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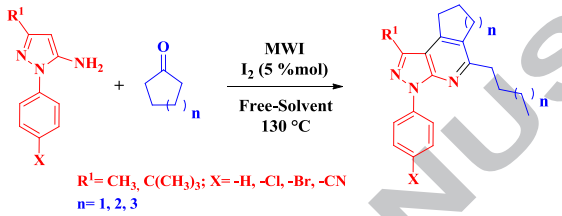

R^1= CH_3, $C(CH_3)_3$; X= -H, -Cl, -Br, -CN
n= 1, 2, 3

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ABSTRACT

5-*n*-Alkylcycloalkane[*d*]pyrazolo[3,4-*b*]pyridines were prepared by a microwave-assisted cyclocondensation reaction between 5-aminopyrazoles and cyclic ketones under solvent-free conditions and catalyzed by iodine. This procedure provides a simple one-step methodology with good yields and environmentally friendly.

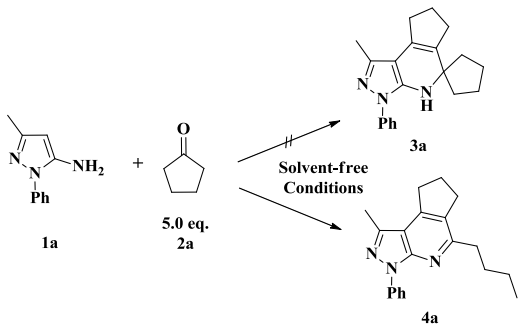
Currently, the Microwave-Assisted Organic Synthesis (MAOS) is a powerful synthetic tool to carry out the synthesis of a variety of organic compounds.[1] Comparing with classical methods, microwave-assisted reactions are a non-conventional efficient energy source for synthetic chemistry and have gained importance because of the simplicity in operation, milder reaction conditions, increasing reaction rates and formation of cleaner products, allowing the development of new molecules with potential biological activity.[1] Moreover, solvent-free microwave-assisted reactions are having more popularity as they provide an opportunity to work under conditions ecologically compatibles.[2]

Pyrazolo[3,4-*b*]pyridines are an important group of nitrogen-containing fused heterocyclics useful for medicinal and organic chemistry because they have shown a wide spectrum of biological and pharmacological activities.[3] Among the most important utilities, these compounds have been found as antibacterial, antidepressant, antihyperglycemic, anti-inflammatory, antitumor and anxiolytic agents and are being used in the treatment of Alzheimer's diseases, drug addiction, and infertility.[4]

On the other hand, molecular iodine has become an important mild and efficient Lewis acid catalyst in organic synthesis due to its benign characteristics as it is inexpensive, non-toxic, insensitive to air and moisture, and can be easily removed from the reaction mixture.[5] Likewise, the molecular iodine has been very useful in the synthesis of fused pyridines and quinolines by Skraup or Doebner-Miller synthesis from anilines and carbonyl compounds; becoming into an easier, regioselective and efficient methodology for the synthesis of this type of compounds.[6]

In our interest to develop synthetic strategies to obtain functionalized and interesting molecules such as pyrazolo[3,4-*b*]pyridines with biological properties,[7] we wish to report an efficient method *via* a one-pot reaction between 5-aminopyrazoles **1**[8] and cyclic ketones **2**, as an useful variant of Skraup-Doebner-Miller fused-pyridine synthesis.[6a]

In an initial study, we tested the reaction between 3-methyl-1-phenyl-1*H*-pyrazol-5-amine **1a** and cyclopentanone **2a** under solvent-free conditions as a template reaction (Entry 2) to obtain the Skraup-Doebner-Miller product, i.e. the spiro-compound **3a** (Scheme 1).[6a]



Scheme 1. Synthesis of alkyl-pyrazolo[3,4-*b*]pyridines.

After purification and opposite to the expected structure **3a**, the obtained product showed by the NMR experiments the characteristics corresponding to the unplanned non-spiro but *n*-alkylated and cycloalkane-fused pyrazolo[3,4-b]pyridine **4a**.

