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Some interesting ^{1}H NMR features of *ortho* substituted N-methoxy-N-methyl benzamides

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During synthetic efforts towards positional isomers of FTY720, using building blocks based on Weinreb amide (WA) functionality, interesting ^{1}H NMR pattern for *ortho*-methyl-*N*-methoxy-*N*-methyl benzamide have been encountered. The ^{1}H NMR spectrum has shown broad humps for *N*-methoxy and *N*-methyl units in WA functionality, whereas the spectrum for the corresponding *meta*-and *para*-isomer, displays two sharp singlets for the same units. This interesting spectral difference has been rationalized. Several *ortho*-substituted *N*-methoxy-*N*-methyl benzamides have been tailor-made and generality has been established. The broadening of the peaks is due to the presence of rotamers and variable temperature NMR study has unraveled that the energy barrier of two rotamers of *ortho*-substituted benzamides is more at room temperature, unlike *para* and *meta* substituted benzamides.

Keywords: Weinreb amide, nuclear magnetic resonance, benzamide, variable temperature, rotamers

Synthesis of FTY720 **1a**, drug approved for the treatment of multiple-sclerosis, has been achieved through the Weinreb amide based building blocks **2x, 2y** (Ref 1). During our ongoing efforts to arrive at the other two positional isomers, **1b** and **1c** of FTY720, through similar concept and corresponding building blocks **3** and **4**, respectively (**Figure 1**), we noted broad humps in ^{1}H NMR spectrum, for *N*-methoxy and *N*-methyl residue of WA functionality in the *ortho*-isomer benzamide **5a**, whereas the corresponding *meta*-and *para*-isomer, **5b** and **5c** respectively displayed two sharp singlets. The rationale to this interesting feature and the generality of the observation is presented herein.

Results and Discussion

The ^{1}H NMR spectrum of *N*,*N*-dimethylformamide is routine text book example[2], illustrating the barrier to the rotation along C-N bond at room temperature, consequential two signals (δ 2.79 and 2.94) for *N*-methyl unit and coalescence of these signals into a broad signal at 65°C. The observation of two signals at room temperature and one signal at 151-152ºC, represents the two extreme cases of slow and rapid exchange respectively of the methyl's between magnetic environment (A and B). In this case the rate constant k_f and k_b are equal, since the two rotamers **X** and **Y** are equal in energy. Similarly, if one applies the same rationale for WA case, there should be two signals for $-OCH_3$ and two signals for $-NCH_3$, as $-OCH_3$ has two different magnetic environments (rotamer **I** and **II**) and similar is the case for $-NCH_3$ case. This would be the case, when the rotation across C-N is slow compared to NMR time-scale. The two peaks, say for $-OCH_3$ (or similarly for $-NCH_3$) need not be of same intensity as these rotamers **I** and **II**, are not of equal energy (hence $k_f \neq k_b$). The intensities would depend upon the relative proportions of **I** and **II** in equilibrium mixture (**Figure 2**). When the rotation across C-N is rapid, the anticipated two signals, say for $-OCH_3$ at ν_A and ν_B (and similarly for $-NCH_3$) would coalesce and the coalesced signal will not be at the mid-point, but at $\nu = \chi_I\nu_A + \chi_{II}\nu_B$, χ_I = mole fractions of rotamer **I** and χ_{II} = mole fractions of rotamer **II**.

The fact that we have been seeing one sharp signal for $-OCH_3$ (around δ 3.55) and similarly another one signal for $-NCH_3$ (around δ 3.35) in WA of *m*-toluic acid **5b** and *p*-toluic acid **5c** (Ref 3), it implies that they are coalesced signals, due to *rapid* rotation (**Figure 3**). However, in the case of WA of *o*-toluic acid, the steric hindrance probably had slowed down the rotation (due to increased barrier) and hence clear sharp signals are not seen due to the presence of several rotamers in equilibrium (**Figure 4**).

