Parallel solution phase synthesis of benzyl (3*S*,4*E*)-4-[(arylamino)methylidene]-5-oxotetrahydrofuran-3-ylcarbamates

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Dedicated to Professor Branko Stanovnik, University of Ljubljana, on the occasion of his 65th anniversary

(received 13 Jun 03; accepted 18 Sep 03; published on the web 19 Sep 03)

Abstract

Benzyl (3*S*,4*E*)-4-[(dimethylamino)methylidene]-5-oxotetrahydrofuran-3-ylcarbamate **5** was prepared in 4 steps from L-aspartic acid **1**. Acid-catalysed treatment of **5** with amines **6** gave the dimethylamine substitution products **7**. Benzyl (3*S*,4*E*)-4-[(arylamino)methylidene]-5-oxotetrahydrofuran-3-ylcarbamates **7c–n** were prepared by parallel solution phase synthesis from **5** and anilines **6c–n** in 45–94% yields. Enaminone **5** reacted with potassium cyanide in the presence of 18-crown-6 to afford benzyl 4-cyanomethyl-5-oxo-2,5-dihydrofuran-3-ylcarbamate **9**. Upon reaction of **9** with nitrile oxide **10** the 1,2,4-oxadiazole derivative **11** was isolated in poor yield, while treatment of **9** with diazomethane **12** furnished the methylation products **13** and **14**.

Keywords: Enaminones, ex-chiral pool, anilines, parallel synthesis, cycloadditions

Introduction

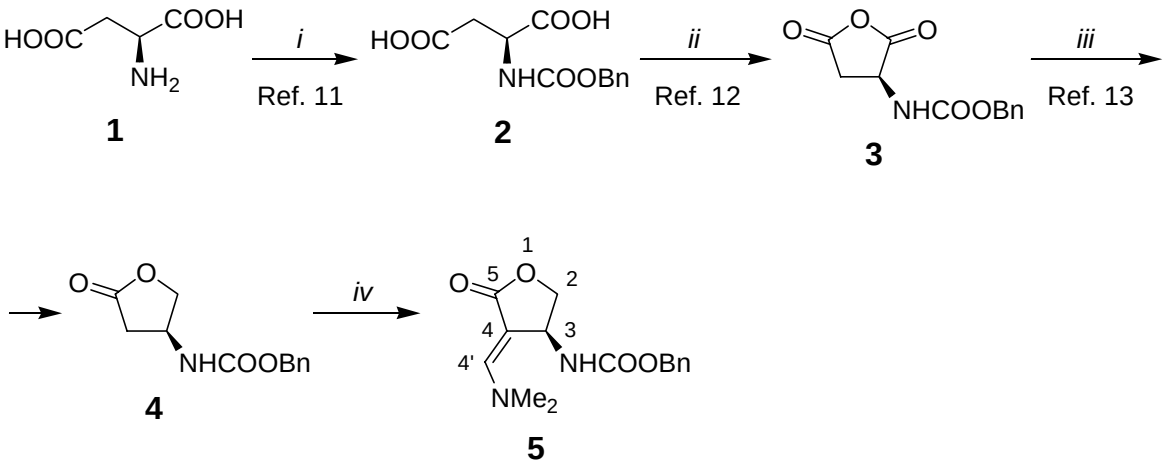
Recently, 5-substituted (*S*)-1-acyl-3-[(dimethylamino)methylidene]pyrrolidin-2-ones and (*S*)-3-[(dimethylamino)methylidene]tetrahydrofuran-2-ones, chiral cyclic analogues of alkyl 2-substituted 3-(dimethylamino)propenoates,[1] were introduced as reagents for the preparation of various functionalised heterocyclic compounds.[2] For example, they were employed in the 'ring switching' preparation of 3-heteroarylalanine-,[3] 3-heteroarylalaninol-,[4] 3-heteroaryllactic acid-,[5] and 3-heteroarylpropan-1,2-diol derivatives,[6] in stereoselective α-amination of γ-lactams and γ-lactones[7], and in stereoselective 1,3-dipolar cycloadditions to 3-cyanomethylidene substituted pyrrolidin-2-ones[8] and tetrahydrofuran-2-ones[9]. Just recently, (1*R*,4*R*)-3-[(*E*)-(dimethylamino)

methylidene]-1,7,7-trimethylbicyclo[2.2.1]heptan-2-one, (1*R*)-(+)-camphor derived *N*,*N*-dimethylenaminone, was used for stereoselecive synthesis of (1*R*,3*R*,4*R*)-3-(1,2,4-triazolo[4,3–*x*]azin-3-yl)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-ones.[10]

In continuation of our research in the field of chiral 3-(dimethylamino)propenoate analogues, we report the preparation and transformations of benzyl (3*S*,4*E*)-4-[(dimethylamino)methylidene]-5-oxotetrahydrofuran-3-ylcarbamate **5**, a novel representative in this series, and its utilisation in the solution phase parallel synthesis of benzyl (3*S*,4*E*)-4-[(arylamino)methylidene]-5-oxotetrahydrofuran-3-ylcarbamates **7c–n**.

Results and Discussion

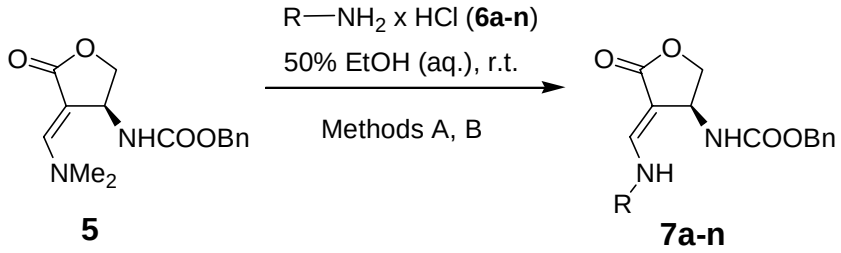
The starting compound, benzyl (*S*)-5-oxotetrahydrofuran-3-ylcarbamate **4** was prepared in 3 steps from L-aspartic acid **1** according to the procedures described in the literature.[11–13] Lactone **4** was then treated with bis(dimethylamino)-*tert*-butoxymethane (Bredereck's reagent) to give benzyl (3*S*,4*E*)-4-[(dimethylamino)methylidene]-5-oxotetrahydrofuran-3-ylcarbamate **5** in 89% yield (Scheme 1).



Scheme 1. Reagents and conditions: *i*) ClCOOBn, NaOH, H_2O, 0 °C; *ii*) Ac_2O, 100 °C; *iii*) $NaBH_4$, THF, 0–20 °C, then benzene, *p*-TsOH (cat.), reflux (Dean-Stark apparatus); *iv*) *t*-$BuOCH(NMe_2)_2$, toluene, 100 °C.

