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Concise Approach towards Tetramic Acid Derivatives via Ugi Reaction/Dieckmann Cyclization Sequence

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Dedication In commemoration of the 300th anniversary of St Petersburg State University's founding

Tetramic acids exhibit intriguing biological activity and are particularly attractive scaffolds for drug design. In this paper, we present a convenient approach based on the Dieckmann cyclization of Ugi adducts of malonic monoesters to afford a series of medically important polysubstituted tetramic acid derivatives. This simple and versatile method tolerates various substituents in both the amine, aldehyde and isocyanide moieties allowing the use of α-substituted malonic acid monoesters. Examples of further functionalization of the free methylene group in the synthesized compounds have been presented.

Introduction

Small bioactive molecules with a simple architecture are very attractive from a medicinal chemistry perspective. Among them, the pyrrolidine-2,4-dione (tetramic acid) scaffold has attracted great interest from synthetic and biosynthetic communities. This heterocyclic motif is found in many natural products of both marine[1] and terrestrial[2] origin (Figure 1). The cyclic keto-enol structure provides intriguing biological profile to these molecules. Tetramic acid derivatives display antifungal,[3] antiviral,[4] antibiotic,[5] cytotoxic,[6] phytotoxic,[7] and other activities.[8] Movento®[9] also known as spirotetramate is a registered trademark that is widely used in agriculture as insecticide. Oxiracetam is a nootropic drug of high importance. The wide range of biological activities, natural abundance of scaffold[10] and structural diversity of pyrrolidine-2,4-diones make them an attractive model for generating libraries of compounds for subsequent biological studies.

Multicomponent reactions (MCRs) are rightly regarded as a versatile tool for assembling different types of heterocycles in a short time. The key advantage of the MCR approach is that large libraries of compounds can be obtained from a small set of commercially available starting materials. Ugi 4-CR by itself or in combination with further post-modification of peptide-like adducts is widely used in the synthesis of various heterocycles and in the total synthesis of natural products.[11] The latest investigations of tetramic acid biosynthesis[12] revealed Dieckmann cyclization of *N*-(β-ketoacyl)-amino acids as a universal scenario for pyrrolidin-2,4-dione ring formation. Recently, a lactamization pathway has been also demonstrated.[13] The synthetic routes to the tetramic acid core, based on MCR approaches, could be divided into two general models (Scheme 1). The first and most common way is based on Dieckmann cyclization[14] of *N*-acyl α-amino carbonyl derivatives providing 3-acyl or 3-aryl pyrrolidinedione framework via a

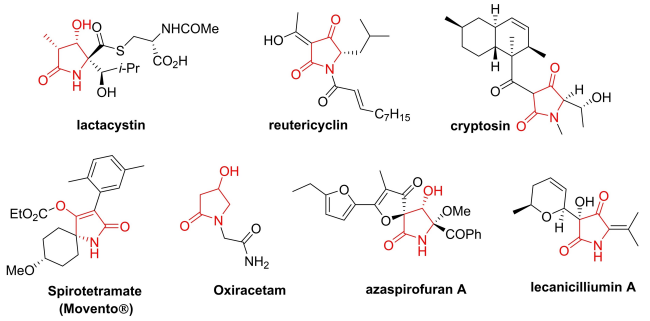
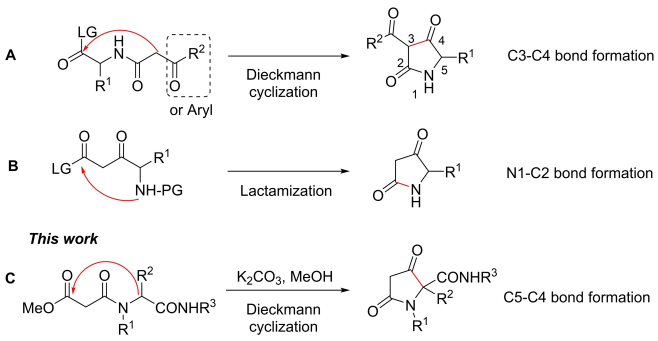


Figure 1. Structure of biologically active tetramic acid derivatives.



