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Short Note

2,2′-((1,4-Dimethoxy-1,4-dioxobutane-2,3-diylidene) bis(azanylylidene))bis(quinoline-3-carboxylic acid)

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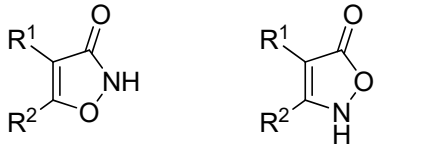
Abstract: The title compound, 2,2′-((1,4-dimethoxy-1,4-dioxobutane-2,3-diylidene)bis(azanylylidene)) bis(quinoline-3-carboxylic acid) was synthesized from isoxazolo[3,4-*b*]quinolin-3(1*H*)-one and dimethyl acetylenedicarboxylate (DMAD) via a double aza-Michael addition followed by [1,3]-H shifts. The product was characterized by infrared and nuclear magnetic resonance spectroscopy, as well as elemental analysis and high-resolution mass spectrometry (HRMS). The proposed reaction mechanism was rationalized by density functional theory (DFT) calculations.

Keywords: [1,3]-H shift; aza-Michael addition; DFT calculations; dimethyl acetylenedicarboxylate; isoxazolo[3,4-*b*]quinolin-3(1*H*)-one

1. Introduction

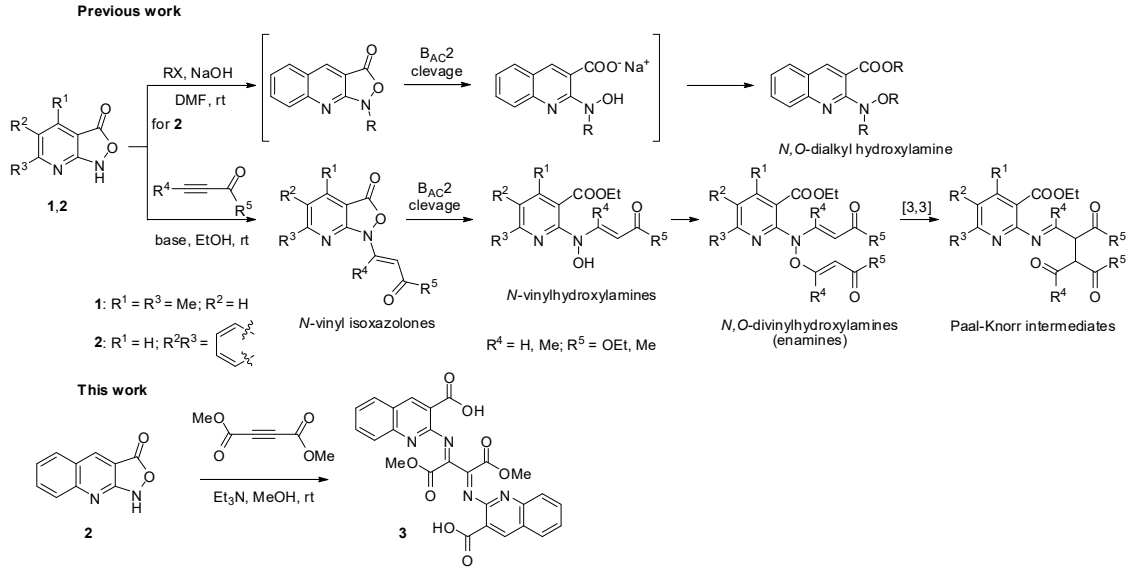
Isoxazol-3(2*H*)-one and isoxazol-5(2*H*)-one derivatives (Figure 1) represent an extensive class of heterocyclic ring systems found in natural products and building blocks employed in medicinal chemistry. They may be treated as useful tools in organic synthesis since they are small and easy to functionalize molecules that can be utilized to design novel bioactive compounds. It has been proven that these synthetic products exhibit antibacterial [1–8], antifungal [7–16], antitubercular [3], anticancer [3,6,17,18], antileucemic [5], antinflammatory [19–21], antiviral [22], anticonvulsant [1], antioxidant [2,7], and antiandrogenic [23,24] properties. They may act as inhibitors of p38 MAP kinases [25], protein kinase C [26], and protein-tyrosine phosphatase 1B, which consequently cause antiobesity effect [27,28]. They also find applications as $GABA_A$ receptor ligands [29] and glutamate receptor agonists [30–32], therefore they can affect learning and memory processes. Despite the molecular mechanism of antifungal action of isoxazol-5(2*H*)-ones such as TAN-950A [16] and drazoxolon [8,15] has not been established, it should be underlined that structurally similar antimicrobial oxazolidones such as posizolid, tedizolid, radezolid and linezolid or cycloserine serve as inhibitors of protein synthesis that prevent binding of *N*-formylmethionyl-tRNA to the ribosome. [33].



