

Mild and Efficient DBU-Catalyzed Amidation of Cyanoacetates

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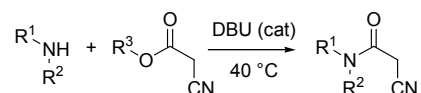
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General Experimental

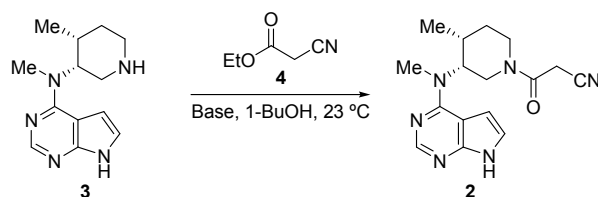
Common substrates and reagents were obtained from commercial suppliers and used without further purification. ^1H NMR and ^{13}C NMR spectra were obtained on a Varian NMR 400 MHz spectrometer in CDCl_3 . IR spectra were obtained on an Avatar 3600 FTIR E.S.P. (Nicolet Smart Sample IR). Elemental analyses were performed by QTI (Quantitative Technologies Inc.). Thin layer chromatography was performed with glass-backed TLC sheets of 250 μm thickness (Silica Gel 60 F₂₅₄). Flash chromatography was performed on a CombiFlash Companion with RediSepRf columns (40 g). HPLC data were collected on an Agilent 1100 Series with a diode array detector. GC/MS data were collected on an Agilent Technologies 6890N Network GC System with an Agilent 5973 Network Mass Selective Detector.

General Procedure for Automated Reaction Monitoring



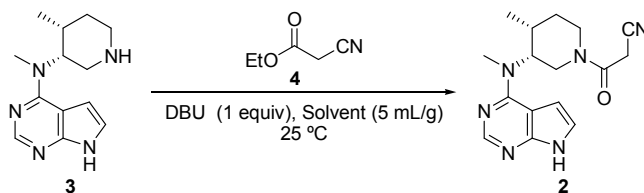
This procedure was used to measure $t_{1/2}$ for the reaction of various amines (**5-8**, Table 1) with ethyl cyanoacetate (**4**) and to monitor the reaction of **5** with various alkyl cyanoacetates (Figure 3). The desired amine (1 g) and DBU (0.5 equiv) were added to 2-methyltetrahydrofuran (4 mL) in a reaction tube. The reaction tube was placed in a React Array RS10 block and heated to the desired temperature. The appropriate alkyl cyanoacetate (2 equiv) was then added. Aliquots were taken and diluted with acetonitrile at pre-programmed intervals. The conversion was determined by HPLC analysis.

Variation of Base in the Reaction of **3** with Ethyl Cyanoacetate (**4**) (Figure 2)



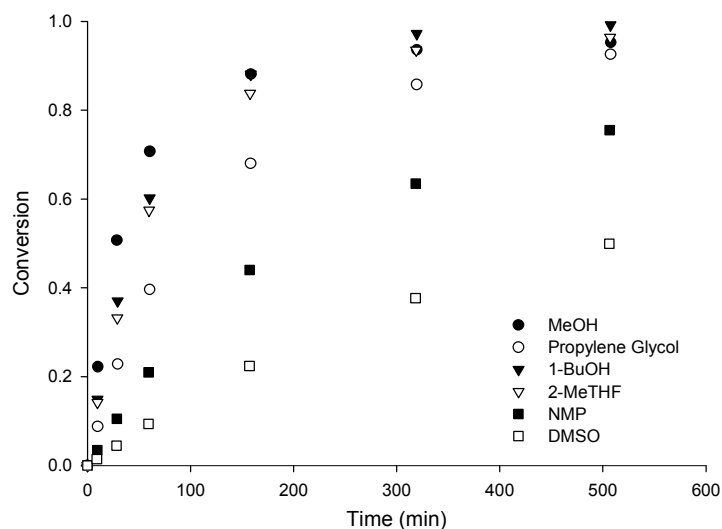
An IKA[®] stir plate fitted with an aluminum vial rack was preheated to the desired temperature. To an HPLC vial, fitted with a small stir bar, were added **3** (100 mg, 0.408 mmol) and 500 μ L of 1-BuOH. The appropriate base (1 equiv, 0.408 mmol) was then added followed by ethyl cyanoacetate (**4**) (86.8 μ L, 0.815 mmol), and the vial was capped. The reaction was then periodically sampled (8 μ L into 1.5 mL acetonitrile) for HPLC analysis.

