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Residual Solvent Signal of $CDCl_3$ as a qNMR Internal Standard for Application in Organic Chemistry Laboratory

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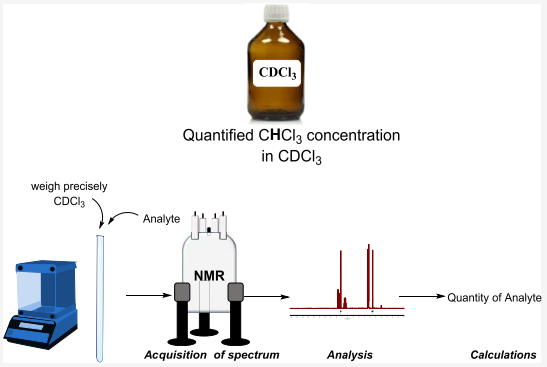
ABSTRACT: A nuclear magnetic resonance (NMR) spectrometer is a key instrument in the organic synthesis laboratory for structure determination, reaction control, and compound purity analysis. In addition to qualitative analysis, the application of NMR for quantitative analysis (qNMR) is gaining popularity. qNMR allows for simple quantification of crude product mixtures, determination of reaction yields, and purity of organic compounds. The determination of NMR yield requires the addition of an internal standard to each sample. Herein, we report a method where $CDCl_3$ residual solvent signal is used as an internal standard for qNMR after quantification in the solvent batch. This method significantly simplifies sample preparation and allows straightforward recovery of the analyte by the simple evaporation of the NMR solvent. The accuracy of the method is comparable to qNMR with 1,3,5-trimethoxybenzene as an internal standard if the herein described guidelines are followed.



INTRODUCTION

A nuclear magnetic resonance (NMR) spectrometer is the most commonly used instrument for structure elucidation in organic chemistry.[1] An access to an NMR spectrometer is a requirement for a modern organic synthesis lab. For example, a research group working in the area of synthetic organic chemistry usually runs hundreds of samples per month.[2] Besides "making sure one made the right compound", chemists use it for determination of purity of a sample, mechanistic experiments, and determination of reaction (NMR) yields by qNMR[3] which requires the addition of an internal standard to the sample. This approach is also used for the quality control of pharmaceutical ingredients[4] and in other areas where quantification of organic compounds is important.[5]

$CDCl_3$ is one of the most commonly used NMR solvents in the organic synthesis lab. It is the preferred solvent due to its affordable price, good solubilizing properties of many organic compounds, and straightforward recovery of the sample after analysis by simple evaporation. The recovery of a sample after qNMR analysis is, however, often problematic even from volatile solvents if the internal standard applied is nonvolatile.[2]

A signal due to incompletely deuterated NMR solvent residue is always present in the NMR spectrum. An experienced chemist would quickly recognize a singlet at 7.26 ppm and might use it to adjust the ppm scale.[6] Here, we propose to take full advantage of this mostly ignored signal in the NMR spectrum as it carries extra valuable information, i.e., a defined concentration of protons in a deuterated NMR solvent batch. Determination of the concentration of the $CHCl_3$ residue for each batch of $CDCl_3$ used in the lab does not require much effort in comparison with the expected value of quantitative information on compound concentrations in all measured samples. We show that the residual solvent signal of $CDCl_3$ can be used as an internal standard for qNMR and that its concentration remains constant for the batch if it is stored properly. Figure 1 shows our approach in comparison with the conventional qNMR method.

There are numerous reports on qNMR[3] including two where residual protons in D_2O and dimethyl sulfoxide (DMSO)-d_6 are considered as potential internal standards for the quantification of natural products.[7,8] However, it is not a common practice in organic synthesis labs to use residual solvent as a qNMR standard. To gain maximum accuracy of this approach, the best practices of the qNMR sample preparation and sample acquisition[3,9] should be taken into consideration. The purpose of this study is to demonstrate the practicality of this approach in an organic synthesis laboratory setting for daily use with simple sample preparation efforts and easy recovery of the analyte.

