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# Simple access toward 3-halo- and 3-nitro-pyrazolo [1,5-a]pyrimidines through a one-pot sequence†

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Herein, a regioselective, time-efficient and one-pot route for the synthesis of diversely substituted 3-haloand 3-nitropyrazolo[1,5-a]pyrimidines in good to excellent yields through a microwave-assisted process is provided. The reaction features a sequential cyclocondensation reaction of  $\beta$ -enaminones with NH-5aminopyrazoles, followed by a regioselective electrophilic substitution with easily available electrophilic reagents. This methodology is distinguished by its short reaction times, high-yield, operational simplicity, broad substrate scope and pot-economy. Furthermore, these 3-functionalized heterocycles have been successfully used in the synthesis of 3-alkynyl and 3-aminopyrazolo[1,5-a]pyrimidines in yields up to 92%.

#### Introduction

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Among the broad range of privileged structures, fusedpyrimidines represents one of the most prominent classes of heterocyclic scaffolds for novel synthetic drug discovery.<sup>1</sup> Particularly, some synthetic purine analogues containing pyrazolo[1,5-*a*]pyrimidine nucleus have received augmented interest in recent years due to their broad range of applications in medicinal chemistry and drug design.<sup>2</sup> For instance, the anxiolytic agent ocinaplon,<sup>3</sup> and the hypnotic drugs indiplon,<sup>4</sup> lorediplon,<sup>5</sup> and zaleplon,<sup>6</sup> among others potential drugs<sup>7</sup> have this structural motif of pyrazolo[1,5-*a*]pyrimidine (Fig. 1). Too, some 3-halopyrazolo[1,5-*a*]pyrimidines have been reported as a nonbenzodiazepinoid class of antianxiety agents.<sup>8</sup>

Besides medicinal applications, pyrazolo[1,5-*a*]pyrimidines and structural analogues have been found in the dyestuff industry (also used as fluorophores),<sup>9</sup> organic light emitting

diodes (OLEDs)10 and semiconductors materials.11 These promising biological and photophysical properties have prompted the development of various methods for the synthesis of functionalized pyrazolo[1,5-a]pyrimidines.<sup>12-16</sup> The vast majority of these methods mostly involve the interaction NH-5-aminopyrazoles with 1,3-bis-electrophilic between reagents (e.g., β-dicarbonyl compounds,<sup>12</sup> β-enaminones,<sup>13</sup> βhaloenones,<sup>14</sup> β-ketonitriles,<sup>15</sup> among others<sup>16</sup>). Although such methodologies are generally reliable, many of them involved harsh reaction conditions, prolonged reaction times and tedious work-up, require use of additives, and often proceed with moderate yields. Particularly, ultrasound- and microwaveassisted reactions using  $\beta$ -enaminones as precursor have been successfully implemented (shorter reaction times and good yields). However, these methods suffer some limitations, including the use of potassium bisulphate as additive or Mg-Al hydrotalcite as solid base catalyst (Scheme 1a).17 Despite the success of different methods to obtain the interesting pyrazolo [1,5-*a*]pyrimidine core, we are surprised that its construction





Fig. 1 Examples of biologically active pyrazolo[1,5-a]pyrimidines.

<sup>†</sup> Electronic supplementary information (ESI) available: Experimental, characterization data, X-ray structures of **4q**, **5g**, and NMR spectra. CCDC 1542479 and 1542481. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c7ra04336h



Scheme 1 Synthesis of pyrazolo[1,5-a]pyrimidines under mild conditions.



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and subsequent functionalization in a single pot has remained largely unexplored. The introduced functional groups in this heterocyclic core are susceptible to undergoing successive postfunctionalization reactions, which is important in drug discovery among other applications. For example, halogenation reactions have been conveniently explored (Scheme 1a)<sup>18</sup> by obtaining suitable substrates for coupling reactions, however, the incorporation of others functional groups such as nitro or sulphonyl is less frequent. From the viewpoint of economy and environmental sustainability, developing operationally simple, high-yielding, and additive-free method for preparing 3-functionalized pyrazolo[1,5-*a*]pyrimidines in a one-pot manner is highly desirable.

