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N–H Insertion reactions of rhodium carbenoids. Part 5: A convenient route to 1,3-azoles☆

James R. Davies,[a] Peter D. Kane[b] and Christopher J. Moody[a,*]

[a]*Department of Chemistry, University of Exeter, Stocker Road, Exeter EX4 4QD, UK*
[b]*Tripos Receptor Research Ltd, Bude-Stratton Business Park, Bude, Cornwall EX23 8LY, UK*

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Abstract—Dirhodium(II) carboxylate catalysed reaction of diazocarbonyl compounds **2** in the presence of primary amides **1** results in the formation of α-acylaminoketones **3** (12 examples) by N–H insertion reaction of the intermediate rhodium carbene. The 1,4-dicarbonyl compounds **3** are readily converted into structurally diverse oxazoles **4** (11 examples) by cyclodehydration, thiazoles **5** (10 examples) by treatment with Lawesson's reagent, or imidazoles **6** (2 examples) by reaction with ammonia or methylamine.

1. Introduction

The 1,3-azoles—oxazoles, thiazoles, imidazoles—have attracted the attention of chemists for many years. The heteroaromatic imidazole ring plays a key role in the chemistry of the proteinogenic amino acid histidine, and oxazoles and thiazoles occur widely in a range of natural products, particularly the non-ribosomal peptides.[2,3] Recently there has been considerable interest in the use of 1,3-azoles as peptide mimetics.[4–6] The structural diversity of complex naturally occurring 1,3-azoles and the biological activity of synthetic analogues has ensured that new methods continue to be developed for their synthesis.[7]

Of the intermediates available for the synthesis of five-membered heteroaromatic rings, 1,4-dicarbonyl compounds are among the most versatile. In the field of 1,3-azole synthesis, the cyclodehydration of such a 1,4-dicarbonyl compound (an α-acylaminoketone) is the basis of the Robinson–Gabriel oxazole synthesis.[7] Although this reaction was discovered some time ago, it continues to undergo modification, for example, the preparation of the intermediate α-acylaminoketone by acylation of α-amino-β-ketoesters,[4,8] or by oxidation of β-hydroxyamides.[9] Recently we reported a new variation on the Robinson–Gabriel synthesis in which the key 1,4-dicarbonyl intermediate was obtained by a rhodium carbene N–H insertion reaction,[10] developed specifically for the synthesis of the amino acid derived oxazole building blocks of the natural products nostocyclamide and promothiocin A.[11,12] Subsequently, others used our protocol for the synthesis of oxazole-containing peptide mimetics,[5] whilst Janda and co-workers have developed a solid-phase variant of this reaction, and applied it to the synthesis of an array of oxazoles.[13,14] We now report further developments in the use of rhodium carbene N–H insertion reactions and their use in a general approach to the synthesis of 1,3-azoles.

2. Results and discussion

A range of primary amides was selected, comprising formamide **1a**, a simple alkanamide **1b**, aromatic and heteroaromatic amides **1c**-**1e**, the amide **1f** derived from piperidine-4-carboxylic acid (isonipecotic acid), and the oxazole amide **1g**. Amide **1d** was readily prepared from 5-methoxysalicylic acid, **1f** from piperidine-4-carboxamide, and **1g** from the corresponding ester **4c** (prepared by the method described herein); the other amides are commercially available. A range of six diazocarbonyl compounds **2** was also selected for study. The α-diazo-β-ketoesters **2a**-**2e** were prepared by diazo-transfer reaction[15] to the corresponding β-ketoesters using 4-acetamidobenzenesulfonyl azide as the reagent,[16] and azibenzil **2f** was obtained by the literature procedure by oxidation of benzil monohydrazone with manganese(IV) oxide.[17] The carbene N–H insertion reactions were generally carried out using dirhodium tetraacetate as catalyst and 1,2-dichloroethane as solvent, the diazocarbonyl compound being added by syringe pump over about 16 h. The resulting α-acylamino ketones **3** were formed in varying yield (13–82%) (Table 1) with no significant by-products being identified.

☆ See Ref. 1.

Keywords: Heterocyclic; Oxazole; Thiazole; Imidazole.
* Corresponding author. Tel.: +44-1392-263429; fax: +44-1392-263434; e-mail address: c.j.moody@ex.ac.uk

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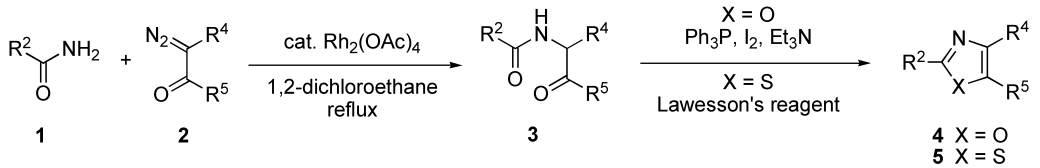
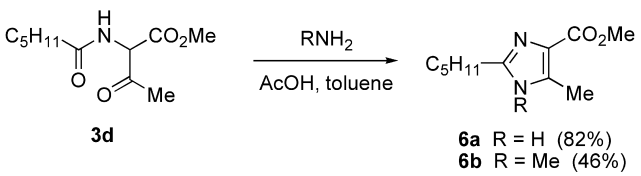
Table 1. Dirhodium(II) catalysed reactions of diazocarbonyl compounds **2** with amides **1**, and subsequent cyclisation of the ketoamides **3** to oxazoles **4** and thaizoles **5**



Amide **1**	R^2	Diazo **2**	R^4	R^5	**3**-**5**	**3** Yield (%)	**4** Yield (%)	**5** Yield (%)
1a	H	**2a**	CO_2Me	Me	**a**	43	45	60
1a	H	**2f**	Ph	Ph	**b**	54	78	94
1a	H	**2a**	CO_2Me	4-Cl–C_6H_4	**c**	55[a]	65	—
1b	C_5H_{11}	**2a**	CO_2Me	Me	**d**	82[b]	79	89
1c	Ph	**2b**	CO_2Et	Me	**e**	62	80	53
1d	2-BnO-5-MeO–C_6H_3	**2a**	CO_2Me	Me	**f**	26	23	55
1d	2-BnO-5-MeO–C_6H_3	**2c**	CO_2Et	Ph	**g**	13	67	—
1e	2-Thienyl	**2a**	CO_2Me	Me	**h**	80	80	69
1e	2-Thienyl	**2d**	CO_2Me	4-Cl–C_6H_4	**i**	36	72	89
1e	2-Thienyl	**2e**	CO_2Me	4-MeO_2C–C_6H_4	**j**	74	54	34
1f	*N*-Boc-piperidin-4-yl	**2a**	CO_2Me	Me	**k**	68	66	74
1g	5-(4-Cl–C_6H_4)oxazol-4-yl	**2a**	CO_2Me	Me	**l**	65	—	40

[a] Dirhodium tetraoctanoate as catalyst in dichloromethane solvent.
[b] Dichloromethane solvent.

With a range of 1,4-dicarbonyl compounds **3** in hand, their conversion into 1,3-azoles was investigated. First, cyclodehydration, using the triphenylphosphine-iodine-triethylamine protocol developed by Wipf and Miller,[9] gave the corresponding oxazoles **4** in 23–80% yield (Table 1), oxazole **4f** being the protected form of the terminal oxazolecarboxylate in the linear lipopeptide amamistatin A.[18] The thiazoles **5** were readily formed from the 1,4-dicarbonyl compounds by thionation with Lawesson's reagent.[19,20] Thus simply heating the α-acylaminoketones **3** with Lawesson's reagent in THF gave the thiazoles **5** in 34–94% yield (Table 1). Finally, two examples of imidazole formation were studied: simply treating 1,4-dicarbonyl compound **3d** with ammonium acetate and methylamine gave the imidazoles **6a** and **6b** in 82 and 46% yield, respectively (Scheme 1).[20]



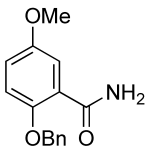
Scheme 1.

Thus by extending the scope of the rhodium carbene N–H insertion reaction, a number of α-acylaminoketones has been obtained. These 1,4-dicarbonyl compounds are useful precursors to a range of structurally diverse 1,3-azoles.

3. Experimental

3.1. General

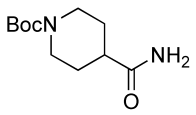
Commercially available reagents were used throughout without further purification unless otherwise stated; solvents were dried by standard procedures. Light petroleum refers to the fraction with bp 40–60 °C and ether refers to diethyl ether. Reactions were routinely carried out under a nitrogen atmosphere. Analytical thin layer chromatography was carried out using aluminium-backed plates coated with Merck Kieselgel 60 GF_{254}. Plates were visualised under UV light (at 254 and /or 360 nm). Flash chromatography was carried out using Merck Kieselgel 60 H silica or Matrex silica 60. Fully characterised compounds were chromatographically homogeneous. IR spectra were recorded in the range 4000–600 cm^{-1} using a Nicolet Magna FT-550 spectrometer. ^1H and ^{13}C NMR spectra were recorded using Bruker 300 and 400 MHz instruments (^1H frequencies, corresponding ^{13}C frequencies are 75 and 100 MHz); *J* values were recorded in Hz. In the ^{13}C NMR spectra, signals corresponding to CH, CH_2 or Me groups are noted; all others are C. High and low-resolution mass spectra were recorded on a Micromass GCT TOF High Resolution Mass Spectrometer, or at the EPSRC Mass Spectrometry Service (Swansea).



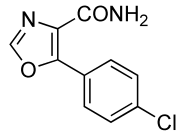
3.1.1. 2-Benzyloxy-5-methoxybenzamide 1d. (a) To a solution of 5-methoxysalicylic acid (2.00 g, 12 mmol) and potassium carbonate (8.20 g, 59 mmol) in DMF (40 ml) cooled to 0 °C was added benzyl bromide (4.24 ml, 36 mmol). The mixture was then stirred at 0 °C for 30 min and then overnight at ambient temperature. Ethyl acetate (100 ml) was added to the mixture and washed with aqueous potassium hydrogen sulfate (1 M; 100 ml), water (100 ml), saturated potassium hydrogen carbonate solution (100 ml) and saturated brine (100 ml). The organic layer was dried ($MgSO_4$) and concentrated to give a dark oil that was then dissolved in methanol (38 ml) and sodium hydroxide solution (40%, 12 ml) and stirred at ambient for 1 h. The reaction mixture was then acidified to pH 1 with dilute

hydrochloric acid solution (30 ml) and extracted with diethyl ether (3×15 ml). The organic extracts were dried ($MgSO_4$) and concentrated to yield the crude compound which was recrystallised from hexane–ethyl acetate (3:2) to yield 2-benzyloxy-5-methoxybenzoic acid as a colourless crystalline solid (1.70 g, 63%); mp 95–96 °C (lit.[18] mp 85–87 °C); ν_{max}(KBr)/cm^{-1} 3440, 3001, 2962, 2929, 2910, 2835, 1695, 1597, 1502, 1454, 1416, 1389, 1329, 1296, 1221, 1047, 1018, 914, 874, 854, 822, 744, 700; δ_H (300 MHz; $CDCl_3$) 9.70 (1H, s br, OH), 7.70 (1H, m, ArH), 7.43 (5H, m, ArH), 7.09 (2H, m, ArH), 5.26 (2H, s, OC*H*$_2$Ph), 3.83 (3H, s, OMe); δ_C (75 MHz; $CDCl_3$) 165.5, 155.0, 151.9, 134.8, 129.6 (CH), 129.5 (CH), 128.4 (CH), 122.5 (CH), 119.0, 116.6 (CH), 115.3 (CH), 73.4 (CH_2), 56.3 (Me).

