Efficient Synthesis of New Tetracyclic Benzofuro[3,2-*d*]-imidazo[1,2-*a*]pyrimidine-2,5-(1*H*,3*H*)-diones

Hu, Yanggen[a,b](胡扬根) Liu, Min[a](刘敏) Ding, Mingwu*,[a](丁明武)

[a] *Key Laboratory of Pesticide & Chemical Biology of Ministry of Education, Central China Normal University, Wuhan, Hubei 430079, China*

[b] *Department of Pharmacy, Taihe Hospital of Yunyang Medical College and Institute of Medicine Chemistry, Yunyang Medical College, Shiyan, Hubei 442000, China*

The aza-Wittig reaction of iminophosphorane (**1**) with aromaic isocyanates gave carbodiimides (**2**), which were allowed to react further with *α*-amino ester in the presence of a catalytic amount of sodium ethoxide to give selectively new tetracyclic benzofuro[3,2-*d*]imidazo[1,2-*a*]pyrimidine-2,5-(1*H*,3*H*)-diones (**5**) in good yields. X-ray structure analysis of **5i** verified the proposed structure and the reaction selectivity.

Keywords benzofuro[3,2-*d*]imidazo[1,2-*a*]pyrimidine-2,5-(1*H*,3*H*)-dione, iminophosphorane, aza-Wittig reaction, isocyanate, carbodiimide

Introduction

Benzofuropyrimidinones are important heterocycles bearing remarkable biological activities. Some of them have shown good analgesic, anti-inflammatory and antimicrobial activities,[1-3] whereas others exhibit good anticoccidial and blood sugar-lowering activities.[4,5] On the other hand, heterocycles containing an imidazolone nucleus also exhibit various biological activities. Several of them have shown good antibacterial, antifungal activities or been used as leukotriene B_4 receptor antagonist and potassium channel openers.[6-10] The introduction of an imidazolone ring to the benzofuro-[3,2-*d*]pyrimidin-4(3*H*)-one system is expected to influence the biological activities significantly. However, this tetracyclic system has been much less investigated[1] and there is no report on synthesis of benzofuro[3,2-*d*]-imidazo[1,2-*a*]pyrimidine-2,5-(1*H*,3*H*)-diones, probably due to the fact that the tetracyclic system is not easily accessible by routine synthetic methods.

The aza-Wittig reactions of iminophosphoranes have received increased attention in view of their utility in the synthesis of nitrogen heterocyclic compounds.[11-14] Annelation of ring systems with *N*-heterocycles by means of an aza-Wittig reaction has been widely utilized because of the availability of functionalized iminophosphoranes. Recently we have been interested in the synthesis of fused pyrimidinones and imidazolones via aza-Wittig reaction, with the aim of evaluating their fungicidal activities.[15-21] We also reported an efficient preparation of benzofuro[3,2-*d*]pyrimidin-4(3*H*)-ones via aza-Wittig reaction of *β*-ethoxycarbonyl-iminophosphorane (**1**) with aromatic isocyanate and subsequent reaction with various nucleophiles under mild conditions.[19] However, the reaction of *α*-amino ester with *β*-ethoxycarbonyl-carbodiimide was not investigated. As a continuation of our research for new biologically active heterocycles, we herein wish to report further an efficient synthesis of the previously unreported benzofuro-[3,2-*d*]imidazo[1,2-*a*]pyrimidine-2,5-(1*H*,3*H*)-diones via the iminophosphorane (**1**).

Experimental

General procedure

Melting points were determined using a Beijing Taike X-4 model apparatus and are uncorrected. MS data were measured on a Finnigan Trace MS instrument. IR spectra were recorded on a PE-983 infrared spectrometer as KBr pellets with absorption in cm^{-1}. NMR spectra were recorded in $CDCl_3$ or DMSO-d_6 on a Varian Mercury 400 spectrometer and resonances are given in δ relative to TMS. Elemental analyses were taken on a Vario EL III elemental analysis instrument. The X-ray diffraction data were collected on a Bruker SMART AXS CCD diffractometer.

