Tetrahedron Letters 52 (2011) 5120–5123

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

A general and convenient route to oxazolyl ligands

Helen C. Aspinall *, Oliver Beckingham, Michael D. Farrar, Nicholas Greeves *, Christopher D. Thomas

Department of Chemistry, University of Liverpool, Crown Street, Liverpool L69 7ZD, UK

ARTICLE INFO

Article history:
Received 24 May 2011
Revised 1 July 2011
Accepted 15 July 2011
Available online 23 July 2011

Keywords:
Oxazolyl ligand
Oxazoline
Chiral ligand
Oxazolyl phenol

ABSTRACT

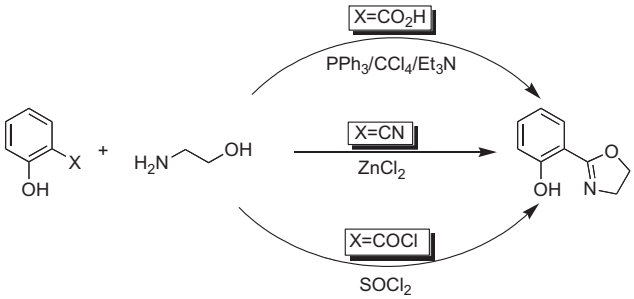
A diverse range of chiral and achiral oxazolyl ligands, which have many applications including catalysis and luminescent devices, are synthesized simply in three steps from readily available and inexpensive phenol and amino alcohol starting materials. The method can be applied to ligands with electron-donating/-withdrawing and sterically demanding/undemanding substituents, and can conveniently be scaled up to >25 g of product.

The oxazolyl group, readily derived from amino alcohols, has long been recognized as a valuable auxiliary in catalysis, and there is a substantial chemistry built on oxazolylphosphine ligands and their applications in asymmetric catalysis.[1] These tertiary phosphine ligands are excellent donors for soft metal centers, but are not ideal for harder Lewis acids such as alkaline earth, rare earth or higher oxidation state transition metals. For these harder Lewis acids the 2-oxazolylphenol ligand is much more suitable, having two hard donor atoms: the phenolic O atom and the imine N atom. Interest in complexes of 2-oxazolylphenols is growing, and there are recent reports of applications in luminescent devices such as OLEDs,[2] 1-D magnetic materials,[3] and coordination polymers,[4] as well as in enantioselective catalysis.[5]

Synthesis of an oxazolyl ring can be achieved by the cyclization reaction of an aminoalcohol with either a nitrile, an acid chloride or a carboxylic acid, and all of these methods have been used in the synthesis of 2-oxazolylphenols (Scheme 1).[6–8] The reaction with a carboxylic acid (the Appel reaction) produces large amounts of Ph_3PO as a by-product; this is extremely troublesome to separate, particularly in large-scale reactions, and can result in low isolated yields. The reaction with acid chlorides can be unreliable, and requires carefully purified $SOCl_2$. The $ZnCl_2$-catalyzed cyclization with a nitrile is undoubtedly the most straightforward, effective and convenient method. However, relatively few 2-cyanophenols are commercially available at low cost, and published synthetic routes to these compounds generally involve cyanation of the corresponding phenol with CuCN (the Rosenmund–von Braun reaction).[9] The toxicity of CuCN makes this procedure undesirable, and a further problem is that the nitrile products frequently form complexes with Cu(I), making them difficult to isolate.

Synthesis of oxazolines from aldehydes (Scheme 2) has been reported more recently; this involves the preparation of an oxazolidine followed by oxidation with a strong halogen-based oxidizing agent such as NBS,[10] I_2[11] or pyridinium hydrobromide perbromide.[12] This method is reasonably successful for a broad range of aromatic aldehydes, however, it is unsuitable for salicylaldehydes as they undergo a rapid electrophilic aromatic halogenation with the oxidizing agent. We investigated the use of non-halogenating oxidizing agents such as $FeCl_3$ and (diacetoxyiodo)benzene, but without success.

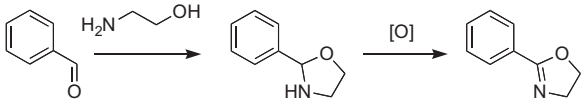
We have therefore developed an adaptation of this process (Scheme 3) where, instead of coupling with the amino alcohol followed by oxidation, the salicylaldehyde is oxidized to a nitrile, followed by cyclization with the amino alcohol. We were primarily interested in the synthesis of oxazolylphenols, but because of the ready availability of thiophene- and furan-2-carbaldehydes (Ta-



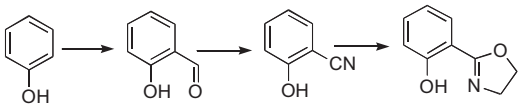
Scheme 1. Synthetic routes to 2-oxazolylphenols.

