ADDITION OF 2-TRIMETHYLSILYLOXYFURAN TO CATALYTICALLY GENERATED *N*-METHYLENEAMINE EQUIVALENTS: SYNTHESIS OF 5-AMINOMETHYL-2,5-DIHYDROFURAN-2-ONES [1]

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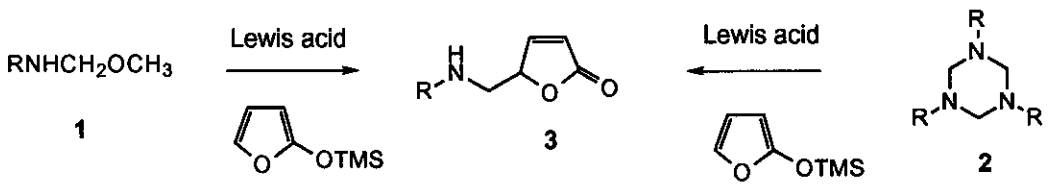
Abstract - Catalytically generated *N*-methyleneamine equivalents from *N*-methoxymethylanilines, 1,3,5-triphenyl- and 1,3,5-tribenzylhexahydro-1,3,5-triazines in the presence of Lewis acid reacted with 2-trimethylsilyloxyfuran to give 5-aminomethyl-2,5-dihydrofuran-2-ones in high yield.

The Mannich reaction as a method introducing nucleophiles at α-position of amines has been widely employed in synthetic chemistry.[2] However, the traditional methods have some drawbacks. The reaction prevents use of compounds with acid sensitive functionalities due to the harsh reaction conditions with iminium ions in acidic protic system. Aminomethylation can not be achieved through the classical method of Mannich reaction. Moreover, one of the simplest imine (monomeric formaldehyde imine) of *N*-methyleneamine for aminomethylation is limited from a synthetic viewpoint because it is difficult to generate the *N*-methyleneamine, which is only known in gas phase through flash vacuum thermolysis.[3] Methods for the preparation of *N*-methyleneamine *in situ* for synthetic purpose have been devised by treating *N*-methoxymethylamines[4] or *N*-cyanomethylamines[5] with alkyllithium for the synthesis of *N*-α-substituted methylamines and β-lactams. Other aminomethylation reactions with silyl enol ethers have also been reported to be achieved from *N*-alkoxymethylamines catalyzed by iodotrimethylsilane,[6] from

hexahydro-1,3,5-triazines catalyzed by trifluoromethanesulfonic acid,[7] and from trimethylsilylmethyl azide with $AlCl_3$.[8]

Recently we reported that *N*-methyleneamine equivalents could be generated from *N*-methoxymethylamines and (or) hexahydro-1,3,5-triazines in the presence of a Lewis acid. Aminomethylations with *N*-methyleneamine equivalents could be carried out with various nucleophiles that were not available under the traditional Mannich reactions. Heteroatom nucleophiles of phosphorus and azide gave aminomethylphosphonates[9] and aminomethyl azides.[10] Reactions with cyanotrimethylsilane yielded the synthetically valuable *N*-substituted aminoacetonitriles.[11] Addition of allyl nucleophiles lead to the synthesis of 1,2,3,4-tetrahydroquinolines and homoallylic amines.[1,12] In this paper we describe the reaction of *N*-methyleneamine equivalents with 2-trimethylsilyloxyfuran as a nucleophile[13] to yield *N*-substituted 5-aminomethyl-2,5-dihydrofuran-2-ones.

Scheme 1



N-Methoxymethylanilines (**1**) were reacted with 2-trimethylsilyloxyfuran in the presence of one molar equivalent of various Lewis acids to get aminomethylated product of 5-anilinomethyl-2,5-dihydrofuran-2-ones (**3**). At first we have tried with $TiCl_4$ as a Lewis acid because it showed the best results for the previous several aminomethylation reactions.[1,9-11] But it was not effective in this reaction. $SnCl_4$ was not good either. With the Lewis acid of $AlCl_3$ much better yield was obtained as 67%. Lewis acids of TMSOTf and $BF_3{\cdot}OEt_2$ were moderate to carry out the reaction in 57 and 48% yields respectively. A relatively weak Lewis acid of $Ti(OiPr)_4$ gave the best result of 86 % yield. Then we tried less and less amount of Lewis acid at room temperature to carry out the reaction catalytically without any sacrifice of the reaction yield. Five mol% of $Ti(OiPr)_4$ was good enough for the reaction to proceed catalytically at room temperature as shown in Scheme 2. At first *N*-methyleneamine equivalent as a coordinated complex of *N*-methoxymethylanilines with Lewis acid was generated and reacted with a nucleophile of 2-