(b) To a solution of the above acid (1.50 g, 58 mmol) and triethylamine (0.81 ml, 58 mmol) in THF (35 ml) cooled to 0 °C was added ethyl chloroformate (0.56 ml, 58 mmol) and stirred for 15 min. Ammonia solution (30%, 35 ml) in THF (15 ml) was then added to the reaction and stirred for 15 min and then concentrated. The solid residue was then partition with dichloromethane (30 ml) and water (30 ml). The aqueous was then washed again with dichloromethane (30 ml) and the combined organics were washed with saturated sodium hydrogen carbonate solution (30 ml), brine (30 ml), dried ($MgSO_4$) and concentrated to yield the title compound as a light brown crystalline solid (1.33g, 89%); mp 121–123 °C; (Found: M$^+$, 257.1064. $C_{15}H_{15}NO_3$ requires 257.1052); ν_{max}(KBr)/cm^{-1} 3452, 2426, 3314, 3252, 3160, 2924, 2827, 1660, 1598, 1578, 1491, 1429, 1368; δ_H (300 MHz; $CDCl_3$) 7.82 (2H, m, ArH), 7.40 (4H, m, ArH), 7.01 (2H, m, ArH), 5.84 (2H, s br, NH_2), 5.14 (2H, s, OC*H*$_2$Ph), 3.83 (3H, s, OMe); *m*/*z* (CI) 257 (M$^+$, 71%), 241 (22), 215 (10), 195 (7), 181 (3), 151 (16), 137 (7), 119 (3), 91 (54).



3.1.2. 1-*tert*-Butoxycarboxypiperidine-4-carboxamide 1f. To a stirred solution of the piperidine-4-carboxamide (1.00 g, 7.8 mmol) and di-*tert*-butyl dicarbonate (2.20 g, 10.1 mmol) in acetonitrile (15 ml) was added DMAP (95 mg, 0.78 mmol). The resulting solution was stirred overnight and then the solvent was removed under reduced pressure. The solid residue was then dissolved in dichloromethane (40 ml) and washed with saturated sodium hydrogen carbonate solution (40 ml). The aqueous was then extracted with dichloromethane (40 ml) and then the combined organic extracts were washed with saturated ammonium chloride solution (60 ml), water (60 ml) and brine (60 ml) and then dried ($MgSO_4$) and concentrated to yield the desired product as a colourless solid (1.70 g, 92%); mp 152–155 °C (lit.[21] mp 154–156 °C); ν_{max}(KBr)/cm^{-1} 3363, 3190, 2976, 2935, 2860, 1687, 1660, 1632, 1479, 1435, 1365, 1288, 1234, 1180, 1146, 1119, 1034, 926, 872, 769; δ_H (300 MHz; $CDCl_3$) 5.79 (1H, s, NH), 5.64 (1H, s, NH), 4.11 (2H, m, 2×CH), 2.72 (2H, m, 2×CH), 2.28 (1H, m, CH), 1.64 (2H, m, 2×CH), 1.57 (2H, m, 2×CH), 1.44 (9H, s, CMe_3); δ_C (75 MHz; $CDCl_3$) 177.4, 155.0, 80.1, 43.6 (CH), 29.0 (CH_2), 43.0 (CH_2), 28.8 (Me); *m*/*z* (CI) 229 (MH$^+$, 15%), 217 (4), 201 (14), 184 (2), 174 (6), 173 (100), 156 (7), 155 (76), 129 (6), 112 (7), 106 (2).



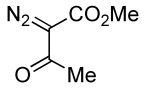
3.1.3. 5-(4-Chlorophenyl)-oxazole-4-carboxamide 1g. (a) A solution of oxazole ester **4c** (500 mg, 2 mmol) and sodium hydroxide (421 mg, 10 mmol) in THF (25 ml) and water (8 ml) was stirred overnight. The reaction mixture was concentrated and the residue was partitioned between dichloromethane (80 ml) and water (80 ml). The aqueous layer was then acidified to pH 1 with diluted hydrochloric acid and extracted with dichloromethane (150 ml). The organic layer was then washed with brine (75 ml), dried ($MgSO_4$) and the solvent removed under reduced pressure to 5-(4-chlorophenyl)oxazole-4-carboxylic acid as a colourless crystalline solid (411 mg, 87%); mp 178–179 °C; (Found: C, 53.5; H, 2.3; N, 6.1. $C_{10}H_6ClNO_3$ requires C, 53.7; H, 2.7; N, 6.3%); (Found: M$^+$, 224.0131. $C_{10}H_6^{35}ClNO_3$ requires 224.0114); ν_{max}(KBr)/cm^{-1} 3128, 3035, 2956, 2924, 2854, 1722, 1701, 1585, 1535, 1491, 1294, 1273, 1234, 1126, 1099, 1068, 1016, 989, 951, 883, 793, 762, 729, 640; δ_H (300 MHz; $CDCl_3$) 8.10 (2H, d, *J*=8.7 Hz, ArH), 7.93 (1H, s, H-2), 7.41 (2H, d, *J*=8.7 Hz, ArH), 5.66 (1H, br s, OH); δ_C (75 MHz; $CDCl_3$) 163.2, 153.1, 151.3 (CH), 135.3, 130.4 (CH), 129.0 (CH), 127.6, 126.0; *m*/*z* (CI) 226/224 (M$^+$, 7/13%), 209 (4), 208/206 (33/100), 182/180 (5/15), 179 (7), 154/152 (3/7), 139 (11), 125 (5).

(b) To a solution of the above acid (480 mg, 2 mmol) and triethylamine (0.30 ml, 2 mmol) in THF (30 ml) cooled to 0 °C was added ethyl chloroformate (0.21 ml, 2 mmol), and the mixture stirred for 15 min at 0 °C. Aqueous ammonia (30% w/w, 20 ml) and THF (15 ml) were then added, and the reaction mixture was stirred at ambient for 15 min. The reaction mixture was then concentrated under reduced pressure and the residue partitioned between water (100 ml) and dichloromethane (100 ml). The aqueous layer was extracted with further dichloromethane (100 ml) and the combined organics were washed with saturated sodium hydrogen carbonate solution (100 ml) and brine (100 ml), dried (Mg_2SO_4) and the solvent removed under reduced pressure to yield the title compound as a colourless crystalline solid (275 mg, 58%); mp 245–247 °C; (Found: M$^+$, 222.0194. $C_{10}H_7^{35}ClN_2O_2$ requires 222.0196); ν_{max}(KBr)/cm^{-1} 2404, 3361, 3290, 3201, 3128, 3080, 2924, 2852, 1699, 1608, 1597, 1533, 1491, 1400, 1329, 1257, 1194, 1119, 1093, 1061, 1016, 987, 953, 835, 793, 742, 708, 667; δ_H (300 MHz; $CDCl_3$) 8.51 (1H, s, H-2), 8.18 (2H, d, *J*=8.7 Hz, ArH), 7.72 (1H, s, NH), 7.60 (1H, s, NH), 7.51 (2H, d, *J*=8.7 Hz, ArH); δ_C (75 MHz; DMSO) 163.0, 150.6 (CH), 150.5, 150.4, 134.8, 129.9 (CH), 128.9 (CH), 126.2; *m*/*z* (CI) 224/222 (M$^+$, 11/17%), 221 (5), 208/206 (34/100), 187 (4), 186 (12).

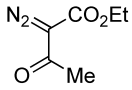
3.2. General method for diazo transfer

To a solution of the β-ketoester substrate (10 mmol) and

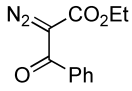
4-acetamidobenzenesulfonyl azide[16] (11 mmol) in acetonitrile (60 ml) at 0 °C was added triethylamine (30 mmol) dropwise. After stirring at room temperature for 16 h the reaction mixture was concentrated in vacuo and the resultant solid was triturated with ether–light petroleum. The filtrate was concentrated in vacuo and purified by flash chromatography on silica gel eluting with ethyl acetate–light petroleum (1:4) to yield the desired product.



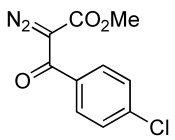
3.2.1. Methyl 2-diazo-3-oxobutanoate 2a. Obtained as a yellow oil according to the general procedure in 92% yield; data as previously described.[10]



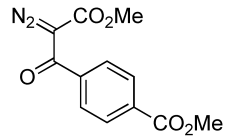
3.2.2. Ethyl 2-diazo-3-oxobutanoate 2b. According to the general procedure the title compound was obtained as a yellow oil (83%) (lit.[22] data not given); (Found: M^+, 156.0531. $C_6H_8N_2O_3$ requires 156.0535); ν_{max}(film)/cm^{-1} 2985, 2939, 2912, 2877, 2141, 1716, 1660, 1595, 1533, 1458, 1373, 1319, 1251, 1155, 1074, 1022, 966, 858, 744, 639; δ_H (300 MHz; $CDCl_3$) 4.24 (2H, q, J=7.1 Hz, OC*H*$_2$Me), 2.41 (3H, s, Me), 1.27 (3H, t, J=7.1 Hz, CH$_2$*Me*); δ_C (75 MHz; $CDCl_3$) 188.4, 159.5, 74.5, 59.6 (CH_2), 26.4 (Me), 12.4 (Me); *m*/*z*(CI) 156 (M^+, 26%), 129 (16), 111 (4), 102 (5), 101 (100), 87 (3), 85 (17), 83 (8).



