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Tetramic acid derivatives via Ugi–Dieckmann-reaction

Julia H. Spatz [a,b,*], Sebastian J. Welsch [a,b], David-Emmanuel Duhaut [a], Nadine Jäger [a], Thomas Boursier [a], Martin Fredrich [a], Lars Allmendinger [c], Günther Ross [a], Jürgen Kolb [a], Christoph Burdack [a], Michael Umkehrer [a]

[a] Priaxon AG, Gmunder Str. 37-37a, D-81379 München, Germany
[b] Technical University Munich, Lichtenbergstrasse 4, D-85747 Garching, Germany
[c] Ludwig-Maximilians-University Munich, Butenandtstr. 7, D-81377 München, Germany

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ABSTRACT

Tetramic acid derivatives constitute an important class of nitrogen containing heterocycles, and are key structural motifs in many natural products of terrestrial and marine origin. The interesting biological and structural diversity of this class of substances makes it a particularly interesting template for the design of compound libraries in search of small molecules that effect cellular signalling pathways. Therefore, a novel combinatorial synthesis of tetramic acids by an Ugi/Dieckmann condensation is described.

Tetramic acid derivatives represent an important class of nitrogen-containing heterocycles with a pyrrolidine-2,4-dione moiety. They are key structural motifs in many natural products of terrestrial and marine origin exhibiting a wide range of biological activities including antibiotic,[1] antiviral,[2] antifungal,[3] phyto-,[4] cytotoxic[5] and enzyme inhibitory activities against bacterial DNA-directed RNA polymerase.[6] Tetramic acids are also found in the agrochemical field, therein they have been patented for fungicidal and herbicidal use. The interesting biological and structural diversity of this compound class makes it a particularly interesting template for the design of compound libraries in search of small molecules that effect cellular signalling pathways. Therefore, several classical synthetic procedures[7] were developed, but with a lack of diversity that is required for an effective lead discovery and optimization. In contrast to the classical organic synthesis, the combinatorial synthesis of 'drug-like' compounds permits the fast preparation of compound libraries suitable for lead finding and optimization.[8–18] Thus, multi-component reactions (MCRs) represent a powerful tool for the high-throughput screening strategy.[19,20] Especially, the Ugi-reaction has generated much interest due to its synthetic potential, and the capacity to generate molecular diversity. In the Ugi-four component reaction,[21] an amine, an aldehyde, a carboxylic acid and an isocyanide react simultaneously to afford peptide-like structures.

In order to reach a maximum of diversity, several research groups have successfully combined different classical methods with multi-component reactions.[22–26] In this context, we wish to introduce a novel reaction type (Ugi–Dieckmann) based on the concept of a 'universal isocyanide'[27] that enables the required post condensation modification after the Ugi-four-component reaction.

1,1,-Dimethyl-2-isocyano-ethyl-methylcarbonate[28] is used as cleavable isocyanide for the Ugi-4CR. In the following post condensation modification the deprotonation of amide **5** initiates the cyclization to the *N*-acyl-5,5-dimethyloxazolidin-2-one **6**. Upon attack by the enolized carboxylic acid moiety 5,5-dimethyloxazolidin-2-one **8** acts as leaving group and a Dieckmann-like cyclization to pyrrolidine-2,4-dione or hydroxy-dihydropyrrolidone structures **7** takes place (Scheme 1). The Ugi-reaction is generally initiated by the condensation of amine **1** with aldehyde **2** leading to an intermediate imine, which subsequently reacts with α-CH-acidic carboxylic acid/acetic acid **3** and isocyanide **4** to afford the desired product **5**. Herein, MeOH turned out to be the best solvent for the MCR, step. After completion of the MCR the solvent was removed in vacuo. The conversions of the MCR products **5a-ae** determined by HPLC–MS[29] were generally good. The clean-up of the crude products was done by column chromatography.[31] The subsequent intramolecular cyclization required a strong base KO*t*Bu in THF (dry) at room temperature. In the case of acetic acid,

* Corresponding author. Tel.: +49 89 45213080; fax: +49 89 452130822.
E-mail address: spatz@priaxon.de (J.H. Spatz).

