Intermolecular Aza-Wittig Reaction: One-Step Synthesis of Pyrazolo[1,5-*a*]pyrimidine and Imidazo[1,2-*b*]pyrazole Derivatives

Magda A. Barsy* and Eman A. El-Rady

Chemistry Department, Faculty of Science, South Valley University
Aswan - 81528, Egypt.

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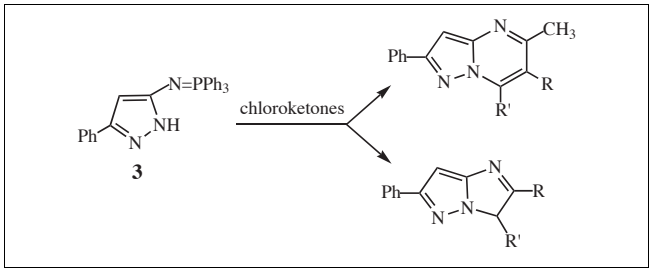

Pyrazolo[1,5-*a*]pyrimidine and imidazo[1,2-*b*]pyrazole derivatives were synthesized *via* intermolecular aza-Wittig reaction of 5-(triphenylphosphoranylideneamino)-3-phenylpyrazole **3** derived from 5-amino-3-phenylpyrazole with some selected α-chloroketones.

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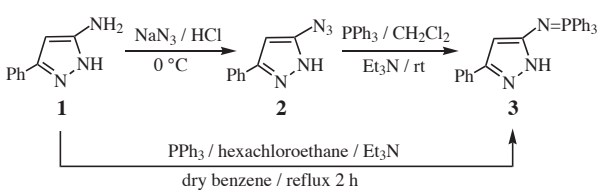
In recent years, there has been significant interest in the chemistry of iminophosphoranes [1-5] because of their utility in the synthesis of a wide variety of nitrogen heterocycles [6-8]. The chemistry of 5-amino-pyrazole derivatives and their use as excellent precursors for the preparation of fused and isolated pyrazoles have received much attention in the last few decades [9-17]. However, their use to prepare fused pyrazolo-pyrimidine ring structure *via* the 5-iminophosphorane derivatives attracted less attention. In the course of our studies directed toward the synthesis of fused heterocycles [18-22], especially those based on Wittig reaction [23, 24], we now report a mild and facile one-step approach for the synthesis of new fused pyrazoles.

Results and Discussion.

The iminophosphorane **3** was prepared very easily through the classical Staudinger reaction [25] of 5-azido-3-phenylpyrazole **2** with triphenylphosphine in dry methylene chloride at room temperature. The iminophosphorane **3** was also prepared by reacting 5-amino-3-phenylpyrazole **1** with triphenylphosphine and hexachloroethane in the presence of triethylamine according to Appel's procedure [26], (Scheme 1).

Scheme 1



The reaction of compound **3** with α-chloroacetylacetone **4** in dry toluene at reflux temperature gave the corresponding pyrazolo[1,5-*a*]pyrimidine **6** in good yield, (Scheme 2). The mechanism of the conversion involves an initial aza-Wittig reaction between the iminophosphorane **3** and α-chloroketone to give **5** as a highly reactive intermediate, which readily undergoes heterocyclization with loss of water rather than elimination of hydrogen chloride, to give the fused pyrazolo[1,5-*a*]-pyrimidine **6**. The mass spectrum of **6** showed the molecular ions at *m/z* 259 (M + 2, 23) and at 257 (M^+, 70) showing the characteristics isotope pattern for one chlorine atom. The ^{1}H NMR spectrum showed one singlet signal at 2.1 ppm assigned to the six protons of two methyl groups, and one singlet signal at 6.9 ppm for the H-4 proton of the pyrazole ring. Similarly, iminophosphorane **3** reacted with α-chloro ethyl acetoacetate **7** to give the pyrazolo[1,5-*a*]pyrimidinone **9** *via* the corresponding intermediate **8** which cyclized with loss of ethanol. The IR spectrum of **9** revealed an absorption band at *v* 1690 cm^{-1} due to a C=O function indicating the elimination of ethanol rather than elimination of water as shown in Scheme 2. Furthermore, the ^{13}C NMR spectrum also showed a signal at 185.6 ppm assigned to the carbonyl carbon and a signal at 45.4 ppm assigned to the sp^3 C-6 bearing the chlorine atom. Also, iminophosphorane **3** easily reacted with α-chloroacetoacetanilide (2-chloro-3-oxo-*N*-phenylbutanamide) **10** to yield the same pyrazolopyrimidinone **9** *via* loss of aniline from intermediate **11**. However, ethyl acetoacetate **12** itself afforded the corresponding 6-dihydro-pyrazolo-pyrimidinone **14** *via* intermediate **13** which eliminated ethanol rather than water, (Scheme 2). The structure of **14** is supported by its molecular ion at *m/z* 225 (100 %), an

