

A Facile Synthesis of 4(3*H*)-Pteridinone Derivatives by Utilizing *N*-{3-[(*N*-Substituted)carbamoyl]-2-pyrazyl}iminophosphoranes

Tomohiro Okawa, Masaru Kawase, Shoji Eguchi*

Department of Molecular Design and Engineering, Graduate School of Engineering, Nagoya University, Furo-cho, Chikusa-ku, Nagoya 464-01, Japan

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Abstract: The intermolecular aza-Wittig reaction of iminophosphoranes **4** derived from 3-aminopyrazine-2-(*N*-substituted)-carboxamide derivatives **2** with various acyl chlorides followed by heterocyclization provided an efficient synthetic route to 2,3-disubstituted 4(3*H*)-pteridinone derivatives **5**.

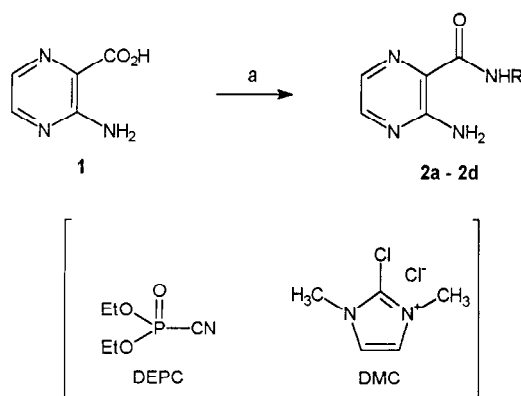
Key words: iminophosphorane, intermolecular aza-Wittig reaction, heterocyclization, 4(3*H*)-pteridinone

Over the past decade, the aza-Wittig methodology¹⁻⁴ has received increased attention for its utility in the formation of C=N bonds and heterocumulative bonds. As well as other workers we have also recently demonstrated that the intramolecular aza-Wittig reaction is a powerful and useful tool for the synthesis of 5–8 membered heterocycles^{2, 5, 6} including natural products such as DC-81,^{7, 8} *l*-vasicinone,⁹ (–)-benzomalvin A,¹⁰ (–)-dendrobine,¹¹ and (+)-fumiquinazoline G¹² etc. On the other hand, the intermolecular aza-Wittig reaction followed by electrocyclization, cycloaddition or heterocyclization, i.e., the tandem aza-Wittig methodology, has been utilized for the synthesis of many important heterocycles by Molina,³ Wamhoff,⁴ Quintela,¹³ Saito,^{14, 15} and Noguchi^{16, 17} and co-workers. We were interested in the preparation and the reactivity of the *N*-heteroaryliminophosphorane derivatives because these species seem to have been less studied, notwithstanding their promising role as building blocks for synthesis of heterocyclic compounds. For example, we have reported the facile synthesis of 4(3*H*)-pteridinone derivatives via the intermolecular aza-Wittig reaction followed by heterocyclization^{18,19} and pyrazino[2,3-*e*]-[1,4]diazepin-5-one derivatives via the intramolecular aza-Wittig reaction.²⁰ In addition, the reaction of the iminophosphorane derivatives with carboxylic acid chlorides to give heterocyclic compounds has been reported by Zbiral,²¹ Wamhoff²² and Molina^{23, 24} et al. They have shown that upon warming or in the presence of *tert*-amines, imidoyl chlorides are formed, which react with internal nucleophiles to afford various heterocyclic compounds such as oxazoles,²¹ 3,1-oxazin-4-ones,²² 1,2,4-triazolo[5,1-*c*]-1,2,4-triazines²³ and 6-substituted quinazolino[4,3-*b*]-quinazolin-8-ones,²⁴ etc.

Folic acid, methotrexate, L-biopterin²⁵ and leucettidine,²⁶ etc. are known as natural products having pteridine skeletons which play an essential role in several biological processes and methotrexate has a long and distinguished history as an antineoplastic and an immunosuppressive drug. Although several methods for the synthesis of these important skeletons, pteridine rings, have been reported,^{27, 28} new technologies that advance the field are still in demand. Recently, Wamhoff et al. reported the synthesis of 4(3*H*)-pteridinone derivatives from 3-arylamino-pyraz-

ine-2-carboxylates or 2-arylpyrazino[2,3-*d*][3,1]oxazin-4-ones.²⁹ Also, we reported the synthetic route to 4(3*H*)-pteridinone derivatives from the corresponding *N*-(2-pyrazyl)iminophosphorane derivatives via intermolecular aza-Wittig reaction followed by addition of alcohols or amines for the desired heterocyclization.^{18, 19} As a part of our continued research programs on the aza-Wittig reaction, we wish to report here that the intermolecular aza-Wittig reaction of iminophosphorane derivatives **4** with various acyl chlorides followed by heterocyclization provides a facile and efficient synthetic route to 2,3-disubstituted 4(3*H*)-pteridinone derivatives **5**.

At first, we investigated the synthesis of the corresponding *sec*-amide derivatives **2**, the precursors of *N*-heteroaryl iminophosphorane derivatives. These required amide derivatives **2** were prepared by the condensation of 3-aminopyrazine-2-carboxylic acid (**1**) and various primary amines (glycine methyl ester, alkyl amines etc.) with the aid of diethylphosphoryl cyanide (DEPC)³⁰ or 2-chloro-1,3-dimethylimidazolinium chloride (DMC) which are two of the most powerful and useful condensation reagents (Scheme 1, Table 1). In the condensation of 3-aminopyrazine-2-carboxylic acid (**1**) and glycine methyl ester hydrochloride (entries 1 and 2 in Table 1), the yield with DEPC was somewhat better than that with DMC (78% vs. 74%).



(a) RNH₂, condensation reagent, Et₃N, DME, 0 °C, 1 h → 40 °C 1 h

Scheme 1

Although the exchange reaction of ester **3** to *tert*-butyl amide derivative **2b** was ineffective (see entry 5 in Table 2), a much better yield was obtained with DMC by the condensation of **1** and *tert*-butylamine (see entries 3 and 4 in Table 1, 13% vs. 68%). Thus, **1** and 1-methylbut-3-enylamine, which was prepared from the corresponding alco-

Table 1. Synthesis of *sec*-Amides **2a–2d** by Condensation Reagents

Entry	R	Condensation Reagents	Product	Yield (%) ^a
1	–CH ₂ CO ₂ CH ₃	DEPC ^b	2a	78
2	–CH ₂ CO ₂ CH ₃	DMC ^c	2a	74
3	<i>t</i> -Bu	DEPC	2b	13
4	<i>t</i> -Bu	DMC	2b	68
5	<i>s</i> -Bu	DMC	2c	45
6	–CH(CH ₃)CH ₂ CH=CH ₂	DMC	2d	32

^a Isolated yields.^b Diethylphosphoryl cyanide.^c 2-Chloro-1,3-dimethylimidazolinium chloride.

hol by Mitsunobu reaction and Gabriel synthesis, were effectively condensed by using DMC (entries 5 and 6 in Table 1).

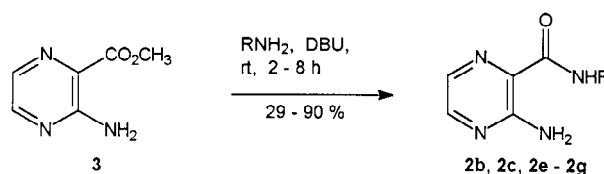
The exchange reactions of ester **3** to *sec*-amide derivatives **2** proceeded using primary amines as solvent in the presence of various bases (Scheme 2, Table 2). When allyl amine and sodium hydride were used at room temperature, the corresponding *sec*-amide derivative **2e** was produced in only 18% yield together with an unidentified product in 18% yield. When potassium hydroxide was used at room temperature, the desired *sec*-amide **2e** was obtained in 51% yield. Also, when 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) was used at room temperature, the desired *sec*-amide **2e** was obtained in quantitative yield. Thus, we decided to employ DBU as the base in the exchange reactions of ester **3** to *sec*-amide derivatives **2b**, **2c** and **2e–2g**. This reaction proceeded quantitatively with allyl-, propyl-, isopropyl- and *sec*-butylamines. But it did not proceed smoothly with hindered amines such as *tert*-BuNH₂, giving only 1% yield (3% based on consumed **3**,

Table 2. Exchange Reaction of Ester **3** to *sec*-Amides **2b**, **2c**, **2e–2g**

Entry	R	Products	Yield (%) ^a
1	allyl	2e	100
2	Pr	2f	100
3	<i>i</i> -Pr	2g	90 (100) ^b
4	<i>s</i> -Bu	2c	100
5	<i>t</i> -Bu	2b	1 (3) ^b

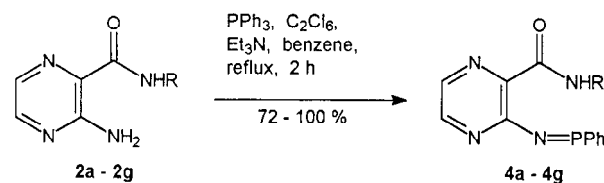
^a Isolated yield.^b Based on consumed **3**.**Table 3.** Characterization (mp, *R*_f, IR) of Compounds **2a–2g** Prepared

Products	mp (°C)	<i>R</i> _f (A/H) ^a	IR (KBr or neat) ν (cm ^{–1})
2a	135–136	0.25	3416, 3382, 3258, 3154, 1757, 1740, 1667, 1616, 1534, 1514, 1213, 1169
2b	84–85	0.67	3407, 2967, 1661, 1611, 1514, 1236, 932, 847, 814
2c	28	0.49	3449, 1692, 1663, 1539, 1412, 1379, 1265, 1219, 1020, 777, 750
2d	oil	0.48	3387, 3324, 2975, 1655, 1597, 1516, 1435, 1235, 1163, 920, 816
2e	63–66	0.52	3399, 3326, 1657, 1597, 1518, 1433, 1236, 1161, 993, 918, 814
2f	oil	0.37	3401, 3320, 2965, 1655, 1601, 1534, 1522, 1435, 1236, 1161, 814
2g	61–62	0.46	3391, 3318, 2973, 1655, 1599, 1514, 1460, 1433, 1179, 959, 910, 810

^a EtOAc/hexane (A/H) (1:1).**Scheme 2**

entry 5 in Table 2, for the characterization of **2a–2g**, see Tables 3–5).