Scheme 1. General routes to tetramic acid core formation. A) synthetic and biosynthetic model of Dieckmann cyclization; B) synthetic and biosynthetic model of C–N bond formation; C) Tandem Ugi/Dieckmann approach proposed in current work.

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C3–C4 bond formation (Scheme 1 A). The second pathway to pyrrolidinedione ring is realized through the intramolecular nucleophilic attack of nitrogen atom of α-amino keto esters onto ester carbonyl group with the formation of N1–C2 bond[15] (Scheme 1 B). Recently, Ugi-4CR/Dieckmann cyclization strategy for the synthesis of 2,2-disubstituted indolinones[16] and pyrrolinones[17] was applied. Inspired by these studies, we became interested whether Ugi adducts of monomethyl malonate could be substrates for these transformations leading to functionalized tetramic acids with a quaternary carbon center.

Herein, we present the results of our study aimed at developing a facile approach providing tetramic acid derivatives via a consistent Ugi reaction/Dieckmann condensation strategy involving C5–C4 bond formation (Scheme 1 C).

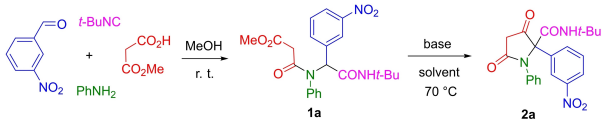
Results and Discussion

To test the feasibility of the outlined approach, a model Ugi amide **1a** was synthesized by stirring *m*-nitrobenzaldehyde, aniline, *tert*-butyl isocyanide and monomethyl malonate in methanol at room temperature overnight. The Ugi adduct precipitated from the reaction mixture and required filtration only. We carried out some optimization studies to find better conditions for the Dieckmann cyclization (Table 1).

It was found that heating **1a** in methanol with DBU at 70 °C for 3 hours led to the desired product **2a** in moderate yield (entry 1). Cyclization did not occur when DIPEA, TEA, or DMAP were used as bases (entries 2–4). We were pleased to observe the formation of target tetramic acid in 83% and 92% yield after replacing the base with cesium carbonate and potassium carbonate respectively (entries 5 and 6). In order to evaluate the influence of the solvent nature the Dieckmann cyclization of **1a** was carried out in various aprotic polar and non-polar solvents in the presence of DBU or K_2CO_3 (entries 7–15). When methanol was replaced by DMF, the yield was drastically reduced with potassium carbonate and almost unchanged with DBU (entries 8 and 7). As it could be seen from table 1 the DBU-promoted cyclization proceeded smoothly in MeCN, THF and DCM leading to the target product **2a** in good yield (entries 10, 12, 14), while the use of toluene led to a decrease in the yield (entry 15). The cyclization did not occur in the presence of K_2CO_3 in THF and DCM (entries 11, 13) even after heating for 3 days. When acetonitrile was used, the cyclized product **2a** was obtained in 37% yield after prolonged heating (entry 9). The observed results for potassium carbonate are probably due to its low solubility in these solvents.

Given that methanol is used in both steps we decided to carry out the reaction in one-pot fashion (Table 1). Upon completion of Ugi adduct formation the solution was diluted to a concentration of 0.13 M, the base was added and the mixture was heated at 70 °C. It was found that one-pot procedure led to the target tetramic acid, albeit with significant drop in yield due to multiple side products formation (entries 1, 5, 6). Based on the results of the optimization, it can be concluded that the use of methanol and potassium carbonate and carrying out the reaction via a step-by-step protocol are the conditions of choice. The advantage of this method is that the tetramic acid obtained does not require any further purification after the reaction work up.

Table 1. Optimization studies for Dieckmann cyclization.

