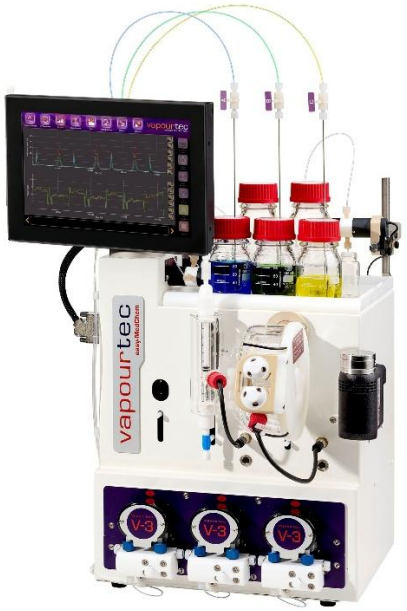

Application Note 53:

Sodium Hydride as a Slurry In Continuous Flow

Produced by Vapourtec

Abstract

The highlights of this application notes are:

- Utilizing sodium hydride slurries in a laboratory scale continuous flow reaction
- Pumping the sodium hydride as a slurry and controlling gas formation by operation ata pressure of 7 bar
- Truly continuous operation demonstrated during a 2-hour synthesis of an alkylcarbazole heterocyclic intermediate
- Fast reaction time of 4 minutes
- 82 % isolated yield, 10.6 gh^{-1} with greater than 98% purity

For more details, please contact:
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Background

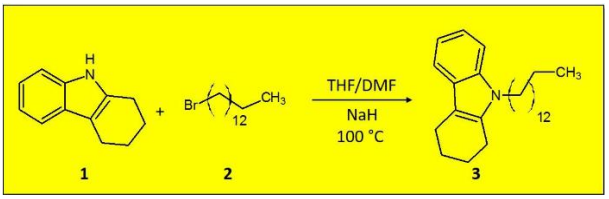

Figure 1: The synthesis of heterocyclic intermediate 3 via the sodium hydride promoted alkylation of 1,2,3,4-tetrahydrocarbazole

As part of our ongoing series of application notes on pumping slurries of reagents (see Vapourtec Application note 51: Palladium on Charcoal Slurries in Continuous Flow Hydrogenation) we now demonstrate the successful pumping of a slurry of sodium hydride dispersion and demonstrate that the technology is compatible with a heterocyclic alkylation reaction.

Sodium hydride is one of the most versatile heterogeneous strong bases available in chemistry and has been widely used in a myriad of applications.[1] Many commercial forms of the reagent are cheaply available. In this work, we choose to use the commonly available 60% dispersion in mineral oil, a relatively stable and easily handled form, compatible with a range of solvents (for example, see MSDS available online from Sigma Aldrich).[2] Sodium hydride derived anions frequently lead to enhancements in yield and selectivity in a large variety of reactions.[3] Many commercially important syntheses use sodium hydride, for example, in fluoxetine synthesis.[4]

Setup

All reactions in this application note were performed using a Vapourtec easy-MedChem E-series, equipped with slurry pump manifolds, and with a Vapourtec 10 ml PFA reactor or a Vapourtec 20 ml Reactor for Rapid Mixing. Reagent bottle A contained a solution of 1,2,3,4-tetrahydrocarbazole, 1 and 1-bromotetradecane, 2 in a molar ration of 1:1.1, and in a mixture of THF and DMF (3:1 v/v respectively), or DMF only. Reagent bottle B contained a continuously stirred suspension of sodium hydride (0.5 and 1 M 60% dispersion in mineral oil, Sigma Aldrich, product code 452912) in anhydrous THF, with a continuous supply of dry nitrogen. A 1.5 mm bore tube was used on pump B to allow easy aspiration into the pump. All reagents were used as supplied. The system was dried prior to use by flushing with anhydrous THF. Pressure was maintained at 7 bar using one of the V-3 positions in back pressure regulation mode. The reactor output was collected directly into deionized water to immediately quench any excess sodium hydride.

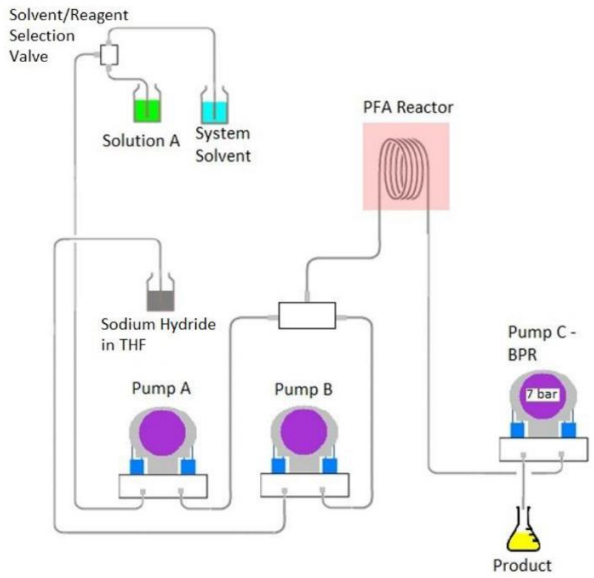

Figure 2: Schematic of the easy-MedChem used during this application note

Reaction Investigation

Alkyl carbazole, 3, is structurally similar to an intermediate in the synthesis of a carbazole-based macrocycle, reported by Moore et al. and was chosen as a target for this application note.[5] An initial experiment was performed using a Vapourtec standard 10 ml PFA reactor at 5 bar and with a 2:1 excess of sodium hydride to 1, Table 1, entry 1. It was considered that the hydrogen released from the reaction could potentially reduce the residence time within the reactor, so the pressure was increased to 7 bar to reduce the size of the gas pockets. Further experiments were performed at conditions similar to those described by Moore et al. with a 1.3 molar excess of sodium hydride to 1, Table 1, entries 2 and 3. Encouragingly, a maximum conversion of 75 % could be obtained, and the sodium hydride pumped continuously without issue or any observable hold-up.

