A versatile and green mechanochemical route for aldehyde-oxime conversions

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General experimental details

^{1}H NMR spectra were recorded on a Varian Unity plus 400 MHz spectrometer in $CDCl_3$ or d_6-DMSO. Data is expressed in parts per million (ppm) downfield shift from tetramethylsilane or residual protiosolvent as internal reference and are reported as position (in ppm), multiplicity (s = singlet, d = doublet, t = triplet, m= multiplet), coupling constant (J in Hz) and integration (number of protons). ^{13}C nuclear magnetic resonance spectra were recorded on a Varian Unity plus 400 MHz spectrometer in $CDCl_3$ or d_6-DMSO with complete proton decoupling. Data is expressed in parts per million (ppm) shift relative to $CDCl_3$ (77.00 ppm) or d_6-DMSO (40.45 ppm) and are reported as position (δ). Melting points were recorded on a Fisher-Johns melting point apparatus and are uncorrected. All the chemicals were purchased from Aldrich and used without further purification, unless otherwise noted. The synthesis of 1,3,5-benzenetricarboxaldehyde[1] and 4-iodobenzaldehyde[2] was carried out according to the published procedures.

X-ray crystallography

Data were collected on a Bruker Kappa APEX II system using APEX2 software.[3] An Oxford Cryostream 700 low-temperature device was used to control temperature. MoKα radiation was used. Initial cell constants were found by small widely separated “matrix” runs. Data collection strategies were determined using COSMO.[4] Scan speeds and scan widths were chosen based on scattering power and peak rocking curves.

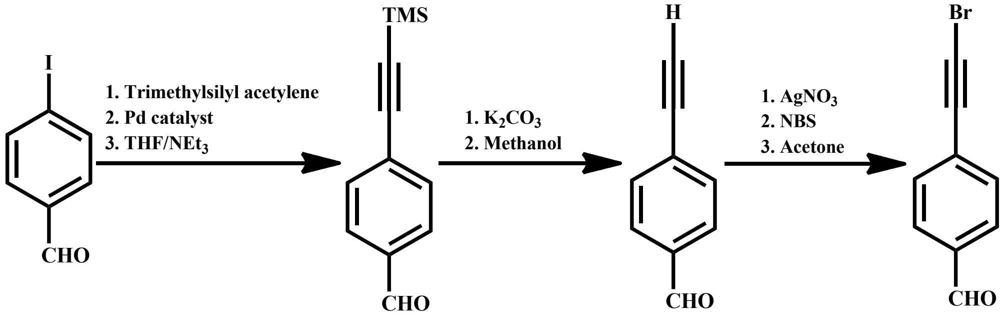
Unit cell constants and orientation matrix were improved by least-squares refinement of reflections thresholded from the entire dataset. Integration was performed with SAINT,[5] using the improved unit cell as a starting point. Precise unit cell constants were calculated in SAINT from the final merged dataset. Lorenz and polarization corrections were applied. An absorption correction was applied using SADABS.[6]

The dataset was reduced with SHELXTL.[7] The structure was solved by direct methods without incident. Friedel opposites were merged, and no attempt was made to determine absolute configuration. Coordinates for the oxime hydrogen atoms were allowed to refine. All other hydrogen atoms were assigned to idealized positions and were allowed to ride. Isotropic thermal parameters for the hydrogen atoms were constrained to be 1.2x (all other) that of the connected atom.

Systematic name	1,3,5-tris-[CH(=NOH)]-benzene
Empirical formula	$C_9H_9N_3O_3$
Molecular weight	207.19
Color, Habit	orange prism
Crystal dimensions	0.30 x 0.22 x 0.14
Crystal system	Orthorhombic
Space group, Z	$Pna2_1$, 4
a, Å	16.6967(11)
b, Å	4.2787(3)
c, Å	13.1262(8)
α, °	90.00
β, °	90.00
γ, °	90.00
Volume, $Å^3$	937.74(11)
X-ray wavelength, Å	0.71073
μ, mm-1	0.113
Absorption corr	multi-scan
Trans min / max	0.9668 / 0.9843
Reflections	
collected	11730
independent	1780
observed	1489
Threshold expression	$>2\sigma$ (I)
R_1 (observed)	0.0499
wR_2 (all)	0.1302
S	1.163

Table S1 Crystallographic data for 1,3,5-tris-[CH(=NOH)]-benzene.