First investigations on reactivity of the enamino lactone **5** towards nucleophiles revealed that, in contrast to previously established general reactivity pattern of various 3-(dimethylamino)propenoates,[1,2] compound **5** is quite unstable under acidic conditions. In most cases, acid-catalysed reactions with various nucleophiles, such as aliphatic and heteroaromatic amines, *N*,*N*-, *C*,*N*-, and *C*,*O*-ambident nucleophiles, and potassium cyanide, gave inseparable mixtures of products. Only upon reaction of **5** with 3-aminoisoxazole **6a** and piperidine **6b**, the dimethylamine substitution products **7a** and **7b** were isolated in poor yields. On the other hand,

preliminary tests showed that dimethylamine substitution in reactions of **5** with anilines **6** in 50% aqueous ethanol proceed smoothly and in good yields. Therefore, we carried out the parallel solution-phase synthesis of benzyl (3*S*,4*E*)-4-[(arylamino)methylidene]-5-oxotetrahydrofuran-3-ylcarbamates **7c–n**, which were prepared in 45–94% yields. In most cases, analytically pure compounds were obtained upon filtration, washing, and thorough drying. Compounds **7a,b,n** were isolated in isomerically pure form, while compounds **7c–m** were obtained as mixtures of the major (*E*)-isomers and the minor (*Z*)-isomers (Scheme 2).

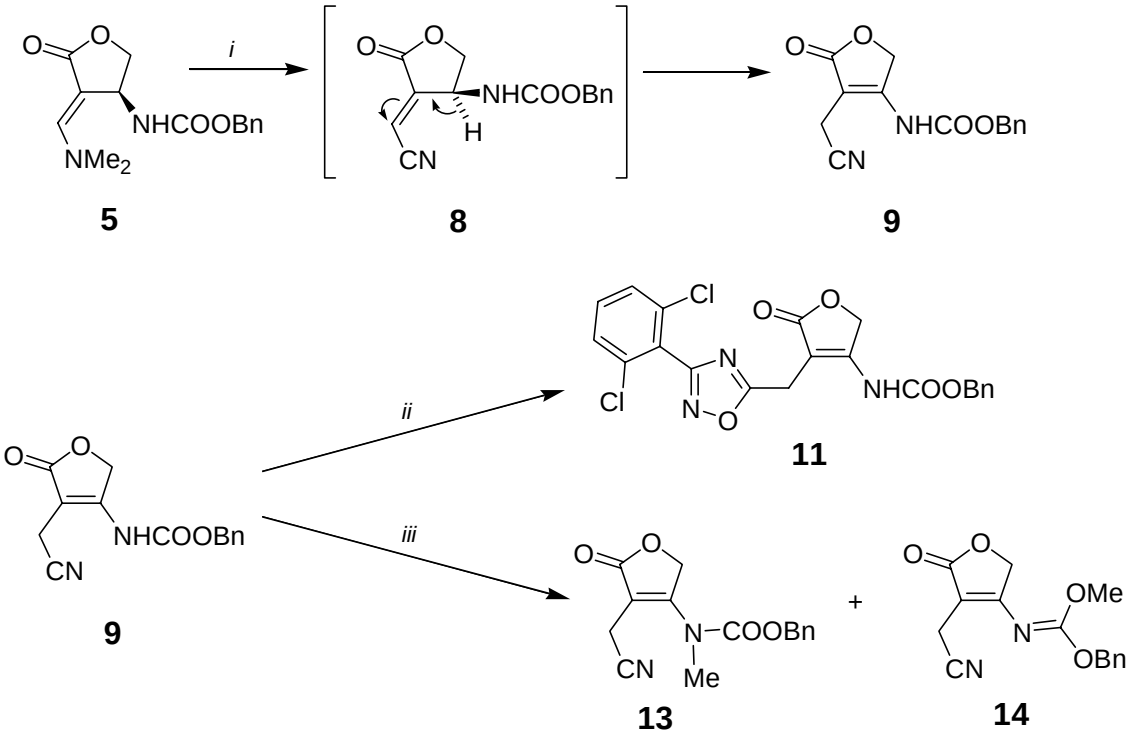


Compound	R	Method	Yield [%]	*E*:*Z*
6a, **7a**	piperidin-1-yl	A	9	100:0
6b, **7b**	isoxazol-3-yl	A	15	100:0
6c, **7c**	phenyl	B	89	93:7
6d, **7d**	2-methylphenyl	B	45	81:19
6e, **7e**	3-methylphenyl	B	76	96:4
6f, **7f**	4-methylphenyl	B	88	93:7
6g, **7g**	2-methoxyphenyl	B	77	81:19
6h, **7h**	3-methoxyphenyl	B	62	87:13
6i, **7i**	4-methoxyphenyl	B	73	99:1
6j, **7j**	2-bromophenyl	B	71	77:23
6k, **7k**	3-bromophenyl	B	70	94:6
6l, **7l**	4-bromophenyl	B	74	90:10
6m, 7m	3-hydroxyphenyl	B	94	90:10
6n, 7n	4-hydroxyphenyl	B	46	100:0

Scheme 2. Method A: classical (single vessel) synthesis (**6a,b→7a,b**); Method B: parallel synthesis (**6c–n→7c–n**).

Attempts to prepare the 4-cyanomethylidene analogue **8** by acid-catalysed dimethylamine substitution under various reaction conditions failed. However, when reaction of **5** with potassium cyanide was carried out in dichloromethane in the presence of 1 equivalent of 18-crown-6, benzyl 4-cyanomethyl-5-oxo-2,5-dihydrofuran-3-ylcarbamate **9** was obtained in 60% yield. Most probably, this transformation proceeds *via* the cyanomethylidene compound **8** as the intermediate, which then isomerises into the cyanomethyl tautomer **9**. Similar base-catalysed

migration of the exocyclic C=C double bond has been observed previously in 3-cyanomethylidene-5-methoxycarbonyl-2-pyrrolidinone series.[8] 1,3-Dipolar cycloaddition of 2,6-dichlorobenzonitrile oxide **10** to dipolarophile **9** in chloroform under reflux afforded cycloadduct **11** in 7% yield. Since IR spectrum of **11** does not exhibit a signal characteristic for the cyano group, we presume, that cycloaddition of **10** to nitrile **9** is taking place to the C≡N triple bond and not to the C=C double bond, thus furnishing the 1,2,4-oxadiazole derivative **11**. On the other hand, treatment of **9** with diazomethane **12** gave the *N*-methylated compound **13** and the *O*-methylated compound **14** in 41% and 7% yield, respectively (Scheme 3).



