Reductive dehalogenation of 4-halogenomethyl azetidin-2-one derivatives. Synthesis of (4-oxo-azetidin-2-yl)acetonitriles†

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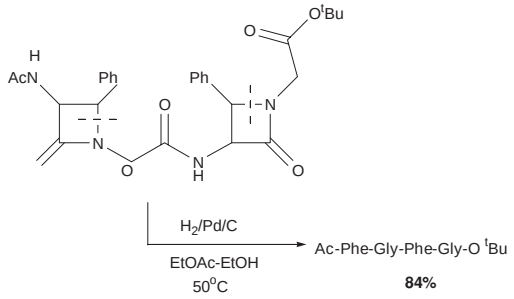
The stability of the β-lactam ring under reductive conditions was examined in order to find a selective method for the synthesis of (4-oxo-azetidin-2-yl)acetonitrile derivatives. Fifteen variously substituted 4-halogenomethyl-β-lactam derivatives were synthesised and dehalogenated by three reductive methods. It was found that both the substituents connected to the four-membered ring and to the halogenomethyl group, as well as the applied method have considerable influence on the ratio of the resulting ring-containing and ring-opened products. The best conditions have been defined to give — state products — in excellent yields.

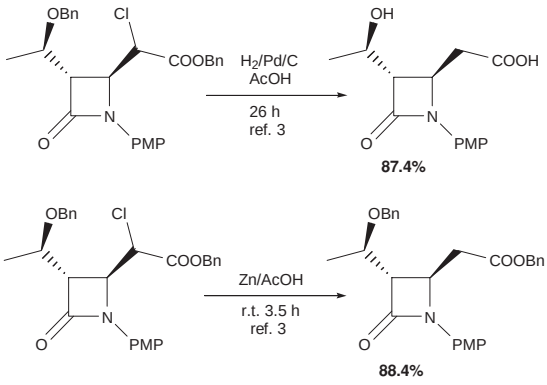
Keywords: (4-oxo-azetidin-2-yl)acetonitriles, reductive dehalogenation, β-lactam ring cleavage, azetidinones

Introduction

β-Lactam chemistry is of great pharmaceutical importance as the β-lactam ring is part of penicillines and several other antibiotics. The behaviour of the β-lactam ring under reductive conditions has been widely investigated.[1-5] Opening of the β-lactam ring under catalytic reductive conditions between N1 and C4 is generally observed when an aryl substituent is connected to C4 of the ring. The optimal conditions and selectivity of this reaction have been already investigated as it provides new possibilities to synthesise oligopeptides using β-lactams as precursors of the amide bonds.[1, 2]



The behaviour of aliphatic substituted β-lactam derivatives under reductive conditions has been also investigated.[3,4] It was found that opening of the ring occurs generally, when radical methods *e.g.* reduction by $Na_2Fe(CO)_4$/THF[5] are applied, but is very unusual in the case of catalytic hydrogenation or when Zn powder in acetic acid is used.[3,4] The ratio of the products was, however, never investigated.



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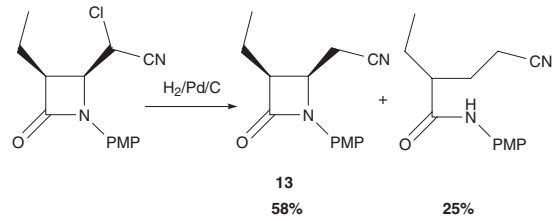
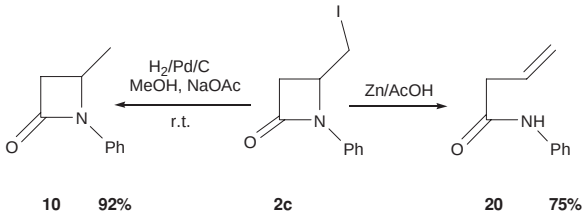
† Dedicated to Professor Károly Lempert on his 80th birthday.

Recently we attempted to synthesise compound **13** by using the appropriate halogenated derivative as the starting material. Unfortunately, under catalytic reductive conditions formation of a ring-opened amide was observed in addition to the expected cyclic product.



In an earlier study[6] it was also found that reduction of compound **2c** results in different products when different reductive methods are used. The only product of the dehalogenation using Pd/C as a catalyst under H_2 is a lactam, whereas reduction with Zn powder in acetic acid results in a ring-opened unsaturated amide.



Here we report our study into the stability of the β-lactam ring under reductive conditions as a function of both the substituents and the reduction method, in order to synthesise variously substituted (4-oxo-azetidin-2-yl)acetonitrile derivatives.

Results and discussion

Fifteen variously substituted 4-halogenomethyl-β-lactam derivatives (Figure 1) were synthesised as model compounds. All Chiral compounds discussed in the present paper are racemic only one enantiomer is shown.

Compounds **2a–c** were synthesised by a previously published method.[6] Compounds **3a–c** were synthesised from the appropriate hydroxy compound[7] by methods well known from the literature (Scheme 1).

Compounds **7a–c, 8a–c** and **9a–c** were synthesised from the appropriate carbaldehydes[11-13] through cyanohydrines (**4, 5, 6**), by methods well known from the literature (Scheme 2).

PAPER: 04/2468

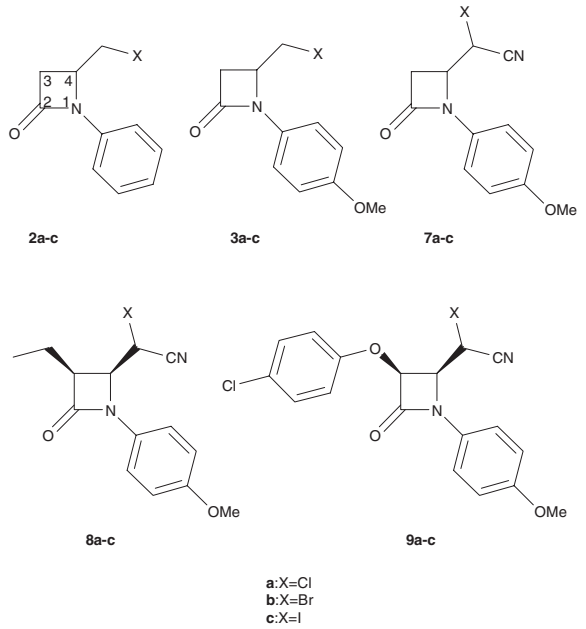
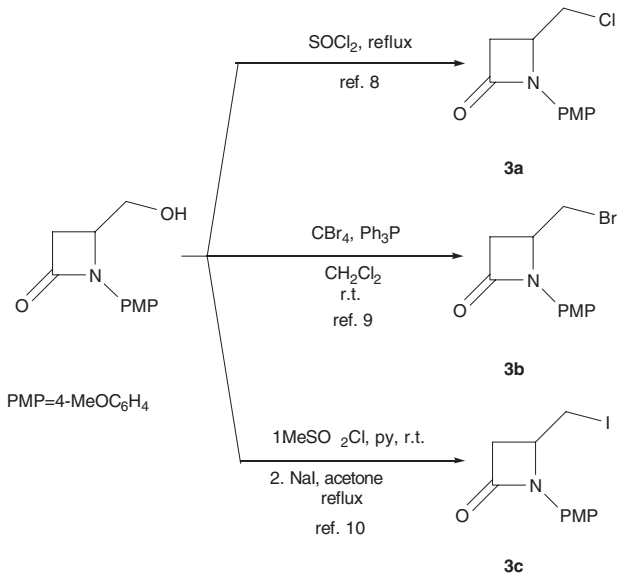


