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Efficient and Selective Construction of Pyrrolo[3,2-*d*]pyrimidine Derivatives

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An efficient and selective method for the synthesis of ethyl 2-amino/aryloxy-3-aryl-4-oxo-5-phenyl-4,5-dihydro-3*H*-pyrrolo[3,2-*d*]pyrimidine-7-carboxylate derivatives has been developed. The main process involved the reaction of diethyl 1-phenyl-3-((triphenylphosphoranylidene)amino)-1*H*-pyrrole-2,4-dicarboxylate and aromatic isocyanates, followed by addition of amines/phenols in the presence of catalytic amount of sodium ethoxide or solid potassium carbonate.

Key Words : Pyrrolo[3,2-*d*]pyrimidine, Aza-Wittig reaction, Iminophosphorane

Introduction

N-heterocycles are widely used as drugs or pesticides because of their good biological activities, and especially the derivatives of fused pyrimidinone have attracted much interest in drug development research. Among them, the pyrrolo[3,2-*d*]pyrimidines, also called 9-deazapurines, are now known to have a wide range of biological properties such as potent purine nucleoside phosphorylase inhibitors,[1-4] potent A_1- and A_2- adenosine receptor antagonists,[5] and some derivatives have also been reported to have anticancer activity.[6,7] Furthermore, in recent years, the chemistry of pyrrolo[3,4-*d*]pyrimidines have also received much attention because their derivatives possess a broad range of biological activities and have been used as potent cystic fibrosis transmembrane conductance regulator inhibitors,[8] A3 adenosine receptor antagonists[9] and β-site APP-cleaving enzyme 1 inhibitors.[10] Recently, Kung *et al.* reported that some derivatives of pyrrolo[3,4-*d*]pyrimidine may be used as inhibitors of heat shock protein 90, which could inhibit multiple pathways in human cancers.[11-13]

On the other hand, the aza-Wittig-mediated annulation strategy has received increased attention in view of their utility in the synthesis of nitrogen-containing heterocyclic compounds.[14-22] We have been interested in the synthesis of fused heterocycles *via* aza-Wittig reaction for some time,[23-29] with the aim of searching for new lead compounds. In the early studies, we reported the synthesis of pyrrolo[3,2-*d*]-pyrimidines from 3-amino-2-carboxylpyrroles,[30] and the synthesis of pyrrolo[3,4-*d*]pyrimidines from 4-amino-3-carboxylpyrroles.[31] Problems may happen if there is a carboxyl group at either side of the amino substituent and the selective ring formation should be carried out. Therefore, it is interesting herein to report the construction of ethyl 2-amino/aryloxy-3-aryl-4-oxo-5-phenyl-4,5-*d*ihydro-3*H*-pyrrolo-[3,2-*d*]pyrimidine-7-carboxylate derivatives from 3-amino-2,4-dicarboxylpyrroles in a selective way.

Experimental

General Procedures. Melting points were determined using a X-4 model apparatus and were uncorrected. MS were measured on a Finnigan Trace MS spectrometer. NMR spectra were recorded in $CDCl_3$ on a Varian Mercury 400 or 600 spectrometer and chemical shifts (δ) were given in ppm using $(CH_3)_4Si$ as an internal reference (δ = 0). IR were recorded on a PE-983 infrared spectrometer as KBr pellets with absorption in cm^{-1}. Elementary analyses were taken on a Vario EL III elementary analysis instrument.

Procedure for the Preparation of Compound 2. Compound **2** was obtained from the reaction of ethyl cyanoacetate with aniline and ethyl orthoformate in the presence of K_2CO_3, followed by reaction with ethyl 2-bromoacetate according to a literature report.[32] White crystals (yield: 82%); mp: 69-70 °C (Lit. mp: 66-68 °C).

