Tetramic acids and indole derivatives from amino acid β -keto esters. Fine-tuning the conditions of the key Cu-catalyzed reaction

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Abstract: 1,3,5-Trisubstituted tetramic acids and 2,3-disubstituted indole derivatives were prepared from β -keto esters derived from amino acids by their reaction with iodophenyl-2-trifluoroacetylamine under Cu-catalysis. Both heterocyclic systems were generated from the same starting materials by choice of the appropriate reaction conditions.

Keywords: 2,3-Disubstituted indoles, Tetramic acids, β -Keto esters, Amino acids, Diversity oriented synthesis

Diversity-Oriented Synthesis (DOS) strategies have successfully been used to identify new ligands for a variety of targets, including protein-protein interactions.¹ These strategies provide skeletal, appendage and stereochemical diversity to give access to collections of complex and diverse small molecules. In the search for bioactive compounds, special efforts have also been directed to develop libraries based on privileged scaffolds, structural motifs common to bioactive molecules, such as indole, quinolone, benzimidazole, dihydropyridine, dihydropyrimidine, benzodiazepine, and others.² Although DOS usually explores the chemical space not occupied by synthetic drugs and natural products, some DOS-based strategies around privileged scaffolds have been described.^{1a,3} These strategies populate the chemical space through the creation of new core skeletons that have embedded privileged motifs, or by generating innovative substitution patterns on privileged structures.

Within privileged scaffolds, the indole ring is probably one of the most important structures in drug discovery,⁴ as well as one of the heterocyclic systems more commonly found in natural products.⁵ Therefore, any method aimed at the preparation of innovative indole derivatives is of invaluable interest in medicinal chemistry. In a similar manner, the tetramic acid is a challenging structure that is present in a high variety of natural products displaying a wide range of biological activities, ranging from antibiotic and antivirals to antineoplastic and fungicides.⁶ Most of the tetramic acid derivatives hitherto described are 1-unsubstituted or 1-alkyl/benzyl derivatives, but very few 1-benzyloxycarbonyl analogues have been reported until now.⁷

It is known that β -keto esters are versatile synthetic intermediates that have been widely used for the preparation of different heterocyclic systems, like dihydropyrimidinones, indoles, pentasubstituted pyrrole rings and pyrazolones.⁸ In particular, we have worked on the transformation of β -keto esters derived from amino acids and dipeptides in different chiral heterocyclic systems, namely 1,3-dioxoperhydropyrido[1,2-c]pyrimidines, and 2-oxopiperazine derivatives.⁹ More recently, we have initiated a program directed to study the use of these β -keto esters as valuable starting materials for DOS approaches, allowing the appendage of the amino acid side-chain in the heterocyclic system, which, in turn, can provide a source of diversification. In this sense, the preparation of highly functionalized β,γ -diamino esters have already been described, along with their conversion into pyrrolidinone derivatives.¹⁰ Now, we illustrate the application of amino-acid-derived β -keto esters to the synthesis of non-conventional 2,3-disubstituted indoles and 1-benzyloxycarbonyl tetramic acid derivatives.

Inspired by the indole synthesis described by Tanimori from 2-iodoaniline and alkyl or aryl β -keto esters,^{8e} we decided to explore the preparation of indole derivatives of general formula **C**, with an unusual α -amino substituent at position 2, using amino acid-derived β -keto esters **1** as key starting materials (Scheme 1). In this copper catalyzed reaction, two intermediates can be envisaged for the generation of the indole ring. These are, the previously proposed condensation to conjugated enamines **A**,¹¹ followed by a Heck-type coupling (i), but also the arylation of the 1,3-dicarbonyl compound to intermediates **B** and subsequent condensation (ii). In fact, the CuI/L-proline catalytic system was previously described as a useful procedure to diverse 2-aryl-1,3-dicarbonyl compounds.¹² If intermediates **B** were formed, under the basic conditions of the reaction, they could also lead to tetramic acid derivatives **D** through lactamization (route iii).

Scheme 1. Initial proposed route to 2,3-disubstituted indoles and tetramic acid derivatives.

