Direct N-Acetyl Enamine Formation: Lithium Bromide Mediated Addition of Methyllithium to Nitriles

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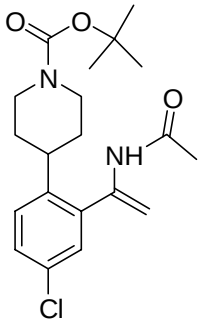
General Methods. Reagents and solvents were obtained from commercial suppliers and were used without further purification or drying unless otherwise noted. Chromatography was done on silica gel (70-230 mesh). ^{1}H NMR and ^{13}C NMR spectra were recorded at 400 or 500 and 100 MHz, respectively as stated in the text.

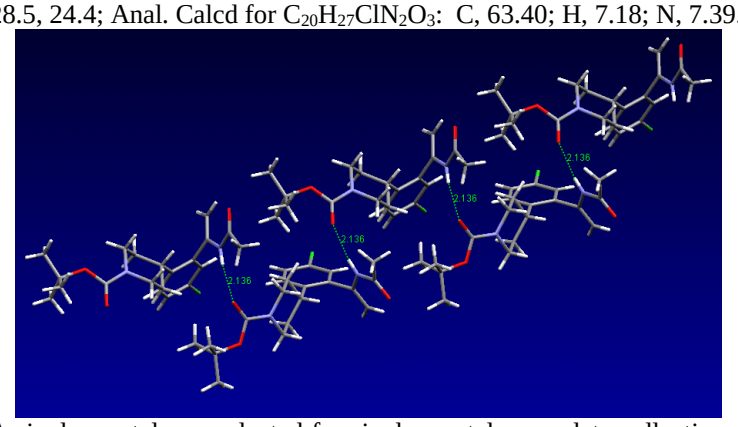
General Procedure. Enamide Formation using MeLi.LiBr as a complex

To a flask under N_2 is added nitrile and MTBE (12 volumes). The homogeneous solution is cooled to -30 ºC (+/- 5 ºC) and MeLi.LiBr (1.5 M in Et2O) is added at a rate such that the temperature remains <-10 ºC. After a 30-60 minute age, the solution is further cooled to -50 ºC (+/- 5 ºC). Acetic anhydride in MTBE (3.4 M) is added at a rate such that the temperature remains <-35 ºC. The reaction is then allowed to warm to room temperature and aged overnight. MTBE and 6.5 wt% K_2HPO_4 (aq) are added. The mixture is stirred, the layers allowed to settle, and the aqueous layer is cut. The organic layer is washed with 6.5 wt% K_2HPO_4 (aq). The solution is solvent switched to EtOH and 5N NaOH is added until the apparent pH=12 and the bis –acetylated compound is consumed. The reaction mixture is either concentrated to dryness and then submitted to column chromatography on silica gel or the enamide is isolated directly by crystallization (EtOAc or MTBE with heptane or hexanes crystallization – alternatively, EtOH:H_2O crystallization can be done and is highly desirable for better subsequent asymmetric hydrogenation at low catalyst loading). In the case of EtOH:H_2O crystallization, H_2O is slowly added to a solution of the enamide in EtOH at rt (seeding the solution saturation point),



4-[2-(1-Acetylaminovinyl)-4-chlorophenyl]-piperidine-1-carboxylic acid *tert*-butyl ester, 1a

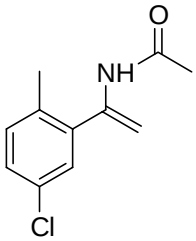
Crystallization from EtOH:H_2O, 2:1 afforded the desired product as white crystals (1.5 g, 80%). mp 213-215 ºC; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.28 (dd, *J* = 8.4, 2.2 Hz, 1H), 7.20 (d, *J* = 2.2 Hz, 1H), 7.17 (d, *J* = 8.4 Hz, 1H), 7.07 (br s, 1H), 5.97 (br s, 1H), 4.64 (br s, 1H), 4.16 (app. d, *J* = 12.8 Hz, , 2H), 2.94 (tt, *J* = 11.6 Hz, 3.2 Hz, 1H), 2.78-2.62 (m, 2H), 2.00 (s, 3H), 1.67-1.51 (m, 4H), 1.44 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 168.6, 154.8, 142.4, 139.5, 138.8, 131.7, 129.4, 129.0, 128.1, 103.6, 79.6, 44.3, 38.2, 33.5, 28.5, 24.4; Anal. Calcd for $C_{20}H_{27}ClN_2O_3$: C, 63.40; H, 7.18; N, 7.39. Found: C, 63.59; H, 7.36; N, 7.61.