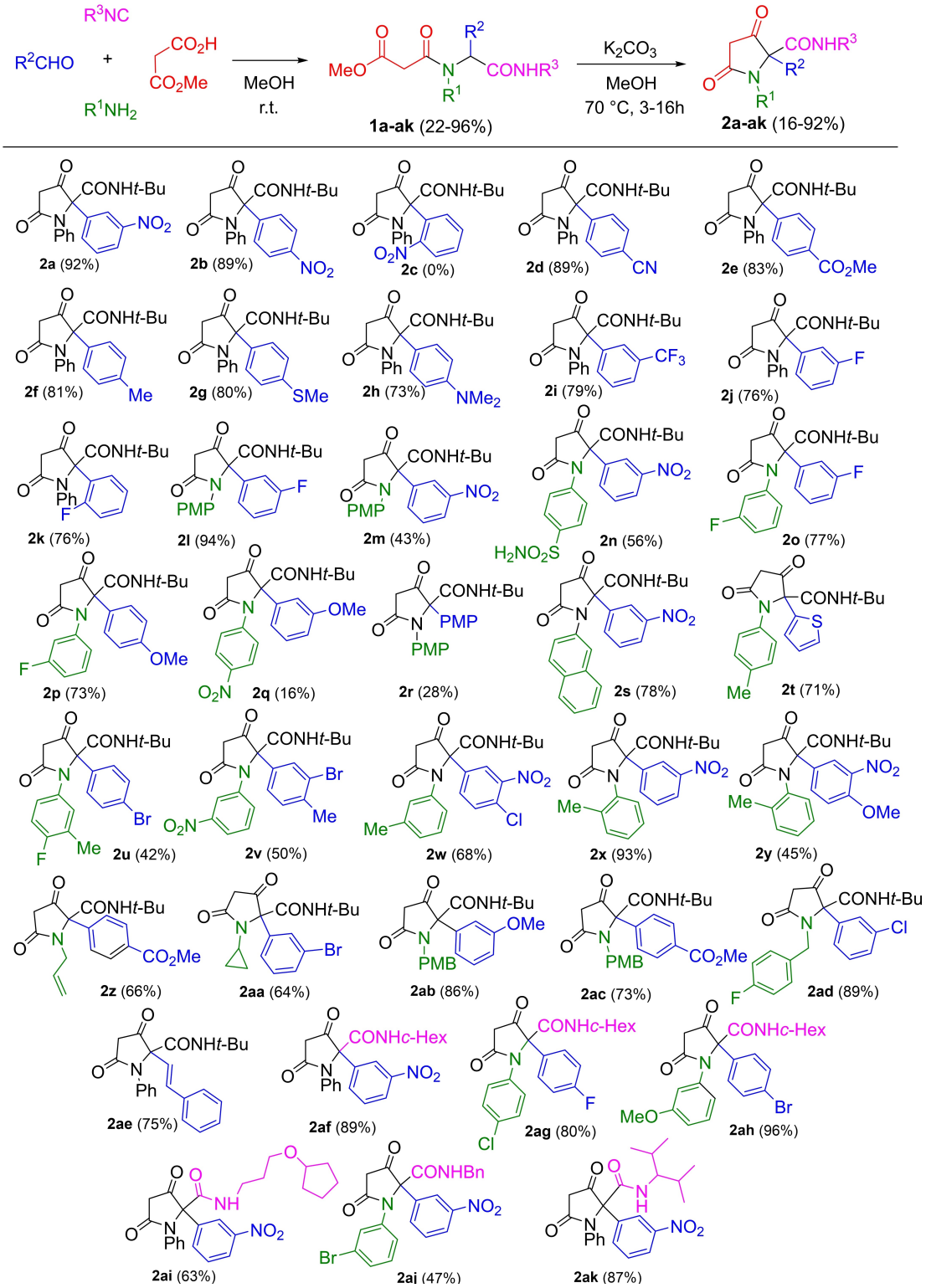


Entry	Base	Solvent	Yield,[a,c] % 1a→2a	Yield,[a,d] % One-pot
1	DBU	MeOH	54	18
2	DIPEA	MeOH	NR[b]	NR
3	TEA	MeOH	NR	NR
4	DMAP	MeOH	NR	NR
5	Cs_2CO_3	MeOH	83	26
6	K_2CO_3	MeOH	92	32
7	DBU	DMF	51	–
8	K_2CO_3	DMF	54	–
9	K_2CO_3	MeCN	37[e]	–
10	DBU	MeCN	72	–
11	K_2CO_3	THF	NR[e]	–
12	DBU	THF	73	–
13	K_2CO_3	DCM	NR[f]	–
14	DBU	DCM	79[f]	–
15	DBU	PhMe	48	–

