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An Approach to α-Substituted Amines

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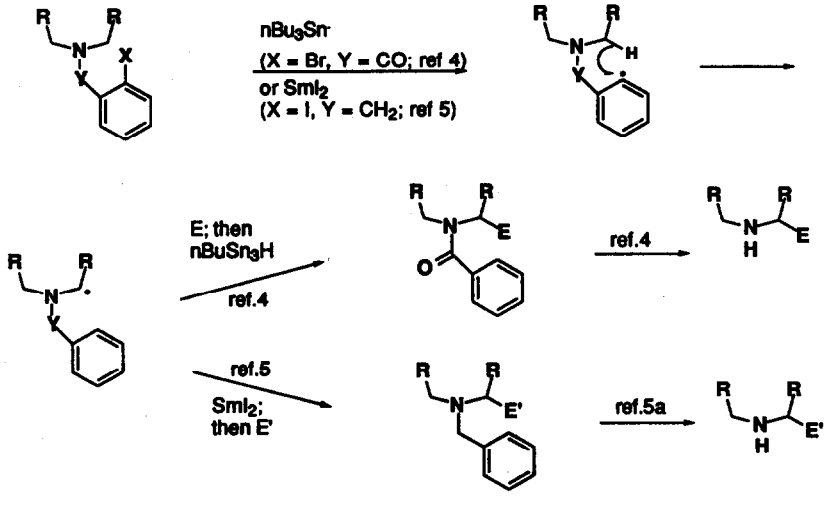
Abstract: A number of amines have been alkylated at the position *alpha* to nitrogen *via* free radical methodology. *N*-(2-Iodobenzyl) and *N*-(2-iodobenzoyl) 'protected' amines have been used to generate radicals which rapidly undergo a 1,5-hydrogen shift to give more stable α-amino radicals. These can subsequently be trapped by electron deficient alkenes to give α-alkylated amines.

The development of methodology for the introduction of substituents at the α-position of amines is important for the synthesis of many nitrogen-containing natural products. Various methods have been employed for substitution at a carbon adjacent to nitrogen.[1] However, these examples are limited and generally involve activation of the α-carbon by an electron withdrawing group on the nitrogen. These methods have proved ineffective in more complex systems where the presence of many nitrogens complicate the course of the desired

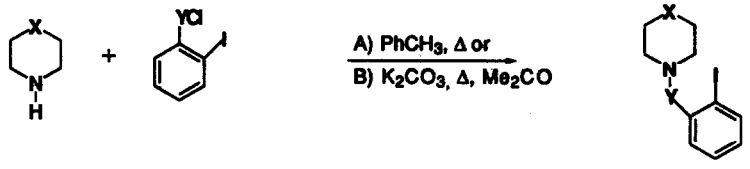


Scheme 1

reaction.[2] We recently reported a reasonably efficient method for the introduction of substituents adjacent to nitrogen *via* radical chemistry,[3] and are prompted to report our complete results.

Curran and coworkers reported that α-benzamidoyl radicals can be generated from *o*-halobenzamides by a 1,5-hydrogen atom transfer and subsequently trapped by inter/intramolecular reaction/addition.[4] A similar process has also been employed by us and by Ito, using a 2-iodobenzyl moiety to generate and alkylate carbanions *alpha* to the nitrogen of amines *via* SmI_2-mediated reaction.[5] Both Curran and Ito had respectively demonstrated the 'protecting group' nature of these groups by their removal through hydrolysis and hydrogenolysis (Scheme 1).

For our studies the required 2-iodoaryl model precursors were synthesised as shown in Scheme 2. The 2-iodoaryl derivatives were prepared in good yield by heating the respective 2-iodoaryl chloride with an excess of the amine in toluene, or with the amine in the presence of an excess of potassium carbonate in acetone.



a) Et_2NH; Y = CH_2; 98 %[b]

b)  ; Y = CH_2; 91 %[b]

c) X = CH_2; Y = CH_2; 98 %[a]

d) X = $(CH_2)_2$; Y = CH_2; 97 %[b]

e) X = O; Y = CO; 87 %[a]

f) X = O; Y = CH_2; 92 %[a]

g) X = S; Y = CH_2; 87 %[b]

h) X = NCHO; Y = CH_2; 66 %[b]

i) X = NMe; Y = CH_2; 72 %[a]

j) X = NCOPh; Y = CH_2; 85 %[b]

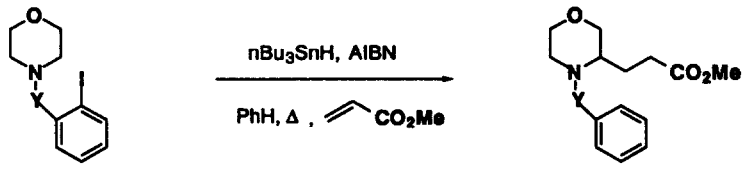
k) X = NCO_2Et; Y = CH_2; 95 %[b]

[a] Formed by heating an excess of the amine with the 2-iodoaryl chloride in toluene.
[b] Formed by heating the amine with 2-iodobenzyl chloride in acetone in the presence of an excess of K_2CO_3

Scheme 2. Preparation of the Radical Precursors

We initially wanted to compare both 'protecting groups' using the tin hydride method for the generation of radicals and chose morpholine as our model substrate. Comparisons using methyl acrylate as the electrophile indicated that the 2-iodobenzyl moiety was more efficient than the 2-iodobenzoyl group (Scheme 3). However, the conditions for optimum formation of the respective morpholinopropanoates differed in that best results were obtained in the presence of 3 equivalents of the electrophile for transformation **1**, and only 1.1 equivalents for **2**. The corresponding α-alkylated adducts were obtained in 46 and 66% respectively, indicating that the corresponding α-amino radical is less stable and therefore more reactive than the α-amido radical.

Transformations were achieved by syringe pump addition of tri-*n*-butyltin hydride (2 eq.) and AIBN (0.1 eq.) in benzene over a period of 9 hours to the radical precursors and the electrophile in refluxing benzene. Other products isolated from the reaction mixtures included some reduction product and telomers produced by subsequent addition of methyl acrylate to the morpholinopropanoate radicals prior to hydrogen abstraction from the tin hydride.



