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Short Note

6′-Amino-5,7-dibromo-2-oxo-3′-(trifluoromethyl)-1′*H*-spiro[indoline-3,4′-pyrano[2,3-*c*]pyrazole]-5′-carbonitrile

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Abstract: The multicomponent reactions are environmentally benign synthetic methods of building-up of complex molecules and several levels of structural diversity for diverse applications. Spirooxindoles are an important synthetic target possessing extended biological activity and drug discovery applications. In this communication, the multicomponent transformation of 5,7-dibromoisatin, malononitrile, and 5-(trifluoromethyl)-2,4-dihydro-3*H*-pyrazol-3-one in EtOH at reflux in the presence of sodium acetate was carefully investigated to give 6′-amino-5,7-dibromo-2-oxo-3′-(trifluoromethyl)-1′*H*-spiro[indoline-3,4′-pyrano[2,3-*c*]pyrazole]-5′-carbonitrile in excellent yield. The structure of the new compound was established by means of elemental analysis, mass and nuclear magnetic resonance, and infrared spectroscopy.

Keywords: 5,7-dibromoisatin; malononitrile; 5-(trifluoromethyl)-2,4-dihydro-3*H*-pyrazol-3-one; spiro[indole-3,4′-pyrano[2,3-*c*]pyrazole]; multicomponent reactions

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1. Introduction

Multicomponent reactions (MCRs) are environmentally benign synthetic methods of the building-up of complex molecules and several levels of structural diversity for diverse applications [1]. Performing MCRs is well regarded as one of the potential techniques in achieving the greenness of a chemical process. The advantages of MCRs over multistep synthesis include atom-economy and step-efficiency, which reduce waste generation in particular [2]. MCRs show a very high bond-forming index (BFI) as several non-hydrogen atom bonds are formed in one synthetic transformation [3]. Hence, MCRs are a very promising synthetic instrument today.

The indole ring system is probably the most ubiquitous heterocycle in nature. Owing to the great structural diversity of biologically active indoles, it is not surprising that the indole ring system has become an important structural component in many pharmaceutical agents [4]. The numerous chemical compounds consisting of indole as a core nucleus exhibit such activities as anti-inflammatory [5], anticonvulsant [6], antidiabetic [7], antimicrobial [8], anticancer [9], and others.

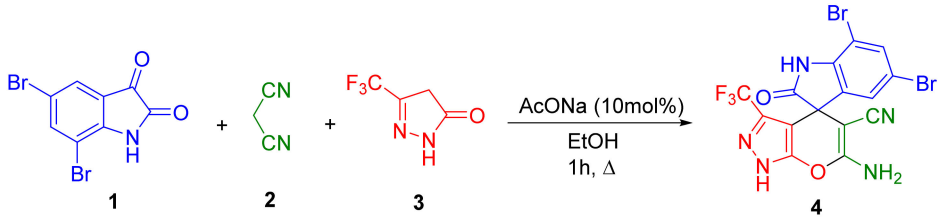
Pyrazole is one of the most popular rings in bioactive compounds, including drugs and agrochemicals [10]. Fluorinated pyrazoles play an important role in medicinal chemistry, drug discovery, agrochemistry, coordination chemistry, and organometallic chemistry [11].

Spirooxindoles are an important synthetic target possessing extended biological activity and drug discovery applications. In the modern broad range of pharmaceuticals, spiro compounds are not widely used, and spirooxindoles are absent. At the same time, this type of core is prevalent in a number of spiro leader-compounds and drug candidates with different directions of action [12], such as anti-cancer [13], antitumor [14], and cardiotonic [14]. Therefore, multicomponent synthesis of new spirooxindoles is a promising area of organic chemistry.

2. Results and Discussion

We previously carried out a multicomponent transformation of isatins, malononitrile, and different C-H acids into functionalized spirooxindoles [15–18]. These reactions were carried out both in solution and in 'on-solvent' and 'solvent-free' formats.