The synthesis of *N*-heteroarylminophosphorane derivatives **4a–4g** was carried out by the Appel method, i.e. the modified Kirsanov reaction.³¹ The *sec*-amide derivatives **2a–2g** were easily and directly converted into the corresponding iminophosphoranes **4a–4g** by a triphenylphosphine/hexachloroethane/triethylamine reagent system in benzene under reflux (Scheme 3, Table 6, for the characterization of **4a–4g**, see Tables 7–9).

**Scheme 3**

Finally, the synthesis of 4(3*H*)-pteridinone derivatives **5a–5m** (Scheme 4) was examined by the intermolecular aza-Wittig reaction and heterocyclization as follows. To a solution of the iminophosphorane derivative **4a** in anhydrous toluene was added dropwise benzoyl chloride (2.0 equiv) and triethylamine (2.0 equiv). The mixture was heated to reflux for 4 hours to provide the desired 4(3*H*)-pteridinone derivative **5a**. Moreover this reaction was performed without triethylamine to realize the mechanism of 4(3*H*)-pteridinone formation (entry 2 in Table 10). As a result, 4(3*H*)-pteridinone derivative **5a** and the *N*-benzoyl amide derivative **7a** were obtained in 12% and 40% yield, respectively (Scheme 5). Taking the isolation of the *N*-benzoyl amide derivative **7a** into consideration, imidoyl chloride **6** must participate as the key intermediate in the consecutive reaction. The imidoyl chloride intermediate **6** could not be isolated due to its high reactivity.

Table 4. Characterization (^1H , ^{13}C NMR) of Compounds **2a–2g** Prepared

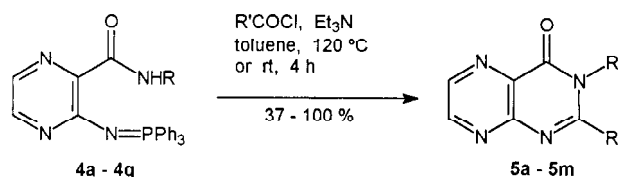
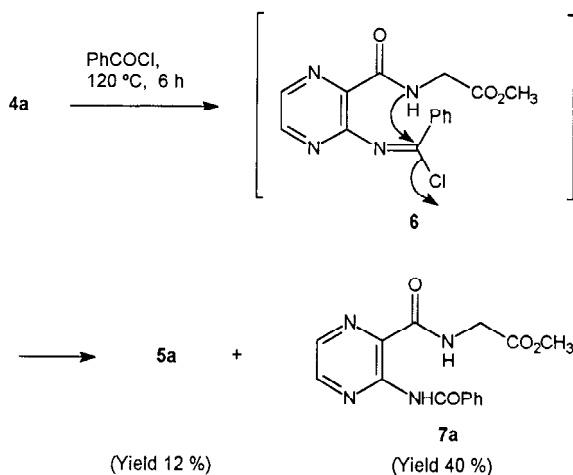
Product	^1H NMR (CDCl_3/TMS , 200 MHz), δ , J (Hz)	^{13}C NMR (CDCl_3/TMS , 50 MHz) δ
2a	8.32 (1H, br s, CONH), 8.17 (1H, d, $J = 2.3$, H-5), 7.83 (1H, d, $J = 2.3$, H-6), 7.0–6.0 (2H, br, NH_2), 4.22 (2H, d, $J = 5.8$, NHCH_2CO), 3.80 (3H, s, OCH_3)	170.57 (CO_2), 166.81 (CONH), 155.46 (C-3), 147.42 (C-5), 132.31 (C-6), 126.32 (C-2), 52.62 (OCH_3), 41.12 (NHCH_2CO)
2b	8.11 (1H, d, $J = 2.4$, H-5), 7.85 (1H, br s, CONH), 7.76 (1H, d, $J = 2.4$, H-6), 7.2–5.5 (2H, br, NH_2), 1.47 [9H, s, $\text{C}(\text{CH}_3)_3$]	165.95 (CONH), 155.53 (C-3), 146.63 (C-5), 131.63 (C-6), 127.86 (C-2), 51.19 [$\text{NHC}(\text{CH}_3)_3$], 28.87 [$\text{C}(\text{CH}_3)_3$]
2c	8.14 (1H, d, $J = 2.4$, H-5), 7.78 (1H, d, $J = 2.4$, H-6), 7.75–7.69 (1H, br, CONH), 7.3–5.5 (2H, br, NH_2), 4.04 [1H, d-sextet, $J = 9.0$, 6.6, $\text{NHCH}(\text{CH}_3)\text{CH}_2$], 1.59 (2H, qd, $J = 7.4$, 6.8, CHCH_2CH_3), 1.24 (3H, d, $J = 6.8$, CHCH_3), 0.96 (3H, t, $J = 7.4$, CH_2CH_3)	165.84 (CONH), 155.56 (C-3), 146.81 (C-5), 131.83 (C-6), 127.25 (C-2), 46.60 [$\text{NHCH}(\text{CH}_3)\text{CH}_2$], 29.82 (CHCH_2CH_3), 20.53 (CHCH_3), 10.49 (CH_2CH_3)
2d	8.13 (1H, d, $J = 2.4$, H-5), 7.78 (1H, d, $J = 2.4$, H-6), 7.82–7.67 (1H, br, CONH), 7.3–6.0 (2H, br, NH_2), 5.84 (1H, ddt, $J = 17.1$, 10.1, 7.2, $\text{CH}_2\text{CH}=\text{CH}_2$), 5.13 [1H, dq, $J = 16.8$, 1.2, $\text{CH}=\text{CH}_2$ (<i>trans</i>)], 5.11 [1H, dq, $J = 10.4$, 1.1, $\text{CH}=\text{CH}_2$ (<i>cis</i>)], 4.20 [1H, d-sextet, $J = 8.6$, 6.6, $\text{NHCH}(\text{CH}_3)\text{CH}_2$], 2.34 (2H, ddt, $J = 7.2$, 6.6, 1.3, $\text{CHCH}_2\text{CH}=\text{CH}_2$), 1.26 (3H, d, $J = 7.0$, CHCH_3)	165.74 (CONH), 155.53 (C-3), 146.83 (C-5), 134.61 ($\text{CH}_2\text{CH}=\text{CH}_2$), 131.87 (C-6), 127.11 (C-2), 118.29 ($\text{CH}=\text{CH}_2$), 44.69 [$\text{NHCH}(\text{CH}_3)\text{CH}_2$], 41.03 ($\text{CHCH}_2\text{CH}=\text{CH}_2$), 20.34 (CHCH_3)
2e	8.15 (1H, d, $J = 2.4$, H-5), 8.10–7.95 (1H, br, CONH), 7.80 (1H, d, $J = 2.4$, H-6), 7.4–5.9 (2H, br, NH_2), 5.94 (1H, ddt, $J = 17.2$, 10.2, 5.4, $\text{CH}_2\text{CH}=\text{CH}_2$), 5.27 [1H, dq, $J = 17.2$, 1.6, $\text{CH}=\text{CH}_2$ (<i>trans</i>)], 5.19 [1H, dq, $J = 10.2$, 1.4, $\text{CH}=\text{CH}_2$ (<i>cis</i>)], 4.06 (2H, ddt, $J = 6.1$, 5.5, 1.6, $\text{NHCH}_2\text{CH}=\text{CH}_2$)	166.37 (CONH), 155.53 (C-3), 147.03 (C-5), 134.31 ($\text{CH}_2\text{CH}=\text{CH}_2$), 131.94 (C-6), 126.88 (C-2), 116.78 ($\text{CH}=\text{CH}_2$), 41.61 ($\text{NHCH}_2\text{CH}=\text{CH}_2$)
2f	8.14 (1H, d, $J = 2.4$, H-5), 8.05–7.85 (1H, br, CONH), 7.78 (1H, d, $J = 2.4$, H-6), 7.5–6.0 (2H, br, NH_2), 3.39 (2H, td, $J = 7.0$, 6.2, NHCH_2CH_2), 1.65 (2H, sextet, $J = 7.3$, $\text{CH}_2\text{CH}_2\text{CH}_3$), 0.99 (3H, t, $J = 7.4$, CH_2CH_3)	166.44 (CONH), 155.51 (C-3), 146.83 (C-5), 131.85 (C-6), 127.16 (C-2), 40.99 (NHCH_2CH_2), 22.93 ($\text{CH}_2\text{CH}_2\text{CH}_3$), 11.48 (CH_2CH_3)
2g	8.13 (1H, d, $J = 2.4$, H-5), 7.78 (1H, d, $J = 2.4$, H-6), 7.83–7.65 (1H, br, CONH), 7.2–6.3 (2H, br, NH_2), 4.21 [1H, d-septet, $J = 8.2$, 6.6, $\text{NHCH}(\text{CH}_3)_2$], 1.27 [6H, d, $J = 6.6$, $\text{CH}(\text{CH}_3)_2$]	165.63 (CONH), 155.54 (C-3), 146.80 (C-5), 131.83 (C-6), 127.23 (C-2), 41.30 [$\text{NHCH}(\text{CH}_3)_2$], 22.81 [$\text{CH}(\text{CH}_3)_2$]

