HETEROCYCLES, Vol. 74, 2007, pp. 383 -396. © The Japan Institute of Heterocyclic Chemistry
Received, 24th July, 2007, Accepted, 18th September, 2007, Published online, 20th September, 2007. COM-07-S(W)16

A NOVEL SODIUM IODIDE-PROMOTED RING TRANSFORMATION OF 2-AMINO-4,5-DIHYDRO-3-FURANCARBONITRILES TO 2-PYRROLIDINONES AND DIHYDROPYRANS

Hiroshi Maruoka, Fumi Okabe, and Kenji Yamagata*

Faculty of Pharmaceutical Sciences, Fukuoka University, 8-19-1 Nanakuma, Jonan-ku, Fukuoka 814-0180, Japan
e-mail:yamagata@fukuoka-u.ac.jp

Abstract – A novel and efficient approach to 2-pyrrolidinones and dihydropyrans *via* the ring transformation of 3-phenacylated tetrahydro-2-imino-3-furancarbonitriles in the presence of sodium iodide is described. The key feature in the ring transformation is that *C*-phenacylation of 2-amino-4,5-dihydro-3-furancarbonitriles using phenacyl bromides, *e.g*. phenacyl bromide, 4-chlorophenacyl bromide and 4-methoxyphenacyl bromide, proceeds smoothly and the ring-opening intermediate having leaving group such as iodide ion is produced.

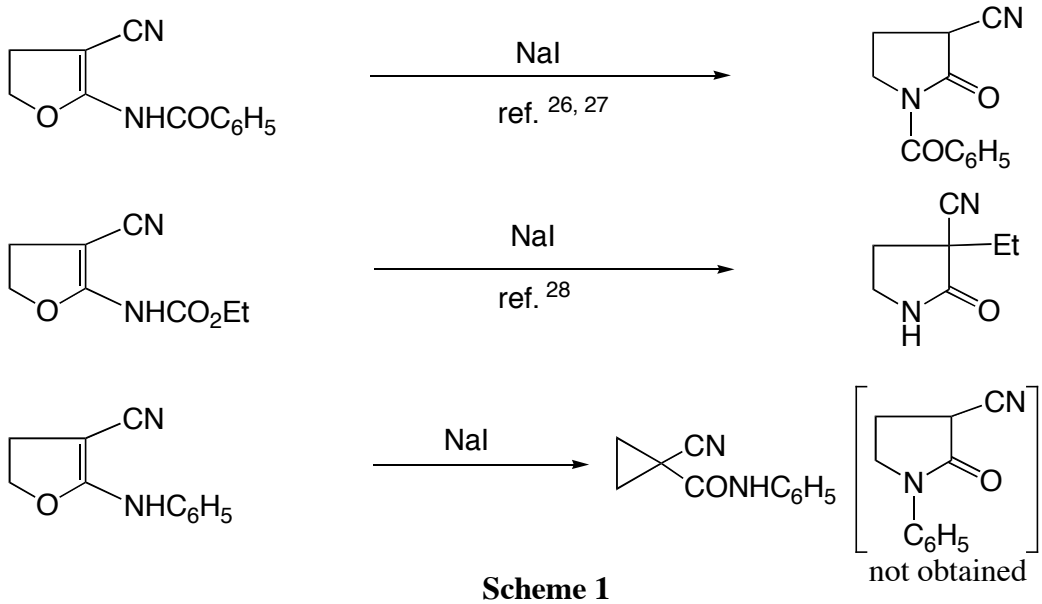
INTRODUCTION

γ-Lactams[1-5] and dihydropyrans[6-8] are important synthetic targets due to their occurrence in numerous natural products and biologically active compounds. The γ-lactam system occurs in pyrrolidine alkaloids and in γ-aminobutyric acid analogues.[9-11] Dihydropyrans have been proven to be particularly useful in the synthesis of cyclic components of macrocyclic antibiotics[12,13] and also as precursors in the preparation of *C*-glycosides.[14] In the past several years, a number of methods for construction of γ-lactams[15-21] and dihydropyrans[22-25] have been developed. Although these methods are efficient and selective pathways for the formation of γ-lactams (2-pyrrolidinones) and dihydropyrans, these are still interest to develop a new methodology for the efficient synthesis of these compounds. Continuing with our interest in this area, we focused our attention on the development of a new method for the synthesis of 2-pyrrolidinones and dihydropyrans, and now report the results of our investigation, a ring transformation of 3-phenacylated tetrahydro-2-imino-3-furancarbonitriles in the presence of sodium iodide.

This paper is dedicated to Professor Dr. Ekkehard Winterfeldt on the occasion of his 75th birthday.

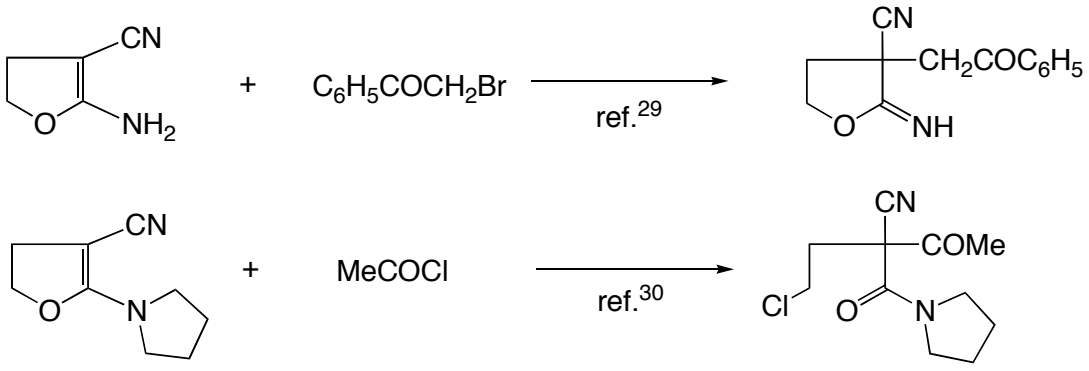
RESULTS AND DISCUSSION

In the course of our studies on heterocyclic β-enaminonitriles, we have already investigated the synthesis of 3-pyrrolidinecarbonitriles by the reaction of 2-amino-4,5-dihydro-3-furancarbonitriles with sodium iodide[26-28] (Scheme 1). However, when we tried the similar sodium iodide-mediated ring transformation using 4,5-dihydro-2-(phenylamino)-3-furancarbonitrile as the substrate, the desired 2-oxo-1-phenyl-3-pyrrolidinecarbonitrile was not detected at all but instead cyclopropane derivative was obtained.