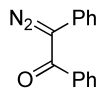
3.2.3. Ethyl 2-diazo-3-oxo-3-phenylpropanoate 2c. According to the general procedure, the title compound was obtained as a yellow oil (99%) (lit.[22] data not given); (Found: C, 60.8; H, 4.8; N, 13.0. $C_{11}H_{10}N_2O_3$ requires C, 60.6; H, 4.6; N, 12.9%); ν_{max}(film)/cm^{-1} 3058, 2976, 2940, 2904, 2868, 2136, 1721, 1685, 1629, 1598, 1578, 1450, 1368, 1301, 1260, 1178, 1112, 1015, 938, 917, 789, 748, 692, 671; δ_H (300 MHz; $CDCl_3$) 7.62 (2H, m, ArH), 7.52 (1H, m, ArH), 7.40 (2H, m, ArH), 4.24 (2H, q, J=7.3 Hz, OC*H*$_2$Me), 1.25 (3H, t, J=7.3 Hz, CH$_2$*Me*); δ_C (75 MHz; $CDCl_3$) 186.9, 160.9, 137.0, 132.2 (CH), 128.4 (CH), 128.0 (CH), 76.1, 61.4 (CH_2), 14.0 (Me); *m*/*z* (CI) 218 (M^+, 8%), 193 (65), 175 (21), 163 (100), 145 (85), 105 (53), 91 (4).



3.2.4. Methyl 3-(4-chlorophenyl)-2-diazo-3-oxopropanoate 2d. According to the general procedure the title compound was obtained as a yellow solid (89%); mp 104 °C (chloroform) (lit.[23] mp 105.5–107.5 °C); (Found: C, 50.1; H, 2.7; N, 11.7. $C_{10}H_7ClN_2O_3$ requires C, 50.3; H, 2.9; N, 11.7%); ν_{max}(KBr)/cm^{-1} 2955, 2919, 2848, 2141, 1716, 1624, 1583, 1434, 1342, 1265, 1127, 1086, 1015, 968, 902, 840, 753, 733, 687; δ_H (300 MHz; $CDCl_3$) 7.51 (2H, d, J=8.7 Hz, ArH), 7.32 (2H, d, J=8.7 Hz, ArH), 3.73 (3H, s, OMe); δ_C (75 MHz; $CDCl_3$) 183.7, 159.3, 136.7, 133.2, 128.0 (CH), 126.3 (CH), 74.6, 50.5 (Me); *m*/*z* (EI) 240/238 (M^+, 10/39%), 212 (7), 210 (15), 154 (4), 152 (8), 141 (67), 139 (100), 123 (48), 111 (78), 75 (47).



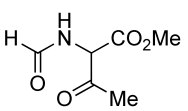
3.2.5. Methyl 2-diazo-3-(4-methoxycarbonylphenyl)-3-oxopropanoate 2e. According to the general procedure the title compound was obtained as a yellow solid (99%); mp 70–72 °C (ethyl acetate–light petroleum); (Found: C, 55.1; H, 3.6; N, 10.8. $C_{12}H_{10}N_2O_5$ requires C, 55.0; H, 3.8; N, 10.7%) (Found: M^+, 262.0588. $C_{12}H_{10}N_2O_5$ requires 262.0590); ν_{max}(KBr)/cm^{-1} 3027, 2950, 2996, 2919, 2853, 2131, 1721, 1624, 1434, 1409, 1281, 1189, 1132, 1107, 1020, 974, 963, 902, 866, 820, 784, 743, 707, 677; δ_H (300 MHz; $CDCl_3$) 8.02 (2H, d, J=8.6 Hz, ArH), 7.59 (2H, d, J=8.6 Hz, ArH), 3.87 (3H, s, OMe), 3.72 (3H, s, OMe); δ_C (75 MHz; $CDCl_3$) 186.8, 166.6, 161.5, 141.2, 133.5, 129.5 (CH), 128.6 (CH), 52.9 (Me), 52.8 (Me), diazo carbon not observed; *m*/*z*(CI) 262 (M^+, 11%), 235 (20), 205 (6), 204 (10), 203 (100), 191 (16), 179 (4), 163 (28), 159 (11), 131 (4).



3.2.6. Azibenzil 2f. Prepared in 87% yield by oxidation of benzil monohydrazone (2.50 g, 11 mmol) in chloroform (38 ml) using activated manganese dioxide (3.90 g, 44 mmol) according to the literature procedure,[17] mp 78–80 °C (lit.[24] mp 79–80 °C).

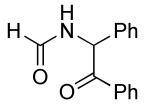
3.3. General procedure for N–H insertion reactions; preparation of α-acylamino ketones 3

To a solution of the amide **1** (5 mmol) and dirhodium tetraacetate (2.5 mol%) in 1,2-dichloroethane (10 ml), heated to reflux, was added a solution of the diazo compound **2** (7 mmol) in 1,2-dichloroethane dropwise over 16 h. The reaction mixture was then heated for a further 2–4 h until TLC analysis showed that the reaction was complete. The mixture was evaporated in vacuo and purified on silica gel eluting with ethyl acetate–light petroleum (1:4) to yield the product.

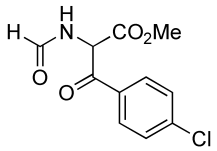


3.3.1. *N*-(1-Methoxycarbonyl-2-oxopropyl)formamide 3a. According to the general procedure, using formamide **1a**, diazo compound **2a** and 1,2-dichloromethane as solvent, the title compound was obtained as a colourless crystalline solid (43%); mp 68–70 °C (ethyl acetate–light petroleum); (Found: C, 45.2; H, 5.7; N, 8.7. $C_6H_9NO_4$ requires C, 45.3; H, 5.7; N, 8.8%); (Found: M^+, 160.0623. $C_6H_9NO_4$ requires 160.0610); ν_{max}(KBr)/cm^{-1} 3319, 3017, 2950, 2925, 2894,

2853, 1747, 1721, 1639, 1521, 1434, 1388, 1373, 1347, 1250, 1209, 1163, 1107, 1035, 968, 933, 886, 758, 661, 600; δ_H (300 MHz; $CDCl_3$) 8.28 (1H, s, CHO), 7.85 (1H, s br, NH), 5.34 (1H, d, *J*=7.0 Hz, C*H*NH), 3.86 (3H, s, OMe), 2.43 (3H, s, Me); δ_C (75 MHz; $CDCl_3$) 198.0, 166.5, 160.8 (CH), 62.0 (CH), 53.9 (Me), 28.4 (Me); *m*/*z* (CI) 160 (M^+, 36%), 156 (6), 132 (100), 128 (53), 117 (11), 85 (6), 83 (16).



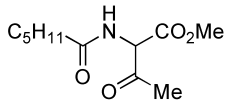
3.3.2. *N*-(2-Oxo-1,2-diphenylethyl)formamide 3b. To a suspension of formamide **1a** (234 mg, 5 mmol) and dirhodium tetraacetate (62 mg, 0.12 mmol) in dichloromethane (20 ml) was added a solution of azibenzil **2f** (1.5 g, 6.7 mmol) in dichloromethane (30 ml) over 15 min and stirred at room temperature overnight. The reaction was the heated to reflux for 4 h and then evaporated in vacuo and purified on silica gel eluting with ethyl acetate–light petroleum (2:3) to yield the title product as a beige solid (670 mg, 54%); mp 119–120 °C (lit.[25] mp 122 °C); (Found: C, 74.9; H, 5.5; N, 5.7. $C_{15}H_{13}NO_2$ requires C, 75.3; H, 5.5; N, 5.9%); ν_{max}(KBr)/cm^{-1} 3370, 3063, 3032, 2919, 2858, 2751, 1690, 1660, 1593, 1578, 1491, 1445, 1383, 1322, 1296, 1255, 1219, 1189, 1066, 984, 933, 881, 851, 779, 758, 738, 692, 677, 656; δ_H (300 MHz; $CDCl_3$) 8.28 (1H, s, CHO), 7.99 (2H, m, ArH), 7.54 (1H, m, NH), 7.42 (4H, m, ArH), 7.32 (4H, m, ArH), 6.66 (1H, d, *J*=7.4 Hz, C*H*NH); δ_C (75 MHz; $CDCl_3$) 195.6, 160.7 (CH), 137.3, 134.5, 134.4 (CH), 129.8 (CH), 129.7 (CH), 129.3 (CH), 129.0 (CH), 128.7 (CH), 57.6 (CH); *m*/*z* (CI) 239 (M^+, 3%), 212 (51), 196 (12), 195 (94), 167 (7), 149 (4), 134 (8), 105 (4).



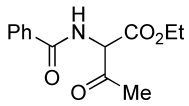
3.3.3. *N*-[2-(4-Chlorophenyl)-1-methoxycarbonyl-2-oxoethyl]formamide 3c. (a) According to the general procedure, using formamide **1a**, diazo compound **2d** and 1,2-dichloroethane as solvent, the title compound was obtained as a colourless solid (21%); mp 116–119 °C (lit.[26] mp 116–118 °C); (Found: C, 51.8; H, 3.7; N, 5.2. $C_{11}H_{10}ClNO_4$ requires C, 51.7; H, 3.9; N, 5.5%); ν_{max}(KBr)/cm^{-1} 3365, 3091, 3076, 3045, 3012, 2958, 2941, 2912, 2877, 2848, 1747, 1699, 1666, 1585, 1570, 1498, 1435, 1406, 1354, 1273, 1252, 1211, 1190, 1167, 1093, 999, 964, 849, 762, 660, 611, 538, 472; δ_H (300 MHz; $CDCl_3$) 8.23 (1H, s, CHO), 8.00 (2H, d, *J*=8.7 Hz, ArH), 7.43 (2H, d, *J*=8.7 Hz, ArH), 6.98 (1H, d, *J*=7.5 Hz, NH), 6.17 (1H, d, *J*=7.5 Hz, C*H*NH), 3.68 (3H, s, OMe); δ_C (75 MHz; $CDCl_3$) 190.2, 166.9, 160.9 (CH), 141.8, 132.5, 131.4 (CH), 129.7 (CH), 56.8 (CH), 54.0 (Me); *m*/*z* (EI) 255/257 (M^+, 7/1%), 227 (4), 224 (16), 223 (3), 196 (31), 168 (7), 140 (100), 139 (64), 133 (47), 113 (84), 112 (99), 111 (96), 104 (28), 85 (23), 77 (45), 75 (69), 51 (59).

(b) According to the general procedure, using dichloromethane as solvent, the title compound was obtained as a colourless solid (41%). See above for data.

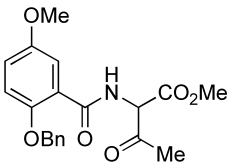
(c) According to the general procedure, using dichloromethane as solvent and dirhodium tetraoctanoate as catalyst, the title compound was obtained as a colourless solid (55%). See above for data.