isoxazol-3(2*H*)-one isoxazol-5(2*H*)-one

Figure 1. The structure of isoxazolone derivatives.

Recently, our research group reported antibacterial [34] and antifungal [35] *N*-substituted derivatives of 4,6-dimethylisoxazolo[3,4-*b*]pyridin-3(1*H*)-one **1**, which were obtained in N1-alkylation, N1-acylation, and N1-sulfonation reactions. Moreover, we have implemented compound **1** and its benzo analogue, isoxazolo[3,4-*b*]quinolone-3(1*H*)-one **2**, to tandem Mannich—electrophilic amination reactions with formaldehyde and (fluoro)quinolones as secondary amines to obtain hybrid quinolone-based quaternary ammonium compounds with proved antibacterial and antibiofilm activities along with enhanced hydrophilic properties [36,37]. Furthermore, our studies aimed at reactivity exploration of isoxazolones proved that under alkaline conditions the said heterocyclic ring system (**2**) undergoes N1-alkylation followed by bimolecular base-catalyzed acyl-oxygen cleavage ($B_{AC}2$) and *O*-alkylation to yield *N*,*O*-dialkyl hydroxylamines (Scheme 1) [38]. Finally, we found that compounds **1** and **2** react with α,β-acetylenic carbonyl compounds (Michael acceptors) to give *N*-vinyl isoxazolones, which transform into *N*-vinylhydroxylamines by means of $B_{AC}2$ cleavage of C-O bond. The later react with an excess of Michael acceptors to yield *N*,*O*-divinylhydroxylamines (enamines) that undergo [3,3]-sigmatropic rearrangement to give Paal–Knorr intermediates (Scheme 1) [39]. These findings prompted us to examine the aza-Michael addition reaction of isoxazolone **2** to double activated electron-deficient acetylene, i.e., dimethyl acetylenedicarboxylate (DMAD).



Scheme 1. Base-promoted reactivity of isoxazolones.

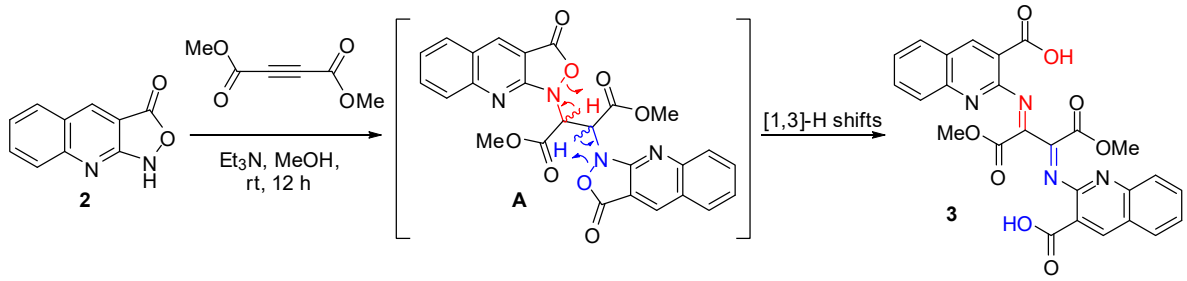
Herein, we describe a facile approach to 2,2′-((1,4-dimethoxy-1,4-dioxobutane-2,3-diylidene)bis (azanylylidene))bis(quinoline-3-carboxylic acid) **3** along with its characterization by experimental methods such as ^{1}H-NMR, IR, HRMS, and elemental analysis, as well as theoretical DFT calculations.

