Regioselective Three-Component Synthesis of Indolylpyrazolo[3,4-*b*]pyridines Induced by Microwave and under Solvent-Free Conditions

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Abstract: New 4-(1*H*-indol-3-yl)-6-arylpyrazolo[3,4-*b*]pyridines **7** have been prepared in a solvent-free three-component reaction induced by microwave from 5-aminopyrazole **1**, benzaldehydes **2** and 3-indolyl-3-oxopropanenitrile **5**. These compounds were also obtained by means of the reaction of aminopyrazole **1** with benzylidene-derivatives of 3-(1*H*-indol-3-yl)-3-oxopropanenitrile **6**, prepared in the reaction of 3-(1*H*-indol-3-yl)-3-oxopropanenitrile and aldehydes.

Keywords: 5-Aminopyrazole, 3-(1*H*-indol-3-yl)-3-oxopropanenitrile, Benzaldehyde, Indolylpyrazolo[3,4-*b*]pyridine, Three-component reaction, Solvent-free procedure, Microwave.

Microwave-assisted solvent-free reactions have received much attention due to their enhanced reaction rates as well as higher yields and purities. These methods are regarded as environmentally benign and easy to perform, paving the way to the development of "Green Chemistry" protocols [1]. Multi-component reactions, an important class of organic tandem reactions, are one-pot processes with at least three components to form a single product, which incorporates most or even all of the starting materials [2], and particularly under solvent-free conditions enhance the reaction efficiency, and simplicity and lessen environmental impact. Multi-component reactions (MCRs) have been oriented during the last years towards developing combinatorial chemistry procedures, because of their high efficiency and convenience in comparison with multistage procedures. Hence, most of the scientific efforts have been focused on the development of multi-component procedures to prepare diverse heterocyclic compound libraries and to afford new and effective MCRs [2b].

Simple nitrogen containing heteroaromatic compounds have received much attention in the literature over the years. They are, among other things, pharmacophores of paramount importance, which have exciting biological properties in their own right and also serve as important synthetic building blocks in drug discovery.

Indole is essential both in nature as well as for commercial drug development. Indole moieties are present in many natural compounds and many drugs, participating in vital biological processes [3]. On the synthetic point of view, it is known that cyanoacetic acid can serve as a building block in various reactions like cyclizations or syntheses of coumarins and others heterocycles [4].

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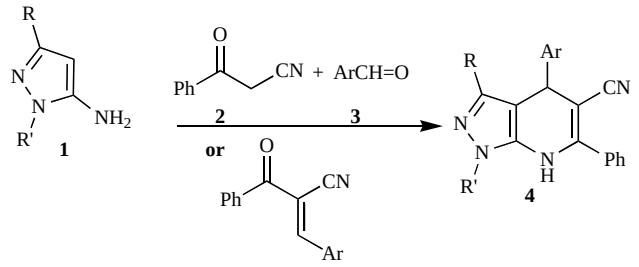
In our search for multicomponent procedure to prepare fused heterocyclic systems such pyrazolo[3,4-*b*]pyridine derivatives, well known for their wide range of biological and pharmacological activities [5], we have already reported several approximations. For example, three-component, one-pot condensation synthesis of 4-aryl-5-cyano-6-phenyl-4,7-dihydropyrazolo-[3,4-*b*]pyridine **4** (Scheme **1**) using microwave irradiation, a process that is adaptable for the assembly of a library of compounds has recently gained much attention in pharmaceutical research [6,7],



Scheme 1.

In this way, we have planned the regioselective synthesis of a new family of pyrazolo[3,4-*b*]pyridines bearing a indolyl residue and a versatile functional group, such as cyanide that can give a higher diversity potential to this family. Thus a new series of pyrazolo[3,4-*b*]pyridines **7** through three-component microwave-assisted reaction of 5-aminopyrazole **1** with 3-(1*H*-indol-3-yl)-3-oxopropanenitrile **5** and aromatic aldehydes **3** is described here.

