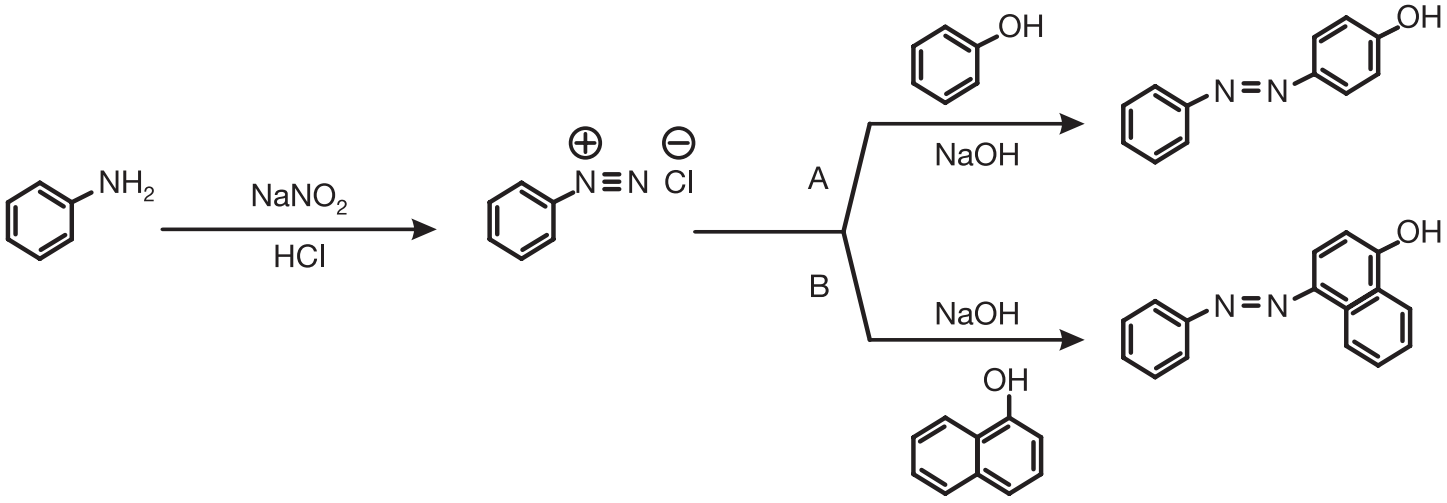
THALESNano

Multistep Azo Dye Formation in the IceCube™ Continuous Flow Reactor

INTRODUCTION

Diazotization and azo-coupling reactions are chemical processes that lead to industrially important azo-dyes and other intermediary molecules. The formed intermediate diazonium salts are unstable above 5°C and might explode when they are left to dry. Both diazotization and azo coupling reactions are always carried out with high precautions in the lab on any scale. The need for a safe and high capacity process for diazotization and azo-coupling made us develop these reactions in a flow manner. The outcome is reported in this application note using the IceCube™ continuous flow reactor.

During a typical diazotization method an aromatic amine is transformed into the respective diazonium salt by a nitrite salt in acidic, aqueous media. The active agent is the nitrous acid, which is liberated from the nitrite by mineral acids. In general, maintaining a low reaction temperature is crucial during diazotization (under conventional batch synthesis <5°C) [1.,2.]. It not only increases the solubility of the *in situ* generated nitrous acid and suppresses its decomposition rate, but it may also prevent the run-away natured diazo decomposition.



Scheme 1. Multistep diazotization and subsequent azo coupling reactions in the IceCube™ flow reactor.
A: Azo coupling with phenol. **B:** Azo coupling with naphthol.

IceCube™ Application Note

In the case of azo dye synthesis, the prepared diazo intermediates are preferably reacted further immediately due to the highly unstable nature of the diazonium salts. In batch, during azo-coupling the acidic cold solution of diazonium salt is added in fractions to the cold, alkaline solution of alcohol. This requires a long-term, effective cooling of the batch reactor, since the addition of the diazonium compound results in rapid heat evolution. However, in a continuous flow system the temperature can be easily controlled and maintained at the desired level due to the improved heat transfer capability of the flow reactor. The IceCube's excellent heat conduction capability coupled with dual reaction zones means hazardous reactive intermediates may be formed and reacted immediately in a safer more controlled way.

INSTRUMENTATION

The IceCube™ is a low temperature, continuous flow reactor. The reagents are continuously pumped through the reaction zone and the product is collected in a flask at the end of the device. The device has two reaction zones, which can each be cooled down or heated up to -70°C – +80°C and -30°C – +80°C respectively, so multi-step reactions may be performed consecutively. This includes reactions where hazardous intermediates are formed, reacted without isolation, and converted into stable final products. The IceCube™ has also been utilized for performing hazardous reactions, such as ozonolysis, Swern oxidation, lithiation, and nitration.

