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Simultaneous Synthesis of Pyrazolopyridines and Pyrazolopyrimidinones Under Microwave Irradiation

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Abstract: The direct reaction of *o*-aminopyrazocarbonitriles and carbonyl compounds to afford pyrazolopyrimidinones was discovered; hence, a simultaneous synthetic method for pyrazolopyridines and pyrazolopyrimidinones was achieved. Under microwave irradiation, better yields of products than those of conventional method were given.

Keywords: Microwave irradiation, pyrazolopyridines, pyrazolopyrimidinones, synthesis

Condensed polyazaheterocycles are an important ring system presenting in a variety of natural products, pharmaceuticals, and agrochemicals.[1] Compounds containing pyrazolopyrimidinone or pyrazolo-pyridine skeletons are important heterocycles and exhibit a wide range of biological and pharmaceutical activities, such as acting as a potent and selective phosphodiesterase type-5 inhibitor and an A_1-adenosine receptor.[2–10] In literature,[11,12] the two skeletons of heterocycles are prepared separately by different reactions; the direct synthesis of pyrazolopyrimidinones from *o*-aminopyrazocarbonitriles and carbonyl compounds has never been

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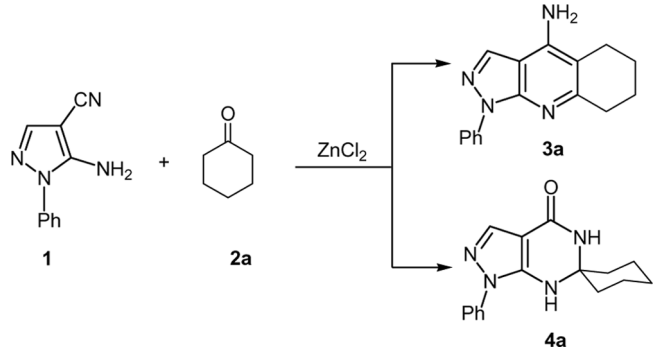


Scheme 1. Reaction of 3-amino-4-cyano-1-phenyl-1*H*-pyrazole and cyclohexanone.

reported. Classically, when catalyzed by Lewis acids, pyrazolopyridines, as exclusive products, were obtained via the reaction of *o*-aminopyrazocarbonitriles and carbonyl compounds; however, during our synthesis of pyrazolopyridines by the condensation of *o*-aminopyrazocarbonitrile **1** and cyclohexanone **2a** in the presence of zinc chloride, two different skeletons of products, pyrazolopyridine **3a** and pyrazolopyrimidinone **4a**, were separated (Scheme 1). By utilizing Boitage microwave reactor, greater product yields than those of conventional methods were afforded.

3-Amino-4-cyano-1-phenyl-1*H*-pyrazole (**1**), the starting material for this work, was conveniently synthesized from the reaction of ethoxymethylenemalononitrile with phenyl hydrazine.[13] Then, the reaction of compound **1** with excessive cyclohexanone, catalyzed by zinc chloride, was carried out at the boiling point of cyclohexanone in an oil bath, and 7 h later, two different skeletons of compounds, **3a** and **4a,** were simultaneously obtained in poor yields (Scheme 1). On the basis of spectral data and elemental analysis, the structure of **4a** was assigned as 1*H*-pyrazolo[3,4-b]-pyrimidin-4-one and the structure of **3a** was assigned as pyrazolopyridine, which was further confirmed by x-ray diffraction of **3c** (Fig. 1) The crystal structure of **3c** has been determined as monoclinic, with space group $P2_1/c$ with lattice parameters $a = 13.694(13)$ Å, $b = 6.888(6)$ Å, $c = 16.929(16)$ Å, $\beta = 112.417(12)^\circ$, $V = 1476(2)$ Å^3, $Z = 4$, and $D_{calc} = 1.252$ Mg/m^3. $T = 293(2)$ K, R indices (all data): $R_1 = 0.0824$, $wR_2 = 0.1597$. CCDC 635028.