A B

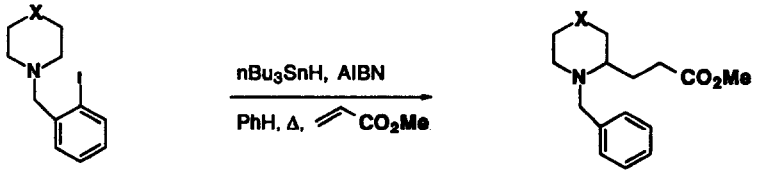
1 Y = CO; 46 %[a]

2 Y = CH_2; 66 %[b]

[a] 3.0 eq.of electrophile used. [b] 1.1 eq. of electrophile used.

Scheme 3. Reaction of 2-Iodoarylmorpholine Derivatives with Methyl Acrylate

Alkylations at the *alpha* position of other amines utilising the 2-iodobenzyl group are shown in Scheme 4. Once again optimum conditions for the transformations shown were as before, with the use of only 1.1 equivalents of the electrophile. Methyl acrylate was again considered as the electrophile and was distilled prior to use. Although reasonable yields were obtained for the piperidine and morpholine derivatives, the formylpiperazine derivative **5B** was yielded in only 12% and the thiomorpholine and methylpiperazine derivatives **4B** and **6B** were not detected in the reaction mixture. Only a noticeable increase in the amount of reduction of the respective radical precursors, and the telomerisation of their corresponding aminopropanoate radicals were observed in these reactions.



A B

2 X = O; 66 %

3 X = CH_2; 52 %

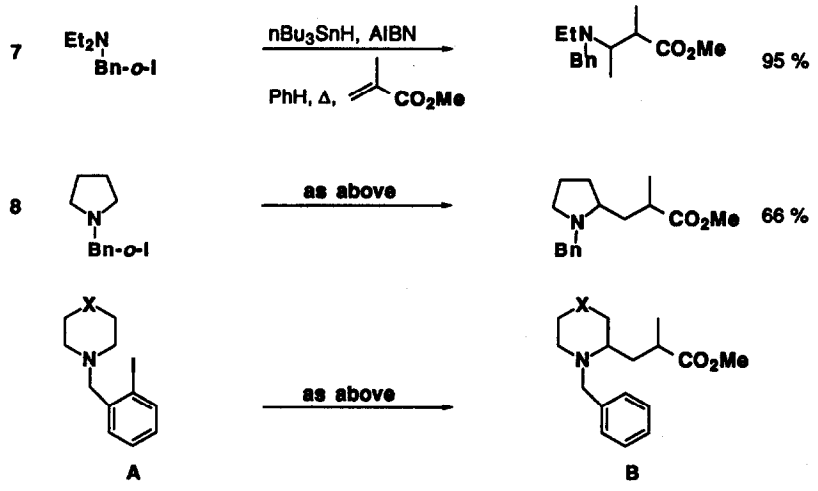
4 X = S; 0 %

5 X = NCHO; 12 %

6 X = NMe; 0 %

Scheme 4. Alkylations of 2-Iodobenzylamines with Methyl Acrylate.

The alkylation of a number of 2-iodobenzylamines with methyl methacrylate (3 equivalents) to give the corresponding α-alkylated adducts is shown in Scheme 5. No significant selectivity was detected during reaction and all products were obtained as a mixture of diastereoisomers. Treatment of the 2-iodobenzyldiethylamine derivative with methyl methacrylate under the standard tin hydride conditions cleanly afforded the aminobutanoate **7B** in 95%. However, extension of this methodology to cyclic amines led to a marked decrease in the amount of the α-alkylated products obtained, as reduction and telomerisation side reactions began to compete. The five, six, and seven-membered cyclic amine precursors yielded the corresponding α-alkylated adducts **8-10B** in reasonable yields decreasing from 66 to 55%.



9 X = CH_2; 65 % **13** X = NCHO; 41 %

10 X = $(CH_2)_2$; 55 % **14** X = NMe; 29 %

11 X = O; 55 % **15** X = NCOPh; 14 %

12 X = S; 23 % **16** X = NCO_2Et; 29 %

Scheme 5. Alkylations of Iodobenzylamines with Methyl Methacrylate.

The introduction of an additional heteroatom into the cyclic systems had quite a marked effect upon the outcome of these alkylations. However the presence of an oxygen atom in the morpholine derivative was tolerated, and the respective morpholinopropanoate **11B** was afforded in 55% yield. Replacement of the oxygen atom by sulphur led to a significant reduction in alkylation, with the thiomorpholine derivative **12B** being obtained in only 23%. It is suggested that the larger size and polarisability of the sulphur atom may influence the stability of the intermediate α-amino radical, and thus affect the overall outcome of the reaction.

Similarly a reduction in yield was also perceived for reaction of piperazine derivatives. The formylpiperazine adduct **13B** was obtained in 41% yield and the methyl and ethoxycarbonyl derivatives **14B** and **16B** were afforded in 29%. The benzoylpiperazinopropanoate **15B** was yielded in only 14%, and in particular the reactions of the 2-iodobenzylpiperazines were accompanied by a vast increase in reduction in addition to other side reactions.

Through our results we have shown that employment of the 2-iodobenzyl moiety as a 'protecting group' in conjunction with the tin hydride method for the generation of radicals, affords α-alkylated amines in moderate to good yields in simple heterocyclic systems. However, the introduction of sulphur or nitrogen into these systems is not tolerated and the desired reaction is impeded. This methodology also appears to work very efficiently with acyclic systems but requires further elaboration.

EXPERIMENTAL

^{13}C NMR spectra were either recorded at 50 MHz or at 75 MHz. Mass spectra were recorded with electron impact (EI) or chemical ionisation (CI) using methane. Reactions were routinely carried out under an inert atmosphere of Ar. Where necessary, solvents and reagents were dried and purified according to recommended methods. Petroleum ether refers to the fraction boiling in the range 40-60 °C.