Fig. 1 Structure and labelling of the studied 4-halogenomethyl β-lactam derivatives.



Scheme 1 Synthesis of the 4-halogenomethyl β-lactam derivatives **3a–c**.

Examination of the products and product ratios of the catalytic, Zn/AcOH, and Bu_3SnH reductions has shown that, in agreement with previous observations, both the applied method and substituents of the ring have considerable effects on the ratio of the reduced lactam and the ring-opened amide (Table 1).

On the basis of the experimental results information can be obtained on the effect of the various substituents. Comparing the products obtained from compounds **2a**–**c** and **3a**–**c** it can be seen that the substituent of the lactam nitrogen does apparently not influence the ratio of the two products. The catalytic and Zn/AcOH reductions of both types resulted in the same product distribution. Surprisingly, when Bu_3SnH was used as the reducing agent, a difference between the phenyl and 4-methoxyphenyl substituted model compounds was observed, as the ratio of the olefin rose in the latter case. The change possibly can be explained by assuming that because of the electron releasing methoxy group, the entire 4-methoxyphenyl substituent becomes electron repelling. In this way it can promote the cleavage of the bond between the nitrogen and the C4 carbon atom.

The effect of the cyano substituent can be established, by comparing the ratios of the products obtained from compounds **3a**–**c** and **8a**–**c**. In the case of unsubstituted halogenomethyl derivatives **3a**–**c** the type of the halogen atom generally does not influence the product distribution, whereas in the case of cyano group containing models **8a**–**c** it usually does. Introduction of a cyano group into the molecule resulted in the decrease of the amount of the ring-containing product under catalytic reductive conditions, and in its increase when using the Zn/AcOH or Bu_3SnH methods. In the latter case the ring-containing product was even the only product of the reaction. The increase in the amount of the reduced lactam when using radical methods is the result of the radical stabilising effect of the cyano group.

Examining the effect of the substituent at C3 of the ring, in the catalytic and Zn/AcOH reductions the amount of the ring-containing product rose in the order H, Et, 4-ClC_6H_4O, in agreement with the increasing ring stabilising effect of these substituents in the same order. On the contrary, applying Bu_3SnH as a reducing agent resulted in an increase of the ring opened product when an ethyl group is present at C3. The change can be explained by the steric effect of the ethyl group which makes it difficult for the large Bu_3SnH molecule to approach the intermediate lactam radical, resulting in a longer lifetime of the radical, which makes the rearrangement more probable.

Conclusion

Many factors do influence the product distribution of the dehalogenation reaction. With these studies we have managed to define conditions to give state products in excellent yields (Table 2). In the case of model compounds that do not contain a cyano group (**2a–c, 3a–c)**, there is generally one major product and only traces of the other product can be detected in the reaction mixture. Since the major product is the reduced lactam when the dehalogenation is carried out under catalytic conditions or with Zn powder in acetic acid, these methods are suitable for the synthesis of such compounds.

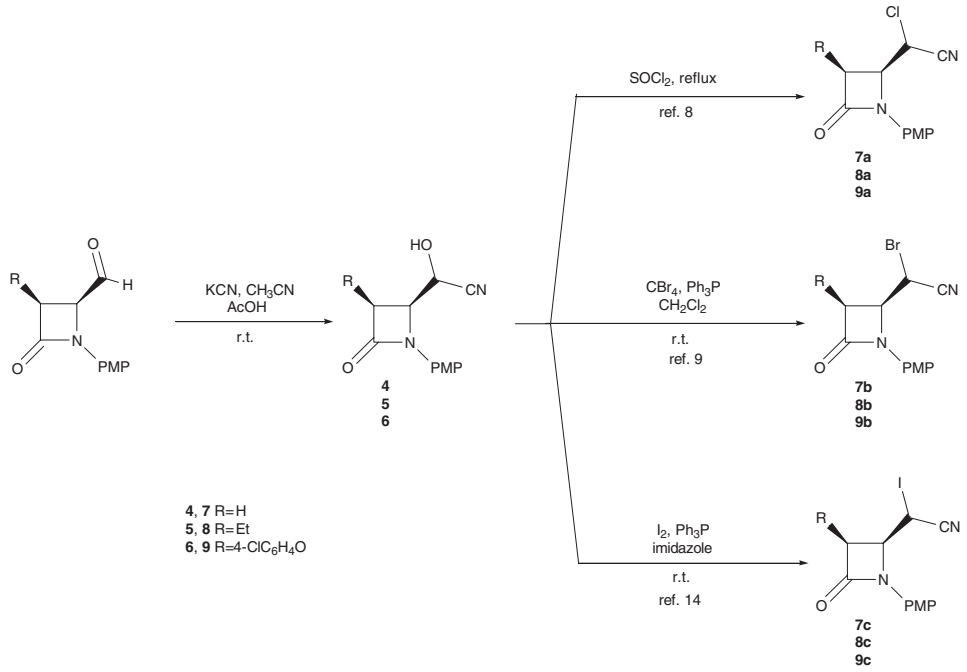
On the other hand, when a cyano group is present, the ratio of the products is generally similar under catalytic or Zn/AcOH conditions, however in most cases it is the reduced lactam which is formed in larger amounts. When reducing with Bu_3SnH, a shift in the ratio towards the cyclic product is observed, which is sometimes the only product of the reaction. Therefore this method is the best way to synthesise (4-oxo-azetidin-2-yl)acetonitrile derivatives in good yields.

Experimental

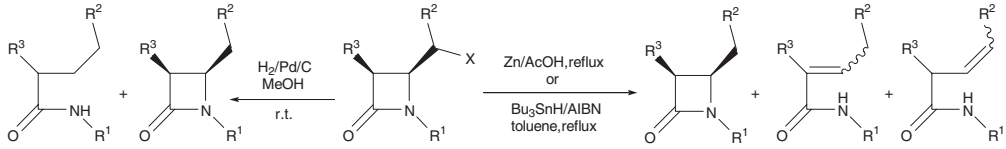
General

Abbreviations: DMB: 2,4-dimethoxybenzyl, PMP: 4-methoxyphenyl, FC: flash column chromatography.

