Preparation of 1-Methylimidazole-*N*-oxide (NMI-O)

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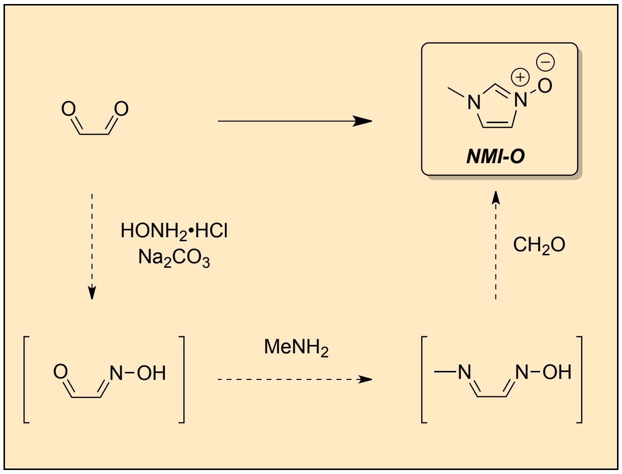

Procedure

1-Methylimidazole-N-oxide (**NMI-O**). A 500 mL, single-necked, round-bottomed flask is charged with an oval 3 cm Teflon coated magnetic stirrer bar. To this flask is added hydroxylamine hydrochloride (11.2 g, 0.161 mol) (Note 1) and sodium carbonate (21.2 g, 0.20 mol, Note 1) followed by distilled water (60 mL) and the resulting white suspension cooled to 0 °C in an ice-water bath (Figure 1A). The headspace in the flask is flushed with nitrogen, the flask fitted with a rubber septum and placed under a positive pressure of nitrogen *via* a syringe needle to a manifold (Figure 1A). After stirring the suspension for 5 min, an aqueous solution of glyoxal (23.0 mL, 40% w/v aq., 8.8 M, 0.20 mol) is added *via* syringe over 5 min resulting in the suspension becoming pale yellow in color (Note 2) (Figure 1B/C). An

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aqueous solution of methylamine (17.0 mL, 40% w/v aq., 11.6 M, 0.20 mol) is added *via* syringe over 5 min. The addition causes an immediate orange/red coloration of the suspension which darkens progressively during the addition to become a red/brown suspension upon complete addition (Note 3) (Figure 1D/E). An aqueous solution of formaldehyde (15.0 mL, 37% w/v aq., 13.4 M, 0.20 mol) is then added *via* syringe over 5 min during which the brown color is maintained (Note 4) (Figure 1F). The reaction mixture is then stirred for 16 h at room temperature under nitrogen.

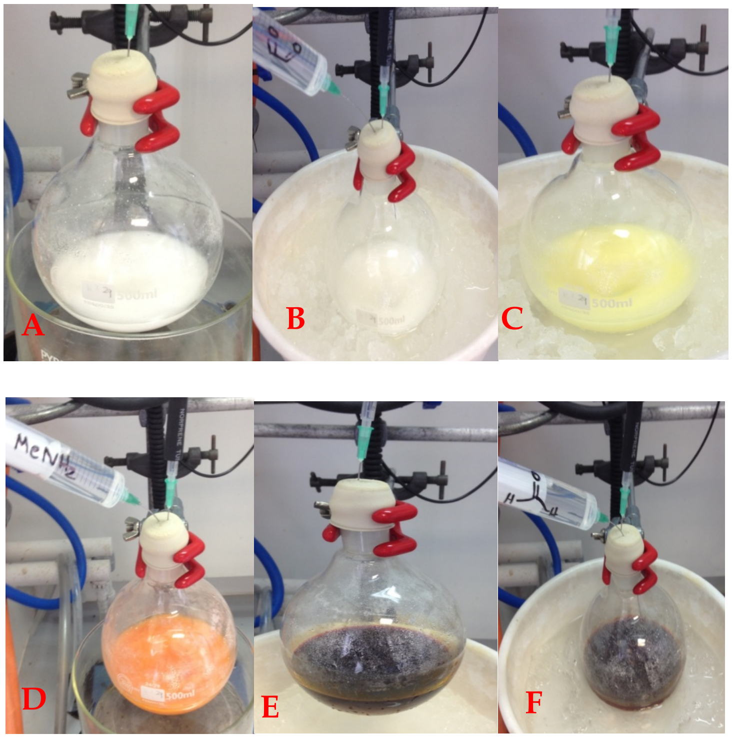


Figure 1. A; Initial appearance of reaction mixture, B; During addition of glyoxal, C; 5 minutes after glyoxal addition, D; During addition of $MeNH_2$, E; 5 min after $MeNH_2$ addition, F; During CH_2O addition.