Table 5. Characterization (MS, HRMS) of Compounds **2a–2g** Prepared

Products	MS (70 eV), m/z (%)	HRMS (70 eV), m/z , Found (Formula, Calcd.)
2a	210 (71, M^+), 178 (23), 167 (15), 151 (88), 123 (31), 122 (95), 95 (37), 94 (100), 68 (13), 67 (24)	210.0751 ($\text{C}_8\text{H}_{10}\text{N}_4\text{O}_3$, 210.0753)
2b	194 (45, M^+), 180 (8), 179 (100), 138 (13), 122 (44), 95 (12), 94 (46), 68 (6), 67 (8)	194.1167 ($\text{C}_9\text{H}_{14}\text{N}_4\text{O}$, 194.1167)
2c	194 (29, M^+), 166 (8), 165 (100), 138 (6), 122 (70), 95 (8), 94 (50), 72 (30), 67 (8)	194.1167 ($\text{C}_9\text{H}_{14}\text{N}_4\text{O}$, 194.1167)
2d	206 (3, M^+), 166 (13), 165 (100), 138 (3), 123 (5), 122 (79), 95 (6), 94 (80), 68 (3), 67 (12)	206.1167 ($\text{C}_{10}\text{H}_{14}\text{N}_4\text{O}$, 206.1168)
2e	178 (100, M^+), 163 (22), 162 (19), 161 (21), 160 (14), 150 (20), 133 (16), 123 (10), 122 (18), 95 (90), 94 (87), 68 (49), 67 (47)	178.0854 ($\text{C}_8\text{H}_{10}\text{N}_4\text{O}$, 178.0855)
2f	180 (62, M^+), 167 (33), 151 (30), 149 (100), 122 (71), 95 (27), 94 (72), 85 (18), 83 (19), 81 (19), 71 (42), 70 (18), 69 (41)	180.1011 ($\text{C}_8\text{H}_{12}\text{N}_4\text{O}$, 180.1011)
2g	180 (55, M^+), 165 (37), 122 (75), 95 (22), 94 (100), 68 (15), 67 (19)	180.1011 ($\text{C}_8\text{H}_{12}\text{N}_4\text{O}$, 180.1011)

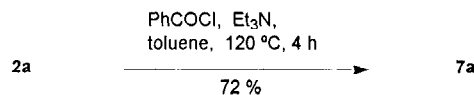
Table 6. Synthesis of Iminophosphoranes **4a–4g** by the Modified Kirsanov Reaction

Entry	R	Products	Yield (%) ^a
1	–CH ₂ CO ₂ CH ₃	4a	100
2	<i>t</i> -Bu	4b	96
3	<i>s</i> -Bu	4c	72
4	–CH(CH ₃)CH ₂ CH=CH ₂	4d	89
5	allyl	4e	100
6	Pr	4f	83
7	<i>i</i> -Pr	4g	93

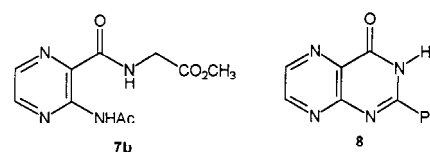
^a Isolated yield**Scheme 4****Scheme 5**

In addition, *N*-benzoyl amide **7a** was also produced in 72% yield by the reaction of *sec*-amide **2a** with benzoyl chloride in the presence of triethylamine at 120 °C for 4 hours to confirm the given structure (Scheme 6).

The other aroyl chlorides were reactive as benzoyl chloride and the substituent effects were not observed (entries 1, 3 and 4 in Table 10). Alkyl acyl chlorides were found to be more reactive than aroyl chlorides and the intermolecular aza-Wittig reaction with acyl chlorides proceeded

**Scheme 6**

even at room temperature in a few hours (entries 5 and 6 in Table 10). The reaction with isobutyryl chloride produced the desired 4(3*H*)-pteridinone derivative **5d** in a moderate yield; however, that with acetyl chloride gave only acetyl amide derivative **7b**. The expected 3-(methoxycarbonylmethyl)-2-methyl-4(3*H*)-pteridinone (**5e**) was not probably produced because it is sensitive to hydrolysis due to less steric hindrance than the other 4(3*H*)-pteridinone derivatives **5a–5d**. Further, the other iminophosphorane derivatives **4c–4g** (R were simple alkyl groups) showed similar reactivity to afford the desired 4(3*H*)-pteridinone derivatives **5f–5k**, **5m** in satisfactory yields (entries 7–12 and 14 in Table 10). However, in the case of the *tert*-butyl amide derivative **4b**, the corresponding 4(3*H*)-pteridinone derivatives **5l** was produced in a low yield accompanied by a small amount of 2-phenyl-4(3*H*)-pteridinone (**8**) as a byproduct (entry 13 in Table 10). Because a *tert*-butyl group is well known as very bulky and sensitive to heat and acid to be removed as isobutene, the above-mentioned side reaction must have occurred. Besides, the reaction of iminophosphorane **4a** and trifluoroacetic anhydride instead of acyl chloride resulted in the formation of unidentified compounds, affording none of the desired product. In the synthesis of a series of these 4(3*H*)-pteridinone derivatives **5**, Chromatorex[®] (NH-DM-1020)³² was used to isolate the desired compounds (e.g. **5h**, **5k–5m**) because *R_f* values of these compounds on silica gel TLC were the same as that of triphenylphosphine oxide, which was the inevitable byproduct in the aza-Wittig reaction.



In addition, we investigated the possibility of extended ring construction of the 4(3*H*)-pteridinone derivative. The reaction of iminophosphorane **4a** and *o*-azidobenzoyl chloride, which was derived from anthranilic acid in two steps, led to the 4(3*H*)-pteridinone derivative **9** having an azide function. This compound **9** was treated with triphenylphosphine to give the corresponding iminophos-

Table 7. Characterization (mp, *R_f*, IR) of Compounds **4a–4g** Prepared

Products	mp (°C)	<i>R_f</i> (EtOAc)	IR (KBr or neat) ν (cm ^{–1})
4a	55–56	0.09 (tailing)	2973, 1750, 1665, 1549, 1512, 1451, 1400, 1219, 1171, 1115, 750, 723, 694
4b	194–200	0.10 (tailing)	3422, 2967, 1665, 1551, 1512, 1439, 1400, 1115, 993, 750, 723, 693
4c	162–165	0.10 (tailing)	2965, 1657, 1547, 1510, 1439, 1399, 1173, 1115, 993, 750, 723, 694
4d	45–50	0.10 (tailing)	2967, 1657, 1547, 1439, 1399, 1171, 1115, 993, 750, 723, 693
4e	132–135	0.10 (tailing)	3420, 3194, 1690, 1618, 1439, 1420, 1200, 654
4f	60–61	0.10 (tailing)	3181, 2965, 1657, 1549, 1512, 1449, 1399, 1175, 1115, 995, 847, 721, 693
4g	202–208	0.10 (tailing)	3428, 2971, 1657, 1545, 1439, 1399, 1161, 1115, 995, 721, 693