Techniques: All reactions were monitored by TLC (DC-Alufolien 60 F_{254}, Merck; visualised by UV_{254} and/or UV_{366} irradiation and/or by dipping into phosphomolybdic acid soln., followed by heating), and allowed to go to completion. Separations of product mixtures by FC were carried out using Kieselgel 60 G (Merck) as the adsorbent unless otherwise stated (pressure differences between the two ends of the columns 65–75 kPa). For preparative TLC separations 20×20 cm glass plates coated with Kieselgel $PF_{254+366}$ (Merck; thickness of adsorbent layer 2.0 mm) were used (home-made ones, except where otherwise noted). The solvents are given in parentheses. The purity of the products was checked in combination with IR spectroscopy, by TLC on DC-Alufolien 60 F_{254} (Merck); the individual compounds were detected by UV irradiation. Evaporations to dryness were carried out at reduced pressure. All new compounds described in the present paper were colorless crystals, unless otherwise stated.



Scheme 2 Synthesis of the cyano group containing 4-halogenomethyl β-lactam derivatives **7–9**.



				R^1	R^2	R^3		
15[16]	**10**[6]		**2a-c**	Ph	H	H	**10**[6]	**20**[17]
16[19]	**11**[18]		**3a-c**	PMP	H	H	**11**[18]	**21**[20]
17[21]	**12**[10]		**7a-c**	PMP	CN	H	**12**[10]	**22**	**23**
18	**13**[15]		**8a-c**	PMP	CN	Et	**13**[15]	**24**	**25**
19	**14**		**9a-c**	PMP	CN	4-ClC_6H_4O	**14**	**26**	

Table 1 Reduction of 4-halogenomethyl-β-lactams (**A**) by various methods to afford dehalogenated β-lactams (**B**) and/or open chain amides (**C, D**)

Method:[a]	Pd/C	Zn/AcOH	Bu_3SnH	
Product ratio:	**B**:**C**	**B**:**D**	**B**:**D**	
A	**X**			
2	R^1=Ph; R^2=H; R^3=H			
a	Cl	**B** + traces of **C**	no reaction	**B** + traces of **D**
b	Br	**B** + traces of **C**	**D** + traces of **B**	**B** + traces of **D**
c	I	**B** + traces of **C**	**D** + traces of **B**	**B** + traces of **D**
3	R^1=PMP; R^2=H; R^3=H			
a	Cl	**B** + traces of **C**	no reaction	5.3:1
b	Br	**B** + traces of **C**	**D** + traces of **B**	6.0:1
c	I	**B** + traces of **C**	**D** + traces of **B**	8.6:1
7	R^1=PMP; R^2=CN; R^3=H			
a	Cl	1.5:1	2.1:1	only **B**
b	Br	2.9:1	3.1:1	only **B**
c	I	1:1.2	3.2:1	only **B**
8	R^1=PMP; R^2=CN; R^3=Et			
a	Cl	2.3:1	4.7:1	14.3:1
b	Br	4.3:1	4.4:1	12.0:1
	I	1.3:1	3.3:1	13.4:1
9	R^1=PMP; R^2=CN; R^3=4-ClC_6H_4O			
a	Cl	1.1:1	3.0:1	
b	Br	1.8:1	1.7:1	
c	I	1.1:1	1.6:1	

[a]The product ratios were established by HPLC (for details see Experimental)

Table 2 Reduction of 4-halogenomethylazetidin-2-ones **2**, **3**, **7**, **8** and **9**

Method[a]:	H_2/Pd/C Method 1			Zn/AcOH Method 2			Bu_3SnH/AIBN Method 3		
Start. mat.	Products	Prod. ratio[c]	Yield/%[b]	Products	Prod. ratio	Yield/%[b]	Products	Prod. ratio	Yield/%[b, e]
2a	**10+15**	**15** in traces	86			no reaction	**10+20**	**20** in traces	>100
2b	**10+15**	**15** in traces	86	**10+20**	**10** in traces	81	**10+20**	**20** in traces	>100
2c	**10+15**	**15** in traces	92	**10+20**	**10** in traces	75	**10+20**	**20** in traces	66
3a	**11+16**	**16** in traces	93			no reaction	**11+21**	5.25:1	92
3b	**11+16**	**16** in traces	88	**11+21**	**11** in traces	95	**11+21**	6.0:1	95
3c	**11+16**	**16** in traces	100	**11+21**	**11** in traces	100	**11+21**	8.6:1	81
7a	**12+17**	1.5:1	69	**12+(22+23)**	2.1:1	100	**12**		78
7b	**12+17**	2.9:1	82	**12+(22+23)**	3.1:1	82	**12**		95
7c	**12+17**	1:1.2	80	**12+(22+23)**	3.2:1	69	**12**		83
8a	**13+18**	2.3:1	83	**13+(24+25)**	4.7:1	76	**13+(24+25)**	14.3:1	76
8b	**13+18**	4.3:1	82	**13+(24+25)**	4.4:1	78	**13+(24+25)**	12.0:1	>100
8c	**13+18**	1.3:1	86	**13+(24+25)**	3.3:1	77	**13+(24+25)**	13.4:1	>100
9a[d]	**14+19**	1.1:1	79	**14+26**	3.0:1	84			
9b[d]	**14+19**	1.8:1	84	**14+26**	1.7:1	75			
9c[d]	**14+19**	1.1:1	72	**14+26**	1.6:1	100			

[a]For further details see general methods 1-3
[b]Total yield of the products
[c]Product ratios were established by HPLC
[d]By preparative work-up of the reaction mixture (preparative TLC or FC)
[e]In the Bu_3SnH reductions the yields calculated on the basis of preparative work-up of the reaction mixtures were often higher than 100% because of the difficult separability of Bu_3SnH. Traces of the reagent do not interfere with the determination of the product ratio by HPLC

Melting point values were determined on a Kofler hot-stage melting point apparatus and are uncorrected. IR spectra were recorded on a Specord-75 or Specord M-80 spectrometer (Zeiss, Jena), measured as film or KBr pellets, absorption bands are in cm^{-1}. NMR spectra were obtained with a Varian XL-400 (^1H: 400 MHz, ^{13}C: 100 MHz) spectrometer, chemical shifts (δ-values) are reported in ppm with respect to Me_4Si (δ= 0 ppm) as the internal standard, coupling constants (J) are given in Hz. ^{13}C NMR Spectra are broad-band-decoupled.

