Short Note

$N^2,N^6$-Bis(6-iodo-2-methyl-4-oxoquinazolin-3(4H)-yl)pyridine-2,6-dicarboxamide

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Abstract: A green chemistry method was applied in the synthesis of $N^2,N^6$-bis(6-iodo-2-methyl-4-oxoquinazolin-3(4H)-yl)pyridine-2,6-dicarboxamide. The desired compound was synthesized mechanochemically, using a choline chloride-based deep eutectic solvent as a catalyst. The synthesis took 20 min and the new compound was characterized using different spectral methods.

Keywords: quinazolinone; pyridine; mechano-synthesis; deep eutectic solvents

1. Introduction

Quinazolinones, a group of nitrogen containing heterocyclic compounds, are very prominent medicinal and pharmaceutical scaffolds, showing a wide range of biological activities. Their activities include antibacterial [1–4], antifungal, antitumor [5–8], antidiabetic [9–11], anti-inflammatory [12–14] and many others. Many researchers these days are investigating their synthesis, finding the most efficient synthetic paths and synthesizing different derivatives and hybrids. Our investigation was based on the synthesis of quinazolinone–pyridine hybrids, since pyridine derivatives have also proven to be biologically active [15,16]. Keeping the green chemistry principles in mind [17], we applied a mechanochemical procedure in the synthesis of such hybrids. Since conventional synthetic methods usually have adverse effects on the environment due to the utilization of high volumes of volatile organic solvents [18], high energy consumption and waste production, green synthetic methods are becoming more prominent in recent times [19]. Mechanochemistry, as one of these methods, has found applications in many chemical processes. Mechanochemical reactions can be performed solvent-free and at low temperatures due to the combination of mechanical and chemical phenomena. Reaction times are usually reduced, while the post-synthetic procedures are minimal, with the overall process being faster and cleaner [20].

2. Results and Discussion

A new compound $N^2,N^6$-bis(6-iodo-2-methyl-4-oxoquinazolin-3(4H)-yl)pyridine-2,6-dicarboxamide was synthesized from 6-iodo-2-methyl-4H-benzo[d][1,3]oxazin-4-one (1) and pyridine-2,6-dicarboxhydrazide (2). First, 6-iodo-2-methyl-4H-benzo[d][1,3]oxazin-4-one (1) was synthesized in a microwave-assisted reaction according to Figure 1, as described in our previous work [21].

Figure 1. Microwave-assisted synthesis of 6-iodo-2-methyl-4H-benzo[d][1,3]oxazin-4-one.
Then, pyridine-2,6-dicarbohydrazide (2) was synthesized (Figure 2) according to Molnar et al. [22].

![Figure 2. Synthesis of pyridine-2,6-dicarbohydrazide.](image)

Afterwards, the synthesis of the desired compound was performed mechanochemically, using freshly prepared 6-iodo-2-methyl-4H-benzo[d][1,3]oxazin-4-one (1) and pyridine-2,6-dicarbohydrazide (2) and 1 mL of choline chloride:urea (1:2) deep eutectic solvent (DES) (Figure 3). The mixture was ball-milled for 20 min and upon completion of the reaction, water was added to the mixture. The new compound was recrystallized from methanol and obtained with 57% yield. The melting point, NMR and mass spectra were recorded.

![Figure 3. Synthesis of N²,N⁶-bis(6-iodo-2-methyl-4-oxoquinazolin-3(4H)-yl)pyridine-2,6-dicarboxamide.](image)

The 1H NMR spectra reveal some characteristic peaks. Quinazolinone C-2 methyl protons show singlet peaks at 2.51 ppm, aromatic protons peaks are found at 7.52-8.47 ppm, while –NH– protons are found at 12.24 and 12.15 ppm. The 13C NMR spectra also show peaks characteristic of a –CH3 carbon at 21.8 ppm and characteristic aromatic carbon peaks (full spectra available in Supplementary Materials).

This synthetic pathway has green character due to utilization of DES as a catalyst, which is biodegradable and non-toxic, while ball-milling proves to be time and energy efficient, yielding the final compound in high purity. The synthesis of similar compounds, using benzoxazinone and different amines, is usually performed conventionally, but in most cases requires longer times, higher temperatures or extensive purification [23–26].