3.3.4. *N*-(1-Methoxycarbonyl-2-oxopropyl)hexanamide 3d. According to the general procedure, using hexanamide **1b**, diazo compound **2a** and dichloromethane as solvent the title compound was isolated as an oily solid (82%); mp 44–46 °C; (Found: MH^+, 230.1387. $C_{11}H_{20}NO_4$ requires 230.1392); ν_{max}(film)/cm^{-1} 3375, 3298, 2960, 2925, 2868, 1752, 1726, 1665, 1511, 1434, 1358, 1271, 1214, 1158, 1025, 968; δ_H (300 MHz; $CDCl_3$) 6.70 (1H, app s, NH), 5.23 (1H, d, *J*=6.5 Hz, C*H*NH), 3.77 (3H, s, CO_2Me), 2.33 (3H, s, Me), 2.23 (2H, t, *J*=7.4 Hz, CH_2CO), 1.58 (2H, m, CH_2), 1.23 (4H, m, 2×CH_2), 0.83 (3H, m, Me); δ_C (75 MHz; $CDCl_3$) 199.1, 173.4, 167.1, 63.2 (Me), 53.7 (CH), 36.3 (CH_2), 31.7 (CH_2), 28.5 (Me), 25.4 (CH_2), 22.7 (CH_2), 14.3 (Me); *m*/*z* (CI) 230 (MH^+, 76%), 228 (14), 215 (13), 187 (25), 155 (4), 133 (7), 132 (100), 131 (4), 117 (4).

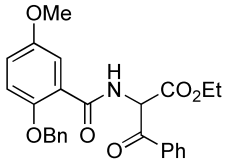


3.3.5. *N*-(1-Ethoxycarbonyl-2-oxopropyl)benzamide 3e. According to the general procedure using benzamide **1c** and diazo compound **2b**, the title compound was obtained as a colourless oil (62%) (lit.[27] data not given); (Found: M^+, 250.1080. $C_{13}H_{15}NO_4$ requires 250.1079); ν_{max}(film)/cm^{-1} 3401, 3058, 3027, 2981, 2940, 2868, 1752, 1726, 1659, 1603, 1578, 1516, 1481, 1445, 1373, 1337, 1265, 1209, 1178, 1102, 1071, 1015, 861, 799, 712, 692; δ_H (300 MHz; $CDCl_3$) 7.83 (2H, m, ArH), 7.46 (3H, m, ArH), 7.41 (1H, d, *J*=6.4 Hz, NH), 5.43 (1H, d, *J*=6.4 Hz, C*H*NH), 4.29 (2H, q, *J*=7.1 Hz, OCH_2Me), 2.46 (3H, s, Me), 1.29 (3H, t, *J*=7.1 Hz, CH_2Me); δ_C (75 MHz; $CDCl_3$) 199.1, 167.2, 166.5, 133.4, 132.5 (CH), 129.0 (CH), 127.6 (CH), 63.9 (CH), 63.1 (CH_2), 20.5 (Me), 14.4 (Me); *m*/*z* (CI) 250 (M^+, 88%), 233 (4), 232 (23), 208 (6), 207 (50), 204 (71), 188 (3), 172 (3), 161 (13), 160 (3), 133 (5), 122 (7), 105 (100).

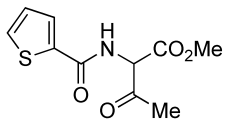


3.3.6. 2-Benzyloxy-5-methoxy-*N*-(1-methoxycarbonyl-2-oxopropyl)benzamide 3f. According to the general procedure using amide **1d** and diazo compound **2a** the title compound was obtained as a colourless solid (26%); mp 65–67 °C (ethyl acetate–light petroleum) (lit.[18] mp not given); (Found: M^+, 371.1362. $C_{20}H_{21}NO_6$ requires 371.1369); ν_{max}(KBr)/cm^{-1} 3437, 3365, 2924, 2356, 2336, 1752, 1721, 1644, 1603, 1496, 1455, 1440, 1388, 1352, 1306, 1281, 1214, 1173, 1143, 1040, 999, 892, 856, 815, 769, 743, 697, 666, 615; δ_H (300 MHz; $CDCl_3$) 9.23

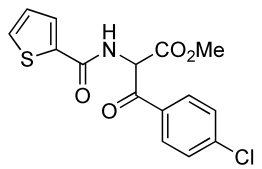
(1H, d, *J*=6.0 Hz, NH), 7.70 (1H, m, ArH), 7.40 (5H, m, ArH), 6.98 (2H, m, ArH), 5.43 (1H, d, *J*=6.0 Hz, C*H*NH), 5.26 (2H, s, OCH_2Ph), 3.80 (3H, s, OMe), 3.74 (3H, s, OMe), 2.36 (3H, s, Me); δ_C (100 MHz; $CDCl_3$) 198.6, 166.6, 164.7, 154.0, 151.4, 135.7, 128.7 (CH), 128.4 (CH), 128.0 (CH), 121.2, 120.2 (CH), 115.3 (CH), 115.0 (CH), 72.1 (CH_2), 63.9 (CH), 55.8 (Me), 53.1 (Me), 27.9 (Me); *m*/*z*(EI) 371 (M^+, 3%), 353 (4), 281 (3), 258 (6), 257 (47), 255 (6), 231 (3), 178 (6), 151 (45), 150 (65), 102 (59), 91 (100), 59 (7).



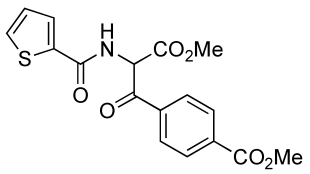
3.3.7. 2-Benzyloxy-*N*-(1-ethoxycarbonyl-2-oxo-2-phenylethyl)-5-methoxybenzamide 3g. According to the general procedure, using amide **1d** and diazo compound **2c**, the title compound was obtained as a colourless solid (13%); mp 85–88 °C (diethyl ether); (Found: C, 69.8; H, 5.5; N, 3.0. $C_{26}H_{25}NO_6$ requires C, 69.8; H, 5.6; N, 3.1%); ν_{max}(KBr)/cm^{-1} 3334, 3088, 3073, 2996, 2976, 2950, 2930, 2899, 2832, 1737, 1690, 1655, 1614, 1598, 1578, 1506, 1486, 1445, 1281, 1224, 1204, 1184, 1158, 1086, 1045, 1025, 979, 948, 902, 815, 769, 743, 687, 645; δ_H (300 MHz; $CDCl_3$) 9.66 (1H, d, *J*=7.1 Hz, NH), 8.34 (2H, d, *J*=7.7 Hz, ArH), 7.94 (1H, s, H-6), 7.82 (1H, m, ArH), 7.71 (3H, m, ArH), 7.62–7.48 (4H, m, ArH), 7.19 (2H, m, ArH), 6.59 (1H, d, *J*=7.1 Hz, C*H*NH), 5.50 (2H, s, OCH_2Ph), 4.36 (2H, q, *J*=7.0 Hz, CH_2Me), 4.01 (3H, s, OMe), 1.34 (3H, t, *J*=7.0 Hz, CH_2*Me*); δ_C (75 MHz; $CDCl_3$) 191.2, 166.4, 164.4, 153.5, 151.0, 135.4, 134.1 (CH), 133.8, 129.1 (CH), 128.4 (CH), 128.3 (CH), 127.9 (CH), 127.4 (CH), 121.1, 119.8 (CH), 114.9 (CH), 114.7 (CH), 71.6 (CH_2), 61.9 (CH_2), 58.8 (CH), 55.4 (Me), 13.5 (Me); *m*/*z* (EI) 447 (M^+, 22%), 429 (53), 401 (16), 357 (20), 340 (26), 339 (44), 297 (20), 258 (28), 257 (100), 239 (57), 212 (28), 151 (50), 150 (85), 91 (94).



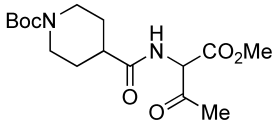
3.3.8. *N*-(1-Methoxycarbonyl-2-oxopropyl)thiophene-2-carboxamide 3h. According to the general procedure, using thiophene-2-carboxamide **1e**, diazo compound **2a** and 1,2-dichloromethane as solvent, the title compound was obtained as a colourless oil (80%); (Found: C, 49.8; H, 4.5; N, 5.4. $C_{10}H_{11}NO_4S$ requires C, 49.8; H, 4.6; N, 5.8%); ν_{max}(film)/cm^{-1} 3334, 3088, 3073, 2996, 2976, 2950, 2930, 2899, 2832, 1737, 1690, 1655, 1614, 1598, 1578, 1506, 1486, 1445, 1281, 1224, 1204, 1184, 1158, 1086, 1045, 1025, 979, 948, 902, 815, 769, 743, 687, 645; δ_H (300 MHz; $CDCl_3$) 7.61 (1H, dd, *J*=1.1, 3.8 Hz, ArH), 7.51 (1H, dd, *J*=1.1, 4.9 Hz, ArH), 7.19 (1H, d, *J*=6.4 Hz, NH), 7.08 (1H, dd, *J*=3.8, 4.9 Hz, ArH), 5.40 (1H, d, *J*=6.4 Hz, C*H*NH), 3.82 (3H, s, OMe), 2.42 (3H, s, OMe); δ_C (75 MHz; $CDCl_3$) 198.7, 166.9, 161.7, 137.6, 131.5 (CH), 129.5 (CH), 128.2 (CH), 63.6 (CH), 53.9 (Me), 28.5 (Me); *m*/*z* (EI) 241 (M^+, 20%), 199 (85), 167 (63), 112 (18), 110 (100), 83 (14).



3.3.9. *N*-[2-(4-Chlorophenyl)-1-methoxycarbonyl-2-oxoethyl)thiophene-2-carboxamide 3i. According to the general procedure, using thiophene-2-carboxamide **1e**, diazo compound **2d** and 1,2-dichloromethane as solvent, the title compound was obtained as a colourless crystalline solid (36%); mp 100 °C (diethyl ether); (Found: C, 53.2; H, 3.4; N, 4.0. $C_{15}H_{12}ClNO_4S$ requires C, 53.3; H, 3.6; N, 4.2%); ν_{max}(KBr)/cm^{-1} 3421, 3314, 3109, 3088, 3073, 3037, 2991, 2950, 2843, 1737, 1685, 1644, 1619, 1578, 1532, 1501, 1432, 1358, 1312, 1271, 1224, 1199, 1158, 1086, 1004, 958, 927, 861, 840, 764, 712, 605; δ_H (300 MHz; $CDCl_3$) 8.12 (2H, d, *J*=8.7 Hz, ArH), 7.64 (1H, dd, *J*=1.1, 3.9 Hz, ArH), 7.54 (1H, dd, *J*=1.1, 5.0 Hz, ArH), 7.50 (2H, d, *J*=8.7 Hz, ArH), 7.32 (1H, d, *J*=7.1 Hz, NH), 7.11 (1H, dd, 3.9, 5.0, ArH), 6.31 (1H, d, *J*=7.1 Hz, C*H*NH), 3.75 (3H, s, OMe); δ_C (75 MHz; $CDCl_3$) 190.7, 167.3, 161.8, 141.7, 137.6, 132.8, 131.6 (CH), 131.4 (CH), 129.7 (CH), 129.6 (CH), 128.2 (CH), 58.5 (CH), 53.5 (Me); *m*/*z* (CI) 340/338 (M^+, 32/100%), 322/320 (3/7), 308/306 (13/39), 278 (3), 254 (6), 226 (4), 140 (3), 138 (6).