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Usually, catalytic amounts of iodine and an excess of ketone are used in a Skraup-Doebner-Miller reaction[6] and in order to obtain the optimal reaction conditions, we performed the optimization varying the equivalents of iodine respect to the 5-aminopyrazole **1a** and testing the effect of conventional heating versus microwave irradiation (Table 1).

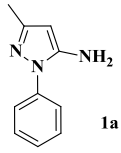
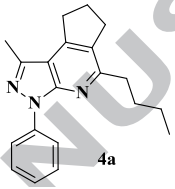
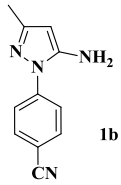
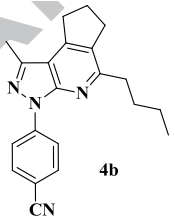
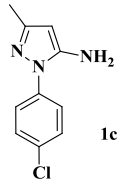
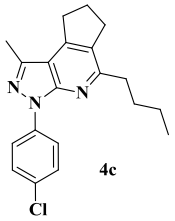
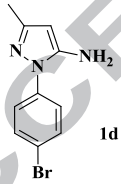
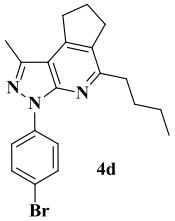
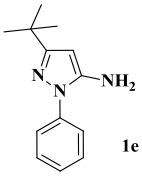
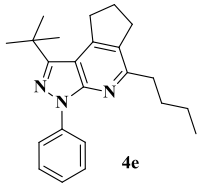
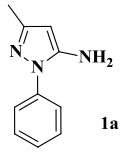
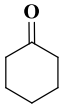
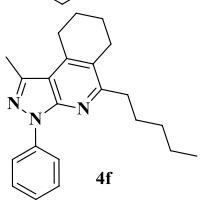
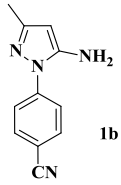
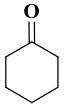
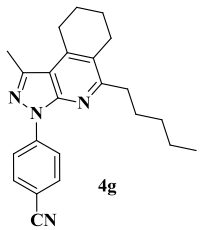
Table 1. Screening and optimization of the reaction conditions.

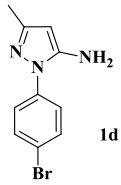
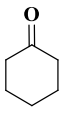
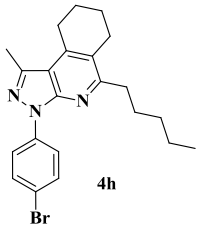
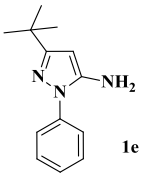
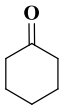
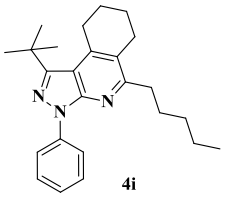
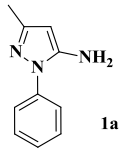
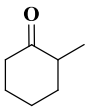
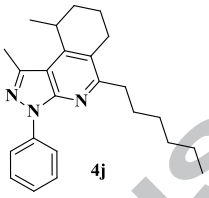
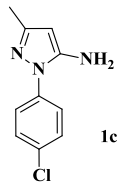
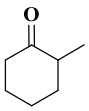
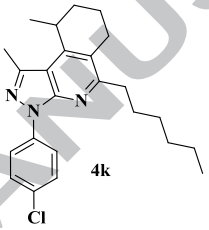
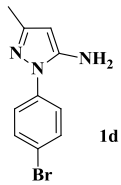
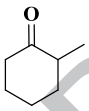
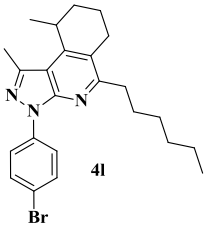
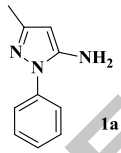
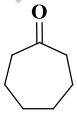
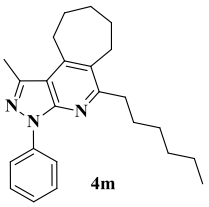
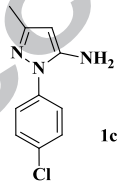
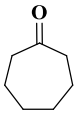
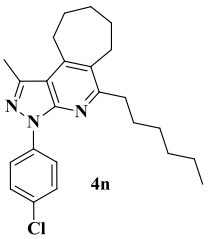
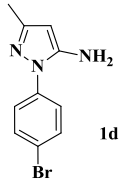
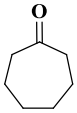
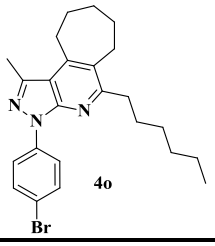
Entry	2a equivalents	Conditions	Time (min)	Yield
1	5.0	20 mol% I_2, Neat, 150 °C	45	20
2	5.0	20 mol% I_2, 300W, 150 °C	20	25
3	3.0	20 mol% I_2, 300W, 130 °C	10	48
4	3.0	10 mol% I_2, 300W, 130 °C	15	70
5	3.0	5 mol% I_2, 300W, 130 °C	25	85

