A FACILE SYNTHESIS OF 6-ALKOXYL (AROXYL)-1,5-DIHYDROPYRAZOLO-[3,4-d]PYRIMIDIN-4-ONE DERIVATIVES

Hong-Qing WANG[1,2] Li-Min Yang[1] Zhao-Jie LIU [1]* Ming-Wu DING[1]

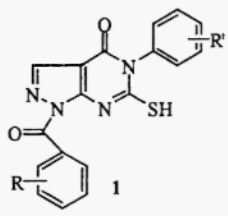
1. Institute of Organic Synthesis, Central China Normal University, Wuhan, 430079, P.R.China.

2. College of Chemistry &Chemical Engineer, NanHua University, Hengyang, 421001, P.R.China.

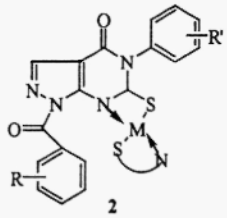
Abstract: Reaction of 3-methylthio-1-phenyl-5-{[(triphenyl-λ^5-phosphanylidene)methane] -amino}-1H-pyrazole-4-carboxylic acid ethyl ester with ROH in the presence of RONa or passium carbonate affords 6-alkoxyl/aroxyl-3-alkylthio-1,5-diphenyl-1,5-dihydropyrazolo[3,4-d]pyrimidin -4-one

Introduction:

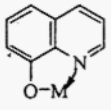
A number of pyrazolo[3,4-d]pyrimidine derivatives had exhibited excellent fungicidal[1], antiphlogistic[2-4] and antiumor[5] activities. The compound **1** by virtue of having SH group adjacent to N-atom served very well as suitable ligand to chelate essential metal which fungus needed in its metabolism[6], which was similar to that of 8-hydroxyquinolin **3** which displayed antibacterials and antifungal[7] activities, and then exhibited excellent antifungal activies[8]. Thus, it was expected that title compound might be promising pesticidal agents. They were generally synthesized from the reaction of 5-alkoxycarbonylamino-1H-pyrazole-4-carboxylic acid with 2-aminoacetate[9] and the reaction of 1,7-dihydropyrazolo[3,4-d]pyrimidin-4,6-dione with iodomethane[10]. In this paper, a facile synthesis access to 6-alkoxyl (aroxyl) -3- methylthio-1,5-diphenyl-1,5- dihydropyrazolo[3,4d]pyrimidin-4-one derivatives via reaction of functionalized carbodiimide with ROH[11] would be reported and a serials of new compounds had been prepared.



1



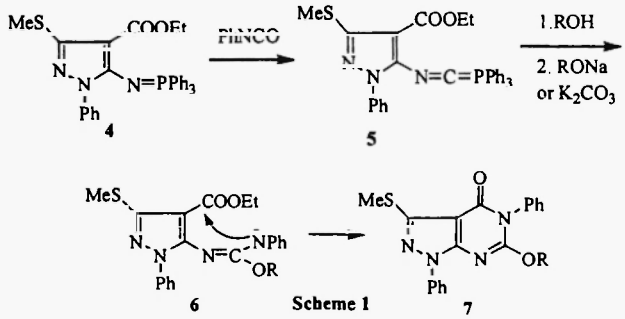
2



3

Results and Discussion:

The imiphosphorane **4** reacted with phenyl isocyanate to afford carbodiimide **5**. The reaction of **5** with ROH was carried out very slowly even at refluxing, however, when R was alkyl, the reaction was undergone smoothly in the presence of catalytic RO^-Na^+, and when R was aryl, the reaction took place smoothly under excess K_2CO_3. The final product obtained was verified to be 6-alkoxyl(aroxyl)-3-meththio-1,5-diphenyl-1,5-dihydropyrazolo[3,4-d]pyrimidin-4-one **7**.