Variation of Solvent in the Reaction of 3 and 4

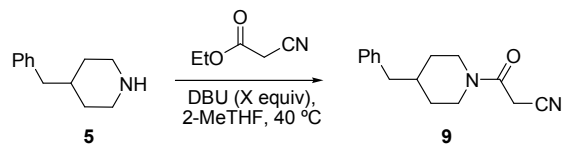


An IKA[®] stir plate fitted with an aluminum vial rack was preheated to the desired temperature. To an HPLC vial, fitted with a small stir bar, were added **3** (40 mg, 0.163 mmol) and 200 μ L of solvent (5 mL/g). DBU (24.5 μ L, 0.163 mmol) was then added followed by ethyl cyanoacetate (**4**) (35 μ L, 0.326 mmol), and the vial was capped. The reaction was then periodically sampled (5-8 μ L into 1.5 mL acetonitrile) for HPLC analysis.

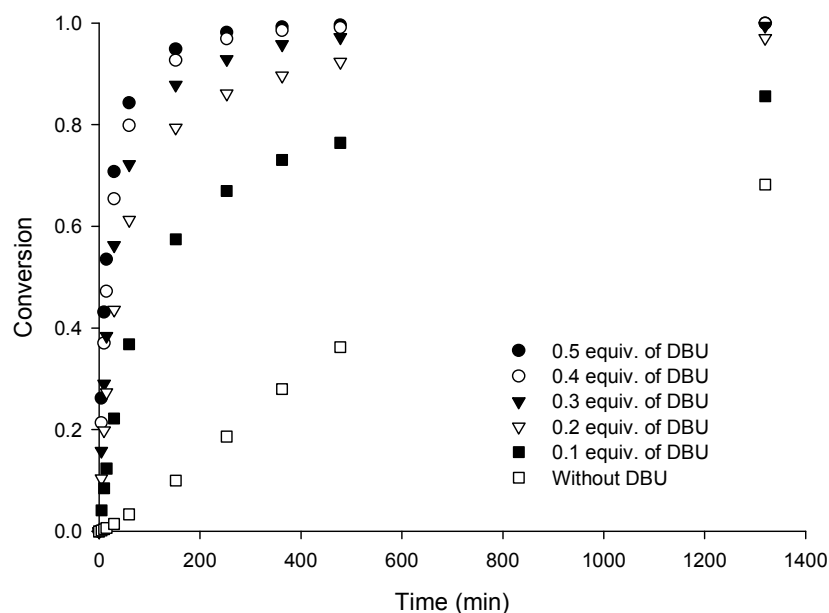
Profiles of the initial reaction between **3**, ethyl cyanoacetate (**4**), and DBU in the presence of various solvents



Variation of DBU Stoichiometry

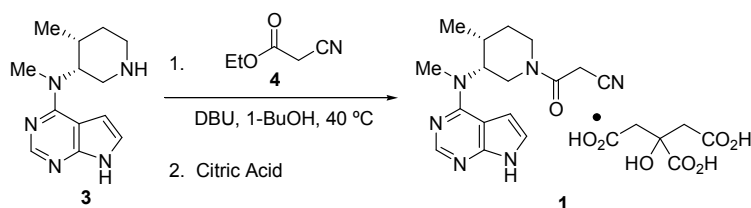


An IKA[®] stir plate fitted with an aluminum vial rack was preheated to the desired temperature. To an HPLC vial, fitted with a small stir bar, were added **5** (120 mg, 0.685 mmol) and 480 μ L of 2-MeTHF (4 mL/g). The appropriate quantity of DBU (0-0.5 equiv) was then added followed by ethyl cyanoacetate (**4**) (146 μ L, 1.37 mmol), and the vial was capped. The reaction was then periodically sampled (8 μ L into 1.5 mL acetonitrile) for HPLC analysis.