### 3. Materials and Methods

All chemicals were purchased from commercial suppliers and were used as such. Choline chloride (99%) was purchased from Acros Organics (Geel, Belgium) and urea (p.a.) was purchased from Gram Mol. Aluminum plates coated with silica gel fluorescent indicator F254 were used for thin-layer chromatography, while benzene: acetone: acetic acid (8:1:1) was used as a mobile phase. TLC plates were monitored using HP-UVIS cabinet (Biostep GmbH, Burkhardtsdorf, Germany). The Electrothermal IA9100 melting point apparatus (Electrothermal Engineering Ltd., Rochford, UK) was used for melting point determination. NMR spectra were recorded on a Bruker 600 MHz spectrometer (Bruker Biospin, Rheinstetten, Germany). Mass spectra were recorded on an LC/MS/MS API 2000 (Foster City, CA, USA). IR spectra were recorded on an Agilent Cary 630 FTIR Spectrometer (Agilent Technologies, Santa Clara, CA, USA). The synthesis was performed using an Omni Bead Ruptor 12 Homogenizer (OMNI International, Kennesaw, GA, USA).

Synthesis of N²,N⁶-bis(6-iodo-2-methyl-4-oxoquinazolin-3(4H)-yl)pyridine-2,6-dicarboxamide.

To a reaction mixture of 6-iodo-2-methyl-4H-benzo[d][1,3]oxazin-4-one (1 mmol, 287.05 mg) and pyridine-2,6-dicarbohydrazide (0.5 mmol, 97.6 mg), 1 mL of ChCl: urea DES and 3 g of ceramic beads was added. The mixture was subjected to ball-milling for 20 min at 6 m/s.
The reaction was monitored by TLC (benzene:acetone:acetic acid 8:1:1) and quenched with water. Upon precipitation, the product was filtered off and recrystallized from methanol with 57% yield.

\[ M_p = 249–251 ^\circ C; \quad R_f = 0.58; \quad MS (ESI): \quad m/z = 732.10 [M-H] - (M_r = 733.26). \]

\[ ^1H \text{NMR (600 MHz, DMSO-}d_6\text{): } \delta / \text{ppm} 12.24 (1H, s, -NH-); 12.15 (1H, s, -NH-); 8.47–8.38 (5H, m, arom.); 8.22–8.18 (2H, m, arom.); 7.52 (2H, dd, \text{ } J = 8.6; 1.2 Hz, arom.); 2.51 (6H, s, -CH_3). \]

\[ ^13C \text{NMR (150 MHz, DMSO-}d_6\text{): } \delta / \text{ppm} 162.9; 162.8; 158.3; 158.1; 157.3; 147.1; 146.3; 144.2; 141.2; 135.1; 129.8; 127.1; 122.6; 92.7; 21.8. \]

4. Conclusions

A new derivative of dipicolinic acid was mechanochemically synthesized. The synthesis was performed using benzoxazinone, pyridine-2,6-dicarbohydrazide and choline chloride: urea DES as a catalyst, and was performed in 10 min. Our method for this synthesis is green, efficient and short.

Supplementary Materials: The following supporting information can be downloaded online, Figure S1: \(^1H\) NMR spectra of N\(^2\),N\(^6\)-bis(6-iodo-2-methyl-4-oxoquinazolin-3(4\(H\))-yl)pyridine-2,6-dicarboxamide; Figure S2: Mass spectra of N\(^2\),N\(^6\)-bis(6-iodo-2-methyl-4-oxoquinazolin-3(4\(H\))-yl)pyridine-2,6-dicarboxamide; Figure S3: \(^13C\) NMR spectra of N\(^2\),N\(^6\)-bis(6-iodo-2-methyl-4-oxoquinazolin-3(4\(H\))-yl)pyridine-2,6-dicarboxamide; Figure S4: IR spectra of N\(^2\),N\(^6\)-bis(6-iodo-2-methyl-4-oxoquinazolin-3(4\(H\))-yl)pyridine-2,6-dicarboxamide; Molfile of N\(^2\),N\(^6\)-bis(6-iodo-2-methyl-4-oxoquinazolin-3(4\(H\))-yl)pyridine-2,6-dicarboxamide.

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