General Procedure for the Coupling of an Amine to an Alkyl / Acyl Halide.

The amine (4 mmol) was added to a stirring solution of the halide (1 mmol) in dry toluene (10 mL) under Ar. The mixture was then heated at reflux until tlc indicated the complete consumption of the starting halide. After cooling, the amine salt was removed by filtration and the solution concentrated. Filtration through a silica pad / purification by column chromatography then afforded the product amine / amide.

The amine (1.1 mmol) was added to a stirring solution of the halide (1 mmol) and potassium carbonate (5 mmol) in dry acetone (10 mL) under an inert atmosphere. The mixture was then heated at reflux until tlc indicated the complete consumption of the starting halide. After cooling, excess potassium carbonate was removed by filtration and the solution concentrated. Filtration through a silica pad / purification by column chromatography then afforded the product amine.

Preparation of 1-(2-Iodobenzyl)-1,1-diethylamine[5a,6]. 1-(2-Iodobenzyl)-1,1-diethylamine was prepared according to general procedure B, by reaction of 2-iodobenzyl chloride (1.0 g, 4 mmol) with diethylamine (0.45 mL, 4.4 mmol). Purification of the crude product by Kugelrohr distillation yielded the product as a clear liquid (1.12 g, 98 %); b.p. 105 °C at 0.5 mm Hg (Lit. b.pt.[6] 106-107 °C at 0.5 mm Hg); R_f 0.50 (EtOAc-hexane, 1:4, v/v); ^1H NMR (200 MHz, $CDCl_3$) δ 7.83 (1H, d, J = 7.9 Hz), 7.53 (1H, t, J = 7.9 Hz), 7.32 (1H, t, J = 7.9 Hz), 6.94 (1H, t, J = 7.9 Hz), 3.58 (2H, s), 2.59 (4H, q, J = 7.1 Hz), 1.06 (6H, t, J = 7.1 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 142.9, 139.6, 130.6, 128.8, 128.5, 100.5, 62.7, 47.6 (2C), 12.5 (2C); IR (neat) 3050, 2975, 1560 cm^{-1}. MS *m/z* (EI) 289 (20), 274 (100), 217 (89). HRMS Calcd for $C_{11}H_{16}IN$ 289.0328, found 289.0317.

Preparation of 1-(2-Iodobenzyl)pyrrolidine[5a]. 1-(2-Iodobenzyl)pyrrolidine was prepared according to general procedure B, by reaction of 2-iodobenzyl chloride (2.7 g, 10.8 mmol) with pyrrolidine (1 g, 14.1 mmol). The product (2.8 g, 91 %) was obtained as a colourless liquid; R_f 0.41 (EtOAc-hexane, 1:2,

v/v); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.83 (1H, d, J = 7.7 Hz), 7.45 (1H, t, J = 7.7 Hz), 7.32 (1H, t, J = 7.7 Hz), 6.94 (1H, t, J = 7.7 Hz), 3.69 (2H, s), 2.62 (4H, bs), 1.82 (4H, bs); ^{13}C NMR (50 MHz, $CDCl_3$) δ 141.6, 139.2, 129.8, 128.4, 128.0, 100.1, 64.4, 54.1 (2C), 23.6 (2C); IR (neat) 3058, 2973, 1575 cm^{-1}. MS *m/z* (EI) 288 ($M+H^+$, 14), 287 (94), 286 (97), 216 (56), 160 (30). HRMS Calcd for $C_{11}H_{14}IN$ 287.0171, found 287.0168.

Preparation of 1-(2-Iodobenzyl)piperidine[7]. 1-(2-Iodobenzyl)piperidine was prepared according to general procedure A outlined earlier, by reaction of 2-iodobenzyl chloride (1.5 g, 6 mmol) with piperidine (2.4 mL, 24 mmol). The product (1.75 g, 98 %) was obtained as a pale yellow solid; m.pt. 34 °C; R_f 0.42 (EtOAc-petroleum ether, 1:8, v/v); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.83 (1H, d, J = 7.9 Hz,), 7.44 (1H, t, J = 7.9 Hz), 7.32 (1H, t, J = 7.9 Hz), 6.94 (1H, t, J = 7.9 Hz), 3.48 (2H, s), 2.46 (4H, t, J = 4.7 Hz), 1.65-1.36 (6H, m); ^{13}C NMR (50 MHz, $CDCl_3$) δ 141.4, 139.5, 130.5, 128.7, 128.5, 101.2, 68.3, 55.7 (2C), 27.6 (2C), 25.9; IR ($CDCl_3$) 3030, 2910, 1570 cm^{-1}. MS *m/z* (CI, CH_4) 302 ($M+H^+$, 76), 301 (85), 300 (100), 217 (27), 176 (35), 175 (40), 174 (54). HRMS Calcd for $C_{12}H_{16}IN$ 301.0328, found 301.0321. Anal. Calcd for $C_{12}H_{16}IN$: C, 47.84; H, 5.36; N, 4.65. Found : C, 47.86; H, 5.35; N, 4.65.

Preparation of 1-(2-Iodobenzyl)hexahydroazepine[5a]. 1-(2-Iodobenzyl)-hexahydroazepine was prepared according to general procedure B, by reaction of 2-iodobenzyl chloride (1.0 g, 4 mmol) with hexahydroazepine (1.6 g, 15.8 mmol). The product (1.2 g, 97 %) was obtained as a colourless liquid; R_f 0.44 (EtOAc-hexane, 1:8, v/v); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.84 (1H, d, J = 7.6 Hz), 7.49 (1H, t, J = 7.6 Hz), 7.32 (1H, t, J = 7.6 Hz), 6.94 (1H, t, J = 7.6 Hz), 3.64 (2H, s), 2.69 (4H, bs), 1.65 (8H, bs); ^{13}C NMR (50 MHz, $CDCl_3$) δ 142.0, 139.2, 130.1, 128.3, 127.8 , 100.2, 66.5, 55.5 (2C), 28.4 (2C), 27.0 (2C); IR (neat) 3051, 2926, 1575 cm^{-1}. MS *m/z* (EI) 316 ($M+H^+$, 12), 315 (88), 314 (32), 300 (12), 286 (39), 272 (12), 246 (13), 217 (100), 202 (19), 200 (13), 188 (52), 146 (22). HRMS Calcd for $C_{13}H_{18}IN$ 315.0488, found 315.0477.

