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A Facile Solid Phase Synthesis of Tetramic Acid

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Abstract—The condensation of *N*-acylated amino acids with polymer-supported cyclic malonic acid ester was carried out in the presence of DCC/DMAP. The cyclisation of the intermediate resin, by heating in an organic solvent, gave the *N*-protected tetramic acid derivatives in good yields and high purity.

Tetramic acid derivatives are a class of natural products that have attracted significant attention over the years as a result of their biological activities and synthetic challenges presented by their complex structures.[1] Tetramic acid derivatives are widely found as a metabolic product and some have various biological activities. Representative examples of this structural class include Streptolydigin,[2] Tirandamycin,[3] BU2313A, BU2313B,[4] BlasticidinA[5] and Vancoresmycin.[6] 5-Oxotetramic acids are known as active glycolic acid oxidase inhibitors.[7]

The construction of heterocycles on solid phase via linkage directly to the ring has proven in general to be a valuable strategy because it permits facile variation of substituents.[8] Recently, several reports have appeared describing the solid phase synthesis of tetramic acids.[9–11] Kulkarni and Ganesan[9] describe the preparation of tetramic acids with substitutents other than acyl at the 3-position. Tetrabutyl ammonium hydroxide was employed as the cyclization reagent. However, this requires further treatment of the product with Amberlyst A-15 ion exchange resin as scavenged reagents. Matthews and Rivero[10] also reported preparation of tetramic acid, heating at 85 °C or 24 h with sodium ethoxide was required to effect cyclization. Campbell[11] reported the solid phase synthesis of tetramic acid by cyclative cleavage of the penultimate intermediate via Dieckmann cyclization in the presence of KOH/MeOH.

There are numerous examples[12] in the literature utilizing standard solution phase chemistry in which *N*-protected amino acid are reacted with Meldrum's acid followed by subsequent cyclisation step to provide the targeted tetramic acid. Meldrum's acid is a remarkable reagent for synthesis of the heterocyclic compounds.[13] In our previous research, we have reported the first application of this chemistry to solid phase synthesis.[14] Herein we wish to report a facile solid phase synthesis of tetramic acid from resin-bound cyclic malonic acid ester.

Our solid phase synthesis route begins with Merrifield resin loaded with cyclic malonic acid ester **1** (Scheme 1), which is prepared according to the prelimary communication.[14a] The C-acylation of polymer supported Meldrum's acid **1** by *N*-protected amino acids **2** was carried out using the *N*,*N*′-dicyclohexylcarbodiimide (DCC) and 4-*N*,*N*-dimethylaminopyridine (DMAP) as the condensing agent. This conversion was proceeded in dry CH_2Cl_2 at room temperature. After formation of the polymer supported acylated compounds **3**, excess reagents were removed by washing with the solvents (DMF, EtOH, CH_2Cl_2). Cyclative cleavage was accomplished by resuspending the resin **3** in $CHCl_3$ or EtOAc under reflux. After cleavage, the resin was filtered and washed completely with EtOAc and MeOH. The filtrates were combined to afford the product by evaporation. The product **4** was obtained in good yield and high purity (determined by ^1H NMR without further purification)(Table 1).

For each resin-bound intermediate, the structure was verified by FT-IR spectra. When the resin **1** was transformed to the resin **3**, the carbonyl peak in IR spectra shifted from 1794, 1760 cm^{-1} to 1731, 1660 cm^{-1} (**3a**, X = C_6H_5CO, R = H). Also a new peak appeared at 3439 cm^{-1} (OH group). After cleavage in $CHCl_3$, the ketone resin **5** was obtained which showed carbonyl peak at 1716 cm^{-1} in IR spectra. The ketone resin **5** can

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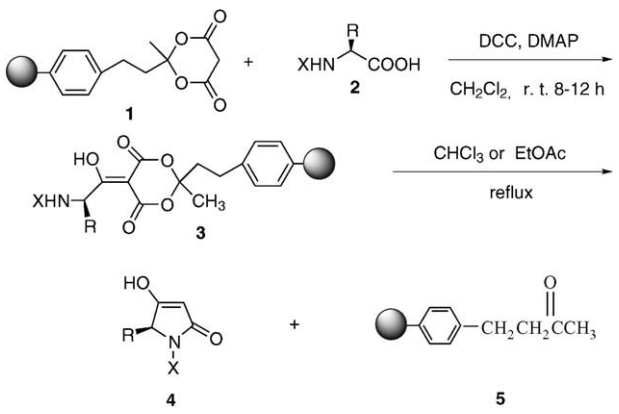

Scheme 1.