To validate these arguments in support of the observed differences in the nature of $-OCH_3$ and $-NCH_3$

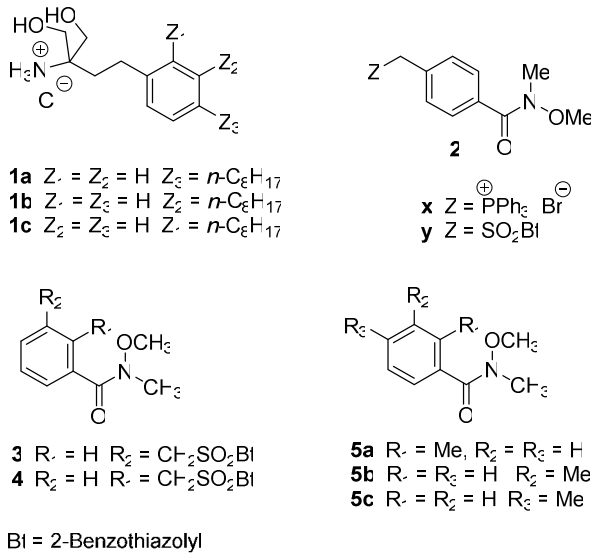


Figure 1

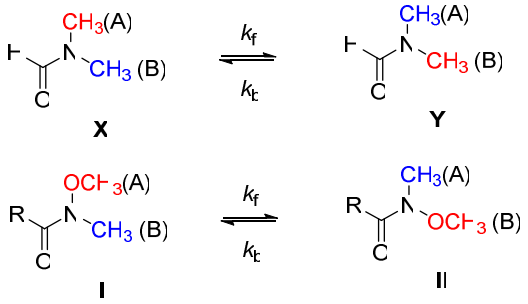


Figure 2

signals for WA of *o*-toluic acid **5a**, *m*-toluic acid **5b** and *p*-toluic acid **5c**, we relied upon variable temperature NMR experiments, since it is well established that variable temperature NMR provides good insight into these dynamic equilibriums[4]. We expect sharpening of the signals on heating. Gratifyingly, to our delight sharpening of signals did occur at high temperature, as it provided sufficient energy for establishing a *rapid* equilibrium among the various rotamers. The ^{1}H NMR spectrum of **5a** in two solvents, $CDCl_3$ and DMSO-d_6 (**Figure 5**) at 25°C ($CDCl_3$), showed two humps in the range δ 3.18-3.42 for-NMe and-OMe protons, but by increasing the temperature to 40°C ($CDCl_3$) these two humps transformed into a singlet peak at δ 3.16 and a broad singlet at δ 3.39 respectively. When the temperature was further increased to 50°C ($CDCl_3$) and 75ºC (DMSO-d_6) two sharp singlets were observed for NMe and OMe protons.

The effect of heating was also seen in the ^{13}C NMR spectra of compound **5a**. At room temperature, although there is a sharp signal at δ 60.8 corresponding to OMe, the signal for N-Me carbon is a mere small hump (almost invisible) around δ 32.5. This becomes prominent with the rise in temperature, and at 75°C in DMSO-d_6, the spectrum shows a sharp peak at δ 32.9 for NMe (**Figure 6**).

To further substantiate these observations and findings, a few other *ortho*-substituted WA-benzamides **6-13** were tailor made and subjected to similar NMR studies (**Table I**). It was observed that the compounds **6-13** also showed only broad humps for the *N*-OMe and *N*-Me units in their respective ^{1}H NMR spectra at room temperature, while at higher temperatures, (40°C→75°C), two sharp signals were seen in all cases.

The ^{1}H NMR spectrum of 2-iodo *N*-methoxy-*N*-methyl benzamide **12** in fact showed four signals (two singlets and two humps) in δ 3.00-3.81 range for the protons in-OMe and-NMe protons, at room temperature, implying slow rotation across C-N and presence of rotamers. By increasing the temperature to 40°C ($CDCl_3$) these peaks transformed into two broad humps between δ 3.14-3.64. When the temperature was further increased to 50°C ($CDCl_3$) and 75°C (DMSO-d_6) two sharp singlets were observed for NMe and OMe protons. A similar pattern was observed with 2-chloro-*N*-methoxy-*N*-methyl benzamide **13**.

Experimental Section

Infrared spectra are reported in cm^{-1}. High resolution NMR experiments were recorded using tetramethylsilane (TMS) as the internal standard on 400 MHz and 500 MHz spectrometer. High-resolution mass spectra (HRMS) were recorded by electrospray ionization (ESI) method on a Q-Tof Micro with lock spray source. Melting points are uncorrected. Dry tetrahydrofuran (THF) was obtained by refluxing the solvent with sodium and benzophenone for several hours. Dimethylformamide (DMF) and dichloromethane (DCM) were dried over CaH_2 followed by distillation and stored under N_2 using 4 Å molecular sieves in air tight bottles. For the reaction purposes and column chromatography distilled solvents were used. The solvent system used throughout unless otherwise specified, was ethyl acetate-hexanes with various percentage of polarity depending on the nature of the substrate.