Recently, we reported a microwave-assisted synthesis of 6aryldiazenylpyrazolo [1,5-a] pyrimidin-7-amines from  $\alpha$ -arylhydrazinylidene-\beta-ketonitriles, and their use in the preparation of substituted pyrazolo[5,1-b]purines.<sup>15b</sup> Inspired by these results, and our continuing interest in the synthesis of biologically active N-heterocycles using green chemistry tools,19 we envisioned that microwave-assisted reactions of β-enaminones with NH-5-aminopyrazoles might generate the pyrazolo[1,5-a] pyrimidine core, which could be halogenated and nitrated at the C-3 position of the heterocycle. As a result, leading to the formation of 3-halo and 3-nitropyrazolo[1,5-a]pyrimidines through a catalyst- and additive-free one-pot approach (Scheme 1b). It is important to note that the cyclocondensationelectrophilic substitution sequence between β-enaminones, NH-5-aminopyrazoles and easily available electrophilic reagents would open a practical and eco-compatible synthetic approach to properly functionalized pyrazolo[1,5-a]pyrimidines through the formation of three new bonds in a single reaction vessel and the release of water as the unique byproduct. In this sense, the microwave-assisted one-pot synthesis has proved to be an extremely powerful tool because several synthetic transformations and bond-forming steps can be carried out in a single pot. Thereby, minimal chemical waste, time saving, and operational simplicity are achieve.20

#### Results and discussion

Considering the aforementioned aspects and prior to test the feasibility of the one-pot approach towards properly functionalized pyrazolo[1,5-a]pyrimidines, we started our investigation by examining a strategy to efficiently prepared  $\beta$ -enaminones under microwave irradiation. Although there are diverse protocols to obtain these 1,3-bis-electrophiles,<sup>21</sup> the development of convenient, high-yielding and sustainable methods are still highly desirable due to their synthetic importance. As a test reaction, we submitted a 1:1.5 mixture of acetophenone (1a) and N,N-dimethylformamide-dimethylacetal under microwave irradiation at 160 °C for 15 min in a sealed tube under solventfree conditions. We were pleased to find that the desired  $\beta$ enaminone 2a could be obtained with high purity and almost quantitative yield after simple evaporation of residues in the reaction (Scheme 2). Stimulated by this result, we examined the scope of this eco-compatible reaction with a variety of



Scheme 2 Solvent-free microwave-assisted synthesis of  $\beta$ -enaminones. Reaction conditions: methyl ketone 1 (8.0 mmol) and *N*,*N*-dimethylformamide-dimethylacetal (12.0 mmol); see ESI† for details. <sup>a</sup> 8.0 mmol of ethyl acetoacetate used.

methylketones **1b–f**, providing the  $\beta$ -enaminones **2b–f** in nearly quantitative yields without further purification (Scheme 2).

Subsequently, our exploratory study toward the synthesis of pyrazolo[1,5-*a*]pyrimidine core began with the model reaction between the phenylpropenone (2a) and 5-amino-3-methyl-1*H*-pyrazole (3a) (Table 1). We carried out the optimization by varying the temperature, the solvent and testing the effect of conventional heating *versus* microwave irradiation. Heating to reflux of an equimolar mixture of 2a and 3a in ethanol or toluene for 12 h did not lead to the pyrazolo[1,5-*a*]pyrimidine 4a (Table 1, entries 1 and 2, respectively). When we performed the reaction in DMF at higher temperature, provided compound 4a in poor yield (Table 1, entry 3). The structure of 4a was confirmed by <sup>1</sup>H NMR, <sup>13</sup>C NMR and mass spectroscopy. These preliminary results, showed that higher temperatures favor the

 Table 1
 Optimization of the reaction parameters for the synthesis of pyrazolo[1,5-a]pyrimidine<sup>a</sup>