[a] Isolated yield. [b] NR = no reaction. [c] Reaction conditions: 1a (0.25 mmol), base (0.3 mmol), solvent 1.8 mL, heating at 70 °C with TLC monitoring. [d] Reaction conditions: amine (0.25 mmol), aldehyde (0.25 mmol), monomethyl malonate (0.25 mmol), *t*-BuNC (0.25 mmol) in 0.5 mL of MeOH and stirred overnight at room temperature, diluted to 0.13 M and base (0.3 mmol) was added, then heating at 70 °C.[e] Heating at 70 °C for 3 days with TLC monitoring. [f] Heating at 40 °C for 3 h.

Thus, a series of adducts **1a–ak** were synthesized via a four-component Ugi reaction of aldehydes, aryl or alkyl amines, isocyanides and monomethyl malonate. Most of the adducts precipitated from the reaction mixture and were isolated by simple filtration. In the case of oily products, the solvent was removed under reduced pressure and the crude material was treated with *n*-hexane prior to the next step. With the optimized conditions in hand, the scope and limitations of the method were investigated (Scheme 2).

As can be seen from Scheme 2, the reaction is tolerant to different substituents in both the amine and isocyanide parts of the molecule, yielding tetramic acids **2** in good to moderate yields. It is worth noting that the ^{1}H NMR spectra of the acids obtained contain only one set of signals attributed to the keto form, no enolization was observed at room temperature. The influence of the substituents in the aldehyde moiety (R^2) of compounds **1** depends both on the position of the group and on its electronic effect. The reaction is slightly sensitive to the electronic effect of the substituent at *p*- and *m*- positions of the aldehyde phenyl ring (see for *para* **2b**, **2d**, **2f**, **2g**, for *meta* **2a,**



Scheme 2. The scope of Ugi reaction/Dieckmann condensation sequential protocol.

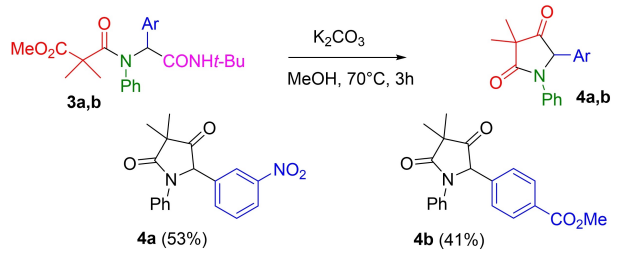
2i, 2j, 2ab). It was found that cyclization of **1c** with the nitro group in the *ortho* position did not lead to the formation of the target product (**2c**), instead resinification was observed. When the *o*-fluoro substituted amide **1k** was used, after heating for 3 h in MeOH at 70 °C, only traces of tetramic acid were detected and the reaction mixture contained unreacted starting material. Prolonged heating for 16 h gave the desired product **2k** in 76% yield. This may be related to steric hindrance caused by an *ortho* group close to the reaction center, which makes nucleophilic attack on the carbonyl group difficult.

In contrast, *N*-*o*-tolyl amides easily underwent Dieckman cyclization to give target products **2x**, **2y**. The use of the Ugi adduct with electron donating groups in both the amine and aldehyde moieties resulted in a significant decrease in yield (**2r**). It should be noted that in this case the reaction also required prolonged heating for 6 h to achieve complete conversion of the starting material. Finally, a dramatic decrease in yield was observed in the case of nitrophenyl substituents on the nitrogen atom (**2q**, **2v**).

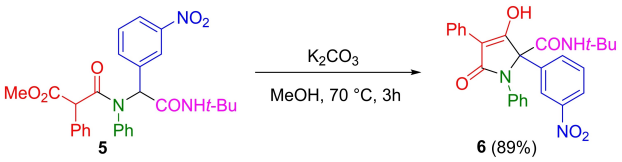
Interestingly, not only aryl aldehydes could be used in the proposed approach, but also cinnamoyl aldehyde derivatives underwent Dieckmann cyclization smoothly, giving compound **2ae** in 75% yield. Variation of the isocyanide moiety has no significant effect on the reaction outcome.