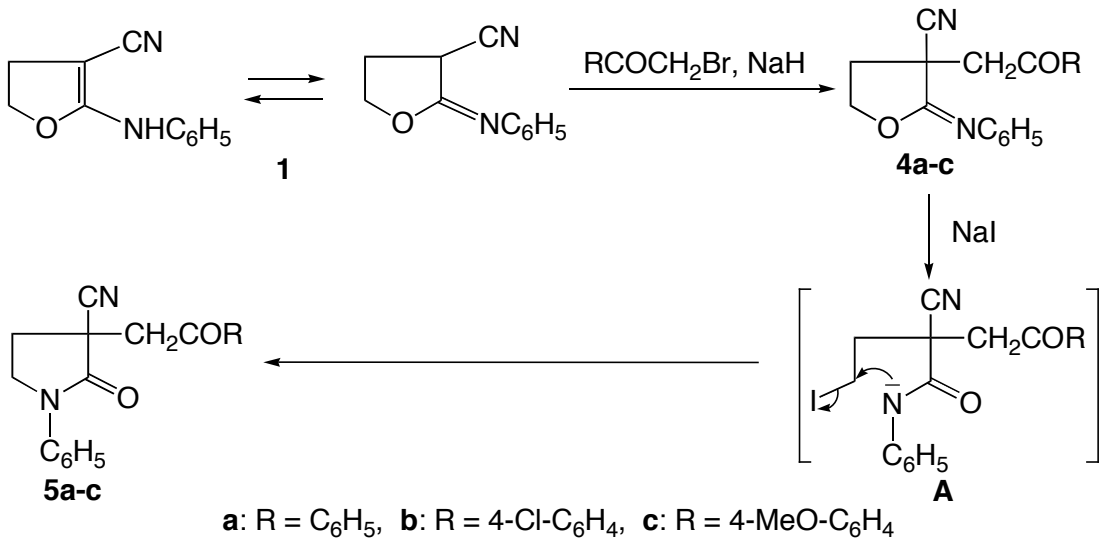


Scheme 1

In our previous paper, we have reported the *C*-phenacylation[29] and *C*-acetylation[30] of 2-amino-4,5-dihydro-3-furancarbonitriles with phenacyl bromide or acetyl chloride (Scheme 2). Encouraged by these results, we envisioned that the ring opening of 3-phenacylated tetrahydro-2-imino-3-furancarbonitriles **4a-c** with iodide ion would afford attractive ring-opening



Scheme 2



Scheme 3

intermediate **A**, and that a subsequent intramolecular cyclization of **A** would give 2-pyrrolidinones **5a-c** (Scheme 3).

When a mixture of 4,5-dihydro-2-(phenylamino)-3-furancarbonitrile (**1**) and phenacyl bromides, *e.g.* phenacyl bromide, 4-cholorophenacyl bromide and 4-methoxyphenacyl bromide, in DMF in the presence of sodium hydride was stirred at room temperature for 1 hour according to our previous procedure,[29] 3-phenacylated tetrahydro-2-imino-3-furancarbonitriles **4a-c** were obtained in moderate yields (Scheme 3 and entries 1-3 in Table 1). The IR spectra of **4a-c** display bands near 2240 cm^{-1} due to a non-conjugated cyano group and near 1720 cm^{-1} due to a carbonyl group. Elemental analyses, mass spectra, ^{1}H and ^{13}C NMR spectra of **4a-c** are consistent with the assigned structures (see experimental section).

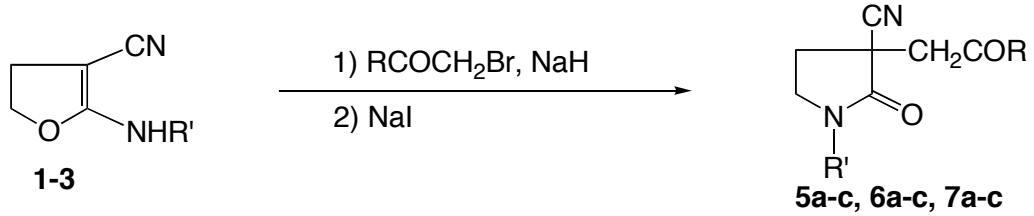
In the next step, we examined the ring transformation of the imino derivatives **4a-c** into the 2-pyrrolidinones **5a-c**. As a consequence, when **4a-c** were treated with sodium iodide in DMF at 150 °C for 2 hours, the expected 2-pyrrolidinones **5a-c** were produced in good yields (Scheme 3 and entries 1-3 in Table 1). The IR spectra of **5a-c** display bands near 2240 cm^{-1} due to a non-conjugated cyano group, near 1710 cm^{-1} due to a carbonyl group and near 1680 cm^{-1} due to an amido group. The ^{1}H NMR spectra of **5a-c** exhibit two one-proton doublets near δ 4 attributable to the phenacyl methylene protons. The ^{13}C NMR spectra of **5a-c** show a signal near δ 118 due to the cyano carbon, a signal near δ 167 due to the amido carbonyl carbon and a signal near δ 193 due to the phenacyl carbonyl carbon. Elemental analyses and spectral data of **5a-c** are consistent with the proposed structures (see experimental section). This indicates that sodium iodide plays a key role in the ring transformation mechanism.

Table 1. Synthesis and reaction of **4a-c** according to Scheme 3.

Entry	R	Product **4**	Yield (%) of **4**	Product **5**	Yield (%) of **5**
1	C_6H_5	**4a**	47	**5a**	95
2	4-Cl-C_6H_4	**4b**	72	**5b**	92
3	4-MeO-C_6H_4	**4c**	76	**5c**	91

On the basis of these results, we have tried to directly convert **1** into 2-pyrrolidinones **5** in a one-pot process. The results are summarized in Table 2. Indeed, when a mixture of **1** and phenacyl bromides in DMF in the presence of sodium hydride was stirred at room temperature for 1 hour and then the reaction mixture was treated with sodium iodide at 150 °C for 2 hours, the 2-pyrrolidinones **5a-c** were obtained in moderate yields (entries 1-3 in Table 2). Similarly, the reactions of 4,5-dihydro-2-(4-substituted phenylamino)-3-furancarbonitriles **2** and/or **3** with phenacyl bromides gave the corresponding ring transformation products **6a-c** and **7a-c** (entries 4-9 in Table 2). By comparison of the IR spectra, NMR spectra, mass spectra and elemental analyses of **6** and **7**, it seems that the structural assignments given to these compounds are correct.

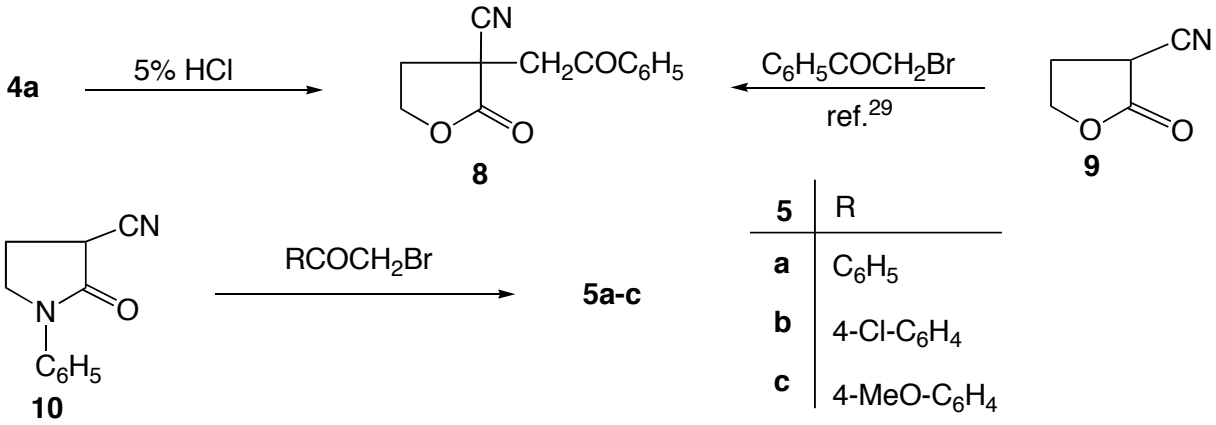
Table 2. Synthesis of 2-pyrrolidinones **5-7** starting from **1-3**.