	Ph + 2a	Me- N-NH 3a	Solvent, t T (°C)	Aa Ph
Entry	Solvent	T (°C)	Time <i>t</i>	$\operatorname{Yield}^{b}(\%)$
1	EtOH	Reflux <sup>c</sup>	12 h	_
2	PhMe	Reflux <sup>c</sup>	12 h	_
3	DMF	$150^{c}$	12 h	15
4	EtOH	$150^d$	3 min	10
5	PhMe	$180^d$	3 min	78
6	DMF	$180^d$	3 min	80
7	—	$180^{e}$	1 min	91
8	_	$180^{e}$	2 min	95
9	—	$180^{e}$	2 min	Quantitative <sup>g</sup>
10	_	180 <sup>f</sup>	30 min	51

<sup>*a*</sup> Reaction conditions: β-enaminone **2a** (0.50 mmol) and NH-5aminopyrazole **3a** (0.50 mmol). <sup>*b*</sup> Isolated yield. <sup>*c*</sup> Conventional heating. <sup>*d*</sup> Run in 10 mL sealed tubes at a power of 300 W in anhydrous solvent (2.0 mL). <sup>*e*</sup> Run in 10 mL sealed tubes at a power of 300 W in the absence of solvent. <sup>*f*</sup> Conventional heating with a sand bath without solvent (fusion procedure). <sup>*g*</sup> Yield is given for the crude product.

#### Paper

formation of the pyrazolo[1,5-a]pyrimidine 4a. To further improve the reaction yield, we examined the influence of microwave irradiation on this reaction in different solvents such as ethanol, toluene, and DMF, and among these, ethanol gave the worst yield of compound 4a (10%) (Table 1, entries 4-6). In the reaction with ethanol as solvent, was not possible to increase the temperature above 150 °C due to system overpressure. In a modified protocol, we performed the solvent-free reaction of 2a and 3a at 180 °C for 1-2 min under microwave irradiation to afford the desired product 4a in high to nearly quantitative yield, after simple collection with mixtures of ethanol-water (Table 1, entries 7 and 8, respectively). Indeed, the reaction proceed in quantitative yield (Table 1, entry 9) after high vacuum removal of all volatiles of the reaction mixture. This result was evidenced by <sup>1</sup>H NMR analysis of the crude product (ESI,† page S22). Therefore, we corroborated the feasibility of our hypothesis to carry out reliable functionalization reactions in the same reactor without further isolation of the pyrazolo[1,5-a]pyrimidine. In order to determine the specific microwave effect on accelerating the reaction vs. conventional heating, a pre-heated sand bath was used as a source of heat in comparative experiments (Table 1, entries 8 vs. 10). The low yield obtained with conventional heating at the same temperature for 30 min, indicated that the effect of microwave irradiation is not purely thermal.

With the optimized reaction conditions in hand (Table 1, entry 8), we then examined the scope of the reaction with a variety of  $\beta$ -enaminones 2a–f and NH-5-aminopyrazoles (3a–e). The results are summarized in Scheme 3. In general, the solvent-free microwave-assisted reaction of  $\beta$ -enaminones 2a–f with a wide range of NH-5-aminopyrazoles (3a–e) bearing both electron-donating and electron-withdrawing substituents



Scheme 3 Microwave-assisted synthesis of  $\beta$ -enaminones and pyrazolo[1,5-a]pyrimidines. Reaction conditions:  $\beta$ -enaminone 2 (0.50 mmol) and NH-5-aminopyrazole 3 (0.50 mmol) at 180 °C for 2 min under solvent-free conditions. <sup>a</sup> 1.50 mmol of 3-(*tert*-butyl)-1*H*-pyrazol-5-amine used. <sup>b</sup> 0.50 mmol of  $\beta$ -enaminoester used.

