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New *one-pot* synthesis of 4-arylpyrazolo[3,4-*b*]pyridin-6-ones based on 5-aminopyrazoles and azlactones

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Abstract

An effective *one-pot* strategy was developed for the synthesis of 4-arylpyrazolo[3,4-*b*]pyridin-6-ones from pyrazolo[3,4-*b*]pyridin-6-ones, obtained by reacting 5-aminopyrazole with 4-arylidene-2-phenyloxazol-5(4*H*)-ones (azlactones) under solvent free conditions, through subsequent elimination of the benzamide molecule in a superbasic medium (*t*-BuOK/DMSO). The fluorescent properties of the synthesized compounds were studied.

Keywords

5-aminopyrazole; azlactone; elimination; fluorescence; *one-pot* synthesis; pyrazolo[3,4-*b*]pyridin-6-one

Introduction

The pyrazolo[3,4-*b*]pyridine scaffold is present in many biologically active compounds [1–12]. Among them, 4-aryl-substituted derivatives should be distinguished, exhibiting antiviral [13] and anti-inflammatory properties [14], being modulators of Estrogen-related Receptor alpha [15], JAK1 kinase inhibitor [16], GSK3 [17] and GyrB [8] inhibitors (Figure 1).

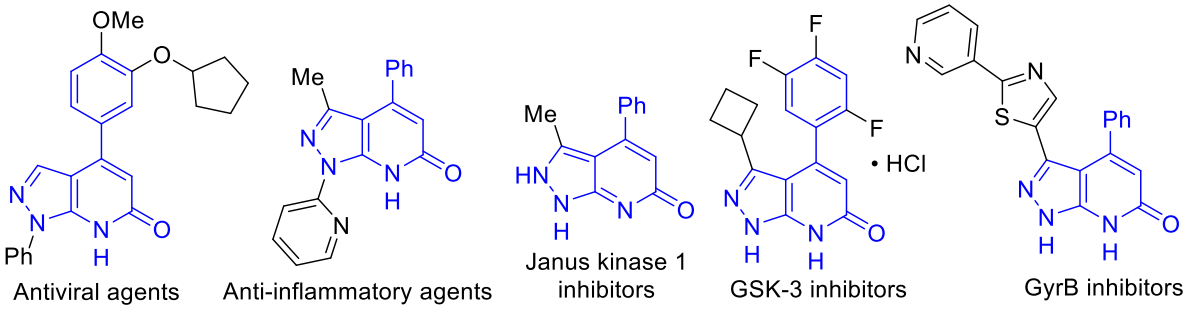
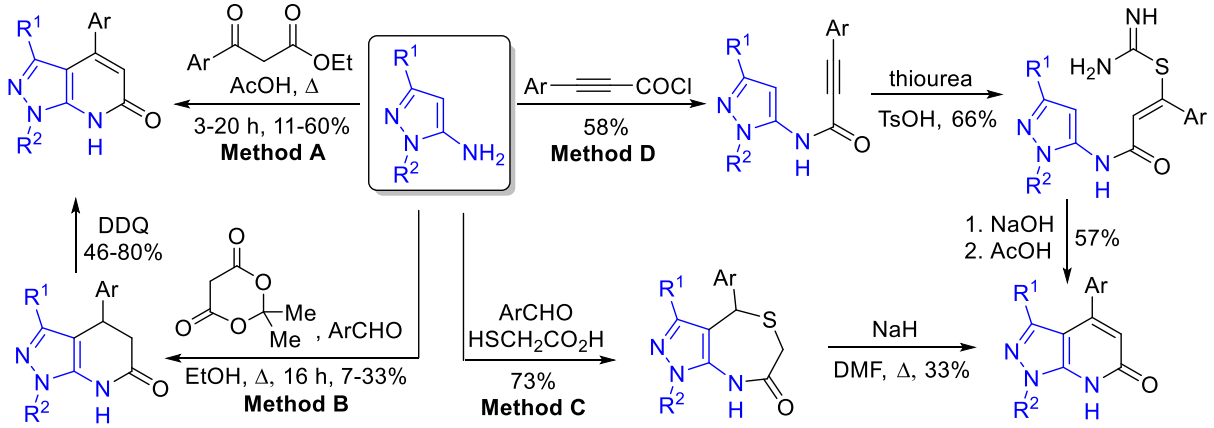


