

## Tetraalkoxysilanes as Convenient and Inexpensive Reagents for Direct Amidation of Carboxylic Acids

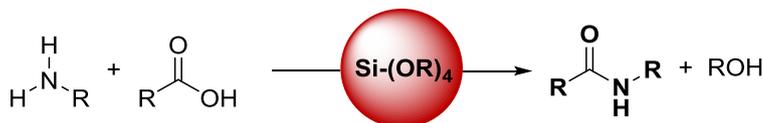
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“Amide formation avoiding poor atom economy reagents” was voted as the top priority research area by the ACS GCI Pharmaceutical Roundtable in 2007<sup>1</sup> and the amide group is present in about 25% of all pharmaceuticals on the market. With the increasing need for green, non-toxic, cost effective organic functional group transformations, catalytic direct amide bond formation is of considerable interest to the pharmaceutical industry. The desire for inexpensive and convenient amidation reagents along with some literature precedent for the use of silicas for amide formation prompted us initially to investigate molecular silanols such as Ph<sub>3</sub>SiOH as direct amidation catalysts. Unfortunately, although several molecular silanols do act as amidation catalysts, yields are not high and catalyst condensation reactions to give siloxanes are a problem. We then turned our attention to tetraalkoxysilanes (see equation, R = Me or Et) and find that (MeO)<sub>4</sub>Si is a particularly effective direct amidation reagent.

We report<sup>2</sup> that tetramethoxysilane is a convenient and high yielding reagent for direct amidation of a range of aliphatic and aromatic carboxylic acids with primary, cyclic and acyclic secondary aromatic amines, and anilines. The method can even be applied successfully to the direct amidation of an aromatic carboxylic acid with an aniline, a particularly difficult transformation. The amide products can be isolated easily and in high yield without the need for chromatographic purification. In addition, we have scaled up the method to mole scale and the process mass intensity compares very favourably with more conventional methods.



- [1] D. J. C. Constable, P. J. Dunn, J. D. Hayler, G. R. Humphrey, J. L. Leazer Jr., R. J. Linderman, K. Lorenz, J. Manley, B. A. Pearlman, A. Wells, A. Zaks, T. Y. Zhang, *Green Chem.* **2007**, *9*, 411–420.
- [2] D. C. Braddock, P. D. Lickiss, B. C. Rowley, D. Pugh, T. Purnomo, G. Santhakumar and S. J. Fussell, *Organic Letters*, **2018**, *20*, 950-953.