



Synthesis of fused 1,2,3-triazolo-1,3,6-triazonines through copper-catalyzed intramolecular Ullmann cross-coupling reaction



José Edmilson R. do Nascimento^a, Lóren C. C. Gonçalves^a, Geert Hooyberghs^b, Erik V. Van der Eycken^{b,*}, Diego Alves^a, Eder J. Lenardão^a, Gelson Perin^a, Raquel G. Jacob^{a,*}

^a Laboratório de Síntese Orgânica Limpa—LASOL, CCQFA, Universidade Federal de Pelotas—UFPEL, PO Box 354, 96010-900 Pelotas, RS, Brazil

^b Laboratory for Organic & Microwave-Assisted Chemistry (LOMAC), Department of Chemistry, University of Leuven (KU Leuven), Celestijnenlaan 200F, 3001 Leuven, Belgium

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ABSTRACT

We describe here an efficient method to synthesize 1-aryl-15*H*-dibenzo[*d,h*][1,2,3]triazolo[1,5-*a*][1,3,6]-triazonines by copper-catalyzed intramolecular Ullmann cross-coupling reaction. Reactions between a range of 5-iodo-1,2,3-triazoyl benzaldehydes and substituted diaminobenzenes in the presence of a catalytic amount of CuI (5 mol %) in DMSO at 100 °C under microwave irradiation have proven to be an efficient way to access new fused 1,2,3-triazolo-1,3,6-triazonines in good to excellent yields.

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Heterocyclic systems have been pointed out as one of the most representative chemical architectures found in several natural and synthetic bioactive compounds, including a large number of commercial drugs. Also, *N*-heterocyclic compounds are important building-blocks for new materials possessing interesting electronic, mechanical, or biological properties.¹

In this context, structures containing medium-sized *N*-heterocycle rings (8- to 11-membered rings) are very important compounds found in biologically active natural products used in modulation of drug candidates,² materials science,³ and catalysis.⁴ Conventional cyclization methods are not effective to access medium-sized rings, once the overall entropy and enthalpy changes in the process are unfavorable, unless to a restrict number of acyclic precursors.⁵ The synthesis of medium-sized *N*-heterocyclic rings therefore remains an important challenge in synthetic organic chemistry.

Azonines are compounds characterized by having in their structure a nine membered *N*-heterocyclic ring.⁶ These compounds have synthetic interest and are present in many naturally occurring and synthetic compounds.⁷ For example, azonines such as Teleocidin A and B (**I** and **II** respectively), were isolated from the fungus *Streptomyces mecliocidicus* (Fig. 1). These azonines stimulate the nervous system and are potent activators of protein kinase C.⁸ Other azonines, such as (–)-Rhazinilam **III** and (–)-Rhazinicine **IV**, are both

members of the *Aspidosperma* class of alkaloids and have been recognized as lead compounds for new antitumor agents.⁹ The synthetic azonine **V**¹⁰ and triazonine **VI**¹¹ show antagonistic activity for CCK receptors.

Regarding the available methods for the synthesis of medium-sized *N*-heterocycles, Buchwald and co-workers¹² developed a simple protocol for the preparation of 7-, 8-, 9-, and 10-membered *N*-heterocycles via a domino process involving a copper-catalyzed C–N coupling reaction followed by a ring-expansion step proceeding through an intramolecular transamidation reaction.^{12a} In another study, Fu and co-workers^{12b} described a method for the preparation of medium- and large-sized *N*-heterocycles via a copper-catalyzed intramolecular *N*-arylation of phosphoramidates and carbamates. Therefore, copper-catalyzed *N*-arylation reactions have been largely used for the preparation of a plethora of nitrogen heterocycles, including 5-, 6-, and 7-membered *N*-heterocycles.¹³

In view of these findings, and due to our interest in copper-catalyzed reactions,¹⁴ we describe herein the synthesis of a range of new fused 1,2,3-triazolo-1,3,6-triazonines **3** by copper-catalyzed intramolecular Ullmann cross-coupling reactions between 5-iodo-1,2,3-triazoyl benzaldehydes **1** and substituted diaminobenzenes **2** (Scheme 1).

We envisioned that the 5-iodo-1,2,3-triazoyl benzaldehydes **1** and diaminobenzene **2** could be used as substrates for the

* Corresponding authors.

