



# Easy access to (2-imidazolin-4-yl)phosphonates by a microwave assisted multicomponent reaction



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## ABSTRACT

An efficient and user-friendly synthetic process involving the combination of multicomponent reaction methodology and microwave heating generates unprecedented (2-imidazolin-4-yl)phosphonates **1–18**. This strategy presents a silver-catalysed, operationally simple and environmentally friendly transformation without the need of anhydrous atmosphere or additional solvents.

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## 1. Introduction

2-Imidazoline-containing compounds constitute a valuable class of agents that modulate the  $\alpha$ 2-adrenergic receptors, and often show a high affinity for imidazoline binding sites (IBS) (Fig. 1).<sup>1</sup> The biological profile of these IBSs has been examined in pharmacological studies due to their involvement in the control of blood pressure, depression, insulin secretion, neurodegenerative disorders, and tolerance and dependence on opioids.<sup>2</sup> Moreover, 2-imidazolines are an important class of heterocyclic scaffolds that can be found in natural product chemistry, organic synthesis, coordination chemistry and homogeneous catalysis.<sup>3</sup>

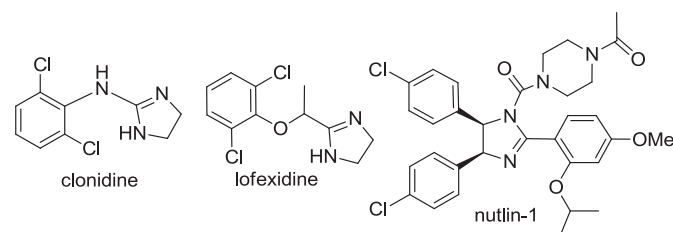


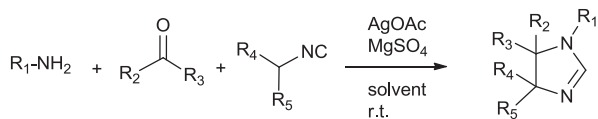
Fig. 1. Biologically active 2-imidazoline-containing compounds.

To meet the demand for 2-imidazoline-containing compounds, many efficient synthetic approximations have been developed, including the synthesis of 2-imidazolines from 1,2-diamines,  $\beta$ -hydroxyamides, *N*-acyldiamines, aziridines, alkenes, azalactones and imines, and isocyanides and imines.<sup>4</sup>

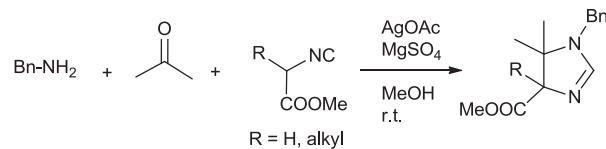
The distinctive reactivity of isocyanides has been recognized as an advantageous characteristic for the construction of nitrogen-containing heterocycles.<sup>5</sup> Their divalent nature makes smooth reactions possible with a myriad of reaction partners of either electrophilic or nucleophilic character. In addition, the facile coordination of isonitriles to metals increases the acidity of the adjacent hydrogen atoms. Deprotonation of metal-complexed isocyanides often proceeds with weak bases, leading to nucleophiles that can be used in, for example, cycloaddition reactions.<sup>6</sup> The rich chemistry of isonitriles has experienced a renaissance due to their crucial role in the fashionable and fascinating field of multicomponent reactions.<sup>7</sup> The isocyanide-based multicomponent reactions (IMCRs) have been widely investigated in organic synthesis owing to their inherent features such as atom- and step economy, convergence and diversity. Thus, IMCRs encode a set of privileged reactions in the toolbox of sustainable synthetic methodologies.<sup>8</sup>

In this framework, the pioneering paper by Orru and co-workers is a key contribution, as it describes an efficient and flexible multicomponent reaction of diversely substituted 2-imidazolines, employing isocyanides bearing an acidic  $\alpha$ -proton (Scheme 1).<sup>9</sup>

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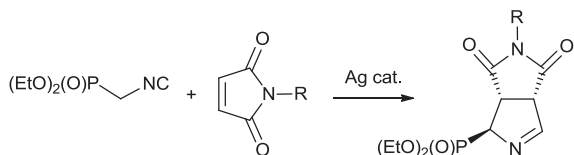


Scheme 1. Orru's synthesis of 2-imidazolines.



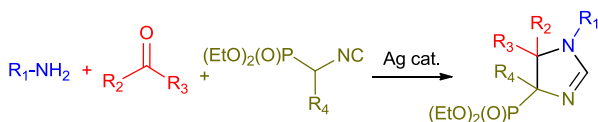
Scheme 4. Orru's examples with methyl isocyanoacetate derivatives.

As part of our ongoing research in  $\alpha$ -metallated isocyanides, we have recently published the first diastereoselective silver-catalysed [3+2]cycloaddition of diethyl isocyanomethylphosphonate (PhosMic) and diversely *N*-substituted maleimides, leading to bicyclic  $\alpha$ -aminophosphonates (Scheme 2).<sup>10</sup>



Scheme 2. Reaction of PhosMic and maleimides.