* Corresponding authors.
E-mail addresses: hca@liv.ac.uk (H.C. Aspinall), ngreeves@liv.ac.uk (N. Greeves).

0040-4039/$ - see front matter © 2011 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2011.07.070



Scheme 2. Synthesis of oxazolines from aldehydes.

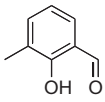
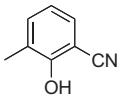
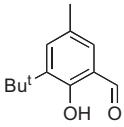
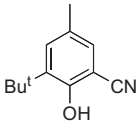
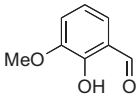
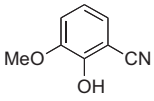
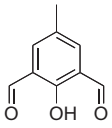
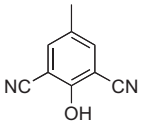
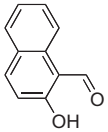
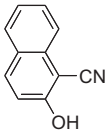


Scheme 3. Synthetic route to oxazolylphenols.

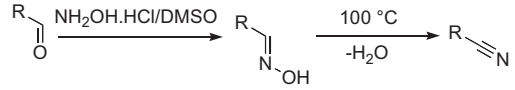
ble 1, **6A**, **7A**) we also applied our methods to these heterocyclic starting materials. Chiral thienyl oxazolines such as **6C** have been used with Pd in enantioselective catalysis,[13] and as intermediates in the synthesis of HetPHOX ligands for the use in the enantioselective Heck reaction.[14] Achiral analogues have been used as precursors to carbene ligands for Au.[15]

Some of the aldehydes (Table 1) are commercially available at low cost, however where this is not the case, there are several options for the formylation step. For the compounds **1A** and **2A** we found Casiraghi's $SnCl_4$-catalyzed method[16] to be the most effective as it gave solely *ortho*-formylated products, avoiding the need for *para*-blocked substrates, and thus expanding the range of commercially available starting materials. It also has the advantages of

Table 1
Synthesis of nitriles

	A Aldehyde	B Nitrile	Isolated yield of nitrile (%)
1[a]			73
2[a]			56
3[b]			91
4[c]			64
5[d]			98
6[b]			73
7[b]			35

[a] Aldehyde synthesized by $SnCl_4$-catalyzed formylation.
[b] Aldehyde commercially available.
[c] Di-aldehyde synthesized by the Duff reaction.
[d] Aldehyde synthesized by Reimer–Tiemann reaction.



Scheme 4. Synthesis of nitriles.

not requiring rigorously anhydrous conditions[17] or the use of pyrophoric reagents.[18] The Casiraghi method does not work for deactivated phenols and so diformyl compound **4A** was synthesized by the Duff reaction,[19] and the naphthyl compound **5A** was synthesized by the Reimer–Tiemann reaction.[20] We found that all of the formyl compounds (apart from **3A**) could be used in the next stage of the synthesis without purification.

Conversion of formyl compounds into the corresponding nitriles proceeds via the aldoxime which dehydrates on heating (Scheme 4). Like the formylation step, this process is robust, converting a broad range of aldehydes in good to excellent yields, on a scale of up to 20 g of the product.[21] We found that phenols required a longer reaction time than expected from the literature[22] (up to 6 h); this could be due to stabilization of the oxime by intramolecular H-bonding with the phenolic OH. All the nitriles were purified simply by recrystallization (apart from **6B** and **7B**, which were purified by distillation).

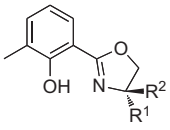
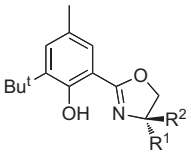
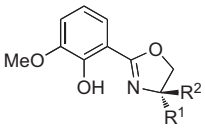
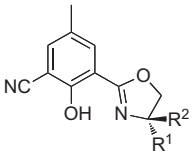
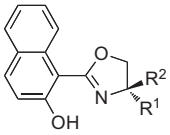
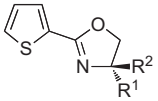
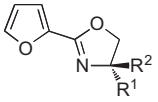
The final step in the synthesis of the oxazolyl compounds was the cyclization reaction of the nitrile with an amino alcohol. For all of the nitriles **1B**–**7B** we used both a chiral aminoalcohol (valinol) and an achiral aminoalcohol (2-amino-2-methylpropanol) with comparable results, and on a scale of up to 25 g of the product. For compounds **1C/D**–**5C/D** (Table 2) this process was achieved under anhydrous conditions with a $ZnCl_2$-catalyzed reaction in refluxing chlorobenzene.[23] Pure products were isolated by column chromatography.