Among all the parameters, the catalyst plays the most important role in leading to different conversion products. Complying with Friedländer reaction,[14] only product **3a** was afforded in 42% yield after pyrazole **1** reacted with **2a** for 4 h in 1,2-dichloroethane and was catalyzed by $AlCl_3$. However, when the same reaction was carried out under $ZnCl_2$, products

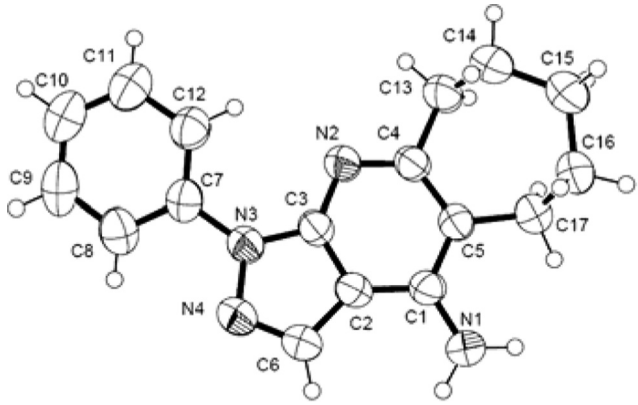


Figure 1. Molecular structure of **3c**, with the atom-labeling scheme. Displacement ellipsoids are drawn at the 50% probability level.

3a and **4a** were obtained in 37% and 21% yields, respectively. Other catalysts such as *p*-$PhSO_3H$, HCl, pyridine, and sodium carbonate failed to give **4a** in a separable yield. After screening a lot of catalysts, we found that $ZnCl_2$ was the best one in promoting the formation of **4a**.

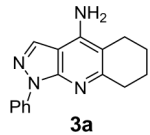
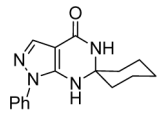
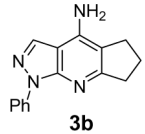
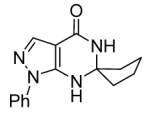
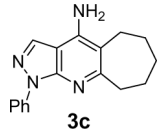
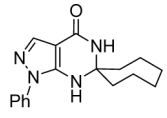
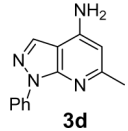
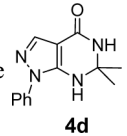
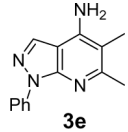
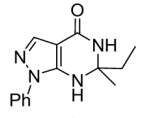
Because the optimization of reaction parameters failed to give acceptable product yields, we adopted microwave irradiation to improve the reaction; fortunately, better yields of both **3a** and **4a** were obtained (Table 1).

To extend the reaction scope, several ketones were employed to react with reactant **1**, and in most cases, pyrazolopyrimidinones **4** were also obtained. As shown in Table 1 for the formation of compound **4**, ketones with six-membered rings were better than others. When compound **1** reacted with cycloheptanone, the new conversion product **4c** was obtained in merely trace amounts. In the case of acetone, only one direction of reactions occurred, and the product **4d** with pyrazolo[3, 4-*d*]pyrimidinone skeleton was isolated in 65% yield.

Based on these observations, the possible mechanism for the formation of compounds **4** is shown in Scheme 2. Intermediate **5** was produced by the addition of the amino group of *o*-aminopyrazonitrile onto the carbonyl of cyclohexanone; then the hydroxyl group of intermediate **5** attacked the nitrile moiety via Pinner reaction[15] to afford an oxazine derivative **6**, which was unstable in reaction sites and quickly rearranged to the new conversion product **4a** (Dimorth rearrangement[16]).

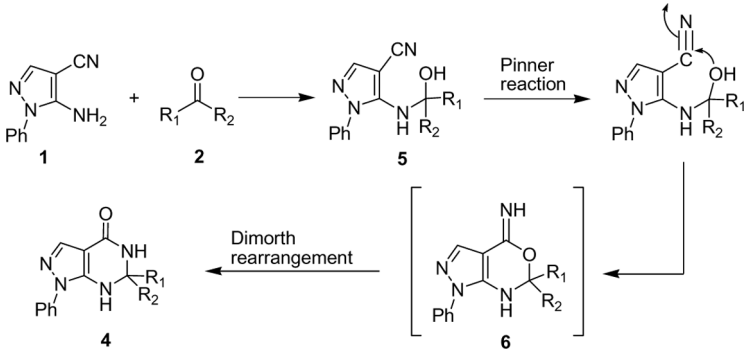
In summary, we have developed a convenient, straightforward method for the construction of the pyrazolopyrimidinone and

Table 1. Synthesis of pyrazolopyridines **3** and pyrazolopyrimidinones **4** catalyzed by $ZnCl_2$ under microwave irradiation[a]

Entry	2	Temperature (°C)	Product	Yield (%)[b]	Product	Yield (%)[b]	Total yield[b] (%)
1		150	 **3a**	43	 **4a**	46	89
2		130	 **3b**	42	 **4b**	29	71
3		150	 **3c**	43	 **4c**	Trace	43
4		110	 **3d**	Trace	 **4d**	65	65
5		130	 **3e**	28	 **4e**	53	81

[a]All reactions were carried out at variable power in a Biotage microwave reactor for 10 min using **1** (4 mmol), $ZnCl_2$ (4.2 mmol), and **2** (3 mL).