trimethylsilyloxyfuran to yield the expected product of 5-anilinomethyl-2,5-dihydrofuran-2-one (**3**) along with methoxytrimethylsilane and free Lewis acid. This catalytic cycle was effectively repeated until all starting material was consumed for the reaction in high yield. Once the reaction condition was established *N*-methoxymethylanilines (**1b, 1c, 1d**) bearing diverse substituents on the benzene ring were reacted to give 5-anilinomethyl-2,5-dihydrofuran-2-ones (**3b, 3c, 3d**) in good yield (Table 1).

Scheme 2

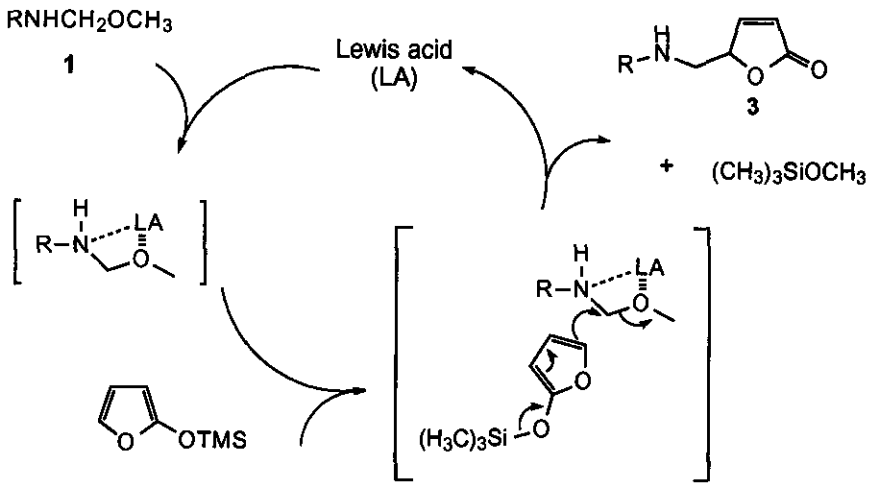
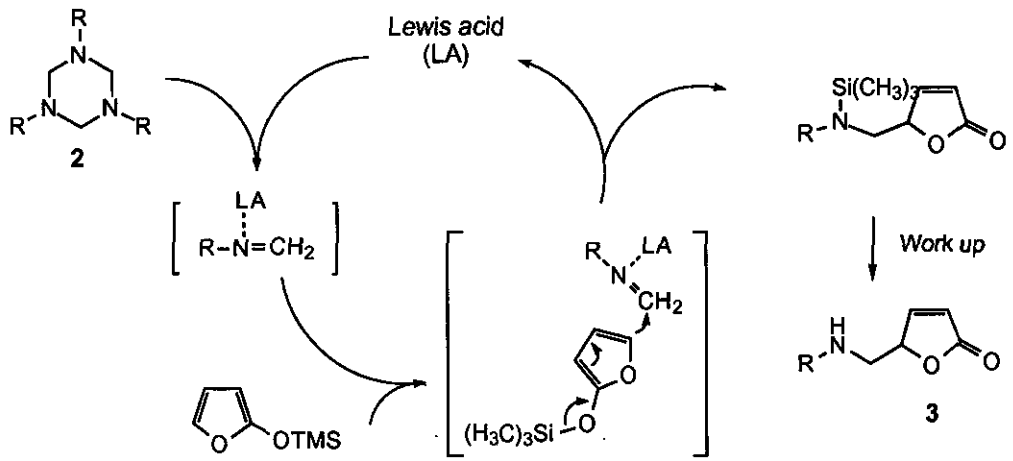


Table 1. Reactions of *N*-methoxymethylanilines (**1**) with 2-trimethylsilyloxyfuran in the presence of Lewis acid.