HPLC: Waters 3000, Waters 990 photodiode detector, Software: Waters 991. Column: Lichrospher-100 5-RP-18, eluent: H_2O:MeOH = 70:30+0.1% H_3PO_4, H_2O: CH_3CN = 85:15 + 0.1% H_3PO_4 or H_2O:MeOH:CH_3CN = 70:18:12 + 0.1% H_3PO_4, v = 1.2 ml/min. Exact molecular mass determinations were made at 70 eV with a Finnigan-MAT 95 SQ hybride – tandem instrument using a heated direct inlet system and perfluorokerosene as the reference.

General method for the catalytic reduction of 4-halogenomethyl-β-lactam derivatives – Method 1

Methanolic suspensions of the substrates (0.4 mmol), NaOAc (0.6 mmol) and 10% Pd/C (0.006 g) were stirred under H_2 at room temperature. After disappearance of the starting material (generally 15 min, depending on the starting material) the reaction mixture was filtered and evaporated *in vacuo*. The residue was dissolved in CH_2Cl_2 and extracted three times with water. The organic phase was dried over $MgSO_4$ and evaporated *in vacuo*. Preparative TLC (eluent: toluene-ethyl acetate = 4: 1) afforded the pure products.

In the case of iodo-acetonitrile derivatives (**7c, 8c, 9c**) a further amount of the catalyst (0.003 g) and therefore a longer reaction time (30 min) was necessary because of deactivation of the catalyst.

General method for the Zn/AcOH reduction of 4-halogenomethyl-β-lactam derivatives – Method 2

A suspension of the substrate (0.4 mmol) and Zn powder (0.06 g) in acetic acid was refluxed until disappearance of the starting material (~15 min). After filtration the reaction mixture was evaporated in vacuo. The residue was worked up as described in Method 1.

General method for the Bu_3SnH/AIBN reduction of 4-halogenomethyl-β-lactam derivatives – Method 3

To a toluenic solution (8 ml) of the substrate (0.4 mmol) were Bu_3SnH (1.3 mmol) and a catalytic amount of azo-bis-isobutironitrile (AIBN) added. The reaction mixture was refluxed under N_2 until the disappearance of the starting material (~15 min), then filtered and evaporated in vacou. The residue was dissolved in acetonitrile and extracted three times with n-hexane. The acetonitrile phase was separated and evaporated *in vacuo*.

General method for the preparation of cyanohydrine derivatives **(4, 5, 6)** *– Method 4*

To AcOH (4,9 ml) containing acetonitrilic solutions of the substrates (71,1 mmol), aqueous solutions of KCN (82,8 mmol) were added slowly under cooling and vigorous stirring. The reaction mixture was stirred for another 1 hour at room temperature, and evaporated in vacuo. In the case of compounds **5** and **6**, the residues were dissolved in water and extracted with ethyl acetate. The crystalline products were filtered and washed with ethyl acetate. In the case of compound **4**, the residue was extracted three times with ethyl acetate. The combined organic phases were extracted with brine, dried over $MgSO_4$ and evaporated in vacuo. The residue was purified by FC (eluent CH_2Cl_2, then CH_2Cl_2-acetone = 10:0.5). The results of the reductions are summarised in Table 2.

4-Chloromethyl-1-(4-methoxyphenyl)azetidin-2-one (**3a**): Compound **3a** was synthesised according to ref. 8.Yield: 58 %, m.p. 83 °C; IR: ν_{max}(KBr)/cm^{-1} 1752 (CO). ^1H NMR ($CDCl_3$): δ 3.00 (1 H, dd, J_g 15.4, J_{tr} 2.4, 3-H), 3.23 (1 H, dd, J_g 15.4, J_c 5.4, 3-H), 3,75 (1 H, dd, J_g 11.9, J_v 6.7, $ClCH_2$), 3.95 (1 H, dd, J_g 11.9, J_v 3.1, $ClCH_2$), 3.79 (3 H, s, OMe), 4.32 (1 H, m, 4-H), 6.88 (2 H, m, C_6H_4OMe) and 7.29 (2 H, m, C_6H_4OMe). HRMS *m/z* (EI) 225.0544 ($M^{\bullet+}$ $C_{11}H_{12}NO_2Cl$ requires 225.0551).

4-Bromomethyl-1-(4-methoxyphenyl)azetidin-2-one (**3b**): Compound **3b** was synthesised according to ref. 9.Yield: 95%, m.p. 75–76 °C; IR: ν_{max}(KBr)/cm^{-1} 1748 (CO). ^1H NMR ($CDCl_3$): δ 2.96 (1 H, dd, J_g 15.4, J_{tr} 2.3, 3-H), 3.25 (dd, J_g 15.4, J_c 5.2, 3-H), 3.54 (1 H, dd, J_g 10.9, J_v 7.8, $ClCH_2$), 3.84 (1 H, dd, J_g 10.9, J_v 2.9, $ClCH_2$), 3.79 (3 H, s, OMe), 4.29 (1 H, m, 4-H), 6.89 (2 H, m, C_6H_4OMe) and 7.29 (2 H, m, C_6H_4OMe). HRMS *m/z* (EI) 269.0038 ($M^{\bullet+}$ $C_{11}H_{12}NO_2Br$ requires 269.0046).

Hydroxy-[1-(4-methoxyphenyl)-4-oxo-azetidin-2-yl]acetonitrile (**4**): Compound **4** was synthesised according to Method 4.

Yield: 65%. A 50:50 mixture of two diastereoisomers; m.p. 104–105 °C; IR: ν_{max}(KBr)/cm^{-1} 1730 (CO) and 3100–3600br (OH). ^1H NMR ($CDCl_3$ + DMSO-d_6) diastereoisomer 1: δ 3.03 (1 H, dd, J_g 15.5, J_{tr} 2.5, 3-H), 3.25 (1 H, dd, Jg 15.5, J_c 5.5, 3-H), 3.77 (3 H, s, OMe), 4.39 (1 H, m, 4-H), 4.95 (1 H, br dd, J_v 5.0, J_v 5.0, CHCN), 6.87 (2 H, m, C_6H_4OMe), 6.79 (1 H, br d, OH) and 7.39 (2 H, m, C_6H_4OMe), diastereoisomer 2: δ 3.10 (1 H, dd, J_g 15.0, J_{tr} 2.5, 3-H), 3.17 (1 H, dd, J_g 15.0, J_c 5.4, 3-H), 3.77 (3 H, s, OMe), 4.41 (1 H, m, 4-H), 4.99 (1 H, br dd, J_v 5.0, J_v 2.5, CHCN), 6.87 (2 H, m, C_6H_4OMe), 6.89 (1 H, br d, OH) and 7.42 (2 H, m, C_6H_4OMe). HRMS *m/z* (EI) 232.0824 ($M^{\bullet+}$ $C_{12}H_{11}N_2O_3$ requires 232.0842).

