THALESNano

Optimization of *N*-alkylation in the Phoenix Flow Reactor using 45 MHz picoSpin™ bench-top NMR for monitoring

In this application note we report on the Thermo Scientific picoSpin™ 45 benchtop proton (^{1}H) NMR that was utilized to monitor the optimization of imidazole alkylation carried out in the Phoenix Flow Reactor™. Flow chemistry is a widely accepted technique in the synthesis field and makes optimization fast and convenient. Benchtop NMR instruments allow chemists to measure ^{1}H NMR spectra directly in the fume hood and monitor pseudo real-time behavior of reaction chemistries. Here we give details on both the flow synthesis at extremely high temperature as well as the following analysis.

INSTRUMENTATION

Flow chemistry reactors are ideal tools for chemists to perform a wide variety of reactions, which take place inside a small volume reaction area, through which the solution or reaction mixture is pumped. Due to the excellent mixing and large exposed surface to volume ratio used during a reaction, reactions are better controlled and the process is more productive then in batch. Using flow technology can dramatically reduce optimization and reaction time. ThalesNano's H-Cube Series is a revolutionary bench top continuous flow system family with built-in hydrogen production capability and a disposable catalyst cartridge system for safe and fast hydrogenation reactions. With no external storage of hydrogen necessary, the members of the H-Cube Series, the H-Cube®, H-Cube Pro™, H-Cube Mini™, and H-Cube Midi™, can be used safely in almost any laboratory environment. The H-Cube Series can be used from mgs to half-kilo production per day. ThalesNano's Phoenix Flow Reactor™ is a high temperature module compatible with the H-Cube Series allowing reactions up to 450°C and 100 bar. The reaction zone in the Phoenix Flow Reactor may vary upon the chemistry and desired scale allowing production in mg-kg/day scale and reactions in fixed bed or loop reactors for heterogeneous or homogeneous reactions, respectively. This module can be used separately from the H-Cube Series reactors when connected with a high pressure providing Valve Module, and a liquid supplier unit.

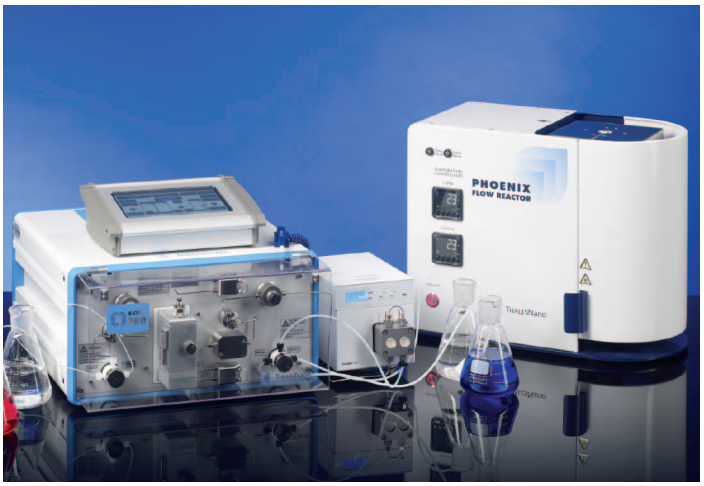

Figure 1: The Phoenix Flow Reactor connected to the H-Cube Pro and HPLC pump.

The picoSpin™ 45 ^{1}H NMR spectrometer is a true breakthrough in chemical instrumentation. It provides the power of NMR spectroscopy in a compact and affordable instrument beneficial to applications in research, manufacturing processes and the teaching classroom. This miniature, portable NMR instrument only weighs 4.76 kg and has a dimension of 20×14×29 cm.

Phoenix Flow Reactor™ – picoSpin™ 45 Application Note

Liquid samples are simply injected into an internal capillary via front-panel fittings, and only 30 microliters of sample fluid is needed to obtain a spectrum. The unit's fluid capillary is contained within a cartridge, so it can be replaced easily by the user in case it becomes blocked or contaminated.

Figure 2: Injection of the sample into the picoSpin™ capillary

Deuterated solvents are not necessary for measurement, though their use can be beneficial when an important analyte signal overlaps with a solvent signal. A highly stable, temperature-controlled permanent magnet ensures easy maintenance-free operation without the need for liquid cryogens. The unit occupies a small fraction of the space of a conventional NMR spectrometer, and it does not require specialized knowledge or training for operation.

NMR data is generated in the industry-standard JCAMP-DX format for compatibility with standard NMR data analysis packages.