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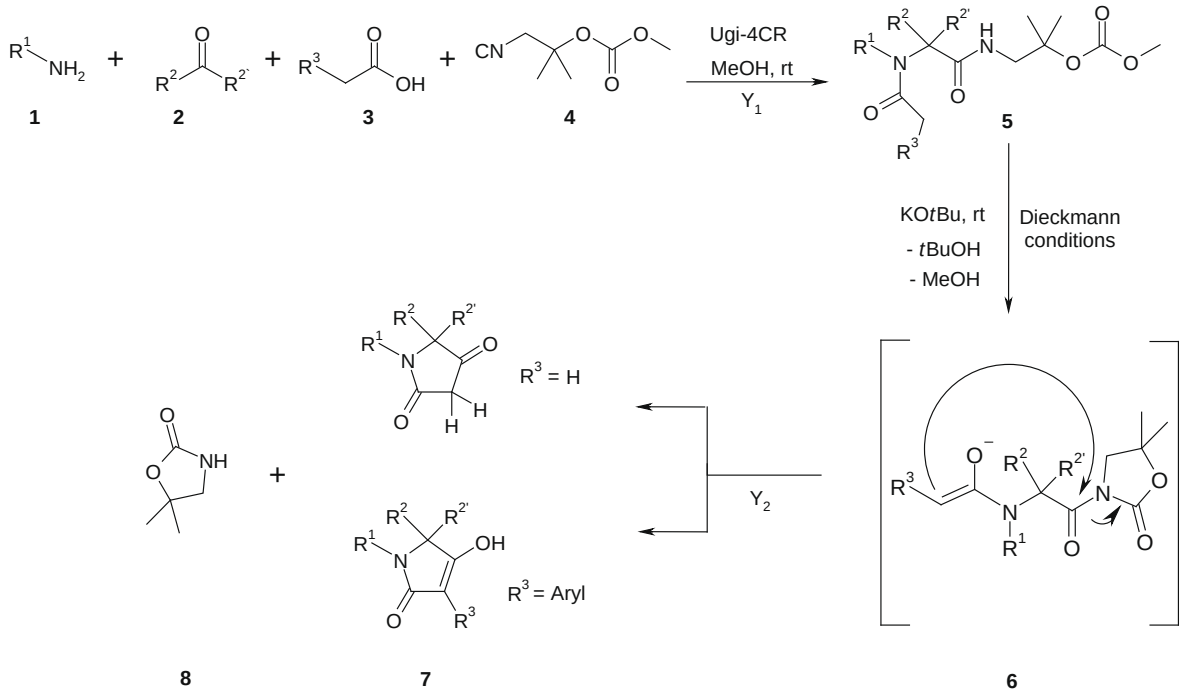


Scheme 1. Combinatorial synthesis of tetramic acids by an Ugi/Dieckmann condensation.

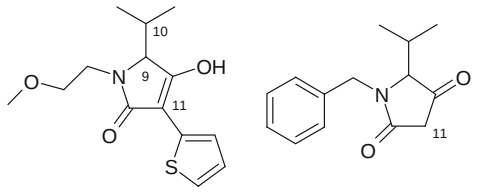
2.0 equiv KO*t*Bu is used to obtain exclusively the cyclization product, whereby for α-CH-acidic carboxylic acids 1.2 equiv was sufficient.