Although cyclization of the thiophene and furan nitriles **6B** and **7B** with amino alcohols proceeds by the $ZnCl_2$-catalyzed route, the high volatility of the oxazolyl compounds **6C/D** and **7C/D** makes them difficult to separate effectively from the high-boiling chlorobenzene solvent. For these compounds we therefore used a method developed by Gomez et al.,[24] which was carried out under basic conditions (0.1 equiv K_2CO_3) in a solvent mixture of ethylene glycol and glycerol. On quenching with aqueous NH_4Cl, the polar ethylene glycol/glycerol solvent mixture dissolves in the aqueous phase and the product is obtained easily and in very high yield by the extraction with Et_2O.[25]

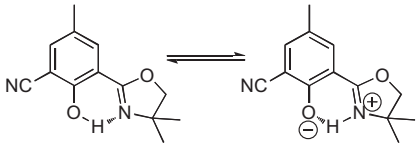
Given the convenience of the Gomez method for the cyclization reaction we investigated its application to a phenol substrate: nitrile compound **3B**. However, rather poor conversions were achieved after 72 h at reflux temperature in the presence of either 0.1 or 1.0 equiv of K_2CO_3. We believe that this is due to deprotonation of the phenol, resulting in the deactivation of the nitrile carbon toward nucleophilic attack by the amino alcohol. This method applied to bis-nitrile **4B** resulted in 45% of conversion into mono-oxazoline after 36 h at reflux.

We had originally hoped that the bis-nitrile compound **4B** could be converted into a bis-oxazolylphenol, and we attempted the cyclization reaction with 2 equiv of aminoalcohol and 20 mol % of $ZnCl_2$. However, this resulted only in the formation of the mono-oxazolyl compounds **4C**/**D**. We considered the possibility that this might be due to Zn being rendered catalytically inactive by forming a complex with the cyclized product, and so we increased the loading of $ZnCl_2$ to 100 mol %. This resulted in an increased yield of mono-oxazolyl product, but still no bis-oxazolyl product. The reason for this failure to form the bis-oxazoline became apparent from the ^1H NMR spectra of mono-cyclized products: the phenolic OH groups have chemical shifts of δ 13.27 (**4C**) and δ 13.10 (**4D**) indicating very strong H-bonding, and the possibility of a zwitterionic

Table 2
Conversion of nitriles into oxazolyl compounds

		C R^1 = ^{i}Pr; R^2 = H Isolated yield (%)	D R^1 = R^2 = Me Isolated yield (%)
1		78	60
2		58	75
3		31	49
4		71	77
5		48	37
6		93	93
7		82	85

structure as shown below. Delocalization of the negative charge on the phenol would render the second nitrile much less susceptible to nucleophilic attack.



In conclusion, we have developed a convenient synthesis of a diverse range of oxazolyl ligands, both chiral and achiral. Our method uses cheap and readily available starting materials and we have shown that it can be applied equally successfully to ligands with electron-donating/-withdrawing and sterically demanding/undemanding substituents. All of the reactions are homogeneous and can be scaled-up without difficulty: we have routinely prepared oxazolyl compounds in quantities of >25 g. We believe that our method will be particularly useful for oxazolylphenols for which there has previously been no general applicable route.

Acknowledgment

We thank EPSRC for support (studentship to O.B.).

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.07.070.