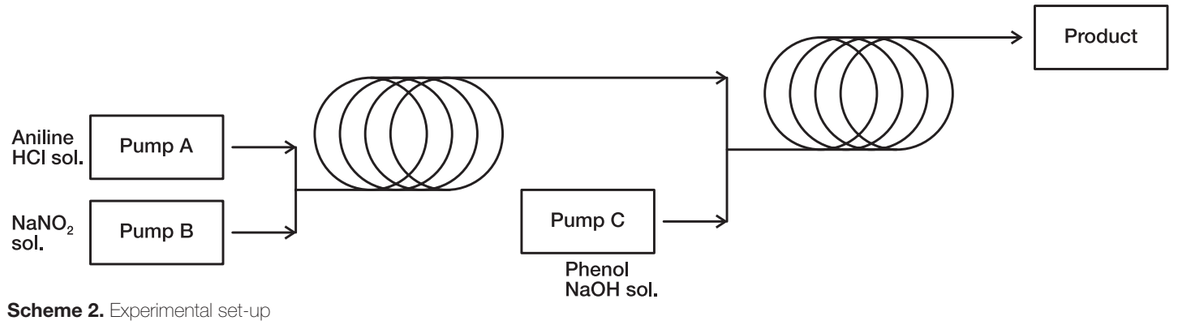
	Solution	Acid/Base	Total Volume	Conc. (M)
A	100 mmol aniline	50 mL cc. HCl 5 mL cc. AcOH	150 mL	0.66
B	250 mmol $NaNO_2$	-	150 mL	1.66
C	100 mmol phenol or naphthol	90 mL 25 % NaOH	150 mL	0.66

Table 1. Reagent solutions

GENERAL EXPERIMENTAL PROTOCOL

Reagent solutions were prepared according to ***Table 1.*** The experimental set-up was realized according to ***Scheme 2.***, where the reactants were passed through the 1/8" PTFE loops.

The acidic amine solution (A) and the sodium nitrite solution (B), both precooled in the IceCube™ reactor, were delivered by two pumps into a T-junction. The resulting reaction mixture was then introduced into a 1.7 mL PTFE reactor loop, where the diazotization occured. Having left the first reactor, the salt solution (A+B) was combined with either the alkaline phenol or naphthol solution(C) in a static mixer. Next, having left the static mixer, the mixture was introduced into the second reactor block, where the azo coupling occured in a 4 mL loop reactor. The final dyes were collected at the end of the IceCube™ reactor without manually handling the diazonium salt.

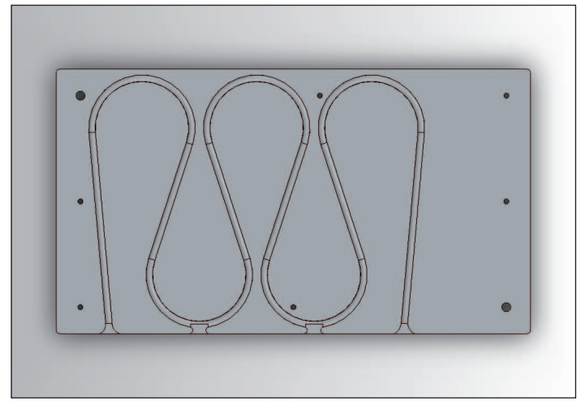


Scheme 2. Experimental set-up

RESULTS AND DISCUSSIONS

The conducted experiments with the applied reaction conditions and collected results are listed in ***Tables 2.*** and ***3.*** The products were identified by LC-MS. The ortho- and para-substituted products were not distinguished.

Increased flow rates provided the same, very good isolated yields, between 84-91%. This shows that both diazotization and coupling occurs instantaneously. Residence times as low as 1.21 – 5.45 mins make it possible to reach high productivity.



Picture 1. Reactor plate for 1/8"-OD PTFE reactor tubes

	Flow rate [mL/min]			T [°C]			
Entry	Aniline	Sodium Nitrite	Phenol	1st reactor	2st reactor	Isolated Yield [%]	Productivity (g/h)
1	0.4	0.4	0.4	0	5	91	8.3
2	0.9	0.9	0.9	0	5	91	18.7
3	0.9	0.9	0.9	10	5	85	17.4
4	1.5	1.5	1.5	10	5	86	29.1
5	1.2	1.2	1.2	15	5	84	22.9
6	1.8	1.8	1.8	15	5	86	35.3

Table 2. Applied reaction conditions and their results during the diazotization and subsequent azo dye formation with phenol in the IceCube™ flow reactor

	Flow rate [mL/min]			T [°C]			
Entry	Aniline	Sodium Nitrite	Phenol	1st reactor	2st reactor	Isolated Yield [%]	Productivity (g/h)
1	0.6	0.6	0.6	0	5	77	13.6
2	1.5	1.5	1.5	0	5	99	43.7
3	1.5	1.5	1.5	15	15	99	43.7

Table 3. Applied reaction conditions and their results during the diazotization and subsequent azo dye formation with naphthol in the IceCube™ flow reactor

ADVANTAGES OF DIAZOTIZATION IN FLOW

- Safe handling of diazonium salts
- Only a small amount of diazonium is present at one time
- Very effective heat conduction. Cooling is very effective, no danger of overheating and explosion
- Diazotization can be driven safely > 5°C, due to very short residence time
- pH can be kept constant during the coupling reaction
- Residence time can be as low as 1.21 – 5.45 min, with concentrations similar to batch conditions (0.66 M solutions)

CONCLUSION

In this application note we demonstrated two multistep flow chemistry applications in the IceCube™ flow reactor via diazonium salt intermediated azo dye syntheses in good yields. We also demonstrated that utilizing flow chemistry allows a safer and more controlled syntheses of short lived intermediates such as diazonium salts.

REFERENCE

1) Patent US3423391; Continuous diazotization process. BASF AG.

2) Patent US 4268437; Continuous diazotization of amines. Hoechst Aktiengesellschaft

For further information please contact us at **flowchemistry@thalesnano.com** or visit our website:

www.thalesnano.com

ThalesNano Nanotechnology Inc.
Zahony u. 7.
H-1031 Budapest
Hungary
Tel.: +36 1 880 8500
Fax.: +36 1 880 8501
E-mail: sales@thalesnano.com

US Office
50 S. Penn St. Suite B-2
Hatboro
PA. 19040
USA
Phone: +1 818 600 1116
E-mail: USAsales@thalesnano.com