Preparation of Diethyl 1-Phenyl-3-((triphenylphosphoranylidene)amino)-1*H*-pyrrole-2,4-dicarboxylate (3). To a mixture of diethyl 3-amino-1-phenyl-1*H*-pyrrole-2,4-dicarboxylate (**2**) (3.02 g, 10 mmol), triphenylphosphine (3.93 g, 15 mmol) and hexachloroethane (2.55 g, 15 mmol) in dry acetonitrile (50 mL), was added dropwise triethylamine (2.52 g, 25 mmol) at room temperature. After the mixture was stirred at room temperature for 6 h, the solvent was removed under reduced pressure, and the residue was recrystallized from a mixture of ethanol and petroleum ether to give iminophosphorane **3** as white crystals, 5.17 g (yield: 92%), mp 126 ºC; MS (*m/z*, %): 562 (M^+, 100), 489 (31), 461 (11), 443 (18), 262 (12), 201 (20), 183 (84), 152 (13), 107 (18), 78 (20), 77 (93); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.79-7.17 (m, 21H, 20Ar-H+C=CH), 3.86 (q, J = 7.2 Hz, 2H, CH_2), 3.75 (q, J = 7.2 Hz, 2H, CH_2), 1.06 (t, J = 7.2 Hz, 3H, CH_3), 0.83 (t, J = 7.2 Hz, 3H, CH_3); Anal. Calcd for $C_{34}H_{31}N_2O_4P$: C, 72.59; H, 5.55; N, 4.98; Found: C, 72.62; H, 5.53; N, 4.95.

General Preparation of Ethyl 2-Amino-3-aryl-4-oxo-5-

phenyl-4,5-dihydro-3*H*-pyrrolo[3,2-*d*]pyrimidine-7-carboxylate (6a-6j). To a solution of iminophosphorane **3** (1.69 g, 3 mmol) in dry methylene dichloride (12 mL), an aryl isocyanate (3 mmol) was added under nitrogen at room temperature. After the reaction mixture was left to stand unstirred for 1 h at room temperature, the solvent was removed under reduced pressure and a mixture of ether/petroleum ether (1:2, 18 mL) was added to precipitate triphenylphosphine oxide. After filtration, the solvent was removed to give carbodiimide **4**, which was used directly without further purification. To the solution of crude **4** in methylene dichloride (10 mL), amine (3 mmol) was added. After the reaction mixture was allowed to stand for 5 h, the solvent was removed and anhydrous ethanol (12 mL) with several drops of sodium ethoxide in ethanol was added. The mixture was stirred for 2 h at room temperature. The solution was then concentrated under reduced pressure and the residual was recrystallized from methylene dichloride/ethanol to give **6a-h**. The characterization data of the compounds are given below:

Ethyl 3-(4-Chlorophenyl)-2-(dipentylamino)-4-oxo-5-phenyl-4,5-dihydro-3*H*-pyrrolo[3,2-*d*]pyrimidine-7-carboxylate (6a). White crystals**,** mp 165-166 ºC; IR (KBr, cm^{-1}): 3120, 2954, 2927, 1696, 1675, 1537, 1494, 1296; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.84 (s, 1H, C=CH), 7.43-7.20 (m, 9H, 9Ar-H), 4.40 (q, *J* = 7.2 Hz, 2H, CH_2), 3.04 (t, *J* = 7.6 Hz, 4H, $2NCH_2$), 1.42 (t, *J* = 7.2 Hz, 3H, CH_3), 1.29-1.08 (m, 12H, $2CH_2CH_2CH_2$), 0.86 (t, *J* = 7.6 Hz, 6H, $2CH_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.3, 154.9, 154.7, 144.5, 138.0, 136.3, 136.1, 133.7, 130.4, 128.8, 128.5, 127.9, 125.4, 114.3, 109.3, 59.9, 51.3, 29.1, 27.0, 22.3, 14.2, 13.8. MS (*m/z*, %): 548 (M^+, 39), 505 (36), 477 (70), 459 (25), 444 (31), 431 (100), 421 (33), 407 (29), 400 (20), 381 (24), 375 (65), 361 (20), 352 (22), 341 (44), 325 (27), 321 (34), 311 (36), 298 (33), 265 (42), 236 (16), 211 (20), 157 (11), 104 (10), 77 (20), 57 (11); Anal. Calcd for $C_{31}H_{37}ClN_4O_3$: C, 67.81; H, 6.79; N, 10.20; Found: C, 67.90; H, 6.83; N, 10.25.

