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Synthesis of novel fluorescent 3-aryl- and 3-methyl-7-aryl-[1,2,3]triazolo[1,5-*a*]pyridines by Suzuki cross-coupling reactions

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Dedicated to Professor Joaquin Plumet on the occasion of his 60th birthday

Abstract—Two series of compounds, 3-aryl- (series A, compounds **2a**–**j**) and 3-methyl-7-aryl-[1,2,3]triazolo[1,5-*a*]pyridines (series B, compounds **3a**–**j**) have been synthesized by Suzuki cross-coupling reactions, with a triazolopyridine halide and an aryl or heteroaryl boronic acid in moderate to good yields. All compounds obtained are fluorescents, the quantum yields, particularly those of compounds **3f**–**j**, are very high.

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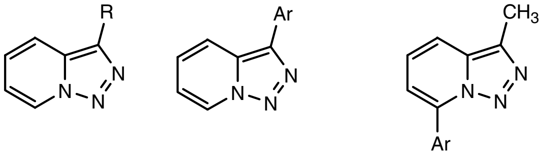
1. Introduction

Biaromatic fluorophores have been exploited in several analytical applications.[1] Heterobiaryls have important biological properties and the biaryl unit is represented in several types of compounds of current interest including natural products, polymers, advanced materials, liquid crystals, luminescent molecular chemosensors, and molecules of medicinal interest.[2,3] The architecture of π-conjugated heteroaromatic compounds assumes significance in view of the applications of these compounds. Recently, we have obtained a sensor of cations and anions based on the fluorogenic properties of a terheteroaryl system in which the [1,2,3]triazolo[1,5-*a*]pyridine nucleus is present.[4] Nevertheless the fluorescence properties of [1,2,3]triazolo[1,5-*a*]pyridines **1** have been scarcely studied. A study of fluorescent spectra of some 7-substituted triazolopyridines showed that only methyl 3-substituted-[1,2,3]triazolo[1,5-*a*]pyridine-7-propenoates showed relatively high fluorescence in methanol.[5,6] A Ni^{+2} complex of 3-(2-pyridyl)-[1,2,3]triazolo[1,5-*a*]pyridine **2h** has been used as a fluorescent indicator.[7] The structural feature of triazolopyridines with conjugated aromatic substituents on 3- or 7-positions should be associated with useful fluorescent properties. This possibility encouraged us to investigate the synthesis and fluorescent properties of two series of compounds, 3-aryl- (series A, compounds **2**) and



1 a R = H
b R = CH_3

2a Ar = C_6H_5
b Ar = *p*-$MeOC_6H_4$
c Ar = *p*-MeC_6H_4
d Ar = *m*-MeC_6H_4
e Ar = *o*-MeC_6H_4
f Ar = *p*-BrC_6H_4
g Ar = 3-pyridyl
h Ar = 2-pyridyl
i Ar = 6-fluor-3-pyridyl
j Ar = 6-chloro-3-pyridyl

3 a Ar = C_6H_5
b Ar = *p*-$MeOC_6H_4$
c Ar = *p*-MeC_6H_4
d Ar = *m*-MeC_6H_4
e Ar = *o*-MeC_6H_4
f Ar = *p*-BrC_6H_4
g Ar = 3-pyridyl
h Ar = 4-pyridyl
i Ar = 6-fluor-3-pyridyl
j Ar = 6-chloro-3-pyridyl

Figure 1.

Keywords: Triazolopyridines; Suzuki cross-coupling reaction; Fluorescence.

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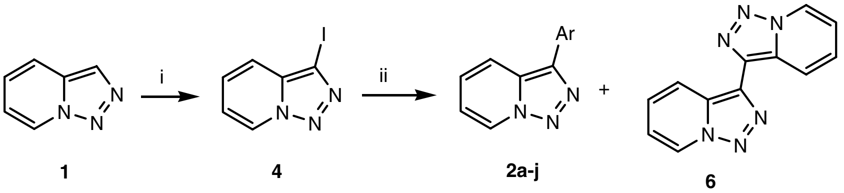
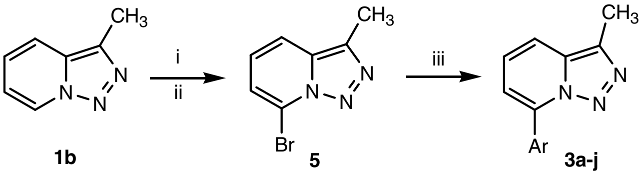


Scheme 1. Reagents and conditions: (i) I_2, DMF, KOH; (ii) $ArB(OH)_2$, dioxane, Na_2CO_3, $Pd(PPh_3)_4$.



Scheme 2. Reagents and conditions: (i) *n*-BuLi/toulene, −40 °C; (ii) DBTCE; (iii) $ArB(OH)_2$, dioxane, Na_2CO_3, $Pd(PPh_3)_4$.

3-methyl-7-aryl-[1,2,3]triazolo[1,5-*a*]pyridines (series B, compounds **3**) (Fig. 1).