Preparation of benzofuro[3,2-*d*]imidazo[1,2-*a*]-pyrimidine-2,5-(1*H*,3*H*)-diones (5a—5k)

To a solution of iminophosphorane (**1**)[19] (0.93 g, 2 mmol) in dry methylene dichloride (15 mL) was added

* E-mail: mwding@mail.ccnu.edu.cn; Tel.: 0086-027-63158845; Fax: 0086-027-67862041
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aromatic isocyanate (2 mmol) under nitrogen in 0—5 ℃. After the reaction mixture stood for 6—8 h in 0—5 ℃, the solvent was removed under reduced pressure and ether/petroleum ether (V∶V=1∶2, 20 mL) was added to precipitate triphenylphosphine oxide. Removal of the solvent gave carbodiimide (**2**), which was directly used without further purification. A mixture of α-amino acid ester hydrochloride (2 mmol) and triethylamine (0.61 g, 4 mmol) in acetonitrile (10 mL) was stirred for 10 min and filtered. Then the filtrate was added to the solution of carbodiimide (**2**) prepared above in dry methylene dichloride (10 mL) at room temperature. After being stirred for 0.5 h, the solution was concentrated and anhydrous EtOH (10 mL) with several drops of EtONa in EtOH was added. The mixture was stirred for 4—6 h at room temperature and concentrated under reduced pressure, and the residual was recrystallized from methylene dichloride/petroleum ether to give benzofuro[3,2-*d*]-imidazo[1,2-*a*]pyrimidine-2,5-(1*H*,3*H*)-diones (**5a**—**5k**).

1-Phenylbenzofuro[3,2-*d*]imidazo[1,2-*a*]pyrimidine-2,5-(1*H*,3*H*)-dione (5a) White solid, m.p.＞300 ℃; ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 7.90—7.41 (m, 9H, Ar-H), 4.79 (s, 2H, CH_2); IR (KBr) v: 1754 (C=O), 1706 (C=O), 1568, 1379, 1048 cm^{-1}; MS m/z (%): 317 (M^+, 100), 288 (58), 260 (59), 185 (12), 130 (62), 101 (32), 77 (12). Anal. calcd for $C_{18}H_{11}N_3O_3$: C 68.14, H 3.49, N 13.24; found C 68.10, H 3.52, N 13.19.

3-Hydroxymethyl-1-phenylbenzofuro[3,2-*d*]imidazo[1,2-*a*]pyrimidine-2,5-(1*H*,3*H*)-dione (5b) White solid, m.p. 255—256 ℃; ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 7.90—7.42 (m, 9H, Ar-H), 5.50 (t, J=6.0 Hz, 1H, CH), 5.15 (s, 1H, OH), 4.54—4.49 (m, 1H, C**H**HO), 4.05—4.00 (m, 1H, CH**H**O); IR (KBr) v: 3419 (O—H), 1765 (C=O), 1705 (C=O), 1599, 1350, 1211 cm^{-1}; MS m/z (%): 347 (17) [M^+], 329 (99), 317 (60), 288 (41), 260 (88), 130 (100), 101 (47), 77 (20). Anal. calcd for $C_{19}H_{13}N_3O_4$: C 65.70, H 3.77, N 12.10; found C 65.93, H 3.62, N 12.05.

3-Ethoxycarbonylmethyl-1-phenylbenzofuro[3,2-*d*]imidazo[1,2-*a*]pyrimidine-2,5-(1*H*,3*H*)-dione (5c) White solid, m.p. 183—184 ℃; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.94—7.34 (m, 9H, Ar-H), 5.02 (t, J=5.6 Hz, 1H, CH), 4.10—4.03 (m, 3H, OCH_2 and C**H**HCOO), 3.38—3.33 (m, 1H, CH**H**COO), 1.18 (t, J=7.2 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 170.1, 169.1, 157.0, 151.2, 151.1, 143.9, 135.7, 131.2, 129.8, 129.3, 129.1, 127.0, 123.8, 122.3, 121.8, 112.8, 61.4, 55.8, 32.2, 13.9; IR (KBr) v: 1764 (C=O), 1727 (C=O), 1705 (C=O), 1604, 1352, 1209, 1129 cm^{-1}; MS m/z (%): 403 (38) [M^+], 357 (15), 329 (100), 275 (15), 260 (27), 130 (16). Anal. calcd for $C_{22}H_{17}N_3O_5$: C 65.50, H 4.25, N 10.42; found C 65.43, H 4.23, N 10.18.

1-Phenyl-3-(*i*-propyl)benzofuro[3,2-*d*]imidazo[1,2-*a*]pyrimidine-2,5-(1*H*,3*H*)-dione (5d) White solid, m.p. 266—267 ℃; ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 7.90—7.43 (m, 9H, Ar-H), 5.02 (d, J=3.2 Hz, 1H, CH), 3.04—2.98 (m, 1H, CH), 1.27 (t, J=7.2 Hz, 3H, CH_3), 0.91 (t, J=7.2 Hz, 3H, CH_3); IR (KBr) v: 1762 (C=O), 1713 (C=O), 1546, 1347, 1189 cm^{-1}; MS m/z (%): 359 (29) [M^+], 316 (38), 287 (23), 277 (100), 260 (25), 130 (33), 101 (16). Anal. calcd for $C_{21}H_{17}N_3O_3$: C 70.18, H 4.77, N 11.69; found C 70.03, H 4.71, N 11.83.

