Pergamon

Tetrahedron Vol. 50, No. 12, pp. 3761-3772, 1994

0040-4020/94 $6.00+0.00

0040-4020(94)E0059-3

The Rhodium Carbenoid Route to Oxazoles. Synthesis of 4-Functionalised Oxazoles; Three Step Preparation of a Bis-Oxazole

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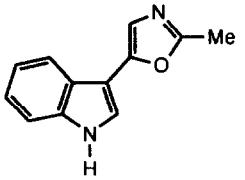
Abstract: *Oxazole-4-sulfones, -phosphonates, and -nitriles are prepared by rhodium(II) catalysed addition of nitriles to the corresponding diazo compound. The effect of the ligand on rhodium was briefly investigated, with rhodium(II) trifluoroacetamide generally proving the most effective catalyst. The 4-cyanooxazole* **9** *is readily converted into the bis-oxazoles* **10-12**.

INTRODUCTION

Oxazoles, which have been known for well over a hundred years, have been of considerable interest to organic chemists ever since the 1940's, when the intense research effort on penicillin led Cornforth and others to develop new routes to the oxazole ring. This work, summarised in the classic treatise in 1949,[1] is the foundation of modern oxazole chemistry. The subsequent discoveries during the 1950's by Kondrat'eva that oxazoles can function as azadienes in the Diels-Alder reaction, and by Huisgen that mesionic oxazoles participate in 1,3-dipolar cycloaddition prompted further research into the ring system. More recently the isolation of a large number of oxazole containing natural products has caused a renewed interest in the chemistry of oxazoles.[2-4] Naturally occurring oxazoles range in structure from relatively simple 2,5-disubstituted derivatives such as pimprinine **1**,[5-9] to the more complex 2,4-disubstituted compounds such as phenoxan **2**,[10,11] calyculin A,[12-17] and rhizoxin.[18,19] Bis-oxazoles such as hennoxazole A **3**,[20] and diazonamide A **4**,[21] and tris-oxazoles such as the ulapualides and kabiramides are also known,[22-25] as is an ever increasing number of oxazole containing cyclic peptides.[3,26,27] In view of the above, it is perhaps not surprising that a number of new synthetic methods for the construction of oxazoles has been published in the last few years.[28-58]



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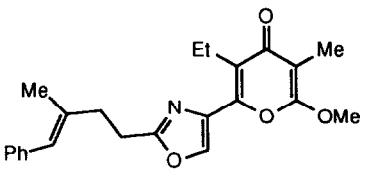

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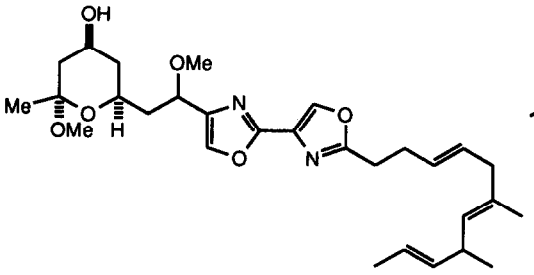

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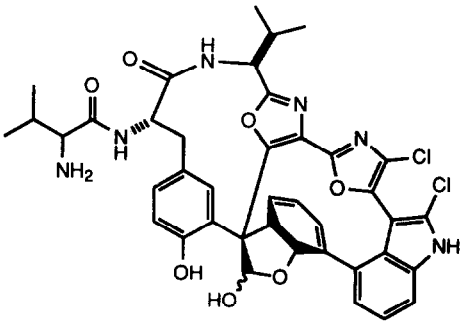

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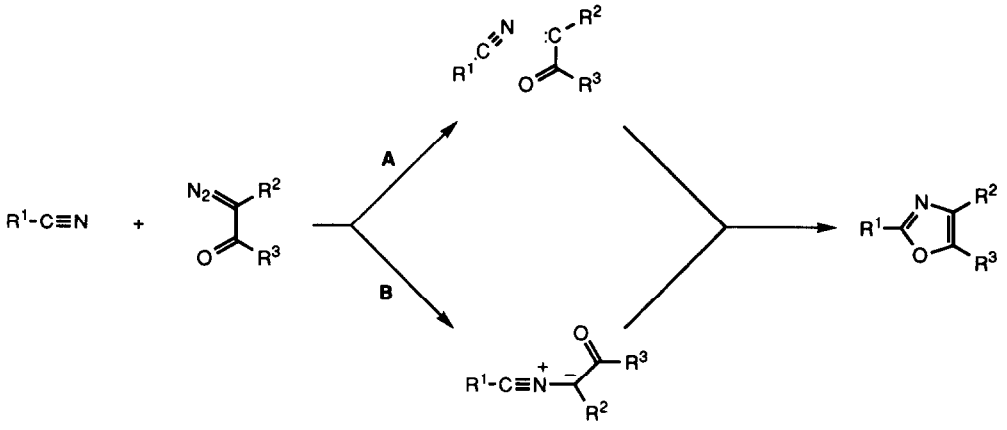
One particular method involves the reaction of diazocarbonyl compounds with nitriles (Scheme 1). The reaction can be carried out under thermal,[59,60] photochemical,[61] or Lewis acid[31,49,62-65] or metal catalysed conditions,[25,29,30,37,46,52,66-71] and presumably involves the 1,3-dipolar cycloaddition of the carbonylcarbene (or its metal carbenoid if a metal catalyst is being used) to the nitrile (path A, Scheme 1) or formation and subsequent 1,5-cyclisation of a nitrile ylide (path B, Scheme 1).