EXPERIMENTAL SETUP

N-alkylation of imidazole was achieved over a zeolite catalyst using high temperature and pressure in the Phoenix Flow Reactor™ connected to the H-Cube Pro™, which supplied the high pressure and liquid delivery system, and also served as a central control unit. The reaction was carried out in a Metal-metal Sealed High Temperature Cartridge. The product solutions were analyzed by picoSpin™ benchtop NMR.

For the chosen reaction a 1 M solution of imidazole was prepared in ethanol. A 250 mm × 10 mm cartridge was filled with acidic zeolite and placed into the Phoenix Flow Reactor™.

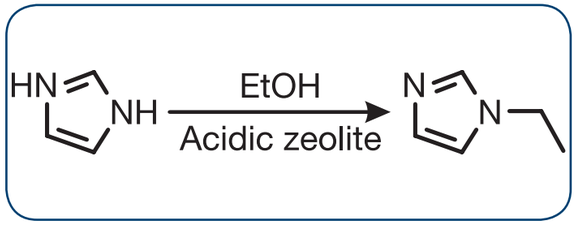

Figure 3: N-alkylation of imidazole

The reaction was carried out initially at 300 °C and 90 bar, using a 1 mL/min flow rate. After obtaining the first results temperature and flow rate were screened to optimize the reaction (see Table 1 with the corresponding results).

SHIMMING OF THE picoSpin™ 45 INSTRUMENT

The picoSpin™ 45 is highly stable with respect to magnet shim. If the unit is powered on continuously and the temperature is stabilized at a fixed temperature, it is only necessary to perform Maintenance Shimming a few times a week. No reshimming is necessary when samples are changed.

SAMPLE PREPARATION AND DATA ACQUISITION

After thorough evaporation of small volumes (2-3 mL) of the reaction mixtures, the samples were diluted with drops of DMSO-d_6 to avoid crystallization of the remaining imidazole. All samples were injected into the picoSpin™ NMR and in parallel, samples were measured by a 300 MHz NMR (Bruker) instrument as well.

With the picoSpin™ spectrometer, deuterated solvents are not necessary for 'locking' purposes, but one might want to use it when there is strong solvent proton signal overlap with important solute signals.

The small sample volume requires an effective lower limit sample concentration of approximately 0.5 M, though neat liquid samples can be analyzed directly without dilution. Solid samples must be fully dissolved in a suitable solvent.

If the sample behaves in a time-dependent way, any number of single scans can be averaged together to improve SNR (Signal-to-Noise Ratio). A single scan is acquired in less than a second.

In our case, 128 scans were collected with the picoSpin™ from each sample.

RESULTS

Due to the lower magnetic field, the signals are broader than they are in the 300 MHz spectra. However, the resolution is sufficient for quantification. MestReNova™ software 8.1. version was used for evaluating spectra.

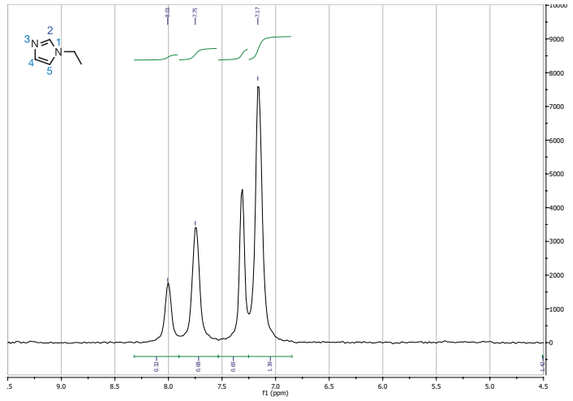

Figure 4: Integration of the aromatic signals of Sample 5. Inset: General parameters data acquisition used with picoSpin™

The singlet found at 8.01 is the C2 proton from the imidazole and the singlet at 7.75 ppm represents the C2 proton from the product. Interestingly, the C4-5 protons of the alkylated imidazole do not split; they appear as a singlet at 7.17 ppm. The peak at 7.31 ppm corresponds to the C4-5 protons in imidazole.

The conversion ratio of reactant to product can be determined by integrating signal areas under the respective peaks. We were pleased to find that values obtained from the two NMR instruments are in correspondence with each other.

The obtained results are summarized in Table 1. GC and HPLC measurements verified that alkylation was indeed selective and there are no other components in the reaction mixture.

In this particular reaction, the lowest amount of starting material that was still distinguishable in the spectrum – based on the signal at 8.01 ppm – was around 5%.