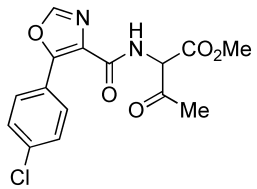


3.3.10. *N*-[1-Methoxycarbonyl-2-(4-methoxycarbonylphenyl)-2-oxoethyl)thiophene-2-carboxamide 3j. According to the general procedure, using thiophene-2-carboxamide **1e**, diazo compound **2e** and 1,2-dichloromethane as solvent the title compound was obtained as a colourless crystalline solid (74%); mp 188–190 °C (diethyl ether); (Found: C, 56.3; H, 4.1; N, 3.7. $C_{17}H_{15}NO_6S$ requires C, 56.5; H, 4.2; N, 3.9%); ν_{max}(KBr)/cm^{-1} 3309, 3249, 3113, 3097, 3067, 3041, 3017, 2957, 2848, 1710, 1690, 1634, 1530, 1502, 1453, 1433, 1421, 1405, 1361, 1317, 1285, 1261, 1237, 1205, 1169, 1113, 1041, 1005, 964, 928, 872; δ_H (300 MHz; $CDCl_3$) 8.22 (2H, d, *J*=8.7 Hz, ArH), 8.17 (2H, d, *J*=8.7 Hz, ArH), 7.65 (1H, dd, *J*=1.1, 3.8 Hz, ArH), 7.54 (1H, dd, *J*=1.1, 4.9 Hz, ArH), 7.33 (1H, d, *J*=7.3 Hz, NH), 7.11 (1H, dd, *J*=3.8, 4.9 Hz, ArH), 6.37 (1H, d, *J*=7.3 Hz, C*H*NH), 3.96 (3H, s, OMe), 3.75 (3H, s, OMe); δ_C (75 MHz; $CDCl_3$) 191.7, 167.1, 166.3, 161.8, 137.7, 137.5, 135.4, 131.6 (CH), 130.4 (CH), 129.9 (CH), 129.7 (CH), 128.2 (CH), 58.8 (CH), 53.9 (Me), 53.0 (Me); *m*/*z* (CI) 362 (M^+, 100%), 344 (7), 330 (25), 278 (3), 176 (3), 163 (8).



3.3.11. 1-*tert*-Butyloxycarbonyl-*N*-(1-methoxycarbonyl-2-oxopropyl)piperidine-4-carboxamide 3k. According to

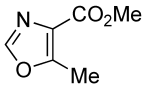
the general procedure the title product was isolated from reaction of amide **1f** and diazo compound **2a** in dichloromethane as an oily solid (68%); mp 76–79 °C; (Found: MH^+, 343.1871. $C_{16}H_{27}N_2O_6$ requires 343.1869); ν_{max}(KBr)/cm^{-1} 3280, 3057, 2978, 2960, 2937, 2860, 1757, 1695, 1639, 1541, 1435, 1365, 1342, 1279, 1250, 1214, 1173, 1107, 968, 764, 661; δ_H (300 MHz; $CDCl_3$) 6.68 (1H, d, *J*=6.3 Hz, NH), 5.24 (1H, d, *J*=6.3 Hz, C*H*NH), 4.14–4.07 (2H, m, 2×CH), 3.81 (3H, s, OMe), 2.81–2.73 (2H, m, 2×CH), 2.39 (4H, m, Me+CH), 1.85–1.81 (2H, m, 2×CH), 1.70–1.56 (2H, m, 2×CH), 1.44 (9H, s, CMe_3); δ_C (75 MHz; $CDCl_3$) 198.7, 174.5, 166.9, 155.0, 80.1, 63.2 (CH), 53.8 (Me), 43.5 (CH_2), 43.0 (CH), 28.8 (Me), 28.7 (CH_2), 28.5 (Me); *m*/*z* (CI) 343 (MH^+, 5%), 327 (2), 315 (6), 299 (2), 288 (7), 287 (73), 269 (40), 241 (10), 218 (12), 186 (7), 174 (22), 173 (100), 155 (21), 133 (6), 131 (83), 115 (7), 102 (7), 75 (17).



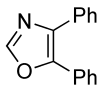
3.3.12. 5-Chlorophenyl-*N*-(1-methoxycarbonyl-2-oxo-propyl)oxazole-4-carboxamide 3l. To a solution of amide **1g** (385 mg, 1.73 mmol) and dirhodium tetraoctanoate (34 mg, 0.04 mmol) in dichloromethane (20 ml) heated to reflux was added a solution of diazo compound **2a** (320 mg, 2.25 mmol) in dichloromethane (10 ml) dropwise over 4 h. The reaction mixture was then concentrated under reduced pressure and the residue was triturated with diethyl ether to yield the title compound as a beige solid (280 mg, 48%). The trituration liquors were then reduced in vacuo and purified by flash column chromatography to yield further title compound (101 mg, 17%, total 381 mg, 65%); mp 122–125 °C; (Found: M^+, 337.0599. $C_{15}H_{13}^{35}ClN_2O_5$ requires 337.0591); ν_{max}(KBr)/cm^{-1} 3401, 3334, 3135, 3083, 3032, 2960, 2930, 2853, 1747, 1660, 1588, 1527, 1496, 1440, 1363, 1332, 1260, 1224, 1163, 1091, 1055, 1009, 979, 943, 927, 840, 784, 743 697, 641; δ_H (300 MHz; $CDCl_3$) 8.31 (1H, m, NH), 8.23 (2H, d, *J*=8.9 Hz, ArH), 7.89 (1H, s, H-2), 7.42 (2H, d, *J*=8.9 Hz, ArH), 5.40 (1H, d, *J*=6.8 Hz, C*H*NH), 3.86 (3H, s, OMe), 2.44 (3H, s, Me); δ_C (75 MHz; $CDCl_3$) 199.5, 168.0, 162.2, 154.0, 149.8 (CH), 137.9, 131.1 (CH), 130.3 (CH), 129.7, 126.7, 64.6 (CH), 55.1 (Me), 29.6 (Me); *m*/*z* (CI) 339/337 (M^+, 23/100%), 333 (9), 319 (5), 307/305 (15/51), 294 (14), 277 (5), 262 (3), 234 (2), 208/206 (3/8).

3.4. General procedure for oxazole formation

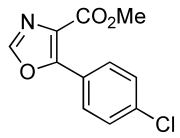
To a solution of triphenylphosphine (0.2 mmol) and iodine (0.2 mmol) in dry dichloromethane (10 ml) was added triethylamine (0.41 mmol) and then a solution of the keto amide substrate **3** in dry dichloromethane (3 ml). The reaction mixture was then stirred for 16 h and then evaporated in vacuo and purified on silica gel eluting with ethyl acetate–light petroleum (3:7) to yield the product.



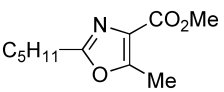
3.4.1. Methyl 5-methyloxazole-4-carboxylate 4a. According to the general procedure the title compound was obtained from **3a** as a colourless crystalline solid (45%); mp 45–47 °C (lit.[28] mp 46–48 °C); ν_{max}(KBr)/cm^{-1} 3114, 3017, 2955, 2925, 2848, 1701, 1603, 1516, 1440, 1393, 1347, 1327, 1235, 1199, 1168, 1096, 1071, 968, 943, 871, 810, 779, 656; δ_H (300 MHz; $CDCl_3$) 7.68 (1H, s, H-2), 3.85 (3H, s, OMe), 2.58 (3H, s, Me); δ_C (75 MHz; $CDCl_3$) 162.9, 157.0, 149.2 (CH), 127.5, 52.4 (Me), 12.2 (Me); *m*/*z* (FI) 141 (M^+, 100%).



3.4.2. 4,5-Diphenyloxazole 4b. According to the general procedure the title compound was obtained from **3b** as a colourless crystalline solid (78%); mp 42–43 °C (lit.[29] mp 44 °C); ν_{max}(KBr)/cm^{-1} 3122, 3076, 3026, 2926, 2852, 1674, 1603, 1510, 1477, 1443, 1363, 1217, 1124, 1107, 1068, 1053, 1026, 955, 912, 839, 762, 692, 644; δ_H (300 MHz; $CDCl_3$) 7.90 (1H, s, H-2), 7.57 (4H, m, ArH), 7.30 (6H, m, ArH); δ_C (75 MHz; $CDCl_3$) 149.5 (CH), 145.5, 134.4, 131.8 (2×C), 128.5 (CH), 128.4 (CH), 128.3 (CH), 127.9 (CH), 127.6 (CH), 126.5 (CH); *m*/*z* (EI) 237 (M^+, 22%), 195 (4), 165 (3).

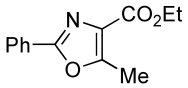


3.4.3. Methyl 5-(4-chlorophenyl)oxazole-4-carboxylate 4c. According to the general procedure the title compound was obtained from **3c** as a colourless crystalline solid (65%); mp 113–115 °C (lit.[30] mp 111–112 °C); (Found: C, 55.5; H, 3.1; N, 5.8. $C_{11}H_8ClNO_3$ requires C, 55.6; H, 3.4; N, 5.9%); ν_{max}(KBr)/cm^{-1} 3126, 3014, 2960, 2924, 2854, 1705, 1618, 1524, 1489, 1441, 1373, 1325, 1250, 1209, 1097, 1072, 1005, 823, 791, 642; δ_H (300 MHz; $CDCl_3$) 7.99 (2H, d, *J*=8.9 Hz, ArH) 7.84 (1H, s, H-2), 7.38 (2H, d, *J*=8.9 Hz, ArH), 3.87 (3H, s, OMe); δ_C (100 MHz; $CDCl_3$) 162.3, 154.7, 149.0 (CH), 136.7,129.7 (CH), 128.9 (CH), 126.6, 125.0, 52.5 (Me); *m*/*z* (CI) 237/239 (M^+, 23/13%), 234 (16), 209 (5), 208/206 (34/100), 186 (7), 139 (3).