Figure 1: Biologically active of 4-arylpyrazolo[3,4-*b*]pyridin-6-ones

Despite the high demand, their synthesis methods are few (Scheme 1). To obtain 4-arylpyrazolo[3,4-*b*]pyridin-6-ones, the only known one-step method is most often used, including the acid-catalyzed condensation of aminopyrazoles with ketoesters [1, 16, 18] (Method A). Its significant disadvantage is the low yields of the target products (11–60%). Yields are also low in two-stage synthesis methods. The first of them is based on the three-component condensation of aminopyrazoles, Meldrum's acid, and aromatic aldehydes, followed by the oxidation of the intermediate with DDQ [13, 16, 19] (Method B). The second one includes the reaction of an aromatic aldehyde with thioglycolic acid and aminopyrazole, followed by the extrusion of sulfur

from the resulting thiazepine [20] (Method C). The three-stage synthesis of 4-arylpyrazolo[3,4-*b*]pyridin-6-ones, involving the preparation of 3-aryl-*N*-(1*H*-pyrazol-5-yl)propiolamides (Method D), also leads to the formation of the target products with low yields [21]. Therefore, the development of a new effective method for the preparation of 4-arylpyrazolo[3,4-*b*]pyridin-6-ones is an urgent task.



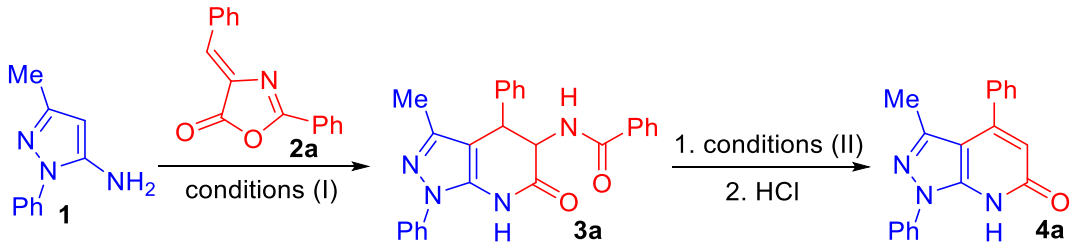
Scheme 1: Methods for the synthesis of 4-arylpyrazolo[3,4-*b*]pyridin-6-ones

Results and Discussion

One of the rational approaches to the synthesis of fused pyridine derivatives is based on the domino reaction of enamines with azlactones [22–30]. We have previously reported a plausible mechanism of such reactions [22, 25]. 1*H*-Pyrazol-5-amines also enter into similar transformations with azlactones in various solvents. The yields of tetrahydro-1*H*-pyrazolo[3,4-*b*]pyridones **3** obtained by this method vary widely [31–33]. Solvent-free reactions are convenient from both economic and environmental points of view. We obtained tetrahydro-1*H*-pyrazolo[3,4-*b*]pyridinone **3a** by heating 5-aminopyrazole **1** with azlactone **2a** in the absence of solvent at 150°C in 62% yield (Table 1). For compound **3a**, the possibility of benzamide elimination was studied. Benzamide fragment is a poor leaving group; however, in a superbasic medium, we were able to eliminate this group in compound **3a**. In order to select optimal synthesis

conditions, we heated compound **3a** in DMSO at temperatures from 90 to 150°C for 1.5, 3.5 and 6 h in the presence of KOH or *t*-BuOK (Table 1).

Table 1: Optimization of the reaction conditions[a]