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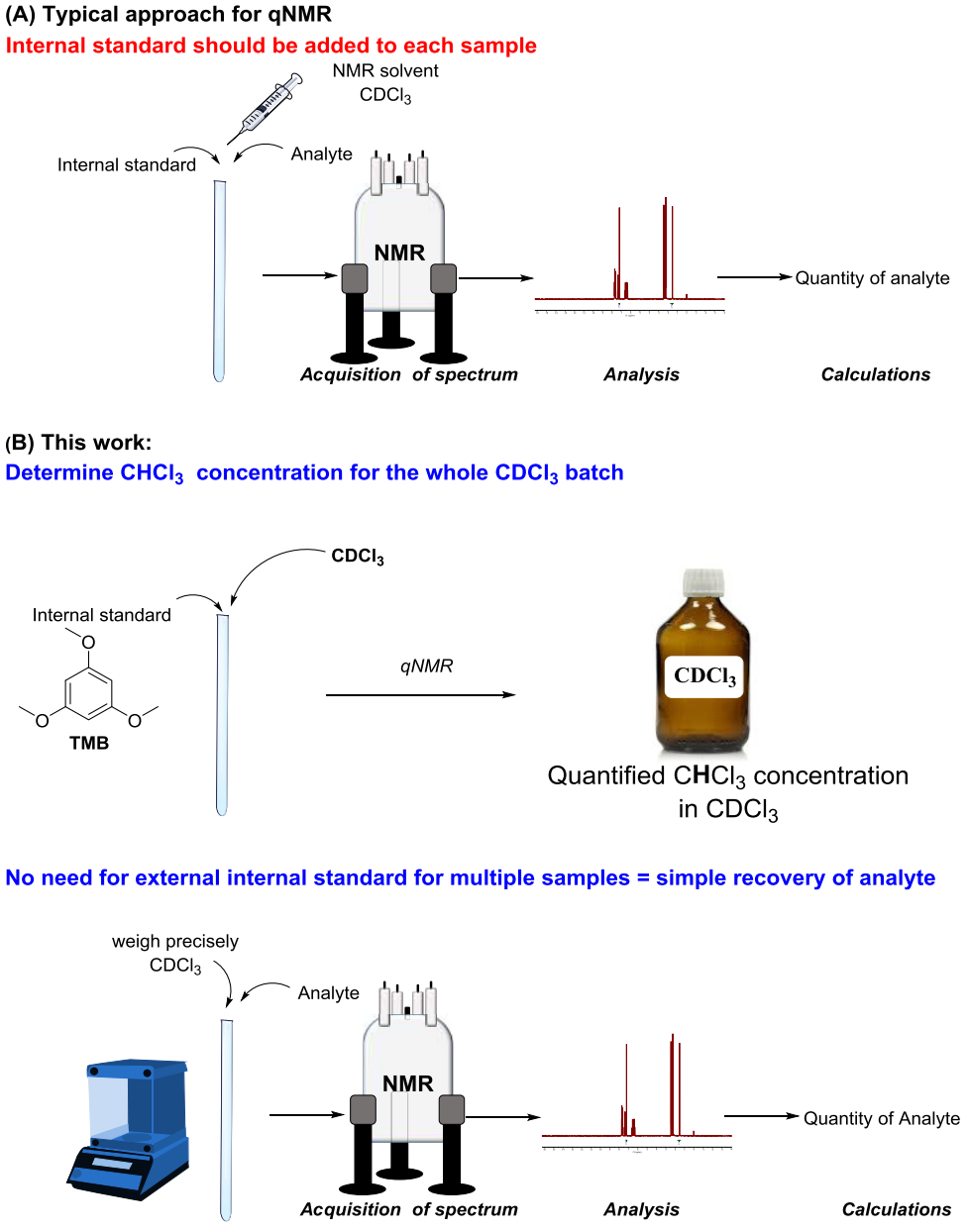

Figure 1. (A) NMR internal standard should be added to each sample. (B) No need for the addition of extra internal standard after the determination of residual $CHCl_3$ concentration in $CDCl_3$.

Table 1. T_1 Relaxation Time for $CHCl_3$ and TMB (400 MHz)

	T_1, s		
	$CHCl_3$	TMB 2,4,6-C**H**	TMB 1,3,5-OCH_3
average (n = 3 measurements)	6.314 ± 0.004	3.688 ± 0.004	1.760 ± 0.002

RESULTS AND DISCUSSION

We started our study with the determination of the concentration of nondeuterated $CHCl_3$ residual solvent in a $CDCl_3$ batch using the internal standard 1,3,5-trimethoxybenzene (TMB).[2] Since $CHCl_3$ is a smaller molecule than the usual internal standards, its relaxation is expected to be slower and care must be taken to use appropriate experimental parameters (pulse length and recycle delay) for the qNMR experiments. Therefore, we determined the T_1 relaxation time for $CHCl_3$ and TMB as a primary internal standard (Table 1).

