{16}FN_3O$·HCl. Calculated, %: C 61.17; H 5.10; N 12.59.

3-Benzyl-2-(*p*-methoxycarbonylphenyl)amino-5,6-dihydropyrimidin-4-one Hydrochloride (7b), Yield 0.402 g (54%); mp 237-238°C (acetonitrile). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.8 (2H, t, *J* = 7.5, CH_2CO); 3.4 (2H, t, *J* = 7.5, CH_2N=C); 3.8 (3H, s, $COOCH_3$); 5.2 (2H, s, C_6H_5-CH_2); 7.1 (2H, d, *J* = 8.5, H-*m*

in $C_6H_4CO_2CH_3$); 7.35-7.5 (5H, m, arom.); 7.9 (2H, d, *J* = 8.5, H-*o* in $C_6H_4CO_2CH_3$). Mass spectrum, *m/z*: 338 [M+H]. Found, %: C 61.39; H 5.79; N 11.22. $C_{19}H_{19}N_3O_3 \cdot HCl$. Calculated, %: C 61.04; H 5.35; N 11.24.

3-Benzyl-2-phenylamino-5,6-dihydropyrimidin-4-one Hydrochloride (7c), yield 0.353 g (56%); mp 228-229°C (2-propanol). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.8 (2H, t, *J* = 7.5, CH_2CO); 3.5 (2H, t, *J* = 7.5, CH_2N=C); 5.4 (2H, s, C_6H_5-CH_2); 7.0 (2H, d, *J* = 8.5, H-*o* in C_6H_5); 7.2 (8H, m, arom.); 9.0 (1H, br. s, NH); 11.0 (1H, br. s, HCl). Mass spectrum, *m/z*: 280 [M+H]. Found, %: C 64.90; H 6.20; N 13.31. $C_{17}H_{17}N_3O \cdot HCl$. Calculated, %: C 64.66; H 5.71; H 13.31.

2-Phenylamino-3-[(2-thienyl)methyl]-5,6-dihydropyrimidin-4-one Hydrochloride (7d), yield 0.394 g (69%); mp 218-219°C (ethanol). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 3.0 (2H, t, *J* = 7.5, CH_2CO); 3.4 (2H, t, *J* = 7.5, CH_2N=C); 5.6 (2H, s, 2-thienyl-CH_2); 6.9 (1H, dd, *J* = 5.4, H-β in thienyl); 7.0 (3H, m, H-β in thienyl + 2H-*o* in C_6H_5); 7.2 (1H, t, *J* = 8.5, H-α in thienyl); 7.3 (3H, m, in C_6H_5); 9.0 (1H, br. s, NH); 11.0 (1H, br. s, HCl). Mass spectrum, *m/z*: 286 [M+H]. Found, %: C 56.30; H 5.26; N 13.13; S 9.84. $C_{15}H_{15}N_3OS \cdot HCl$. Calculated, %: C 56.00; H 4.98; H 13.06; S 9.96.

2-(*p*-Methoxyphenyl)amino-3-[(2-thienyl)methyl]-5,6-dihydropyrimidin-4-one Hydrochloride (7e), yield 0.382 g (61%); mp 230-231°C (ethanol). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.9 (2H, t, *J* = 7.5, CH_2CO); 3.4 (2H, t, *J* = 7.5, CH_2N=C); 3.8 (3H, s, OCH_3); 5.5 (2H, s, 2-thienyl-CH_2); 7.02 (1H, dd, *J* = 5.4, *J* = 4.0, H-β in thienyl); 7.06 (2H, d, *J* = 8.5); 7.10 (2H, d, *J* = 8.5); 7.23 (1H, d, *J* = 4.0); 7.50 (1H, d, *J* = 5.4); 9.0 (1H, br. s, NH); 11.0 (1H, br. s, HCl). Mass spectrum, *m/z*: 316 [M+H]. Found, %: C 54.83; H 5.14; N 12.08; S 9.28. $C_{16}H_{17}N_3O_2S \cdot HCl$. Calculated, %: C 54.63; H 5.12; N 11.95; S 9.10.

3-[(2-Furyl)methyl]-2-phenylamino-5,6-dihydropyrimidin-4-one Hydrochloride (7f), yield 0.321 g (58%); mp 185-186°C (2-propanol). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.9 (2H, t, *J* = 7.5, CH_2CO); 3.5 (2H, t, *J* = 7.5, CH_2N=C); 5.4 (2H, s, 2-furyl-CH_2); 6.5 (1H, d, *J* = 3.6); 6.6 (1H, d, *J* = 3.6); 7.2 (2H, d, *J* = 8.5); 7.3 (1H, t, *J* = 8.5); 7.5 (2H, d, *J* = 8.5); 7.7 (1H, d, *J* = 1.8); 9.0 (1H, br. s, NH); 11.0 (1H, br. s, HCl). Mass spectrum, *m/z*: 270 [M+H]. Found, %: C 59.20; H 5.64; N 13.78. $C_{15}H_{15}N_3O_2 \cdot HCl$. Calculated, %: C 58.92; H 5.24; N 13.75.

3-Cyclopentyl-2-phenylamino-5,6-dihydropyrimidin-4-one (7g), yield 0.341 g (65%); mp 133-134°C (ethyl acetate). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.5 (2H, m); 1.7 (4H, m); 2.1 (2H, m); 2.6 (2H, t, *J* = 7.5); 3.1 (2H, t, *J* = 7.5); 5.1 (1H, m); 6.1 (1H, br. s); 6.7 (2H, d, *J* = 8.5); 6.9 (1H, t, *J* = 8.5); 7.2 (2H, t, *J* = 8.5). Mass spectrum, *m/z*: 258 [M+H]. Found %: C 70.57; H 7.96; N 16.05. $C_{15}H_{19}N_3O$. Calculated, %: C 70.01; H 7.44; N 16.33.

2-(*p*-Methoxycarbonylphenyl)amino-3-phenyl-5,6-dihydropyrimidin-4-one (7h), yield 0.281 g (44%); mp 227-228°C (ethyl acetate). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.8 (2H, t, *J* = 7.5, CH_2CO); 3.4 (2H, t, *J* = 7.5, CH_2N=C); 3.8 (3H, s, $COOCH_3$); 5.2 (2H, s, $PhCH_2$); 7.1 (2H, d, *J* = 8.5); 7.35-7.5 (5H, m, arom.); 7.9 (2H, d, *J* = 8.5). Mass spectrum, *m/z*: 324 [M+H]. Found, %: C 67.09; H 5.54; N 12.94. $C_{18}H_{17}N_3O_3$. Calculated, %: C 66.86; H 5.30; N 13.00.

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