Regioselective Synthesis of the 5,6-Dihydro-4*H*-furo[2,3-*c*]pyrrol-4-one Skeleton: A New Class of Compounds

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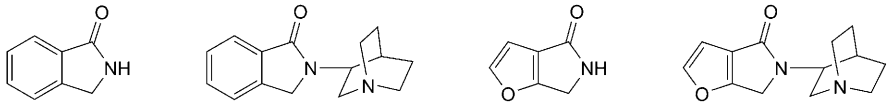
We hereby report the first preparation of the 5,6-dihydro-4*H*-furo[2,3-*c*]pyrrol-4-one (**3**) and its derivatives starting from methyl 3-(methoxycarbonyl)furan-2-acetate (**8**). The ester functionality connected to the methylene group was regiospecifically converted to the desired monohydrazide **9**. Conversion of **9** into the acyl azide **10** followed by *Curtius* rearrangement gave the corresponding isocyanate derivative **11** (*Scheme 2*). Reaction of **11** with different nucleophiles produced urethane and urea derivatives (*Scheme 3*). Intramolecular cyclization reactions provided the target compounds (*Scheme 5*). Removal of the amine-protecting group formed the title compound **3**.

Introduction. – Isoindolinone (=2,3-dihydro-1*H*-isoindol-1-one; **1**) derivatives show a wide range of important biological activities. A series of isoindolinone derivatives have recently been synthesized and screened. Some substituted isoindolinone derivatives have quite potent metabotropic glutamate receptor 1 antagonist activity [1]. Moreover, it has been demonstrated that some derivatives show an antipsychotic-like effect in an animal model.

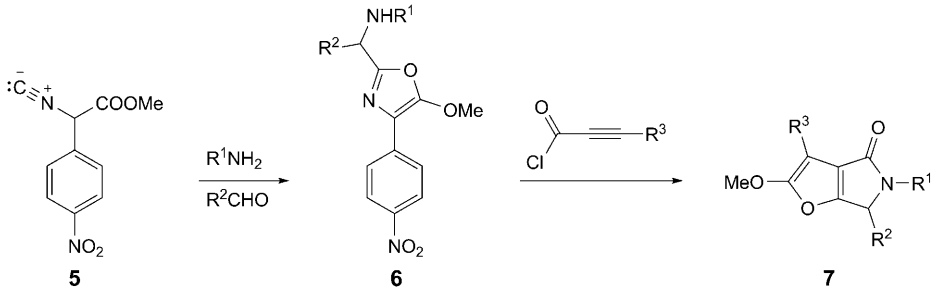


1 **2** **3** **4**

Furthermore, it has been shown that the isoindolinone derivative **2** [2], having a 1-azabicyclo[2.2.2]octane unit, can bind nicotinic acetylcholine receptors in the treatment of a range of disorders [3], and furopyrrolone derivatives (such as **4**) are claimed to be useful in the treatment of psychotic disorders or intellectual impairment disorders including *Alzheimer*'s disease [2].

Recently, *Zhu et al.* [4] developed a four-component synthesis of furopyrrolones on the basis of the unique reactivity of methyl α-isocyano-4-nitrobenzeneacetate (**5**) (*Scheme 1*). A three-component reaction of **5** with an aldehyde and amine gave the corresponding methoxyoxazole derivative **6**. The reaction of oxazole **6** with prop-2-ynoyl chloride produced the furopyrrolone **7** [4]. This methodology is useful for the synthesis of furopyrrolidone derivatives substituted at certain positions. Therefore, an efficient method for the preparation of the unknown parent compound **3** would be of

Scheme 1

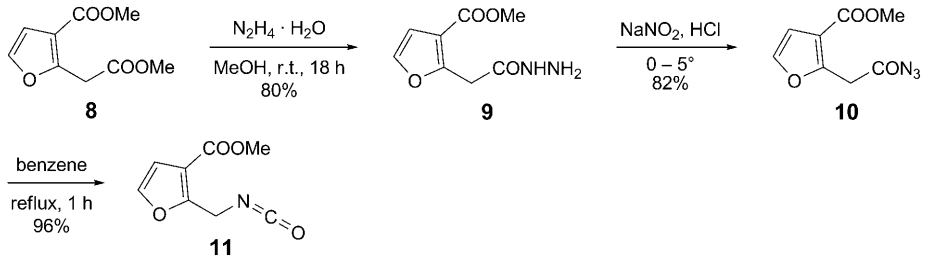


interest. In this article, we describe a method for the synthesis of **3**, which may also be applied for the synthesis of specifically substituted derivatives of **3**.