A single crystal was selected for single crystal x-ray data collection on a Bruker Smart Apex system. The crystal was colorless polyhedron with dimensions of 0.28 mm x 0.26 mm x 0.14 mm. The unit cell was collected on 10 second scan rate and indexing gave the cell setting to be monoclinic. The structure was solved in the monoclinic P21/c space group after a full quadrant data collection using 10 second scan rate. See Table 1 for tabulated information pertaining to the final specifications of the solved structure.

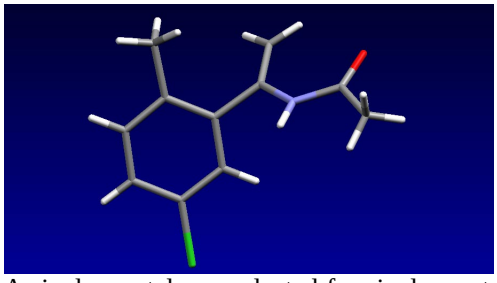
Table 1. Crystal data and structure refinement for jrc0931m.

Identification code	jrc0931m		
Empirical formula	C20 H27 Cl N2 O3		
Formula weight	378.89		
Temperature	298(2) K		
Wavelength	0.71073 A		
Crystal system, space group	Monoclinic,	P2(1)/c	
Unit cell dimensions	a = 10.658(5) A	alpha = 90 deg.	
	b = 15.006(7) A	beta = 109.975(7) deg.	
	c = 13.850(6) A	gamma = 90 deg.	
Volume	2081.9(16) A^3		
Z, Calculated density	4,		1.209 Mg/m^3
Absorption coefficient	0.204 mm^-1		
F(000)	808		
Crystal size	0.28 x 0.26 x 0.14 mm		
Theta range for data collection	2.03 to 23.25 deg.		
Limiting indices	-11<=h<=11,		
	-16<=k<=16,		
	-15<=l<=15		
Reflections collected / unique	16863 / 2991 [R(int) = 0.0671]		
Completeness to theta = 23.25	100.0 %		
Absorption correction	None		
Refinement method	Full-matrix least-squares on F^2		
Data / restraints / parameters	2991 / 0 / 239		
Goodness-of-fit on F^2	1.074		
Final R indices [I>2sigma(I)]	R1 = 0.0426,	wR2 = 0.1169	
R indices (all data)	R1 = 0.0534,		wR2 = 0.1230
Largest diff. peak and hole	0.285 and -0.330 e.A^-3		



***N*-(1[-3-chloro-5-tolyl]vinyl)-acetamide, 1b**

Crystallization from EtOH:H_2O afforded the desired product as white crystals (1.6 g, 90%). mp 109-110 ºC; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.22-7.18 (m, 2H), 7.12 (d, *J* = 8.0 Hz, 1H), 6.93 (br s, 1H), 5.95 (s, 1H), 4.67 (s, 1H), 2.29 (s, 3H), 1.99 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 168.8, 140.0, 139.3, 134.3, 131.7, 131.4, 129.0, 128.4, 103.2, 24.3, 19.0.

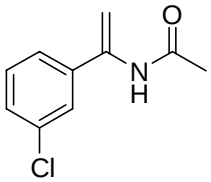


A single crystal was selected for single crystal x-ray data collection on a Bruker Smart Apex system. The crystal was pale yellow polyhedron with dimensions of 0.45 mm x 0.25 mm x 0.22 mm. The unit cell was collected on 5 second scan rate and indexing gave the cell setting to be triclinic. The structure was solved in the triclinic P1 space group after a quadrant data collection using 5 second scan rate. See Table 1 for tabulated information pertaining to the final specifications of the solved structure.