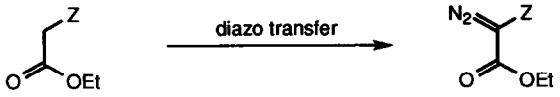


Scheme 1

As with many other reactions of diazocarbonyl compounds,[72-77] the transition-metal catalysed processes are often the higher yielding and most synthetically useful. Thus the addition of diazo carbonyl compounds to nitriles has been subject to copper,[66,69,70] tungsten,[67] palladium[68] and rhodium catalysis.[25,29,30,37,46,52,71] Despite the vast increase in interest in rhodium carbenoids, the rhodium(II) catalysed variant is still somewhat poorly described and is limited to simple diazoesters. Therefore in continuation of our work on the use of other functionalised diazocarbonyl compounds such as diazo-sulfones, -phosphonates and -nitriles,[78,79] we were keen to investigate their reactions with nitriles to give 4-functionalised oxazoles, and we now report our results in full.[80]

RESULTS AND DISCUSSION

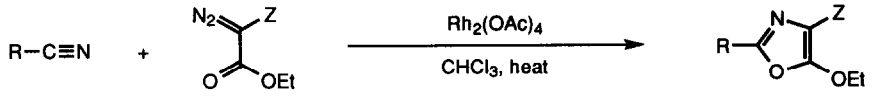
The starting diazo compounds **6** were prepared from the corresponding methylene compounds by diazotransfer techniques[81] as indicated in the Experimental Section. The diazosulfone **6a** reacted with a range of nitriles in refluxing chloroform in the presence of rhodium(II) acetate to give 4-benzenesulfonyloxazoles **7a** - **7g** in varying yield (Table 1). Although 4-benzenesulfonyloxazoles are known,[28,60] the present use of diazosulfones represents a useful extension of the rhodium carbenoid methodology. The reaction of the diazosulfone **6a** with propionitrile was further investigated using a range of rhodium(II) catalysts. The results (Table 2) demonstrate that there is little variation in the yield of oxazole, although the rate of reaction is somewhat increased using rhodium(II) trifluoroacetamide, a catalyst we have found useful for other rhodium carbenoid transformations.[82]



5 **6**

Scheme 2 [**a**, Z = SO_2Ph; **b**, Z = $PO(OEt)_2$; **c**, Z = CN]

Table 1. Synthesis of 4-functionalised oxazoles **7** by rhodium(II) acetate catalysed addition of diazo compounds **6** to nitriles

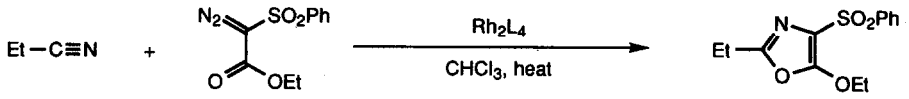


6 **7**

Diazo	*Z*	*R*	*Oxazole*	*Yield(%)*
6a	SO_2Ph	Et	**7a**	52[a]
6a	SO_2Ph	Ph	**7b**	71
6a	SO_2Ph	2-Cl-C_6H_4	**7c**	56
6a	SO_2Ph	4-Cl-C_6H_4	**7d**	46
6a	SO_2Ph	3-MeO-C_6H_4	**7e**	24
6a	SO_2Ph	4-MeO-C_6H_4	**7f**	28
6a	SO_2Ph	2-thienyl	**7g**	22
6b	$PO(OEt)_2$	Ph	**7h**	16(53)[b]
6c	CN	Ph	**7i**	25

Notes: [a] yield increased slightly using other Rh(II) catalysts - see Table 2
[b] yield increased to 53% using $Rh_2(NHCOCF_3)_4$ as catalyst.

Table 2. Catalyst effect in the formation of 4-benzenesulfonyl-5-ethoxy-2-ethyloxazole **7a** by reaction of propionitrile with diazosulfone **6a**



6a **7a**

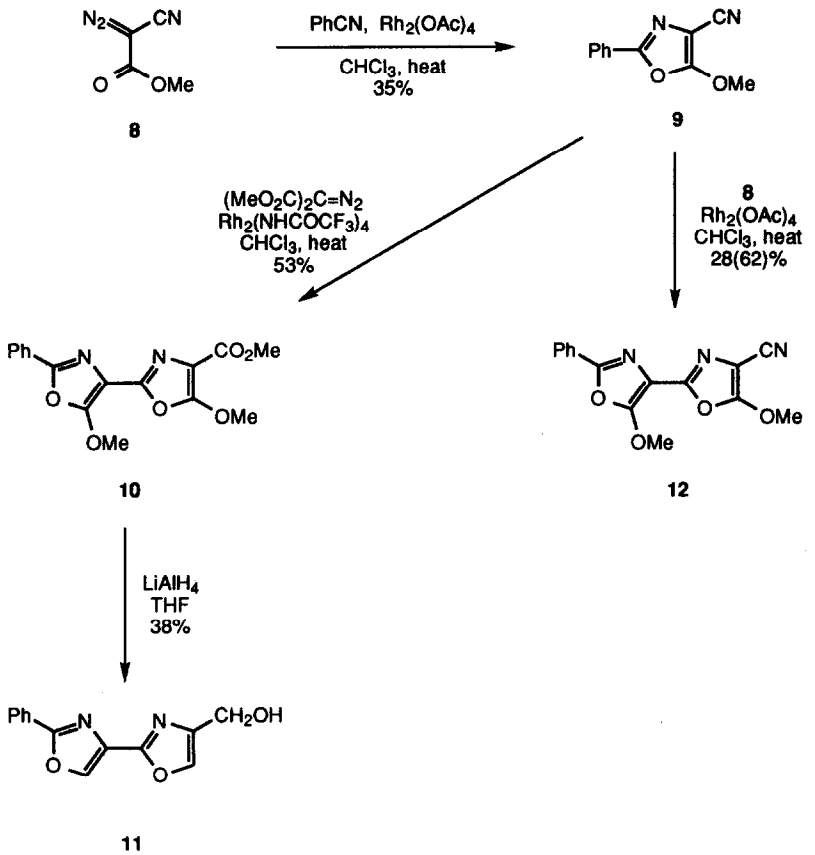
L	*Yield 7a (%)*
$MeCO_2$-	52
CF_3CONH-	64
$PhCH(OH)CO_2$-	68
1-$C_{10}H_7CO_2$-	65
1-benzenesulfonylprolinate	44

