Supplementary Information

Selective monomethylation of primary amines with simple electrophiles

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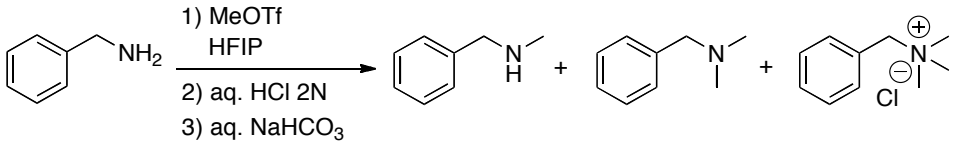
General remarks

^{1}H NMR spectra were obtained on a Bruker 300. In all measurements CD_3OD was used as solvent unless otherwise noted. Chemical shifts δ are given in ppm relative to TMS as internal standard. Microflow reactions were performed with Harvard Apparatus syringe pumps (Pump 11 Elite) equipped with Hamilton gastight syringes. Peek (P-885) T-shaped micromixers with swept volume of 29 nL were manufactured by IDEX Health & Science. Peek (1532) microtubes with inner diameter of 500 µm and peek fittings were also purchased from IDEX Health & Science. All chemicals were used as provided without further purification. The conversion of amine into products was measured by ^{1}H NMR spectra directly from the crude product for benzylamine derivatives and for the other ones was added 3-bromotoluene as an internal standard.

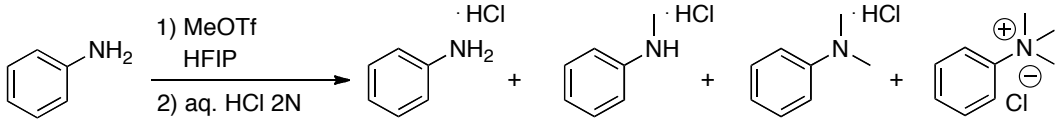
Experimental procedures

Typical procedure for the methylation of benzylamine



To a solution of HFIP (1.0 mL, 10 mmol) and benzylamine (109 µL, 1 mmol) was added MeOTf (164 µL, 1.5 mmol). The mixture was stirred for 1 h at room temperature and then quenched by a solution of HCl (2N, 1 mL). Volatiles were evaporated under reduced pressure, and the resulting mixture was neutralised with a saturated aqueous solution of $NaHCO_3$ and extracted with CH_2Cl_2 (3×5 mL). Combined organic phases were dried over $MgSO_4$, filtered and solvent was removed under reduced pressure. The crude product was analysed by ^{1}H NMR.

Typical procedure for the methylation of aniline



To a solution of HFIP (1.0 mL, 10 mmol) and aniline (91 µL, 1 mmol) was added MeOTf (164 µL, 1.5 mmol). The mixture was stirred for 1 h at room temperature and then quenched by a solution of HCl (2N, 1 mL). Volatiles were evaporated under reduced pressure. 3-Bromotoluene (123 µL, 1 mmol) was added to the crude product and a ^{1}H NMR analysis was performed.

Further experimental data

Kinetic study of the methylation of benzylamine

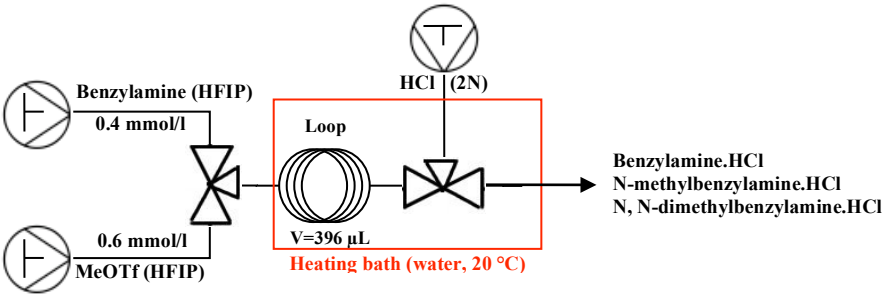


Figure S1: A flow microreactor for the methylation of benzylamine

Kinetic study was performed in a flow microreactor (Figure 1). The first syringe (3 mL) was filled with a mixture of benzylamine (330 µL, 3.03 mmol) in HFIP (1.67 mL). The second syringe (3 mL) contained a mixture of MeOTf (495 µL, 4.52 mmol) and HFIP (1.51 mL, 14.33 mmol). The reaction was quenched *in-situ* by a solution of aq. HCl (2N). Results of this study are shown below (Table S1 and Fig S2).

Table S1: Methylation of benzylamine with 1.5 equivalent of MeOTf in a flow microreactor

Time (min)	Benzylamine	N-methylbenzylamine	N, N-dimethylbenzylamine
0.5	70%	27%	3%
3	57%	41%	3%
7	41%	54%	5%
15	32%	62%	7%

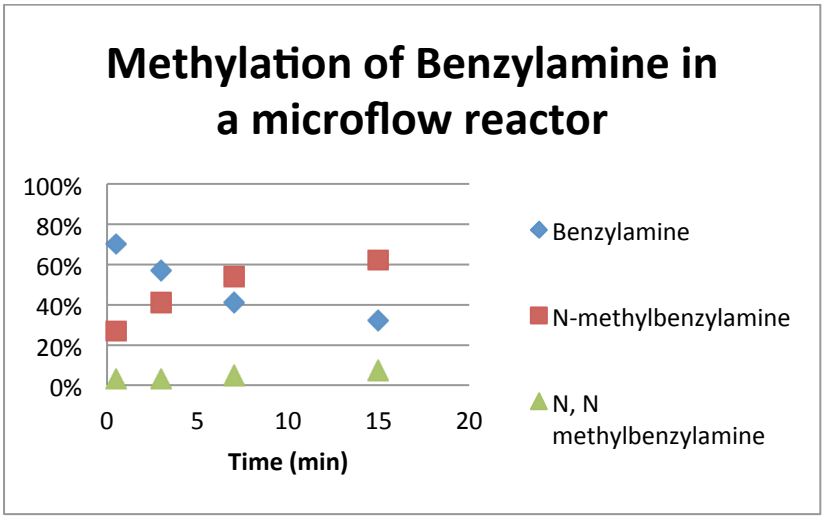
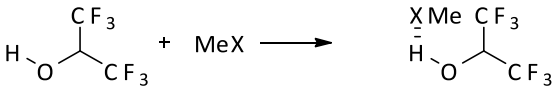


Figure S2: Methylation of benzylamine with 1.5 equivalent of MeOTf

Influence of HFIP on the methylating reagent

This study was performed to show the influence of HFIP on the methylating reagent. The variation of δ_{OH} (HFIP) in ^{1}H NMR according to the number of equivalents of methylating reagent was monitored.

Typical procedure



HFIP (50 µL, 475 µmol) and 600 µL of $CDCl_3$ were added into a NMR tube and a ^{1}H NMR spectrum was taken. The amount of methylating reagent was increased step by step (0, 0.5, 1, 1.5 and 2 eq) and each time a ^{1}H NMR spectrum was recorded (Fig S3).

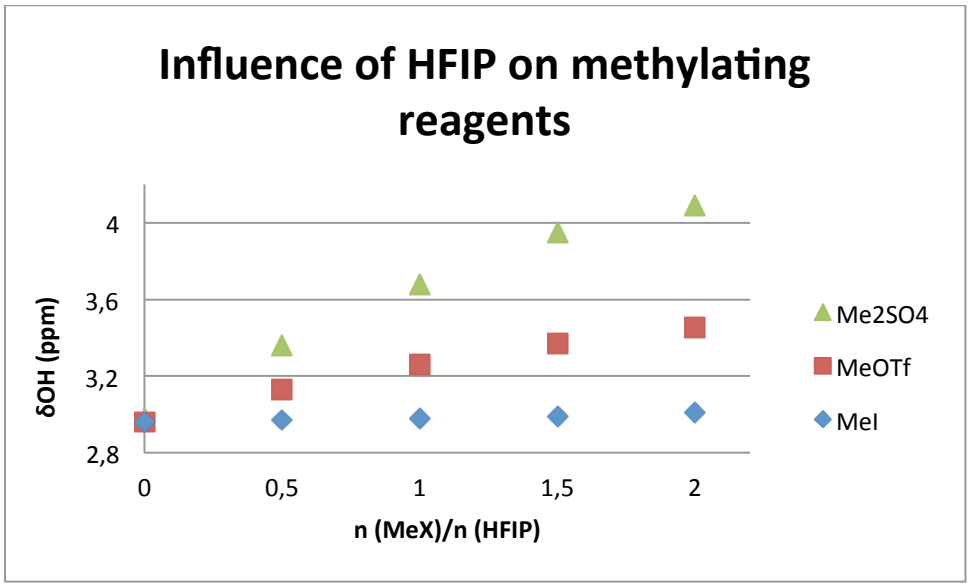


Figure S3 $\Delta\delta_{OH}$ according to MeX (MeOTf, Me_2SO_4 or MeI)

^{1}H NMR spectra

Amines are under hydrochloride salt form and the corresponding ^{1}H NMR spectra were recorded in CD_3OD, except where indicated.

