SYNTHESIS OF TRI-ARM STAR SHAPED 1,3,5-TRIAZINES CATALYZED BY 1,5,7-TRIAZABICYCLO[4.4.0]DEC-5-ENE (TBD)

MARZIE KARIMI, ALI REZA KARIMI*

Department of Chemistry, Faculty of Science, Arak University, Arak 38156-8-8349, Iran.

ABSTRACT

Facile solution method for the synthesis of tri-arm star shaped 1,3,5-triazines was developed using 1,5,7-Triazabicyclo[4.4.0]dec-5-ene (TBD) by reaction of cyanuric chloride with *O*-nucleophiles.

Keywords: Cyanuric chloride; 1,3,5-Triazines; Nucleophilic reactions; TBD.

INTRODUCTION

2,4,6-Trisubstituted-1,3,5-triazine derivatives are very efficient and important compounds having considerable properties like antifungal,¹ antitumor,² antibacterial³ and antiviral⁴ activities.

Diverse bases such as NaOH, K₂CO₃, NaH, DIPEA have been utilized for synthesis of 2,4,6-trisubstituted-1,3,5-triazine. There are different conditions such as use of various solvents like THF, acetone, mixture of acetone and water, acetonitrile. Also some of reactions are performed under inert atmosphere using Ar.⁵⁻⁸ Industrially, synthesis of these compounds are carried out in homogeneous phase with KOH or NaOH as catalysts.⁹

Moreover, application of metal catalysts in the synthesis of bioactive compounds is sometimes unwanted since the presence of even minute amount of residual metal would lead to serious consequences. Loss of catalyst due to the separation difficulties and corrosion problems in the equipments are other disadvantages of these catalysts.

The known methods⁵⁻⁹ suffered from the drawbacks of low yield, prolonged reaction time, separation difficulties, by-products and the use of toxic solvents and catalysts. The above disadvantages make these methods a little bit complicated to use. Consequently, there is a need for a convenient, facile and efficient method and better yields.

1,5,7-Triazabicyclo[4.4.0]dec-5-ene (TBD) is a bicyclic guanidine base that is known as super base. Among super bases, TBD has high pKa value (pKa = 24.97) and has been widely utilized in organic synthesis.¹⁰ For example, it can promote diverse organic reactions including Wittig reaction, Horner-Wadsworth-Emmons reactions,¹¹ secondary amine alkylation,¹² carboxylation of propylene glycol with CO₂,¹³ synthesis of symmetrically *N,N*-substituted ureas,¹⁴ 5- and 6-enoloxo aldolisation of acyclic ketoaldehydes,¹⁵ intramolecular aldolization of acyclic ketoaldehydes¹⁶ and etc. Considering what was mentioned above, we were interested to develop facile methods for the synthesis of tri-arm star shaped 1,3,5-triazines by reaction of cyanuric chloride with some *O*- and *N*-nucleophiles (Scheme 1).

EXPERIMENTAL

Materials

All chemicals were purchased from Merck Chemical Co. (Germany), Fluka Chemical Co. (Switzerland) and Acros Organics N.V./S.A. (Belgium).

Techniques

Mps were measured on an Electrothermal 9100 apparatus. ¹H-NMR and ¹³C-NMR spectra were recorded on a Bruker 300 MHz instrument (Germany). Fourier transform infrared (FTIR) spectra were recorded on Galaxy series FTIR 5000 spectrophotometer (England). Spectra of solid were performed by using KBr pellets. Vibration transition frequencies were reported in wave numbers (cm⁻¹).

General procedure for preparation of 3a-g using TBD in solution phase: Crushed ice/water (10 mL) was added to stirred solution of 2,4,6-trichloro-1,3,5-triazine (1 mmol) in acetone (10 mL). To the resulting fine white slurry, compounds **2a-2g** (3.2 mmol) and 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD) (30 mol%) dissolved in 5 mL acetone/water mixture (1:1) were added dropwise with vigorous stirring. The reaction mixture was stirred for 2 h at 0 °C and then warmed to room temperature. After stirring for 2 h at room temperature the reaction mixture was refluxed for 18 h and then the resulting

suspension solution was filtered and washed with cold water (3×20 mL) to give the compounds **3a-3g** as the only products.

General procedure for preparation of 3a, 3d, 3f using DBU in solution phase: Crushed ice/water (10 mL) was added to stirred solution of 2,4,6-trichloro-1,3,5-triazine (1 mmol) in acetone (10 mL). To the resulting fine white slurry, compounds **2a, 2d, 2f** (3.2 mmol) and 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU) (3 equiv), dissolved in 5 mL acetone/water mixture (1:1) were added dropwise with vigorous stirring. The reaction mixture was stirred for 2 h at 0 °C and then warmed to room temperature. After stirring for 2 h at room temperature the reaction mixture was refluxed for 18 h and then the resulting suspension solution was filtered and washed with cold water (3×20 mL) to give the compounds **3a, 3d, 3f** as the only products.