Unexpectedly, when *gem*-dimethyl Ugi adducts **3a,b** were subjected to Dieckmann condensation under the above conditions, it was found that the cyclization was accompanied by decarbamoylation resulting in tetramic acids **4** lacking exocyclic amide function (Scheme 3).

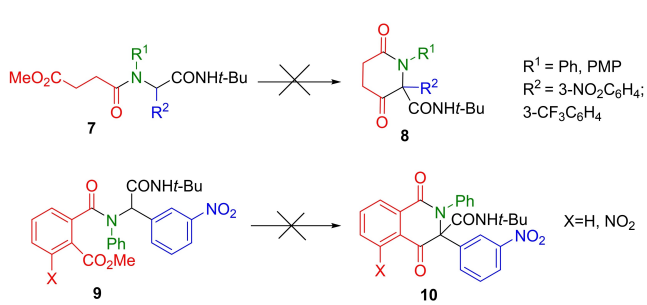
To further investigate the influence of the substituent in the α-position of the β-oxopropionic moiety, amide **5** was subjected to Dieckmann cyclization (Scheme 4). The target tetramic acid **6** was obtained in 89% yield; no product of carbamoyl function loss was detected. The ^{1}H NMR spectrum showed that compound **6** exists in enol form.



Scheme 3. Dieckmann condensation of *gem*-dimethyl Ugi adducts **3a,b**.



Scheme 4. Dieckmann cyclization of compound **5**.



Scheme 5. Evaluation of the method scope involving Ugi adducts **7** and **9**.

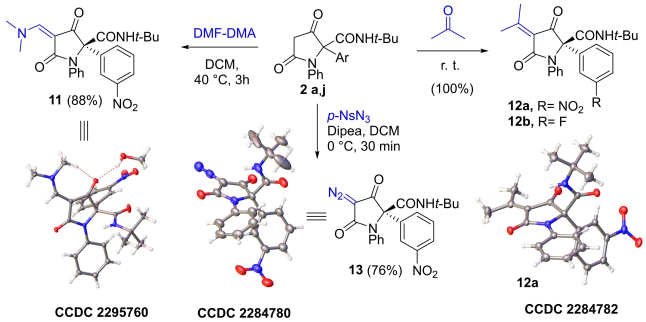
Following our continuing interest in the synthesis of medicinally relevant isoquinolones[18] and pyridinones[19] we further focused on the possibility of extending our approach for piperidinedione (**8**) and isoquinolinedione (**10**) ring formation. To this end, Ugi adducts **7** and **9** were subjected to Dieckmann condensation (Scheme 5). Unfortunately, no cyclized products were observed even when harsh conditions were applied (*t*-BuOK in DMSO at 150 °C). The ^{1}H NMR spectra of the reaction mixtures contained signals from the starting compounds and products of their decomposition.

The presence of free methylene group in tetramic acids obtained in the present work opens a wide field for post modification. It was found that the acidity of CH_2-protons is enough to react readily with acetone at room temperature to give products **12a,b** in quantitative yield (Scheme 6). Acetone was used as both solvent and reagent. Interaction with *N,N*-dimethylformamide dimethyl acetal (DMF–DMA) in DCM gave product **11** in 88% yield after stirring for 3 h at 40 °C. The diazo transfer reaction of tetramic acid **2a** proceeds smoothly in DCM at 0 °C to afford the diazo compound **13** in 76% yield. The formation of stable diazo derivative opens the possibility for the synthesis of fused[20] or spiro heterocycles[21] or the insertion of various groups that are difficult to incorporate by other methods.

All structures were confirmed by the standard set of analytical data, including ^{1}H NMR, ^{13}C NMR, HRMS, IR, and X-ray for selected structures.