[b]Isolated yield.



Scheme 2. Mechanism for the formation of **4**.

pyrazoloquinoline frameworks that involves the direct cyclization of *o*-aminocyanopyrazoles with ketones in the presence of a Lewis acid catalyst; thus, a new method to afford pyrazolopyrimidinones was discovered. With microwave assistance, the reaction was completed quickly and gave good yields of products. It may represent a potentially useful route to otherwise laboriously accessible polyazaheterocycles. Further work is under way.

EXPERIMENTAL

Melting points were determined using an XT4 microscope melting-point apparatus and are uncorrected. Infrared (IR) spectra were recorded on a Perkin-Elmer Fourier transform (FT)–IR spectrophotometer and were run as KBr pellets. ^{1}H and ^{13}C NMR spectra were recorded at 400 MHz on a Bruker 400 spectrometer. Chemical shifts were reported in δ (ppm) relative to internal tetramethylsilane (TMS). Mass spectra were recorded on a ZAB-HS mass spectrometer using electrospray ionization (ESI). Elemental analyses were within ±0.4% of theoretical values and were performed on an Elementar Vario EL instrument. X-ray diffraction data were collected at 113(2) *K* on a Rigaku MM-007 Rotating anode diffractometer equipped with Saturn 70 CCD, using confocal Mo *K*α radiation (λ = 0.71070 Å), and the structure was solved by direct methods using the program SHELXS6.12. Refinements were done by the full-matrix least-squares on F^2 using SHELXL6.12.

General Procedure

A solution of corresponding ketone (3 mL), *o*-aminopyrazocarbonitrile **1** (4 mmol), and anhydrous $ZnCl_2$ (4.2 mmol) was added in a 5-mL tube, which was sealed and put into the microwave reactor (“Initiator,” manufactured by Biotage, formerly Personal Chemistry). The time (10 min) and different temperatures were set up (Table 1). (The power is variable during the reaction stage). After the completion of the reaction as indicated by thin-layer chromatography (TLC), the hot mixture was quenched with water (10 mL) and neutralized to pH 10–12 with 20% sodium hydroxide. The organic layer was dried over anhydrous sodium sulfate and filtered, and the solvent was evaporated. The resulting solid was isolated by column chromatography (200 to 300-mesh silica gel, ethyl acetate–petroleum 1:2) to give pyrazolopyridines **3** and pyrazolopyrimidinones **4**.

Data

1-Phenyl-5,6,7,8-tetrahydro-1H-pyrazolo[3,4-b]quinolin-4-amine (**3a**)

White crystal; mp 194–195°C; IR (KBr) ν (cm^{-1}): 3335 and 3230 (NH), 2937 and 2855 (CH aliph.), 1648, 1597, 1567, 1502, 1355, 1255, 1154; ^1H NMR (400 MHz, $CDCl_3$, δ ppm): 1.85–1.93 (m, 4 H, aliph-H), 2.49–2.52 (t, 2 H, aliph-H), 2.96–2.99 (t, 2 H, aliph-H), 4.59 (s, 2 H, NH_2), 7.21–7.26 (t, 1 H, $J = 7.4$ Hz, Ph-H), 7.45–7.49 (t, 2 H, $J = 7.5$ Hz, Ph-H), 7.98 (s, 1 H, pyrazole-H), 8.30–8.32 (d, 2 H, $J = 7.6$ Hz, Ph-H); ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm): 22.84, 22.86, 22.91, 34.19, 105.47, 107.67, 120.80 (2C), 125.25, 128.90 (2C), 130.44, 140.10, 144.88, 150.04, 158.53; MS-ESI (MH^+, 100%): 265.1. Anal. calcd. for $C_{16}H_{16}N_4$: C, 72.70; H, 6.10; N, 21.20. Found: C, 72.41; H, 6.08; N, 21.47.