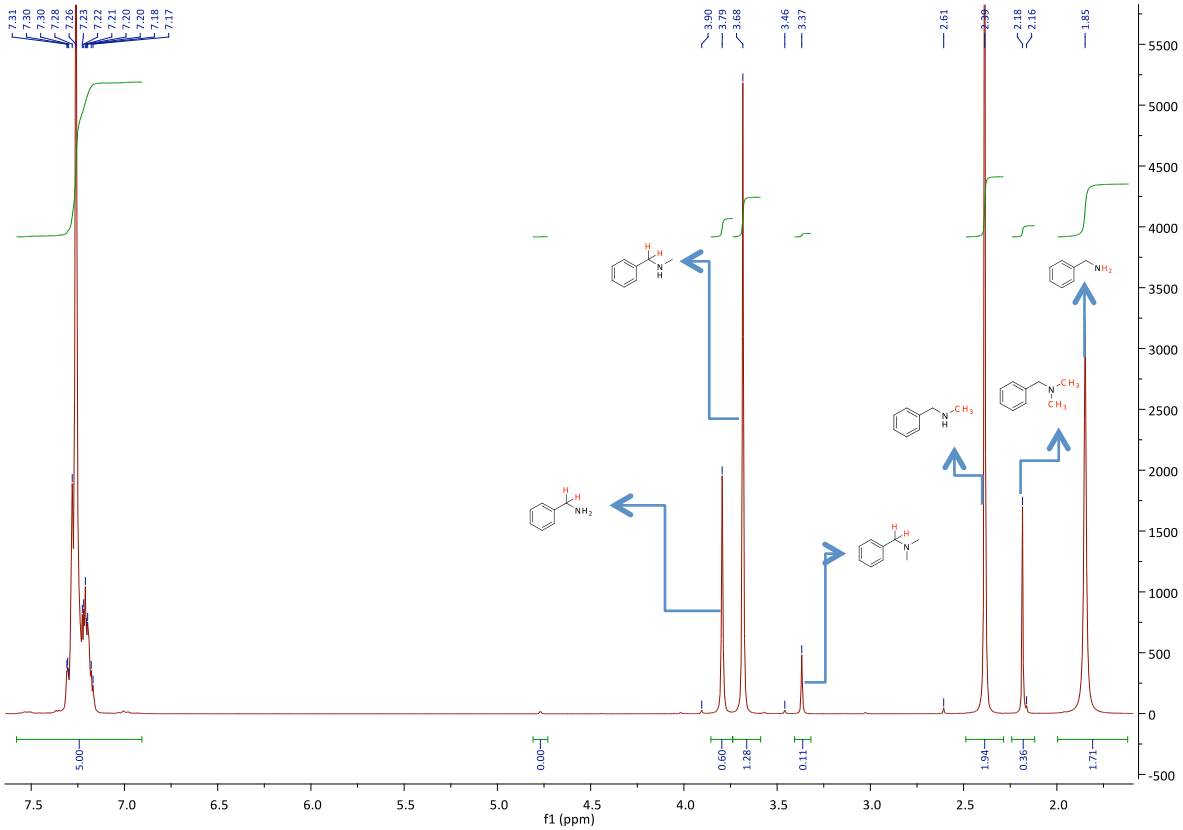


Table 1 ($CDCl_3$, free amine)

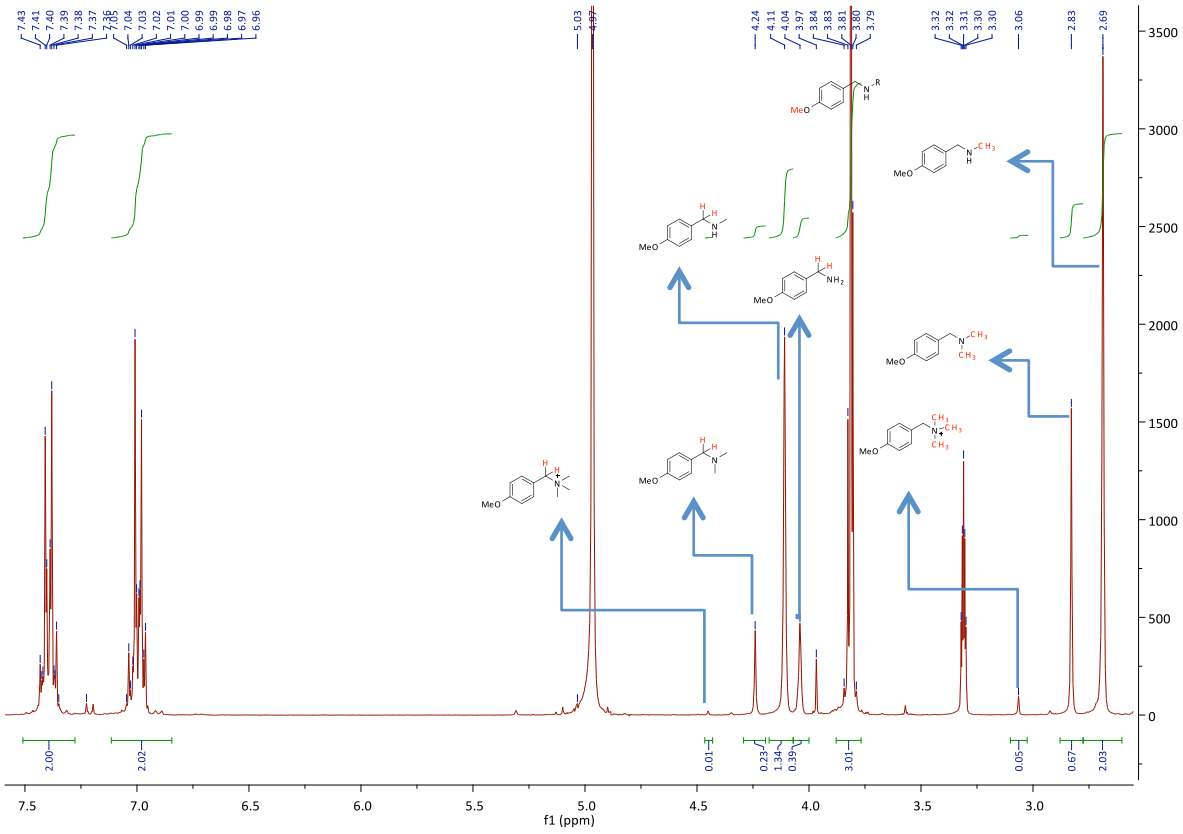
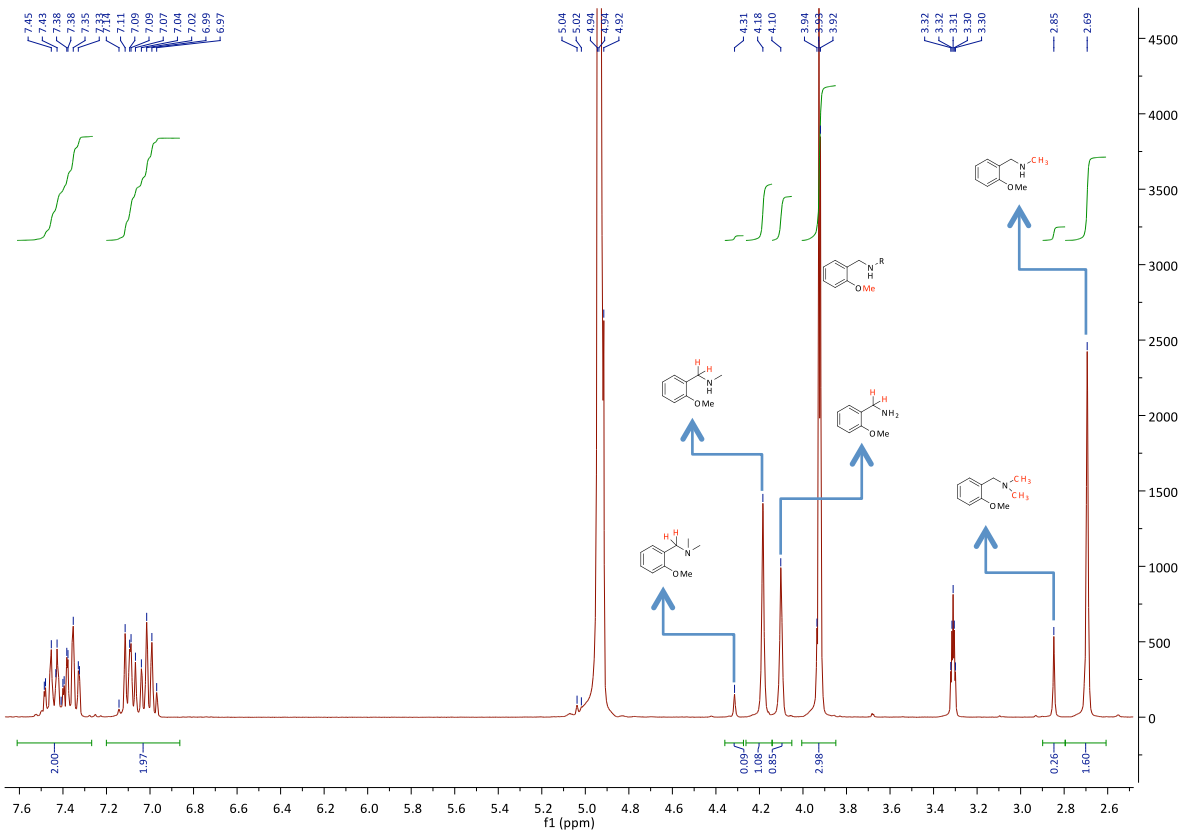