The reaction mixture is cooled to 0 °C with an ice-water bath before adding *conc*. hydrochloric acid (5.3 mL, 37% aq., 12.2 M) (Note 5) over a period of ~ 2 min *via* syringe. The reaction mixture becomes a yellow/orange suspension and this suspension is stirred for a further 2 h at room temperature (Figure 2A).

The reaction mixture is filtered using a Büchner funnel (5 cm diameter) and the filtrate concentrated at reduced pressure on a rotary evaporator (45 °C, 100 mmHg) to afford a brown slurry (Figure 2B). To this residue is added a mixture of dichloromethane/methanol/triethylamine (300 mL, 80:15:5) and after vigorous swirling the resulting mixture is filtered again using a 5 cm diameter Büchner funnel (Note 6). The collected solid residue is washed with a further 100 mL of dichloromethane/methanol/triethylamine (80:15:5 v/v) and the filtrates combined (TLC; 20% methanol in dichloromethane + 0.5% triethylamine, R_f = 0.37, Figure 2C). To the resulting combined brown filtrate solution is added silica gel (15 g) (Note 7) and the mixture concentrated at reduced pressure on a rotary evaporator (45 °C, 100 mmHg) to afford an orange solid. This solid is dry-loaded and purified by flash chromatography (Note 8) to afford the product as brown oil which solidifies upon standing in a fridge or freezer (10.8 g, 68%) (Notes 9 and 10) (Figure 3).

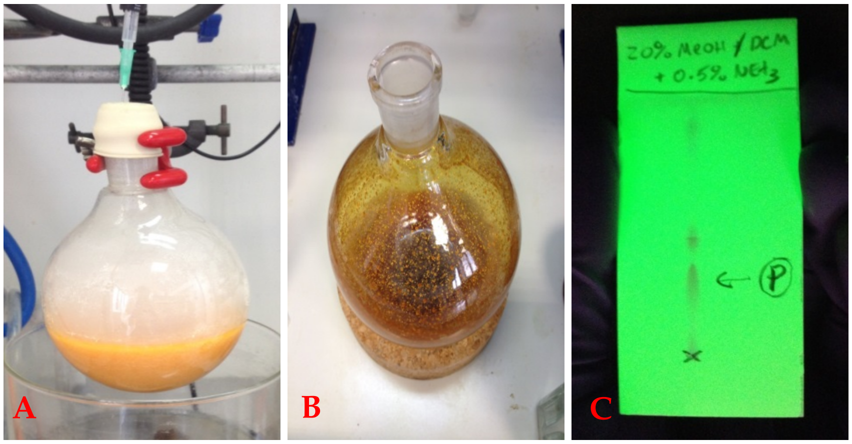


Figure 2. A; After addition of HCl, B; after reaction mixture concentrated, C; TLC of crude reaction mixture P = product.

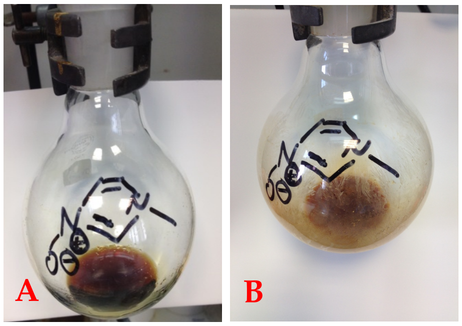


Figure 3. A; Product as an oil directly after concentration of column fractions on rotary evaporator, B; Product as a solid after standing in freezer for 24 h.