Ethyl 3-(4-Chlorophenyl)-2-(dipropylamino)-4-oxo-5-phenyl-4,5-dihydro-3*H*-pyrrolo[3,2-*d*]pyrimidine-7-carboxylate (6b). White crystals, mp 154-155 ºC; IR (KBr, cm^{-1}): 3066, 2964, 2873, 1697, 1554, 1537, 1491, 1306; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.84 (s, 1H, C=CH), 7.43-7.20 (m, 9H, 9Ar-H), 4.40 (q, *J* = 6.8 Hz, 2H, CH_2), 3.02 (t, *J* = 7.6 Hz, 4H, $2NCH_2$), 1.42 (t, *J* = 6.8 Hz, 3H, CH_3), 1.33-1.28 (m, 4H, $2CH_2$), 0.75 (t, *J* = 7.6 Hz, 6H, $2CH_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.4, 155.0, 154.7, 144.6, 138.1, 136.4, 136.2, 133.8, 130.5, 128.9, 128.6, 128.0, 125.5, 114.4, 109.3, 59.9, 53.1, 20.7, 14.3, 11.4. MS (*m/z*, %): 492 (M^+, 35), 449 (77), 421 (20), 403 (100), 375 (51), 353 (24), 340 (35), 311 (69), 293 (36), 265 (48), 236 (15), 210 (30), 155 (10), 103 (15), 77 (26); Anal. Calcd for $C_{27}H_{29}ClN_4O_3$: C, 65.78; H, 5.93; N, 11.36; Found: C, 65.69; H, 5.89; N, 11.44.

Ethyl 2-Morpholino-4-oxo-3,5-diphenyl-4,5-dihydro-3*H*-pyrrolo[3,2-*d*]pyrimidine-7-carboxylate (6c). White crystals, mp 250-251 ºC; IR (KBr, cm^{-1}): 3073, 2980, 2963 2851, 1714, 1696, 1558, 1415, 1295; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.84 (s, 1H, C=CH), 7.47-7.31 (m, 10H, 10Ar-H), 4.40 (q, *J* = 7.2 Hz, 2H, CH_2), 3.41 (t, *J* = 4.8 Hz, 4H, $2OCH_2$), 3.19 (t, *J* = 4.8 Hz, 4H, $2NCH_2$), 1.42 (t, *J* = 7.2 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.9, 154.4, 144.0, 137.8, 136.6, 135.9, 128.6, 128.4, 127.8, 125.4, 114.9, 109.1, 65.7, 59.8, 49.1, 14.2. MS (*m/z*, %): 444 (M^+, 77), 399 (51), 387 (46), 367 (11), 353 (62), 341 (100), 311 (26), 304 (21), 277 (12), 265 (48), 236 (8), 209 (5), 183 (7), 103 (8), 77 (17); Anal. Calcd for $C_{25}H_{24}N_4O_4$: C, 67.55; H, 5.44; N, 12.60; Found: C, 67.62; H, 5.51; N, 12.55.

Ethyl 4-Oxo-3,5-diphenyl-2-(piperidin-1-yl)-4,5-dihydro-3*H*-pyrrolo[3,2-*d*]pyrimidine-7-carboxylate (6d). White crystals**,** mp 221-222 ºC; IR (KBr, cm^{-1}): 3112, 3069, 2936, 2846, 1690, 1560, 1540, 1293; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.82 (s, 1H, C=CH), 7.45-7.29 (m, 10H, 10Ar-H), 4.40 (q, *J* = 7.2 Hz, 2H, CH_2), 3.18 (t, *J* = 5.6 Hz, 4H, $2NCH_2$), 1.44-1.39 (m, 5H, CH_3+CH_2), 1.24-1.21 (m, 4H, $2CH_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.2, 155.9, 155.0, 144.7, 138.1, 137.5, 136.0, 129.0, 128.6, 128.5, 127.9, 127.7, 125.6, 114.9, 109.1, 60.0, 50.1, 24.8, 24.0, 14.3. MS (*m/z*, %): 442 (M^+, 79), 413 (25), 395 (23), 367 (92), 339 (20), 314 (18), 291 (29), 265 (53), 236 (14), 199 (18), 160 (100), 128 (8), 103 (16), 77 (22); Anal. Calcd for $C_{26}H_{26}N_4O_3$: C, 70.57; H, 5.92; N, 12.66; Found: C, 70.52; H, 6.04; N, 12.75.