Table 2, entry 1



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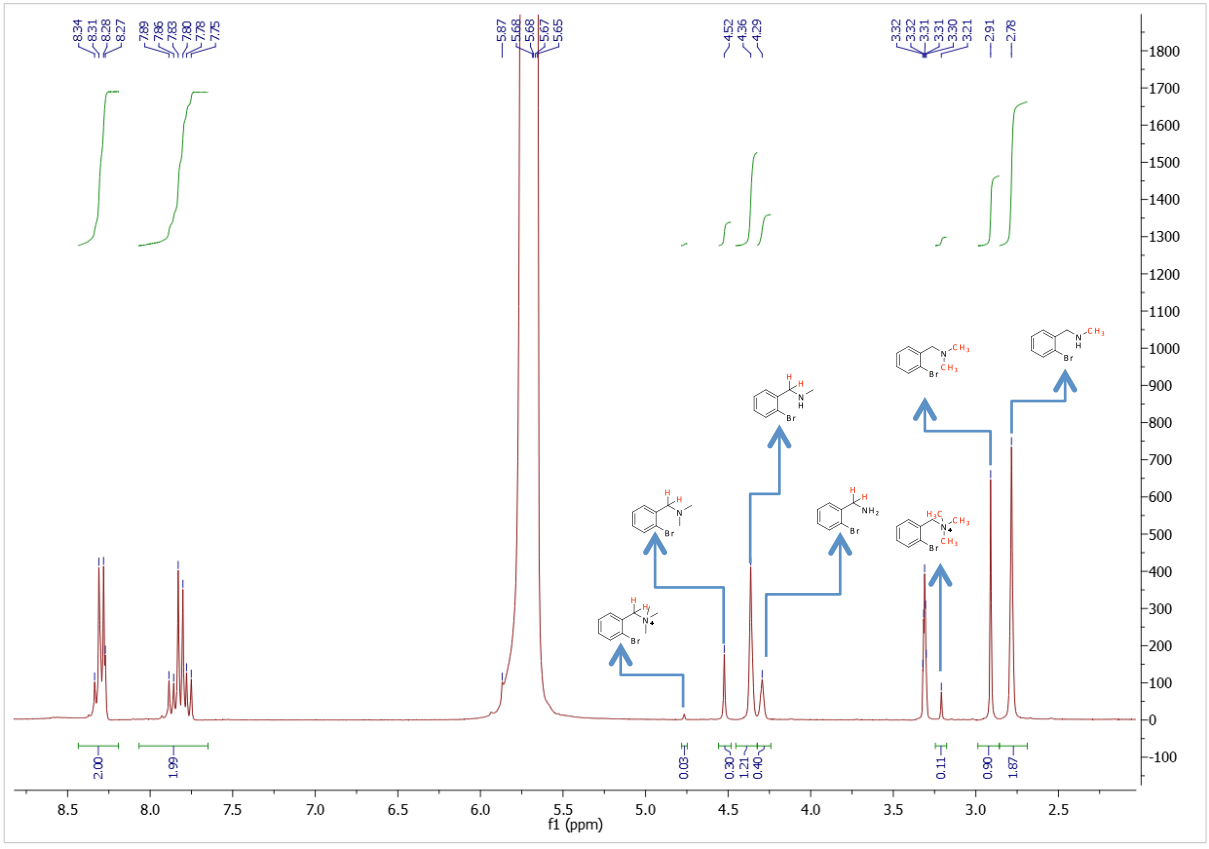

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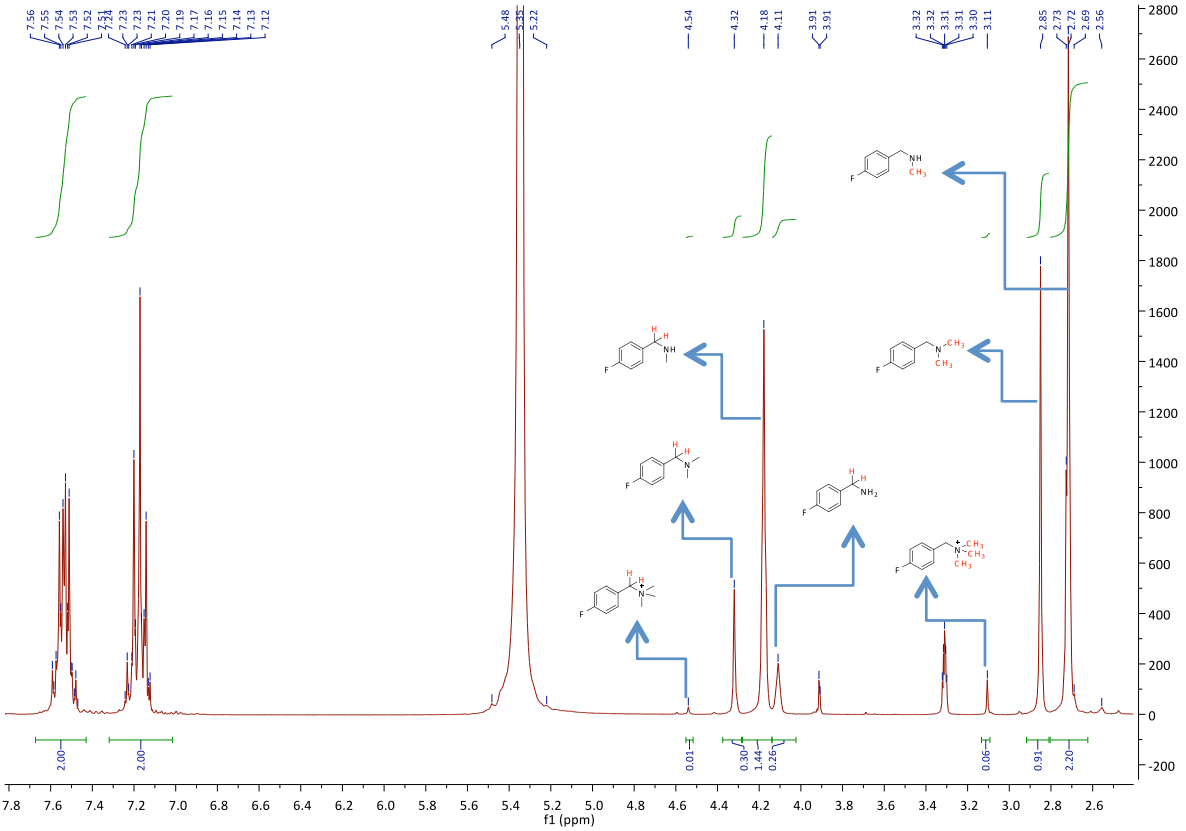