Results and Discussion. – Our plan for the construction of the desired heterocyclic ring system **3** involved an intramolecular cyclization reaction of the isocyanate **11**, which can be generated by *Curtius* rearrangement [5] of the corresponding acyl azide **10**. The most general and versatile synthesis of acyl azides involves the reaction of acyl chlorides with NaN_3 in an aqueous medium. Problems associated with this method and others turned our attention to the generation of acyl azides *via* acyl hydrazides. The starting diester **8** was synthesized by treatment of dimethyl 3-oxopropanedioate with chloroacetaldehyde in the presence of pyridine as described in [6].

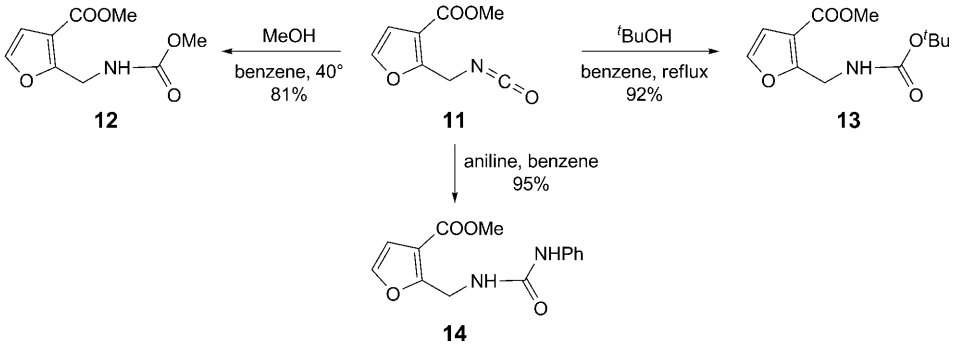
Recently, we have reported that diester **8** was successfully converted to the corresponding dihydrazide by refluxing in MeOH [7]. However, we noted that the reactivity of the ester carbonyl groups of **8** is different. The ester functionality connected to the CH_2 group is more reactive than the other. Therefore, for regiospecific hydrazide formation, the diester **8** was treated with hydrazine at room temperature for 18 h. The desired monohydrazide derivative **9** was formed in 80% yield (*Scheme 2*). The hydrazide derivative **9** was treated with $NaNO_2$ and HCl at low temperature to give monoazide derivative **10** in 82% yield. Finally, **10** was refluxed in benzene for 1 h to give the corresponding isocyanate derivative **11** in high yield.

Scheme 2. *Synthesis of Isocyanate* **11**



Isocyanate derivative **11** was chosen as a model to explore further reactions, *e.g.*, the isocyanate can be trapped by a variety of nucleophiles. Treatment of **11** in benzene with MeOH at 40° for 1 h gave the urethane derivative **12** in 81% yield (*Scheme 3*). When

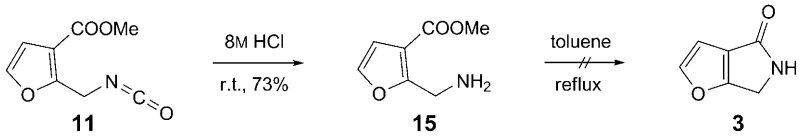
Scheme 3. *Reaction of Isocyanate* **11** *with Various Nucleophiles*



the reaction was carried out in the presence of ^{t}BuOH at reflux temperature, Boc-protected amine derivative **13** was generated, which is a useful intermediate [8] in organic synthesis. The urea derivative **14** was obtained from **11** in 95% yield after treatment with aniline in benzene.