Based on the measured T_1 values, we chose the qNMR acquisition parameters as follows: 14° pulse, recycle delay 30 s, and 32−128 scans yielding experiment times of 21−75 min (on a 400 and 300 MHz instrument, respectively). The theoretical recovery of the $CHCl_3$ magnetization during the recycle delay is 99.97% and practically 100% for TMB protons as well as other compounds of similar or larger size. Reduction of the recycle delay to 7 s would yield an experiment time of 8−26 min and still ensure >99% recovery of the $CHCl_3$ magnetization. As expected, on both instruments, we observed a good linear correlation (linearity) between the concentration

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of the internal standard $c_{(TMB)}$ and its corresponding integral value $I_{(TMB)}$, when the integral value $I_{(CHCl3)}$ of the $CHCl_3$ signal was set to 100 (for 400 MHz data see Figure 2, for 300 MHz data see the Supporting Information).

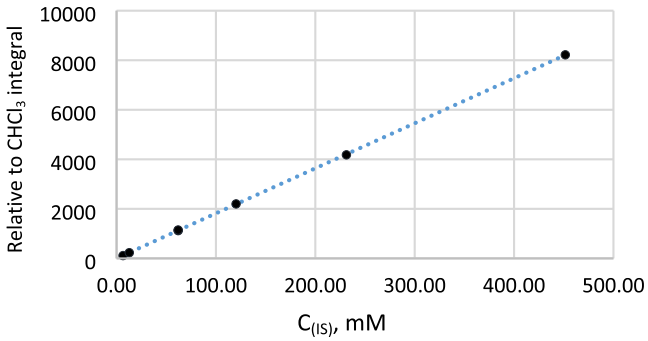

Figure 2. Integral value of internal standard 1,3,5-trimethoxybenzene (TMB) as a function of its concentration, when residual $CHCl_3$ integral value is set to 100 (400 MHz).

To determine the $CHCl_3$ concentration in our $CDCl_3$ batch, we prepared three independent samples and performed three measurements for each sample. The obtained $c_{(CHCl3)}$ was 16.231 ± 0.138 mM (standard deviation of 0.85%). To test the stability of the $CHCl_3$ content in $CDCl_3$, we repeated the determination of $CHCl_3$ concentration after 1 month and obtained 16.144 ± 0.037 mM (standard deviation of 0.23%). The difference of −0.087 mM or −0.54% is within the standard deviation of the first measurement, which indicates that the $CHCl_3$ concentration remains constant for at least 1 month.

Once the precise $CHCl_3$ concentration in a $CDCl_3$ batch has been determined, the residual solvent signal can be used as an internal standard for qNMR. To assess the accuracy of this approach, we used it to determine the weight $m_{(qNMR\ CHCl3)}$ of nine compounds and compared the obtained values with the balance weight $m_{(balance)}$ as well as cross-checked the results with those from qNMR using the accepted internal standard TMB (Table 2). All measurements were repeated three times and the standard deviation was calculated to determine the precision of the measurement. The accuracy of the method was evaluated by calculating the percentage errors of the determined qNMR weight $m_{(qNMR)}$ with respect to the balance weight $m_{(balance)}$ using both $CHCl_3$ and TMB as internal standards. The sample purity provided by the suppliers was taken into account. All samples were measured on both 400 MHz and 300 MHz instruments and the results were compared.

The selected test compounds include common solvents (Table 2, **1**−**3**), reagents in different states of matter (solid **4**, **5**; oil **7**), a pharmaceutical drug (**6**), and a compound with limited solubility in $CDCl_3$ (**8**, with MeCN additive as a solubilizing cosolvent). On average, the obtained $m_{(qNMR\ CHCl3)}$ values differ by 3.0% from the balance weight $m_{(balance)}$ and by 2.5% from the weight determined using TMB as internal standard $m_{(qNMR\ TMB)}$. At the same time, the $m_{(qNMR\ TMB)}$ values differ by about 2.5% from the balance weight $m_{(balance)}$. The difference between the results obtained from two different $CDCl_3$ solvent batches is similarly in a range of 2−3% (Table 2, 1). The maximum qNMR error between the measurements with $CHCl_3$ as internal standard is 6.2 and 8.8% using 400 and 300 MHz instruments, respectively. Among the measurements using TMB, the corresponding maximum errors are 5.2 and 8.6%. These results indicate that the accuracy of our proposed method is comparable to the conventional approach using TMB as an internal standard.