Notes

1. Hydroxylamine hydrochloride (HONH2·HCl, 99%) and sodium carbonate (Na2CO3, 99.5%) were purchased from Sigma Aldrich and used as received.
2. Glyoxal solution [(HCO)2, ~40% w/v aq., ~8.8 M] was purchased from Sigma Aldrich and used as received.
3. Methylamine (MeNH2) solution (40% w/v aq., 1.6 M) was purchased from Sigma Aldrich and used as received.
4. Formaldehyde (HCO2H) solution (37% w/v aq., 13.4 M, containing 10-15% MeOH as stabilizer) was purchased from Sigma Aldrich and used as received.
5. Conc. HCl (~37% w/v aq., 12.2 M) was purchased from Sigma Aldrich and used as received.
6. Dichloromethane, methanol and triethylamine were HPLC grade, purchased from Sigma Aldrich and used as received.
7. Silica Gel (high purity grade, pore size 60 Å, 230-400 mesh particle size.
8. Silica gel column (6 cm x 24 cm, 280 g Si). The column is eluted with 10% methanol in dichloromethane + 0.5% triethylamine (1500 mL, first 500 mL discarded) followed by 20% methanol in dichloromethane + 0.5% triethylamine (2000 mL). Fractions were collected in 40 mL test tubes and the desired product is typically obtained in fractions 27–77, which are concentrated by rotary evaporation (45 °C, 100 mmHg) to afford the hygroscopic product as a brown oil. The Rf of the purified product was found to be strongly dependent on the amount of material spotted onto the TLC plate and usually lay in the range of 0.1 to 0.3 (20% methanol in dichloromethane + 0.5% triethylamine).

9. A reaction run at half-scale provided 6.22 g (78%) of 1-methylimidazole-*N*-oxide.
10. Physical characteristics of 1-methylimidazole-*N*-oxide: low melting point waxy brown solid with 99.0% purity as determined by quantitative ^{1}H NMR using ethylene carbonate as an internal standard. mp 41–44 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.66 (s, 3H), 6.68 (s, 1H), 7.10 (s, 1H), 7.84 (s, 1H) (the submitters reported observing ^4J coupling of 1.9 Hz in the heterocycle ^{1}H NMR resonances); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 35.7, 117.6, 122.7, 126.9. HRMS (*m*/*z*) (M, $C_4H_6N_2O$) Calcd 98.0480), Found 98.0475; IR (film) 3142, 2929, 1651, 1551, 1316, 1165, 1090, 1027, 609, 479 cm^{-1}. Elemental analysis could not be secured by either submitters or checkers as a result of the hygroscopic nature of 1-methylimidazole-*N*-oxide. The coordinates from a single crystal X-ray structure determination on the monohydrate of 1-methylimidazole-N-oxide (obtained following atmospheric hydration of a sample of the anhydrous product prepared using this *Organic Syntheses* method) have been deposited at the Cambridge Crystallographic Data Centre: CCDC 1509924.

Working with Hazardous Chemicals

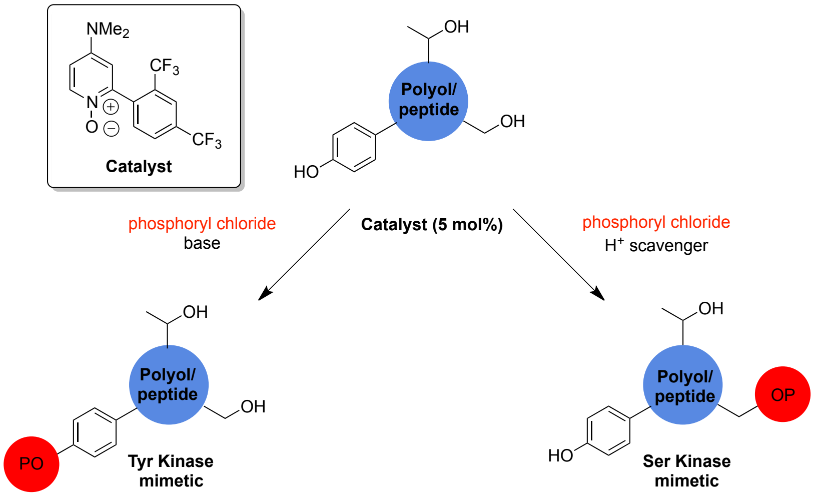
The procedures in *Organic Syntheses* are intended for use only by persons with proper training in experimental organic chemistry. All hazardous materials should be handled using the standard procedures for work with chemicals described in references such as "Prudent Practices in the Laboratory" (The National Academies Press, Washington, D.C., 2011; the full text can be accessed free of charge at http://www.nap.edu/catalog.php?record_id=12654). All chemical waste should be disposed of in accordance with local regulations. For general guidelines for the management of chemical waste, see Chapter 8 of Prudent Practices.

