

## Selective Sonogashira Couplings in 1,2,4,5-tetrazine derivatives

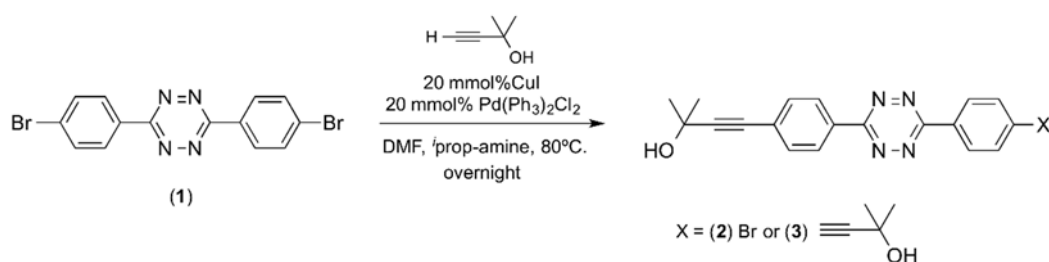
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1,2,4,5-Tetrazines are six-membered heterocyclic compounds in which the four nitrogen atoms are displayed in a symmetric fashion. Their reactivity is quite different from other heterocyclic aromatic systems due to its unique electron-withdrawing character, comparable to tetra-nitrobenzene.<sup>1</sup> In particular, 1,2,4,5-tetrazines are known to take part in [4+2] inverse-Diels–Alder cycloaddition processes which efficiently lead to the construction of substituted pyridazine systems that are important in drug development and biomarker applications.<sup>2</sup> However, the electronic character of 1,2,4,5-tetrazines hampered the development of 3-ethynyl- and 3,6-diethynyl-1,2,4,5-tetrazine derivatives for molecular electronic applications, proved by the scarcity of examples found in the literature.<sup>3</sup>

Herein, we describe the synthesis and characterization of two novel ethynyl-based 1,2,4,5-tetrazine derivatives. Synthesis of 3,6-(4-bromophenyl)-1,2,4,5-tetrazine precursor (**1**) was achieved in good yield by Pinner's method, starting from 4-bromobenzonitrile. Despite its low solubility in common organic solvents, this precursor was found to react smoothly under typical Sonogashira coupling conditions to selectively afford the 3-ethynyl (**2**) and 3,6-diethynyl (**3**) protected derivatives (**Figure 1**). Reaction conditions were evaluated in order to provide the best yields and to promote selectivity of the mono- or disubstituted ethynyl derivatives. Finally, deprotection was achieved affording, in the case of compound **3**, an unprecedented 3,6-diethynyl-1,2,4,5-tetrazine compound.



**Figure 1:** Selective Sonogashira Coupling of 1,2,4,5-tetrazine derivatives.

Time-Dependent Density Functional Theory (TDDFT) calculations for both deprotected ethynyl derivatives were used to simulate electronic spectra. A deep knowledge of the relevant electronic transitions involved and quantitatively satisfactory results of the calculated electronic excitations in comparison with experimental data were obtained.

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