Ethyl 4-Oxo-3,5-diphenyl-2-(pyrrolidin-1-yl)-4,5-dihydro-3*H*-pyrrolo[3,2-*d*]pyrimidine-7-carboxylate (6e). White crystals, mp 230-231 ºC; IR (KBr, cm^{-1}): 2978, 2887, 1721, 1685, 1534, 1414; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.80 (s, 1H, C=CH), 7.45-7.28 (m, 10H, 10Ar-H), 4.40 (q, *J* = 7.2 Hz, 2H, CH_2), 3. 10 (t, *J* = 6.0 Hz, 4H, $2NCH_2$), 1.74-1.71 (m, 4H, $2CH_2$), 1.43 (t, *J* = 7.2 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.4, 154.9, 153.2, 146.0, 138.2, 137.4, 136.1, 129.4, 128.8, 128.5, 127.9, 127.7, 125.4, 113.3, 108.3, 59.9, 49.9, 25.3, 14.4. MS (*m/z*, %): 429 (M^+, 100), 399 (26), 382 (24), 371 (76), 353 (41), 330 (23), 325 (60), 278 (29), 250 (41), 211 (15), 154 (16), 103 (13), 77 (25). Anal. Calcd for $C_{25}H_{24}N_4O_3$: C, 70.08; H, 5.65; N, 13.08; Found: C, 69.99; H, 5.70; N, 13.01.

Ethyl 2-(Diethylamino)-4-oxo-3,5-diphenyl-4,5-dihydro-3*H*-pyrrolo[3,2-*d*]pyrimidine-7-carboxylate (6f). White crystals, mp 117-118 ºC; IR (KBr, cm^{-1}): 3129, 2979, 2933, 1717, 1690, 1577, 1553, 1415, 1290; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.83 (s, 1H, C=CH), 7.45-7.26 (m, 10H, 10Ar-H), 4.40 (q, *J* = 7.2 Hz, 2H, CH_2), 3.14 (q, *J* = 7.1 Hz, 4H, $2NCH_2$), 1.42 (t, *J* = 7.0 Hz, 3H, CH_3), 0.84 (t, *J* = 6.8 Hz, 6H, $2CH_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.0, 154.9, 154.6, 144.3, 137.8, 137.4, 135.8, 128.8, 128.4, 128.2, 127.5, 127.4, 125.1, 114.3, 108.8, 59.5, 44.9, 14.0, 12.0. MS (*m/z*, %): 430 (M^+, 62), 401 (78), 355 (100), 325 (11), 311 (14), 279 (39), 211 (11), 153 (11), 128 (17), 103 (20), 77 (38); Anal. Calcd for $C_{25}H_{26}N_4O_3$: C, 69.75; H, 6.09; N, 13.01; Found: C, 69.82; H, 6.02; N, 13.05.

Ethyl 2-(*Tert*-butylamino)-3-(4-chlorophenyl)-4-oxo-5-phenyl-4,5-dihydro-3*H*-pyrrolo[3,2-*d*]pyrimidine-7-carboxylate (6g). White crystals, mp 223-224 ºC; IR (KBr, cm^{-1}): 3439, 2986, 2865, 1711, 1680. ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.56-7.22 (m, 10H, C=CH+Ar-H), 4.26 (q, *J* = 7.2 Hz, 2H, CH_2), 3.87 (s, 1H, NH), 1.45 (s, 9H, $3CH_3$), 1.32 (t, *J* = 7.2

Hz, 3H, CH_3); MS (*m/z*, %): 466 (M^+, 3), 361 (41), 336 (15), 278 (15), 211 (12), 154 (27), 77 (64), 44 (100). Anal. Calcd for $C_{25}H_{25}ClN_4O_3$: C, 64.58; H, 5.42; N, 12.05; Found: C, 64.56; H, 5.51; N, 12.10.

Ethyl 2-(Cyclohexylamino)-3-(4-fluorophenyl)-4-oxo-5-phenyl-4,5-dihydro-3*H*-pyrrolo[3,2-*d*]pyrimidine-7-carboxylate (6h). White crystals, mp 217-218 ºC; IR (KBr, cm^{-1}): 3437, 2999, 2880, 1717, 1684. ^1H NMR ($CDCl_3$, 600 MHz) δ 7.82 (s, 1H, C=CH), 7.44-7.23 (m, 9H, Ar-H), 4.40 (q, *J* = 7.2 Hz, 2H, CH_2), 4.06-4.04 (m, 1H, CH), 3.80 (d, *J* = 7.2 Hz, 1H, NH), 2.04-2.02 (m, 2H, CH_2), 1.63-1.06 (m, 11H, $4CH_2$+CH_3). MS (*m/z*, %): 474 (M^+, 2), 391 (7), 345 (17), 181 (12), 121 (19), 104 (41), 91 (40), 77 (54), 55 (100). Anal. Calcd for $C_{27}H_{27}FN_4O_3$: C, 68.34; H, 5.74; N, 11.81; Found: C, 68.28; H, 5.71; N, 11.90.