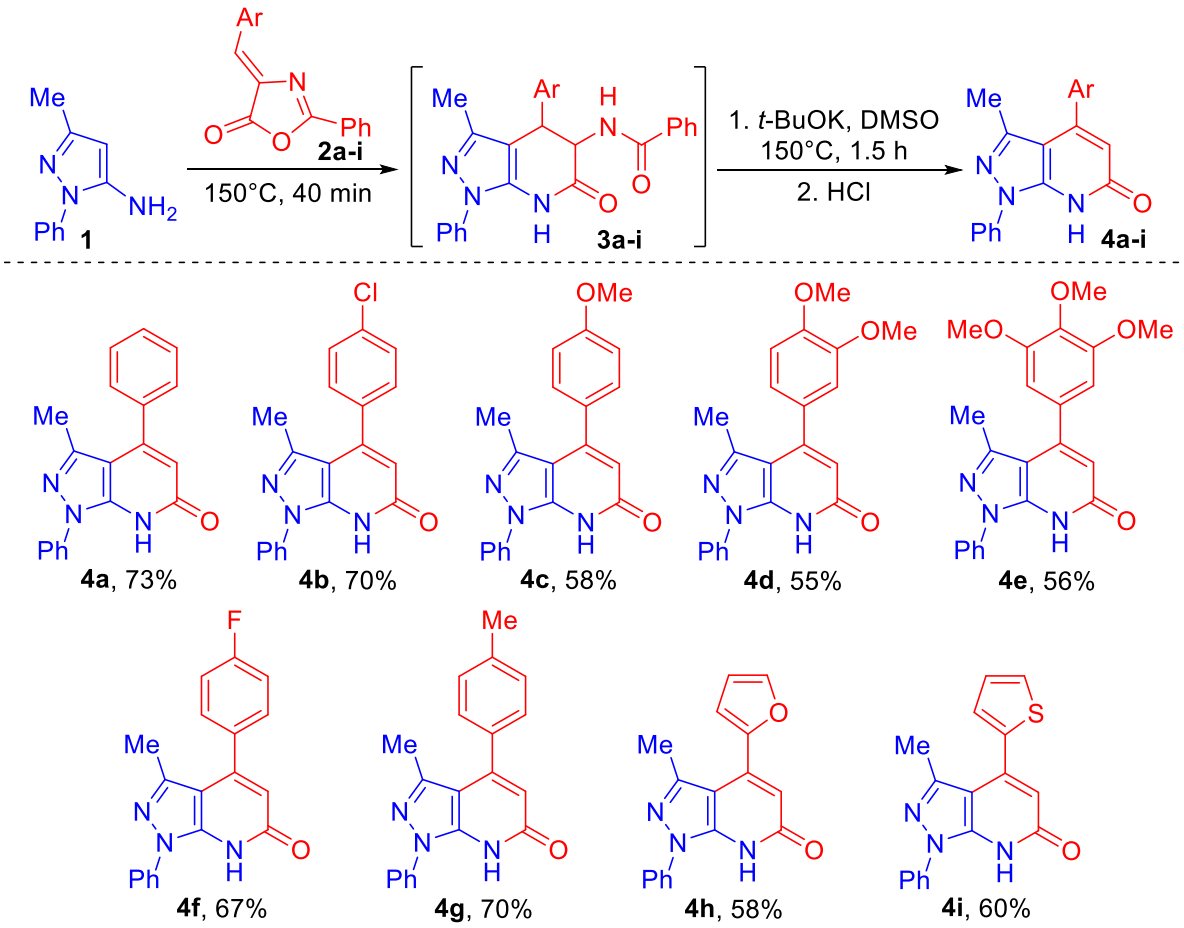


entry	conditions (I)	conditions (II)	yield of **4a** (%)[b]
1	150°C, 40 min, (62%)[b]	KOH (1 equiv), DMSO, 90°C, 6 h	traces
2		KOH (1 equiv), DMSO, 150°C, 6 h	58[c]
3		KOH (1.5 equiv), DMSO, 150°C, 3.5 h	63
4		*t*-BuOK (1.5 equiv), DMSO, 150°C, 1.5 h	81
5[d]	150°C, 40 min then *t*-BuOK (1.5 equiv), DMSO, 150°C, 1.5 h		73
6[d]	DMSO, 150°C, 2.5 h then *t*-BuOK (1.5 equiv), 150°C, 1.5 h		60

[a]Reaction conditions: **1** (2 mmol), **2a** (2 mmol). [b]Isolated yield after column chromatography purification. [c]Compound **3a** was additionally isolated in 6% yield. [d]*One-pot* method

