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Note

Green synthesis of 3-(2-oxo-2*H*-chromenyl)-1-[3-(4-methoxyphenyl)[1,8]naphthyridin-2-yl]-1*H*-4-pyrazolecarbaldehydes under microwave irradiation

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An efficient and convenient method is described for the synthesis of 3-(2-oxo-2*H*-chromenyl)-1-[3-(4-methoxyphenyl)-[1,8]naphthyridin-2-yl]-1*H*-4-pyrazolecarbaldehydes from 3-[2-(3-(4-methoxyphenyl)[1,8]-naphthyridin-2-yl)ethanhydrazonyl]-2*H*-2-chromenones (hydrazones) in the presence of DMF-$POCl_3$ (Vilsmeier-Haack reagent) using silica gel as solid support under microwave irradiation.

Keywords: 1,8-Naphthyridine, 2*H*-2-chromenones, pyrazolecarbaldehydes, Vilsmeier-Haack reagent, solid support, microwave irradiation

1,8-Naphthyridine derivatives have attracted a great deal of interest owing to their diverse biological activities[1,2]. Various 2*H*-2-chromenones[3,4] and pyrazoles derivatives[5,6] occupy an important place in medicinal chemistry as they show a variety of pharmacological and microbiological activities. Therefore, it was envisaged that chemical entities with 1,8-naphthyridines, 2*H*-2-chromenone and pyrazole might result in compounds with interesting biological activity. The solvent-free organic reactions[7,8], in general and inorganic solid supports[9] assisted by microwaves have gained special attention in recent years. The use of microwave activation in organic synthesis can increase the purity of the resulting products, enhance the chemical yields and shorten the reaction time. Solvent-free reaction leads to a clean, eco-friendly and economic technology. In view of this and in continuation of the work on microwave assisted organic transformation of 1,8-naphthyridine derivatives[10-12], is now described a convenient, efficient and high yielding protocol for the synthesis of chromenyl 1,8-naphthyridinyl pyrazoles using Vilsmeier-Haack reagent with silica gel as solid support under microwave irradiation.

Condensation of 2-hydrazino-3-(4-methoxyphenyl)-1,8-naphthyridine **1** with different 3-acetylcoumarins (3-acetyl-2*H*-2-chromenones) **2** in the presence of catalytic amount of DMF under microwave irradiation afforded the corresponding 3-[2-(3-(4-methoxyphenyl)[1,8]naphthyridin-2-yl)ethan-hydrazonyl]-2*H*-2-chromenones (hydrazones) **3** in excellent yields.

The hydrazones **3** when subjected to the Vilsmeier-Haack reaction with $POCl_3$-DMF/SiO_2 under microwave irradiation furnished the respective 3-(2-oxo-2*H*-3-chromenyl)-1-[3-(4-methoxyphenyl)[1,8]naphthyridin-2-yl]-1*H*-4-pyrazole-carbaldehydes **4** (**Scheme I**). The reaction proceeds efficiently in very good yields within a few minutes and in the absence of solvent. The products were obtained in a state of high purity. The experimental procedure is very simple. The process is environmentally benign.

Interestingly, this reaction proceeds only to a minor extent (5-10% in 2.5 to 4.0 min) when conducted under conventional conditions in an oil-bath preheated to 110ºC (highest observed temperature during irradiation) which confirms the rate increase during microwave heating.