At first, the hydrolysis of isocyanate derivative **11** was carried out to synthesize the amine derivative **15** and to study its cyclization. Treatment of **11** with 8M HCl at room temperature gave **15** in 73% yield (*Scheme 4*). However, all efforts to convert **15** into the target compound **3** failed. Therefore, we turned our attention to the synthesis of the carboxylic acids **16**–**18**.

Scheme 4. *Synthesis of Methyl 2-(Aminomethyl)furan-3-carboxylate* (**15**)

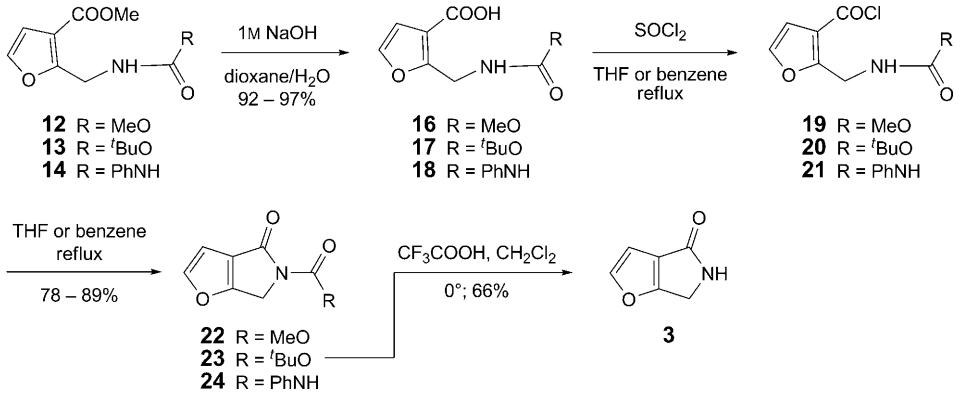


To increase the reactivity of the ester C=O groups in **12**–**14**, which is necessary for the cyclization reaction, the ester functionalities in **12**–**14** should be converted into acyl chlorides **19**–**21**. The ester derivatives **12**–**14** were first hydrolyzed to the corresponding acids **16**–**18** by treatment with 1M NaOH in dioxane/H_2O at room temperature for 2 h (*Scheme 5*). The acids **16**–**18** were then treated with $SOCl_2$ in THF or benzene at 75°. The acyl chlorides **19**–**21** were obtained in high yields. For the ring-closing reaction, acyl chlorides **19**–**21** were refluxed in benzene or THF to give the desired 5,6-dihydro-4*H*-furo[2,3-*c*]pyrrol-4-one derivatives **22**–**24** in high yields.

Finally, hydrolysis of the cyclization product **23** with CF_3COOH in CH_2Cl_2 at 0° gave the target compound 5,6-dihydro-4*H*-furo[2,3-*c*]pyrrol-4-one (**3**) in 66% yield. The spectral data of **3** were fully in accord with the proposed structure.

Conclusions. – The presented results establish that cyclization of acyl azides is a valuable method for the synthesis of heterocyclic compounds with new skeletons. Furthermore, controlling the number of the CH_2 groups separating the ester

Scheme 5. *Synthesis of Substituted Furopyrrolone Derivatives* **22**–**24** *Starting from* **12**–**14** *and Hydrolysis to the Target Compound, Dihydrofuropyrrolone* **3**



functionalities from the furan ring will be a useful approach for the synthesis of six- and seven-membered heterocycles fused to a furan ring [9].

The authors are indebted to the *Scientific and Technological Research Council of Turkey* (*TUBITAK*, Grant 108-M168), the Department of Chemistry at Middle East Technical University, and the *Turkish Academy of Sciences* (*TUBA*) for their financial support of this work. *G. K.* thanks *TUBITAK* for a postdoctoral fellowship.