2. Results and discussion

2.1. Chemistry

We have performed the reaction of isoxazolone **2** with DMAD in anhydrous methanol at room temperature. Triethylamine was used as a base to deprotonate the acidic isoxazolone ring and hence form an ambident nucleophile capable to serve as a Michael donor. We reasoned that in the case of the reaction between compound **2** and double activated acetylene derivatives such as DMAD, dual addition to the Michael acceptor would occur (product **A**, Scheme 2). Unexpectedly, the isolated compound proved alternate structure as evidenced by ^{1}H-NMR spectrum (Supplementary Materials). The analysis of the spectrum revealed a lack of the aliphatic signal of the methine CH groups as depicted in structure **A**. Instead, two acidic protons were observed as broad singlet at δ = 13.85. Presumably, the initial step of the reaction sequence involved nucleophilic attacks of isoxazolones on the α,β-unsaturated carbonyl

compound. The initially formed intermediate **A** undergoes base-promoted [1,3]-hydrogen shifts with isoxazolone rings cleavage to yield 2,3-diiminosuccinate derivative **3**. The elucidated structure was supported by the results of the high-resolution mass spectrometry and elemental analysis.

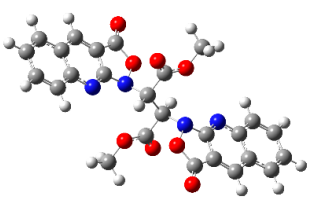
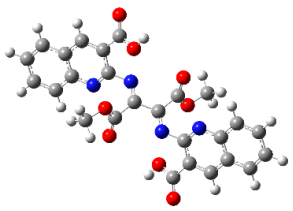


Scheme 2. The synthesis of **3** (2,2′-((1,4-dimethoxy-1,4-dioxobutane-2,3-diylidene)bis(azanylylidene)) bis(quinoline-3-carboxylic acid).

2.2. DFT Calculations

Quantum-chemical calculations were carried out to rationalize the formation of product **3**. The results obtained with density functional calculations (DFT) revealed that compound **3** is more favorable than the double Michael addition product **A**, both in gas phase and in the solvent (Table 1). Hence, the data obtained with use of B3LYP, ωB97XD, and APFD methods indicate that isomer **3** is 36.8 to 51.4 kcal/mol more stable than the intermediate **A**. Albeit the predictions are to some extent sensitive to variation of the functional type applied, the results unequivocally prove that the base-promoted [1,3] proton shifts that comprise isoxazolone ring opening transformations are intensely exothermic.

Table 1. Relative electronic energies (ΔE), and Gibbs free energies (ΔG) for isomers **A** and **3** calculated using B3LYP, ωB97XD, and APFD density functionals and 6-31G+(d) basis set in vacuum and with PCM (MeOH) solvation model.

Relative Energy		
Vacuum	**A**	**3**
ΔE (kcal/mol)		
B3LYP	0	−46.5
ωB97XD	0	−40.5
APFD	0	−36.8
ΔG (kcal/mol)		
B3LYP	0	−50.9
ωB97XD	0	−45.7
APFD	0	−40.6
MeOH	**A**	**3**
ΔE (kcal/mol)		
B3LYP	0	−47.8
ωB97XD	0	−42.2
APFD	0	−38.4
ΔG (kcal/mol)		
B3LYP	0	−51.4
ωB97XD	0	−47.4
APFD	0	−41.1

3. Materials and Methods

3.1. General Methods

All reagents and solvents were purchased from commercial sources (Acros Organics, Geel, Belgium; Alfa-Aesar, Haverhill, MA, USA; or Sigma-Aldrich, Saint Louis, MO, USA) and used without further purification. Isoxazolo[3,4-*b*]quinolin-3(1*H*)-one **2** was obtained according to the known procedure [40,41]. Analytical TLC was performed on silica gel Merck 60 F254 plates (0.25 mm) with UV light visualization. Melting point was determined on an X-4 melting point apparatus with a microscope and was uncorrected. The IR spectrum was recorded on a Thermo Scientific Nicolet 380 FT-IR spectrometer. The ^{1}H NMR spectrum was registered on a Varian Unity Plus 500 MHz spectrometer. ^{1}H NMR data were internally referenced to DMSO-d_6 (2.50 ppm). The ESI-MS spectra were recorded on Shimadzu single quadrupole LCMS 2010 eV mass spectrometer (Shimadzu, Kyoto, Japan). The HRMS spectra were obtained using Agilent LC/MS Q-TOF 6550 mass spectrometer (Agilent Technologies, Santa Clara, CA, USA). Elemental analysis was performed with Elementar Vario El Cube CHNS (Elementar Analysensysteme GmbH, Langenselbold, Germany).