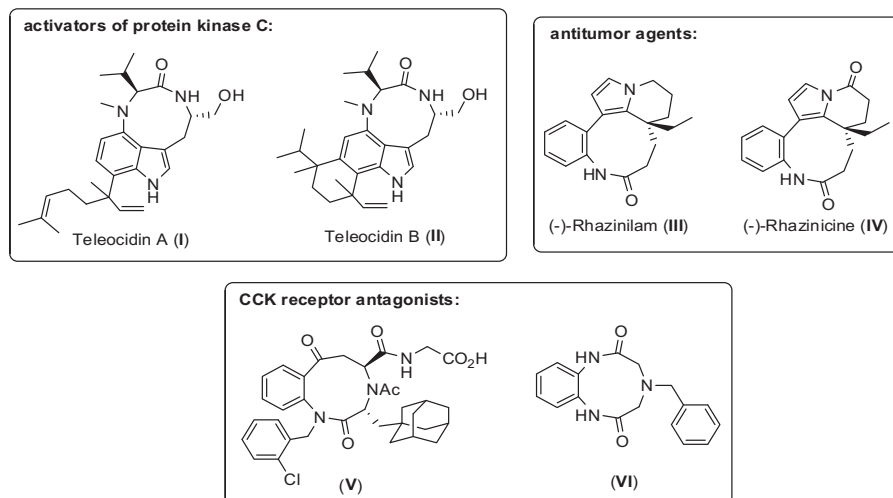
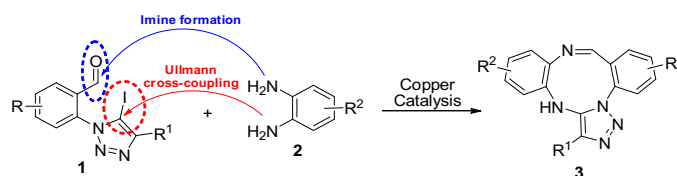


Figure 1. Selected examples of bioactive benzoazonines.



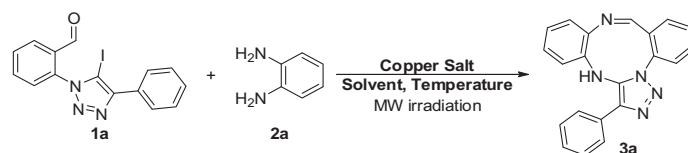
Scheme 1. General scheme of the reaction.

synthesis of fused 1,2,3-triazolo-1,3,6-triazonines **3** in a sequential imine formation and Ullmann cross-coupling reaction.

According to previous reports on copper-catalyzed reactions,^{12a,b,13} a homogeneous mixture of 2-(5-iodo-4-phenyl-1H-

1,2,3-triazol-1-yl)benzaldehyde **1a**¹⁵ (0.6 mmol) and *o*-phenylenediamine **2a** (0.6 mmol) in DMSO (0.6 mL) was stirred at 100 °C in the presence of 10 mol % of CuI as catalyst, providing a good yield (78%) of the desired product **3a** after 15 h (Table 1, entry 1). It has been shown that organic reactions can be influenced by microwave irradiation (MW).¹⁶ In all these cases, the authors demonstrated that the use of MW irradiation can considerably decrease the reaction time, often accompanied by an increase in product yields. Therefore, the above described reaction was evaluated under focused microwave irradiation at 100 °C, 200 W for 1 h, delivering product **3a** in 85% yield (Table 1, entry 2). Encouraged by this result, we further optimized the conditions under microwave irradiation varying time and

Table 1
Optimization of the reaction conditions^a



Entry	Temp (°C)	Time (h)	Solvent	Catalyst (mol %)	Yield (%) ^b
1	100	15	DMSO	CuI (10)	78 ^c
2	100	1.0	DMSO	CuI (10)	85
3	100	0.5	DMSO	CuI (10)	76
4	60	1.0	DMSO	CuI (10)	75
5	80	1.0	DMSO	CuI (10)	80
6	100	1.0	DMSO	CuI (10)	82 ^d
7	100	1.0	DMSO	CuI (10)	77 ^e
8	100	1.0	DMF	CuI (10)	58
9	100	1.0	THF	CuI (10)	54
10	100	1.0	Toluene	CuI (10)	61
11	100	1.0	Glycerol	CuI (10)	37
12	100	1.0	DMSO	CuCl (10)	71
13	100	1.0	DMSO	CuBr (10)	62
14	100	1.0	DMSO	Cu(OAc) ₂ (10)	81
15	100	1.0	DMSO	CuI (5)	86
16	100	1.0	DMSO	CuI (20)	83
17	100	1.0	DMSO	CuI (3)	71
18	150	0.3	DMSO	CuI (5)	68

^a Reactions were performed with 2-(5-iodo-4-phenyl-1H-1,2,3-triazol-1-yl)benzaldehyde **1a** (0.6 mmol) and *o*-phenylenediamine **2a** (0.6 mmol) under focused microwave irradiation (200 W).

^b Yields are given for isolated products.

^c Reaction was performed with conventional heating.

^d Reaction was performed using 1.2 equiv of *o*-phenylenediamine **2a**.

^e Reaction was performed using 1.2 equiv of 2-(5-iodo-4-phenyl-1H-1,2,3-triazol-1-yl)benzaldehyde **1a**.

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