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Short Note

2,4-Diamino-5-(nitromethyl)-5*H*-chromeno[2,3-*b*]pyridine-3-carbonitrile

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Abstract: Dimethyl sulfoxide (DMSO) is a cheap polar aprotic solvent used in organic synthesis and in pharmacology because of its low cost, high stability, and non-toxicity. Multicomponent reactions (MCRs) are highly convergent processes and have good atom, step, and pot economies. In this communication, the multicomponent transformation of salicylaldehyde, malononitrile dimer, and nitromethane in DMSO at room temperature was investigated to give 2,4-diamino-5-(nitromethyl)-5*H*-chromeno[2,3-*b*]pyridine-3-carbonitrile in good yield. The structure of the earlier unknown compound was confirmed by means of elemental analysis, mass-, nuclear magnetic resonance, and infrared spectroscopy.

Keywords: salicylaldehyde; malononitrile dimer; nitromethane; chromeno[2,3-*b*]pyridines; multicomponent reaction

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1. Introduction

Sustainable trends in chemistry are gaining momentum [1]. Organic chemistry is becoming "greener", it reduces waste and uses more effective approaches. Dimethyl sulfoxide (DMSO) meets modern challenges in organic chemistry as it has aprotic properties, it is eco-friendly and it simplifies the treatment of a reaction mixture. Thus, it may be one of the most effective solvents today.

Multicomponent reactions (MCRs) are highly convergent processes that include two or more chemical reactions. These processes are often related to the PASE principles—atom, step, and pot economies [2]. Such a convergence leads to the formation of several bonds at once and, thus, to high bond-forming index (BFI) of the whole process [3]. Apparently, the mentioned advantages of MCRs in corporation with advantages of DMSO as a solvent are supposed to be even more effective, eco-friendly and useful for the development of new synthetic approaches [4]. In the literature, there is not a very large variety of multicomponent reactions in DMSO. In general, these are reactions in the iodine–DMSO system [5–7].

Chromeno[2,3-*b*]pyridines are an interesting class of three-fused heterocycles with broad medicinal, biological and industrial importance. Depending on their structure, these compounds show different kinds of pharmacological activity, such as antimicrobial [8], anticancer [9], antimyopic [10], neuroprotective [11], and other properties. In addition, 5-*S*-substituted chromeno[2,3-*b*]pyridines can inhibit the corrosion of mild steel [12]. At present, the best known are two anti-inflammatory commercial drugs: amlexanox and pranoprofen (Figure 1). Thus, the multicomponent design of new chromeno[2,3-*b*]pyridines is an important goal for organic and medicinal chemistry.

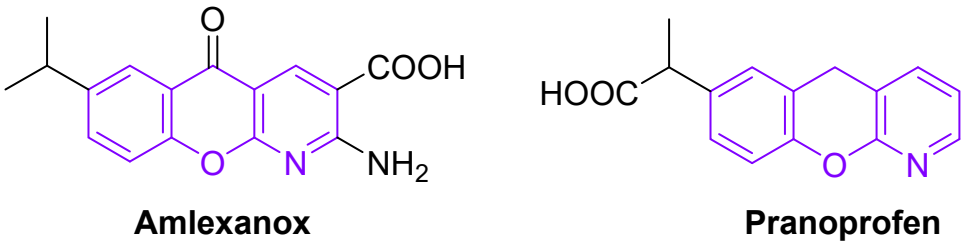
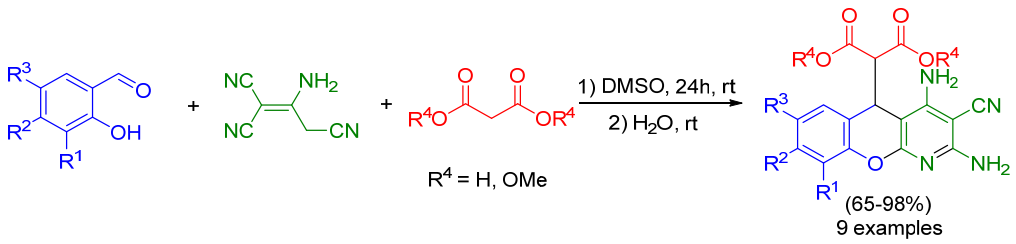


Figure 1. Some biologically active chromeno[2,3-*b*]pyridines.

In the synthesis of different types of chromeno[2,3-*b*]pyridines, both multistep classical and multicomponent methods [13] are used. We have already published different multicomponent transformations leading to 5-*C*- and 5-*P*-substituted chromeno[2,3-*b*]pyridines [14–18].