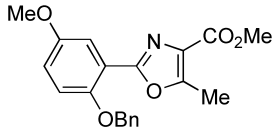


3.4.4. Methyl 5-methyl-2-pentyloxazole-4-carboxylate 4d. According to the general procedure the title compound was isolated from **3d** as a colourless oil (79%); (Found: MH^+, 212.1287. $C_{11}H_{18}NO_3$ requires 212.1287); ν_{max}(film)/cm^{-1} 2950, 2930, 2862, 1716, 1622, 1591, 1441, 1387, 1352, 1203, 1178, 1097, 980, 825, 789, 723, 641; δ_H (300 MHz; $CDCl_3$) 3.82 (3H, s, CO_2Me), 2.66 (2H, m, CH_2), 2.52 (3H, s, Me), 1.69 (2H, m, CH_2), 1.27 (4H, m, 2×CH_2), 0.83 (3H, m, Me); δ_C (75 MHz; $CDCl_3$) 163.9,

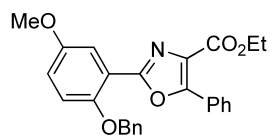
163.7, 156.8, 127.8, 52.6 (Me), 32.1 (CH_2), 28.8 (CH_2), 27.5 (CH_2), 23.1 (CH_2), 14.7 (Me), 12.7 (Me); *m/z* (CI) 212 (MH^+, 100%), 210 (8), 196 (3), 181 (5), 180 (41), 168 (6), 155 (8), 136 (2), 123 (4), 109 (1), 85 (1).



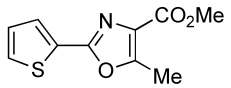
3.4.5. Ethyl 5-methyl-2-phenyloxazole-4-carboxylate 4e. According to the general procedure the title product was obtained from **3e** as a colourless solid (80%); mp 51–52 °C (ethyl acetate–light petroleum) (lit.[31] oil); (Found: C, 67.4; H, 5.7; N, 5.9. $C_{13}H_{13}NO_3$ requires C, 67.5; H, 5.7; N, 6.1%); ν_{max}(KBr)/cm^{-1} 3066, 2999, 2981, 2960, 2924, 2906, 2852, 1732, 1564, 1468, 1450, 1404, 1375, 1347, 1325, 1304, 1225, 1190, 1124, 1105, 1059, 1022, 841, 787, 710, 690; δ_H (300 MHz; $CDCl_3$) 8.07 (2H, m, ArH), 7.45 (3H, m, ArH), 4.45 (2H, q, *J*=7.1 Hz, OCH_2Me), 2.71 (3H, s, Me), 1.42 (3H, t, *J*=7.1 Hz, OCH_2*Me*); δ_C (75 MHz; $CDCl_3$) 162.9, 160.0, 156.6, 131.1 (CH), 129.2, 129.1 (CH), 127.0 (CH), 61.4 (CH_2), 14.8 (Me), 12.6 (Me), 1 Ar C unobserved; *m/z*(CI) 231 (M^+, 15%), 214 (6), 187 (4), 186 (28), 185 (4).



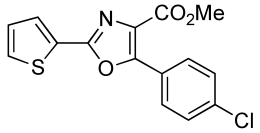
3.4.6. Methyl 2-(2-benzyloxy-5-methoxyphenyl)-5-methyloxazole-4-carboxylate 4f. According to the general procedure the title compound was obtained from **3f** as a white crystalline solid (23%); mp 96–99 °C (ethyl acetate–light petroleum) (lit.[18] mp 98–100 °C); ν_{max}(KBr)/cm^{-1} 3062, 3030, 3003, 2953, 2920, 2854, 2839, 1711, 1616, 1541, 1491, 1448, 1383, 1348, 1267, 1234, 1209, 1107, 1043, 868, 808, 781, 733, 692; δ_H (400 MHz; $CDCl_3$) 7.54 (3H, m, ArH), 7.42 (3H, m, ArH), 6.98 (2H, m, ArH), 5.14 (2H, s, OCH_2Ph), 3.95 (3H, s, CO_2Me), 3.83 (3H, s, OMe), 2.68 (3H, s, Me); δ_C (100 MHz; $CDCl_3$) 175.5, 163.0, 156.4, 153.8, 151.1, 137.0, 128.4 (CH), 128.1, 127.8 (CH), 127.0 (CH), 118.7 (CH), 117.1, 115.9 (CH), 114.3 (CH), 71.7 (CH_2), 56.0 (Me), 52.0 (Me), 12.1 (Me); *m/z*(EI) 353 (M^+, 67%), 336 (19), 321 (10), 310 (16), 279 (11), 278 (25), 277 (57), 262 (100), 231 (30), 224 (53), 216 (34), 202 (22), 174 (14), 167 (22) 150 (28), 149 (65), 125 (14), 111 (23), 97 (35), 91 (83), 71 (39), 57 (52).



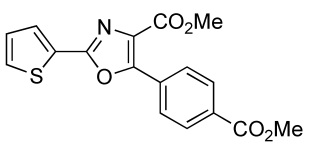
3.4.7. Ethyl 2-(2-benzyloxy-5-methoxyphenyl)-5-phenyloxazole-4-carboxylate 4g. According to the general procedure the title compound was obtained from **3g** as colourless crystalline solid (67%); mp 115–116 °C (ethyl acetate–light petroleum); (Found: C, 72.9; H, 5.4; N, 3.1. $C_{26}H_{23}NO_5$ requires C, 72.7; H, 5.4; N, 3.3%); ν_{max}(KBr)/cm^{-1} 3053, 3027, 2996, 2971, 2925, 2863, 1711, 1588, 1537, 1491, 1419, 1373, 1224, 1107, 1035, 1015, 866, 815, 743, 687; δ_H (300 MHz; $CDCl_3$) 7.71 (2H, m, ArH), 7.45 (1H, m, ArH), 7.31 (2H, m, ArH), 7.14 (6H, m, ArH), 6.83 (2H, m, ArH), 4.93 (2H, s, OCH_2Ph), 4.24 (2H, q, *J*=7.1 Hz, OCH_2Me), 3.66 (3H, s, OMe), 1.21 (3H, t, *J*=7.1 Hz, OCH_2*Me*); δ_C (75 MHz; $CDCl_3$) 162.9, 159.2, 155.6, 154.1, 151.8, 137.1, 130.4 (CH), 128.9 (2×CH), 128.7 (CH), 128.4 (CH), 128.2 (CH), 128.1, 127.6, 119.3 (CH), 117.0, 115.6 (CH), 115.1 (CH), 72.0 (CH_2), 61.8 (CH_2), 56.4 (Me), 14.7 (Me); *m/z*(EI) 429 (M^+, 34%), 412 (7), 383 (4), 355 (7), 338 (45), 324 (8), 293 (4), 279 (10), 277 (6), 224 (15), 167 (26), 151 (45), 149 (100), 139 (9), 113 (13), 105 (28), 91 (66), 71 (38), 57 (55).



3.4.8. Methyl 5-methyl-2-(thien-2-yl)oxazole-4-carboxylate 4h. According to the general procedure the title compound was obtained from **3h** as a colourless crystalline solid (80%), 158–159 °C (diethyl ether); (Found: C, 53.8; H, 3.9; N, 6.2. $C_{10}H_9NO_3S$ requires C, 53.8; H, 4.1; N, 6.3%); ν_{max}(KBr)/cm^{-1} 3078, 3063, 2991, 2945, 2914, 2852, 1726, 1639, 1603, 1588, 1496, 1440, 1414, 1368, 1317, 1260, 1219, 1178, 1107, 1055, 1015, 984, 856, 810, 779, 769, 712, 646, 630; δ_H(300 MHz; $CDCl_3$) 7.72 (1H, dd, *J*=1.1, 3.8 Hz, ArH), 7.45 (1H, dd, *J*=1.1, 5.1 Hz, ArH), 7.10 (1H, dd, *J*=3.8, 5.1 Hz, ArH), 3.93 (3H, s, OMe), 2.69 (3H, s, Me); δ_C (75 MHz; $CDCl_3$) 164.9, 158.1, 131.1 (CH), 131.0, 130.7 (CH), 130.5, 130.4, 130.1 (CH), 54.3 (Me), 14.3 (Me); *m/z* (EI) 223 (M^+, 58%), 192 (23), 163 (46), 130 (100), 110 (60), 95 (77), 60 (25).

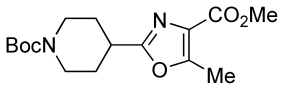


3.4.9. Methyl 5-(4-chlorophenyl)-2-(thien-2-yl)oxazole-4-carboxylate 4i. According to the general procedure the title compound was obtained from **3i** as a colourless crystalline solid (72%); mp 138–139 °C (methanol); (Found: C, 56.1; H, 2.9; N, 4.2. $C_{15}H_{10}ClNO_3S$ requires C, 56.3; H, 3.2; N, 4.4%); ν_{max}(KBr)/cm^{-1} 3117, 3093, 3065, 3001, 2953, 2917, 2844, 1718, 1606, 1578, 1554, 1486, 1441, 1421, 1353, 1309, 1221, 1185, 1093, 1037, 1017, 1005, 948, 924; δ_H (300 MHz; $CDCl_3$) 8.10 (2H, d, *J*=8.6 Hz, ArH), 7.82 (1H, dd, *J*=1.1, 3.8 Hz, ArH), 7.51 (1H, dd, *J*=1.1, 5.0 Hz, ArH), 7.47 (2H, d, *J*=8.6 Hz, ArH), 7.15 (1H, dd, *J*=3.8, 5.0 Hz, ArH), 3.97 (3H, s, OMe); δ_C (75 MHz; $CDCl_3$) 162.9, 156.6, 154.1, 136.9, 130.1 (2×CH), 129.7 (CH), 129.2 (CH), 128.7, 128.5 (CH), 128.4, 125.5, 53.0 (Me); *m/z* (EI) 321/319 (M^+, 30/43%), 316 (12), 291 (3), 290/288 (17/45), 284 (27).