Under conventional heating the product was formed very slowly and in low yield (Entry 1). Microwave irradiation made faster the reaction but when 5 equivalents of **2a** or a high load of iodine (10 or 20 mol%) were used the product was obtained in lower yields (Entries 2-4). Finally, ahead with others reports at reflux or neat conditions, the reaction was optimized at 300W, 130 °C, using lesser amount of ketone with 3.0 equivalents of cyclopentanone and 5 mol% of iodine (Entry 5) to obtain the *n*-alkylated-cyclopentane[*d*]pyrazolo[3,4-*b*]pyridine **4a**.[9]

The scope and generality of the optimized method was further demonstrated by the reaction of 5-aminopyrazoles **1** with different cyclic ketones. In each case, the angular regioisomers **4a-o** were obtained in good to excellent yields and high regioselectivity (Table 2).

Table 2. Synthesis of 5-alkyl-pyrazolo[3,4-*b*]pyridines **3a-h**.[9]

Entry	5-aminopyrazol	Ketone	Product	Time (min)	Yield[a]
1	 **1a**	 **2a**	 **4a**	25	85
2	 **1b**	 **2a**	 **4b**	5	65
3	 **1c**	 **2a**	 **4c**	15	75
4	 **1d**	 **2a**	 **4d**	15	70
5	 **1e**	 **2a**	 **4e**	20	80
6	 **1a**	 **2b**	 **4f**	15	80
7	 **1b**	 **2b**	 **4g**	30	78

8	 **1d**	 **2b**	 **4h**	17	72
9	 **1e**	 **2b**	 **4i**	16	58
10	 **1a**	 **2c**	 **4j**	25	90
11	 **1c**	 **2c**	 **4k**	10	68
12	 **1d**	 **2c**	 **4l**	12	60
13	 **1a**	 **2d**	 **4m**	20	68
14	 **1c**	 **2d**	 **4n**	13	55
15	 **1d**	 **2d**	 **4o**	10	64

[a]Isolated yields.

The structures of all compounds were confirmed by ^{1}H NMR, ^{13}C NMR, 2D NMR spectra and MS analysis. Due to the double nucleophilic nature of the 5-aminopyrazoles **1** we could expect the formation of either a linear regioisomer type **4'** or an angular regioisomer type **4**.