Scheme 1

The reaction condition was related to R group. When R was alkyl, the reaction was undergone at room temperature in good yield, but when R was bulky (R = ios-Pr), the yield decreased; when R was aryl, the reaction was carried out at refluxing temperature and the yield was less than that of alkyl group. The stronger of electron-drawing of the group which Ar bore, the less of the yield (see **Table 1**). The formation of 7 could be rationalized in terms of an initial nucleophilic addition of RO^- to afford the intermediate **6** which directly cyclized to give 7 (see **Scheme 1**).

The structure of the title compounds had been confirmed by elemental analytical results and spectral data IR, ^1H NMR, EI-MS. Taken compound 7a as representative example, which gave correct elemental analysis, in IR spectra showed the strong stretching resonance peak of C=O at 1704 cm^{-1} and 1600 cm^{-1}, 1572 cm^{-1}, 1549 $cm^{-1}$for aromatic ring. ^1H NMR spectrum displayed a sharp singlet at δ2.66ppm for SCH_3, 3.97ppm for OCH_3, a multiplet at 7.18 ~ 8.11ppm for aromatic protons. The EI-MS spectra showed strong molecule peak (100 %).

Experimental:

Melting points were determined with a WRS-1B Digital melting point apparatus and were uncorrected. EI-MS was measured on a FinnigenTrace Mass 2000 Spectrometer. IR was recorded on a Avatar 360 Spectrometer. ^1H NMR was taken on a Varian Mercury Plus-300 Spectrometer with TMS as the internal and with $CDCl_3$ as the solvent. Elementary Analysis were taken on a Vario EL III elementary analysis instrument. All of the solvents and materials were reagent grade and purified as required.

Table1. Compounds of 6-alkoxyl

(aroxyl)-3-methylsulfanyl-1,5-diphenyl-1,5–dihydropyrazolo [3,4-d]pyrimidin-4-one

compound	R	condition	Yield/%*
7a	Me	r.t./1 h	85.8
7b	Et	r.t./2 h	86.6
7c	n-Pr	r.t./2 h	82.7
7d	iso-Pr	r.t./3 h	36.4
7e	Ph	reflux/3h	43.8
7f	p-CH_3Ph	reflux/3h	50.8
7g	m-CH_3Ph	reflux/3h	60.2
7h	p-ClPh	reflux/3h	81.2
7i	o-ClPh	reflux/5h	42.0
7j	2,4-2ClPh	reflux/8h	18.2
7k	p-O_2NPh	reflux/8h	13.7
7l	m-O_2NPh	reflux/8h	32.5

* isolated yields based on iminophosphorane **4**

General procedure for the preparation of iminophosphorane 4 [12].

A solution of triphenylphosphine (13.1g, 50mmoles) in dichloromethane (120mL) at 0°C was treated with bromine (8.0g, 50mmoles). The resulting reaction mixture was stirred at 0°Cfor 30 minutes and then treated with triethylamine (10.1g, 100mmoles) followed immediately by the addition of 5-amino-pyrazole **1** (13.9g, 50mmoles). After **1** added, the cooling bath was removed and the reaction mixture was allowed to stir at 25°C for 26 hours. The reaction mixture was washed by water for three times and then was dried over anhydrous sodium sulfate. After removing off the solvent, the residues were recrystallized with benzene/n-hexane gave 22.63g (26.85g theoretical ,84.28%) of **2** as a pale yellow crystal, m.p. 192.1~193.8□. ^{1}H NMR($CDCl_3$, TMS, 300Hz): 7.16 ~ 7.70 (20H, m, Ph), 3.61 (2H, q, J = 7.2Hz), 2.51 (3H, s), 1.44 (3H, t, J = 7.2Hz).

