Tetrahedron Letters 53 (2012) 3486–3489

Contents lists available at SciVerse ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Microwave-assisted S_NAr reaction of 2,4,6-trichloro-1,3,5-triazine for the rapid synthesis of C_3-symmetrical polycarboxylate ligands

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ARTICLE INFO

Article history:
Received 23 December 2011
Revised 18 April 2012
Accepted 27 April 2012
Available online 2 May 2012

Keywords:
Microwave-assisted synthesis
1,3,5-Triazine
Polycarboxylate ligand
Metal–organic frameworks

ABSTRACT

The microwave-assisted S_NAr reaction of 2,4,6-trichloro-1,3,5-triazine with various unprotected amino acids was developed for the synthesis of C_3-symmetrical polycarboxylate ligands which can be used as structural directing units in metal–organic frameworks. The reactions were performed in water using a domestic microwave oven as the heating device. In comparison to the reactions performed under conventional heating, the reactions under microwave irradiation proceeded much more rapidly within 20 min to afford the desired ligands in comparative yields to those obtained by conventional heating.

Rational design of new polymeric coordination compounds, also known as metal–organic frameworks (MOFs), has become an increasingly important research field due to the intriguing structural diversity and potential applications of these functional materials.[1–3] Based on self-assembly of metallic centers and bridging organic linkers, the precisely controlled formation of complex structural architectures can be achieved depending on the shapes of the organic molecules and the specific interactions within the frameworks.

Recently, many studies have focused on the use of polycarboxylate triazine-based ligands as the structural directing units in the construction of novel functional MOFs.[4–14] Due to the stability of the triazine ring and the reactivity of chlorine substituents atoms toward nucleophiles,[15] new ligands can be synthesized by substitution of 2,4,6-trichloro-1,3,5-triazine (TCT) with various types of nucleophiles containing carboxyl groups. Tri-substituted C_3-symmetrical triazine derivatives such as *N,N′,N″*-1,3,5-triazine-2,4,6-triyltris-glycine (TTG),[9,10,13] 1,3,5-triazine-2,4,6-triamine hexaacetic acid (TTHA),[5,7,11] 1,1′,1″-(benzene-1,3,5-triyl)tripiperidine-4-carboxylic acid,[12] 1,3,5-triazine-2,4,6-trithiotri-3-benzoic acid,[6] and 1,3,5-triazine-2,4,6-triaminetri-4-benzoic acid[4,8] have been applied successfully in the construction of MOFs with new structural architectures and unique properties. Generally, the syntheses of C_3-symmetrical triazine carboxylate ligands were performed at high temperature over a long period of time. New energy and time efficient methods are thus potentially useful for the synthesis of highly structurally diverse ligands having unique properties.

Microwave-assisted organic synthesis has proved to be a useful technique in enhancing the reaction rate relative to conventional heating.[16,17] By taking advantage of the ability of some liquids and solids to transform electromagnetic radiation into heat, the heating rate under microwave irradiation is several-fold higher than heating with traditional equipment. In addition, since the heat generated by microwave irradiation is proportional to the dielectric constant (ε) of the media, water ($\varepsilon = 78$) is an excellent solvent for microwave synthesis which can lead to cleaner and more environmentally benign processes.[18,19]

Although microwave-assisted synthesis has been applied to a variety of reactions,[16,17] it has not been explored in the S_NAr reaction of TCT, neither in organic solvents nor in aqueous media. To our surprise, only one example has reported the S_NAr reaction of aryl halides with amino acids in water under microwave irradiation.[20] The reactions of highly activated 2,4-dinitrofluorobenzene with natural amino acids in a monomode microwave reactor were complete within 40 s at 80 °C to afford the N-arylated amino acids in excellent yields using 2 equiv of $NaHCO_3$ as base.

Herein, we report the microwave-assisted synthesis of C_3-symmetrical polycarboxylate triazine-based ligands via S_NAr reaction of TCT with unprotected amino acids. All the reactions were carried out in a domestic microwave oven (Samsung GB872, 850 W, 2.54 GHz) using water as the solvent in an open-vessel.