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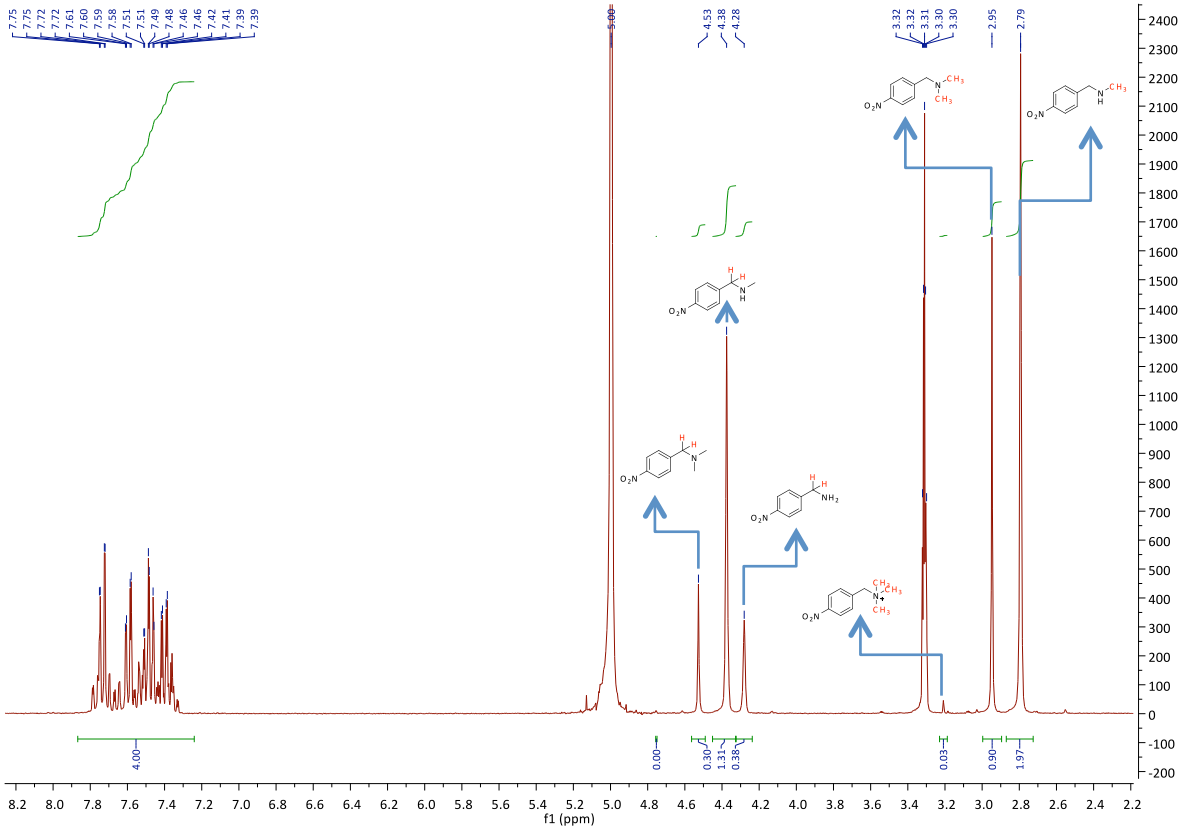

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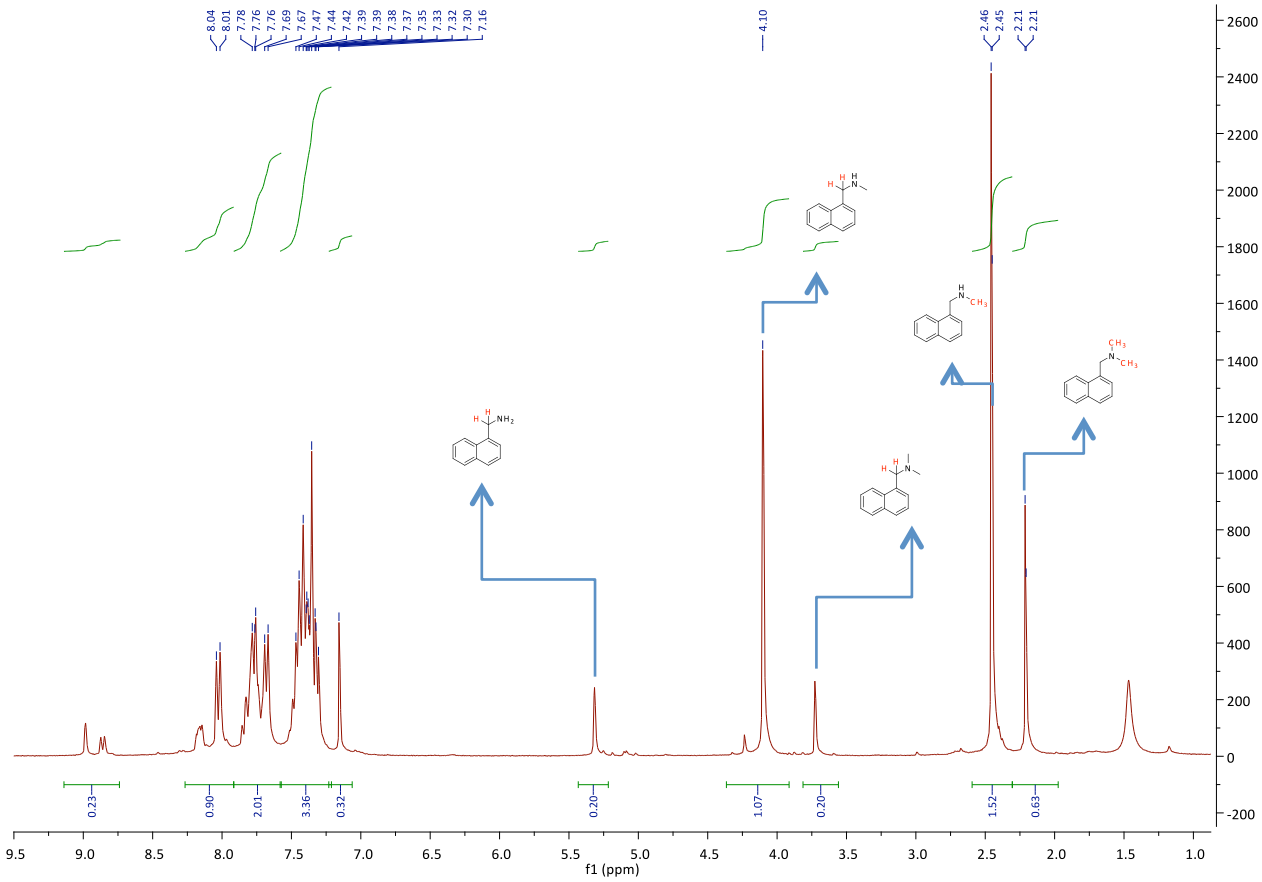
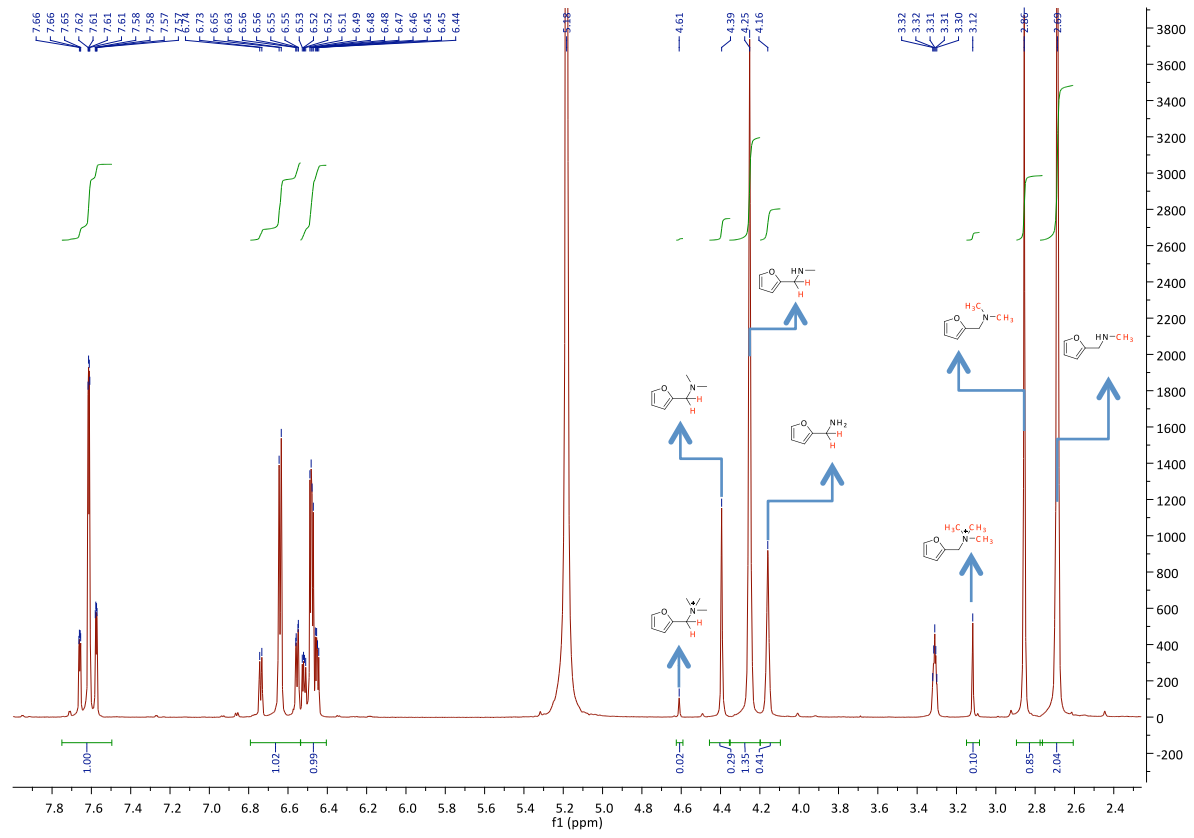