Conclusions

In summary, we have developed a convenient approach toward medicinally relevant tetramic acids based on the Ugi reaction/Dieckmann cyclization sequence. The reaction is tolerant to various substituents in the amine, aldehyde and isocyanide moieties opening up the possibility of three points of structural diversity. Cyclization of α,α-dimethyl-3-oxopropanoate derivatives resulted in the pyrrolidine-2,4-dione core with loss of the exocyclic amide function. All tetramic acids synthesized in this work exist in the tautomeric keto form, with the exception of the fully enolized 4-phenylpyrrolidinedione. Several routes for post-modification of the free methylene group in tetramic acids obtained were proposed.



Scheme 6. Variants for the post-modification of synthesized tetramic acids.

Experimental section

General information

NMR spectroscopic data were recorded using a 400 MHz spectrometer (400.13 MHz for ^{1}H and 100.61 MHz for $^{13}C\{1H\}$, and 376 MHz for $^{19}F\{1H\}$) in $CDCl_3$ and were referenced to residual solvent proton signal ($\delta H = 7.26$) and solvent carbon signal ($\delta C = 77.0$). Melting points were determined with a melting point apparatus RD-MP in the open capillary tubes. Mass spectra were recorded using a HRMS-ESI-qTOF spectrometer Nexera LCMS-9030 (electrospray ionization mode). IR spectra were recorded using a Fourier transform infrared Shimadzu spectrophotometer IRAffinity-1. Analytical thin-layer chromatography was carried out on UV-254 silica gel Macherey-Nagel plates using appropriate eluents. Compounds were visualized with short-wave-length UV light. Column chromatography was carried out on silica gel Merk grade 60 (0.040–0.063 mm) 230–400 mesh. Single crystal X-ray data were obtained using an Agilent Technologies SuperNova Atlas diffractometer. The crystals of compound **11** were obtained by slow evaporation from $CHCl_3$/MeOH solution at room temperature; the crystals of products **12a**, **13** were obtained by slow evaporation of $CDCl_3$ solutions at room temperature. The crystals of **11**, **12a**, **13** were kept at 293(2)K during data collection. Using Olex2[22] the structure was solved with the ShelXT[23] structure solution program using Intrinsic Phasing and refined with the ShelXL[24] refinement package using Least Squares minimization.

General procedure for the synthesis of compounds 2, 4 and 6

The corresponding amine (1 mmol) and aldehyde (1 mmol) were mixed in 2 mL of MeOH, the mixture was stirred for 10 min, followed by addition of monomethyl malonate (1 mmol, 118 mg) and isocyanide (1 mmol). The mixture was stirred overnight at room temperature. In the case of solid products, the precipitate was filtered off and dried in air. When no precipitate was formed, the solvent was removed under reduced pressure, the crude was ultrasonicated with *n*-hexane, hexane fraction was discarded and the residue was used in the next step.

To 10 mL vial with a screwing cap equipped with a magnetic stirring bar Ugi adduct (0.4 mmol) and K_2CO_3 (0.5 mmol, 69 mg) were added and dissolved in 3 mL of MeOH. The reaction mixture was stirred for 3 h at 70 °C (6 h for compound **2r**; 16 h for compound **2k**). Upon the completion, the solvent was removed under reduced pressure. The obtained crude material was quenched with water (4 mL) and acidified with 1 M HCl to adjust pH 2–3. The precipitate formed was extracted with $CHCl_3$ (3 × 15 mL), washed with brine, and dried over Na_2SO_4. The solvent was removed under reduced pressure to give target tetramic acids.

Supporting Information

The Supporting Information contains experimental procedures, characterization data, copies of ^{1}H,^{13}C, and ^{19}F NMR spectra, IR spectra as well as X-ray data.

Acknowledgements

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Conflict of Interests

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

Keywords: tetramic acid · pyrrolidine-2,4-dione · Ugi reaction · Dieckmann condensation · MCR

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[25] Deposition Numbers 2295760 (for **11**), 2284782 (for **12a**), and 2284780 (for **13**) contain the supplementary crystallographic data for this paper. These data are provided free of charge by the joint Cambridge Crystallographic Data Centre and Fachinformationszentrum Karlsruhe Access Structures service.

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