2. Results and Discussion

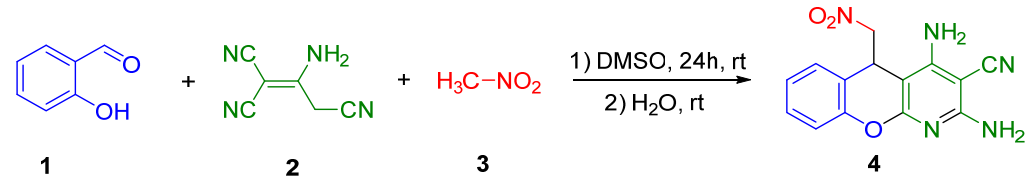
We previously realized multicomponent reactions of salicylaldehydes, 2-aminoprop-1-ene-1,1,3-tricarbonitrile and malonic acid or dimethyl malonate into 2-(2,4-diamino-3-cyano-5*H*-chromeno[2,3-*b*]pyridin-5-yl)malonic acids or dimethyl 2-(2,4-diamino-3-cyano-5*H*-chromeno[2,3-*b*]pyridin-5-yl)malonate [19,20] (Scheme 1). These reactions were the first examples of a multicomponent synthesis of chromeno[2,3-*b*]pyrnidines in DMSO.



Scheme 1. Reaction of salicylaldehyde, malononitrile dimer, and malonic acid or dimethyl malonate.

The application of this technique made it possible to obtain previously inaccessible heterocyclic compounds. Therefore, we decided to try to synthesize other chromeno[2,3-*b*]pyridines that were previously inaccessible to us under these conditions.

Now, we wish to report our results on the efficient multicomponent transformation of salicylaldehyde **1**, 2-aminoprop-1-ene-1,1,3-tricarbonitrile **2**, and nitromethane **3** into the novel 2,4-diamino-5-(nitromethyl)-5*H*-chromeno[2,3-*b*]pyridine-3-carbonitrile **4** in DMSO at room temperature (23 °C) for 24 h, as shown in Scheme 2.



Scheme 2. Reaction of salicylaldehyde **1**, malononitrile dimer **2**, and nitromethane **3**.

When the reaction in DMSO was completed, water was added to the reaction mixture and the final chromeno[2,3-*b*]pyridine **4** was crystallized in pure form. Compound **4** was synthesized in 73% yield.

We also carried out the transformation described above in other aprotic solvents and catalyst–solvent systems developed by us (Table 1).

Table 1. Optimization of multicomponent reaction conditions [1].

Entry	Solvent	Catalyst	Time (h)	Temp. (°C)	Water Volume (mL)	Yield (%)
1	DMSO	-	24	23 (rt)	15	73 [2]
2	DMF	-	24	23 (rt)	15	52 [2]
3	NMP	-	24	23 (rt)	15	50 [2]
4	Py	-	4	115	-	-
5	EtOH	Et_3N	4	79	-	-
6	MeCN	Et_3N	4	82	-	13
7	*n*-PrOH	Et_3N	4	97	-	-
8	*i*-PrOH	KF	4	83	-	-
9	EtOH/Py (3:1)	-	4	81	-	8

[1] Reaction conditions: salicylaldehyde **1a** (1 mmol), malononitrile dimer **2** (1 mmol), and nitromethane **3** (1 mmol) were stirred in 5 mL of solvent at room temperature or reflux in the presence of a catalyst or without it, and then H_2O was added or not. [2] Isolated yields, in other cases NMR data.

In aprotic polar solvents, the reaction proceeds with good yields (Table 1, Entries 1–3). The use of systems developed earlier by us did not give such good results (Table 1, Entries 4–9). In most cases, the target was not fixed (Table 1, Entries 4, 5, 7, and 8). In two cases (Table 1, Entries 6 and 9), there were very small yields of the compound, calculated from the ^{1}H-NMR spectra. The best conditions were confirmed by our research (Table 1, Entry 1).

The BFI (bond-forming index) of this transformation was four since four new bonds were formed in one stage, namely 2 C–C bonds, 1 C–N, and 1 C–O bonds.