In the first attempt to afford the pyrazolo[3,4-*b*]pyridine derivatives **7**, a two-component classical reaction was carried out, where 1-(1*H*-indol-3-yl)-3-aryl-2-cyano-1-propenones **6** was prepared through a simple solvent-free reaction of equimolar amounts of benzaldehydes **3** and 3-(1*H*-indol-3-yl)-3-oxopropanenitrile **5** (Scheme **2**), using a focused microwave reactor (CEM Discover TM) [8].

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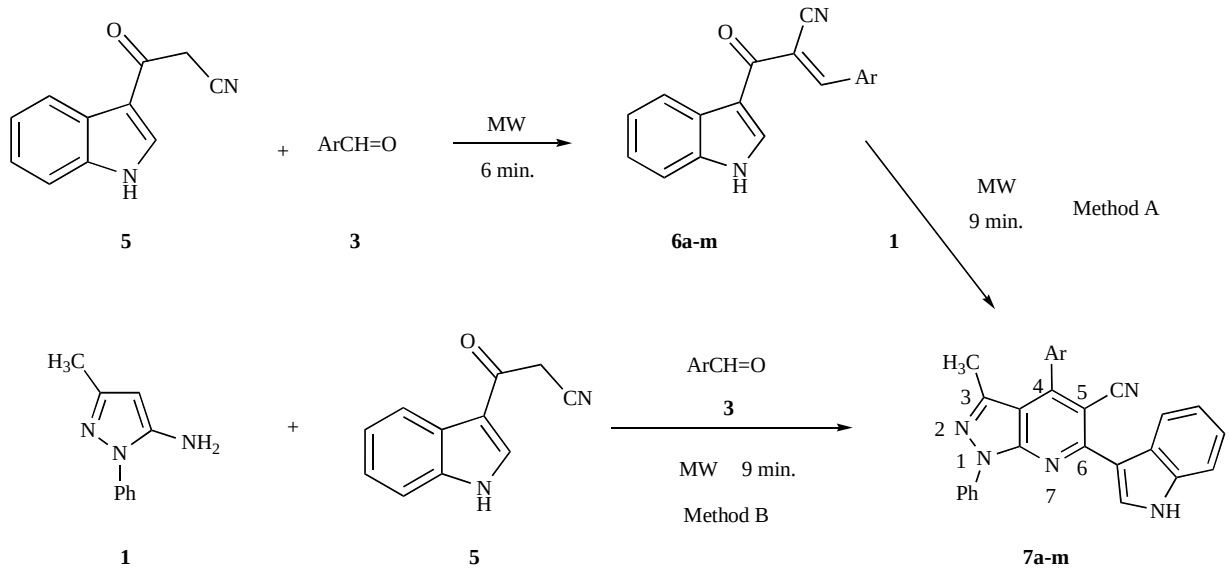

Scheme 2.

Then, to afford the pyrazolo[3,4-*b*]pyridine derivatives **7** aminopyrazoles **1** and 1-(1*H*-indol-3-yl)-3-aryl-2-cyano-1-propenone **6** were reacted by induction with microwave irradiation with isolated yields never exceeding 35 % (method A, Scheme **2** and Table **1**) [9]. A three-component one-pot cyclocondensation was then tried in a similar fashion to a previously reported method using 5-aminopyrazole **1**, aromatic aldehydes **3** and 3-(1*H*-indol-3-yl)-3-oxopropanenitrile **5** rendering compounds **7** with good to excellent yields (51-98%, method B, Scheme **2**, and Table **1**) [9].

We have also studied different reaction conditions concluded that when reactions were carried out under conventional heating conditions (reflux in ethanol and/or DMF) the expected products were not obtained.

The structures of all indolyl-chalcone analogs **6** and indolylpyrazolo[3,4-*b*]pyridines **7** were appropriately established by IR, ^{1}H NMR, ^{13}C NMR and MS spectra. Single crystal X-ray diffraction analysis of compounds **7c**, **7f** and **7k** was used to corroborate the postulated structures [10].