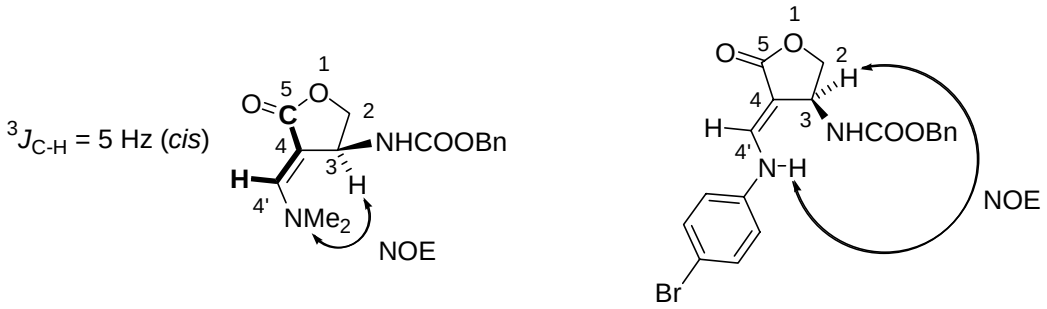
Scheme 3. Reagents and conditions: *i*) KCN, CH_2Cl_2, 18-crown-6, 20 °C; *ii*) 2,6-dichlorobenzonitrile oxide **10**, $CHCl_3$, reflux; *iii*) CH_2N_2 **12**, Et_2O, THF, 20 °C.

Structure determination

Structures of novel compounds **5**, **7a–n**, **9**, **11**, **13**, and **14** were determined by spectroscopic methods (IR, NMR, MS) and by elemental analyses for C, H, and N. Compounds **7a,b,d,j,n**, **11**, and **14** were not prepared in analytically pure form; their identity was confirmed by HRMS.

The (*E*)-configuration around the exocyclic C=C double bond in compound **5** was determined by NMR on the basis of NOE between *H*–C(3) and N*Me*$_2$ group. Similarly, the (*E*)-configuration was established for compound **7l** on the basis of NOE between *H*–C(3) and *H*–N–C(4'). In the case of enaminone **5**, the (*E*)-configuration was additionally confirmed by 2D HMBC techique on the basis of magnitude of the heteronuclear long range coupling constant, $^3J_{C–H}$. Generally, the magnitude of coupling constans $^3J_{C–H}$ for nuclei with *cis*-orientation around

the C=C double bond are smaller (2–6 Hz) than those for the *trans*-oriented nuclei (8–12 Hz).[14] In compound **5**, the magnitude of coupling constant, $^{3}J_{C–H}$ = 5 Hz, showed the *cis*-configuration between *H*–C(4') and *C*(5), and was in agreement with the magnitudes determined previously for analogous compounds (Scheme 4).[8–10,14,15]



compound **5** (*E*)-isomer

compound **7l** (*E*)-isomer

Scheme 4

Conclusions

Benzyl (3*S*,4*E*)-4-[(dimethylamino)methylidene]-5-oxotetrahydrofuran-3-ylcarbamate **5**, a novel chiral 3-dimethylaminopropenoate analogue, is available in 4 steps from L-aspartic acid. Parallel treatment of **5** with 12 aromatic amines under mild conditions afforded the corresponding dimethylamine substitution products in good yields. However, with respect to previously prepared 3-(dimethylamino)propenoates and their analogues, enamino lactone **5** turned out to be quite unstable under acidic conditions, which are usually employed for reactions of related *N*,*N*-dimethylenaminones with nucleophiles. On the other hand, substitution of the dimethylamino group in compound **5** by the cyano group was achieved under basic conditions. However, this substitution was accompanied by migration of the exocyclic C=C double bond into the ring and by loss of chirality.

Experimental Section

General Procedures. Parallel synthesis of compounds **7c–n** was carried out on a Mettler-Toledo Bohdan MiniBlock™ Compact Shaking and Washing Station and Vacuum Collection Base (12 positions). Melting points were taken with a Kofler micro hot stage. The ^{1}H NMR spectra (300 MHz) and ^{13}C NMR (75.5 MHz) spectra were obtained with a Bruker Avance DPX 300 (300 MHz) spectrometer with DMSO-d_6 and $CDCl_3$ as solvents and Me_4Si as internal standard. IR spectra were recorded with a Perkin-Elmer 1310 and Perkin-Elmer Spectrum BX FTIR

spectrophotometers (KBr discs). The microanalyses for C, H, and N were obtained with a Perkin-Elmer CHN Analyser 2400. Optical rotations were measured by a Perkin-Elmer-241-MC polarimeter. The MS spectra were recorded with an Autospeck Q (VG-Analytical) spectrometer in Laboratory for Mass Spectroscopy (J. Stefan Institute, Ljubljana). TLC: Merck, Alufolien Kieselgel 60 F 254, 0.2 mm. Column chromatography was performed on a silica gel (Fluka, Kieselgel 60, 0.04–0.063 mm).

All starting materials were commercially available (in most cases from Fluka) and purified following the standard techniques. Benzyl (*S*)-5-oxotetrahydrofuran-3-ylcarbamate **4**,[13] 2,6-dichlorobenzonitrile oxide **10**,[16] and diazomethane **12**[17] were prepared according to the procedures described in the literature.

Benzyl (3*S*,4*E*)-4-[(dimethylamino)methylidene]-5-oxotetrahydrofuran-3-ylcarbamate (5). A mixture of **4** (2.35 g, 10 mmol), anhydrous toluene (20 mL), and bis(dimethylamino)-*tert*-butoxymethane (Bredereck's reagent) (2.61 g, 15 mmol) was stirred at 90–100 °C for 2 h. Volatile components were evaporated *in vacuo* and the residue was purified by column chromatography (ethyl acetate). Fractions containing the product were combined, evaporated *in vacuo*, and the residue was crystallised from ethyl acetate to give **5**. Yield: 2.58 g (89%), pale yellow crystals; mp 130–133 °C (from ethyl acetate), $[\alpha]_D^{20}$ –155.9 ° (*c* = 1.00, CH_2Cl_2). IR (KBr, cm^{-1}): 1710, 1680, 1630 (C=O). ^{1}H NMR (DMSO-d_6): δ 3.01 (6H, s, NMe_2), 3.94 (1H, dd, *J* = 1.1, 9.4 Hz, 5–Ha), 4.21 (1H, dd, *J* = 6.4, 9.4 Hz, 5–Hb), 4.97–5.10 (1H, m, 4–H), 5.04 (2H, s, C*H*$_2$Ph), 7.15 (1H, d, *J* = 0.8 Hz, 3'–H), 7.27–7.40 (5H, m, Ph), 7.86 (1H, d, *J* = 6.8 Hz, NH). ^{13}C NMR (DMSO-d_6): δ 39.9, 49.1, 65.6, 72.3, 86.7, 127.9, 128.1, 128.7, 137.5, 149.8, 155.6, 173.7. Anal. Calcd. for $C_{15}H_{18}N_2O_4$ (290.13): C, 62.06; H 6.25; N 9.65. Found: C, 62.41; H 6.10; N 9.66.

