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Solid-phase synthesis of tetramic acids

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Abstract

Upon treatment with base, *N*-acylated α-amino acids loaded on Wang resin undergo cyclative Claisen-type condensation to release the tetramic acid in high yield and purity. The use of tetrabutylammonium hydroxide as base simplifies product purification, as it can be scavenged by acidic Amberlyst A-15 ion exchange resin. The diversity of the tetramic acids can be further increased by reductive alkylation of the starting amino acid.

Keywords: combinatorial chemistry; solid-phase synthesis; pyrrolidinones; condensations

The combinatorial synthesis of chemical libraries is now an established source of molecular diversity [1,2]. Initial focus on linear oligomers has shifted to more conformationally restricted small molecules, particularly heterocycles [3], for drug discovery applications. Such chemical libraries fall into one of two general categories. 'Focused' libraries explore diversity space around a narrowly defined structure and are best suited for lead optimization, whereas 'prospecting' libraries [4] are intended for the discovery of novel leads against a variety of assay targets.

In their seminal solid-phase syntheses, Ellman [5] and the Parke-Davis group [6] chose the benzodiazepine and hydantoin scaffolds, as many pharmacologically active examples were already known. Natural products represent another profitable source of suitable core structures for prospecting. For example, the use of diketopiperazines as constrained dipeptidomimetics was recognized by nature long before the advent of medicinal chemistry. Similarly, we were interested in exploiting the 2,4-pyrrolidinedione or tetramic acid template. Many naturally occurring tetramic acids have been isolated, and exhibit a broad range of biological activities [7]. Recently, we devised [8] a solution-phase combinatorial synthesis of tetramic acids in which an ion exchange resin served the dual functions of a basic reagent and a purification method. Here, we report the adaptation of this protocol to solid-phase.

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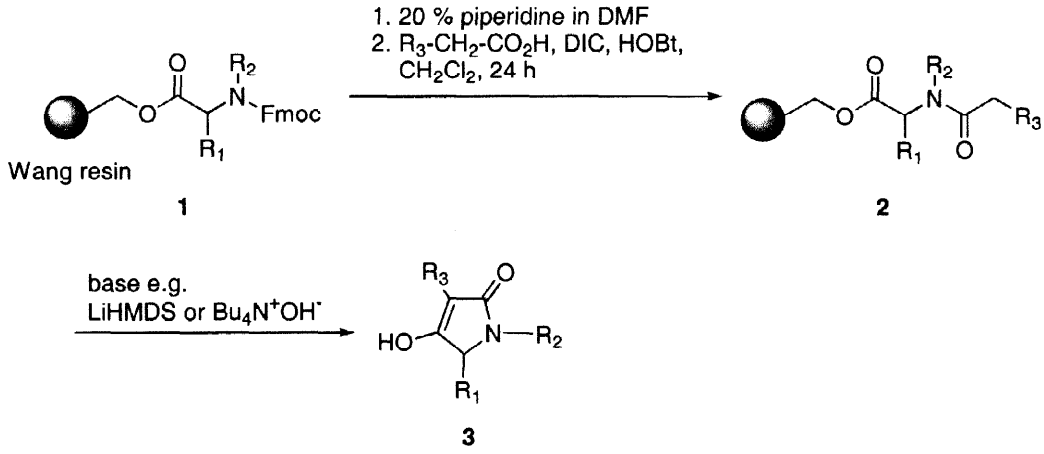
Amino acids (**1**, Scheme 1, R_2 = H) loaded on Wang resin were acylated with carboxylic acids bearing electron-withdrawing groups (R_3) to give amides **2**. Upon base treatment, these amides undergo cyclative Claisen-like condensation to release the tetramic acid (**3**). Crowley and Rapoport carried out a pioneering study [9,10] on the solid-phase Dieckmann condensation of diesters and the factors determining the direction of cyclization. In our case (R_3 = carbanion-stabilizing), the amide α-protons are much more acidic than the ester α-proton, resulting in unidirectional cyclative cleavage. Furthermore, some of our R_3 substituents are not capable of being attacked nucleophilically, thus limiting the cyclization to a single pathway. Despite the potential of the reaction, we are unaware of other Dieckmann-like condensations in the modern era [11] of solid-phase organic synthesis.



Scheme 1

Most of the tetramic acids give a positive reaction with iron (III) chloride solution, providing a sensitive and rapid method of monitoring product formation. The optimum base for the cyclization is dictated by the convenience of product purification. Thus, with potassium *tert*-butoxide and lithium hexamethyldisilazane, removal of the inorganic salts is necessary. We find it more convenient to use tetrabutylammonium hydroxide. This is effectively scavenged after the reaction by treatment with acidic Amberlyst A-15 resin[1] [12]. Other groups have also reported the use of ion exchange resins in the cleanup of solid-phase reaction products [13,14]. Following resin treatment, a final wash with hexanes removes any hydrophobic impurities.

