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DIC-MEDIATED COUPLING OF CARBOXYLIC ACIDS TO (4R, 5S)-4-METHYL-5-PHENYL-2-OXAZOLIDINONE

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Abstract: The use of diisopropylcarbodiimide as an agent to effect the coupling of carboxylic acids to Evans' chiral auxiliary (4R, 5S)-4-methyl-5-phenyl-2-oxazolidinone provides the corresponding acyl derivatives in good yields.

The utility of chiral oxazolidinone auxiliaries developed by Evans[2-6] have become a staple in the synthetic organic chemist's arsenal for the production of enantiomerically enriched compounds. High degrees of relative asymmetric induction have been realized in α-alkylation,[2] α-hydroxylation,[3] aldol condensations,[4] acylations[5] and Diels-Alder reactions[6] of N-acylated chiral oxazolidinones. Production of the starting acyl oxazolidinone is typically accomplished through formation of the lithium derivative of the oxazolidinone followed by acylation with the acid chloride or acid anhydride derivative of the corresponding carboxylic acid.[2-5] Several alternative methods have been developed for efficient N-acylation of these oxazolidinones. These methods include derivatization of the oxazolidinone as its magnesium salt,[6] as its trimethylsilyl derivative

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Table 1

Entry	Substituents	Yield	Melting Point (lit.)[a]	$[\alpha]^D$ (lit.)[b]
1	R_1, R_2 = H	61%	105-106 °C	+14.5° (c 1.12)
2	R_1 = OCH_3; R_2 = H	77%	106-107 °C	+9.89° (c 1.17)
3	R_2 = OCH_3; R_1 = H	77%	125.5-126.5 °C	-11.9° (c 1.62)
4	R_1 = $N(CH_3)_2$; R_2 = H	72%	120-121 °C	+4.84° (c 1.22)

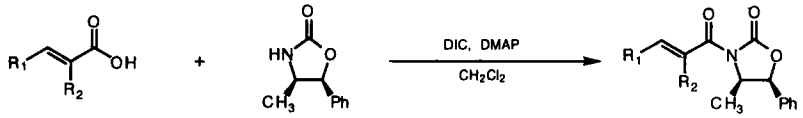
a) All melting points are uncorrected. b) Optical rotations were obtained as $CHCl_3$ solutions at the concentration given.

with excess acid chloride in the presence of copper salts,[7] the use of triethylamine and catalytic 4-N,N-dimethylaminopyridine (DMAP)[8] and the lithium chloride-initiated acylation.[9] However, each of these protocols require the intermediate preparation of the activated acylating agent prior to coupling to the oxazolidinone or oxazolidinone derivative.

We required several phenylacetic acid oxazolidinone derivatives (entries **1-4**, Table 1) in the preparation of mandelic acid derivatives.[3] We report here that coupling of the underivatized acid under the influence of diisopropylcarbodiimide and 1 equivalent of 4-N,N-dimethylaminopyridine (DMAP) proceeds smoothly with a series of substituted phenylacetic acids (Table 1).

It should be noted that addition of the carboxylic acids over shorter periods of time leads to isolation of appreciable amounts of the carboxylic acid anhydride, presumably arising from attack of an acid molecule on a DIC-activated acid molecule. Therefore, a slow introduction of the acid is required to suppress this anhydride formation. An alternative method to affect this transformation was also investigated wherein all of the requisite reagents were introduced at the

Table 2



Entry [a]	Substituents	Yield	Melting Point (lit.)[b]	[a]^D (lit.)[c]
1	R_1 = CH_3, R_2 = H	62%	64.5-65.5 °C (68.0-66.5 °C)[6] (63-65 °C)[7]	+43.5 ° (c 1.16) (+42°)[7] (+52.5°)[6]
2	R_1 = H, R_2 = CH_3	66%	80.5-81.5 °C (80.0-80.5 °C)[6]	+36.6 ° (c 1.17) (+36.8°)[6]
3	R_1 = Ph R_2 = H	84%	113-114° C (113-114° C)[7]	91.1 ° (c 1.90) (+94°)[7]

a) Physical data obtained for these compounds were identical in all respects with that obtained from literature reports (see reference 6). b) All melting points are uncorrected. c) Optical rotations were obtained as $CHCl_3$ solutions at the concentration given.

outset of the reaction into the reaction flask (with both catalytic and molar equivalents of DMAP present). To date these attempts have provided the target compounds in inferior yields.