No.	T (°C)	p (bar)	Flow (mL/min)	Conv. (300 MHz NMR)	Conv. (picoSpin™)
1	300	90	1	31	37
2	300	90	0.75	44	43
3	300	90	1.25	32	30
4	300	90	1.5	27	26
5	320	90	1	67	68
6	340	90	1	89	90
7	350	90	1	94	93
8	350	90	0.75	97.5	100

Table 1: Reaction parameters and conversion values measured with the two NMR instruments.

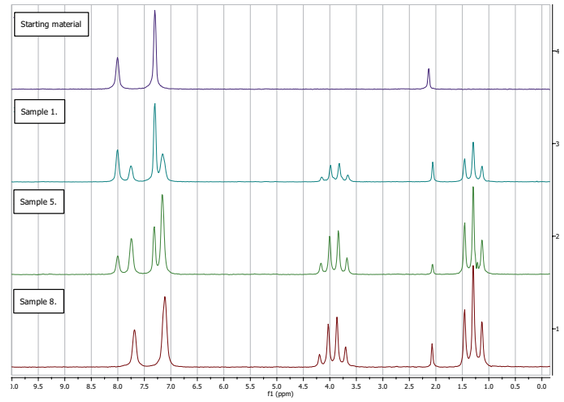

Figure 5: ^{1}H NMR spectra of the starting material and 3 reaction samples (1, 5, 8) acquired with the picoSpin™ 45. Solvent: DMSO-d_6.

We also investigated the minimum number of scans necessary to obtain spectra suitable of quantification since collecting scans can be time consuming. Therefore, different number of scans (16, 32, 64 and 128) were collected at reaction conditions of 2 M, 350°C, 90 bar and 1 mL/min flow rate, where the product is in large excess relative to the starting material, 85% conversion by picoSpin 45 NMR.

Figure 6 shows stacked spectra of the sample obtained at 16, 32, 64 and 128 scans. With increasing number of scans, the baseline of the spectrum becomes smoother; the SNR changes from 22 to 66 for the smallest intensity (7.95 ppm) peak.

However, even at 16 scans the spectrum can be integrated. Table 2 summarizes the integral values obtained from each spectrum (only the aromatic region was evaluated). Interestingly, there is no significant deviation among the values originating from the scan number. When analysis time matters, 16 scans can provide sound data and acquisition takes less than 3 mins.

Another positive phenomenon is that despite the low magnetic field, the NH group of the imidazole appears sharp in the spectra and the integration value is in agreement with the other peaks.

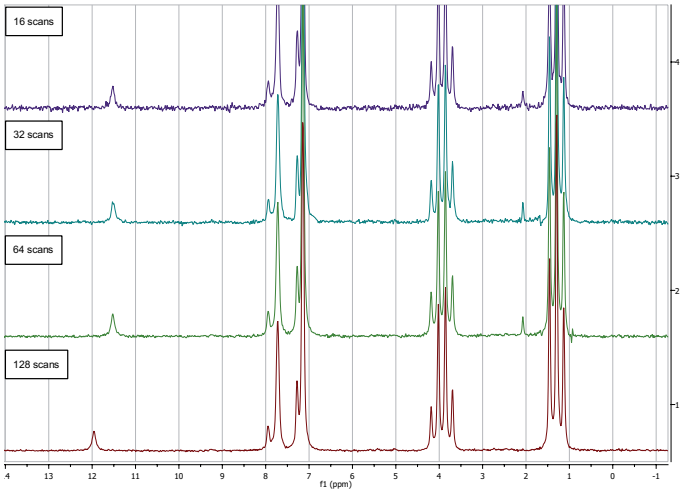

Figure 6: Spectra of Sample 9, obtained from different number of scans

Number of scans	Integral value of peak			Remaining starting material (%)
	11.5 ppm (NH)	7.95 ppm (C2)	7.28 ppm (C3-4)	
16	0.16	0.17	0.195	17
32	0.17	0.14	0.145	14
64	0.18	0.14	0.17	14
128	0.16	0.15	0.165	15

Table 2: Integration values due to the number of scans.

CONCLUSION

We were able to achieve full conversion of the imidazole starting material at 350 °C, 90 bar and 0.75 mL/min flow rate in the Phoenix Flow Reactor™ during the optimization process confirmed by the picoSpin™ benchtop NMR system from Thermo Scientific. Moreover, we found the reaction fully selective towards the *N*-alkylated product.

The 45 MHz picoSpin™ instrument was effectively implemented for monitoring the conversion in *N*-alkylation of imidazole in flow. The acquired data are in good agreement with those from a 300 MHz NMR, while providing NMR spectra in the same fume hood as the instrument used for synthesis within few minutes.

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