Table 8. Characterization (^1H , ^{13}C NMR) of Compounds **4a–4g** Prepared

Product	^1H NMR (CDCl_3/TMS , 200 MHz), δ , J (Hz)	^{13}C NMR (CDCl_3/TMS , 50 MHz), δ , J (Hz)
4a	11.52 (1H, br s, CONH), 7.99 (1H, d, $J = 2.4$, H-5), 7.86–7.74 (1H + 6H, m, H-6 + C_6H_5), 7.63–7.42 (9H, m, C_6H_5), 4.41 (2H, d, $J = 5.6$, NHCH_2CO), 3.73 (3H, s, OCH_3)	171.19 (CO_2), 165.97 (CONH), 158.66 (d, $J = 7.3$, C-3), 143.33 (C-5), 136.53 (d, $J = 4.2$, C-2), 133.75 (C-6), 133.45 (d, $J = 9.9$, C-2'), 132.64 (d, $J = 2.8$, C-4'), 129.02 (d, $J = 12.3$, C-3'), 128.53 (d, $J = 101.1$, C-1'), 52.15 (OCH_3), 41.78 (NHCH_2CO)
4b	10.52 (1H, br s, CONH), 7.96 (1H, d, $J = 2.4$, H-5), 7.80–7.69 (1H + 6H, m, H-6 + C_6H_5), 7.64–7.41 (9H, m, C_6H_5), 1.43 [9H, s, $\text{C}(\text{CH}_3)_3$]	164.62 (CONH), 158.22 (d, $J = 7.5$, C-3), 142.52 (C-5), 138.48 (d, $J = 19.6$, C-2), 133.79 (C-6), 133.50 (d, $J = 9.9$, C-2'), 132.61 (d, $J = 2.6$, C-4'), 128.98 (d, $J = 12.3$, C-3'), 128.84 (d, $J = 101.0$, C-1'), 50.95 [$\text{C}(\text{CH}_3)_3$], 29.10 [$\text{C}(\text{CH}_3)_3$]
4c	10.90 (1H, d, $J = 8.2$, CONH), 8.00 (1H, d, $J = 2.4$, H-5), 7.81–7.69 (1H + 6H, m, H-6 + C_6H_5), 7.63–7.43 (9H, m, C_6H_5), 4.25 [1H, d-sextet, $J = 8.2$, 6.6, $\text{NHCH}(\text{CH}_3)\text{CH}_2$], 1.52 (2H, qd, $J = 7.4$, 6.6, CHCH_2CH_3), 1.21 (3H, d, $J = 6.6$, CHCH_3), 0.87 (3H, t, $J = 7.4$, CH_2CH_3)	164.91 (CONH), 158.41 (d, $J = 7.6$, C-3), 142.73 (C-5), 137.70 (d, $J = 19.1$, C-2), 133.86 (C-6), 133.39 (d, $J = 10.0$, C'-2), 132.68 (d, $J = 2.8$, C'-4), 129.03 (d, $J = 12.4$, C'-3), 128.74 (d, $J = 101.1$, C'-1), 46.52 [$\text{NHCH}(\text{CH}_3)\text{CH}_2$], 29.86 (CHCH_2CH_3), 20.88 (CHCH_3), 10.51 (CH_2CH_3)
4d	10.97 (1H, d, $J = 8.0$, CONHCH_2), 8.00 (1H, d, $J = 2.4$, H-5), 7.81–7.69 (1H + 6H, m, H-6 + C_6H_5), 7.65–7.43 (9H, m, C_6H_5), 5.76 (1H, ddt, $J = 18.0$, 9.2, 7.1, $\text{CH}_2\text{CH}=\text{CH}_2$), 4.91 [1H, dq, $J = 9.2$, 0.8, $\text{CH}=\text{CH}_2$ (cis)], 4.89 [1H, dq, $J = 18.0$, 0.8, $\text{CH}=\text{CH}_2$ (trans)], 4.44 [1H, d-sextet, $J = 8.2$, 6.6, $\text{NHCH}(\text{CH}_3)\text{CH}_2$], 2.27 (2H, tt, $J = 6.8$, 1.2, $\text{CHCH}_2\text{CH}=\text{CH}_2$), 1.22 (3H, d, $J = 6.8$, CHCH_3)	164.80 (CONH), 158.31 (d, $J = 7.4$, C-3), 142.81 (C-5), 137.58 (d, $J = 19.2$, C-2), 135.57 ($\text{CH}_2\text{CH}=\text{CH}_2$), 133.88 (C-6), 133.43 (d, $J = 10.0$, C'-2), 132.71 (d, $J = 2.8$, C'-4), 129.05 (d, $J = 12.6$, C'-3), 128.72 (d, $J = 101.3$, C'-1), 117.32 ($\text{CH}=\text{CH}_2$), 44.63 [$\text{NHCH}(\text{CH}_3)\text{CH}_2$], 41.24 ($\text{CHCH}_2\text{CH}=\text{CH}_2$), 20.68 (CHCH_3)
4e	11.26 (1H, br s, CONH), 8.01 (1H, d, $J = 2.4$, H-5), 7.81–7.69 (1H + 6H, m, H-6 + C_6H_5), 7.63–7.41 (9H, m, C_6H_5), 6.01 (1H, ddt, $J = 17.2$, 10.2, 5.8, $\text{CH}_2\text{CH}=\text{CH}_2$), 5.29 [1H, dq, $J = 17.2$, 1.6, $\text{CH}=\text{CH}_2$ (trans)], 5.14 [1H, dq, $J = 10.2$, 1.5, $\text{CH}=\text{CH}_2$ (cis)], 4.23 (2H, tt, $J = 5.7$, 1.5, $\text{NHCH}_2\text{CH}=\text{CH}_2$)	165.58 (CONH), 158.39 (d, $J = 7.5$, C-3), 143.01 (C-5), 137.36 (d, $J = 19.1$, C-2), 135.50 ($\text{CH}_2\text{CH}=\text{CH}_2$), 133.87 (C-6), 133.38 (d, $J = 9.8$, C'-2), 132.68 (d, $J = 2.8$, C'-4), 129.05 (d, $J = 12.5$, C'-3), 128.62 (d, $J = 101.2$, C'-1), 116.56 ($\text{CH}=\text{CH}_2$), 42.59 ($\text{NHCH}_2\text{CH}=\text{CH}_2$)
4f	11.09 (1H, br s, CONH), 8.00 (1H, d, $J = 2.4$, H-5), 7.81–7.69 (1H + 6H, m, H-6 + C_6H_5), 7.64–7.43 (9H, m, C_6H_5), 3.52 (2H, td, $J = 7.0$, 5.6, NHCH_2CH_2), 1.62 (2H, sextet, $J = 7.3$, $\text{CH}_2\text{CH}_2\text{CH}_3$), 0.90 (3H, t, $J = 7.4$, CH_2CH_3)	165.65 (CONH), 158.29 (d, $J = 7.8$, C-3), 142.80 (C-5), 137.61 (d, $J = 19.2$, C-2), 133.82 (C-6), 133.32 (d, $J = 10.1$, C'-2), 132.68 (d, $J = 2.9$, C'-4), 129.02 (d, $J = 12.1$, C'-3), 128.66 (d, $J = 101.1$, C'-1), 41.63 (NHCH_2CH_2), 22.81 ($\text{CH}_2\text{CH}_2\text{CH}_3$), 11.75 (CH_2CH_3)
4g	10.89 (1H, d, $J = 7.6$, CONHCH_2), 7.99 (1H, d, $J = 2.2$, H-5), 7.82–7.70 (1H + 6H, m, H-6 + C_6H_5), 7.64–7.43 (9H, m, C_6H_5), 4.41 [1H, d-septet, $J = 7.6$, 6.6, $\text{NHCH}(\text{CH}_3)_2$], 1.23 [6H, d, $J = 6.6$, $\text{CH}(\text{CH}_3)_2$]	164.72 (CONH), 158.29 (d, $J = 7.5$, C-3), 142.77 (C-5), 137.63 (d, $J = 19.1$, C-2), 133.83 (C-6), 133.40 (d, $J = 9.9$, C'-2), 132.68 (d, $J = 2.8$, C'-4), 129.03 (d, $J = 12.5$, C'-3), 128.72 (d, $J = 101.2$, C'-1), 41.22 [$\text{NHCH}(\text{CH}_3)_2$], 23.20 [$\text{CH}(\text{CH}_3)_2$]

Table 9. Characterization (MS, HRMS) of Compounds **4a–4g** Prepared

Products	MS (70 eV), m/z (%)	HRMS (70 eV), m/z , Found (Formula, Calcd.)
4a	471 (26, $M + 1$), 470 (89, M^+), 412 (11), 411 (42), 398 (7), 397 (27), 382 (7), 355 (21), 354 (100), 352 (8), 262 (12), 201 (9), 183 (24)	470.1497 ($\text{C}_{26}\text{H}_{23}\text{N}_4\text{O}_3\text{P}$, 470.1508)
4b	455 (19, $M + 1$), 454 (62, M^+), 440 (11), 439 (38), 398 (22), 397 (11), 382 (24), 355 (26), 354 (100), 262 (14), 212 (13), 183 (30)	454.1923 ($\text{C}_{27}\text{H}_{27}\text{N}_4\text{OP}$, 454.1923)
4c	455 (16, $M + 1$), 454 (52, M^+), 425 (13), 383 (11), 382 (16), 355 (28), 354 (100), 262 (11), 208 (8), 183 (17)	454.1922 ($\text{C}_{27}\text{H}_{27}\text{N}_4\text{OP}$, 454.1923)
4d	466 (17, M^+), 426 (14), 425 (50), 383 (10), 382 (30), 355 (22), 354 (100), 262 (15), 205 (9), 183 (25), 178 (11), 108 (9)	466.1922 ($\text{C}_{28}\text{H}_{27}\text{N}_4\text{OP}$, 466.1923)
4e	439 (18, $M + 1$), 438 (61, M^+), 397 (12), 394 (9), 355 (25), 354 (100), 262 (12), 201 (9), 183 (22)	438.1607 ($\text{C}_{26}\text{H}_{23}\text{N}_4\text{OP}$, 438.1609)
4f	441 (19, $M + 1$), 440 (61, M^+), 425 (6), 411 (8), 397 (12), 383 (7), 382 (7), 355 (27), 354 (100), 262 (10), 183 (21), 108 (6)	440.1766 ($\text{C}_{26}\text{H}_{25}\text{N}_4\text{OP}$, 440.1766)
4g	441 (16, $M + 1$), 440 (54, M^+), 397 (12), 355 (31), 354 (100), 183 (20)	440.1765 ($\text{C}_{26}\text{H}_{25}\text{N}_4\text{OP}$, 440.1766)