General procedure for the preparation of 6-alkoxyl-3-alkylthio-1,5-diphenyl-1,5-dihydro -pyrazolo[3,4-d] pyrimidin-4-one 7a ~ 7d

To a solution of iminophosphorane **2** (1.61g, 3mmol) in dry methylene dichloride (20mL) phenyl isocyanate (0.36g, 3mmol) was added under nitrogen at room temperature. After the reaction mixture was stirred for 1.5 hours, the solvent was removed off under reduced pressure and 25mL anhydrous ROH and catalytic sodium alkoxide was added to the mixture. After stirring for 1 ~ 3 hours at room temperature, the solution was condensed under reduce pressure, the mixture was cooled and filtered, white solid was obtained. Recrystallized from dichloromethane/petroleum ether to give pure 6-alkoxyl-3-alkylthio-1,5-diphenyl-1,5-dihydro-pyrazolo[3,4-d]pyrimidin-4 -one **7a ~ 7d.**

General procedure for the preparation of 6-aroxyl-3-alkylthio-1,5-diphenyl-1,5-dihydro -pyrazolo[3,4-d] pyrimidin-4-one 7e ~ 7l

To a solution of iminophosphorane **2** (1.61g, 3mmol) in dry methylene dichloride (20mL) phenyl isocyanate (0.36g, 3mmol) was added under nitrogen at room temperature. After the reaction mixture was stirred for 1.5 hours, the solvent was removed off under reduced pressure and 25mL anhydrous acetonitrile and 1.5g anhydrous passium carbonate was added to the mixture. After stirring for 3 ~ 8 hours at refluxing and filtrating, the solution was condensed under reduce pressure, white solid was obtained. Recrystallized from ethanol or purified by a silica gel column to give pure 6-aroxyl-3-alkylthio-1,5-diphenyl-1,5-dihydro -pyrazolo[3,4-d] pyrimidin-4-one **7e ~ 7l**

7a: 6-methoxyl-3-methylthio-1,5-diphenyl-1,5–dihydropyrazolo [3,4-d]pyrimidin-4-one

White crystals, m.p. 233.9~235.3 °C, **^{1}H NMR** ($CDCl_3$, 300MHz) δ:2.66 (s, 3H, **SCH_3**), 3.97 (s, 3H, **OCH_3**), 7.18 ~ 8.11 (m, 10H, **Ph**); **IR** (KBr)ν(cm^{-1}): 1704, 1600, 1572, 1549,1383, 1344, 1038; **EI-MS** (70eV, m/z) (relative intensity %): 365 (M+1, 24), 364 (M+, 100), 331 (34), 119 (22), 91 (17), 77 (32); **Elemental Anal.** Calcd. for $C_{19}H_{16}N_4O_2S$: C, 62.62; H, 4.43; N, 15.37; Found: C, 62.86; H, 4.30; N, 15.49.

7b: 6-ethoxyl-3-methylthio-1,5-diphenyl-1,5–dihydropyrazolo [3,4-d]pyrimidin-4-one

White crystals, m.p. 164.7~166.5 °C, **^{1}H NMR** ($CDCl_3$, 300MHz) δ: 1.28 (t, 3H, J = 7.2Hz, CH_2**CH_3**), 2.67 (s, 3H, SCH_3), 4.45 (q, 2H, J = 7.2Hz, **CH_2**CH_3), 7.18 ~ 8.10 (m, 10H, Ph); **IR** (KBr) ν (cm^{-1}): 1705, 1600, 1570, 1549 1396, 1330, 1015; **EI-MS** (70eV, m/z) (relative intensity %): 379 (M+1,40), 378 (M+, 100), 345 (31), 317 (11), 258 (6), 231 (10), 91 (12), 77 (41); **Elemental Anal.** Calcd. for $C_{20}H_{18}N_4O_2S$: C, 63.47; H, 4.79; N,

14.80; Found: C, 63.12; H, 4.73; N, 14.68.

