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Enabling Modular Click Chemistry Library through Sequential Ligations of Carboxylic Acids and Amines
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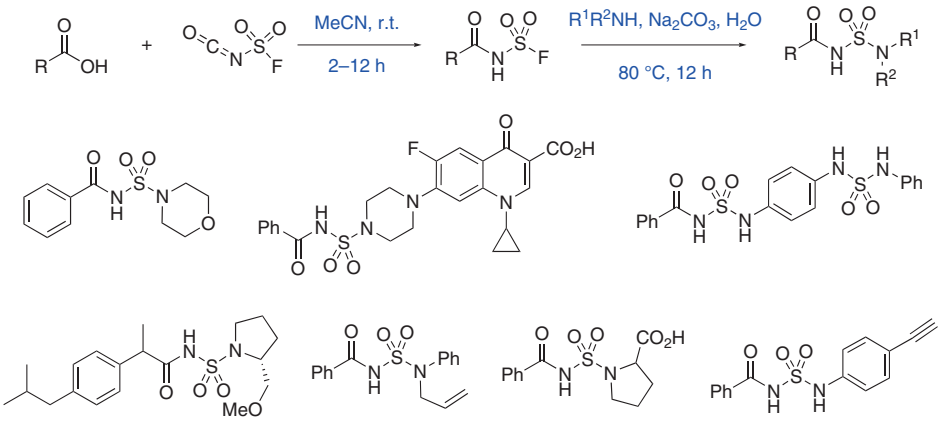
High-Throughput Access to Libraries of *N*-Acylsulfamide Derivatives, a Bioisostere of Carboxylic Acids



Significance: *N*-Acylsulfamides have been established as bioisosteres of carboxylic acids, notably in the HCV NS5B polymerase inhibitor beclabuvir which was approved in Japan, the Nav1.7 inhibitor GDC-0276 and the herbicide safluenacil. The process developed in this article is mild and high yielding, amenable to the generation of large libraries of *N*-acylsulfamide derivatives with products typically isolated by a simple filtration after acidification of the reaction mixture The process was demonstrated with a range of carboxylic acid derivatives that explored only relatively benign substituents (for example, there was an absence of alcohols or amides in the acids), although the amines contained a broader range of functionality that included acids, tertiary amines, and alkynes. Bis-carboxylic acids could be fully or partially converted by controlling the ratio of reagents. The process has potential for late-stage functionalization of carboxylic acids, the scope of which will depend on the functionality inherent to a molecule.

Comment: Exposure of a carboxylic acid to the highly electrophilic but readily available fluorosulfuryl isocyanate in CH_3CN, determined to be the crucial solvent, at room temperature afforded an *N*-fluorosulfonyl amide in yields typically >90%. The scope of the process extended to aromatic, heteroaromatic and aliphatic carboxylic acids with limited polar functionality, although NH-sulfonamide and imide functionality were compatible, and the reaction was tolerant of steric encumbrance. Electron-deficient acids required heating to 50–60 °C in order to complete the reaction. Reaction of the *N*-fluorosulfonyl amides with aromatic and aliphatic amines occurred in H_2O with Na_2CO_3 as the base heated at 80 °C for 12 hours to afford *N*-acylsulfamides in good to excellent yields, with the products typically isolated by acidification and simple filtration to afford the product. Execution of a 13x24 library in 96 well plates generated 312 products, with 281 proceeding with >90% conversion and 97% proceeding with >80% conversion.

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