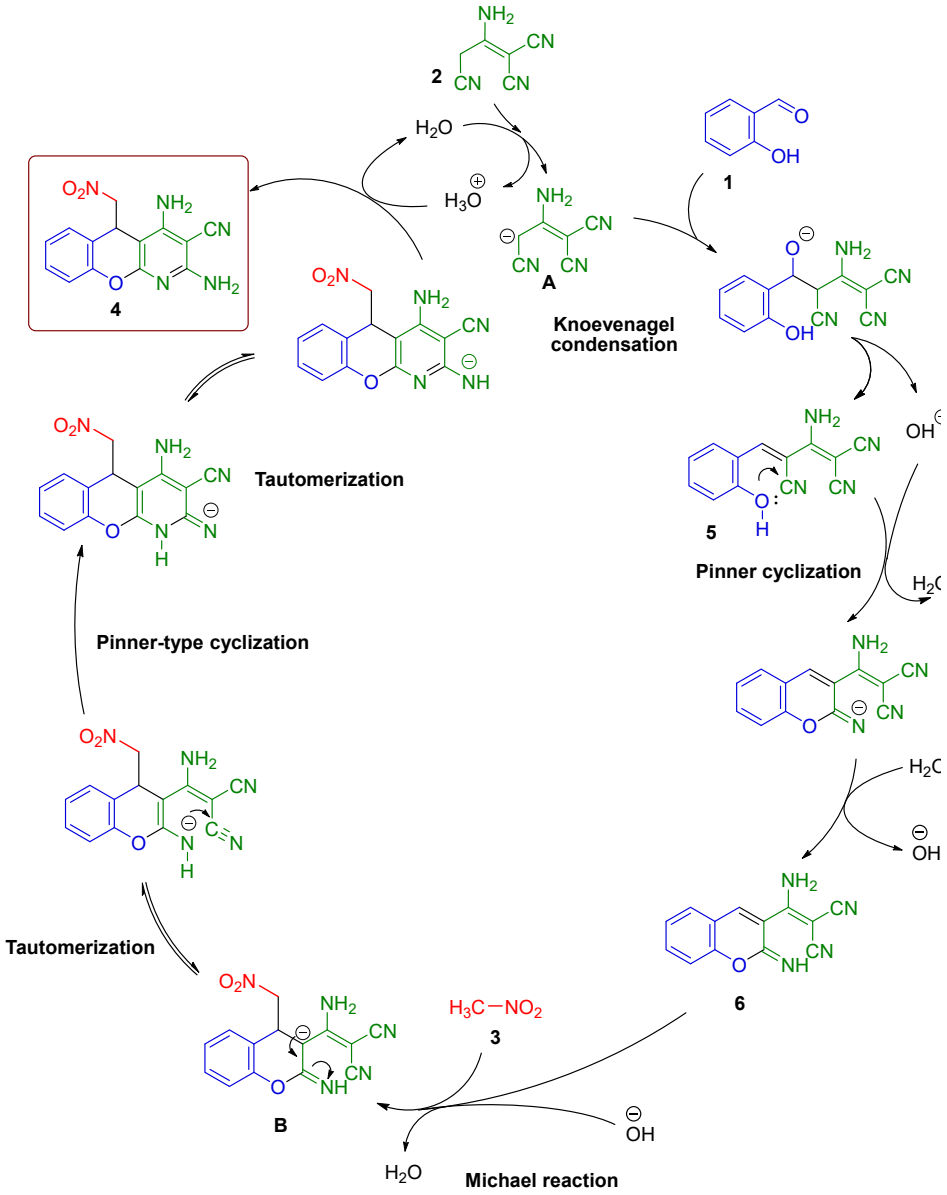
The structure of novel chromeno[2,3-*b*]pyridine **4** was confirmed by ^{1}H, ^{13}C NMR, and IR spectroscopy data, mass spectrometry data and elemental analysis (see Supplementary Materials). Only one set of signals was recorded in ^{1}H and ^{13}C-NMR spectra.

In 2017, 12-nitromethyl-12*H*-chromeno[2,3-*c*]isoquinolin-5-amines were synthesized from salicylaldehydes, homophthalonitrile and nitromethane using one-pot transformation in 20–92% yields [21]. The process proceeds in two stages without the isolation of intermediate compounds under the action of microwave radiation.

Earlier in our scientific group, 2-amino-4-(1-nitroalkyl)-4*H*-chromenes were synthesized from salicylaldehydes, nitroalkanes and malononitrile derivatives [22,23].

Taking into consideration our previous results and ^{1}H-NMR monitoring data [19,24], the following mechanism for the multicomponent reaction of salicylaldehyde **1**, 2-aminoprop-1-ene-1,1,3-tricarbonitrile **2**, and nitromethane **3** was suggested, as shown in Scheme 3.

The first stage of the process was a rapid formation of Knoevenagel adduct **5** with the expulsion of a hydroxide anion [25]. This hydroxide anion instantly catalyzed a rapid Pinner cyclization of adduct **5** into intermediate **6**. Then, the Michael addition of nitromethane **3** occurred to form anion **B**. Next, there were successive tautomerizations and Pinner-type cyclization to the final 2,4-diamino-5-(nitromethyl)-5*H*-chromeno[2,3-*b*]-pyridine-3-carbonitrile **4**.



Scheme 3. Mechanism of salicylaldehyde **1**, malononitrile dimer **2**, and nitromethane **3** transformation into chromeno[2,3-*b*]pyridine **4**. Catalytic cycles are simplified.

3. Materials and Methods

3.1. General Methods

The solvents and reagents were purchased from commercial sources and used as received. 2-Aminoprop-1-ene-1,1,3-tricarbonitrile **2** (malononitrile dimer) was obtained from malononitrile according to the literature [26].