Table 2, entry 6 ($CDCl_3$, free amine)



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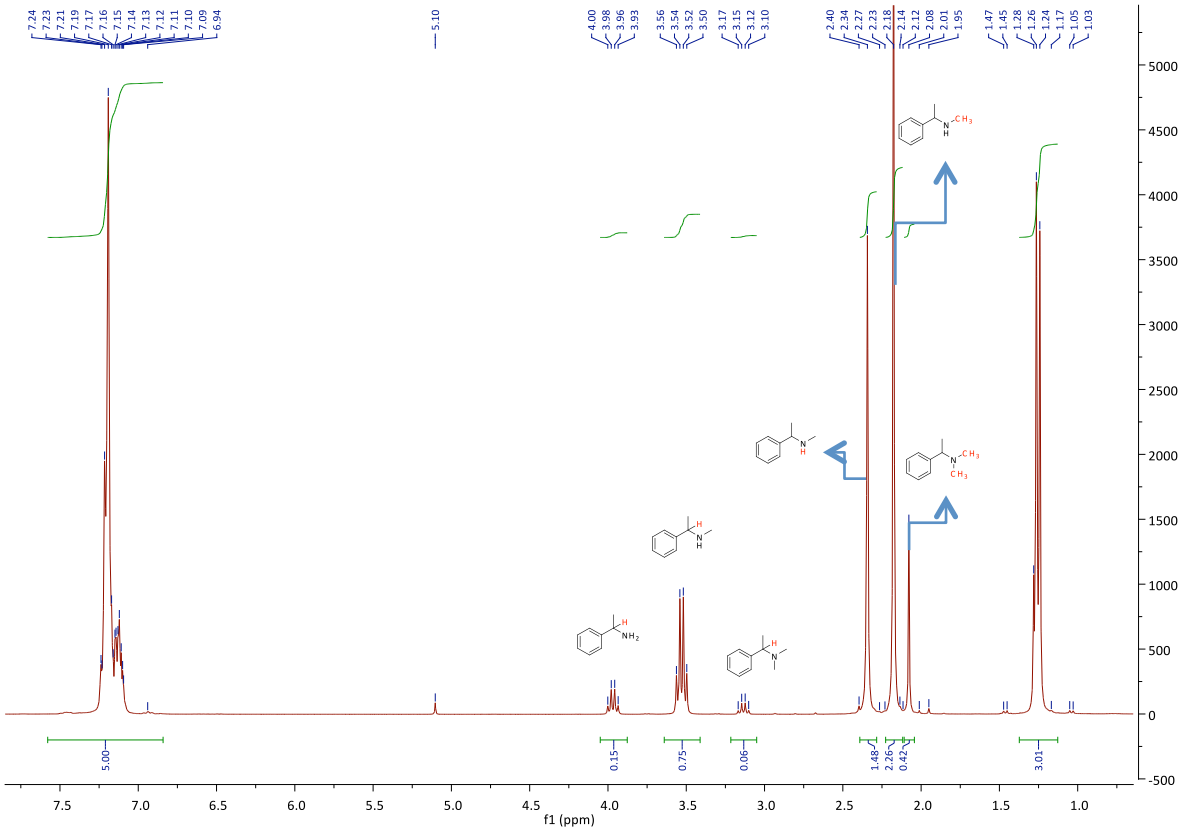

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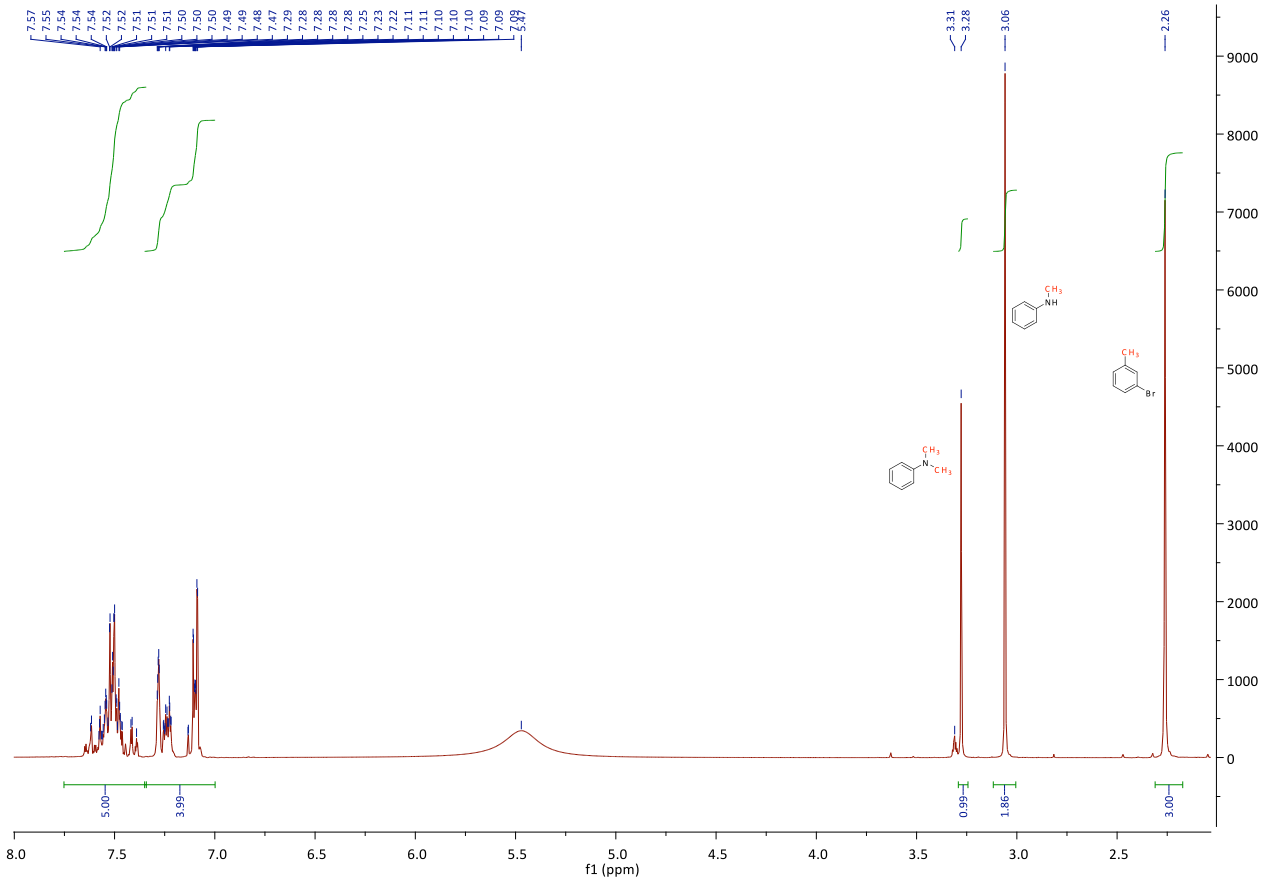

