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A four-component, one-pot synthesis of highly substituted 1,4-dihydro-1,8-naphthyridine-3-carboxamides

Ahmad Shaabani *, Mozhdeh Seyyedhamzeh, Ali Maleki, Maryam Behnam

Department of Chemistry, Shahid Beheshti University, PO Box 19396-4716, Tehran, Iran

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ABSTRACT

A new, one-pot, four-component reaction for the synthesis of a novel class of highly substituted 1,4-dihydro-1,8-naphthyridine-3-carboxamide derivatives starting from readily available inputs including aliphatic or aromatic amines, diketene, aromatic aldehydes, and 2-aminopyridines in the presence of a catalytic amount of *p*-toluenesulfonic acid under mild reaction conditions and in good yields at ambient temperature is described.

Naphthyridine derivatives have received significant attention due to their exceptionally broad spectrum of biological activity. Substituted 1,8-naphthyridine derivatives are used for diagnosis and treatment of human diseases such as AIDS[1] and allergies.[2] Very recently, substituted naphthyridines were reported as HIV-1 integrase inhibitors.[3] The 1,8-naphthyridine core is incorporated in numerous biologically active compounds and drugs which act as antibacterials,[4] anticonvulsants,[5] antihypertensives[6] as well as inhibitors of platelet aggregation.[7]

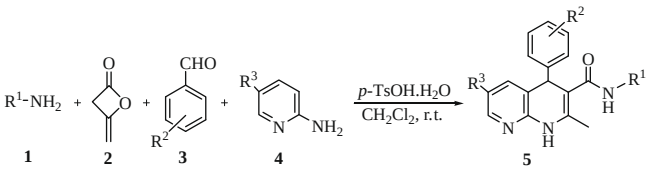
1,8-Naphthyridine derivatives are used in cancer chemotherapy. One such example is SNS-595, a cell cycle modulator, in second phase clinical trials.[8] 1,8-Naphthyridines were found to display moderate cytotoxic activity against murine P388 leukemia.[8] They also show promising cytotoxicity, anticancer, and anti-inflammatory activities based on the molecular link between cancer and inflammation.[9]

Multicomponent reactions (MCRs) are powerful synthetic tools which have changed the landscape of organic and medicinal chemistry due to their environmental friendliness, atom economy, and their ability to generate large libraries of compounds in one or two synthetic steps.[10]

Due to the biological and pharmacological importance of naphthyridine-3-carboxamides, and in continuation of our interest in MCRs,[11] we describe herein the synthesis of a new class of highly substituted 1,4-dihydro-1,8-naphthyridine-3-carboxamide derivatives **5**. The products were prepared via a one-pot process involving a four-component condensation reaction of an aliphatic or aromatic amine **1**, diketene **2**, an aromatic aldehyde **3,** and a 2-aminopyridine **4** in the presence of a catalytic amount of *p*-toluenesulfonic acid (p-TsOH·H_2O) under mild reaction conditions and in good yields at ambient temperature (Scheme 1).

In a pilot experiment, the reaction of *N*-alkyl-3-oxobutanamide **6**, which was prepared by addition of benzylamine to diketene **2**, with 4-chlorobenzaldehyde and 2-aminopyridine in the presence of catalytic p-TsOH·H_2O was performed in dry dichloromethane at ambient temperature. The progress of the reaction was monitored by TLC. After completion of the reaction, the product, *N*-benzyl-4-(4-chlorophenyl)-2-methyl-1,4-dihydro-1,8-naphthyridine-3-carboxamide **5a** was obtained in 73% yield.[12]

Three substituents in the products can be varied independently of each other. We have shown that the use of a wide range of



R^1 = Bn, 4-Me$C_6H_4CH_2$, *n*Pr
R^2 = 4-Cl, 4-Br, 4-F, 4-CH_3, 3-NO_2
R^3 = H, Br, CH_3

Scheme 1.

* Corresponding author. Tel.: +98 21 29902800; fax: +98 21 22431663.
E-mail address: a-shaabani@cc.sbu.ac.ir (A. Shaabani).