The precision expressed as a standard deviation for repeated measurements using $CHCl_3$ as an internal standard was in the range of 0.06−1.66% with one exception. The results for the aldehyde **4** displayed lower repeatability (standard deviation of 4.36%) at 300 MHz, which could be explained by the instability of the sample during a longer measurement time, as was required for this instrument. The standard deviation of the measurements using TMB was between 0.02 and 0.86%. This indicates that the precision is notably higher than the accuracy using both approaches.

As with qNMR in general, the present method requires good solubility of the tested compounds in the NMR solvent. The compound **8** displayed only partial solubility in $CDCl_3$; therefore, cosolvent was added to improve solubility. The obtained results for this compound show some of the largest errors with respect to balance weight; however, also, in this case, the results using $CHCl_3$ or TMB as an internal standard are comparable. Another limitation of the method is the potential overlap of the analyte signals with $CHCl_3$ signal, which limits its applicability to compounds that do not show signals around 7.26 ppm. With regard to the detection limit and useful $CHCl_3$ concentration, the number of scans may need to be adjusted to reach the desirable S/N ratio for the signals under analysis taking into consideration the best practices of qNMR.[2] Additionally, the analyte concentration may need to be adjusted by dilution using an appropriate volume of $CDCl_3$ to obtain both $CHCl_3$ and analyte signal intensities at the desired signal-to-noise ratio as well as in the working range of the spectrometer's analog-to-digital converter. For this purpose, the sample can be prepared in appropriate size vials (equipped with a screwing cap to avoid evaporation losses), which would allow us to use a higher volume of $CDCl_3$. For the best result, a precise determination of $CDCl_3$ weight is crucial. Therefore, we recommend using a balance for measuring the $CDCl_3$ weight, as this is very easy to do and guarantees the best accuracy. We do not recommend using simple hypodermic syringes for this purpose, as this will add extra uncertainty to the measurement (see the Supporting Information). The concentration of $CHCl_3$ should be determined for each bottle regardless if it has the same or different LOT number. This will remove any uncertainties that might arise due to varying manufacturing, packing, storage, and shipment conditions. For example, two different $CDCl_3$ batches with D 99.8% content used for the experiments in Table 2 (batch A and B) have approximately a 3% difference in the $CHCl_3$ concentration.

To exemplify the utility of the current technique in the organic synthesis laboratory, we present its application in the synthesis of vinyl sulfone **9**. The compound **9** can be prepared in three steps (Scheme 1 and Table 3) starting from 1-phenyl-1*H*-tetrazole-5-thiol (**10**), which is alkylated with 1,2-dichloromethane to yield 5-((2-chloroethyl)thio)-1-phenyl-1H-tetrazole (**11**). Further, oxidation of sulfide **11** to a corresponding sulfone **12** can be accomplished using $NaIO_4$ in the presence of catalyst $RuCl_3{\cdot}H_2O$.[10] Purity of the crude intermediate **12** was determined using the herein described qNMR method, which helped to adjust the quantity of the required base in the next step (Table 3). The desired product, vinyl sulfone **9**, turned out to be unstable in dichloromethane when using

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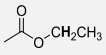
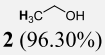
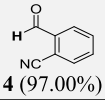
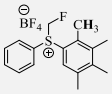
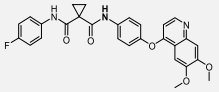
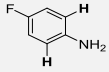
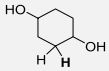
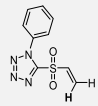
Table 2. Compound Weight Determined by qNMR $m_{(qNMR)}$ Using $CHCl_3$ or 1,3,5-Trimethoxybenzene and Balance $m_{(balance)}$

