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Synthesis and herbicidal activity of novel pyrazolo[3,4-*d*]pyrimidin-4-one derivatives containing aryloxyphenoxypropionate moieties

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Abstract—The 6-(4-alkoxycarbonylalkoxy)phenoxy-3-alkylthio(alkylsulfonyl)-1-phenyl-5-(substituted phenyl)pyrazolo[3,4-*d*]pyrimidin-4-ones **6** and **7** have been synthesized via the tandem aza-Wittig and annulation reactions of the corresponding iminophosphoranes **4**, aromatic isocyanates, and substituted phenols **2** in 52–98% yields. Their structures were clearly verified by spectroscopic data (IR, ^{1}H NMR, ^{13}C NMR, MS, and elemental analysis or X-ray diffraction crystallography). And the results of preliminary bioassay indicated that these title compounds possess potential herbicidal activity against the root of rape and barnyard grass.

The derivatives of fused pyrimidinones have been the focus of great interest over many years due to the fact that many compounds containing a fused pyrimidinone ring play an important role in the biochemistry of the living cell.[1] Pyrazolo[3,4-*d*]pyrimidin-4-one derivatives also have extremely rich biological activities because of their structural similarity with purines,[2] they exhibit excellent antibacterial, antiphlogistic, and antitumor activities,[3] and they are employed in the treatment of erectile dysfunction in male animals.[4] In previous reports, various synthetic procedures have been devised for the conversion of *o*-aminonitriles and *o*-aminoesters bearing pyrazole ring to pyrazolopyrimindinone derivatives.[5] However, 3-substituted-6-(4-alkoxycarb-onylalkoxy)phenoxy pyrazolo[3,4-*d*]pyrimidin-4-ones are not easily accessible by these existing methods.

Aryloxyphenoxypropionate (APP) derivatives are a very important class of herbicides in the international market.[6] In recent years, heterocycles were introduced to the structures of APP, which lead to the development of a new series of highly efficient herbicides, such as whip, fenthiaprop-ethyl, quizalofop-ethyl, and heloxyfop-methyl.[7] Furthermore, some heteroaryloxo-phenoxy carbonates are of good fungicidal activity and anti-cancer activity.[8]

Aza-Wittig reactions of iminophosphoranes have received increasing attention in view of their utility in the synthesis of nitrogen-containing heterocyclic compounds.[9] Recently, aza-Wittig reactions of isocyanates were used to synthesize carbodiimides, which, in turn, were able to undergo a plethora of cyclization reactions, leading to the preparation of thienodipyrimidinones,[10] quinazolines,[11] imidazolinones,[12] pteridinones,[13] and fused pyrimidines.[14] As the continuing work of our search for new herbicidal active heterocycles,[15] we designed the structures which contain both pyrazolo-[3,4-*d*]pyrimidin-4-one and aryloxyphenoxypropionate (APP) moieties based on biochemical reasoning, and developed a new annulation process (Scheme 1), which proceeded smoothly via a tandem aza-Wittig and cyclization reaction to afford the novel title compounds 6-(4-alkoxycarbonylalkoxy)phenoxy-3-alkylthio(alkylsulfonyl)-1-phenyl-5-(substituted phenyl)pyrazolo[3,4-*d*]pyrimidin-4-ones **6** and **7**, in order to obtain better herbicidal activity.

The iminophosphorane **4**, which was prepared from 3-alkylthio-5-amino-4-ethoxycarbonyl-1-phenylpyrazole **3**, reacted with aromatic isocyanate to afford carbodiimide **5**. Then reaction of 2-(4-hydroxyphenoxy)-carboxylate **2** with **5** provides intermediate guanidine **8**. In the presence of catalytic amount of potassium carbonate,

