One-Step Synthesis of Diarylpyrazolo[3,4-*b*]pyridines from Isoflavones

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A new concise, facile, and efficient method for the synthesis of 3-hydroxy-5,6-diphenylpyrazolo[3,4-*b*]pyridine derivatives has been described. The cyclocondensation of isoflavones with 3-amino-5-hydroxypyrazole in the presence of sodium methoxide gave fused heteroaromatic 3-hydroxy-5,6-diphenylpyrazolo[3,4-*b*]pyridines in moderate to good yields.

Introduction

Fused heteroaromatic compounds containing ring-junction nitrogen atoms are important for the preparation of biologically active molecules.[1,2] One such heteroaromatic class of compounds is an important pharmaceutical target (Scheme 1).[3] The structural diversity and biological importance of substituted pyridines have made them attractive targets for synthesis for many years.[4] The 4,5-dihydropyrazolo[3,4-*b*]pyridine systems are also convenient models for investigating the reactivity, chemical stability, and tautomerism of partially hydrogenated azoloazines. As a result, these compounds have become interesting substances for the preparation of novel analogues of new fused or substituted derivatives.[5]

One of the most common approaches used for the syntheses of the pyrazolo[3,4-*b*]pyridine core has been with the annulation of the pyridine ring onto appropriately substituted pyrazole, or its reverse.[6] The described bicyclic core was also prepared by the cyclocondensation of 5-aminopyrazole with 1,3-dicarbonyl compounds[7−9] or their ethoxymetylene derivatives.[10] Moreover, a one-pot synthesis of 1*H*-pyrazolo[3,4-*b*]pyridines by condensation of dihydropyrazolone, ethyl acetoacetate, and a convenient aldehyde was also described.[11] The promising Diels−Alder cycloaddition of pyrazolylimine as diene with nitroalkene was recently reported.[12]

Natural isoflavones display a wide range of biological activities.[13,14] It was reported that the chromone fragment present in isoflavones can generate a 1,3-diketone equivalent in the presence of alkali, which readily reacts with amidines,[15] guanidine,[16] and hydrazine[17] to form the corresponding 2-substituted pyrimidines and diarylpyrazoles. Recently, we have reported the high-throughput synthesis of 3,4-diarylpyrazoles, 4,5-biphenyl-2-pyrimidinylguanidine, and 2,3-diarylpyrimido[1,2-*a*]benzimidazole via a one-pot reaction of hydrazine,[17] bisguanidine,[18] or 2-aminobenzimidazole[19] with isoflavones. Herein, we now report an effective, concise, and facile synthesis of 5,6-diphenylpyrazolo[3,4-*b*]pyridines obtained by treating 3-amino-5-hydroxypyrazole and varied isoflavones under basic condition.

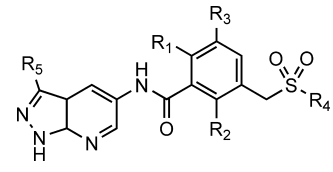
Results and Discussion

On the basis of our previous results,[17−19] we envisioned the synthesis of 2-hydroxy-6-phenyl-7-(2-hydroxy-4-isopropoxy)pyrazolo[1,5-*a*]pyrimidine **3a** by the condensation of **1a** (4-isopropoxyisoflavone, 1.0 equiv) with 3-amino-5-hydroxypyrazole **2** (1.1 equiv) under basic conditions (Scheme 2). Surprisingly, the unexpected compound **4a** (3-hydroxy-5-phenyl-6-(2-hydroxy-4-isopropoxy)pyrazolo[3,4-*b*]pyridine) was obtained and elucidated by spectroscopic analyses (^{1}H- and ^{13}C NMR, IR) and elemental analysis.