1-3 **5a-c, 6a-c, 7a-c**

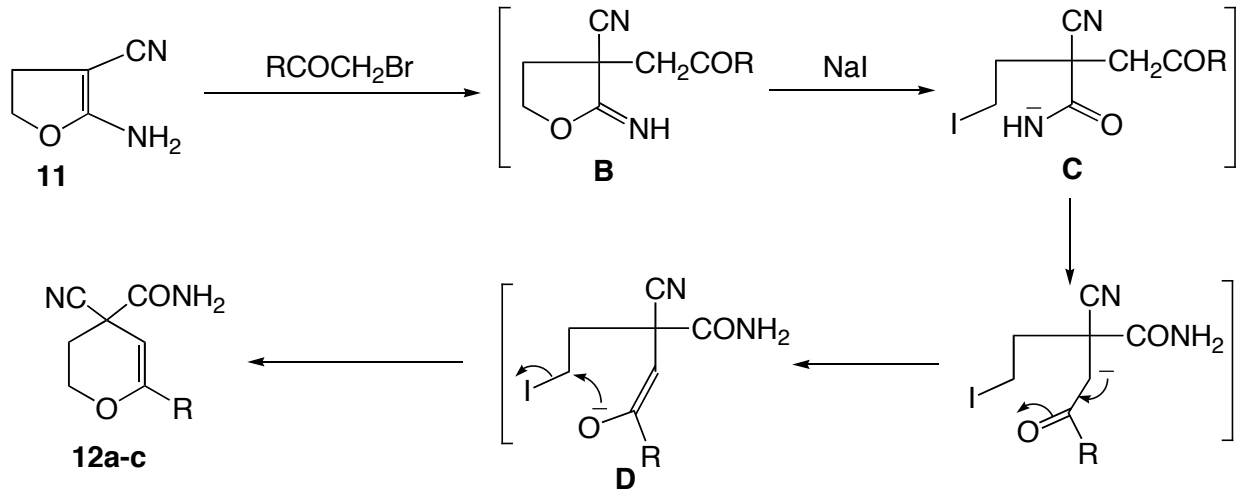
Entry	Substrate	R'	R	Product	Yield (%)
1	**1**	C_6H_5	C_6H_5	**5a**	67
2	**1**	C_6H_5	4-Cl-C_6H_4	**5b**	71
3	**1**	C_6H_5	4-MeO-C_6H_4	**5c**	72
4	**2**	4-Cl-C_6H_4	C_6H_5	**6a**	55
5	**2**	4-Cl-C_6H_4	4-Cl-C_6H_4	**6b**	70
6	**2**	4-Cl-C_6H_4	4-MeO-C_6H_4	**6c**	75
7	**3**	4-MeO-C_6H_4	C_6H_5	**7a**	79
8	**3**	4-MeO-C_6H_4	4-Cl-C_6H_4	**7b**	68
9	**3**	4-MeO-C_6H_4	4-MeO-C_6H_4	**7c**	67

We have examined the hydrolysis of **4a** in order to confirm its structure (Scheme 4). Treatment of compound **4a** with 5% hydrochloric acid produced the γ-lactone **8** (85%), which was identical with an authentic sample prepared from γ-lactone **9** and phenacyl bromide.[29] Furthermore, the reactions of 2-pyrrolidinone **10**[31] with phenacyl bromides in the presence of sodium hydride gave the corresponding 2-pyrrolidinones **5a-c** (**5a**: 78%, **5b**: 82%, **5c**: 76%), which were identical with authentic samples prepared according to Scheme 3.



Scheme 4

During the aforementioned sodium iodide-promoted ring transformation of 2-amino-4,5-dihydro-3-furancarbonitriles, we found that 3-phenacylated imines **B**, which were readily produced from **11**[32] and phenacyl bromides, reacted with sodium iodide to yield dihydropyrans **12a-c** (**12a**: 32%, **12b**: 27%, **12c**: 8%) (Scheme 5). The IR spectra of **12a-c** display bands near 2240 cm^{-1} due to a non-conjugated cyano group, near 1700 cm^{-1} due to an amido carbonyl group. The ^{1}H NMR spectra of **12a-c** exhibit a one-proton singlet near δ 5.7 attributable to the olefin proton and two one-proton singlets near δ 7.7 assignable to the amido protons. The ^{13}C NMR spectra of **12a-c** show a signal near δ 120 due to the cyano carbon and a signal near δ 168 due to the amido carbonyl carbon. Elemental analyses and spectral data of **12a-c** are consistent with the proposed structures (see experimental section). In this case, the expected 2-pyrrolidinones were not detected at all. The reason for this change of behavior is not clear at present. The formation of dihydropyrans **12** can be rationalized by the mechanism shown in Scheme 5. One explanation could reply on the fact that a transformation of the carboxamide anion **C** to the enolate anion **D** easily occurs because the intramolecular cyclization of **D** is more reactive than that of **C**. Therefore, it is proposed that in the reaction of **B** with sodium iodide, the intermediate **D** could undergo intramolecular cyclization with elimination of iodide ion to form dihydropyrans **12a-c**.



a: R = C_6H_5, **b**: R = 4-Cl-C_6H_4, **c**: R = 4-MeO-C_6H_4

Scheme 5

In conclusion, we have developed a novel and efficient methodology to prepare 2-pyrrolidinones and dihydropyrans *via* the ring transformation of 2-amino-4,5-dihydro-3-furancarbonitriles. A key step is the generation of an intermediate carboxamide anion having leaving group such as iodide ion through the ring opening of 3-phenacylated tetrahydro-2-imino-3-furancarbonitriles, which are produced by the reaction of 2-amino-4,5-dihydro-3-furancarbonitriles with phenacyl bromides, in the presence of sodium iodide. This method is useful because of the easy of operation.

EXPERIMENTAL

All melting points are uncorrected. The IR spectra were recorded on a JASCO FT/IR-230 spectrometer or FT/IR-4100 spectrometer. The ^{1}H and ^{13}C NMR spectra were measured with a JEOL JNM-A500 spectrometer at 500.0 and 125.65 MHz, respectively. The ^{1}H and ^{13}C chemical sifts (δ) are reported in parts per million (ppm) relative to tetramethylsilane as internal standard. Positive FAB mass spectra were obtained on a JEOL JMS-700T spectrometer. Elemental analyses were performed on YANACO MT-6 CHN analyzer.

General procedure for the preparation of starting compounds 1-3.

A mixture of **11**[32] (2.20 g, 20 mmol) and aniline hydrochloride (2.85 g, 22 mmol), 4-chloroaniline hydrochloride (3.61 g, 22 mmol) or 4-methoxyaniline hydrochloride (3.51 g, 22 mmol) in 1,4-dioxane (10 mL) was stirred at rt for 2 h. After removal of the solvent *in vacuo*, cold water was added to the residue. The precipitate was collected by filtration, washed with water, dried and recrystallized from an appropriate solvent to yield **1-3**.