Table 10. Synthesis of 4(3*H*)-Pteridinone Derivatives **5a–5m** via the Intermolecular Aza-Wittig Reaction Followed by Heterocyclization

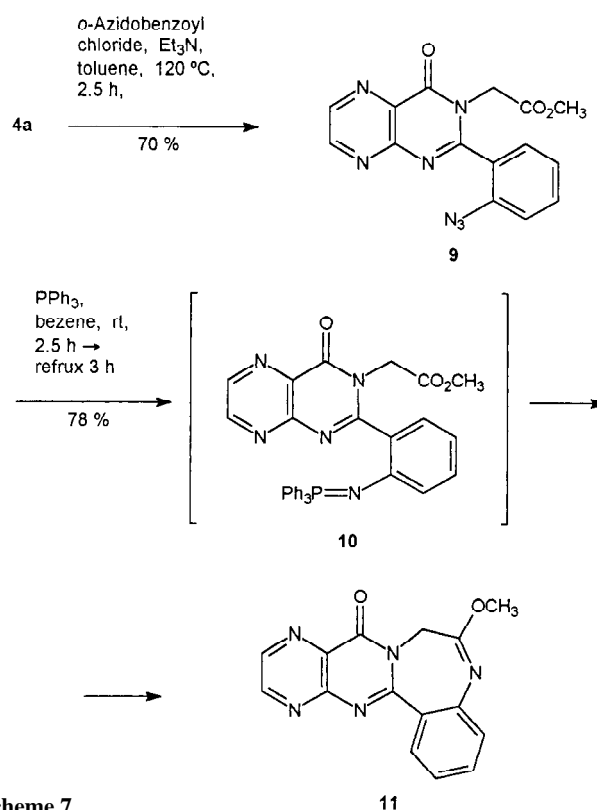
Entry	R	R'	Products	Yield (%) ^a
1	–CH ₂ CO ₂ CH ₃	Ph	5a	68
2 ^b	–CH ₂ CO ₂ CH ₃	Ph	5a + 7a ^c	12 + 40
3	–CH ₂ CO ₂ CH ₃	4-CH ₃ OC ₆ H ₄	5b	52
4	–CH ₂ CO ₂ CH ₃	4-NO ₂ C ₆ H ₄	5c	61
5	–CH ₂ CO ₂ CH ₃	<i>i</i> -Pr	5d	47
6	–CH ₂ CO ₂ CH ₃	CH ₃	5e	0 ^d
7	–CH ₂ CH=CH ₂	Ph	5f	89
8	Pr	Ph	5g	53
9	<i>i</i> -Pr	Ph	5h	91
10	<i>i</i> -Pr	4-CH ₃ OC ₆ H ₄	5i	49
11	<i>i</i> -Pr	4-NO ₂ C ₆ H ₄	5j	67
12	<i>s</i> -Bu	Ph	5k	98
13	<i>t</i> -Bu	Ph	5l + 8	37 + 14
14	–CH(CH ₃)CH ₂ CH=CH ₂	Ph	5m	89

^a Isolated yield.^b Absence of Et₃N.^c *Vide infra*.^d Obtained compound was only **7b**.

phorane intermediate **10** via Staudinger reaction, which was then heated without purification to produce the seven membered ring compound **11**, 4(3*H*)-pteridinone fused with a 1,4-benzodiazepine skeleton, via intramolecular aza-Wittig reaction with the ester carbonyl function (Scheme 7).

In conclusion, a facile and efficient method for synthesis of 4(3*H*)-pteridinone derivatives via *N*-pyrazylimino-phosphorane derivatives has been established.

Mps were determined with a Yanagimoto micro-melting-point hot-stage apparatus and were uncorrected. IR spectra were recorded on a JASCO FT/IR 5300 spectrophotometer. ¹H and ¹³C NMR spectra were obtained with a Varian GEMINI-200 or 500 spectrometer at 200 or 500 and 50 or 125 MHz, respectively, for samples in CDCl₃ or DMSO-*d*₆ solution with TMS as an internal standard. Chemical shifts were reported in ppm (δ). MS and HRMS were recorded on a JEOL JMS-AX 505 HA mass spectrometer (EI and CI, 70 eV). Flash chromatography was performed with a silica gel column (Fuji-Davison BW-300) and Chromatorex® (NH-DM-1020).³² TLC was performed on Merck Kieselgel 60 F₂₅₄ pre-coated silica plates (0.15 mm layer thickness). All reactions except for amide exchange reactions were

**Scheme 7**

carried out under N₂ or argon. 3-Aminopyrazine-2-carboxylic acid (**1**) and DMC were supplied by Nippon Soda Co., Ltd. and Shiratori Pharmaceutical Co., Ltd., respectively. Methyl 3-aminopyrazine-2-carboxylate (**3**) and DEPC were purchased from Sigma-Aldrich Japan K. K. and Tokyo Kasei Co., Ltd., respectively. These reagents were used without further purification.

3-Amino-*N*-(methoxycarbonylmethyl)pyrazine-2-carboxamide (**2a**); Typical Procedure:

The condensation reaction (see Scheme 1).

To a mixture of 3-aminopyrazine-2-carboxylic acid (**1**) (714 mg, 5.13 mmol) and glycine methyl ester hydrochloride (773 mg, 6.16 mmol) in anhyd DME (30.0 mL) was added dropwise DEPC (93%, 1.00 mL, 6.16 mmol) and Et₃N (1.70 mL, 12.2 mmol) respectively at 0 °C. The resultant solution was stirred at 0 °C for 1 h and at 40 °C for 1 h under N₂. The mixture was diluted with EtOAc (500 mL)

Table 11. Characterization (mp, *R*_f, IR) of Compounds **5a–5m** Prepared

Products	mp (°C)	<i>R</i> _f (Solvent) ^a	IR (KBr or neat) ν (cm ⁻¹)
5a	178–179	0.08 (A/H 2:1)	3343, 1753, 1696, 1659, 1589, 1489, 1451, 1256, 704
5b	228.5–229	0.27 (A)	1742, 1701, 1609, 1586, 1561, 1543, 1518, 1426, 1366, 1258, 1225, 1175
5c	86–90	0.41 (A)	3007, 1752, 1705, 1580, 1543, 1524, 1420, 1350, 1229, 752
5d	oil	0.29 (A)	2978, 1752, 1701, 1588, 1561, 1543, 1464, 1424, 1373, 1217, 752
5f	159–160	0.29 (A)	1686, 1543, 1408, 1366, 1337, 1265, 1217, 926, 704
5g	164–165	0.24 (A)	2955, 1692, 1561, 1543, 1449, 1418, 1368, 1211, 1140, 704
5h	235	0.10 (2:1)	2998, 2920, 1694, 1576, 1541, 1416, 1395, 1345, 1215, 1074, 745, 704
5i	237.5–238	0.30 (A)	2932, 1692, 1607, 1561, 1537, 1510, 1418, 1294, 1260, 1073, 1032, 831, 750
5j	>300	0.30 (A)	3079, 1692, 1576, 1545, 1520, 1414, 1350, 1290, 1202, 1071, 858, 714
5k	160–166	0.19 (A/H 3:1)	1699, 1578, 1439, 1416, 1395, 1343, 1194, 1121, 721, 696
5l	277–285 (dec.)	0.36 (A)	3056, 1696, 1555, 1535, 1483, 1402, 1370, 1343, 1314, 1287, 675
5m	127–131	0.36 (A)	3056, 1699, 1580, 1541, 1416, 1395, 1345, 1290, 1209, 1119, 914, 828, 698

^a EtOAc (A) and hexane (H)