Benzyl (3*S*,4*E*)-4-[(piperidin-1-yl)methylidene]-5-oxotetrahydrofuran-3-ylcarbamate (7a). Compound **5** (0.145 g, 0.5 mmol) was added to a stirred solution of piperidine **6a** (0.045 g, 0.5 mmol) in a mixture of ethanol (2 mL), water (2 mL), and hydrochloric acid (37%, 2 drops, ~0.6 mmol) and the mixture was stirred at room temperature for 12 h. Volatile components were evaporated *in vacuo* (T < 40 °C) and the residue was purified by column chromatography (ethyl acetate). Fractions containing the product were combined and evaporated *in vacuo* to give **7a**. Yield: 0.015 g (9%), colourless oil. ^{1}H NMR ($CDCl_3$): δ 1.50–1.70 (6H, m, 6H of piperidine), 3.28–3.45 (4H, m, 4H of piperidine), 4.17 (1H, d, *J* = 9.8 Hz, 2–Ha), 4.28–4.39 (1H, m, 2–Hb), 5.00–5.20 (2H, m, 3–H and N*H*COOBn), 5.12 (2H, s, C*H*$_2$Ph), 7.25 (1H, br s, =CH), 7.29–7.40 (5H, m, Ph). Anal. Calcd. for $C_{18}H_{22}N_2O_4$ (330.16): C, 65.44; H 6.71; N 8.48. Found: C, 64.78; H 6.88; N 7.92. Exact mass Calcd. for $C_{18}H_{22}N_2O_4$: *m*/*z* = 330.157957. Found: *m*/*z* = 330.158660.

Benzyl (3*S*,4*E*)-4-{[(isoxazol-3-yl)amino]methylidene}-5-oxotetrahydrofuran-3-ylcarbamate (7b). Compound **5** (0.145 g, 0.5 mmol) was added to a stirred solution of 3-aminoisoxazole **6** (0.042 g, 0.5 mmol) in a mixture of ethanol (2 mL), water (2 mL), and hydrochloric acid (37%, 2 drops, ~0.6 mmol) and the mixture was stirred at room temperature for 12 h. The precipitate was collected by filtration, washed with water, and dried *in vacuo* over sodium hydroxide pellets for

12 h to give **7b**. Yield: 0.025 g (15%), m.p. 146–149° C, white solid. IR (KBr, cm^{-1}): 1740, 1680, 1640 (C=O). ^{1}H NMR ($CDCl_3$): δ 4.13 (1H, dd, *J* = 2.3, 10.6 Hz, 2–Ha), 4.57 (1H, dd, *J* = 8.3, 10.6 Hz, 2–Hb), 5.04–5.22 (1H, m, 3–H), 5.18 (2H, s, C*H*$_2$Ph), 5.64 (1H, d, *J* = 7.5 Hz, N*H*COOBn), 6.12 (1H, d, *J* = 1.9 Hz, 4'–H), 7.29–7.40 (5H, m, Ph), 7.85 (1H, dd, *J* = 1.5, 13.2 Hz, =C*H*NH), 8.23 (1H, d, *J* = 1. 9 Hz, 5'–H), 9.17 (1H, d, *J* = 13.2 Hz, N*H*CH=). Anal. Calcd. for $C_{16}H_{15}N_3O_5$ (329.10): C, 58.36; H 4.59; N 12.76. Found: C, 56.87; H 4.30; N 12.34. Exact mass Calcd. for $C_{16}H_{15}N_3O_5$: *m*/*z* = 329.101171. Found: *m*/*z* = 329.101850.

Parallel synthesis of benzyl (3*S*,4*E*)-4-[(arylamino)methylidene]-5-oxotetrahydrofuran-3-ylcarbamates (7c–n). MiniBlock™ parallel synthesiser with 12 positions was equipped with glass reaction vessels (20 mL each) with fritted bottom. The frits were wetted with ethanol (~ 0.5 mL each), the MiniBlock^{TM} was closed, and mounted onto the shaking and washing station. The reaction vessels were loaded *via* syringe with aqueous solutions of anilines hydrochlorides **6c–n** (0.25 *M* in water, 2 mL = 0.5 mmol to each position). Then a warm ethanolic solution of compound **5** (~ 40 – 50°C, 0.25 *M* in ethanol, 2 mL = 0.5 mmol) was added *via* syringe to each reaction vessel. The reaction mixtures were stirred (350 r.p.m., Vortex stirring) at room temperature for 12 h. During this time, precipitation of the products occurred. The MiniBlock™ was removed from the shaking and washing station, put onto the vacuum collection base, and opened. The reaction mixtures were filtered and the precipitates were washed with water (2 × 5 mL). The reaction vessels with products were taken out from the MiniBlock™ and put into a dessiccator. The products were dried *in vacuo*, first over sodium hydroxide pellets for 3 days, and then over phosphorous pentoxide for 2 days. The dried precipitates were collected to give the substitution products **7c–n**.

The following compounds were prepared in this manner:

Benzyl (3*S*,4*E*)-4-[(phenylamino)methylidene]-5-oxotetrahydrofuran-3-ylcarbamate (7c). This compound was prepared from **5** and aniline hydrochloride **6c**. Yield: 0.151 g (89%), *E*:*Z* = 93:7; m.p. 161–165 °C, white solid; $[\alpha]_D^{21}$ –119.4° (*c* = 0.39, CH_2Cl_2). IR (KBr, cm^{-1}): 1711, 1691, 1641 (C=O). ^{1}H NMR (DMSO-d_6) major isomer: δ 4.12 (1H, dd, *J* = 2.3, 9.8 Hz, 2–Ha), 4.42 (1H, dd, *J* = 7.4, 9.6 Hz, 2–Hb), 4.97 (1H, br t, *J* = 6.6 Hz, 3–H), 5.10 (2H, s, C*H*$_2$Ph), 7.02 (1H, t, *J* = 7.3 Hz, 1H of Ar), 7.14 (2H, d, *J* = 7.9 Hz, 1H of Ar), 7.27–7.40 (7H, m, 7H of Ar), 7.77 (1H, d, *J* = 13.6 Hz, =C*H*NH), 7.97 (1H, d, *J* = 6.0 Hz, N*H*COOBn), 9.31 (1H, d, *J* = 13.6 Hz, N*H*CH=); minor isomer: δ 9.52 (1H, d, *J* = 12.4 Hz, N*H*CH=). Anal. Calcd. for $C_{19}H_{18}N_2O_4$ (338.36): C, 67.44; H 5.36; N 8.28. Found: C, 67.27; H 5.35; N 8.56.