The preparation of 5-ethoxy-oxazole-4-phosphonates and -nitriles from the corresponding diazophosphonate **6b** and diazonitrile **6c** was also briefly investigated. Diazo compound **6b** gives a poor yield (16%) of the oxazole **7h** on reaction with benzonitrile in the presence of rhodium(II) acetate. However, the yield was increased to 53% when rhodium(II) trifluoroacetamide was used as catalyst. The corresponding reaction with diazonitrile **6c**, however, could not be improved upon by change in catalyst, and the yield of the oxazolenitrile **7i** remained poor (Table 1), although another product (a bis-oxazole) was formed in the reaction (see below).

The need to prepare oxazoles with a functional group at the 4-position was stimulated by our interest in the synthesis of oxazole containing natural products, in particular, the hennoxazoles **4**[20] and diazonamides **5**[21] in which the two heterocyclic rings are directly linked through their 4- and 2-positions. Although, in principle, the 4-sulfonyl group can be substituted, thereby allowing the preparation of more complex linked oxazoles, the corresponding 4-cyano derivative (*e.g.* **7i**) could act as a direct precursor to bis-oxazoles. Bis- and tris-oxazoles have been prepared previously by iterative cyclisations,[24] double cyclisations,[50] or repetitive rhodium(II) acetate catalyzed addition reactions of diazomalonates to nitriles.[25] Our present use of diazonitriles which leads directly to a 4-cyanooxazoles obviates the need for the 4-step conversion of the oxazole-4-ester to the corresponding nitrile.[25]

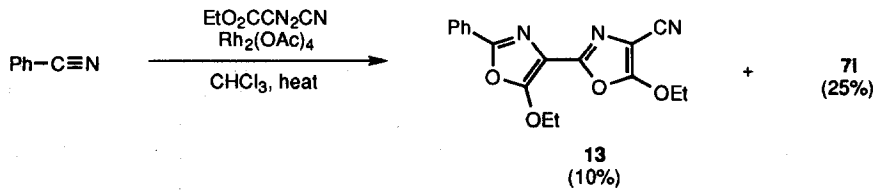
Thus, although ethyl diazocyanoacetate **6c** only gave a poor yield of the 4-cyano oxazole **7i** (see below also), the corresponding methyl ester **8** reacted with benzonitrile in the presence of rhodium(II) acetate to give the 4-cyanooxazole **9** in acceptable yield (35%). In contrast to the related work referred to above,[25] no attempt was made to remove the 5-methoxy group at this stage. Rather, reaction of the 4-cyanooxazole **9** with dimethyl diazomalonate under similar conditions gave the desired bis-oxazole **10** but in only 4% yield; possibly the presence of the 5-methoxy group adversely affects the reaction (*cf.* ref. 25). However, using rhodium(II) trifluoroacetamide as catalyst the yield of bis-oxazole **10** was improved to 53%. Finally, as had been hoped, *both* methoxy groups were cleaved from the bis-oxazole, with concomitant reduction of the ester, by reaction with lithium aluminium hydride to give the bis-oxazole **11** (Scheme 3). Use of the diazocyanoacetate **8** in the second rhodium mediated oxazole forming step should lead directly to a bis-oxazole nitrile, and this indeed proves to be the case (Scheme 3), reaction of the 4-cyanooxazole **9** with diazonitrile **8** giving the bis-oxazole **12** in 28% yield (62% based on recovered starting material). Thus, this first use of diazonitriles in oxazole

synthesis represents a useful advance, bis-oxazoles being available in just 2 steps from the original nitrile precursor.



Scheme 3

Interestingly, some "double addition" also occurred to a small extent in the original preparation of cyanooxazole **7i**; careful examination of the reaction mixture indicated that in addition to the oxazole **7i** (25%), the bis-oxazole **13** (the diethoxy equivalent of **12**) is also formed (Scheme 4). Although the yield of **13** is low (10%), the conversion of a simple nitrile into a relatively complex bis-oxazole in a *single* step is a remarkable transformation. As expected, reaction of oxazole nitrile **7i** with diazonitrile **6c** also gives the bis-oxazole **13**.



Scheme 4

EXPERIMENTAL

For general experimental points, see ref. 79.

Preparation of Diazo Compounds

Ethyl benzenesulfonylacetate **5a**

A solution of ethyl bromoacetate (5.0 g, 30 mmol) and benzenesulfinic acid, sodium salt (5.9 g, 1.2 equivalents) in ethanol (200 mL) was refluxed for 3 h. Excess solvent was removed *in vacuo*. The remaining precipitate was dissolved in ether (200 mL) and washed with water (2 x 200 mL) and brine (50 mL). The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure. The product was then recrystallised from dichloromethane to give the *title compound* as a colourless crystalline solid (5.92 g, 86 %), m.p. 39 - 41°C (lit.,[83] 42-43°C); $\nu_{max.}$ (KBr); 3006, 1742, 1325, 1154 cm^{-1}; δ_H (250 MHz; $CDCl_3$); 1.17 (3 H, t, J 7.1), 4.05-4.17 (4 H, m), 7.55-7.69 (3 H, m), 7.93-7.97 (2 H, m); δ_C (62.5 MHz; $CDCl_3$); 13.8, 61.0, 62.3, 128.5, 129.2, 134.3, 138.5, 162.5; *m/z* (EI) 229 (MH^+, 80%), 164 (80%), 141 (100%), 91 (95%), 78 (75%); (Found: M^+ 228.0456. $C_{10}H_{12}O_4S$ requires 228.0456).