Preparation of 4-(2-Iodobenzoyl)morpholine. Treatment of 2-iodobenzoyl chloride (0.5 g, 2 mmol) with morpholine (0.65 mL, 7.5 mmol) gave 4-(2-iodobenzoyl)morpholine (0.52 g, 87 %) as a white crystalline solid according to general procedure A; m.p. 86-7 °C; R_f 0.43 (EtOAc-petroleum ether, 1:2, v/v); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.83 (1H, d, J = 7.5 Hz), 7.40 (1H, t, J = 7.5 Hz), 7.19 (1H, t, J = 7.5 Hz), 7.09 (1H, t, J = 7.5 Hz), 3.95-3.67 (4H, m), 3.66-3.50 (2H, m), 3.38-3.10 (2H, m); ^{13}C NMR (50 MHz, $CDCl_3$) δ 169.2, 142.0, 139.5, 130.6, 128.8, 127.4, 93.2, 67.7, 67.6, 48.5, 43.3; IR ($CHCl_3$) 3030, 2945, 1575 cm^{-1}. MS *m/z* (CI, CH_4) 346 ($M+C_2H_5^+$, 9), 318 ($M+H^+$, 100), 231 (53), 190 (30). HRMS Calcd for $C_{11}H_{12}INO_2$ 316.9913, found 316.9908. Anal. Calcd for $C_{11}H_{12}INO_2$: C, 41.66; H, 3.81. Found : C, 41.99; H, 3.79.

Preparation of 4-(2-Iodobenzyl)morpholine. Treatment of 2-iodobenzyl chloride (0.5 g, 2 mmol) with morpholine (0.76 mL, 8.7 mmol) gave some recovery of the starting halide (0.08 g, 15 %) and 4-(2-iodobenzyl)morpholine (0.47 g, 92 % based on reacted starting material) as a white crystalline solid according to general procedure A; m.p. 44-5 °C; R_f 0.43 (EtOAc-petroleum ether, 1:2, v/v); ^{1}H NMR (200

MHz, $CDCl_3$) δ 7.83 (1H, d, J = 7.5 Hz), 7.40 (1H, t, J = 7.5 Hz), 7.31 (1H, t, J = 7.5 Hz), 6.96 (1H, t, J = 7.5 Hz), 3.72 (4H, t, J = 4.7 Hz), 3.53 (2H, s), 2.53 (4H, t, J = 4.7 Hz,); ^{13}C NMR (50 MHz, $CDCl_3$) δ 140.3, 139.7, 130.6, 129.1, 128.3, 101.2, 68.0 (3C), 54.6 (2C); IR ($CHCl_3$) 3030, 2940, 1575 cm^{-1}. MS *m/z* (CI, CH_4) 304 ($M+H^+$, 100), 217 (34), 109 (29). HRMS Calcd for $C_{11}H_{14}INO$ 303.0120, found 303.0126. Anal. Calcd for $C_{11}H_{14}INO$: C, 43.59; H, 4.66; N, 4.62. Found : C, 43.58; H, 4.65; N, 4.62.

Preparation of 4-(2-Iodobenzyl)thiomorpholine. Treatment of 2-iodobenzyl chloride (1.0 g, 4 mmol) with thiomorpholine (0.4 mL, 4.4 mmol) gave 4-(2-iodo-benzyl)thiomorpholine (1.1 g, 87 %) as a white crystalline solid according to general procedure B; m.p. 63-4 °C; R_f 0.59 (EtOAc-hexane, 1:8, v/v); ^1H NMR (200 MHz, $CDCl_3$) δ 7.83 (1H, dd, J = 7.8, 1.2 Hz), 7.41-7.27 (2H, m), 6.95 (1H, dt, J = 7.8, 1.2 Hz), 3.52 (2H, s), 2.76 (4H, m), 2.70 (4H, m); ^{13}C NMR (50 MHz, $CDCl_3$) δ 140.8, 140.7, 130.6, 129.1, 128.3, 101.2, 68.0, 55.8 (2C), 29.2 (2C); IR (nujol) 3010, 2900, 1445 cm^{-1}. MS *m/z* (EI) 319 (59), 291 (20), 192 (29), 164 (25), 146 (99). HRMS Calcd for $C_{10}H_{11}INS$ 303.9657, found ($M-CH_3$) 303.9670. Anal. Calcd for $C_{11}H_{14}INS$: C, 41.34; H, 4.45; N, 4.47; S, 10.01. Found : C, 41.39; H, 4.42; N, 4.38; S, 10.05.

Preparation of 1-Formyl-4-(2-iodobenzyl)piperazine. Treatment of 2-iodobenzyl chloride (1.0 g, 4 mmol) with formylpiperazine (0.5 g, 5.9 mmol) gave 1-formyl-4-(2-iodobenzyl)piperazine (0.9 g, 66 %) as a white crystalline solid according to general procedure B; m.p. 107 °C; R_f 0.63 (EtOAc-methanol, 10:1, v/v); ^1H NMR (200 MHz, $CDCl_3$) δ 8.24 (1H, s), 8.08 (1H, d, J = 7.9 Hz), 7.70-7.45 (2H, m), 7.18 (1H, t, J = 7.9 Hz), 3.76 (4H, m), 3.66 (2H, s), 2.72 (4H, m); ^{13}C NMR (50 MHz, $CDCl_3$) δ 161.2, 140.4, 140.2, 130.8, 129.5, 128.6, 101.2, 66.8, 53.8, 52.6, 46.2, 40.5; IR (nujol) 3040, 2900, 1640, 1435 cm^{-1}. MS *m/z* (CI, CH_4) 359 ($M+C_2H_5^+$, 27), 331 ($M+H^+$, 99), 303 (17), 233 (21), 217 (28), 205 (81), 203 (38), 129 (21), 127 (21), 113 (100). HRMS Calcd for $C_{12}H_{15}IN_2O$ 330.0229, found 330.0219. Anal. Calcd for $C_{12}H_{15}IN_2O$: C, 43.65; H, 4.58; N, 8.48. Found : C, 43.60; H, 4.49; N, 8.52.