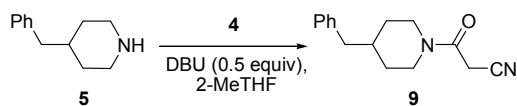
Preparative Examples:

CP-690550-10 (1)



To a round-bottomed flask fitted with a temperature probe, condenser, nitrogen source, and heating mantle, amine **3** (5.0 g, 20.4 mmol) was added followed by 1-butanol (15 mL), ethyl cyanoacetate (**4**) (4.6 g, 40.8 mmol), and DBU (1.6 g, 10.2 mmol). The resulting amber solution was stirred at 40 °C for 20 h. Upon reaction completion, citric acid monohydrate (8.57 g, 40.8 mmol) was added followed by water (7.5 mL) and 1-butanol (39.5 mL). The mixture was heated to 81 °C and held at that temperature for 30 min. The mixture was then cooled slowly to 22 °C and stirred for 2 h. The slurry was filtered and washed with 1-butanol (20 mL). The filter cake was dried in a vacuum oven at 80 °C to afford 9.6 g (93%) of **1** as an off-white solid. ^1H NMR spectrum was consistent with literature values (Ruggeri, S. G.; Hawkins, J. M.; Makowski, T. M.; Rutherford, J. L.; Urban, F. J. WO 2007/012953 A2, 2007).

3-(4-Benzylpiperidin-1-yl)-3-oxopropanenitrile (**9**)



DBU (0.86 mL, 5.71 mmol) and 4-benzylpiperidine (**5**) (2.01 mL, 11.41 mmol) were added to 2-methyltetrahydrofuran (8 mL) and the mixture was stirred at 40 °C. Ethyl cyanoacetate (2.43 mL, 22.82 mmol) was added and the reaction was stirred for 12 hours at 40 °C. Upon reaction completion, the mixture was washed with 0.1 N aqueous hydrochloric acid (2 × 20 mL) and water (1 × 10 mL). The organic layer was dried over MgSO₄, filtered and concentrated. The residue was purified by column chromatography (SiO₂; 30 to 60% ethyl acetate in heptanes) to give 2.62 g (95%) of a pale pink solid. NMR and IR spectra are attached. Anal. Calcd for C₁₅H₁₈N₂O : C, 74.35; H, 7.49; N, 11.57. Found : C, 74.11; H, 7.51; N, 11.57.

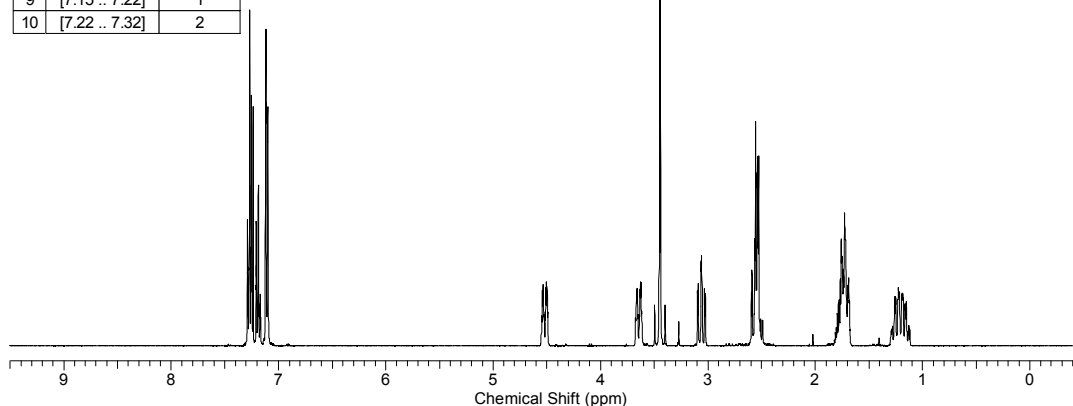
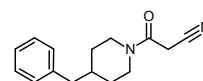
Characterization of Compound 9