Experimental Part

General. TLC: anal. aluminium plates coated with SiO_2 *60* F_{254} (0.2 mm, *Merck*). Column chromatography (CC): silica gel (SiO_2; 60 mesh; *Merck*). M.p.: *Gallenkamp*; uncorrected. IR Spectra: FT-IR *Bruker-Vertex-70* instrument; ATR = attenuated total reflectance; soln. in 0.1 mm cells or KBr pellets; $\tilde{\nu}$ in cm^{-1}. ^1H- and ^{13}C-NMR Spectra: *Bruker-BioSpin* (*DPX-400*) instrument; δ in ppm rel. to Me_4Si as internal standard, *J* in Hz; apparent splitting is given in all cases.

Methyl 2-(2-Hydrazinyl-2-oxoethyl)furan-3-carboxylate (**9**). To a stirred soln. of diester **8** (10.0 g, 50.5 mmol) in MeOH (100 ml) at 0° was added hydrazine monohydrate (7.4 ml, 151.5 mmol) followed by stirring without removing the ice bath for 18 h. The solvent was evaporated and the crude product purified by extraction with $CHCl_3$ (200 ml) and H_2O (40 ml). The aq. layer was re-extracted with $CHCl_3$ (2 × 70 ml) and the combined org. extract washed with H_2O (40 ml), dried ($MgSO_4$), and concentrated: **9** (8.0 g, 80%). White solid. M.p. 143–144°. IR (KBr): 3301, 1712, 1644, 1540, 1439, 1312, 1205, 1068, 755. ^1H-NMR (400 MHz, $(D)_6$DMSO): 9.03 (br. *s*, NH); 7.45 (*d*, *J* = 2.0, =CH); 6.48 (*d*, *J* = 2.0, =CH); 4.24 (br. *s*, NH_2); 3.60 (*s*, CH_2); 3.53 (*s*, MeO). ^{13}C-NMR (100.6 MHz, (D_6)DMSO): 166.4; 163.3; 155.9; 142.4; 114.4; 110.3; 51.4; 32.7. Anal. calc. for $C_8H_{10}N_2O_4$ (198.18): C 48.48, H 5.09, N 14.14; found: C 48.51, H 5.05, N 14.12.

Methyl 2-(2-Azido-2-oxoethyl)furan-3-carboxylate (**10**). To a stirred soln. of **9** (2.5 g, 12.6 mmol) in 1M aq. HCl (40 ml) at 0° was added dropwise a soln. of $NaNO_2$ (0.91 g, 13.3 mmol) in H_2O (10 ml) followed by stirring at 0–5° for 30 min. The mixture was extracted with Et_2O (2 × 60 ml) and the combined org. phase washed with sat. aq. Na_2CO_3 soln. (40 ml) and then brine (30 ml), dried ($MgSO_4$), and concentrated: **10** (2.16 g, 82%). Colorless oil. IR (KBr): 2956, 2143, 1718, 1613, 1443, 1315, 1205, 1158, 1034. ^1H-NMR (400 MHz, $CDCl_3$): 7.29 (*d*, *J* = 2.0, =CH); 6.64 (*d*, *J* = 2.0, =CH); 4.02 (*s*, CH_2); 3.77 (*s*, MeO). ^{13}C-NMR (100.6 MHz, $CDCl_3$,): 175.3; 163.7; 153.1; 142.2; 116.1; 110.8; 51.6; 35.7.

Methyl 2-(Isocyanatomethyl)furan-3-carboxylate (**11**). A soln. of **10** (2.1 g, 10.0 mmol) in dry benzene (30 ml) was heated under reflux for 1 h. The solvent was evaporated: **11** (1.72 g, 95%). Colorless

oil. IR (KBr): 2956, 2258, 1720, 1612, 1515, 1414, 1312, 1081. ^{1}H-NMR (400 MHz, $CDCl_3$): 7.32 (*d*, *J* = 2.0, =CH); 6.64 (*d*, *J* = 2.0, =CH); 4.67 (*s*, CH_2); 3.80 (*s*, MeO). ^{13}C-NMR (100.6 MHz, $CDCl_3$): 163.3; 155.1; 142.3; 125.3; 115.1; 111.0; 51.8; 38.6.