1-Phenyl-1,5,6,7-tetrahydrocyclopenta[b]pyrazolo[4,3-e]pyridin-4-amine (**3b**)

White crystal; mp 188–189°C; IR (KBr) ν (cm^{-1}): 3397 and 3337 (NH), 2955 and 2838 (CH aliph.), 1659, 1591, 1576, 1505, 1363; ^1H NMR (400 MHz, $CDCl_3$, δ ppm): 2.15–2.22 (qt, 2 H, CH_2), 2.73–2.77 (t, 2 H, CH_2), 3.03–3.07 (t, 2 H, CH_2), 4.57 (br, 2 H, NH_2), 7.22–7.24 (t, $J = 7.4$ Hz, 1 H, Ph-H), 7.45–7.49(t, $J = 7.7$ Hz, 2 H, Ph-H), 7.99 (s, 1 H, pyrazole-H), 8.22–8.24 (d, $J = 7.8$ Hz, 2 H, Ph-H); ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm): 23.12, 26.33, 34.97, 105.94, 112.54, 121.32 (2C), 125.56, 128.94 (2C), 130.55, 139.94, 142.74, 152.40, 167.80; MS-ESI (MH^+, 100%): 251.15. Anal. calcd. for $C_{15}H_{14}N_4$: C, 71.98; H, 5.64; N, 22.38. Found: C, 71.72; H, 5.66; N, 22.39.

1-Phenyl-1,5,6,7,8,9-hexahydrocyclopenta[b]pyrazolo[4,3-e]pyridin-4-amine (**3c**)

White crystal; mp 194–195°C; IR (KBr) ν (cm^{-1}): 3482, 3350, 2922, 1638, 1594, 1501, 1358; ^1H NMR (400 MHz, $CDCl_3$, δ ppm): 1.62–1.90 (m, 6 H, C*6*H_2, C*7*H_2 and C8 H_2), 2.66–2.69 (t, 2 H, C*5*H_2), 3.08–3.01 (t, 2 H, C9 H_2), 4.60 (s, 2 H, N*H*$_2$), 7.22–7.26 (t, $J = 7.4$ Hz, 1 H), 7.46–7.50 (t, $J = 7.5$ Hz, 2 H), 7.98 (s, 1 H, pyrazole-H), 8.30–8.32 (d, $J = 7.6$ Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm): 25.40, 26.79, 27.56, 32.16, 39.81, 106.11, 113.24, 120.91 (2C), 125.37, 128.89 (2C), 130.61, 140.02, 143.69, 149.52, 165.25; MS-ESI (MH^+, 100%): 279.1. Anal. calcd. for $C_{15}H_{14}N_4$: C, 73.35; H, 6.52; N, 20.13. Found: C, 73.17; H, 6.52; N, 19.99.

5,6-Dimethyl-1H-Pyrazolo[3,4-b]pyridin-4-amine (**3e**)

White powder; mp 170–172°C; IR (KBr) ν (cm^{-1}): 3399, 3347, 1658, 1600, 1571, 1504, 1351, 1288; ^1H NMR (400 MHz, $CDCl_3$, δ ppm): 2.16 (s, 3 H), 2.61 (s, 3 H), 4.60 (s, 2 H, NH_2), 7.24–7.27 (t, 1 H, $J = 7.4$ Hz), 7.47–7.51 (t, $J = 7.5$ Hz, 2 H), 8.0 (s, pyrazole-H), 8.31–8.33 (d, 2 H, $J = 7.6$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm): 11.70, 24.44, 105.81, 106.31, 120.86 (2C), 125.37, 128.90 (2C), 130.34, 140.01, 144.84, 149.68, 157.98; MS-ESI (MH^+, 100%): 239.15. Anal. calcd. for $C_{14}H_{14}N_4$: C, 70.57; H, 5.92; N, 23.51. Found: C, 70.30; H, 5.88; 23.62.

1′-Phenyl-spiro[Cyclohexane-1,6′-[6H]pyrazolo[3,4-d]pyrimidin]-4′(5′h)-one (**4a**)

White crystal; mp 164–166°C; IR (KBr) ν (cm^{-1}): 3204 (NH), 2952, 2936 (CH_2), 1649, 1598, 1545, 1458, 1309, 1216; ^1H NMR (400 MHz, $CDCl_3$, δ ppm): 1.21–1.93 (m, 10 H), 4.36 (s, 1 H, NH), 5.67 (s, 1 H, NH), 7.37–7.41 (t, 1 H, $J = 7.4$ Hz), 7.50–7.54 (t, 2 H, $J = 7.5$ Hz), 7.59–7.62 (d, 2 H, $J = 7.8$ Hz), 7.90 (s, pyrazole-H); ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm): 22.10 (2C), 27.01, 37.41 (2C), 71.47, 122.23 (2C), 127.72, 129.79 (2C), 137.83, 137.97, 138.63, 147.02, 161.90; MS-ESI (MH^+, 100%): 283.1. Anal. calcd. for $C_{16}H_{18}N_4O$: C, 68.06; H, 6.43; N, 19.84. Found: C, 67.98; H, 6.47; N, 20.13.