Synthesis of 4-(bromoethynyl)benzaldehyde



Scheme S1 Synthesis of 4-(bromoethynyl)benzaldehyde.

Step 1: Synthesis of 4-((trimethylsilyl)ethynyl)benzaldehyde

A mixture of 4-iodobenzaldehyde (0.80 g, 3.45 mmol), trimethylsilylacetylene (0.59 mL, 4.14 mmol), copper(I) iodide (0.021 g, 0.11 mmol), triphenylphosphine (0.082 g, 0.31 mmol), and *bis*(triphenylphosphine)palladium(II) dichloride (0.077 g, 0.11 mmol) were added to a round bottom flask. Tetrahydrofuran (30 mL) and triethylamine (30 mL) were added and dinitrogen bubbled through the resultant mixture for 10 minutes. A condenser was attached and the mixture heated at 65 ˚C under a dinitrogen atmosphere. The reaction was monitored by TLC and allowed to cool to room temperature on completion (26 hours). The solution was then diluted with ethyl acetate (50 mL), washed with water (3 x 50 mL) then washed with saturated aqueous sodium chloride (1 x 50 mL). The organic layer was separated and dried over magnesium sulfate. The solvent was removed on a rotary evaporator and the residue chromatographed on silica with hexane/ethyl acetate mixture as the eluant. The product was isolated as a dark yellow solid. Yield: 0.61 g (88%); mp 61-63˚C (lit., 66˚C)[8]; ^{1}H NMR (δH; $CDCl_3$, 400MHz): 0.28 (9 H, s), 7.61 (2 H, d, *J*=8.20 Hz), 7.83 (2 H, d, *J*=8.20 Hz), 10.01 (1 H, s).

Step 2: Synthesis of 4-ethynylbenzaldehyde

A mixture of 4-((trimethylsilyl)ethynyl)benzaldehyde (0.50 g, 2.47 mmol) and potassium carbonate (0.51g, 3.71 mmol) were stirred in methanol (30 mL) at room temperature for 1 hour. The solution was then diluted with ethyl ether (30 mL) and washed with water (4 x 50 mL). The solvent was removed on a rotary evaporator and the product was isolated as a yellow solid. Yield: 0.29 g (90%); mp 84-86˚C (lit., 87˚C)[9]; ^{1}H NMR (δH; $CDCl_3$, 400MHz): 3.30 (1 H, s), 7.66 (2 H, d, *J*=8.20 Hz), 7.86 (2 H, d, *J*=8.20 Hz), 10.03 (1 H, s).

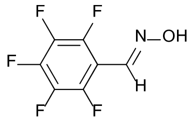
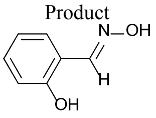
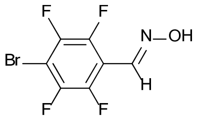
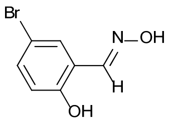
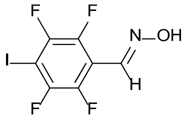
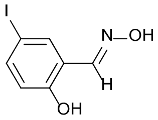
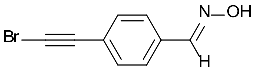
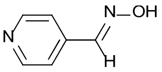
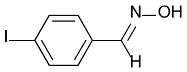
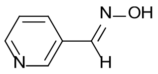
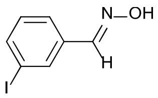
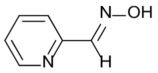
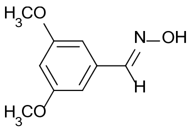
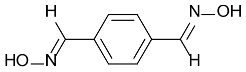
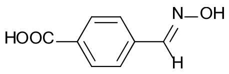
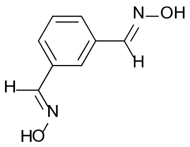
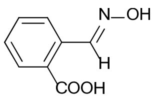
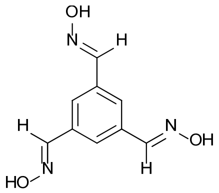
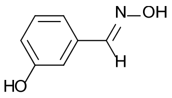
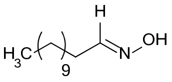
Step 3: Synthesis of 4-(bromoethynyl)benzaldehyde

