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A CONVENIENT AND PRACTICAL METHOD FOR N-ACYLATION OF 2-OXAZOLIDINONE CHIRAL AUXILIARIES WITH ACIDS

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Abstract: A one-pot, convenient and practical method for N-acylation of 2-oxazolidinone chiral auxiliaries directly with acids in the presence of pivaloyl chloride and triethylamine is described.

Pioneering work of Evans[1] has resulted in the development of 2-oxazolidinones as popular and widely used chiral auxiliaries in asymmetric synthesis.[2,3] The resulting asymmetric induction using these auxiliaries is high in carbon-carbon bond formation reactions such as alkylation,[4] aldol reaction,[5] acylation[6] and Diels-Alder reactions.[7] We recently required an efficient and large scale synthesis of ß-(R)-(hydroxymethyl)benzenepropionitrile. Asymmetric alkylation of (R)-4-substituted-N-phenylacetyl-2-oxazolidinones with bromoacetonitrile[8] was an obvious route, which was well precedented. The first step in this approach required a coupling of 2-oxazolidinone chiral auxiliary with the substrate. A common method to accomplish this coupling is the reaction of the acid chloride or mixed anhydride of the substrate with the lithium salt of the chiral auxiliary.[9] Recently, a few other methods have been reported using triethylamine-LiCl,[10] triethylamine-DMAP,[11] triethylamine-DMAP-CuCl-Cu[12] as coupling agents. N-Trimethylsilyl derivative of 2-oxazolidinones have also been acylated in the presence of $CuCl_2$ and copper powder.[13] Not only do these methods require a separate step for the preparation of acid chloride or mixed anhydride, they have not been used for the acylation of 2-oxazolidinones with phenylacetyl chloride.[2] The coupling of acid chlorides or mixed anhydrides of arylacetic acids with 2-oxazolidinones is especially challenging because of the ease of ketene formation from these intermediates, which could lead to poor yields.[14] This problem could possibly be circumvented by generating the mixed anhydride *in situ* during the coupling reaction. In this paper we describe a one-pot, convenient and practical method for N-acylation of 2-oxazolidinones directly with arylacetic acids in the presence of pivaloyl chloride and triethylamine. Acylation of 2-oxazolidinones directly with acids is a topic of interest.[15]

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Table 1: N-Acylation of 2-Oxazolidinone Chiral Auxiliaries with Acids (2.0 eq.)

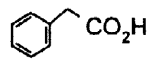
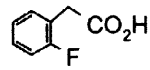
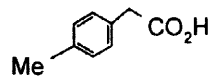
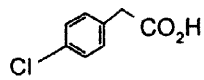
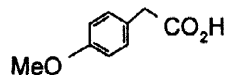
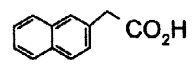
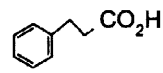
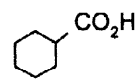
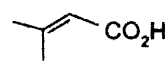
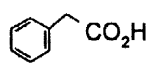
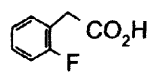
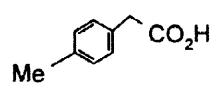
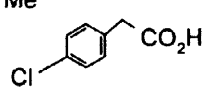
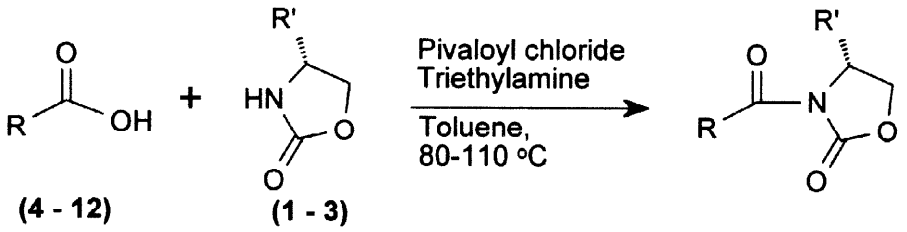
Entry	R⌒CO_2H		% Yield of N-acylated products (1)	(2)	(3)
1		**(4)**	80	72	80
2		**(5)**	85	87	76
3		**(6)**	92	88	80
4		**(7)**	93	85	70
5		**(8)**	92	90	88
6		**(9)**	75	85	80
7		**(10)**	87	80	55
8		**(11)**	50	50	62
9		**(12)**	57	44	14

Table 2: N-Acylation of 2-Oxazolidinone Chiral Auxiliaries with Acids (1.14 eq.) at different temperatures

Entry	R⌒CO_2H		% Yield of N-acylated products (1)		(3)	
			80 °C	110 °C	80 °C	110 °C
1		**(4)**	74	-	41	74
2		**(5)**	70	-	40	68
3		**(6)**	47	82	-	-
4		**(7)**	49	80	-	-



(4 - 12) (1 - 3)