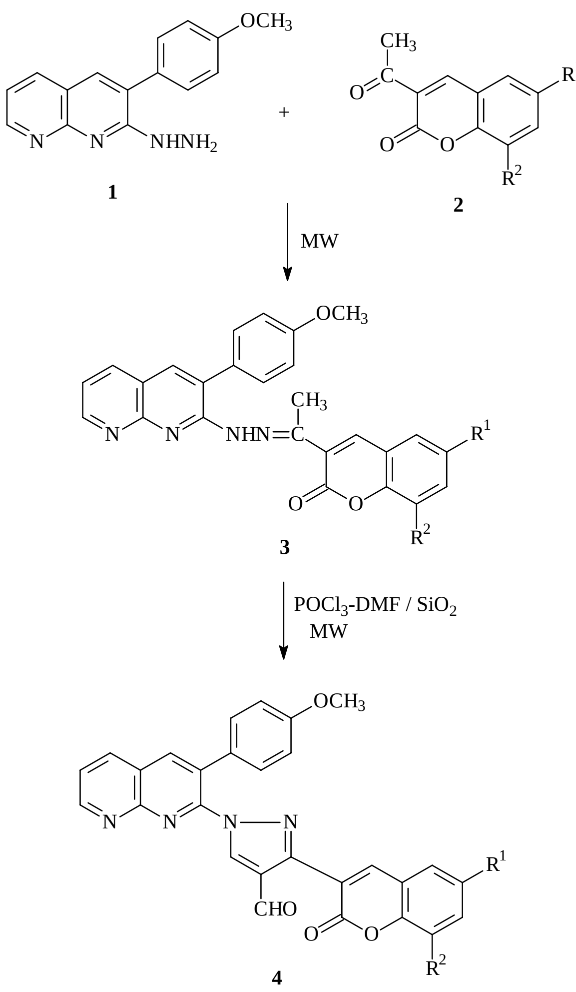
The structural assignments of compounds **3** and **4** were based on their elemental analyses and spectral (IR and ^{1}H NMR) data.

The significant advantages of this method are the simple operation, clear reaction profiles, high yields, excellent purity and short reaction times, and the elimination of solvent.

Experimental Section

Melting points were determined in open capillaries on a Cintex melting point apparatus and are uncorkrected. Homogeneity of the compounds was checked by precoated TLC plates (Merck, 60F-254). IR spectra were recorded in KBr on a Perkin-Elmer spectrum BX series FT-IR spectrophotometer and ^{1}H NMR spectra on a Varian Gemini 400 MHz spectrometer using TMS as internal standard. Microwave irradiations were carried out using domestic microwave oven (LG MG 556P, 2450 MHz).

General procedure for the synthesis of 3-[2-(3-(4-methoxy-phenyl)[1,8]-naphthyridin-2-yl)ethanhydra-



	R^1	R^2
a :	H	H
b :	H	OCH_3
c :	Cl	H
d :	Cl	Cl
e :	Br	H
f :	Br	Br
g :	NO_2	H
h :	5,6-benzo	

Scheme I

zonyl]-2*H*-2-chromenones (hydrazones), 3. A mixture of 2-hydrazino-3-(4-methoxyphenyl)-1,8-naphthyridine **1** (0.01 mole), 3-acetylcoumarin **2** (0.01 mole) and DMF (5 drops) was subjected to microwave irradiation at 200 W intermittently at 10 s intervals for the specified time (**Table I**). After completion of the reaction as indicated by TLC, the reaction mixture was cooled and treated with water. The separated solid was filtered, washed with water and purified by recrystallization from ethanol to afford **3** (**Table I**).

Spectral data

3a: IR (KBr): 3362 (NH), 1725 (lactone, C=O), 1619 (C=N), 1588 cm^{-1} (C=C); ^1H NMR ($CDCl_3$ + DMSO-d_6): δ 2.38 (s, 3H, CH_3), 3.85 (s, 3H, OCH_3), 7.75 (m, 1H, C_6-H), 8.00 (m, 2H, C_4-H, C_5-H), 8.38 (m, 1H, C_7-H), 8.60 (s, 1H, C_4-H of coumarin), 7.00-7.72 (m, 8H, Ar-H), 10.55 (s, 1H, NH).

3b: IR (KBr): 3411 (NH), 1712 (lactone, C=O), 1611 (C=N), 1585 cm^{-1} (C=C); ^1H NMR ($CDCl_3$ + DMSO-d_6): δ 2.40 (s, 3H, CH_3), 3.85 (s, 3H, OCH_3), 3.94 (s, 3H, OCH_3), 7.80 (m, 1H, C_6-H), 7.95 (m, 2H, C_4-H, C_5-H), 8.40 (m, 1H, C_7-H), 8.55 (s, 1H, C_4-H of coumarin), 6.98-7.68 (m, 7H, Ar-H), 10.50 (s, 1H, NH).