We have also found that acryloyl derivatives can be efficiently prepared via this method. The following reactions were conducted on a 0.010 mole scale utilizing the reaction conditions described above to provide the α,β-unsaturated acylated (4R, 5S)-4-methyl-5-phenyl-2-oxazolidinone in the yields described in Table 2. One noted exception to this list of successful acylations is the coupling acrylic acid which proceeded in low yield (~20%).

This method adds another entry to the acylation protocols used to prepare these acylated chiral auxiliaries. This method circumvents the preparation of the labile acylating partner (either acid chloride or acid anhydride) and foregoes any modification of the oxazolidinone (generation of the lithium, magnesium or trimethylsilyl derivative). This procedure may prove especially useful on more sensitive carboxylic acid substrates. Current efforts involve further examination of the scope and limitations of this methodology involving acylation of other oxazolidinones as well as the production of N-acylated bornane-2,10-sultam systems.

Experimental

Infrared spectra were recorded on a Perkin Elmer 1600 or Spectrum BX spectrophotometer. Nuclear magnetic resonance spectra were recorded on a Varian Gemini 400 FT NMR instrument operating at 400 MHz (^{1}H) and 100 MHz (^{13}C). Chemical shifts for ^{1}H NMR spectra are reported in ppm relative to Me_4Si (δ 0.00) and chemical shifts for ^{13}C NMR spectra are reported in ppm relative to the center line of the triplet corresponding to $CDCl_3$ (δ 77.00). Splitting patterns for ^{1}H NMR spectral absorptions are recorded as follows: br, broad; s, singlet; d, doublet; dd, doublet of doublets; t, triplet; q, quartet; m, multiplet. Thin layer chromatography (TLC) was performed on Merck silica gel 60 pre-coated TLC plates (layer thickness 0.25mm) containing fluorescent indicator. Flash column chromatography was performed using Merck silica gel 60 (230-400 mesh) according to the method of Still.[10] Dichloromethane was distilled from CaH_2 immediately before used. All of the carboxylic acids used were purchased from Aldrich Chemical company and used without further purification and (4R,5S)-4-methyl-5-phenyl-2-oxazolidinone was obtained according to literature preparation.[11] All reactions were performed under a positive pressure of nitrogen in either flame-dried or oven-dried glassware. Optical rotations were recorded on an Autopol III Automatic Polarimeter, Rudolph Research, Flanders, New Jersey. Elemental analyses were performed by National Chemical Consulting, Inc., Tenafly, New Jersey.

General Experimental - Preparation of Entry 3 (Table 1)

To a flame dried 500 mL three-neck round bottom flask equipped with a magnetic stir bar and an equalizing addition funnel was added (4R, 5S)-4-methyl-5-phenyl-2-oxazolidinone (8.8 g, 50 mmol), 4-N,N-dimethylaminopyrine (6.10 g, 50 mmol) and diisopropylcarbodiimide (7.82 mL. 6.3 g, 50 mmol) in dry CH_2Cl_2 (75 mL). 2-Methoxyphenylacetic acid, dissolved in dry CH_2Cl_2 (125 mL), was added dropwise at room temperature via the addition funnel over 5 h. The reaction was stirred for an additional 24 h at room temperature and then was partitioned between water and CH_2Cl_2 (250 mL each). The aqueous layer was extracted with CH_2Cl_2 (2 x 250 mL) and the combined extracts were dried ($MgSO_4$). The solution was filtered and the solvent was evaporated to

give a solid residue which was chromatographed on silica gel (650 g) utilizing hexanes/ethyl acetate (3:1) as eluent to provide 12.5 g (77%) of a white crystalline solid. All known compounds (entry 1, Table 1, entries 1-4, Table 2) exhibited characteristic ^1H and ^{13}C NMR spectral properties consistent with their assigned structure and were identical to those reported.