Benzyl (3*S*,4*E*)-4-{[(2-methylphenyl)amino]methylidene}-5-oxotetrahydrofuran-3-ylcarbamate (7d). This compound was prepared from **5** and 2-methylaniline hydrochloride **6d**. Yield: 0.079 g (45%), *E*:*Z* = 81:19; mp 61–85 °C, pale brown amorphous solid; $[\alpha]_D^{21}$ –116.3° (*c* = 0.26, CH_2Cl_2). MS (EI): *m*/*z* = 352 (M^+). IR (KBr, cm^{-1}): 1689, 1641 (C=O). ^{1}H NMR (DMSO-d_6) major isomer: δ 2.27 (3H, s, Me), 4.14 (1H, dd, *J* = 2.4, 9.6 Hz, 2–Ha), 4.46 (1H, dd, *J* = 7.9, 9.8 Hz, 2–Hb), 5.01–5.09 (1H, br m, 3–H), 5.10 (2H, s, C*H*$_2$Ph), 6.92–7.05 (1H, m, 1H of Ar), 7.12–7.40 (8H, m, 5H of Ph and 3H of Ar), 7.68 (1H, d, *J* = 13.2 Hz, =C*H*NH), 8.22 (1H, d, *J* = 7.12 Hz, N*H*COOBn), 8.60 (1H, d, *J* = 13.2 Hz, N*H*CH=); minor isomer: δ 2.24 (3H, s, Me), 4.87–5.05 (1H, br m, 3–H), 9.62 (1H, d, *J* = 12.4 Hz, N*H*CH=). ^{13}C NMR (DMSO-d_6): δ 18.1,

49.1, 66.9, 70.4, 97.9, 116.9, 124.2, 127.5, 128.1, 128.6, 128.8, 129.2, 131.8, 137.5, 140.0, 140.7, 158.2, 172.6. Anal. Calcd. for $C_{20}H_{20}N_2O_4$ (352.38): C, 68.17; H 5.72; N 7.95. Found: C, 66.01; H, 5.69; N, 7.78. Exact mass Calcd. for $C_{20}H_{20}N_2O_4$: *m*/*z* = 352.143150. Found: *m*/*z* = 352.142307.

Benzyl (3*S*,4*E*)-4-{[(3-methylphenyl)amino]methylidene}-5-oxotetrahydrofuran-3-ylcarbamate (7e). This compound was prepared from **5** and 3-methylaniline hydrochloride **6e**. Yield: 0.134 g (76%), *E*:*Z* = 96:4; mp 128–131 °C, white solid; $[\alpha]_D^{21}$ –131.5° (*c* = 0.30, CH_2Cl_2). IR (KBr, cm^{-1}): 1715, 1680 (C=O). ^1H NMR (DMSO-d_6) major isomer: δ 2.29 (3H, s, Me), 4.11 (1H, dd, *J* = 2.3, 9.8 Hz, 2–Ha), 4.42 (1H, dd, *J* = 7.5, 9.4 Hz, 2–Hb), 4.96 (1H, br t, 3–H), 5.10 (2H, s, C*H*$_2$Ph), 6.84 (1H, d, *J* = 7.2 Hz, 1H of Ar), 6.93 (1H, br d, *J* = 7.9 Hz, 1H of Ar), 6.98 (1H, br s, 1H of Ar), 7.20 (1H, t, *J* = 7.7 Hz, 1H of Ar), 7.27–7.40 (5H, m, Ph), 7.76 (1H, d, *J* = 13.3 Hz, =C*H*NH), 7.97 (1H, d, *J* = 6.4 Hz, N*H*COOBn), 9.24 (1H, d, *J* = 13.6 Hz, N*H*CH=); minor isomer: δ 9.48 (1H, d, *J* = 12.8 Hz, N*H*CH=). Anal. Calcd. for $C_{20}H_{20}N_2O_4$ (352.38): C, 68.17; H 5.72; N 7.95. Found: C, 67.85; H, 5.73; N, 8.15.

Benzyl (3*S*,4*E*)-4-{[(4-methylphenyl)amino]methylidene}-5-oxotetrahydrofuran-3-ylcarbamate (7f). This compound was prepared from **5** and 4-methylaniline hydrochloride **6f**. Yield: 0.154 g (88%), *E*:*Z* = 93:7, mp 162–165 °C, white solid; $[\alpha]_D^{21}$ –117.8° (*c* = 1.00, CH_2Cl_2). IR (KBr, cm^{-1}): 1713, 1680 (C=O). ^1H NMR (DMSO-d_6) major isomer: δ 2.25 (3H, s, Me), 4.10 (1H, dd, *J* = 2.1, 9.6 Hz, 2–Ha), 4.40 (1H, dd, *J* = 7.4, 9.6 Hz, 2–Hb), 4.95 (1H, br t, *J* = 6.6 Hz, 3–H), 5.10 (2H, s, C*H*$_2$Ph), 7.04 (2H, d, *J* = 8.7 Hz, 2H of Ar), 7.13 (2H, d, *J* = 8.3 Hz, 2H of Ar), 7.25–7.41 (5H, m, Ph), 7.73 (1H, d, *J* = 13.9 Hz, =C*H*NH), 7.96 (1H, d, *J* = 6.4 Hz, N*H*COOBn), 9.25 (1H, d, *J* = 13.6 Hz, N*H*CH=), minor isomer δ 5.06 (2H, s, C*H*$_2$Ph), 9.47 (1H, d, *J* = 13.2 Hz, N*H*CH=). Anal. Calcd. for $C_{20}H_{20}N_2O_4$ (352.14): C, 68.17; H 5.72; N 7.95. Found: C, 68.27; H 5.59; N 7.89.

