SYNLETT
Spotlight 434

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

2-Cyanoacetamide

Compiled by Anna Zdzienicka

Anna Zdzienicka was born in Łódź (Poland) in 1987. She received her M.Sc. degree in chemistry in 2011 working in the group of Professor Janusz Zakrzewski at the Department of Organic Chemistry, University of Łódź. Currently, she is continuing her research at the Bioorganic Chemistry Laboratory, Faculty of Pharmacy, Medical University of Łódź, working in the group of Professor Andrzej E. Wróblewski. Her research interests focus on synthesis of new 1,2,3-triazolylalkylphosphonates.

Bioorganic Chemistry Laboratory, Faculty of Pharmacy, Medical University of Łódź, Muszyńskiego 1, 90-151 Łódź, Poland
E-mail: anna.zdzienicka@umed.lodz.pl

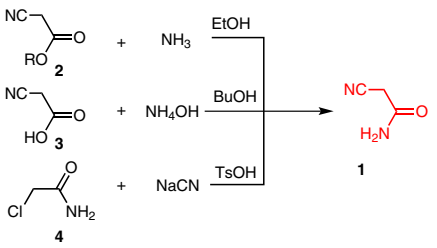
Introduction

Cyanoacetic acid derivatives are important intermediates in the synthesis of various organic heterocyclic compounds. Among these derivatives, 2-cyanoacetamide deserves attention since it is a useful reagent for the synthesis of a variety of novel compounds possessing biological activity and other special properties.[1]

It possesses electrophilic C1 and C3 carbons and nucleophilic C2 and NH centers responsible for the high reactivity and importance of this compound. The acidic C2 hydrogen prompts an extensive application in a variety of condensation and cycloaddition reactions. Moreover, 2-cyanoacetamide can take part in substitution reactions.[2]

Preparation:

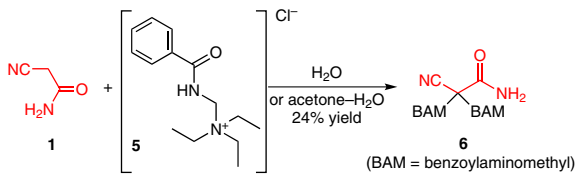
2-Cyanoacetamide (**1**) is commercially available. It can be prepared by several literature procedures from: cyanoacetates **2** and ammonia, from cyanoacetic acid (**3**) and NH_4OH, and from chloracetamide (**4**) and NaCN.[1]



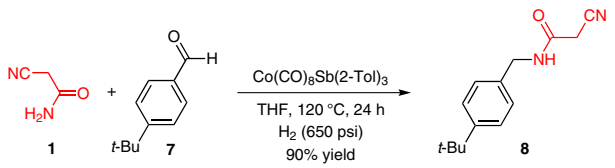
Scheme 1

Abstracts

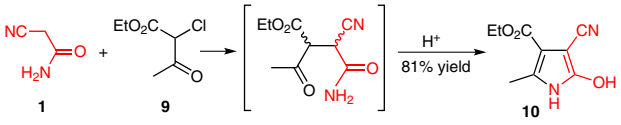
(A) 2-Cyanoacetamide (**1**) can be readily alkylated at C2. Nucleophilic substitution in (benzamidomethyl)triethylammonium chloride (**5**) occurred under mild conditions in aqueous media and at ambient temperature to give disubstituted cyanoacetamide **6** without any catalyst.[3]



(B) Triarylstibine-modified $Co_2(CO)_8$ appeared to be an efficient homogeneous catalytic system for the synthesis of secondary amides by direct reductive N-alkylation of a variety of substituted aryl aldehydes with aryl-, heteroaryl- and aliphatic primary amides. Reaction of 4-*tert*-butyl benzaldehyde (**7**) and 2-cyanoacetamide (**1**) gave compound **8** in 90% yield.[4]



(C) The triethylamine-catalyzed alkylation of 2-cyanoacetamide (**1**) with 2-chloroacetoacetate (**9**) followed by nucleophilic attack of the amide nitrogen on the carbonyl group and acid-catalyzed dehydration led to the formation of substituted pyrrole **10** in good yield.[5]



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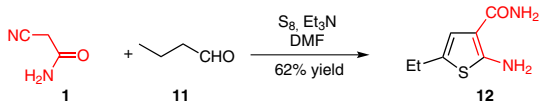
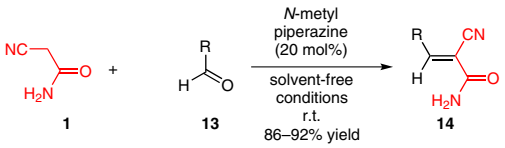
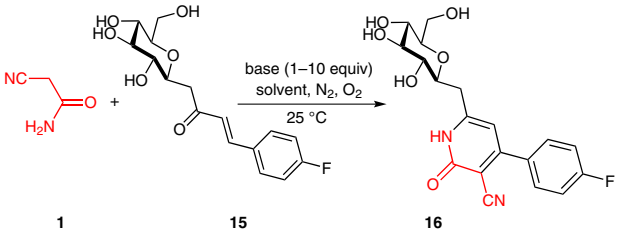
(D) The Gewald reaction of a ketone or aldehyde with 2-cyanoacetamide in the presence of a base and elemental sulfur affords substituted 2-aminothiophenes. T. Horiuchi and co-workers described the preparation of thiophene **12** from butyraldehyde (**11**), 2-cyanoacetamide (**1**) and elemental sulfur in DMF.[6]



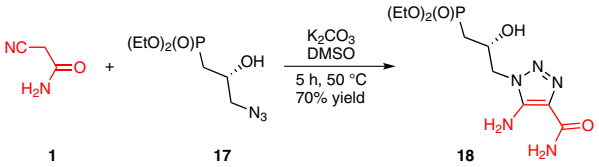
(E) α,β-Unsaturated nitrile derivatives (Knoevenagel condensation products) are among the most important precursors of heterocycles. Various aliphatic, aromatic and heteroaromatic aldehydes **13** reacted with 2-cyanoacetamide (**1**) in the presence of *N*-methylpiperazine under solvent-free conditions to give the Knoevenagel condensation products **14**.[7]



(F) 1,4-Conjugate addition (Michael reaction) of 2-cyanoacetamide (**1**) to butenonyl *C*-glycoside **15** was carried out in the presence of various organic bases in organic solvents and under a nitrogen atmosphere followed by oxidative aromatization to form glycopyranosyl methylpyridone **16**.[8]



(G) [3+2] Dipolar cycloaddition of azides and 2-cyanoacetamide gave substituted 5-amine-4-carbamoyl-1,2,3-triazoles. Cycloaddition of diethyl (*R*)-3-azidophosphonate **17** and 2-cyanoacetamide (**1**) in DMSO in the presence of potassium carbonate provided phosphonate **18** in 70% yield.[9]



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