(4R,5S)-3-(4-Methoxyphenyl)acetyl-4-methyl-5-phenyl-2-oxazolidinone (Entry 2, Table 1)

R_f = 0.45 (7:3 hexanes/ethyl acetate) IR (Nujol) 1775, 1700, 1614, 1513, 1247, 1247, 1028, 790, 765, 696 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.43-7.32 (m, 3H), 7.29-7.25 (m, 4H), 6.87 (d, 2H, J = 8.42 Hz), 5.62 (d, 1H, J = 7.33 Hz), 4.74 (dq, apparent pentet, 1H, J = 6.96, 6.59 Hz), 4.24 (nearly convergent AB_q, 2H, J_{AB} = 16.11 Hz, Δν = 14.91 Hz), 3.78 (s, 3H), 0.87 (d, 3H, J = 6.59 Hz) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz) δ 171.0, 158.6, 152.8, 133.2, 130.6, 128.6, 128.6, 125.6, 113.9, 78.9, 55.0, 40.9, 14.6 ppm. Anal. Calcd. for $C_{19}H_{19}NO_4$: C, 70.14; H, 5.89; N 4.30. Found: C, 70.40; H, 5.98; N, 4.23.

(4R,5S)-3-(2-Methoxyphenyl)acetyl-4-methyl-5-phenyl-2-oxazolidinone (Entry 3, Table 1)

R_f = 0.41 (3:1 hexanes/ethyl acetate) IR (Nujol) 1775, 1706, 1602, 1493, 1204, 756, 723, 692 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.43-7.32 (m, 3H), 7.30-7.22 (m, 3H), 7.16 (d, 1H, J = 7.32 Hz), 6.91 (t, 1H, J = 7.32), 6.87 (d, 1H, J = 8.06 Hz), 5.62 (d, 1H, J=7.32 Hz), 4.75 (dq, apparent pentent, 1H, J = 6.96, 6.59 Hz), 4.27 (AB_q, 2H, J_{AB} = 17.57, Δν = 35.42 Hz), 3.77 (s, 3H), 0.88 (d, 3H, J = 6.59 Hz) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.7, 157.4, 153.1, 133.4, 131.1, 128.59, 128.56, 125.6 122.8, 120.5, 110.5, 79.0, 55.5, 55.0, 37.5, 14.7 ppm. Anal. Calcd. for $C_{19}H_{19}NO_4$: C, 70.14; H, 5.89; N 4.30. Found: C, 70.24; H, 5.79; N, 4.39.

(4R,5S)-3-(4-Dimethylaminophenyl)acetyl-4-methyl-5-phenyl-2-oxazolidinone (Entry 4, Table 1)

R_f = 0.27 (7:3 hexanes/ethyl acetate) IR (Nujol) 3056, 3034, 1778, 1697, 1617, 1524, 1204,

1067, 1028, 806, 765, 734, 697 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.43-7.33 (m, 3H), 7.31-7.24 (m, 2H), 7.19 (d, 2H, J = 8.79 Hz), 6.70 (d, 2H, J = 8.79 Hz), 5.63 (d, 1H, J = 7.32 Hz), 4.74 (dq, apparent pentet, 1H, J = 6.96, 6.59 Hz), 4.20 (Abq, 2H, JAB = 15.74 Hz, Δν = 25.57 Hz), 2.93 (s, 6H), 0.88 (d, 3H, J = 6.59 Hz) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz) δ 171.6, 153.0, 149.8, 133.4, 130.3, 128.7, 128.7, 125.7, 121.4, 112.8, 79.0, 55.2, 40.92, 40.85, 14.8 ppm. Anal. Calcd. for $C_{20}H_{22}N_2O_3$: C, 70.99; H, 6.55; N 8.28. Found: C, 70.96; H, 6.40; N, 8.19.

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