regioselectively afforded pyrazolo[1,5-a]pyrimidines 4a-p in 85-97% yields, without tedious purification (Scheme 3). Almost no loss of efficiency was observed for the substrates tested, which indicated the low electronic influence of the substituents on the reactivity. This methodology also provided an interesting synthetic access to the valuable product 4q which could be used to synthesize pyrazolo[1,5-a]pyrimidine-based dendritic architectures with potential applications in pharmaceutical and medicinal chemistry, as well as in materials science.<sup>22</sup> The structure of the tris-pyrazolo[1,5-a]pyrimidine 4q was solved by single-crystal X-ray diffraction analysis.23 Additionally, β-enaminone 2f exhibit two different types of carbonyl groups, which reacted chemo- and regioselectively with 3-methyl-1H-pyrazol-5amine (3a) under optimized conditions, to give ethyl 2,7-dimethylpyrazolo [1,5-a] pyrimidine-6-carboxylate (4r) in 89% isolated yield. Also, aminopyrazol 3f substituted with an electronwithdrawing group (R: 4-NO<sub>2</sub>Ph) reacted efficiently with  $\beta$ enaminone 2c (Ar: 4-MeOPh) under optimized conditions, giving the corresponding pyrazolo[1,5-a]pyrimidine 4s in 87% isolated yield (Scheme 3). Notably, this synthetic methodology to obtain pyrazolo[1,5-a]pyrimidines 4a-s was distinguished by its broad substrate scope, operational simplicity, no additives, no solvent, no excess of substrate is used, short reaction times, high-yielding without chromatographic purification, and ecocompatibility in terms of energy and waste.

Halogenated pyrazolo[1,5-a]pyrimidines belong to a class of important building blocks and versatile synthons, which could be converted into more complex molecules by cross-coupling reactions.25 Nevertheless, existing methods to synthesize 3-halopyrazolo[1,5-a]pyrimidines are scarcely reported. Most of these involve the cyclocondensation reaction between 1,3-biselectrophilic reagents and 5-amino-4-halopyrazoles<sup>25a</sup> or by multistep sequences that proceed with the preformation of pyrazolo[1,5-a]pyrimidines and subsequent halogenation reaction with diverse halogen sources such as N-halosuccinimides,<sup>18,24</sup> iodine monochloride,<sup>25b</sup> bromine<sup>25c</sup> and 1chlorobenzotriazole.25d The drawbacks of these strategies include: long reaction times, large volume of hazardous solvents, as well as difficult protocols. Therefore, and continuing with the implementation of greener and economic strategies, the development of an efficient and practical one-pot approach to halogenated pyrazolo [1,5-a] pyrimidines that allows use of readily available starting materials, short reaction times, and easier workup is highly desirable. Consequently, and according to the noteworthy results obtained in our former synthetic method (Scheme 3), we planned to study a consecutive approach toward 3-halopyrazolo[1,5-*a*]pyrimidine 5 in a single reaction vessel, starting from an equimolar mixture of  $\beta$ enaminone 2 and NH-5-aminopyrazole (3), and finishing with the addition of 1 equiv. of N-iodosuccinimide (NIS). Usually, halogenation reactions have been carried out successfully in chlorinated solvents, thus we decided to use 1,2-dichloroethane (EDC) instead of dichloromethane (DCM) to evaluate the effect of temperature. In addition, the first step reaction was performed using conditions analogous to those previously optimized (Table 1, entry 8), while the second step was optimized as indicated below (Table 2).

Table 2Optimization of the reaction parameters for the one-potsynthesis of 3-iodopyrazolo[1,5-a]pyrimidine  $\mathbf{5f}^a$ 



Entry	T (°C)	Time t	Yield <sup>b</sup> (%)
1	80 <sup>c</sup>	5 min	96
2	60 <sup>c</sup>	5 min	94
3	$40^{c}$	5 min	95
4	$30^c$	5 min	62
5	$40^c$	2 min	70
6	Reflux <sup>d</sup>	20 min	73
7	$25^{e}$	20 min	94
8	$25^{e}$	10 min	76

<sup>*a*</sup> Reaction conditions: β-enaminone **2a** (0.25 mmol) and NH-5aminopyrazole **3a** (0.25 mmol) at 180 °C under microwave irradiation for 2 min; after cooling by airflow addition of NIS (0.25 mmol) and EDC (2.0 mL). <sup>*b*</sup> Isolated yield. <sup>*c*</sup> Run in 10 mL sealed tubes under microwave irradiation. <sup>*d*</sup> Run in a 10 mL round-bottom flask with 2.0 mL of EDC under reflux (not one-pot procedure). <sup>*e*</sup> Run in 10 mL sealed tubes at 25 °C.