These results prompted us to turn our attention to optimizing the conditions for the efficient formation of **4a** (Table 1). When NaOH (5 M) was used as base, **4a** was obtained in 40% yield (entry 1). It was found that Et_3N was ineffective in providing the desired product (entry 2). Examination of the effects of the other bases on yield showed NaOMe to be the most effective for the condensation (entries 1−3). Further studies with varying amounts of NaOMe revealed that 4.0 equiv of base are necessary to obtain a high yield of **4a** (entries 3−6). MeOH was an ideal solvent, since reactions in tetrahydrofuran (THF), *N*,*N*-dimethylformamide (DMF), or EtOH gave lower yields with higher temperature (entries 6−8). The best condition to obtain the maximum yield (81%) was using NaOMe (4.0 equiv) as base in methanol with 1:1.2 as the ratio of **1a/2**.

Having the optimized conditions, the scope of the reaction was examined and summarized in Table 2. All products were characterized by IR, ^{1}H NMR, ^{13}C NMR, mass spectrometry (MS), and elemental analysis. Also single crystal X-ray dif-

Scheme 1. Pyrazolo[3,4-*b*]pyridine as a Raf Kinases Inhibitor



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Scheme 2. Designed Synthetic Route for the Synthesis of **3a**

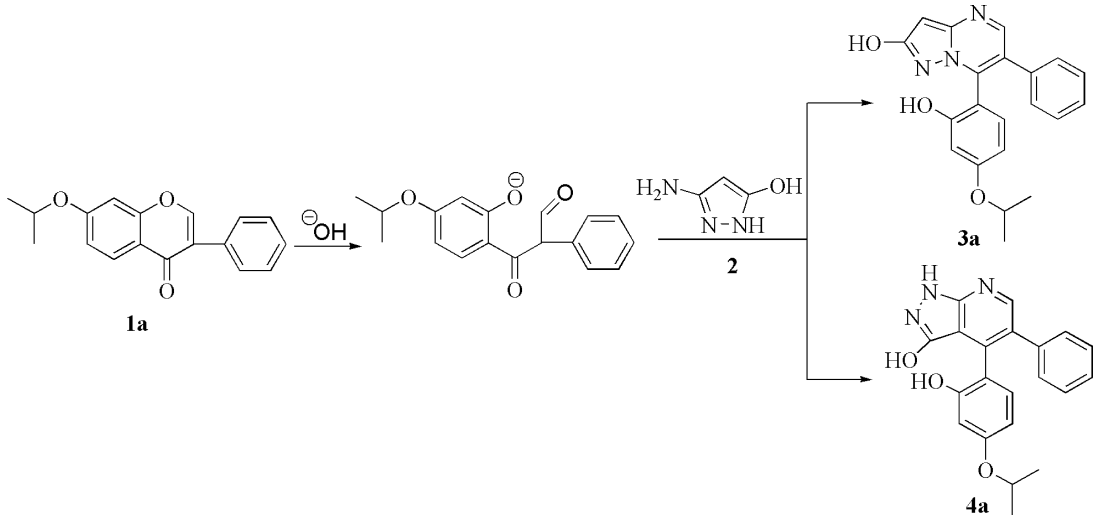
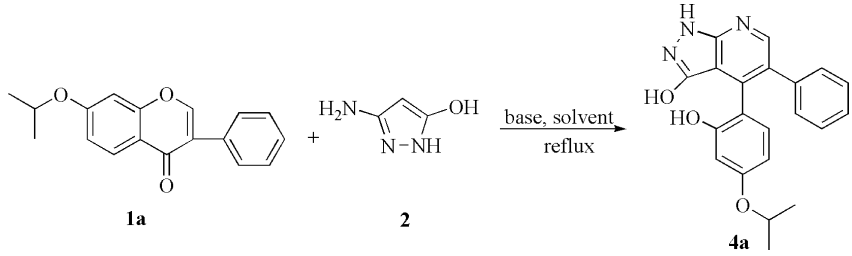


