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Short Note

Dimethyl 2-(2,4-Diamino-3-cyano-5*H*-chromeno[2,3-*b*]pyridin-5-yl)malonate

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Abstract: Dimethyl sulfoxide (DMSO) is widely used as a solvent in organic synthesis and in pharmacology because of its low cost, stability, and non-toxicity. Multicomponent reactions are a powerful synthetic tool for the rapid and efficient construction of complicated molecular frameworks. In this communication, the multicomponent transformation of salicylaldehyde, malononitrile dimer, and dimethyl malonate in DMSO at room temperature was carefully investigated to give dimethyl 2-(2,4-diamino-3-cyano-5*H*-chromeno[2,3-*b*]pyridin-5-yl)malonate with good yield. The structure of the new compound was established by means of elemental analysis and mass, nuclear magnetic resonance, and infrared spectroscopy.

Keywords: salicylaldehyde; malononitrile dimer; dimethyl malonate; chromeno[2,3-*b*]pyridines; multicomponent reactions

Citation: Ryzhkova, Y.E.; Maslov, O.I.; Elinson, M.N. Dimethyl 2-(2,4-Diamino-3-cyano-5*H*-chromeno[2,3-*b*]pyridin-5-yl)malonate. *Molbank* **2022**, *2022*, M1308. https://doi.org/10.3390/M1308

Academic Editor: Raffaella Mancuso

Received: 14 December 2021
Accepted: 21 December 2021
Published: 22 December 2021

1. Introduction

Dimethyl sulfoxide (DMSO) is widely used as a solvent in organic synthesis and in pharmacology because of its low cost, stability, and non-toxicity [1]. However, in the last decade, DMSO has also attracted the attention of scientists as a source of oxygen, carbon, or sulfur in a wide range of organic reactions [2].

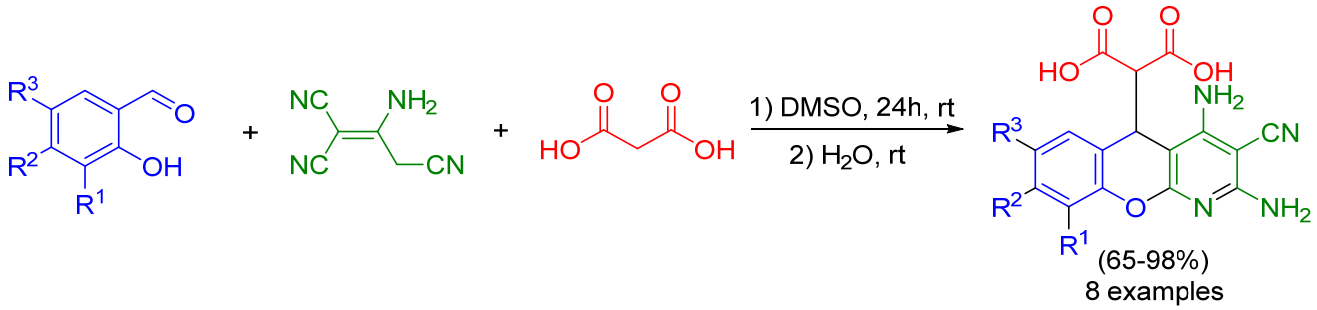
Multicomponent reactions (MCRs) are a powerful synthetic tool for the rapid and efficient construction of complicated molecular frameworks [3]. The advantages of MCRs over multistep synthesis include atom-economy and step-efficiency, which also reduce waste generation [4]. MCRs show a very high bond-forming index (BFI), as several non-hydrogen atom bonds are formed in one synthetic transformation [5]. Hence, MCRs are the best instrument for modern organic synthesis.

Chromeno[2,3-*b*]pyridines are the important classes of heterocyclic compounds from the point of view of medicinal chemistry as well as industry. Depending on the structure, they demonstrate different types of biological activity, such as antimicrobial [6], anticancer [7], antirheumatic [8], antimyopic [9], neuroprotective [10], and hypotensive [11] properties. In addition, chromeno[2,3-*b*]pyridines are known as inhibitors of the corrosion of mild steel [12]. Thus, the multicomponent synthesis of novel chromeno[2,3-*b*]pyridines is an important aim for modern organic chemistry.

In the synthesis of chromeno[2,3-*b*]pyridines, both multistep classical and multicomponent approaches [13] are applied. We have already published different multicomponent transformations leading to chromeno[2,3-*b*]pyridines [14–19].