1′-Phenyl-spiro[cyclopentane-1,6′-[6H]pyrazolo[3,4-d]pyrimidin]-4′(5′h)-one (**4b**)

White crystal; mp 161–163°C; IR (KBr) ν (cm^{-1}): 3378, 3229, 2957, 1650, 1578, 1500, 1382, 777; ^1H NMR (400 MHz, $CDCl_3$, δ ppm): 1.78–2.0 (m, 4 H, $2CH_2$), 1.86–2.02 (m, 4 H, $2CH_2$), 4.43 (s, 1 H, NH), 6.15 (s, 1 H, NH), 7.38–7.40 (t, 1 H, $J = 7.3$ Hz, Ph-H), 7.48–7.53 (t, 2 H, $J = 7.4$ Hz, Ph-H), 7.59–7.61 (d, 2 H, $J = 7.5$ Hz, Ph-H), 7.90 (s, 1 H, pyrazole-H); ^{13}C NMR (400 MHz, $CDCl_3$, δ ppm): 22.23 (2C), 39.82 (2C), 80.14, 122.17, 122.19, 123.78, 127.62, 129.67, 129.74, 137.95, 138.54, 147.68, 162.72; MS-ESI (MH^+, 100%): 269.2. Anal. calcd. for $C_{15}H_{16}N_4O$: C, 67.15; H, 6.01; N, 20.88. Found: C, 67.01; H, 5.99; N, 20.96.

6,6-Dimethyl-1-phenyl-6,7-dihydro-1H-pyrazolo[3,4-d]pyrimidin-4(5H)-one (**4d**)

White crystal; mp 213–214°C; IR (KBr) ν(cm^{-1}): 3267, 3188, 1655, 1637, 1577, 1542, 1386; ^1H NMR (400 MHz, $CDCl_3$, δ ppm): 1.61 (s, 6 H), 4.52

(s, 1 H, NH), 6.22 (s, 1 H, NH), 7.36–7.40 (t, 1 H, $J = 7.2$ Hz), 7.49–7.53 (t, 2 H, $J = 7.6$ Hz), 7.56–7.59 (d, 2 H, $J = 7.5$ Hz), 7.89 (s, pyrazole-H); ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm): 29.24 (2C), 70.38, 99.99, 122.41 (2C), 127.71, 129.71 (2C), 137.85, 138.57, 147.35, 162.33; MS-ESI (MH^+, 100%): 243.15. Anal. calcd. for $C_{13}H_{14}N_4O$: C, 64.45; H, 5.82; N, 23.13. Found: C, 64.20; H, 5.78; N, 23.21.

6-Ethyl-6-methyl-1-phenyl-6,7-dihydro-1H-pyrazolo[3,4-d]pyrimidin-4(5h)-one (**4e**)

White crystal; mp 165–166°C; IR (KBr) ν(cm^{-1}): 3211, 2968, 2927, 2876, 2855, 1649, 1600, 1578, 1560, 1504, 1458, 1272; ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 0.98–1.02 (t, 3 H, $J = 7.4$ Hz), 1.55 (s, 3 H), 1.84–1.89 (q, $J = 7.4$ Hz), 4.51 (s, 1 H, NH), 6.29 (s, 1 H, NH), 7.36–7.40 (t, 1 H, $J = 7.3$ Hz), 7.49–7.53 (t, 2 H, $J = 7.4$ Hz), 7.56–7.58 (d, 2 H, $J = 7.6$ Hz), 7.87 (s, pyrazole-H); ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm): 8.35, 27.07, 34.29, 73.08, 99.59, 122.45 (2C), 127.77, 129.78 (2C), 137.84, 138.59, 147.40, 162.55; MS-ESI (MH^+, 100%): 257.15. Anal. calcd. for $C_{14}H_{16}N_4O$: C, 65.61; H, 6.29; N, 21.86. Found: C, 65.40; H, 6.25; N, 22.08.

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