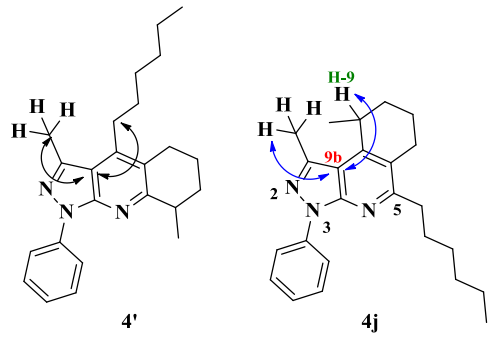
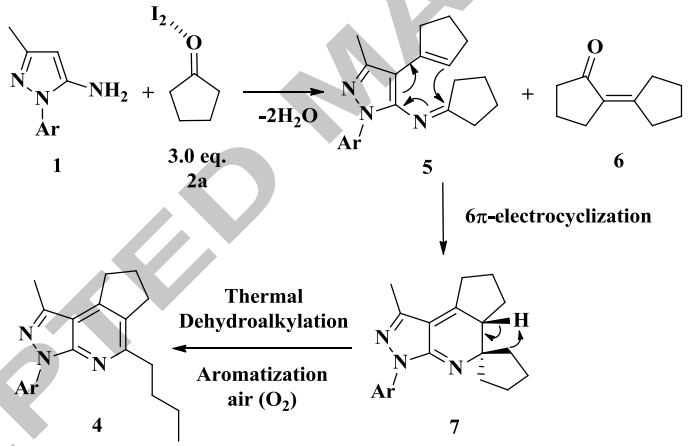


Figure 1. HMBC correlations in the obtained pyrazolo[3,4-*b*]pyridines **4**.

To determine the above, through HMBC experiment, compound **4j** was chosen due to its cyclohexyl fragment is substituted with a methyl group being the 9-H proton and the C-9b carbon atom exactly assigned from their ^{1}H NMR and ^{13}C NMR spectra, respectively. Hence, a three-bonds HMBC correlation observed between C-9b and H-9 atoms unequivocally confirmed the angular regiochemistry for compounds **4**, but not the linear one (Figure 1).

A possible mechanistic route for the described cyclocondensation reaction is outlined in the Scheme 2. According to Fotie[6a] presumably the first step involved the condensation of the cyclopentanone with both nucleophilic centers (i.e. 5-amino group and the C-4 carbon atom) of the 5-aminopyrazol **1** leading to the formation of the Schiff base intermediate **5**. Then, the subsequent intramolecular 6π-electrocyclization of **5** should afford the spiro-intermediate **7**, and although a spiro-dihydroderivative **3a** is expected by a 1,5-sigmatropic rearrangement of **7**, instead it is finally oxidized by air under thermal conditions and undergoes an aromatization toward the isolated pyrazolo[3,4-*b*]pyridines **4**.[6] According to our studies about pyrazolopyridine derivates, under air atmosphere and thermal conditions is possible to obtain both dihydro and oxidized derivates and the final product will depend on the stability of the dihydroderivate and/or reaction conditions.[7] It is worth mentioning that the formation of the α,β-unsaturated adduct **6** was observed and in some cases it was isolated and characterized. Adduct **6** was in competence with the formation of Schiff-base intermediate **5**, for that reason it was necessary to use an excess of the cyclic ketone in all cases.



Scheme 2. Proposed mechanism for the formation of the 5-alkylpyrazolo[3,4-*b*]pyridines **4a-o**.

In summary, we obtained the unplanned 5-alkyl-pyrazolo[3,4-*b*]pyridines in good yields by an easy, direct and regioselective cyclocondensation-aromatization reaction catalyzed by molecular iodine under microwave irradiation. This methodology offers a non-metal and solvent-free reaction conditions and operational simplicity from inexpensive reagents. Currently, this procedure is being extended to other nucleophilic heterocyclic amines and the biological and fluorescent properties of the new obtained compounds are under investigation.

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Supplementary Data

Supplementary data (^{1}H NMR, ^{13}C NMR spectra, experimental procedure and characterization data of the obtained compounds are given in supplementary material) associated with this article can be found, in the online version, at http://.