Inspired by Orru's study and seeking new applications of isocyanide derivatives, we envisaged the possibility of performing a multicomponent reaction between PhosMic or  $\alpha$ -substituted PhosMic derivatives, ketones and amines (Scheme 3). Notably, although isocyanide derivatives can be found extensively in the literature as reactants in multicomponent reactions, the use of PhosMic in IMCRs has received less attention.<sup>11</sup> It is worth noting that the proposed reaction would give direct access to (2-imidazolin-4-yl) phosphonate compounds. The potential biological interest of these new azaheterocyclic phosphonates is mostly associated with the tetrahedral structure of the phosphonyl group, which may act as a 'transition state analogue' in enzymatic peptide hydrolysis.<sup>12</sup>



Scheme 3. Proposed reaction to access (2-imidazolin-4-yl)phosphonates.

This work addresses the synthesis of 2-(imidazolin-4-yl)phosphonates through an environmentally friendly multicomponent heterocyclic reaction following green chemistry considerations. To this end, we envisioned the use of microwave irradiation, which is an outstanding tool for sustainable organic chemistry, maximizing synthetic efficiency, diversity and complexity.<sup>13</sup> In particular, we disclose a general microwave protocol for a silver-catalysed three-component reaction towards the synthesis of (2-imidazolin-4-yl) phosphonates. The reactivity outcome is rationalized by theoretical calculations.

## 2. Results and discussion

As mentioned above, Orru and co-workers were able to obtain methyl 1-benzyl-5,5-dimethyl-4,5-dihydro-1*H*-imidazole-4-carboxylate (R=H, Scheme 4) in 89% yield by stirring a suspension of benzylamine, acetone and methyl isocyanoacetate in methanol for 5 h at room temperature in the presence of an equimolar amount of magnesium sulfate. Using  $\alpha$ -alkyl substituted isocyanide derivatives (R=alkyl, Scheme 4), the process required the presence of a catalytic amount of silver acetate and a considerable increase in the reaction time for the reaction to occur.

In this work, an analogous multicomponent reaction using PhosMic was examined with the aim of finding the easiest to handle and eco-friendly reaction conditions different factors were considered. First of all, removal of methanol as the solvent and the use of acetone were studied. Thus, acetone would act both as reagent and solvent in a very concentrated reaction without exclusion of air and humidity. Secondly, the use of microwave irradiation was envisaged as an optimal technique to carry out the reaction in the shortest possible time.

Since active hydrogen atoms in the  $\alpha$ -isocyanophosphonate Schiff bases are less acidic than their corresponding counterpart  $\alpha$ -isocyanoesters, the proposed transformation needed to be performed under silver catalytic conditions. As previously reported, when PhosMic is stirred in the presence of silver acetate, a self-cyclodimerization product is observed.<sup>14</sup> In order to avoid this side product, a weaker base salt, AgNO<sub>3</sub>, was employed as the catalyst. In this process, a series of experiments were conducted to study the impact of the temperature, the catalyst and the reaction time on the yield. Finally, the optimized reaction conditions consisted of irradiating a mixture of PhosMic (1 equiv), amine (1.5 equiv), MgSO<sub>4</sub> (1.8 equiv) and AgNO<sub>3</sub> (10%-mmol) and acetone in a microwave oven during 10 min at 40 °C.<sup>15</sup> The reaction was examined with a range of diversely substituted alkyl amines and the results are given in Table 1.

Table 1  
Yields (%) of the phosphono-2-imidazolines **1–10**<sup>a</sup>

Entry	RNH <sub>2</sub>	With MgSO <sub>4</sub> <sup>b</sup>	Without MgSO <sub>4</sub> <sup>b</sup>
1	Propylamine	<b>1</b> 30	53
2	Cyclohexylamine	<b>2</b> 57	62
3	2-Ethylhexylamine	<b>3</b> 52	89
4	1-Adamantanemethylamine	<b>4</b> 49	72
5	Benzylamine	<b>5</b> 62	66
6	Phenethylamine	<b>6</b> 91	89
7	Tryptamine	<b>7</b> 50	87
8	1-(1-Adamantyl)ethylamine	<b>8</b> nd	71 <sup>c</sup>
9	1-Methylbenzylamine	<b>9</b> nd	60 <sup>d</sup>
10	2-Methylphenethylamine	<b>10</b> nd	69

<sup>a</sup> Reagents and conditions: (i) PhosMic (1 equiv), amine (1.5 equiv), MgSO<sub>4</sub> (1.8 equiv) or without MgSO<sub>4</sub>, AgNO<sub>3</sub> (10%-mmol) and acetone in a microwave oven 10 min at 40 °C; **1–10** (yields, see Table 1).

<sup>b</sup> Yields refer to isolated products.

<sup>c</sup> Reaction carried out at rt for 24 h.

<sup>d</sup> Reaction carried out at rt for 48 h. nd=not done.

Propylamine, cyclohexylamine and 2-ethylhexylamine gave expected final products **1–3** in 30, 57 and 52% yield, respectively (entries 1–3). Compound **3** was isolated as a single diastereoisomer. Notably, the reaction also occurred with the hindered adamantane moiety to furnish **4** in 49% yield (entry 4). When benzylamine, phenethylamine and tryptamine were employed, the reaction gave **5–7** in 62, 91 and 50% yield, respectively (entries 5, 6 and 7). After confirming that the reaction occurs with a considerable range of amines in the presence of acetone playing the dual role of reagent and solvent, removal of MgSO<sub>4</sub> was envisaged to achieve the

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