2-Methyl-*N*-methoxy-*N*-methylbenzamide, **5a**: R_f: 0.43 in 2:3 EtOAc/Hexane, liquid. IR: 3021, 2401, 1646, 1450.2, 1379, 1223, 992, 753 cm^{-1}; ^{1}H NMR

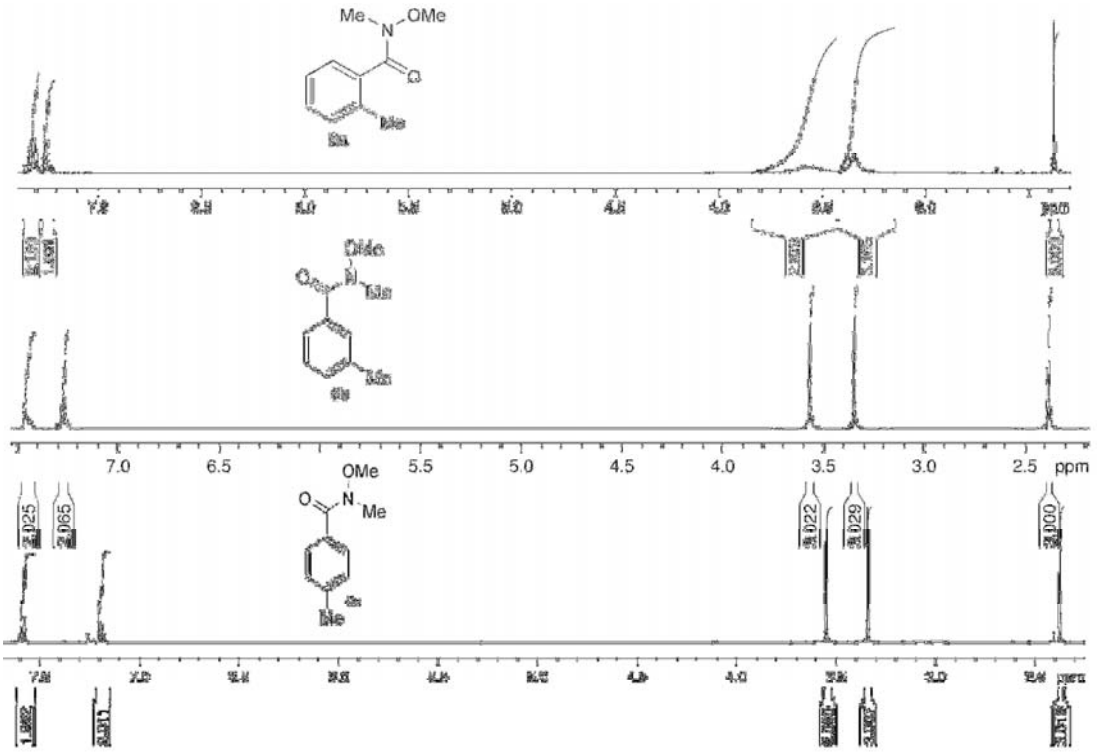


Figure 3 — ^{1}H NMR of compounds **5a**, **5b** and **5c** in $CDCl_3$

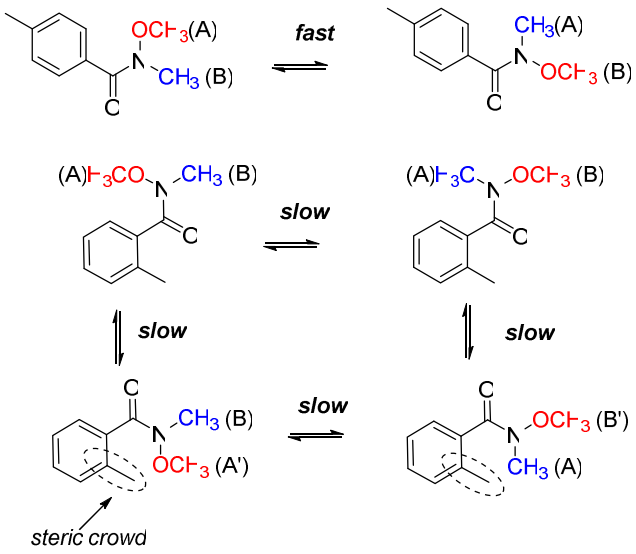


Figure 4

(400 MHz, $CDCl_3$/TMS, at 25°C): δ 2.23 (s, 3H, CH_3), 3.42-318 (Two broad humps, 6H, NCH_3, OCH_3), 7.10-7.06 (m, 2H, ArH), 7.19-7.14 (m, 2H, ArH); ^{13}C NMR ($CDCl_3$/TMS, 100 MHz): δ 18.8, 32.5, 60.8, 125.2, 125.9, 129.0, 129.9, 134.5, 140.1, 169.6; ^{1}H NMR (400 MHz, DMSO-d_6, at 75°C): δ 3.19 (s, 3H, NMe), 3.47 (s, 3H, OMe); ^{13}C NMR: δ 32.6 (NMe), 60.1 (OMe); HRMS (ESI): *m/z* Calcd for $C_{10}H_{14}NO_4[M+H]^+$ 179.0992. Found 179.0988.

2-(Methoxy(methyl)carbamoyl)phenyl pivalate, **6**: To a solution of salicylic acid (1.00 g, 8.20 mmol) in dry DCM, pivaloyl chloride (2.52 mL, 20.49 mmol) and Et_3N (3.41 mL, 24.58 mmol) were added at 0°C under N_2 atmosphere. It was stirred at RT for 4 hr.