Table 1

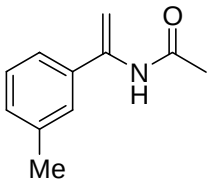
Identification code	jrc1001m	
Empirical formula	C_{11} H_{12} Cl N O	
Formula weight	209.67	
Temperature	298(2) K	
Wavelength	0.71073 A	
Crystal system, space group	Triclinic,	P-1
Unit cell dimensions	a = 9.577(3) A	alpha = 70.632(4) deg.
	b = 11.401(3) A	beta = 81.354(4) deg.
	c = 11.847(3) A	gamma = 68.533(4) deg.
Volume	1135.1(5) A^3	
Z, Calculated density	4, 1.227 Mg/m^3	
Absorption coefficient	0.305 mm^{-1}	
F(000)	440	
Crystal size	0.45 x 0.25 x 0.22 mm	
Theta range for data collection	1.82 to 23.25 deg.	
Limiting indices	-10<=h<=10,	
	-12<=k<=12,	
	-13<=l<=13	
Reflections collected / unique	9424 / 3269 [R(int) = 0.2564]	
Completeness to theta = 23.25	100.0 %	
Absorption correction	None	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3269 / 0 / 257	
Goodness-of-fit on F^2	1.065	

Final R indices [I>2sigma(I)]	R1 = 0.0682,	wR2 = 0.1602
R indices (all data)	R1 = 0.0906,	wR2 = 0.1760
Largest diff. peak and hole	0.276 and -0.523 e.A^{-3}	



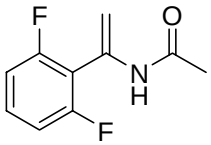
***N*-[1-(3-chlorophenyl)-vinyl]-acetamide, 1c**[1]

The amide was purified via column chromatography on silica gel (2:1, Hexanes:EtOAc) to afford the desired product as a yellow oil (19.88g, 70% yield). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.40 (s, 1H), 7.34-7.28 (m, 2H), 6.99 (br s, 1H), 5.81 (br s, 1H), 5.11 (br s, 1H), 2.12 (s, 3H).



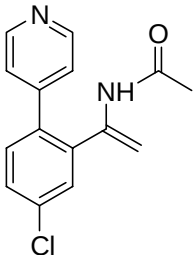
***N*-(1-*m*-tolylvinyl)-acetamide, 1d**[2]

The enamide was purified via column chromatography on silica gel (3:1, Hexanes:EtOAc) to afford the desired product as white solid (5.43 g, 73% yield). mp 103-105 ºC; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.28-7.07 (m, 5H), 5.82 (s, 1H), 5.06 (s, 1H), 2.37 (s, 3H), 2.09 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 169.1, 140.6, 138.3, 129.3, 128.5, 126.7, 123.1, 102.1, 24.4, 21.3; Anal. Calcd for $C_{11}H_{13}NO$: C, 75.40; H, 7.48; N, 7.99. Found: C, 75.43; H, 7.55; N, 7.93.



***N*-[1-(2,6-difluorophenyl)-vinyl]-acetamide, 1e**[3]

The enamide was purified via column chromatography on silica gel (3:1, Hexanes:EtOAc) to afford the desired product as white solid (2.41 g, 85% yield). mp 130-132 ºC; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.32-7.24 (m, 1H), 7.02-6.88 (m, 3H), 6.06 (s, 1H), 4.94 (s, 1H), 2.04 (s, 3H).



***N*-[1-(5-Chloro-2-pyridin-4-yl-phenyl)-vinyl]-acetamide, 1f**

The enamide was purified via column chromatography on silica gel (1:4, Hexanes:EtOAc to 1:1:0.1 Hexanes:EtOAC:MeOH) to afford the desired product as white solid (0.25 g, 76% yield). mp 170-172 ºC; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.55 (dd, *J* = 4.4, 1.6 Hz, 2H), 7.46 (d, *J* = 2.4 Hz, 1H), 7.41 (dd, *J* = 8.0, 2.4

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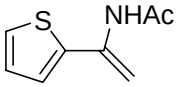
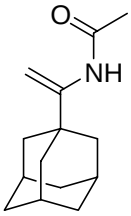
[1] Gridnev, H. D.; Yasutake, M.; Higashi, N.; Imamoto, T. *J. Am. Chem. Soc.* **2001**, *123*, 22, 5268-5276.
[2] Zhu, G.; Zhang, X. *J. Org. Chem.* **1998**, *63*, 25, 9590-9593.
[3] Burk, M. J.; Wang, Y. M.; Lee, J. R. *J. Am. Chem. Soc.* **1996**, *118*, 21, 5142-5143.

