SYNLETT
Spotlight 458

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

1-Cyanoacetyl-3,5-dimethylpyrazole

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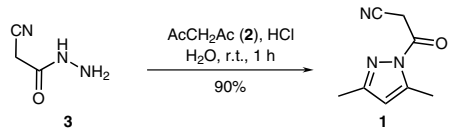
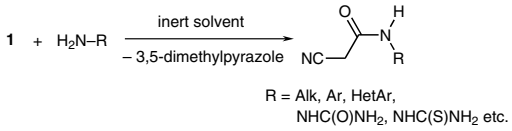
Introduction

1-Cyanoacetyl-3,5-dimethylpyrazole (**1**) is a white crystalline solid with a melting point of 118–121 °C,[1] stable at room temperature in air. In the 1950s, Ried and Meyer[1] were the first to describe it as a mild cyanoacetylating reagent, being more reactive than ethyl cyanoacetate. Pyrazole **1** is a cheap, handy, and non-toxic reagent that proved to be superior to cyanoacetyl chloride and cyanoacetyl azide in terms of stability and convenience. It is commercially available and can be prepared in about 90% yield by condensation of acetylacetone (**2**) with cyanoacetohydrazide (**3**) in aqueous hydrochloric acid (Scheme 1).[2]



Scheme 1 Preparation of 1-cyanoacetyl-3,5-dimethylpyrazole

The first and most common application of 1-cyanoacetyl-3,5-dimethylpyrazole (**1**) is the synthesis of N-substituted cyanoacetamides, which are known as versatile building blocks for heterocyclic synthesis.[3,4] **1** readily reacts with various N-nucleophiles (amines, hydrazines, hydrazides, semicarbazides) in an inert solvent (ether, benzene, toluene, dioxane) under mild conditions.

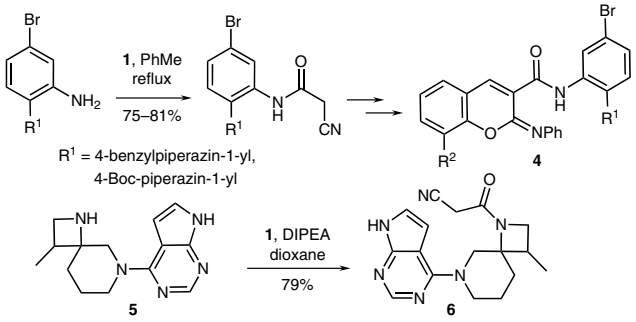


Scheme 2 Synthesis of s-substituted cyanoacetamides

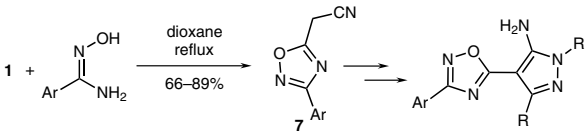
The N-cyanoacetylation products can be isolated from the reaction mixture in crystalline form, while the 3,5-dimethylpyrazole by-product remains in the mother liquor. The yields are usually high and sometimes nearly quantitative.

Abstracts

(A) *Synthesis of Biologically Active Amides*
The reaction of **1** with various amine substrates was successful for the synthesis of biologically active compounds. Thus, imino-2H-chromen-3-carboxamide derivatives **4**, inhibitors of β-secretase, were obtained in three steps starting from substituted anilines and pyrazole **1**.[5] The reaction of spirocyclic amine **5** with a two-fold excess of **1** led to *N*-cyanoacetyl derivative **6**, an inhibitor of Janus kinase 3.[6,7]



(B) *Synthesis of Oxadiazoles*
New 5-cyanomethyl-1,2,4-oxadiazoles **7** have been synthesized by the reaction of pyrazole **1** with arylamidoximes. The obtained compounds **7** are recognized as valuable building blocks for heterocyclic synthesis.[8,9]



