New 3,7-dihydro-4*H*-pyrazolo[3',4':2,3]pyrido[4,5-*d*]pyrimidin-4-ones

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Thirteen novel pyrazolo[3",4":2,3]pyrido[4,5-*d*]pyrimidin-4-ones **7a–m** were synthesised via tandem aza-Wittig and annulation reactions of the corresponding iminophosphoranes **5**, phenylisocyanate, and substituted amine in 56–86% yields. Their structures were verified by IR, ^{1}H NMR, EI-MS spectroscopy and elemental analysis. Preliminary bioassay indicated that some compounds possess inhibition activity against *Brassica napus* (rape) and *Echinochloa crusgalli* (barnyard grass).

Keywords: fused pyrazoles, pyridines, pyrimidines, aza-Wittig reactions, herbicides

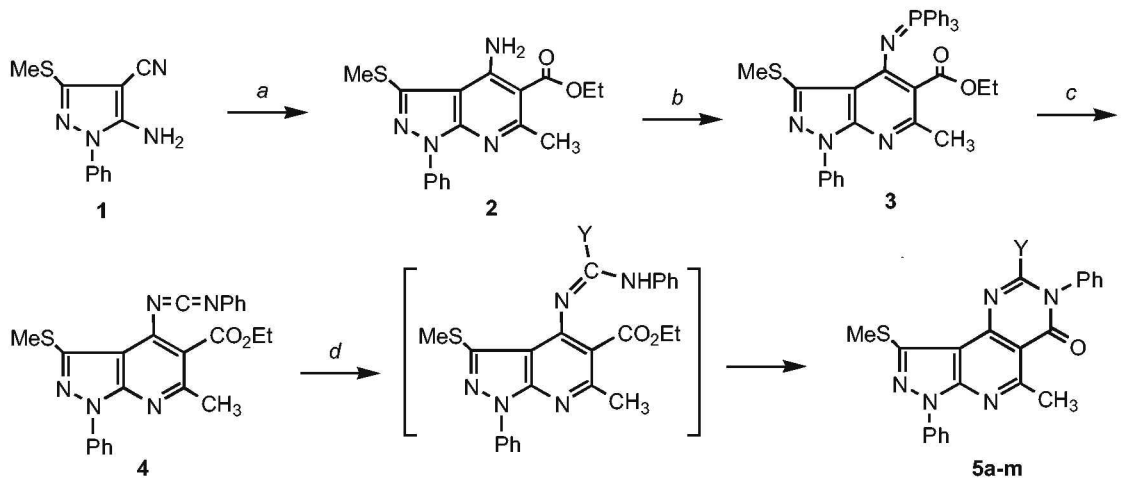
Derivatives of pyridopyrimidines have been the focus of interest for many years. This is due to the wide range of biological activities associated with this heterocyclic scaffold. Some derivatives have shown remarkable biological properties such as antitumour, antiviral, antibacterial, antihypertensive, antibronchitics, antiallergic, antiarthritic and anti-HIV activities,[1-18] while others exhibited insecticidal, growth regulator, herbicidal and fungicidal properties.[19-22] Heterocycles containing the pyrazole nucleus also exhibit various biological activities; several of them have been used as fungicides, bactericides and insecticides.[23-25] The introduction of a pyrazole ring to the pyrido[4,3-*d*]pyrimidin-4-one system may be expected to influence the biological activities significantly. However, this heterocyclic scaffold system has been much less investigated and there is no report on the synthesis of new tricyclic pyrazolo[3',4':2,3]pyrido[4,5-*d*] pyrimidin-4-ones.

The aza-Wittig reactions of iminophosphoranes have received increasing attention in view of their utility in the synthesis of N-heterocyclic compounds.[26-30] We have recently become interested in the synthesis of new heterocycles such as pyrido[4,3-*d*]pyrimidines from various iminophosphoranes, with the aim of exploring their biological activity. Here we describe a facile synthesis of 2-substituted 3,7-dihydro-5-methyl-9-methylthio-3,7-diphenyl-4*H*-pyrazolo[3',4':2,3]pyrido[4,5-*d*] pyrimidin-4-ones via tandem aza-Wittig and cyclisation reactions.