Integrals

No.	(ppm)	Value
1	[1.08 .. 1.32]	2
2	[1.64 .. 1.85]	3
3	[2.46 .. 2.62]	3
4	[2.99 .. 3.14]	1
5	[3.38 .. 3.51]	2
6	[3.59 .. 3.69]	1
7	[4.47 .. 4.57]	1
8	[7.07 .. 7.15]	2
9	[7.15 .. 7.22]	1
10	[7.22 .. 7.32]	2

Annotations

No.	(ppm)	Annotation
1	7.27	Chloroform



Peaks

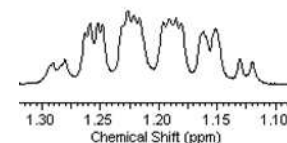
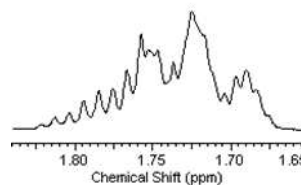
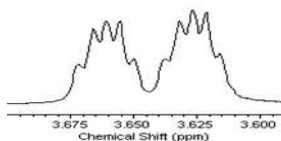
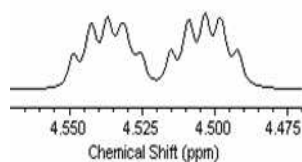
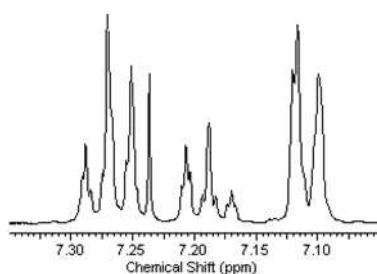
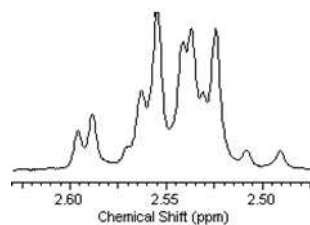
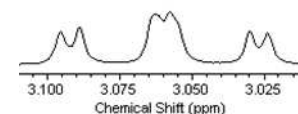
(ppm)	(Hz)
7.29	2913.3
7.28	2911.7
7.25	2898.7
7.24	2892.8
7.21	2882.2
7.21	2880.9
7.20	2879.6
7.19	2875.6
7.19	2873.6
7.18	2871.2
7.17	2867.5
7.17	2866.3
7.12	2846.3
7.12	2844.8
7.10	2838.0
4.55	1818.2
4.54	1815.6

(ppm)	(Hz)
4.54	1813.4
4.53	1811.4
4.53	1809.2
4.51	1804.8
4.51	1802.5
4.50	1800.1
4.50	1798.2
4.49	1795.9
3.67	1467.9
3.67	1465.5
3.66	1463.5
3.66	1461.3
3.65	1459.1
3.64	1454.1
3.63	1451.8
3.63	1449.7
3.62	1447.7

(ppm)	(Hz)
3.62	1445.5
3.49	1397.0
3.45	1379.4
3.44	1376.3
3.40	1358.5
3.10	1237.5
3.09	1234.8
3.06	1224.3
3.06	1222.3
3.03	1211.1
3.02	1208.7
2.60	1037.7
2.59	1034.8
2.56	1024.5
2.55	1021.2
2.54	1015.9
2.54	1014.1

