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Nucleophilic substitution of hydrogen–the Boger reaction sequence as an approach towards 8-(pyridin-2-yl)coumarins

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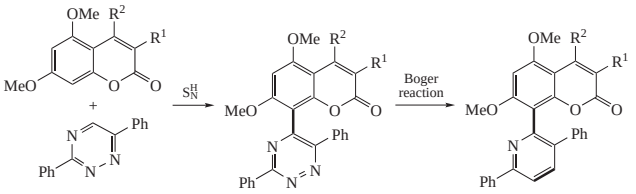
5,7-Dimethoxy-8-(3,6-diphenylpyridin-2-yl)coumarins were obtained from 5,7-dimethoxycoumarins and 3,6-diphenyl-1,2,4-triazines *via* the protocol comprising aromatic S_N^H substitution in the triazine ring followed by the Boger transformation of formed triazine moiety into the pyridine one. The advantages of the suggested method are simple procedures, high yields, and the absence of transition-metal catalysts.



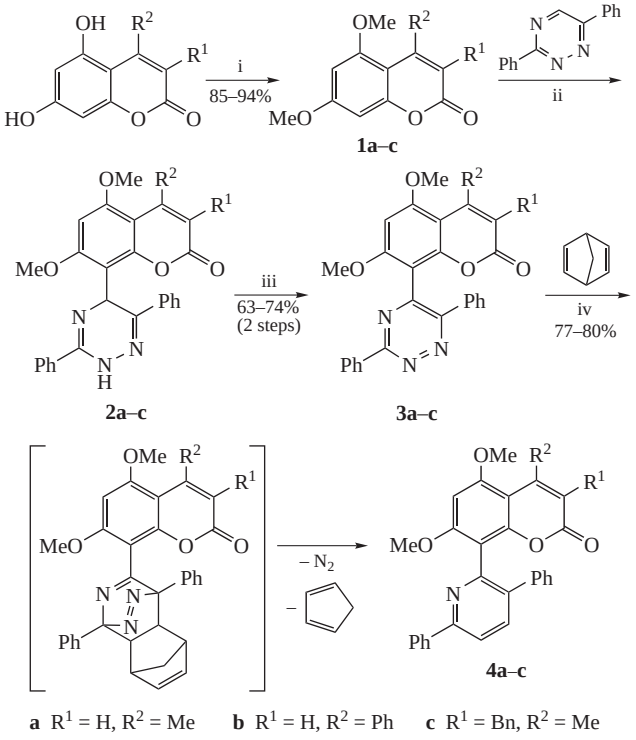
Coumarin derivatives bearing pyridine fragments are of particular interest due to their wide spectrum of physiological activity.[1] The reported synthetic approaches include multistep reaction sequences involving acylation of coumarins, halogenation of the acyl derivatives, halogen substitution and the Kröhnke ring formation.[2]

Noteworthy that aromatic nucleophilic substitution of hydrogen (S_N^H)[3] is a versatile tool for the single-step modification of various π-deficient heterocycles, in particular, 1,2,4-triazines,[4] by the incorporation of electron-rich residues. Unfortunately, the reactivity of pyridine ring is generally insufficient for its modification by direct substitution of hydrogen. At the same time, the Boger pyridine synthesis[5] involving hetero-Diels–Alder reaction of 1,2,4-triazines followed by extrusion of N_2 provides simple conversion of triazines into pyridines. This protocol is widely used, *e.g.*, for the synthesis of (bi)pyridines with such substituents as (het)aryl, alkylthio, ester and chloromethyl groups.[6] Therefore, S_N^H reaction of 1,2,4-triazines or its activated forms (1,2,4-triazine 4-oxides) followed by the Boger reaction represent an effective strategy for the synthesis of substituted pyridines. In this way, various 2,2′-bi- and 2,2′:6′,2″-terpyridines were obtained *via* ring transformation of the corresponding 5-Nu-1,2,4-triazine precursors. Such nucleophiles as cyanide anion,[7] resorcinol, thiophene, lithium acetylides,[8] lithiocarboranes,[8,9] lithium salts of polynuclear aromatic compounds[10] and C–H-active compounds[11] were successfully employed in this strategy. Moreover, the possibility of combination of S_N^H, S_N^{ipso} and the Boger reactions for the preparation of 2,2′-bipyridines bearing aniline,[12] amine or alcohol[13] functional groups should be noted. Recently, this strategy has been extended onto *in situ* generated aryne intermediates as dienophiles.[14]

The aim of this communication is to describe a convenient synthetic approach towards 8-(pyridin-2-yl)coumarin derivatives comprising S_N^H reaction at the first step and Boger reaction at the second step (Scheme 1).

5,7-Dimethoxycoumarins **1** were synthesized by methylation of the corresponding known[15] 5,7-dihydroxy precursors according to the procedure reported for other analogous compounds.[16]

The C–C coupling of 5,7-dimethoxycoumarins **1a–c** at the 5-position of 3,6-diphenyl-1,2,4-triazine[17] was processed *via* aromatic nucleophilic addition followed by oxidation of initially formed dihydroadducts **2a–c**.† We have found that the earlier described conditions[18] for the addition of 1,2,4-triazines to 5,7-dihydroxycoumarins (3 equiv. MsOH, 24 h, ambient temperature) could be successfully applied to methoxy derivatives



a R^1 = H, R^2 = Me **b** R^1 = H, R^2 = Ph **c** R^1 = Bn, R^2 = Me

Scheme 1 *Reagents and conditions*: i, Me_2SO_4, K_2CO_3, acetone, reflux, 8 h; ii, MsOH, CH_2Cl_2, room temperature, 24 h; iii, DDQ, $C_2H_2Cl_2$, reflux, 6 h; iv, 1,2-$Cl_2C_6H_4$, 215 °C (autoclave), 20 h.