Ethyl diazo(benzenesulfonyl)acetate **6a**

(a) To a stirred solution of ethyl benzenesulfonylacetate **5a** (5.8 g, 25.4 mmol) and 4-acetamidobenzenesulfonyl azide[84] (9.16 g, 1.5 equiv.) in acetonitrile (200 mL) at 0°C, was added triethylamine (5.31 mL, 1.5 equiv.) dropwise. The reaction mixture was then stirred at room temperature for 16 h. After this time it was concentrated *in vacuo*, and the resulting precipitate was triturated (3 x 200 mL, 1 : 1 ether : light petroleum). The combined organics were concentrated under reduced pressure. Purification by flash chromatography (eluant ether : light petroleum) yielded the *title compound* as a pale yellow solid (4.76 g, 74%), data given below.

(b) A solution of 1-ethyl-2-chloropyridinium tetrafluoroborate[85] (2.40 g, 1.2 equivalents) and sodium azide (678 mg, 1.2 equivalents) in 70% methanolic solution (100 mL), at 0°C, was stirred for 10 min. Ethyl benzenesulfonylacetate **5a** (2.0 g, 8.7 mmol) and sodium acetate (856 mg, 1.2 equivalents) were added as a solution in 70 % methanolic solution (50 mL). The reaction mixture was stirred for 24 h, after which time excess solvent was removed under reduced pressure. The residue was diluted with ether (150 mL) and washed with water (2 x 50 mL) and brine (50 mL). The organic layer was dried ($MgSO_4$) and concetrated *in vacuo*. The product was purified by flash chromatography (eluant ethyl acetate : light petroleum) to yield the *title compound* as a yellow solid (1.45 g, 65%), m.p. 51 - 53°C; $\nu_{max.}$ ($CHCl_3$) 2129, 1416, 1345, 1160 cm^{-1}; δ_H (250 MHz; $CDCl_3$) 1.25 (3 H, t, J 7.1), 4.18 (2 H, q, J 7.1), 7.53-7.66 (3 H, m), 8.01-8.05 (2 H, m); δ_C (62.5 MHz; $CDCl_3$) 14.0, 62.0, 127.0, 129.0, 133.9 (diazo and carbonyl carbons not observed); *m/z* (E.I.) 254 (M^+, 20%), 226 (10%), 209 (20%), 182 (20%), 141 (100%); (Found: M^+ 254.0362 $C_{10}H_{10}N_2O_4S$ requires 254.0361).

Triethyl diazophosphonoacetate **6b**

Prepared by the literature method from triethyl phosphonoacetate and azidotris(diethylamino)phosphonium bromide.[86]

Ethyl diazocyanoacetate **6c**

A mixture of 1-ethyl-2-chloropyridinium tetrafluoroborate (12.1 g, 1.2 equiv) and sodium azide (3.4 g, 1.2 equiv) in 70% methanolic solution (140 mL), at 0°C, was stirred for 15 min. Ethyl cyanoacetate **5c** (5 g, 44.2 mmol) and sodium acetate (4.3 g, 1.2 equiv.) was added to the reaction mixture as a solution in 70% methanolic solution (60 mL). After stirring for 15 min, the reaction mixture was diluted with ether (100 mL). The resulting solution was washed with water (70 mL). The organic layer was washed with brine (20 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by dry-flash chromatography (gradient of light

petroleum to light petroleum-ethyl acetate) gave the *title compound* as a yellow oil (4.89 g, 80%) (lit.,[87] oil), $\nu_{max.}$ (neat) 2230, 2137, 1719 cm^{-1}; δ_H (250 MHz; $CDCl_3$) 1.34 (3 H, t, J 7.1), 4.35 (2 H, q, J 7.2); δ_C (62.5 MHz; $CDCl_3$) 14.3, 63.45 (diazo and carbonyl carbons not seen); *m/z* (EI) 139 (*M* +, 30%), 94 (20%), 44 (30%), 129 (100%); (Found: *M* + 139.03817. $C_5H_5N_3O_2$ requires 139.03817)