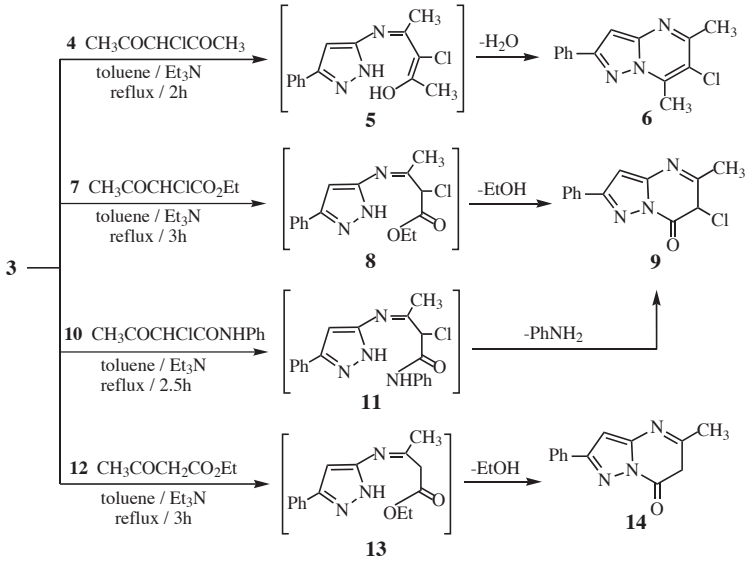
intense carbonyl absorption at ν 1695 cm^{-1}, the ^{13}C resonance for the methylene carbon at 32.2 ppm and for the carbonyl group at 187.1 ppm as well as the ^{1}H signals at 1.3 and 2.4 ppm for the methyl and the methylene groups.

However, reaction of **3** with ethyl-2-chloro-3-oxo-2-phenylazobutanoate **15**, (Scheme 3) yielded the new oligo-substituted 6-chloro-7-ethoxy-5-methyl-2-phenyl-pyrazolo[1,5-*a*]pyrimidine **18**. It appears that a conden–sation step yielded the intermediate **16** *via* elimination of triphenylphosphine oxide, followed by a nucleophilic attack of pyrazole N-1 on the carbonyl carbon affording the cyclic intermediate **17**.

On the other hand, reaction of iminophosphorane **3** with 2-chloro-2-phenylacetophenone **19a**, chloroacetylchloride **19b** and α-chloro-α-phenylazoacetone **19c** afforded the imidazo[1,2-*b*]pyrazole derivatives **21a-c** *via* elimination of hydrogen cholride from the initially formed intermediate **20**, (Scheme 4). The mass spectra of **21a** (R = Ph) showed *m/z* at 335 (M^+, 9), of **21b** (R = Cl) at 219 (M + 2, 6) and of **21c** at 301 (M^+, 20).

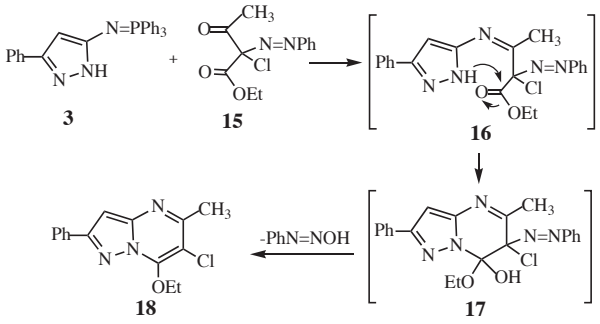
Also the pyrazolo[1,5-*a*]pyrimidine ring structure **24** was obtained when compound **3** reacted with α-cyanoacetophenone **22** *via* a nucleophilic addition of the pyrazole N-1 to the cyano function of intermediate **23**. The IR spectrum of **24** showed the lack of a cyano group

Scheme 2



Subsequent elimination of phenyldiazonium hydroxide finally yielding the pyrazolo[1,5-*a*]pyrimidine **18**.