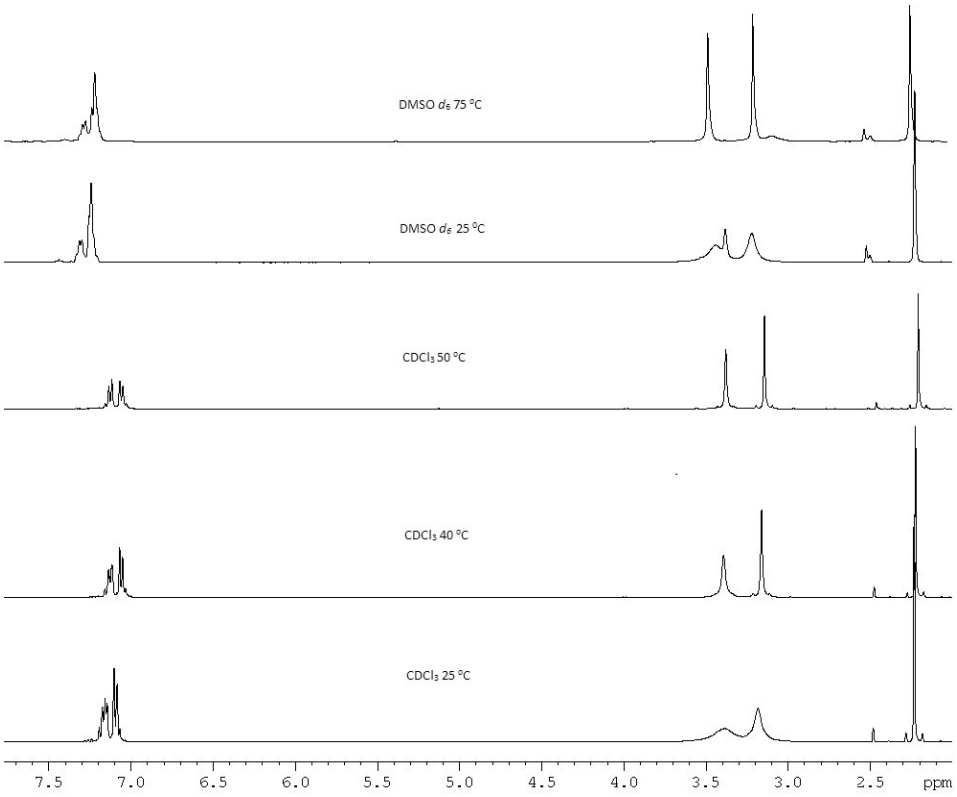


Figure 5 — Variable temperature ^{1}H NMR spectra of compound **5a**

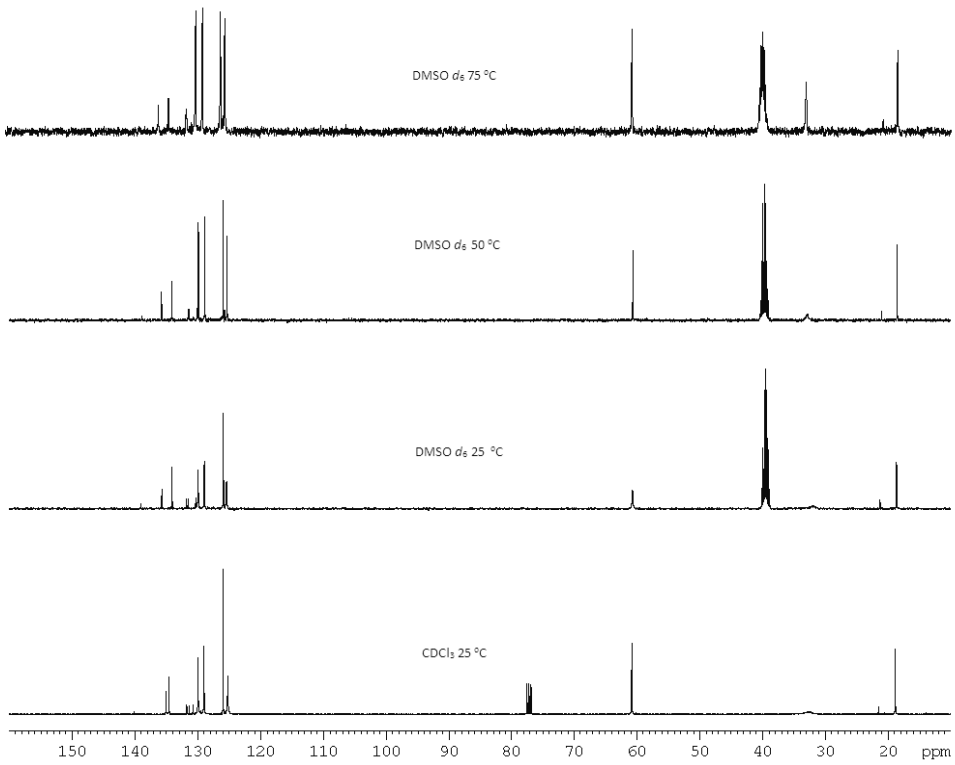
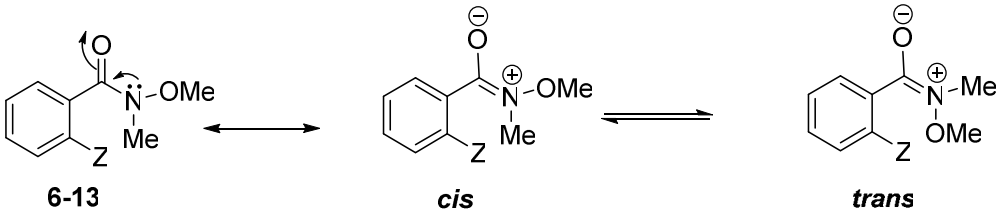
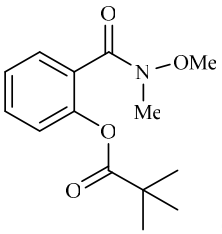
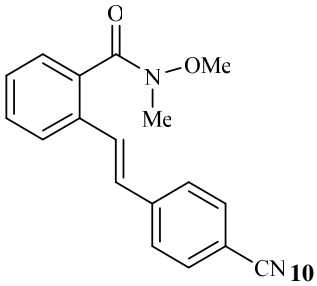
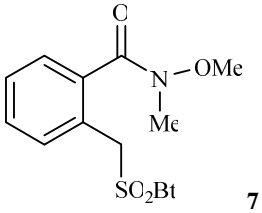
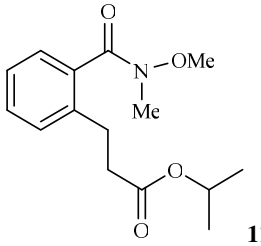
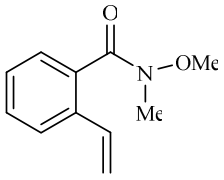
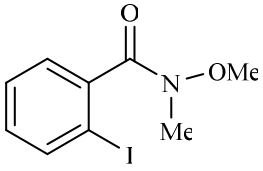
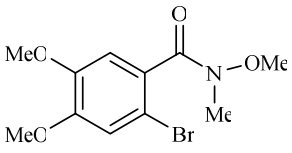
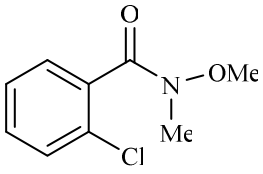