Results and discussion

5-Amino-3-(methylthio)-1-phenylpyrazole-4-carbonitrile **1**, prepared from [bis(methylthio)methylene]malononitrile according to the literature[31], was converted into the pyrazolo[3,4-*b*]pyridine derivative **2** by heating with acetoacetic ester and tin tetrachloride. The iminophosphorane **3** was obtained in a satisfactory yield when **2** was treated with triphenylphosphine, hexachloroethane and triethylamine in acetonitrile. The iminophosphorane reacted with phenyl isocyanate to give the carbodiimide **4**. Direct reaction of carbodiimide **4** with a substituted amine did not produce the desired cyclisation product **5**. However, in CH_2Cl_2 and in the presence of a catalytic amount of EtONa, compounds **4** were converted smoothly into the 2-substituted 3,7-dihydro-5-methyl-9-methylthio-3,7-diphenyl-4*H*-pyrazolo[3',4':2,3]pyrido[4,5-*d*]pyrimidin-4-ones **5** in satisfactory yields at room temperature for 0.5–2 h when either primary or secondary amines were used (Scheme 1).

The results of bioassay indicated that these compounds possess herbicidal activity resulting from their action against the roots of *Brassica napus* (rape) and *Echinochloa crusgalli* (barnyard grass).



Scheme 1

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Experimental

Melting points were measured on an Electrothermal melting point apparatus. Mass spectra (EI, positive-ion detection) were obtained using a Finnigan Trace MS 2000 spectrometer. IR spectra were recorded on an FTS-185 IR spectrometer as KBr pellets. ^{1}H NMR were recorded in DMSO-d_6 or $CDCl_3$ as solvent on a Bruker AC-P400 spectrometer; resonances are given in ppm (δ) relative to TMS. Elemental analyses were taken on a Vario EL III elemental analysis instrument. All of the solvents and materials were reagent grade and purified as required.

Ethyl 4-amino-6-methyl-3-methylthio-1-phenyl-1*H*-pyrazolo[3,4-*b*] pyridine-5-carboxylate **2** was prepared via the pyrazole **1** according to the literature.[32]

Synthesis of iminophosphorane **3**

To a solution of the amino-ester **2** (5.13 g, 15 mmol) in CH_3CN (60 ml) was added Ph_3P (7.86 g, 30 mmol), C_2Cl_6 (7.11 g, 30 mmol) and finally Et_3N (8.3 ml). The mixture was stirred for 6–7 h at r.t. The solvent was then removed, and the residue was recrystallised from EtOH to give **3** in 94% yield, m.p. 152–153 °C. NMR ($CDCl_3$): δ_H 1.39 (t, 3H, $CH_2C\underline{H}_3$, J = 6.8 Hz), 2.77 (s, 3H, SCH_3), 3.05 (s, 3H, CH_3), 4.67 (q, 2H, $C\underline{H}_2CH_3$, J = 7.2 Hz), 7.22–7.68 (m, 20H, ArH). MS: *m/z* (%) 602 (M^+, 43), 539 (22), 463 (44), 262 (58), 201 (45), 183 (100), 108 (40), 77 (56). Anal. Calcd for $C_{35}H_{31}N_4O_2PS$: C, 69.75; H, 5.18; N, 9.30. Found: C, 71.49; H, 5.28; N, 9.67%.

Preparation of 2-(substituted amino)-3,7-dihydro-5-methyl-9-methylthio-3,7-diphenyl-4H-pyrazolo[3',4':2,3]pyrido[4,5-d]pyrimidin-4-ones (**5**): *general procedure*

To a solution of iminophosphorane **3** (1.1 g, 2 mmol) in dry methylene chloride (10 ml), phenyl isocyanate(0.21 g, 2 mmol) was added under nitrogen at room temperature. After mixing, the reaction mixture was left unstirred for 10–12 h, the solvent was removed under vacuum and anhydrous ethanol (10 ml) was added to precipitate triphenylphosphine oxide. Removal of the solvent gave carbodiimide **4**, which were used directly without further purification.

