

SYNLETT Spotlight 433

Chloroacetonitrile

Compiled by Rajni Sharma



This feature focuses on a reagent chosen by a postgraduate, highlighting the uses and preparation of the reagent in current research

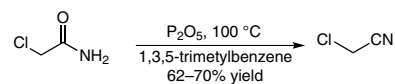
Rajni Sharma was born in Jammu, India. She received her B.Sc in 2006 from Jammu University and her M.Sc in 2008 from Chaudhary Charan Singh University, Meerut, India. Afterwards, she joined the research group of Dr. R. A. Vishwakarma at the Indian Institute of Integrative Medicine pursuing her Ph.D. Her research interests focus on semi-synthetic studies on bioactive natural products, non-natural products and on the development of new synthetic methodologies.

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Introduction

Chloroacetonitrile is a simple organic compound with a linear chemical structure. Both ends of this molecule have a reactive group: a cyano group on one side and a chloro substituent on the other side. The nitrile can be converted into an amine, amide, amidine, etc., whereas the chloro group plays an important role in different alkylation reactions. Chloroacetonitrile is known for the synthesis of

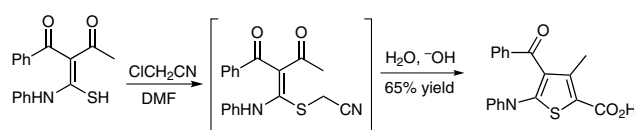
heterocycles including thiophenes,¹ thiazoles² and thiazolo[3,2-*b*][1,2,4]triazoles.³ Chloroacetonitrile is commercially available and can be synthesized by dehydration of chloroacetamide with phosphorous pentoxide.⁴



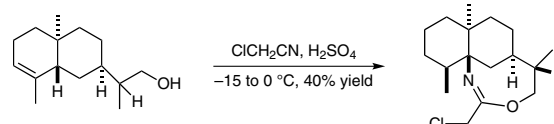
Scheme 1

Abstract

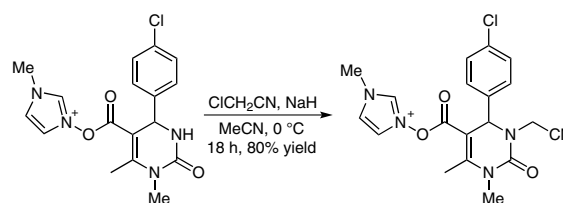
(A) Fadda et al.¹ reported the conversion of thiocarbamoyl compounds into active thiophene derivatives using chloroacetonitrile.



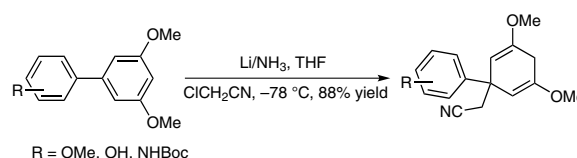
(B) Chloroacetonitrile played an important role in the synthesis of the azatricyclo intermediate in the stereoselective synthesis of (–)-4-epiaxinysamine.⁵



(C) Legeay et al.⁶ reported the N-alkylation of 3,4-dihydropyrimidine-2(1*H*)-one using chloroacetonitrile via ionic liquid-phase technology.



(D) Regioselective Birch reductive alkylation of biaryls using chloroacetonitrile was achieved in the presence of Li/NH₃.⁷



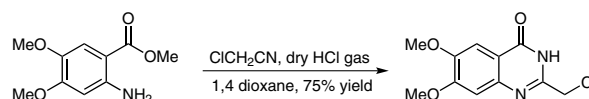
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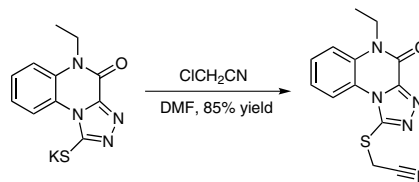
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(E) M. R. Yadav et al.⁸ reported the synthesis of biological active quinazolines by cyclization and effective alkylation of anthranilamide ester in the presence of chloroacetonitrile.



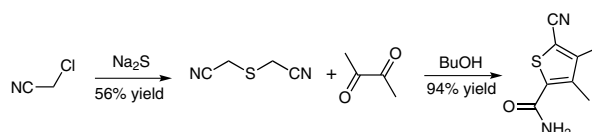
(F) The S-alkylation of mercapto-1,2,4-triazole quinoxalinones was achieved using chloroacetonitrile.⁹



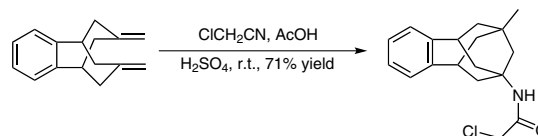
(G) Alkylation of the phenolic hydroxyl group using chloroacetonitrile in the presence of K_2CO_3 and NaI gave the cyanomethylated product in 92% yield. These compounds are important intermediates for synthesis of various heterocycles possessing VEGFR-2 inhibitory activity.¹⁰



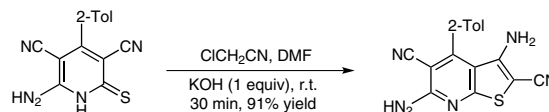
(H) Chloroacetonitrile was also used in the preparation of important thiophene intermediates.¹¹



(I) E. Torres et al.¹² reported the synthesis of benzopolycyclic cage amines using chloroacetonitrile as one of the key reagents.



(J) W. Fugel et al.¹³ reported the synthesis of 3,6-diamino-4-arylthieno[2,3-b]pyridine-5-carbonitriles as selective inhibitors of *Plasmodium falciparum* glycogen synthase kinase-3 from 2-thioxo-1,2-dihydropyridines using chloroacetonitrile.



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