The melting point was measured with Gallenkamp melting-point apparatus (Gallenkamp & Co., Ltd., London, UK). ^{1}H and ^{13}C-NMR spectra were recorded in DMSO-d_6 temperature. IR spectrum was registered with a Bruker ALPHA-T FT-IR spectrometer (Bruker Corporation, Billerica, MA, USA) in KBr pellets. The MS spectrum (EI = 70 eV) was obtained directly with a Kratos MS-30 spectrometer (Kratos Analytical Ltd., Manchester, UK). For elemental analysis, a 2400 Elemental Analyzer (Perkin Elmer Inc., Waltham, MA, USA) was used.

3.2. Multicomponent Synthesis of 2,4-Diamino-5-(nitromethyl)-5H-chromeno[2,3-b]pyridine-3-carbonitrile 4

Salicylaldehyde **1** (0.122 g, 1 mmol), 2-aminoprop-1-ene-1,1,3-tricarbonitrile **2** (0.132 g, 1 mmol) and nitromethane **3** (0.061 g, 1 mmol) were stirred in 5 mL of DMSO for 24 h at ambient temperature. After the reaction was completed, 15 mL of water was added to the solution. The formed solid was filtered, washed with well-chilled ethanol (3 mL × 2), and dried to isolate pure 2,4-diamino-5-(nitromethyl)-5*H*-chromeno[2,3-*b*]pyridine-3-carbonitrile **4**.

2,4-Diamino-5-(nitromethyl)-5H-chromeno[2,3-b]pyridine-3-carbonitrile (4): Yellowish solid; yield—73% (0.217 g); mp = 271–272 °C (decomp.) (from DMSO-H_2O); FTIR (KBr) cm^{-1}: 3466 (NH_2), 3337 (NH_2), 3247 (NH_2), 3153 (NH_2), 2205 (CN), 1637 (C–C Ar), 1600 (C–C Ar), 1568 (C–C Ar), 1229 (NO_2). ^{1}H-NMR (300 MHz, DMSO-d_6): δ 4.68 (d, ^3J = 4.8 Hz, 1H, CH_2), 4.86 (t, ^3J = 4.8 Hz, 1H, CH), 6.52 (s, 2H, NH_2), 6.78 (s, 2H, NH_2), 7.07 (d, ^3J = 8.0 Hz, 1H, CH Ar), 7.16 (t, ^3J = 8.0 Hz, 1H, CH Ar), 7.24–7.36 (m, 2H, 2 CH Ar) ppm; ^{13}C-NMR (75 MHz, DMSO-d_6): δ 32.6 (C(5)H), 70.7 (C(3)-CN), 79.3 (CH_2), 85.1 (C(4a)), 116.4 (C(9)H Ar), 120.3 (CN), 124.0 (2C, C(5a) and C(7)H Ar), 128.4 (C(8)H Ar), 128.9 (C(6)H Ar), 151.2 (C(9a)), 156.7 (C(2)-NH_2), 159.9 (C(4)-NH_2), 160.1 (C(1a)) ppm; MS (*m/z*, relative intensity %): 297 $[M]^+$ (3), 250 $[M - NO_2 - H]^+$ (3), 237 $[M - CH_2NO_2]^+$ (100), 77 $[C_6H_5]^+$ (5); Anal. calcd. for $C_{14}H_{11}N_5O_3$: C, 56.57; H, 3.73; N, 23.56%; found: C, 56.65; H, 3.77; N, 23.47%.

4. Conclusions

The title compound, 2,4-diamino-5-(nitromethyl)-5*H*-chromeno[2,3-*b*]pyridine-3-carbonitrile, was synthesized in good yield using the mild and efficient multicomponent method with simple implementation and equipment and available starting materials. The new synthesized compound was characterized by spectroscopic methods (NMR, IR and MS-EI), and elemental analysis.

Supplementary Materials: The following are available online, compound **4** spectra: Figure S1. ^{1}H-NMR spectrum of 2,4-diamino-5-(nitromethyl)-5*H*-chromeno[2,3-*b*]pyridine-3-carbonitrile **4** in DMSO-d_6; Figure S2. ^{13}C-NMR spectrum of 2,4-diamino-5-(nitromethyl)-5*H*-chromeno[2,3-*b*]pyridine-3-carbonitrile **4** in DMSO-d_6; Figure S3. MS (EI) spectrum of 2,4-diamino-5-(nitromethyl)-5*H*-chromeno[2,3-*b*]pyridine-3-carbonitrile **4**; Figure S4. IR spectrum of 2,4-diamino-5-(nitromethyl)-5*H*-chromeno[2,3-*b*]pyridine-3-carbonitrile **4.**

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