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**DIRECT COUPLING PROCEDURE FOR THE SYNTHESIS OF
N-ACYL-2-OXAZOLIDINONES DERIVED FROM
 α,β -UNSATURATED CARBOXYLIC ACIDS**

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Abstract: An efficient direct coupling procedure for the synthesis of *N*-acyl-2-oxazolidinones derived from α,β -unsaturated carboxylic acids is described in which 2-chloro-1-methylpyridinium iodide is employed as the dehydrating agent.

N-acyl-2-oxazolidinones derived from α,β -unsaturated carboxylic acids have proven to be the dienophiles of choice in many recent studies concerning chiral Lewis acid catalyzed enantioselective Diels Alder reactions.¹ Due to the bidentate chelating properties² of this type of dienophiles high levels of

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asymmetric induction have been reported in catalytic studies by various groups.³ Traditionally, these compound are prepared by reaction of the *N*-lithiated 2-oxazolidinone with the α,β -unsaturated acid chloride.^{4,5} Literature reports indicate low to moderate yields when unsubstituted 2-oxazolidinone is employed. In our search for a direct coupling procedure, which could circumvent the use of *n*-butyllithium and α,β -unsaturated acid chlorides, we examined 2-chloro-1-methylpyridinium iodide **1** as a dehydrating agent.⁶ Coupling reactions of several α,β -unsaturated carboxylic acids were performed in dichloromethane with nearly stoichiometric molar ratios of carboxylic acid, 2-oxazolidinone and **1** (1 : 1.1 : 1.2) in the presence of triethylamine (2.4 eq.) as a base. When the latter was added to a suspension of the acid, 2-oxazolidinone and the pyridinium salt, an exothermal reaction occurred and the dichloromethane insoluble pyridinium salt was progressively dissolved as the reaction proceeded. Furthermore, monitoring the conversion with TLC (SiO₂) indicated clean product formation in all cases. Purification was easily performed by direct transfer of the reaction mixture to a silica gel column and subsequent elution with hexane/ethyl acetate mixtures. In this way the pure product was easily separated from 1-methyl-1-pyridone **2**. From the results (table) it can be seen that moderate to good yields of *N*-acyloxazolidinones are obtained in general via this simple procedure. A clear difference in reactivity was observed for the different α,β -unsaturated carboxylic acids employed. Acrylic, crotonic and cinnamic acid gave only moderate yields of the known *N*-acyloxazolidinones **3** - **5** after several days of reflux. The previously unreported

Table. Synthesis of *N*-acyl-2-oxazolidinones in the presence of 2-chloro-1-methylpyridinium iodide.

<i>N</i> -acyl-2-oxazolidinone (yield (%)) ^a
3 (40)	7 (80)
4 (50)	8 (71)
5 (35)	9 (73)
6 (26)	

a) Isolated yields: see experimental section for specific reaction conditions and purification procedures.

N-acyloxazolidinone **6**, derived from phenylpropionic acid was obtained in only 26% yield. Significantly higher yields were obtained when fumaric acid monomethyl ester⁷ was used. As expected this acid proved to be much more reactive in the coupling reaction. The corresponding *N*-acyloxazolidinone **7** was obtained in 80% after 48 h at room temperature. This is a substantial

improvement compared to the synthesis reported so far.⁸ The coupling of substituted 2-oxazolidinones like 4,4-dimethyl-1,3-oxazolidin-2-one and 4(*S*)-(phenylmethyl)-1,3-oxazolidin-2-one allowed isolation of the products **8** and **9** in respectively 71 and 73% chemical yield.

In conclusion, we have demonstrated a simple new procedure for the synthesis of *N*-acyl-2-oxazolidinones derived from α,β -unsaturated carboxylic acids.