We can conclude that the reported one-step procedure is efficient, simple and very regioselective alternative for the preparation of indolylpyrazolo[3,4-*b*]pyridines *via* a three-component cyclocondensation reaction of 5-aminopyrazole, aromatic aldehydes and 3-(1*H*-indol-3-yl)-3-oxopropanenitrile in solvent-free conditions under microwave irradiation. The best results were obtained with a three-component cyclocondensation reaction, compared to the two-component cyclocondensation reaction and conventional

Table 1. Synthesis of 1-(1*H*-indol-3-yl)-3-aryl-2-cyano-1-propenone 6 and Indolylpyrazolo[3,4-*b*]pyridine 7 in Solvent-Free Conditions Induced by Microwave for 6 and 9 min Respectively

Entry	Ar	Compound 6		Compound 7	
		M.p. ºC	Yield (%)	M.p. ºC	*Yield (%)
a	4-ClC_6H_4	253-255	70	286-288	61
b	4-$NO_2C_6H_4$	246-248	87	300-302	59
c	4-$OCH_3C_6H_4$	212-214	71	270-272	85
d	C_6H_5	231-233	93	288-290	62
e	4-BrC_6H_4	221-223	88	306-308	72
f	4-$CH_3C_6H_4$	204-206	83	273-275	89
g	4-FC_6H_4	244-246	81	338-340	98
h	2-$CF_3C_6H_4$	201-203	83	288-289	87
i	2-FC_6H_4	215-217	82	296-298	53
j	3,4-$OCH_2OC_6H_3$	237-239	77	278-280	75
k	3,4,5-tri-$CH_3OC_6H_2$	167-169	87	273-275	89
l	3-piridil	214-216	88	297-299	51
m	C_6H_5-CH=CH-CHO	259-261	72	318-320	70

*The reported yield were obtain by method B. By the Method A the isolated yields never exceeded 35 %.

heating conditions. Prominent advantages of this new method are operational simplicity, good yields, short reaction times and easy workup. The readily obtainable 3-functionally substituted indole has shown to be an excellent precursor to obtain heterocycle fused systems.

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[8] General procedure for the preparation of 1-(1*H*-indol-3-yl)-3-aryl-2-cyano-1-propenone 6 under microwave irradiation. Microwave experiment was carried out using a focused microwave reactor (CEM Discover TM). The 3-(1*H*-indol-3-yl)-3-oxopropanenitrile **5** (0.5 mmol) was mixed with equimolar amounts of aromatic aldehydes **2** (0.5 mmol). The mixture was exposed to microwave radiation at a 200 ºC with a maximum power of 300 W for 6 min. The solid was dissolved in hot ethanol-DMF solution (2:1). After cooling, the solid product was filtrated and washed with ethanol and ether to afford the pure product. Selective spectral and physical/chemical data for compound **6k**: 1-(1*H*-indol-3-yl)-3-(3,4,5-trimethoxyphenyl)-2-cyano-1-propenone. Brown dark solid. m.p. 167-169 ºC, yield 87 %. ^{1}H NMR: δ = 3.79 (*s*, 3H, OCH_3); 3.85 (*s*, 6H, OCH_3); 7.27-7.35 (*m*, 2H, H-5 and H-6); 7.51 (*s*, 2H, H*o*); 7.56 (*d*, 1H, H-7); 8.19 (*d*, 1H, H-4); 8.21 (*s*, 1H, H-10); 8.45 (*s*, 1H, H-2); 12.28 (*s*, 1H, NH). ^{13}C NMR: δ = 56.0 (OCH_3); 60.3 (OCH_3); 108.3 (C_o trimethoxyphenyl); 110.0 (C-9); 112.4 (C-7); 113.6 (C-3); 118.1 (CN); 121.3 (C-4); 122.3 (C-5); 123.5 (C-6); 126.1 (C-7a); 127.6 (C_i trimethoxyphenyl); 135.4 (C-2); 136.6 (C-3a); 141.1 (C_p Ph); 152.2 (C-10); 152.8 (C_m Ph); 181.3 (C=O). The mass spectrum shows the following peaks: MS (70 eV) *m/z* (%): 362(28, M^+), 144(100), 116(35), 89(27), 44(18), 43(26), 41(27), 40(19). HR-MS (EI): $C_{21}H_{18}N_2O_4$ calcd 362.1267, found 362.1263.

