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A facile KF/Al_2O_3 mediated method for the synthesis of substituted oxazolidinones

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Abstract

2-Substituted oxazolidinones are prepared by a KF/Al_2O_3 mediated reaction of an oxazolidinone with an alkyl bromide, isocyanate, or sulfonyl chloride.

Over the past several years, the field of combinatorial chemistry has grown into an accepted practice in drug discovery.[1] While the vast majority of the reported literature to date has focused on the application of resin-based technologies, we have been exploring an additional avenue to the preparation of combinatorial libraries, the use of reagents on solid support. This approach, which sits between conventional solution phase chemistry and resin bound techniques, shares several advantages of both fields. As with solid phase synthesis, excess support bound reagents can be used to drive reactions to completion and then be removed by filtration, avoiding cumbersome work-ups. Unlike resin-based chemistry, however, the target compound is not covalently bound to the solid support, so monitoring of the reactions and analysis can be accomplished using standard methods (thin layer chromatography, solution ^1H NMR, etc.). Finally, the products are isolated by filtration and removal of the solvents, eliminating the need for the cleavage step required in solid phase preparations.

Recently, we have been investigating the use of solid supported reagents for the preparation of libraries of functionalized oxazolidinones. As a class, oxazolidinones have been shown to possess a wide range of biological activity, including antidepressant, antihistaminic, antifungal, antihypertensive, and antibacterial activity.[2] A brief examination of the literature revealed that most common methods for the preparation of functionalized oxazolidinones require the use of strong bases (i.e. *n*-BuLi, NaH, etc.) and an aqueous work-up.[3] The preparation of combinatorial libraries of oxazolidinones would be greatly simplified if both of these steps could be avoided. To that end, we have found that the functionalization of oxazolidinones in the 2-position can be accomplished using potassium fluoride on alumina (KF/Al_2O_3) as a base in the presence of a suitable electrophile (Scheme 1).

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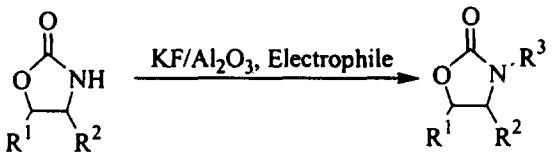

Scheme 1.

Table 1
Representative examples of condensation of a 2-oxazolidinone with an electrophile[7]

Entry	R^1	R^2	Electrophile	R^3	% Yield
1	Ph	CH_3	PhNCO	CONHPh	81
2	Ph	CH_3	TsCl	Ts	86
3	H	Ph	n-C_4H_9Br	n-C_4H_9	83
4	H	Bn	n-C_3H_7Br	n-C_3H_7	77
5	Ph	CH_3	$C_6H_{11}NCO$	$CONHC_6H_{11}$	90
6	H	Bn	$C_6H_5CH_2Br$	CH_2Ph	82

The use of KF/Al_2O_3 for the functionalization of amides was initially reported in 1981 by Yamawaki,[4] but has received little attention since then. The major advantage claimed in this paper is the suppression of competing *O*-alkylation that is generally observed in the alkylation of amides. Morgan extended the utility of KF/Al_2O_3 by demonstrating that it could be used to facilitate the alkylation of a series of 2,4-dinitrophenylhydrazones.[5] In addition, Tius recently reported the synthesis of various α-heterosubstituted Weinreb amides using a KF/Al_2O_3 mediated alkylation of an α-chloro amide by a series of nucleophiles.[6] We now wish to report that 2-oxazolidinones readily react with a range of electrophiles in the presence of KF/Al_2O_3. Alkylation was readily accomplished with 1.0 equivalents of an alkyl bromide in the presence of KF/Al_2O_3 in a number of solvents (DME, EtOAc, CH_3CN, THF, 1,4-dioxane) at 25°C over 24 h (Table 1). Interestingly, protic solvents (MeOH, EtOH) could not be used for this application as they leach the KF off of the solid support, leaving undesired amounts of KF in the end product. This would make the procedure less attractive from the standpoint of library production. Sulfonyl chlorides reacted with 2-oxazolidinones to produce the corresponding sulfonamide product at room temperature in CH_2Cl_2 or DCE. The desired product was observed in other more polar solvents (DMF, 1,4-dioxane, etc.), but it was contaminated with varying levels of the corresponding sulfonic acid. This suggests that the rate of hydrolysis of the sulfonyl chloride approaches that of the desired reaction in more polar solvents. Similar results were obtained with isocyanates, as the desired urea was the exclusive product in CH_2Cl_2 and $CHCl_3$, but in more polar solvents, symmetrical ureas (the result of hydrolysis of the starting isocyanate) were observed. Other electrophiles, such as acid chlorides, anhydrides, and epoxides failed to produce the desired products under any of the conditions examined.

In summary, we have developed a novel method for the functionalization of 2-oxazolidinones using KF/Al_2O_3. The products are obtained in good to excellent yield and purity, and the reaction is amenable to the production of combinatorial libraries.

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7. All of the products described in Table 1 are known compounds. Synthetic samples gave spectral data identical to previously reported literature values. All crude reaction products were characterized without further purification. Typical experimental procedures are as follows. Alkylation: 4-Benzyl-2 oxazolidinone (150 mg, 0.85 mmol) and 1.5 g of KF/Al_2O_3 (40% by weight) are dissolved/suspended in 15.0 mL of DME and 145 mg (101 μL, 0.85 mmol) of benzyl bromide is added. The reaction is stirred vigorously at room temperature for 24 h, filtered, and stripped of solvent to yield 186 mg (82%) of the desired product. Urea synthesis: 4-Methyl-5-phenyl-2-oxazolidinone (150 mg, 0.85 mmol) and 1.5 g of KF/Al_2O_3 (40% by weight) are dissolved/suspended in 15.0 mL of $CHCl_3$ and 101 mg (92 μL, 0.85 mmol) of phenyl isocyanate is added. The reaction is stirred vigorously at room temperature for 24 h, filtered, and stripped of solvent to yield 203 mg (81%) of the desired product. Sulfonylation: 4-Methyl-5-phenyl-2-oxazolidinone (150 mg, 0.85 mmol) and 1.5 g of KF/Al_2O_3 (40% by weight) are dissolved/suspended in 15.0 mL of CH_2Cl_2 and 161.4 mg (0.85 mmol) of *p*-toluenesulfonyl chloride is added. The reaction is stirred vigorously at room temperature for 24 h, filtered, and stripped of solvent to yield 241 mg (86%) of the desired product.