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A novel conversion of acetylenic 1,2,4-triazoles into 3-alkyl-5-arylpyridazines

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Abstract—Bromination of 2-aryl-1-[1,2,4]triazol-1-ylalk-3-yn-2-ols gives 6-bromo-7-hydroxy-5-alkyl-7-aryl-7,8-dihydro-[1,2,4]triazolo[1,2-*a*]pyridazin-4-ylium salts, which are converted by treatment with strong alkali into novel 3-alkyl-5-arylpyridazines.
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1. Introduction

Pyridazines are an important class of heterocycle, which have been the subject of extensive research, particularly in the pharmaceutical and agrochemical areas, and their synthesis and applications have been comprehensively reviewed.[1–4] While there are numerous general methods for the synthesis of pyridazines, there are only few methods for making 3-substituted-5-arylpyridazines. These have usually been based on cycloaddition chemistry, for example, alkyl or alkylstannyl acetylenes undergo [4+2] cycloaddition with 3-aryl-1,2,4,5-tetrazines to give mixtures of regioisomers, which can be manipulated to give a variety of 3,5-diarylpyridazines,[5] and monohaloazodienes react with enamines to give 3-alkyl-5-arylpyridazines in variable yields.[6] In another approach, addition of diazomethane to diarylcyclopropene carboxylates gives diazabicyclohexenes, which lose nitrogen in situ to give diarylpyridazine esters, which are in turn hydrolysed and decarboxylated to give 3,5-diarylpyridazines.[7] In this paper, we wish to report a novel route to 3-alkyl-5-arylpyridazines from 1,2,4-triazolyl alkynols. Our route involves the intramolecular attack of the triazole ring nitrogen on a bromonium ion or bromovinyl cation generated by bromination of an acetylene to give a fused triazolium salt, which then breaks down on treatment with aqueous alkali to give the 3-alkyl-5-arylpyridazines.

Substituted 1,2,4-triazoles have received a great deal of attention owing to their biological activity against both agricultural[8] and human fungi.[9] In particular, tertiary triazolyl alcohols of general type **1** have been of great interest because of their outstanding potency on a wide range of fungal pathogens. In the agrochemical field extensive work by many groups[10] has shown that R and R^1 in **1** can be aryl rings or alkyl chains, which in turn can be substituted by many different groups such as ethers, ketones, esters or even another triazole ring. Important examples of antifungal triazoles are the agricultural fungicide epoxiconazole[11] **2** and the pharmaceutical fungicide fluconazole **3**[9] (Fig. 1).

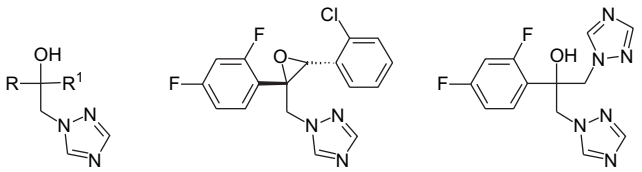

Figure 1. Structures of fungicidal 1,2,4-triazoles **1**–**3**.

2. Results

During our research into fungicides for agricultural use we found that triazoles **1** where R was a substituted phenyl group and R^1 was an alkenyl or alkynyl group, showed high fungicidal activity. We developed a simple synthesis of acetylenic triazoles **6a**–**f**[12] (Scheme 1). Lithium acetylides, generated from the acetylenes by treatment with *n*-butyl lithium, were added smoothly to chloroacetophenones **4a**–**f** to give moderate to excellent yields of the chlorohydrins **5a**–**f**. The crude chlorohydrins were reacted directly with the anion of 1,2,4-triazole, generated with sodium hydride in DMF, to give the 1,2,4-triazolyl alkynols **6a**–**f** in moderate to good yields. For the synthesis of the ethynyl compound **6a**, the trimethylsilyl acetylene chlorohydrin **5a** was used and the trimethylsilyl group was removed by acidic work-up after reaction with 1,2,4-triazole.

Keywords: Pyridazines; Triazoles; Acetylenes; Triazolium; Cyclisation.
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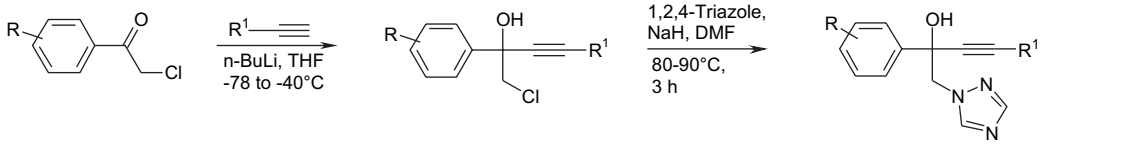


4a R = 2,4-di-Cl
4b R = 4-Cl
4c R = 2,4-di-F

	crude yield
5a R = 2,4-di-Cl, R^1 = $Si(CH_3)_3$,	88%
5b R = 2,4-di-Cl, R^1 = CH_3,	92%
5c R = 2,4-di-Cl, R^1 = C_2H_5,	37%
5d R = 2,4-di-Cl, R^1 = n-C_5H_{11},	100%
5e R = 4-Cl, R^1 = C_2H_5,	100%
5f R = 2,4-di-F, R^1 = C_2H_5	85%

	yield from **4a-e**
6a R = 2,4-di-Cl, R^1 = H,	41%
6b R = 2,4-di-Cl, R^1 = CH_3,	20%
6c R = 2,4-di-Cl, R^1 = C_2H_5,	58%
6d R = 2,4-di-Cl, R^1 = n-C_5H_{11},	59%
6e R = 4-Cl, R^1 = C_2H_5,	41%
6f R = 2,4-di-F, R^1 = C_2H_5,	55%