Conversions were monitored by HPLC–MS, generally after 1 h of reaction time a maximum of conversion was reached, and the reaction mixture was neutralized with 6 N HCl (pH 6–7). All compounds were isolated by column chromatography on silica in good yields (Y_2) and purities.[32]

Table 1 shows the results for the synthesized tetramic acids[33–38] **7a–ae** with specific yields for each step (Y_1 = MCR, Y_2 = cyclization). Aliphatic, aromatic and benzylic amines, aldehydes as well as ketones, aliphatic as well as α-CH-acidic carbox-

Table 1
Synthesized tetramic acid derivatives

R^1	R^2	$R^{2'}$	R^3	Y_1 (%)	MCR	Y_2 (%)	Cyclization
4-CH_3O–C_6H_4	4-CH_3O–C_6H_4	H	C_6H_5	64	**5a**	13	**7a**
4-CH_3O–C_6H_4	CH_3	CH_3	C_6H_5	51	**5b**	21	**7b**
C_6H_5–CH_2	2-F–C_6H_4	H	4-Cl–C_6H_4	65	**5c**	74	**7c**
C_6H_5–CH_2	4-CH_3O–C_6H_4	H	2-Thienyl	64	**5d**	26	**7d**
C_6H_5–CH_2	4-CH_3O–C_6H_4	H	4-Cl–C_6H_4	43	**5e**	78	**7e**
C_6H_5–CH_2	H	H	4-Cl–C_6H_4	60	**5f**	45	**7f**
C_6H_5–CH_2	$(CH_3)_2$–CH	H	2-F–C_6H_4	28	**5g**	48	**7g**
C_6H_5–CH_2	$(CH_3)_2$–CH	H	2-Thienyl	54	**5h**	43	**7h**
C_6H_5–CH_2	$(CH_3)_2$–CH	H	4-Cl–C_6H_4	75	**5i**	81	**7i**
C_6H_5–CH_2	$(CH_3)_2$–CH	H	4-CH_3O–C_6H_4	79	**5j**	81	**7j**
C_6H_5–CH_2	$(CH_3)_2$–CH	H	4-NO_2–C_6H_4	79	**5k**	82	**7k**
C_6H_5–CH_2	$(CH_3)_2$–CH	H	$COOC_2H_5$	20	**5l**	73	**7l**
C_6H_5–CH_2	$(CH_3)_2$–CH	H	H	79	**5m**	68	**7m**
C_6H_5–CH_2	$(CH_3)_2$–CH	H	O–C_6H_5	74	**5n**	24	**7n**
C_6H_5–CH_2	$(CH_3)_2$–CH	H	C_6H_5	85	**5o**	99	**7o**
C_6H_5–CH_2	$(CH_3)_2$–CH	H	$PO(OC_2H_5)_2$	72	**5p**	99	**7p**
C_6H_5–CH_2	$(CH_3)_2$–CH	H	S–CH_2–C_6H_5	73	**5q**	55	**7q**
C_6H_5–CH_2	CH_3	CH_3	2-Thienyl	45	**5r**	18	**7r**
C_6H_5–CH_2	CH_3	CH_3	4-Cl–C_6H_4	47	**5s**	69	**7s**
C_6H_5–CH_2	CH_3	CH_3	C_6H_5	71	**5t**	32	**7t**
C_6H_5–CH_2	C_6H_5	H	4-Cl–C_6H_4	42	**5u**	68	**7u**
C_6H_5–CH_2	$(CCH_3)_3$	H	4-Cl–C_6H_4	50	**5v**	46	**7v**
C_6H_5–CH_2	$(CH_3)_2$–CH	H	4-Cl–C_6H_4	53	**5w**	35	**7w**
$(CH_2)_2$–OCH_3	4-CH_3O–C_6H_4	H	2-Thienyl	76	**5x**	99	**7x**
$(CH_2)_2$–OCH_3	4-CH_3O–C_6H_4	H	4-Cl–C_6H_4	58	**5y**	93	**7y**
$(CH_2)_2$–OCH_3	4-CH_3O–C_6H_4	H	4-CH_3O–C_6H_4	61	**5z**	13	**7z**
$(CH_2)_2$–OCH_3	4-CH_3O–C_6H_4	H	C_6H_5	73	**5aa**	80	**7aa**
$(CH_2)_2$–OCH_3	$(CH_3)_2$–CH	H	2-Thienyl	57	**5ab**	85	**7ab**
$(CH_2)_2$–OCH_3	$(CH_3)_2$–CH	H	4-Cl–C_6H_4	67	**5ac**	72	**7ac**
$(CH_2)_2$–OCH_3	$(CH_3)_2$–CH	H	4-CH_3O–C_6H_4	57	**5ad**	99	**7ad**
$(CH_2)_2$–OCH_3	$(CH_3)_2$–CH	H	C_6H_5	89	**5ae**	99	**7ae**