[9] General procedure for the preparation of 6-(1H-indol-3-yl)-3-methyl-1-phenyl-4-aryl-1H-pyrazolo[3,4-b]pyridine-5-carbonitrile **7** under microwave irradiation. Microwave experiment was carried out a focused microwave reactor (CEM Discover TM). Method A. The 5-aminopyrazole **1** and 1-(1*H*-indol-3-yl)-3-aryl-2-cyano-1-propenone **6** was exposed to microwave radiation at 200 °C with a maximum power of 300 W for 9 min. The reaction mixture was dissolved in hot ethanol-DMF solution (2:1) and solid product was filtrated and washed with ethanol and diethyl ether to afford the pure products **6** in lower yields than 35%. Method B. The 5-aminopyrazole **1** (0.5 mmol) was mixed with equimolar amounts of 3-(1*H*-indol-3-yl)-3-oxopropanenitrile **5** (0.5 mmol) and aromatic aldehydes **3** (0.5 mmol); and the mixture exposed to microwave radiation at 200 °C with a maximum power of 300 W for 9 min. The reaction mixture was dissolved in hot ethanol-DMF solution (2:1) and solid product was filtrated and washed with ethanol and diethyl ether to afford the pure products **7** in goods yields. Selective spectral and physical/chemical data for compound **7k**: 6-(1*H*-indol-3-yl)-4-(3,4,5-trimethoxyphenyl)-3-methyl-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carbonitrile**.** Yellow crystalline solid m.p. 273-275 ºC, yield 89 %. ^{1}H NMR: δ = 2.14 (*s*, 3H, CH_3);3.82 (*s*, 3H, OCH_3); 3.86 (*s*, 6H, OCH_3); 7.02 (*s*, 2H, H_o trimethoxyphenyl); 7.19 (*t*, 1H, H-5´); 7.27 (*t*, 1H, H-6´); 7.41 (*t*, 1H, H_p of Ph); 7.57 (*d*, 1H, H-7´); 7.60 (*t*, 2H, H_m of Ph); 8.28 (*d*, 2H, H_o of Ph); 8.44 (*s*, 1H, H-2´); 8.47 (*d*, 1H, H-4´); 11.89 (*s*, 1H, NH). ^{13}C NMR: δ = 14.4 (CH_3); 56.2 (OCH_3); 60.22 (OCH_3); 99.2 (C-5); 106.8 (C_o trimethoxyphenyl); 111.7 (C-3a); 112.2 (C-7´); 112.8 (C-3´); 118.7 (CN); 120.9 (C-5´); 121.1 (C_o Ph); 121.4 (C-2´); 122.6 (C-6´); 126.0 (C_i trimethoxyphenyl); 126.4 (C_p Ph); 129.1 (C_m Ph); 129.2 (C_p trimethoxyphenyl); 129.4 (C-4´); 136.4 (C-7´a); 138.3 (C-3´a); 138.4 (C_i Ph); 144.0 (C-3); 150.1 (C-6a); 152.6 (C-4); 152.8 (C_m trimethoxyphenyl); 155.4 (C-6). The mass spectrum shows the following peaks: MS (70eV) *m/z* (%) = 515 (100, M^+), 484 (23), 414 (8), 258 (10), 77 (31), 51 (13). HR-MS (EI): $C_{31}H_{25}N_5O_3$ calcd 515.1957 found 515.1967.

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