To a stirred solution of 4-ethynylbenzaldehyde (0.14 g, 1.08 mmol) in acetone (20 mL) was added 19 mg of silver(I) nitrate (0.11 mmol). The mixture was stirred for 30 minutes, then N-bromosuccinimide (0.48 g, 2.69 mmol) was added. The mixture was protected from light and stirred for 3 days. Upon completion of the reaction, acetone was evaporated under vacuum and the solid mixture was chromatographed over a short pad of silica gel with hexane as the eluant and the product was isolated as a yellow solid. Yield: 0.21 g (91%); mp 96-98˚C; ^{1}H NMR (δH; $CDCl_3$, 400MHz):[10] 7.60 (2 H, d, *J*=8.06 Hz), 7.84 (2 H, d, *J*=1.00 Hz), 10.01 (1 H, s); ^{13}C NMR (δc; $CDCl_3$, 400MHz): 54.65, 79.29, 128.84, 129.50, 132.57, 135.75, 191.29.

General synthesis of the aldoximes

In a mortar, 1.0 mole of aldehyde and 1.2 moles (per aldehyde present) of hydroxylamine hydrochloride is ground together with a pestle. Then, 1.2 moles (per aldehyde present) of crushed sodium hydroxide is added and the mixture is ground further with the addition of 2-4 drops of methanol, for 2 minutes at room temperature. The reaction mixture is left for 5 minutes, after which it is ground for another 2 minutes with 2-4 drops of methanol. At this stage the reaction is monitored by TLC. Upon completion of the reaction, a ^{1}H NMR of the crude mixture is taken in d_6 DMSO to confirm the formation of aldoxime. The crude mixture is washed with water to get rid of any inorganic salts and it is air dried, after which the melting point is taken to confirm the formation of pure product.

Characterization of the aldoximes

#	Product	M.p. (^{0}C)	Yield (%)[a]	#	Product	M.p. (^{0}C)	Yield (%)[a]
1		128-132 (133)[11]	78	**11**		110-116 (117)[12]	71
2		138-140 dec (138 dec)[11]	80	**12**		112-114	83
3		165-169	87	**13**		124-126	76
4		119-121	85	**14**		130-132 (132)[13]	83
5		101-103	61	**15**		146-148 (150)[13]	81
6		66-68	59	**16**		110-114 (114)[13]	65
7		112-114 (117)[14]	89	**17**		202-204 (201-202)[15]	69
8		212-216 (218)[16]	67	**18**		180-182 (181-184)[17]	67
9		126-128 (128-130)[18]	73	**19**		239-241	64
10		83-90 (87-88)[19]	62	**20**		70-72 (72)[20]	77

[a] % yield calculated based on the mass of product obtained after washing the crude mixture with water. Lower yield in some cases is due to loss of product during the washing procedure as some oximes are partially soluble in water. Yields could be improved to 95-100% by carrying out a normal extraction work up.

4-(bromoethynyl)benzaldehyde oxime (4): ^{1}H NMR (δH; d_6 DMSO, 400MHz): 7.50 (2 H, d, *J*=1.00 Hz), 7.59 (2 H, d, *J*=1.00 Hz), 8.15 (1 H, s), 11.42 (1 H, br. s.); ^{13}C NMR (δc; d_6 DMSO, 400MHz): 54.20, 79.55, 122.40, 126.52, 132.13, 133.58, 147.47.

4-iodobenzaldehyde oxime (5):[21] ^{1}H NMR (δH; d_6 DMSO, 400MHz): 7.38 (2 H, d, *J*=1.00 Hz), 7.76 (2 H, d, *J*=1.00 Hz), 8.10 (1 H, s), 11.34 (1 H, s).

3-iodobenzaldehyde oxime (6):[22] ^{1}H NMR (δH; d_6 DMSO, 400MHz): 7.20 (1 H, t, *J*=7.79 Hz), 7.61 (1 H, d, *J*=7.79 Hz), 7.73 (1 H, d, *J*=7.79 Hz), 7.94 (1 H, s), 8.10 (1 H, s), 11.41 (1 H, br. s.).