3-Methyl-1-phenylbenzofuro[3,2-*d*]imidazo[1,2-*a*]-pyrimidine-2,5-(1*H*,3*H*)-dione (5e) White solid, m.p. 290—291 ℃; ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 7.90—7.41 (m, 9H, Ar-H), 5.07 (q, J=7.2 Hz, 1H, CH), 1.80 (d, J=7.2 Hz, 3H, CH_3); IR (KBr) v: 1764 (C=O), 1715 (C=O), 1548, 1341, 1172 cm^{-1}; MS m/z (%): 331 (100) [M^+], 302 (30), 287 (51), 275 (51), 130 (40), 101 (25), 91 (13). Anal. calcd for $C_{19}H_{13}N_3O_3$: C 68.88, H 3.95, N 12.68; found C 68.83, H 3.70, N 12.84.

1-(3-Tolyl)benzofuro[3,2-*d*]imidazo[1,2-*a*]pyrimidine-2,5-(1*H*,3*H*)-dione (5f) White solid, m.p.＞300 ℃; ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 7.91—7.33 (m, 8H, Ar-H), 4.78 (s, 2H, CH_2), 2.42 (s, 3H, CH_3); MS m/z (%): 331 (100) [M^+], 302 (30), 287 (51), 275 (51), 130 (40), 101 (25), 91 (13). Anal. calcd for $C_{19}H_{13}N_3O_3$: C 68.88, H 3.95, N 12.68; found C 68.61, H 3.89, N 12.73.

1-(4-Chlorophenyl)-3-(*i*-propyl)benzofuro[3,2-*d*]-imidazo[1,2-*a*]pyrimidine-2,5-(1*H*,3*H*)-dione (5g) White solid, m.p. 266—267 ℃; ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 7.91—7.43 (m, 8H, Ar-H), 5.01 (d, J=3.2 Hz, 1H, CH), 3.03—2.99 (m, 1H, CH), 1.26 (d, J=7.2 Hz, 3H, CH_3), 0.90 (d, J=7.2 Hz, 3H, CH_3); IR (KBr) v: 1757 (C=O), 1722 (C=O), 1600, 1498, 1368, 1188 cm^{-1}; MS m/z (%): 393 (23) [M^+], 350 (24), 310 (100), 287 (12), 130 (29), 101 (21). Anal. calcd for $C_{21}H_{16}ClN_3O_3$: C 64.05, H 4.09, N 10.67; found C 63.99, H 4.02, N 10.75.

1-(4-Fluorophenyl)-3-(*i*-propyl)benzofuro[3,2-*d*]-imidazo[1,2-*a*]pyrimidine-2,5-(1*H*,3*H*)-dione (5h) White solid, m.p. 216—218 ℃; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.95—7.25 (m, 8H, Ar-H), 4.95 (d, J=3.6 Hz, 1H, CH), 3.29—3.21 (m, 1H, CH), 1.38 (d, J=7.2 Hz, 3H, CH_3), 0.94 (d, J=7.2 Hz, 3H, CH_3); MS m/z (%): 377 (25) [M^+], 335 (24), 295 (100), 279 (20), 130 (26), 101 (18), 83 (14). Anal. calcd for $C_{21}H_{16}FN_3O_3$: C 66.84, H 4.27, N 11.14; found C 66.79, H 4.22, N 11.05.

3-Ethoxycarbonylmethyl-1-(4-fluorophenyl)benzofuro[3,2-*d*]imidazo[1,2-*a*]pyrimidine-2,5-(1*H*,3*H*)-dione (5i) White solid, m.p. 204—206 ℃; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.94—7.25 (m, 8H, Ar-H), 5.02 (t, J=3.6 Hz, 1H, CH), 4.10—4.04 (m, 3H, OCH_2 and C**H**HCO$_2$), 3.35 (dd, J_1=18.0 Hz, J_2=3.2 Hz, 1H, CH**H**CO$_2$), 1.19 (t, J=7.2 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 170.2, 169.2, 163.8, 161.3, 157.0, 151.2, 151.1, 143.8, 135.7, 129.8, 129.1, 129.0, 127.1, 123.8, 122.3, 121.7, 116.5, 116.3, 112.8, 61.4, 55.8, 32.2, 13.9; IR (KBr) v: 1772 (C=O), 1745 (C=O), 1712 (C=O), 1584, 1352, 1186 cm^{-1}; MS m/z (%): 421 (10) [M^+], 347 (70), 294 (21), 279 (59), 222 (13), 130 (100), 101 (80), 95 (27). Anal. calcd for $C_{22}H_{16}FN_3O_5$: C 62.71, H 3.83, N 9.97; found: C 62.62, H 3.95, N 10.05.