In a preliminary study, the effects of the microwave conditions including microwave power and exposure time were investigated on the synthesis of the known ligand, TTG. For safety considerations and ease of manipulation, irradiation of the reaction mixture was performed repeatedly over a short period of time to avoid vigorous boiling and superheating of the solution which may cause an

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http://dx.doi.org/10.1016/j.tetlet.2012.04.124

explosion. After each MW irradiation period, the sample was cooled for 1 min in a water bath. The synthetic conditions were adapted from the previously reported procedure for the synthesis of TTHA.[5] Typically, a mixture of 1.0 equiv of TCT, 3.6 equiv of glycine, and 10 equiv of NaOH in water was irradiated using a microwave oven according to the conditions listed in Table 1. Upon completion of the reaction as monitored by TLC, the cooled reaction mixture was acidified with concentrated hydrochloric acid and filtered. The filtrate was washed several times with water then ethanol to afford the tri-substituted product in high purity; no further purification was necessary.

As shown in Table 1, slightly lower yields of TTG were obtained at low irradiation power (100 W, entries 1 and 2). The highest yield (81%) was produced with a minimum exposure time of 5 × 2 min at 180 W (entry 3). Prolonged irradiation at the same microwave power resulted in product loss through vigorous boiling of the reaction mixture (entry 4). At 300 W, the reaction mixture goes to complete boiling within 1 min and again a low yield was isolated due to escape of the reaction mixture (entry 5).

The microwave conditions were further optimized by varying the type and quantity of base (Table 2). The highest yield of TTG was generated using 10 equiv of NaOH. Attempts to lower the amount of NaOH or use a weaker base such as sodium carbonate or potassium carbonate resulted in poorer conversion which complicated the reaction work-up. An excess of strong base is presumably required to shift the equilibrium toward the reactive amino acid anions through deprotonation of the $-NH_3^+$ group of the amino acid zwitterions.

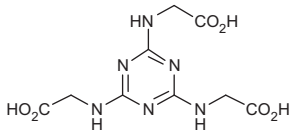
The efficiency of the microwave method was compared with that of conventional heating. TCT was reacted with glycine in the presence of 10 equiv of NaOH under reflux in an oil bath for 10 min. In this case, the reaction was incomplete and TTG was isolated in only 32% yield. As expected, an enhancement in the reaction rate and a shorter reaction time were achieved under microwave heating.

To expand the scope of this reaction, a variety of amino acids were employed in the synthesis of polycarboxylate triazine-based ligands under the optimized microwave conditions. Unless otherwise specified, all the reactions were carried out in water with TCT (0.54 mmol), amino acid (1.94 mmol), and NaOH (5.4 mmol) at 180 W for 5 × 2 min. For comparison, the same reactions were conducted under reflux conditions for 12 h. The isolated yields from both methods are summarized in Table 3.

It was found that under MW irradiation, the reaction time was reduced by several-fold when compared with reactions performed under conventional heating. Diverse amino acids containing primary, secondary, or aromatic amino groups were sufficiently reactive to afford the corresponding tri-substituted products in good yields. Racemic α-amino acids such as tyrosine, aspartic acid, and glutamic acid (entries 3–5) could be applied directly in the substitution reaction without side-chain protection. However, when using phenylalanine and proline as the nucleophiles, the desired products could not be isolated from the residual starting amino acids, while histidine gave complicated product mixtures possibly through side reactions from the side-chain imidazole (data not shown).

Nevertheless, the yields of the tri-substituted products from microwave heating were in most cases comparable to those of the standard heating method, except for compound **1i** where a

Table 1
Effect of microwave conditions on the percentage yield of TTG[a]



TTG

Entry	Microwave power (W)	Exposure time (min)	Isolated yield (%)
1	100	5 × 2	76
2	100	5 × 3	80
3	180	5 × 2	81
4	180	2 × 5	72
5	300	5 × 1	78

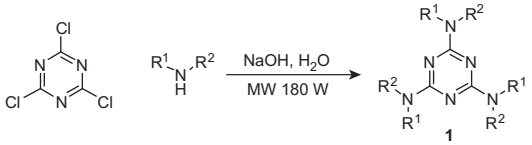
[a] All reactions were carried out with TCT (0.54 mmol), glycine (1.94 mmol), and NaOH (5.4 mmol) in H_2O (2 mL).