3.2. Synthesis of 2,2′-((1,4-dimethoxy-1,4-dioxobutane-2,3-diylidene)bis(azanylylidene))bis(quinoline-3-carboxylic acid) (**3**)

Isoxazolo[3,4-*b*]quinolin-3(1*H*)-one **2** (0.186 g, 1 mmol), dimethyl acetylenedicarboxylate (0.123 mL, 1 mmol), and triethylamine (0.139 mL, 1 mmol) were dissolved in 10 mL of anhydrous methanol. The reaction was stirred at room temperature and the reaction progress was monitored by TLC (chloroform). After 12 h, the reaction mixture was concentrated to 5 mL under reduced pressure. Upon cooling, the precipitated solid was filtered off and washed with diethyl ether (3 × 3 mL). The product was obtained as a yellow solid. Yield 0.162 g (63%); mp 240 °C (with decomposition); IR (KBr) ν_{max} 2952, 1747, 1736, 1627, 1610, 1574, 1557, 1454, 1204, 1133, 1064, 787, 759 cm^{-1}; ^{1}H-NMR (500 MHz, DMSO-D$_6$) δ 3.76 (s, 6H, OCH_3), 7.35 (t, *J* = 7.8 Hz, 2H, CH), 7.41 (d, *J* = 7.8 Hz, 2H, CH), 7.79 (t, *J* = 7.8 Hz, 2H, CH), 7.99 (d, *J* = 7.8 Hz, 2H, CH), 8.71 (s, 2H, CH), 13.65 (bs, 2H, COOH); ESI-MS positive ionization *m/z* 515 [M + 1]$^{+}$, negative ionization *m/z* 513 [M − 1]$^{-}$; HRMS *m/z* 515.1194 [M + 1]$^{+}$ (calcd for $C_{26}H_{19}N_4O_8^{+}$, 515.1197); anal. C 59.61, H 3.59, N 10.74%, calcd for $C_{26}H_{18}N_4O_8 \cdot 0.5H_2O$, C 59.66, H 3.66, N 10.70%.

3.3. DFT Calculations

All calculations have been performed with the Gaussian 16 [42] using standard algorithms and thresholds. The hybrid Becke-3–Lee–Yang–Parr functional (B3LYP) [43], long-range-corrected hybrid functional ωB97XD [44], as well as Austin–Frisch–Petersson hybrid density functional with dispersion (APFD) [45] were utilized. The bulk solvent effects were taken into account for the DFT calculations by means of polarizable continuum model (IEF-PCM) [46]. The 6-31G+(d) standard basis set has been used in the course of this study. The geometry optimizations for the studied molecules were carried out in their ground states with the inclusion of solvent effects. Vibrational analyses were used to verify that the optimized structures correspond to local minima on the energy surface. Gibbs energies including zero-point corrections, temperature corrections, and vibrational energies were computed for standard conditions (T = 298.15 K, P = 1.0 atm) using the harmonic oscillator approximation.

4. Conclusions

In summary, we have shown that isoxazolone **2** in the presence of triethylamine reacts with highly electrophilic DMAD via double aza-Michael addition followed by [1,3]-H shifts to give 2,2′-((1,4-dimethoxy-1,4-dioxobutane-2,3-diylidene)bis(azanylylidene))bis(quinoline-3-carboxylic acid) **3** in good yield. The structure of compound **3** was confirmed by spectroscopic characterization. Finally, compound **3** was proven to be significantly more stable than intermediate **A** as evidenced by DFT calculations.

Supplementary Materials: The following are available online. ^{1}H-NMR spectrum of compound **3** and HRMS Qualitative Compound Report.

Author Contributions: Conceptualization, J.F. and J.S.; Synthesis, J.F.; Molecule characterization, J.F. and P.W.; NMR data analysis, J.F.; DFT calculation and visualization, K.G. and J.S.; Data evaluation, J.F., K.G., P.W., and J.S.; Writing—original draft preparation, J.F.; Writing—review and editing, J.S.; Supervision and project administration, J.S. All authors read and approved the final manuscript.

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Conflicts of Interest: The authors declare no conflict of interest. The funders had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript, or in the decision to publish the results.

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