3c: IR (KBr): 3329 (NH), 1724 (lactone, C=O), 1615 (C=N), 1584 cm^{-1} (C=C); ^1H NMR ($CDCl_3$ + DMSO-d_6): δ 2.42 (s, 3H, CH_3), 3.86 (s, 3H, OCH_3), 7.78 (m, 1H, C_6-H), 8.12 (m, 2H, C_4-H, C_5-H), 8.22 (m, 1H, C_7-H), 8.42 (s, 1H, C_4-H of coumarin), 6.95-7.67 (m, 7H, Ar-H), 10.52 (s, 1H, NH).

3d: IR (KBr): 3420 (NH), 1725 (lactone, C=O), 1620 (C=N), 1590 cm^{-1} (C=C); ^1H NMR ($CDCl_3$ + DMSO-d_6): δ 2.39 (s, 3H, CH_3), 3.89 (s, 3H, OCH_3), 7.85 (m, 1H, C_6-H), 8.18 (m, 2H, C_4-H, C_5-H), 8.20 (m, 1H, C_7-H), 8.42 (s, 1H, C_4-H of coumarin), 7.00-7.68 (m, 6H, Ar-H), 10.26 (s, 1H, NH).

3e: IR (KBr): 3414 (NH), 1734 (lactone, C=O), 1610 (C=N), 1592 cm^{-1} (C=C); ^1H NMR ($CDCl_3$ + DMSO-d_6): δ 2.42 (s, 3H, CH_3), 3.92 (s, 3H, OCH_3), 7.90 (m, 1H, C_6-H), 8.20 (m, 2H, C_4-H, C_5-H), 8.35 (m, 1H, C_7-H), 8.50 (s, 1H, C_4-H of coumarin), 6.90-7.78 (m, 7H, Ar-H), 10.28 (s, 1H, NH).

3f: IR (KBr): 3435 (NH), 1736 (lactone, C=O), 1611 (C=N), 1585 cm^{-1} (C=C); ^1H NMR ($CDCl_3$ + DMSO-d_6): δ 2.40 (s, 3H, CH_3), 3.88 (s, 3H, OCH_3), 7.80 (m, 1H, C_6-H), 8.15 (m, 2H, C_4-H, C_5-H), 8.25 (m, 1H, C_7-H), 8.40 (s, 1H, C_4-H of coumarin), 6.82-7.70 (m, 6H, Ar-H), 10.20 (s, 1H, NH).

3g: IR (KBr): 3435 (NH), 1737 (lactone, C=O), 1614 (C=N), 1584 cm^{-1} (C=C); ^1H NMR ($CDCl_3$ + DMSO-d_6): δ 2.42 (s, 3H, CH_3), 3.85 (s, 3H, OCH_3), 7.70 (m, 1H, C_6-H), 8.25 (m, 2H, C_4-H, C_5-H), 8.37 (m, 1H, C_7-H), 8.50 (s, 1H, C_4-H of coumarin), 6.84-7.60 (m, 8H, Ar-H), 10.38 (s, 1H, NH).

3h: IR (KBr): 3317 (NH), 1725 (lactone, C=O), 1618 (C=N), 1586 cm^{-1} (C=C); ^1H NMR ($CDCl_3$ + DMSO-d_6): δ 2.45 (s, 3H, CH_3), 3.90 (s, 3H, OCH_3), 7.98 (m, 1H, C_6-H), 8.20 (m, 2H, C_4-H, C_5-H), 8.50 (m, 1H, C_7-H), 9.00 (s, 1H, C_4-H of coumarin), 6.95-7.82 (m, 10H, Ar-H), 10.40 (s, 1H, NH).

General procedure for the synthesis of 3-(2-oxo-2*H*-3-chromenyl)-1-[3-(4-methoxyphenyl)[1,8]naphthyridin-2-yl)-1*H*-4-pyrazolecarbaldehydes 4. To the Vilsmeier-Haack reagent (0.03 mole) at 0-5ºC, compound **3** (0.01 mole) was added portion-wise. After the addition was complete, the reaction flask was kept at RT for 5 min and silica gel (3 g) was added and properly mixed with the help of a glass rod, till free flowing powder was obtained. The powder was then irradiated in microwave oven at 400 W intermittently at 30 s intervals for the specified time (**Table I**). On completion of reaction (monitored by TLC), the reaction mixture was cooled, treated with chilled water and filtered. The solid obtained by the neutralization of the filtrate with $NaHCO_3$ was filtered, washed with water and purified by recrystallization from ethanol to furnish **4** (**Table I**).