(ppm)	(Hz)
2.53	1011.7
2.52	1009.1
1.79	717.2
1.78	713.4
1.78	709.7
1.77	706.2
1.76	702.6
1.75	700.6
1.75	698.2
1.74	694.2
1.72	689.4
1.70	681.2
1.70	678.2
1.69	675.7
1.68	672.7
1.26	505.0
1.26	503.3

(ppm)	(Hz)
1.25	500.6
1.25	499.1
1.23	492.3
1.23	490.3
1.22	488.1
1.22	486.1
1.20	478.1
1.19	476.0
1.19	473.8
1.18	472.2
1.16	464.5
1.15	460.1



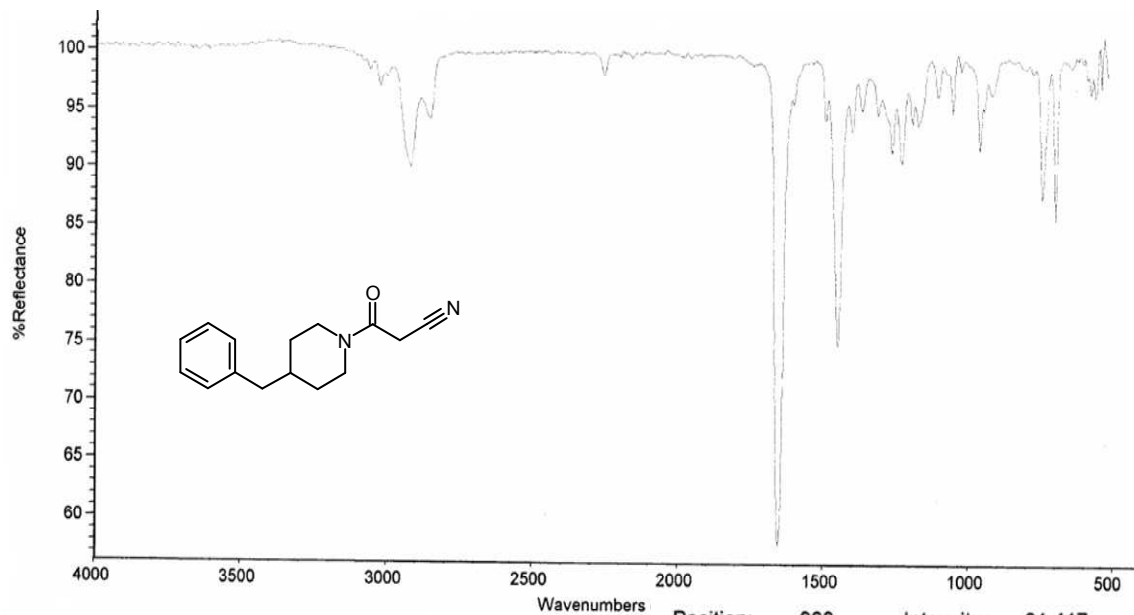
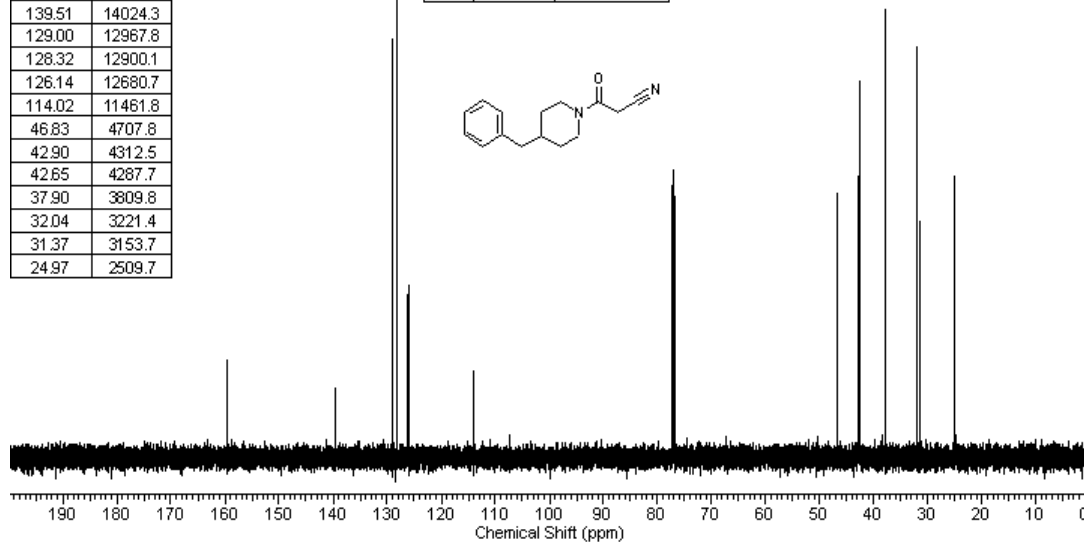
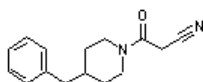
Characterization of Compound 9

