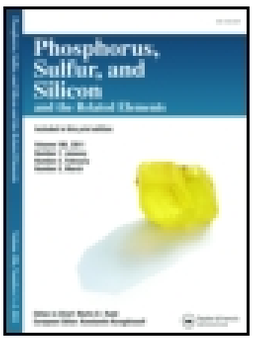

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Synthesis and herbicidal activity of novel 6-arylthio-3-methylthio-1*H*-pyrazolo[3,4-d]pyrimidin-4(5*H*)-ones

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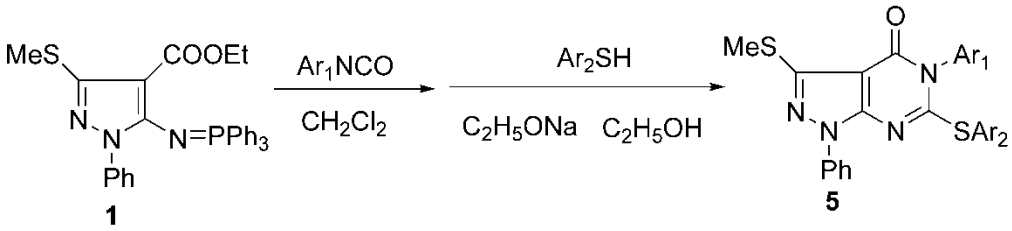
Abstract: A series of pyrazolo[3,4-d]pyrimidine-4-one derivatives were conveniently synthesized via tandem aza-Wittig and annulation reactions of the corresponding iminophosphoranes, arylisocyanate, and substituted thiophenols. The structures of the target compounds were confirmed by IR, ^{1}H NMR, ^{13}C NMR, LC-MS, and elemental analysis. The preliminary bioassay demonstrated that some title compounds such as 6-(3-chlorophenylthio)-1-phenyl-3-methylthio-5-(4-chlorophenyl)-1*H*-pyrazolo[3,4-d]-pyrimidin-4(5*H*)-one and 6-(4-fluorophenylthio)-1-phenyl-3-methylthio-5-(3-chlorophenyl)-1*H*-pyrazolo[3,4-d]pyrimidin-4(5*H*)-one showed good inhibition activities against the root of *Brassica napus* (rape) and *Echinochloa crusgalli* (barnyard grass) at a dosage of 100 mg/L.

Keywords: Pyrazolo[3,4-d]pyrimidin-4-one derivatives; synthesis; preliminary bioassay; inhibition activities

Graphical Abstract



Introduction

N-Containing heterocycles have received extensive attention as they are widely found in natural products, agrochemicals, and drug molecules. Among the fused *N*-heterocycles, pyrazolopyrimidins are described as a charismatic target owing to their remarkable biological activities such as antibacterial,[1] antiviral,[2] antiphlogosis,[3] antipodagric,[4] antihistamine,[5] antitumor,[6] and herbicidal.[7,8] Some of them are used clinically as antipodagric (allopurinol)[9] and erectile dysfunction (viagra)[10,11] drugs. In recent years, the synthesis and biological activity of these derivatives have become one of hot topics in current biological and pharmacological studies.

Pyrazolo[3,4-d]pyrimidine, one of the isomers of the pyrazolopyrimidine series, has been the focus of drug investigations due to the ease of synthesis and high stability of these compounds. There are various methods reported in the literature for the preparation of pyrazolo[3,4-d]pyrimidine.[12-26] For example, the reaction of 5-amino-3-methyl-sulfanyl-1*H*-pyrazole-4-carbonitrile with formic acid, phosphorus oxychloride, and aromatic aldehydes produced a class of pyrazolo[3,4-d]pyrimidines. These compounds were found to exhibit anti-breast cancer activity.[18] Shi and coworkers reported an effective one-pot multicomponent reaction for the synthesis of pyrazolo[3,4-d]pyrimidinone derivatives from hydrazine, methylenemalononitrile, and aldehyde.[26] In our previous work, sixteen pyrazolo[3,4-d]pyrimidinone derivatives were designed and synthesized, and the subsequent herbicidal testing showed that two compounds possessed 100% inhibition rate to rape and barnyard grass at 100 mg/L.[27] Recently, we have become interested in the synthesis of new bioactive, fused heterocycles, such as pyrazolo[3,4-d]pyrimidine-4-ones from various iminophosphoranes, with

