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New efficient synthesis of 2,5,6-trisubstituted oxazolo[5,4-d]pyrimidi-7(6*H*)-ones *via* an oxazolyliminophosphorane

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ABSTRACT

A new efficient synthesis of 2,5,6-trisubstituted oxazolo[5,4-d]pyrimidi-7(6*H*)-ones by consecutive aza-Wittig reaction was developed. The sequential three-component reaction of oxazolyliminophosphorane **4**, isocyanates and amines produced 2,5,6-trisubstituted oxazolo[5,4-d]pyrimidi-7(6*H*)-ones **7** in good overall yields in the presence of catalytic amount of EtONa.

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1. Introduction

Oxazoles represent an important class of heterocycles because they are found as the building block in a multitude of natural products and possess broad spectrum of biological properties in medicinal chemistry [1–3]. The structural diversity and complexity of the oxazoles has generated much interest in the development of mild methods for their synthesis. The oxazolo[5,4-d]pyrimidi-7(6*H*)-one system, a kind of fused oxazole, is of great importance because of its structural similarity with guanine. Some derivatives of oxazolo[5,4-d]pyrimidi-7(6*H*)-one have shown remarkable biological properties such as antitumor activities [4], whereas others were evaluated as brain A2A adenosine receptor antagonists or as ricin and shiga toxin inhibitors [5,6]. The methods described for the preparation of this ring system either involves cyclization of properly substituted 5-(acylamino)-4-hydroxypyrimidines in the presence of dehydrating agent, or reaction starting from 5-amino-4-ethoxycarbonyl(cyano)oxazoles [7–14]. However, most of the methods often require relatively harsh acid, dehydrating conditions or heating at high temperature, and there is no report of a generally useful synthesis of 2,5,6-trisubstituted oxazolo[5,4-d]pyrimidi-7(6*H*)-ones starting from easily accessible 5-amino-4-ethoxycarbonyloxazoles.

The aza-Wittig reactions of iminophosphoranes with carbonyl compounds provide one of the best method for the construction of C=N double bond under mild and neutral conditions. This type of reaction has recently applied widely in the synthesis of nitrogen-containing heterocyclic compounds with structural diversity [15–18]. The aza-Wittig reactions between iminophosphoranes with isocyanates produce high reactive carbodiimides, which may be used in preparing many heterocycles in further sequential reactions [19,20]. Recently we have been interested in the synthesis of various heterocycles *via* aza-Wittig reaction, with the aim of evaluating their biological activities [21–26]. Herein we wish to reported a new efficient synthesis of 2,5,6-trisubstituted oxazolo[5,4-d]pyrimidi-7(6*H*)-ones from an oxazolyliminophosphorane **4**, isocyanates and amines.

2. Experimental

Unless otherwise noted, all materials were commercially available and were used directly without further purification. All solvents were redistilled before use. ^{1}H NMR spectra were recorded on a Mercury-Plus 400 spectrometer in $CDCl_3$ with TMS as the internal reference. MS spectra were determined using a Trace MS 2000 organic mass spectrometer. IR were recorded on a PE-983 infrared spectrometer as KBr pellets with absorption in cm^{-1}. Elemental analyses were performed on a Vario EL III elemental analysis instrument. Melting points were taken on an X-4 binocular microscope melting point apparatus (Beijing Tech

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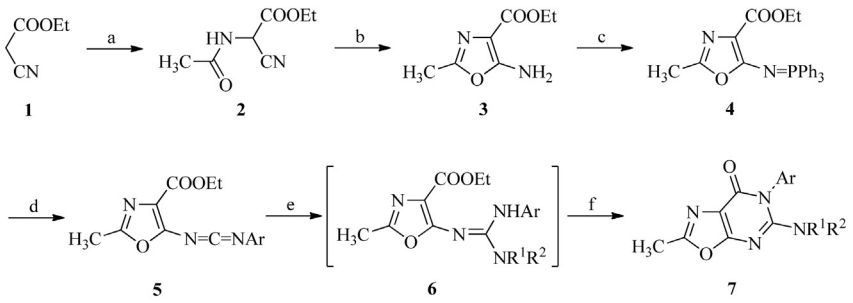