Substrate	R	Lewis Acid	mol %	Temp (°C)	Time (h)	Yield (%)
1a	Ph	$TiCl_4$	100	rt	0.2	27
1a	Ph	$SnCl_4$	100	rt	0.2	27
1a	Ph	$AlCl_3$	100	rt	0.3	67
1a	Ph	TMSOTf	100	rt	0.2	57
1a	Ph	$BF_3{\cdot}OEt_2$	100	rt	0.3	48
1a	Ph	$Ti(OiPr)_4$	100	rt	0.5	86
1a	Ph	$Ti(OiPr)_4$	10	rt	2	84
1a	Ph	$Ti(OiPr)_4$	5	rt	3	82
1b	2-Me-C_6H_4	$Ti(OiPr)_4$	5	rt	3	56
1c	2-MeO-C_6H_4	$Ti(OiPr)_4$	5	rt	3	73
1d	2,5-Cl_2-C_6H_3	$Ti(OiPr)_4$	5	rt	3	52

The aminomethylation reactions from 1,3,5-triphenylhexahydro-1,3,5-triazines (**2**) as another source for *N*-methyleneamine equivalents were succeeded to give the similar results as from *N*-methoxymethylanilines shown in Table 2. The reaction was carried out at room temperature with 5 mole% of $Ti(OiPr)_4$ catalyst. This reaction proceeded quite well with 1,3,5-triphenylhexahydro-1,3,5-triazines (**2b**, **2c**, **2d** and **2e**) with substituents of 2-Me, 2-OMe, 2,5-Cl_2 and 4-F on the benzene ring respectively. Slightly better yield was obtained with 10 mol% of the catalyst at -78°C. The catalytic mechanism as shown in Scheme 3 is a little different from the reaction with *N*-methoxymethylanilines. *N*-Methyleneamine equivalents induced by Lewis acid from hexahydro-1,3,5-triazines (**2**) were reacted with 2-trimethylsilyloxyfuran to give free Lewis acid and *N*-trimethylsilyl-5-anilinomethyl-2,5-dihydrofuran-2-ones that were hydrolized to the product of 5-anilinomethyl-2,5-dihydrofuran-2-ones (**3**). This reaction is different from that of *N*-methoxymethylanilines. An ineffective Lewis acid catalyst TMSOTf to *N*-methoxymethylanilines was quite good, sometimes even better than $Ti(OiPr)_4$ with the substrate of 1,3,5-triphenylhexahydro-1,3,5-triazines.

Scheme 3



The same reaction was applied to 1,3,5-tribenzylhexahydro-1,3,5-triazines (**2f**). It has an advantage getting synthetically valuable 5-aminomethyl-2,5-dihydrofuran-2-ones[14] by catalytic hydrogenation of the aminomethylated product of 5-benzylaminomethyl-2,5-dihydrofuran-2-ones. However the reaction with tribenzylhexahydro-1,3,5-triazines was different from the previous one. It is quite sensitive to the reaction

temperature and the catalyst $Ti(OiPr)_4$ was not effective anymore. After several trials by changing various catalysts under different reaction temperature we have obtained 5-benzylaminomethyl-2,5-dihydrofuran-2-one (**3f**) with 10 mole% of $SnCl_4$ at -78°C in 54% yield as shown in Table 2. Catalytic hydrogenation in MeOH and conc-HCl with Pd·C catalyst under atmospheric H_2 gas at room temperature gave the expected product of 5-aminomethyltetrahydrofuran-2-one hydrochloride (**4**) in 85% yield.

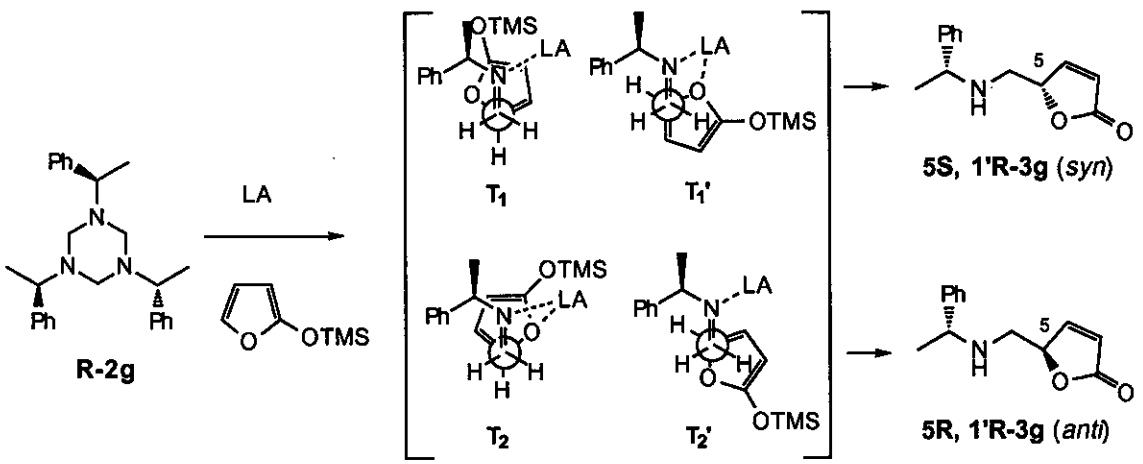
Table 2. Reactions of 1,3,5-trisubstituted hexahydro-1,3,5-triazine (**2**) with 2-trimethylsilyloxyfuran in the presence of Lewis acid.