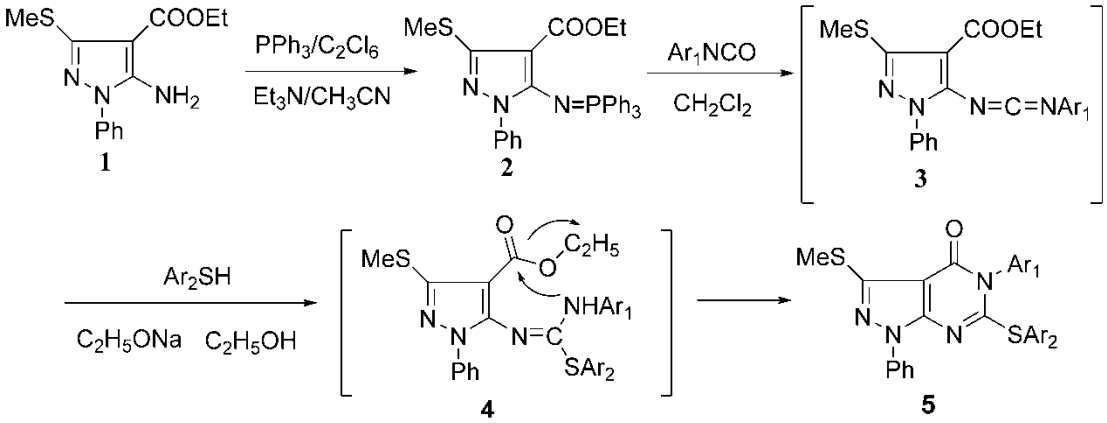
the aim to evaluate their biological activities. Herein, we utilized iminophosphoranes **2**, arylisocyanate, and substituted thiophenols as the substrates to synthesize pyrazolo[3,4-d]pyrimidine-4-ones **5** via tandem aza-Wittig and annulation reactions. A preliminary bioassay of these title compounds was studied and many compounds possessed herbicidal activity against the root and stalk of *Brassica napus* (rape) and *Echinochloa crusgalli* (barnyard grass).

Results and discussion

Synthesis and spectroscopic characterization

The synthetic procedures of the newly designed pyrazolo[3,4-d]pyrimidin derivatives are demonstrated in Scheme 1. 5-Amino-3-methylthio-1-phenyl-1*H*-pyrazole-4-carboxylic acid ethyl ester **1**, which was obtained as reported,[28] reacted with triphenylphosphine, hexachloroethane, and triethylamine to give iminophosphorane **2** in satisfactory yield. Iminophosphorane **2** was converted to carbodiimides **3** via reaction with arylisocyanate. **3** reacted with various thiophenols in the presence of a catalytic amount of sodium ethoxide (Table 1) to produce the corresponding target compounds **5** conveniently.

<Insert Scheme 1 here>



<Insert Table 1 here>

The title compounds **5** were characterized by IR, ^{1}H NMR, and ^{13}C NMR spectra. In the ^{1}H NMR spectra, the single peaks at 2.66 ppm and 2.51 ppm were attributed to the methyl of SCH_3 and Ph-CH_3, respectively. The signals at 7.14-7.74 ppm could be assigned to the protons of Ar-H. The ^{13}C NMR peak at 13.6 ppm was attributed to the carbon of SCH_3, and the peak at 21.5 ppm was attributed to Ph-CH_3. The typical carbon resonance of 164.0 ppm was indicative of the carbonyl group (C=O). In the IR spectrum, the C=O vibration appeared at 1705 cm^{-1}.

Herbicidal Activity

The herbicidal activity of compounds **5a-o** against rape and barnyard grass has been studied at the dosage of 100 mg/L and 10 mg/L using a reported procedure.[29] Table S 1 (Supplemental Materials shows the inhibition rates of these compounds. The results of the bioassay illustrate that many of these compounds exhibited good herbicidal activity. For example, **5j** and **5k** show >90% inhibition rates to root of barnyard grass at 100 mg/L. **5j** and **5l** displayed >90% inhibition rate to root of rape at 100 mg/L.