1-(4-Fluorophenyl)-3-methylbenzofuro[3,2-*d*]imidazo[1,2-*a*]pyrimidine-2,5-(1*H*,3*H*)-dione (5j) White solid, m.p. 230—232 ℃; ^{1}H NMR ($CDCl_3$, 400 MHz) δ:

7.90—7.42 (m, 8H, Ar-H), 5.07 (q, J=7.2 Hz, 1H, CH), 1.80 (d, J=7.2 Hz, 3H, CH_3); IR (KBr) ν: 1760 (C=O), 1720 (C=O), 1590, 1352, 1192 cm^{-1}; MS *m*/*z* (%): 349 (100) [M^+], 320 (60), 295 (26), 279 (54), 130 (54), 101 (28), 95 (14). Anal. calcd for $C_{19}H_{12}FN_3O_3$: C 65.33, H 3.46, N 12.03; found C 65.28, H 3.39, N 11.90.

3-(*s*-Butyl)-1-(4-fluorophenyl)-benzofuro[3,2-*d*]-imidazo[1,2-*a*]pyrimidine-2,5-(1*H*,3*H*)-dione (5k) White solid, m.p. 224—226 ℃; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.94—7.25 (m, 8H, Ar-H), 5.04 (d, J=3.2 Hz, 1H, CH), 3.03—2.98 (m, 1H, CH), 1.93—1.69 (m, 2H, CH_2), 1.11 (t, J=7.6 Hz, 3H, CH_3), 0.89 (d, J=6.8 Hz, 3H, CH_3); IR (KBr) ν: 1760 (C=O), 1718 (C=O), 1578, 1352, 1129 cm^{-1}; MS *m*/*z* (%): 391 (17) [M^+], 335 (100), 295 (88), 279 (45), 222 (9), 130 (12). Anal. calcd for $C_{22}H_{18}FN_3O_3$: C 67.51, H 4.64, N 10.74; found C 67.41, H 4.60, N 10.65.

X-ray crystal structure analysis for compound (5i) formula $C_{22}H_{16}FN_3O_5$, colorless crystal. The crystal is of triclinic, space group $P\bar{1}$ with a=5.7933(9) Å, b=9.1494(14) Å, c=10.2380(16) Å, β=96.327(2)°, V=477.97(13) $Å^3$, Z=1, D_c=1.464 g/cm^3, F(000)=218, μ=0.122 mm^{-1}, R=0.0342 and wR=0.0957 for 1941 observed reflections with $I>2\sigma(I_0)$. Crystallographic data (excluding structure factors) for the structure of **5i** reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-714882. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax.: (internat.) 00 44 1223/336-033; e-mail: deposit@ccdc.cam.ac.uk].

Results and discussion

Iminophosphorane (**1**) was reacted with aromatic isocyanates to give carbodiimides (**2**), which were allowed to react with α-amino ester at room temperature in the presence of a catalytic amount of sodium ethoxide to give benzofuro[3,2-*d*]imidazo[1,2-*a*]pyrimidine-2,5-(1*H*,3*H*)-diones (**5**) selectively. A variety of α-amino esters and isocyanates could be used for this synthetic strategy and the products **5** were obtained in good yields (Scheme 1). Presumably the reaction of carbodiimides **2** with α-amino ester should afford primarily guanidine intermediates of type **3**. From these intermediates **3**, the formation of two cyclized products imidazolone **4** (via path a), and benzofuro[3,2-*d*]pyrimidin-4(3*H*)-one (**6**) (via path b) could in principle take place. The formation of **5** might probably be due to a consecutive cyclization of **3** to imidazolone intermediate **4** and further base catalytic cyclization between the imidazolone ring NH and ethoxylcarbonyl. The result illustrated also that the imidazolone (**4**) was more easily produced from intermediate **3** than benzofuro[3,2-*d*]pyrimidin-4(3*H*)-one (**6**).