Benzyl (3*S*,4*E*)-4-{[(2-methoxyphenyl)amino]methylidene}-5-oxotetrahydrofuran-3-ylcarbamate (7g). This compound was prepared from **5** and 2-methoxyaniline hydrochloride **6g**. Yield: 0.141 g (77%), *E*:*Z* = 81:19, mp 163–167 °C, white solid; $[\alpha]_D^{21}$ –136.9° (*c* = 0.32, CH_2Cl_2). IR (KBr, cm^{-1}): 1742, 1673, 1643 (C=O). ^1H NMR (DMSO-d_6) major isomer: δ 3.82 (3H, s, OMe), 4.09 (1H, dd, *J* = 2.6, 9.8 Hz, 2–Ha), 4.47 (1H, dd, *J* = 8.3, 9.4 Hz, 2–Hb), 5.02–5.11 (1H, m, 3–H), 5.12 (2H, s, C*H*$_2$Ph), 6.90–7.09 (3H, m, 3H of Ar), 7.23–7.40 (6H, m, 6H of Ar), 7.76 (1H, d, *J* = 13.6 Hz, =C*H*NH), 8.10 (1H, d, *J* = 7.5 Hz, N*H*COOBn), 8.65 (1H, d, *J* = 13.6 Hz, N*H*CH=), minor isomer δ 3.87 (3H, s, OMe), 4.82–4.87 (1H, m, 3–H), 5.13 (2H, s, C*H*$_2$Ph), 9.76 (1H, d, *J* = 13.2 Hz, N*H*CH=). Anal. Calcd. for $C_{20}H_{20}N_2O_5$ (368.38): C, 65.21; H 5.47; N 7.60. Found: C, 65.22; H, 5.47; N, 7.54.

Benzyl (3*S*,4*E*)-4-{[(3-methoxyphenyl)amino]methylidene}-5-oxotetrahydrofuran-3-ylcarbamate (7h). This compound was prepared from **5** and 3-methoxyaniline hydrochloride **6h**. Yield: 0.114 g (62%), *E*:*Z* = 87:13, mp 127–133 °C, pale brown solid; $[\alpha]_D^{21}$ –123.2° (*c* = 0.28, CH_2Cl_2). IR (KBr, cm^{-1}): 1722, 1691, 1647 (C=O). ^1H NMR (DMSO-d_6) major isomer: δ 3.76 (3H, s, OMe), 4.11 (1H, dd, *J* = 2.1, 10.0 Hz, 2–Ha), 4.41 (1H, dd, *J* = 7.5, 9.8 Hz, 2–Hb), 4.95 (1H, br t, *J* = 6.4 Hz, 3–H), 5.10 (2H, s, C*H*$_2$Ph), 6.58–6.61 (1H, m, 1H of Ar), 6.70–6.73 (1H, m, 1H of Ar), 7.12–7.40 (7H, m, 5H of Ph and 2H of Ar), 7.79 (1H, d, *J* = 14.3 Hz, =C*H*NH),

7.96 (1H, d, *J* = 6.4 Hz, N*H*COOBn), 9.29 (1H, d, *J* = 13.6 Hz, N*H*CH=), minor isomer δ 3.73 (3H, s, OMe), 4.20 (1H, dd, *J* = 6.6, 9.6 Hz, 2–Ha), 4.49 (1H, dd, *J* = 7.5, 9.4 Hz, 2–Hb), 4.82–4.91 (1H, m, 3–H), 9.49 (1H, d, *J* = 13.2 Hz, N*H*CH=). Anal. Calcd. for $C_{20}H_{20}N_2O_5$ (368.38): C, 65.21; H 5.47; N 7.60. Found: C, 64.95; H, 5.46; N, 7.65.

Benzyl (3*S*,4*E*)-4-{[(4-methoxyphenyl)amino]methylidene}-5-oxotetrahydrofuran-3-ylcarbamate (7i). This compound was prepared from **5** and 4-methoxyaniline hydrochloride **6i**. Yield: 0.134 g (73%), *E*:*Z* = 99:1, mp 162–165 °C, white solid; $[\alpha]_D^{21}$ –129.5° (*c* = 0.292, CH_2Cl_2). IR (KBr, cm^{-1}): 1709, 1689, 1640 (C=O). ^{1}H NMR (DMSO-d_6) major isomer: δ 3.72 (3H, s, OMe), 4.09 (1H, dd, *J* = 1.9, 9.8 Hz, 2–Ha), 4.39 (1H, dd, *J* = 7.5, 9.8 Hz, 2–Hb), 4.94 (1H, br t, *J* = 6.4 Hz, 3–H), 5.09 (2H, s, C*H*$_2$Ph), 6.91 (2H, dt, *J* = 2.8, 9.1 Hz, 1H of Ar), 7.09 (2H, d, *J* = 8.7 Hz, 1H of Ar), 7.25–7.42 (5H, m, 5H of Ph), 7.67 (1H, d, *J* = 13.6 Hz, =C*H*NH), 7.93 (1H, d, *J* = 6.0 Hz, N*H*COOBn), 9.21 (1H, d, *J* = 13.6 Hz, N*H*CH=), minor isomer δ 5.05 (2H, s, C*H*$_2$Ph), 9.46 (1H, d, *J* = 12.1 Hz, N*H*CH=). Anal. Calcd. for $C_{20}H_{20}N_2O_5$ (368.38): C, 65.21; H 5.47; N 7.60. Found: C,64.92; H, 5.40; N, 7.54.

Benzyl (3*S*,4*E*)-4-{[(2-bromophenyl)amino]methylidene}-5-oxotetrahydrofuran-3-ylcarbamate (7j). This compound was prepared from **5** and 2-bromoaniline hydrochloride **6j**. Yield: 0.149 g (71%), *E*:*Z* = 77:23, mp 133–140 °C, pale yellowish solid; $[\alpha]_D^{21}$ –93.8° (*c* = 0.26, CH_2Cl_2). MS (EI): *m*/*z* = 416, 418 (1:1, M^+, ^{79}Br, ^{81}Br). IR (KBr, cm^{-1}): 1722, 1669, 1642 (C=O). ^{1}H NMR (DMSO-d_6) major isomer: δ 4.11 (1H, dd, *J* = 2.6, 9.8 Hz, 2–Ha), 4.50 (1H, dd, *J* = 7.9, 9.8 Hz, 2–Hb), 5.05–5.16 (3H, m, 3–H and C*H*$_2$Ph), 7.00–7.05 (1H, m, 1H of Ar), 7.22–7.47 (7H, m, 5H of Ph and 2H of Ar), 7.58–7.71 (2H, m, 1H of Ar and =C*H*NH), 8.15 (1H, d, *J* = 7.2 Hz, N*H*COOBn), 8.48 (1H, d, *J* = 12.4 Hz, N*H*CH=), minor isomer δ 4.87–4.95 (1H, m, 3–H), 9.92 (1H, d, *J* = 12.4 Hz, N*H*CH=). ^{13}C NMR (DMSO-d_6): δ 48.3, 66.3, 70.3, 100.0, 112.7, 118.3, 124.2, 125.1, 128.3, 128.7, 129.5, 133.5, 137.0, 138.9, 139.1, 157.4, 171.7. Anal. Calcd. for $C_{19}H_{17}BrN_2O_4$ (417.25): C, 54.69; H 4.11; N 6.71. Found: C, 53.82; H, 3.97; N, 6.52. Exact mass Calcd. for $C_{19}H_{17}BrN_2O_4$: *m*/*z* = 416.038620. Found: *m*/*z* = 416.037168.