Spectral data

4a: IR (KBr): 1726 (lactone, C=O), 1683 (aldehyde, C=O), 1608 (C=N), 1565 cm^{-1} (C=C); ^1H NMR ($CDCl_3$ + DMSO-d_6): δ 3.92 (s, 3H, OCH_3), 7.80 (m, 1H, C_6-H of naphthyridine), 8.15 (m, 2H, C_4-H, C_5-H of naphthyridine), 8.32 (m, 1H, C_7-H of naphthyridine), 8.45 (s, 1H, C_4-H of coumarin), 6.90-7.72 (m, 9H, CH of pyrazole, 8Ar-H), 9.62 (s, 1H, CHO).

4b: IR (KBr): 1725 (lactone, C=O), 1682 (aldehyde, C=O), 1609 (C=N), 1585 cm^{-1} (C=C); ^1H NMR ($CDCl_3$ + DMSO-d_6): δ 3.87 (s, 3H, OCH_3), 3.95 (s, 3H, OCH_3), 7.84 (m, 1H, C_6-H of naphthyridine), 8.12 (m, 2H, C_4-H, C_5-H of naphthyridine), 8.35 (m, 1H, C_7-H of naphthyridine), 8.42 (s, 1H, C_4-H of coumarin), 6.95-7.70 (m, 8H, CH of pyrazole, 7Ar-H), 9.65 (s, 1H, CHO).

4c: IR (KBr): 1727 (lactone, C=O), 1686 (aldehyde, C=O), 1605 (C=N), 1565 cm^{-1} (C=C); ^1H NMR ($CDCl_3$ + DMSO-d_6): δ 3.95 (s, 3H, OCH_3), 7.78 (m, 1H, C_6-H of naphthyridine), 8.18 (m, 2H, C_4-H, C_5-H of naphthyridine), 8.42 (m, 1H, C_7-H of naphthyridine), 8.50 (s, 1H, C_4-H of coumarin), 6.92-7.65 (m, 8H, CH of pyrazole, 7Ar-H), 9.60 (s, 1H, CHO).

4d: IR (KBr): 1730 (lactone, C=O), 1685 (aldehyde, C=O), 1607 (C=N), 1576 cm^{-1} (C=C); ^1H NMR ($CDCl_3$ + DMSO-d_6): δ 3.94 (s, 3H, OCH_3), 7.80 (m, 1H, C_6-H of naphthyridine), 8.20 (m, 2H, C_4-H, C_5-H of naphthyridine), 8.40 (m, 1H, C_7-H of naphthyridine), 8.44 (s, 1H, C_4-H of coumarin), 6.96-7.70 (m, 7H, CH of pyrazole, 6Ar-H), 9.65 (s, 1H, CHO).