2. Results and discussion

The preparation of heterobiaryls using the Suzuki coupling reaction, in which the aryl moieties are one heterocyclic and one carbocyclic ring or both heterocycles, has attracted considerable attention, and there are many examples of this type of synthesis.[2] We have used Suzuki methodology,[8] with a triazolopyridine halide and an aryl or heteroaryl boronic acid in dioxane, sodium carbonate as base, and tetrakistriphenylphosphine palladium as catalyst, for the synthesis of all new compounds in the two series. We obtained compounds **2b–g,i,j** and **3a–g** in very good yields (60–90%). 3-Phenyl-[1,2,3]triazolo[1,5-*a*]pyridine **2a** and 3-(2-pyridyl)-[1,2,3]triazolo[1,5-*a*]pyridine **2h** had been obtained previously from the corresponding 2-pyridylarylketone by reaction with hydrazine hydrate and further oxidation with manganese dioxide in chloroform.[9,10] 7-Pyridyltriazolopyridines **3h–j** were also previously synthesized, in low yield, also by Suzuki type reactions, but in this case with pinacol ester of 7-boronictriazolopyridine acid and the corresponding aryl halide.[11]

As starting triazolopyridines halides we used the new 3-iodo-[1,2,3]triazolo[1,5-*a*]pyridine **4**, synthesized by Bocchi procedure,[12] with iodine in dimethylformamide and potassium hydroxide, and 3-methyl-7-bromo-[1,2,3]triazolo[1,5-*a*]pyridine **5** that was prepared, as described,[13] from 3-methyltriazolopyridine **1b** by regioselective lithiation at position 7 followed by reaction with dibromotetrachloroethane (DBTCE).

3-Iodo-[1,2,3]triazolo[1,5-*a*]triazolopyridine **4** reacted, under the conditions of the Suzuki reaction,[8] with the corresponding commercial aryl boronic acid to give 3-aryltriazolopyridines **2b–g,i,j** in medium to good yields (27–81%).[†] A secondary compound, 3,3′-bitri-azolopyridine **6**,[10,14] was also formed as the consequence of a homocoupling Ullman reaction[15] (Scheme 1).

The cross-coupling reactions between 3-methyl-7-bromo-[1,2,3]triazolo[1,5-*a*]pyridine **5** with aryl boronic acids gave clean reactions in average to very good yields (52–96%) to give compounds **3a–g** (Scheme 2).[‡] The analytical and spectroscopic data for all new compounds are in agreement with the proposed structures (see Supplementary data).

All compounds studied are highly fluorescent. The fluorescence excitation, emission maxima, and quantum yields of both series, are recorded in Table 1. As we can see the conjugation of triazolopyridine with an aryl or heteroaryl group gives highly fluorescent compounds. It does not matter if the conjugation is through 3-position or through 7-position because no significant difference in the emission band is noted. In both series, the presence of one halogen in the 6-position of a 3-pyridyl group does not have significant effect in the fluorescence emission band, but these halo derivatives have the greatest relative fluorescence intensity. The quantum yields have been calculated taking anthracene dissolved in

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[†] *General procedure for the preparation of 3-aryl-[1,2,3]triazolo[1,5-a]pyridines* **2**. To a mixture of 3-iodo[1,2,3]triazolo[1,5-*a*]pyridine **4** (1 mmol), the corresponding arylboronic acid (1.2 mmol), and $Pd(PPh_3)_4$ (4–5%) in dioxane (15 mL), was added a solution of sodium carbonate (2.4 mmol) in water (3 mL). The reaction mixture was heated at 85 °C with vigorous stirring and the rate of reaction was followed by TLC. Water was added at room temperature and the mixture was extracted with dichloromethane. The organic layer was dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The reaction crude was purified by chromatotron using ethyl acetate/hexane in increasing amounts as eluent. Triphenylphosphine oxide, 3,3′-bi[1,2,3]triazolo[1,5-*a*]pyridine **6**, and starting material were isolated in some reactions in low proportions.

[‡] *General procedure for the preparation of 7-aryl-3-methyl-[1,2,3]triazolo[1,5-a]pyridines* **3**. To a mixture of 7-bromo-3-methyl-[1,2,3]triazolo[1,5-*a*]pyridine **5** (1 mmol), the corresponding arylboronic acid (1.2 mmol), and $Pd(PPh_3)_4$ (4–5%) in dioxane (15 mL), was added a solution of sodium carbonate (2.4 mmol) in water (3 mL). The reaction mixture was heated at 85 °C with vigorous stirring, the rate of reaction was followed by TLC. Water was added at room temperature and the mixture was extracted with dichloromethane. The organic layer was dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The reaction crude was purified by chromatotron using ethyl acetate/hexane in increasing amounts as eluent. Triphenylphosphine oxide was isolated together with 3-methyltriazolopyridine as secondary products in some reactions.

Table 1. Relative fluorescence intensities and quantum yields of triazolopyridines

Compound	λ_{max} (nm)		Relative fluorescence intensity (**2j** = 100)	Φ
	Excitation	Emission		
2a	360	431	9.61	0.12
2b	370	448	43.55	0.44
2c	364	440	18.53	0.29
2d	361	432	12.24	0.54
2e	348	431	7.34	0.40
2f	363	431	11.89	0.38
2g	357	424	5.64	—
2h	361	412	6.09	—
2i	364	432	93.88	—
2j	365	431	100	0.10
3a	365	436	9.35	0.13
3b	363	428	8.31	0.12
3c	372	428	13.59	0.25
3d	368	437	4.01	0.12
3e	351	430	4.40	0.08
3f	377	442	3.75	0.62
3g	374	438	1.21	0.69
3h	378	448	22.15	0.89
3i	351	439	22.64	—
3j	359	439	36.09	0.52

Series A and B.

CH_2Cl_2 as a reference ($\Phi_{ant} = 0.42$). In general, the quantum yields are very high. Particularly, compounds **3g** and **3h** having pyridyl functions attached to the six-membered ring, display quantum yield that is almost double than that of the reference.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2006.09.051.

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