Hz, 1H), 7.33 (dd, *J* = 4.4, 1.6 Hz, 2H), 7.24 (d, *J* = 8. 0 Hz, 1H), 5.59 (s, 1H), 4.84 (s, 1H), 1.55 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 168.2, 149.7, 147.7, 139.3, 138.6, 135.2, 134.8, 131.2, 130.2, 129.1, 123.2, 106.4, 23.5; HRMS 272.0716 for $C_{15}H_{13}ClN_2O$ (real – [M+H] 273.0800, 4 ppm error).



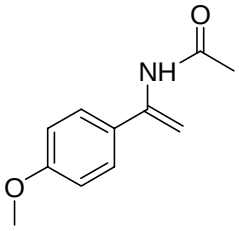
***N*-(1-Thiophene-2-yl-vinyl)-acetamide, 1f**[4]

The enamide was purified via column chromatography to afford the desired product as colorless oil (0.3 g, 60 % yield); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.56 (br s, 1H), 7.18 (d, *J* = 4.0 Hz, 1H), 7.08 (d, *J* = 4.0 Hz, 1H), 6.94 (t, *J* = 4.0 Hz, 1H), 5.63 (br s, 1H), 5.20 (br s, 1H), 2.04 (s, 3H).



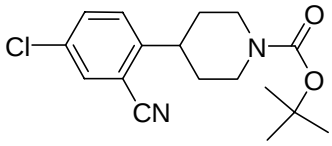
***N*-(1-Adamantan-1-yl-vinyl)-acetamide, 1h**[5]

The enamide was purified via crystallization from EtOH:H_2O, 2:1 to afford the desired product as a white solid (2.21 g, 79 % yield). mp 155-156 ºC; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.45 (br s, 1H), 5.54 (br s, 1H), 4.75 (br s, 1H), 2.09-2.05 (m, 6H), 1.77-1.65 (m, 12H).



***N*-[1-(4-Methoxyphenyl-vinyl]-acetamide, 1i**[6]

The enamide was purified via column chromatography on silica gel to afford the desired product as a white solid (0.2 g, 62 % yield). mp 105-106 ºC; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.35 (d, *J* = 8.2 Hz, 2H), 6.88 (d, *J* = 8.2 Hz, 2H), 6.81 (br s, 1H), 5.77 (br s, 1H), 5.02 (br s, 1H), 3.82 (s, 3H), 2.13 (s, 3H).



***tert*-Butyl 4-(4-chloro-2-cyanophenyl)piperidine-1-carboxylate, 2a**

Prepared as previously described in the literature.[7] mp 97–99 ºC; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.61 (d, *J* = 2.2 Hz, 1H), 7.55 (dd, *J* = 8.6, 2.2 Hz, 1H), 7.29 (d, *J* = 8.6 Hz, 1H), 4.28 (br s, 2H), 3.11 (tt, *J* = 12.2, 3.5 Hz, 1H), 2.87 (app t, *J* = 12.0 Hz, 2H), 1.85 (app d, *J* = 13.1 Hz, 2H), 1.66–1.54 (m, 2H), 1.49 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 154.5, 147.5, 133.3, 132.5, 132.4, 127.8, 116.5, 113.3, 79.6, 43.9, 40.4,

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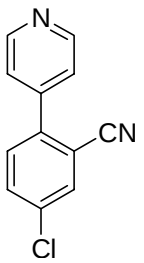
[4] Minnaard, A. J.; Vries, A. H. de; Vries, J. G. de; Feringa, B. L. *Adv. Synth. Catal.* **2002**, *344*, 9, 1003-1007.

[5] Burk, M. J.; Casy, G.; Johnson, N. B. *J. Org. Chem.* **1998**, *63*, 6084-6085.

[6] Zhu, G.; Zhang, X. *J. Org. Chem.* **1998**, *63*, 25, 9590-9593.