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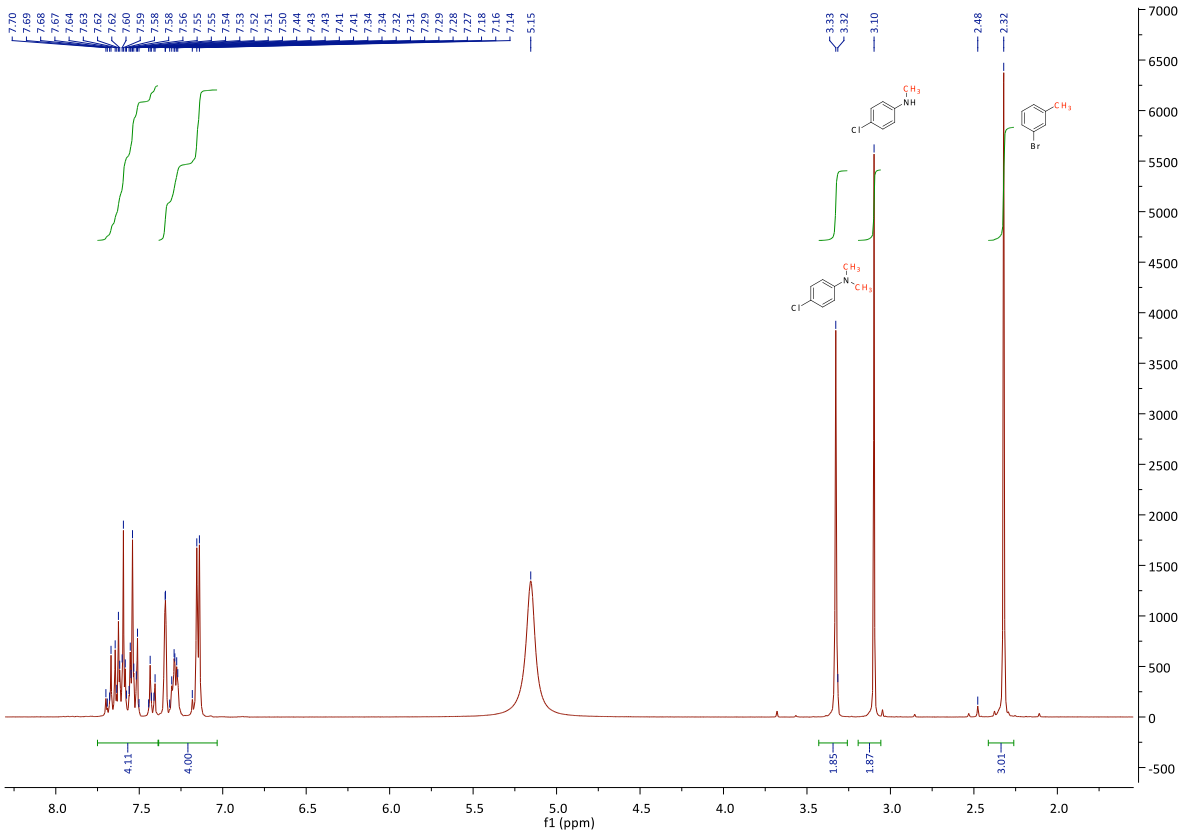

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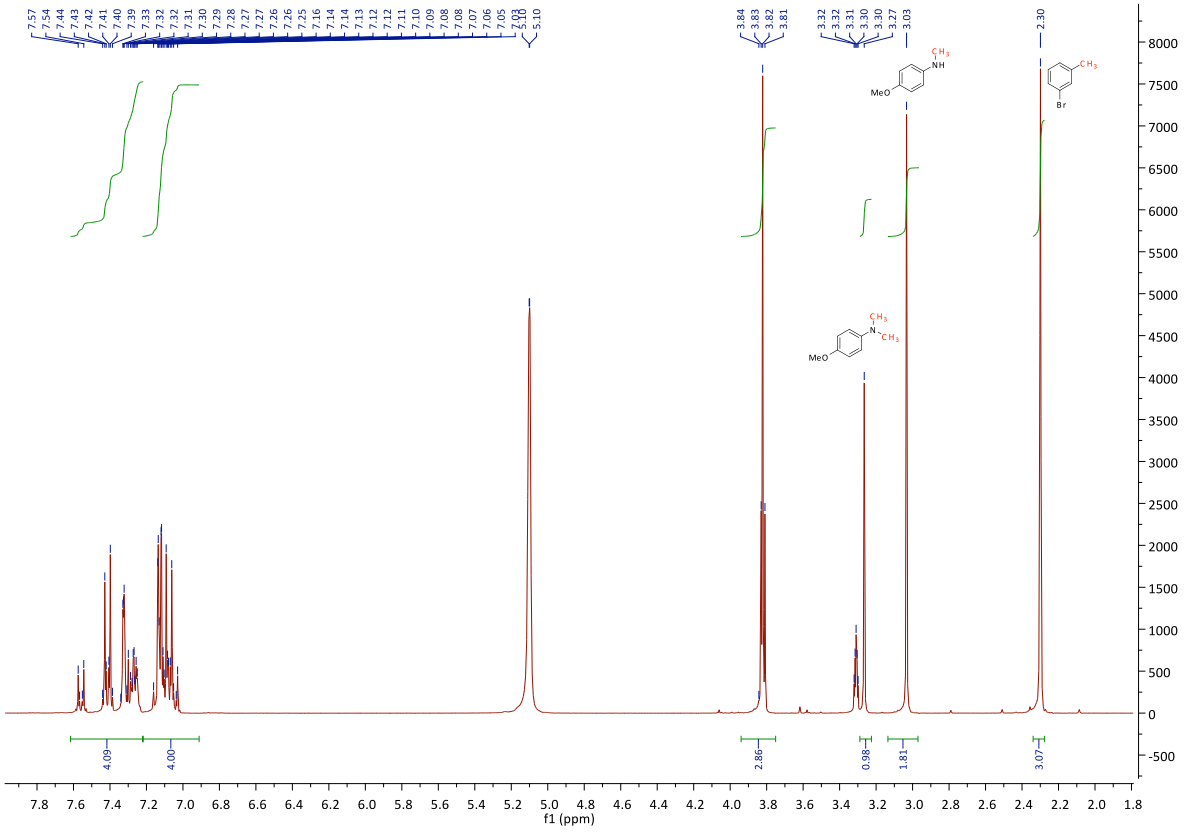