General Procedure for Preparation of Oxazoles 7

4-Benzenesulfonyl-5-ethoxy-2-ethyloxazole **7a**

(a) To a refluxing solution of propionitrile (0.357 mL 5 equiv) and rhodium(II) acetate (3 mg, 1% mol. equiv) in ethanol-free chloroform (3 mL) was added a solution of ethyl diazo(benzenesulfonyl)acetate **6a** (254 mg, 1 mmol) in ethanol-free chloroform (7 mL) over a 7 h period. After the addition was finished, the reaction mixture was refluxed for a further hour, after which time it was concentrated *in vacuo*. Purification by flash chromatography (eluant: ethyl acetate-light petroleum) followed by recrystallisation from ethyl acetate gave the *title compound* as a colourless solid (147 mg, 52%), m.p. 101-103°C; (Found C, 55.6; H, 5.10; N, 4.9. $C_{13}H_{15}NO_4S$ requires C, 55.5; H, 5.37; N, 5.0 %); $\nu_{max.}$ (KBr) 2360, 1633, 1327, 1150 cm^{-1}; δ_H (250 MHz; $CDCl_3$) 1.26 (3 H, t, J 7.6), 1.47 (3 H, t, J 7.1), 2.65 (2 H, q, J 7.6), 4.45 (2 H, q, J 7.1), 7.48-7.59 (3 H, m), 8.01-8.04 (2 H, m); δ_C (62.5 MHz; $CDCl_3$) 13.8, 14.8, 63.4, 70.7, 114.1, 127.4, 129.0, 131.4, 141.5 (C-4), 155.7 (C-5), 157.9 (C-2); *m/z* (FAB) 282 (*MH*+, 100%), 236 (*M*-45, 10), 197 (20), 135 (25), 125 (20); (Found: *MH* + 282.080. $C_{13}H_{15}NO_4S$ + *H* requires 282.0799).

(b) The above reaction was carried out using rhodium(II) trifluoroacetamide (6.5 mg, 1% mol equiv.) as catalyst to give the *title compound* (180 mg, 64%).

(c) The above reaction was carried out using rhodium(II) (*S*)-mandelate (8.1 mg, 1% mol equiv.) as catalyst to give the *title compound* (190 mg, 68%).

(d) The above reaction was carried out using rhodium(II) 1-naphthoate (8.9 mg, 1% mol equiv.) as catalyst to give the *title compound* (183 mg, 65%).

(e) The above reaction was carried out using rhodium(II) 1-benzenesulfonyl-(S)-prolinate (12.0 mg, 1% mol equiv.) as catalyst to give the *title compound* (125 mg, 44%).

4-Benzenesulfonyl-5-ethoxy-2-phenyloxazole **7b**

Yield 71%

m.p. 110-112°C; (Found: C, 61.8; H, 4.64; N, 4.2. $C_{17}H_{15}NO_4S$ requires C, 62.0; H, 4.59; N, 4.2%); $\nu_{max.}$ (KBr) 1615, 1343, 1163 cm^{-1}; δ_H (250 MHz; $CDCl_3$) 1.54 (3 H, t, J 7.1), 4.58 (2 H, q, J 7.1), 7.40-7.57 (6 H, m), 7.88-7.92 (2 H, m), 8.06-8.10 (2 H, m); δ_C (62.5 MHz; $CDCl_3$) 14.9, 71.1, 116.0, 126.0, 127.5, 128.7, 129.1, 130.8, 133.3, 141.5 (C-4), 151.5 (C-5), 158.0 (C-2); *m/z* (FAB) 330 (*MH* +, 100%), 284 (M-45, 40%), 154 (35%), 122 (45%); (Found: *M*+ 329.0721. $C_{17}H_{15}NO_4S$ requires 329.0722).

4-Benzenesulfonyl-2-(2-chlorophenyl)-5-ethoxyoxazole **7c**

Yield 56%

m.p. 145-147°C; (Found C, 56.2; H, 4.0; N, 3.8. $C_{17}H_{14}ClNO_4S$ requires C, 56.1; H, 3.9; N, 3.85 %); $\nu_{max.}$ (KBr) 1612, 1341, 1157 cm^{-1}; δ_H (250 MHz; $CDCl_3$) 1.53 (3 H, t, J 7.1), 4.59 (2 H, q, J 7.1), 7.32-7.58 (6 H, m), 7.92 (1 H, m), 8.07-8.11 (2 H, m); δ_C (100 MHz; $CDCl_3$) 14.7, 70.8, 115.3, 124.8, 126.8, 127.4, 128.9, 130.8, 131.0, 131.5, 132.0, 133.2, 141.3 (C-4), 149.3 (C-5), 158.0 (C-2); *m/z* (E.I.) 363 (*M* +, 30%), 358 (50 %), 286 (100%); (Found: *MH* + 364.0410. $C_{17}H_{14}ClNO_4S$ + *H* requires 364.0410).

4-Benzenesulfonyl-2-(4-chlorophenyl)-5-ethoxyoxazole **7d**

Yield 46%

m.p. 127-129°C (decomposes); $\nu_{max.}$ (KBr) 1622, 1302, 1155 cm^{-1}; δ_H (250 MHz; $CDCl_3$) 1.52 (3 H, t, J 7.1), 4.57 (2 H, q, J 7.1), 7.36-7.39 (2 H, m), 7.52-7.55 (3 H, m), 7.80-7.83 (2 H, m), 8.04-8.08 (2 H, m);

δ_C (62.5 MHz; $CDCl_3$) 14.9, 71.2, 124.4, 127.2, 128.7, 129.0, 133.3, 136.9, 141.2 (C-4), 150.6 (C-5), 158.0 (C-2); *m/z* (FAB) 364 (*MH* +, 100%), 318 (*M* -45, 6%), 307 (18%), 289 (18%); (Found: *MH* + 364.041. $C_{17}H_{14}ClNO_4S$ + *H* requires 364.0410).

4-Benzenesulfonyl-5-ethoxy-2-(3-methoxyphenyl)oxazole **7e**
Yield 24%
m.p.121-123°C; (Found C, 59.9; H, 4.7; N, 3.9. $C_{18}H_{17}NO_5S$ requires C, 60.2; H, 4.8; N, 3.9 %); $\nu_{max.}$ (KBr) 2957, 1618, 1345, 1157 cm^{-1}; δ_H (250 MHz; $CDCl_3$) 1.53 (3 H, t, J 7.1) 3.84 (3 H, s), 4.57 (2 H, q, J 7.1) 6.99 (1 H, m), 7.31-7.60 (6 H, m) 8.05-8.09 (2 H, m); δ_C (100 MHz; $CDCl_3$) 14.8, 55.3, 71.0, 110.7, 116.0, 117.0, 118.3, 127.0, 127.4, 128.9, 129.7, 133.1, 141.3 (C-4), 151.3 (C-5), 157.8, 159.7 (C-2); (Found: *MH* + 360.091. $C_{18}H_{17}NO_5S$ + *H* requires 360.0905).