An alkylamine (2 mmol) was added into the solution of **4** prepared as above in CH_2Cl_2 (10 ml). After the reaction mixture was stirred continuously for an additional 10–12 h, the solvent was removed and anhydrous ethanol (10 ml) was added, followed by several drops of sodium ethoxide in ethanol (3M). After stirring for another 0.5–2 h, the solution was concentrated and the residue was recrystallised from dichloromethane/petroleum ether to give pure 2-(substituted amino)-3,7-dihydro-5-methyl-9-methylthio-3,7-diphenyl-4*H*-pyrazolo[3',4':2,3]pyrido[4,5-*d*]pyrimidin-4-one (**5a–m**), in every case as a white crystalline solid. Yields are of isolated products, based on the amount of iminophosphorane taken.

2-(Diethylamino)-3,7-dihydro-5-methyl-9-methylthio-3,7-diphenyl-4H-pyrazolo[3',4':2,3]pyrido[4,5-d]pyrimidin-4-one (**5a**): Yield 68%, m.p. 208–209 °C. IR: ν_{max} 3081 (PhH), 2927 (C–H), 1697 (C=O), 1586 (C=C), 1505 cm^{-1} (C=N). NMR ($CDCl_3$): δ_H 1.36 (t, 6H, $2NCH_2C\underline{H}_3$, J = 7.2 Hz), 2.76 (s, 3H, SCH_3), 3.05 (s, 3H, CH_3), 4.64–4.69 (m, 4H, $2NC\underline{H}_2CH_3$), 7.25–8.38 (m, 10H, ArH). Anal. Calcd for $C_{26}H_{26}N_6OS$: C, 66.36; H, 5.57; N, 17.86. Found: C, 66.29; H, 5.57; N, 18.12%.

2-(Di-n-propylamino)-3,7-dihydro-5-methyl-9-methylthio-3,7-diphenyl-4H-pyrazolo[3',4':2,3]pyrido[4,5-d]pyrimidin-4-one (**5b**): Yield 63%, m.p. >280 °C. IR: ν_{max} 3136 (PhH), 2997 (C–H), 1688 (C=O), 1579 (C=C), 1501 cm^{-1} (C=N). NMR (DMSO-d_6) δ_H 1.16 (t, 6H, $2NCH_2CH_2C\underline{H}_3$), 2.77 (s, 3H, SCH_3), 2.82 (s, 3H, CH_3), 3.11–3.17 (m, 4H, $2NCH_2C\underline{H}_2CH_3$), 3.58–3.64 (m, 4H, $2NC\underline{H}_2CH_2CH_3$), 7.33–8.54 (m, 10H, ArH). Anal. Calcd for $C_{28}H_{30}N_6OS$: C, 67.44; H, 6.06; N, 16.85. Found C, 67.68; H, 6.27; N, 16.98%.

2-(Di-n-butylamino)-3,7-dihydro-5-methyl-9-methylthio-3,7-diphenyl-4H-pyrazolo[3',4':2,3]pyrido[4,5-d]pyrimidin-4-one (**5c**): Yield 60%, m.p. 225–226 °C. IR: ν_{max} 3084 (PhH), 2925 (C–H), 1690 (C=O), 1596 (C=C), 1505 cm^{-1} (C=N). NMR (DMSO-d_6): δ_H 0.93–0.99 (m, 6H, $2NCH_2CH_2CH_2C\underline{H}_3$), 1.24–1.46 (m, 8H, $2NCH_2C\underline{H}_2C\underline{H}_2CH_3$), 2.77 (s, 3H, SCH_3), 3.01 (s, 3H, CH_3), 3.14–3.38 (m, 4H, $2NC\underline{H}_2$), 7.26–8.28 (m, 10H, ArH). Anal. Calcd for $C_{30}H_{34}N_6OS$: C, 68.41; H, 6.51; N, 15.96. Found C, 68.26; H, 6.68; N, 16.13%.