To explore the possibilities of this synthetic scheme, we prepared the corresponding β -keto esters derived from Z-Ala-OH, both L and D, and Z-Phe-OH, using described strategies.^{9c,13} In our hands, following the Tanimori conditions,¹⁷ the reaction of β -keto esters **1** with 2-iodoaniline led to complex mixtures, both using BINOL and L-Pro as additives. Similar disappointing results were obtained when the reaction was carried out by conventional heating and under MW irradiation. Considering that the primary amine group could be the responsible for the undesired side reactions, we decided to protect it with a trifluoroacetyl group, following a procedure previously described by Chen and coworkers.¹⁴ This modification would diminish the risk of side reactions and, at the same time, it would permit to take profit of the accelerating effect described for an *ortho*-amide group in Ullman-type reactions.¹⁵

Scheme 2. Synthesis of 2,3-disubstituted indoles and tetramic acids from amino acid-derived β -keto esters.

As depicted in Scheme 2, treatment of a mixture of the corresponding β -keto ester, **1a-c**, and iodophenyl-2-trifluoroacetylamine with copper iodide, in the presence of an excess of cesium carbonate (4 equiv) as base and L-Pro (0.4 equiv) as additive in DMSO,¹⁴ did not lead to the expected open 2-aryl-1,3-dicarbonyl derivatives **2**. Instead, under these conditions, the tetramic acid derivatives **3a-c** were

isolated in good yield. The structure of compounds **3**, which should come from the nucleophilic addition of the carbamate NH to the methyl ester group of compounds **2**, through type-B intermediates, was confirmed by mass spectrometry that showed the loss of 31 mass units, which corresponds to the loss of a MeO-group, as well as the absence of the corresponding signal in the ^1H NMR spectra. On the contrary, when we tried milder conditions for the coupling reaction, using room temperature and only 1 equivalent of cesium carbonate as base, the expected coupling products **2a-c** were isolated as the main reaction products.¹⁶ Heating compounds **2a-c** with 2 equivalents of cesium carbonate in methanol led, again, to the tetramic acid derivatives **3a-c**.¹⁷ This is in agreement with the direct formation of these compounds from **1a-c** when the first reaction was performed under excess of base (Scheme 2).

Deprotection of the *o*-amino group of compounds **2** either in basic or in acidic conditions would permit the cyclization to the desired indole derivative.^[9b] Thus, removal of the trifluoroacetyl group of compounds **2a-c** by treatment with hydrochloric acid finally led to the expected indole derivatives **4a-c** in good yield.¹⁸ In addition, these compounds were also obtained by a similar acidic treatment of the tetramic acid analogues **3a-c**. In general terms, for the preparation of indole derivatives **4** the route **1**→**3**→**4** led to better yields than the alternative **1**→**2**→**4** pathway.

Chiral HPLC experiments on these indole derivatives indicated a partial loss of optical purity, probably due to the instability of the β -keto esters or of the intermediate compounds **2** or **3** under the basic reaction conditions. A similar stereochemical integrity loss was described in the reductive amination reaction of these β -keto esters.¹⁰

The carbamate group (**Z**) in compounds **3** and **4** can be easily removed by hydrogenation, as illustrated by the preparation of tetramic acids **5a-c**, and indole **6a**, respectively, having appropriate functional groups for further transformations. Thus, the primary amino group in compounds **6a** is susceptible of new reactions, offering the possibility of increasing the molecular diversity by introducing different substituents and functionalities to that position. To exemplify this, and to explore the reactivity of the amino group at this position, compound **6a** was reacted with an isocyanate, an acyl chloride and a sulfonyl chloride to lead to urea **7a**, amide **8a** and sulfonamide **9a**, with good/acceptable yields (Scheme 3). Reactions with the acyl and sulfonyl chlorides were performed in the presence of excess of propylene oxide as acid scavenger, leading to cleaner crude products and higher yield than with TEA.

Scheme 3. Incorporation of diversity at the free amino group.

In summary, starting from β -keto esters derived from amino acids we have developed a simple and practical method that permits the preparation of either 1-benzyloxycarbonyl-3,5-disubstituted tetramic acid derivatives or 2,3-disubstituted indole systems. The thorough control of the reaction conditions, by means of the amount of base and the temperature, allowed us to stop the reaction in the linear 2-aryl-1,3-dicarbonyl derivatives or progress it to the tetramic acids, both precursors of the indole derivatives upon acid hydrolysis. The obtained indole systems are substituted in position 2 by an amino methyl group, also supporting an amino acid side-chain (R^1) at the methylene group. Therefore, different R^1 substituents could be introduced by using different amino acids as starting materials. Additionally, the primary amino group on the substituent in position 2, as well as the carboxylate group in position 3 of the indole ring are both susceptible of further modification, providing new opportunities for diversification. The synthetic approach described here could have application in the generation of libraries based on two biologically relevant heterocyclic systems, indole and tetramic acids, with new substitution patterns.

