Method Article

Protocol for synthesis of di- and tri-substituted s-triazine derivatives

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A B S T R A C T

The present protocol describes the synthesis of di and tri-substituted s-triazine derivatives

\begin{itemize}
  \item s-Triazine undergoes sequential nucleophilic substitution reaction but order of nucleophile is very crucial.
  \item It is very difficult to substitute any nucleophile except amine once amine is incorporated onto s-triazine.
  \item During the synthesis of O,N-type substituted s-triazine, always O-type should be incorporated first.
\end{itemize}

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Specification Table

Subject Area:  
- Chemistry  
- More specific  
- Orthogonal chemoselective

Method name:  Sequential nucleophilic substitution

Name and reference of original method:  N/A

Resource availability:  N/A

Method details

Method details involves synthesis of di- and tri-substituted s-triazine derivatives as drawn in below scheme.

![synthesis scheme]

**Synthesis of di-substituted s-triazine using two sequential amines**

**Step 1: Synthesis of 4-[(4,6-dichloro-1,3,5-triazin-2-yl)amino]benzonitrile**

**Materials required**

- Cyanuric chloride
- Potassium carbonate (K₂CO₃)
- 4-Aminobenzonitrile
- Solvent [acetone, methanol (MeOH) and chloroform]
- Crushed ice and distilled H₂O
- Rotary evaporator
- Glassware (Round bottom flask, beakers and conical flask)
- Silica-gel coated Aluminum TLC plates

**Procedure**

*Note: Cyanuric chloride is fuming solid. So, care must be taken to weigh it. Bottle must be opened in the fume hood with exhaust on.*

1. Cyanuric chloride (10 mmol) and 4-aminobenzonitrile (10 mmol) were dissolved in acetone (50 mL each) separately in conical flask.
2. Both solutions were cooled to 0 °C.
3. K₂CO₃ (10 mmol) was added to cyanuric chloride solution while stirring vigorously at 0 °C in a round bottom flask.
4. A cold solution of 4-aminobenzonitrile was added dropwise to the stirring solution of cyanuric chloride and K₂CO₃.
The reaction was stirred for 4 h at 0 °C (Note: maintaining temperature at 0 °C is very crucial for the reaction to avoid double incorporation).

(6) Monitor the reaction by TLC using 20% MeOH in chloroform as mobile phase in a closed system.

(7) Once no starting material appears on TLC, pour the reaction mixture onto crushed ice (1 L) in a beaker.

(8) Filter the solid product with distilled H₂O (3 × 500 mL) and dry under high vacuum to obtain pure product.

Note: The current procedure is applicable for all amines (In case of aromatic amines the time consumed is 4 h whereas in case of aliphatic amine it only requires 30 min)

**Step 2: Synthesis of 4-[4-chloro-6-substituted(1,3,5-triazin-2-yl)amino]benzonitrile**

**Materials required**
- K₂CO₃
- Piperidine
- Morpholine
- N,N’-Diethylamine
- Solvents [THF, ethyl acetate (EtOAc), hexane]
- Ice cold water and crushed ice
- Rotary evaporator
- Glassware (Round bottom flask, beakers and conical flask)
- Silica-gel coated Aluminum TLC plates

**Procedure**

(1) 4,6-Dichloro (1,3,5-triazin-2-yl) aminobenzonitrile (10 mmol) and respective amine (piperidine, morpholine and diethyl amine) were dissolved in THF (50 mL each) separately in conical flask.

(2) K₂CO₃ (10 mmol) was added to 4,6-dichloro (1,3,5-triazin-2-yl) aminobenzonitrile solution while stirring vigorously at rt in a round bottom flask.

(3) Solution of respective amine was added dropwise to the stirring solution of 4,6-dichloro (1,3,5-triazin-2-yl) aminobenzonitrile and K₂CO₃.

(4) The reaction was stirred for 24 h at rt.

(5) Monitor the reaction by TLC using EtOAc-hexane (6:4) in a closed system.

(6) Once no starting material appears on TLC, THF was removed using rotary evaporator.

(7) Remaining reaction mixture was poured onto crushed ice (1 L) in a beaker.

(8) Filter the solid product with distilled H₂O (3 × 500 mL) and dry under high vacuum to obtain product.

(9) The crude was recrystallized from EtOAc.

**Synthesis of trisubstituted triazines containing one alkoxy substituent and two amino substituents [1]**

**Step 1: Synthesis of 2,4-dichloro-6-methoxy-1,3,5-triazine [2]**

**Materials required**
- Cyanuric chloride
- Sodium bicarbonate (NaHCO₃)
- Solvents (MeOH, EtOAc, hexane)
- Crushed ice and distilled H₂O
- Rotary evaporator
- Glassware (Round bottom flask, beakers and conical flask)
- Silica-gel coated Aluminum TLC plates
Procedure

Note: Cyanuric chloride is fuming solid. So, care must be taken to weigh it. Bottle must be opened in the fume hood with exhaust on.

