

MILD AND EFFECTIVE METHOD FOR THE CROSS-COUPLING OF GLYCOSYL THIOLS IN AQUEOUS SURFACTANT SOLUTION

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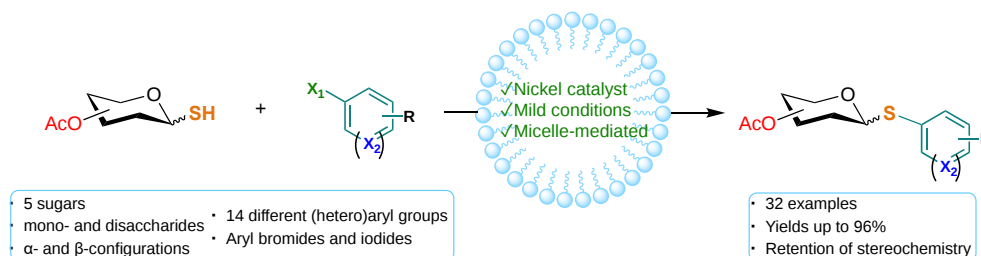
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Thioglycosides have become universal in carbohydrate chemistry not only as oligosaccharide building blocks, but also as enzymatically stable glycomimetics [1]. In both cases, the identity of the aglycon and the anomeric configuration can greatly affect the properties of the glycoside [2]. Traditionally, aryl thioglycosides have been synthesised by reaction of a glycosyl acetate with an aryl thiol in the presence of excess Lewis acid, but this method can have drawbacks including necessity of foul-smelling thiol reagents, limitation of available thiols, and difficulty in obtaining 1,2-*cis* stereochemistry. Conversely, by using glycosyl thiols as starting material, aryl thioglycosides can be generated through transition metal catalysed cross coupling with a breadth of aryl halides while retaining anomeric stereochemistry [3].

Recently, Lipschutz and coworkers reported a surfactant-mediated, nickel catalysed C-S cross coupling which can be carried out in aqueous solution [4]. Using *bis*-phenanthroline Ni (II) catalyst and surfactant TPGS-750-m, we demonstrate an analogous cross coupling reaction for glycosyl thiols, achieving arylation with inexpensive and abundant nickel, and avoiding the need for toxic or environmentally harsh organic solvents. We have shown this methodology to be effective in the coupling of multiple mono- and disaccharide 1-glycosyl thiols with aryl- and heteroaryl halides bearing both electron-donating and electron-withdrawing substituents. The reaction proceeds under mild conditions in yields of up to 96% with retention of native anomeric stereochemistry [5].



References:

1. G. Lian, X. Zhang, B. Yu, *Carbohydr. Res.* **2015**, 403, 13-22.
2. (a) R. Smith, H. Müller-Bunz, X. Zhu, *Org. Lett.* **2016**, 18, 3578-81. (b) A. C. Broussard, M. Boyce, *Mol. Biol. Cell.* **2019**, 30, 525-9.
3. N. Ibrahim, A. Mouad, S. Messaoudi, *Asian J. Org. Chem.* **2018**, 7, 2026-38.
4. T-Y. Yu, H. Pang, Y. Cao, F. Gallou, B. Lipschutz, *Angewandte Chem. Int. Ed.* **2020**, 60, 3708-16.
5. Z. Beato, S. Howard Ihle, X. Zhu, *J. Org. Chem.* **2024**, <https://doi.org/10.1021/acs.joc.4c02233>.