7c: 6-propoxyl-3-methylthio-1,5-diphenyl-1,5–dihydropyrazolo [3,4-d]pyrimidin-4-one

White crystals, m.p. 191.5~193.0 °C, **^{1}H NMR** ($CDCl_3$, 300MHz) δ: 0.80 (t, 3H, J = 7.2Hz, $OCH_2CH_2\mathbf{CH_3}$), 1.63 ~ 1.70 (m, 2H, $OCH_2\mathbf{CH_2}$), 2.66 (s, 3H, SCH_3), 4.33 (t, 2H, J = 6.2Hz, OCH_2CH_2), 7.18 ~ 8.09 (m, 10H, Ph); **IR** (KBr) ν (cm^{-1}): 1713, 1597, 1569, 1543, 1394, 1346, 1039; **EI-MS** (70eV, m/z) (relative intensity %): 393 (M+1, 56), 392 (M+, 100), 359 (37), 350 (57), 317 (58), 258 (67), 231 (79), 198 (74), 145 (89), 119 (41), 91 (72), 77 (93); **Elemental Anal.** Calcd. for $C_{21}H_{20}N_4O_2S$: C, 64.27; H, 5.14; N, 14.28; Found: C, 64.44; H, 4.97; N, 14.35.

7d:

6-iso-propoxyl-3-methylthio-1,5-diphenyl-1,5–dihydropyrazolo[3,4-d]pyrimidin-4-one

White crystals, m.p. 248.6~249.9 °C, **^{1}H NMR** ($CDCl_3$, 300MHz) δ: 1.27 (d, 6H, J = 5.7Hz, $OCH\mathbf{Me_2}$), 2.67 (s, 3H, SCH_3), 5.33 ~ 5.53 (m, 1H, $O\mathbf{CH}Me_2$), 7.13 ~ 8.11 (m, 10H, Ph); **IR** (KBr) ν (cm^{-1}): 1700, 1602, 1567, 1538, 1393, 1037; **EI-MS** (70eV, m/z) (relative intensity %): 393 (M+1, 31), 392 (M+, 87), 377 (22), 359 (30), 317 (32), 258 (34), 231 (45), 198 (59), 145 (69), 119 (32), 91 (53), 77 (100); **Elemental Anal.** Calcd. for $C_{21}H_{20}N_4O_2S$: C, 64.27; H, 5.14; N, 14.28; Found: C, 64.51; H, 5.21; N, 14.02.

7e: 6-phenoxyl-3-methylthio-1,5-diphenyl-1,5–dihydropyrazolo [3,4-d]pyrimidin-4-one

White crystals, m.p. 240.4~242.6 °C, **^{1}H NMR** ($CDCl_3$, 300MHz) δ: 2.66 (s, 3H, $\mathbf{SCH_3}$), 7.06 ~ 8.07 (m, 15H, **Ph**); **IR** (KBr) ν (cm^{-1}): 1706, 1646, 1597, 1548, 1392, 1329, 1038; **EI-MS** (70eV, m/z) (relative intensity %): 427 (M+1, 29), 426 (M+, 100), 393 (30.), 333 (53), 220 (23), 169 (29), 77 (98); **Elemental Anal.** Calcd. for $C_{24}H_{18}N_4O_2S$: C, 67.59; H, 4.25; N, 13.14; Found: C, 67.83; H, 4.44; N, 13.46.

7f:

6-(p-methylphenoxyl)-3-methylthio-1,5-diphenyl-1,5–dihydropyrazolo[3,4-d]pyrimidin-4 - one

White crystals, m.p. 219.1~221.7 °C, **^{1}H NMR** ($CDCl_3$, 300MHz) δ: 2.37 (s, 3H, $\mathbf{CH_3}PhO$), 2.67 (s, 3H, SCH_3), 6.40 ~ 7.90 (m, 14H, Ph); **IR** (KBr) ν (cm^{-1}): 1712, 1600, 1572, 1547, 1385, 1346, 1036; **EI-MS** (70eV, m/z) (relative intensity %): 441 (M+1, 46), 440 (M+,80), 407 (49), 333 (82), 285 (36), 258 (28), 220 (62), 169 (71), 145 (45), 91 (48), 77 (100); **Elemental Anal.** Calcd. for $C_{25}H_{20}N_4O_2S$: C, 68.16; H, 4.58; N, 12.72; Found: C, 67.81; H, 4.42; N, 13.03.