Now, we wish to report our results on the efficient multicomponent transformation of 5,7-dibromoisatin **1**, malononitrile **2**, and 5-(trifluoromethyl)-2,4-dihydro-3*H*-pyrazol-3-one **3** into the previously unknown 6′-amino-5,7-dibromo-2-oxo-3′-(trifluoromethyl)-1′*H*-spiro[indoline-3,4′-pyrano[2,3-*c*]pyrazole]-5′-carbonitrile **4** in boiling ethanol in the presence of sodium acetate for 1 h, as shown in Scheme 1.



Scheme 1. Reaction of 5,7-dibromoisatin **1**, malononitrile **2,** and 5-(trifluoromethyl)-2,4-dihydro-3*H*-pyrazol-3-one **3**.

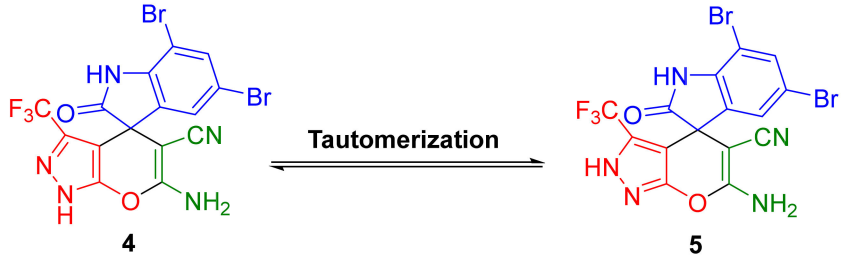
When the reaction was finished, the final compound **4** was directly crystallized in pure form. Compound **4** was synthesized in a 91% yield.

The BFI of this process was three, since three new bonds were formed in one stage, namely 2 C-C bonds, and 1 C-O bonds.

Previously, similar spiro[indole-3,4′-pyrano[2,3-*c*]pyrazoles] were obtained by a four-component reaction of trifluoacetoacetic ether, hydrazine, isatins, malononitrile, and 5-(trifluoromethyl)-2,4-dihydro-3*H*-pyrazol-3-ones; however, the isolated residue had to be purified by column chromatography [19]. Spiro[indole-3,4′-pyrano[2,3-*c*]pyrazoles] with a trifluoromethyl group can inhibit the enzyme *Plasmodial* serine hydroxymethyltransferase, which makes them promising antimalarial drugs [20].

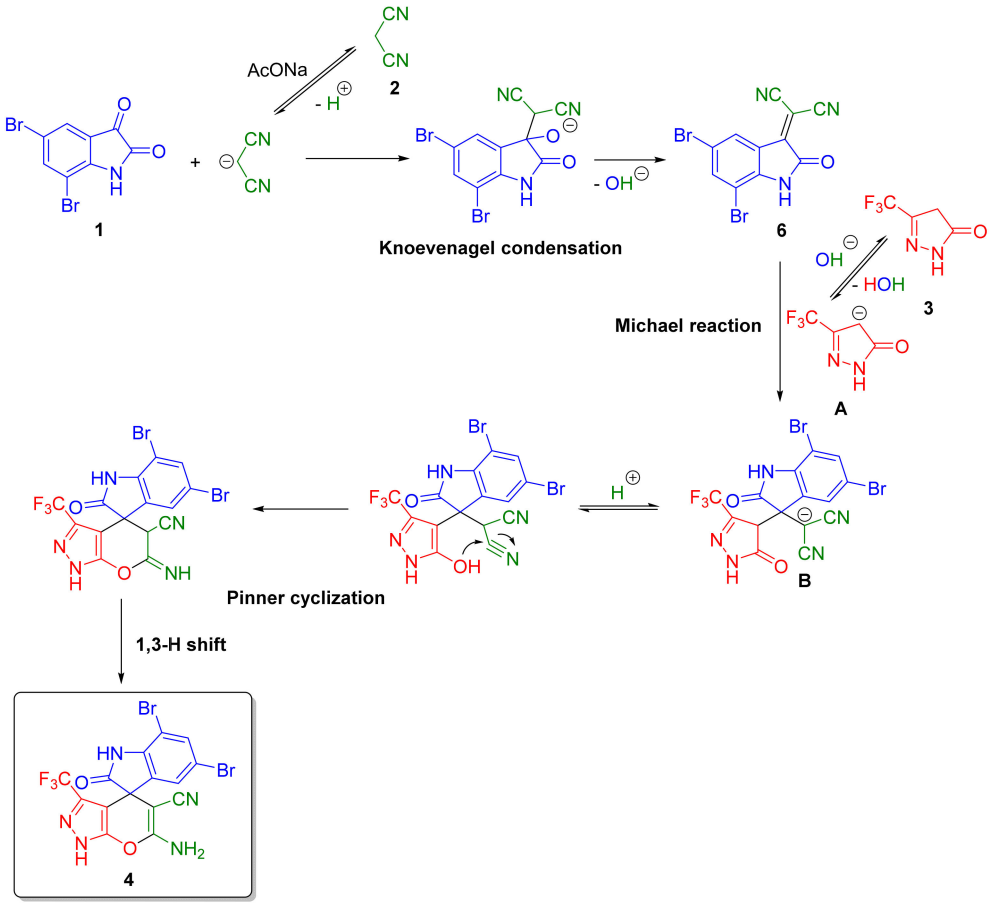
The structure of compound **4** was confirmed by ^{1}H, ^{13}C and ^{19}F NMR, and IR spectroscopy as well as mass spectrometry data and elemental analysis (Supplementary Materials). Only one set of signals was observed in ^{1}H, ^{13}C, and ^{19}F NMR spectra.