Scheme 1. Preparation of oxazolo[5,4-d]pyrimidi-7(6*H*)-ones **7**. (a) $NaNO_2$/HOAc, then $Na_2S_2O_4$/Ac_2O, H_2O, 0–5 °C, 3 h, 66%; (b) HCl, then $NaHCO_3$, CH_3COCH_3, r.t., 2 h, 89%; (c) Ph_3P, C_2Cl_6, Et_3N, CH_2Cl_2, r.t., 3 h, 78%; (d) ArNCO, CH_2Cl_2, 0–5 °C, 8–12 h; (e) HNR^1R^2, CH_3CN, r.t., 0.5–4 h; (f) EtONa, CH_3CN, r.t., 4–8 h, 72%–87%.

Instruments Co., Beijing, China) and are uncorrected. The ethyl 5-amino-2-methyloxazole-4-carboxylate **3** were prepared according to the reported method [27].

2.1. Preparation of iminophosphorane 4

To a mixture of ethyl 5-amino-2-methyloxazole-4-carboxylate **3** (1.36 g, 8 mmol), PPh_3 (3.14 g, 12 mmol) and C_2Cl_6 (2.84 g, 12 mmol) in dry CH_2Cl_2 (40 mL), was added dropwise Et_3N (2.42 g, 24 mmol) at room temperature. After stirred for 3 h, the solvent was removed under reduced pressure and the residue was recrystallized from ethanol–ether (1:3) to give iminophosphorane **4** as pale yellow crystals (2.68 g, yield 78%), mp: 121–123 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.82–7.27 (m, 15*H*, Ar–H), 4.31 (q, 2*H*, J = 6.8 Hz, OCH_2), 2.12 (s, 3*H*, CH_3), 1.37 (t, 3*H*, J = 7.0 Hz, CH_3). IR (KBr, cm^{-1}): 1699, 1621, 1563, 1439, 1268, 1172. MS (70 eV) *m*/*z* (%): 430 (M^+, 50), 262 (100), 183 (51), 108 (13). Anal. Calcd. for $C_{25}H_{23}N_2O_3P$ (430.4): C, 69.76; H, 5.39; N, 6.51. Found: C, 70.01; H, 5.25; N, 6.27.

2.2. General preparation of 2-methyl-5-amino-6-aryl-oxazolo[5,4-d]pyrimidi-7(6H)-ones 7a–7i

To a solution of iminophosphorane **4** (0.86 g, 2 mmol) in dry methylene dichloride (15 mL) was added aromatic isocyanate (2 mmol) under nitrogen at room temperature. After the reaction mixture was left unstirred for 8–12 h at 0–5 °C, the solvent was removed off under reduced pressure and Et_2O/petroleum ether (1:2, 10 mL) was added to precipitate triphenylphosphine oxide. Removal of the solvent gave carbodiimide **5**, which were used directly without further purification. To the solution of carbodiimide **5** prepared above in CH_3CN (15 mL) was added an amine (2 mmol). After the mixture was stirred for 0.5–4 h, several drops of EtONa in EtOH was added. The mixture was stirred for 4–8 h at room temperature under dry N_2 protection. The solution was condensed and the residual was recrystallized from ethanol to give 2-methyl-5-amino-6-aryl-oxazolo[5,4-d]pyrimidi-7(6*H*)-ones **7a–7i**.

3. Results and discussion

The ethyl 5-amino-2-methyloxazole-4-carboxylate **3** was easily prepared by acid catalytic cyclization of compound **2**, which was obtained from ethyl cyanoactate **1**, nitrous acid, $Na_2S_2O_4$ and acetic anhydride [27]. Further treatment of **3** with triphenylphosphine, hexachloroethane and triethylamine produced iminophosphorane **4** in good yield (Scheme 1). The conversion of 5-amino-2-methyloxazole-4-carboxylate **3** to iminophosphorane **4** involves initial formation of dichlorotriphenyl phosphorane between reaction of triphenylphosphine with hexachloroethane, and further reaction with compound **3** to give iminophosphorane **4** in the presence of triethylamine.