Preparation of 1-(2-Iodobenzyl)-4-methylpiperazine. Treatment of 2-iodobenzyl chloride (1.0 g, 4 mmol) with methylpiperazine (1.8 mL, 16 mmol) gave 1-(2-iodobenzyl)-4-methylpiperazine (0.9 g, 72 %) as a white crystalline solid according to general procedure A; m.p. 189 °C; R_f 0.40 (methanol); ^1H NMR (200 MHz, $CDCl_3$) δ 7.82 (1H, d, J = 7.8 Hz), 7.44-7.21 (2H, m), 6.93 (1H, t, J = 7.8 Hz), 3.51 (2H, s), 2.71-2.43 (8H, m), 2.31 (3H, s); ^{13}C NMR (50 MHz, $CDCl_3$) δ 139.8, 138.8, 129.7, 128.1, 127.3, 100.3, 66.4, 55.3 (2C), 53.0 (2C), 46.2; IR (nujol) 3030, 2910, 1455 cm^{-1}. MS *m/z* (EI) 316 (99), 245 (48), 217 (69), 99 (100). HRMS Calcd for $C_{12}H_{17}IN_2$ 316.0437, found 316.0435. Anal. Calcd for $C_{12}H_{17}IN_2$: C, 45.55; H, 5.34; N, 8.84. Found : C, 45.59; H, 5.42; N, 8.86.

Preparation of 1-Benzoyl-4-(2-iodobenzyl)piperazine. Treatment of 2-iodobenzyl chloride (1.0 g, 4 mmol) with 1-benzoylpiperazine (0.83 g, 4.36 mmol) gave 1-benzoyl-4-(2-iodobenzyl)piperazine (1.37 g, 85 %) as a white crystalline solid according to general procedure B; m.pt. 95-6 °C; R_f 0.49 (EtOAc-hexane, 2:1, v/v); ^1H NMR (200 MHz, $CDCl_3$) δ 7.84 (1H, d, J = 7.8 Hz), 7.48-7.35 (6H, m), 7.31 (1H, t, J = 7.8 Hz), 6.96 (1H, t, J = 7.8 Hz), 3.80 (2H, bs), 3.56 (2H, s), 3.44 (2H, bs), 2.58 (2H, bs), 2.48 (2H, bs); ^{13}C NMR (50 MHz, $CDCl_3$) δ 170.1, 140.2, 139.8, 130.6, 129.9, 129.3 (2C), 128.8 (2C), 128.4 , 127.4 (2C), 101.3, 67.3, 54.2 (2C), 49.0, 43.4; IR ($CHCl_3$) 3058, 2998, 1647 cm^{-1}. MS *m/z* (EI) 406 (23), 301

(13), 285 (13), 279 (20), 273 (14), 272 (100), 260 (58), 258 (26), 247 (31), 217 (98), 148 (24). HRMS Calcd for $C_{18}H_{19}IN_2O$ 406.0542, found 406.0536. Anal. Calcd for $C_{18}H_{19}IN_2O$: C, 53.22; H, 4.71; N, 6.90. Found : C, 53.32; H, 4.74; N, 6.84.

Preparation of 4-Ethoxycarbonyl-1-(2-iodobenzyl)piperazine. Treatment of 2-iodobenzyl chloride (1.0 g, 4 mmol) with 1-carboethoxypiperazine (0.65 mL, 4.21 mmol) gave some recovery of the starting halide (0.19 g, 19 %) and 4-ethoxy-carbonyl-1-(2-iodobenzyl)piperazine (1.14 g, 95 % based on reacted starting material) as a colourless oil according to general procedure B; R_f 0.44 (EtOAc-hexane, 1:2, v/v); ^1H NMR (200 MHz, $CDCl_3$) δ 7.83 (1H, d, J = 7.8 Hz), 7.42-7.27 (2H, m), 6.95 (1H, t, J = 7.8 Hz), 4.13 (2H, q, J = 7.1 Hz), 3.52 (2H, s), 3.48 (4H, t, J = 5.0 Hz), 2.47 (4H, t, J = 5.0 Hz), 1.25 (3H, t, J = 7.1 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 155.5, 140.4, 139.8, 130.6, 129.2, 128.3, 101.3, 67.4, 62.4, 53.8 (2C), 45.0 (2C), 16.3; IR (nujol) 3050, 2860, 1675, 1440 cm^{-1}. MS *m/z* (EI) 374 (58), 272 (61), 260 (43), 258 (21), 217 (100), 171 (22), 157 (22). HRMS Calcd for $C_{14}H_{19}IN_2O_2$ 374.0491, found 374.0473. Anal. Calcd for $C_{14}H_{19}IN_2O_2$: C, 44.93; H, 5.12; N, 7.45. Found : C, 44.98; H, 5.13; N, 7.49.

General Procedure for the α-Alkylation of Amines / Amides. Tri-*n*-butyltin hydride (2 mmol) and AIBN (0.1 mmol) in dry, degassed benzene (10 mL) were added over a period of 9 h to the amine / amide (1 mmol) and electrophile (3 mmol) in dry, degassed benzene (40 mL) at reflux under argon. After cooling the solvent was removed under reduced pressure and the crude product diluted with wet ether (50 mL). DBU[8] (3 mmol) was then added and the mixture stirred for 30 min before being filtered through a silica plug and concentrated to afford the crude product. Purification by flash chromatography on silica gel yielded the pure product.

