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A novel synthesis of new 2-aryl-6-(arylamino)-1*H*-imidazo[1,2-*b*]pyrazole-7-carbonitrile derivatives

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ABSTRACT

New 2-aryl-6-(arylamino)-1*H*-imidazo[1,2-*b*]pyrazole-7-carbonitriles are synthesized in good yields, via cyclocondensation of 5-amino-1-(2-oxo-2-arylethyl)-3-(arylamino)-1*H*-pyrazole-4-carbonitriles, which are prepared by the reaction of 5-amino-3-arylamino-1*H*-pyrazole-4-carbonitriles and α-bromoacetophenone derivatives in the presence of K_2CO_3 using acetone as the solvent.

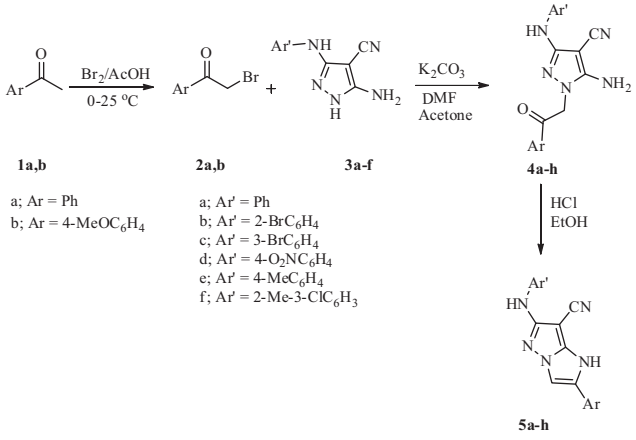
The development of new methods for the synthesis of nitrogen-containing heterocycles is very important in organic chemistry. Among various biheterocyclic compounds, bicyclic imidazo[1,2-*b*]pyrazoles exhibit a wide range of biological and pharmaceutical activities such as antitumor,[1–3] herbicidal,[4] anti-inflammatory,[5] antiviral,[6] and antineoplastic[7] activities.

Despite there being many literature reports on the synthesis of fused pyrazole derivatives, imidazopyrazoles have rarely been reported. However, there are a variety of methods for the synthesis of imidazo[1,2-*b*]pyrazoles,[8–21] among which, many involve tedious and time-consuming multi-step procedures.

As part of our studies on the synthesis of tri- and tetracyclic heterocycles,[22–25] herein we report a facile method for the synthesis of new derivatives of 1*H*-imidazo[1,2-*b*]pyrazole (**5a**–**h**) with possible pharmaceutical applications. The synthetic procedure involves the cyclocondensation of 5-amino-1-(2-oxo-2-arylethyl)-3-(arylamino)-1*H*-pyrazole-4-carbonitriles **4a**–**h**, which were prepared by the reaction of 5-amino-3-arylamino-1*H*-pyrazole-4-carbonitriles **3a**–**f** and α-bromoacetophenone derivative **2a**,**b** in the presence of K_2CO_3 using acetone as the solvent.

Bromination of acetophenones **1a**,**b** in Br_2/AcOH gave the corresponding α-bromoacetophenones **2a**,**b**.[26] Although the synthesis of 5-amino-3-arylamino-1*H*-pyrazole-4-carbonitrile **3a**–**f** derivatives has been reported,[27] we prepared these by a different method.[28] Reaction of α-bromoacetophenones **2a**,**b** with pyrazole derivatives **3a**–**f** gave the corresponding pyrazole intermediates (**4a**–**h**). Finally, cyclocondensation of compounds **4a**–**h** by refluxing in ethanol in the presence of hydrochloric acid gave the desired products **5a**–**h** in 78–93% yields (Scheme 1).