Iminophosphorane **4** had good reactivity as it reacted with aromatic isocyanates even at low temperature (0–5 °C). The carbodiimide intermediates **5** were produced and were then allowed to react with secondary amines to generate guanidines **6**. In the presence of catalytic amount of sodium ethoxide, **6** were easily converted to 5-dialkylamino oxazolo[5,4-d]pyrimidi-7(6*H*)-ones **7** in satisfactory yields at room temperature under dry N_2 protection. It is noteworthy that the reaction proceeds under mild conditions to give various substituted oxazolo[5,4-d]pyrimidi-7(6*H*)-ones **7**, and the overall transformation is run in a simple one-pot procedure from iminophosphorane **4** in good overall yields. The results are listed in Table 1. As indicated in Table 1, good yields were obtained whenever dialkylamines (compounds **7a**, **7c** and **7h**), cyclic amines (compounds **7e**, **7f**, **7g** and **7i**) or alkylarylamines (compound **7d**) were used. The isolated yield of **7** was good even as the bulky di-*iso*-propylamine was applied (compound **7b**).

The structure of compounds **7** was confirmed by their spectra data (Table 2). For example, the ^{1}H NMR spectrum of **7a** shows doublets at δ 2.84 due to –NCH_2– group. The signals of CH_3 appear at δ 2.54 as singlet. The signals of $CH(CH_3)_2$ appear at δ 1.84–1.80 as

Table 1
Synthesis of 2,5,6-trisubstituted oxazolo[5,4-d]pyrimidi-7(6*H*)-ones **7a-7i** by aza-Wittig reaction at room temperature.

Compd.	Ar	NR^1R^2	Time (h)	Yield (%)	Elementary analysis (%, calcd.)		
					C	H	N
7a	Ph	N(*i*-Bu)$_2$	8	80	67.51 (67.77)	7.30 (7.39)	15.98 (15.81)
7b	Ph	N(*i*-Pr)$_2$	8	77	66.11 (66.24)	6.94 (6.79)	17.45 (17.17)
7c	Ph	N(*c*-Hex)$_2$	6	75	71.02 (70.91)	7.25 (7.44)	13.58 (13.78)
7d	Ph	N(Me)Ph	8	81	68.44 (68.66)	5.01 (4.85)	16.99 (16.86)
7e	Ph	1-Piperidinyl	4	75	65.96 (65.79)	5.91 (5.85)	18.30 (18.05)
7f	Ph	4-Morpholinyl	4	87	61.45 (61.53)	5.20 (5.16)	18.03 (17.94)
7g	4-ClC_6H_4	1-Piperidinyl	4	83	59.44 (59.22)	5.02 (4.97)	16.38 (16.25)
7h	4-FC_6H_4	NPr_2	5	78	62.50 (62.78)	6.30 (6.15)	16.34 (16.27)
7i	4-FC_6H_4	1-Piperidinyl	4	72	62.08 (62.19)	5.46 (5.22)	17.28 (17.06)

Table 2
Mp, IR, MS and ^{1}H NMR of **7a–7i**.