Substrate	R	Lewis Acid	mol %	Temp (°C)	Time (h)	Yield (%)	*syn:anti*
2a	Ph	$Ti(OiPr)_4$	5	rt	3	73	
2a	Ph	$Ti(OiPr)_4$	10	-78	3	80	
2a	Ph	TMSOTf	5	rt	3	79	
2b	2-Me-C_6H_4	$Ti(OiPr)_4$	5	rt	2	71	
2c	2-MeO-C_6H_4	$Ti(OiPr)_4$	5	rt	2	63	
2d	2,5-Cl_2-C_6H_3	$Ti(OiPr)_4$	5	rt	2	41	
2d	2,5-Cl_2-C_6H_3	TMSOTf	5	rt	2	46	
2e	4-F-C_6H_4	$Ti(OiPr)_4$	5	rt	2	52	
2e	4-F-C_6H_4	TMSOTf	5	rt	2	77	
2f	$PhCH_2$	$Ti(OiPr)_4$	10	-78	3	n.r.	
2f	$PhCH_2$	$TiCl_2(OiPr)_2$	10	-78	3	17	
2f	$PhCH_2$	$TiCl_4$	10	-78	2	42	
2f	$PhCH_2$	$SnCl_4$	10	-78	2	54	
2f	$PhCH_2$	$AlCl_3$	10	-78	1.5	27	
2f	$PhCH_2$	TMSOTf	10	-78	2	28	
R-**2g**	(R)-PhMeCH	$SnCl_4$	10	-78	1.5	81	76:24
R-**2g**	(R)-PhMeCH	$SnCl_4$	5	-78	3	64	-
R-**2g**	(R)-PhMeCH	$SnCl_4$	10	0	0.5	69	56:44
R-**2g**	(R)-PhMeCH	$TiCl_4$	10	-78	1.5	65	69:31
R-**2g**	(R)-PhMeCH	TMSOTf	10	-78	1.5	38	65:35
R-**2g**	(R)-PhMeCH	$BF_3{\cdot}OEt_2$	10	-78	1.5	44	71:29
S-**2g**	(S)-PhMeCH	$SnCl_4$	10	-78	1.5	80	78:22

The same reactions of 1,3,5-tris-(*R*)- (*R*-**2g**) or 1,3,5-tris-(*S*)-1-phenylethylhexahydro-1,3,5-triazine (*S*-**2g**) yielded a diastereomeric mixture of 5-(1-phenylethylaminomethyl)-2,5-dihydrofuran-2-ones (**3g**) in good yield with catalytic amount of $SnCl_4$ at -78°C. The reaction product from 1,3,5-tris-

(*R*)-1-phenylethylhexahydro-1,3,5-triazine with 2-trimethylsilyloxyfuran in the presence of $SnCl_4$ catalyst was hydrogenated in methanol and conc-HCl with Pd·C catalyst under atmospheric H_2 gas at room temperature to yield 5-aminomethyltetrahydrofuran-2-one hydrochloride (**4**) with $[\alpha]_D^{20}$ of + 42.9° at c = 0.4 in MeOH that correspond to 53% ee. The absolute stereochemistry of the newly formed bond in major diastereomer was identified as 5*S*.[14(c)] Though the diastereomeric mixture was not separable by column chromatography hplc on reverse phase column was successful to separate with the eluent of $MeOH/H_2O/Et_3N$ (100:8:1). The diastereomeric ratio was dependent on the reaction temperature and the best result could be obtained at -78°C as *syn*:*anti* of 76:24. The opposite stereochemical outcome of 5*R* in a major isomer was obtained from the reaction of 1,3,5-tris-(*S*)-1-phenylethylhexahydro-1,3,5-triazines.

