Diazoacetonitrile: Safe and Green Synthesis through Continuous Processing

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Supporting Information
available online

Diazo compounds, although possessing unique reactivity, have been widely rejected due to their highly hazardous preparation protocols. Diazoacetonitrile (DAN), a relatively stable diazo compound, has been overlooked despite its potential in chemical synthesis. The present study describes a microflow process for the simultaneous preparation of DAN in aqueous solution and its extraction in dichloromethane. The DAN productivity was optimized in terms of solvent, temperature, residence time, and pressure. This experimental work represents a breakthrough in delivering DAN continuously in a stable CH_2Cl_2 solution, enabling its utilization as a versatile building block for various synthetic processes and contributing to the development of new green synthetic processes.

Keywords: Continuous processing, Diazo compounds, Green chemistry, Hazardous chemistry

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1 Introduction

In the search for efficient and environmentally friendly synthetic processes, researchers have avoided hazardous reagents and building blocks, in compliance with the principles of green chemistry [1]. Diazo compounds have been among the chemicals widely rejected due to their inherent negative environmental impact and the risks associated with their use [2, 3]. However, these compounds possess unique reactivity, making them potentially useful in chemical synthesis. But with increasing implementation of continuous synthesis methods and flow chemistry, and the associated ability to generate hazardous substances on demand and in situ, the use of diazo compounds has also been on the rise.

For example, ethyl diazoacetate is an increasingly used diazo compound in preparative chemistry and has already been studied quite extensively [4, 5]. In contrast, diazoacetonitrile (DAN) has been largely overlooked despite its stability compared to diazomethane. DAN was first synthesized in 1898 by Curtius [6] using aminoacetonitrile and sodium nitrite, but attempts to replicate the synthetic protocol resulted in violent explosions [7]. In 1956, Pettit and Dewar developed an alternative method using diethyl ether as a solvent [8].

Compared to diazomethane, DAN is more stable due to the conjugation of the diazo moiety with the nitrile group, which also stabilizes the diazo moiety through the inductive effect. Consequently, DAN can be utilized as both a nucleophile [9, 10] and an electrophile [11], as well as in [3+2] cycloadditions with alkynes [12, 13]. Despite its potential, the use of DAN in chemical synthesis has been limited. However, recent extensive work by Mykhailiuk and Koenigs [14] and Mykhailiuk [15, 16] has shown that DAN has the potential to accelerate several synthetic paths, thereby reducing the global warming potential (GWP) of the process. Additionally, the use of reactive building blocks like DAN can significantly reduce the number of reactants employed in a process, ultimately contributing to a lower overall human toxicity potential (HTP). Mykhailiuk [13] in 2015 established a method that allowed for in situ formation of DAN using acetonitrile as a solvent, and, more recently, Empel et al. [17] developed a promising new method in flow, which was performed in aqueous solution.

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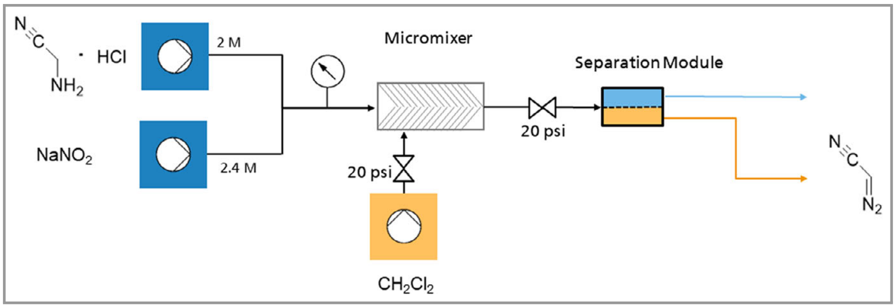


Figure 1. Schematic representation of the flow setup used for DAN synthesis.

The development of alternative green synthetic routes is hindered by the complete avoidance of certain chemicals, despite their potential use in chemical synthesis. Recent work has shown that DAN can be used as a valuable building block in chemical synthesis by taking proper safety precautions and handling procedures.

In this work, we aim to further exploit the potential of DAN by developing a microflow process for the simultaneous preparation and extraction of DAN in an organic solvent. The extraction step is crucial in processing the prepared building block for the synthesis of valuable specialty chemicals. This microflow process will contribute to the advancement of more sustainable and efficient processes in chemical synthesis.

