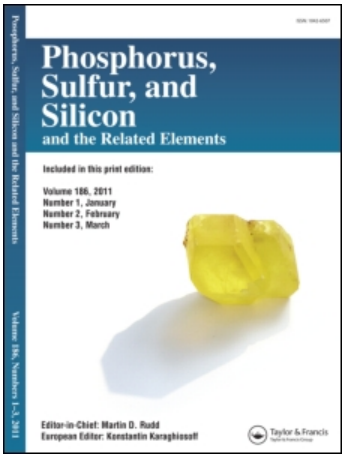

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SYNTHESIS OF THE CHIRAL α,β-UNSATURATED N-ACYL-OXAZOLIDIN-2-ONES BY WITTIG REACTION

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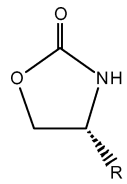
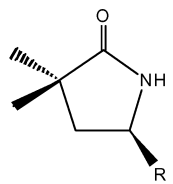
*A new, universal, and versatile method has been developed for the synthesis of the chiral α,β-unsaturated N-acyl-oxazolidin-2-ones **4** based on the Wittig reaction of the triphenylphosphonium salt **7** derived from the (R)-3-(2-Chloro-acetyl)-5,5-dimethyl-4-phenyl-oxazolidin-2-one **6**.*

Keywords: Chiral auxiliaries; oxazolidin-2-one; Wittig reaction

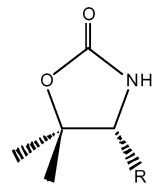
One of the most popular and reliable methods of asymmetric synthesis has proved to be via stoichiometric chiral auxiliaries.[1] The role of chiral auxiliaries in asymmetric synthesis for the preparation of homochiral molecules is now firmly established in organic synthesis.[2] In this area the versatile oxazolidin-2-one based chiral auxiliaries **1** developd by Evans et al. has been widely used for the preparation of highly functionalized homochiral molecules.[3] Recently Davies et al. reported the synthesis and application of Quats **2** and SuperQuats **3** which had the advantage of completely clean removal and recycling of the auxiliary while maintaining effective stereocontrol in a variety of reactions.[4]



Evans 1



Quats 2



SuperQuats 3

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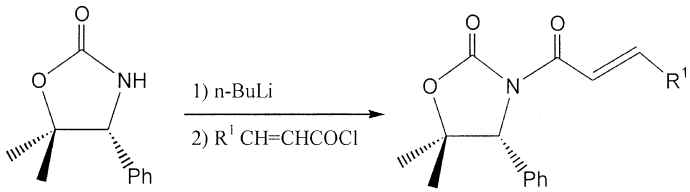
This methodology generally involves coupling the auxiliary to an acyl fragment which is then chemically derivatized to afford ideally a single diastereoisomer with one or more new stereocenters. Subsequent cleavage and purification of the transformed acyl fragment affords the desired homochiral product and the chiral auxiliary which may be recycled as required.[5]

The α,β-unsaturated N-acyl-oxazolidin-2-ones **5**, are important acceptor reactants in many type of transformations. The use of chiral auxiliary attached to an activated alkene in alkylation and conjugate additions, cyclization, and cycloaddition reactions of attached N-acyl moieties has been briefly described.[6] The most popular method of N-acylation of oxazolidin-2-one is the reaction of its Li salt (generated with BuLi at -78°C) with an acyl chloride (Scheme 1).[5b]



4 5 (a, b)