References and notes

1. Helmchen, G.; Pfaltz, A. *Acc. Chem. Res.* **2000**, *33*, 336.
2. (a) Katkova, M. A.; Balashova, T. V.; Ilichev, V. A.; Konev, A. N.; Isachenkov, N. A.; Fukin, G. Y.; Ketkov, S. Y.; Bochkarev, M. N. *Inorg. Chem.* **2010**, *49*, 5094; (b) Rai, V. K.; Srivastava, R.; Kamalasanan, M. N. *Synth. Met.* **2009**, *159*, 234; (c) Kim, D.-E.; Kim, W.-S.; Kim, B.-S.; Lee, B.-J.; Kwon, Y.-S. *Thin Solid Films* **2008**, *516*, 3637.
3. Zhang, Y.; Wang, X. T.; Zhang, X. M.; Liu, T. F.; Xu, W. G.; Gao, S. *Inorg. Chem.* **2010**, *49*, 5868.
4. Zhang, J.; Gao, S.; Che, C.-M. *Eur. J. Inorg. Chem.* **2004**, 956.
5. (a) Allen, L. E. N.; Clarkson, G. J.; Fox, D. J.; Gott, A. L.; Scott, P. *J. Am. Chem. Soc.* **2010**, *132*, 15308; (b) Corbin, R. A.; Ison, E. A.; Abu-Omar, M. M. *Dalton Trans.* **2009**, 2850; (c) Braun, I.; Rudroff, F.; Mihovilovic, M. D.; Bach, T. *Angew. Chem., Int. Ed.* **2006**, *45*, 5541.
6. Peterson, T.; Falk, K.-E.; Leong, S. A.; Klein, M. P.; Neilands, J. B. *J. Am. Chem. Soc.* **1980**, *102*, 7715.
7. Scheurer, A.; Mosset, P.; Bauer, W.; Saalfrank, R. W. *Eur. J. Org. Chem.* **2001**, 3067.
8. Mugesh, G.; Singh, H. B.; Butcher, R. J. *Eur. J. Inorg. Chem.* **2001**, 669.
9. Ellis, G. P.; Romney-Alexander, T. M. *Chem. Rev.* **1987**, *87*, 779.
10. Schwekendick, K.; Glorius, F. *Synthesis* **2006**, 2996.
11. Ishihara, M.; Togo, H. *Tetrahedron* **2007**, *63*, 1474.
12. Sayama, S. *Synlett* **2006**, 1479.
13. Frost, C. G.; Williams, J. M. J. *Tetrahedron Lett.* **1993**, *34*, 2015.
14. Fitzpatrick, M. O.; Muller-Bunz, H.; Guiry, P. J. *Eur. J. Org. Chem.* **2009**, 1889.
15. Desmet, M.; Raubenheimer, H. G.; Kruger, G. J. *Organometallics* **1997**, *16*, 3324.
16. Casiraghi, G.; Casnati, G.; Puglia, G.; Sartori, G.; Terenghi, G. *J. Chem. Soc., Perkin Trans. 1* **1980**, 1862.
17. Hansen, T. V.; Skattebøl, L. S. *Org. Synth.* **2005**, *82*, 64.
18. Casiraghi, G.; Casnati, G.; Cornia, M.; Pochini, A.; Puglia, G.; Sartori, G.; Ungaro, R. *J. Chem. Soc., Perkin Trans. 1* **1978**, 318.
19. Lindoy, L. F.; Meehan, G. V.; Svenstrup, N. *Synthesis* **1998**, 1029.
20. Kalechits, G. V.; Osinovskii, A. G.; Matveenko, Y. V.; Ol'khovik, V. K. *Russ. J. Appl. Chem.* **2002**, *75*, 962.
21. 2-*Hydroxy-3-methylbenzonitrile* (**1B**): Salicylaldehyde (**1A**) (28.86 g, 1 equiv) was dissolved in DMSO (200 ml) to give an orange solution. Hydroxylamine hydrochloride (29.31 g, 2.2 equiv) was charged and the mixturewas stirred at rt for 20 min to give a yellow solution, this was heated to 100 °C for 6 h before being allowed to cool. The reaction was quenched into H_2O (300 ml) and extracted with Et_2O (5 × 100 ml). The combined organic layer was washed with brine (2 × 50 ml), dried ($MgSO_4$), and evaporated to give a foul smelling red-brown solid (30.53 g). Semi-pure material suitable for subsequent reactions was obtained by the extraction of impurities into refluxing heptane (100 ml) followed by cooling and trituration with cold heptane. Pure material for characterization was obtained by flash chromatography (product adhered to silica, eluting with 1:9 EtOAc in hexane, R_f = 0.32) which yielded the title compound as an orange-red solid (20.58 g, 73%).
IR (NaCl, Nujol mull): ArOH 3301.5, C≡N 2233.8; MS (CI+, NH_3): *m*/*z* = 151.1 ($M+NH_4^+$, 100%); ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.35 (1H, t, *J* = 1.0 Hz, H4), 7.33 (1H, t, *J* = 1.0 Hz, H6), 6.90 (1H, t, *J* = 7.7 Hz, H5), 5.93 (1H, s, OH), 2.29 (3H, s, CH_3) ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 157.4 (COH), 136.4 (C4), 130.5 (C6), 126.6 (C3), 121.4 (C5), 117.2 (CN), 99.2 (C1), 16.3 (CH_3); CHN ($C_{12}H_{16}O_2$) found: C 72.35, H 5.28N 10.39; required: C 72.16, H 5.30, N 10.52.
22. Chill, S. T.; Mebane, R. C. *Synth. Commun.* **2009**, *39*, 3601.
23. *(S)-2-(4-Isopropyl-4,5-dihydrooxazol-2-yl)-6-methylphenol* (**1C**): $ZnCl_2$ (2.18 g, 0.1 equiv) was charged into a 250 ml Schlenk flask and heated under vacuum until molten (heatgun) before being allowed to cool under an argon atmosphere. *S*-valinol (23.92 g, 1.5 equiv) and nitrile **1B** (20.58 g, 1.0 equiv) were dissolved in chlorobenzene (100 ml) and charged into the flask in one go. The resulting dark red solution was heated to 131 °C for 72 h, before being cooled and the solvent was evaporated. The resulting dark oil was quenched into 2 M HCl (200 ml) and extracted with CH_2Cl_2 (5 × 100 ml). The combined organic phase was washed with H_2O (100 ml) which was back-extracted with CH_2Cl_2 (2 × 50 ml). The combined organic phase was dried ($MgSO_4$) and the solvent evaporated to give a dark red oil (31.48 g). This was purified by flash chromatography (product adhered to silica, eluting with 1:9 EtOAc in hexane, R_f = 0.73) to yield the title compound as a pale orange oil which slowly crystallized on standing (26.50 g, 78%). IR (ATR): Ar-H 2958.3, C=N 1635.3; MS (CI+, NH_3): *m*/*z* = 220 (M+H+, 100%); ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 12.59 (1H, br s, OH), 7.49 (1H, dd, *J* = 7.8, 1.6 Hz, H5), 7.23 (1H, dd, *J* = 7.3, 0.8 Hz, H3), 6.77 (1H, pent, *J* = 7.6 Hz, H4), 4.37–4.46 (1H, m, H4′), 4.06–4.17 (2H, m, H5′), 2.29 (3H, s, CH_3), 1.79 (1H, dq, *J* = 13.3, 6.7 Hz, $CH(CH_3)_2$), 0.98 (6H, dd, *J* = 28.6, 6.5 Hz, $CH(CH_3)_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.8 (C2′), 158.7 (COH), 134.6 (C5), 126.1 (C6), 125.9 (C3), 118.4 (C4), 110.3 (C2), 71.9 (C5′), 70.3 (C4′), 33.5 ($CH(CH_3)_2$), 19.1 ($CH(CH_3)_2$), 16.3 (CH_3); CHN ($C_{13}H_{17}NO_2$) found: C 71.21, H 7.81, N 6.42; required: C 71.21, H 7.81, N 6.39.
24. Gomez, M.; Jansat, S.; Muller, G.; Aullon, G.; Maestro, M. A. *Eur. J. Inorg. Chem.* **2005**, 4341.