General procedure for preparation of 3a-g using NaOH in solid phase: NaOH (3.2 mmol) and compounds **2a-2g** (3.2 mmol) in 1 mL water was mixed in a mortar. After the solvent evaporated, cyanuric chloride (1 mmol) was added to the dry residue and the mixture was grounded in a mortar until a fine powder was formed. After storage at 0 °C for 2 h, the mixture warmed to room temperature. After being placed for 2 h at room temperature the reaction mixture was heated on the oil bath at 100 °C for 18 h. The contents were cooled to room temperature and mixed thoroughly with 10 mL of ethanol. The products were filtered off and washed with cold water and ethanol.

RESULTS AND DISCUSSION

In liquid phase, the nucleophiles **2a-g** and TBD as base were dissolved in acetone/water and were added to a suspension solution of cyanuric chloride in iced water/acetone. The reaction mixture was stirred for 2 h at 0 °C, 2 h at room temperature and 18 h at 60 °C. The resulting suspension solution was filtered and washed with cold water to yield the compounds **3a-3g** (Scheme 1 and Table 1).

An investigation of base quantity and the solvent effect on the reaction indicated that the best yield was obtained using 30 mol% of TBD at acetone/water solution. The reactions were completed in 22 h and after separation, gave excellent isolated yields (Table 1). The amount of base could be reduced to 20 mol% (Table 1, entries **3a-3b**) without affecting the yield.

Table 1. Synthesis of tri-arm star shaped 1,3,5-triazines **3a-g** in different conditions.

Product	TBD ^a (Solution phase) ^b Yields ^d	DBU ^a (Solution phase) ^b Yields ^d	NaOH (Solid phase) ^c Yields ^d
3a	85% ^a / 81% ^e	41%	78%
3b	85% ^a / 80% ^e	-	76%
3c	78% ^a	-	75%
3d	85% ^a	38%	85%
3e	84% ^a	-	75%
3f	86% ^a	35%	82%
3g	84% ^a	-	74%

^aTBD: 30 mol%. ^bAcetone/water (1:1); Reaction times at three different temperatures: 0 °C=2 h, r.t.=2 h, 60 °C=18 h. ^cReaction times at three different temperatures: 0 °C=2h, r.t.=2h, 100 °C=18 h. ^dYields refer to isolated products. ^eTBD: 20 mol%.

Scheme 1. Synthesis of tri-arm star shaped 1,3,5-triazines.

Next we examined the solid phase synthesis of **3a-3g** by using NaOH as base. In this method, NaOH and compounds **2a-2g** in 1 mL water were mixed in a mortar. After the solvent evaporated, cyanuric chloride was added to the dry residue and the mixture was ground in a mortar until a fine powder was formed. The mixture was placed for 2h at 0 °C, 2h at room temperature and 18 h at 100 °C. Contents were cooled to room temperature and mixed thoroughly with 10 mL of ethanol. The product was filtered off and washed with cold water and ethanol.

The solution phase of above reaction using DBU at acetone/water was also investigated (Table 1). We compared the results obtained from TBD with DBU as another organobase. As it is shown in Table 1, TBD is an effective base for this reaction and the yield of reaction using TBD is higher than DBU.

In these methods the products did not need any additional purification. The reaction was performed in a simple way and the precipitates were separated from the reaction medium easily. The solvent-free condition by using NaOH was simple and did not need to use of solvent, but the yield of the products was a little bit. TBD and DBU did not respond to this method.

Thus due to these results and disadvantage of metal catalysts application in the synthesis of bioactive compounds, it can be deduced that using TBD in the synthesis of these compounds is better than NaOH.

Chemical structure and purity of **3a-g** were proved by using FTIR, ¹H-NMR and ¹³C-NMR spectroscopic techniques. These data are shown in Table 2.

As an example, the FTIR data for compound **3c** showed absorption around 2835 cm⁻¹, which was assigned to the C–H stretching vibration of CHO groups. The peak appearing at 1707 cm⁻¹ confirmed the presence of aldehyde groups in this compound (Fig. 1). The ¹H-NMR spectrum of compound **3c** showed peak at 3.94 ppm as a singlet, which was assigned for CH₃ group. The peaks at 7.98 and 8.24 ppm were assigned to aromatic protons. Also a singlet peak in 10.00 ppm was assigned to CHO group (Fig. 1). The ¹³C NMR spectrum also shows 9 signals for the product **3c**.

Table 2. ¹H-NMR, ¹³C-NMR, FTIR spectra data of **3a-g**.