2 Materials and Methods

2.1 Chemicals and Equipment

The chemicals used in this work were all commercially available. Sources and purity are reported as: aminoacetonitrile hydrochloride (AAN HCl, 98+ %; Thermo Scientific), sodium nitrite (p.s.; Sigma-Aldrich), dichloromethane.

Equipment used for the continuous reaction: pumps: HiTec Zang (SyrDos), Sykam, Harvard (PHD 2000); water bath: IKA; reactor: LTF (ST design); backpressure valve: Upchurch (pressure valve); membrane separation module: Zaiput (SEP-10).

2.2 Continuous Synthesis of DAN

2.2.1 Laboratory Setup Description

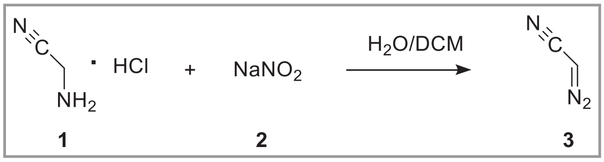
Aqueous solutions of 2 M aminoacetonitrile hydrochloride, 2.4 M sodium nitrite and dichloromethane were delivered by pumps via 1/16″ polytetrafluoroethylene (PTFE) capillaries into a glass microreactor in a water bath (Fig. 1). The reactor consists of a single channel with a chaotic mixing structure (ST design, Little Things Factory) with the following approximate dimensions: a hydraulic diameter of 0.5 mm, a channel length of 86 cm, and a volume of 1.4 mL. The pressure was kept by a 100-psi pressure relief valve. After the back-pressure valve, the reaction mixture passed a membrane separation module for phase separation. The measurements were performed inline with an infrared-attenuated total reflectance (IR-ATR) flow cell after the phase separation (measurement of the CH_2Cl_2 phase only due to strong gas formation in the water phase).

2.2.2 Reaction Description

Due to its challenging synthesis in aqueous media associated with poor stability as a product in water, DAN (**3**) is usually generated "in situ" and considered a sort of invisible intermediate. Diazo compounds decompose in the presence of both nucleophiles or electrophiles, generating further reactive species (for instance carbene) and molecular nitrogen. Additionally, due to its extremely high nitrogen content (63 wt %), DAN is highly explosive and should never be handled as a pure liquid or in highly concentrated solutions. The proposed reaction pathway involves a continuous reaction/extraction process that enables DAN (**3**) as a stable solution in an organic solvent (Scheme 1). This simultaneous process, however, implies that the productivity of the reaction is influenced by both the reactivity and the extraction efficiency, which in turn depends on the species concentration and temperature.

2.3 Analytical Methods

IR measurements were taken with a Bruker Matrix MF equipped with an optical fiber ATR diamond probe head mounted into a flow cell, which was placed after the membrane separation unit. Measurement parameters were: 32 scans for background and sample, spectra were collected from 3200 to 850 cm^{-1}, with a resolution of 4 cm^{-1}. A minimum of five measurements were made. As mentioned before, it is not possible to isolate DAN for calibration, and indirect methods for calibration are prone to errors due to its instability. Consequently, the band area of the N=N asymmetric stretching band of the diazo group was used for direct comparison of the product contents of different



Scheme 1. DAN synthesis starting from aminoacetonitrile.

experiments. Therefore, the spectra were integrated from 2125 to 2070 cm^{-1} with Bruker Opus and Spectragryph software. Additional details, such as example spectra and software details, can be found in the Supporting Information.

3 Results and Discussion

Preliminary experiments were performed by mixing the two aqueous solutions of aminoacetonitrile (**1**) hydrochloride and sodium nitrite (**2**) without adding any solvent for the extraction. However, this protocol, due to the fast decomposition of DAN (**3**), hampers the further implementation of the obtained diazo compound as building block in organic synthesis and had to be integrated with an extraction process.

Aiming to select a solvent for extraction that shows stability under an oxidizing environment, dichloromethane, chloroform, and toluene were considered for the subsequent attempts. Analyzing the distribution of DAN in the organic and aqueous phases with IR-ATR, only dichloromethane led to satisfactory results, allowing both high concentrations of DAN in the extract and high extraction efficiency.

Once the standard conditions for the continuous synthesis of **3** were defined, standard parameters (residence time, pressure, water/organic solvents ratio) were deliberately changed to find the best settings for the synthetic process. The following experiments were carried out measuring DAN in the organic phase by online IR-ATR in a flow cell after phase separation.