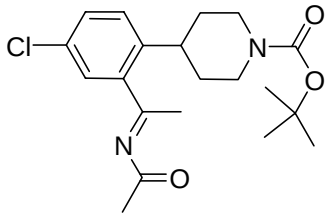
[7] Corley, E.; Conrad, K.; Murry, J.; Savarin, C.; Holko, J.; Boice, G. *J. Org. Chem.* **2004**, *69*, 5120-5123.

32.2, 28.3; IR (thin film) 3072, 2975, 2929, 2858, 2235, 1681 cm^{-1}; Anal. Calcd for $C_{17}H_{21}ClN_2O_2$: C, 63.64; H, 6.60; N, 8.73. Found: C, 63.85; H, 6.49; N, 8.60.



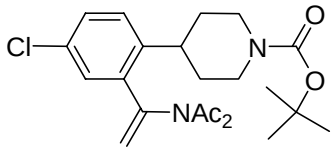
5-Chloro-2-pyridin-4-yl-benzonitrile, 2f

A flask under N_2 was charged with 2-bromo-5-chlorobenzonitrile **8** (2.1 g, 9.6 mmol), pyridine-4-boronic acid (2.0g, 16.3 mmol), K_3PO_4 (4.7 g, 22.1 mmol), $Pd(PPh_3)_4$ (0.55 g, 0.5 mmol), Dioxane (90 mL), and H_2O (18 mL). The reaction mixture was heated to 85 ºC. A second charge of pyridine-4-boronic acid (0.1 g, 0.8 mmol) was added after 5 h. After 6 h, the reaction mixture was cooled to rt. Saturated $NaHCO_3$(aq) (80 mL) and EtOAc (90 mL) were added and the resulting layers were separated. The aqueous layer was extracted with EtOAc (40 mL) and the combined organic layers were dried over Na_2SO_4. The organic layer was concentrated to a golden oil. Purification by silica gel chromatography (2:1 EtOAc/Hexanes to 100% EtOAc) afforded the product as an off-white solid (1.69 g, 82%). mp 143–145 ºC; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.75 (dd, *J* = 4.5, 1.7 Hz, 2 H), 7.79 (d, *J* = 2.1 Hz, 1H), 7.68 (dd, *J* = 8.4, 2.1 Hz, 1H), 7.49–7.46 (m, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 150.2, 144.4, 140.7, 135.3, 133.50, 133.48, 131.0, 123.0, 116.5, 112.5; IR (thin film) 3350, 3065, 2228, 1598 cm^{-1}; Anal. Calcd for $C_{12}H_7ClN_2$: C, 67.15; H, 3.29; N, 13.05. Found: C, 67.04; H, 2.96; N, 12.86.



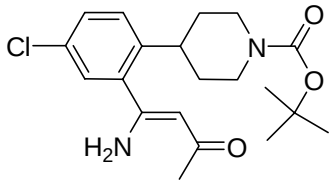
4-(2-{1-[-Acetylimino]-ethyl}-4-chlorophenyl)-piperidine-1-carboxylic acid *tert*-butyl ester, 4a

^{1}H NMR (CD_3CN, 500.13 MHz) δ 7.37 (dd, J=8.3,2.4, 1H), 7.33 (d, J=8.3,1H), 7.31 (d, J=2.4, 1H), 4.15 (br m, 2H), 2.94 (m, 1H), 2.73 (brm, 2H), 2.11 (s, 3H), 1.93 (s, 3H), 1.74 (br d, J=13.1, 2H), 1.55 (m, 2H), 1.44 (s, 9H); ^{13}C NMR (CD_3CN, 125.77 MHz) δ 185.9, 166.6, 155.5, 142.4, 141.3, 132.3, 130.3, 129.9, 127.3, 79.9, 45.2 (broad, 2C), 39.5, 33.9 (2C), 28.7 (3C), 25.8, 25.4; ^{15}N NMR (CD_3CN, 50.69 MHz) δ ~352 *(footnote: BOC- N too broad to observe*)



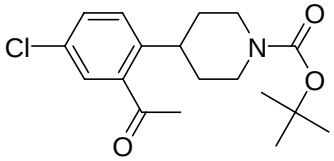
4-[4-Chloro-2-(1-diacetylaminovinyl)phenyl]-piperidine-1-carboxylic acid *tert*-butyl ester, 5a