Signals from four carbon atoms in the ^{13}C spectrum (carbons of the pyrazole fragment) are not observed due to too large line broadening caused by the tautomerism of the pyrazole N–H proton (Scheme 2).



Scheme 2. Tautomerization of spiro[indole-3,4′-pyrano[2,3-*c*]pyrazole] **4**.

Taking into consideration our previous results [16,17] and literature data [19], the following mechanism for the multicomponent transformation of 5,7-dibromoisatin **1**, malononitrile **2**, and 5-(trifluoromethyl)-2,4-dihydro-3*H*-pyrazol-3-one **3** was proposed, as shown in Scheme 3.



Scheme 3. Mechanism of 5,7-dibromoisatin **1**, malononitrile **2**, and 5-(trifluoromethyl)-2,4-dihydro-3*H*-pyrazol-3-one **3** transformation into spiro[indole-3,4′-pyrano[2,3-*c*]pyrazole] **4**.

The first stage of the process is a rapid Knoevenagel condensation with the formation of intermediate **6** with the expulsion of a hydroxide anion [21]. This hydroxide anion instantly catalyzes a rapid Michael addition of electron-deficient intermediate **6** to anion **A**. Then, the resulting anion **B** is protonated and undergoes Pinner cyclization. Next, 1,3-proton shift occurs, leading to 6′-amino-5,7-dibromo-2-oxo-3′-(trifluoromethyl)-1′*H*-spiro[indoline-3,4′-pyrano[2,3-*c*]pyrazole]-5′-carbonitrile **4**.

3. Materials and Methods

3.1. General Methods

The solvents and reagents were purchased from commercial sources and used as received. 5,7-Dibromoisatin **1** was obtained from isatin according to the literature [22]. 5-(Trifluoromethyl)-2,4-dihydro-*3H*-pyrazol-3-one **3** was synthesized according to the standard procedure [23].

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 and acetone-d_6 with Bruker AM300 spectrometer (Bruker Corporation, Billerica, MA, USA) at ambient 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 6′-Amino-5,7-dibromo-2-oxo-3′-(trifluoromethyl)-1′H-spiro[indoline-3,4′-pyrano[2,3-c]pyrazole]-5′-carbonitrile 4

5,7-Dibromoisatin **1** (0.305 g, 1 mmol), malononitrile **2** (0.066 g, 1 mmol), 5-(trifluoromethyl)-2,4-dihydro-*3H*-pyrazol-3-one **3** (0.152 g, 1 mmol), and sodium acetate (0.008 g, 0.1 mmol) were refluxed in 3 mL of EtOH for 1 h. After the reaction was completed, the formed solid was filtered, washed with well-chilled ethanol (3 mL × 2 mL), and dried to isolate pure 6′-amino-5,7-dibromo-2-oxo-3′-(trifluoromethyl)-1′*H*-spiro[indoline-3,4′-pyrano[2,3-*c*]pyrazole]-5′-carbonitrile **4**.