compound (purity)[c]	$m_{(balance)}$[d], mg	NMR spectrometer	Error of $m_{(qNMR)}\% = (m_{(balance)} \times purity - m_{(qNMR)}) \times 100\%/(m_{(balance)} \times purity)$[e]			
			$CHCl_3$ method		1,3,5-trimethoxybenzene	
			Error, %	Stdev.S, % (3 repeats)[f]	Error, %	Stdev.S, % (3 repeats)[f]
 **1** (99.99%)	14.87 *batch A*[a]	400 MHz	4.08	*0.25*	2.14	*0.04*
		300 MHz	4.24	*1.66*	2.77	*0.04*
	12.16 *batch B*[b]	400 MHz	2.22	*0.06*	-1.09	*0.08*
		300 MHz	0.67	*0.34*	-0.88	*0.13*
 **2** (96.30%)	16.37	400 MHz	3.72	*0.12*	4.18	*0.07*
		300 MHz	7.17	*1.54*	3.94	*0.14*
 **3** (99.90%)	16.86	400 MHz	-1.08	*0.46*	-0.98	*0.02*
		300 MHz	-0.15	*0.99*	0.18	*0.11*
 **4** (97.00%)	11.16	400 MHz	0.81	*0.38*	-3.22	*0.13*
		300 MHz[g]	8.78	*4.36*	-4.28	*0.62*
 **5** (98.00%)	11.69	400 MHz	-0.78	*0.38*	-0.92	*0.11*
		300 MHz	0.20	*0.75*	0.55	*0.20*
 **6** (98.00%)	13.43	400 MHz	2.32	*0.37*	1.10	*0.31*
		300 MHz	-0.39	*0.60*	4.80	*0.64*
 **7** (99.00%)	22.30	400 MHz	-1.01	*0.06*	-0.04	*0.10*
		300 MHz	-3.14	*1.32*	-0.42	*0.27*
 **8** (98.00%) +MeCN 100 μL	11.54	400 MHz	6.15	*0.49*	5.15	*0.13*
		300 MHz	7.67	*1.46*	8.64	*0.86*
 **9** (99.0%)	12.32	400 MHz	-0.27	*0.35*	-2.22	*0.25*
		300 MHz	-5.24	*0.55*	-1.65	*0.38*
Average of absolute values of errors, %			**3.00**		**2.46**	

[a]All calculations were performed using $CDCl_3$ batch A (Eurisotop, chloroform D, 99.80% D, Lot: S1541) $c_{(CHCl3)}$ = 16.231 mmol/L unless otherwise stated. [b]$CDCl_3$ batch B (Aldrich, chloroform-*d*, 99.80% D, Lot # STBJ5818) $c_{(CHCl3)}$ = 16.700 mmol/L. Signals of protons highlighted in bold were used for integration. [c]As indicated in the certificate of analysis provided by the supplier. [d]Sample weight measured on analytical balance *d* = 0.01 mg. [e]Error calculated as the difference between the balance weight and qNMR weight taking into consideration the compound purity. [f]Three independent measurements for each sample. [g]Due to compound **4** instability in solution, lowered accuracy was observed on 300 MHz instrument (acquisition time 1 h 15 min).

excess Et_3N as a base (Table 3, entry 1). Therefore, a careful adjustment of the reaction conditions (entries 2−4) was performed to find an optimal reaction solvent and stoichiometry of base. Using the $CDCl_3$ qNMR method, both, ^1H NMR yields and the purity of product **9** was easily evaluated for the crude and the isolated product **9**, thereby allowing rapid identification of optimal reaction conditions (entry 4). The elimination reaction from **12** to product **9**

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Scheme 1. Synthesis of Sulfone 12

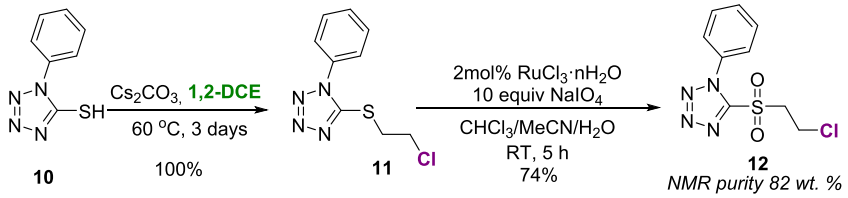
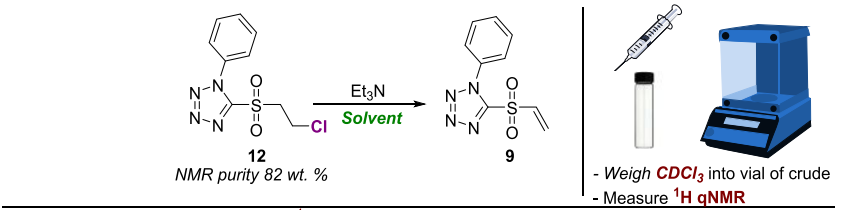


Table 3. Reaction Optimization Using $CDCl_3$ qNMR Technique



		NMR yield of **9**, %[b]			
entry	conditions[a]	crude[c]	isolated[d]	balance yield of **9**, %	NMR purity of **9**, %[b,e]
1	DCM, RT, 4 h, 2.5 equiv TEA	4.8			
2	Et_2O, 0 °C, 15 min, 2.27 equiv TEA	87.0	86.4	97	89
3	Et_2O, 0 °C, 15 min, 1.12 equiv TEA	100	97.1	103	95
4	MTBE, 0 °C, 15 min, 1.12 equiv TEA	100	99.5	103	97