Scheme 4



The stereochemical outcome of the reaction can be speculated from the transition structure. Four possible transition structure models (T_1, T_1', T_2 and T_2') can be postulated for the reaction with 1,3,5-tris-(*R*)-1-phenylethylhexahydro-1,3,5-triazine based on minimization of steric hindrance for 2-trimethylsilyloxyfuran to approach to *N*-methyleneamine equivalent (Scheme 4). Lewis acids on T_1 and T_2' as non-chelated models are coordinated with only nitrogen of *N*-methyleneamine equivalent to leave oxygen of furan ring free while both atoms of nitrogen and oxygen are coordinated with Lewis acid in T_1' and T_2. Models of T_1 and T_2 have orbital interaction as "*Diels-Alder like*" while T_1' and T_2' are "*non-*

Diels-Alder like".[13] Getting the stereochemical outcome of 5*S* as a major from the reaction of *R*-**2g** with 2-trimethylsilyloxyfuran the aminomethylation occurred from the *re*-face of furan ring with transition states of either T_1 or T_1'. The difference in two possibilities is whether the Lewis acid is coordinated with only nitrogen or with both atoms of nitrogen and oxygen. If the coordination complex at the transition state model like T_1' is involved during the reaction, changing the coordination pattern by non-metallic Lewis acid of TMSOTf and $BF_3 \cdot OEt_2$ instead of metallic Lewis acids of $SnCl_4$ and $TiCl_4$ could induce any difference in the stereochemical outcome or diastereomeric ratio. However, as shown in Table 2, no significant difference was observed.[13,15] This implies that a possible transition state model to lead the major product was speculated as a non-chelated and "*Diels-Alder like*" arrangement of T_1. The transition state structure of "*Diels-Alder like*" arrangement was observed in common to most reactions of imines and iminium ions with 2-trimethylsilyloxyfuran.[16]

In conclusion 5-aminomethyl-2,5-dihydrofuran-2-one was obtained by the aminomethylation reactions of catalytically generated *N*-methyleneamine equivalents from *N*-methoxymethylamines or hexahydro-1,3,5-triazines with 2-trimethylsilyloxyfuran.

EXPERIMENTAL

^{1}H Nmr and ^{13}C-Nmr spectra were recorded on a Gemini 200 (200 MHz for ^{1}H and 50.3 MHz for ^{13}C). Chemical shifts were given in ppm using TMS as internal standard. Mass spectra were obtained using a Hewlett Packard Model 5985B spectrometer or a Kratos Concept 1-S double focusing mass spectrometer. Elemental analysis was taken on a Perkin-Elmer 240 DS elemental analyzer. Optical rotation was measured with Rudolph Research Autopole 3 polarimeter. Melting point was measured by Mel-II capillary melting point apparatus. The silica gel used for column chromatography was Merck 200-230 mesh. Thin layer chromatography was carried out with Merck 60F-254 plates with 0.25 mm thickness. *N*-Methoxymethylanilines were prepared by the reported method.[9a] 2-Trimethylsilyloxyfuran purchased from Aldrich was distilled prior to use. All the other chemicals were reagent grade and used without further purification. 1,3,5-Trisubstituted hexahydro-1,3,5-triazines were obtained by the conventional method with amine and formaldehyde. Some of the *N*-methoxymethylanilines and 1,3,5-triphenylhexahydro-1,3,5-triazines were inter-convertible.[11]

General Procedure for the Synthesis of *N*-Substituted 5-Aminomethyl-2,5-dihydrofuran-2-one: To a stirred solution of *N*-methoxymethylaniline (**1**) (6.0 mmol) or 1,3,5-trisubstituted hexahydro-1,3,5-triazine (**2**) (2.0 mmol) in CH_2Cl_2 (25 ml) under nitrogen atmosphere was slowly added the Lewis acid at the specified temperature in the Table. After being stirred for 10 min 2-trimethylsilyloxyfuran (0.95 g, 6.1 mmol) was added to it. The resulting solution was stirred at the

specified temperature until all starting material was consumed on tlc. The reaction mixture was poured into ice-water. The resulting solution was neutralized with cold sat. $NaHCO_3$ solution. The reaction product was extracted with CH_2Cl_2. Organic layer was washed successively with water and brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude reaction product was purified by flash chromatography to give the *N*-substituted 5-aminomethyl-2,5-dihydrofuran-2-one.