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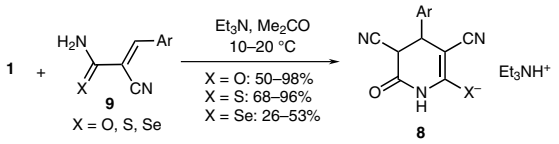
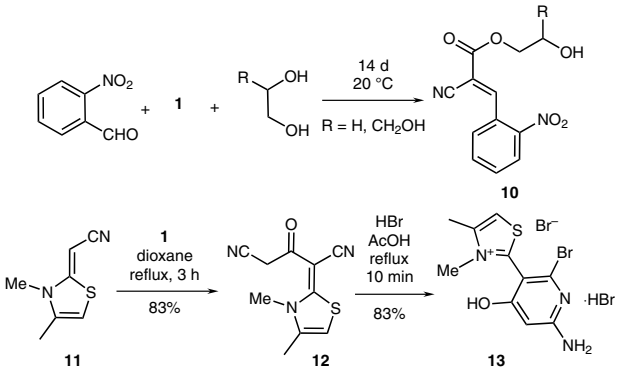
(C) *Synthesis of Guareschi Imides*

Pyrazole **1** can be used as an active methylene compound capable of successfully replacing ethyl cyanoacetate in most cases. Thus, the Guareschi condensation could be vastly improved by replacing ethyl cyanoacetate with **1**. The Guareschi imides as well as their sulfur and selenium analogues were obtained as triethylammonium salts **8** by a Michael-type addition of **1** to 2-cyanoacrylamides **9** followed by subsequent cyclocondensation.[10–14]



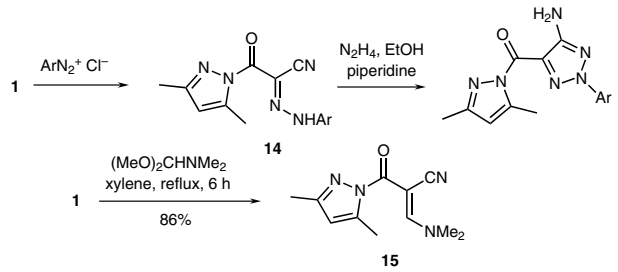
(D) *O- and C-Cyanoacetylation*

While a number of papers have focused on the reactions of **1** with various N-nucleophiles, the reactions of cyanoacetylpyrazole with C- and O-nucleophiles have been neglected. The only examples of such reactions were reported by Swellem et al.[15] and Tverdokhlebov and co-workers.[16] Ternary condensation of 2-nitrobenzaldehyde with pyrazole **1** and ethylene glycol or glycerol gives 2-cyanoacrylates **10** in about 40% yield.[15] Despite the low yields, this approach is the method of choice in cases where the corresponding cyanoacetates are not readily available. The first examples of C-cyanoacetylation with **1** were reported a few years ago. The hetarylideneacetonitrile **11** reacts with **1** to give β-keto glutaronitrile **12**. The latter upon treatment with HBr readily cyclizes to pyridine **13** in good yield.[16]



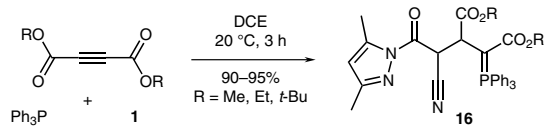
(E) *Azo Coupling and Related Reactions*

As an active methylene compound, **1** readily reacts with diazonium salts to afford hydrazone products **14**, which were found to be good starting materials for the synthesis of a variety of functionalized heterocycles.[17] In a similar manner, **1** gives dimethylaminomethylene derivative **15** upon treatment with DMF dimethyl acetal.[18]



(F) *Functionalized Phosphorus Ylides*

The highly functionalized phosphorus ylides **16** are accessible in high yield by a three-component reaction of triphenylphosphine, dialkyl acetylene-dicarboxylates, and pyrazole **1**.[19]



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