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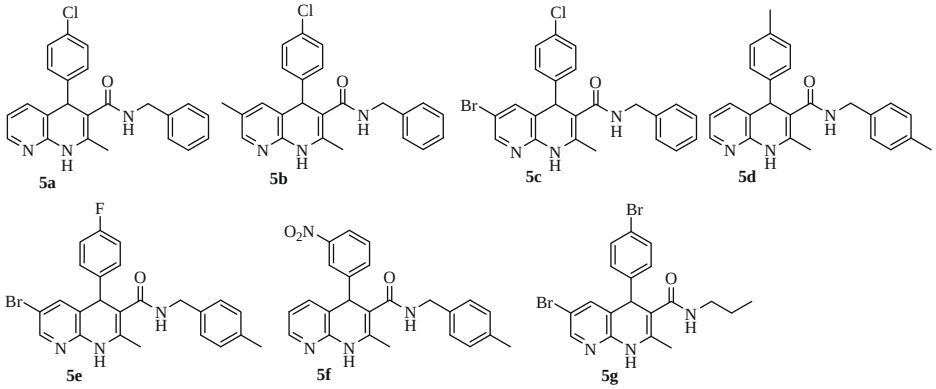
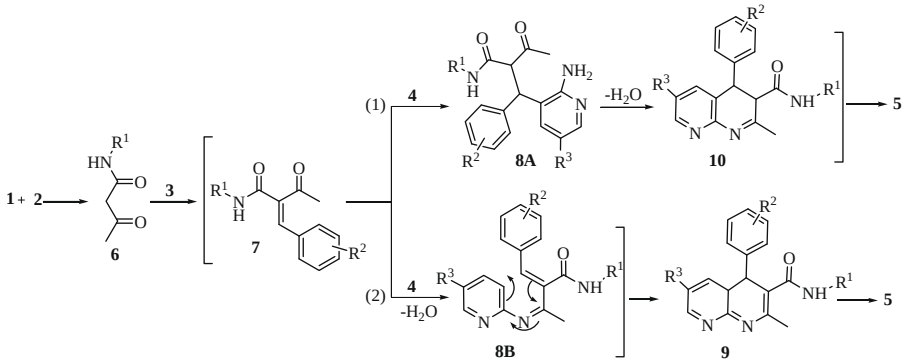


Figure 1.



Scheme 2. Possible mechanisms for the formation of compounds **5a–g**.

amines **1**, aromatic aldehydes **3** and 2-aminopyridines **4** in this four-component reaction make possible the syntheses of libraries of compounds. The results are shown in Table 1. As anticipated from our initial results, these reactions proceeded very cleanly under mild conditions at room temperature and no undesirable side reactions were observed. All the compounds described in this Letter are new (Fig. 1).

It is noteworthy that aromatic aldehydes possessing both electron-withdrawing and electron-releasing substituents were converted into the corresponding 1,4-dihydro-1,8-naphthyridine-3-carboxamide derivatives in good yields. We also reacted aliphatic propylamine to assess the scope and generality of this reaction (Table 1).

Compounds **5a–g** are stable solids whose structures were determined by IR, ^{1}H and ^{13}C NMR spectroscopy, mass spectrometry, and elemental analysis. The mass spectra of products **5a–g** displayed molecular ion peaks at values consistent with the proposed structures.

Possible mechanisms for the formation of products **5a–g** are illustrated in Scheme 2. It is rational to assume that intermediate **7** results from the initial condensation of the aldehyde **3** with *N*-alkylated-3-oxobutanamide **6**, itself derived from the addition of amine **1** to diketene **2**. Next, a Michael-type addition of 2-aminopyridine **4** to **7** would produce intermediate **8A**. Alternatively, condensation of **4** with **7** gives imine **8B**. Intramolecular condensation of **8A** or cyclization of **8B** would give **10** or **9**. Finally, aromatization of **9** or imine-enamine tautomerization of **10** yields product **5** (Scheme 2).

In summary, we have described an efficient four-component, one-pot approach for the synthesis of highly substituted 1,4-dihydro-1,8-naphthyridine-3-carboxamide derivatives via cyclocondensation of a primary aliphatic or aromatic amine, diketene, aromatic aldehydes, and 2-aminopyridines in CH_2Cl_2 using *p*-TsOH·H_2O as the catalyst at ambient temperature. All the products were obtained in high purity and in good yields. We hope that this novel class of compounds will meet with success as biologically active substances.