Figure 6 — Variable temperature ^{13}C NMR spectra of compound **5a**

Table I — *Ortho*-substituted benzamides



Compd	Structure	Compd	Structure
6		**10**	
7		**11**	
8		**12**	
9		**13**	

N,O-Dimethyl hydroxylamine hydrochloride (0.958 g, 9.83 mmol) and Et_3N (1.14 mL,8.20 mmol) were added to it at 0°C. It was allowed to attain RT gradually and stirred for 3 hr. The reaction mass was extracted with DCM and washed successively with water (2 × 20mL), and aq. $NaHCO_3$ (4 × 20 mL) solutions. The DCM layer was dried over anhyd.Na_2SO_4 and evaporated under vacuum to give **6** (1.786g, 82%) as greenish liquid after silica gel column chromatography. R_f: 0.35 in 1:4 EtOAc/Hexane; Greenish liquid. IR: 3014, 2976, 1749, 1641, 1515, 1480, 1448, 1382 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$/TMS, at 25°C): δ 1.12 (s, 9H, $C(CH_3)_3$), 3.32-3.14 (Two broad humps, 6H, OCH_3, NCH_3), 7.0 (d, 1H, J = 7.2 Hz, ArH), 7.10 (t, 2H, J = 7.2 Hz, ArH), 7.28 (d, 1H, J = 6.4 Hz, ArH); ^{13}C NMR (100 MHz, $CDCl_3$/TMS): δ 27.0, 32.1(bs), 38.8, 60.9, 125.7, 125.3, 128.0, 130.4, 147.4, 175.9; ^{1}H NMR (400 MHz, DMSO-d_6, at 75°C): δ 3.18 (s, 3H, NMe), 3.47 (s, 3H, OMe); ^{13}C NMR: δ 32.6 (NMe), 60.7 (OMe); HRMS (ESI): *m/z* Calcd for $C_{14}H_{20}NO_4[M+H]^+$ 66.1392. Found 266.1388.

Benzo[*d*]thiazol-2-ylsulfonyl)methyl)-*N*-methoxy-*N*-methyl benzamide[5], **7**: White solid. m.p. 117-119°C, IR ($CHCl_3$): 1014, 1330, 1466, 1644, 2998, 3291 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, at 25°C): δ 3.15-4.00 (Two broad humps, 6H, NCH_3, OCH_3), 5.04 (s, 2H, SCH_2), 7.13-7.29 (m, 3H, ArH), 7.43 (t, 1H, *J* = 7.2 Hz, ArH), 7.31-7.57 (m, 3H, ArH), 7.81 (d, 1H, *J* = 8.0 Hz, ArH), 8.10 (d, 1H, *J* = 8.0 Hz, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 32.7, 57.2, 122.1, 124.6, 127.5, 127.9, 128.5, 129.9, 132.9, 136.7, 152.4, 165.1, 168.2; ^1H NMR (400 MHz, DMSO-d_6, at 75°C): δ 3.24 (s, 3H, NMe) and 3.59 (s, 3H, OMe); ^{13}C NMR: δ 33.6 (NMe), 60.6 (OMe); HRMS (ESI): *m*/*z* Calcd for $C_{17}H_{17}N_2O_4S_2[M+H]^+$ 377.0630. Found 377.0640.

***N*-Methoxy-*N*-methyl-2-vinylbenzamide**[5], **8**: Colourless liquid. IR ($CHCl_3$): 1076, 1446, 1645, 2938 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, at 25°C): δ 3.00-3.60 (Two broad humps, 6H, NCH_3,OCH_3), 5.26 (d, 1H, *J* = 11.2 Hz, ArCHCH_2), 5.68 (d, 1H, *J* = 17.2 Hz, ArCHCH_2), 6.71 (dd, 1H, *J* = 11.2 Hz, *J* = 17.6 Hz), 7.32-7.19 (m, 3H), 7.52 (d, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 32.1, 60.8, 111.7, 116.3, 122.0, 123.7, 125.0, 126.4, 129.2, 133.4, 134.4, 135.7, 172.1; ^1H NMR (400 MHz, $CDCl_3$, at 50°C): δ 3.32 (s, 3H, NMe), 3.49 (s, 3H, OMe); ^{13}C NMR: δ 33.0 (NMe), 60.6 (OMe); HRMS (ESI): *m*/*z* Calcd for $C_{11}H_{14}NO_2[M+H]^+$ 192.1025. Found 192.1034.

