A One-Pot Synthesis of 2-Aryl-4,5-*anti*-diphenyloxazolines

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Received 10 July 2009

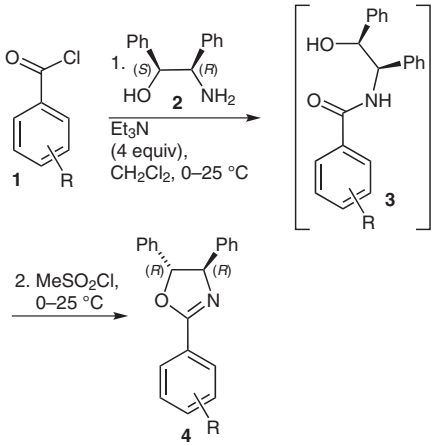
Abstract: A one-pot procedure for the synthesis of oxazolines was developed. An amino alcohol was coupled with benzoyl chlorides in the presence of triethylamine to produce a β-hydroxyamide. Direct treatment with methanesulfonyl chloride forms oxazolines in good yields.

Key words: oxazoline, arenes, heterocycle substitutions, auxiliary

Oxazolines have been used to direct a broad range of asymmetric reactions[1] – for instance, as features of chiral ligands for asymmetric catalysis[2] or as chiral auxiliaries for diastereoselective couplings, substitution[3] or dearomatising additions.[4] The oxazoline ring's resistance to hydrolysis or attack by nucleophiles, bases or radicals confers applicability to a wide variety of reaction conditions – the oxazoline ring itself reacts only with strong Brønsted acids or powerful electrophiles.[1]

2-Aryl oxazolines have been made[1,5] principally (a) by reaction of an amino alcohol with an activated benzoic acid derivative,[6] (b) by rearrangement of an N-acyl aziridine,[7] or (c) by formation of an amide by acylation of an amino alcohol, followed by cyclisation with invertive displacement of the hydroxyl group (for example, Scheme 1).[8–10] Epimerisation or racemisation by non-stereospecific displacement is a danger in the synthesis of oxazolines bearing a stereogenic centre at the 5-position (adjacent to oxygen).

Following our recent demonstration of the utility of 4,5-*anti*-diphenyloxazolines **4** for the activation of benzenoid rings towards dearomatising attack by organolithiums,[4b] an extension of the work by Meyers et al. on naphthyl and pyridyloxazolines,[1,4a] we sought a reliable, stereospecific route to enantiomerically pure oxazolines **4** bearing a range of substituents R. The ready availability of amino alcohol **2** in enantiomerically pure form encouraged us to employ strategy (c), since invertive displacement provides the required *anti* relative stereochemistry. Linclau[9] used *N*,*N*′-diisopropylcarbodiimide and $Cu(OTf)_2$ to cyclise *N*-(2-hydroxyethyl)amides to oxazolines, however, this reaction required either reflux or microwave irradiation, and the presence of substituents α- to the oxygen gave reduced yields. Du[10] showed that both *syn*- and *anti*-4,5-diphenyloxazolines **4** can be formed by substitution of the hydroxyl group of amides **3** by mesylation followed by reflux with NaOH in methanol. Inversion adjacent to oxygen was observed as expected for an S_N2 displacement.



Scheme 1 One-pot oxazoline synthesis

However, we found that isolation of the intermediate hydroxyamides **3** is complicated by their insolubility in a variety of solvents. It was envisaged that a one-pot synthesis of oxazolines direct from the amino alcohol **2** and acyl chloride **1** would avoid the need for isolation of amides **3** and could provide a general, simple and scalable procedure for oxazoline synthesis.[11]

Four equivalents of triethylamine were used both to effect amide formation and to facilitate the subsequent hydroxyl substitution – by increasing the amount of base we avoided the need for a reflux step. The cyclisation itself was promoted by methanesulfonyl chloride. The result is an uncomplicated stereoselective one-pot synthesis of 2-aryl oxazolines, which is applicable to a range of substituted products as shown in Table 1. The presence of electron-withdrawing and electron-donating groups was well tolerated, and yields were generally good to excellent. In some cases, the carboxylic acids themselves were used, the acyl chlorides being formed with thionyl chloride in situ prior to addition of the amino alcohol and triethylamine. The synthesis of **4b** was successfully carried out on a 10 g scale.