7ab **7m**

Figure 1. Compounds **7ab** and **7m**.

ylic acid could successfully be involved in the reaction. The reaction time (rt) for the cyclization is generally short, and the conversions are moderate to good for all compounds. The chromatographic methods used allow the isolation of products with high purity (>95%). All compounds were characterized by NMR[30] and HPLC–MS data.

The observable tautomer (Fig. 1) in ^{1}H NMR spectra (DMSO-d_6) depends on the substituent at **C-11**. If the starting material is acetic acid there is no substituent at **C-11** of the resulting product, and so only the pyrrolidine-2,4-dione-tautomer is observed (CH_2-group at 3.02 ppm, carbonyl-carbon at 206 ppm). If an α-CH-acidic carboxylic acid is used, the resulting products contain a phenyl moiety at **C-11**, and therefore the hydroxy-dihydropyrrolidone tautomer is the exclusively observable structure in ^{1}H NMR spectra (DMSO-d_6). The enolic structure of compound **7ab** was confirmed by NOE-experiments. In DPFGSE-NOE-spectra of compound **7ab** NOEs with methine-proton 9 (δ 4.11 ppm) and methine-proton 10 (δ 2.36 ppm) of the isopropyl-group were observed upon excitation of enol-proton at (δ 11.47 ppm) and vice versa.

In summary, a novel two-step synthetic procedure for the preparation of substituted tetramic acid derivatives has been described. Amines, carbonyls and α-CH-acidic carboxylic acid can be varied broadly, leading to compounds with three potential points of diversity.