Scheme 3



The mass spectrum of **18** showed *m/z* at 289 (M + 2, 2), and the ^{1}H NMR revealed the characteristic absorption pattern of ethoxy protons at δ 1.3 and 3.5 ppm in support for the proposed pathway in Scheme 3.

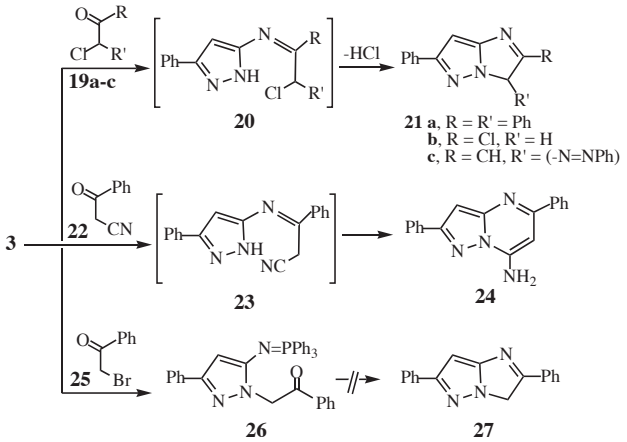
but exhibited an absorption band at ν 3320 cm^{-1} due to the NH_2 function. The mass spectrum of **24** showed the molecular ion as the base peak at *m/z* 286 (100 %).

In contrast, it was expected that the reaction of **3** with phenacylbromide **25** would afford the imidazolopyrazole **27**. However, based on the spectral data this assumption had to be ruled out. The mass spectrum of the product showed *m/z* at 537 (30 %). The IR spectrum revealed an intense absorption band at ν 1701 cm^{-1} assigned to an acyclic carbonyl group. The ^{1}H NMR spectrum showed several multiplets at δ 7.1-7.8 and a singlet signal at δ 4.3 ppm for two protons. Thus, structure **26** was suggested as the reaction product, which seemed thermodynamically stable, insoluble in most organic solvents and remain unreacted. This may be due to the steric hindrance as was previously observed for the aza-Wittig cyclization of lactam carbonyl groups [27].

It should be noted that the C-Cl bond in intermediates **5**, **8** and **11** is strong enough and elimination of water, ethanol or aniline is highly favoured over the elimination

of hydrogen chloride even in the presence of triethylamine unless there is no other option such as in the case of formation of **21**.

Scheme 4



EXPERIMENTAL

Preparation of 5-(triphenylphosphoranylideneamino)-3-phenylpyrazole (**3**).

Method A.

5-Amino-3-phenylpyrazole **1**, (90 mg, 0.57 mmol), hexachloroethane (134 mg, 0.57 mmol, 1.0 equiv.) and triphenylphosphine (150 mg, 0.57 mmol, 1.0 equiv.) were dissolved in 5.0 mL anhydrous benzene and stirred for 10 minutes. Triethylamine 0.16 mL, (1.15 mmol, 2.0 equiv.) was added dropwise over 5 minutes with stirring and the reaction mixture was kept at reflux for 2 hours. After cooling, the solid formed was filtered off and the mother liquor was concentrated under vacuum and the residue was subjected to column chromatography using mixture of ethylacetate / hexane (1:2, v/v) as eluent to afford **3** (0.18 g, 77 %).

Method B.