SCHEME 1

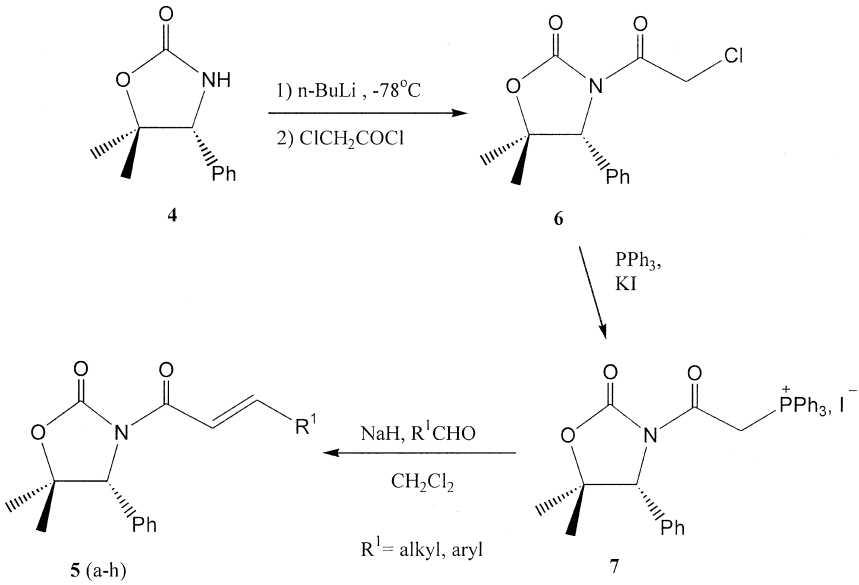
Generally, this procedure leads to N-acyl-oxazolidin-2-ones in good yields, but there are some limitations: 1) Acryloyl derivatives tend to polymerize under these conditions; 2) β,γ-unsaturated carboxylic-acid derivatives isomerize to the α,β-unsaturated compounds; 3) the method is not applicable to carboxylic acids, which do not form stable acid halides; 4) due to the basicity of the lithiated oxazolidinone group, substrates with relatively acidic H-atoms or with a propensity for elimination cannot be employed; and 5) the use of Ri at -78°C is not desirable from an economic point of view (at least in larg-scale application).[7,8] To circumvent these limitations, we report our results on the use of Wittig reaction as an alternative method for preparation of the α,β-unsaturated N-acyl-oxazolidin-2-ones.

RESULTS AND DISCUSSION

The (R)-4-phenyl-5,5-dimethyl oxazolidin-2-ones **4** is readily available from the ®-phenylglycine according to the Davies protocol.[9] N-Acylation of this auxiliary was achieved via deprotonation with BuLi followed

by quenching with chloroacetylchloride. This gave the ®-3-(2-chloroacetyl)-5,5-dimethyl-4-phenyl-oxazolidin-2-one **6** in 93% yield, which was then treated with PPh_3 in the presence of KI.

It is known that α-haloamides can be reduced in some cases when reacted with PPh_3.[10] The interaction of compound **6** with PPh_3 under heating in ethanolic or dioxane solutions proceeds with low yields and in some cases is accompanied by the formation of side products.[11] We succeeded in finding of reaction conditions which afford phosphonium salt **7** in 85% yield (Scheme 2).



SCHEME 2

The Wittig reaction is one of the most powerful methods for the preparation of carbon-carbon double bonds[12] and is used as a key step in this synthesis. The required alkylidenephosphorane was prepared by deprotonation of phosphonium salt **7**. We searched for a strong base that work efficiently and eliminate the hydrogen halide to produce the corresponding ylide.[13] When the mixture of benzaldehyde and phosphonium salt **7** treated either with DBU or with NaOH in aq. THF at 0°C gave only exocyclic cleavage and regeneration of auxiliary **4** in 95% yield. After testing several bases, it was found that NaH is a very effective base for the Wittig reaction and no exocyclic cleavage occurs in this process. Our results are shown in Table I.

TABLE I Products Obtained from the Wittig Reaction of Phosphonium Salt **7** with Several Aldehydes

Entry	Aldehyde	R^1	Yield **5**(%)[a,b]
a	Benzaldehyde	Ph	80
b	Acetaldehyde	Me	73
c	4-chlorobenzaldehyde	4-Cl-C_6H_5	82
d	4-nitrobenzaldehyde	4-NO2-C_6H_5	84
e	4-methylbenzaldehyde	4-Me-C_6H_5	77
f	4-methoxybenzaldehyde	4-OMe-C_6H_5	78
g	4-pyridinecarbaldehyde	4-Py	82
h	3-pyridinecarbaldehyde	3-Py	75

[a]All products were analyzed by comparison of their physical and spectroscopic data (^{1}H NMR, IR) with those of authentic samples.
[b]Yields are based on isolated products.

^{1}H NMR spectroscopic analysis of each of the products indicated that the generated ylide was particularly stable and yielded the E isomer of **5** as a major product.

In conclution the results presented in this communication show that the Wittig reaction is a very useful and effective method for the preparation of α,β-unsaturated N-acyl-oxazolidin-2-ones.