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9. *General procedure for the preparation of 5-alkyl-pyrazolo[3,4-b]pyridines**4a-h***: Microwave experiment was carried out using a focused microwave reactor (CEM Discover TM). A mixture of 5-aminopyrazol **1** (1 mmol), cyclic ketone **2** (3 mmol) and iodine (0.05 mmol), was subjected to microwave irradiation for 20-30 min. at 125-135 °C and a maximum power of 300W. The obtained compounds were purified on silica gel column by using a mixture of dichlorometane:hexanes (1:1) as eluent. *Data for **5-butyl-1-methyl-3-phenyl-3,6,7,8-tetrahydrocyclopentane[d]pyrazolo[3,4-b]pyridine*** **4a**. Yellow solid, Yield 85%, **m.p.**: 63-65 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm: 1.00 (t, *J*=7.4 Hz, 3H), 1.41-1.53 (m, 2H), 1.77-1.88 (m, 2H), 2.25 (quin, *J*=7.5 Hz, 2H), 2.67 (s, 3H), 2.83-2.90 (m, 2H), 2.99 (t, *J*=7.4 Hz, 2H), 3.28 (t, *J*=7.5 Hz, 2H), 7.19-7.26 (m, 1H), 7.45-7.53 (m, 2H), 8.40 (dd, *J*=8.8, 1.0 Hz, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ ppm: 13.9 (CH_3), 14.0 (CH_3), 22.6 (CH_2), 24.5 (CH_2), 30.2 (CH_2), 30.4 (CH_2), 31.6 (CH_2), 36.0 (CH_2), 113.1 (C), 120.3 (CH), 124.7 (C), 128.8 (CH), 131.4 (C), 140.3 (C), 141.7 (C), 147.0 (C), 150.9 (C), 158.4 (C). **MS** (70 eV) m/z (%): 305 (M^+, 10), 290 (5), 276 (10), 264 (20), 263 (100), 262 (20), 77 (7).
1-methyl-5-pentyl-3-phenyl-6,7,8,9-tetrahydro-3H-pyrazolo[3,4-c]isoquinoline **4f**. Yellow oil, Yield 78%, **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm: 0.90-1.00 (m, 3H), 1.41-1.49 (m, 4H), 1.80-1.95 (m, 6H), 2.72 (s, 3H), 2.76 (t, *J*=4.5 Hz, 2H), 2.83 (t, *J*=7.6, 2H), 3.19 (t, *J*=4.5 Hz, 2H), 7.19-7.25 (m, 1H), 7.44-7.51 (m, 2H), 8.37 (dd, *J*=8.7, 1.1 Hz, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ ppm: 14.1 (CH_3), 15.8 (CH_3), 21.8 (CH_2), 22.7 (CH_2), 22.8 (CH_2), 25.8 (CH_2), 27.0 (CH_2), 27.6 (CH_2), 31.9 (CH_2), 35.2 (CH_2), 114.1 (C), 120.2 (CH), 123.8 (C), 124.6 (CH), 128.8 (CH), 140.1 (C), 140.8 (C), 142.0 (C), 149.3 (C), 161.5 (C). **MS** (70 eV) m/z (%): 333 (M^+, 10), 305 (12), 290 (19), 277 (62), 263 (100), 77 (20).
***5-hexyl-1-methyl-3-phenyl-3,6,7,8,9,10-hexahydrocycloheptane[d]pyrazo-lo[3,4-b]pyridine 4m*.** Yellow solid, Yield 68%, **m.p.**: 89-91 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm: 0.89-0.98 (m, 3H), 1.31-1.42 (m, 4H), 1.42-1.52 (m, 2H), 1.65 (dt, *J*=10.6, 5.6 Hz, 2H), 1.70-1.84 (m, 4H), 1.87-1.95 (m, 2H), 2.74 (s, 3H), 2.92-3.00 (m, 4H), 3.19-3.25 (m, 2H), 7.19-7.26 (m, 1H), 7.48 (t, *J*=8.0 Hz, 2H), 8.37-8.42 (m, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ ppm: 14.1 (CH_3), 16.2 (CH_3), 22.6 (CH_2), 26.4 (CH_2), 27.3 (CH_2), 28.4 (CH_2), 29.1 (CH_2), 29.3 (CH_2), 29.6 (CH_2), 31.8 (CH_2), 32.1 (CH_2), 37.0 (CH_2), 114.1 (C), 120.2 (CH), 124.5 (CH), 128.7 (CH), 130.4 (C), 140.0 (C), 141.7 (C), 147.4 (C), 149.6 (C), 159.9 (C). **MS** (70 eV) m/z (%): 361 (M^+, 15), 332 (5), 318 (10), 304 (19), 291 (100), 276 (33), 262 (30), 43 (61).