Benzyl (3*S*,4*E*)-4-{[(3-bromophenyl)amino]methylidene}-5-oxotetrahydrofuran-3-ylcarbamate (7k). This compound was prepared from **5** and 3-bromoaniline hydrochloride **6k**. Yield: 0.147 g (70%), *E*:*Z* = 94:6, mp 162–164 °C, white solid; $[\alpha]_D^{21}$ –118.6° (*c* = 0.23, CH_2Cl_2). IR (KBr, cm^{-1}): 1713, 1690, 1643 (C=O). ^{1}H NMR (DMSO-d_6) major isomer: δ 4.12 (1H, dd, *J* = 1.9, 9.8 Hz, 2–Ha), 4.42 (1H, dd, *J* = 7.2, 9.4 Hz, 2–Hb), 4.95 (1H, br t, *J* = 6.4 Hz, 3–H), 5.10 (2H, s, C*H*$_2$Ph), 7.11–7.21 (2H, m, 2H of Ar), 7.23–7.42 (7H, m, 5H of Ph and 2H of Ar), 7.79 (1H, d, *J* = 13.6 Hz, =C*H*NH), 7.95 (1H, d, *J* = 6.0 Hz, N*H*COOBn), 9.36 (1H, d, *J* = 13.2 Hz, N*H*CH=), minor isomer δ 9.55 (1H, d, *J* = 13.2 Hz, N*H*CH=). Anal. Calcd. for $C_{19}H_{17}BrN_2O_4$ (417.25): C, 54.69; H 4.11; N 6.71. Found: C, 54.91; H, 4.29; N, 6.72.

Benzyl (3*S*,4*E*)-4-{[(4-bromophenyl)amino]methylidene}-5-oxotetrahydrofuran-3-ylcarbamate (7l). This compound was prepared from **5** and 4-bromoaniline hydrochloride **6l**. Yield: 0.154 g (74%), *E*:*Z* = 90:10, mp 177–182 °C, white solid; $[\alpha]_D^{21}$ –125.2° (*c* = 0.26, CH_2Cl_2). IR (KBr, cm^{-1}): 1711, 1690, 1641 (C=O). ^{1}H NMR (DMSO-d_6) major isomer: δ 4.11 (1H, dd, *J* = 1.9, 9.8 Hz, 2–Ha), 4.42 (1H, dd, *J* = 7.3, 9.6 Hz, 2–Hb), 4.95 (1H, br t, *J* = 6.4 Hz, 3–H), 5.09 (2H, s, C*H*$_2$Ph), 7.13 (2H, d, *J* = 9.0 Hz, 2H of Ar), 7.29–7.38 (5H, m, Ph), 7.47 (2H, dt, *J* = 2.6,

9.0 Hz, 2H of Ar), 7.75 (1H, d, *J* = 13.2 Hz, =C*H*NH), 7.96 (1H, d, *J* = 6.0 Hz, N*H*COOBn), 9.38 (1H, d, *J* = 13.2 Hz, N*H*CH=), minor isomer δ 4.49 (1H, dd, *J* = 7.5, 9.4 Hz, 3–H), 5.06 (2H, s, CH_2Ph), 9.56 (1H, d, *J* = 12.8 Hz, N*H*CH=). Anal. Calcd. for $C_{19}H_{17}BrN_2O_4$ (417.25): C, 54.69; H 4.11; N 6.71. Found: C, 54.56; H, 3.97; N, 6.59.

Benzyl (3*S*,4*E*)-4-{[(3-hydroxyphenyl)amino]methylidene}-5-oxotetrahydrofuran-3-ylcarbamate (7m). This compound was prepared from **5** and 3-hydroxyaniline hydrochloride **6m**. Yield: 0.166 g (94%), *E*:*Z* = 90:10, mp 182–186 °C, white solid; $[\alpha]_D^{21}$ –162.8° (*c* = 0.22, THF). IR (KBr, cm^{-1}): 1728, 1712, 1660, 1647 (C=O). ^{1}H NMR (DMSO-d_6) major isomer: δ 4.10 (1H, dd, *J* = 2.1, 9.6 Hz, 2–Ha), 4.40 (1H, dd, *J* = 7.3, 9.6 Hz, 2–Hb), 4.95 (1H, br t, *J* = 6.8 Hz, 3–H), 5.10 (2H, s, CH_2Ph), 6.44 (1H, dd, *J* = 2.1, 8.1 Hz, 1H of Ar), 6.51–6.61 (2H, m, 2H of Ar), 7.11 (1H, t, *J* = 8.1 Hz, 1H of Ar), 7.27–7.39 (5H, m, Ph), 7.66 (1H, d, *J* = 13.6 Hz, =C*H*NH), 7.95 (1H, d, *J* = 6.0 Hz, N*H*COOBn), 9.25 (1H, d, *J* = 13.2 Hz, N*H*CH=), 9.51 (1H, s, OH), minor isomer δ 9.41 (1H, d, *J* = 13.2 Hz, N*H*CH=). Anal. Calcd. for $C_{19}H_{18}N_2O_5$ (354.36): C, 64.40; H 5.12; N 7.91. Found: C, 64.43; H, 4.98; N, 7.87.