In some articles in *Organic Syntheses*, chemical-specific hazards are highlighted in red “Caution Notes” within a procedure. It is important to recognize that the absence of a caution note does not imply that no significant hazards are associated with the chemicals involved in that procedure. Prior to performing a reaction, a thorough risk assessment should be carried out that includes a review of the potential hazards associated with each chemical and experimental operation on the scale that is planned for the procedure. Guidelines for carrying out a risk assessment and for analyzing the hazards associated with chemicals can be found in Chapter 4 of Prudent Practices.

Discussion

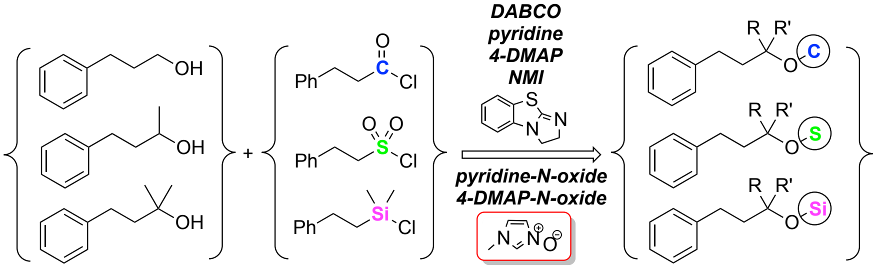
1-Methylimidazole-*N*-oxide (NMI-O) has been an underused member of the aryl-*N*-oxides, primarily due to its problematic synthesis.[2,3] Tsai *et al.* mistakenly reported the use of NMI-O as an efficient catalyst in the Morita-Baylis-Hillman reaction.[2] However, these authors were subsequently shown by Laus *et al.*[3] to have employed the *N*-methylimidazole (NMI) semiperhydrate (NMI.½H_2O_2) for these studies. The error resulted from the use of hydrogen peroxide (H_2O_2) for the direct oxidation of NMI, which has been repeatedly reported not to yield the desired *N*-oxide.[4] It is likely that NMI-O is concomitantly deoxygenated by H_2O_2 and by peracids during attempted preparation in this fashion.[5] Laus *et al.*[3] demonstrated the first synthesis of authentic NMI-O, requiring an 8 step synthesis from glyoxal.

Our group have reported the use of aryl-*N*-oxides as highly efficient catalysts for the phosphorylation of alcohols,[6] and recently reported the use of 2-aryl-4-dimethylaminopyridine-*N*-oxides for site-selective phosphorylation of polyols and peptides (Scheme 1).[7]



Scheme 1. Aryl-*N*-oxide catalysed site selective phosphorylation of polyols and peptides.

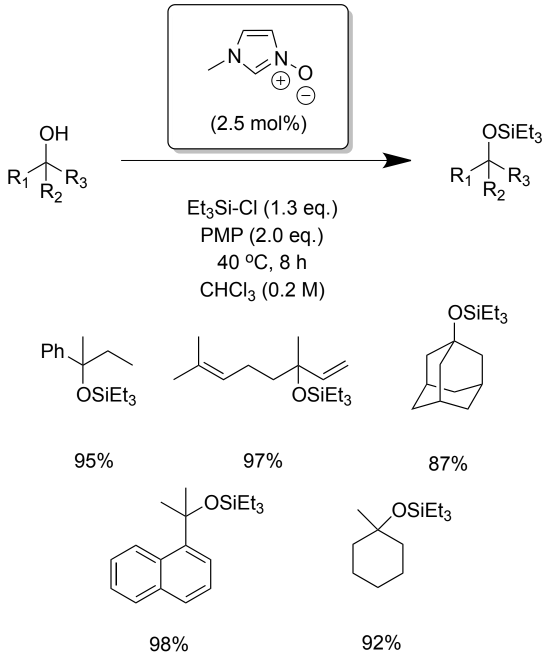
As such, we were interested in the comparative catalytic efficiencies of commonly used *N*-heterocycles and their *N*-oxide counterparts for acylation, sulfonylation and silylation reactions (Scheme 2).[8]