This approach is termed one-pot when the last reaction occurred in the same microwave tube. In this sense, we carried out the optimization by varying the temperature and testing the effect of microwave irradiation in contrast to conventional heating. The reaction of the crude product 4a with 1 equiv. of NIS in 2.0 mL of EDC using temperatures between 30-80 °C for 2-5 minutes under microwave irradiation afforded the desired product 5f in good to nearly quantitative yield (Table 2, entries 1-5). However, the reaction at reflux was not completely satisfactory due to loss of precursor mass during the transfer process from the microwave tube to the round-bottom flask (Table 2, entry 6). Pleasingly, this one-pot synthesis could be performed at room temperature without microwave heating, affording the 3-iodoheterocycle 5f in good to excellent yields and short reaction times (Table 2, entries 7 and 8, respectively). These results evidenced the high electron density of carbon atom at position 3 of the pyrazolo[1,5-a]pyrimidine ring (see <sup>13</sup>C NMR spectra of compounds 4a-s in the ESI<sup>†</sup>). In consequence, the optimum conditions for the regioselective 3-iodination of the pyrazolo [1,5-*a*]pyrimidine 4a were achieved using a stoichiometric amount of N-iodosuccinimide by a simple and energy-saving protocol (Table 2, entry 7). With the optimized reaction conditions, we explored the scope of this one-pot synthesis with diverse N-halosuccinimides and pyrazolo[1,5-a]pyrimidines preformed. The microwave-assisted reaction between β-enaminones 2 and NH-5-aminopyrazoles (3) afforded the crude products 4, which were subsequently halogenated using diverse N-halosuccinimides in 1,2-dichloroethane as solvent at room temperature for 20 min. As shown in Scheme 4, the 3-halopyrazolo[1,5-a]pyrimidines 5a-i were successfully obtained in 89-96% yields. The structure of the 3-iodopyrazolo[1,5-a]pyrimidine 5g was solved by single-crystal X-ray diffraction analysis.<sup>26</sup>



Scheme 4 Synthesis of 3-halopyrazolo[1,5-a]pyrimidines. Reaction conditions:  $\beta$ -enaminone 2 (0.50 mmol) and NH-5-aminopyrazole 3 (0.50 mmol) at 180 °C under microwave irradiation for 2 min; after cooling by airflow addition of *N*-halosuccinimide (0.50 mmol) and EDC (2.0 mL) at 25 °C for 20 min.<sup>a</sup> From 4q, 1.50 mmol of NBS used.

Although some publications are devoted to the linear synthesis of halogenated pyrazolo[1,5-a]pyrimidines, the regioselective incorporation of others functional groups such as nitroso, nitro, sulphonyl and amine have been poorly explored. In fact, most of the existing reports are patents. Thereby, we propose the introduction of diverse functional groups on this heterocyclic core through a one-pot approach according to our former results, starting from  $\beta$ -enaminone 2 (or another 1,3-bisappropriate electrophilic reagents) and the NH-5aminopyrazole (3). Particularly, nitroaromatic compounds have been employed to develop not only bioreductive prodrugs27a but also fluorescent probes for the detection of nitroreductase and tumor hypoxia.<sup>27b,c</sup> These results encouraged us to investigate the cyclocondensation-nitration sequence under microwave irradiation in order to afford 3-nitropyrazolo[1,5-a] pyrimidines 6 within a single reaction vessel (Scheme 5). Our initial testing of the nitration reaction proceeded under conventional heating, attempting to carry out the reaction in the same microwave tube. The crude product 4 with 4 equiv. of the nitrating mixture  $(HNO_3 : H_2SO_4, 2 : 1)$  in 2.0 mL of EDC or water as solvent, and with temperatures between 5-45 °C for 1-3 hours, did not work without microwave irradiation. However, microwave-assisted reactions at 60 °C for 10 min under solventfree conditions, enabled the regioselective formation of the 3nitrosubstituted products 6a-d in yields up to 89% (Scheme 5). Remarkably, these 3-nitropyrazolo [1,5-a] pyrimidines 6 could be used as potential colorimetric or fluorescent probes for the