Table 1. Optimization of the Reaction Conditions[a]



entry	solvent[b]	base	molar ratios **1a**/**2**/base	**4a** yield/%[c]
1	EtOH	NaOH	1/1.1/3	40
2	EtOH	Et_3N	1/1.1/3	0
3	EtOH	NaOMe	1/1.1/2	58
4	EtOH	NaOMe	1/1.1/3	66
5	EtOH	NaOMe	1/1.1/4	72
6	EtOH	NaOMe	1/1.1/5	45
7	THF	NaOMe	1/1.1/4	38
8	DMF[d]	NaOMe	1/1.1/4	34
9	MeOH	NaOMe	1/1.2/4	82
10	MeOH	NaOMe	1/1.3/4	81
11	MeOH	NaOMe	1/1.4/4	80
12	MeOH	NaOMe	1/1.5/4	78

[a] All reactions were carried out with isoflavone **1a** (2 mmol), 3-amino-5-hydroxypyrazole **2**, and varying bases in indicated solvents (20 mL) for 24 h. [b] Reactions with EtOH, MeOH, and THF as solvent were carried out at reflux. [c] Isolated yield based on isoflavone (**1a**). [d] Carried out at 100 °C.

fraction analysis was realized on **4d** (Figure 1). As shown in the Table 2, the yield decreases as the number of hydroxyl groups on the aryl rings of the isoflavones increase. For example, isoflavones **1a**, **1b**, **1d**, **1f**, **1i**, **1k**, **1l**, **1m**, **1p**, **1q**, and **1s**, (Table 2, entries 1, 2, 4, 6, 9, 10−13, 16, 17, and 19) lacking a hydroxyl group, afforded **4** in near 80% yield. Isoflavones with one hydroxyl group, **1c**, **1e**, **1j**, and **1o** (entries 3, 5, 10, and 15) afforded **4** in about 65% yield while isoflavones with two hydroxyl groups such as **1g**, **1h**, and **1s** (entries 7, 8, and 18) gave desired products in about 60%. It is even more difficult for Genistein (4′,5,7-trihydroxyisoflavone, entry 14) to produce **4** (39%). It seems possible that the hydroxyl groups of the isoflavones can deprotonate under basic reaction conditions, increasing the electron-donating ability of the hydroxyisoflavones more than the corresponding alkoxy and benzoxyisoflavones, preventing condensation with **2**.

Further experimental and mechanistic studies are required to fully understand the differences of chemoselective condensation of isoflavone **1** with pyrazole **2**. As reported,[20]

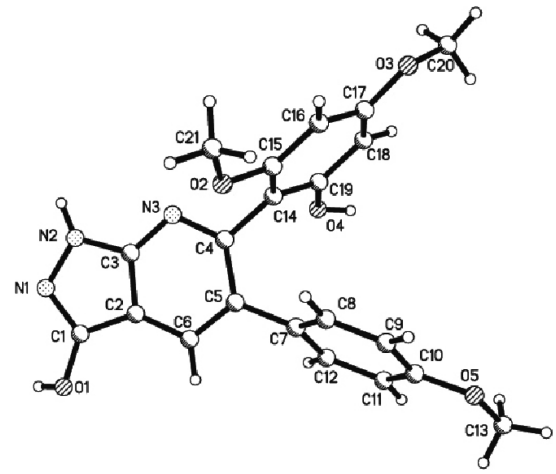
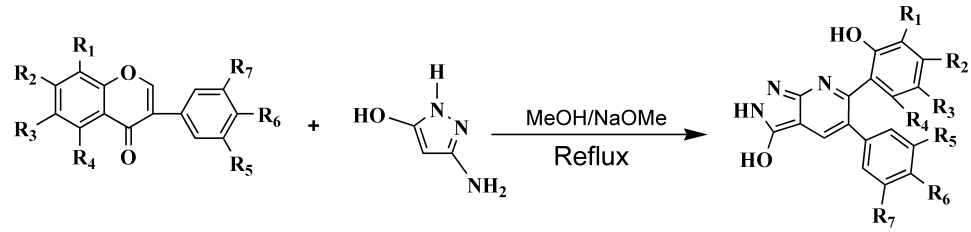