Methyl 2-{[(Methoxycarbonyl)amino]methyl}furan-3-carboxylate (**12**). To a stirred soln. of **11** (0.42 g, 2.3 mmol) in dry benzene (20 ml) at 40° was added MeOH (0.6 ml, 14.7 mmol) and stirred for 1 h. The solvent was evaporated to give the crude product which was then purified by CC (SiO_2; AcOEt/hexane 2:1): **12** (0.4 g, 81%). White solid. M.p. 60–62°. IR (ATR): 3338, 3150, 2938, 1694, 1601, 1540, 1433, 1353, 1310, 1260, 1199, 1144, 1087. ^{1}H-NMR (400 MHz, $CDCl_3$): 7.33 (*d*, *J* = 1.8, =CH); 6.69 (*d*, *J* = 1.8, =CH); 5.51 (br. *s*, NH); 4.68 (*d*, *J* = 6.1, CH_2); 3.87 (*s*, MeO); 3.71 (*s*, MeO). ^{13}C-NMR (100.6 MHz, $CDCl_3$): 164.0; 158.1; 156.9; 141.5; 114.7; 110.8; 52.3; 51.7; 37.5. Anal. calc. for $C_9H_{11}NO_5$ (213.19): C 50.70, H 5.20, N 6.57; found: C 50.75, H 5.13, N 6.59.

*Methyl 2-{[(*tert*-Butoxycarbonyl]amino}methyl}furan-3-carboxylate* (**13**). To a stirred soln. of **11** (2.81 g, 15.5 mmol) in dry benzene (40 ml) was added excess ^{t}BuOH (25 ml), followed by heating under reflux for 2 d. The solvent and excess ^{t}BuOH were evaporated: **13** (3.2 g, 92%). White solid. M.p. 93–95°. IR (ATR): 3360, 3155, 2996, 1716, 1687, 1604, 1524, 1432, 1405, 1315, 1266, 1251, 1199, 1164, 1126, 1088, 1034. ^{1}H-NMR (400 MHz, $CDCl_3$): 7.23 (*d*, *J* = 1.9, =CH); 6.59 (*d*, *J* = 1.9, =CH); 5.19 (br. *s*, NH); 4.53 (*d*, *J* = 5.6, CH_2); 3.78 (*s*, MeO); 1.37 (*s*, ^{t}Bu). ^{13}C-NMR (100.6 MHz, $CDCl_3$,): 165.0; 159.3; 156.5; 142.3; 115.4; 111.7; 80.7; 52.6; 38.0; 29.3. Anal. calc. for $C_{12}H_{17}NO_5$ (255.27): C 56.46, H 6.71, N 5.49; found: C 56.56, H 6.80, N 5.56.

Methyl 2-{[[(Phenylamino)carbonyl]amino}methyl}furan-3-carboxylate (**14**). To a stirred soln. of **11** (1.7 g, 9.4 mmol) in dry benzene (25 ml) at r.t. was added aniline (1.2 ml, 13.3 mmol), and the resulting mixture was stirred for 5 min. The precipitate was filtered and washed with a mixture of hexane (30 ml) and CH_2Cl_2 (25 ml): **14** (2.45 g, 95%). White solid. M.p. 153–154°. IR (ATR): 3305, 3155, 2955, 1709, 1636, 1597, 1568, 1519, 1498, 1313, 1241, 1196, 1130, 1088. ^{1}H-NMR (400 MHz, $CDCl_3$): 7.24 (*d*, *J* = 2.0, =CH); 7.19–7.29 (*m*, 4 H, =CH); 7.00 (*tt*, *J* = 7.2, 1.4, =CH); 6.72 (br. *s*, NH); 6.58 (*d*, *J* = 2.0, =CH); 5.56 (br. *t*, *J* = 6.4, NH); 4.64 (*d*, *J* = 6.4, CH_2); 3.77 (*s*, MeO). ^{13}C-NMR (100.6 MHz, $CDCl_3$): 164.6; 158.8; 155.7; 141.6; 138.6; 129.1; 123.6; 120.7; 114.5; 110.6; 51.8; 36.7. Anal. calc. for $C_{14}H_{14}N_2O_4$ (274.27): C 61.31, H 5.14, N 10.21; found: C 61.18, H 5.25, N 10.26.