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.14 (s, 2H), 6.97 (s, 1H), 5.37 (s, 1H), 5.24 (s, 1H), 4.11 (br s, 2H), 3.24 (tt, *J* = 11.8, 3.4 Hz, 1H), 2.63 (t, *J* = 12.8 Hz, 2H), 2.30 (s, 6H), 1.66-1.58 (m, 2H), 1.57-1.44 (m, 2H), 1.34 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 172.7, 154.7, 143.2, 141.5, 137.4, 131.5, 129.2, 128.8, 126.0, 119.7, 79.4, 37.4, 33.7, 28.4, 26.2; ^{15}N NMR (CD_3CN, 50.69 MHz) δ~193. *(footnote: BOC- N too broad to observe*)



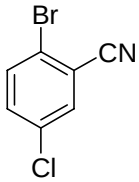
4-[2-(-1-Amino-3-oxo-but-1-Z-enyl)-4-chlorophenyl]-piperidine-1-carboxylic acid *tert*-butyl ester, 6a

^{1}H NMR (CD_3CN, 500.13 MHz) δ 9.64 (br s, 1H), 7.38 (dd, J=8.3, 2.4, 1H), 7.34 (d, J=8.3, 1H), 7.25 (d, J=2.4, 1H), 5.85 (br s. 1H), 5.04 (s, 1H), 4.13 (br d, J=11.9, 2H), 2.97 (m. 1H), 2.72 (br m, 2H), 2.02 (s, 3H), 1.69 (m, 2H), 1.56 (m,2H), 1.44 (s, 9H); ^{13}C NMR (CD_3CN, 125.77 MHz) δ 197.7, 161.2, 155.6, 143.2, 139.8, 132.0, 130.2, 129.6, 128.9, 97.6, 79.9, 45.2 (2C), 39.3, 34.2 (2C), 29.9, 28.7 (3C), ^{15}N NMR (CD_3CN, 50.69 MHz) δ ~96 *(footnote: BOC- N too broad to observe*)



***tert*-Butyl 4-(2-acetyl-4-chlorophenyl)piperidine-1-carboxylate, 7a**

mp 76–79 ºC; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.53 (d, *J* = 2.3 Hz, 1H), 7.40 (dd, *J* = 8.5, 2.2 Hz, 1H), 7.29 (d, *J* = 14.4 Hz, 1H), 4.22 (br s, 2H), 3.22 (tt, *J* = 12.0, 3.4 Hz, 1H), 2.79 (app t, *J* = 11.9 Hz, 2H), 2.58 (s, 3H), 1.79 (app d, *J* = 1.6 Hz, 2H), 1.64–1.52 (m, 2H), 1.48 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 201.4, 154.7, 143.3, 139.8, 131.6, 131.2, 128.7, 128.1, 79.4, 44.2 (br), 37.7, 33.1, 30.3, 28.4; IR (thin film) 2975, 2927, 2844, 1689 cm^{-1}; Anal. Calcd for $C_{18}H_{24}ClNO_3$: C, 63.99; H, 7.16; N, 4.15. Found: C, 63.73; H, 7.07; N, 4.06.



2-Bromo-5-chlorobenzonitrile, 8

To a solution of 3-chlorobenzonitrile (50 g, 360 mmol) in trifluoroacetic acid (180 mL) was added sulfuric acid (24 mL) and then 1,3-dibromo-5,5-dimethylhydantoin (67 g, 234 mmol) in portions over 8 min. The reaction temperature was allowed to reach 31 ºC and then cooling was applied to bring the temperature to 24 ºC. After a 6 h age the heterogeneous reaction was cooled to 10 ºC and water (250 mL) was added. Following a 10 min ages, the reaction was filtered and the product cake was washed twice with water (250 and 100 mL) to afford a white solid (52.4 g, 63%). mp 137–140 ºC; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.64–7.62 (m, 2H), 7.44 (dd, *J* = 8.6, 2.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 134.2, 134.1, 133.9, 133.8, 123.3, 117.2, 115.8; IR (thin film) 3086, 3052, 2228 cm^{-1}; Anal. Calcd for C_7H_3BrClN: C, 38.84; H, 1.40; N, 6.47. Found: C, 38.64; H, 1.18; N, 6.35