Figure 1. Single-crystal X-ray structural analysis of **4d**.

isoflavone may undergo ring-opening reaction in the presence of alkali to form an α,β-unsaturated ketone intermediate **6**

Table 2. Synthesis of 3-Hydroxy-5,6-diphenylpyrazolo[3,4-*b*]pyridines **4**[a]

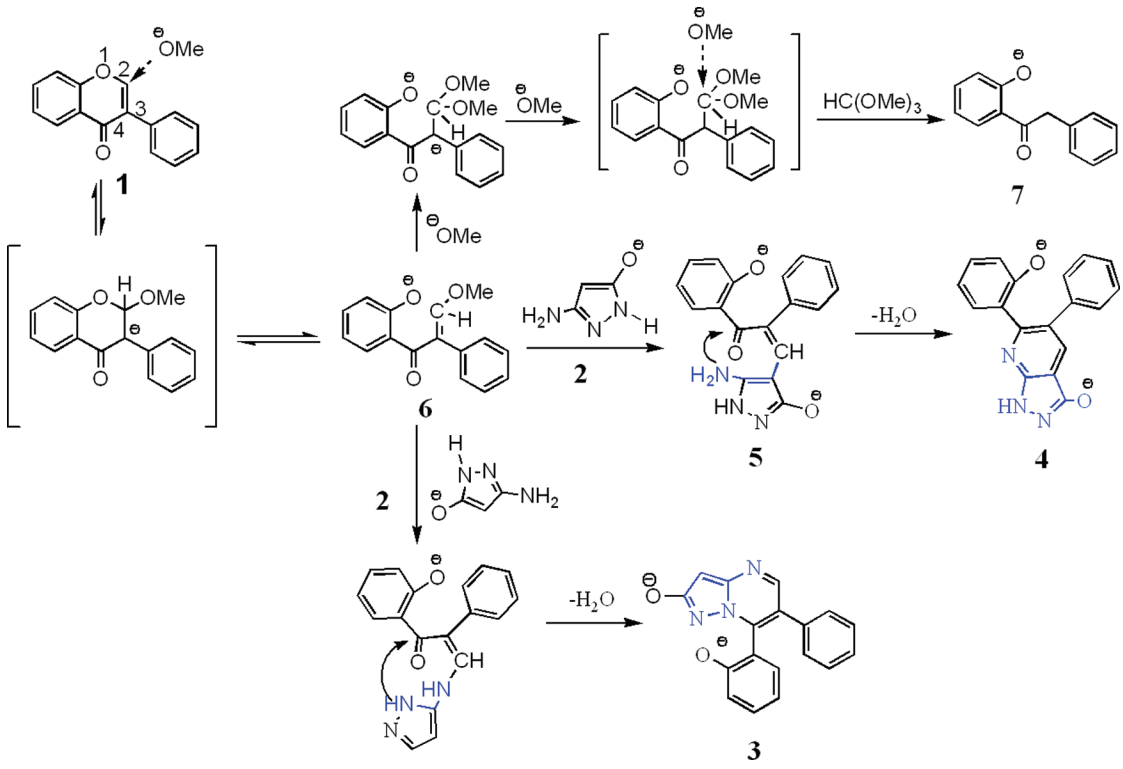


1 **2** **4**

entry	substrate	R_1	R_2	R_3	R_4	R_5	R_6	R_7	product	yield [b]	time/h
1	**1a**	H	*i*-OPr	H	H	H	H	H	**4a**	82	14
2	**1b**	H	OMe	H	Me	H	H	H	**4b**	77	16
3	**1c**	H	OH	H	H	H	OMe	H	**4c**	66	25
4	**1d**	H	OMe	H	OMe	H	OMe	H	**4d**	78	19
5	**1e**	H	OH	H	H	H	H	H	**4e**	60	24
6	**1f**	H	OMe	H	H	H	OMe	H	**4f**	81	14
7	**1g**	H	OH	H	H	H	OH	H	**4g**	56	36
8	**1h**	H	OH	H	H	*i*-Pr	OH	*i* -Pr	**4h**	64	38
9	**1i**	H	OMe	H	H	H	H	H	**4i**	76	16
10	**1j**	H	OMe	H	H	H	OH	H	**4j**	70	27
11	**1k**	Br	*i* -OPr	H	H	H	H	H	**4k**	84	15
12	**1l**	H	OMe	H	H	*i*-Pr	OMe	*i* -Pr	**4l**	73	20
13	**1m**	H	OMe	OMe	OMe	H	OMe	H	**4m**	84	19
14	**1n**	H	OH	H	OH	H	OH	H	**4n**	39	48
15	**1o**	H	OMe	H	H	*i*-Pr	OH	*i* -Pr	**4o**	77	31
16	**1p**	H	OMe	H	OMe	*i* -Pr	OMe	*i* -Pr	**4p**	76	27
17	**1q**	Br	OMe	H	H	H	OMe	H	**4q**	78	16
18	**1r**	H	OH	H	H	H	OH	NO2	**4r**	52	38
19	**1s**	H	OBn	H	H	H	OMe	H	**4s**	85	17

[a] Isoflavones **1** (2 mmol), **2** (2.4 mmol), $NaOCH_3$ (8, 10, 12, and 14 mmol were used for 0, 1, 2, and 3 hydroxyl groups in **1**, respectively), in methanol. [b] Isolated yield.

Scheme 3. Proposed Mechanism for the Formation of **4**



(Scheme 3). If the primary amine group of the 3-amino-5-hydroxylpyrazole **2** attacks the β-carbon of **6**, followed by ring closure, **3** is formed. However, if C4 of the 3-amino-5-hydroxypyrazole **2** attacks the β-carbon in **6**, followed by ring closure between the primary amine and the carbonyl carbon in the intermediate of **5** would give **4**. The intermediate **5n** was successfully isolated from the crude reaction mixture of **2** and