4,5-Dihydro-2-(phenylamino)-3-furancarbonitrile (1)

Colorless columns (2.06 g, 55%), mp 112-115 °C (acetone/petroleum ether); IR (KBr): 3208 (NH), 2192 (C≡N) cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.50–2.65 (m, 1.6H, 4-H), 2.93 (t, J = 8.9 Hz, 0.4H, 4-H), 3.92 (t, J = 8.7 Hz, 0.8H, 3-H), 4.30-4.38 (m, 0.8H, 5-H), 4.43-4.52 (m, 0.8H, 5-H), 4.55 (t, J = 8.9 Hz, 0.4 H, 5-H), 4.79 (br. s, 0.2H, NH), 7.04-7.16 (m, 3H, aryl H), 7.21-7.38 (m, 2H, aryl H); ^{13}C NMR ($CDCl_3$): δ 28.4, 28.5 (C-4), 33.0, 53.5 (C-3), 69.8, 71.8 (C-5), 116.5, 119.0 (C≡N), 120.1, 122.8, 123.9, 124.8, 128.7, 129.1, 137.6, 145.2 (C aryl), 155.1, 165.2 (C-2); MS: *m/z* 187 $[M+H]^+$. Anal. Calcd for $C_{11}H_{10}N_2O$: C, 70.95; H, 5.41; N, 15.04. Found: C, 70.97; H, 5.50; N, 14.99.

2-[(4-Chlorophenyl)amino]-4,5-dihydro-3-furancarbonitrile (2)

Colorless columns (3.34 g, 76%), mp 141-143 °C (acetone/petroleum ether); IR (KBr): 3211 (NH), 2185 (C≡N) cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.52–2.67 (m, 1.2H, 4-H), 2.94 (t, J = 8.7 Hz, 0.8H, 4-H), 3.91 (t, J = 8.7 Hz, 0.6H, 3-H), 4.34-4.39 (m, 0.6H, 5-H), 4.48-4.54 (m, 1.0H, 5-H), 4.51 (br. s, 0.4H, NH), 4.56 (t, J = 8.7 Hz, 0.4 H, 5-H), 7.07-7.12 (m, 2H, aryl H), 7.22-7.28 (m, 2H, aryl H); ^{13}C NMR ($CDCl_3$): δ 28.39, 28.44 (C-4), 33.1, 54.0 (C-3), 70.0, 71.9 (C-5), 116.3, 118.8 (C≡N), 121.1, 124.4, 128.7, 129.0, 129.1, 130.1, 136.3, 143.7 (C aryl), 155.5, 164.8 (C-2); MS: *m/z* 221 $[M+H]^+$. Anal. Calcd for $C_{11}H_9ClN_2O$: C, 59.88; H, 4.11; N, 12.70. Found: C, 59.92; H, 4.14; N, 12.78.

4,5-Dihydro-2-[(4-methoxyphenyl)amino]-3-furancarbonitrile (3)

Colorless prisms (3.06 g, 71%), mp 99-101 °C (acetone/petroleum ether); IR (KBr): 3212 (NH), 2188 (C≡N) cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.49–2.64 (m, 1.4H, 4-H), 2.92 (t, J = 8.7 Hz, 0.6H, 4-H), 3.78 (s, 0.9H, OCH_3), 3.79 (s, 2.1H, OCH_3), 3.89 (t, J = 8.5 Hz, 0.7H, 3-H), 4.33-4.38 (m, 0.6H, 5-H), 4.48-4.53 (m, 1.4H, 5-H), 6.60 (br. s, 0.3H, NH), 6.82-6.86 (m, 2H, aryl H), 7.06-7.10 (m, 0.6H, aryl H), 7.16-7.22 (m, 1.4H, aryl H); ^{13}C NMR ($CDCl_3$): δ 28.5, 28.7 (C-4), 33.1, 52.1 (C-3), 55.4, 55.5 (OCH_3), 69.7, 71.5 (C-5), 113.8, 114.3 (C aryl), 116.7, 119.2 (C≡N), 123.1, 124.8, 130.3, 138.0, 153.9, 156.9 (C aryl), 157.0, 165.6 (C-2); MS: *m/z* 217 $[M+H]^+$. Anal. Calcd for $C_{12}H_{12}N_2O_2$: C, 66.65; H, 5.59; N, 12.95. Found: C, 66.64; H, 5.69; N, 12.88.

General procedure for the preparation of imino derivatives 4a-c from 1 and phenacyl bromides.

To an ice-cooled and stirred mixture of **1** (2.79 g, 15 mmol) in DMF (15 mL) was added 60% NaH (0.60 g, 15 mmol). The stirring was continued at rt until evolution of gas ceased. To the obtained solution was added phenacyl bromide (2.99 g, 15 mmol), 4-chlorophenacyl bromide (3.50 g, 15 mmol) or 4-methoxyphenacyl bromide (3.44 g, 15 mmol) with stirring and ice-cooling and the mixture was stirred at rt for 1 h. After removal of the solvent *in vacuo*, cold water added to the residue. The resulting mixture

was extracted with AcOEt. The extract was washed with water, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by column chromatography on alumina with CH_2Cl_2 as the eluent to give **4a-c**.

Tetrahydro-3-(2-oxo-2-phenylethyl)-2-(phenylimino)-3-furancarbonitrile (4a)

Colorless prisms (2.14 g, 47%), mp 126-127 °C (acetone/petroleum ether); IR (KBr): 2235 (C≡N), 1700 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.46–2.52 (m, 1H, 4-H), 3.04 (ddd, J = 3.1, 6.0, 13.3 Hz, 1H, 4-H), 3.63 (d, J = 18.3 Hz, 1H, C<u>H</u>COC_6H_5), 4.10 (d, J = 18.3 Hz, 1H, C<u>H</u>COC_6H_5), 4.49-4.56 (m, 2H, 5-H), 7.08-7.14 (m, 3H, aryl H), 7.28-7.32 (m, 2H, aryl H), 7.48-7.52 (m, 2H, aryl H), 7.60-7.64 (m, 1H, aryl H), 7.99-8.01 (m, 2H, aryl H); ^{13}C NMR ($CDCl_3$): δ 34.4 (C-4), 41.2 (C-3), 44.1 (<u>C</u>$H_2COC_6H_5$), 68.7 (C-5), 118.9 (C≡N), 122.7, 124.7, 128.1, 128.7, 128.9, 134.0, 135.8, 145.3 (C aryl), 157.8 (C-2), 194.5 (C=O); MS: *m/z* 305 $[M+H]^+$. Anal. Calcd for $C_{19}H_{16}N_2O_2$: C, 74.98; H, 5.30; N, 9.20. Found: C, 75.03; H, 5.32; N, 9.10.

3-[2-(4-Chlorophenyl)-2-oxoethyl]tetrahydro-2-(phenylimino)-3-furancarbonitrile (4b)

Colorless prisms (3.66 g, 72%), mp 205-206 °C (acetone/petroleum ether); IR (KBr): 2251 (C≡N), 1690 (C=O) cm^{-1}; ^1H NMR (DMSO-d_6): δ 2.53–2.60 (m, 1H, 4-H), 2.87 (ddd, J = 4.9, 7.2, 13.3 Hz, 1H, 4-H), 3.97 [d, J = 18.6 Hz, 1H, C<u>H</u>COC_6H_4-Cl(4)], 4.05 [d, J = 18.6 Hz, 1H, C<u>H</u>COC_6H_4-Cl(4)], 4.43-4.48 (m, 1H, 5-H), 4.50-4.55 (m, 1H, 5-H), 7.04-7.10 (m, 3H, aryl H), 7.30-7.33 (m, 2H, aryl H), 7.62-7.65 (m, 2H, aryl H), 8.04-8.07 (m, 2H, aryl H); ^{13}C NMR (DMSO-d_6): δ 33.2 (C-4), 41.0 (C-3), 43.4 [<u>C</u>$H_2COC_6H_4$-Cl(4)], 69.2 (C-5), 119.6 (C≡N), 122.5, 124.2, 128.6, 128.9, 130.0, 134.5, 138.7, 145.5 (C aryl), 159.2 (C-2), 194.5 (C=O); MS: *m/z* 339 $[M+H]^+$. Anal. Calcd for $C_{19}H_{15}ClN_2O_2 \bullet 0.1\ H_2O$: C, 67.00; H, 4.50; N, 8.22. Found: C, 67.04; H, 4.57; N, 8.09.