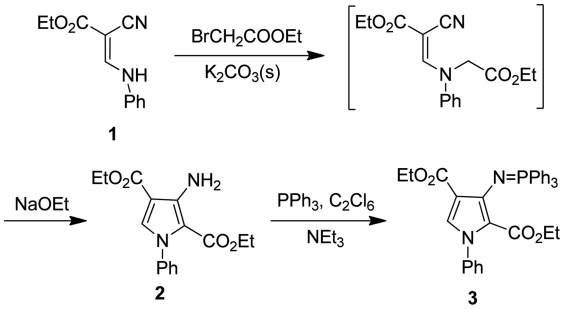
General Preparation of Ethyl 2-aryloxy-3-aryl-4-oxo-5-phenyl-4,5-dihydro-3*H*-pyrrolo[3,2-*d*]pyrimidine-7-carboxylate (6i, 6j). To the solution of crude carbodiimide **4** (3 mmol) in anhydrous acetonitrile (10 mL), phenol (3 mmol) and potassium carbonate (0.2 g, 1.5 mmol) were added. The mixture was stirred at 50 ºC for 4 h. After cooling, 20 mL water was added and stirring was continued until all the product was precipitated. The reaction mixture was filtered and washed with ethanol, and then the residue was recrystallized from methylene dichloride/ethanol to give **6i-6j** in good yields. The characterization data of the compounds are given below:

Ethyl 3-(4-Fluorophenyl)-2-(4-methoxyphenoxy)-4-oxo-5-phenyl-4,5-dihydro-3*H*-pyrrolo[3,2-*d*]pyrimidine-7-carboxylate (6i). White crystals, mp 215-216 ºC; IR (KBr, cm^{-1}): 3121, 2954, 2925, 2877, 1699, 1681; ^1H NMR ($CDCl_3$, 600 MHz) δ 7.87 (s, 1H, C=CH), 7.45-6.89 (m, 13H, 13Ar-H), 4.26 (q, *J* = 7.2 Hz, 2H, CH_2), 3.80 (s, 3H, OCH_3), 1.22 (t, *J* = 7.2 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.1, 161.8, 157.0, 154.0, 152.4, 145.4, 142.8, 137.7, 136.3, 130.6, 130.0, 128.7, 128.2, 125.5, 122.1, 116.4, 114.9, 114.1, 109.9, 60.1, 55.5, 13.9. MS (*m/z*, %): 499 (M^+, 1), 290 (26), 211 (9), 123 (60), 95 (81), 77 (100). Anal. Calcd for $C_{28}H_{22}FN_3O_5$: C, 67.33; H, 4.44; N, 8.41; Found: C, 67.41; H, 4.37; N, 8.38.

Ethyl 3-(4-Fluorophenyl)-2-(2-methoxyphenoxy)-4-oxo-5-phenyl-4,5-dihydro-3*H*-pyrrolo[3,2-*d*]pyrimidine-7-carboxylate (6j). White crystals, mp 208-209 ºC; IR (KBr, cm^{-1}): 3122, 2964, 2915, 2871, 1695, 1680; ^1H NMR ($CDCl_3$, 600 MHz) δ 7.87 (d, *J* = 4.2 Hz, 1H, C=CH), 7.46-7.00 (m, 13H, Ar-H), 4.26-4.23 (m, 2H, CH_2), 2.35 (d, *J* = 9.0 Hz, 3H, Ar-CH_3), 1.21-1.16 (m, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.0, 162.9, 161.4, 153.8, 152.0, 151.9, 151.6, 149.5, 142.5, 139.1, 137.5, 136.1, 134.9, 130.5, 129.8, 129.4, 128.7, 128.4, 128.0, 126.1, 125.3, 121.5, 120.8, 118.1, 116.1, 115.9, 114.7, 110.0, 59.8, 20.9, 20.5, 13.6. MS (*m/z*, %): 483 (M^+, 3), 274 (26), 121 (15), 91 (18), 77 (100). Anal. Calcd for $C_{28}H_{22}FN_3O_4$: C, 69.56; H, 4.59; N, 8.69; Found: C, 69.63; H, 4.54; N, 8.72.