Eight examples of the conversion of α-bromoacetophenones **2a**,**b** into the corresponding substituted 5-amino-1-(2-oxo-2-arylethyl)-3-(arylamino)-1*H*-pyrazole-4-carbonitriles **4a**–**h** and 2-aryl-6-(arylamino)-1*H*-imidazo[1,2-*b*]pyrazole-7-carbonitiles **5a**–**h** along with reaction conditions, reaction times, melting points, and yields are listed in Tables 1 and 2, respectively.



Scheme 1. Synthesis of 2-aryl-6-(arylamino)-1*H*-imidazo[1,2-*b*]pyrazole-7-carbonitiles **5a**–**h**.

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Table 1
Physical properties and reaction conditions for the synthesis of compounds **4a–h**

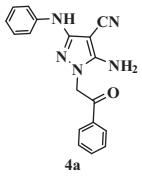
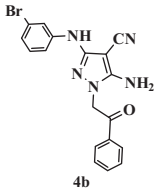
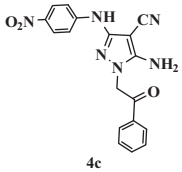
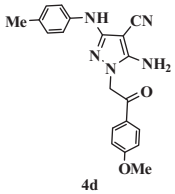
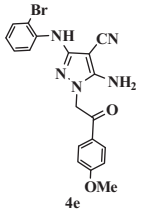
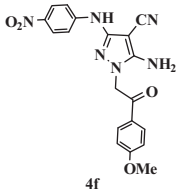
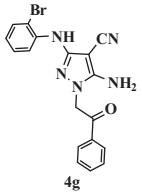
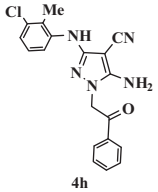
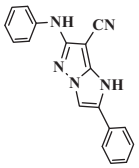
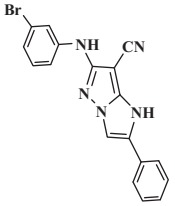
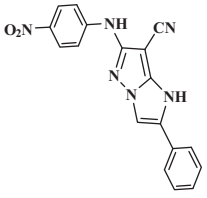
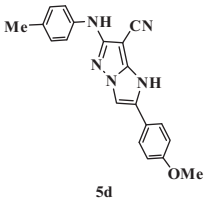
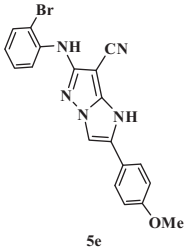
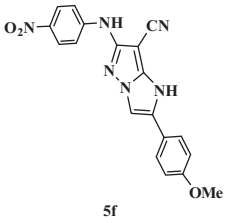
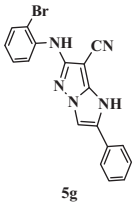
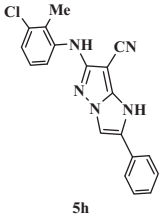
Entry	Intermediate	Temp	Time (h)
1	 4a	Reflux	1
2	 4b	Reflux	1
3	 4c	rt	8
4	 4d	rt	10
5	 4e	rt	4
6	 4f	rt	4.5
7	 4g	rt	7
8	 4h	Reflux	2

Table 2
Physical properties, yields, and reaction times for the synthesis of compounds **5a–h**

Entry	Product	Time (h)	Mp (°C)	Yield (%)
1	 5a	1.5	265–266 (dec.)	85
2	 5b	1	285–286 (dec.)	93
3	 5c	1	330 (dec.)	84
4	 5d	1	280 (dec.)	78
5	 5e	0.5	268–270 (dec.)	90
6	 5f	0.75	275 (dec.)	88
7	 5g	1	296–298 (dec.)	90
8	 5h	2	249	83

The proposed mechanisms for the sequence are shown in Scheme 2. The first step involves the attack of the endocyclic nitrogen atom of 5-amino-3-arylamino-1*H*-pyrazole-4-carbonitrile **3a–f**, which is more nucleophilic due to the electron-withdrawing effect of the pyrazole ring, onto α-bromoacetophenone **2a**,**b** to