Conclusions

In summary, fifteen novel pyrazolo[3,4-d]pyrimidine-4-ones have been successfully synthesized and their structures confirmed by ^{1}H NMR, ^{13}C NMR, IR, LC-MS, and elemental analysis. The preliminary bioassay displayed that some of the compounds exhibit good herbicidal activity against the root and stalk of rape and barnyard grass. The study in this work will provide useful information for the design and discovery of fused heterocycles containing a pyrazolo[3,4-d]pyrimidine moiety with high herbicidal activity.

Experimental

Melting points (mp.) were measured on an electrothermal melting-point apparatus and are temperature uncorrected. LC-MS spectra were measured on a 1100LC/MSD Trap spectrometer. A FTS-185 IR spectrometer was used to record IR spectra (KBr pellets). ^{1}H, ^{13}C, and ^{19}F NMR were recorded on a Bruker 400 spectrometer with $CDCl_3$ as the solvent at 400 MHz (^{1}H), 100 MHz (^{13}C), and 376 MHz (^{19}F). The elementary analyses were taken on a Vario EL III elementary analysis instrument. Ph_3P, hexachloroethane (C_2Cl_6), arylisocyanate, and substituted thiophenols were purchased from Aladdin Reagent (China). Et_3N and CH_3CN were dried by standard methods and distilled before use. 5-Amino-3-alkylthio-1-phenyl-1H-pyrazole-4-carboxylate **1** was synthesized according to the literature.[28] The Supplemental Materials contains sample ^{1}H, ^{13}C NMR and FT-IR spectra for products 5, together with full characterization data (Figures S 1 – S 50)

Synthesis of Iminophosphorane 2

Ph_3P (7.86 g, 30mmol), C_2Cl_6 (7.11 g, 30mmol), and Et_3N (6.06 g, 60 mmol) were added to a solution of **1** (4.155g, 15 mmol) in dry acetonitrile (60 mL) under nitrogen atmosphere. After stirring the reaction mixture at room temperature for 5 h, the solution was concentrated under vacuum, and the solid residue was washed with ethanol to give compound **2** in 88% yield. Mp. 192-194 °C; ^{1}H NMR δ: 7.19-7.72 (m, 20H, Ph), 3.60-3.65 (q, 2H, J = 7.0 H_Z, OCH_2), 2.52 (s, 3H, SCH_3), 0.91-0.95 (t, 3H, J = 7.1 H_Z, CH_2CH_3); ^{13}C NMR δ: 163.7, 149.3, 140.1, 132.5, 132.4, 132.1, 131.5, 128.3, 128.2, 128.1, 126.0, 125.1, 58.6, 14.4, 13.1.

6-Arylthio-3-methylthio-1H-pyrazolo[3,4-d]pyrimidin-4(5H)-ones 5 (General Procedure)

Arylisocyanate (2 mmol) was added to a solution of iminophosphorane **2** (2 mmol) in dry CH_2Cl_2 (25 mL) under N_2 at room temperature. After 6 h, substituted thiophenol (2 mmol) was

added and the solution was stirred for additional 30 min. Then the solvent was removed under vacuum, and anhydrous ethanol (25 mL) and a catalytic amount of EtONa was added to the mixture. After stirring for 6 h at room temperature, the mixture was filtered to obtain a white solid which was recrystallized from CH_2Cl_2/petroleum ether to provide the pure 6-arylthio-3-methylthio-1*H*-pyrazolo[3,4-d] pyrimidin-4(5*H*)-ones **5**. ^{1}H, ^{19}F and ^{13}C NMR and IR spectra of products **5a**-**5o** are presented in the Supplemental Materials (Figures S 3-S 50).

6-Phenylthio-3-methylthio-1,5-diphenyl-1*H*-pyrazolo[3,4-d]pyrimidin-4(5*H*)-one (**5a**). White crystals; yield: 70.4%; mp. 280-282 °C; IR: 3053, 2925, 1700 (C=O), 1598, 1530, 1506, 1033, 754, 687 cm^{-1}; ^{1}H NMR δ: 7.14-7.73 (m, 15H, Ar-H), 2.66 (s, 3H, SCH_3); ^{13}C NMR δ: 164.0, 157.4, 151.4, 147.0, 138.7, 136.4, 135.3, 130.3, 130.1, 129.9, 129.6, 129.4, 128.6, 128.2, 125.7, 119.7, 102.8, 13.6; LC-MS (ESI) *m/z*: 443.1 $[M+H]^+$; Anal. Calcd.(%) for $C_{24}H_{18}N_4OS_2$: C 65.13, H 4.10, N 12.66; Found C 65.36, H 4.16, N 12.71.

