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A SIMPLE APPROACH SYNTHESIS OF BENZO[*b*]PYRAZOLO[3,2-*h*] [1,6] NAPHTHYRIDIN-1(2*H*)-ONES

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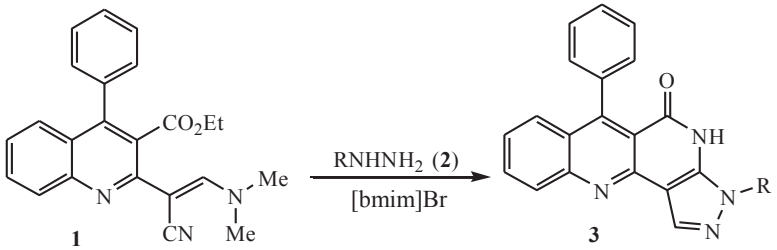
Abstract – A simple method for the synthesis of benzo[*b*]pyrazolo[3,2-*h*][1,6]-naphthyridin-1(2*H*)-ones by a tandem addition-elimination-cyclization reaction strategy from *α*-(dimethylaminomethylene)-2-cyanomethylquinoline-3-carboxylate and hydrazine has been developed.

Naphthyridines are fused nitrogen heterocycles present in many natural and synthetic compounds of particular interest in medicinal chemistry due to their diverse biological activities.[1] Therefore, great attention has been directed toward the development of efficient methods for the selective functionalization of the naphthyridine cores. In particular, a variety of synthetic fused 1,6-naphthyridines exhibited various biological properties, such as anticancer,[2] anti-HIV-1,[3] anti-inflammatory,[4] and cytotoxic activity.[5] Although many studies on the preparation of fused 1,6-naphthyridine derivatives have been developed,[6] these methods suffer multistep syntheses. Thus, the development of general and efficient routes to synthesis of fused 1,6-naphthyridine is still challenging.

Recently, we described an efficient synthesis of fused naphthyridines. Due to our interest in continuation to our work on the synthesis of naphthyridines,[7] herein, we reported the simple and facile protocol for the synthesis of pyrazolo[3,2-*h*][1,6]naphthyridinones with *α*-(dimethylaminomethylene)-2-cyanomethyl-quinoline-3-carboxylate **1**[7c] and hydrazine **2** by a novel domino reaction in [bmim]Br (Scheme 1).



Scheme 1. Synthesis of benzo[*b*]pyrazolo[3,2-*h*][1,6]naphthyridin-1(2*H*)-ones

In our initial study, various reaction conditions including solvents and temperatures were tested in the one-pot synthesis of the pyrazolo[3,2-*h*][1,6]naphthyridinone **3**. Among different polar solvents, such as ethanol, acetic acid, glycol, DMF and ionic liquid 3-butyl-1-methylimidazolium bromide ([bmim]Br), the best result was obtained when the reaction was carried out in [bmim]Br at 90 °C. [bmim]Br was chosen as the solvent for all further reactions as it is environmentally friendly and the toxic organic reagents can be avoided. Under these optimized reaction conditions, a series of pyrazolo[3,2-*h*][1,6]naphthyridinone derivatives **3** were synthesized.

As shown in Table 1, the reaction was successful for hydrazine **2** incorporating alkyl (entries 1-2), and aromatic (entries 3-10) R groups carrying either electron-donating or electron-withdrawing substituents reacted efficiently giving good yields (70-85%).