Table 12. Characterization (^1H , ^{13}C NMR) of Compounds **5a–5m** Prepared

Product	^1H NMR (CDCl_3/TMS , 200 MHz) δ , J (Hz)	^{13}C NMR (CDCl_3/TMS , 50 MHz) δ
5a	9.01 (1H, d, $J = 2.0$, H-7), 8.88 (1H, d, $J = 2.0$, H-6), 7.65–7.48 (5H, m, C_6H_5), 4.78 (2H, s, NCH_2CO), 3.78 (3H, s, OCH_3)	168.12 (CO_2), 161.59 (C-8a), 160.26 (C-4), 154.00 (C-2), 151.08 (C-7), 145.45 (C-6), 134.08 (C-4a), 132.53 (C'-1), 131.37 (C'-4), 129.36 (C'-2), 128.27 (C'-3), 53.06 (OCH_3), 48.41 (NCH_2CO)
5b	8.99 (1H, d, $J = 2.0$, H-7), 8.85 (1H, d, $J = 2.0$, H-6), 7.64–7.57 (2H, m, C_6H_4), 7.06–6.99 (2H, m, C_6H_4), 4.82 (2H, s, NCH_2CO), 3.89 (3H, s, $\text{C}_6\text{H}_4\text{OCH}_3$), 3.80 (3H, s, CO_2CH_3)	168.34 (CO_2), 162.22 (C'-4), 161.90 (C-4), 160.24 (C-8a), 154.10 (C-2), 151.05 (C-7), 145.23 (C-6), 132.41 (C-4a), 130.36 (C'-2), 126.32 (C'-1), 114.70 (C'-3), 55.67 ($\text{C}_6\text{H}_4\text{OCH}_3$), 53.10 (CO_2CH_3), 48.79 (NCH_2CO)
5c	9.05 (1H, d, $J = 2.0$, H-7), 8.93 (1H, d, $J = 2.2$, H-6), 8.45–8.38 (2H, m, C_6H_4), 7.89–7.83 (2H, m, C_6H_4), 4.73 (2H, s, NCH_2CO), 3.80 (3H, s, OCH_3)	167.95 (CO_2), 161.15 (C-4), 158.11 (C-8a), 153.77 (C-2), 151.31 (C-7), 149.61 (C'-4), 146.13 (C-6), 139.72 (C'-1), 132.78 (C-4a), 129.80 (C'-2), 124.63 (C'-3), 53.40 (OCH_3), 48.15 (NCH_2CO)
5d	8.96 (1H, d, $J = 2.0$, H-7), 8.82 (1H, d, $J = 2.0$, H-6), 5.03 (2H, s, NCH_2CO), 3.83 (3H, s, OCH_3), 2.98 [1H, septet, $J = 6.6$, $\text{CH}(\text{CH}_3)_2$], 1.45 [6H, d, $J = 6.6$, $\text{CH}(\text{CH}_3)_2$]	168.10 (CO_2), 166.44 (C-8a), 161.70 (C-4), 154.09 (C-2), 150.83 (C-7), 144.99 (C-6), 132.23 (C-4a), 53.24 (OCH_3), 44.86 (NCH_2CO), 33.05 [$\text{CH}(\text{CH}_3)_2$], 21.05 [$\text{CH}(\text{CH}_3)_2$]
5f	9.00 (1H, d, $J = 2.2$, H-7), 8.87 (1H, d, $J = 2.0$, H-6), 7.70–7.46 (5H, m, C_6H_5), 5.93 (1H, ddt, $J = 17.3$, 10.3, 5.2, $\text{CH}_2\text{CH}=\text{CH}_2$), 5.23 [1H, ddd, $J = 10.4$, 2.3, 1.5, $\text{CH}=\text{CH}_2$ (<i>cis</i>)], 5.00 [1H, ddd, $J = 17.2$, 2.4, 1.6, $\text{CH}=\text{CH}_2$ (<i>trans</i>)], 4.74 (2H, dt, $J = 5.4$, 1.6, $\text{NCH}_2\text{CH}=\text{CH}_2$)	161.58 (C-4), 161.04 (C-8a), 153.92 (C-2), 150.95 (C-7), 145.31 (C-6), 134.62 (C'-1), 132.71 (C-4a), 131.69 ($\text{CH}_2\text{CH}=\text{CH}_2$), 131.08 (C'-4), 128.92 (C'-2), 128.44 (C'-3), 118.88 ($\text{CH}=\text{CH}_2$), 49.36 ($\text{NCH}_2\text{CH}=\text{CH}_2$)
5g	8.98 (1H, d, $J = 2.0$, H-7), 8.86 (1H, d, $J = 2.0$, H-6), 7.63–7.51 (5H, m, C_6H_5), 4.08 (2H, t, $J = 7.7$, NCH_2CH_2), 1.70 (2H, sextet, $J = 7.6$, $\text{CH}_2\text{CH}_2\text{CH}_3$), 0.79 (3H, t, $J = 7.5$, CH_2CH_3)	161.76 (C-4), 161.00 (C-8a), 153.80 (C-2), 150.84 (C-7), 145.21 (C-6), 134.98 (C'-1), 132.72 (C-4a), 130.85 (C'-4), 129.09 (C'-2), 128.21 (C'-3), 48.58 (NCH_2CH_2), 21.90 ($\text{CH}_2\text{CH}_2\text{CH}_3$), 11.08 (CH_2CH_3)
5h	8.96 (1H, d, $J = 2.0$, H-7), 8.83 (1H, d, $J = 2.0$, H-6), 7.60–7.54 (5H, m, C_6H_5), 4.48 [1H, septet, $J = 6.8$, $\text{NCH}(\text{CH}_3)_2$], 1.64 [6H, d, $J = 6.8$, $\text{CH}(\text{CH}_3)_2$]	161.93 (C-4), 161.29 (C-8a), 153.40 (C-2), 150.69 (C-7), 145.08 (C-6), 135.75 (C'-1), 133.51 (C-4a), 130.73 (C'-4), 129.21 (C'-2), 127.72 (C'-3), 55.57 [$\text{NCH}(\text{CH}_3)_2$], 19.47 [$\text{CH}(\text{CH}_3)_2$]
5i	8.94 (1H, d, $J = 1.6$, H-7), 8.80 (1H, d, $J = 1.8$, H-6), 7.62–7.54 (2H, m, C_6H_4), 7.08–7.01 (2H, m, C_6H_4), 4.58 [1H, septet, $J = 6.8$, $\text{NCH}(\text{CH}_3)_2$], 3.90 (3H, s, OCH_3), 1.67 [6H, d, $J = 6.8$, $\text{CH}(\text{CH}_3)_2$]	162.20 (C'-4), 161.74 (C-4), 161.28 (C-8a), 153.47 (C-2), 150.65 (C-7), 144.86 (C-6), 133.36 (C-4a), 129.77 (C'-2), 127.96 (C'-1), 114.51 (C'-3), 55.61 [OCH_3 and $\text{NCH}(\text{CH}_3)_2$ may be overlapped], 19.65 [$\text{NCH}(\text{CH}_3)_2$]
5j	8.99 (1H, d, $J = 2.0$, H-7), 8.88 (1H, d, $J = 2.2$, H-6), 8.47–8.40 (2H, m, C_6H_4), 7.84–7.77 (2H, m, C_6H_4), 4.31 [1H, septet, $J = 6.8$, $\text{NCH}(\text{CH}_3)_2$], 1.67 [6H, d, $J = 6.8$, $\text{CH}(\text{CH}_3)_2$]	161.51 (C-4), 158.98 (C-8a), 153.18 (C-2), 150.92 (C-7), 149.30 (C'-4), 145.77 (C-6), 141.47 (C'-1), 133.75 (C-4a), 129.10 (C'-2), 124.61 (C'-3), 55.98 [$\text{NCH}(\text{CH}_3)_2$], 19.56 [$\text{NCH}(\text{CH}_3)_2$]
5k	8.96 (1H, d, $J = 2.0$, H-7), 8.84 (1H, d, $J = 2.0$, H-6), 7.75 (5H, s, C_6H_5), 4.20 [1H, d-quintet, $J = 9.0$, 6.5, $\text{NCH}(\text{CH}_3)\text{CH}_2$], 2.36 [1H, d-quintet, $J = 15.5$, 7.5, CHCH_2CH_3], 1.88 (1H, dqd, $J = 14.0$, 7.5, 6.5, CHCH_2CH_3), 1.67 (3H, d, $J = 7.0$, CHCH_3), 0.73 (3H, t, $J = 7.5$, CH_2CH_3)	161.74 (C-4), 161.64 (C-8a), 153.27 (C-2), 150.58 (C-7), 144.99 (C-6), 135.72 (C'-1), 133.22 (C-4a), 130.56 (C'-4), 129.11 (C'-2), 127.56 (C'-3), 61.68 [$\text{NCH}(\text{CH}_3)\text{CH}_2$], 25.99 (CHCH_2CH_3), 18.21 (CHCH_3), 11.60 (CH_2CH_3)
5l	8.90 (1H, d, $J = 2.2$, H-7), 8.77 (1H, d, $J = 2.2$, H-6), 7.71–7.66 (2H, m, C_6H_5), 7.55–7.45 (3H, m, C_6H_5), 1.55 [9H, s, $\text{C}(\text{CH}_3)_3$]	165.07 (C-4), 161.55 (C-8a), 152.41 (C-2), 150.34 (C-7), 144.58 (C-6), 140.06 (C'-1), 133.41 (C-4a), 130.98 (C'-4), 128.85 (C'-2), 128.57 (C'-3), 65.71 [$\text{NC}(\text{CH}_3)_3$], 31.08 [$\text{C}(\text{CH}_3)_3$]
5m	8.96 (1H, d, $J = 2.0$, H-7), 8.83 (1H, d, $J = 2.0$, H-6), 7.55 (5H, s, C_6H_5), 5.49 (1H, dddd, $J = 17.0$, 10.0, 8.4, 6.3, $\text{CH}_2\text{CH}=\text{CH}_2$), 4.97 [1H, dq, $J = 16.8$, 1.0, $\text{CH}=\text{CH}_2$ (<i>trans</i>)], 4.92 [1H, dq, $J = 10.0$, 1.0, $\text{CH}=\text{CH}_2$ (<i>cis</i>)], 4.36 [1H, dqd, $J = 9.1$, 6.8, 6.1, $\text{NCH}(\text{CH}_3)\text{CH}_2$], 3.15 (1H, dddd, $J = 14.2$, 9.2, 8.4, 1.0, $\text{CHCH}_2\text{CH}=\text{CH}_2$), 2.53 (1H, dtt, $J = 14.2$, 6.3, 1.3, $\text{CHCH}_2\text{CH}=\text{CH}_2$), 1.69 (3H, d, $J = 6.8$, CHCH_3)	161.97 (C-4), 161.75 (C-8a), 153.40 (C-2), 150.73 (C-7), 145.16 (C-6), 135.80 (C'-1), 134.34 ($\text{CH}_2\text{CH}=\text{CH}_2$), 133.39 (C-4a), 130.72 (C'-4), 129.22 (C'-2), 127.97 (C'-3), 118.92 ($\text{CH}=\text{CH}_2$), 59.46 [$\text{NCH}(\text{CH}_3)\text{CH}_2$], 36.99 ($\text{CHCH}_2\text{CH}=\text{CH}_2$), 18.00 (CHCH_3)

and washed with water (50 mL), sat. Na_2CO_3 (50 mL), water (50 mL) and sat. brine (50 mL) successively. The combined organic layer was dried (MgSO_4) and evaporated under reduced pressure to afford the crude product, which was purified by recrystallization from EtOAc and hexane to give secondary amide derivative **2a** (pale yellow needles, 841 mg, 78%). The other secondary amide derivatives **2b–2d** were also obtained by the similar method (see, Table 1).