[a]All reactions were performed on 0.301 mmol scale of **12**. [b]qNMR performed on a 400 MHz instrument using residual $CHCl_3$ as an internal standard. [c]The crude **9** used for analysis. [d]Product isolated using silica gel column chromatography (PE/EtOAc 5:1 to 1:1). Balance yield, NMR yield, and purity determined for the same sample. [e]NMR purity calculated following eq 5, see Experimental Section.

under the optimized conditions turned out to be a quantitative process. The balance yield of isolated **9** includes the weight of impurities, whereas the qNMR yield is calculated for a pure substance in a sample, thereby allowing us to estimate the sample purities (entries 2−4). Application of the residual $CHCl_3$ as an internal standard made possible the complete recovery of the analyzed samples by simple solvent evaporation.

We advise chemists who routinely use NMR in their work to quantify the $CHCl_3$ concentration of the particular solvent batch and label the bottle with the determined concentration, which is a simple task to do. This needs to be done once for each batch of $CDCl_3$ and, if properly stored, the value should be constant for at least 1 month. Our results show that the present method is sufficiently accurate and precise for qNMR applications in routine organic chemistry. This method offers a simple alternative to an external standard or the ERETIC qNMR methods.[12] According to the literature, ERETIC gives approximately 3% of error,[12a] which is comparable to the average error of using $CHCl_3$ (3.00%) and TMB (2.46%) as internal standards (Table 2). To adopt it as an analytical chemistry tool or evaluate its suitability for other purposes, we suggest to validate this method for the compound of interest using an established internal standard on your own instrument and determine the uncertainties of the measurement.

CONCLUSIONS

We have proposed a very simple approach for the fast determination of NMR yield in the organic synthesis lab by the determination of residual solvent concentration in each $CDCl_3$ batch and using the residual solvent signal as an internal standard. The valuable quantitative information carried by the residual solvent adds an extra dimension besides the usual qualitative interpretation of the ^1H NMR data. Our results indicate that the residual $CHCl_3$ gives comparable accuracy with 1,3,5-trimethoxybenzene as an internal standard. In addition, the use of NMR solvent residue as an internal standard simplifies qNMR sample preparation and provides an opportunity for very straightforward sample recovery by simple NMR solvent evaporation. This approach has a huge potential in reaction optimization and fast purity assessment of the reaction intermediates and common lab chemicals without the necessity to add any foreign materials to the sample.

EXPERIMENTAL SECTION

General Experimental Details. The weights of the internal standard 1,3,5-trimethoxybenzene (TMB), $CDCl_3$, and compounds **1**−**9** were measured using analytical balance BOECO d = 0.01 mg placed on a stone table. All of the prepared samples were measured within 24 h to avoid errors from solvent evaporation losses. Spectra were recorded on (1) a 400 MHz Bruker Avance Neo spectrometer equipped with 5 mm double-resonance broadband CryoProbe Prodigy using the parameters: 14° pulse (90° pulse = 12 μs), d_1 = 30 s, ns = 32, acquisition time = 4.19 s (32k points), spectral width 19.5333 ppm centered at 6.175 ppm and (2) a 300 MHz Bruker Fourier spectrometer equipped with 5 mm dual-channel EasyProbe using the parameters: 14° pulse (90° pulse = 14.5 μs), d_1 = 30 s, ns = 128, acquisition time = 5.37 s (32k points), spectral width 20.3339 ppm centered at 6.175 ppm. The chosen interscan (pulse) delay d_1 was based on the measured T_1 relaxation times of the standard and analyte to ensure a near-complete (>99.97%) relaxation of $CHCl_3$.[3] However, in most cases, the interscan delay can be reduced to approximately 10 s (which ensures 99.4% relaxation using 14° pulse tip angle) without deteriorating the accuracy of the method (as

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demonstrated in the Supporting Information). Each qNMR spectrum was taken three times (two for only $CDCl_3$). 1,3,5-Trimethoxybenzene TraceCERT, purity = 99.96% (Lot# BCBW3670) and 99.82 (Lot# BCC9688) was purchased from Sigma-Aldrich. $CDCl_3$ batch A: Eurisotop, chloroform D, 99.80% D, (Lot: S1541). $CDCl_3$ batch B: Aldrich, chloroform-*d*, 99.80% D, (Lot # STBJ5818). ^1H NMR spectra were transformed and analyzed with Mestrenova software (Mestrelab Research). All spectra before integration were transformed with the baseline correction (Whittaker Smoother).