3.1 Variation of Standard Parameters

First, a set of nine experiments with three different temperatures (35, 55, 70 °C) and three flow rates were tested to identify the best reaction conditions. The pressure was set to 1.4 bar for experiments at 35 and 55 °C and to 2.8 bar for experiments at 70 °C, to keep dichloromethane in the liquid state. The spectroscopic analyses clearly show a positive effect of the temperature on the reaction, with a significant increase of the DAN signal from 35 to 70 °C (Fig. 2). Similarly, prolonging the residence time from 52 to 104 s has a positive effect on the DAN production. At 35 and 70 °C, a further increase of the residence time still has a positive effect. The results obtained in this first set of reactions are used as a reference for the following experiments.

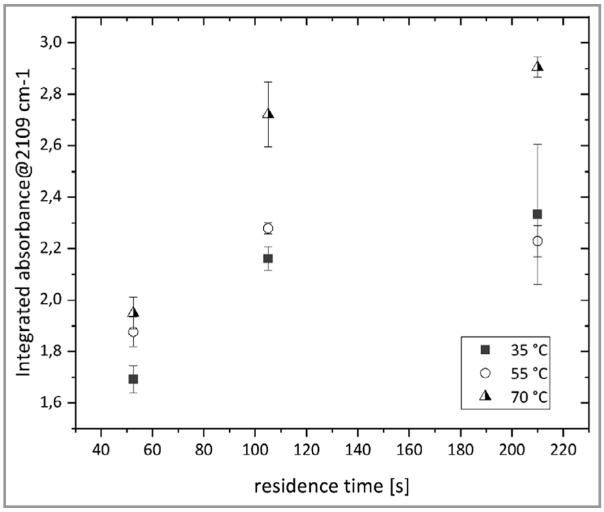


Figure 2. Effects of the temperature and the residence time on DAN (**3**) production.

However, it must be considered that the results are not only influenced by conversion and/or the kinetics of DAN formation, but also by the decomposition of DAN and associated gas evolution (especially at higher temperatures) and the efficiency of extraction, which are both assumed to be more efficient at higher temperatures.

The band area increases with longer residence time under standard parameters at 70 °C. To further study the influence of the residence time and mixing, the reactor volume was doubled by introducing a second micromixer in subsequent experiments. Fig. 3 illustrates the comparison of the band areas between the standard parameters and the results obtained with the doubled reaction volume. A slight improvement is observed at 420 s compared to 210 s, albeit with a larger error.

As the flow rate was doubled to result in a comparable residence time for the doubled reactor volume, the mixing efficiency also increased. Surprisingly, this resulted in a slightly lower product amount. This indicates that mixing and mass transfer have a remarkable influence on the process. Consequently, further experiments were designed to examine the impact of the extraction solvent amount and the reaction pressure.

Additional experiments were undertaken to assess the possibility of enhancing the yield through the utilization

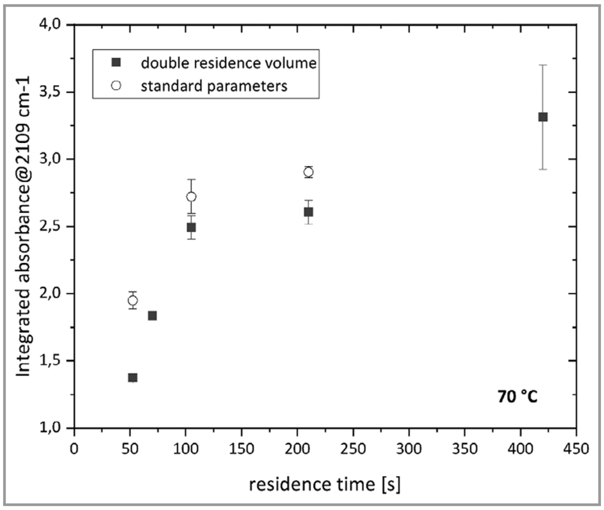


Figure 3. Effect of the reactor volume on DAN (**3**) production.