Table 2
Effect of base on the percentage yield of TTG[a]

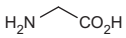
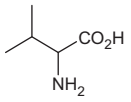
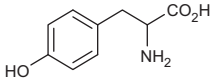
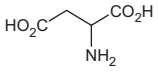
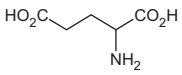
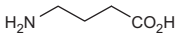
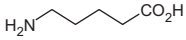
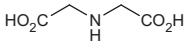
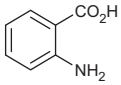
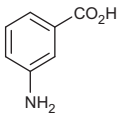
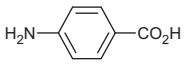
Entry	Base (equiv)	Isolated yield (%)
1	NaOH (10)	81
2	NaOH (7.2)	32
3	NaOH (3.6)	13
4	Na_2CO_3 (10)	63
5	K_2CO_3 (10)	56
6	NaOH/$NaHCO_3$ (5/3.3)	51

[a] All reactions were carried out with TCT (0.54 mmol) and glycine (1.94 mmol) in H_2O (2 mL) at 180 W, 5 × 2 min.

Table 3
Synthesis of polycarboxylate ligands containing a 1,3,5-triazine core



1

Entry	NHR^1R^2	Product[Ref.]	Isolated yield (%)	
			Microwave	Reflux
1		**1a**[21]	81	80
2		**1b**	78[a]	73
3		**1c**	80	83
4		**1d**	54[a]	67
5		**1e**	87	86
6		**1f**[21]	89[a]	87
7		**1g**[21]	78[a]	70
8		**1h**[5]	89	86
9		**1i**[22]	28[a]	75
10		**1j**	7[a]	85
11		**1k**[4,23]	87	80

[a] 180 W, 10 × 2 min.

significantly lower yield was produced under microwave irradiation (entry 9). Attempts to drive the reaction to completion by raising the microwave power under prolonged irradiation failed to give good conversion. Intramolecular hydrogen bonding is seemingly responsible for the poor nucleophilicity of 2-aminobenzoic acid. Under microwave conditions, where the reaction was heated and cooled down intermittently, the amount of free amino group may be insufficient to react with TCT and thus leads to a slower rate of reaction. It should be noted also that although TCT has a tendency to hydrolyze under aqueous alkaline conditions,[24] by-products such as 2,4-dichloro-6-hydroxy-1,3,5-triazine, 2-chloro-4,6-dihydroxy-1,3,5-triazine, and 2,4,6-dihydroxy-1,3,5-triazine (cyanuric acid) were not observed suggesting that the rate of TCT hydrolysis was much slower than amine substitution.

To demonstrate the practicality of the developed microwave protocol, large-scale experiments (5.0 g, 27 mmol of TCT) were carried out in the synthesis of TTG and TTHA using a 250 mL Erlenmeyer flask as the reaction vessel. High yields of TTG (82%) and TTHA (91%) were afforded under microwave irradiation at 180 W with exposure times of 10 × 3 min.

In summary, a straightforward and effective method to synthesize C_3-symmetrical polycarboxylate triazine-based ligands has been developed using microwave-assisted synthesis. The ligands were obtained in good yields and in short reaction times. Compared to conventional heating, the microwave technique provides a rapid, simple, and effective method to generate a variety of polycarboxylate ligands with potential applications in the design of MOFs. Further efforts toward this end will be reported in due course.

General procedure for the microwave-assisted synthesis

A solution of amino acid (1.94 mmol) and NaOH (0.22 g, 5.40 mmol) in H_2O (1 mL) was added dropwise into a 20 mL test tube containing a 1 mL aqueous solution of TCT (0.1 g, 0.54 mmol) at 0 °C. The mixture was allowed to warm to room temperature, boiling chips were added and the reaction vessel was placed on the center of the turn-table in a domestic microwave oven (Samsung GB872, 850 W, 2.54 GHz). The mixture was then irradiated at the specified power for the prescribed time. After the microwave was switched off, the reaction mixture was cooled and acidified with concentrated HCl. The precipitate was collected by filtration, washed successively with H_2O and EtOH before drying at 80 °C to afford the pure product. Novel compounds **1b–e** and **1j** were fully characterized by ^{1}H NMR, ^{13}C NMR, FT-IR, and HRMS analyses. Spectroscopic data for known compounds **1a, 1f–i** and **1k** were consistent with those reported in the literature.

N,N′,N″-1,3,5-Triazine-2,4,6-triyltris-valine (1b)

White powder; mp 267–270 °C; R_f = 0.49 (60% MeOH/EtOAc); ^{1}H NMR (D_2O, 400 MHz): δ 0.67 (dd, J = 28.6, 6.8, 18H), 1.65–1.70 (m, 3H) 2.82 (dd, J = 5.2 Hz, 3H) ppm; ^{13}C NMR (D_2O, 100 MHz) δ 17.0, 31.8, 61.7, 168.5, 183.1 IR (KBr) 2969, 1727, 1615, 1510, 1397 cm^{-1}. HRMS Calcd for $C_{18}H_{29}N_6O_6$ $[M-H]^-$ 425.2154. Found 425.2134.