Table 1
Synthesis of 1,4-dihydro-1,8-naphthyridine-3-carboxamides **5a–g**

R^1	R^2	R^3	Product	Time (h)	Yield[a] (%)
$PhCH_2$	4-Cl	H	**5a**	8	73
$PhCH_2$	4-Cl	CH_3	**5b**	6	69
$PhCH_2$	4-Cl	Br	**5c**	8	71
4-$MeC_6H_4CH_2$	4-CH_3	H	**5d**	6	67
4-$MeC_6H_4CH_2$	4-F	Br	**5e**	7	71
4-$MeC_6H_4CH_2$	3-NO_2	H	**5f**	9	77
n-C_3H_7	4-Br	Br	**5g**	10	76

[a] Isolated yield.

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12. *Typical procedure for the synthesis of N-benzyl-4-(4-chlorophenyl)-2-methyl-1,4-dihydro-1,8-naphthyridine-3-carboxamide* (**5a**): A solution of benzylamine (0.107 g, 1.0 mmol) and diketene (0.084 g, 1.0 mmol) was magnetically stirred in 5 mL of dry CH_2Cl_2 for 2 h. Then, 4-chlorobenzaldehyde (0.140 g, 1.0 mmol), 2-aminopyridine (0.094 g, 1.0 mmol), and *p*-TsOH·H_2O (0.019 g, 0.1 mmol) were added simultaneously. The reaction mixture was allowed to stir for 8 h until a precipitate appeared. After completion of the reaction, as indicated by TLC (EtOAc:*n*-hexane, 1:2), the reaction mixture was filtered and the residue was washed with water and then with ethanol and dried in vacuo to give **5a**.

N-Benzyl-4-(4-chlorophenyl)-2-methyl-1,4-dihydro-1,8-naphthyridine-3-carboxamide **5a**: White powder (0.28 g, 73%): mp 167–169 °C. IR (KBr) cm^{-1}: 3463, 3335, 3069, 2916, 1654, 1565, 1491, 1448, 1388. ^1H NMR (300.13 MHz, DMSO-d_6) δ 2.28 (3H, s, CH_3), 4.32–4.42 (2H, m, CH_2), 5.44 (1H, s, CH), 6.60–6.65 (2H, m, H-Ar), 7.00–7.16 (3H, m, H-Ar), 7.41–7.48 (3H, m, H-Ar), 7.84–7.93 (2H, m, H-Ar), 8.26–8.51 (3H, m, H-Ar and NH), 9.74 (1H, br s, NH). ^{13}C NMR (75.47 MHz, DMSO-d_6) δ 21.3 (CH_3), 42.2 (CH_2), 90.3 (CH), 113.5, 114.9, 125.9, 126.7, 128.4, 128.7, 129.2, 129.9, 132.2, 134.0, 136.6, 138.5, 138.9, 142.4, 145.5 (C-Ar and C=C), 150.4, 166.7 (CO). MS *m*/*z*: 389 (M^+, 2), 302 (15), 283 (25), 255 (45), 218 (30), 172 (32), 107 (50), 91 (100), 65 (46). Anal. Calcd for $C_{23}H_{20}ClN_3O$: C, 70.85; H, 5.17; N, 10.78. Found: C, 70.73; H, 5.23; N, 10.75.

N-Benzyl-4-(4-chlorophenyl)-2,6-dimethyl-1,4-dihydro-1,8-naphthyridine-3-carboxamide **5b**: White powder (0.28 g, 69%): mp 178–179 °C. IR (KBr) cm^{-1}: 3332, 3117, 2928, 1678, 1588, 1565, 1491, 1450, 1379. ^1H NMR (300.13 MHz, DMSO-d_6) δ 2.23 (3H, s, CH_3), 2.28 (3H, s, CH_3), 4.33–4.45 (2H, m, CH_2), 5.06 (1H, br s, CH), 6.63 (2H, d, $^3J_{HH}$ = 6.2 Hz, H-Ar), 6.98 (1H, d, $^3J_{HH}$ = 8.9 Hz, H-Ar), 7.07–7.16 (2H, m, H-Ar), 7.41–7.51 (3H, m, H-Ar), 7.76 (1H, d, $^3J_{HH}$ = 8.8 Hz, H-Ar), 8.13 (1H, br s, H-Ar), 8.40–8.46 (2H, m, H-Ar and NH), 9.58 (1H, br s, NH). ^{13}C NMR (75.47 MHz, DMSO-d_6) δ 17.4, 21.2 (CH_3), 42.2 (CH_2), 90.1 (CH), 114.6, 122.7, 125.9, 126.7, 127.3, 128.3, 129.2, 129.9, 130.7, 134.0, 136.8, 138.4, 138.9, 144.5, 145.6 (C-Ar and C=C), 148.9, 166.8 (CO). MS *m*/*z*: 297 (M^+-106, 6), 271 (10), 229 (14), 172 (15), 106 (100), 91 (80), 65 (42). Anal. Calcd for $C_{24}H_{22}ClN_3O$: C, 71.37; H, 5.49; N, 10.40. Found: C, 71.25; H, 5.43; N, 10.35.

