MethodsX 7 (2020) 100825

Contents lists available at ScienceDirect

MethodsX

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

Method Article

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

Ayman El-Faham[a,b,*], Anamika Sharma[c], Muhammad Farooq[d], Zainab Almarhoon[a], Rakia Abd Alhameed[a], Mohammad A.M. Wadaan[d], Beatriz G. de la Torre[e], Fernando Albericio[a,c,f,*]

[a] Department of Chemistry, College of Science, King Saud University, P.O. Box 2455, Riyadh 11451, Saudi Arabia
[b] Department of Chemistry, Faculty of Science, Alexandria University, P.O. Box 426, Alexandria 21321, Egypt
[c] School of Chemistry and Physics, University of KwaZulu-Natal, University Road, Westville, Durban 4001, South Africa
[d] Department of Zoology, Bioproducts Research Chair, College of Science, King Saud University, P.O. Box 2455, Riyadh 11451, Saudi Arabia
[e] KRISP, College of Health Sciences, University of KwaZulu-Natal, Westville, Durban 4001, South Africa
[f] Department of Organic Chemistry, CIBER-BBN, Networking Centre on Bioengineering, Biomaterials and Nanomedicine, University of Barcelona, Martí i Franqués 1-11, Barcelona 08028, Spain

A B S T R A C T

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

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

A R T I C L E I N F O
Method name: Sequential nucleophilic substitution
Keywords: Orthogonal chemoselectivity, Cyanuric chloride, Nucleophilic substitution, Amines, Alcohol
Article history: Received 31 October 2019; Accepted 3 February 2020; Available online 20 February 2020

DOI of original article: 10.1016/j.bioorg.2019.103397
* Corresponding authors.
E-mail addresses: fmuhammad@ksu.edu.sa (M. Farooq), zalmarhoon@ksu.edu.sa (Z. Almarhoon), Wadaan@ksu.edu.sa (M.A.M. Wadaan), Garciadelatorreb@ukzn.ac.za (B.G. de la Torre), albericio@ukzn.ac.za (F. Albericio).

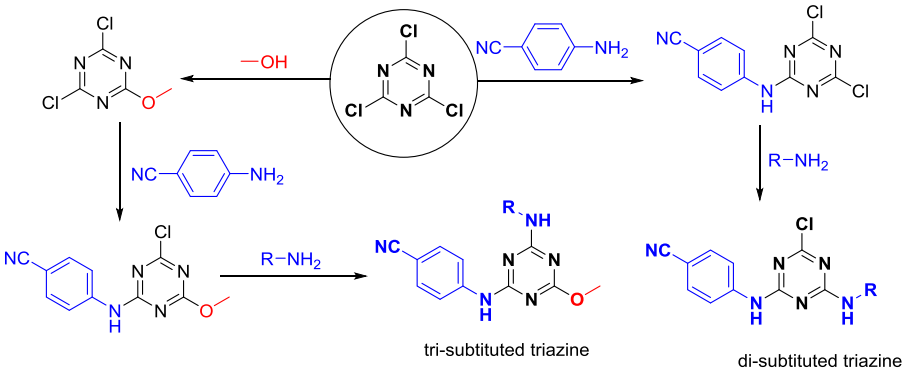
https://doi.org/10.1016/j.mex.2020.100825

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 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 (K_2CO_3)
- 4-Aminobenzonitrile
- Solvent [acetone, methanol (MeOH) and chloroform]
- Crushed ice and distilled H_2O
- 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) K_2CO_3 (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 K_2CO_3.

(5) 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 H_2O (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

- K_2CO_3
- 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) K_2CO_3 (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 K_2CO_3.
(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 H_2O (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 ($NaHCO_3$)
- Solvents (MeOH, EtOAc, hexane)
- Crushed ice and distilled H_2O
- 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) $NaHCO_3$ (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 H_2O (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

- $NaHCO_3$
- 4-Aminobenzonitrile
- Solvents (acetone, EtOAc, hexane)
- Crushed ice and distilled H_2O
- 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) $NaHCO_3$ (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 $NaHCO_3$.
(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 H_2O (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

- K_2CO_3
- 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 H_2O
- 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) K_2CO_3 (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 K_2CO_3.
(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 H_2O (3 $\times$ 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 ^{1}H-NMR and ^{13}C-NMR.

Acknowledgments

The work was funded in part by the following: the Deanship of Scientific Research at King Saud University Research Group no. RGP-234, Saudi Arabia.; the National Research Foundation (NRF) (Blue Sky's Research Programme # 110960) and the University of KwaZulu-Natal (South Africa); and the Spanish Ministry of Science, Innovation, and Universities (CTQ2015-67870-P) and the Generalitat de Catalunya (2017 SGR 1439; Spain).

Declaration of Competing Interest

The authors declare no conflicts of interest.

References

[1] A. Sharma, A. El-Faham, B.G. de la Torre, F. Albericio, Exploring the orthogonal chemoselectivity of 2, 4, 6-Trichloro-1, 3, 5-Triazine (TCT) as a trifunctional linker with different nucleophiles: rules of the game, Front. Chem. 6 (2018) 516.
[2] H. Tanaka, A. Wada, M. Shiro, Synthesis of aza-bridged calix (4-methoxy) triazines toward flattened π-conjugated macrocycles, Heterocycles 79 (2009) 609.