Table 1. Solid phase synthesis of tetramic acid

Entry	Product	X	R	Yield (%)[a]	Purity (%)[b]
1	4a	C_6H_5CO	H	92	>93
2	4b	4-$CH_3OC_6H_4$ CO	H	90	>90
3	4c	4-$CH_3C_6H_4$ CO	H	78	>92
4	4d	4-ClC_6H_4CO	H	67	>90
5	4e	$COOCH_2CH_3$	H	88	>94
6	4f	$COOCH_3$	H	78	>91
7	4g	$COOCH_2C_6H_5$	H	76	>90
8	4h	$COCH_3$	H	90	>95
9[c]	4a	C_6H_5CO	H	92	>93
10	4i	C_6H_5CO	CH_3	80	>95
11	4j	Boc	Bu[i]	84	>92
12	4k	Boc	$C_6H_5CH_2$	81	>90
13	4l	Boc	CH_3	88	>90

[a]The yield was based on the loading of resin 1.
[b]Determined by ^1H NMR (400 MHz).
[c]Using the regenerated resin.

be recovered and reused to prepare the cyclic malonic acid ester resin 1.[15] The good result was also obtained when the regenerated resin was used (Table 1, entry 9).

The synthesis of optically active tetramic acid is a research field of major importance as it has relevance to virtually all areas of pharmaceutical industries. The development of such enantiomerically pure compounds has gained increasing interest in organic and medicinal chemistry. [16] So we use an *N*-protected L-amino acid to run this reaction. It was found that the reaction worked very well and give the optically active compounds (**4i**–**4l**) with good yield and high purity. The optical purity of the amino acids is retained in the tetramic acids during the synthesis.

Typical Procedure for the Solid Phase Synthesis of Tetramic Acid

To the suspension of cyclic malonic acid ester resin 1 (500 mg, 1.20 mmol/g) in CH_2Cl_2 (5 mL), *N*-protected amino acid (3 mmol), DMAP (4.5 mmol, 0.55 g) were added. Then the solution of DCC (3.6 mmol, 0.72 g) in CH_2Cl_2 (5 mL) was added dropwise under nitrogen. The mixture was stirred at room temperature for 10 h. The resin was filtered and washed completely with DMF, AcOH/MeOH (1:10), MeOH, CH_2Cl_2. The newly formed resin in $CHCl_3$ or EtOAc (20 mL) was refluxed for 2 h. The resin was filtered and washed with EtOH and acetone completely. The filtrates were combined to afford the product by evaporation.[17]

In summary, we have developed an efficient, facile method of solid phase synthesis of tetramic acid from polymer supported cyclic malonic acid ester. This is a traceless cyclative cleavage under mild conditions. The *N*-protected tetramic acid was prepared with good yield and high purity. Further work is in progress on the solid phase synthesis of heterocyclic compounds via the resin-bound cyclic malonic ester.

Acknowledgements

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15. The loading of the regenerated cyclic malonic acid ester is 1.20 mmol/g which is determined by reversed titration with hydrochloride acid after saponification with excess NaOH in EtOH.

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17. Sample analysis: **4a**: 1-benzoyl-4-hydroxy-3-pyrrolin-2-one. white solid. mp. 179–180 °C (lit[12a] 180 °C). ^{1}H NMR (DMSO-d_6): δ 4.40 (s, 2H), 4.96 (s, 1H), 7.34–7.41 (m, 2H), 7.47–7.51 (m, 3H), 12.57 (s, 1H). IR (KBr): ν_{max} (cm^{-1}). 2928, 1671, 1620, 1574, 1353, 1330, 1286. MS *m*/*z* (relative intensity) (EI, 70 eV) 203 (M^+, 8), 175 (12) 105 (100) 77 (64).