4-Benzenesulfonyl-5-ethoxy-2-(4-methoxyphenyl)oxazole **7f**
Yield 28%
m.p. 125-127°C; (Found C, 60.1; H, 4.74; N, 4.0. $C_{18}H_{17}NO_5S$ requires C, 60.2; H, 4.77; N, 3.9 %) $\nu_{max.}$ (KBr) 3003, 1605, 1323, 1155 cm^{-1}; δ_H (250 MHz, $CDCl_3$) 1.53 (3 H, t, J 7.1), 3.84 (3 H, s), 4.55 (2 H, q, J 7.1), 6.90-6.93 (2 H, m), 7.52-7.59 (3 H, m), 7.82-7.85 (2 H, m), 8.06-8.10 (2 H, m); δ_C (100 MHz; $CDCl_3$) 14.9, 55.3, 71.0, 114.1, 118.6, 127.4, 127.7,128.9, 129.0, 133.1, 141.4 (C-4), 151.8 (C-5), 157.6, 161.6 (C-2); *m/z* (FAB) 360 (MH+, 85%), 314 (M-45, 10), 135 (100); *m/z* (E.I.) 359 (*M* +, 30%), 286 (100%); (Found: MH+ 360.0906. $C_{18}H_{17}NO_5S$ + H requires 360.0905).

4-Benzenesulphonyl-5-ethoxy-2-(2-thienyl)oxazole **7g**
Yield 22%
m.p. 96-98°C; $\nu_{max.}$ (KBr) 1621, 1331, 1160 cm^{-1}; δ_H (250 MHz; $CDCl_3$) 1.53 (3 H, t, J 7.0), 3.48 (2 H, q, J 7.0), 7.07 (1 H, dd, J 3.7, J' 4.9), 7.41 (1 H, dd, J 1.2, J' 5.0), 7.49 - 7.63 (4 H, m), 8.05 - 8.10 (2 H, m) ; δ_C (62.5 MHz; $CDCl_3$) 14.8, 71.3, 116.0, 127.4, 127.8, 128.3, 128.9, 129.0, 133.3, 141.2 (C-5), 148.0 (C-4), 157.4 (C-2) ; *m/z* (E.I.) 336 (*MH*+, 100%), 272 (25%), 168 (30%), 111 (10%); (Found *MH*+ 336.0364. $C_{15}H_{13}NO_4S_2$ + *H* requires 336.0364)

Diethyl 5-ethoxy-2-phenyloxazole-4-phosphonate **7h**
(a) To a refluxing solution of benzonitrile (309 mg, 1.5 equiv) and rhodium(II) trifluoroacetamide (13 mg, 1% mol equiv) in ethanol-free chloroform (5 mL) was added a solution of triethyl diazophosphonoacetate **6b** (468 mg, 2 mmol) in ethanol-free chloroform (16 mL) over a 6 h period. The reaction mixture was refluxed for a further hour, after which time it was concentrated *in vacuo*. Purification by flash chromatography (eluant ethyl acetate: light petroleum) gave the *title compound* as an oil (254 mg, 53% yield). $\nu_{max.}$ (neat); 2985, 1614, 1248, 1023, 735 cm^{-1}; δ_H (250 MHz; $CDCl_3$) 1.37 (6 H, dt, J 2.6), 1.51 (3 H, t, J 7.1), 4.14-4.30 (4 H, m), 4.54 (2 H, q, J 7.1) , 7.41-7.44 (3 H, m), 7.93-7.97 (2 H, m); δ_C (62.5 MHz; $CDCl_3$) 14.1, 16.1 and 16.2 (J_{CP} 6.8), 62.4 and 62.5 (J_{CP} 5.3), 70.2, 125.7, 126.5, 128.6, 130.1, 131.8 (C-5), 152.6 and 153.0 (C-2, J_{CP} 22.6), 163.1 and 163.6 (C-4, J_{CP} 34.5); *m/z* (FAB); 326 (*MH* +, 100%), 297 (*M* -28, 8%), 280 (*M* -45, 15%); (Found:*MH*+ 326.1157. $C_{15}H_{20}NO_5P$ + *H* requires 326.1157).
(b) The above reaction was carried out on the 3mmol scale using rhodium(II) acetate (26 mg, 2% mol equiv.) as catalyst, to give the *title compound* (161 mg, 16%).