Compd.	Mp (°C)	IR (KBr, cm^{-1})	MS (*m*/*z*, %)	^{1}H NMR ($CDCl_3$, 400 MHz, δ, ppm)
7a	122–124	1713, 1624, 1513, 1139	354 (M^+, 93), 310 (100), 254 (67), 226 (41), 179 (10), 117 (10)	7.52–7.28 (m, 5*H*, Ar–H), 2.84 (d, 4*H*, *J* = 7.2 Hz, $2NCH_2$), 2.54 (s, 3*H*, CH_3), 1.84–1.80 (m, 2*H*, 2CH), 0.78 (d, 12*H*, *J* = 6.8 Hz, $4CH_3$)
7b	147–149	1713, 1624, 1513, 1139	326 (M^+, 89), 311 (25), 283 (51), 269 (90), 207 (100), 119 (41)	7.48–7.24 (m, 5*H*, Ar–H), 3.60–3.53 (m, 2*H*, 2NCH), 2.53 (s, 3*H*, CH_3), 1.07 (d, 12*H*, *J* = 6.8 Hz, $4CH_3$)
7c	179–181	1717, 1613, 1517, 1332	406 (M^+, 79), 349 (97), 323 (100), 248 (95), 199 (44), 82 (25)	7.48–7.25 (m, 5*H*, Ar–H), 3.08–3.04 (m, 2*H*, 2NCH), 2.53 (s, 3*H*, CH_3), 1.81–1.07 (m, 20*H*, $10CH_2$)
7d	199–200	1720, 1522, 1354, 1056	332 (M^+, 100), 226 (35), 200 (65), 145 (16)	7.09–6.54 (m, 10*H*, Ar–H), 3.29 (s, 3*H*, NCH_3), 2.59 (s, 3*H*, CH_3)
7e	150–151	1719, 1615, 1527, 1275	310 (M^+, 100), 226 (11), 219 (13), 200 (41), 84 (11)	7.50–7.32 (m, 5*H*, Ar–H), 3.13 (t, 4*H*, *J* = 5.6 Hz, $2NCH_2$), 2.55 (s, 3*H*, CH_3), 1.44–1.26 (m, 6*H*, $3CH_2$)
7f	210–211	1723, 1615, 1529, 1112	312 (M^+, 100), 255 (27), 200 (38), 77 (13)	7.52–7.33 (m, 5*H*, Ar–H), 3.44 (t, 4*H*, *J* = 4.8 Hz, $2OCH_2$), 3.15 (t, 4*H*, *J* = 4.8 Hz, $2NCH_2$), 2.57 (s, 3*H*, CH_3)
7g	192–193	1725, 1613, 1527, 1452, 1275, 1138	344 (M^+, 74), 234 (35), 194 (59), 111 (56), 84 (100)	7.48–7.27 (m, 4*H*, Ar–H), 3.12 (t, 4*H*, *J* = 5.6 Hz, $2NCH_2$), 2.54 (s, 3*H*, CH_3), 1.49–1.29 (m, 6*H*, $3CH_2$)
7h	110–112	1715, 1507, 1327, 1138, 1052	344 (M^+, 100), 315 (50), 179 (58), 109 (26)	7.27–7.18 (m, 4*H*, Ar–H), 2.99 (t, 4*H*, *J* = 6.8 Hz, $2NCH_2$), 2.53 (s, 3*H*, CH_3), 1.34–1.29 (m, 4*H*, $2CH_2$), 0.75 (t, 6*H*, *J* = 7.2 Hz, $2CH_3$)
7i	133–134	1721, 1615, 1529, 1326, 1138	328 (M^+, 100), 218 (49), 178(70), 95 (75)	7.33–7.16 (m, 4*H*, Ar–H), 3.12 (t, 4*H*, *J* = 5.6 Hz, $2NCH_2$), 2.54 (s, 3*H*, CH_3), 1.46–1.28 (m, 6*H*, $3CH_2$)

multiplets and δ 0.78 as doublets, respectively. The signals attributable to the Ar–Hs are found at δ 7.52–7.28 as mutiplets. The IR spectra of **7a** revealed C=O absorption bands at 1713 cm^{-1}. The MS spectrum of **7a** shows molecular ion peak at *m*/*z* 354 with 93% abundance.

4. Conclusion

We described a new efficient synthesis of 2,5,6-trisubstituted oxazolo[5,4-d]pyrimidi-7(6*H*)-ones, which are of considerable interest as potential biological active compounds or pharmaceuticals, by the aza-Wittig reaction. This protocol presented many advantages, such as good yields, mild reaction condition, readily available starting material, and simple purification procedure.

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