Methyl 2-(Aminomethyl)furan-3-carboxylate (**15**). A soln. of **11** (4.0 g, 22.1 mmol) in 8M HCl (20 ml) was stirred for 2 h at r.t. After the completion of the reaction, the mixture was washed with petroleum ether (80 ml), and the pH value of the aq. phase was adjusted to pH 10 by the addition of 10% NaOH soln. at 5°. The mixture was extracted with Et_2O (2 × 50 ml). The combined org. extract was washed with brine (50 ml), dried ($MgSO_4$), and concentrated: **15** (2.5 g, 73%). Yellow oil. IR (KBr): 3381, 3154, 2953, 1716, 1597, 1441, 1306, 1201, 1148, 1053. ^{1}H-NMR (400 MHz, $CDCl_3$): 7.22 (*d*, *J* = 2.0, =CH); 6.59 (*d*, *J* = 2.0, =CH); 4.03 (*s*, CH_2); 3.77 (*s*, MeO); 1.62 (br. *s*, NH_2). ^{13}C-NMR ($CDCl_3$, 100.6 MHz): 164.1; 162.7; 140.9; 113.1; 110.8; 51.5; 38.6. Anal. calc. for $C_7H_9NO_3$ (155.15): C 54.19, H 5.85, N 9.03; found: C 54.49, H 6.09, N 9.29.

2-{[(Methoxycarbonyl)amino]methyl}furan-3-carboxylic Acid (**16**). To a stirred soln. of **12** (0.94 g, 4.4 mmol) in dioxane (45 ml) and H_2O (20 ml) was added dropwise 1M aq. NaOH (8.83 ml, 8.83 mmol), and the resulting mixture was stirred at 30° for 2 h (TLC monitoring). After the completion of the reaction, the soln. was acidified to pH 2 with 1M HCl and then extracted with AcOEt (3 × 70 ml). The combined org. extract was washed with brine (80 ml), dried ($MgSO_4$), and concentrated, and the crude product purified by crystallization from CH_2Cl_2/AcOEt 1:1 (80 ml): **16** (0.85 g, 97%). White solid. M.p. 183–185°. IR (ATR): 3324, 3154, 2983, 1680, 1594, 1543, 1518, 1429, 1310, 1261, 1221, 1181, 1145, 1122, 1982, 1022. ^{1}H-NMR (400 MHz, (D_6)DMSO): 12.76 (br. *s*, COOH); 7.66 (*d*, *J* = 1.9, =CH); 7.63 (*t*, *J* = 5.8, NH); 6.65 (*d*, *J* = 1.9, =CH); 4.52 (*d*, *J* = 5.8, CH_2); 3.54 (*s*, MeO). ^{13}C-NMR ((D_6)DMSO, 100.6 MHz): 164.5; 157.7; 157.0; 142.4; 114.8; 111.1; 51.7; 36.8. Anal. calc. for $C_8H_9NO_5$ (199.16): C 48.25, H 4.55, N 7.03; found: C 48.03, H 4.44, N 7.05.

*2-{[(*tert*-Butoxycarbonyl)amino]methyl}furan-3-carboxylic Acid* (**17**). As described for **16**, with **13** (6.0 g, 23.5 mmol), at 30° for 1.5 h: **17** (5.47 g, 96%). White solid, which was crystallized from hexane/AcOEt 1:1. M.p. 142–144°. IR (ATR): 3379, 3152, 2988, 1680, 1600, 1519, 1464, 1436, 1367, 1321, 1280, 1251, 1160, 1125, 1086, 1029. ^{1}H-NMR (400 MHz, (D_6)DMSO): 12.72 (br. *s*, COOH); 7.65 (*d*, *J* = 1.8, =CH); 7.30 (*t*, *J* = 5.7, NH); 6.64 (*d*, *J* = 1.8, =CH); 4.46 (*d*, *J* = 5.7, CH_2); 1.38 (*s*, ^{t}Bu). ^{13}C-NMR

