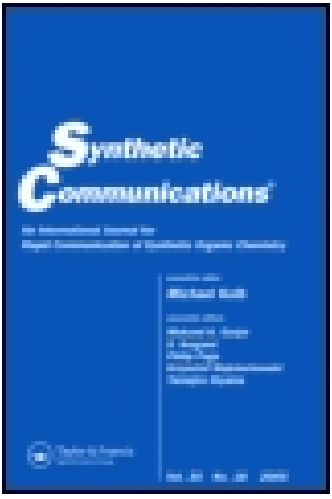

Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

# Direct Coupling Procedure for the Synthesis of N-Acyl-2-oxazolidinones Derived from α,β-Unsaturated Carboxylic Acids

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Published online: 21 Aug 2006.

To cite this article: Joop Knol & Ben L. Feringa (1996) Direct Coupling Procedure for the Synthesis of N-Acyl-2-oxazolidinones Derived from α,β-Unsaturated Carboxylic Acids, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 26:2, 261-268, DOI: 10.1080/00397919608003613

To link to this article: http://dx.doi.org/10.1080/00397919608003613

SYNTHETIC COMMUNICATIONS, 26(2), 261-268 (1996)

# 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 properties[2] of this type of dienophiles high levels of

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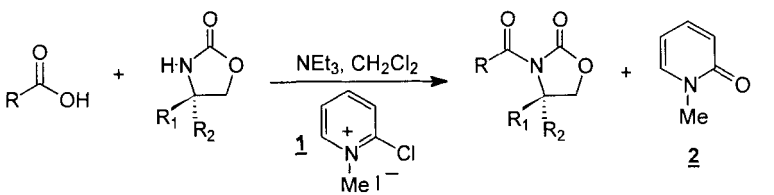
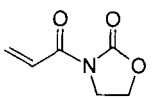
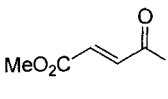
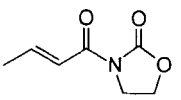
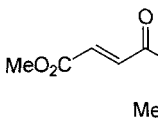
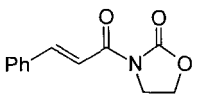
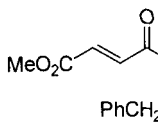
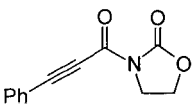
asymmetric induction have been reported in catalytic studies by various groups.[3] Traditionally, these compound are prepared by reaction of the *N*-lithiated 2-oxazolidinone with the α,β-unsaturated acid chloride.[4,5] Literature reports indicate low to moderate yields when unsubstituted 2-oxazolidinone 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 stochiometric 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 ($SiO_2$) 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.




| *N*-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 phenylpropiolic acid was obtained in only 26% yield. Significantly higher yields were obtained when fumaric acid monomethyl ester[7] 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 sofar.[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 $SiO_2$ (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 ($SiO_2$: 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 ($SiO_2$: 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 ($SiO_2$: 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 phenylpropiolic acid (0.73 g, 5 mmol) and following the general procedure, the mixture was refluxed for 4 h. Purification by column chromatography ($SiO_2$: 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, $CDCl_3$) δ 4.11 (t, $J$ = 8 Hz, 2H), 4.47 (t, $J$ = 8 Hz, 2H), 7.42 (m, 3H), 7.68 (m, 2H); $^{13}C$ NMR (50.3 MHz, $CDCl_3$) 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 $C_{12}H_9NO_3$: 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 ($SiO_2$: 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; $^1$H NMR (200 MHz, $CDCl_3$) 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). $^{13}$C NMR (50.3 MHz, $CDCl_3$) 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 $C_{10}H_{13}NO_5$: 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* ***9***:

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 ($SiO_2$: ethyl acetate/petroleum ether (40-60) 3/7) which afforded **9** 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; $[\alpha]_D^{RT}$ +69.5° (c 0.994, $CHCl_3$); $^1$H NMR (200 MHz, $CDCl_3$) 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); $^{13}$C NMR (50.3 MHz, $CDCl_3$) 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.

**Acknowledgement**

This research was financially supported by the Innovation Oriented Research Program (IOP) on Catalysis (no. 90031) of the Dutch Ministry of Economic Affairs.



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(Received in The Netherlands 19 June 1995)