3.4.10. Methyl 5-(4-methoxycarbonylphenyl)-2-(thien-2-yl)oxazole-4-carboxylate 4j. According to the general procedure the title compound was obtained from **3j** as a colourless crystalline solid (54%); mp 168 °C (methanol);

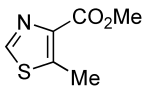
(Found: C, 59.2; H, 3.6; N, 3.9. $C_{17}H_{13}NO_5S$ requires C, 59.5; H, 3.8; N, 4.1%); ν_{max}(KBr)/cm^{-1} 3109, 3088, 3032, 2996, 2950, 2843, 1716, 1609, 1578, 1501, 1434, 1404, 1347, 1281, 1224, 1189, 1107, 1091, 1020, 1015, 943, 861, 810, 774, 723, 692; δ_H (300 MHz; DMSO) 8.26 (2H, d, J=8.7 Hz, ArH), 8.13 (2H, d, J=8.7 Hz, ArH), 7.96 (2H, m, ArH), 7.32 (1H, app t, J=4.1 Hz, ArH), 3.93 (3H, s, OMe), 3.90 (3H, s, OMe); δ_C (75 MHz; DMSO) 165.9, 162.0, 156.3, 152.8, 131.7 (CH), 131.1, 130.8, 130.3 (CH), 129.6 (CH), 129.2, 129.1 (CH), 128.7 (CH), 128.0, 52.8 (Me), 52.6 (Me); m/z (CI) 343 (M$^+$, 33%), 340 (5), 314 (3), 313 (6), 312 (29).



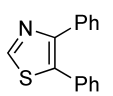
3.4.11. Methyl 2-(1-*tert*-butoxycarbonylpiperidin-4-yl)-5-methyloxazole-4-carboxylate 4k. According to the general procedure the title compound was isolated from **3k** as a colourless crystalline solid (66%); mp 101–103 °C; (Found: C, 59.1; H, 7.6; N, 8.5. $C_{16}H_{24}N_2O_5$ requires C, 59.2; H, 7.5; N, 8.6%); ν_{max}(KBr)/cm^{-1} 2981, 2962, 2937, 2850, 1718, 1682, 1622, 1425, 1346, 1252, 1234, 1211, 1167, 1107, 1026, 937, 783; δ_H (300 MHz; $CDCl_3$) 4.09 (2H, m, 2×CH), 3.87 (3H, s, CO_2Me), 2.90 (3H, m, 3×CH), 2.58 (3H, s, Me), 1.97 (2H, m, 2×CH), 1.75 (2H, m, 2×CH), 1.43 (9H, s, CMe_3); δ_C (75 MHz; $CDCl_3$) 164.8, 163.2, 156.5, 155.0, 127.5, 80.0, 52.3 (Me), 43.5 (CH), 36.0 (CH), 29.7 (CH_2), 28.8 (Me), 12.3 (Me); m/z (CI) 324 (M$^+$, 2%), 298 (3), 297 (11), 271 (3), 270 (15), 269 (100), 251 (55), 226 (4), 225 (25), 223 (32), 193 (3), 168 (14), 155 (2), 136 (5), 83 (5).

3.5. General procedure for thiazole formation

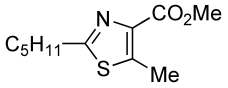
A solution of the keto amide substrate **3** (1.5 mmol) and Lawesson's reagent (3.0 mmol) in dry THF (10 ml) was heated to reflux for 4–6 h. The reaction mixture was then evaporated in vacuo and purified on silica gel eluting with ethyl acetate–light petroleum (3:7) to yield the product.



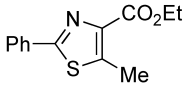
3.5.1. Methyl 5-methylthiazole-4-carboxylate 5a. According to the general procedure the title compound was obtained from **3a** as a colourless crystalline solid (60%); mp 62–65 °C (diethyl ether) (lit.[32] mp not given); (Found: M$^+$, 157.0200. $C_6H_7NO_2S$ requires 157.0198); ν_{max}(KBr)/cm^{-1} 3035, 2958, 2924, 2850, 1722, 1597, 1518, 1433, 1372, 1333, 1288, 1203, 1124, 1066, 955, 881, 831, 785, 762, 627; δ_H (300 MHz; $CDCl_3$) 8.51 (1H, s, H-2), 3.87 (3H, s, OMe), 2.73 (3H, s, Me); δ_C (75 MHz; $CDCl_3$) 163.2, 149.6 (CH), 145.4, 142.1, 52.6 (Me), 13.4 (Me); m/z (EI) 157 (M$^+$, 17%), 127 (6), 126 (65), 125 (100), 98 (12), 97 (23), 72 (4), 71 (11), 59 (8), 54 (3).



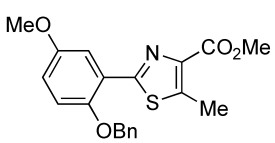
3.5.2. 4,5-Diphenylthiazole 5b. According to the general procedure the title compound was obtained from **3b** as a colourless crystalline solid (94%); mp 59–61 °C (lit.[33] mp 60–61 °C); (Found: C, 75.7; H, 4.6; N, 5.8. $C_{15}H_{11}NS$ requires C, 75.9; H, 4.7; N, 5.9%); ν_{max}(KBr)/cm^{-1} 3053, 2926, 2854, 2808, 1497, 1475, 1441, 1414, 1338, 1279, 1070, 1026, 999, 966, 899, 825, 766, 694; δ_H (300 MHz; $CDCl_3$) 8.84 (1H, s, H-2), 7.54 (2H, m, ArH), 7.34 (8H, m, ArH); δ_C (75 MHz; $CDCl_3$) 151.5 (CH), 151.0, 135.0, 133.4, 132.2, 130.1 (CH), 129.4 (CH), 129.2 (CH), 128.73, 128.71, 128.3 (CH); m/z (EI) 237 (M$^+$, 24%), 236 (6).



3.5.3. Methyl 5-methyl-2-pentylthiazole-4-carboxylate 5d. According to the general procedure the title compound was isolated from **3d** as a colourless oil (89%); (Found: MH$^+$, 228.1050. $C_{11}H_{18}NO_2S$ requires 228.1058); ν_{max}(film)/cm^{-1} 2954, 2929, 2858, 1716, 1504, 1437, 1221, 1068, 962, 866, 789, 768; δ_H (300 MHz; $CDCl_3$) 3.88 (3H, s, OMe), 2.91 (2H, t, J=7.8 Hz, CH_2), 2.69 (3H, s, Me), 1.70 (2H, m, CH_2), 1.34 (4H, m, 2×CH_2), 0.85 (3H, t, J=7.0 Hz, Me); δ_C (75 MHz; $CDCl_3$) 168.2, 163.3, 144.9, 140.5, 52.4 (Me), 33.8 (CH_2), 31.6 (CH_2), 30.2 (CH_2), 22.7 (CH_2), 14.3 (Me), 13.4 (Me); m/z (CI) 228 (MH$^+$, 100%), 226 (8), 212 (3), 197 (4), 196 (31), 184 (3), 171 (11), 139 (3).

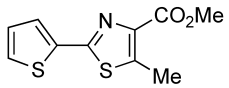


3.5.4. Ethyl 5-methyl-2-phenylthiazole-4-carboxylate 5e. According to the general procedure the title product was obtained from **3e** as a colourless solid (53%); mp 80–81 °C (ethyl acetate–light petroleum) (lit.[34] mp 59–61 °C); (Found: C, 63.1; H, 5.2; N, 5.6. $C_{13}H_{13}NO_2S$ requires C, 63.1; H, 5.3; N, 5.7%); ν_{max}(KBr)/cm^{-1} 2980, 2927, 2902, 2868, 2852, 1707, 1517, 1466, 1443, 1367, 1327, 1242, 1219, 1165, 1065, 1018, 974, 777, 698, 638; δ_H (300 MHz; $CDCl_3$) 8.15 (2H, m, ArH), 7.65 (3H, m, ArH), 4.66 (2H, q, J=7.1 Hz, OCH_2Me), 3.03 (3H, s, Me), 1.67 (3H, t, J=7.1 Hz, OCH$_2$*Me*); δ_C (75 MHz; $CDCl_3$) 164.1, 163.1, 144.9, 142.7, 133.3, 130.7 (CH), 129.3 (CH), 127.1 (CH), 61.6 (CH_2), 14.8 (Me), 13.8 (Me); m/z(CI) 247 (M$^+$, 13%), 230 (5), 203 (4), 202 (30), 201 (4).

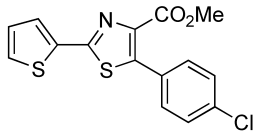


3.5.5. Methyl 2-(2-benzyloxy-5-methoxyphenyl)-5-methylthiazole-4-carboxylate 5f. According to the general procedure the title product was obtained from **3f** as a colourless crystalline solid (55%); mp 115–117 °C (methanol); (Found: C, 64.9; H, 5.0; N, 3.6. $C_{20}H_{19}NO_4S$ requires C, 65.0; H, 5.2; N, 3.8%); ν_{max}(KBr)/cm^{-1} 3058, 3032, 2996, 2946, 2914, 2868, 2838, 1701, 1650, 1609, 1506, 1455, 1440, 1414, 1388, 1312, 1276, 1235, 1173, 1117, 1071, 1035, 999, 871, 805, 779, 733, 692, 666; δ_H (400 MHz; $CDCl_3$) 7.94 (1H, d, J=3.1 Hz, ArH), 7.41 (5H, m, ArH), 6.95 (2H, m, ArH), 5.23 (2H, s, OCH_2Ph), 3.96 (3H, s, OMe), 3.87 (3H, s, OMe), 2.75 (3H, s, Me); δ_C

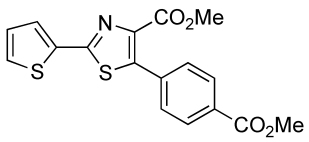
(100 MHz; $CDCl_3$) 163.4, 158.1, 154.0, 149.9, 145.6, 139.8, 136.3, 128.6 (CH), 128.2 (CH), 127.8 (CH), 122.7, 117.9 (CH), 114.4 (CH), 112.0 (CH), 71.6 (CH_2), 56.0 (Me), 52.0 (Me), 12.9 (Me); *m/z*(EI) 369 (M^+, 8%), 352 (7), 279 (5), 278 (16), 246 (5), 218 (8), 205 (7), 177 (7), 149 (100), 125 (5), 111 (8), 97 (12), 91 (23), 83 (12), 55 (16).