5-Anilinomethyl-2,5-dihydrofuran-2-one (3a): oil; δ_H (200 MHz; $CDCl_3$) 3.23 (1 H, dd, J = 14.2 and 6.4 Hz, CH_AN), 3.43 (1 H, dd, J = 14.2 and 2.6 Hz, CH_BN), 3.98 (1 H, brs, NH), 5.07 (1 H, brs, HCO), 5.97 (1 H, d, J = 5.8 Hz, =CHC=O), 6.49 (2 H, d, J = 7.1 Hz, ArH), 6.62 (1 H, t, J = 7.0 Hz, ArH), 7.08 (2 H, t, J = 7.2 Hz, ArH) and 7.35 (1 H, d, J = 5.8 Hz, OC=CH); δ_C (50.3 MHz, $CDCl_3$) 45.4, 82.0, 112.8, 117.9, 121.9, 129.2, 146.9, 154.6 and 172.8; m/z 189 (M^+, 9%), 107 (12), 106 (100), 93 (14), 79 (11) and 77 (25). Anal. Calcd for $C_{11}H_{11}NO_2$: C, 69.8; H, 5.86; N, 7.40. Found: C, 70.1; H, 5.88; N, 7.31.

5-(2-Methylanilinomethyl)-2,5-dihydrofuran-2-one (3b): oil; δ_H (200 MHz; $CDCl_3$) 2.00 (3 H, s), 3.28 (1 H, dd, J = 14.0 and 6.6 Hz), 3.51 (1 H, dd, J = 14.0 and 4.5 Hz), 3.69 (1 H, t, J = 4.8 Hz), 5.11 (1 H, brs), 6.00 (1 H, d, J = 5.6 Hz), 6.48 (1 H, d, J = 8.0 Hz), 6.58 (1 H, t, J = 7.4 Hz), 6.97 (2 H, t, J = 8.2 Hz), and 7.36 (1 H, d, J = 5.8 Hz, O-C=CH); δ_C (50.3 MHz, $CDCl_3$) 16.8, 45.3, 81.8, 109.4, 117.5, 121.7, 122.2, 126.7, 130.1, 144.6, 154.3 and 172.5; m/z 203 (M^+, 11%), 121 (12), 120 (100), 106 (10), 91 (25) and 65 (10) [HREIMS. Found: 203.0952. $C_{12}H_{13}NO_2(M^+)$ requires: 203.0946].

5-(2-Methoxyanilinomethyl)-2,5-dihydrofuran-2-one (3c): oil; δ_H (200 MHz; $CDCl_3$) 3.33 (1 H, dd, J = 14.1 and 6.3 Hz), 3.51 (1 H, dd, J = 14.1 and 4.5 Hz), 3.72 (3 H, s), 4.24 (1 H, brs), 5.14 (1 H, dd, J = 6.3, 4.5 Hz), 6.03 (1 H, d, J = 5.8 Hz), 6.49 - 7.18 (4 H, m) and 7.39 (1 H, d, J = 5.8 Hz); δ_C (50.3 MHz, $CDCl_3$) 45.6, 55.2, 82.1, 109.6, 109.9, 117.5, 121.0, 122.2, 136.8, 147.0, 154.4 and 172.8; m/z 219 (M^+, 15%), 136 (100), 121 (43), 120 (33), 108 (12) [HREIMS. Found: 219.0911. $C_{12}H_{13}NO_3(M^+)$ requires: 219.0895].