Benzyl (3*S*,4*E*)-4-{[(4-hydroxyphenyl)amino]methylidene}-5-oxotetrahydrofuran-3-ylcarbamate (7n). This compound was prepared from **5** and 4-hydroxyaniline hydrochloride **6n**. Yield: 0.081 g (46%), *E*:*Z* = 100:0, mp 168–170 °C, white solid; $[\alpha]_D^{21}$ –164.8° (*c* = 0.22, THF). MS (EI): *m*/*z* = 354 (M^+). IR (KBr, cm^{-1}): 1717, 1662 (C=O). ^{1}H NMR (DMSO-d_6) δ 4.08 (1H, dd, *J* = 1.9, 9.8 Hz, 2–Ha), 4.38 (1H, dd, *J* = 7.3, 9.6 Hz, 2–Hb), 4.92 (1H, br t, *J* = 6.6 Hz, 3–H), 5.09 (2H, s, CH_2Ph), 6.73 (2H, dd, *J* = 2.7, 8.7 Hz, 2H of Ar), 6.96 (2H, d, *J* = 8.7 Hz, 2H of Ar), 7.26–7.42 (5H, m, Ph), 7.61 (1H, d, *J* = 13.9 Hz, =C*H*NH), 7.91 (1H, d, *J* = 6.4 Hz, N*H*COOBn), 9.14 (1H, d, *J* = 13.9 Hz, N*H*CH=), 9.21 (1H, s, OH). ^{13}C NMR (DMSO-d_6): δ 48.8, 66.1, 70.9, 94.5, 116.4, 117.7, 128.1, 128.2, 128.7, 133.1, 137.2, 140.0, 153.7, 157.3, 172.3. Anal. Calcd. for $C_{19}H_{18}N_2O_5$ (354.36): C, 64.40; H 5.12; N 7.91. Found: C, 63.73; H, 4.95; N, 7.77. Exact mass Calcd. for $C_{19}H_{18}N_2O_5$: *m*/*z* = 354.122450. Found: *m*/*z* = 354.121572.

Benzyl 4-cyanomethyl-5-oxo-2,5-dihydrofuran-3-ylcarbamate (9). Potassium cyanide (0.390 g, 6 mmol) and 18-crown-6 (1.58 g, 6 mmol) were added to a solution of **5** (1.45 g, 5 mmol) in dichloromethane (50 mL) and the mixture was heated under reflux for 6 h. Volatile components were evaporated *in vacuo* and the residue was purified by column chromatography (ethyl acetate). Fractions containing the product were combined, evaporated *in vacuo*, and the solid residue was crystallised from ethyl acetate to give **9**. Yield: 0.816 g (60%), white crystals, mp 198–200 °C (from ethyl acetate). IR (KBr, cm^{-1}): 2260 (C≡N), 1740, 1660 (C=O). ^{1}H NMR ($CDCl_3$): δ 3.26 (2H, t, *J* = 1.1 Hz, CH_2CN), 5.23 (2H, s, CH_2Ph), 5.26 (2H, br s, 5–CH_2), 7.35–7.43 (5H, m, Ph), 7.73 (1H, br s, NH). Anal. Calcd. for $C_{14}H_{12}N_2O_4$ (272.26): C, 61.76; H 4.44; N 10.29. Found: C, 61.48; H 4.45; N 10.26.

Benzyl 4-{[3-(2,6-dichlorophenyl)-1,2,4-oxadiazol-5-yl]methyl}-5-oxo-2,5-dihydrofuran-3-ylcarbamate (11). A mixture of **5** (0.136 g, 0.5 mmol), 2,6-dichlorobenzonitrile oxide **10** (0.094 g, 0.5 mmol), and chloroform (10 mL) was heated under reflux for 4 h. Volatile components were evaporated *in vacuo* and the residue was purified by column chromatography (diethyl ether). Fractions containing the product were combined, evaporated *in vacuo* to give **11**. Yield: 0.015 g (7%), white crystals, mp 55–59 °C. IR (KBr, cm^{-1}): 1750, 1660 (C=O). ^{1}H NMR ($CDCl_3$): δ 4.09

(2H, t, *J* = 1.1 Hz, CH_2–C(4)), 5.14 (2H, s, C*H*$_2$Ph), 5.26 (2H, br s, 5–CH_2), 7.26–7.40 (8H, m, 5H of Ph and C_6H_3), 9.81 (1H, br s, NH). Anal. Calcd. for $C_{21}H_{15}Cl_2N_3O_5$ (460.24): C, 54.80; H 3.28; N 9.13. Found: C, 54.85; H 3.50; N 8.29. Exact mass Calcd. for $C_{21}H_{15}Cl_2N_3O_5$: *m/z* = 459.038876. Found: 459.039850.

Benzyl 4-cyanomethyl-5-oxo-2,5-dihydrofuran-3-yl(methyl)carbamate 13 and benzyl methyl 4-cyanomethyl-5-oxo-2,5-dihydrofuran-3-ylimidocarbonate (14). A solution of **9** (0.190 g, 0.7 mmol) in tetrahydrofuran (8 mL) was added to a solution of diazomethane **12** in diethyl ether (~0.4 M, 7.5 mL, ~3 mmol) and the mixture was left at room temperature for 20 h. Volatile components were left to evaporated in a ventilated hood and the residue was purified by column chromatography (ethyl acetate–petroleum ether, 2:1). Fractions containing the products were combined and evaporated *in vacuo* to give **13** and **14**.

Benzyl 4-cyanomethyl-5-oxo-2,5-dihydrofuran-3-yl(methyl)carbamate (13). Yield: 0.082 g (41%), colourless crystals, mp 71–72 °C ($CHCl_3$–petroleum ether). IR (KBr, cm^{-1}): 2240 (C≡N), 1720, 1630 (C=O). ^{1}H NMR ($CDCl_3$): δ 3.47 (3H, s, NMe), 3.49 (2H, br s, C*H*$_2$CN), 5.06 (2H, br s, 5–CH_2), 5.27 (2H, s, C*H*$_2$Ph), 7.35–7.40 (5H, m, Ph). Anal. Calcd. for $C_{15}H_{14}N_2O_4$ (286.28): C, 62.93; H 4.93; N 9.79. Found: C, 62.73; H 4.63; N, 9.70.

Benzyl methyl 4-cyanomethyl-5-oxo-2,5-dihydrofuran-3-ylimidocarbonate (14). Yield: 0.013 g (7%), colourless crystals, mp 79–82 °C. IR (KBr, cm^{-1}): 2230 (C≡N), 1740, 1680 (C=O). ^{1}H NMR ($CDCl_3$): δ 3.58 (2H, br s, C*H*$_2$CN), 3.79 (3H, s, OMe), 5.42 (2H, br s, 5–CH_2), 5.49 (2H, s, C*H*$_2$Ph), 7.36–7.48 (5H, m, Ph). Anal. Calcd. for $C_{15}H_{14}N_2O_4$ (286.28): C, 62.93; H 4.93; N 9.79. Found: C, 63.57; H 5.06; N, 9.40. Exact mass Calcd. for $C_{15}H_{14}N_2O_4$: *m/z* = 286.095357. Found: 286.096150.

Acknowledgements

The financial support from the Ministry of Education, Science, and Sport (project number: PS-0502-0103), Slovenia, is gratefully acknowledged.

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