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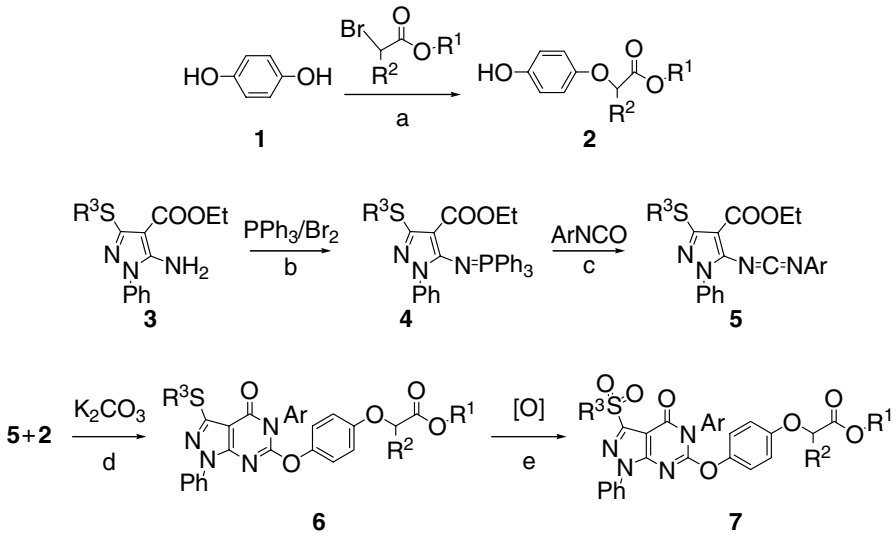
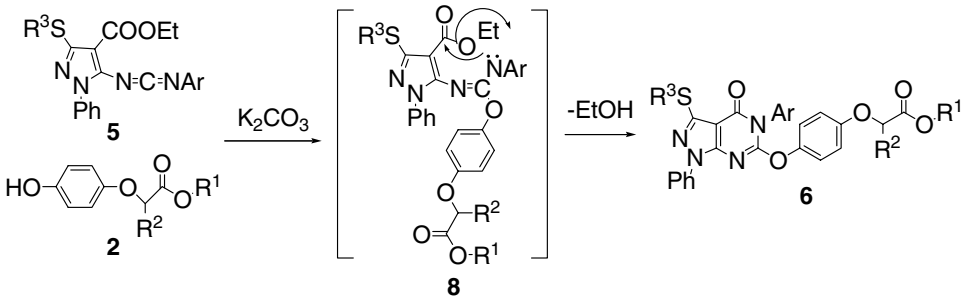


Scheme 1. Synthesis of the title compounds **6** and **7**. Reagents and conditions: (a) R^1ONa, R^1OH, 0–35 °C, 6 h, yields 57–66%; (b) Et_3N, CH_2Cl_2, 0 °C for 30 min then 25 °C for 26 h, yields 84%; (c) CH_2Cl_2, rt, 2–5 h; (d) K_2CO_3, CH_3CN, reflux, 5 h, yields 52–84%; (e) $Na_2WO_4{\cdot}H_2O$, AcOH, 30% H_2O_2, 50 °C, 5 h, yields 75–98%.



Scheme 2. The cyclization of carbodiimide **5** to synthesize the title compounds **6**.

the reaction took place to give **6** in moderate to good yields after recrystallization. This process can be rationalized in Scheme 2.

In this reaction, a variety of substituents can be tolerated in Ar group, such as electron-withdrawing groups (F, Cl) or electron-donating group (Me). R^1, R^2, and R^3 also could be various alkyl groups. Satisfactory yields of **6** were obtained when polar solvent acetonitrile was used;[16] furthermore, compounds **6** could be oxidized by hydrogen peroxide (H_2O_2) using sodium wolframate (Na_2WO_4) as catalyst to give the corresponding compounds **7** at about 40 °C. The results are listed in Table 1.

Table 1. Yields of compounds **6** and **7**

Compounds	R =	R^3	R^2	R^1	Yields of **6** (%)	Yields of **7** (%)
6a, **7a**	H	Me	Me	Me	80	75
6b, **7b**	*o*-Cl	Me	Me	Me	73	78
6c, **7c**	*m*-Me	Me	Me	Me	80	91
6d, **7d**	*o*-F	Me	Me	Me	65	85
6e, **7e**	H	Me	Me	Et	84	98
6f, **7f**	*o*-Cl	Me	Me	Et	71	83
6g, **7g**	*m*-Me	Me	Me	Et	78	86
6h, **7h**	*m*-Me	Me	H	Et	82	77
6i, **7i**	*m*-Me	Bn	Me	Et	52	90
6j, **7j**	*m*-Me	Bn	H	Et	66	82
6k, **7k**	H	Me	Me	*n*-Pr	82	78
6l, **7l**	*o*-Cl	Me	Me	*n*-Pr	72	95
6m, **7m**	*m*-Me	Me	Me	*n*-Pr	74	77

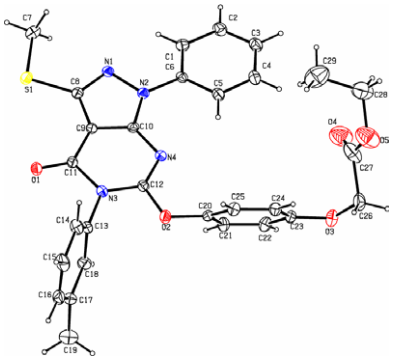


Figure 1. View and atom labeling of **6h**.