



Synthesis of 2,5-diaryl-4-halo-1,2,3-triazoles and comparative study of their fluorescent properties

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ABSTRACT

A convenient method for arylation of mono- and disubstituted 1,2,3-triazoles by copper-catalyzed Chan-Lam coupling was developed. The method is applicable for the regioselective synthesis of fluorescent 4-halogen-substituted (Hal = F, Cl, Br) 2,5-diaryl-1,2,3-triazoles in high yields. Comparative study of their fluorescent properties revealed that 4-fluorosubstituted triazoles possess the highest quantum yield (up to 0.69) among halogenated triazoles possessing Cl and Br in the position 4.

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1. Introduction

At the present time fluorescent compounds gain considerable attention of chemists. The design of new fluorophores is an attractive field due to possible application in molecular imaging, preparation of OLED and chemosensors.¹ These various uses require compounds with ranging characteristics, such as absorbance and emission maxima, quantum yield, fluorescence intensity. Recently, *N*-2-aryl substituted 1,2,3-triazoles were demonstrated as a new class of the blue-light emitting fluorophores.² Thus, importance of triazole scaffold in the medicinal and material chemistry areas^{3,4} makes them promising substrates for novel fluorophore development. We were particularly interested in fluorine-containing triazoles and their properties.⁵ Indeed, incorporation of fluorine atom is known to affect both physical and chemical properties of molecules, such as stability, polarity or lipophilicity.⁶ There are examples of increasing in quantum yields upon fluorine introduction.⁷ Importantly, presence of fluorine may also increase

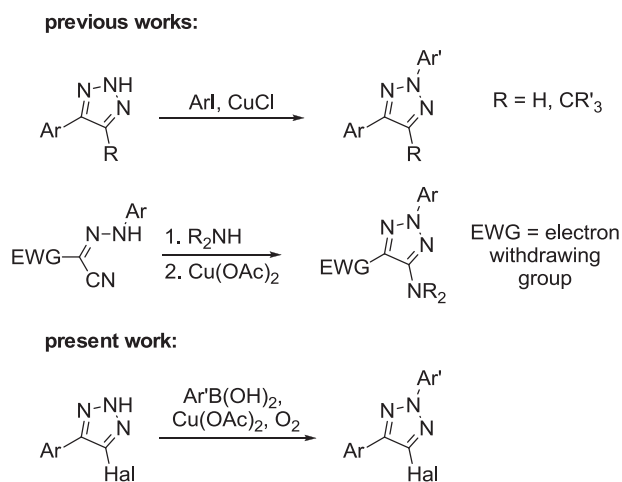
photochemical stability of target molecules.^{7a,8} Despite the influence of various functional groups (alkyl, amino) on the optical characteristics of 1,2,3-triazoles is rather well-studied,^{2,9} the effect of halogen substituents is almost not investigated (Scheme 1). In the present paper we report a method for the synthesis of 2,5-diaryl-4-fluoro-1,2,3-triazoles and comparative study of their fluorescent properties.

2. Results and discussion

For the synthesis of target arylated triazoles copper-catalyzed reaction with boronic acids (Chan-Lam coupling) was chosen.^{10,11} Nowadays, this method is widely used for the arylation of different *N*-nucleophiles, such as amines, anilines, as well as imidazoles, pyrazoles and pyrroles.¹² However, Chan-Lam coupling for regioselective arylation of π -deficient heterocycles such as 1,2,3-triazoles is studied only for 4,5-disubstituted examples and remains being a challenging task.¹³ We initiated our studies with arylation of 4-fluoro-1,2,3-NH-triazole **1a** by benzenboronic acid in the common Chan-Lam coupling conditions using 1 equiv. $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ as a copper source under air (Table 1).¹⁴ Screening of

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Scheme 1. Approaches toward fluorescent N2-aryl-1,2,3-triazoles.

various solvents (Entries 1–4) and basic additives (Entries 5–9) showed CH_2Cl_2 as the optimal solvent and pyridine (2 equiv.) as the optimal base in the case of the stoichiometric reaction with copper acetate (entry 5). In such conditions model triazole **2a** was isolated in reasonably high yield (63%, entry 9). Further improvement was achieved when 2 equiv. of boronic acid was used (71% yield, entry 10).