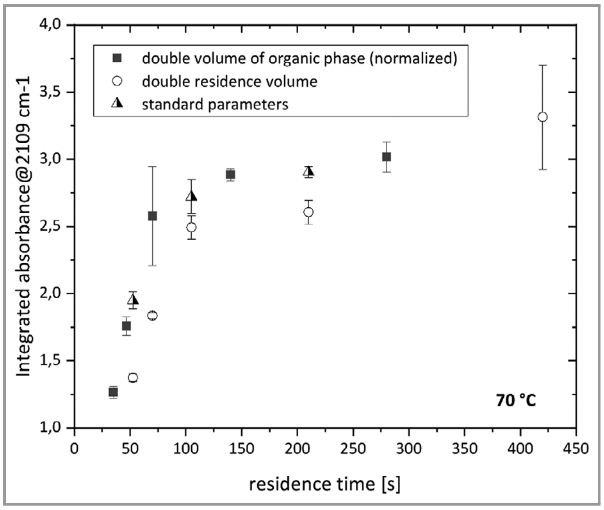


Figure 4. Effect of the extraction volume on DAN (**3**) production.

Table 1. Effect of the pressure on DAN (**3**) production.

Entry[a]	V_{aq}	V_{org}	T [°C]	RT [s]	P [bar]	IR area[b]
1	0.2	0.2	35	210.0	1.4	2.334 ± 0.272
2	0.4	0.4	35	105.0	1.4	2.161 ± 0.045
3	0.8	0.8	35	52.5	1.4	1.693 ± 0.053
4	0.2	0.2	55	210.0	1.4	2.230 ± 0.060
5	0.4	0.4	55	105.0	1.4	2.279 ± 0.021
6	0.8	0.8	55	52.5	1.4	1.876 ± 0.057
7[c]	0.2	0.2	70	210.0	2.8	2.905 ± 0.040
8[c]	0.4	0.4	70	105.0	2.8	2.721 ± 0.126
9[c]	0.8	0.8	70	52.5	2.8	1.950 ± 0.062
10	0.2	0.2	35	210.0	5.2	2.437 ± 0.070
11	0.4	0.4	35	105.0	5.2	2.107 ± 0.057
12	0.8	0.8	35	52.5	5.2	1.880 ± 0.048
13	0.2	0.2	55	210.0	5.2	2.349 ± 0.039
14	0.4	0.4	55	105.0	5.2	2.515 ± 0.025
15	0.8	0.8	55	52.5	5.2	2.144 ± 0.013
16	1.2	1.2	55	35.0	5.2	1.427 ± 0.031
17	0.2	0.2	70	210.0	5.2	2.211 ± 0.085
18	0.4	0.4	70	105.0	5.2	2.431 ± 0.024
19	0.8	0.8	70	52.5	5.2	2.245 ± 0.011
20	1.2	1.2	70	35.0	5.2	1.708 ± 0.015
21	0.2	0.2	35	210.0	6.9	1.832 ± 0.036
22	0.4	0.4	35	105.0	6.9	1.535 ± 0.091
23	0.8	0.8	35	52.5	6.9	1.368 ± 0.022
24	1.2	1.2	35	35.0	6.9	0.956 ± 0.024
25	0.2	0.2	55	210.0	6.9	1.528 ± 0.015
26	0.4	0.4	55	105.0	6.9	1.528 ± 0.011
27	0.8	0.8	55	52.5	6.9	1.464 ± 0.017
28	1.2	1.2	55	35.0	6.9	1.304 ± 0.018
29	0.2	0.2	70	210.0	6.9	1.626 ± 0.023
30	0.4	0.4	70	105.0	6.9	1.789 ± 0.026
31	0.8	0.8	70	52.5	6.9	1.761 ± 0.032
32	1.2	1.2	70	35.0	6.9	1.611 ± 0.029

RT, Residence time.
[a] Reaction performed according to the description in Sect. 2.2.2.
[b] Measurements carried out as described in Sect. 2.3. [c] Experiments at 70 °C were performed at the pressure of 2.8 bar, which allows maintaining DAN in the liquid phase.

of a higher volume of extraction solvent. Fig. 4 presents a comparison between the standard parameters at 70 °C and the normalized values achieved with a doubled volume of extracting solvent. No noteworthy increase in the band area is discernible and the concentration of DAN in the product solution is lower, which is undesirable for DAN utilization in a subsequent reaction and for the overall solvent consumption.