The method gave lower yields of 2-oxazolines when electron-withdrawing substituents were present in the *ortho*-position, presumably due to the inductive decrease in the nucleophilicity of the amide C=O bond, which reduces the rate of cyclisation. However, alternative methods exist for the efficient stereoselective synthesis of these compounds, such as rearrangement of the corresponding *N*-acyl aziridine.[4b,7]

SYNLETT 2009, No. 17, pp 2836–2838
Advanced online publication: 24.09.2009
DOI: 10.1055/s-0029-1217985; Art ID: D18209ST

Table 1 Synthesis of Oxazolines by the One-Pot Method Shown in Scheme 1

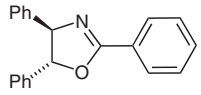
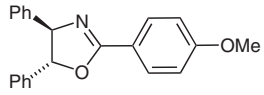
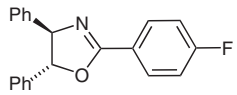
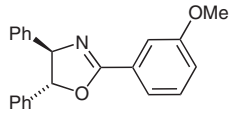
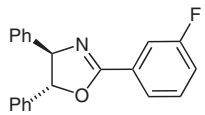
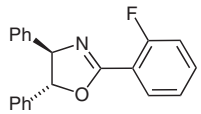
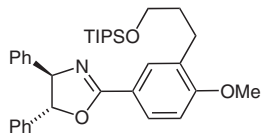
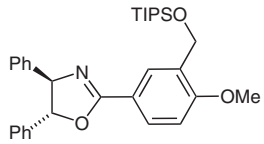
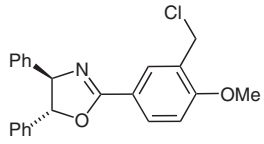
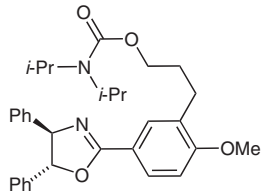
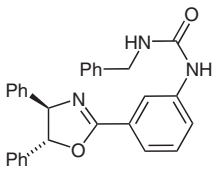
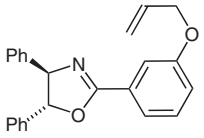
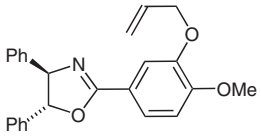
Entry	Oxazoline **4**	Yield from **1** (%)
1	 **4a**	71
2	 **4b**	89[a]
3	 **4c**	90
4	 **4d**	88
5	 **4e**	80
6	 **4f**	46
7	 **4g**	88[b]
8	 **4h**	67[b]
9	 **4i**	67[b]
10	 **4j**	90[b]

Table 1 Synthesis of Oxazolines by the One-Pot Method Shown in Scheme 1 (continued)

Entry	Oxazoline **4**	Yield from **1** (%)
11	 **4k**	67[b]
12	 **4l**	66[b]
13	 **4m**	20[b]

[a] On a 10 g scale.
[b] Yield from carboxylic acid, forming acyl chloride in situ by reflux with thionyl chloride.

The one-pot procedure forms, to the limit of detection, only the *anti*-diphenyloxazoline product of inversion at the oxazoline C-5 position.[12]

In summary, we have developed an operationally simple one-pot synthesis of enantiomerically pure 2-aryl-4,5-*anti*-diphenyl oxazolines from the corresponding commercially available amino alcohol **2**.[13,14]

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

Acknowledgment

We are grateful for studentship support from the EPSRC and GlaxoSmithKline, and we thank Dr. Diane Coe for valuable discussions.

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(12) The *syn*- and *anti*-diphenyloxazolines display characteristic differences in the chemical shifts of the benzylic protons α to N and O, see: Parris, S. *PhD Thesis*; University of Manchester: **2008**. No *syn*-diphenyloxazoline was identified in the ^{1}H NMR spectra of the crude products.