25. *(S)-4-Isopropyl-2-(thien-2-yl)-4,5-dihydrooxazole* (**6C**): K_2CO_3 (0.12 g, 0.1 equiv) and glycerol (5 ml) were charged into a Schlenk flask and placed under an argon atmosphere. To this was added nitrile **6B** (1.0 g, 1.0 equiv), *S*-valinol (1.64 g, 1.7 equiv), and dry ethylene glycol (10 ml). The resulting clear colorless solution was heated to 110 °C for 72 h to form a purple solution. This was cooled and quenched into satd aq NH_4Cl (100 ml) before being extracted with Et_2O (3×100 ml). The combined organic phase was dried ($MgSO_4$) and the solvent evaporated to give a purple oil. This was purified by filtration through an alumina plug (washing with Et_2O) to give a pale yellow oil (1.52 g, 93%).IR (NaCl, thin film): C–H 2959.4, C=N 1651.5; MS (CI+, NH_3): m/z = 196.2 ($M+H^+$, 100%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 (1H, dd, J = 3.7, 1.2 Hz, H3′), 7.35 (1H, dd, J = 5.0, 1.2 Hz, H5′), 6.98 (1H, dd, J = 5.0, 3.7 Hz, H4′), 4.31 (1H, td, J = 8.1, 1.2 Hz, H4), 3.96–4.12 (2H, m, H5), 1.79 (1H, pseudo sext, J = 13.1, 6.7, 6.7, 6.7, 6.7, 6.7 Hz, $CH(CH_3)_2$), 0.89 (6H, dd, J = 39.9, 6.8 Hz, $CH(CH_3)_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 159.4 (C2), 130.9 (C2′), 130.6 (C3′), 130.0 (C4′), 127.9 (C5′), 73.0 (C5), 70.8 (C4), 33.1 ($CH(CH_3)_2$), 19.4 ($CH(CH_3)_2$); CHN ($C_{10}H_{13}NOS$) found: C 61.35, H 6.84, N 7.55; required: C 61.50, H 6.71, N 7.17.