Application Note 57:

Automated Library Synthesis

Produced by Vapourtec

Abstract

Equipping a Vapourtec R-Series with a liquid handler creates a powerful, automated library synthesis platform that has been used to carry out reaction screening of nucleophilic aromatic substitution partners, including volatile amines.

This application note describes:

- Automated reaction screening using automated reagent loading and collection
- Safe out-of-hours operation permitted by flow control software.
- The use of highly volatile amines and ammonia at 160 °C through the application of high pressures difficult to achieve in batch

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Background

The chemical validation of the potential scope for synthesis of a chemical library can be a time consuming and expensive part of a research program.[1] Moreover, as the complexity and cost of reaction inputs to library synthesis continue to grow, such as the use of advanced synthetic intermediates, natural products, peptides etc., economic use of these materials also becomes an important factor.

Within this application note, we demonstrate the use of the Vapourtec R-Series in conjunction with an autosampler, as a versatile and efficient method of addressing these issues. Using examples of S_NAr chemistry, Figure 1, we were very quickly able to identify reaction partners for synthesis using a range of nitro-aryl halides and amine nucleophiles. These included ammonia and dimethylamine which, although often challenging to heat in batch due to boiling the volatile amine out of solution, are easily handled at high temperature and pressure within the Vapourtec R-Series.

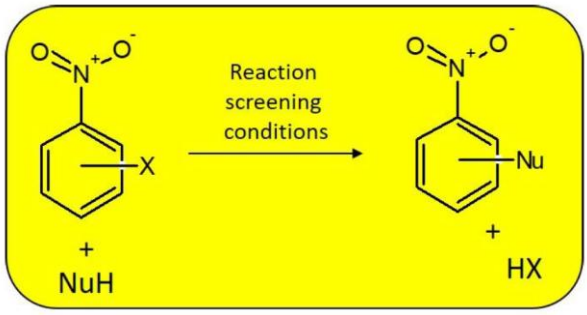


Figure 1: Reaction screening of a nucleophilic aromatic substitution using a range of nitro-aryl halides and amine nucleophiles

Setup

All reactions were performed using a Vapourtec R-Series equipped with an R2C+ pump module and a 5 ml high temperature stainless-steel reactor, as shown in Figure 2. A Gilson X241 automated liquid handler was connected to the system and controlled by flow control software, and used to load the two 2 ml sample loops and to collect product as determined by the flow control software dispersion model.

All reagents were used as supplied by Sigma-Aldrich. The electrophile reagent solutions, 3,4-difluoronitrobenze (34DFNB), 2-fluoronitrobenzene (2FNB) and 2,4-dichloronitrobenzene (24DCNB) were prepared to 0.1 M in 1-methyl-2-pyrrolidone (NMP), and the nucleophile solutions, morpholine, piperidine, dimethyl amine (from 2.0 M dimethyl amine in methanol solution) and ammonia (from 7 N ammonia in methanol solution) were prepared to 0.25 M in NMP; a second equivalent of the nucleophile is required to remove the halogen-acid generated during the reaction. All reagents were transferred to 20 ml scintillation vials and loaded into a code 24 20 ml rack. A second code 24 rack was prepared with empty vials and designated as collection sites. All reactions were performed with a system pressure of 22 bar and at 140 °C using morpholine and piperidine, and 160 °C for dimethyl amine and ammonia.

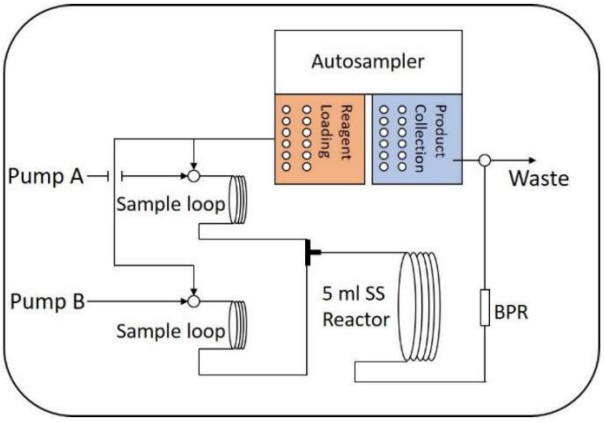


Figure 2: Reactor configuration used to screen reactions using a range of nucleophilic amines. An automated liquid handler permits loading of reagents into the sample loops, allowing a large number of experiments to be performed without direct control of the user