6′-Amino-5,7-dibromo-2-oxo-3′-(trifluoromethyl)-1′H-spiro[indoline-3,4′-pyrano[2,3-c]pyrazole]-5′-carbonitrile (4). White solid; yield 91% (0.460 g); mp = 305–306 °C (decomp.) (from EtOH); FTIR (KBr) cm^{-1}: 3405 (N-H), 3316 (NH_2), 3176 (N-H), 2205 (CN), 1715 (C = O), 1654 (C-C Ar), 1163 (C-F), 1147 (C-F). ^{1}H NMR (300 MHz, DMSO-d_6):δ 7.51 (d, ^4J = 1.4 Hz, 1H, CH Ar), 7.61 (s, 2H, NH_2), 7.74 (d, ^4J = 1.4 Hz, 1H, CH Ar), 11.19 (s, 1H, NH isatin), 14.43 (br s, 1H, NH pyrazole) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ 48.4 (C(3)-CN), 55.2 (br s, C(4) spiro), 102.8 (C(7′)-Br Ar), 114.5 (C(5′)-Br Ar), 117.5 (CN), 127.0 (C(4′)H Ar), 134.0 (C(6′)H Ar), 136.0 (C(3a′) Ar), 140.7 (C(7a′) Ar), 161.1 (C(2)-NH_2), 177.0 (C = O) ppm (pyrazolone moiety C-signals were not detected due to tautomerism); ^{19}F NMR (282 MHz, acetone-d_6): δ –62.62 (s, CF_3) ppm; MS (*m/z*, relative intensity %): 507 [^{81}Br, ^{81}Br, M]$^+$ (26), 505 [^{81}Br, ^{79}Br, M]$^+$ (52), 503 [^{79}Br, ^{79}Br, M]$^+$ (27), 479 [^{81}Br, ^{81}Br, M - CN]$^+$ (63), 477 [^{81}Br, ^{79}Br, M - CN]$^+$ (100), 475 [^{79}Br, ^{79}Br, M - CN]$^+$ (45), 422 [^{81}Br, ^{81}Br, M - $C_3H_3N_2O$]$^+$ (12), 420 [^{81}Br, ^{79}Br, M - $C_3H_3N_2O$]$^+$ (25), 418 [^{79}Br, ^{79}Br, M - $C_3H_3N_2O$]$^+$ (12), 410 [^{81}Br, ^{81}Br, M - C_2F_3N]$^+$ (15), 408 [^{81}Br, ^{79}Br, M - C_2F_3N]$^+$ (30), 406 [^{79}Br, ^{79}Br, M - C_2F_3N]$^+$ (16), 355 [^{81}Br, ^{81}Br, $C_{11}H_5Br_2N_3O$]$^+$ (3), 353 [^{81}Br, ^{79}Br, $C_{11}H_5Br_2N_3O$]$^+$ (6), 351 [^{79}Br, ^{79}Br, $C_{11}H_5Br_2N_3O$]$^+$ (4), 229 [$C_8H_4F_3N_4O$]$^+$ (5), 152 [$C_4H_3F_3N_2O$]$^+$ (3); Anal. calcd. for $C_{15}H_6Br_2F_3N_5O_2$: C, 35.67; H, 1.20; N, 13.87%; found: C, 35.72; H, 1.23; N, 13.83%.

4. Conclusions

The title compound, 6′-amino-5,7-dibromo-2-oxo-3′-(trifluoromethyl)-1′*H*-spiro[indoline-3,4′-pyrano[2,3-*c*]pyrazole]-5′-carbonitrile, was synthesized in excellent yield using the simple and efficient multicomponent approach with available equipment and starting compounds. The previously unknown compound was characterized by spectroscopic methods (NMR, IR and MS-EI) and elemental analysis.

Supplementary Materials: Compound **4** spectra: ^{1}H NMR (Figure S1), ^{13}C NMR (Figure S2), ^{19}F NMR (Figure S3), IR (Figure S4), MS (Figure S5).

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