Experimental

General coupling procedure as illustrated for 3-((E)-3-(methoxycarbonyl)propenoyl)-1,3-oxazolidin-2-one 7:

To a stirred suspension of fumaric acid mono methyl ester (1.30 g, 10 mmol), 2-chloro-1-methylpyridinium iodide (3.07 g, 12 mmol) and 2-oxazolidinone (0.96 g, 11 mmol) in dry dichloromethane (25 ml) under an atmosphere of nitrogen was added triethylamine (2.42 g, 24 mmol). The mixture, which quickly turned into a brown homogeneous solution, was stirred for 48 h at room temperature. After evaporation of the solvent in vacuo the residu was purified by flash chromatography over SiO₂ (ethyl acetate/hexane 1/1). A slightly yellow solid (mp 81.4-81.9 °C, lit.^{3a} 80.5-81.0 °C) was obtained which was pure according to ¹H NMR (1.60 g, 80%). Spectroscopic and analytical data were completely in accordance with those reported in the literature.^{3a}

3-(2-Propenoyl)-1,3-oxazolidin-2-one **3**:

Starting from acrylic acid (0.72 g, 10 mmol) and following the general procedure the mixture was refluxed for 4 days. Purification by column chromatography (SiO₂: ethyl acetate/hexane 1/1) afforded the product (0.56 g, 40%) as a yellow solid (mp 79.0-81.8 °C, lit.^{3a} 82.0-83.0 °C). Spectroscopic data were identical to those reported in the literature^{3a} and of an independently prepared sample.⁴

3-((E)-3-Butenoyl)-1,3-oxazolidin-2-one **4**:

Starting from crotonic acid (0.86 g, 10 mmol) and following the general procedure the mixture was refluxed for 3 days. Purification by column chromatography (SiO₂: ethyl acetate/hexane 4/6) afforded the product as a colorless oil (0.78 g, 50%). Spectroscopic and analytical data were in complete accordance with those reported in the literature.^{3a}

3-((E)-3-Phenyl-2-propenoyl)-1,3-oxazolidin-2-one **5**:

Starting from trans cinnamic acid (1.48 g, 10 mmol) and following the general procedure the mixture was refluxed for 7 days. Purification by column chromatography (SiO₂: ethyl acetate/hexane 3/7) afforded the product (0.77 g,

35%) as a yellow solid (mp 144.0-145.6 °C, lit.^{3a} 151.0-152.5 °C). Spectroscopic data were identical to those reported in the literature.^{3a}

*3-(3-(Phenyl-2-propynoyl)-1,3-oxazolidin-2-one **6**:*

Starting from phenylpropionic acid (0.73 g, 5 mmol) and following the general procedure, the mixture was refluxed for 4 h. Purification by column chromatography (SiO₂: ethyl acetate/petroleum ether (40-60) 35/65) afforded the product (0.282 g, 26%) as a yellow solid which was pure according to ¹H NMR. An analytical sample was obtained by recrystallization from a cyclohexane/dichloromethane mixture as slightly yellow needles: mp 158.0-158.9 °C; ¹H NMR (200 MHz, CDCl₃) δ 4.11 (t, *J* = 8 Hz, 2H), 4.47 (t, *J* = 8 Hz, 2H), 7.42 (m, 3H), 7.68 (m, 2H); ¹³C NMR (50.3 MHz, CDCl₃) δ 42.17 (t), 61.84 (t), 80.70 (s), 94.54 (s), 119.49 (s), 128.42 (d), 130.89 (d), 133.13 (d), 150.73 (s), 151.88 (s); Anal. Calcd for C₁₂H₉NO₃: C, 66.97; H, 4.22; N, 6.51. Found C, 66.79; H, 4.22; N, 6.58.

*3-((E)-3-(Methoxycarbonyl)propenoyl)-4,4-(dimethyl)-1,3-oxazolidin-2-one **8**:*

Starting from fumaric acid mono methyl ester (0.65 g, 5 mmol) and 4,4-dimethyl-1,3-oxazolidin-2-one (0.63 g, 5.5 mmol) and following the general procedure, the mixture was refluxed for 4 h. Purification by column chromatography (SiO₂: ethyl acetate/petroleum ether (40-60) 3/7) afforded the

product as a slightly yellow viscous oil which solidified upon standing (0.81 g, 71%). An analytical sample was obtained by crystallization from a cyclohexane/dichloromethane mixture as colorless plates: mp 79.8-80.9 °C; ¹H NMR (200 MHz, CDCl₃) δ 1.61 (s, 6H), 3.81 (s, 3H), 4.08 (s, 2H), 6.85 (d, *J* = 15.4 Hz, 1H), 7.96 (d, *J* = 15.4 Hz, 1H). ¹³C NMR (50.3 MHz, CDCl₃) δ 24.25 (q), 52.07 (q), 60.51 (s), 75.39 (t), 132.34 (d), 134.28 (d), 153.55 (s), 164.34 (s), 165.19 (s); Anal. Calcd for C₁₀H₁₃NO₅: C, 52.84; H, 5.77; N, 6.17. Found C, 52.79; H, 5.69; N, 6.13.