Peaks

(ppm)	(Hz)
159.64	16048.0
139.51	14024.3
129.00	12967.8
128.32	12900.1
126.14	12680.7
114.02	11461.8
46.83	4707.8
42.90	4312.5
42.65	4287.7
37.90	3809.8
32.04	3221.4
31.37	3153.7
24.97	2509.7

Annotations

No.	(ppm)	Annotation
1	77.00	Chloroform



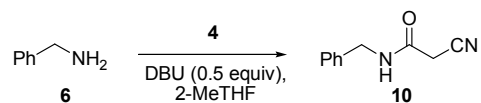
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Position: 1266

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Intensity: 74.678
Intensity: 85.614
Intensity: 87.331
Intensity: 90.064
Intensity: 90.474
Intensity: 91.368

Position: 963
Position: 1403
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Position: 565
Position: 544
Position: 3025

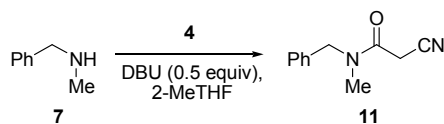
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Intensity: 93.937
Intensity: 94.099
Intensity: 94.226
Intensity: 94.869
Intensity: 95.086
Intensity: 96.308
Intensity: 96.264
Intensity: 96.866
Intensity: 96.932

***N*-Benzyl-2-cyanoacetamide (10)**



DBU (6.98 mL, 46.66 mmol) and benzylamine (**6**) (10.19 mL, 93.33 mmol) were added to 2-methyltetrahydrofuran (40 mL) and the mixture was stirred at room temperature. Ethyl cyanoacetate (19.86 mL, 186.65 mmol) was added and the reaction was stirred for 12 hours at ambient temperature. Upon reaction completion, the mixture was washed with 0.1 N aqueous hydrochloric acid (2×20 mL) and water (1×10 mL). The organic layer was dried over MgSO_4 , filtered and concentrated. The residue was recrystallized from ethyl acetate/heptanes to give 15.39 g (95%) of a white crystalline solid. ^1H NMR and ^{13}C NMR spectra were consistent with literature values (Bhawal, B.M.; Khanapure, S.P.; Biehl, E.R. *Synth. Commun.* **1990**, *20*, 3235-3243).

***N*-benzyl-*N*-methyl-2-cyano-acetamide (11)**



DBU (1.24 mL, 8.25 mmol) and *N*-benzylmethylamine (**7**) (2.13 mL, 16.50 mmol) were added to 2-methyltetrahydrofuran (8 mL) and the reaction was stirred at room temperature. Ethyl cyanoacetate (3.52 mL, 33.01 mmol) was added and the reaction was stirred for 12 hours. The reaction mixture was concentrated to dryness and the residue was purified by column chromatography (SiO₂; 30 to 60% ethyl acetate in heptanes) to give 2.77 g (89%) of a pale yellow oil. NMR and IR spectra are attached.