N-Benzyl-6-bromo-4-(4-chlorophenyl)-2-methyl-1,4-dihydro-1,8-naphthyridine-3-carboxamide **5c**: White powder (0.33 g, 71%): mp 170–171 °C. IR (KBr) cm^{-1}: 3342, 3177, 3108, 2924, 1675, 1652, 1566, 1490, 1374. ^1H NMR (300.13 MHz, DMSO-d_6) δ 2.28 (3H, s, CH_3), 4.34–4.39 (2H, m, CH_2), 6.41 (1H, s, CH), 7.08–8.20 (11H, m, H-Ar), 9.01 (1H, br s, NH), 9.97 (1H, br s, NH). ^{13}C NMR (75.47 MHz, DMSO-d_6) δ 21.2 (CH_3), 42.8 (CH_2), 103.2 (CH), 111.2, 115.3, 125.9, 128.6, 128.9, 129.1, 129.8, 131.9, 132.8, 134.4, 135.2, 138.4, 138.8, 145.7, 146.0 (C-Ar and C=C), 156.0, 167.0 (CO). MS *m*/*z*: 361 (M^+-106, 6), 333 (12), 295 (35), 202 (8), 174 (30), 157 (50), 106 (100), 91 (84), 65 (34). Anal. Calcd for $C_{23}H_{19}BrClN_3O$: C, 58.93; H, 4.09; N, 8.96. Found: C, 58.97; H, 4.16; N, 8.89.

2-Methyl-N-(4-methylbenzyl)-4-p-tolyl-1,4-dihydro-1,8-naphthyridine-3-carboxamide **5d**: White powder (0.26 g, 67%): mp 159–161 °C. IR (KBr) cm^{-1}: 3416, 3328, 3113, 2916, 1678, 1653, 1574, 1439, 1379. ^1H NMR (300.13 MHz, DMSO-d_6) δ 2.23 (3H, s, CH_3), 2.28 (3H, s, CH_3), 2.37 (3H, s, CH_3), 4.22–4.34 (2H, m, CH_2), 5.01 (1H, br s, CH), 6.57 (2H, d, $^3J_{HH}$ = 7.7 Hz, H-Ar), 6.90 (2H, d, $^3J_{HH}$ = 7.6 Hz, H-Ar), 6.96–7.48 (5H, m, H-Ar), 7.83–7.91 (1H, m, H-Ar), 8.26–8.36 (2H, m, H-Ar and NH), 8.43 (1H, br s, NH). ^{13}C NMR (75.47 MHz, DMSO-d_6) δ 21.1 (CH_3), 21.3 (CH_3), 25.0 (CH_3), 53.2 (CH_2), 90.3 (CH), 113.3, 114.9, 125.9, 126.9, 128.6, 128.9, 129.8, 132.2, 135.9, 138.3, 138.8, 145.9 (C-Ar and C=C), 150.4, 166.8 (CO). MS *m*/*z*: 263 (M^+-120, 14), 223 (6), 195 (30), 172 (18), 145 (16), 120 (100), 105 (32), 91 (60), 79 (82), 65 (30). Anal. Calcd for $C_{25}H_{25}N_3O$: C, 78.30; H, 6.57; N, 10.96. Found: C, 78.38; H, 6.53; N, 10.91.

