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A Facile and Single-pot Procedure for Synthesis of Altretamine

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ABSTRACT On the basis of D.W. Kaiser's report (1951), an improved, simple, and practical procedure for the synthesis of altretamine (**1**), an antitumor drug in large scale has been successfully developed. The synthesis method involves the conversion of cyanuric chloride (**2**) into altretamine (**1**) by dimethylamination of **2** with aqueous solution of 40% dimethylamine and sodium hydroxide in acetone with only one step to afford altretamine (**1**) in high yield (90%) and its quality in respect to the United State Pharmacopeia (USP 38).

KEYWORDS Altretamine, Antitumor, Cyanuric chloride, Dimethylamine, Hexamethylmelamine.

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INTRODUCTION

Altretamine (**1**) is described chemically as hexamethylmelamine (HMM) (2,4,6-tris(dimethylamino)-*s*-triazine or *N*,*N*,*N*′,*N*′,*N*″,*N*″-hexamethyl [1,3,5]triazin-2,4,6-triamine. It was approved worldwide under the brand name Hexalen® by the FDA in 1990[1] and various trade names such as Hexastat (Roger Bellon) and Hexamethylmelamine (Rhone-Poulenc). Altretamine is a potential anticancer (antineoplastic) drug used in the treatment of lung, breast, and ovarian cancer.[2] Altretamine also has the advantage of being less toxic than the others.

There have been a number of publications regarding the synthesis of altretamine (**1**) started from various input materials such as cyanuric chloride,[3] *N*,*N*-dimethylamino-cyanamide,[4] melamine,[5] halogeno-*s*-triazine,[6] and acid cyanuric acid[7] and reaction conditions including reaction types, different catalysts, and manners of product purification.[3,4]

Due to increasing requirements, it becomes evident that the previous synthetic methods of altretamine (**1**) remain disadvantage, especially for industrial scale, as whether using expensive materials or operation in uncertain conditions (microwave, temperature, and pressure).[3c,5,7] For example, the well-documented method of D.W. Kaiser[3a] with input materials of cyanuric chloride, aqueous dimethylamine solution, and sodium hydroxide was the most practical and feasible for the industrial scale, though the yield of preparation **1** remained low (only 37%).

Kaiser *et al.*[3a] synthesized altretamine (**1**) by dimethylaminolation of cyanuric chloride (**2**) with dimethylamine and sodium hydroxide in acetone through 2,4-dichloro-6-(dimethylamino)-*s*-triazine (**3**), followed by the conversion of **3** into **1** and 2-chloro-4,6-bis-(dimethylamino)-*s*-triazine (**4**) [**Scheme 1**].

To the best of our knowledge, the unsatisfactory factors of this method were as follows. Overall, the entire procedure was relatively complicated as many steps for handling and, especially, the key point was of molar ratio between reagents (CYC: DMA: NaOH) using in the reaction (1:3.3:3) was not reasonable, it was very absent, because the boiling point of DMA is very low (7°C), leading to light evaporation. Recently, Dinh *et al.*[3e] modified the D.W. Kaiser's procedure by changing the reaction conditions, work-up, separation, crystallization, and purification to improve the yield of altretamine (*ca.* 70%), but till under industrially desired.

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(s, 3C, $C_{triazine}$); and 35.78 (s, 6C, 6 N-CH_3) (Supporting Information).

CONCLUSIONS

A facile route for a safe, simple, and practical and economically competitive synthesis of altretamine (**1**) has been provided. This synthesis used inexpensive, commercially available materials. The parameters of procedure were optimized to reduce materials or eliminate the use of toxic or expensive reagents, the synthesis procedure was carried out with only one stage, which enhances yield to 89–91% (purity 99.74% by HPLC). Moreover, total preparation time was significantly reduced compared to those methods described previously. This method of synthesis has shown to be easily scaled up and industrially feasible. To the best of our best knowledge, this synthesis method is economically advantageous compared with earlier reports in terms of consumption of raw materials and overall yield.

ASSOCIATED CONTENT

Supporting information

Experimental details, optimization results [**Tables S1-S6**]; MS, ^{1}H-NMR and ^{13}C-NMR spectra, HPLC, and GLP analysis certificate of altretamine. This material is available with authors.

Authors' contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript. The authors declare no conflicts of interest.

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