5-bromosalicylaldehyde oxime (12):[23] ^{1}H NMR (δH; d_6 DMSO, 400MHz): 6.87 (1 H, d, *J*=8.60 Hz), 7.32 (1 H, dd, *J*=8.73, 2.28 Hz), 7.61 (1 H, d, *J*=2.42 Hz), 8.26 (1 H, s), 11.21 (1 H, br. s.).

5-iodosalicylaldehyde oxime (13):[24] ^{1}H NMR (δH; d_6 DMSO, 400MHz): 6.74 (1 H, d, *J*=8.60 Hz), 7.45 (1 H, d, *J*=8.60 Hz), 7.77 (1 H, s), 8.23 (1 H, s), 11.11 (1 H, br. s.).

1,3,5-benzenetrisaldoxime (19):[25] ^{1}H NMR (δH; d_6 DMSO, 400MHz): 7.80 (3 H, s), 8.19 (3 H, s), 11.41 (3 H, s).

Note: Some yields listed in the ESI are lower than those reported in the main text of the paper. However, the 100% conversions reported in the main text are based upon NMR data and reflect the analysis on the crude solid straight out of the mortar. In order to obtain a pure material suitable for melting point determination, we washed with water which in some cases reduced the final yield because some oximes were partially soluble in water. If a regular extraction was carried out, however, the yields were always 95-100%.