(4S)-3-((E)-3-(Methoxycarbonyl)propenoyl)-4-(phenylmethyl)-1,3-oxazolidin-2-one 2:

Starting from fumaric acid mono methyl ester (1.30 g, 10 mmol) and 4(*S*)-benzyl-1,3-oxazolidin-2-one (1.95 g, 11 mmol) and following the general procedure, the mixture was refluxed for 2 h. Purification by column chromatography (SiO₂: ethyl acetate/petroleum ether (40-60) 3/7) which afforded **2** as a white solid. Recrystallization from a cyclohexane/dichloromethane mixture afforded analytically pure white crystals (2.12 g, 73%): mp 77.9-78.9 °C; [α]_D^{RT} +69.5° (c 0.994, CHCl₃); ¹H NMR (200 MHz, CDCl₃) δ 2.83 (dd, *J* = 13.7, 9.4 Hz, 1H), 3.35 (dd, *J* = 13.7, 3.4 Hz, 1H), 3.83 (s, 3H), 4.25 (m, 2H), 4.75 (m, 1H), 6.99 (d, *J* = 15.6 Hz, 1H), 7.28 (m, 5H), 8.16 (d, *J* = 15.6 Hz, 1H); ¹³C NMR (50.3 MHz, CDCl₃) δ 37.34 (t), 52.16 (q), 55.08 (d), 66.31 (t), 127.27 (d), 128.83 (d), 129.21 (d), 132.32 (d),

133.59 (d), 134.70 (s), 152.85 (s), 163.42 (s), 165.07 (s); Anal. Calcd for $C_{15}H_{15}NO_5$: C, 62.28; H, 5.23; N, 4.84. Found C, 62.33; H, 5.26; N, 4.77.

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References

1. For a recent review see: Kagan, H.B.; Riant, O. *Chem. Rev.* **1992**, *92*, 1007.
2. (a) Castellino, S.; Dwight, J. *J. Am. Chem. Soc.* **1993**, *115*, 2986. (b) Gothelf, K.V.; Hazell, R.G.; Jørgensen, K.A. *J. Am. Chem. Soc.* **1995**, *117*, 4435.
3. Selected examples: (a) Narasaka, K.; Iwasawa, N.; Inoue, M.; Yamada, T.; Narashima, M.; Sugimori, J. *J. Am. Chem. Soc.* **1989**, *111*, 5340. (b) Evans, D.A.; Miller, S.J.; Leckta, T. *J. Am. Chem. Soc.* **1993**, *115*, 6460. (c) Kobayashi, S.; Hachiya, I.; Ishitani, H.; Araki, M. *Tetrahedron Lett.* **1993**, *34*, 4535. (d) Evans, D.A.; Leckta, T.; Miller, S.J. *Tetrahedron Lett.* **1993**, *34*, 7027. (e) Seebach, D.; Dahinden, R.; Marti, R.E.; Beck, A.K.; Plattner, D.A.; Kühnle, F.N.M. *J. Org. Chem.* **1995**, *60*, 1788.
4. Evans, D.A.; Chapman, K.T.; Bisaha, J. *J. Am. Chem. Soc.* **1988**, *110*, 1238.
5. For recent modified procedures, see: (a) Thom, C.; Kociński, P. *Synthesis*, **1992**, 582. (b) Ho, G.-J.; Mathre, D.J. *J. Org. Chem.* **1995**, *60*, 2271.
6. This reagent is commercially available; for a review see: Mukaiyama, T. *Angew. Chem. Int. Ed. Engl.* **1979**, *18*, 707.
7. Spatz, S.M.; Stone, H. *J. Org. Chem.* **1958**, *23*, 1559.
8. See supplementary material of ref. 3b.

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