Characterization of Compound 11

Peaks

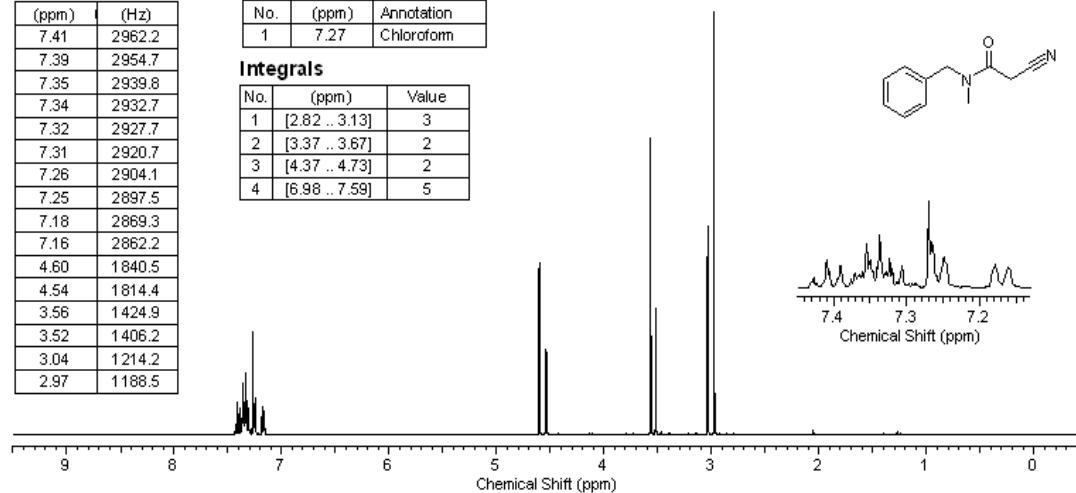
(ppm)	(Hz)
7.41	2962.2
7.39	2954.7
7.35	2939.8
7.34	2932.7
7.32	2927.7
7.31	2920.7
7.26	2904.1
7.25	2897.5
7.18	2869.3
7.16	2862.2
4.60	1840.5
4.54	1814.4
3.56	1424.9
3.52	1406.2
3.04	1214.2
2.97	1188.5

Annotations

No.	(ppm)	Annotation
1	7.27	Chloroform

Integrals

No.	(ppm)	Value
1	[2.82 .. 3.13]	3
2	[3.37 .. 3.67]	2
3	[4.37 .. 4.73]	2
4	[6.98 .. 7.59]	5