Scheme 2. Comparative study of *N*-heterocycle and *N*-oxide catalysts for the acylation, sulfonylation and silylation of alcohol derivatives.[8]

These studies revealed that whilst *N*-heterocycles were generally more efficient than their *N*-oxide analogues in the acylation process, *N*-oxides were generally more active for the sulfonylation and silylation of alcohol derivatives. In particular, 1-methylimidazole-*N*-oxide (NMI-O) was found to be a highly efficient catalyst both for sulfonylation and silylation. NMI-O was found to be the only amine or *N*-oxide Lewis basic organocatalyst capable of promoting the efficient silylation of tertiary alcohol derivatives with low catalyst loading (2.5 mol%) and under mild reaction conditions (45 °C, CH_2Cl_2) (Scheme 3).[8]

The efficiency of NMI-O as a highly active catalyst for the sulfonylation and silylation of alcohols should mean that it becomes widely used in synthesis. The operationally facile synthesis presented in this *Org. Synth.* preparation allows for multi gram-scale preparation of this highly active Lewis-basic catalyst and so should enable its widespread use and the development of novel derivatives.



Scheme 3. *N*-Methylimidazole-*N*-oxide (NMIO) catalyzed triethylsilylation of *tert*-alcohols.[8]

References

1. Department of Chemistry, South Kensington Campus, Imperial College London, United Kingdom, SW7 2AZ. Email: a.c.spivey@imperial.ac.uk. This work was financially supported by the Imperial College Institute of Chemical Biology and the EPSRC. J.I.M gratefully acknowledges the SCI for a Messel Scholarship.
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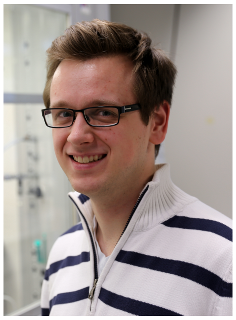
Appendix
Chemical Abstracts Nomenclature (Registry Number)