The best yields of 4-phenylpyrazolo[3,4-*b*]pyridin-6-one **4a** (81%) were achieved at 150°C in DMSO containing 1.5 equiv. of *t*-BuOK for 1.5 h. Obviously, the preparation of 4-phenylpyrazolo[3,4-*b*]pyridin-6-one **4a** could be carried out as *one-pot* synthesis, without isolation of the intermediate dihydro derivative **3a**. In this case, the solvent (DMSO) could be added at the stage of obtaining dihydro derivative **3a** or introduced into the reaction together with *t*-BuOK. We have explored both variants. When intermediate **3a** was obtained under solvent free conditions followed by the addition of *t*-BuOK in DMSO, the yield of pyrazolo[3,4-*b*]pyridin-6-one **4a** was higher (73%) (Table 1, entry 5) than when performing the reaction in a solvent (60%) (Table 1, entry 6). Therefore, this procedure was used for the synthesis of compounds **4b–i**.

The yields of pyrazolo[3,4-*b*]pyridin-6-ones **4a–i** obtained by this method are in the range of 55–73% (Scheme 2).



Scheme 2: *One-pot* synthesis of 4-arylpyrazolo[3,4-*b*]pyridin-6-ones **4a–i**

It should be noted that for compounds containing an electron-donating substituent in the C-4 position, such as 4-methoxyphenyl- (**4c**), 3,4-dimethoxyphenyl- (**4d**), 3,4,5-trimethoxyphenyl- (**4e**), 2-furyl- (**4h**) and 2-thienyl- (**4i**), the product yields are reduced to 55–60% (Scheme 2).

All the compounds obtained are colorless crystalline substances. When dissolved, they produce colorless solutions exhibiting distinct fluorescent properties with blue emission when exposed to UV light. We recorded absorption and fluorescence spectra of ethanolic solutions of compounds **4a-i**. The emission and absorption

spectra of all the compounds differ little from each other. Their spectral parameters are presented in Table 2.

Table 2: The data of absorption and fluorescence spectra of compounds **4a–i**

Compound	UV-VIS				Photoluminescence	
	$^{max}\lambda_{abs}$, nm	ε, 10^3, $M^{-1}\cdot cm^{-1}$ (λ, nm)	λ_{ex}, nm	$^{max}\lambda_{em}$, nm	Stokes shift, nm; eV	Quantum yield Φ_{fl}[a]
4a	260; 302	30.3 ± 0.7 (λ 260 nm)	300; 320	419	117; 1.15	0.22 ± 0.01
4b	260; 302	38.3 ± 0.7 (λ 260 nm)	300; 320	428	126; 1.21	0.23 ± 0.01
4c	262; 302	22.2 ± 0.8 (λ 262 nm)	300; 320	409	107; 1.07	0.16 ± 0.01
4d	260; 301	35.1 ± 0.9 (λ 260 nm)	300; 320	414	113; 1.12	0.15 ± 0.01
4e	262; 301	22.7 ± 0.9 (λ 262 nm)	300; 320	416	115; 1.14	0.18 ± 0.01
4f	260; 302	27.6 ± 0.8 (λ 260 nm)	300; 320	415	113; 1.12	0.20 ± 0.01
4g	261; 300	41.5 ± 0.9 (λ 261 nm)	300; 320	411	111; 1.12	0.20 ± 0.01
4h	265; 305	32.4 ± 1.0 (λ 265 nm)	300; 310	421	116; 1.12	0.23 ± 0.01
4i	263; 301	26.2 ± 0.8 (λ 263 nm)	300; 310	431	130; 1.24	0.09 ± 0.00

[a]Quantum yield determined relative to quinine sulfate standard in 0.5 M H_2SO_4(Φ_f=0.546)

In the UV spectra of ethanolic solutions of compounds **4a–i**, a band with a maximum at 260–265 nm is observed, which has a shoulder at 300–305 nm. These signals seem to correspond to π–π* and n–π* transitions. In the luminescence spectra of compounds **4a–l,** there is one broadened band with an emission maximum at 409–431 nm (Figure 2). Their diluted alcohol solutions luminesce with a quantum yield of 0.09–0.23. Pyrazolo[3,4-*b*]pyridinones **4a–i** are characterized by an abnormally high Stokes shift (107–130 nm) (Table 2). Such luminophores, which are colorless in

daylight but become colored when irradiated with UV light, are used in forensics, in protection against forgery of banknotes, securities, and other important documents [34].