A sample (630 mg, 3.96 mmol) of the amine **1** was dissolved in a mixture of water (4.5 mL) and conc. H_2SO_4 (0.8 mL) and cooled to 0 °C. A cooled solution of $NaNO_2$ (350 mg, 5.2 mmol) in 3.2 mL of water was added dropwise and the reaction mixture was stirred at 0 °C for 30 min. Then a cooled solution of sodium azide (470 mg, 7.3 mmol) in 3 mL of water was added with stirring and the mixture was kept in a refrigator for 12 hours. The solid formed was separated by filtration to give the azide **2** which was crystallized from methylene chloride to give (151 mg, 82 %) of colourless crystals, mp 127 °C. The azide **2** (170 mg, 0.93 mmol) was dissolved in 10 ml of dry methylene chloride and then added dropwise to a solution of 10 mL of dry methylene chloride containing 240 mg of triphenylphosphine (0.93 mmol) at room temperature under nitrogen and the mixture was stirred for one hour. The solid product was collected by filtration and crystallized from ethyl acetate as colourless crystals, mp 198-200 °C; IR: ν 3134 cm^{-1} (NH); ^{1}H NMR (DMSO) *δ*: 6.8 (s, 1H, CH-pyrazole), 7.1-7.9 (m, 20H, Ar-H), 9.5 (s, 1H, NH); *m/z* (%): 419 (M^+, 91), 265 (5), 183(100), 157 (6), 108 (50).

Anal. Calcd. for $C_{27}H_{22}N_3P$: C, 77.31; H, 5.29; N, 10.02. Found: C, 77.61; H, 5.48; N, 10.13.

Reaction of Iminophosphorane 3 with Ketones.

General Procedure.

To a solution of iminophosphorane **3** (419 mg, 1.0 mmol) in 20 mL dry toluene the appropriate ketone (1.0 mmol) and triethylamine (0.2 mL, 2 mmol) were added, and the reaction mixture was refluxed for 5 h. After cooling the solid that precipitated was separated by filtration, dried and recrystallized from proper solvent.

6-Chloro-2-phenyl-5,7-dimethylpyrazolo[1,5-*a*]pyrimidine (**6**).

Colourless crystals from methanol (0.18 g, 70 %), mp >300 °C; ^{1}H NMR (DMSO) *δ*: 2.1 (*s*, 6H, 2 CH_3), 6.9 (*s*, 1H, CH-pyrazole), 7.4-7.9 (*m*, 5H, Ar-H); *m/z* (%) 259 (M + 2, 23), 257 (M^+, 70), 242 (15), 227(19), 191 (6), 114 (50).

Anal. Calcd. for $C_{14}H_{12}ClN_3$: C, 65.25; H, 4.69; N, 16.30; Cl, 13.76. Found: C, 65.47; H, 4.89; N, 16.76; Cl, 13.69.

6-Chloro-5-methyl-2-phenyl-6*H*-pyrazolo[1,5-*a*]pyrimidin-7-one (**9**).

Colourless crystals from methanol (0.17 g, 66 %), mp 340 °C; IR: *ν* 1690 (CO) cm^{-1}; ^{1}H NMR (DMSO) *δ* : 1.9 (*s*, 3H, CH_3), 3.8 (s, 1H, 6-H), 7.1-7.8 (*m*, 6H Ar-H); ^{13}C NMR: 185.6 (C=O), 144.7 (C-3a), 142.5 (C-2), 140.6 (C-5), 138.7 (C-3), 128-135 (C-Phenyl), 45.4 (C-6), 18.3 (CH_3). *m/z* (%) 261 (M + 2, 34), 259 (M^+, 100), 225 (14), 169 (8), 183 (6).

Anal. Calcd. for $C_{13}H_{10}ClN_3O$: C, 60.12; H, 3.88; N, 16.18; Cl, 13.65. Found: C, 60.22; H, 3.79; N, 16.25; Cl, 13.47.

5-Methyl-2-phenyl-6-dihydropyrazolo[1,5-*a*]pyrimidin-7-one (**14**).

Colourless crystals from methanol (0.18 g, 80 %), mp 310 °C; IR : *ν* 1695 (C=O) cm^{-1}; ^{1}H NMR (DMSO) *δ*: 1.3, (*s*, 3H, CH_3), 2.4 (*s*, 2H, CH_2), 7.1-7.9 (*m*, 6H Ar-H); ^{13}C NMR: 187.1 (C=O), 147.1 (C-3a), 141.1 (C-2), 140.1 (C-5), 136.9 (C-3), 128-133 (C-Phenyl), 32.2 (C-6), 17.2 (CH_3). *m/z* (%) 225 (M^+, 100), 169 (38), 168 (30), 145 (11), 102 (22).

Anal. Calcd. for $C_{13}H_{11}N_3O$: C, 69.32; H, 4.92; N, 18.66. Found: C, 69.44; H, 4.45; N, 18.77.