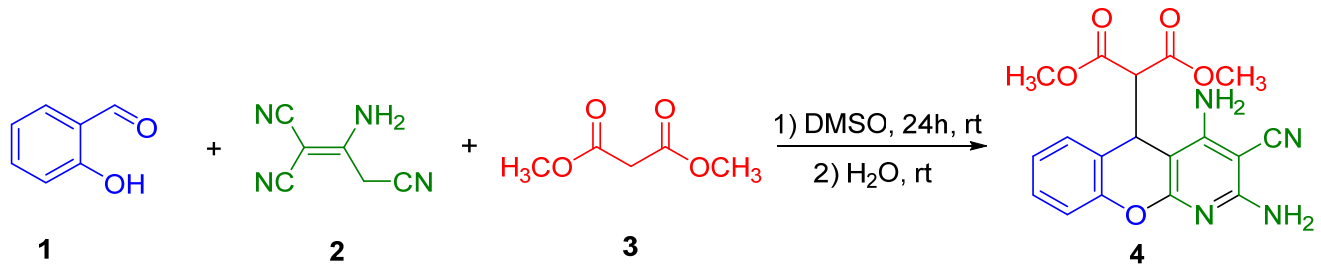
2. Results and Discussion

We previously carried out a multicomponent transformation of salicylaldehydes, 2-aminoprop-1-ene-1,1,3-tricarbonitrile, and malonic acid into 2-(2,4-diamino-3-cyano-5*H*-chromeno[2,3-*b*]pyridin-5-yl)malonic acids [20] (Scheme 1). This reaction was the first example of a multicomponent synthesis of chromeno[2,3-*b*]pyrnidines in DMSO.



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

Now, we wish to report our results that are a continuation of previous research. These results concern the efficient multicomponent transformation of salicylaldehyde **1**, 2-aminoprop-1-ene-1,1,3-tricarbonitrile **2**, and dimethyl malonate **3** into the previously unknown dimethyl 2-(2,4-diamino-3-cyano-5*H*-chromeno[2,3-*b*]pyridin-5-yl)malonate **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 dimethyl malonate **3**.

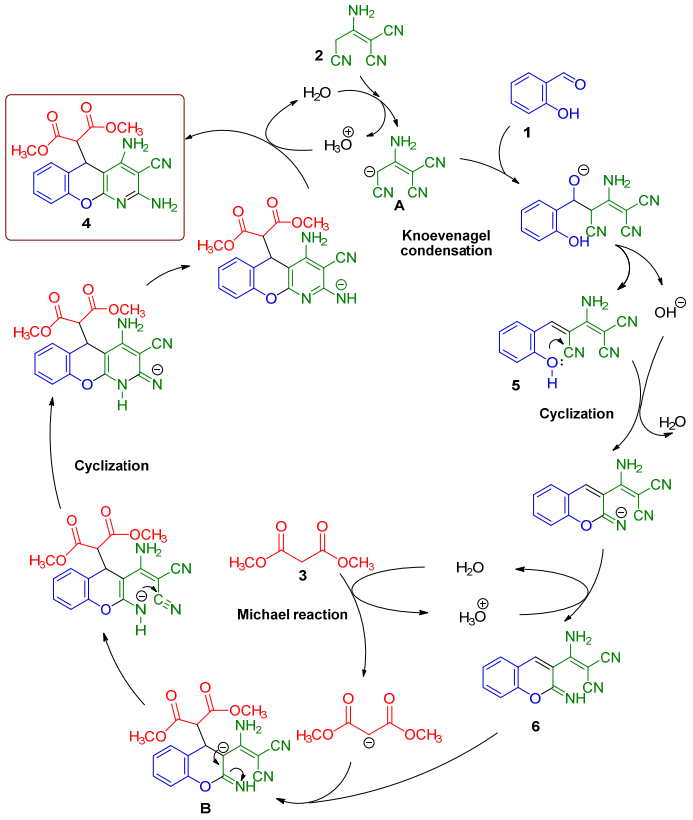
When the reaction in DMSO had finished, water was added to the reaction mixture and the final compound **4** was directly crystallized in pure form. Compound **4** was synthesized with 90% yield.

The BFI (bond forming index) of this process 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 compound **4** was confirmed by ^{1}H, ^{13}C NMR, and IR spectroscopy as well as mass spectrometry data and elemental analysis (Supplementary Materials). Only one set of signals was observed in ^{1}H and ^{13}C NMR spectra.

Taking into consideration the results of the ^{1}H NMR monitoring of the reaction of salicylaldehyde, malononitrile dimer, and malonic acid [20], the following mechanism for the multicomponent transformation of salicylaldehyde **1**, 2-aminoprop-1-ene-1,1,3-tricarbonitrile **2**, and dimethyl malonate **3** was proposed, as shown in Scheme 3.

The first stage of the process was a rapid formation of intermediate **5** with the expulsion of a hydroxide anion [21]. This hydroxide anion instantly catalyzed a rapid cyclization of intermediate **5** into intermediate **6**. Then, the Michael addition of dimethyl malonate **3** occurred to form anion **B**. Next, there were successive cyclization and isomerizations to the final dimethyl 2-(2,4-diamino-3-cyano-5*H*-chromeno[2,3-*b*]pyridin-5-yl)malonate **4**.