Next, we made several attempts to reduce the copper amount to switch the reaction to catalytic version (0.1 equiv. of $\text{Cu}(\text{OAc})_2$) using oxygen as external oxidant. However, the reaction with catalytic amount of copper salt resulted in significant drop in yield in CH_2Cl_2 (entry 11). Fortunately, heating (100°C) the mixture in DMSO under oxygen atmosphere (balloon) afforded excellent yield of 96% (entry 12). Finally conditions employing 1.5 equiv. of boronic acid and 0.1 equiv. of $\text{Cu}(\text{OAc})_2$ in DMSO under O_2 atmosphere were chosen as optimal ones giving target 2-phenyl-triazole **2a** in 92% yield (Entry 13). Decrease in amount of boronic acid (Entry 14),

decrease of oxygen concentration (Entry 15) or decrease in temperature (Entry 16) led to lower yield of target triazole. It's worth noting that usually non-polar solvents are used for Chan-Lam arylation of N-nucleophiles in the literature.¹¹ However, our procedure resembles recently developed protocol for arylation of tetrazoles, where heating with Cu_2O in DMSO was used.^{14c}

With optimized conditions in hand (Entry 13) a set of potentially fluorescent arylated fluorotriazoles **2a–2g** was synthesized (Scheme 2). The coupling proceeded smoothly with halogen-substituted (products **2b**, **2d**) and electron-rich 4-methoxyphenylboronic (**2c**) acids producing arylated fluorotriazoles with excellent yields after 2 h of heating. Electron-poor 4-cyanophenylboronic acid (product **2e**) afforded lower yield, which corresponds to the general tendencies in Chan-Lam coupling.¹¹ Product structures were supported by ^1H , ^{13}C and 2D NMR spectra as well as by HRMS data.

Next, optical properties of prepared fluorinated N-2-aryl-triazoles **2a–g** were investigated (Table 2, Entries 1–7, Figs. 1–2). Since solvent choice (MeCN, EtOAc, *i*-PrOH, MeOH, see SI for full details) showed nearly no influence on both absorbance and fluorescence, MeCN was chosen for further experiments. Triazoles **2a–g** gave colorless solutions that absorb in near- and middle-ultraviolet regions. Their UV–Vis spectra demonstrated strong maxima at 300–325 nm with a shoulder at 290–300 nm. In turn, under irradiation they emit light in near-UV to visible violet-blue region. Similar to non-halogenated triazoles^{2a} excitation and emission wavelengths can be tuned by altering either C-aryl or N-aryl substituent leaving quantum yield reasonably high up to 0.69 (Table 2, Entries 1, 3–7). Particularly, incorporation of donating *p*-MeO-group into N2-aryl unit gave red shift in emission maxima (cf. **2c** and **2d**; **2f** and **2g**) and, hence, larger Stokes shifts. Bathochromic shift of both absorbance and emittance can be achieved by introduction of *p*-cyano substituent, that elongate conjugated system of the molecule (**2e**, Entry 5). However, fluorescence was almost quenched for *p*-bromophenyl substituted triazole **2b** due to heavy atom effect (Entry 2).¹⁵

The efficiency of our arylation method was tested on the other

Table 1
Optimization of conditions for triazole arylation.

Entry	$\text{PhB}(\text{OH})_2$, equiv.	$\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ equiv	Additives	Conditions	Yield 2a , % ^a
1	1.1	1	–	THF, air, rt, 16 h	23
2	1.1	1	–	DMF, air, rt, 16 h	trace
3	1.1	1	–	DMSO, air, rt, 16 h	34
4	1.1	1	–	CH_2Cl_2 , air, rt, 16 h	37
5	1.1	1	1 equiv. Py	CH_2Cl_2 , air, rt, 16 h	60
6	1.1	1	1 equiv. DMAP	CH_2Cl_2 , air, rt, 16 h	18
7	1.1	1	1 equiv. Phen	CH_2Cl_2 , air, rt, 16 h	46
8	1.1	1	1 equiv. TMEDA	CH_2Cl_2 , air, rt, 16 h	50
9	1.1	1	2 equiv. Py	CH_2Cl_2 , air, rt, 16 h	63
10	2	1	2 equiv. Py	CH_2Cl_2 , air, rt, 16 h	71
11	2	0.1	2 equiv. Py	CH_2Cl_2 , O_2 (1 atm), rt, 16 h	15
12	2	0.1	–	DMSO, O_2 (1 atm), 100°C , 2 h	96
13	1.5	0.1	–	DMSO, O_2 (1 atm), 100°C , 2 h	92
14	1.1	0.1	–	DMSO, O_2 (1 atm), 100°C , 2 h	75
15	1.5	0.1	–	DMSO, air, 100°C , 2 h	22 (50) ^b
16	1.5	0. ^b	–	DMSO, O_2 (1 atm), rt, 16 h	trace (12) ^b

^a Determined by ^{19}F NMR using PhCF_3 as internal standard.

^b Yield of Starting triazole **1a** is indicated in brackets.

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