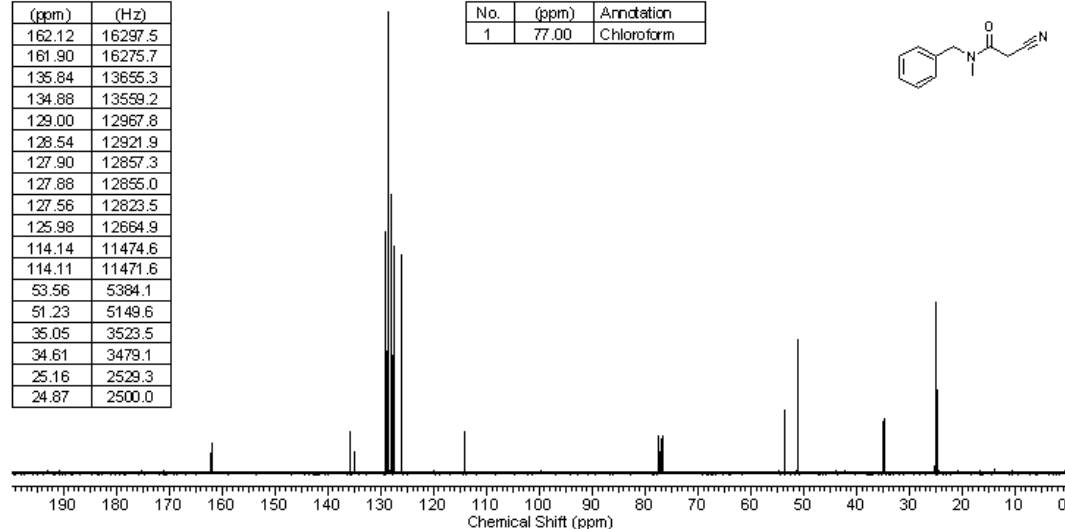


Peaks

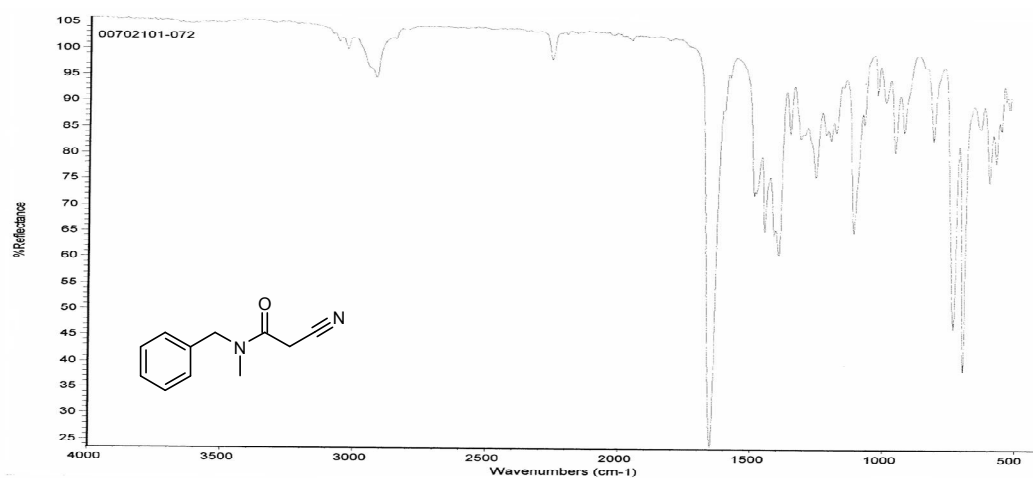
(ppm)	(Hz)
162.12	16297.5
161.90	16275.7
135.84	13655.3
134.88	13559.2
129.00	12967.8
128.54	12921.9
127.90	12857.3
127.88	12855.0
127.56	12823.5
125.98	12664.9
114.14	11474.6
114.11	11471.6
53.56	5384.1
51.23	5149.6
35.05	3523.5
34.61	3479.1
25.16	2529.3
24.87	2500.0

Annotations

No.	(ppm)	Annotation
1	77.00	Chloroform



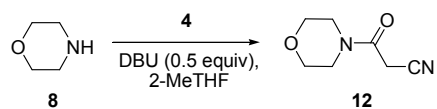
Characterization of Compound 11



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Position:	962	Intensity:	80.206
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Position:	638	Intensity:	84.852
Position:	999	Intensity:	90.074
Position:	1029	Intensity:	91.227
Position:	2921	Intensity:	94.399
Position:	2260	Intensity:	97.965

3-morpholine-3-oxopropanenitrile (**12**)



DBU (1.73 mL, 11.48 mmol) and morpholine (**8**) (2.00 mL, 22.96 mmol) were added to 2-methyltetrahydrofuran (8 mL) and the reaction was stirred at 40 °C. Ethyl cyanoacetate (4.89 mL, 45.91 mmol) was added and the mixture was stirred for 4 hours. The mixture was concentrated and purified by column chromatography (SiO₂; 2% methanol in methylene chloride) to give 3.08 g (87%) of an off-white crystalline solid. ¹H and ¹³C NMR spectra were consistent with literature values (Bhawal, B.M.; Khanapure, S.P.; Biehl, E.R. *Synth. Commun.* **1990**, *20*, 3235-3243).