(1) NaHCO₃ (10 mmol) was dissolved in water and cooled to 0 °C.
(2) MeOH (50 mL) is added to the above solution and stirred vigorously at 0 °C.
(3) Cyanuric chloride (10 mmol) was added to the above stirring solution.
(4) The reaction was stirred for 3 h at 0 °C (Note: maintaining temperature at 0 °C is very crucial for the reaction to avoid double incorporation).
(5) Monitor the reaction by TLC using EtOAc-hexane (6:4) in a closed system.
(6) Once no starting material appears on TLC, excess of MeOH was removed under rotary evaporator.
(7) The residue was poured onto crushed ice (1 L) in a beaker.
(8) Filter the solid product with distilled H₂O (3 × 500 mL) and dry under high vacuum to obtain pure product.

Step 2: Synthesis of 4-chloro-6-methoxy(1,3,5-triazin-2-yl)amino)benzonitrile

Materials required

- NaHCO₃
- 4-Aminobenzonitrile
- Solvents (acetone, EtOAc, hexane)
- Crushed ice and distilled H₂O
- Rotary evaporator
- Glassware (Round bottom flask, beakers and conical flask)
- Silica-gel coated Aluminum TLC plates

Procedure

(1) 2,4-dichloro-6-methoxy-1,3,5-triazine (10 mmol) and 4-aminobenzonitrile (10 mmol) were dissolved in acetone (50 mL each) separately in conical flask.
(2) NaHCO₃ (1.38 g) was added to 2,4-dichloro-6-methoxy-1,3,5-triazine solution while stirring vigorously at 0 °C in a round bottom flask.
(3) Solution of 4-aminobenzonitrile was added dropwise to the stirring solution of 2,4-dichloro-6-methoxy-1,3,5-triazine and NaHCO₃.
(4) The reaction was stirred for 24 h at rt.
(5) Monitor the reaction by TLC using EtOAc-hexane (6:4) in a closed system.
(6) Once no starting material appears on TLC, acetone was removed using rotary evaporator.
(7) Remaining reaction mixture was poured onto crushed ice (1 L) in a beaker.
(8) Filter the solid product with distilled H₂O (3 × 500 mL) and dry under high vacuum to obtain product.

Step 3: Synthesis of 4-substituted-6-methoxy((1,3,5-triazin-2-yl)aminobenzonitrile

Materials required

- K₂CO₃
- Piperidine
- Morpholine
- Pyrrolidine
- 4-Methylpiparizine
- 2-Hydroxyethylamine
- N,N'-Diethylaniline
• 4-Bromoaniline
• 4-Methoxyaniline
• Aniline
• Solvents [acetonitrile, EtOAc, ethanol (EtOH), hexane]
• Crushed ice and distilled H₂O
• Rotary evaporator
• Glassware (Round bottom flask, beakers and conical flask)
• Silica-gel coated Aluminum TLC plates

Procedure

(1) 4-chloro-6-methoxy(1,3,5-triazin-2-yl)amino)benzonitrile (10 mmol) and 4-aminobenzonitrile (10 mmol) were dissolved in acetonitrile (50 mL each) separately in conical flask.
(2) K₂CO₃ (10 mmol) was added to 4-chloro-6-methoxy(1,3,5-triazin-2-yl)amino)benzonitrile solution while stirring vigorously at rt in a round bottom flask.
(3) Solution of respective amine (piperidine, morpholine, pyrrolidine, N-methyl piperazine, 1-amino ethanol, N,N'-diethylamine, aniline, 4-bromoaniline and 4-methoxyaniline) dissolved in 10 mL acetonitrile was added to the stirring solution of 4-chloro-6-methoxy(1,3,5-triazin-2-yl)amino)benzonitrile and K₂CO₃.
(4) The reaction was refluxed for 18 h in an oil bath.
(5) Monitor the reaction by TLC using EtOAc-hexane (6:4) in a closed system.
(6) Once no starting material appears on TLC, acetonitrile was removed using rotary evaporator.
(7) Remaining reaction mixture was poured onto crushed ice (1 L) in a beaker.
(8) Filter the solid product with distilled H₂O (3 x 500 mL) and dry under high vacuum to obtain product.
(9) The crude was recrystallized from 3:1 EtOAc-EtOH solvent mixture.

Method validation

All the compounds were obtained in high yields and high purity as confirmed by ¹H-NMR and ¹³C-NMR.

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Declaration of Competing Interest

The authors declare no conflicts of interest.

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