Tetrahydro-3-[2-(4-methoxyphenyl)-2-oxoethyl]-2-(phenylimino)-3-furancarbonitrile (4c)

Colorless prisms (3.82 g, 76%), mp 142-143 °C (acetone/petroleum ether); IR (KBr): 2245 (C≡N), 1693 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.46–2.53 (m, 1H, 4-H), 3.02 (ddd, J = 3.1, 6.0, 13.2 Hz, 1H, 4-H), 3.56 [d, J = 18 Hz, 1H, C<u>H</u>COC_6H_4-OCH_3(4)], 3.88 (s, 3H, OCH_3), 4.04 [d, J = 18 Hz, 1H, C<u>H</u>COC_6H_4-OCH_3(4)], 4.48-4.53 (m 2H, 5-H), 6.94-6.97 (m, 2H, aryl H), 7.08-7.25 (m, 3H, aryl H), 7.29-7.32 (m, 2H, aryl H), 7.95-7.99 (m, 2H, aryl H); ^{13}C NMR ($CDCl_3$): δ 34.4 (C-4), 41.3 (C-3), 43.8 [<u>C</u>$H_2COC_6H_4$-OCH_3(4)], 55.5 (OCH_3), 68.7 (C-5), 114.0 (C aryl), 119.0 (C≡N), 122.7, 124.6, 128.6, 128.9, 130.5, 145.4, 158.0 (C aryl), 164.2 (C-2), 192.8 (C=O); MS: *m/z* 335 $[M+H]^+$. Anal. Calcd for $C_{20}H_{18}N_2O_3$: C, 71.84; H, 5.43; N, 8.38. Found: C, 71.86; H, 5.50; N, 8.38.

General procedure for the preparation of 2-pyrrolidinones 5a-c from 4a-c and sodium iodide.

A mixture of **4a-c** (5 mmol) and NaI (1.50 g, 10 mmol) in DMF (5 mL) were stirred at 150 °C for 2 h. After removal of the solvent *in vacuo*, cold water was added to the residue. The resulting mixture was extracted with AcOEt. The extract was washed with water, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel with CH_2Cl_2 as the eluent to afford **5a-c**.

2-Oxo-3-(2-oxo-2-phenylethyl)-1-phenyl-3-pyrrolidinecarbonitrile (5a)

Colorless prisms (1.45 g, 95%), mp 139-140 °C (acetone/petroleum ether); IR (KBr): 2241 (C≡N), 1712, 1687 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.42–2.49 (m, 1H, 4-H), 2.93 (ddd, J = 2.7, 7.6, 13.4 Hz, 1H, 4-H), 3.61 (d, J = 18 Hz, 1H, C<u>H</u>COC_6H_5), 3.94-3.98 (m, 1H, 5-H), 3.95 (d, J = 18 Hz, 1H, C<u>H</u>COC_6H_5), 4.08-4.15 (m, 1H, 5-H), 7.21-7.26 (m, 1H, aryl H), 7.40-7.43 (m, 2H, aryl H), 7.47-7.51 (m, 2H, aryl H), 7.60-7.64 (m, 3H, aryl H), 7.96-7.98 (m, 2H, aryl H); ^{13}C NMR ($CDCl_3$): δ 29.6 (C-4), 42.87 (<u>C</u>$H_2COC_6H_5$), 42.91 (C-3), 46.0 (C-5), 118.8 (C≡N), 120.5, 125.8, 128.1, 128.9, 129.1, 134.0, 135.7, 138.5 (C aryl), 166.8 (C-2), 194.5 (C=O); MS: *m/z* 305 $[M+H]^+$. Anal. Calcd for $C_{19}H_{16}N_2O_2$: C, 74.98; H, 5.30; N, 9.20. Found: C, 75.07; H, 5.44; N, 9.06.

3-[2-(4-Chlorophenyl)-2-oxoethyl]-2-oxo-1-phenyl-3-pyrrolidinecarbonitrile (5b)

Colorless prisms (1.56 g, 92%), mp 158-159 °C (acetone/petroleum ether); IR (KBr): 2231 (C≡N), 1713, 1685 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.41–2.48 (m, 1H, 4-H), 2.93 (ddd, J = 2.8, 7.4, 13.4 Hz, 1H, 4-H), 3.56 [d, J = 18 Hz, 1H, C<u>H</u>COC_6H_4-Cl(4)], 3.91 [d, J = 18 Hz, 1H, C<u>H</u>COC_6H_4-Cl(4)], 3.92-3.97 (m, 1H, 5-H), 4.08-4.15 (m, 1H, 5-H), 7.21-7.26 (m, 1H, aryl H), 7.39-7.43 (m, 2H, aryl H), 7.46-7.48 (m, 2H, aryl H), 7.60-7.63 (m, 2H, aryl H), 7.89-7.92 (m, 2H, aryl H); ^{13}C NMR ($CDCl_3$): δ 29.6 (C-4), 42.8 [<u>C</u>$H_2COC_6H_4$-Cl(4)], 42.9 (C-3), 46.0 (C-5), 118.6 (C≡N), 120.5, 125.9, 129.1, 129.2, 129.5, 134.1, 138.4, 140.7 (C aryl), 166.7 (C-2), 193.3 (C=O); MS: *m/z* 339 $[M+H]^+$. Anal. Calcd for $C_{19}H_{15}ClN_2O_2$: C, 67.36; H, 4.46; N, 8.27. Found: C, 67.35; H, 4.54; N, 8.17.

3-[2-(4-Methoxyphenyl)-2-oxoethyl]-2-oxo-1-phenyl-3-pyrrolidinecarbonitrile (5c)

Colorless columns (1.53 g 91%), mp 91-92 °C (acetone/petroleum ether); IR (KBr): 2246 (C≡N), 1708, 1668 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.43–2.50 (m, 1H, 4-H), 2.91 (ddd, J = 2.8, 7.6, 13.4 Hz, 1H, 4-H), 3.55 [d, J = 18 Hz, 1H, C<u>H</u>COC_6H_4-OCH_3(4)], 3.88 (s, 3H, OCH_3), 3.89 [d, J = 18 Hz, 1H, C<u>H</u>COC_6H_4-OCH_3(4)], 3.92-3.96 (m 1H, 5-H), 4.06-4.12 (m, 1H, 5-H), 6.94-6.96 (m, 2H, aryl H), 7.20-7.24 (m, 1H, aryl H), 7.39-7.42 (m, 2H, aryl H), 7.62-7.63 (m, 2H, aryl H), 7.93-7.95 (m, 2H, aryl H); ^{13}C NMR ($CDCl_3$): δ 29.6 (C-4), 42.5 [<u>C</u>$H_2COC_6H_4$-OCH_3(4)], 43.0 (C-3), 46.0 (C-5), 55.5 (OCH_3),

114.0 (C aryl), 119.0 (C≡N), 120.5, 125.8, 128.9, 129.1, 130.5, 138.5, 164.2 (C aryl), 167.0 (C-2), 192.8 (C=O); MS: *m/z* 335 $[M+H]^+$. Anal. Calcd for $C_{20}H_{18}N_2O_3$: C, 71.84; H, 5.43; N, 8.38. Found: C, 71.80; H, 5.49; N, 8.31.