6-(4-Fluorophenylthio)-3-methylthio-1,5-diphenyl-1*H*-pyrazolo[3,4-d]pyrimidin-4(5*H*)-one (**5c**). White crystals; yield: 79.4%; mp. 295-296 °C; IR: 3067, 2924, 1699 (C=O), 1590, 1528, 1504, 1036, 778, 688 cm^{-1}; ^{1}H NMR δ: 7.17-7.72 (m, 14H, Ar-H), 2.66 (s, 3H, SCH_3); ^{19}F NMR δ: -109.8; ^{13}C NMR δ: 165.4, 163.7, 162.9, 157.4, 151.3, 147.1, 138.6 (d, J = 8.6 H_Z), 135.2, 130.4, 129.9, 129.4, 128.6, 126.0, 123.6, 119.8, 116.9, 116.7 (d, J = 22.1 Hz), 102.7, 13.5; LC-MS (ESI) *m/z*: 461.1 $[M+H]^+$; Anal. Calcd.(%) for $C_{24}H_{17}FN_4OS_2$: C 62.59, H 3.72, N 12.17; Found C 62.38, H 3.96, N 12.32.

6-(4-Fluorophenylthio)-1-phenyl-3-methylthio-5-(4-chlorophenyl)-1*H*-pyrazolo [3,4-d]pyrimidin-4(5*H*)-one (**5h**). White crystals; yield 83.2%; mp.: 275-276 °C; IR: 3072, 2925, 1704 (C=O), 1589, 1530, 1505, 1027, 741, 687 cm^{-1}; ^{1}H NMR δ: 7.19-7.70 (m, 13H, Ar-H),

2.67(s, 3H, SCH_3); ^{19}F NMR δ: -109.5; ^{13}C NMR δ: 165.4, 163.3, 162.9, 157.2, 151.2, 147.2, 138.7-138.5 (t, *J* = 40.0 Hz), 136.6, 133.6, 130.8, 130.2, 128.6, 126.1, 123.3, 119.8, 116.8 (d, *J* = 22.2 Hz), 102.5, 13.5.; LC-MS (ESI) *m/z*: 495.0 $[M+H]^+$; Anal. Calcd.(%) for $C_{24}H_{16}ClFN_4OS_2$: C 58.23, H 3.26, N 11.32; Found C 58.35, H 3.43, N 11.51.

6-(3-Chlorophenylthio)-1-phenyl-3-methylthio-5-(3-chlorophenyl)-1*H*-pyrazolo[3,4-d]pyrimidin-4(5*H*)-one (**5o**). White crystals; yield: 73.5%; mp. 237-238 °C; IR: 2927, 1712(C=O), 1597, 1530, 1506, 1036, 745, 689 cm^{-1}; ^1H NMR δ: 7.15-7.68 (m, 13H, Ar-H), 2.66(s, 3H, SCH_3); ^{13}C NMR δ: 162.5, 157.0, 151.1, 147.2, 138.5, 136.2, 136.1, 135.5, 135.1, 134.3, 130.8, 130.8, 130.6, 130.4, 129.8, 129.5, 128.7, 127.8, 126.1, 112.0, 102.6, 13.5; LC-MS (ESI) *m/z*: 511.0 $[M+H]^+$; Anal. Calcd.(%) for $C_{24}H_{16}Cl_2N_4OS_2$: C 56.36, H 3.15, N 10.95; Found C 56.45, H 3.28, N 11.02.

Acknowledgments

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Table 1. Structures of products **5a-o**.

Compound	Ar^1	Ar^2
5a	Ph	Ph
5b	Ph	4-CH_3Ph
5c	Ph	4-FPh
5d	Ph	4-ClPh
5e	Ph	3-ClPh
5f	4-ClPh	Ph
5g	4-ClPh	4-CH_3Ph
5h	4-ClPh	4-FPh
5i	4-ClPh	4-ClPh
5j	4-ClPh	3-ClPh
5k	3-ClPh	Ph
5l	3-ClPh	4-CH_3Ph
5m	3-ClPh	4-FPh
5n	3-ClPh	4-ClPh
5o	3-ClPh	3-ClPh