EXPERIMENTAL SECTION

Chemicals were purchased from Merck and Fluka. Melting points were measured on an Electrothermal 9100 apparatus. Elemental analyses were performed using a Heraeus CHN-O-Rapid analyzer. These results agreed favorably with the calculated values. IR spectra were determined on a Shimadzo IR-470 spectrometer. ^{1}H NMR spectra were recorded on a 500 MHz Bruker DRX-500 in $CDCl_3$ as solvent and TMS as internal standard. Preparative thin layer chromatography was prepared from Merck Kieselgel 60 H, F_{254}, Art No 7730. GC was carried out using Buck Scientific 910 (capillary column, MXT-5, 15 m). All solvents used were dried and distilled according to standard procedures.

General Procedure for the Synthesis of ®-3-(2-Chloroacetyl)-5,5-dimethyl-4-phenyl-oxazolidin-2-one 6

n-Buthyllithium (1.3 M, 38.8 mL, 52 mmol) was added dropwise via syringe to a stirred solution of the auxiliary **4** (9.5 g, 50 mmol) in THF (300 mL) at −78°C under nitrogen atmosphere and the mixture allowed to stir for 15 min. Chloroacetylchloride (5.3 mL, 56 mmol) was added at

−78°C and the reaction stirred at this temperature for 30 min, then allowed to warm to room temperature over 2 h. Saturated NH_4Cl (aq.) was added and the reaction extracted with ethyl acetate (3×). The combined organic extracts were washed with $NaHCO_3$ (aq.), brine, dried ($MgSO_4$), and evaporated to give the title compound **6** as a white solid, (12.4 g, 93%, m.p. = 123–125°C), (Found: C, 58.25; H, 5.33; Cl, 13.15; N, 5.33 $C_{13}H_{14}ClNO_3$ requires C, 58.32; H, 5.27; Cl, 13.24; N, 5.23%), IR (film, cm^{-1}); 1780, 1720, 1360, 1340, 700, $[\alpha]_D^{26} = +45.9$ (c 1 in $CHCl_3$),^{1}H NMR ($CDCl_3$, δ); 1.05 (s, 3H), 1.67 (s, 3H), 4.21 (s, 2H), 5.30 (s, 1H), 7.10–7.30 (m, 5H).

General Procedure for the Synthesis of Phosphonium Salt 7

KI (7.64 g, 46 mmol) and Ph_3P were added to a solution of **6** (10.70 g, 40 mmol) in DMF at 0°C. The reaction mixture was kept at 0–7°C for 2–3 days and then poured into a 30% aqueous solution of KI (100 mL) and then kept at the same temperature for 8 h. After adding water (100 mL) the residue was kept until crystallization occurred. The product was filtered off, recrystallized from chloroform-ether, and dried over P_4O_{10} to give the title compound **7** as a solid, (26.40 g, 85%, m.p. > 300°C), (Found: C, 59.85; H, 4.76; N, 2.30 $C_{31}H_{29}INO_3P$ requires C, 59.92; H, 4.70; N, 2.25%), IR (film, cm^{-1}); 3010, 1785, 1722, 1364, 1347, ^{1}H NMR ($CDCl_3$, δ); 1.11 (s, 3H), 1.70 (s, 3H), 2.28 (s, 2H), 5.43 (s, 1H), 7.10–7.64 (m, 15H).

General Procedure for the Wittig Reactions

To a stirred solution of NaH (0.12 g, 5 mmol, prepared from 0.22g of sodium hydride mineral oil dispersion by several washings with dry hexane) in CH_2Cl_2 (15 mL) the phosphonium salt **7** (3.1 g, 5 mmol) was added at room temperature. After stirring for 30 min, a solution of the aldehyde (5 mmol) in CH_2Cl_2 (10 mL) was added to the resulting red ylide solution. Stirring was continued for 12 h at the same temperature, and then the mixture poured into large excess of ice-water mixture and extracted with ether. The ethereal layer was washed with water and brine, dried over $MgSO_4$, and evaporated in vacuo to provide a crude product. This product was purified by column chromatography (petroleum ether/ethyl acetate 3:2) to give adducts in 73–84% yield. The isolated yield for each product is given in parentheses and IR, ^{1}H NMR data for the compounds **5a–h** are given below.

5a: white solid (80%, m.p. 149–150°C), (Found: C, 74.80; H, 5.93; N, 4.33 $C_{20}H_{19}NO_3$ requires C, 74.75; H, 5.97; N, 4.36%), IR (film, cm^{-1});

1771, 1682, 1615, $[\alpha]_D^{26} = +25.9^\circ$ (c 1 in $CHCl_3$), ^{1}H NMR ($CDCl_3$, δ); 1.04 (s, 3H), 1.65 (s, 3H), 5.24 (s, 1H), 7.20–7.64 (m, 10H), 7.80 (d, J15.8, 1H), 8.07 (d, J15.8, 1H).