The following tests were performed at different pressures using different Upchurch pressure valves and setting the pressure to 1.4, 5.2, and 6.9 bar. For the low-pressure experiments at 70 °C, a pressure valve of 2.8 bar was used to keep dichloromethane and DAN in the liquid state. Independently from the temperature, the pressure of 6.9 bar had a negative impact on the reaction. A higher DAN production was observed at 5.2 bar for residence times of up to 52 s. However, with prolonged residence time, this effect ceased and, independently from the reaction temperature, a better DAN yield was found at 1.4 bar. Intensifying the reaction at higher pressures probably promotes the concurrent DAN decomposition.

As 55 and 70 °C are above the boiling points of both dichloromethane and DAN, a higher pressure also means less gas volume in the reaction channel. This could hinder DAN from being extracted from the water phase, where it is more prone to decompose. Therefore, it was confirmed that the best results were obtained at lower pressure and residence times longer than 104 s.

Another interesting inquiry stemming from the preceding experiments pertains to the possibility of augmenting the extraction of higher quantities of the product through the application of elevated pressure in conjunction with an increased solvent volume. Consequently, an accurate replication of the experiments was carried out under conditions of increased pressure, with the solvent volume being doubled accordingly. The data obtained at 70 °C and 2.8 bar pressure manifest the highest outcomes, surpassing the best results achieved under the standard set, exhibiting an approximate band area of 3.2 (Supporting Information Table S1; entry 7) as opposed to the standard set band area of approximately 2.9 (Table 1; entry 7). Nevertheless, the increase in DAN production is rather modest; considering the lower DAN concentration obtained (due to the doubled organic solvent volume) and the remarkable amount of CH_2Cl_2 needed, these operation parameters are not optimal for the further use of DAN as building block in organic synthesis. All other findings demonstrate a deteriorating trend under intensified pressure conditions (the experimental details are reported in Supporting Information Table S1).

The experimental findings demonstrate the nontrivial nature of continuous synthesis and extraction of DAN. The variation of parameters is associated with competitive processes that hinder a straightforward increase in production. While prolonging the residence time positively impacts the yield, lower flow rates do not facilitate reaction intensification. However, a higher yield can be achieved by elevating the temperature to 70 °C. On the other hand, lower pressure exerts a favorable effect on the reaction. This can be attributed to the promotion of mass transfer through gas flow in the reactor, which is supported by maintaining the lower pressure. Notably, conducting experiments at higher flow rate (see the experiments with a larger reactor volume; Fig. 3), which usually enhances mixing in chaotic mixers, resulted in a lower yield, likely due to the inherent rise in pressure caused by the higher flow rate. Apart from that, also the intensified contact between the organic and the water phase due to the better mixing efficiency can promote decomposition in the aqueous phase. In general, efficient DAN generation can only be achieved if the reaction conditions do not simultaneously intensify DAN decomposition, which occurs at a faster rate under harsher conditions.

4 Conclusions

In conclusion, this comprehensive study provides valuable insights into the optimization of the extraction and synthesis of DAN.

The immediate extraction of the formed DAN into an organic phase decreases the decomposition of DAN and enables the versatile use of DAN in subsequent synthesis processes.

The critical factors of solvent selection, temperature, residence time, and pressure were carefully evaluated to enhance the DAN yield and provide guidance for future investigations. Increasing the temperature and residence time positively influenced DAN production, by increasing the mixing efficiency, and increasing the extraction solvent volume yielded only marginal improvements. Tests at different pressures revealed that an increased pressure of up to 6.9 bar had unfavorable effects on the reaction, with the best results consistently obtained at 1.4 bar and residence times of 105 s or longer.

Furthermore, this research presents a significant breakthrough in delivering DAN continuously in a stable organic solution, using dichloromethane. This advancement enables the utilization of DAN as a versatile building block for various synthetic processes, including cycloaddition reactions, carbene reactivity reactions as C-nucleophile, and reactions as N-electrophile. The availability of DAN in a stable organic solution streamlines the preparation of chemicals that were previously challenging to synthesize, contributing to the development of green synthetic processes. By eliminating the need for complex and time-consuming multistep procedures, this approach offers a more efficient and sustainable pathway.

This research contributes to the overall understanding of DAN extraction and synthesis, paving the way for future investigations aimed at improving production efficiency. Ultimately, the advancements achieved in this study have the potential to impact the field of green chemistry and advance the development of environmentally friendly synthetic processes.

Supporting Information

Supporting Information for this article can be found under DOI: https://doi.org/10.1002/cite.202300187.

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