



## A NOVEL SYNTHESIS OF 3,4,5-TRIARYL-1,2,4-*H*-TRIAZOLES FROM 2,5-DIARYL-1,3,4-OXADIAZOLES AND ALUMINIUM ANILIDES

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3,4,5-Triaryl-1,2,4-*H*-triazoles have been prepared in 70-91% yields by a simple and easy to control one-pot procedure from 2,5-diaryl-1,3,4-oxadiazoles and aluminium anilides.

### INTRODUCTION

1,2,4-Triazoles are basic aromatic heterocycles that can be prepared using the Einhorn-Brunner reaction (from imides and alkyl hydrazines to form a mixture of isomeric 1,2,4-triazoles) or the Pellizzari reaction (between an amide and a hydrazide).<sup>1</sup> 1,2,4-Triazole derivatives find use in a wide variety of applications, most notably as antifungals (such as fluconazole and itraconazole) or fungicides for plants protection.

Many diaryl or triaryl substituted triazoles are known to be potential antibacterial, mostly antituberculous,<sup>2</sup> as well as antimicrobial agents.<sup>3</sup> There are in the literature a few reactions used in the synthesis of 3,4,5-triaryl-1,2,4-*H*-triazoles starting from 2,5-diaryl-1,3,4-oxadiazoles and aromatic amines. These reactions take place at high temperatures<sup>4</sup> or in the presence of polyphosphoric acid.<sup>5</sup> They also can be prepared from diaroilylhydrazines and aryloxyphosphazone,<sup>6</sup> or from 5-substituted tetrazoles and carboxylic acid imide chlorides,<sup>7</sup> but these are laborious protocols and use aggressive reagents (*i. e.*,  $\text{PCl}_3$ ). Several other methods, such as condensation of symmetrically substituted bis( $\alpha$ -chlorobenzylidene)hydrazine with an aniline derivative, direct condensation of aroylhydrazine with an appropriately substituted *N*-phenylbenzimidoyl chloride,<sup>2</sup> *in situ* solvothermal

generation from organonitriles and hydrazine hydrate,<sup>8</sup> are also used but involve multistep difficult syntheses.

In this paper, we introduce a novel synthesis of 3,4,5-triaryl-1,2,4-*H*-triazoles starting from 2,5-diaryl-1,3,4-oxadiazoles and aluminium anilides as reagents, in the presence of NMP as solvent, at reflux, for 7-10 h, by a simple and easy to control one-pot procedure, when anilides are prepared *in situ*.

### RESULTS AND DISCUSSION

Metal anilides are well known reagents in organic chemistry due to their specific reactivity,<sup>9,10</sup> namely enhanced basicity and nucleophilicity.

Aluminium anilides  $(\text{Ar-NH})_3\text{Al}$ , although less studied and used, have attractive properties which make them suitable reagents for condensation reactions. They can be prepared from the corresponding aromatic amines and aluminium chloride,<sup>11</sup> in a molar ratio of 4:1, where the amino compound is employed in excess.

We have recently found that these aromatic aluminium anilides can react with 2,5-diaryl-1,3,4-oxadiazoles by opening the oxadiazole cycle and a subsequent cyclization with the formation of a triazole cycle. By stepwise investigation, we

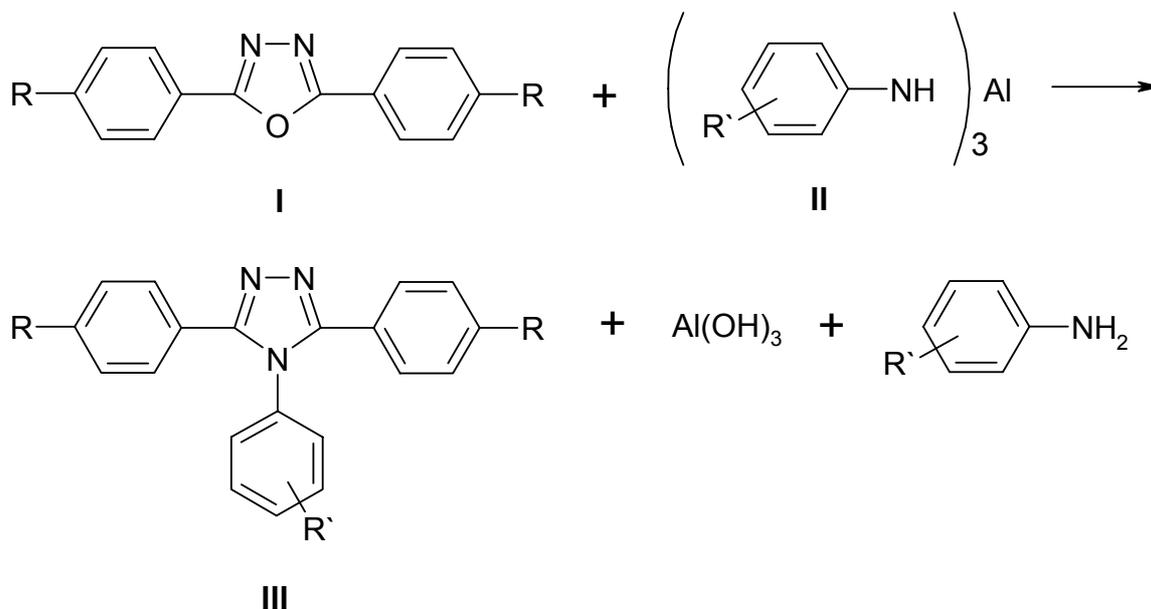
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established that 2,5-diaryl-1,3,4-oxadiazoles **I** can react with aluminium anilides **II**, in the molar ratio of 1:2 (aromatic anilides in excess), resulting in 3,4,5-triaryl-1,2,4-*H*-triazoles **III**, as presented in Scheme 1.