Hydroxy-[3-ethyl-1-(4-methoxyphenyl)-4-oxo-azetidin-2-yl]acetonitrile (**5**): Compound **5** was synthesised according to Method 4. Yield: 70 %. A 65:35 mixture of two diastereoisomers; m.p. 135–145°C; IR: ν_{max}(KBr)/cm^{-1} 1716 (CO) and 3100–3600br (OH). ^1H NMR ($CDCl_3$) diastereoisomer 1: δ 1.18 (3 H, t, J_v 7.5, CH_3), 1.80-1.95 (2 H, m, CH_2), 3.39 (1 H, m, 3-H), 3.65 (1 H, d, J_v 5.0, OH), 3.80 (3 H, s, OMe), 4.34 (1 H, dd, J_c 5.5, J_v 3.5, 4-H), 4.94 (1 H, dd, J_v 5.0, J_v 3.5, CHCN), 6.91 (2 H, m, C_6H_4OMe) and 7.27 (2 H, m, C_6H_4OMe), diastereoisomer 2: δ 1.18 (3 H, t, J_v 7.5, CH_3), 2.0–2.13 (2 H, m, CH_2), 3.39 (1 H, m, 3-H), 3.57 (1 H, d, J_v 6.5, OH), 3.80 (3 H, s, OMe), 4.45 (1 H, dd, J_c 6.2, J_v 5.5, 4-H), 4.76 (1 H, dd, J_v 6.5, J_v 5.5, CHCN), 6.90

(2 H, m, C_6H_4OMe) and 7.32 (2 H, m, C_6H_4OMe). HRMS *m/z* (EI) 260.1129 ($M^{\bullet+}$ $C_{14}H_{16}N_2O_3$ requires 260.1155).

Hydroxy-[3-(4-chlorophenoxy)-1-(4-methoxyphenyl)-4-oxo-azetidin-2-yl]acetonitrile (**6**): Compound **6** was synthesised according to Method 4. Yield: 95 %. A 60:40 mixture of two diastereoisomers; m.p. 136 °C; IR: ν_{max}(KBr)/cm^{-1} 1736 (CO) and 3200–3500br (OH). ^{1}H NMR ($CDCl_3$+ DMSO-d_6) diastereoisomer 1: δ 3.79 (3 H, s, OMe), 4.81 (1 H, dd, J_c 5.4, J_v 7.5, 4-H), 4.90 (1 H, dd, J_v 6.4, J_v 7.5, CHCN), 5.52 (1 H, d, *J*c 5.4, 3-H), 6.88 (2 H, m, C_6H_4Cl), 6.92 (1 H, d, J_v 6.4, OH), 7.16 (2 H, m, C_6H_4OMe), 7.28 (2 H, m, C_6H_4OMe) and 7.56 (2 H, m, C_6H_4Cl), diastereoisomer 2: δ 3.79 (3 H, s, OMe), 4.73 (1 H, dd, J_c 5.4, J_v 2.6, 4-H), 4.99 (1 H, dd, J_v 5.2, J_v 2.6, CHCN), 5.53 (1 H, d, *J*c 5.4, 3-H), 6.90 (2 H, m, C_6H_4Cl), 6.91 (1 H, d, J_v 5.2, OH), 7.14 (2 H, m, C_6H_4OMe), 7.29 (2 H, m, C_6H_4OMe) and 7.61 (2 H, m, C_6H_4Cl). HRMS *m/z* (EI) 331.0598 ($M^{\bullet+}$ $C_{17}H_{14}NO_4Cl$ requires 331.0606).

Chloro-[1-(4-methoxyphenyl)-4-oxo-azetidin-2-yl]acetonitrile (**7a**): Compound **7a** was synthesised according to ref. 8. Yield: 100 %. A 80:20 mixture of two diastereoisomers; m.p. 97–99 °C; IR: ν_{max}(KBr)/cm^{-1} 1736 (CO). ^{1}H NMR ($CDCl_3$) diastereoisomer 1: δ 3.22 (1 H, dd, J_g 15.1, J_{tr} 2.3, 3-H), 3.35 (1 H, dd, J_g 15.1, J_c 5.1, 3-H), 3.80 (3 H, s, OMe), 4.57 (1 H, m, 4-H), 4.93 (1 H, d, J_v= 3.7, CHCN), 6.90 (2 H, m, C_6H_4OMe) and 7.27 (2 H, m, C_6H_4OMe), diastereoisomer 2: δ 3.23 (1 H, dd, J_g 15.5, J_{tr} 2.2, 3-H), 3.40 (1 H, dd, J_g 15.5, J_c 5.2, 3-H), 3.80 (3 H, s, OMe), 4.46 (1 H, m, 4-H), 4.95 (1 H, d, J_v= 3.9, CHCN), 6.90 (2 H, m, C_6H_4OMe) and 7.27 (2 H, m, C_6H_4OMe). HRMS *m/z* (EI) 250.0500 ($M^{\bullet+}$ $C_{12}H_{11}N_2O_2Cl$ requires 250.0504).

Bromo-[1-(4-methoxyphenyl)-4-oxo-azetidin-2-yl]acetonitrile (**7b**): Compound **7b** was synthesised according to ref. 9. Yield: 79 %. A 60:40 mixture of two diastereoisomers; m.p. 105–107 °C; IR: ν_{max}(KBr)/cm^{-1} 1740 (CO). ^{1}H NMR ($CDCl_3$) diastereoisomer 1: δ 3.22 (1 H, dd, J_g 15.7, J_{tr} 2.5, 3-H), 3.34 (1 H, dd, J_g 15.7, J_c 5.1, 3-H), 3.80 (3 H, s, OMe), 4.44 (1 H, m, 4-H), 4.80 (1 H, d, J_v 3.6, CHCN), 6.91 (2 H, m, C_6H_4OMe) and 7.26 (2 H, m, C_6H_4OMe), diastereoisomer 2: δ 3.16 (1 H, dd, J_g 15.5, J_{tr} 2.3, 3-H), 3.39 (1 H, dd, J_g 15.5, J_c 5.1, 3-H), 3.80 (3 H, s, OMe), 4.41 (1 H, m, 4-H), 4.78 (1 H, d, J_v 4.2, CHCN), 6.91 (2 H, m, C_6H_4OMe) and 7.26 (2 H, m, C_6H_4OMe). HRMS *m/z* (EI) 293.9981 ($M^{\bullet+}$ $C_{12}H_{11}N_2O_2Br$ requires 293.9998).