genistein **1n**. The 5-hydroxy group of pyrazole **2** would become an oxyanion in basic condition, enhancing the electrophilic substitution reaction at the β-carbon of **6** with C4 of **2** leading to different chemoselectivity of the cyclocondensation between **1** and **2**. Additionally, the concentration of base is important for the cyclocondensations. Intermediate **6** would convert to ketone

7 at high concentration of base by elimination of $HC(OMe)_3$. However, it would be too difficult for isoflavones to produce the intermediate **6** in low base concentration.

Conclusions

An efficient, concise one-step synthesis of the functionalized 3-hydroxy-5,6-diphenylpyrazolo[3,4-*b*]pyridines is described. The method employs a moderate heating of isoflavones with 3-amino-5-hydroxypyrazole in the presence of strong base to afford the fused 3-hydroxy-5,6-diphenylpyrazolo[3,4-*b*]pyridines biological core chemoselectively. The 5-hydroxyl group of 3-amino-5-hydroxypyrazole is probably one of the key factors that will affect the results of the reaction.

Experimental Section

General Procedure. The corresponding isoflavone **1** (2 mmol), 1*H*-3-amine-5-hydroxypyrazol **2** (2.4 mmol), and sodium methoxide (8 mmol) were refluxed in methanol (20 mL) for 16−48 h. All reactions were monitored by thin-layer chromatography (TLC), which showed the disappearance of **1** that was indicative of the reaction being complete. The reaction mixture was concentrated to 5 mL by a rotary evaporator. The condensate was poured into ice water (20 mL) and adjusted to neutrality with the solution of 5% HCl. A yellow precipitate appeared and was filtered after 15 minutes. Then the precipitate was dissolved and dried over $MgSO_4$, then concentrated under reduced pressure, and purified by column chromatography on silica gel column, using chloroform−methanol (15:1) to give the corresponding pure product **4**.