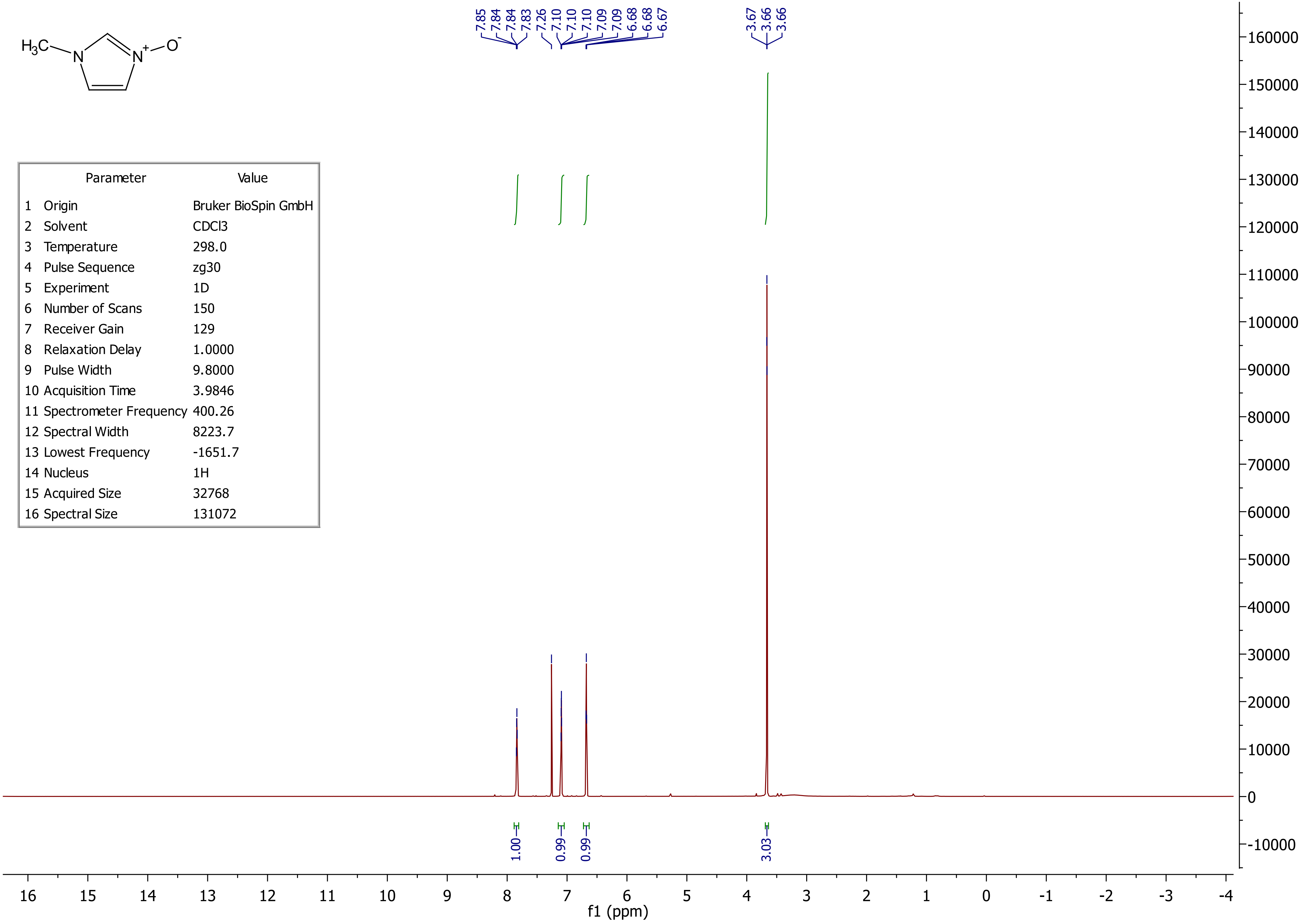
$HONH_2 \cdot HCl$: hydroxylamine hydrochloride; (5470-11-1)
Na_2CO_3: sodium carbonate; (497-19-8)
Glyoxal: ethanedial; (107-22-2)
$MeNH_2$: methylamine; (74-89-5)
Formaldehyde (50-00-0)
HCl: hydrochloric acid; (7647-01-0)

James Murray completed his undergraduate studies at Trinity College Dublin under the supervision of Prof. Stephen Connon. During this time, he conducted a one-year placement as a medicinal chemist at GlaxoSmithKline, Stevenage, and as a process chemist at Hoffman-La Roche, Basel. He is currently a 4th year doctoral student in the Spivey Group at Imperial College London where his research is focused on the development of aryl-*N*-oxide catalysts for acylation, sulfonylation and phosphorylation reactions.

Alan Spivey completed his BSc Chemistry degree at the University of Nottingham in 1988 and DPhil at the University of Oxford in 1991 with Prof. Jack. E. Baldwin. Following post-doctoral studies with Prof. Wolfgang Oppolzer at the Université de Genève, Switzerland and with Prof. Alan R. Battersby at the University of Cambridge, he began his independent career in the Department of Chemistry, University of Sheffield in 1995. In 2003 he moved to Imperial College where he was promoted to Professor in 2008. The focus of the Spivey group's research is the development of useful new synthetic concepts and methods.



Moritz Hönig completed his undergraduate studies at Ludwigs-Maximilians-Universität München in 2014 before he moved to the University of Cambridge for his M.Phil. studies, working in the area of C–H activation in total synthesis under the direction of Professor Matthew J. Gaunt. He is currently a Ph.D. student in the group of Professor Erick M. Carreira at the Eidgenössische Technische Hochschule Zürich. His research focus resides in the total synthesis of natural products.