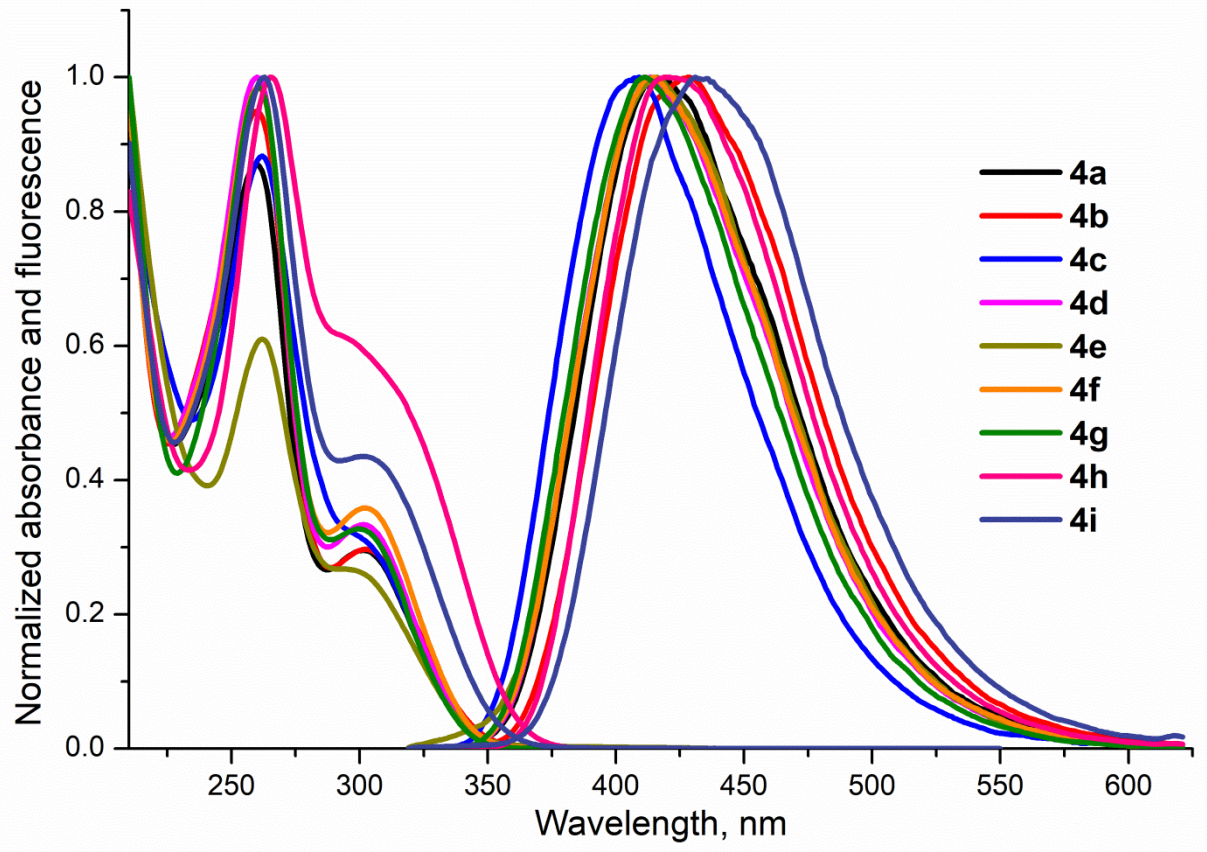


Figure 2: Normalized absorption and fluorescence spectra of solutions of compound **4a–i** in EtOH.

Conclusion

In summary, we developed a simple *one-pot* synthesis of 4-arylpyrazolo[3,4-*b*]pyridin-6-ones, based on the solvent-free reaction of the available starting compounds: 5-aminopyrazole **1** and azlactones **2a–i**, followed by heating the resulting intermediate in DMSO in the presence of *t*-BuOK. Photophysical properties of the obtained compounds were studied.

Supporting Information

Supporting Information File 1

Experimental procedures, characterization data, ^{1}H and ^{13}C spectra for all new compounds.

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