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Biaryl-4-hidroxi-1,2,3-triazoles as a platform for new fluorene-triazole hybrids

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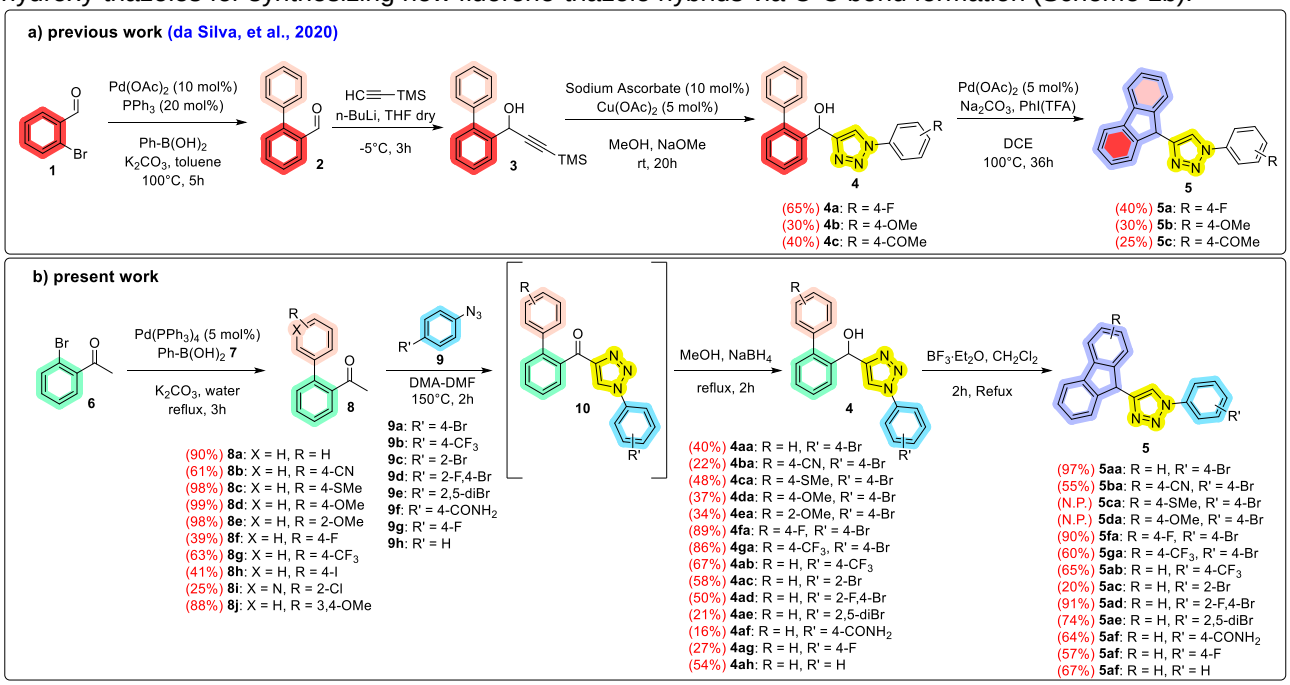
ABSTRACT

Fluorenes are important scaffolds often targeted in medicinal chemistry[1,2]. In 2019, our research group reported the activity of three fluorene-triazole (**5**) against *Leishmania amazonensis*, obtained through a Friedel-Crafts alkylation of biaryl-4-hydroxy-1,2,3-triazoles (**4**), obtained via CuAAC (Scheme 1a)[2]. Since 4-acyl-1,2,3-triazoles (**10**) are readily available, we aim to leverage our expertise[3] in the biaryl system to obtain biaryl-hydroxy-triazoles for synthesizing new fluorene-triazole hybrids via C-C bond formation (Scheme 1b).



Scheme 1 – Overview of the synthesis of 9*H*-fluorene-1,2,3-triazoles

Biaryl acetophenones (**8**) were synthesized via a Suzuki reaction between acetophenone (**6**) and boronic acids (**7**) using, after optimizations, K_2CO_3, water and $Pd(PPh_3)_4$, achieving yields of up to 99%. Biaryl hydroxy-triazoles (**4**) were obtained in a tandem reaction between biaryl acetophenone (**8**), aryl azide (**9**), and DMA-DMF, followed by carbonyl reduction using $NaBH_4$, achieving yields from 16 to 89%. For the C-C bond formation, a Friedel-Crafts alkylation methodology was employed using BF_3. Eleven fluorene-triazole hybrids were obtained in yields of up to 97%.

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