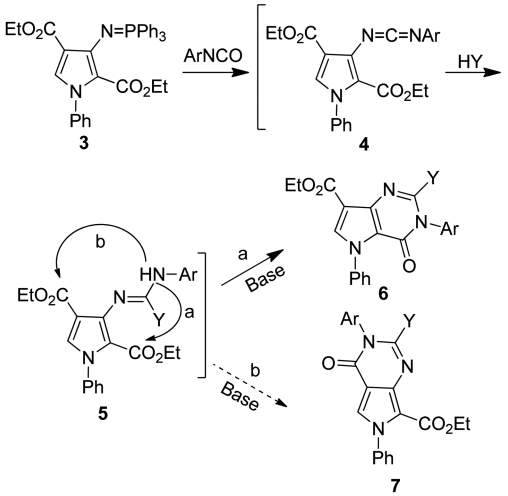
Results and Discussion

The diethyl 3-amino-1-phenyl-1*H*-pyrrole-2,4-dicarboxylate **2**, easily prepared by reaction of compound **1** with ethyl bromoacetate under basic conditions, was converted into iminophosphorane **3** *via* reaction with triphenylphosphine, hexachloroethane and triethylamine in a dried acetonitrile solution in good yield (Scheme 1).

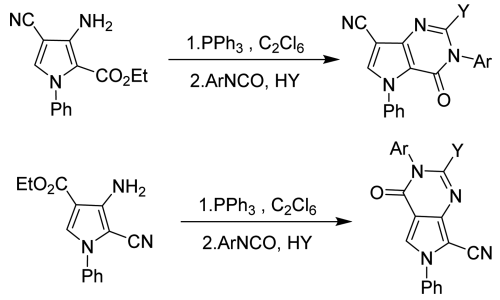


Scheme 1. Preparation of iminophosphorane **3**.

Then the iminophosphorane **3** was allowed to react with aromatic isocyanates to form carbodiimides **4**, which were allowed further to react with amines to obtain guanidine intermediates **5**. Although guanidines **5** did not cyclize in refluxing toluene, in the presence of a catalytic amount of sodium ethoxide, guanidines **5** were easily converted to ethyl 2-amino-3-aryl-4-oxo-5-phenyl-4,5-dihydro-3*H*-pyrrolo[3,2-*d*]pyrimidine-7-carboxylate derivatives **6**, one of the possible regioisomers, all in moderate to high yields at room temperature (Scheme 2). The results are listed in Table 1 (entry **6a-6h**). As shown in Scheme 3, the 3-amino-2-carboxylpyrroles can be used for the synthesis of pyrrolo[3,2-*d*]pyrimidines and the pyrrolo[3,4-*d*]pyrimidines can be constructed from 4-amino-3-carboxylpyrroles.[30,31] However, when there are two carboxyl groups at the *ortho* position of the amino substituent, only compound **6** was monitored by thin layer chromatography (TLC) and obtained from the reaction mixture after recrystallization. Compound **6** appears to be far more stable than **7** because of **6** is highly conjugated and the similar regioselective formation of pyrrolo[3,2-*d*]pyrimidine derivatives have been observed in literatures.[34-39] The proposed mechanism for the reaction is shown in Scheme 2, a



Scheme 2. Selective synthesis of pyrrolo[3,2-*d*]pyrimidine.



Scheme 3. Synthesis of pyrrolo[3,2-*d*]pyrimidines[30] and pyrrolo-[3,4-*d*]pyrimidines.[31]

Table 1. Synthesis of ethyl 2-amino/aryloxy-3-aryl-4-oxo-5-phenyl-4,5-dihydro-3*H*-pyrrolo[3,2-*d*]pyrimidine-7-carboxylate derivatives **6**

6	Ar	Y	Yield (%)[a]
a	4-Cl-ph	N(n-C_5H_{11})$_2$	85
b	4-Cl-Ph	N(n-Pr)$_2$	90
c	Ph	morpholin-4-yl	86
d	Ph	piperidin-1-yl	89
e	Ph	pyrrolidin-1-yl	90
f	Ph	NEt_2	80
g	4-Cl-Ph	NHBu-*t*	86
h	4-F-Ph	NH-C_6H_{11}	80
I	4-F-Ph	-OPh-OCH_3-*p*	88
J	4-F-Ph	-OPh-CH_3-*o*	80

[a]Isolated yields.

key transient state intermediate **5** was assumed in the process, and followed by catalyzed cyclization, leading to the formation of compound **6** due to its lower activation energy for the formation than **7**.