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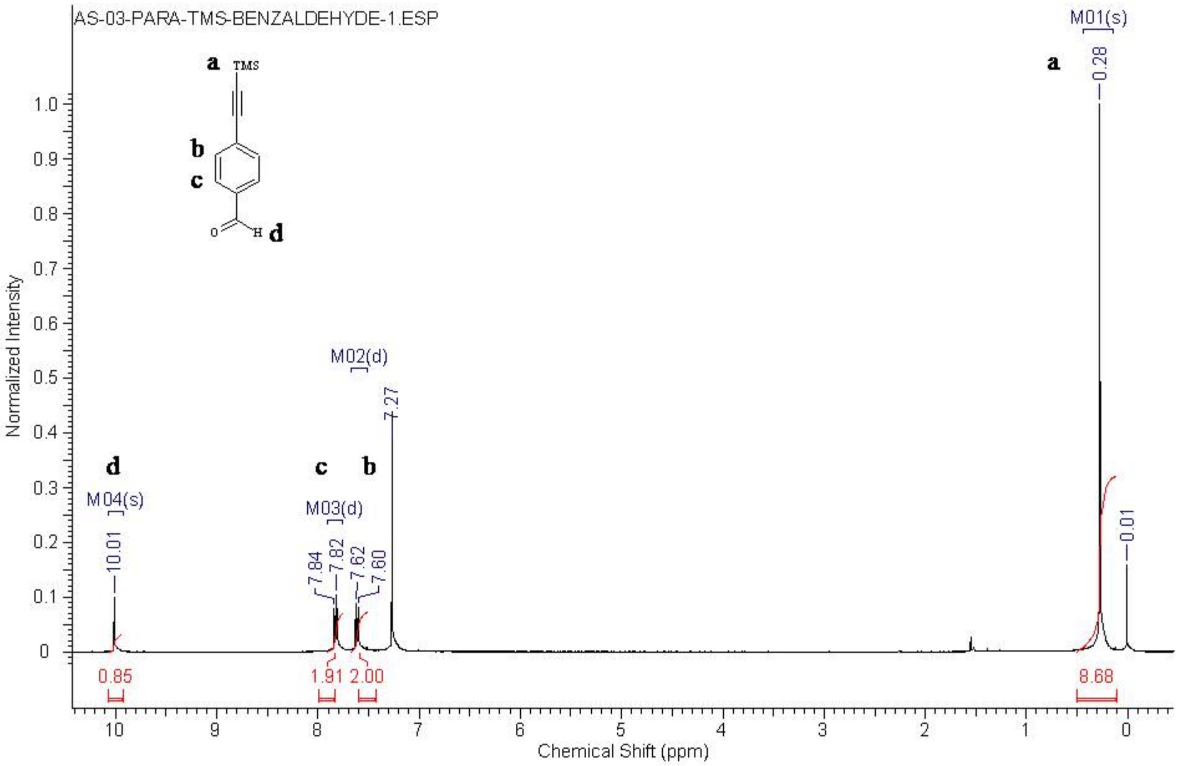
NMR data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M02(d)
7.27
d
c
b
M04(s)
M03(d)
10.01
7.84
7.82
7.62
7.60
0.01
0.85
1.91
2.00
8.68
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
10
9
8
7
6
5
4
3
2
1
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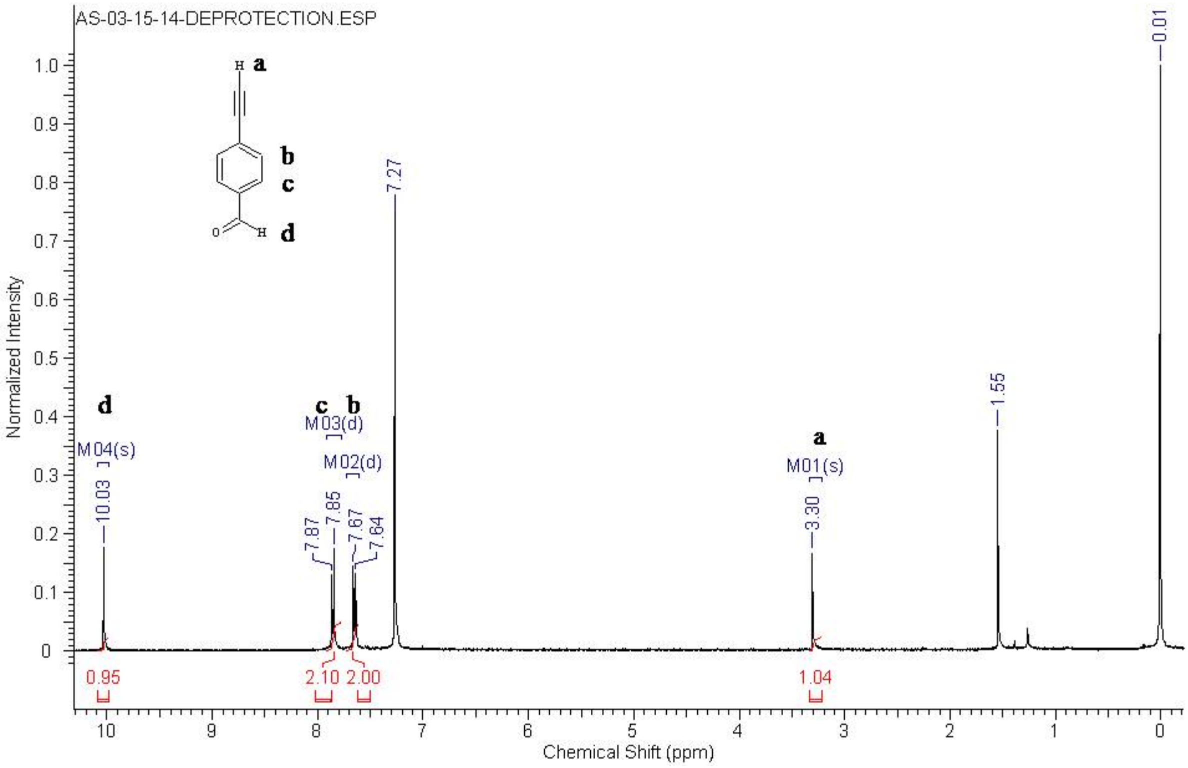
Chemical Shift (ppm)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d