The structure of benzofuro[3,2-*d*]imidazo[1,2-*a*]-pyrimidine-2,5-(1*H*,3*H*)-diones (**5**) was confirmed by

Scheme 1 Preparation of compounds **5**

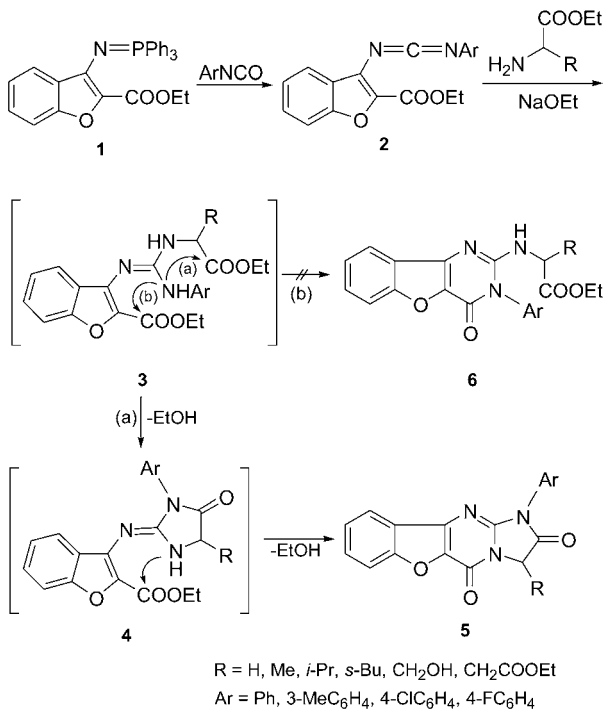

Table 1 Preparation of compounds **5a**—**5k** from iminophosphorane **1**

Compd.	Ar	R	Yield[a]/%
5a	Ph	H	81
5b	Ph	CH_2OH	76
5c	Ph	CH_2COOEt	86
5d	Ph	*i*-Pr	79
5e	Ph	Me	83
5f	3-$CH_3C_6H_4$	H	80
5g	4-ClC_6H_4	*i*-Pr	81
5h	4-FC_6H_4	*i*-Pr	78
5i	4-FC_6H_4	CH_2COOEt	85
5j	4-FC_6H_4	Me	79
5k	4-FC_6H_4	*s*-Bu	74

[a] Isolated yields based on iminophosphorane **1**.

their spectrum data. For example, the ^{1}H NMR spectrum of **5e** shows the signal of CH at δ 5.07 as quartet and signal of CH_3 at δ 1.80 as doublet. The signals attributable to the Ar-Hs are found in δ 7.90—7.41 as mutiplets. The IR spectra of **5e** revealed two C=O absorption bands at 1764 and 1715 cm^{-1} due to the imidazolone and pyrimidinone carbonyl groups, respectively. The mass spectrum of **5e** shows a strong molecular ion peak at *m*/*z* 331 with 100% abundance. Furthermore, a single crystal of **5i** was obtained from a CH_2Cl_2 solution of **5i**. X-ray structure analysis verified again the proposed structure, and showed that all ring atoms in the tetracyclic moiety were nearly coplanar and the fluorophenyl ring was twisted with respect to the pyrimidinone ring system by 62.9(2)°. The C atoms of the ethyl side chain

were disordered over two positions, with site occupancy factors 0.60 and 0.40, and were refined using a split model.

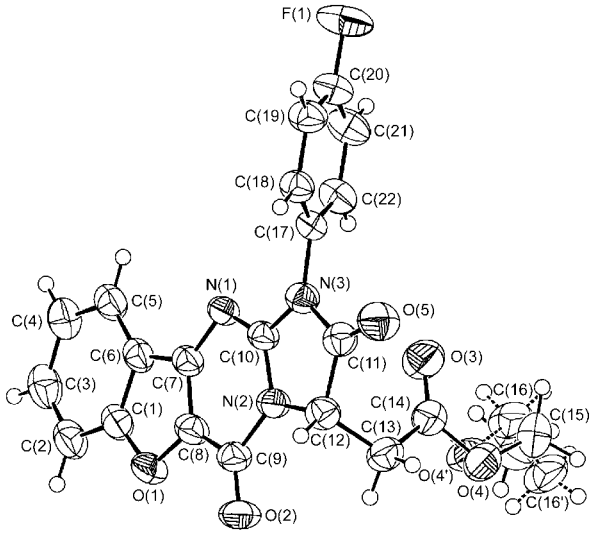

Figure 1 ORTEP diagram of the crystal structure of tetracyclic compound **5i** (Drawn at the 50% thermal ellipsoids).

In conclusion, we have developed a new efficient synthesis for benzofuro[3,2-*d*]imidazo[1,2-*a*]pyrimidine-2,5-(1*H*,3*H*)-diones via an iminophosphorane. This method utilizes easily accessible starting materials and allows mild one-pot reaction conditions, straightforward product isolation and good yields.

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