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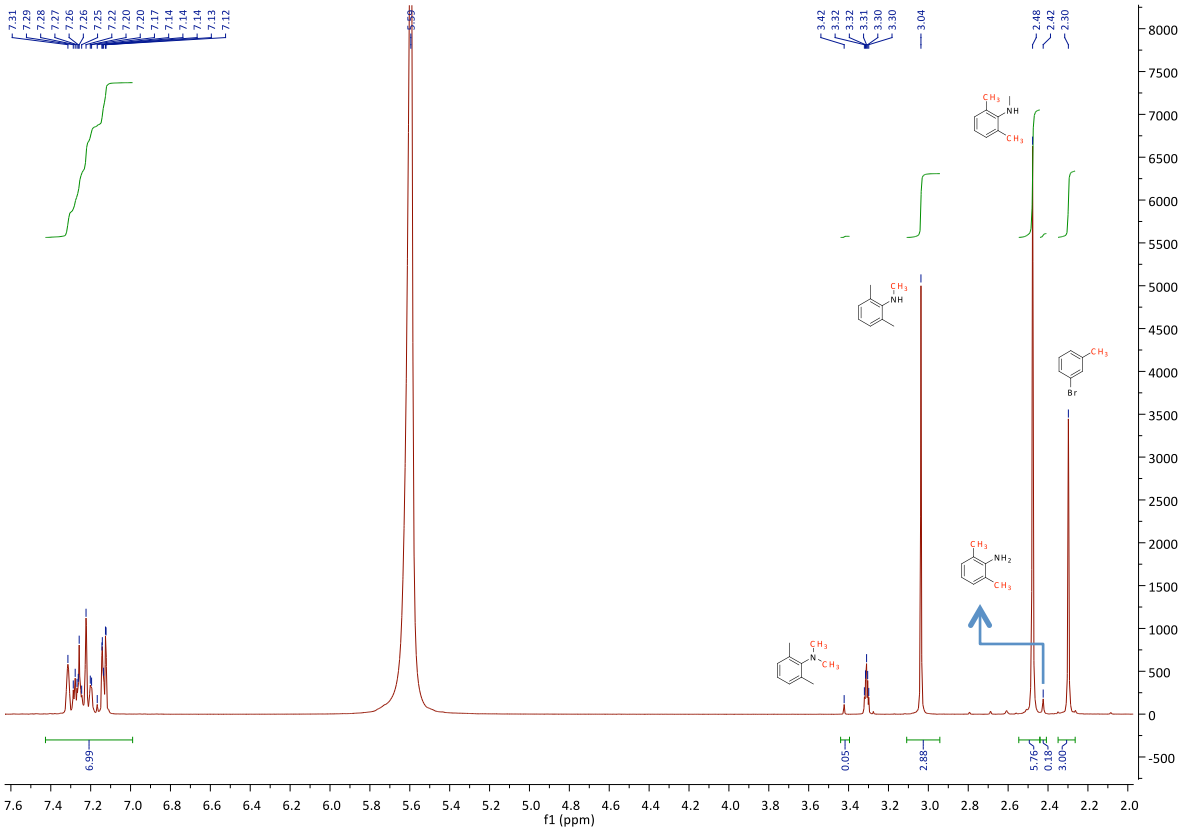

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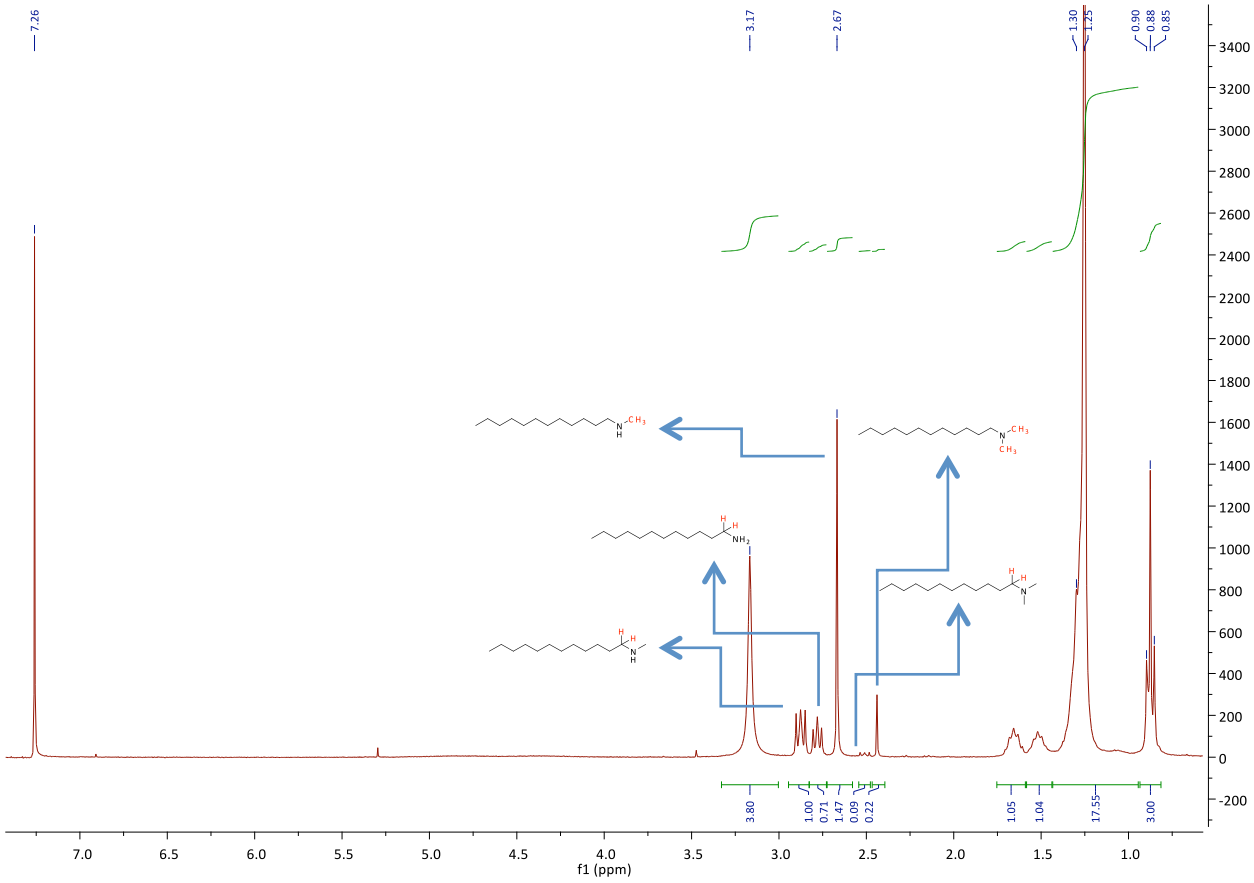

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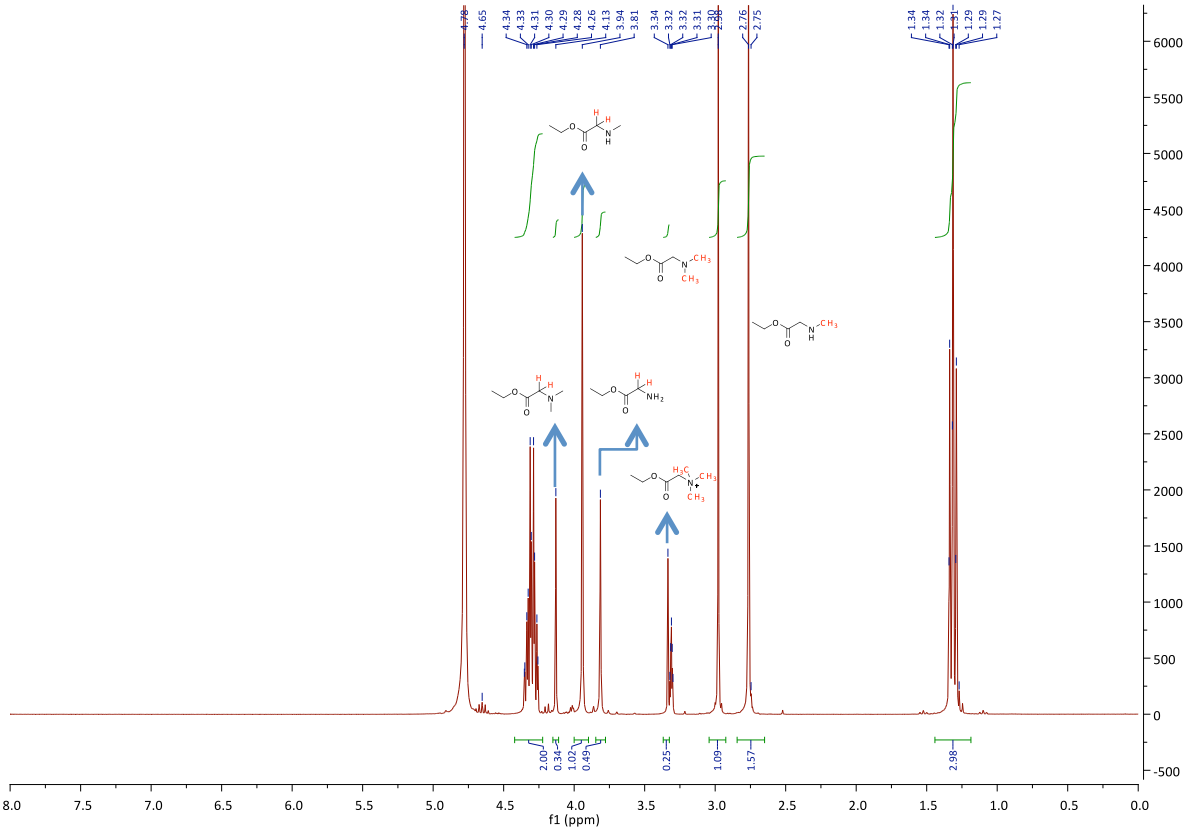