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29. HPLC–MS/MS spectra (Varian 1200), Polaris, RP C18 column, 3 × 150 mm, 5 μm, ProStar 325 (254 nm), 1 ml/min, 3 min gradient from 10% ACN to 90% ACN (0.1% HCOOH) versus H_2O, coupled with a Quadrupol MS/MS mass spectrometer using electrospray ionization (ESI).
30. NMR: ^{1}H/^{13}C: Bruker AV 250: 250.13 MHz, ^{1}H–^{1}H NOESY: Jeol ECP500: 500.16 MHz.
31. *General procedure* (**GP 1**) *for the synthesis of MCR products* **5a–ae**: Amine **1** (1 mmol) and aldehyde **2** (1 mmol) were stirred in 3 mL methanol for 2 h. Then, carboxylic acid **3** (1 mmol) and isocyanide **4** (1 mmol) were added, and the reaction mixture was stirred for 16 h at room temperature. The solvent was removed in vacuo. The resulting crude product was purified by flash chromatography on silica (ethyl cetate/hexane).
32. *General procedure* (**GP 2**) *for the synthesis of tetramic acid derivatives* **6a–ae**: 0.2 mmol of MCR product **5a–ae** was dissolved in 4 mL THF (dry), and 0.24 mmol KO*t*Bu were added under nitrogen atmosphere. The reaction mixture was stirred at room temperature for 1 h. After 1 h of reaction time a maximum of conversion was reached, and the reaction mixture was neutralized with 6 N HCl (pH 6–7). The solvent was removed in vacuo. The resulting crude product was purified by flash chromatography on silica (ethyl acetate/hexane).
33. Compound **7o** was prepared according to **GP 2**, and purified by flash chromatography on silica gel with eluent ethyl acetate/hexane = 1:2 (61 mg of a colourless solid, 99%). m/z = 308 $[M+H]^+$, m/z = 330 $[M+Na]^+$. ^{1}H NMR (250.13 MHz, $CDCl_3$): δ 11.25 (br s, 1H, O*H*), 7.92–7.90 (m, 2H, CH_{ar}), 7.36–7.20 (m, 8H, CH_{ar}), 5.00 (d, J = 15.7 Hz, 1H, PhCH_2), 4.20 (d, J = 15.7 Hz, 1H, PhCH_2), 3.73 (d, J = 2.3 Hz, 1H, NC*H*), 2.23–2.29 (m, 1H, $(CH_3)_2CH$), 0.96 (d, J = 6.9 Hz, 3H, CH(CH_3)$_2$), 0.81 (d, J = 6.9 Hz, 3H, CH(CH_3)$_2$). ^{13}C NMR (62.90 MHz, $CDCl_3$): δ 172.8 (C_q, CON), 170.0 (C_q, HOC_q), 139.2 (C_q, CH_2C_{ar}), 132.7 (C_q, C_{ar}), 129.5 (CH, C_{ar}H), 128.9 (CH, C_{ar}H), 128.5 (CH, C_{ar}H), 128.3 (CH, C_{ar}H), 127.8 (CH, C_{ar}H), 126.8 (CH, C_{ar}H), 105.5 (C_q, PhC_q), 63.7 (CH, NCH), 45.2 (CH_2, PhCH_2), 29.6 (CH, $(CH_3)_2CH$), 19.9 (CH_3, CH(CH_3)$_2$), 16.4 (CH_3, CH(CH_3)$_2$).
34. Compound **7s** was prepared according to **GP 2** and purified by flash chromatography on silica gel with eluent ethyl acetate/hexane = 1:1 (19 mg of a white solid, 69%). m/z = 294 $[M+H]^+$, m/z = 316 $[M+Na]^+$. ^{1}H NMR (250.13 MHz, DMSO): δ 8.12–8.06 (m, 2H, CH_{ar}), 8.01 (br s, 1H, O*H*), 7.19–7.41 (m, 7H, CH_{ar}), 4.53 (s, 2H, NCH_2), 1.32 (s, 6H, CH_3).