The structures of the compound **6** were deduced based on their NMR, MS, IR and elementary analysis. For example, the IR spectral data of **6e** revealed the groups of O=C-O and C=O absorption bands at 1721 and 1685 cm^{-1}, respectively. The ^1H NMR spectrum of **6e** shows the signals of NCH_2 and CH_3 groups at 3.10 and 1.43 ppm as two triplets, signals of OCH_2 at 4.40 ppm as a quartet, and the two CH_2 signals of the pyrrolidine ring appeared at 1.74-1.71 ppm. The signals attributable to the Ar-Hs and 5-H of the pyrrole ring are found at 7.28-7.45 and 7.80 ppm as multiplet and singlet, respectively. In the MS spectrum of **6e**, the molecular ion peak (M^+) at *m/z* 429 is observed with 100% abundance. Furthermore, the structure of **6** was confirmed again by X-ray crystallographic analysis. A single crystal of **6f** was obtained from a dichloromethane solution of **6f** (Figure 1). X-ray structure analysis verified the proposed structure, and showed that the two fused rings of pyrrolo[3,2-*d*]pyrimidine is approximately planar.[33]

In order to extend this method for preparation of ethyl 2,3,5-trisubstituted 4,5-dihydro-4-oxo-3*H*-pyrrolo[3,2-*d*]-pyrimidine-7-carboxylate derivatives, phenols were further used to react with carbodiimides **4**. When carbodiimides **4** reacted with phenols, the presence of a catalytic amount of

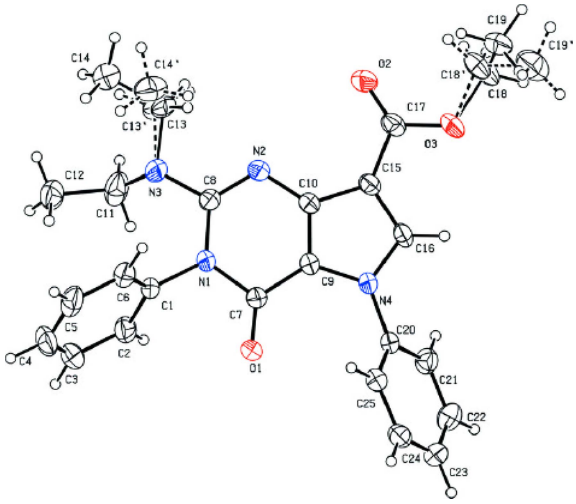


Figure 1. Single crystal X-ray structure of compound **6f**.

potassium carbonate produces ethyl 2-aryloxy-3-aryl-4-oxo-5-phenyl-4,5-dihydro-3*H*-pyrrolo[3,2-*d*]pyrimidine-7-carboxylate derivatives **6** (Y = OAr) directly in good yields, and no pyrrolo[3,4-*d*]pyrimidine **7** was monitored by thin layer chromatography(TLC) in the reactions. The results are listed in Table 1 (entries **6i-6j**). It is reasonable to assume that the reactions of carbodiimides **4** with phenols take place through an initial nucleophilic addition to give the intermediates **5**, which subsequently cyclized to produce ethyl 2-aryloxy-3-aryl-4-oxo-5-phenyl-4,5-dihydro-3*H*-pyrrolo[3,2-*d*]pyrimidine-7-carboxylate **6** under the basic conditions.

Conclusion

In conclusion, we have developed an efficient method to construct the previously unknown ethyl 2-amino/aryloxy-3-aryl-4-oxo-5-phenyl-4,5-dihydro-3*H*-pyrrolo[3,2-*d*]pyrimidine-7-carboxylate derivatives **6** *via* reaction of carbodiimides with a variety of amines and phenols in a selective way. Because of the mild reaction conditions, satisfactory yields and versatile starting materials, this method may potentially be used for the synthesis of many pharmaceutically active ethyl 2,3,5-trisubstituted 4,5-dihydro-4-oxo-3*H*-pyrrolo[3,2-*d*]pyrimidine-7-carboxylate derivatives.

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