(13) (4*R*,5*R*)-2,4,5-Triphenyloxazoline (**4a**): Benzoyl chloride (0.59 mL, 1.1 equiv) was added dropwise over a period of 5 min to a stirred solution of the amine [(1*R*,2*S*)-2-amino-1,2-diphenylethanol, 1 g, 1.0 equiv] in CH_2Cl_2 (100 mL) and Et_3N (2.6mL, 4 equiv) at 0 °C under a nitrogen atmosphere. The solution was stirred for 16 h. The white suspension was cooled to 0 °C and methanesulfonyl chloride (0.54 mL, 1.5 equiv) was added dropwise over 5 min (the solution clarified as the oxazoline formed). The reaction was monitored by TLC and quenched with excess aqueous NH_4Cl after all the amide had been consumed. The solution was partitioned between CH_2Cl_2 and aqueous NH_4Cl and extracted with CH_2Cl_2. The organic layers were washed with aqueous sodium hydrogen carbonate and brine. The solution was dried with $MgSO_4$ and concentrated under reduced pressure, leaving approximately 5 mL solvent to load the crude reaction mixture onto silica gel. Purification using flash chromatography (10% EtOAc in petroleum ether) gave oxazoline **4a** in 71% yield. Mp 116 °C (EtOAc–Petrol) (Lit.[15] 93–95 °C, Et_2O); $[\alpha]_D^{22}$ +17.6 (*c* 1, $CHCl_3$); 1H NMR ($CDCl_3$, 300 MHz): δ = 8.07 (d, *J* = 8 Hz, 2 H, CH C-2, C-6), 7.32 (m, 13 H, Ar), 5.35 (d, *J* = 8 Hz, CH-5′), 5.17 (d, *J* = 8 Hz, 1 H, CH-4′); 13C NMR ($CDCl_3$, 75.5 MHz): δ = 164.1, 141.9, 140.5, 131.8, 128.9, 128.9, 128.7, 128.5, 128.4, 127.8, 127.4, 126.7, 125.8, 89.0, 78.0.

(14) (*4R*,*5R*)-2-(4′-Methoxy-3′-triisopropylsilyloxymethyl)-phenyl-4,5-diphenyloxazoline (**4h**): 4-Methoxy-3-(triisopropylsilyloxymethyl)benzoic acid (0.45 g, 1.3 mmol) was stirred in thionyl chloride–CH_2Cl_2 (1:1 mL) until IR indicated complete conversion into the acyl chloride. The solvent and thionyl chloride was removed under reduced pressure. The crude benzoyl chloride (1.3 mmol) in CH_2Cl_2 (2 mL) was then added dropwise to a stirred solution of the (1*R*,2*S*)-2-amino-1,2-diphenylethanol (0.277 g, 1.3 mmol) in CH_2Cl_2 (15 mL) and Et_3N (0.725 mL, 5.2 mmol) at 0 °C under nitrogen. The reaction mixture was warmed to r.t. and stirred until TLC indicated the reaction was complete. Methane sulfonyl chloride (0.151 mL, 1.95 mmol) was added and the solution was stirred until no amide remained by TLC. Saturated NH_4Cl (5 mL) was added and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL), the combined organic extracts were dried ($NaSO_4$) and the solvent was removed under reduced pressure to give the crude oxazoline. Purification by flash column chromatography (Petrol–EtOAc, 8:2) gave oxazoline **4h** (0.49 g, 67%) as a yellow gum. R_f = 0.73 (Petrol–EtOAc, 2:1); $[\alpha]_D^{19.5}$ –48.2 (*c* 1.025, $CDCl_3$); MS (ES^+): *m*/*z* (%) = 516.3 (100) [MH^+]; HRMS: *m*/*z* [MH^+] calcd for $C_{32}H_{42}O_3NSi$: 516.2928; found: 516.2931; IR:(film): 2945, 2865, 1647, 1497, 1259 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 8.25 (s, 1 H, C-2), 7.96 (dd, *J* = 2, 9 Hz, 1 H, C-5), 6.79 (d, *J* = 9 Hz, 1 H, C-4), 7.31–7.17 (m, 10 H, ArH), 5.31 (d, *J* = 7 Hz, 1 H, CH-5′), 5.1 (d, *J* = 7 Hz, 1 H, CH-4′), 4.78 (s, 2 H, ArCH_2), 3.76 (s, 3 H, OCH_3), 1.07 [m, 21 H, Si(*i*-Pr)$_3$]; ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 163.3, 157.8, 141.5, 139.9, 129.2, 127.8, 127.1, 126.6, 126.6, 125.8, 124.4, 118.8, 108.4, 87.5, 77.9, 59.2, 54.4, 17.0, 16.7, 13.0, 11.5, 11.3, 11.1, 10.7.

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