General procedure for the preparation of 2-pyrrolidinones 5a-c, 6a-c and 7a-c from 1-3.

To an ice-cooled and stirred mixture of **1** (1.86 g, 10 mmol) in DMF (10 mL) was added 60% NaH (0.40 g, 10 mmol). The stirring was continued at rt until evolution of gas ceased. To the obtained mixture was added phenacyl bromide (1.99 g, 10 mmol), 4-chlorophenacyl bromide (2.33 g, 10 mmol) and 4-methoxyphenacyl bromide (2.29 g, 10 mmol) with stirring and ice-cooling, and the mixture was stirred at rt for 1 h. To the resulting mixture was added NaI (3.00 g, 20 mmol) with stirring, and then the mixture was stirred at 150 °C for 2 h. After work-up as described for the preparation of **5a-c**, 2-pyrrolidinones **5a-c** (**5a**: 67 %, **5b**: 71 %, **5c**: 72 %), **6a-c** and **7a-c** were obtained.

1-(4-Chlorophenyl)-2-oxo-3-(2-oxo-2-phenylethyl)-3-pyrrolidinecarbonitrile (6a)

Colorless plates (1.88 g, 55%), mp 113-114 °C (acetone/petroleum ether); IR (KBr): 2252 (C≡N), 1705, 1687 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.44–2.51 (m, 1H, 4-H), 2.91 (ddd, J = 2.8, 7.6, 13.4 Hz, 1H, 4-H), 3.64 (d, J = 18.3 Hz, 1H, C<u>H</u>COC_6H_5), 3.91-3.96 (m, 1H, 5-H), 3.93 (d, J = 18.3 Hz, 1H, C<u>H</u>COC_6H_5), 4.05-4.11 (m, 1H, 5-H), 7.35-7.39 (m, 2H, aryl H), 7.47-7.51 (m, 2H, aryl H), 7.57-7.63 (m, 3H, aryl H), 7.94-7.97 (m, 2H, aryl H); ^{13}C NMR ($CDCl_3$): δ 29.4 (C-4), 42.8 ($\underline{C}H_2COC_6H_5$), 42.9 (C-3), 45.9 (C-5), 118.6 (C≡N), 121.6, 128.1, 128.9, 129.2, 131.1, 134.1, 135.7, 137.0 (C aryl), 166.9 (C-2), 194.4 (C=O); MS: *m/z* 339 $[M+H]^+$. Anal. Calcd for $C_{19}H_{15}ClN_2O_2$: C, 67.36; H, 4.46; N, 8.27. Found: C, 67.41; H, 4.51; N, 8.21.

1-(4-Chlorophenyl)-3-[2-(4-chlorophenyl)-2-oxoethyl]-2-oxo-3-pyrrolidinecarbonitrile (6b)

Colorless prisms (2.63 g, 70%), mp 146-148 °C (acetone/petroleum ether); IR (KBr): 2232 (C≡N), 1701, 1682 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.43–2.50 (m, 1H, 4-H), 2.91 (ddd, J = 2.8, 7.5, 13.4 Hz, 1H, 4-H), 3.59 [d, J = 18.3 Hz, 1H, C<u>H</u>COC_6H_4-Cl(4)], 3.89 [d, J = 18.3 Hz, 1H, C<u>H</u>COC_6H_4-Cl(4)], 3.91-3.96 (m, 1H, 5-H), 4.06-4.11 (m, 1H, 5-H), 7.35-7.39 (m, 2H, aryl H), 7.45-7.48 (m, 2H, aryl H), 7.56-7.60 (m, 2H, aryl H), 7.88-7.91 (m, 2H, aryl H); ^{13}C NMR ($CDCl_3$): δ 29.4 (C-4), 42.7 [$\underline{C}H_2COC_6H_4$-Cl(4)], 42.8 (C-3), 45.9 (C-5), 118.5 (C≡N), 121.6, 129.2, 129.3, 129.5, 131.2, 134.0, 137.0, 140.8 (C aryl), 166.7 (C-2), 193.3 (C=O); MS: *m/z* 374 $[M+H]^+$. Anal. Calcd for $C_{19}H_{14}Cl_2N_2O_2$: C, 61.14; H, 3.78; N, 7.51. Found: C, 61.17; H, 3.84; N, 7.36.

1-(4-Chlorophenyl)-3-[2-(4-methoxyphenyl)-2-oxoethyl]-2-oxo-3-pyrrolidinecarbonitrile (6c)

Colorless prisms (2.77 g, 75%), mp 164-165 °C (acetone/petroleum ether); IR (KBr): 2322 (C≡N), 1713, 1671 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.45–2.52 (m, 1H, 4-H), 2.89 (ddd, J = 2.9, 7.5, 13.3 Hz, 1H, 4-H), 3.59 [d, J = 18 Hz, 1H, C<u>H</u>COC_6H_4-OCH_3(4)], 3.87 [d, J = 18 Hz, 1H, C<u>H</u>COC_6H_4-OCH_3(4)], 3.88 (s, 3H, OCH_3), 3.90-3.95 (m 1H, 5-H), 4.04-4.10 (m, 1H, 5-H), 6.93-6.96 (m, 2H, aryl H), 7.35-7.38 (m, 2H, aryl H), 7.58-7.61 (m, 2H, aryl H), 7.92-7.95 (m, 2H, aryl H); ^{13}C NMR ($CDCl_3$): δ 29.4 (C-4), 42.4 [<u>C</u>$H_2COC_6H_4$-OCH_3(4)], 42.9 (C-3), 45.9 (C-5), 55.6 (OCH_3), 114.1 (C aryl), 118.8 (C≡N), 121.6, 128.8, 129.1, 130.5, 131.0, 137.1, 164.3 (C aryl), 167.1 (C-2), 192.8 (C=O); MS: *m/z* 369 $[M+H]^+$. Anal. Calcd for $C_{20}H_{17}ClN_2O_3$: C, 65.13; H, 4.65; N, 7.60. Found: C, 65.14; H, 4.67; N, 7.50.

1-(4-Methoxyphenyl)-2-oxo-3-(2-oxo-2-phenylethyl)-3-pyrrolidinecarbonitrile (7a)

Colorless needles (2.21 g, 79%), mp 119-120 °C (acetone/petroleum ether); IR (KBr): 2238 (C≡N), 1730, 1679 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.40–2.47 (m, 1H, 4-H), 2.91 (ddd, J = 2.9, 7.5, 13.4 Hz, 1H, 4-H), 3.59 (d, J = 18 Hz, 1H, C<u>H</u>COC_6H_5), 3.81 (s, 3H, OCH_3), 3.87-3.92 (m, 1H, 5-H), 3.94 (d, J = 18 Hz, 1H, C<u>H</u>COC_6H_5), 4.03-4.09 (m, 1H, 5-H), 6.91-6.95 (m, 2H, aryl H), 7.47-7.53 (m, 4H, aryl H), 7.59-7.63 (m, 1H, aryl H), 7.95-7.98 (m, 2H, aryl H); ^{13}C NMR ($CDCl_3$): δ 29.7 (C-4), 42.7 (C-3), 42.9 (<u>C</u>$H_2COC_6H_5$), 46.4 (C-5), 55.5 (OCH_3), 114.3 (C aryl), 118.9 (C≡N), 122.4, 128.1, 128.8, 131.6, 134.0, 135.8, 157.6 (C aryl), 166.6 (C-2), 194.5 (C=O); MS: *m/z* 335 $[M+H]^+$. Anal. Calcd for $C_{20}H_{18}N_2O_3$: C, 71.84; H, 5.43; N, 8.38. Found: C, 71.82; H, 5.46; N, 8.29.