2-Bromo-4,5-dimethoxy-*N*-Methoxy-*N*-methylbenzamide[5], **9**: R_f: 0.25 (Hexanes/Ethyl acetate, 3:2). Yield 82%, White crystalline solid. m.p. 80-82°C. IR ($CHCl_3$): 1430, 1512, 1652, 2941, 2980, 3052 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$, at 25°C): δ 3.01-3.52 (Two broad humps, 6H, NCH_3, OCH_3), 3.78, 3.80 (2 × s, 6H, $ArOCH_3$), 6.75 (s, 1H, ArH), 6.94 (s, 1H, ArH); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 32.4, 56.1, 61.1, 110.6, 115.2, 128.4, 128.5, 131.9, 132.0, 148.2, 150.0; ^1H NMR (500MHz, $CDCl_3$, at 50°C): δ 3.24 (s, 3H, NMe), 3.57 (s, 3H, OMe); ^{13}C NMR: δ 33.7 (NMe), 61.1 (OMe); HRMS (ESI): *m*/*z* Calcd for $C_{11}H_{15}NO_4Br$ $[M+H]^+$ 304.0184. Found 304.0193.

(*E*)-2-(4-Cyanostyryl)-*N*-methoxy-*N*-methylbenzamide[6], **10**: A solution of 2-((benzo[*d*]thiazol-2-ylsulfonyl)methyl)-*N*-methoxy-*N*-methylbenzamide (200 mg, 0.55 mmol) in dry DMF (4 mL) was added to 60% sodium hydride (28 mg, 0.71 mmol) under N_2 atmosphere and stirred for 2 minutes at 0°C. Then the solution of 4-cyano benzaldehyde (86 mg, 0.66 mmol) in dry DMF (1 mL) was added and the reaction mass stirred for 2 hr. On completion of reaction as indicated by TLC, the reaction mixture was quenched with saturated NH_4Cl (15 mL) solution and extracted with ethyl acetate (3×10 mL). The combined ethyl acetate extracts was washed with ice-cold 10% aq NaOH (10 mL). Solvent was removed under vacuum to afford **10** as colourless gummy liquid (137 mg, 85%) after silica gel column chromatography. IR ($CHCl_3$): 1032,1485, 2215, 3019 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, at 25°C): δ 3.22-3.45 (Two broad humps, 6H, NCH_3, OCH_3), 7.02 (d, 1H, *J* = 16.0 Hz, ArH), 7.27-7.36 (m, 2H, ArH), 3.38-3.46 (m, 1H, ArH), 7.52 (d, 2H, *J* = 8.0 Hz, ArH), 7.59 (d, 2H, *J* = 7.2 Hz, ArH), 7.69 (d, 2H, *J* = 8.0 Hz, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 32.6, 61.2, 110.8, 118.9, 125.6, 127.1, 127.2, 128.0, 129.0, 129.6, 132.4, 133.5, 133.6, 134.7, 141.5; ^1H NMR (400 MHz, $CDCl_3$, at 50°C): δ 3.22 (s, 3H, NMe), 3.44 (s, 3H, OMe); ^{13}C NMR: δ 33.6 (NMe), 61.2 (OMe); HRMS (ESI): *m*/*z* Calcd for $C_{18}H_{17}N_2O_2$ $[M+H]^+$: 293.1290. Found 293.1302.