Preparation of Methyl 3-[2-(1-benzoylmorpholino)]propanoate (1B). Reaction of 1-(2-iodobenzoyl)morpholine (150 mg, 0.47 mmol) with methyl acrylate (0.1 mL, 1.1 mmol) under the typical standard conditions given above, yielded **1B** (60 mg, 46 %) as a yellow liquid; R_f 0.63 (EtOAc-methanol, 10:1, v/v); ^1H NMR (200 MHz, $CDCl_3$) δ 7.43-7.15 (5H, m), 4.00-3.27 (8H, m), 2.65-1.75 (6H, m); ^{13}C NMR (50 MHz, $CDCl_3$) δ 173.8, 171.2, 139.7, 130.3, 129.1, 129.0, 127.5, 127.3, 70.3 and 70.1 (rotamer), 67.6 and 67.2 (rotamer), 52.4, 52.3 and 52.2 (rotamer), 47.7, 32.2 and 31.2 (rotamer), 24.7; IR ($CHCl_3$) 3040, 2930, 1725, 1620, 1415 cm^{-1}. MS *m/z* (CI, CH_4) 306 ($M+C_2H_5^+$, 8), 278 ($M+H^+$, 25), 190 (11), 172 (11), 156 (11), 105 (100). HRMS Calcd for $C_{15}H_{18}NO_4$ 276.1230, found M-1 276.1236.

Preparation of Methyl 3-[2-(1-benzylmorpholino)]propanoate (2B). Reaction of 1-(2-iodobenzyl)morpholine (300 mg, 1 mmol) with methyl acrylate (0.1 mL, 1.1 mmol) under the typical standard conditions given above, gave the starting material (25 mg, 8 %) and **2B** (160 mg, 66 % based on reacted starting material) as a yellow liquid; R_f 0.42 (EtOAc-hexane, 1:2, v/v); ^1H NMR (200 MHz, $CDCl_3$) δ 7.43-7.15 (5H, m), 4.04 (1H, d, J = 13.3 Hz), 3.79-3.29 (8H, m), 3.20 (1H, d, J = 13.3 Hz), 2.70-1.85 (6H, m); ^{13}C NMR (50 MHz, $CDCl_3$) δ 174.1, 138.7, 129.3, 129.2, 128.9, 128.7, 127.5, 70.6, 67.7, 59.5, 58.8, 52.5, 51.3, 30.7, 23.4 ; IR ($CHCl_3$) 3040, 2930, 1725, 1485 cm^{-1}. MS *m/z* (CI, CH_4) 292 ($M+C_2H_5^+$, 15), 264 ($M+H^+$, 100), 232 (9), 186 (15), 176 (54), 142 (24). HRMS Calcd for $C_{15}H_{20}NO_3$ 262.1435, found M-1 262.1443.

Preparation of Methyl 3-[2-(1-benzylpiperidino)]propanoate (3B). Reaction of 1-(2-iodobenzyl)piperidine (150 mg, 0.5 mmol) with methyl acrylate (0.13 mL, 1.5 mmol) under the typical standard conditions given above, gave **3B** (68 mg, 52 %) as a yellow liquid; R_f 0.22 (EtOAc-petroleum ether, 1:8, v/v); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.40-7.10 (5H, m), 3.97 (1H, d, J = 13.6 Hz), 3.87-3.50 (4H, m), 3.23 (1H, d, J = 13.6 Hz), 2.85-1.30 (12H, bm); ^{13}C NMR (50 MHz, $CDCl_3$) δ 175.1, 140.1, 129.3 (2C), 128.4 (2C), 127.2, 60.0, 57.9, 52.1, 51.7, 30.3, 30.2, 27.1, 25.2, 23.4; IR ($CHCl_3$) 3040, 2910, 1725, 1585 cm^{-1}. MS *m/z* (CI, CH_4) 290 ($M+C_2H_5^+$, 17), 262 ($M+H^+$, 100), 174 (69), 140 (33). HRMS Calcd for $C_{16}H_{22}NO_2$ 260.1648, found M-1 260.1651.

Preparation of Methyl 3-[3-(4-benzyl-1-formylpiperazino)]propanoate (5B). Reaction of 1-formyl-4-(2-iodobenzyl)piperazine (150 mg, 0.45 mmol) with methyl acrylate (0.12 mL, 1.3 mmol) under the typical standard conditions given above, afforded **5B** (15 mg, 12 %) as a yellow liquid; R_f 0.52 (EtOAc-methanol, 10:1, v/v); ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.03 (1H, d, J = 4.3 Hz), 7.44-7.16 (5H, m), 3.94 (1H, d, J = 13.5 Hz), 3.74-2.99 (8H, m), 2.83-2.65 (1H, m), 2.64-2.18 (4H, m), 2.11-1.73 (2H, m); ^{13}C NMR (50 MHz, $CDCl_3$) δ 173.8, 160.8, 139.9, 138.5, 130.6, 129.3, 128.7, 127.6, 59.3, 58.6, 54.4, 53.2 and 52.8 (rotamer), 49.9 and 49.4 (rotamer), 46.9 and 46.1 (rotamer), 31.3, 23.7 and 23.3 (rotamer); IR ($CHCl_3$) 3064, 2963, 1738, 1677, 1443 cm^{-1}. MS *m/z* (EI) 290 (6), 272 (11), 217 (19), 203 (69), 98 (27), 91 (100). HRMS Calcd for $C_{16}H_{22}N_2O_3$ 290.1630, found 290.1623.

Preparation of Methyl 2,4-dimethyl-(1-benzyl-1-ethylamino)butanoate (7B). Reaction of 1-(2-iodobenzyl)-1,1-diethylamine (150 mg, 0.5mmol) with methyl methacrylate (0.17 mL, 1.6 mmol) under the typical standard conditions given above, gave **7B** (120 mg, 95 %) as a pale yellow liquid; R_f 0.43 (EtOAc-hexane, 1:8, v/v); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.42-7.18 (5H, m), 3.80-3.54 (4H, m), 3.33 (1H, d, J = 14.0 Hz), 2.91-2.60 (1H, m), 2.59-2.22 (2H, m), 2.06-1.91 (1H, m), 1.78-1.40 (2H, m), 1.13 (3H, d, J = 7.2 Hz,), 1.02 (6H, m); ^{13}C nmr (50 MHz, $CDCl_3$) δ 178.0, 141.9, 129.3 (2C), 128.9 (2C), 127.0, 54.0, 51.9, 51.3, 43.7, 36.9, 18.8, 17.2, 16.2, 13.7; IR (neat) 3067, 2969, 1741, 1458 cm^{-1}. MS *m/z* (EI), 263 (19), 262 (100), 129 (25). HRMS Calcd for $C_{16}H_{24}NO_2$ 262.1807, found M-1 262.1794.