6-Bromo-4-(4-fluorophenyl)-2-methyl-N-(4-methylbenzyl)-1,4-dihydro-1,8-naphthyridine-3-carboxamide **5e**: White powder (0.33 g, 71%): mp 157–159 °C. IR (KBr) cm^{-1}: 3344, 3178, 3008, 2925, 1675, 1569, 1508, 1437, 1375. ^1H NMR (300.13 MHz, DMSO-d_6) δ 2.23 (3H, s, CH_3), 2.29 (3H, s, CH_3), 4.20–4.34 (2H, m, CH_2), 5.07 (1H, br s, CH), 6.55 (2H, d, $^3J_{HH}$ = 7.5 Hz, H-Ar), 6.90–7.64 (8H, m, H-Ar), 8.38 (1H, br s, NH), 9.95 (1H, br s, NH). ^{13}C NMR (75.47 MHz, DMSO-d_6) δ 21.2 (CH_3), 21.6 (CH_3), 42.6 (CH_2), 92.8 (CH), 111.5, 117.4, 123.9, 126.9, 127.4, 128.9, 129.7, 129.9, 133.2, 134.8, 136.3, 137.5, 138.8, 143.4, 146.5 (C-Ar and C=C), 152.7, 168.7 (CO). MS *m*/*z*: 345 (M^+-120, 4), 317 (14), 280 (6), 238 (8), 212 (12), 172 (48), 120 (100), 105 (30), 91 (55), 65 (28). Anal. Calcd for $C_{24}H_{21}BrFN_3O$: C, 61.81; H, 4.54; N, 9.01. Found: C, 61.86; H, 4.59; N, 9.08.

2-Methyl-N-(4-methylbenzyl)-4-(3-nitrophenyl)-1,4-dihydro-1,8-naphthyridine-3-carboxamide **5f**: White powder (0.32 g, 77%): mp 147–149 °C. IR (KBr) cm^{-1}: 3391, 3267, 3083, 2924, 1715, 1642, 1603, 1554, 1519, 1480, 1419. ^1H NMR (300.13 MHz, DMSO-d_6) δ 2.21 (3H, s, CH_3), 2.23 (3H, s, CH_3), 4.07–4.29 (2H, m, CH_2), 5.81–5.90 (1H, m, CH), 6.43–8.09 (11H, m, H-Ar), 8.29 (1H, br s, NH), 8.73 (1H, br s, NH). ^{13}C NMR (75.47 MHz, DMSO-d_6) δ 21.1 (CH_3), 28.7 (CH_3), 42.5 (CH_2), 109.3 (CH), 113.1, 122.2, 122.5, 122.6, 127.0, 127.3, 128.0, 128.9, 129.2, 129.9, 135.4, 136.1, 144.6, 148.0 (C-Ar and C=C), 157.9, 165.6 (CO). MS *m*/*z*: 323 (M^+-91,10), 226 (6), 202 (12), 176 (20), 160 (12), 120 (100), 105 (18), 91 (12), 79 (22), 65 (25). Anal. Calcd for $C_{24}H_{22}N_4O_3$: C, 69.55; H, 5.35; N, 13.52. Found: C, 69.51; H, 5.33; N, 13.57.

6-Bromo-4-(4-bromophenyl)-2-methyl-N-propyl-1,4-dihydro-1,8-naphthyridine-3-carboxamide **5g**: White powder (0.35 g, 76%): mp 164–166 °C. IR (KBr) cm^{-1}: 3374, 3335, 3066, 2963, 1711, 1659, 1592, 1548, 1479, 1408, 1366. ^1H NMR (300.13 MHz, DMSO-d_6) δ 0.48–0.74 (3H, m, CH_3), 1.23–1.33 (2H, m, CH_2), 2.09 (3H, s, CH_3), 2.90–3.01 (2H, m, CH_2), 5.60 (1H, br s, CH), 6.43–6.57 (1H, m, H-Ar), 7.25–7.52 (5H, m, H-Ar), 7.92–8.00 (1H, m, NH), 8.06–8.14 (1H, m, NH). ^{13}C NMR (75.47 MHz, DMSO-d_6) δ 11.6, 22.2, 22.5, 28.3, 29.2 (CH_3, CH_2), 106.4 (CH), 111.2, 120.4, 120.6, 129.9, 130.2, 131.4, 132.1, 139.6, 141.2, 141.4, 148.1 (C-Ar and C=C), 156.7, 167.2 (CO). MS *m*/*z*: 377 (M^+-86, 14), 339 (18), 157 (100), 102 (10), 78 (32), 57 (25). Anal. Calcd for $C_{19}H_{19}Br_2N_3O$: C, 49.06; H, 4.12; N, 9.03. Found: C, 49.01; H, 4.19; N, 9.09.