5b: white solid (73%, m.p. 104–105°C), (Found: C, 69.39; H, 6.73; N, 5.33 $C_{15}H_{17}NO_3$ requires C, 69.48; H, 6.61; N, 5.40%), IR (film, cm^{-1}); 1769, 1687, 1618, $[\alpha]_D^{26} = -82.5^\circ$ (c 1 in $CHCl_3$), ^{1}H NMR ($CDCl_3$, δ); 0.99 (s, 3H), 1.60 (s, 3H), 1.93 (d, J5.4, 3H), 5.14 (s, 1H), 7.02–7.40 (m, 7H).

5c: white solid (82%, m.p. 165–166°C), (Found: C, 67.45; H, 5.13; N, 3.88 $C_{20}H_{18}ClNO_3$ requires C, 67.51; H, 5.10; N, 3.94%), IR (film, cm^{-1}); 1776, 1687, 1619, $[\alpha]_D^{26} = +36.8^\circ$ (c 1 in $CHCl_3$), ^{1}H NMR ($CDCl_3$, δ); 1.06 (s, 3H), 1.68 (s, 3H), 5.28 (s, 1H), 7.10–7.64 (m, 9H), 7.86 (d, J15.9, 1H), 8.16 (d, J15.9, 1H).

5d: pale yellow solid (84%, m.p. 173–175°C), (Found: C, 65.58; H, 4.93; N, 7.72 $C_{20}H_{18}N_2O_5$ requires C, 65.57; H, 4.95; N, 7.65%), IR (film, cm^{-1}); 1780, 1690, 1620, $[\alpha]_D^{26} = -45.9$ (c 1 in $CHCl_3$), ^{1}H NMR ($CDCl_3$, δ); 1.08 (s, 3H), 1.70 (s, 3H), 5.30 (s, 1H), 7.10–8.15 (m, 11H).

5e: white solid (77%, m.p. 141–142°C), (Found: C, 75.15; H, 6.38; N, 4.23 $C_{21}H_{21}NO_3$ requires C, 75.20; H, 6.31; N, 4.18%), IR (film, cm^{-1}); 1770, 1680, 1613, $[\alpha]_D^{26} = +35.4^\circ$ (c 1 in $CHCl_3$), ^{1}H NMR ($CDCl_3$, δ); 1.03 (s, 3H), 1.64 (s, 3H), 2.37 (s, 3H), 5.23 (s, 1H), 7.20–7.66 (m, 9H), 7.78 (d, J15.6, 1H), 8.03 (d, J15.6, 1H).

5f: white solid (78%, m.p. 157–158°C), (Found: C, 71.80; H, 5.97; N, 4.15 $C_{21}H_{21}NO_4$ requires C, 71.78; H, 6.02; N, 3.99%), IR (film, cm^{-1}); 1777, 1685, 1619, $[\alpha]_D^{26} = +55.9^\circ$ (c 1 in $CHCl_3$), ^{1}H NMR ($CDCl_3$, δ); 1.07 (s, 3H), 1.67 (s, 3H), 3.70 (s, 3H), 5.28 (s, 1H), 7.21–7.65 (m, 9H), 7.84 (d, J15.8, 1H), 8.11 (d, J15.8, 1H).

5g: pale yellow solid (82%, m.p. 163–165°C), (Found: C, 70.82; H, 5.72; N, 8.55 $C_{19}H_{18}N_2O_3$ requires C, 70.79; H, 5.63; N, 8.69%), IR (film, cm^{-1}); 1778, 1689, 1621, $[\alpha]_D^{26} = -64.6^\circ$ (c 1 in $CHCl_3$), ^{1}H NMR ($CDCl_3$, δ); 1.07 (s, 3H), 1.72 (s, 3H), 5.33 (s, 1H), 7.10–8.61 (m, 11H).

5h: pale yellow solid (75%, m.p. 143–145°C), (Found: C, 70.83; H, 5.71; N, 8.51 $C_{19}H_{18}N_2O_3$ requires C, 70.79; H, 5.63; N, 8.69%), IR (film, cm^{-1}); 1777, 1690, 1625 $[\alpha]_D^{26} = -56.6^\circ$ (c 1 in $CHCl_3$), ^{1}H NMR($CDCl_3$, δ); 1.06 (s, 3H), 1.74 (s, 3H), 5.35 (s, 1H), 7.10–8.60 (m, 11H).

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