The preparation and isolation of acid chlorides or mixed anhydrides require operations which are undesirable for large-scale preparations. We envisioned that the coupling of 2-oxazolidinones could be carried out directly with acids by generating the mixed anhydride *in situ*. Thus, reaction of (R)-4-phenyl-2-oxazolidinone (**1**) with 2.0 equivalents of phenylacetic acid (**4**) in toluene at 110 °C in the presence of pivaloyl chloride and triethylamine yielded the desired N-acylated product in 80% yield (Table 1).[16] Similar results were obtained for the acylation of (R)-4-benzyl (**2**) and (R)-4-isopropyl-2-oxazolidinone (**3**) auxiliaries with phenylacetic acid (entry 1; Table 1). To test the general synthetic utility of this method, several acids (**4-12**) were reacted with these auxiliaries (**1-3**) and the results are listed in Table 1.[17] Generally, arylacetic acids, possessing either an electron withdrawing or electron donating group in the aromatic ring, gave good to excellent yields of the acylated products (entries 1-6). Hydrocinnamic acid also yielded the acylated products in good yields (entry 7). Acylation of **1-3** with cyclohexanecarboxylic acid gave modest yields of N-acyl-2-oxazolidinones (entry 8). α,ß-Unsaturated acid, such as 3,3-dimethylacrylic acid, gave modest yields of the acroylated products with auxiliaries **1** and **2**, but the yields were poor with the auxiliary **3** (entry 9). Thus, this one-pot method is convenient and highly efficient for the acylation of 2-oxazolidinone chiral auxiliaries, in particular with arylacetic acids.

These general reaction conditions could be further optimized using 1.14 equivalents of the acid on a case by case basis (Table 2).[18] The coupling of (R)-4-phenyl-2-oxazolidinone (**1**) with acids **4** and **5** yielded N-acylated products in good yields at 80 °C (entries 1 and 2; Table 2), although these yields were lower when compared to conditions utilizing 2.0 equivalents of acids (entries 1 and 2; Table 1). In contrast, coupling of **1** with 1.14 equivalents of acids **6** and **7** at 80 °C afforded acylated products in poor yields (47 and 49% respectively). In these cases the yields were improved to 82 and 80%, respectively, by increasing the temperature to 110 °C (entries 3 and 4; Table 2). A similar trend was observed during the coupling of the auxiliary **3** with acids **4** and **5** (entries 1 and 2; Table 2).

Because 2-oxazolidinone auxiliaries are relatively more expensive than the acids, conditions involving 2.0 equivalents of the acid would be more economical for this coupling. In cases of acids that are expensive and

not available readily, conditions utilizing 1.14 equivalents of the acid will be more suitable, even though the yields of N-acylated products may be somewhat lower.

In summary, a one-pot, convenient and practical method for N-acylation of 2-oxazolidinone chiral auxiliaries directly with acids in the presence of pivaloyl chloride and triethylamine is described.

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14. Decomposition of N-acylated-2-oxazolidinones under basic conditions via a ketene pathway is aslo known. Hoekstra, M. S.; Sobieray, D. M.; Schwindt, M. A.; Mulhern, T. A.; Grote, T. M.; Huckabee, B. K.; Hendrickson, V. S.; Franklin, L. C.; Granger, E. J.; Karrick, G. L. *Org. Proc. Res. Dev.* **1997**, 1, 26-38.
15. Knol, J.; Feringa, B. L. *Synth. Commun.* **1996**, 26, 261-268.
16. Typical procedure (Table 1): To a mixture of 2-oxazolidinone chiral auxiliary (1 eq.), acid (2 eq.) in toluene (1.6 mL / mmol) was added triethylamine (4 eq.). The mixture was heated to an internal temperature of 80 °C to obtain a solution. To the reaction mixture was added a solution of pivaloyl chloride (2 eq.) in toluene (0.2 mL / mmol) at a rate to maintain an internal temperature of 80 °C. The mixture was then heated to an internal temperature of 110 °C and stirred at this temperature for 14 h (overnight). The reaction mixture was cooled to room temperature and was washed with 2 N hydrochloric acid, 5% aqueous sodium carbonate, and brine. The organic layer was concentrated and the crude product was purified by silica gel chromatography.
17. All the compounds gave satisfactory spectral data.
18. Procedure (Table 2): To a mixture of 2-oxazolidinone chiral auxiliary (1 eq.), arylacetic acid (1.14 eq.) in toluene (1.6 mL / mmol) was added triethylamine (3 eq.). The mixture was heated to an internal temperature of 80 °C to obtain a solution. To the reaction mixture was added pivaloyl chloride (1.19 eq.) in toluene (0.2 mL / mmol) at a rate to maintain an internal temperature of 80 °C. The mixture was stirred at 80 °C (or 110 °C; Table 2) for 2 h and additional pivaloyl chloride (0.6 eq.) was added while maintaining the internal temperature at 80 °C (or 110 °C). The mixture was stirred for an additional 3 h at 80 °C (or 110 °C). The reaction mixture was cooled to room temperature and was washed with 2 N hydrochloric acid, 5% aqueous sodium carbonate, and brine. The organic layer was concentrated and the crude product was purified by silica gel chromatography.