***N*-Allyl-3-aminopyrazine-2-carboxamide (2e); Typical Procedure:**

The exchange reactions of ester derivative **3** to *sec*-amide derivatives (see Scheme 2).

Methyl 3-aminopyrazine-2-carboxylate (**3**) (308 mg, 2.01 mmol) was dissolved in allylamine (10.0 mL) and to this solution was added DBU (0.30 mL, 2.01 mmol). The resultant solution was stirred at r.t.

Table 13. Characterization (MS, HRMS) of Compounds **5a–5m** Prepared

Products	MS (70 eV), m/z (%)	HRMS (70 eV), m/z , Found (Formula, Calcd.)
5a	297 (15, $M+1$), 296 (100, M^+), 295 (50), 264 (11), 263 (11), 237 (68), 236 (33), 235 (9), 209 (15), 165 (8), 79 (13)	296.0911 ($C_{15}H_{14}N_4O_3$, 296.0909)
5b	327 (17, $M+1$), 326 (100, M^+), 325 (66), 294 (7), 293 (10), 267 (24), 266 (14), 265 (8), 252 (6), 239 (9), 133 (7), 79 (6)	326.1017 ($C_{16}H_{14}N_4O_4$, 326.1015)
5c	342 (15, $M+1$), 341 (100, M^+), 340 (28), 311 (8), 310 (9), 295 (8), 294 (9), 282 (12), 281 (10), 236 (27), 79 (21)	341.0747 ($C_{15}H_{11}N_5O_5$, 314.0760)
5d	263 (14, $M+1$), 262 (80, M^+), 248 (18), 247 (100), 234 (55), 231 (12), 203 (23), 189 (22), 177 (12), 175 (40), 79 (15)	262.1064 ($C_{12}H_{14}N_4O_3$, 262.1066)
5f	265 (12, $M+1$), 264 (74, M^+), 263 (100), 249 (8), 235 (8), 187 (8), 181 (14), 132 (7), 104 (9), 103 (14)	264.1038 ($C_{15}H_{12}N_4O$, 264.1011)
5g	267 (18, $M+1$), 266 (100, M^+), 265 (46), 238 (18), 225 (13), 224 (87), 223 (26), 196 (12), 121 (21), 104 (12), 103 (12)	266.1169 ($C_{15}H_{14}N_4O$, 266.1168)
5h	267 (16, $M+1$), 266 (100, M^+), 265 (86), 225 (13), 224 (76), 223 (28), 196 (15), 195 (8), 121 (34), 104 (14), 103 (14), 93 (8)	266.1168 ($C_{15}H_{14}N_4O$, 266.1168)
5i	297 (16, $M+1$), 296 (100, M^+), 295 (73), 255 (12), 254 (74), 253 (54), 223 (6), 211 (14), 134 (11), 133 (12), 121 (7)	296.1271 ($C_{16}H_{16}N_4O_2$, 296.1273)
5j	311 (52, M^+), 310 (57), 295 (17), 294 (71), 270 (19), 269 (100), 268 (11), 264 (17), 239 (10), 223 (61), 195 (11), 121 (22)	311.1015 ($C_{15}H_{13}N_5O_3$, 311.1018)
5k	280 (28, M^+), 279 (12), 226 (6), 225 (50), 224 (100), 223 (18), 196 (13), 121 (26), 104 (11), 103 (9)	280.1326 ($C_{16}H_{16}N_4O$, 280.1324)
5l	280 (10, M^+), 225 (31), 224 (100), 223 (20), 196 (14), 195 (5), 121 (26), 104 (7), 103 (8), 93 (6), 77 (5)	280.1322 ($C_{16}H_{16}N_4O$, 280.1324)
5m	292 (22, M^+), 291 (41), 251 (30), 226 (12), 225 (100), 224 (41), 223 (13), 207 (8), 196 (8), 121 (10), 104 (8), 103 (8)	292.1324 ($C_{14}H_{16}N_4O$, 292.1324)

for 4 h. The mixture was diluted with water (50 mL) and extracted with $CHCl_3$ (3×50 mL). The combined organic layer was dried ($MgSO_4$) and evaporated under reduced pressure to afford the crude product, which was purified on a silica gel column (EtOAc/hexane 1:2) to give secondary amide derivative **2e** (307 mg, 86%). Other *sec*-amide derivatives **2b**, **2c**, **2f**, **2g** were also obtained by a similar method (Table 2). The characterization data of **2a–2g** are summarized in Tables 3–5.

***N*-(Methoxycarbonylmethyl)-3-(triphenylphosphoranylideneamino)pyrazine-2-carboxamide (**4a**); Typical Procedure:** (see Scheme 3.)

To a stirred mixture of the corresponding 3-aminopyrazine-2-carboxamide **2a** (360 mg, 1.71 mmol), hexachloroethane (405 mg, 1.71 mmol) and PPh_3 (449 mg, 1.71 mmol) in anhyd benzene (20.0 mL) was added dropwise Et_3N (0.48 mL, 3.44 mmol). The resultant solution was heated at reflux for 2 h. After cooling, the mixture was filtered under pressure in order to remove the precipitates and the filtrate was evaporated under reduced pressure to give a solid residue, which was purified on a silica gel column (EtOAc/hexane 1:1 \rightarrow 2:1 \rightarrow EtOAc only) to afford the iminophosphorane derivative **4a** (795 mg, 99%). The other iminophosphorane derivatives **4b–4g** were also obtained by a similar method (Table 6). The characterization data of **4a–4g** are summarized in Tables 7–9.

3-(Methoxycarbonylmethyl)-2-phenyl-4(3H)-pteridinone (5a**); Typical Procedure:** (see Scheme 4.)

To a stirred solution of the iminophosphorane **4a** (86 mg, 0.18 mmol) in anhyd toluene (2.0 mL) was added dropwise benzoyl chloride

(0.040 mL, 0.34 mmol) and Et_3N (0.050 mL, 0.36 mmol). The mixture was heated at reflux for 4 h. After completion of the reaction (monitored by TLC), the mixture was diluted with water (10 mL) and extracted with $CHCl_3$ (2×30 mL). The combined extracts were dried ($MgSO_4$) and evaporated under reduced pressure and the crude product was purified on a silica gel column (EtOAc/hexane 1:1) to give the 4(3H)-pteridinone derivative **5a** (37 mg, 68%). The other 4(3H)-pteridinone derivatives **5b–5d**, **5f–5m**, **8**, **9** were synthesized using similar conditions (Table 10). The characterization data of **5a–5d**, **5f–5m** are summarized in Tables 11–13.

2-(2-Azidophenyl)-3-(methoxycarbonylmethyl)-4(3H)-pteridinone (9**):** pale yellow solid;

yield: 70%; R_f 0.17 (EtOAc/hexane 3:1); mp 188–192 °C.

IR (KBr): ν = 2133, 1752, 1705, 1584, 1414, 1366, 1304, 1227, 752 cm^{-1} .

1H NMR ($CDCl_3$, 200 MHz): δ = 9.02 (1H, d, J = 2.0 Hz, H-7), 8.90 (1H, d, J = 2.0 Hz, H-6), 7.65–7.47 (2H, m, C_6H_4), 7.34–7.26 (2H, m, C_6H_4), 5.22 (1H, d, J = 17.2 Hz, NCH_2CO), 4.26 (1H, d, J = 17.2 Hz, NCH_2CO), 3.68 (3H, s, OCH_3).

^{13}C NMR ($CDCl_3$, 50 MHz): δ = 167.82 (CO_2), 161.16 (C-4), 157.66 (C-8a), 154.15 (C-2), 151.02 (C-7), 145.67 (C-6), 138.13 (C'-2), 132.87 (C-4a), 132.61 (C'-4 or C'-6), 130.69 (C'-4 or C'-6), 125.72 (C'-3 or C'-5), 125.43 (C'-1), 118.77 (C'-3 or C'-5), 52.95 (OCH_3), 46.99 (NCH_2CO).