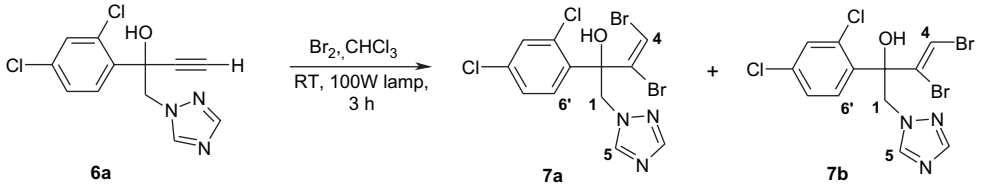
Scheme 1. Synthesis of triazolyl alkynols **6a–f**.

We wished to make some triazoles of type **1** where R was a substituted phenyl group and R^1 was a halogenated alkyl group, and it seemed likely that with the alkynyl analogues **6a–f** in hand, simple addition of halogens would quickly give examples for biological testing. Accordingly bromine was added to the ethynyl compound **6a** in chloroform at room temperature, but gave no reaction. However, in the presence of light (100 W tungsten lamp) smooth bromination took place and after 3 h a nearly quantitative yield of *E*- and *Z*-isomers **7a** and **7b** in an approximately 2:5 ratio was obtained (Scheme 2). The stereochemistry of **7a** and **7b** was assigned by ^{1}H NMR. In the *Z*-isomer **7b** the protons H-1, H-5 and H-6′ showed an NOE when olefinic proton H-4 was irradiated, whereas in the *E*-isomer **7a**, when proton H-4 was irradiated no NOEs were detected.

In the expectation that the alkyl acetylenes **6b–f** would undergo similar radical bromination, we were surprised to find that when bromine was added to the compounds in chloroform at room temperature preparatory to carrying out the light reaction, an exothermic reaction occurred, leading to a rapid decolourisation followed by gradual precipitation of white crystalline solids. After treatment with aqueous alkali to neutralise the reaction these solids yielded new compounds, identified as the novel pyridazines **8b–f** (Scheme 3).

The mass spectra for each of **8b–f** showed a major ion for the loss of two carbon atoms, one nitrogen atom and water from the starting materials **6b–f**, with no incorporation of bromine. There was no alcohol present in their IR spectra. In the ^{1}H NMR spectrum, the triazole protons, typically as singlets at around 7.80 and 8.20 ppm, were replaced by new singlets at around 7.30 and 9.30 ppm. An ^{1}H–^{13}C HMBC study of compound **8e** confirmed all the key connectivities. Pyridazine proton H-4 correlated with carbons C-6 and C-1′, pyridazine proton H-6 correlated with C-4 and C-5 and the ethyl CH_2 protons correlated with C-3 and C-4. Additionally, when pyridazine proton H-6 was irradiated an NOE was shown by the benzene proton H-2′ and when the ethyl CH_2 protons were irradiated an NOE was shown by H-4. The microanalyses were in agreement with the proposed structures.

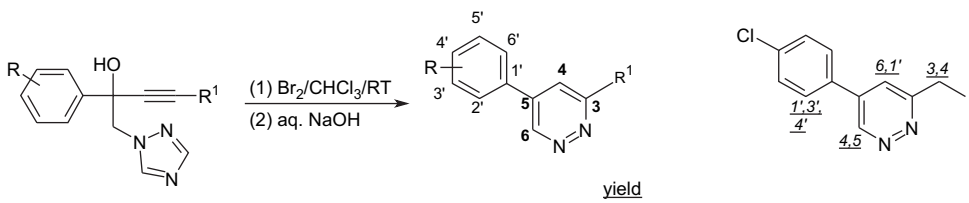
Having identified the final products we then turned our attention to the precipitates formed in the bromination



6a **7a** **7b**

7a:**7b**, 2:5

Scheme 2. Reaction of triazolyl alkynol **6a** with bromine.



6b R = 2,4-di-Cl, R^1 = CH_3
6c R = 2,4-di-Cl, R^1 = C_2H_5
6d R = 2,4-di-Cl, R^1 = n-C_5H_{11}
6e R = 4-Cl, R^1 = C_2H_5
6f R = 2,4-di-F, R^1 = C_2H_5

	yield
8b R = 2,4-di-Cl, R^1 = CH_3	89%
8c R = 2,4-di-Cl, R^1 = C_2H_5	26%
8d R = 2,4-di-Cl, R^1 = n-C_5H_{11}	40%
8e R = 4-Cl, R^1 = C_2H_5	57%
8f R = 2,4-di-F, R^1 = C_2H_5	80%

8e
^{1}H-^{13}C correlations

Scheme 3. Bromination of triazolyl alkynols **6b–f** to give pyridazines **8b–f**.

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