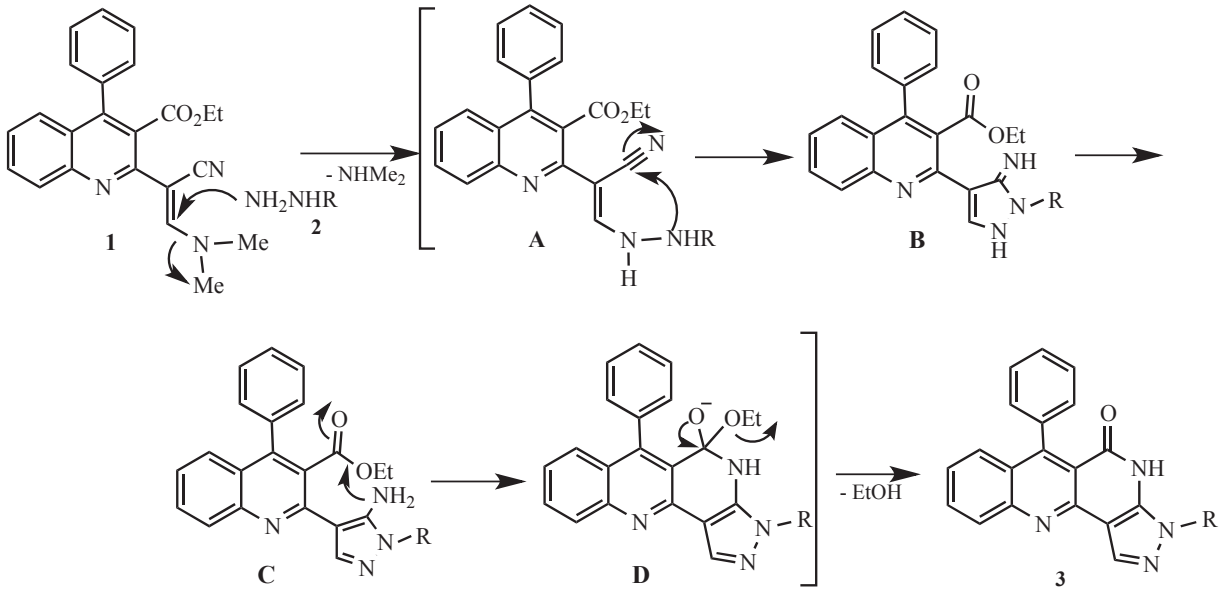
Table 1. Synthesis of benzo[*b*]pyrazolo[3,2-*h*][1,6]naphthyridin-1(2*H*)-ones **3**[8]

Entry	**2** / R		Time (h)	Product	Yield (%)
1	**2a**	H	2	**3a**	74
2	**2b**	Me	1	**3b**	78
3	**2c**	C_6H_5	3	**3c**	82
4	**2d**	2-MeC_6H_4	3	**3d**	80
5	**2e**	4-MeC_6H_4	2	**3e**	85
6	**2f**	2,4-$Me_2C_6H_3$	3	**3f**	78
7	**2g**	4-$MeOC_6H_4$	1	**3g**	75
8	**2h**	4-FC_6H_3	2	**3h**	76
9	**2i**	4-ClC_6H_4	4	**3i**	74
10	**2j**	4-$NO_2C_6H_4$	4	**3j**	70

The products **3** were completely characterized by IR, NMR, and elemental analyses. The IR spectra of compounds **3** are characterized by absorption bands of stretching vibrations (3382-3415 cm^{-1}) and bending vibrations (1657-1676 cm^{-1}) of the amino and amide groups. The ^1H NMR spectra of compounds **3a**-j show characteristic singlets of 3-H protons of the pyrazole ring at 7.25-7.30 ppm. The NH proton resonance at 9.25-9.32 ppm disappeared after addition of D_2O to the DMSO-d_6 solution of **3**. All aromatic protons showed expected chemical shifts and splitting patterns which resembles with the structure of **3**.

The proposed mechanism of the process is summarized in Scheme 2. The sequence involves an initial conjugate addition of the hydrazine **2** on the double bond of the enamine **1** accompanied with the departure of dimethylamine Me_2NH, followed by an intramolecular cyclization and isomerization,

resulting in the formation of 5-aminopyrazoles **C**. Next, this then undergoes intramolecular cyclization *via* loss of ethanol leading to yield benzo[*b*]pyrazolo[3,2-*h*][1,6]naphthyridin-1(2*H*)-one **3**.