MS (EI): m/z (%) = (337.30) 310 (15, $M^+ - 28 + 1$), 309 (90, $M - 28$), 277 (14), 251 (14), 250 (100), 222 (20), 221 (21), 168 (12), 129 (6), 102 (6).

MS (CI): 338 (MH).

Table 14. Characterization (mp, R_f , IR) of Compounds **7a**, **7b**, **8** Prepared

Products	mp (°C)	R_f (Solvent) ^a	IR (KBr or neat) ν (cm ⁻¹)
7a	188–189	0.17 (A/H 2:1)	1753, 1713, 1671, 1406, 1323, 1252, 1217, 1179, 982, 694
7b	149–151	0.10 (A/H 2:1)	3382, 1744, 1715, 1665, 1589, 1530, 1491, 1445, 1370, 1233, 1190, 1121, 721, 696
8	217–218	0.13 (A)	1692, 1603, 1545, 1464, 1391, 1292, 1217, 833, 702

^a EtOAc (A) and hexane (H).**Table 15.** Characterization (¹H, ¹³C NMR) of Compounds **7a**, **7b**, **8** Prepared

Product	¹ H NMR (CDCl ₃ /TMS, 200 MHz) δ , J (Hz)	¹³ C NMR (CDCl ₃ /TMS, 50 MHz) δ
7a	12.70 (1H, br s, NHCOC_6H_5), 8.71 (1H, d, $J = 2.4$, H-5), 8.65 (1H, br s, CONHCH_2), 8.29 (1H, d, $J = 2.2$, H-6), 8.14–8.07 (2H, m, C_6H_5), 7.64–7.49 (3H, m, C_6H_5), 4.29 (2H, d, $J = 5.6$, NHCH_2CO), 3.83 (3H, s, OCH_3)	169.98 (CO_2), 166.39 (NHCOPh), 165.15 (CONHCH_2), 150.27 (C-2), 147.41 (C-6), 137.27 (C-5), 134.66 (C'-1), 132.85 (C'-4), 129.34 (C-3), 129.26 (C'-2), 128.12 (C'-3), 52.82 (OCH_3), 41.32 (NHCH_2CO)
7b	11.70 (1H, br s, NHAc), 8.60 (1H, d, $J = 2.4$, H-5), 8.58 (1H, br s, CONHCH_2), 8.24 (1H, d, $J = 2.4$, H-6), 4.24 (2H, d, $J = 5.6$, NHCH_2CO), 3.83 (3H, s, OCH_3)	169.98 (CO_2), 169.55 (NHCOCH_3), 166.07 (CONHCH_2), 149.58 (C-2), 146.98 (C-6), 137.04 (C-5), 128.79 (C-3), 52.80 (OCH_3), 41.25 (NHCH_2CO), 26.09 (COCH_3)
8 ^a	13.09 (1H, br s, NH), 9.02 (1H, d, $J = 2.2$, H-7), 8.83 (1H, d, $J = 2.0$, H-6), 8.26–8.21 (2H, m, C_6H_5), 8.26–8.21 (3H, m, C_6H_5)	161.93 (C-4), 156.28 (C-8a), 155.48 (C-2), 150.87 (C-7), 144.50 (C-6), 133.52 (C'-1), 132.59 (C'-4), 132.37 (C-4a), 129.09 (C'-2), 128.63 (C'-3)

^a This compound was measured by DMSO- d_6 /TMS.**Table 16.** Characterization (MS, HRMS) of Compounds **7a**, **7b**, **8** Prepared

Products	MS (70 eV), m/z (%)	HRMS (70 eV), m/z , Found (Formula, Calcd.)
7a	315 (17, $M + 1$), 314 (100, M^+), 282 (8), 254 (13), 226 (19), 198 (13), 197 (7), 106 (6), 105 (93), 77 (28)	314.1014 ($\text{C}_{15}\text{H}_{14}\text{N}_4\text{O}_4$, 314.1015)
7b	252 (38, M^+), 211 (10), 210 (100), 193 (12), 178 (19), 167 (12), 164 (40), 151 (77), 136 (13), 123 (21), 122 (68), 120 (10), 95 (34), 94 (54), 67 (11)	252.0860 ($\text{C}_{10}\text{H}_{12}\text{N}_4\text{O}_4$, 252.0859)
8	225 (12, $M + 1$), 224 (100, M^+), 223 (12), 196 (16), 180 (8), 121 (44), 104 (15), 103 (11), 93 (18), 77 (16), 76 (4), 66 (4)	224.0698 ($\text{C}_{12}\text{H}_8\text{N}_4\text{O}$, 224.0698)

HRMS calcd for $\text{C}_{15}\text{H}_{11}\text{N}_7\text{O}_3$ 337.0923, $\text{C}_{15}\text{H}_{11}\text{N}_7\text{O}_3$ ($-\text{N}_2$) 309.0862, found 309.0866.

3-(Methoxycarbonylmethyl)-2-phenyl-4(3H)-pteridinone (5a) and 3-(Benzoylamino)-N-(methoxycarbonylmethyl)pyrazine-2-carboxamide (7a):

(see Scheme 5.)

To a stirred solution of the iminophosphorane **4a** (53 mg, 0.11 mmol) in anhyd toluene (2.0 mL) was added dropwise benzoyl chloride (0.025 mL, 0.22 mmol). The mixture was heated at reflux for 4 h. After completion of the reaction (monitored by TLC), the mixture was diluted with water (10 mL) and extracted with CHCl_3 (2 \times 30 mL). The combined extracts were dried (MgSO_4) and evaporated under reduced pressure and the crude product was purified on a silica gel column (EtOAc/hexane 1:1) to give **5a** (4.0 mg, 12%) and **7a** (14.0 mg, 40%).

3-(Benzoylamino)-N-(methoxycarbonylmethyl)pyrazine-2-carboxamide (7a):

(see Scheme 6.)

To a stirred solution of the *sec*-amide **2a** (41 mg, 0.20 mmol) in anhyd toluene (2.0 mL) was added dropwise benzoyl chloride (0.045 mL, 0.39 mmol) and Et_3N (0.055 mL, 0.39 mmol). The mixture was heated at reflux for 4 h. After completion of the reaction (monitored by TLC), the mixture was diluted with water (10 mL) and extracted with

CHCl_3 (2 \times 30 mL). The combined extracts were dried (MgSO_4) and evaporated under reduced pressure and the crude product was purified on a silica gel column (EtOAc/hexane 1:1) to give **7a** (44 mg, 72%). The characterization data of **7a**, **7b** and **8** are summarized in Tables 14–16.

6-Methoxy-7H-1,4-benzodiazepino[5,4-b]pteridin-9-one (11):

(see Scheme 7.)

The mixture of the 4(3H)-pteridinone derivative having an azide function **9** (47.5 mg, 0.14 mmol) and PPh_3 (41.0 mg, 0.16 mmol) was stirred in benzene (5.0 mL) at r.t. for 2.5 h. After **9** disappeared (monitored by TLC) to form the corresponding iminophosphorane **10**, the mixture was heated at reflux for 3 h to provide desired compound **11** whose R_f value on silica gel TLC was eventually almost the same as **10**. The solvent was evaporated under reduced pressure and the crude product was purified on a silica gel column (EtOAc/hexane 1:1 \rightarrow EtOAc only) to give **11** (32.1 mg, 78%); $R_f = 0.27$ (EtOAc); white solid; mp 270–278 °C (subl.).

IR (KBr): $\nu = 2943, 1690, 1665, 1572, 1537, 1441, 1410, 1379, 1265, 1219, 1128, 1020, 777, 654 \text{ cm}^{-1}$.

¹H NMR (CDCl_3 , 200 MHz): $\delta = 9.01$ (1H, d, $J = 2.0$ Hz, H-12), 8.84 (1H, d, $J = 2.0$ Hz, H-11), 8.33 (1H, ddd, $J = 8.0, 1.6, 0.4$ Hz, H-1 or H-4), 7.63 (1H, ddd, $J = 7.8, 7.4, 1.5$ Hz, H-2 or H-3), 7.36 (1H, ddd, $J = 8.0, 7.4, 1.2$ Hz, H-2 or H-3), 7.31 (1H, ddd, $J = 8.0, 1.4, 0.4$ Hz, H-1 or H-4), 5.89 (2H, br s, NCH_2C), 3.95 (3H, s, OCH_3).

^{13}C NMR (CDCl_3 , 50 MHz) δ = 162.22 (C-9), 160.24 (C-6), 157.65 (C-13a), 154.43 (C-14a), 151.16 (C-12), 146.16 (C-4a), 144.89 (C-11), 133.56 (C-1 or C-3), 132.67 (C-1 or C-3), 132.13 (C-9a), 127.25 (C-2 or C-4), 126.03 (C-14b), 125.34 (C-2 or C-4), 55.15 (OCH_3), 41.30 (NCH_2C).

MS (EI): m/z (%) = (293.29) 294 (12, $\text{M} + 1$), 293 (70, M^+), 264 (16), 250 (7), 237 (14), 236 (100), 208 (5), 79 (7).

MS (CI): 294 (MH).

HRMS calcd for $\text{C}_{15}\text{H}_{11}\text{N}_5\text{O}_2$ 293.0913, found 293.0907.

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