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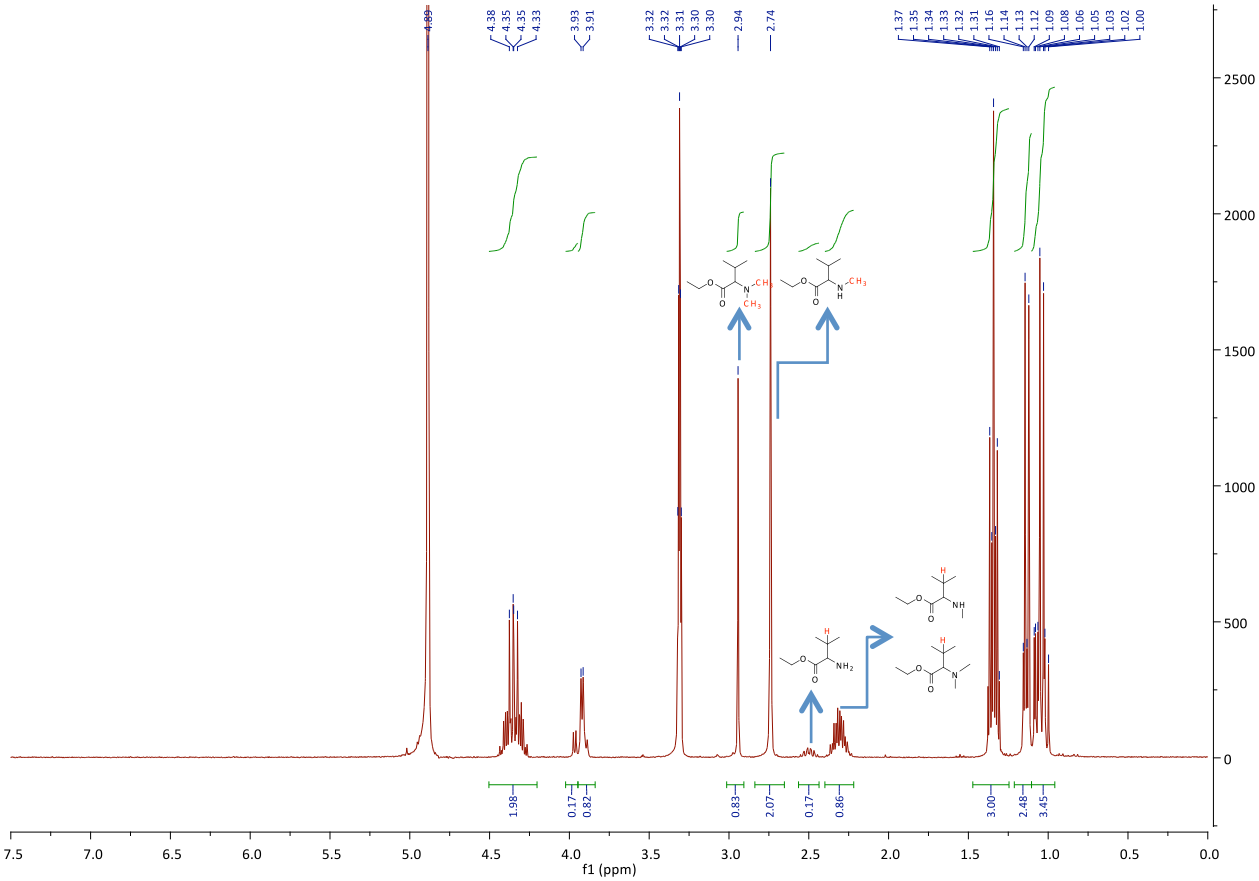

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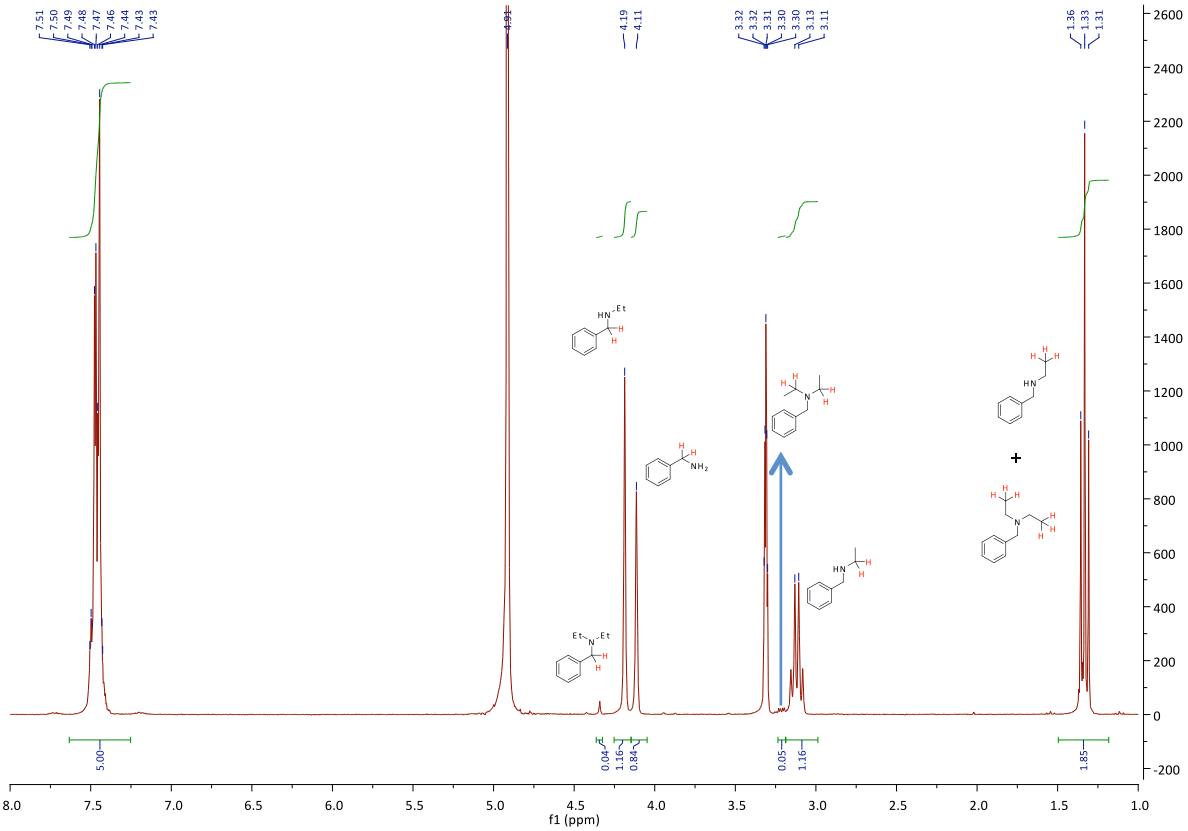

Ethylation of benzylamine