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Short Note

tert-Butyl 2-Amino-3-cyano-5-oxo-4-phenyl-5,7-dihydropyrano[2,3-*c*]pyrrole-6(4*H*)-carboxylate

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Abstract: Organocatalyzed synthesis of *tert*-butyl 2-amino-3-cyano-5-oxo-4-phenyl-5,7-dihydropyrano [2,3-*c*]pyrrole-6(4*H*)-carboxylate, prepared from Boc-tetramic acid and benzylidenemalononitrile, is disclosed. Two bifunctional noncovalent organocatalysts were employed, yielding the product as a racemic mixture in both cases. The structure of the new synthesized compound was confirmed by high resolution mass-spectrometry, ^{1}H- and ^{13}C-NMR, HSQC, and IR spectroscopy.

Keywords: bifunctional noncovalent organocatalysts; tetramic acids; Michael addition; pyrano[2,3-*c*]pyrrole; benzylidenemalononitrile

Citation: Hozjan, M.; Ciber, L.; Požgan, F.; Svete, J.; Štefane, B.; Grošelj, U. *tert*-Butyl 2-Amino-3-cyano-5-oxo-4-phenyl-5,7-dihydropyrano[2,3-*c*]pyrrole-6(4*H*)-carboxylate. *Molbank* **2023**, *2023*, M1575. https://doi.org/10.3390/M1575

Academic Editors: Fawaz Aldabbagh and Hideto Miyabe

Received: 30 November 2022
Revised: 23 December 2022
Accepted: 31 January 2023
Published: 3 February 2023

1. Introduction

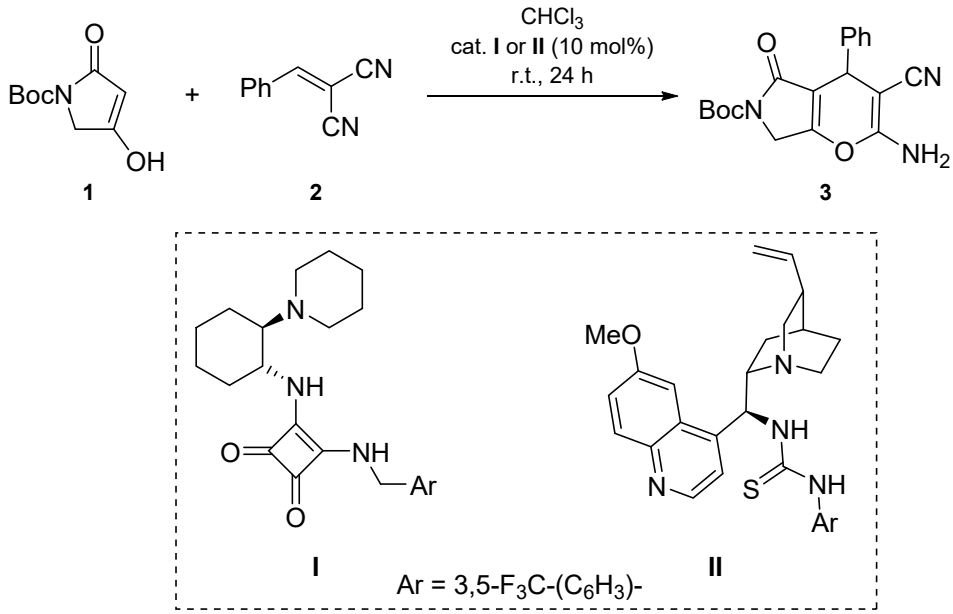
Tetramic acids (pyrrolidine-2,4-dione derivatives) represent an important, structurally diverse group of naturally occurring compounds isolated from various terrestrial and marine species, such as sponges, bacteria, and fungi. Both naturally occurring tetramic acids and their synthetic analogues attracted considerable attention due to their diverse and promising bioactivities [1–5].

Different synthetic protocols have been applied for the construction of the tetramic acid scaffold [6]. C-3/5 unsubstituted tetramic acids are conveniently prepared in two steps via the C-acylation reaction of Meldrum's acid with activated, *N*-protected α-amino acid followed by thermal decomposition of the meldrumate intermediate [7–11]. C-3/5 unsubstituted tetramic acids represent viable building blocks for the construction of libraries of more complex tetramic acid derivatives with potentially beneficial biological activities.