5-(2,5-Dichloroanilinomethyl)-2,5-dihydrofuran-2-one (3d): oil; δ_H (200 MHz; $CDCl_3$) 3.47 (1 H, dd, J = 14.1 and 6.2 Hz), 3.59 (1 H, dd, J = 14.1 and 3.6 Hz), 4.52 (1 H, brs), 5.19 (1 H, brs), 6.12 (1 H, d, J = 7.6 Hz), 6.57 (2 H, s), 7.09 (1 H, d, J = 7.6 Hz) and 7.45 (1 H, d, J = 5.4 Hz); δ_C (50.3 MHz, $CDCl_3$) 45.2, 81.6, 111.0, 117.8, 118.0, 122.9, 130.1, 133.5, 143.8, 153.7 and 172.4; m/z 259 (5), 257 (M^+, 7%), 178 (12), 176 (68), 174 (100), 161 (12), 111 (14)[HREIMS. Found: 257.0014. $C_{11}H_9NO_2Cl_2(M^+)$ requires: 257.0010].

5-(4-Fluoroanilinomethyl)-2,5-dihydrofuran-2-one (3e): oil; δ_H (200 MHz; $CDCl_3$) 3.24 (1 H, dd, J = 13.6 and 6.3 Hz), 3.51 (1 H, dd, J = 13.6 and 3.1 Hz), 3.76 (1 H, brs), 5.16 (1 H, t, J = 4.2 Hz), 6.08 (1 H, d, J = 5.6 Hz), 6.48 - 6.52 (2 H, m), 6.81 (2 H, dd J = 8.4 and 5.4 Hz) and 7.42 (1 H, d, J = 5.6 Hz); δ_C (50.3 MHz, $CDCl_3$) 46.6, 82.1, 114.1, 114.2, 115.6, 116.1, 122.6, 143.3, 153.9, 154.3, 158.6 and 172.8; m/z 207 (M^+, 8%), 125 (9), 124 (100), 111 (13), 96 (12) [HREIMS. Found: 207.0701. $C_{11}H_{10}NO_2F(M^+)$ requires: 207.0695].

5-Benzylaminomethyl-2,5-dihydrofuran-2-one (3f): oil; δ_H (200 MHz; $CDCl_3$) 1.78 (1 H, bs), 2.81 (1 H, dd, J = 14.4 and 6.6 Hz), 2.99 (1 H, dd, J = 14.4 and 4.8 Hz), 3.47 (2 H, s), 5.04 (1 H,

dd, J = 6.6 and 4.8 Hz), 6.04 (1 H, d, J = 6.4 Hz), 7.23 (5 H, brs), and 7.31 (1 H, d, J = 5.6 Hz); δ_C (50.3 MHz, $CDCl_3$) 55.8, 59.3, 81.7, 121.0, 126.5, 127.4, 127.7, 137.0, 154.1 and 171.7 [HREIms. Found: 203.0952. $C_{12}H_{13}NO_2(M^+)$ requires: 203.0946].

5-(1-Phenylethylaminomethyl)-2,5-dihydrofuran-2-one (3g): Though it has been separable on hplc with analytical column we could not obtain sufficient to get a set of spectra corresponding to each diastereomers. The spectral data of diastereomeric mixture is as follows. δ_H (200 MHz; $CDCl_3$) 1.31 (3 H, d, J = 6.8 Hz, CH_3CN), 1.96 (1 H, brs, NH), 2.76 - 2.87 (2 H, m, CH_2N), 3.98 (1 H, q, J = 6.7 Hz, CHN), 4.91 - 5.05 (1 H, m, HCO), 5.59 - 6. 10 (1 H, m, =CHC=O), 7.21 - 7.27 (5 H, m, ArH) and 7.35 (1 H, d, J = 5.6 Hz, O-C=CH. Anal. Calcd for $C_{13}H_{15}NO_2$: C, 71.9; H, 6.96; N, 6.45. Found: C, 71.7; H, 6.84; N, 6.51.

5-Aminomethyltetrahydrofuran-2-one hydrochloride (4): The foregoing 5-benzylaminomethyl-2,5-dihydrofuran-2-one (**3f**, 365 mg, 1.8 mmol) or 5-phenylethylaminomethyl-2,5-dihydrofuran-2-one (**3g**, 391 mg, 1.8 mmol) in 10 ml of MeOH and 2 ml of conc-HCl was stirred with 30% Pd·C catalyst (130 mg) under atmospheric H_2 gas at room temperature. After 2 h the reaction mixture was filtered through Celite to remove catalyst and concentrated under reduced pressure. The crude product was purified by recrystallization with acetone/MeOH to give crystalline solid product in 85% yield. mp 165-166 °C (lit.,[14(c)] 169-170°C).

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REFERENCES AND NOTES

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