6-Chloro-7-ethoxy-5-methyl-2-phenylpyrazolo[1,5-*a*]pyrimidine (**18**).

Colourless crystals from ethylacetate/methanol (0.22 g, 77 %), mp 220 °C; ^{1}H NMR (DMSO) *δ* : 1.3 (*t*, 3H, CH_3), 2.2 (*s*, 3H, CH_3), 3.5 (*q*, 2H, CH_2), 7.1-7.8 (*m*, 6H, Ar-H); *m/z* (%) : 289 (M + 2, 2), 287 (M^+, 5), 259 (50), 225 (100), 196 (37).

*Anal.*Calcd. for $C_{15}H_{14}ClN_3O$: C, 62.61; H, 4.90; N, 14.60; Cl, 12.32. Found: C, 62.75; H, 4.99; N, 14.97; Cl, 12.45.

2,3,6-Triphenyl-3*H*-imidazo[1,2-*b*]pyrazole (**21a**).

Buff crystals from ethyl acetate, (0.25 g, 75 %), mp 270 °C; ^{1}H NMR (DMSO) *δ*: 5.6 (*s*, 1H, 3-H), 6.8-7.9 (*m*, 16H, Ar-H); *m/z* (%): 335 (M^+, 9), 313 (13), 286 (12),

225 (8).

Anal. Calcd. for $C_{23}H_{17}N_3$: C, 82.36; H, 5.11; N, 12.53. Found: C, 82.47; H, 5.25; N, 12.64.

2-Chloro-3-dihydro-6-phenylimidazo[1,2-*b*]pyrazole (**21b**).

Colourless crystals from ethyl acetate/methanol (2:1), (0.17 g, 78 %), mp 220 °C; ^{1}H NMR (DMSO) δ : 3.6 (*s*, 2H, CH_2), 7.1-7.8 (*m*, 6H, Ar-H); *m/z* (%) : 219 (M + 2, 6), 217 (M^+, 20), 140 (15), 104 (12).

Anal. Calcd for $C_{11}H_8N_3Cl$: C, 60.70; H, 3.70; N, 19.31; Cl, 16.29. Found: C, 60.95; H, 3.69; N, 19.45; Cl, 16.38.

2-Methyl-6-phenyl-3-phenylazo-3*H*-imidazo[1,2-*b*]pyrazole (**21c**).

Colourless crystals from ethyl acetate/methanol (0.26 g, 86 %), mp 210 °C; ^{1}H NMR (DMSO) δ: 2.1 (*s*, 3H, CH_3), 5.9 (*s*, 1H, 3-H), 7.1-7.9 (*m*, 11H, Ar-H and 7-H); *m/z* (%): 301 (M^+, 20), 286 (45), 209 (30), 181 (35).

Anal. Calcd. for $C_{18}H_{15}N_5$: C, 71.74; H, 5.02; N, 23.24. Found: C, 71.86; H, 5.15; N, 23.37.

7-Amino-2,5-diphenylpyrazolo[1,5-*a*]pyrimidine (**24**).

Colourless crystals from ethyl acetate (0.20 g, 70 %), mp 265 °C; IR: *v* 3320 cm^{-1} (NH_2); ^{1}H NMR (DMSO) δ: 7.1-7.9 (*m*, 12H, Ar-H), 9.1 (*s*, 2H, NH_2); *m/z* (%): 286 (M^+, 100), 248 (10), 143 (5), 128 (3) 102 (11).

Anal. Calcd. for $C_{18}H_{14}N_4$: C, 75.50; H, 4.93; N, 19.57. Found: C, 75.65; H, 4.74; N, 19.66.

5-(Triphenylphosphoranylideneamino)-1-(2-oxo-2-phenylethyl)-3-phenylpyrazole (**26**).

Colorless crystals from ethyl acetate (0.42 g, 78 %), mp 240 °C; IR : *v* 1701 cm^{-1} (C=O) ^{1}H NMR (DMSO) δ: 4.3 (*s*, 2H, CH_2), 7.1-7.8 (*m*, 26H, Ar-H); *m/z* (%): 537 (M^+, 30), 430 (15), 262 (50), 183 (75).

Anal. Calcd. for $C_{35}H_{28}N_3OP$: C, 78.20; H, 5.25; N, 7.81. Found: C, 78.32; H, 5.37; N, 7.29.

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