35. Compound **7t** was prepared according to **GP 2** and purified by flash chromatography on silica gel with eluent ethyl acetate/hexane = 1:2 (45 mg of a colourless oil, 69%). m/z = 328 $[M+H]^+$, m/z = 350 $[M+Na]^+$. ^{1}H NMR (250.13 MHz, $CDCl_3$): δ 7.98 (d, J = 7.4 Hz, 1H, CH_{ar}), 7.40–7.18 (m, 9H, CH_{ar}), 4.53 (s, 2H, PhCH_2), 1.26–1.08 (m, 6H, CH(CH_3)$_2$). ^{13}C NMR (62.90 MHz, $CDCl_3$): δ 174.0 (C_q, CON), 169.5 (C_q, HOC_q), 140.1 (C_q, CH_2C_{ar}), 128.4 (CH, C_{ar}H), 128.2 (C_q, C_{ar}), 127.7 (CH, C_{ar}H), 127.4 (CH, C_{ar}H), 126.7 (CH, C_{ar}H), 125.7 (CH, C_{ar}H), 101.2 (C_q, PhC_{ar}), 60.6 (C_q, NC$_q$(CH_3)$_2$), 41.1 (CH_2, PhCH_2), 23.5 (CH_3, C$_q$(CH_3)$_2$), 23.0 (CH_3, C$_q$(CH_3)$_2$).
36. Compound **7y** was prepared according to **GP 2** and purified by flash chromatography on silica gel with eluent ethyl acetate/hexane = 9:1 (68 mg of a colourless oil, 93%). m/z = 374 $[M+H]^+$, m/z = 396 $[M+Na]^+$. ^{1}H NMR (250.13 MHz, $CDCl_3$): δ 7.96 (d, ^3J = 8.1 Hz, 2H, CH_{ar}), 7.21 (d, ^3J = 8.1 Hz, 2H, CH_{ar}), 7.08 (d, ^3J = 8.6 Hz, 2H, CH_{ar}), 6.77 (d, ^3J = 8.6 Hz, 2H, CH_{ar}), 4.74 (s, 1H, NC*H*), 3.74 (s, 3H, OCH_3), 3.53–3.71 (m, 2H, CH_2), 3.34–3.38 (m, 1H, CH_2), 3.20 (s, 3H, CH_2OCH_3), 2.77–2.86 (m, 1H, CH_2).
37. Compound **7ab** was prepared according to **GP 2** and purified by flash chromatography on silica gel with eluent ethyl acetate/hexane = 9:1 (48 mg of a white solid, 85%). m/z = 282 $[M+H]^+$, m/z = 304 $[M+Na]^+$. ^{1}H NMR (500.16 MHz, d_6-DMSO): δ 11.47 (br s, 1H, O*H*), 7.47 (dd, J = 1.1, 2.5 Hz, 1H, CH_{ar}), 7.24 (dd, J = 1.1, 2.5 Hz, 1H, CH_{ar}), 6.92 (dd, J = 1.6, 8.7 Hz, 1H, CH_{ar}), 4.00 (s, 1H, H_3COCH_2), 3.85–3.75 (m, 1H, H_3COCH_2), 3.47–3.43 (m, 2H, NCH_2), 3.13 (s, 3H, OCH_3), 3.08–2.98 (m, 1H, NC*H*), 2.35 (m, 1H, $(CH_3)_2CH$), 0.90 (d, J = 7.0 Hz, 3H, CH(CH_3)$_2$), 0.67 (d, J = 7.0 Hz, 3H, CH(CH_3)$_2$). ^{13}C NMR (62.90 MHz, DMSO-d_6): δ 171.0 (C_q, HOC_q), 167.2 (C_q, CON), 143.7 (C_q, SC_{ar}), 133.3 (CH, C_{ar}H), 126.9 (CH, C_{ar}H), 124.0 (CH, C_{ar}H), 102.3 (C_q, C_{ar}), 78.1 (CH, NCH), 70.5 (CH_2, H_3COCH_2), 64.1 (CH_3, OCH_3), 58.6 (CH_2, NCH_2), 29.5 (CH, $(CH_3)_2CH$), 19.8 (CH_3, CH(CH_3)$_2$), 15. (CH_3, CH(CH_3)$_2$).
38. Compound **7ae** was prepared according to **GP 2** and purified by flash chromatography on silica gel with eluent ethyl acetate/hexane = 9:1 (54 mg of a white solid, 99%). m/z = 276 $[M+H]^+$, m/z = 298 $[M+Na]^+$. ^{1}H NMR (250.13 MHz, $CDCl_3$): δ 7.73 (d, J = 8.5 Hz, 2H, CH_{ar}), 7.23 (t, J = 7.5 Hz, 2H, CH_{ar}), 7.09 (d, J = 7.4 Hz, 1H, CH_{ar}), 3.93 (d, J = 2.2 Hz, 1H, NC*H*), 3.85–3.75 (m, 2H, H_3COCH_2), 3.14 (s, 3H, OCH_3), 3.10–2.98 (m, 2H, NCH_2), 2.19 (m, 1H, $(CH_3)_2CH$), 0.89 (d, J = 7.0 Hz, 3H, CH(CH_3)$_2$), 0.75 (d, J = 7.0 Hz, 3H, CH(CH_3)$_2$). ^{13}C NMR (62.90 MHz, $CDCl_3$): δ 171.6 (C_q, CON), 169.2 (C_q, HOC_q), 132.1 (C_q, C_{ar}), 128.0 (CH, C_{ar}H), 127.7 (CH, C_{ar}H), 126.1 (CH, C_{ar}H), 105.1 (C_q, PhC_{ar}), 70.3 (CH, NCH), 63.5 (CH_2, H_3COCH_2), 58.2 (CH_3, OCH_3), 38.7 (CH_2, NCH_2), 30.0 (CH, $(CH_3)_2CH$), 18.9 (CH_3, CH(CH_3)$_2$), 16.1 (CH_3, CH(CH_3)$_2$).