2-(Di-n-pentylamino)-3,7-dihydro-5-methyl-9-methylthio-3,7-diphenyl-4H-pyrazolo[3',4':2,3]pyrido[4,5-d]pyrimidin-4-one (**5d**), yield 56%, m.p. 194–195 °C. IR: ν_{max} 3075 (PhH), 2925 (C–H), 1694 (C=O), 1594 (C=C), 1503 cm^{-1} (C=N). NMR (DMSO-d_6): δ_H 1.05 (t, 6H, $2NCH_2CH_2CH_2CH_2C\underline{H}_3$, J = 7.2 Hz), 1.22–1.27 (m, 8H, $2NCH_2CH_2C\underline{H}_2C\underline{H}_2CH_3$), 2.77 (s, 3H, SCH_3), 2.81 (s, 3H, CH_3), 3.47–3.53 (m, 4H, $2NCH_2C\underline{H}_2CH_2CH_2CH_3$), 3.67–3.73 (m, 4H, $2NC\underline{H}_2$), 7.14–8.36 (m, 10H, ArH). Anal. Calcd for $C_{32}H_{38}N_6OS$: C, 69.28; H, 6.90; N, 15.15. Found C 69.10, H 7.18, N 15.34%.

3,7-Dihydro-5-methyl-9-methylthio-3,7-diphenyl-2-piperidino-4H-pyrazolo[3',4':2,3]pyrido[4,5-d]pyrimidin-4-one (**5e**): Yield 72%, m.p. 199–200 °C. IR: ν_{max} 3066 (PhH), 2924 (C–H), 1692 (C=O), 1594 (C=C), 1504 cm^{-1} (C=N). NMR (DMSO-d_6): δ_H 1.16 (t, 2H, $2NCH_2CH_2C\underline{H}_2$, J = 7.2 Hz), 2.77 (s, 3H, SCH_3), 2.82 (s, 3H, CH_3), 3.11–3.17 (m, 4H, $2NCH_2C\underline{H}_2CH_2$), 3.62(t, 4H, $2NC\underline{H}_2CH_2$, J = 6.8 Hz), 7.34–8.54 (m, 10H, ArH). MS: *m/z* (%) 482 (M^+ 1.2), 443 (6.8), 415 (32), 382 (30), 268 (32), 119 (60), 91 (68), 77 (100), 65 (24). Anal. Calcd for $C_{27}H_{26}N_6OS$: C, 67.20; H, 5.43; N, 17.41. Found: C, 67.01; H, 5.61; N, 17.68%.

3,7-Dihydro-5-methyl-9-methylthio-2-morpholino-3,7-diphenyl-4H-pyrazolo[3',4':2,3]pyrido[4,5-d]pyrimidin-4-one (**5f**): Yield 76%, m.p. 194–196 °C. IR: ν_{max} 3064 (PhH), 2925 (C–H), 1698 (C=O), 1593 (C=C), 1504 cm^{-1} (C=N). NMR (DMSO-d_6): δ_H 2.74 (s, 3H, SCH_3), 2.81 (s, 3H, CH_3), 3.26 (t, 4H, $2NCH_2$, J = 6.4 Hz), 3.63 (t, 4H, $2OC\underline{H}_2$, J = 6.2 Hz), 7.27–8.36 (m, 10H, ArH). Anal. Calcd for $C_{26}H_{24}N_6O_2S$: C, 64.44; H, 4.99; N, 17.34. Found: C, 64.25; H, 5.21; N, 17.53%.