Isopropyl 3-(2-(methoxy(methyl)carbamoyl)phenyl)propanoate, **11**: A solution of 2-((benzo[*d*]thiazol-2-ylsulfonyl)methyl)-*N*-methoxy-*N*-methylbenzamide (200 mg, 0.55 mmol) in dry DMF (4 mL) was added to 60% sodium hydride (28 mg, 0.71 mmol) under N_2 atmosphere and stirred for 2 minutes at 0°C. Then the solution of isopropyl glyoxalate (0.66 mmol) in dry DMF (1 mL) was added and the mass stirred for 2 hr. On completion of reaction as indicated by TLC, the reaction mixture was quenched with saturated NH_4Cl (15 mL) solution and extracted with ethyl acetate (3 ×10 mL). The combined ethyl acetate extracts was washed with ice-cold 10% aq NaOH (10 mL). Solvent was removed under vacuum to afford the olefin as *E*/*Z* mixture, which on catalytic hydrogenation using 10% Pd/C in EtoAc resulted **11** as colourless gummy liquid. IR ($CHCl_3$): 1032, 1485, 2215, 3019 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, at 25°C): δ 1.12 (d, 6H, 2 × CH_3), 2.52 (t, 2H, *J* = 7.6 Hz, CH_2), 2.87 (t, 2H, *J* = 7.6 Hz, CH_2), 3.10-3.70 (Two broad humps, 6H, NCH_3, OCH_3), 4.90 (sep, 1H, *J* = 6.4 Hz, -OCH), 7.10-7.30 (m, 4H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.8, 28.4, 35.6, 61.0, 67.6, 126.0, 126.5, 129.2, 129.4, 135.0, 137.7, 172.4; ^1H NMR (400 MHz, $CDCl_3$, at 50°C): δ 3.21 (s, 3H, NMe), 3.45 (s, 3H, OMe); ^{13}C NMR: δ 33.5 (NMe), 61.0 (OMe); HRMS (ESI): *m*/*z* Calcd for $C_{18}H_{21}NO_4K$ $[M+H]^+$: 318.1111. Found 318.1108.

Preparation of of 2-iodo-*N*-methoxy-*N*-methylbenzamide (12) and 2-chloro-*N*-methoxy-*N*-methylbenzamide, **13**: Both these compounds were

made from the corresponding acids, using the procedure described for compound **12** in our recent report[5].

12: R_f: 0.34 in 2:3 EtOAc/Hexane. Yellow liquid. IR: 3015, 1649, 1586, 1460, 1431, 1385, 1216, 1017, 987, 759 cm^{-1}; ^{1}H NMR (400 MHz,CDCl/TMS, at 25°C) mixture of rotamers: δ 3.92-3.04 (6H, NCH_3, OCH_3; details of the scenario in this region: 3.04-3.15, broad hump; 3.25-3.50, 2 × bs; 3.80-3.92, broad hump), 7.21 (t, 1H, *J* = 7.2 Hz, ArH), 7.37 (d, 1H, *J* = 8.0 Hz, ArH), 7.49 (t, 1H, *J* =7.2 Hz, ArH), 7.89 (d, 1H, *J* = 8.0 Hz, ArH); ^{13}C NMR (100 MHz, $CDCl_3$/TMS): δ 32.1, 61.0, 93.1, 127.4, 128.6, 130.4, 138.3, 141.8, 161.8; ^{1}H NMR (400 MHz, DMSO-d_6 at 75°C): δ 3.20 (s, 3H, NMe), 3.51 (s, 3H, OMe); ^{13}C NMR: δ 33.2 (broad hump, NMe), 61.2 (OMe); HRMS (ESI): *m*/*z* Calcd for $C_9H_{11}NO_2$ I $[M+H]^+$ 291.9835. Found 291.9843.

13: R_f: in 1:4 EtOAc/Hexane. Yellow liquid. IR: 3021, 2928, 1648, 1423, 1389 cm^{-1}. ^{1}H NMR: (400 MHz, $CDCl_3$/TMS, at 25°C): mixture of two rotamers δ 3.82-2.98 (6H, NCH_3, OCH_3; details of the scenario in this region: 2.98-3.10, broad hump; 3.20-3.45, 2 × bs; 3.70-3.82, broad hump), 7.26-7.18 (m, 4H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$/TMS) : δ 31.8, 60.9, 126.2, 127.2, 128.9, 129.9, 132.1, 134.7, 167.9. ^{1}H NMR (400 MHz, $CDCl_3$, at 50°C): δ 3.10-3.30 (s, 3H, NCH_3), 3.30-3.70 (s, 3H, OCH_3); ^{13}C NMR: δ 32.1(broad hump, NMe), 60.9 (OMe); HRMS (ESI): *m*/*z* Calcd for $C_9H_{11}NO_2Cl$ $[M+H]^+$ 200.0478. Found 200.0473.

Conclusion

Several *ortho*-substituted *N*-methoxy-*N*-methyl benzamides were synthesized and NMR signals associated with N-methoxy and N-methyl units were closely observed both in ^{1}H NMR and ^{13}C NMR spectra. Signals for *N*-Me and *O*-Me appeared as two humps in ^{1}H NMR at room temperature. Variable temperature NMR experiment helped explain their departure from the expected two singlet pattern.

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