	Parameter	Value
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3	Temperature	298.0
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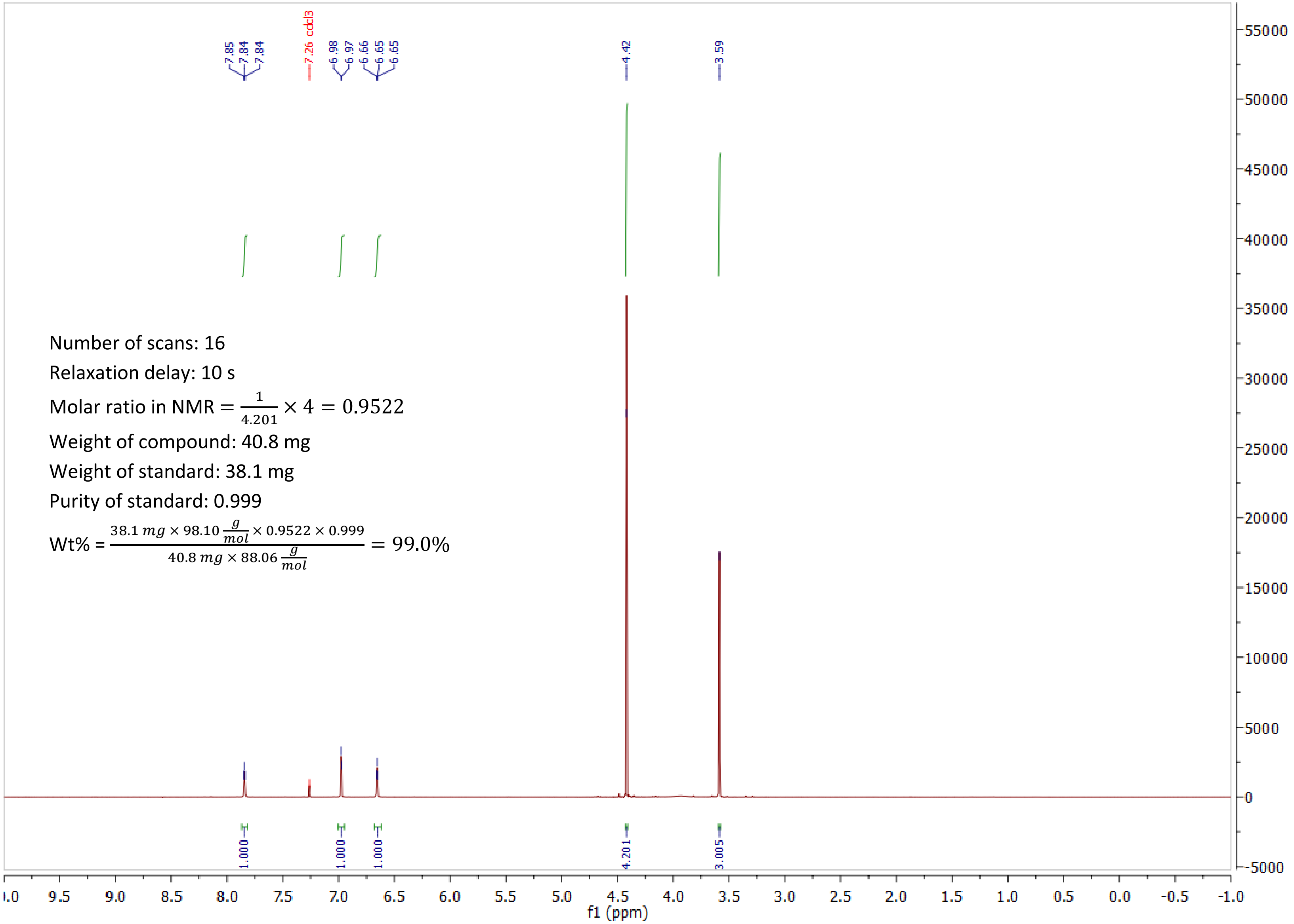
5	Experiment	1D
6	Number of Scans	150
7	Receiver Gain	129
8	Relaxation Delay	1.0000
9	Pulse Width	9.8000
10	Acquisition Time	3.9846
11	Spectrometer Frequency	400.26
12	Spectral Width	8223.7
13	Lowest Frequency	-1651.7
14	Nucleus	1H
15	Acquired Size	32768
16	Spectral Size	131072