Table I — Characterization data for compounds **3** and **4**

Compd	Reaction time (min)	m.p. °C	Yield (%)	Mol. Formula	Found (%) (Calcd) C	H	N
3a	0.5	190	96	$C_{26}H_{20}N_4O_3$	71.72 (71.55	4.66 4.62	12.92 12.84)
3b	0.25	172	98	$C_{27}H_{22}N_4O_4$	69.70 (69.52	4.80 4.75	12.08 12.01)
3c	0.25	200	97	$C_{26}H_{19}N_4O_3Cl$	66.57 (66.32	4.11 4.07	11.98 11.90)
3d	0.5	210	96	$C_{26}H_{18}N_4O_3Cl_2$	61.96 (61.80	3.63 3.59	11.16 11.09)
3e	0.5	198	97	$C_{26}H_{19}N_4O_3Br$	60.78 (60.60	3.76 3.72	10.92 10.87)
3f	0.5	190	95	$C_{26}H_{18}N_4O_3Br_2$	52.70 (52.55	3.09 3.05	9.50 9.43)
3g	0.25	192	96	$C_{26}H_{19}N_5O_5$	65.02 (64.86	4.02 3.98	14.63 14.55)
3h	0.5	220	95	$C_{30}H_{22}N_4O_3$	74.24 (74.06	4.60 4.56	11.60 11.52)
4a	2.5	112	86	$C_{28}H_{18}N_4O_4$	71.05 (70.88	3.86 3.82	11.89 11.81)
4b	3.0	130	88	$C_{29}H_{20}N_4O_5$	69.20 (69.04	4.04 4.00	11.20 11.11)
4c	3.5	230	87	$C_{28}H_{17}N_4O_4Cl$	66.25 (66.08	3.40 3.37	11.10 11.01)
4d	4.0	225	86	$C_{28}H_{16}N_4O_4Cl_2$	62.06 (61.89	3.01 2.97	10.38 10.31)
4e	3.5	132	87	$C_{28}H_{17}N_4O_4Br$	60.95 (60.77	3.15 3.10	10.20 10.12)
4f	4.0	170	86	$C_{28}H_{16}N_4O_4Br_2$	53.37 (53.19	2.60 2.55	8.93 8.86)
4g	3.5	180	84	$C_{28}H_{17}N_5O_6$	64.99 (64.74	3.34 3.30	13.55 13.48)
4h	3.5	242	85	$C_{32}H_{20}N_4O_4$	73.44 (73.28	3.88 3.84	10.75 10.68)

4e: IR (KBr): 1736 (lactone, C=O), 1684 (aldehyde, C=O), 1608 (C=N), 1587 cm^{-1} (C=C); ^1H NMR ($CDCl_3$ + DMSO-d_6): δ 3.94 (s, 3H, OCH_3), 7.90 (m, 1H, C_6-H of naphthyridine), 8.10 (m, 2H, C_4-H, C_5-H of naphthyridine), 8.38 (m, 1H, C_7-H of naphthyridine), 8.43 (s, 1H, C_4-H of coumarin), 6.90 – 7.76 (m, 8H, CH of pyrazole, 7Ar-H), 9.60 (s, 1H, CHO).

4f : IR (KBr): 1736 (lactone, C=O), 1680 (aldehyde, C=O), 1609 (C=N), 1561 cm^{-1} (C=C); ^1H NMR ($CDCl_3$ + DMSO-d_6): δ 3.92 (s, 3H, OCH_3), 7.88 (m, 1H, C_6-H of naphthyridine), 8.15 (m, 2H, C_4-H, C_5-H of naphthyridine), 8.40 (m, 1H, C_7-H of naphthyridine), 8.43 (s, 1H, C_4-H of coumarin), 6.95-7.80 (m, 7H, CH of pyrazole, 6Ar-H), 9.62 (s, 1H, CHO).

4g: IR (KBr): 1743 (lactone, C=O), 1682 (aldehyde, C=O), 1612 (C=N), 1565 cm^{-1} (C=C); ^1H NMR ($CDCl_3$ + DMSO-d_6): δ 3.96 (s, 3H, OCH_3), 7.90 (m, 1H, C_6-H of naphthyridine), 8.10 (m, 2H, C_4-H, C_5-H of naphthyridine), 8.35 (m, 1H, C_7-H of naphthyridine), 8.42 (s, 1H, C_4-H of coumarin), 6.85-7.70 (m, 8H, CH of pyrazole, 7Ar-H), 9.95 (s, 1H, CHO).

4h: IR (KBr): 1725 (lactone, C=O), 1684 (aldehyde, C=O), 1609 (C=N), 1572 cm^{-1} (C=C); ^1H NMR ($CDCl_3$ + DMSO-d_6): δ 3.90 (s, 3H, OCH_3), 7.92 (m, 1H, C_6-H of naphthyridine), 8.18 (m, 2H, C_4-H, C_5-H of naphthyridine), 8.42 (m, 1H, C_7-H of naphthyridine), 8.62 (s, 1H, C_4-H of coumarin), 6.90-7.82 (m, 11H, CH of pyrazole, 10Ar-H), 9.65 (s, 1H, CHO).

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