Preparation of Methyl 2-methyl-3-[2-(1-benzylpyrrolidino)]propanoate (8B). Reaction of 1-(2-iodobenzyl)pyrrolidine (150 mg, 0.5 mmol) with methyl methacrylate (0.17 mL, 1.6 mmol) under the typical standard conditions given above, gave **8B** (90 mg, 66 %) as a pale yellow liquid ; R_f 0.17 (EtOAc-hexane, 1:2, v/v); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.33 (5H, m), 4.03 (1H, d, J = 12.9 Hz), 3.66 (3H, s), 3.20 (1H, d, J = 12.9 Hz), 2.80 (1H, m,), 2.53 (2H, m), 2.15 (1H, m), 2.04-1.40 (6H, m), 1.20 (3H, d, J = 6.0 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 176.9, 141.6, 129.7 (2C), 128.7 (2C), 127.5, 62.9, 59.1, 54.4, 52.1, 37.6, 30.8, 22.7, 18.0, 17.9; IR ($CHCl_3$) 3064, 2952, 1740 cm^{-1}. MS *m/z* (EI) 261 (2), 161 (12), 160 (100). $C_{16}H_{22}NO_2$ 260.1651, found M-1 260.1637.

Preparation of Methyl 2-methyl-3-[2-(1-benzylpiperidino)]propanoate (9B). Reaction of 1-(2-iodobenzyl)piperidine (150 mg, 0.5 mmol) with methyl methacrylate (0.16 mL, 1.5 mmol) under the typical standard conditions given above, gave the starting material (34 mg, 23 %) and **9B** (70 mg, 65 % based

on reacted starting material) as a pale yellow liquid; Rf 0.34 (EtOAc-hexane, 1:2, v/v); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.40-7.15 (5H, m), 3.84 (1H, d, *J* = 13.7 Hz), 3.72-3.52 (4H, m), 3.37 (1H, d, *J* = 13.7 Hz), 2.80-1.70 (11H, bm), 1.15 (3H, d, *J* = 5.7 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 177.9, 139.9, 129.4 (2C), 128.7 (2C), 127.4, 58.5, 57.7, 52.1, 50.3, 37.2, 30.2, 26.4, 24.3, 22.8, 18.0; IR ($CHCl_3$) 3056, 2939, 1743, 1457 cm^{-1}. MS *m/z* (EI) 275 (5), 274 (20), 175 (19), 174 (100). HRMS Calcd for $C_{17}H_{24}NO_2$ 274.1808, found M-1 274.1801.

Preparation of Methyl 2-methyl-3-[2-(1-benzylhexahydroazepino)]-propanoate (10B). Reaction of 1-(2-iodobenzyl)hexahydroazepine (160 mg, 0.5 mmol) with methyl methacrylate (0.16 mL, 1.5 mmol) under the typical standard conditions given above, afforded the starting material (9 mg, 6 %) and **10B** (76 mg, 55 % based on reacted starting material) as a pale yellow liquid; Rf 0.51 (EtOAc-hexane, 1:2, v/v); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.48-7.20 (5H, m), 3.89-3.58 (5H, m), 2.91-2.47 (3H, m), 2.09-1.91 (1H, m), 1.90-1.41 (10H, m), 1.12 (3H, d, *J* = 6.9 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 174.2, 139.1, 129.4 (2C), 128.6 (2C), 127.1, 59.9, 54.5, 52.0, 50.1, 37.2, 28.4 (2C), 27.3 (2C), 26.1, 17.6; IR (neat) 3065, 2931, 1738, 1457 cm^{-1}. MS *m/z* (EI) 289 (3), 288 (6), 189 (19), 188 (100). HRMS Calcd for $C_{18}H_{26}NO_2$ 288.1964, found M-1 288.1970.

Preparation of Methyl 2-methyl-3-[2-(1-benzylmorpholino)]propanoate (11B). Reaction of 1-(2-iodobenzyl)morpholine (150 mg, 0.5 mmol) with methyl methacrylate (0.16 mL, 1.5 mmol) under the typical standard conditions given above, gave the starting material (50 mg, 33 %) and **11B** (50 mg, 55 % based on reacted starting material) as a pale yellow liquid; Rf 0.39 (EtOAc-hexane, 1:2, v/v); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.31 (5H, m), 3.99 (1H, d, *J* = 13.6, Hz), 3.88-3.39 (8H, m), 3.26 (1H, d, *J* = 13.6 Hz), 2.73-1.42 (4H, m), 1.62-1.42 (1H, m), 1.17 (3H, d, *J* = 6.0 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 176.7, 138.9, 129.2 (2C), 128.9, 127.7, 127.0, 71.1, 68.0, 59.3, 58.9, 52.8 , 51.0, 37.8, 32.5, 20.1; IR ($CHCl_3$) 3066, 2962, 1740 cm^{-1}. MS *m/z* (EI) 277 (4), 177 (10), 176 (82). HRMS Calcd for $C_{16}H_{22}NO_3$ 276.1600, found M-1 276.1590

Preparation of Methyl 2-methyl-3-[2-(1-benzylthiomorpholino)]propanoate (12B). Reaction of 1-(2-iodobenzyl)thiomorpholine (150 mg, 0.5 mmol) with methyl methacrylate (0.15 mL, 1.5 mmol) under the typical standard conditions given above, yielded **12B** (32 mg, 23 %) as a pale yellow liquid; Rf 0.37 (EtOAc-hexane, 1:8, v/v); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.41-7.19 (5H, m), 3.71 (2H, s), 3.62 (3H, s), 3.09-2.85 (3H, m), 2.82-2.19 (5H, m), 2.15-1.97 (1H, m), 1.96-1.79 (1H, m), 1.16 (3H, d, *J* = 6.0 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 177.6, 139.4, 129.1 (2C), 128.9 (2C), 127.5, 57.4, 55.7, 52.1, 47.1, 37.1, 31.8, 28.5, 24.1, 18.3; IR (neat) 3063, 2955, 1739, 1456 cm^{-1}. MS *m/z* (EI) 293 (10), 292 (51), 246 (15), 91 (100). HRMS Calcd for $C_{16}H_{22}NO_2S$ 292.1371, found M-1 292.1368.