In order to optimize the reaction system, we tested several solvents, such as DMF, DMSO,

NMP, HMPTA, and we selected NMP because it is a good solvent for the considered reagents and products, is stable under the reaction conditions and has a high boiling point (202°C).

The synthesis we propose requires high temperatures (reflux at 205-215°C), for 7-10h (see Table 1), for the reaction to be completed.



triazole	IIIa	IIIb	IIIc	IIId	IIIe	IIIf	IIIg	IIIh
R	<i>p</i> -CH <sub>3</sub>	<i>p</i> -CH <sub>3</sub>	H	H	H	H	H	H
R'	<i>p</i> -CH <sub>3</sub>	H	H	<i>p</i> -CH <sub>3</sub>	<i>m</i> -CH <sub>3</sub>	<i>p</i> -OCH <sub>3</sub>	<i>p</i> -Cl	<i>m</i> -Cl

Scheme 1 – Synthesis of 3,4,5-triaryl-1,2,4-*H*-triazoles from 2,5-diaryl-1,3,4-oxadiazoles and aluminium anilides.

Table 1

Triazoles obtained with aluminium anilides

Triazoles <sup>a</sup>	Yield <sup>b</sup> (%)	Reaction time (h)	M.p. <sup>c</sup> (°C)	Literature m.p. (°C)
IIIa	91	7	241-243	242-243 <sup>12</sup>
IIIb	88	7	297-298	297-298 <sup>12</sup>
IIIc	77	9	299-300	299-300 <sup>6</sup>
IIId	74	10	301-302	300-302 <sup>6</sup>
IIIe	72	8	255-257	256-257 <sup>6</sup>
IIIf	78	10	240-242	241-242 <sup>6</sup>
IIIg	73	9	261-262	261-262 <sup>6</sup>
IIIh	70	10	258-259	258-259 <sup>13</sup>

<sup>a</sup> Triazoles obtained were identified by comparison of their IR and <sup>13</sup>C NMR spectra with authentic samples.

<sup>b</sup> Yields calculated based on the oxadiazoles **I** employed.

<sup>c</sup> After recrystallization.

As can be seen in Table 1, triazoles **III** were obtained in yields ranging from 70 to 91%, depending on the structure of their corresponding oxadiazoles. Triazoles **IIIa** and **IIIb** were obtained from the same oxadiazole **Ia** where the

substituent R is *p*-CH<sub>3</sub>, an electron releasing group which increases the oxadiazole reactivity and, consequently, the yield in final product.

The reaction conditions also determine the yield of this reaction. At low temperatures, the yield

decreased. For example, for the product **IIIa** the yield decreased to 43-45% when the reaction was performed at 150-160°C. The experimental results are comparable with those reported in the literature using different procedures.<sup>1,4-8</sup>

## EXPERIMENTAL

General procedure for the synthesis of 3,4,5-triaryl-1,2,4-4*H*-triazoles. In a 100mL three-necked Claisen flask, fitted with a mechanical stirrer and a thermometer, anhydrous aluminium chloride (0.0066 mol, 0.88g) was slowly added to the aromatic amine (0.0266 mol) corresponding to aluminium anilide II and the resulted mixture was heated up to 130-140°C under stirring for 2-2.5 h, when aluminium anilide II results. Then, 2,5-diaryl-1,3,4-oxadiazole I (0.01 mol) and NMP (3 mL) were added and the obtained mixture was heated at reflux for 7-10 h, without stirring (see Table 1). Then the solution was treated with HCl solution 15-20% (70-80 mL), when the triazoles III precipitated. After 2-3 h of stirring on an ice bath, the final product III was filtered, washed with cold water (15-20 mL) and dried.

IR spectra were recorded on a Bruker Vertex 79 FTIR spectrophotometer, using the KBr pellet technique. Melting points were determined with a Gallenkamp hot-block point apparatus. <sup>13</sup>C-NMR spectra were recorded on a Bruker Avance DRX 400 device. All solvents and reagents were purchased from Fluka and were used, when necessary, after purification.

In conclusion, we have introduced a novel synthesis for the preparation of 3,4,5-triaryl-1,2,4-4*H*-triazoles starting from 2,5-diaryl-1,3,4-oxadiazoles and aluminium anilides. This method is a simple and efficient synthesis and a very effective alternative to the classical syntheses of triazoles.

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