3-[2-(4-Chlorophenyl)-2-oxoethyl]-1-(4-methoxyphenyl)-2-oxo-3-pyrrolidinecarbonitrile (7b)

Colorless prisms (2.49 g, 68%), mp 179-180 °C (acetone/petroleum ether); IR (KBr): 2232 (C≡N), 1694, 1681 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.39–2.46 (m, 1H, 4-H), 2.91 (ddd, J = 2.8, 7.4, 13.4 Hz, 1H, 4-H), 3.54 [d, J = 18 Hz, 1H, C<u>H</u>COC_6H_4-Cl(4)], 3.81 (s, 3H, OCH_3), 3.86-3.91 (m, 1H, 5-H), 3.90 [d, J = 18 Hz, 1H, C<u>H</u>COC_6H_4-Cl(4)], 4.03-4.09 (m, 1H, 5-H), 6.91-6.94 (m, 2H, aryl H), 7.44-7.51 (m, 4H, aryl H), 7.88-7.91 (m, 2H, aryl H); ^{13}C NMR ($CDCl_3$): δ 29.7 (C-4), 42.6 (C-3), 42.9 [<u>C</u>$H_2COC_6H_4$-Cl(4)], 46.4 (C-5), 55.5 (OCH_3), 114.3 (C aryl), 118.9 (C≡N), 122.4, 129.2, 129.5, 131.4, 134.1, 140.6, 157.6 (C aryl), 166.4 (C-2), 193.4 (C=O); MS: *m/z* 369 $[M+H]^+$. Anal. Calcd for $C_{20}H_{17}ClN_2O_3$: C, 65.13; H, 4.56; N, 7.60. Found: C, 65.21; H, 4.65; N, 7.50.

1-(4-Methoxyphenyl)-3-[2-(4-methoxyphenyl)-2-oxoethyl]-2-oxo-3-pyrrolidinecarbonitrile (7c)

Colorless prisms (2.43 g, 67%), mp 162-164 °C (acetone); IR (KBr): 2242 (C≡N), 1701, 1683 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.41–2.48 (m, 1H, 4-H), 2.90 (ddd, J = 2.9, 7.5, 13.4 Hz, 1H, 4-H), 3.53 [d, J = 18 Hz, 1H, C<u>H</u>COC_6H_4-OCH_3(4)], 3.81 (s, 3H, OCH_3), 3.86-3.90 (m, 1H, 5-H), 3.87 (s, 3H, OCH_3), 3.88 [d, J = 18 Hz, 1H, C<u>H</u>COC_6H_4-OCH_3(4)], 4.01-4.07 (m, 1H, 5-H), 6.91-6.96 (m, 4H, aryl H), 7.26-7.53

(m, 2H, aryl H), 7.92-7.95 (m, 2H, aryl H); ^{13}C NMR ($CDCl_3$): δ 29.7 (C-4), 42.5 [$\underline{C}H_2COC_6H_4$-OCH_3(4)], 42.7 (C-3), 46.4 (C-5), 55.48, 55.53 (OCH_3), 114.0, 114.3 (C aryl), 119.0 (C≡N), 122.3, 128.9, 130.4, 131.6, 157.5, 164.2 (C aryl), 166.7 (C-2), 192.9 (C=O); MS: *m/z* 365 $[M+H]^+$. Anal. Calcd for $C_{21}H_{20}N_2O_4$: C, 69.22; H, 5.53; N, 7.69. Found: C, 69.20; H, 5.57; N, 7.61.

The preparation of 8 from 4a.

After a mixture of **4a** (1.54 g, 5 mmol) and 5% HCl (40 mL) was stirred at rt for 20 h, cold water was added to the reaction mixture. The precipitate was collected by filtration, washed with water, dried and recrystallized from acetone/petroleum ether to yield **8** (85%), which was identical with an authentic sample[29] prepared from **9** and phenacyl bromide on the basis of a mixed melting point determination and comparison of the IR spectra.

The preparation of 5a-c from 10 and phenacyl bromides.

To an ice-cooled and stirred mixture of **10**[31] (0.56 g, 3 mmol) in DMF (3 mL) was added 60% NaH (0.12 g, 3 mmol). The stirring was continued at rt until evolution of gas ceased. To the obtained mixture was added phenacyl bromide (0.60 g, 3 mmol), 4-chlorophenacyl bromide (0.70 g, 3 mmol) or 4-methoxyphenacyl bromide (0.69 g, 3 mmol) with stirring and ice-cooling, and then the mixture was stirred at rt for 2 h. After removal of the solvent *in vacuo*, cold water was added to the residue. The resulting mixture was extracted with AcOEt. After work-up as described for the preparation of **4a-c**, **5a-c** were obtained in 78%, 82% and 76% yields, respectively. The melting points and IR spectra of **5a-c** coincided with those of authentic samples prepared from **4a-c** and phenacyl bromides.

General procedure for the preparation of dihydropyrans 12a-c from 11.

To an ice-cooled and stirred mixture of **11** (1.10 g, 10 mmol) in DMF (10 mL) was added 60% NaH (0.40 g, 10 mmol). The stirring was continued at rt until evolution of gas ceased. To the obtained mixture was added phenacyl bromide (1.99 g, 10 mmol), 4-chlorophenacyl bromide (2.33g, 10 mmol) or 4-methoxyphenacyl bromide (2.29 g, 10 mmol) with stirring and ice-cooling, and then the mixture was stirred at rt for 1 h. To the resulting mixture was added NaI (1.50 g, 10 mmol) with stirring, and then the mixture was stirred at 100 °C for 4 h. After removal of the solvent *in vacuo*, cold water was added to the residue. The resulting mixture was extracted with AcOEt. The extract was washed with water, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel with CH_2Cl_2 as the eluent to give **12a-c**.

4-Cyano-3,4-dihydro-6-phenyl-2*H*-pyran-4-carboxamide (12a)

Colorless needles (0.73 g, 32%), mp 167-169 °C (acetone/petroleum ether); IR (KBr): 3410, 3169 (NH), 2234 (C≡N), 1690 (C=O) cm^{-1}; ^1H NMR (DMSO-d_6): δ 2.30 (ddd, J = 3.4, 7.0, 14.0 Hz, 1H, 3-H), 2.45 (ddd, J = 3.4, 7.7, 13.8 Hz, 1H, 3-H), 4.19-4.30 (m, 2H, 2-H), 5.69 (s, 1H, 5-H), 7.39-7.43 (m, 3H, aryl H), 7.60-7.64 (m, 2H, aryl H), 7.72 (s, 1H, NH), 7.79 (s, 1H, NH); ^{13}C NMR (DMSO- d_6): δ 29.4 (C-3), 40.5 (C-4), 63.3 (C-2), 92.5 (C-5), 120.5 (C≡N), 124.9, 128.3, 129.2, 133.8 (C aryl), 153.5 (C-6), 168.0 (C=O); MS: *m/z* 229 $[M+H]^+$. Anal. Calcd for $C_{13}H_{12}N_2O_2$: C, 68.41; H, 5.30; N, 12.27. Found: C, 68.51; H, 5.37; N, 12.29.