Results

The reaction screening library was programmed into flow control software to pair each nucleophile with each electrophile, and collect the product into separate vials, yielding the results in Table 1. The total library of 12 compounds was completed under fully automated operation in just 5.5 hours. Due to the inherent safety afforded by flow control software and the R-Series, the experiment was prepared at 4 pm, and allowed to run after working hours, under the control of flow control software.

Table 1: Results of the flow reaction screening library. [a] Determined by HPLC. [b] Determined by NMR

Experiment	Nucleophile	Electrophile	Conversion[a]
A	Morpholine	34DFNB	100
B	Morpholine	2FNB	82
C	Morpholine	24DCNB	33
D	Piperidine	34DFNB	86
E	Piperidine	2FNB	84
F	Piperidine	24DCNB	41
G	Dimethyl amine	34DFNB	100
H	Dimethyl amine	2FNB	100
I	Dimethyl amine	24DCNB	85[b]
J	Ammonia	34DFNB	22
K	Ammonia	2FNB	27
L	Ammonia	24DCNB	0

Using this screening method, it is possible to quickly compare the relative reactivities of different reagent pairs under these conditions. For example, it is clear from experiments C, F, I and L that 2,4-dichloronitrobenzene is less reactive under these conditions than the other electrophiles. Interestingly however, it is also clear that dimethyl amine reacts considerably faster than the other nucleophiles, and with a ratio of approximately 5:1 between the 2, and 4-dimethyl substituted isomers (isomers not assigned).

It is also clear that the use of ammonia as a nucleophile is a feasible route to the production of the nitro-anilines; although the conversion is low, we have quickly identified interesting reactions that could be independently optimized.

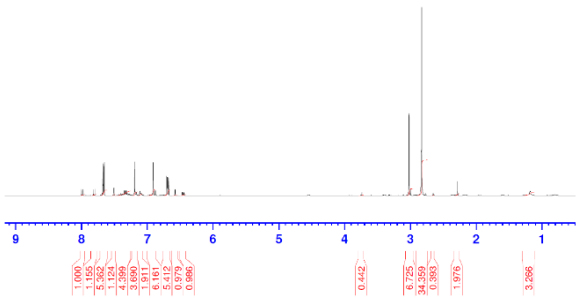
Conclusion

The use of an automated liquid handler and R-Series permitted the rapid screening of reaction partners under conditions that would be difficult to replicate using traditional batch techniques.

The use of highly volatile reagents such as dimethyl amine and ammonia can cause a significant challenge under ambient pressure, as elevated temperatures cause boiling-out of the reagent, making it inaccessible to the reaction. As such, low reaction temperatures are needed, resulting in long reaction times if any reaction occurs at all. Conversely, using the R-Series equipped with a high temperature stainless-steel reactor it is possible to use ammonia and dimethyl amine at 160 °C under pressures of over 20 bar, preventing the reagent boiling out. This permitted reaction times of 5 minutes, and enabled us to screen nucleophiles that may be overlooked using conventional techniques. The automated control afforded by Flow Commander™ enables out-of-hours operation, essentially doubling the available work time of the laboratory, and frees the user from an otherwise labor-intensive process.

Analysis

Samples were automatically collected by the liquid handler and manually analyzed by HPLC. Experiment I resulted in an unresolved peak between the starting material and product. To extract the product for NMR, the fraction collected from the reactor was added to 50 ml of a 50% saturated brine solution, and the product extracted into toluene. The toluene was washed with 3 x 25 ml water to remove residual NMP, and the sample was evaporated using a V10 evaporation system.



References

1. Hamley, P., Czechtizky, W., John Wiley & Sons, New Jersey, 2015