5-Ethoxy-2-phenyloxazole-4-carbonitrile **7i** and *5-Ethoxy-2-[5-ethoxy-2-phenyloxazol-4-yl]oxazole-4-carbonitrile* **13**
To a refluxing solution of benzonitrile (1.21 g, 3 equiv) and rhodium(II) acetate (86.2 mg, 5% mol equiv) in ethanol-free chloroform (4 mL) was added a solution of ethyl diazocyanoacetate (546 mg, 4 mmol) in ethanol-free chloroform (10 mL) over a 10 h period. The reaction mixture was refluxed for a further hour. The reaction

mixture was concentrated *in vacuo* to yield a crude mixture. This was purified by flash chromatography (eluant diethyl ether : light petroleum) to yield the (i) *title compound* **7i** as a colourless crystalline solid (209 mg, 25%), m.p. 78-80°C; (Found C, 67.3, H, 4.6, N, 13.1. $C_{12}H_{10}N_2O_2$ requires C, 67.3, H, 4.7, N, 13.1 %); $\nu_{max.}$ (KBr) 2989, 2223, 1616, 1604, 1568 cm^{-1}; δ_H (400 MHz; $CDCl_3$) 1.54 (3 H, t, J 7.1), 4.60 (2 H, q, J 7.0), 7.43-7.46 (3 H, m), 7.87-7.90 (2 H, m); δ_C (100 MHz; $CDCl_3$) 14.6, 69.9, 89.0, 112.9, 125.6, 125.8, 128.8, 130.8, 152.1, 163.8; *m/z* (EI); 214 (*M* +, 20%), 186 (40%), 105 (100%); (Found: M^+ 214.0742. $C_{12}H_{10}N_2O_2$ requires 214.0742), and *5-ethoxy-2-[5-ethoxy-2-phenyloxazol-4-yl]oxazole-4-carbonitrile* **13** as a colourless crystalline solid (64 mg, 10%); data given below.

5-Ethoxy-2-[5-ethoxy-2-phenyloxazol-4-yl]oxazole-4-carbonitrile **13**

To a refluxing solution of 5-ethoxy-2-phenyloxazole-4-carbonitrile **7i** (80 mg, 0.37 mmol) and rhodium(II) acetate (8.0 mg, 5% molar equivalents) in ethanol-free chloroform (1 mL) was added a solution of ethyl diazocyanoacetate (103.9 mg, 2.0 equivalents) in ethanol-free chloroform (6 mL) over a 6 h period. After the addition was complete the reaction mixture was refluxed for a further 4 h. The reaction mixture was allowed to cool, then concentrated *in vacuo*. Purification by flash chromatography (eluant ethyl acetate-light petroleum) gave the title compound as a crystalline solid (19 mg, 16%), $\nu_{max.}$ ($CDCl_3$) 2254, 1629, 1618, 1348 cm^{-1}; δ_H (400 MHz; $CDCl_3$) 1.52-1.58 (6 H, m), 4.59 (4 H, quintet, J 7.0, J' 7.1), 7.43-7.53 (3 H, m), 7.80-7.99 (2 H, m); δ_C (100 MHz; $CDCl_3$) 14.6, 14.9, 70.0, 70.35, 112.9, 125.8, 126.2, 128.5, 128.7, 130.4, 146.3, 152.3, 157.2, 163.3; *m/z* (FAB) 326 (*MH* +, 65%), 281(40%), 207(25%), 147 (35%), 136 (35%), 105 (65%), 73 (100%); (Found *MH* + 326.114. $C_{17}H_{15}N_3O_4 + H$ + requires 326.114.)

Methyl diazocyanoacetate **8**

A mixture of 1-ethyl-2-chloropyridinium tetrafluoroborate (7.64 g, 1.1 equiv) and sodium azide (2.19 g, 1.1 equiv) in acetonitrile : water solution (7:3; 200 mL), at 0°C, was stirred for 15 min. Methyl cyanoacetate (3.0 g, 30.3 mmol) was added to the solution, followed by a catalytic amount of potassium carbonate. After stirring for 10 min, the reaction mixture was diluted with ether (100 mL). The resulting solution was washed with water (70 mL). The organic layer was washed with brine (20 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by dry-flash chromatography (gradient of light petroleum to light petroleum-ethyl acetate) gave the *title compound* **8** (2.37 g, 62%) as a yellow oil (lit.,[88] oil), $\nu_{max.}$ (neat) 2231, 2142, 1729 cm^{-1}; δ_H (250 MHz; $CDCl_3$) 3.90 (3 H, s); δ_C (62.5 MHz; $CDCl_3$) 53.6 (nitrile, diazo and carbonyl carbons not observed); *m/z* (EI) 125 (*M* +, 50%), 97 (*M* -28, 15%), 94 (20%), 54 (100%); (Found *M* + 125.0223. $C_4H_3N_3O_2$ requires 125.0225).

5-Methoxy-2-phenyloxazole-4-carbonitrile **9**

To a refluxing solution of benzonitrile (3.3 g, 2 equiv) and rhodium(II) acetate (70 mg, 1% molar equiv) in ethanol-free chloroform (10 mL) was added a solution of methyl diazocyanoacetate **8** (2.0 g, 16 mmol) in ethanol-free chloroform (40 mL) over a 20 h period. The reaction mixture was refluxed for a further 2 h, after which time it was then concentrated *in vacuo*. The product was purified by flash chromatography (eluant light petroleum : ethyl acetate) to yield a crystalline compound. Recrystallisation from light petroleum gave the *title compound* as a colourless crystalline solid (1.10 g, 35%), m.p. 107-108°C, (Found; C, 66.0; H, 4.0; N, 13.9. $C_{11}H_8N_2O_2$ requires C, 66.0; H, 4.0; N, 14.0%); $\nu_{max.}$ (KBr) 2228, 1628 cm^{-1}; δ_H (250 MHz; $CDCl_3$) 4.31 (3 H, s), 7.44-7.48 (3 H, m), 7.88-7.93 (2 H, m); δ_C (62.5 MHz; $CDCl_3$) 59.3, 112.8, 125.5, 125.8, 128.8, 130.9, 152.5, 162.1; *m/z* (EI) 200 (M^+, 100%), 157 (*M* -43, 30), 105 (*M* -95, 100); (Found: *M* + 200.0586. $C_{11}H_8N_2O_2$ requires 200.0586).