(100.6 MHz, (D_6)DMSO): 164.3; 157.8; 155.5; 142.0; 114.3; 110.8; 78.0; 36.3; 28.1. Anal. calc. for $C_{11}H_{15}NO_5$ (241.24): C 54.77, H 6.27, N 5.81; found: C 54.88, H 6.15, N 5.87.

2-{{[(Phenylamino)carbonyl]amino}methyl}furan-3-carboxylic Acid (**18**). As described for **16**, with **14** (1.1 g, 4.01 mmol), at 35° for 2.5 h: **18** (0.96 g, 92%). White solid, which was crystallized from acetone/AcOEt 1:1 (150 ml). M.p. 212–213°. IR (ATR): 3330, 3146, 2970, 1680, 1637, 1595, 1563, 1513, 1435, 1423, 1309, 1220, 1128, 1083, 1021. ^{1}H-NMR (400 MHz, (D_6)DMSO): 12.82 (br. *s*, COOH); 8.63 (br. *s*, NH); 7.66 (*d*, *J* = 1.9, =CH); 7.38 (br. *d*, *J* = 7.6, 2 =CH); 7.23 (br. *t*, *J* = 7.9, 2 =CH); 6.90 (br. *t*, *J* = 7.3, =CH); 6.68 (*d*, *J* = 1.9, =CH); 6.59 (*t*, *J* = 6.0, NH); 4.60 (*d*, *J* = 6.0, CH_2). ^{13}C-NMR ((D_6)DMSO, 100.6 MHz): 164.7; 158.8; 155.2; 142.3; 140.5; 128.9; 121.5; 118.0; 114.8; 111.2; 35.8. Anal. calc. for $C_{13}H_{12}N_2O_4$ (260.25): C 60.00, H 4.65, N 10.76; found: C 60.21, H 4.78, N 10.81.

*Methyl 4,6-Dihydro-4-oxo-5*H*-furo[2,3-c]pyrrole-5-carboxylate* (**22**). To a stirred soln. of **16** (0.2 g, 1.0 mmol) in dry THF (15 ml) was added $SOCl_2$ (0.15 ml, 2.0 mmol), followed by heating under reflux for 3 h (TLC monitoring). After the completion of the chlorination, the solvent and excess $SOCl_2$ were evaporated. The residue was dissolved in dry benzene (20 ml) and the soln. heated under reflux for 18 h. The solvent was evaporated and the crude product purified by CC (SiO_2; hexane/AcOEt 1:1): **22** (0.14 g, 78%). White solid. M.p. 173–175°. IR (ATR): 3135, 2973, 1764, 1691, 1607, 1437, 1393, 1325, 1255, 1194, 1130, 1074. ^{1}H-NMR (400 MHz, $CDCl_3$): 7.49 (*d*, *J* = 2.0, =CH); 6.61 (*d*, *J* = 2.0, =CH); 4.66 (*s*, CH_2); 3.86 (*s*, MeO). ^{13}C-NMR (100.6 MHz, $CDCl_3$): 167.5; 161.2; 152.5; 149.3; 120.7; 106.3; 53.7; 45.8. Anal. calc. for $C_8H_7NO_4$ (181.15): C 53.04, H 3.89, N 7.73; found: C 53.21, H 3.86, N 7.82.