7g:

6-(m-methylphenoxyl)-3-methylthio-1,5-diphenyl-1,5–dihydropyrazolo[3,4-d]pyrimidin-4-one

White crystals, m.p. 261.3~263.4 °C, **^{1}H NMR** ($CDCl_3$, 300MHz) δ: 2.39 (s, 3H, $\mathbf{CH_3}PhO$), 2.67 (s, 3H, SCH_3), 6.40 ~ 7.91 (m, 14H, **Ph**); **IR** (KBr) ν (cm^{-1}): 1711, 1646, 1597, 1554, 1382, 1037; **EI-MS** (70eV, m/z) (relative intensity %): 441 (M+1, 5), 440 (M+, 15), 378 (100), 345 (45), 317 (33), 258 (36), 231 (39), 169 (28), 145 (56), 91 (45), 77 (83); **Elemental Anal.** Calcd. for $C_{25}H_{20}N_4O_2S$: C, 68.16; H, 4.58; N, 12.72; Found: C, 67.95; H, 4.52; N, 12.66.

7h:

6-(p-chlorophenoxyl)-3-methylthio-1,5-diphenyl-1,5–dihydropyrazolo[3,4-d]pyrimidin-4-one

White crystals, m.p. 285.4~286.6 °C, **^{1}H NMR** ($CDCl_3$, 300MHz) δ: 2.67 (s, 3H, SCH_3), 7.07 ~ 8.09 (m, 14H, Ph); **IR** (KBr) ν (cm^{-1}): 1713, 1599, 1571, 1548, 1384, 1347, 1037; **EI-MS** (70eV, m/z) (relative intensity %): 462 (M+1, 51), 461 (M+, 45), 460 (M-1, 83), 427 (48), 378 (22), 333 (80), 285 (22), 169 (36), 145 (22), 99 (30), 77 (100); **Elemental Anal.** Calcd. for $C_{24}H_{17}ClN_4O_2S$: C, 62.54; H, 3.72; N, 12.16; Found: C, 62.70; H, 3.87; N, 12.51.

7i:

6-(o-chlorophenoxyl)-3-methylthio-1,5-diphenyl-1,5–dihydropyrazolo[3,4-d]pyrimidin-4-one

White crystals, m.p. 228.9~232.4 °C, **^{1}H NMR** ($CDCl_3$, 300MHz) δ: 2.67 (s, 3H, SCH_3), 7.123 ~ 8.112 (m, 14H, Ph); **IR** (KBr) ν (cm^{-1}): 1713, 1598, 1568, 1542, 1345, 1037; **EI-MS** (70eV, m/z) (relative intensity %): 462 (M+1, 23), 461 (M+, 18), 460 (M-1, 59), 427 (33), 426 (68), 333 (71), 220 (25), 169 (31), 77 (100); **Elemental Anal.** Calcd. for $C_{24}H_{17}ClN_4O_2S$: C, 62.54; H, 3.72; N, 12.16; Found: C, 62.30; H, 3.69; N, 12.11.

7j: 6-(2,4-dichlorophenoxyl)-3-methylthio-1,5-diphenyl-1,5–dihydropyrazolo[3,4-d] pyrimidin-4-one

White crystals, m.p. 246.9~249.2 °C, **^{1}H NMR** ($CDCl_3$, 300MHz) δ: 2.67 (s,3H, SCH_3), 7.133 ~ 8.095 (m, 13H, Ph); **IR** (KBr) ν (cm^{-1}): 1714, 1573, 1550, 1515, 1494, 1390, 1351, 1038; **EI-MS** (70eV, m/z) (relative intensity %): 496 (M+1, 52), 495 (M+, 41), 494 (M-1, 70), 378 (50), 333 (77), 285 (48), 258 (42), 220 (61), 169 (67), 145 (56), 91 (40), 77 (100); **Elemental Anal.** Calcd. for $C_{24}H_{16}Cl_2N_4O_2S$: C, 58.19; H, 3.26; N, 11.31; Found: C, 57.85; H, 3.12; N, 11.01.