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Supplementary data

Supplementary data (1H NMR and 13C NMR spectra for all new compounds **2a–9a** associated with this article can be found, in the online version, at <http://dx.doi...>

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- Representative procedure for the preparation of (2-trifluoroacetamido)phenyl-2-pentenoate derivatives 2.** A solution of the corresponding β -keto ester **1** (0.3 mmol) in dry DMSO (3 ml) was treated with 2-iodotrifluoroacetamidobenzene (0.33 mmol), CuI (0.066

mmol), L-Pro (0.13 mmol) and Cs₂CO₃ (0.33 mmol), and stirred at room temperature for 3 days. Then the reaction mixture was neutralized with 1M HCl and extracted with EtOAc. The organic phase was washed with brine and dried over Na₂SO₄. The solvent was evaporated and the raw material was purified by chromatography (20% EtOAc/Hexane). As an example: **(4S)-Methyl 4-(benzyloxycarbonyl)amino-3-hydroxy-2-(2-trifluoroacetamido)phenyl-2-pentenoate (2a)**: From **1a** (0.3 mmol). Brownish solid (84 mg, 60%). HPLC: *t_R* = 11.55 min, m.p. 130-132 °C, [α]_D²⁵ = -13.5 (*c* = 1.0, MeOH). ¹H NMR (CDCl₃, 300MHz): δ = 13.0 (d, 1H, *J* = 1.6 Hz, 3-OH), 9.66 (s, 1H, NH-COCF₃), 7.77 (d, 1H, *J* = 7.8 Hz, Ar), 7.48 (td, 1H, *J* = 7.8, 1.3 Hz, Ar), 7.44-7.30 (m, 6H, Ar); 7.17 (dd, 1H, *J* = 7.8, 1.3 Hz, Ar), 5.16-5.04 (m, 3H, 2H CH₂, 1H 4-NH), 3.99 (m, 1H, *J* = 6.8, 1.5Hz, 4-H), 3.67 (s, 3H, OCH₃), 1.37 (d, 3H, *J* = 6.8 Hz, 5-CH₃) ppm. ¹³C NMR (CDCl₃, 75MHz): δ = 173.7 (3-C), 172.0 (CO), 156.0 (CO), 155.57 (q, *J* = 32 Hz, COCF₃), 135.7 (C Ar), 134.6 (C Ar), 131.9 (CH Ar), 129.2 (CH Ar), 128.5 (2C, CH Ar), 128.4 (2C, CH Ar), 128.3 (CH Ar), 128.1 (CH Ar), 127.0 (CH Ar), 126.2 (C Ar), 116.1 (q, *J* = 288 Hz, COCF₃), 99.9 (2-C), 67.2 (Z-CH₂), 52.1 (OCH₃), 47.6 (4-C), 17.5 (5-C) ppm. C₂₂H₂₁F₃N₂O₆ (466.41): calcd. C, 56.65; H, 4.54; N, 6.01; found C, 56.55; H, 4.41; N, 5.92. ESI-MS: *m/z* = 489.0 [M+Na]⁺, 467.0 [M+H]⁺.

17. **General procedure for the synthesis of 3-(2-trifluoroacetamido)phenyl-3-pyrrolin-2-one derivatives 3.**

Method A: A solution of the corresponding β-keto ester **1** (0.4 mmol), in dry DMSO (2 ml) was treated with 2-trifluoroacetamidobenzene (0.44 mmol), CuI (0.088 mmol), L-Pro (0.17 mmol) and Cs₂CO₃ (1.76 mmol), and heated at 50°C for 24 h. Then the reaction mixture was neutralized with 1M HCl and extracted with EtOAc. The organic phase was washed with brine and dried over Na₂SO₄. The solvent was evaporated and the raw material was purified by chromatography (5% MeOH/DCM).