Additional diversity in the tetramic acids can be achieved by using *N*-alkyl amino acids (R_2 ≠ H). These were either obtained commercially or by solid-phase reductive alkylation [15].

[1] Purchased from Fluka (loading of 4.6 meq sulfonic acid/gm). The resin was washed with dry methanol and dried under vacuum prior to use.

Subsequent acylation and cyclization then gives *N*-substituted tetramic acids. Representative examples of the tetramic acids we have prepared are provided in Table 1.

Tetramic acid	R_1	R_2	R_3	Yield [%][a]	Purity [%]
3a	H	H	CN	83	88
3b	H	CH_3	2-NO_2-C_6H_4	85	65
3c	CH_3	CH_2Ph[c]	CN	91	63
3d	CH_2Ph	H	CN	85	90
3e	CH_2Ph	H	$P(O)(OEt)_2$	81	96
3f	CH_2Ph	H	2-NO_2-C_6H_4	80	92
3g	CH_2OH[b]	H	CN	88	91
3h	CH_2OH[b]	H	$P(O)(OEt)_2$	86	60
3i	$CH_2C_6H_4OH$[b]	$CH_2C_6H_4$-4-OMe[c]	SPh	68	91
3j	$CH_2CH(CH_3)_2$	$CH_2C_6H_4$-4-OMe[c]	SPh	78	70
3k	$CH(CH_3)_2$	$CH_2C_6H_4$-4-OMe[c]	CN	91	95

[a]All compounds were fully characterized spectroscopically. Purity was determined by reverse-phase HPLC with diode array UV detection at 254 nm.

[b]Removal of the serine and tyrosine side-chain *tert*-butyl ether protecting groups occurred during the Amberlyst A-15 treatment.

[c]These groups were introduced by reductive alkylation of the amino acid (aldehyde 10 mol eq, $NaBH(OAc)_3$ 15 mol eq, CH_2Cl_2, 8 h).

Table 1
Yield and purity of representative tetramic acids.

Typical experimental procedure:

Val-Wang resin (300 mg, 0.20 mmol) was suspended in CH_2Cl_2 (10 mL), followed by the addition of *p*-anisaldehyde (248 μL, 10 mol eq) and sodium triacetoxyborohydride (649 mg, 15 mol eq). After agitation for 8 h, the resin was filtered, washed [DMF, MeOH, CH_2Cl_2, 3x5 mL each] and dried. The resin was resuspended (CH_2Cl_2,10 mL), followed by the addition of hydroxybenzotriazole hydrate (413 mg, 15 mol eq) and cyanoacetic acid (260 mg, 15 mol eq). The reaction mixture was cooled to 0 °C, and diisopropylcarbodiimide (638 μL, 20 mol eq) added slowly. After warming to room temperature, the resin was agitated for 18 h, filtered, washed [DMF, MeOH, CH_2Cl_2, 3x5 mL each] and dried.

Cyclative cleavage was accomplished by resuspending the resin in THF (10 mL) and tetrabutylammonium hydroxide (816 μL of 1M solution in MeOH) and agitation for 6 h. The product was filtered off, the resin washed [THF, 3x10 mL] and the combined filtrates concentrated. The residue was stirred vigorously for 1 h in THF (10 mL) and Amberlyst A-15 resin (710 mg), followed by filtration and washing [THF, 3x10 mL] of the ion exchange resin. The combined filtrates were concentrated, and the Amberlyst A-15 treatment repeated. The residue was then washed with hexane [2x5 mL] to yield tetramic acid **3k** as a solid (53 mg, 91

% overall): mp 101-103 °C; IR (Nujol) 2223, 1651 cm^{-1}; ^1H NMR (400 MHz, acetone-d_6) δ 0.85 (3H, d, J = 6.9 Hz), 1.04 (3H, d, J = 6.9 Hz), 2.33 (1H, m), 3.77 (3H, s), 3.90 (1H, m), 4.15 (1H, d, J = 15.3 Hz), 4.93 (1H, d, J = 15.3 Hz), 6.89 (2H, d, J = 8.4 Hz), 7.22 (2H, d, J = 8.4 Hz); ^{13}C NMR (100 MHz, acetone-d_6) δ 17.2, 18.5, 44.8, 56.1, 66.2, 84.3, 113.3, 115.5, 130.66, 130.72, 168.9, 184.0; HRMS calcd for $C_{16}H_{18}N_2O_3$ 286.13174 (M^+), found 286.13174.

In summary, we have developed an efficient solid-phase synthesis of tetramic acids, which uses simple building blocks as reaction inputs. The procedure is complementary to our previous [8] solution-phase methodology. The solid-phase version has certain advantages for micro-scale synthesis of large libraries, including the possibility of split-and-mix synthesis [16,17] to generate pooled samples.

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