6-(4-Chlorophenyl)-4-cyano-3,4-dihydro-2*H*-pyran-4-carboxamide (12b)

Colorless columns (0.72 g, 27%), mp 164-165 °C (acetone/petroleum ether); IR (KBr): 3377, 3163 (NH), 2245 (C≡N), 1700 (C=O) cm^{-1}; ^1H NMR (DMSO- d_6): δ 2.31 (ddd, J = 3.7, 6.6, 14.0 Hz, 1H, 3-H), 2.43 (ddd, J = 3.7, 7.7, 13.9 Hz, 1H, 3-H), 4.20-4.30 (m, 2H, 2-H), 5.74 (s, 1H, 5-H), 7.45-7.48 (m, 2H, aryl H), 7.63-7.66 (m, 2H, aryl H), 7.73 (s, 1H, NH), 7.79 (s, 1H, NH); ^{13}C NMR (DMSO- d_6): δ 29.3 (C-3), 40.5 (C-4), 63.4 (C-2), 93.1 (C-5), 120.4 (C≡N), 126.7, 128.3, 132.7, 133.8 (C aryl), 153.5 (C-6), 167.9 (C=O); MS: *m/z* 263 $[M+H]^+$. Anal. Calcd for $C_{13}H_{11}ClN_2O_2$: C, 59.44; H, 4.22; N, 10.66. Found: C, 59.56; H, 4.31; N, 10.62.

4-Cyano-3,4-dihydro-6-(4-methoxyphenyl)-2*H*-pyran-4-carboxamide (12c)

Colorless prisms (0.21 g, 8%), mp 163-164 °C (acetone/petroleum ether); IR (KBr): 3429, 3156 (NH), 2239 (C≡N), 1715 (C=O) cm^{-1}; ^1H NMR (DMSO- d_6): δ 2.28 (ddd, J = 2.7, 6.6, 14.9 Hz, 1H, 3-H), 2.43 (ddd, J = 3.7, 6.9, 15.0 Hz, 1H, 3-H), 3.78 (s, 3H, OCH_3), 4.18-4.27 (m, 2H, 2-H), 5.55 (s, 1H, 5-H), 6.93-6.97 (m, 2H, aryl H), 7.54-7.57 (m, 2H, aryl H), 7.68 (s, 1H, NH), 7.75 (s, 1H, NH); ^{13}C NMR (DMSO- d_6): δ 29.4 (C-3), 40.6 (C-4), 55.1 (OCH_3), 63.2 (C-2), 90.7 (C-5), 113.6 (C aryl), 120.7 (C≡N), 126.3, 126.4 (C aryl), 153.4 (C-6), 160.0 (C aryl), 168.2 (C=O); MS: *m/z* 259 $[M+H]^+$. Anal. Calcd for $C_{14}H_{14}N_2O_3$: C, 65.11; H, 5.46; N, 10.85. Found: C, 65.12; H, 5.54; N, 10.86.

REFERENCES

1. A. I. Meyers and L. J. Snyder, *J. Org. Chem.,* 1993, **58**, 36.
2. N. J. Ede, I. D. Rae, and M. T. W. Hearn, *Aust. J. Chem.,* 1991, **44**, 891.
3. B. M. Nilsson, B. Ringdahl, and U. Hacksell, *J. Med. Chem.,* 1990, **33**, 580.
4. R. Bergmann and R. Gericke, *J. Med. Chem.*, 1990, **33**, 492.
5. D. S. Garvey, P. D. May, and A. M. Nadzan, *J. Org. Chem.,* 1990, **55**, 936.
6. J. A. Marco, M. Carda, J. Murga, and E. Falomir, *Tetrahedron,* 2007, **63**, 2929.
7. M. C. Elliott, *J. Chem. Soc., Perkin Trans. 1,* 2002, 2301.

8. M. M. Faul and B. E. Huff, *Chem, Rev.,* 2000, **100**, 2407.
9. B. B. Sinder, Y. Ahn, and B. M. Foxman, *Tetrahedron,* 1999, **40**, 3339.
10. L. E. Burgess and A. I. Meyers, *J. Org. Chem.,* 1992, **57**, 1656.
11. Z. Y. Wei and E. E. Knays, *Synlett,* 1991, 295.
12. I. Paterson, J. G. Cumming, R. A. Ward, and S. Lamboley, *Tetrahedron,* 1995, **51**, 9393.
13. I. Paterson, J. D. Smith, R. A. Ward, and S. Lamboley, *Tetrahedron,* 1995, **51**, 9413.
14. K. A. Parker, C. A. Coburn, and Y. –H. Koh, *J. Org. Chem.,* 1995, **60**, 2938.
15. N. J. Bennett, J. C. Prodger, and G. Pattenden, *Tetrahedron,* 2007, **63**, 6216.
16. P. Haldar, G. Barman, and J. K. Ray, *Tetrahedron,* 2007, **63**, 3049.
17. Y. Kobayashi, H. Kamisaki, H. Takeda, Y. Yasui, R. Yanada, and Y. Takemoto, *Tetrahedron,* 2007, **663**, 2978.
18. H. Twin, W. W. –H. Wen, D. A. Powell, A. J. Lough, and R. A. Batey, *Tetrahedron Lett.,* 2007, **48**, 1841.
19. A. Bassoli, G. Borgonovo, G. Busnelli, and G. Morini, *Eur. J. Org. Chem.,* 2006, 1656.
20. M. Gao, D. –X. Wang, Q. –Y. Zheng, and M. –X. Wang, *J. Org. Chem.,* 2006, **71**, 9532.
21. I. Kanizsai, Z. Szakonyi, R. Sillanpää, M. D'hooghe, N. De Kimpe, and F. Fülöp, *Tetrahedron: Asymmetry,* 2006, **17**, 2857.
22. X. Huang, H. Zhou, and W. Chen, *J. Org. Chem.,* 2004, **69**, 839.
23. I. Paterson and C. A. Luckhurst, *Tetrahedron Lett.,* 2003, **44**, 3749.
24. V. S. Kumar and P. E. Floreancing, *J. Am. Chem. Soc.,* 2001, **123**, 3842.
25. J. Mulzer and M. Hanbauer, *Tetrahedron Lett.,* 2000, **41**, 33.
26. K. Yamagata, H. Maruoka, Y. Hashimoto, and M. Yamazaki, *Heterocycles,* 1989, **29**, 5.
27. K. Yamagata, F. Okabe, H. Maruoka, and Y. Tagawa, *J. Heterocycl. Chem.,* 2005, **42**, 543.
28. H. Maruoka, K. Yamagata, and M. Yamazaki, *Liebigs Ann. Chem.,* 1993, 625.
29. K. Yamagata, Y. Tomioka, and M. Yamazaki, *Chem. Pharm. Bull.,* 1986, **34**, 590.
30. K. Yamagata, F. Okabe, and Y. Tagawa, *Eur. J. Org. Chem.,* 2003, 2383.
31. H. Maruoka, F. Okabe, and K. Yamagata, *J. Heterocycl. Chem.,* 2007, **44**, 201.
32. T. Mastuda, K. Yamagata, Y. Tomioka, and M. Yamazaki, *Chem. Pharm. Bull.*, 1985, **33**, 937.