



Synthesis of 1,4,5-trisubstituted-1,2,3-triazoles via coupling reaction of diaminomaleonitrile with aromatic diazonium salts



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ABSTRACT

A mild procedure for the preparation of 2-(5-amino-1-aryl-1*H*-1,2,3-triazol-4-yl)-2-iminoacetoneitriles and 2-(5-amino-1-aryl-1*H*-1,2,3-triazol-4-yl)-2-oxoacetoneitriles was achieved by the reaction of diaminomaleonitrile and phenyl/substituted phenyl diazonium chlorides. 4-Nitrophenyl diazonium chloride afforded 2-amino-3-(3-(4-nitrophenyl)triaz-1-en-1-yl)maleonitrile. Triazole iminoacetoneitrile and maleonitrile derivatives were reacted further with excess acetone and benzaldehyde with a catalytic amount of 1,8-diazabicyclo[5.4.0]undec-7-ene to yield 5-(5-imino-2,2-dimethyl-2,5-dihydrooxazol-4-yl)-3-aryl-3*H*-1,2,3-triazol-4-amine and (*E*)-*N*-benzylidene-5-(5-imino-2-aryl-2,5-dihydrooxazol-4-yl)-3-aryl-3*H*-1,2,3-triazol-4-amine, respectively. Two competitive reactions, i.e., nucleophilic substitution and nucleophilic addition, were observed when triazole oxoacetoneitrile and maleonitrile derivatives were reacted with hydroxylamine hydrochloride in the presence of sodium acetate.

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1. Introduction

Since the synthesis of 1,2,3-triazoles from Huisgen 1,3-dipolar cycloaddition of azides and alkynes,¹ this class of heterocycles has gained great importance worldwide,^{2–4} as they have found a wide range of applications as pharmaceuticals, catalysts and ligands in transition-based catalyst systems and molecular design.^{2a,5–11} The strong demand for these interesting heterocyclic compounds has prompted several research groups to study new routes for their synthesis, particularly using ‘click chemistry’. Several organic chemists have reported the preparation of 1,2,3-triazoles via the reaction of azides with not only terminal and internal alkynes but also calcium carbides¹² using various metal catalysts, such as copper,^{4,13–22} palladium^{23–25} and ruthenium.²⁶ Other researchers have described a transition metal-free catalytic synthesis procedure.^{26–28}

Wang et al.²⁶ obtained 1,4,5-trisubstituted 1,2,3-triazoles from a regioselective synthesis procedure using enamide-azide cycloaddition. Cao and co-workers¹⁴ showed that 1,4-disubstituted 1,2,3-triazoles could be obtained by a one-pot three-component reaction of primary alcohols, sodium azides and terminal alkynes utilising a Cu^I-catalyst. A recent paper by König et al.¹³ described a solid-state synthesis protocol using a modified Wang resin for the synthesis

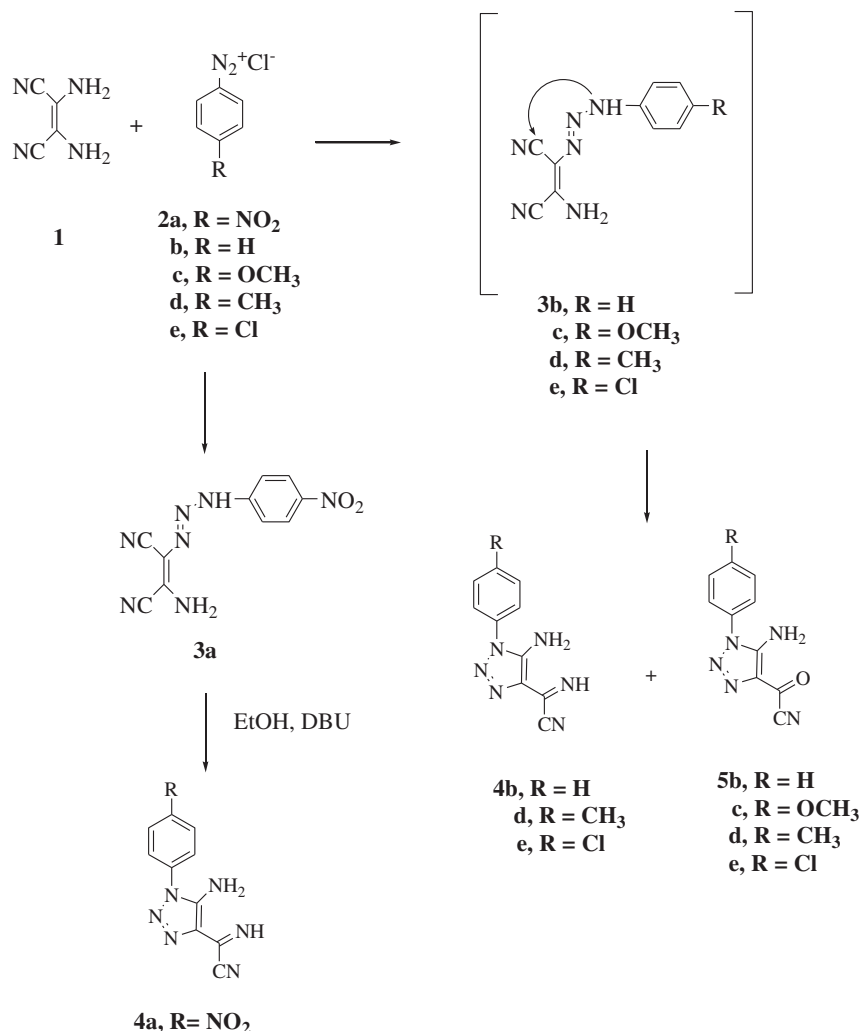
of a series of substituted diaryltriazoles that have the potential to work as selective inhibitors for protein–protein interactions.