7k:

6-(p-nitrophenoxyl)-3-methylthio-1,5-diphenyl-1,5–dihydropyrazolo[3,4-d]pyrimidin-4-one

White crystals, m.p. 166.7~167.4 °C, **^{1}H NMR** ($CDCl_3$, 300MHz) δ: 2.68 (s,3H, SCH_3), 6.677 ~ 8.103 (m, 14H, Ph); **IR** (KBr) ν (cm^{-1}): 1702, 1649, 1589, 1539, 1391, 1336, 1037; **EI-MS** (70eV, m/z) (relative intensity %): 471 (M+, 14), 425 (100), 392 (35),333 (32), 285 (7), 220 (8), 169 (8), 145 (6), 91 (9), 77 (47); **Elemental Anal.** Calcd. for $C_{24}H_{17}N_5O_4S$: C, 61.14; H, 3.63; N, 14.85; Found: C, 60.79; H, 4.00; N, 15.11.

7l:

6-(m-nitrophenoxyl)-3-methylthio-1,5-diphenyl-1,5–dihydropyrazolo[3,4-d]pyrimidin-4-one

White crystals, m.p. 251.9~253.2 °C, **^{1}H NMR** ($CDCl_3$, 300MHz) δ: 2.67 (s, 3H, SCH_3), 7.194 ~ 8.183 (m, 14H, Ph); **IR** (KBr) ν (cm^{-1}): 1708, 1604, 1574, 1551, 1340, 1037; **EI-MS** (70eV, m/z) (relative intensity %): 472 (M+1, 42), 471 (M+, 91), 438 (74), 425 (36), 378 (24), 333 (74), 285 (33), 220 (41), 169 (60), 145 (37), 91 (24), 77 (100); **Elemental Anal.** Calcd. for $C_{24}H_{17}N_5O_4S$: C, 61.14; H, 3.63; N, 14.85; Found: C, 61.52; H, 3.72; N, 15.18.

Reference:

1. W.-Q. Chen, G.-Y. Jin, *Phosphorus, Sulfur, and Silicon, and The Related Elements*, 177, 1193 ~ 1200 (2002)

2. A. Ali, G.E. Taylor, D.W. Graham, WO 0129045 (2001); Chem. Abstr., 134, 311225u (2001).
3. S.A. Armstrong, J.M. Berge, P. Brown, J.S. Elder, A.K. Forrest, D.W. Hamprecht, R.L. Javest, WO 0071524 (2000).
4. E.R. EI Bendary, F.A. Badria, *Arch. Pharm.*, 333 (4), 99 ~ 103 (2000).
5. A. Tetsuya, M. Shogo, I.Fumio, Y. Masuo, N. Masafuml, EP 0733633 (1996).
6. A. Albert, S.D. Rubbo, Brit. *J. Exptl. Patha.*, 1953, 34, 199
7. G.A. Zentmyer, *Science*, 100, 294 (1944).
8. S. Giri, A.K. Shukla, Nizamuddin, *J. Indian Chem. Soc.*, 67,153 ~ 155 (1990)
9. O. EI Mahdi, A. Sedqui, *Bull. Soc. Chim. Fr.* 132 (7), 675 ~ 680 (1995).
10. K. Avasthi, T. Chandra, D.S. Rawat, D.S. Bhakuni, *Indian J. Chem., Sect B: Org. Chem. Incl Med. Cehm.*, 37 (12), 1228 ~ 1233 (1998).
11. M. W. Ding, Y. Sun, X. P. Liu, Zh. J. Liu, *Heterocyclic Communications*, 9 (2), 135 ~ 138 (2003).
12. H. Wamhoff, C. Bamberg, S. Herrmann, M. Nieger, *J.Org.Chem.*, 59, 3985 ~ 3993 (1994)

Received on December 17, 2003.