Iodo-[1-(4-methoxyphenyl)-4-oxo-azetidin-2-yl]acetonitrile (**7c**): Compound **7c** was synthesised according to refs. 14 and 15. Yield: 44 %. A 80:20 mixture of two diastereoisomers; m.p. 128–129 °C. IR: ν_{max}(KBr)/cm^{-1} 1736 (CO) and 2240 (CN). ^{1}H NMR ($CDCl_3$) diastereoisomer 1: δ 3.02 (1 H, dd, J_g 15.6, J_{tr} 2.4, 3-H), 3.32 (1 H, dd, J_g 15.6, J_c 5.3, 3-H), 3.79 (3 H, s, OMe), 3.83 (1 H, ddd, J_v 4.7, J_c 5.3, J_{tr} 2.4, 4-H), 4.73 (1 H, d, J_v 4.7, CHCN), 6.90 (2 H, m, C_6H_4OMe) and 7.24 (2 H, m, C_6H_4OMe), diastereoisomer 2: δ 3.17 (1 H, dd, J_g 15.5, J_{tr} 2.5, 3-H), 3.35 (1 H, dd, J_g 15.5, J_c 5.1, 3-H), 3.79 (3 H, s, OMe), 4.36 (1 H, ddd, J_v 3.5, J_c 5.1, J_{tr} 2.5, 4-H), 4.75 (1 H, d, J_v 3.5, CHCN), 6.90 (2 H, m, C_6H_4OMe) and 7.24 (2 H, m, C_6H_4OMe). HRMS *m/z* (EI) 341.9819 ($M^{\bullet+}$ $C_{12}H_{11}N_2O_2I$ requires 341.9860).

Chloro-[3-ethyl-1-(4-methoxyphenyl)-4-oxo-azetidin-2-yl]acetonitrile (**8a**): Compound **8a** was synthesised according to ref. 8. Yield: 70 %. A 60:40 mixture of two diastereoisomers; m.p. 95–97 °C; IR: ν_{max}(KBr)/cm^{-1} 1732 (CO). ^{1}H NMR ($CDCl_3$) diastereoisomer 1: δ 1.24 (3 H, t, J_v 7.5, CH_3), 1.85–2.20 (2 H, m, CH_2), 3.49 (1 H, m, 3-H), 3.79 (3 H, s, OMe), 4.59 (1 H, dd, J_c 5.5, J_v 5.3, 4-H), 4.83 (1 H, d, J_v 5.3, CHCN), 6.90 (2 H, m, C_6H_4OMe) and 7.33 (2 H, m, C_6H_4OMe), diastereoisomer 2: δ 1.23 (3 H, t, J_v 7.5, CH_3), 1.85-2.20 (2 H, m, CH_2), 3.49 (1 H, m, 3-H), 3.79 (3 H, s, OMe), 4.55 (1 H, dd, J_c 5.5, J_v 5.4, 4-H), 4.89 (1 H, d, J_v 5.4, CHCN), 6.90 (2 H, m, C_6H_4OMe) and 7.60 (2 H, m, C_6H_4OMe). HRMS *m/z* (EI) 278.0811 ($M^{\bullet+}$ $C_{14}H_{15}N_2O_2Cl$ requires 278.0817).

Bromo-[3-ethyl-1-(4-methoxyphenyl)-4-oxo-azetidin-2-yl]acetonitrile (**8b**): Compound **8b** was synthesised according to ref. 9. Yield: 45 %. A 55:45 mixture of two diastereoisomers; m.p. 102–111 °C; IR: ν_{max}(KBr)/cm^{-1} 1736 (CO). ^{1}H NMR ($CDCl_3$) diastereoisomer 1: δ 1.24 (3 H, t, J_v 7.5, CH_3), 1.94 & 2.20 (2 H, m, CH_2), 3.49 (1 H, m, 3-H), 3.79 (3 H, s, OMe), 4.52 (1 H, dd, J_c 5.8, J_v 5.0, 4-H), 4.74 (1 H, d, J_v 5.0, CHCN), 6.90 (2 H, m, C_6H_4OMe) and 7.28 (2 H, m, C_6H_4OMe), diastereoisomer 2: δ 1.25 (3 H, t, J_v 7.5, CH_3), 1.98–2.10 (2 H, m, CH_2), 3.46 (1 H, m, 3-H), 3.79 (3 H, s, OMe), 4.59 (1 H, dd, J_c 5.2, J_v 5.9, 4-H), 4.62 (1 H, d, J_v 5.9, CHCN), 6.90 (2 H, m, C_6H_4OMe) and 7.32 (2 H, m, C_6H_4OMe). HRMS *m/z* (EI) 322.0298 ($M^{\bullet+}$ $C_{14}H_{15}N_2O_2Br$ requires 322.0311).

Iodo-[3-ethyl-1-(4-methoxyphenyl)-4-oxo-azetidin-2-yl]acetonitrile **(8c):** Compound **8c** was synthesised according to ref. 14. Yield: 68 %. A 53:47 mixture of two diastereoisomers; m.p. 111–118 °C; IR: ν_{max}(KBr)/cm^{-1} 724 (CO) and 2240 (CN). ^{1}H NMR ($CDCl_3$) diastereoisomer 1: δ 1.25 (3 H, t, J_v= 7.5, CH_3), 2.10 & 2.25 (2 H, m, CH_2), 3.46 (1 H, m, 3-H), 3.80 (3 H, s, OMe), 4.38 (1 H, dd, J_c 5.5, J_v 4.6, 4-H), 4.72 (1 H, d, J_v 4.6, CHCN), 6.91 (2 H, m, C_6H_4OMe) and 7.27 (2 H, m, C_6H_4OMe), diastereoisomer 2: δ 1.26 (3 H, t, J_v= 7.5, CH_3), 1.95–2.10 (2 H, m, CH_2), 3.41 (1 H, m, 3-H), 3.80 (3 H, s, OMe), 4.46 (1 H, dd, J_c 5.5, J_v 6.6, 4-H), 4.53 (1 H, d, J_v 6.6, CHCN), 6.90 (2 H, m, C_6H_4OMe) and 7.32 (2 H, m, C_6H_4OMe). HRMS *m/z* (EI) 370.0147 ($M^{\bullet+}$ $C_{14}H_{15}N_2O_2I$ requires 370.0173).