Scheme 3. Mechanism of salicylaldehyde **1**, malononitrile dimer **2**, and dimethyl malonate **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 as described in the literature [22].

The melting point was measured with a Gallenkamp melting-point apparatus (London, UK). ^{1}H and ^{13}C NMR spectra were recorded in DMSO-d_6 with a Bruker AM300 spectrometer (Billerica, MA, USA) at ambient temperature. The IR spectrum was registered with a Bruker ALPHA-T FT-IR spectrometer (Billerica, MA, USA) in KBr pellets. The MS spectrum (EI = 70 eV) was obtained directly with a Kratos MS-30 spectrometer (Manchester, UK). For elemental analysis, a 2400 Elemental Analyzer (Perkin Elmer Inc., Waltham, MA, USA) was used.

3.2. Multicomponent Synthesis of Dimethyl 2-(2,4-Diamino-3-cyano-5H-chromeno[2,3-b]pyridin-5-yl)malonate 4

Salicylaldehyde **1** (0.122 g, 1 mmol), 2-aminoprop-1-ene-1,1,3-tricarbonitrile **2** (0.132 g, 1 mmol), and dimethyl malonate **3** (0.132g, 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 mL), and dried to isolate pure dimethyl 2-(2,4-diamino-3-cyano-5*H*-chromeno[2,3-*b*]pyridin-5-yl)malonate **4**.

Dimethyl 2-(2,4-diamino-3-cyano-5H-chromeno[2,3-b]pyridin-5-yl)malonate (4). Yellowish solid; yield 90% (0.331 g); mp = 197–198 °C (decomp.) (from DMSO-H_2O); FTIR (KBr) cm^{-1}: 3483 (NH_2), 3384 (NH_2), 2199 (CN), 1749 (C=O), 1724 (C=O), 1639 (C–C Ar), 1594 (C–C Ar), 1237 (C–O), 1215 (C–O); ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.39 (s, 3H, COOMe), 3.57 (d, ^{3}J = 5.1 Hz, 1H, CH), 3.61 (s, 3H, COOMe), 4.92 (d, ^{3}J = 5.1 Hz, 1H, CH), 6.48 (s, 2H, NH_2), 6.60 (s, 2H, NH_2), 7.00–7.16 (m, 2H, 2 CH Ar), 7.28 (t, ^{3}J = 7.4 Hz, 1H, CH

Ar), 7.43 (d, ^{3}J = 7.4 Hz, 1H, CH Ar) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ 33.0 (C(5)H), 52.0 (COO$\underline{C}$H$_3$), 52.2 (COO$\underline{C}$H$_3$), 56.3 (CH malonic), 70.9 ($\underline{C}$(3)-CN), 87.8 (C(4a)), 116.1 (C(9)H Ar), 116.4 (CN), 121.8 (C(5a)), 123.5 (C(7)H Ar), 128.5 (C(6)H Ar), 129.3 (C(8)H Ar), 152.0 (C(9a)), 156.5 (C(4)-NH$_2$), 159.7 (C(2)-NH$_2$), 160.9 (C(1a)), 167.3 ($\underline{C}$OOCH$_3$), 167.4 ($\underline{C}$OOCH$_3$) ppm; MS (*m/z*, relative intensity %): 368 [M]$^+$ (1), 303 [C$_{15}$H$_{15}$N$_2$O$_5$]$^+$ (1), 277 [C$_{12}$H$_{13}$N$_4$O$_4$]$^+$ (2), 237 [M–C$_5$H$_7$O$_4$]$^+$ (100), 69 [C$_3$H$_5$N$_2$]$^+$ (5), 15 [CH$_3$]$^+$ (2); Elemental analysis. Calculated for C$_{18}$H$_{16}$N$_4$O$_5$: C, 58.69; H, 4.38; N, 15.21%; found: C, 58.79; H, 4.45; N, 15.14%.

4. Conclusions

The title compound, dimethyl 2-(2,4-diamino-3-cyano-5*H*-chromeno[2,3-*b*]pyridin-5-yl)malonate, was synthesized with good yield using the facile and efficient multicomponent approach with simple equipment and available starting compounds. The novel compound was characterized by spectroscopic methods (NMR, IR, and MS-EI) and elemental analysis.

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

Author Contributions: Conceptualization, Y.E.R. and M.N.E.; methodology, Y.E.R. and M.N.E.; investigation, Y.E.R. and O.I.M.; writing—original draft preparation, Y.E.R.; writing—review and editing, M.N.E.; supervision, M.N.E. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Data Availability Statement: The data for the compounds presented in this study are available in the Supplementary Materials of this article.

Conflicts of Interest: The authors declare no conflict of interest.

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