2-Ethylamino-3,7-dihydro-5-methyl-9-methylthio-3,7-diphenyl-4H-pyrazolo[3',4':2,3]pyrido[4,5-d]pyrimidin-4-one (**5g**): Yield 86%, m.p. >280 °C. IR: ν_{max} 3428 (N–H), 3065 (PhH), 2922 (C–H), 1696 (C=O), 1574 (C=C), 1505 (C=N). NMR ($CDCl_3$): δ_H 1.23 (t, 3H, J = 7.2 Hz, $NCH_2C\underline{H}_3$), 2.68 (s, 3H, SCH_3), 2.86 (s, 3H, CH_3), 3.50–3.56 (m, 2H, NCH_2), 4.38 (s, 1H, NH), 7.12–8.34 (m, 10H, ArH). EI MS: *m/z* (%) 442 (M^+, 8.9), 415 (34), 382 (29), 268 (38), 119 (61), 91 (79), 77 (100), 65 (30). Anal. Calcd for $C_{24}H_{22}N_6OS$: C, 65.14; H, 5.01; N, 18.99. Found C, 65.32; H, 5.23; N, 19.14%.

2-n-Propylamino-3,7-dihydro-5-methyl-9-methylthio-3,7-diphenyl-4H-pyrazolo[3',4':2,3]pyrido[4,5-d]pyrimidin-4-one (**5h**): Yield 83%, m.p. >280 °C. IR: ν_{max} 3436 (N–H), 3077 (PhH); 2928 (C–H), 1667 (C=O), 1570 (C=C), 1504 (C=N). NMR ($CDCl_3$): δ_H 0.90 (t, 3H, J = 7.2 Hz, $NCH_2CH_2C\underline{H}_3$), 1.53–1.64 (m, 2H, $NCH_2C\underline{H}_2CH_3$), 2.68 (s, 3H, SCH_3), 2.86 (s, 3H, CH_3), 3.46–3.57 (m, 2H, NCH_2), 4.38 (s, 1H, NH), 7.12–8.34 (m, 10H, ArH). EI MS: *m/z* (%) 456 (M^+ 1.2), 415 (22), 382 (27), 268 (39), 119 (62), 91 (87), 77 (100), 65 (14). Anal. Calcd for $C_{25}H_{24}N_6OS$: C, 65.77; H, 5.30; N, 18.41. Found C, 65.86; H, 5.48; N, 18.63%.

3,7-Dihydro-2-isopropylamino-5-methyl-9-methylthio-3,7-diphenyl-4H-pyrazolo[3',4':2,3]pyrido[4,5-d]pyrimidin-4-one (**5i**): Yield 79%, m.p. >280 °C. IR: ν_{max} 3347(N–H), 3081 (PhH), 2927 (C–H), 1664 (C=O), 1574 (C=C), 1505 cm^{-1} (C=N). NMR ($CDCl_3$): δ_H 1.22 (d, 6H, J = 6.8 Hz, 2×CH_3), 2.68 (s, 3H, SCH_3), 2.86 (s, 3H, CH_3), 3.90–4.01 (m, H, CH), 4.34 (d, 1H, J = 6.8 Hz, NH), 7.12–8.34 (m, 10H, ArH). EI MS: *m/z* (%) 456 (M^+ 6.3), 415 (35), 382 (43), 268 (40), 119 (66), 91 (86), 77 (100), 65 (29). Anal. Calcd for $C_{25}H_{24}N_6OS$: C, 65.77; H, 5.30; N, 18.41. Found C, 65.91; H, 5.44; N, 18.65%.

2-n-Butylamino-3,7-dihydro-5-methyl-9-methylthio-3,7-diphenyl-4H-pyrazolo[3',4':2,3]pyrido[4,5-d]pyrimidin-4-one (**5j**): Yield 76%, m.p. >280 °C. IR: ν_{max} 3285 (N–H), 3071 (PhH), 2927 (C–H), 1678 (C=O), 1575 (C=C), 1505 (C=N). NMR ($CDCl_3$): δ_H 0.93 (t, 3H, J = 7.2 Hz, $CH_2CH_2CH_2C\underline{H}_3$), 1.22–1.36 (m, 2H, J = 7.2 Hz, $CH_2CH_2C\underline{H}_2CH_3$), 1.54–1.62(m, 2H, J = 7.2 Hz, $CH_2C\underline{H}_2CH_2CH_3$), 2.68 (s, 3H, SCH_3), 2.86 (s, 3H, CH_3), 3.50(q, 2H, J = 6.2 Hz, $NC\underline{H}_2CH_2CH_2CH_3$), 4.36 (s, 1H, NH), 7.12–8.34 (m, 10H, ArH). EI MS: *m/z* (%) 470 (M^+ 7.9), 415 (38), 382 (33), 268 (39), 119 (51), 91 (80), 77 (100), 65 (35). Anal. Calcd for $C_{26}H_{26}N_6OS$: C, 66.36; H, 5.57; N, 17.86. Found C, 66.29; H, 5.66; N, 18.08%.