General Procedure A for the $CHCl_3$ Concentration Determination in $CDCl_3$. In a 4 mL vial equipped with a screwing cap internal standard 1,3,5-trimethyoxybenzole (TMB) (>∼11 mg) was precisely weighed. The capped vial with TMB was placed on an analytical balance and tare was measured. To the vial, $CDCl_3$ (∼1 mL) was added, the vial immediately sealed with a screwing cap, and the precise weight of $CDCl_3$ was measured by analytical balance. The sample was shaken till all TMB dissolved. The clear TMB solution was transferred to an NMR tube and ^1H NMR spectrum was recorded using the above-described parameters. The signals of $CHCl_3$ at 7.26 ppm and those of 1,3,5-trimethyoxybenzole at 6.09 and 3.77 ppm were integrated. Average $c_{(CHCl3)}$ was calculated from three independent measurements (three repeats for each) using eq 1

$$c_{(CHCl_3)} = \frac{I_{(CHCl_3)} \times c_{(TMB)} \times N_{(TMB)}}{I_{(TMB)}} \quad (1)$$

where $c_{(CHCl3)}$ is the concentration of the $CHCl_3$ residue in $CDCl_3$, $c_{(TMB)}$ is the concentration of internal standard, and $N_{(TMB)}$ is the ratio of the number of protons of the signal used for integration in internal standard (TMB) and the number of protons in solvent residue ($CHCl_3$). $I_{(CHCl3)}$ is the integral of solvent residue (at 7.26 ppm) and $I_{(TMB)}$ is the integral of the internal standard signal (for TMB, the aromatic CH signal at 6.09 ppm was used).

General Procedure B for the Analyte Weight Determination by ^1H NMR Using $CDCl_3$ Solvent Residue or TMB as an Internal Standard. The analyte (>∼11 mg) was weighed in a 4 mL vial equipped with a screwing cap. To crosscheck the results, TMB (∼11 mg) was also added to the reference samples listed in Table 2. The capped vial with a sample was placed on an analytical balance and tare was measured. To the vial, $CDCl_3$ (∼1 mL) was added, the vial was immediately sealed with a screwing cap, and the precise weight of $CDCl_3$ was measured by an analytical balance. The sample was shaken till all of the analyte dissolved. The sample solution was transferred to the NMR tube and ^1H NMR spectrum was recorded. The signal of $CHCl_3$ at 7.26 ppm and a signal of choice from the analyte were integrated. The analyte weight was calculated using the previously determined $C_{(CHCl3)}$ concentration following eq 2

$$m_{(qNMR\ CHCl_3)} = \frac{c_{(CHCl_3)} \times I_{(X)} \times M_{(X)} \times m_{(CDCl_3)}}{I_{(CHCl_3)} \times N_{(X)} \times \rho_{(CDCl_3)}} \quad (2)$$

For comparison, the compound weight $m_{(qNMR\ IS)}$ using 1,3,5-trimethoxybenzene (TMB) as the internal standard was calculated following eq 3

$$m_{(qNMR\ TMB)} = \frac{I_{(X)} \times N_{(TMB)} \times M_{(X)} \times m_{(TMB)}}{I_{(TMB)} \times N_{(X)} \times M_{(TMB)}} \times \text{TMB purity} \quad (3)$$

where $c_{(CHCl3)}$ is the calculated protonated chloroform concentration [mM/L], $I_{(X)}$ is the integral intensity of the studied compound, $I_{(CHCl3)}$ is the integral intensity of protonated chloroform [100], $M_{(X)}$ is the molecular weight test item [g/mol], $m_{(CDCl3)}$ is the sample weight of chloroform [g], $N_{(X)}$ is the number of protons for the integrated signal in the molecule of an analyte, $\rho_{(CDCl3)}$ is the density of chloroform [1500 mg/mL], $N_{(TMB)}$ is the number of protons for the integrated signal in the molecule of standard, $m_{(TMB)}$ is the sample weight of standard [mg], and $M_{(TMB)}$ is the molecular weight standard [g/mol].

The errors were calculated using the equation error% = $(m_{(balance)} \times \text{purity} - m_{(qNMR)})/(m_{(balance)} \times \text{purity}) \times 100\%$.