Preparation of Methyl 2-methyl-3-[3-(4-benzyl-1-formylpiperaz-ino)]propanoate (13B). Reaction of 1-formyl-4-(2-iodobenzyl)piperazine (150 mg, 0.45 mmol) with methyl methacrylate (0.15 mL, 1.4 mmol) under the typical standard conditions given above, gave **13B** (57 mg, 41 %) as a pale yellow liquid; Rf 0.30 (EtOAc-hexane, 2:1, v/v); ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.07 (1H, d, *J* = 3.0 Hz), 7.46-7.15 (5H, m), 3.82 (1H, d, *J* = 13.0 Hz), 3.78-3.12 (8H, m), 2.82-2.25 (4H, m), 2.20-1.97 (1H, m), 1.53-1.32

(1H, m) 1.17 (3H, d, J = 6.6 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 177.3, 161.5, 139.6, 129.2 (2C), 128.8 (2C), 127.7, 58.1, 57.3 and 56.7 (rotamer), 52.1, 48.8 and 48.0 (rotamer), 47.2 and 46.1 (rotamer), 45.1 and 44.8 (rotamer), 37.6 and 37.1 (rotamer), 30.9 and 30.2 (rotamer), 19.0 and 18.2 (rotamer) ; υ_{max} (neat) 3067, 2957, 1748, 1673, 1443 cm^{-1}. MS *m/z* (EI) 304 (11), 232 (16), 204 (13), 203 (95), 91 (100). HRMS Calcd for $C_{17}H_{24}N_2O_3$ 304.1787, found 304.1785.

Preparation of Methyl 2-methyl-3-[2-(1-benzyl-4-methylpiperaz-ino)]propanoate (14B). Reaction of 1-(2-iodobenzyl)-4-methylpiperazine (150 mg, 0.5 mmol) with methyl methacrylate (0.16 mL, 1.5 mmol) under the typical standard conditions given above, afforded **14B** (40 mg, 29 %) as a pale yellow liquid; R_f 0.46 (methanol); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.38-7.15 (5H, m), 3.98 (1H, d, J = 13.0 Hz), 3.66 (3H, s), 3.54 (1H, m), 3.25 (1H, d, J = 13.0 Hz), 2.85-1.96 (10H, m), 1.85 (1H, m), 1.52 (1H, m), 1.17 (3H, d, J = 6.9 Hz; ^{13}C NMR (50 MHz, $CDCl_3$) δ 176.9, 139.3, 129.0 (2C), 128.3 (2C), 127.2, 60.3, 58.8, 58.5, 55.3, 52.8, 51.0, 47.5, 38.0, 35.0, 20.0; IR (neat) 3056, 2935, 1734, 1452 cm^{-1}. MS *m/z* (EI) 290 (8), 232 (23), 189 (78), 119 (17), 91 (100). HRMS Calcd for $C_{17}H_{26}N_2O_2$ 290.1994, found 290.2006.

Preparation of Methyl 2-methyl-3-[3-(1-benzoyl-4-benzylpiperaz-ino)]propanoate (15B). Reaction of 1-benzyl-4-(2-iodobenzyl)piperazine (150 mg, 0.37 mmol) with methyl methacrylate (0.12 mL, 1.1 mmol) under the typical standard conditions given above, afforded **15B** (20 mg, 14 %) as a pale yellow liquid; R_f 0.23 (EtOAc-hexane, 2:1, v/v); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.70-6.96 (10H, m), 3.95-1.60 (15H, m), 1.19 (3H, d, J = 6.2 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 177.0, 171.0, 139.5, 136.3, 130.2-127.5 (10C and rotamers), 59.7, 58.1, 56.0, 52.2, 51.9 and 51.5 (rotamer), 48.8 and 48.2 (rotamer), 37.4 and 37.1(rotamer), 32.4, 19.5; IR (neat) 3063, 2937, 1734, 1636, 1433 cm^{-1}. MS *m/z* (EI) 380 (5), 279 (46), 188 (14), 137 (23). HRMS Calcd for $C_{23}H_{27}N_2O_3$ 379.2022, found M-1 379.2017.

Preparation of Methyl 2-methyl-3-[3-(4-benzyl-1-ethoxycarbonylpiperazino)]-propanoate (16B). Reaction of 4-ethoxycarbonyl-1-(2-iodobenzyl)piperazine (150 mg, 0.4 mmol) with methyl methacrylate (0.13 mL, 1.2 mmol) under the typical standard conditions given above, yielded the starting material (14 mg, 9 % recovery) and **16B** (36 mg, 29 % based on reacted starting material) as a pale yellow liquid; R_f 0.35 (EtOAc-hexane, 1:2, v/v); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.38-7.19 (5H, m), 4.13 (2H, q, J = 7.1 Hz), 3.91-3.22 (9H, m), 2.76-2.48 (3H, m), 2.45-2.19 (1H, m), 2.17-1.76 (1H, m), 1.60-1.35 (1H, m), 1.25 (3H, t, J = 7.1 Hz), 1.18 (3H, d, J = 5.8 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 176.7, 155.8, 139.0, 129.1 (2C), 128.7 (2C), 127.4, 62.4, 58.8, 57.7, 52.8, 48.5, 47.5, 44.1, 38.1, 32.0, 20.0, 16.3; IR (neat) 3061, 2991, 1738, 1703, 1446 cm^{-1}. MS *m/z* (EI) 348 (11), 347 (17), 248 (16), 247 (96), 232 (14). HRMS Calcd for $C_{19}H_{27}N_2O_4$ 347.1971, found M-1 347.1965.

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