Chloro-[3-(4-chlorophenoxy)-1-(4-methoxyphenyl)-4-oxo-azetidin-2-yl]acetonitrile (**9a)**: Compound **9a** was synthesised according to ref. 8. Yield: 52 %, m.p. 142–145 °C; IR: ν_{max}(KBr)/cm^{-1} 1756 (CO). ^{1}H NMR ($CDCl_3$): δ 3.81 (3 H, s, OMe), 4.86 (1 H, dd, J_c 5.0, J_v 5.2, 4-H), 5.02 (1 H, d, J_v= 5.2, CHCN), 5.44 (1 H, d, J_c 5.0, 3-H), 6.93 (2 H, m, C_6H_4OMe), 7.12 (2 H, m, C_6H_4Cl), 7.30 (2 H, m, C_6H_4Cl) and 7.44 (2 H, m, C_6H_4OMe). HRMS *m/z* (EI) 376.0374 ($M^{\bullet+}$ $C_{18}H_{14}N_2O_3Cl_2$ requires 376.0376).

Bromo-[3-(4-chlorophenoxy)-1-(4-methoxyphenyl)-4-oxo-azetidin-2-yl]acetonitrile (**9b**): Compound **9b** was synthesised according to ref. 9. Yield: 85 %. A 55:45 mixture of two diastereoisomers; m.p. 140–155 °C; IR: ν_{max}(KBr)/cm^{-1} 1740 (CO) and 2250 (CN). ^{1}H NMR ($CDCl_3$) diastereoisomer 1: δ 3.81 (3 H, s, OMe), 4.90 (1 H, dd, J_c 5.1, J_v 6.3, 4-H), 4.83 (1 H, d, J_v 6.3, CHCN), 5.45 (1 H, d, J_c= 4.9, 3-H), 6.93 (2 H, m, C_6H_4OMe), 7.15 (2 H, m, C_6H_4Cl), 7.30 (2 H, m, C_6H_4Cl) and 7.44 (2 H, m, C_6H_4OMe), diastereoisomer 2: δ 3.81 (3 H, s, OMe), 4.84 (1 H, dd, J_c 4.9, J_v 5.4, 4-H), 4.87 (1 H, d, J_v 5.4, CHCN), 5.41 (1 H, d, J_c= 5.1, 3-H), 6.93 (2 H, m, C_6H_4OMe), 7.13 (2 H, m, C_6H_4Cl), 7.30 (2 H, m, C_6H_4Cl) and 7.40 (2 H, m, C_6H_4OMe). HRMS *m/z* (EI) 419.9847 ($M^{\bullet+}$ $C_{18}H_{14}N_2O_3ClBr$ requires 419.9871).

Iodo-[3-(4-Chlorophenoxy)-1-(4-methoxyphenyl)-4-oxo-azetidin-2-yl]acetonitrile (**9c**): Compound **9c** was synthesised according to ref. 14.Yield: 51 %. A 55:45 mixture of two diastereoisomers; m.p. 145-158 °C; IR: ν_{max}(KBr)/cm^{-1} 1740 (CO). ^{1}H NMR ($CDCl_3$) diastereoisomer 1: δ 3.81 (3 H, s, OMe), 4.61 (1 H, dd, J_c 5.1, J_v 4.2, 4-H), 4.87 (1 H, d, J_v 4.2, CHCN), 5.34 (1 H, d, J_c 5.2, 3-H), 6.94 (2 H, m, C_6H_4OMe), 7.17 (2 H, m, C_6H_4Cl), 7.31 (2 H, m, C_6H_4Cl) and 7.38 (2 H, m, C_6H_4OMe), diastereoisomer 2: δ 3.81 (3 H, s, OMe), 4.72 (1 H, d, J_v 7.5, CHCN), 4.82 (1 H, dd, J_c 5.2, J_v 7.5, 4-H), 5.41 (1 H, d, J_c 5.1, 3-H), 6.92 (2 H, m, C_6H_4OMe), 7.16 (2 H, m, C_6H_4Cl), 7.31 (2 H, m, C_6H_4Cl) and 7.42 (2 H, m, C_6H_4OMe). HRMS *m/z* (EI) 467.9701 ($M^{\bullet+}$ $C_{18}H_{14}N_2O_3ClI$ requires 467.9732).

[3-(4-Chlorophenoxy)-1-(4-methoxyphenyl)-4-oxo-azetidin-2-yl]acetonitrile (**14**): Compound **14** was synthesised according to Methods 1–3.M.p. 115 °C; IR: ν_{max}(KBr)/cm^{-1} 1752 (CO) and 2248 (CN). ^{1}H NMR ($CDCl_3$): δ 2.92-3.04 (2 H, m, CH_2CN), 3.81 (3 H, s, OMe), 4.70 (1 H, m, 4-H), 5.39 (1 H, d, J_c= 5.0, 3-H), 6.93 (2 H, m, C_6H_4OMe), 7.13 (2 H, m, C_6H_4Cl), 7.3 (2 H, m, C_6H_4Cl) and 7.44 (2 H, m, C_6H_4OMe). HRMS *m/z* 342.0750 (EI) ($M^{\bullet+}$ $C_{18}H_{15}N_2O_3Cl$ requires 342.0766).

4-Cyano-2–ethyl-N-(4-methoxyphenyl)butyric amide (**18**): Compound **18** was synthesised according to Method 1. M.p. 99 °C; IR: ν_{max}(KBr)/cm^{-1} 1652 (CO), 2248 (CN) and 3304 (NH). ^{1}H NMR ($CDCl_3$): δ 1.00 (3 H, t, CH_3), 1.60 (1 H, m, ethyl CH_2), 1.77 (1 H, m, ethyl CH_2), 1.82 (1 H, m, 3-H), 2.08 (1 H, m, 3-H), 2.35 (1 H, m, 2-H), 2.39 (1 H, ddd, J_g 17.0, J_v 6.1, J_v 9.4, CH_2CN), 2.47 (1 H, ddd, J_g 17.0, J_v 6.4, J_v 5.2, CH_2CN), 3.79 (3 H, s, OMe), 6.87 (2 H, m, C_6H_4OMe) and 7.42 (2 H, m, C_6H_4OMe). HRMS *m/z* (EI) 246,1365 ($M^{\bullet+}$ $C_{14}H_{18}N_2O_2$ requires 246.1363).

2-(4-Chlorophenoxy)-4-cyano-N-(4-methoxyphenyl)butyric amide (**19**): Compound **19** was synthesised according to Method 1. M.p. 130 °C; IR: ν_{max}(KBr)/cm^{-1} 1664 (CO), 2248 (CN) and 3232 (NH). ^{1}H NMR ($CDCl_3$): δ 2.30–2.46 (2 H, m, 3-H), 2.59 (2 H, t, J_v 7.5, CH_2CN), 3.79 (3 H, s, OMe), 4.71 (1 H, dd, J_v 4.7, J_v 6.8, 2-H), 6.86 (2 H, m, C_6H_4OMe), 6.95 (2 H, m, C_6H_4Cl), 7.31 (2 H, m, C_6H_4Cl), 7.40 (2 H, m, C_6H_4OMe) and 8.0 (1 H, br s, NH). HRMS *m/z* (EI) 344,0913 ($M^{\bullet+}$ $C_{18}H_{17}N_2O_3Cl$ requires 344.0922).