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d
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M03(d)
M04(s)
M02(d)
a
M01(s)
10.03
7.87
7.85
7.67
7.64
3.30
0.95
2.10
2.00
1.04
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
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7
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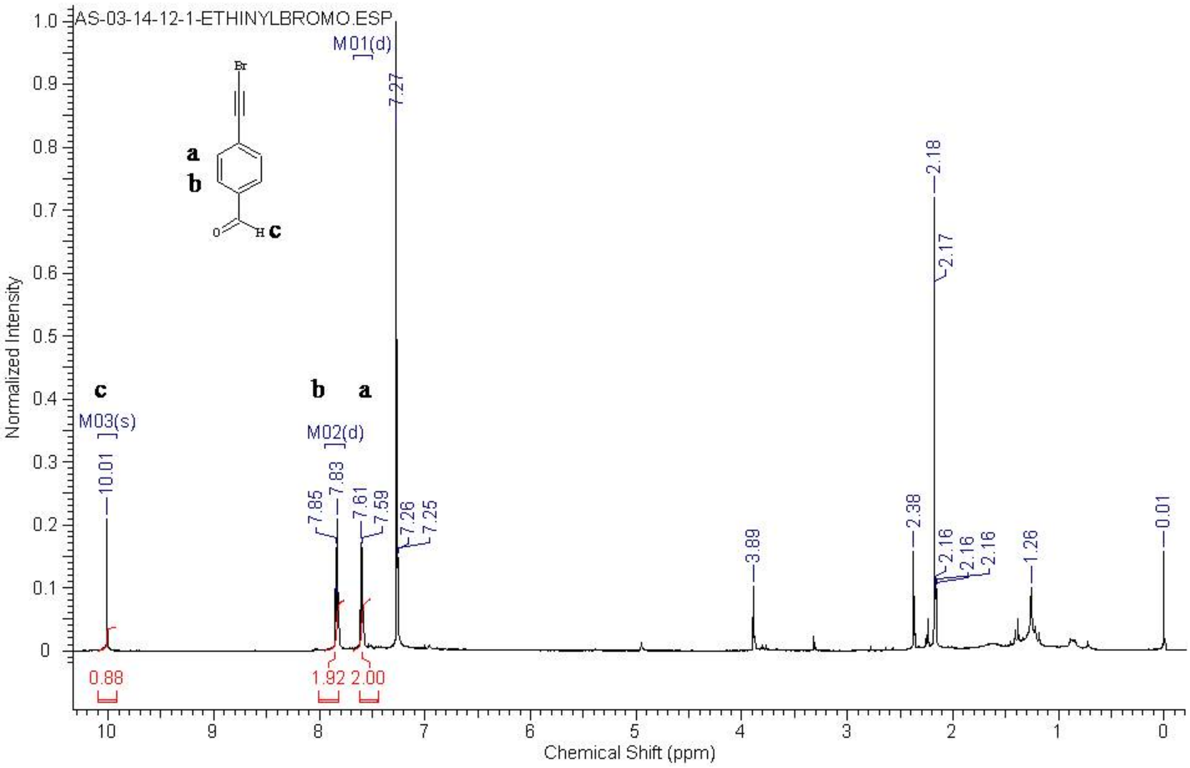
Chemical Shift (ppm)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b
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7.85