Scheme 2. Proposed mechanism for the synthesis of compounds **3**

In conclusion, we have described an efficient method for generating the pyrazole-annulated [1,6]-naphthyridine ring through a novel domino reaction from *α*-(dimethylaminomethylene)-2-cyano-methylquinoline-3-carboxylate and hydrazine in [bmim]Br. This method has the advantages of mild reaction conditions, easy work-up, inexpensive reagents and good yields.

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8. The general procedure is represented as follow: To a solution of *α*-(dimethylaminomethylene)-2-cyanomethylquinoline-3-carboxylate **1** (1.0 mmol) in ionic liquid [bmim]Br (2.0 mL) hydrazine **2** (1.0 mmol) was added, and the mixture was heated at 90 °C. After completion monitored by TLC, the reaction mixture was allowed to cool to room temperature, and then water (20 mL) was added to the mixture. The solid was filtered and recrystallized from AcOH to give crystalline powder **3** (yield of the products is summarized in Table 1). Selected data of compound. **3a**: mp > 300 °C; IR (KBr): *v* 3382, 3343 (NH), 1657 cm^{-1} (C=O); ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.25 (1H, s), 7.29-7.32 (4H, m), 7.80-7.84 (1H, m), 8.11-8.18 (2H, m), 8.72-8.75 (1H, m), 8.90-8.93 (1H, m), 9.16 (1H, s), 9.25 (1H, s). ^{13}C NMR (100 MHz, DMSO-d_6): δ 115.1, 116.3, 118.0, 124.4, 126.5, 128.5, 129.1, 130.2, 130.8, 132.6, 139.7, 140.4, 143.9, 144.5, 156.0, 159.1, 168.5. *Anal*. Calcd for $C_{19}H_{12}N_4O$: C 73.07, H 3.87, N 17.94. Found: C 73.13, H 3.95, N 18.03. **3c**: mp > 300 °C; IR (KBr): *v* 3398 (NH), 1676 cm^{-1} (C=O). ^{1}H NMR (400 MHz, DMSO-d_6): δ 6.98-7.00 (2H, m), 7.28 (1H, s), 7.47-7.49 (4H, m), 7.83-7.88 (3H, m), 8.20-8.22 (2H, m), 8.66-8.68 (1H, m), 8.90-8.92 (1H, m), 9.27 (1H, s). ^{13}C NMR (100 MHz, DMSO-d_6): δ 111.5, 113.9, 116.5, 119.3, 124.1, 126.2, 128.2, 128.5, 129.1, 129.3, 130.1, 130.3, 130.6, 132.7, 139.5, 140.7, 143.7, 144.7, 155.1, 159.1, 168.9. *Anal*. Calcd for $C_{25}H_{16}N_4O$: C 77.30, H 4.15, N 14.42. Found: C 77.43, H 4.29, N 14.55. **3g**: mp > 300 °C; IR (KBr, cm^{-1}): *v* 3415 (NH), 1674 (C=O). ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.98 (3H, s), 7.18 (2H, d, J = 8.4 Hz), 7.30 (1H, s), 7.32-7.39 (4H, m), 7.85-7.89 (2H, m), 8.17-8.20 (2H, m), 8.71-8.73 (1H, m), 8.93-8.95 (1H, m), 9.32 (1H, s). ^{13}C NMR (100 MHz, DMSO-d_6): δ 62.1, 114.2, 115.7, 116.7, 119.0, 124.3, 126.2, 128.5, 128.7, 129.0, 129.4, 130.1, 130.5, 130.8, 132.7, 139.6, 140.7, 143.9, 144.6, 155.3, 159.5, 167.9. *Anal*. Calcd for $C_{26}H_{18}N_4O_2$: C 74.63, H 4.34, N 13.39. Found: C 74.76, H 4.52, N 13.57.