Method B: A solution of compound **2a** (80 mg, 0.017 mmol) in MeOH (5 ml) and H₂O (2.5 ml) was treated with Cs₂CO₃ (0.034 mmol) and heated at 80 °C for 2h. The reaction was allowed to recover room temperature, neutralized with 1M HCl, and extracted with EtOAc. The workup was continued as described in method A. As an example: **(5S)-1-Benzoyloxycarbonyl-4-hydroxy-5-methyl-3-(2-trifluoroacetamido)phenyl-3-pyrrolin-2-one (3a)**: From **1a** (0.4 mmol) by Method A or **2a** (0.017 mmol) by Method B. (100 mg, 60% and 3.5 mg, 47% respectively). Brownish solid, HPLC: *t_R* = 9.57 min, m.p. 168-171 °C, [α]_D²⁵ = +36.7 (*c* = 1.0, MeOH). ¹H NMR (DMSO-*d*₆, 300MHz): δ = 13.27 (s, 1H, 4-OH), 7.81 (dd, 1H, *J* = 6.2, 3.3 Hz, Ar), 7.57 (m, 1H, Ar), 7.49-7.26 (m, 7H, 5H Ar-Z, 1H Ar, and 1H NHCOCF₃); 7.11 (dd, 1H, *J* = 5.7, 3.5 Hz, 3-H Ar), 5.24 (d, 1H, *J* = 12.9 Hz, CH₂), 5.17 (d, 1H, *J* = 12.9 Hz, CH₂), 3.94 (q, 1H, 5-H, *J* = 6.3Hz), 1.33 (d, 3H, *J* = 6.5 Hz, 5-CH₃) ppm. ¹³C NMR (DMSO-*d*₆, 75MHz): δ = 187.6 (4-C-OH), 169.7 (CO), 154.2 (q, *J* = 36 Hz, COCF₃), 151.2 (COO), 136.5 (C Ar), 132.4 (C Ar), 129.17 (CH Ar), 128.8 (2C, CH Ar), 127.8 (CH Ar), 127.5 (2C, CH Ar), 124.7 (C Ar), 124.41 (CH Ar), 124.0 (CH Ar), 123.6 (CH Ar), 116.4 (q, *J* = 286 Hz, COCF₃), 94.4 (3-C), 66.0 (Z-CH₂), 56.1 (5-C), 17.7 (5-CH₃) ppm. C₂₁H₁₇F₃N₂O₅ (434.37): calcd. C, 58.07; H, 3.94; N, 6.45; found C, 57.98; H, 3.88; N, 6.32. ESI-MS: *m/z* = 435.2 [M + H]⁺.

18. **General procedure for the synthesis of 2,3-disubstituted indole derivatives 4.** A solution of the corresponding compound **2** or **3** (0.17 mmol) in MeOH (5 ml) was treated with concentrated HCl (1 ml) and heated at 80°C for 2 h. After recovering room temperature, the reaction mixture was neutralized with 10% NaHCO₃ and EtOAc was added. The organic phase was separated, washed with brine, dried with Na₂SO₄. After removing the solvent, the residue was purified by column chromatography (20% EtOAc/Hexane). As an example: **(1'S)-2-[1'-(Benzyloxycarbonyl) amino]ethyl-3-methoxycarbonylindole (4a)**: From **2a** (0.17 mmol). White solid (38 mg, 63%), HPLC: *t_R* = 9.95 min, m.p. 143-146°C, [α]_D²⁵ = -8.7 (*c* = 1.0, MeOH). ¹H NMR (DMSO-*d*₆, 300MHz): δ = 11.69 (s, 1H, NH), 7.93 (dd, 1H, *J* = 5.2, 3.8 Hz, 4-H_{Indol}), 7.64 (d, 1H, *J* = 4.5 Hz, NHCO), 7.46 (m, 1H, 7H_{Indol}), 7.34 (m, 5H, H Ar), 7.15 (m, 2H, 5-H_{Indol}, 6-H_{Indol}), 5.58 (m, 1H, CHCH₃), 5.00 (m, 2H, CH₂), 3.82 (s, 3H, OCH₃), 1.44 (d, 3H, *J* = 7.0 Hz, CHCH₃) ppm. ¹³C NMR (DMSO-*d*₆, 75MHz): δ = 165.6 (3-CO), 155.7 (NHCO), 150.6 (2-C_{Indol}), 137.2 (C Ar), 135.0 (7'-C_{Indol}), 128.7 (2C, CH Ar), 128.2 (2C, CH Ar), 128.0 (CH Ar), 126.8 (3'-C_{Indol}), 122.4 (6-C_{Indol}), 121.6 (4-C_{Indol}), 121.0 (5-C_{Indol}), 112.4 (7-C_{Indol}), 101.5 (3-C_{Indol}), 65.9 (Z-CH₂), 51.0 (OCH₃), 45.0 (CHCH₃), 21.4 (CHCH₃) ppm. C₂₀H₂₀N₂O₄ (352.38): calcd. C, 68.17; H, 5.72; N, 7.95; found C, 68.02; H, 5.68; N, 7.84. ESI-MS: *m/z* = 375.3 [M+Na]⁺, 353.3 [M+H]⁺.