7.83
7.61
7.59
M01(d)
7.27
7.26
7.25
3.89
2.38
2.18
2.17
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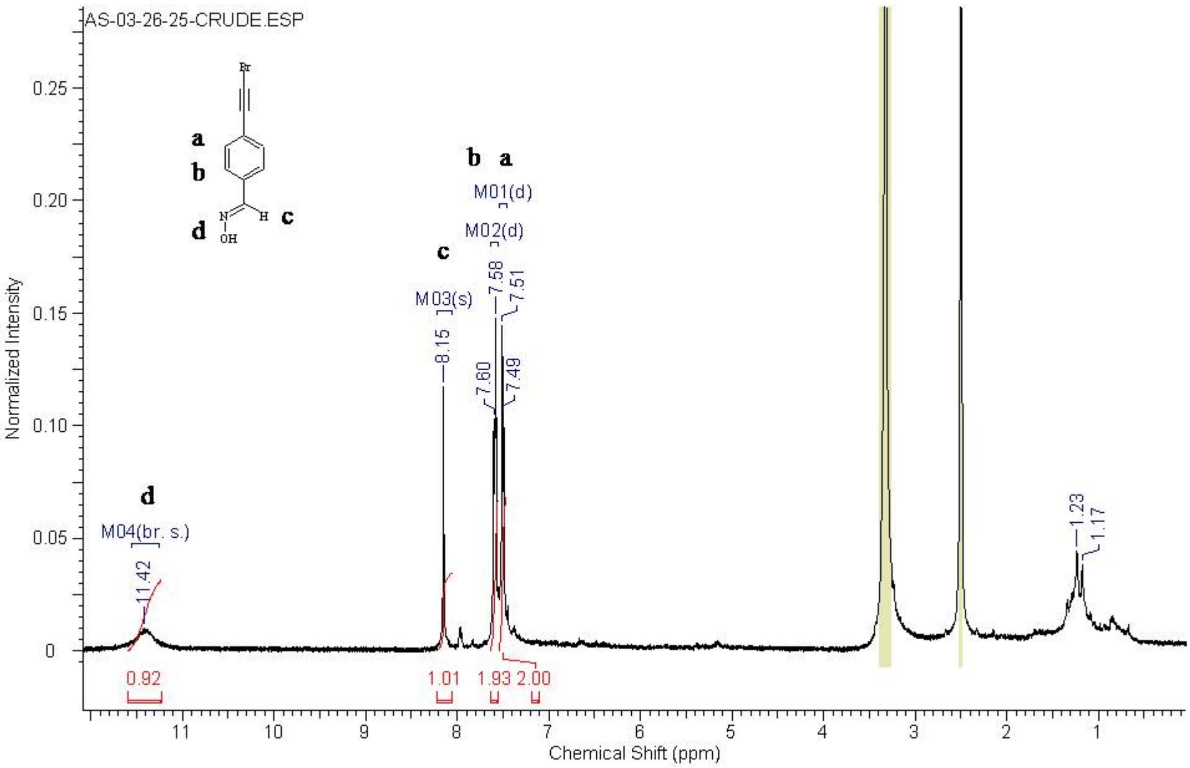
Normalized Intensity
Chemical Shift (ppm)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d
N
OH
H
c
d
M04(br. s.)
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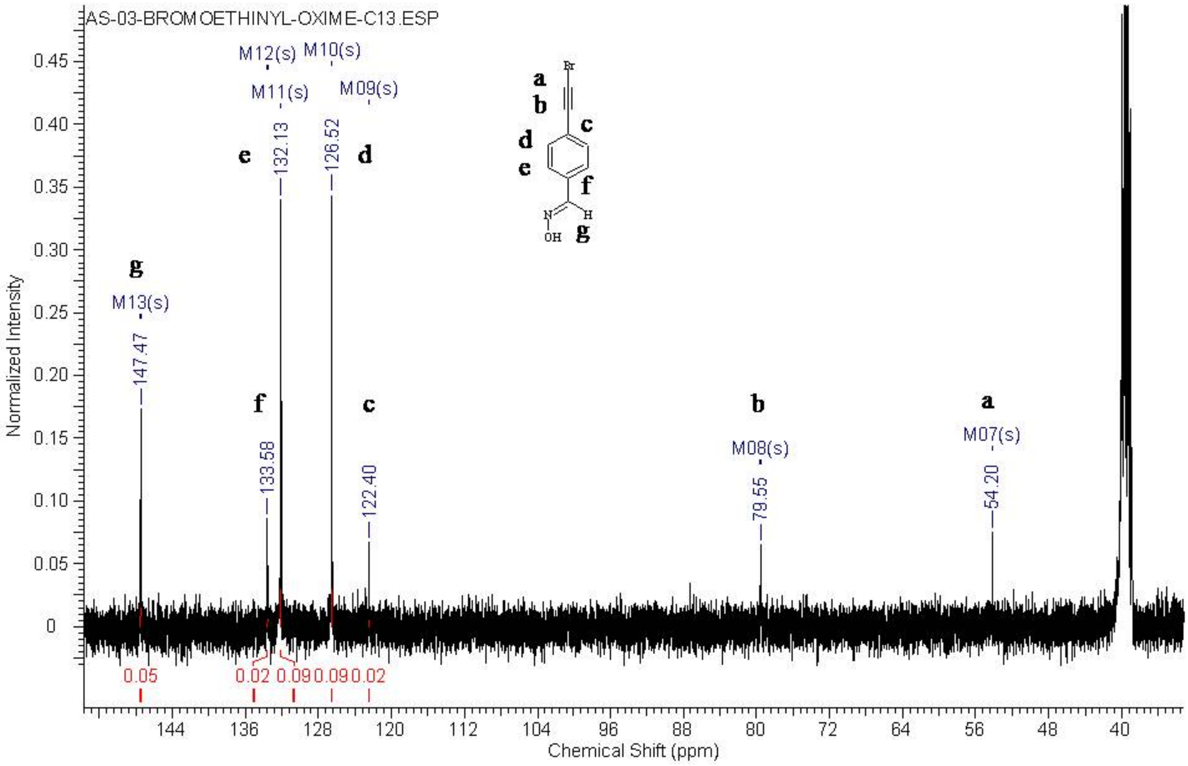
M03(s)
8.15
b a
M01(d)
M02(d)
7.60
7.58
7.51
7.49
1.23
1.17
0.92
1.01
1.93
2.00
Normalized Intensity
Chemical Shift (ppm)