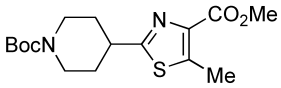
3.5.6. Methyl 5-methyl-2-(thien-2-yl)thiazole-4-carboxylate 5h. According to the general procedure the title product was obtained from **3h** as a colourless crystalline solid (69%); mp 113–115 °C (methanol); (Found: C, 49.9; H, 3.6; N, 5.7. $C_{10}H_9NO_2S_2$ requires C, 50.2; H, 3.8; N, 5.9%); ν_{max}(KBr)/cm^{-1} 3109, 2991, 2950, 2919, 2843, 1711, 1521, 1470, 1440, 1419, 1378, 1317, 1240, 1219, 1163, 1071, 912, 856, 840, 825, 781, 764, 702, 630; δ_H (300 MHz; $CDCl_3$) 7.47 (1H, d, *J*=3.7 Hz, ArH), 7.40 (1H, d, *J*=5.0 Hz, ArH), 7.06 (1H, dd, *J*=3.7, 5.0 Hz, ArH), 3.94 (3H, s, OMe), 2.78 (3H, s, Me); δ_C (75 MHz; $CDCl_3$) 163.2, 158.1, 144.8, 141.7, 136.8, 128.5 (CH), 128.2 (CH), 127.6 (CH), 52.6 (Me), 13.6 (Me); *m/z*(EI) 239 (M^+, 64%), 209 (8), 208 (21), 207 (65), 181 (8), 179 (47), 136 (4), 129 (9), 127 (100), 111 (5), 99 (4), 71 (8), 59 (10).



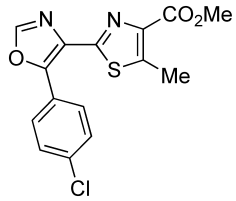
3.5.7. Methyl 5-(4-chlorophenyl)-2-(thien-2-yl)thiazole-4-carboxylate 5i. According to the general procedure the title compound was obtained from **3i** as a pale crystalline solid (89%); mp 146–149 °C (methanol); (Found: C, 53.2; H, 2.8; N, 4.0. $C_{15}H_{10}ClNO_2S_2$ requires C, 53.6; H, 3.0; N, 4.2%); ν_{max}(KBr)/cm^{-1} 3109, 3088, 3068, 3049, 3032, 2996, 2951, 2924, 1716, 1647, 1541, 1466, 1431, 1417, 1400, 1335, 1201, 1169, 1088, 1016, 999; δ_H (300 MHz; $CDCl_3$) 7.55 (1H, dd, *J*=1.1, 3.7 Hz, ArH), 7.46 (3H, m, ArH), 7.41 (2H, d, *J*=8.7 Hz, ArH), 7.10 (1H, dd, *J*=3.7, 5.0 Hz, ArH), 3.86 (3H, s, CO_2Me); δ_C (75 MHz; $CDCl_3$) 163.0, 160.8, 145.1, 141.2, 136.7, 136.3, 132.0 (CH), 129.6, 129.3 (CH), 129.1 (CH), 128.8 (CH), 128.5 (CH), 52.9 (Me); *m/z* (CI) 335/337 (M^+, 41/34%), 332 (12), 307 (5), 306/304 (27/60), 300 (7).



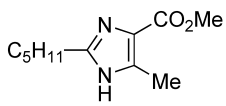
3.5.8. Methyl 5-(4-methoxycarbonylphenyl)-2-(thien-2-yl)thiazole-4-carboxylate 5j. According to the general procedure the title compound was obtained from **3j** as a pale crystalline solid (34%); mp 165–167 °C (methanol); (Found: C, 56.6; H, 3.5; N, 3.7. $C_{17}H_{13}NO_4S_2$ requires C, 56.8; H, 3.7; N, 3.9%); ν_{max}(KBr)/cm^{-1} 3119, 3117, 2955, 2914, 2848, 1721, 1654, 1603, 1537, 1470, 1424, 1327, 1281, 1260, 1214, 1178, 1112, 1081, 963, 917, 851, 764, 702; δ_H (300 MHz; DMSO) 8.06 (2H, d, *J*=8.5 Hz, ArH), 7.87 (1H, dd, *J*=1.1, 4.9 Hz, ArH), 7.82 (1H, dd, *J*=1.1, 3.8 Hz, ArH), 7.75 (2H, d, *J*=8.5 Hz, ArH), 7.25 (1H, dd, *J*=3.8, 4.9 Hz, ArH), 3.92 (3H, s, OMe), 3.78 (3H, s, OMe); δ_C (75 MHz; DMSO) 166.1, 162.0, 160.0, 143.3, 141.0, 135.5, 134.6, 130.7 (CH), 130.5 (CH), 130.4, 129.5 (CH), 129.3 (CH), 129.1 (CH), 52.7 (Me), 52.5 (Me); *m/z* (CI) 359 (M^+, 30%), 356 (3), 329 (7), 328 (32), 285 (3).



3.5.9. Methyl 2-(1-*tert*-butoxycarbonylpiperidin-4-yl)-5-methylthiazole-4-carboxylate 5k. According to the general procedure the title compound was isolated from **3k** as a colourless crystalline solid (74%); mp 75–77 °C; (Found: M^+, 340.1439. $C_{16}H_{24}N_2O_4S$ requires 340.1457); ν_{max}(KBr)/cm^{-1} 3174, 2980, 2958, 2933, 2872, 1741, 1709, 1597, 1454, 1377, 1338, 1306, 1265, 1238, 1205, 1155, 1111, 1088, 1053, 933, 856, 746; δ_H (300 MHz; $CDCl_3$) 4.20 (2H, m, 2×CH), 3.90 (3H, s, OMe), 3.16 (1H, m, CH), 2.79 (2H, m, 2×CH), 2.73 (3H, s, Me), 2.04 (2H, m, 2×CH), 1.63 (2H, m, 2×CH), 1.44 (9H, s, CMe_3); δ_C (75 MHz; $CDCl_3$) 168.9, 161.0, 152.7, 142.4, 138.3, 77.8, 50.2 (Me), 41.6 (CH_2), 39.0 (CH), 30.5 (CH_2), 26.5 (Me), 11.3 (Me); *m/z* (CI) 340 (M^+, 3%), 314 (3), 313 (14), 287 (5), 286 (9), 285 (100), 267 (40), 253 (4), 242 (9), 241 (56), 239 (33), 210 (2), 209 (7), 197 (3), 184 (24), 171 (3), 152 (9), 83 (7).

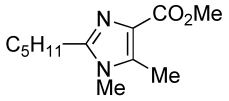


3.5.10. Methyl 2-[5-(4-chlorophenyl)oxazol-4-yl]-5-methylthiazole-4-carboxylate 5l. According to the general procedure **3l** was treated with Lawesson's reagent to yield the title compound as a colourless crystalline solid (40%); mp 210–212 °C; (Found: C, 53.6; H, 3.0; N, 8.2. $C_{15}H_{11}ClN_2O_3S$ requires C, 53.8; H, 3.3; N, 8.4%); ν_{max}(KBr)/cm^{-1} 3129, 3058, 3037, 2955, 2909, 2843, 1701, 1511, 1470, 1434, 1327, 1230, 1112, 1091, 1066, 1030, 1009, 912, 876, 839, 769, 744, 625; δ_H (300 MHz; $CDCl_3$) 8.47 (2H, d, *J*=8.7 Hz, ArH), 7.88 (1H, s, H-2), 7.42 (2H, d, *J*=8.7 Hz, ArH), 3.93 (3H, s, OMe), 2.79 (3H, s, Me); δ_C (75 MHz; $CDCl_3$) 160.9, 154.6, 147.2 (CH), 145.0, 144.2, 139.6, 133.7, 127.2, 126.8 (CH), 126.7 (CH), 123.8, 50.2 (Me), 11.1 (Me); *m/z* (FI) 334 (M^+, 100%).



3.5.11. Methyl 5-methyl-2-pentyl-1*H*-imidazole-4-carboxylate 6a. Ketoamide **3a** (1.0 g, 4.4 mmol), ammonium acetate (510 mg, 6.6 mmol) and glacial acetic acid (2 ml) were dissolved in toluene (50 ml) and heated under reflux for 2 h. The reaction was cooled, washed with brine, dried ($MgSO_4$), reduced in vacuo and purified by column chromatography to yield the title product as a colourless oil (756 mg, 82%); (Found: MH^+, 211.1454. $C_{11}H_{19}N_2O_2$ requires 211.1447); ν_{max}(film)/cm^{-1} 3399, 3308, 2956,

2928, 2866, 1739, 1602, 1539, 1434, 1373, 1292, 1264, 1187, 1106; δ_H (300 MHz; $CDCl_3$) 6.30 (1H, s, NH), 3.63 (3H, s, OMe), 2.24 (2H, t, J=7.4 Hz, CH_2), 1.91 (3H, s, Me), 1.71–1.61 (2H, m, CH_2), 1.35–1.29 (4H, m, 2×CH_2), 0.88 (3H, t, J=6.8 Hz, Me); δ_C (75 MHz; $CDCl_3$) 174.5, 171.6, 168.4, 93.3, 51.0 (Me), 36.8 (CH_2), 31.7 (CH_2), 25.9 (CH_2), 22.8 (CH_2), 19.5 (Me), 14.2 (Me); *m/z* (CI) 211 (MH^+, 28%), 198 (12), 197 (100), 195 (8), 179 (5), 157 (5), 154 (3), 131 (6), 130 (46), 129 (13), 113 (3), 99 (5), 98 (2), 70 (3).



3.5.12. Methyl 1,5-dimethyl-2-pentyl-1*H*-imidazole-4-carboxylate 6b. Ketoamide **3a** (250 mg, 1.1 mmol) and glacial acetic acid (2 ml) were dissolved in toluene (50 ml) to which was then added a solution of methylamine (2 M in THF, 0.82 ml, 1.7 mmol) and heated under reflux for 2 h. The reaction was cooled, washed with brine, dried ($MgSO_4$), reduced in vacuo and purified by column chromatography to yield the title product as an orange oil (114 mg, 46%); (Found: MH^+, 225.1603. $C_{12}H_{21}N_2O_6$ requires 225.1603); ν_{max}(film)/cm^{-1} 2958, 2928, 2858, 1701, 1577, 1530, 1439, 1373, 1216, 1068; δ_H (300 MHz; $CDCl_3$) 3.81 (3H, s, OMe), 3.42 (3H, s, NMe), 2.63 (2H, t, J=7.7 Hz, CH_2), 2.46 (3H, s, Me), 1.65–1.62 (2H, m, CH_2), 1.30–1.28 (4H, m, 2×CH_2), 0.84 (3H, t, J=6.6 Hz, Me); δ_C (75 MHz; $CDCl_3$) 164.7, 148.7, 136.5, 127.1, 51.5 (Me), 31.9 (CH_2), 30.5 (Me), 27.9 (CH_2), 27.6 (CH_2), 22.6 (CH_2), 14.2 (Me), 10.4 (Me); *m/z* (CI) 225 (MH^+, 100%), 224 (8), 209 (3), 195 (3), 194 (6), 193 (56), 181 (6), 169 (2), 168 (14), 150 (2), 136 (5), 116 (2), 99 (3).

Acknowledgements

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