Product	Spectral data
3a	¹ H-NMR (CDCl ₃ , δ ppm): 7.34 (d, 6H, <i>J</i> = 8.2 Hz, H _{arom}), 7.93 (d, 6H, <i>J</i> = 8.2 Hz, H _{arom}), 10.00 (s, 3H, CHO). ¹³ C-NMR (CDCl ₃ , δ ppm): 122.2, 131.3, 134.3, 155.6, 173.2, 190.6. FT-IR Peaks (cm ⁻¹): 3103, 3070, 2835, 1703, 1568, 1371, 1213, 808. Anal. Calcd for C ₂₄ H ₁₅ N ₃ O ₆ : C, 65.31; H, 3.43; N, 9.52. Found: C, 65.54; H, 3.76; N, 9.88.
3b	¹ H-NMR (CDCl ₃ , δ ppm): 7.41 (d, 3H, <i>J</i> = 8.1 and 1.1 Hz, H _{arom}), 7.57 (t, 3H, <i>J</i> = 7.8 Hz, H _{arom}), 7.65 (s, 3H, <i>J</i> = 1.0 Hz, H _{arom}), 7.77 (d, 3H, <i>J</i> = 7.2 and 1.0 Hz, H _{arom}), 10 (s, 3H, CHO). FT-IR Peaks (cm ⁻¹): 3080, 2823, 2735, 1701, 1570, 1377, 1228, 842. Anal. Calcd for C ₂₄ H ₁₅ N ₃ O ₆ : C, 65.31; H, 3.43; N, 9.52. Found: C, 65.62; H, 3.70; N, 9.76.
3c	¹ H-NMR (DMSO- <i>d</i> ₆ , δ ppm): 3.94 (s, 9H, OCH ₃), 7.98 (d, 3H, <i>J</i> = 1.5 Hz, H _{arom}), 8.24 (d, 3H, <i>J</i> = 1.5 Hz, H _{arom}), 10.00 (s, 3H, CHO). ¹³ C-NMR (DMSO- <i>d</i> ₆ , δ ppm): 57.8, 117.3, 118.5, 134.9, 137.4, 142.6, 153.4, 169.3, 191.1. FT-IR Peaks (cm ⁻¹): 3084, 2835, 1707, 1537, 1465, 1357, 1292. Anal. Calcd for C ₂₇ H ₁₈ N ₆ O ₉ : C, 48.66; H, 2.72; N, 12.61. Found: C, 48.96; H, 2.92; N, 12.96.
3d	¹ H-NMR (CDCl ₃ , δ ppm): 7.36 (d, 6H, <i>J</i> = 7.6 Hz, H _{arom}), 8.32 (d, 6H, <i>J</i> = 7.6 Hz, H _{arom}). FT-IR Peaks (cm ⁻¹): 3117, 3082, 1616, 1601, 1568, 1487, 1373, 1348, 1207, 858. Anal. Calcd for C ₂₁ H ₁₂ N ₆ O ₉ : C, 51.23; H, 2.46; N, 17.07. Found: C, 51.46; H, 2.72; N, 17.36.
3e	¹ H-NMR (DMSO- <i>d</i> ₆ , δ ppm): 7.46 (d, 6H, <i>J</i> = 8.4 Hz, H _{arom}), 7.93 (d, 6H, <i>J</i> = 8.4 Hz, H _{arom}). FT-IR Peaks (cm ⁻¹): 3103, 3047, 2235, 1608, 1570, 1500, 1369, 1215. Anal. Calcd for C ₂₄ H ₁₂ N ₆ O ₉ : C, 66.67; H, 2.80; N, 19.44. Found: C, 66.95; H, 3.10; N, 19.76.
3f	¹ H-NMR (CDCl ₃ , δ ppm): 2.61 (s, 3H, CH ₃), 7.23 (d, 6H, <i>J</i> = 8.6 Hz, H _{arom}), 7.99 (d, 6H, <i>J</i> = 8.6 Hz, H _{arom}). FT-IR Peaks (cm ⁻¹): 3070, 2920, 1687, 1568, 1502, 1379, 1265, 850. Anal. Calcd for C ₂₇ H ₂₁ N ₃ O ₆ : C, 67.07; H, 4.38; N, 8.69. Found: C, 67.35; H, 4.50; N, 8.96.
3g	¹ H-NMR (DMSO- <i>d</i> ₆ , δ ppm): 6.67 (3H, s, CH ₃ methine), 7.35-7.83 (m, 12H, H _{arom}). ¹³ C-NMR (DMSO- <i>d</i> ₆ , δ ppm): 91.4, 116.2, 116.8, 123.6, 124.3, 133.1, 150.3, 153.9, 162.4, 166.1. FT-IR Peaks (cm ⁻¹): 3080, 3061, 1736, 1645, 1554, 1340, 845. Anal. Calcd for C ₃₀ H ₁₅ N ₃ O ₉ : C, 64.18; H, 2.69; N, 7.48. Found: C, 64.65; H, 2.82; N, 7.78.

Fig. 1. FT-IR and ¹H-NMR spectrum (DMSO-*d*₆) of compound **3c**.

CONCLUSIONS

In conclusion, we have reported a simple, high yielding and convenient protocol for the synthesis of tri-arm star shaped 1,3,5-triazines in solution and

solid phase. This reaction is easy to perform and the purification protocol is simple. No side products were observed for this reaction.

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