3,7-Dihydro-2-isobutylamino-5-methyl-9-methylthio-3,7-diphenyl-4H-pyrazolo[3',4':2,3]pyrido[4,5-d]pyrimidin-4-one (**5k**): Yield 73%, m.p. >280 °C. IR: ν_{max} 3405 (N–H), 3064 (PhH), 2926 (C–H), 1680 (C=O), 1570 (C=C), 1504 (C=N). NMR ($CDCl_3$): δ_H 0.86 (d, 6H, J = 6.8 Hz, 2×CH_3), 1.86–1.96 (m, 1H, CH), 2.68 (s, 3H, SCH_3), 2.86 (s, 3H, CH_3), 3.30 (d, 2H, J = 6.2 Hz, $NC\underline{H}_2CH$), 4.36 (s, 1H, NH), 7.12–8.34 (m, 10H, ArH). EI MS: *m/z* (%) 470 (M^+ 12), 415 (22), 382 (28), 268 (39), 119 (69), 91 (87), 77 (100), 65 (24).Anal. Calcd for $C_{26}H_{26}N_6OS$: C, 66.36; H, 5.57; N, 17.86. Found C, 66.26; H, 5.75; N, 18.12%.

3,7-Dihydro-5-methyl-9-methylthio-3,7-diphenyl-2-phenylamino-4H-pyrazolo[3',4':2,3]pyrido[4,5-d]pyrimidin-4-one (**5l**): Yield 79%, m.p. >280 °C. IR: ν_{max} 3425 (N–H), 3087 (PhH), 2924 (C–H), 1682 (C=O), 1573 (C=C), 1501 (C=N). NMR ($CDCl_3$): δ_H 2.68 (s, 3H, SCH_3), 2.86 (s, 3H, CH_3), 4.38 (s, 1H, NH), 7.12–8.34 (m, 15H, ArH). EI MS: *m/z* (%) 490 (M^+ 14), 443 (3.8), 415 (31), 382 (30), 268 (24), 119 (51), 91 (79), 77 (100), 65 (22). Anal. Calcd for $C_{28}H_{22}N_6OS$: C, 68.55; H, 4.52, N; 17.13. Found C, 68.36; H, 4.70; N, 17.36%.

2-Benzylamino-3,7-dihydro-5-methyl-9-methylthio-3,7-diphenyl-4H-pyrazolo[3',4':2,3]pyrido[4,5-d]pyrimidin-4-one (**5m**): Yield 82%, m.p. >280 °C. IR: ν_{max} 3429 (N–H), 3062 (PhH), 2925 (C–H), 1686 (C=O), 1536 (C=C), 1504 (C=N). NMR ($CDCl_3$): δ_H 2.68 (s,

3H, SCH_3), 2.86 (s, 3H, CH_3), 4.12 (d, 2H, J = 6.2 Hz, NCH_2Ph), 4.38 (s, 1H, J = 5.4 Hz, NH), 7.20–8.14 (m, 15H, ArH). EI MS: *m/z* (%) 504 (M^+, 22), 415 (36), 382 (40), 268 (37), 119 (41), 91 (88), 77 (100), 65 (21). Anal. Calcd for $C_{29}H_{24}N_6OS$: C, 69.03; H, 4.79; N, 16.65. Found C, 69.30; H, 4.94; N, 16.82%.

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