Methyl 5-methoxy-2-[5-methoxy-2-phenyloxazol-4-yl]oxazole-4-carboxylate **10**

To a refluxing solution of 5-methoxy-2-phenyloxazole-4-carbonitrile **9** (150 mg, 0.75 mmol) and rhodium(II) trifluoroacetamide (9.8 mg, 2% molar equiv) in ethanol-free chloroform (3 mL) was added a solution of

dimethyl diazomalonate (216.2 mg, 2 equiv) in ethanol-free chloroform (10 mL) over a 10 h period. The reaction mixture was refluxed for a further 2 h, after which time it was concentrated *in vacuo*. The residue was purified by flash chromatography (eluant light petroleum : ethyl acetate) to give the *title compound* as a colourless crystalline compound (131 mg, 53%), m.p. 144-146°C; (Found C, 58.3; H, 4.12; N, 8.4. $C_{16}H_{14}N_2O_6$ requires C, 58.2; H, 4.27; N, 8.5 %); $\nu_{max.}$ (KBr) 2956, 1713, 1615 cm^{-1}; δ_H (400 MHz; $CDCl_3$) 3.88 (3 H, s), 4.25 (3 H, s), 4.26 (3 H, s), 7.43-7.45 (3 H, m), 7.98-7.99 (2 H, m); δ_C (100 MHz; $CDCl_3$) 51.5, 59.8, 60.0, 104.8, 107.0, 125.6, 126.4, 128.6, 130.2, 144.8, 151.7, 157.5, 161.3, 161.7; *m/z* (EI) 330 (*M* +, 50%), 287 (*M* -43, 30), 202 (50), 105 (100); (Found: *M* + 330.0850. $C_{16}H_{14}N_2O_6$ requires 330.0852).

2-(2-Phenyloxazol-4-yl)oxazole-4-methanol **11**

To a stirred solution of methyl 5-methoxy-2-[5-methoxy-2-phenyloxazol-4-yl] oxazole-4-carboxylate **10** (43 mg, 0.13 mmol) in THF (5 mL) at -78°C under a nitrogen atmosphere, was added lithium aluminium hydride (0.195 mL, 1.0 M solution in THF, 2 equiv). The reaction mixture was stirred at -70°C for 1.5 h, then allowed to warm up to room temperature. The reaction was then worked-up by the successive addition of water (0.1 mL), NaOH solution (15%; 0.1 mL) then diluted with diethyl ether (20 mL), which was then filtered. The organic layer was then washed with brine (10 mL) and dried ($MgSO_4$), then concentrated under reduced pressure. The residue was purified by flash chromatography (eluant light petroleum : ethyl acetate) to yield the *title compound* as a colourless solid (13 mg, 38% yield), m.p. 142-144°C, $\nu_{max.}$ (KBr) 3293, 1635, 1523, 1456, 1330, 1114, 1034 cm^{-1}; δ_H (400 MHz; $CDCl_3$) 2.26 (1 H, br s, exchangeable D_2O), 4.69 (2 H, s), 7.44-7.52 (3 H, m), 7.67 (1 H, s), 8.12-8.17 (2 H, m), 8.27 (1 H, s); δ_C (100 MHz; $CDCl_3$) 56.9, 126.3, 126.8, 128.7, 131.0, 131.5, 134.9, 138.2, 141.4, 155.6, 162.7; *m/z* (EI) 242 (*M* +, 100%), 172 (*M* -70, 80), 80 (50); (Found: *M* + 242.0690. $C_{13}H_{10}N_2O_3$ requires 242.0691).

5-Methoxy-2-[5-methoxy-2-phenyloxazol-4-yl]oxazole-4-carbonitrile **12**

To a refluxing solution of 5-methoxy-2-phenyloxazole-4-carbonitrile **9** (250 mg, 1.25 mmol) and rhodium(II) acetate (27.6 mg, 5% molar equivalents) in ethanol-free chloroform (5 mL) was added a solution of methyl diazocyanoacetate **8** (187 mg, 1.2 equivalents) in ethanol-free chloroform (10 mL) over a 10 h period. After the addition was complete the reaction mixture was refluxed for a further 4 h. The reaction mixture was allowed to cool, then concentrated *in vacuo*. Purification by flash chromatography (eluant ethyl acetate-light petroleum) gave the starting nitrile (137 mg), and the *title compound* as a colourless solid (104 mg, 28% yield, 62% based upon recovered starting material), m.p. 140-142 °C; (Found C, 60.6; H, 3.60; N, 14.1. $C_{15}H_{11}N_3O_4$ requires C, 60.6; H, 3.73; N, 14.2 %); $\nu_{max.}$ (KBr) 2230, 1654, 1627, 1582, 1377, 1221, 1138, 1041, 700 cm^{-1}; δ_H (400 MHz; $CDCl_3$) 4.27 (3 H, s), 4.29 (3 H, s), 7.43-7.46 (3 H, m), 7.95-8.00 (2 H, m); δ_C (100 MHz; $CDCl_3$) 60.12, 60.14, 88.5, 104.4, 112.6, 125.7, 126.1, 128.7, 130.4, 146.2, 152.0, 157.8, 163.9; *m/z* (E.I.) 297 (*M* +, 40%), 254 (*M* -43, 50%), 105 (100%); (Found *M* + 297.0750. $C_{15}H_{11}N_3O_4$ requires 297.0749).

ACKNOWLEDGEMENTS

We thank Fisons Pharmaceuticals for their generous support of our research programme, and the S.E.R.C. MS and NMR Services at Swansea and Warwick respectively for spectroscopic data.

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(*Received in UK* 20 *December* 1993; *accepted* 14 *January* 1994)