Annulation of either acyclic or (hetero)cyclic Michael acceptors with malononitrile is a convenient approach for the stereoselective synthesis of amino-cyano-substituted 4*H*-pyran heterocycles and their fused analogues [12–15]. In continuation of our research on the implementation of pyrrolone derivatives in organocatalyzed asymmetric transformations, [16–20] we herein report the application of *N*-Boc substituted tetramic acids **1** in the construction of dihydropyrano[2,3-*c*]pyrrole heterocycle **3** via organocatalyzed conjugative addition to benzylidenemalononitrile (**2**) followed by cyclization.

2. Results and Discussion

Recently, we reported the application of C-3/5 unsubstituted tetramic and tetronic acid derivatives in the organocatalyzed alkylation with *trans*-β-nitrostyrene derivatives and their aliphatic analogues [21]. Among the screened catalysts, the best results were obtained with cyclohexane-1,2-diamine derived squaramide catalyst **I** [22], yielding 1,4-addition products with enantioselectivities up to 94% *ee*. In continuation of our studies on the implementation of tetramic acid derivatives in organocatalyzed functionalizations, benzylidenemalononitrile (**2**) was applied as the Michael acceptor in the reaction with Boc-tetramic acid **1** [21] using **I** as the catalyst (Scheme 1). Dihydropyrano[2,3-*c*]pyrrole **3** was formed in 36% yield, presumably via the initial Michael addition, followed by 6-*exo-dig* enolate-to-nitrile cyclisation, and final tautomerization of the imine into enamine.



Scheme 1. Organocatalyzed synthesis of dihydropyrano[2,3-*c*]pyrrole **3**.

Unexpectedly, the product **3** was formed as a racemate, as confirmed by HPLC analysis. Repeating the reaction with quinuclidine-derived thiourea catalyst **II** [23] furnished dihydropyrano[2,3-*c*]pyrrole **3** in 32% yield as a racemate as well. Other organocatalysts have not been employed. Enantiomerically enriched dihydropyrano[3,2-*b*]pyrrole analogues have been successfully prepared via organocatalyzed annulation of arylidene-Δ^2-pyrrolin-4-ones with malononitrile [20]. For the synthesis of racemic dihydropyrano[2,3-*c*]pyrroles, an achiral organocatalyst, 3-((3,5-bis(trifluoromethyl)benzyl)amino)-4-((2-(dimethylamino)ethyl)amino)cyclobut-3-ene-1,2-dione, could be used [24].

The structure of compound **3** was confirmed by spectroscopic methods (^{1}H- and ^{13}C-NMR, HSQC, IR, and high-resolution mass spectrometry (HRMS)). The racemic nature of product **3** was confirmed by HPLC analysis.

In conclusion, dihydropyrano[2,3-*c*]pyrrole **3** was successfully synthesized as a racemic mixture from Boc-tetramic acid **1** and benzylidenemalononitrile (**2**). In view of the commercial availability of arylidene-malononitrile derivatives and straightforward preparation of tetramic acid derivatives from amino acids [21], a library of (racemic) dihydropyrano[2,3-*c*]pyrroles can easily be prepared and studied further.

3. Materials and Methods

Solvents for extractions and chromatography were of technical grade and were distilled prior to use. Extracts were dried over technical grade anhydrous Na_2SO_4. Melting points were determined on a Kofler micro hot stage and on SRS OptiMelt MPA100—Automated Melting Point System (Stanford Research Systems, Sunnyvale, CA, USA). The NMR spectra were obtained on a Bruker UltraShield 500 plus (Bruker, Billerica, MA, USA) at 500 MHz for ^{1}H and 126 MHz for ^{13}C nucleus, using DMSO-d_6 and $CDCl_3$ with TMS as the internal standard, as solvents. Mass spectra were recorded on an Agilent 6224 Accurate Mass TOF LC/MS (Agilent Technologies, Santa Clara, CA, USA), IR spectra on a Perkin-Elmer Spectrum BX FTIR spectrophotometer (PerkinElmer, Waltham, MA, USA). Column chromatography (CC) was performed on silica gel (Silica gel 60, particle size: 0.035–0.070 mm (Sigma-Aldrich, St. Louis, MI, USA)). HPLC analyses were performed on an Agilent 1260 Infinity LC (Agilent Technologies, Santa Clara, CA, USA) using CHIRALPAK AD-H (0.46 cm ø × 25 cm) as the chiral column (Chiral Technologies, Inc., West Chester, PA, USA). All the commercially available chemicals used were purchased from Sigma-Aldrich (St. Louis, MI, USA).