1a–**c**. Adducts **2** can be readily isolated (*e.g.* **2a** can be easily purified by single recrystallization from benzene) and subjected to the aromatization.

Although coumarins **1a**–**c** contain two nucleophilic centres (C^6 and C^8 carbon atoms), they add 3,6-diphenyltriazine exclusively at the 8-position. This was based on 2D HMBC experiment data for adduct **2a** revealing cross-peaks between C^6 hydrogen and the C^5 and C^7 carbon atoms (see Online Supplementary Materials), which was in good agreement with published data.[18,19]

To restore aromaticity of 1,2,4-triazine ring, dihydroadducts **2a**–**c** were oxidized by refluxing with 1.5 equiv. DDQ in 1,2-dichloroethane thus yielding triazines **3a**–**c** (see Scheme 1).

According to our strategy, the last step of the pyridine ring synthesis is the replacement of N=N fragment in 1,2,4-triazines **3a**–**c** with the CH=CH moiety originating from 2,5-norbornadiene as a dienophile (see Scheme 1). However, attempts to conduct this reaction in high-boiling solvents such as toluene, *o*-xylene or 1,2-dichlorobenzene failed, and only starting materials were recovered. It worth noting that carrying out such a reaction under elevated pressure and temperature was described.[20] For example, 5-aryl-2,2′-bipyridines bearing alcohol or amine moiety at the C^6 position were obtained *via* the reaction of the 1,2,4-triazine precursors with 2,5-norbornadiene in an autoclave at 215 °C in 1,2-dichlorobenzene.[13] This procedure proved to be applicable to the preparation of coumarins **4a**–**c** containing pyridine residues, and after carrying out the reaction for 20 h the complete conversion of the starting 1,2,4-triazines **3** into the products did occur.‡

NMR spectra provide evidence of replacing the N=N fragment with the CH=CH one when two characteristic pyridine doublets were observed. Other proton signals underwent noticeable upfield shift (see Online Supplementary Materials).

In conclusion, the suggested S_N^H substitution–the Boger reaction sequence is a simple and useful tool to access pyridine-containing coumarins. This protocol provides wide diversity within the chemotype of such compounds.

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† MsOH (195 μl, 3 mmol) was added to a solution of the corresponding coumarin **1** (1 mmol) and 3,6-diphenyltriazine (233 mg, 1 mmol) in CH_2Cl_2 (7 ml). The mixture was left at room temperature for 24 h, then diluted with CH_2Cl_2 (10 ml), basified with saturated solution of Na_2CO_3, the organic layer was separated, and the solvent was removed under reduced pressure to leave product **2**.

*8-(3,6-Diphenyl-2,5-dihydro-1,2,4-triazin-5-yl)-5,7-dimethoxy-4-methyl-2*H*-chromen-2-one* **2a**. Mp 238–240 °C (benzene). ^{1}H NMR (DMSO-d_6) δ: 2.43 (s, 3H, Me), 3.86 (s, 3H, OMe), 3.93 (s, 3H, OMe), 5.99 (s, 1H, H-3), 6.40 [s, 1H, H-5(triazine)], 6.58 (s, 1H, H-6), 7.20–7.30 (m, 3H, Ph), 7.36–7.46 (m, 3H, Ph), 7.61–7.63 (m, 2H, Ph), 7.80–7.82 (m, 2H, Ph). ^{13}C NMR (DMSO-d_6) δ: 23.8, 45.8, 56.2, 56.4, 92.6, 103.6, 110.5, 111.3, 124.9, 126.2, 128.2, 128.7, 130.2, 133.2, 135.9, 139.4, 149.4, 153.4, 154.4, 158.6, 159.0, 160.7. Found (%): C, 71.45; H, 5.15; N, 9.18. Calc. for $C_{27}H_{21}N_3O_4$ (%): C, 71.51; H, 5.11; N, 9.27.

‡ The mixture of the corresponding triazine **3** (0.3 mmol), 2,5-norbornadiene (325 μl, 3.2 mmol) and 1,2-dichlorobenzene (25 ml) was stirred in autoclave under argon atmosphere at 215 °C for 20 h. The solvent was removed under reduced pressure, the residue was purified by flash chromatography (chloroform as eluent).

*8-(3,6-Diphenylpyridin-2-yl)-5,7-dimethoxy-4-methyl-2*H*-chromen-2-one* **4a**. Mp 209–211 °C. ^{1}H NMR ($CDCl_3$) δ: 2.38 (s, 3H, Me), 3.52 (s, 3H, OMe), 3.73 (s, 3H, OMe), 5.76 (s, 1H, H-3), 6.11 (s, 1H, H-6), 7.05–7.14 (m, 5H, Ph), 7.26–7.27 (m, 1H, Ph), 7.32–7.34 (m, 2H, Ph), 7.65 and 7.68 [both d, 1H, ^3J 8.0 Hz, H-3,4 (Py)], 7.90–7.92 (m, 2H, Ph). ^{13}C NMR ($CDCl_3$) δ: 24.4, 55.7, 55.8, 91.1, 104.6, 111.5, 111.6, 119.9, 127.1, 127.4, 127.7, 128.4, 128.5, 128.6, 137.5, 138.0, 139.6, 139.7, 150.3, 153.9, 154.2, 156.5, 159.2, 160.2, 160.7. Found (%): C, 77.33; H, 4.97; N, 3.44. Calc. for $C_{29}H_{23}NO_4$ (%): C, 77.49; H, 5.16; N, 3.12.

Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2019.05.019.

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