Application of qNMR $CDCl_3$ Technique in the Reaction Optimization Experiments.[10] *5-((2-Chloroethyl)sulfonyl)-1-phenyl-1H-tetrazole (**12**).*[10] To a mixture of 1-phenyl-1H-tetrazole-5-thiol (**10**) (3.178 g, 17.83 mmol, 1.00 equiv) and Cs_2CO_3 (17.4 g, 53.5 mmol, 3.0 equiv) was added 1,2-dichloroethane (116 mL, 1480 mmol, 93 equiv) and MeCN (4 mL) at RT. The reaction mixture was stirred at 60 °C for 3 days. TLC (PE/EtOAc 5:1) showed full conversion. The reaction mixture was diluted with water (150 mL) and extracted with DCM (3 × 200 mL). The combined organic phases were dried over anh. $NaSO_4$, filtered, and evaporated to give the intermediate product 5-((2-chloroethyl)thio)-1-phenyl-1H-tetrazole (**11**) (4.30 g, 100%) as an off-white solid, which was subjected to the next step without additional purification. ^1H NMR (400 MHz, $CDCl_3$) δ 7.56−7.44 (m, 3H), 3.91−3.86 (m, 2H), 3.72−3.62 (m, 2H).[10,11] To a mixture of crude sulfide from previous step (4.212 g, 17.50 mmol, 1.0 equiv) in $CHCl_3$ (12 mL) and MeCN (12 mL) was added $NaIO_4$ (37.4 g, 175 mmol, 10 equiv). To the mixture, a solution of $RuCl_3$ hydrate (83 mg, 0.37 mmol, 0.02 equiv) in water (42 mL) was added dropwise over 10 min at room temperature. The reaction mixture was stirred for 5 h at room temperature. The reaction progress was monitored by TLC (PE/EtOAc 5:1). After the completion, 100 mL of water was added to the mixture. The reaction mixture was extracted with MTBE (3 × 50 mL). The combined organic phases were washed with sat. $NaHCO_3$ and filtered through a plug of silica gel covered with anh. Na_2SO_4. The plug was washed with MTBE till no more product was detected by TLC in the filtrate. The filtrate was evaporated under reduced pressure to give the desired product (3.549 g, 74%, $NMR_{(qNMR\ CDCl3)}$ purity = 82%) as an off-white solid.

^1H NMR (400 MHz, $CDCl_3$) δ 7.75−7.48 (m, 5H), 4.23−4.07 (m, 2H), 4.10−3.96 (m, 2H).[10,11]

*Reaction Optimization for the Synthesis of 1-Phenyl-5-(vinylsulfonyl)-1H-tetrazole (**9**).* To a chloride **12** (100 mg, 82% purity, 0.301 mmol, 1.0 equiv) in a solvent (4 mL) (see Table 3) at 0 °C was added triethylamine (46.9 μL, 0.337, 1.12 equiv). A white precipitate formed. The reaction mixture was stirred for 15 min at 0 °C. The white precipitate was filtered off, filter-cake washed with solvent (1 mL), and the filtrate was evaporated under reduced pressure. To the crude product, ∼3 g of precisely weighted $CDCl_3$ with previously determined $CHCl_3$ concentration was added (following general procedure **B**). After the measurement of ^1H NMR under qNMR conditions, the product weight in the sample was determined according to eq 2. The NMR yield for the crude was calculated by eq 4

$$\text{yield}_{(qNMR)} = \frac{m_{(qNMR\ CDCl_3)}}{m_{(theoretical)}} \times 100\% \quad (4)$$

The NMR sample was completely recovered by solvent evaporation under reduced pressure and the obtained residue was purified by silica gel column chromatography (PE/EtOAc 5:1 to 1:1) to give product **2**. The qNMR yield for the isolated product was obtained as previously mentioned using eq 4. The product qNMR purity was calculated by eq 5

$$\text{purity}_{(qNMR)} = \frac{m_{(qNMR\ CDCl_3)}}{m_{(balance)}} \times 100\% \quad (5)$$

^1H NMR (400 MHz, chloroform-*d*) δ 7.71−7.56 (m, 5H), 7.13 (dd, J = 16.5, 9.8 Hz, 1H), 6.71−6.62 (m, 1H), 6.49 (dd, J = 9.9, 1.1 Hz, 1H).

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.0c02744.

The tables with data and NMR spectra (PDF)

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Notes

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