Number of scans: 16

Relaxation delay: 10 s

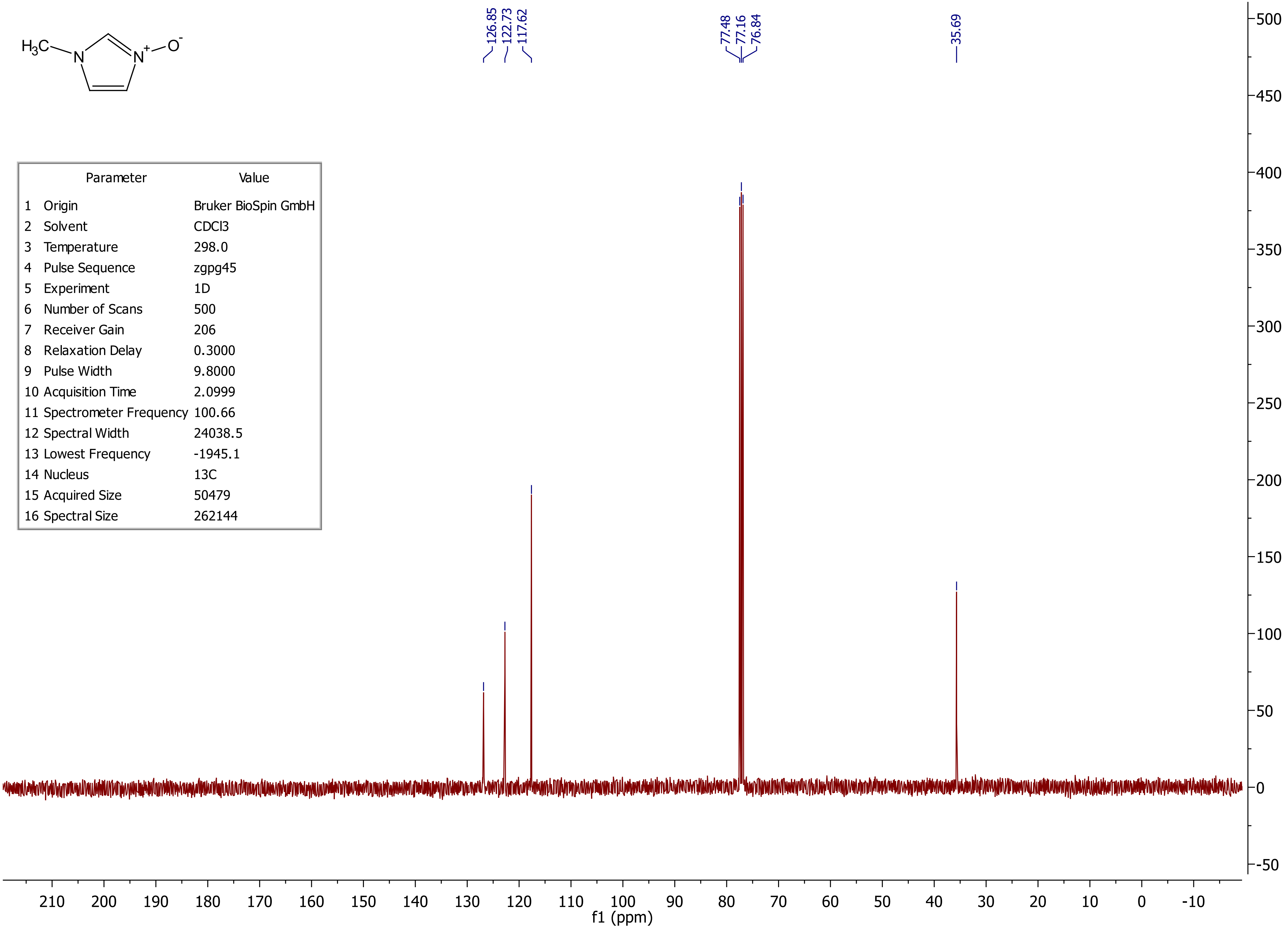
Molar ratio in NMR $= \frac{1}{4.201} \times 4 = 0.9522$

Weight of compound: 40.8 mg

Weight of standard: 38.1 mg

Purity of standard: 0.999

$$\text{Wt\%} = \frac{38.1\ mg \times 98.10\,\frac{g}{mol} \times 0.9522 \times 0.999}{40.8\ mg \times 88.06\,\frac{g}{mol}} = 99.0\%$$



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12	Spectral Width	24038.5
13	Lowest Frequency	-1945.1
14	Nucleus	13C
15	Acquired Size	50479
16	Spectral Size	262144