Scheme 5 Synthesis of 3-nitropyrazolo[1,5-a]pyrimidines. Reaction conditions:  $\beta$ -enaminone 2 (0.50 mmol) and NH-5-aminopyrazole 3 (0.50 mmol) at 180 °C under microwave irradiation for 2 min; after cooling by airflow addition of nitric acid (2.0 mmol) and sulfuric acid (1.0 mmol) at 60 °C under solvent-free microwave irradiation for 10 min.

detection of nitroreductase and hypoxic tumor cell imaging, because the reduced systems have interesting photophysical properties, as well as their unsubstituted precursors 4 (Image 1 in the ESI<sup>†</sup>).

Notably, the synergy between functionality and modularity is the key aspect of this consecutive one-pot approach towards the syntheses of properly functionalized pyrazolo[1,5-*a*]pyrimidines **5a–i** and **6a–d**. This is important because such structures are attractive scaffolds for medicinal chemistry and can be prepared by convenient and eco-compatible one-pot synthetic methods. For example, the chemically manipulating the halogen and nitro groups in the functionalized heterocycles **5** and **6** was briefly explored. Because of easy availability of water, we choose to use this green solvent and microwave heating in order to start our studies using some iodine-derivatives **5**. Gratifyingly, the palladium-catalyzed Sonogashira crosscoupling reaction of phenylacetylene with 3-iodopyrazolo[1,5*a*]pyrimidines **5f** and **5g** using 10% Pd/C–PPh<sub>3</sub>–CuI as a catalyst system, afforded the corresponding 3-phenylethynyl derivatives



Scheme 6 Post-functionalization of 3-halo- and 3-nitropyrazolo[1,5a]pyrimidines. Reaction conditions: (i) substrate 5f or 5g (0.25 mmol), phenylacetylene (0.38 mmol), 1:4:2 ratio of 10% Pd/C–PPh<sub>3</sub>–Cul and Et<sub>3</sub>N (5.0 equiv.) in water (2.0 mL) at 80 °C under microwave irradiation for 1 h; (ii) substrate 6a or 6b (0.50 mmol) and 10% Pd/C (5 wt%) under an H<sub>2</sub> atmosphere in EtOH (5.0 mL) at 25 °C for 3 h.

7**a** and 7**b** in 75% and 60% yields, respectively (Scheme 6, right). Further applications of this methodology is under active investigation due to their interesting extended  $\pi$ -conjugation.<sup>27c</sup> Furthermore, the palladium-catalyzed reduction of representative 3-nitropyrazolo[1,5-*a*]pyrimidines **6a** and **6b** was explored. As expected, the reduction of the nitro group was achieved at 25 °C under H<sub>2</sub> atmosphere at ambient pressure using Pd/C as catalyst in ethanol, giving the corresponding pyrazolo[1,5-*a*] pyrimidin-3-amines **8a** and **8b** in good yields, which have inherent synthetic utility (Scheme 6, left).

#### Conclusions

In summary,  $\beta$ -enaminones and pyrazolo[1,5-*a*]pyrimidines can be easily and conveniently prepared in excellent yields from methylketones via microwave irradiation under catalyst- and solvent-free conditions, and easy purification. These protocols provide a better and practical alternative to existing procedures. Likewise, we have developed an efficient and expeditious microwave-assisted synthesis of functionalized pyrazolo[1,5-a] pyrimidines in good to excellent yields with the formation of three new bonds in a one-pot manner. Interestingly, the timeefficient construction of a pyrazolo[1,5-a]pyrimidine core and subsequent regioselective functionalization on the pyrazole moiety with functional groups such as halogen or nitro in a single reaction vessel has not been previously reported. This cyclocondensation-electrophilic substitution sequence offers marked improvements in terms of general applicability, efficacy, simplicity, and eco-compatibility. Also, this one-pot methodology could be used to introduce others electrophilic substituents on the pyrazolo [1,5-a] pyrimidine core. Finally, some representative post-functionalization reactions have also been developed, affording heteroamines and  $\pi$ -extended heterocycles of valuable synthetic and medicinal interest.

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