Amongst these reported procedures, azides appear to be the common reactant. However, in 1986 Vaughan reported an azide free route to 1,2,3-triazoles,²⁹ diazotization of aryl amines followed by coupling with α -aminoacetoneitrile gave cyanomethyltriazene derivatives, which were cyclised to 1,2,3-triazoles using alumina as a catalyst. The extensive search for a mild, inexpensive and easily applicable approach continues to this day. Our group has investigated the chemistry of diaminomaleonitrile (DAMN) **1** for over a decade.^{30a} Diazotization of DAMN **1** or *N*-[2-amino-1,2-dicyanovinyl]alkanimides yields 4,5-disubstituted 1,2,3-triazoles.^{30b} Our motivation for extending work in this area is based on further explorations of the reactions of DAMN **1** with aryl diazonium salts. Herein, we report a method for preparing 1,4,5-trisubstituted 1,2,3-triazoles via reaction of DAMN **1** with various aryl diazonium salts.

2. Results and discussion

4-Nitrophenyl diazonium salt **2a** was freshly prepared^{31a} and added to a mixture of DAMN **1** in ethanol. A yellow solid was isolated by filtration from the reaction mixture and all spectroscopic analyses showed the expected 2-amino-3-(3-(4-nitrophenyl)triaz-1-en-1-yl)maleonitrile **3a** indicated in Scheme 1. Isolation of **3a** prompted us to prepare different derivatives that could be utilised as precursors in various transformations. Hence, phenyl diazonium salts **2b–e** were synthesised and allowed to react with DAMN **1** in

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Scheme 1.

ethanol. None of the isolated products showed an imine–NH–signal during ¹H NMR spectroscopy, and the IR spectra obtained showed only a very weak CN peak in addition to a carbonyl function. Molecular ions detected in the mass spectra identified the triazoles **5b–e** shown in Scheme 1. Isolation of maleonitrile derivative **3a** from the 4-nitrophenyl diazonium salt could only result from the strong electron-withdrawing effect of the nitro group in the *para*-position of the benzene ring. This group reduces the electron density around the nitrogen atom in the N=N–NH–moiety, which survives cyclisation and, consequently, hydrolysis. Isolation of triazoles **5b–e** indicates that maleonitrile derivatives **3b–e** are formed as intermediates after the reaction of diazonium salts **2b–e** with DAMN **1**. Due to their instability, maleonitrile derivatives **3b–e** are cyclised to triazoles of type **4b–e**, which are hydrolysed spontaneously to give the more stable triazoles **5b–e**. Triazoles **5b–e** were characterized by spectroscopic data. All of them contain the alpha-ketonitrile group. In their ¹³C NMR spectra, the carbonyl function of these groups appears at δ 160.3–156.7 ppm. This is not surprising as it has been reported before to appear at δ 164.7–167.6.^{31b,c}

In an attempt to obtain compounds **3b–e** and **4b–e**, the reaction conditions were modified, as shown in Table 1.

Initially, all of the reactions were carried out in the presence of sodium acetate to prevent protonation of the amino groups in

DAMN **1** prior to addition of the diazonium salts. Under these conditions, 4-nitrophenyl diazonium salt **2a** coupled with DAMN **1** to yield **3a**. However, when the same conditions were applied using diazonium salts **2b**, **d** and **e**, triazoles **5b**, **d** and **e** were obtained.

Table 1
Reaction conditions for the coupling of DAMN **1** with diazonium salts **2**

Entry	Diazonium salt	Reaction condition	Product	Yield
1	2a	DAMN, EtOH, rt	3a	44%
2	2a	DAMN, EtOH, rt, CH ₃ CO ₂ Na	3a	35%
3	2a	DAMN, EtOH, rt, CH ₃ CO ₂ Na and ice	Traces of 3a	
4	2b	DAMN, EtOH, rt	5b	15%
5	2b	DAMN, EtOH, rt, CH ₃ CO ₂ Na	5b	12%
6	2b	DAMN, EtOH, rt, CH ₃ CO ₂ Na and ice	Traces of 4b	
7	2c	DAMN, EtOH, rt	5c	9%
8	2c	DAMN, EtOH, rt, CH ₃ CO ₂ Na	Decomposed	
9	2c	DAMN, EtOH, rt, CH ₃ CO ₂ Na and ice	Decomposed	
10	2d	DAMN, EtOH, rt	5d	21%
11	2d	DAMN, EtOH, rt, CH ₃ CO ₂ Na	5d	7%
12	2d	DAMN, EtOH, rt, CH ₃ CO ₂ Na and ice	Traces of 4d	
13	2e	DAMN, EtOH, rt	5e	24%
14	2e	DAMN, EtOH, rt, CH ₃ CO ₂ Na	5e	13%
15	2e	DAMN, EtOH, rt, CH ₃ CO ₂ Na and ice	Traces of 4e	

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