Organocatalysts **I** [22], **II** [23] and tetramic acid, *tert*-butyl 4-hydroxy-2-oxo-2,5-dihydro-1*H*-pyrrole-1-carboxylate (**1**) [21], were prepared following the literature procedures.

*Synthesis of tert-Butyl 2-Amino-3-cyano-5-oxo-4-phenyl-5,7-dihydropyrano[2,3-c]pyrrole-6(4H)-carboxylate (**3**)*

To a mixture of *tert*-butyl 2,4-dioxopyrrolidine-1-carboxylate (**1**) (49.1 mg, ω = 81% (the purity of tetramic acid **1** was determined by ^{1}H-NMR analysis using 1,3,5-trimethoxybenzene as the internal standard [21]), 0.20 mmol), benzylidenemalononitrile (**2**) (46.3 mg, 0.30 mmol), and organocatalyst **I** (10.1 mg, 0.02 mmol) or **II** (10.1 mg, 0.02 mmol), chloroform (1 mL) was added. The reaction mixture under argon was left to stir at 25 °C for 24 h. Volatile components were evaporated in vacuo. The residue was purified by column chromatography (Silica Gel 60; 1. EtOAc/petroleum ether = 1:2 to remove the nonpolar impurities, 2. EtOAc to elute the product **3**). Fractions containing product **3** were combined and volatile components evaporated in vacuo. Product **3** formed as a racemic mixture. Yield: 25.4 mg (0.0720 mmol, 36%) of white solid; mp 166–169 °C. EI-HRMS: *m/z* = 298.0821 (M-*t*Bu)H$^+$; $C_{15}H_{12}N_3O_4$ requires: *m/z* = 298.0822 (M-*t*Bu)H$^+$; ν_{max} 3479, 3310, 2978, 2198, 1761, 1703, 1630, 1577, 1455, 1419, 1383, 1343, 1310, 1265, 1252, 1199, 1148, 1093, 983, 946, 915, 841, 821, 804, 773, 735, 700, 654, 623 cm^{-1}. ^{1}H-NMR (500 MHz, DMSO-d_6): δ 1.43 (*s*, 9H, *t*Bu); 4.24 (*s*, 1H); 4.42 (*dd*, *J* = 1.9; 17.7 Hz, 1H); 4.51 (*dd*, *J* = 1.0; 17.7 Hz, 1H); 7.22–7.29 (*m*, 5H); 7.31–7.36 (*m*, 2H). ^{13}C-NMR (126 MHz, DMSO-d_6): δ 27.70, 35.23, 46.31, 57.80, 81.87, 108.51, 119.47, 127.13, 127.83, 128.40, 142.11, 148.95, 159.20, 161.81, 164.81. HPLC: Chiralpak AD-H, *n*-Hexane/*i*-PrOH = 90:10, flow rate 1.0 mL/min, λ = 230 nm. Enantiomers: *t*R = 13.5 min; 25.9 min—racemate (supplementary materials).

Supplementary Materials: Synthesis and characterization data; HPLC data; Copies of ^{1}H- and ^{13}C-NMR spectra; Copies of HRMS reports; IR spectra.

Author Contributions: Conceptualization, L.C., U.G., J.S. and B.Š.; methodology, L.C. and U.G.; software, L.C., U.G., J.S. and B.Š.; validation, L.C., U.G., J.S., F.P. and B.Š.; formal analysis, U.G., M.H. and L.C.; investigation, M.H. and U.G.; resources, L.C., U.G. and J.S.; data curation, L.C., U.G., J.S. and B.Š.; writing—original draft preparation, U.G., J.S. and B.Š.; writing—review and editing, L.C., U.G., J.S., F.P. and B.Š.; visualization, L.C., U.G., B.Š. and J.S.; supervision, U.G.; project administration, U.G. and J.S.; funding acquisition, U.G. and J.S. All authors have read and agreed to the published version of the manuscript.

Funding: This research was funded by the Slovenian Research Agency through grant P1-0179.

Data Availability Statement: Not applicable.

Acknowledgments: We thank the EN-FIST Centre of Excellence, Dunajska 156, 1000 Ljubljana, Slovenia, for the use of their BX FTIR spectrophotometer and Agilent 1260 Infinity LC for the HPLC analyses.

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

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