Table 1: Initial experiments using the sodium hydride slurry at a residence time of 6 minutes.

Experiment	Temperature/ °C	Pressure/bar	Conversion/%
Exp1	50	5	50
Exp2	80	7	75
Exp3	100	7	50
Exp4	80	7	> 90

During these experiments, it was observed that a gradual beige solid deposit formed on the inside of the standard 10 ml reactor. Sodium bromide is a known by-product of this reaction, and over time began to accumulate on the reactor walls. This was easily removed after the reaction had completed by washing the reactor with a small quantity of water. Further improvement to conversion was accomplished by increasing the molar excess of sodium hydride to 1 to 2.6, achieved by increasing the slurry concentration from 0.5 M to 1 M, and operating at 100 °C. Under

these conditions, it was found that conversions of greater than 99% could be obtained, with a residence time of 4 minutes, as shown in Figure 3.

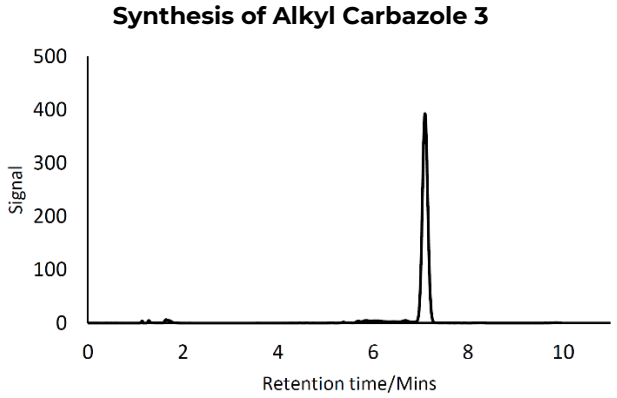

Figure 3: HPLC chromatogram of the crude reactor output, showing greater than 99% conversion to the product. The peaks are assigned as follows: 1.16 min, unknown, suspect mineral oil from NaH dispersion; 1.3 min, 1,2,3,4-tetrahydrocarbazole; 1.69 min, 1-bromotetradecane; 7 min, alkylated carbazole product 3.

To establish the long-term feasibility of pumping the sodium hydride slurry a 2-hour synthesis was performed under the previously obtained high yielding conditions, however we became concerned that gas partitioning, created by the release of hydrogen, had the potential to compromise the mixing of the reagent with the solid sodium hydride. To prevent any potential partitioning caused by gas evolution the reactor was changed for a Vapourtec 20 ml Reactor for Rapid Mixing, with static mixers running the length of the reactor ensuring an intense mixing environment. This guaranteed good mixing of the liquid reagents with the solid sodium hydride, and also prevented the evolved hydrogen from forming plugs which could separate the flow.

To further ensure long term running, the substrate solution of 1 and 2 was prepared to a concentration of 0.17 M in DMF only, which assisted in the solvation of the sodium bromide by-product and reduced the effect of any fouling restricting the flow path. In batch systems, sodium hydride and DMF have been identified as a potential safety hazard,[6] however using a flow method, exotherms and rapid gas evolution are significantly more controllable and there is only one reactor volume of material available to react, permitting access to chemical environments that would be otherwise challenging in batch. During these experiments, no decomposition of DMF was observed. Using this reactor, a synthesis of 3 was performed for a duration of 2 hrs without any detrimental fouling of the reactor, resulting in a theoretical throughput of 13.0 gh^{-1}. The product was isolated in a yield of 82% and purity of over 98% were achievable following a simple recrystallisation from methanol, resulting in an isolated throughput of 10.6 gh^{-1}.

Conclusion

Using a Vapourtec easy-MedChem it has been possible to use sodium hydride as a slurry in THF to perform the alkylation of 1,2,3,4-tetrahydrocarbazole to form heterocyclic intermediate 3 with an isolated yield of 82% and throughput scale of 10.6 gh^{-1}. A Vapourtec Reactor for Rapid Mixing ensured that gas evolution did not compromise the mixing in this complex reactive environment of solid, liquid and gas. To demonstrate the suitability of this process for continuous operation, a continuous synthesis for 2 hours was performed.

Analysis

Immediate reaction analysis was performed using thin-layer chromatography at 250 nm. Further analysis was performed using HPLC and ^{1}H NMR,

see figure 4. Percentage conversion is calculated against the starting 1,2,3,4-tetrahydrocarbazole, 1.

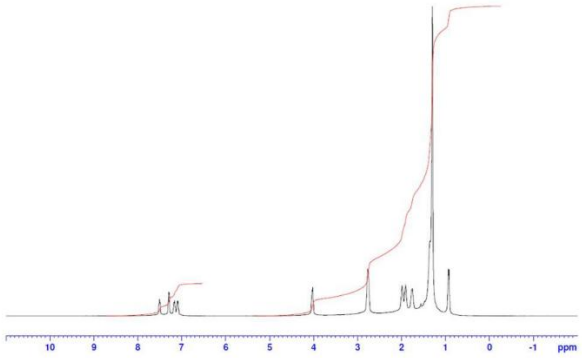

Figure 4: ^{1}H NMR ($CDCL_3$, 400 MHz) of alkylated carbazole 3 following purification.

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