tert-*Butyl 4,6-Dihydro-4-oxo-5*H*-furo[2,3-c]pyrrole-5-carboxylate* (**23**). To a stirred suspension of **17** (2.0 g, 8.29 mmol) in dry benzene (40 ml) was added $SOCl_2$ (1.3 ml, 17.11 mmol), and the resulting mixture was heated under reflux for 2 h. The solvent and excess $SOCl_2$ were evaporated. The residue was dissolved in dry benzene (50 ml) and heated under reflux for 48 h. After evaporation of the solvent, the crude product was separated and purified by CC (SiO_2, hexane/AcOEt 3:1): **23** (1.46 g, 79%). White solid. M.p. 82–83°. IR (KBr): 3127, 2980, 1770, 1703, 1616, 1495, 1459, 1369, 1323, 1257, 1152, 1067. ^{1}H-NMR (400 MHz, $CDCl_3$): 7.47 (*d*, *J* = 2.0, =CH); 6.59 (*d*, *J* = 2.0, =CH); 4.59 (*s*, CH_2); 1.50 (*s*, ^{t}Bu). ^{13}C-NMR (100.6 MHz, $CDCl_3$): 167.3; 161.7; 150.2; 149.0; 121.0; 106.2; 83.0; 45.7; 28.1. Anal. calc. for $C_{11}H_{13}NO_4$ (223.23): C 59.19, H 5.87, N 6.27; found: C 59.31, H 5.87, N 6.18.

*4,6-Dihydro-4-oxo-*N*-phenyl-5*H*-furo[2,3-c]pyrrole-5-carboxamide* (**24**). To a stirred soln. of **18** (0.45 g, 1.75 mmol) in dry THF (50 ml) was added $SOCl_2$ (0.25 ml, 3.46 mmol), followed by heating under reflux for 4 h. The workup of the mixture was done as described above. The crude product was purified by CC (SiO_2; AcOEt/hexane/CH_2Cl_2 1:1:1): **24** (0.37 g, 89%). White solid. M.p. 172–174°. IR (ATR): 3113, 2971, 1709, 1679, 1596, 1557, 1462, 1438, 1398, 1308, 1275, 1239, 1152, 1126, 1069. ^{1}H-NMR (400 MHz, $CDCl_3$): 10.4 (br. *s*, NH); 7.53 (*d*, *J* = 2.0, =CH); 7.49 (*m*, 2 =CH); 7.28 (*m*, 2 =CH); 7.05 (*tt*, *J* = 7.4, 1.1, 1 H); 6.63 (*d*, *J* = 2.0, =CH); 4.77 (*s*, CH_2). ^{13}C-NMR (100.6 MHz, $CDCl_3$): 168.2; 165.3; 150.5; 149.5; 137.5; 129.0; 124.1; 120.6; 120.1; 106.0; 45.0. Anal. calc. for $C_{13}H_{10}N_2O_3$ (242.23): C 64.46, H 4.16, N 11.56; found: C 64.23, H 4.16, N 11.63.

*5,6-Dihydro-4*H*-furo[2,3-c]pyrrol-4-one* (**3**). To a stirred soln. of Boc-protected **23** (0.30 g, 1.35 mmol) in CH_2Cl_2 (30 ml) at 0° was added dropwise CF_3COOH (1 ml, 13 mmol), and the resulting mixture was stirred for 1 h at r.t. (TLC monitoring). After the completion of the reaction, 2M aq. NaOH (6.5 ml) was added to remove excess acid. Then, the mixture was extracted with CH_2Cl_2 (2 × 50 ml), the combined org. extract dried ($MgSO_4$) and concentrated, and the crude product purified by CC (SiO_2; AcOEt): **3** (0.1 g, 66%). White solid. M.p. 141–143°. IR (ATR): 3185, 3093, 1726, 1677, 1462, 1443, 1296, 1262, 1173, 1117, 1059, 1037. ^{1}H-NMR (400 MHz, $CDCl_3$): 7.45 (*d*, *J* = 2.0, =CH); 6.58 (*d*, *J* = 2.0, =CH); 5.83 (br. *s*, NH); 4.29 (*s*, CH_2). ^{13}C-NMR (100.6 MHz, $CDCl_3$): 169.0; 167.7; 148.5; 121.1; 105.9; 42.4. Anal. calc. for $C_6H_5NO_2$ (123.11): C 58.54, H 4.09, N 11.38; found: C 58.46, H 4.09, N 11.28.

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Received December 15, 2009