N,N′,N″-1,3,5-Triazine-2,4,6-triyltris-tyrosine (1c)

White powder; mp (dec) ⩾270 °C; R_f = 0.09 (80% MeOH/EtOAc); ^{1}H NMR (D_2O, 400 MHz): δ 2.30 (dd, J = 13.7, 7.4 Hz, 3H), 2.48 (dd, J = 13.6, 5.2 Hz, 3H), 3.05 (t, J = 8.7 Hz, 3H), 6.22 (d, J = 8.3 Hz, 6H), 6.63 (d, J = 8.3 Hz, 6H) ppm; ^{13}C NMR (D_2O, 100 MHz) δ 39.9, 57.9, 117.9, 123.7, 131.1, 164.4, 168.4, 182.9 ppm. IR (KBr) 3207, 2935, 1588, 1454, 1451, 1412, 1246 cm^{-1}. HRMS Calcd for $C_{30}H_{29}N_6O_9$ $[M-H]^-$ 617.2002. Found 617.2007.

N,N′,N″-1,3,5-Triazine-2,4,6-triyltris-aspartic acid (1d)

White powder; mp (dec) ⩾270 °C; R_f = 0.08 (60% MeOH/EtOAc); ^{1}H NMR (D_2O, 400 MHz): δ 1.96 (dd J = 15.3, 9.1 Hz, 3H), 2.23 (dd, J = 15.2, 4.4 Hz, 3H), 3.16 (dd, J = 9.1, 4.4 Hz, 3H) ppm; ^{13}C NMR (D_2O, 100 MHz) δ 32.2, 62.1, 168.3, 181.0, 183.4 ppm. IR (KBr) 3021, 1692, 1645, 1600, 1512, 1423, 1326, 1250 cm^{-1}. HRMS Calcd for $C_{15}H_{17}N_6O_{12}$ $[M-H]^-$ 473.0910. Found 473.0906.

N,N′,N″-1,3,5-Triazine-2,4,6-triyltris-glutamic acid (1e)

White powder; mp 240–242 °C; R_f = 0.12 (80% MeOH/EtOAc); ^{1}H NMR (D_2O, 400 MHz): δ 1.93–2.31 (m, 6H), 2.45 (t, J = 6.9 Hz, 6H) 4.43–4.55 (m, 3H) ppm; ^{13}C NMR (D_2O, 100 MHz) δ 26.8, 30.7, 56.0, 155.8, 176.5, 178.0. IR (KBr) 3563, 1739, 1631, 1412, 1231 cm^{-1}. HRMS Calcd For $C_{18}H_{23}N_6O_2$ $[M-H]^-$ 515.1379. Found 515.1382.

N,N′,N″-1,3,5-Triazine-2,4,6-triaminetri-3-benzoic acid (1j)

White powder; mp (dec) ⩾300 °C; R_f = 0.08 (60% MeOH/EtOAc); ^{1}H NMR (D_2O, 400 MHz): δ 7.24 (t, J = 7.9 Hz, 3H), 7.43 (d, J = 7.7 Hz, 3H), 7.51 (d, J = 7.9 Hz, 3H), 7.74 (s, 3H) ppm; ^{13}C NMR (DMSO-d_6, 100 MHz) δ 171.6, 165.9, 138.5, 136.8, 128.6, 124.5, 123.8, 122.0. IR (KBr) 3294, 1697, 1542, 1397, 1271, 1008 cm^{-1}. HRMS Calcd for $C_{24}H_{19}N_6O_6$ $[M+H]^+$ 487.1366. Found 487.1363.

Caution! The level of the filled solvent line should not exceed 1/3 of the reaction vessel. Heating under microwave irradiation can produce superheating and explosions. All experiments should thus be performed in a fume hood with an explosion shield.

Acknowledgements

This research was supported by a grant under the program Strategic Scholarships for Frontier Research Network for the Ph.D. Program Thai Doctoral degree from the Commission on Higher Education (CHE), Thailand (to W. Karuehanon). The authors also gratefully acknowledge the Center of Excellence for Innovation in Chemistry (PERCH-CIC), the National Research University Project under Thailand's Office of the Higher Education Commission, and the Graduate School, Chiang Mai University for financial support of this research.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.04.124.

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