Mixture of 4-cyano-N-(4-methoxyphenyl)but-2-enoic amide (**22**) *and 4-cyano-N-(4-methoxyphenyl)but-3-enoic amide* (**23**): Compounds **22** and **23** were synthesised according to Methods 2 and 3, and they were not separated in the course of the preparative work-up. The isomers were assignated by NMR spectroscopy. M.p. 104–105 °C; IR: ν_{max}(KBr)/cm^{-1} 1652 (CO), 2248 (CN) and 3304 (NH). HRMS *m/z* (EI) 216.0893 ($M^{\bullet+}$ $C_{12}H_{12}N_2O_2$ requires 216.0893).

22: ^{1}H NMR ($CDCl_3$): δ 3.33 (2 H, dd, J_v 4.8, J_a 2.0, CH_2CN), 3.80 (3 H, s, OMe), 6.35 (1 H, dt, J_{tr} 15.2, J_a 2.0, 2-H), 6.84 (1 H, dt, J_{tr} 15.2, J_v 4.8, 3-H), 6.88 (2 H, m, C_6H_4OMe), 7.10 (1 H, br s, NH) and 7.48 (2 H, m, C_6H_4OMe). ^{13}C NMR ($CDCl_3$): δ 20.23 (1 C, C4), 55.53 (1 C, OMe), 114.35 (2 C, C_6H_4OMe), 121.87 (2 C, C_6H_4OMe), 128.01 (1 C, C2) and 131,82 (1 C, C3).

23: ^{1}H NMR ($CDCl_3$): δ 3.30 (2 H, dd, J_v 7.0, J_a 1.7, CH_2), 3.79 (3 H, s, OMe), 5.58 (1 H, dt, J_{tr} 16.8, J_a 1.7, CHCN), 6.87 (2 H, m, C_6H_4OMe), 6.90 (1 H, dt, J_{tr} 16.8, J_v 7.0, 3-H), 7.06 (1 H, br s, NH)

and 7.37 (2 H, m, C_6H_4OMe). ^{13}C NMR ($CDCl_3$): δ 40.86 (1 C, C2), 55.53 (OMe), 103.68 (1 C, C4), 114.35 (2 C, C_6H_4OMe), 116.55 (CN), 122.12 (2 C, C_6H_4OMe), 130.08 (1 C, C_6H_4OMe), 147.12 (1 C, C3), 157.04 (1 C, C_6H_4OMe) and 165.46 (1 C, CO).

Mixture of 4-cyano-2-ethyl-N-(4-methoxyphenyl)but-2-enoic amide (**24**) *and 4-cyano-2-ethyl-N-(4-methoxyphenyl)but-3-enoic amide* (**25**): Compounds **24** and **25** were synthesised according to Methods 2 and 3, and they were not separated in the course of the preparative work-up. The isomers were assignated by NMR spectroscopy. M.p. 47–48°C; IR: ν_{max}(film)/cm^{-1} 1712 (CO), 2224 (CN) and 3312 (NH). HRMS *m/z* (EI) 244.1206 ($M^{\bullet+}$ $C_{14}H_{16}N_2O_2$ requires 244.1206).

(E)-**24**: ^1H NMR ($CDCl_3$): δ 1.13 (3 H, t, J_v 7.5, CH_3), 2.44 (2 H, q, J_v 7.5, ethyl CH_2), 3.47 (2 H, d, J_v 7.0, CH_2CN), 3.80 (3 H, s, OMe), 5.63 (1 H, t, J_v 7.0, 3-H), 6.87 (2 H, m, C_6H_4OMe), 7.34 (1 H, br s, NH) and 7.45 (2 H, m, C_6H_4OMe).

(Z)-**24**: ^1H NMR ($CDCl_3$): δ 1.13 (3 H, t, J_v 7.5, CH_3), 2.44 (2 H, q, J_v 7.5, ethyl CH_2), 3.25 (2 H, d, J_v 7.0, CH_2CN), 3.80 (3 H, s, OMe), 6.13 (1 H, t, J_v 7.0, 3-H), 6.87 (2 H, m, C_6H_4OMe), 7.34 (1 H, br s, NH) and 7.45 (2 H, m, C_6H_4OMe).

(E)-**25** : ^1H NMR $CDCl_3$): δ 1.00 (3 H, t, J_v 7.5, CH_3), 1.73 & 1.98 (2 H, m, ethyl CH_2), 2.95 (1 H, m, 2-H), 3.80 (3 H, s, OMe), 5.53 (1 H, dd, J_a 1.2, J_{tr} 16.4, CHCN), 6.82 (1 H, dd, J_v 8.4, J_{tr} 16.4, 3-H), 6.89 (2 H, m, C_6H_4OMe), 7.02 (1 H, br s, NH) and 7.38 (2 H, m, C_6H_4OMe).

(Z)-**25**: ^1H NMR ($CDCl_3$): δ 1.00 (3 H, t, J_v 7.5, CH_3), 1.73 & 1.98 (2 H, m, ethyl CH_2), 3.38 (1 H, m, 2-H), 3.80 (3 H, s, OMe), 5.49 (1 H, dd, J_a 1.0, J_c 11.0, CHCN), 6.69 (1 H, dd, J_v 10.0, J_c 11.0, 3-H), 6.89 (2 H, m, C_6H_4OMe), 7.02 (1 H, br s, NH) and 7.38 (2 H, m, C_6H_4OMe).

2-(4-Chlorophenoxy)-4-cyano-N-(4-methoxyphenyl)but-2-enoic amide (**26**): Compound **26** was synthesised according to Method 2. Yellow oil, IR: ν_{max}(KBr)/cm^{-1} 1656 (CO), 2256 (CN) and 3328 (NH). ^1H NMR ($CDCl_3$): δ 3.15 (2 H, d, J_v 7.5, CH_2CN), 3.78 (3 H, s, OMe), 6.65 (1 H, t, J_v 7.5, J_v 6.8, 3-H), 6.85 (2 H, m, C_6H_4OMe), 7.0 (2 H, m, C_6H_4Cl), 7.34 (2 H, m, C_6H_4Cl), 7.37 (2 H, m, C_6H_4OMe) and 7.78 (1 H, br s, NH). HRMS *m/z* (EI) 342.0748 ($M^{\bullet+}$ $C_{18}H_{15}N_2O_3Cl$ requires 342.0766).

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