

# SYNLETT Spotlight 458

## 1-Cyanoacetyl-3,5-dimethylpyrazole

Compiled by Elena A. Chigorina



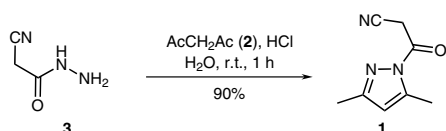
This feature focuses on a reagent chosen by a postgraduate, highlighting the uses and preparation of the reagent in current research

Elena Chigorina was born in Vladikavkaz (North Ossetia, Russian Federation) in 1983. She received her M.Sc. in chemistry from the Hetagurov North Ossetian State University. Currently she is working towards her Ph.D. degree under the supervision of Dr. Victor V. Dotsenko at the Chemical Diversity Research Institute in Khimki. Her work focuses on the use of 1-cyanoacetyl-3,5-dimethylpyrazole and related azolides in organic synthesis.

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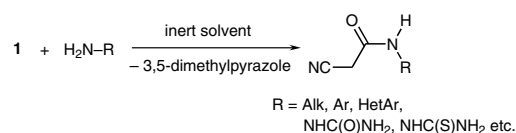
### Introduction

1-Cyanoacetyl-3,5-dimethylpyrazole (**1**) is a white crystalline solid with a melting point of 118–121 °C,<sup>1</sup> stable at room temperature in air. In the 1950s, Ried and Meyer<sup>1</sup> 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 cyanoaceto-hydrazide (**3**) in aqueous hydrochloric acid (Scheme 1).<sup>2</sup>



**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.<sup>3,4</sup> **1** readily reacts with various N-nucleophiles (amines, hydrazines, hydrazides, semicarbazides) in an inert solvent (ether, benzene, toluene, dioxane) under mild conditions.



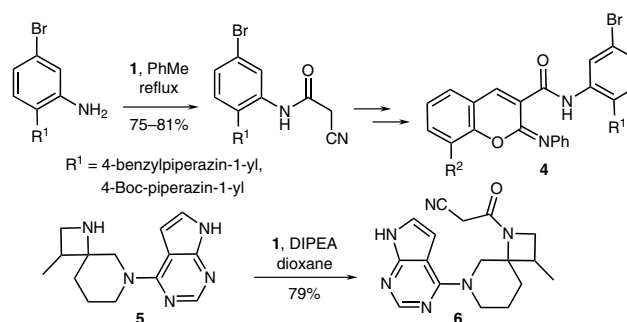
**Scheme 2** Synthesis of s-substituted cyanoacetamides

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

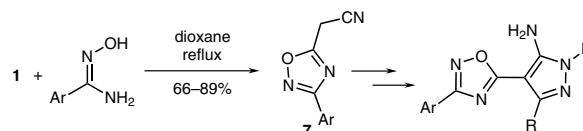
#### (A) Synthesis of Biologically Active Amides

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  $\beta$ -secretase, were obtained in three steps starting from substituted anilines and pyrazole **1**.<sup>5</sup> 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.<sup>6,7</sup>



#### (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.<sup>8,9</sup>



SYNLETT 2014, 25, 0453–0454

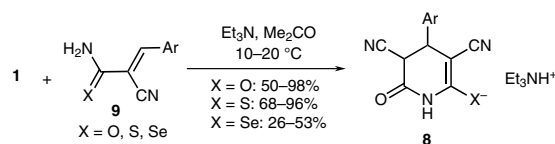
Advanced online publication: 12.12.2013

DOI: 10.1055/s-0033-1340469; Art ID: ST-2013-V0465-V

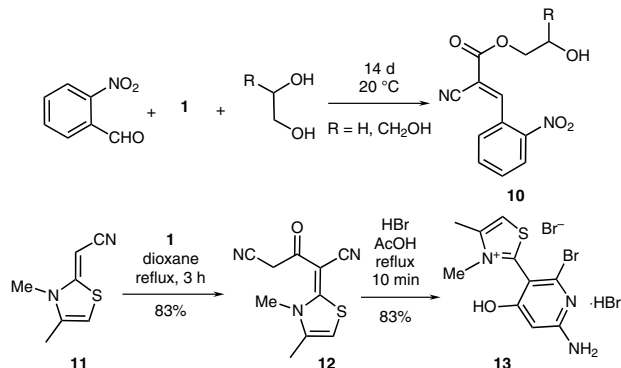
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(C) *Synthesis of Guareschi Imides*

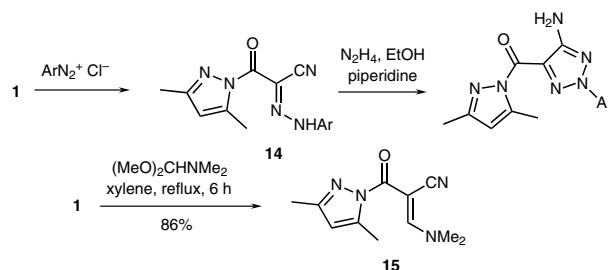
Pyrazole **1** can be used as an active methylene compound capable of successfully replacing ethyl cyanoacetate in most cases. Thus, the Guareschi condensation could be vastly improved by replacing ethyl cyanoacetate with **1**. The Guareschi imides as well as their sulfur and selenium analogues were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

(D) *O- and C-Cyanoacetylation*

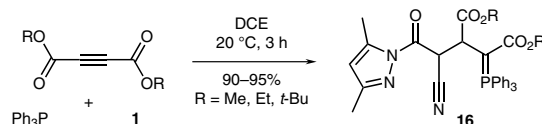
While a number of papers have focused on the reactions of **1** with various N-nucleophiles, the reactions of cyanoacetylpyrazole with C- and O-nucleophiles have been neglected. The only examples of such reactions were reported by Swellem et al.<sup>15</sup> and Tverdokhlebov and co-workers.<sup>16</sup> Ternary condensation of 2-nitrobenzaldehyde with pyrazole **1** and ethylene glycol or glycerol gives 2-cyanoacrylates **10** in about 40% yield.<sup>15</sup> 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 hetarylidenacetone nitrile **11** reacts with **1** to give  $\beta$ -keto glutaronitrile **12**. The latter upon treatment with HBr readily cyclizes to pyridine **13** in good yield.<sup>16</sup>

(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.<sup>17</sup> In a similar manner, **1** gives dimethylaminomethylene derivative **15** upon treatment with DMF dimethyl acetal.<sup>18</sup>

(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**.<sup>19</sup>



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