3-Hydroxy-5-phenyl-6-(2-hydroxy-4-isopropoxyphenyl)-1*H*-pyrazolo[3,4-*b*]pyridine (4a) (Entry 3a, Table 2). mp 248−250 °C. IR (KBr), ν (cm^{-1}): 3314, 2977, 1684, 1610, 1519, 1423, 1386, 1235, 1113, 993, 837, 796, 699. ^{1}H NMR [300 MHz, DMSO/TMS, δ (ppm)]: 1.22(d, J = 5.7 Hz, 6H), 4.49(m, 1H), 6.24(s, 2H), 6.89(d, J = 8.8 Hz, 1H), 7.21−7.23(m, 5H), 7.96(s, 1H), 9.85(s, 1H), 10.96(s, 1H), 12.04(s, 1H); ^{1}H NMR [300 MHz, DMSO-d_6+D_2O/TMS, δ (ppm)]: 1.17(d, J = 3.3 Hz, 6H), 4.44(s, 1H), 6.21−6.25(m, 2H), 6.87(d, J = 6.0 Hz, 1H), 7.14−7.19(m, 5H), 7.99(s, 1H); ^{13}C NMR [75 MHz, DMSO-d_6/TMS), δ (ppm)]: 21.7, 69.1, 102.8, 103.6, 106.0, 119.2, 126.3, 127.9, 129.0, 129.2, 131.1, 131.8, 140.9, 151.2, 154.5, 156.0, 156.5, 158.4. ^{13}C NMR [75 MHz, DMSO-d_6/TMS), δ (ppm), DEPT ^{90}]: 21.9, 69.9, 103.0, 106.6, 127.1, 128.4, 129.4, 132.1. EIMS: *m*/*z* (rel intensity) 384 (M+Na, 15), 362 (M+1, 100). Anal. Calcd for $C_{21}H_{19}N_3O_3$: C, 69.79; H, 5.30; N, 11.63; Found C, 69.92; H, 5.25; N, 11.76.

2-(3-hydroxy-1*H*-pyrazol-5-ylimino)-2-(4-hydroxyphenyl)-1-(2,4,6-trihydroxyphenyl)ethanone (5n). mp 246−248 °C. IR (KBr), ν (cm-1): 3599, 3227, 2908, 2684, 1631, 1414, 1243, 1053, 839. ^{1}H NMR [300 MHz, DMSO-d_6/TMS, δ (ppm)]: 5.67(s, 2H), 6.58(m, 4H), 7.11(d, J = 7.78 Hz, 2H), 7.82(s, 1H), 8.74(s, 1H), 9.26(s, 1H), 9.33(s, 1H). ^{1}H NMR [300 MHz, DMSO-d_6+D_2O/TMS, δ (ppm)]: 6.51(s, 2H), 6.58(d, J = 8.1 Hz, 2H), 7.10(d, J = 8.1 Hz, 2H), 7.86(s, 1H). ^{13}C NMR [75 MHz, DMSO-d_6/TMS, δ (ppm)]: 87.2, 103.8, 104.2, 112.8, 114.4, 129.7, 131.1, 131.3, 133.7, 152.4, 155.1, 155.6, 168.1. Anal. Calcd for $C_{18}H_{12}N_4O_6$: C, 56.85; H, 3.18; N, 14.73; Found C, 56.87; H, 3.17; N, 14.75.

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Note Added after ASAP Publication. There were errors in the structures of Table 1 and Schemes 3 and 4 in the version of this paper published ASAP June 4, 2010; the correct version published on June 9, 2010.

Supporting Information Available. Synthetic procedures; characterization data, copies of ^{1}H and ^{13}C NMR spectra of all compounds; crystal and structure refinement data for **4d**. This material is available free of charge via the Internet at http://pubs.acs.org.

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