AS-03-BROMOETHINYL-OXIME-C13.ESP
Normalized Intensity
Chemical Shift (ppm)
M13(s) 147.47 g
M12(s) M11(s) 133.58 132.13 e f
M10(s) 126.52 d
M09(s) 122.40 c
M08(s) 79.55 b
M07(s) 54.20 a
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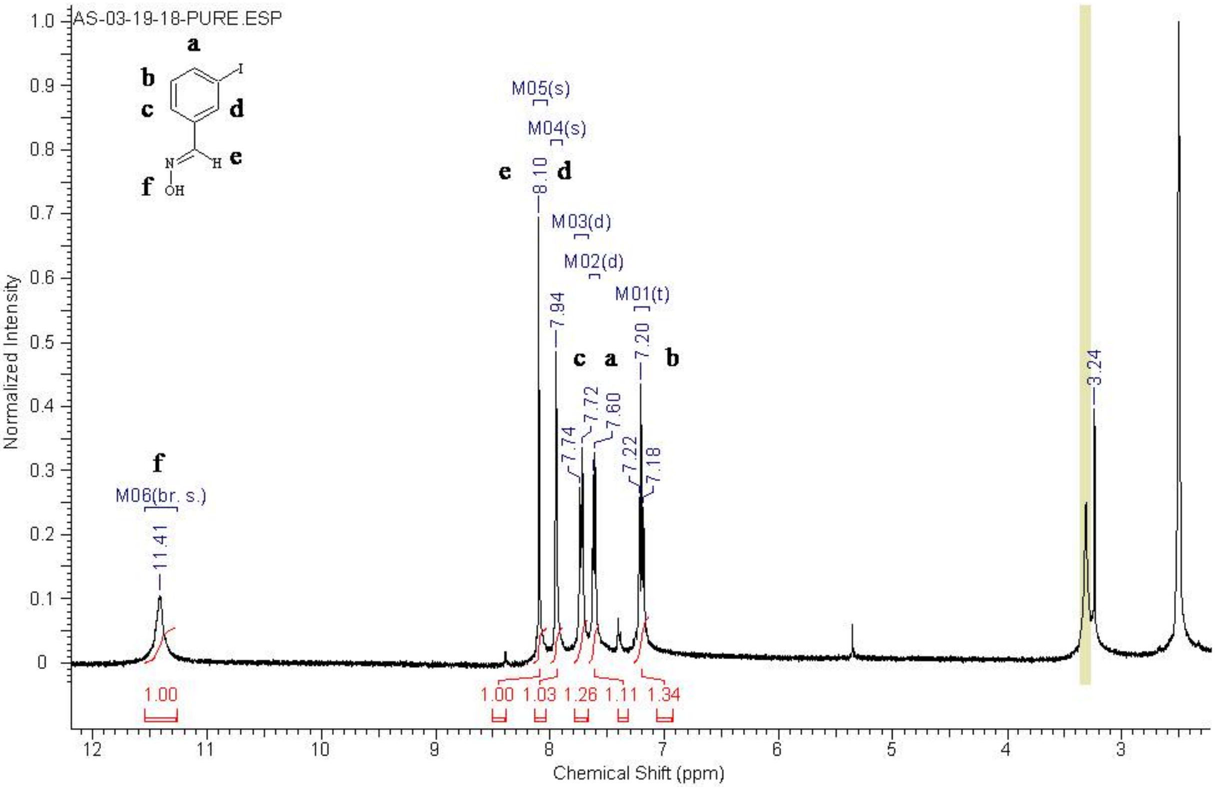
Br
H
N
OH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Normalized Intensity
Chemical Shift (ppm)
M06(br. s.) 11.41 f
M05(s) 8.10 e
M04(s) 7.94 d
M03(d) 7.74 7.72 c
M02(d) 7.60 a
M01(t) 7.22 7.20 7.18 b
3.24
1.00 1.00 1.03 1.26 1.11 1.34
I
H
N
OH