Photochemical Flow Oximation of Alkanes

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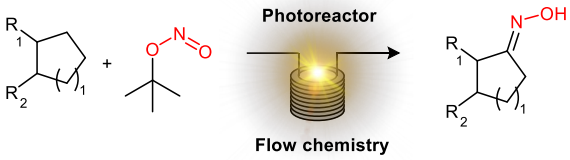

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Abstract: The nitrosation of several alkanes using *t*-butyl nitrite has been performed in flow showing a remarkable reduction in the reaction time compared with batch processing. Due to the necessity for large excesses of the alkane component a continuous recycling process was devised for the preparation of larger quantities of material.

Key words Nitrosation, oximes, flow chemistry, Toray process, photochemistry

Oximes are an important class of molecules that have found numerous applications in many different fields such as coordination chemistry,[1] material science[2] and medicinal chemistry.[3] The further importance of these molecules is also highlighted by the large number of important biologically active compounds possessing this chemical moiety.[4] However, the greatest application of oximes is often as intermediates in cascades such as the named Beckmann Rearrangement or the related Fragmentation, and in their reactions leading to nitriles.[5]

Cyclohexanone oxime is a compound that exemplifies the aforementioned rearrangement chemistry being a precursor of caprolactam, itself a starting material for Nylon-6 synthesis. Because of the immense industrial demand for Nylon there has been significant research into the preparation of all the intermediates along the chemical pipeline. Since the discovery of the Toray photonitrosation of cyclohexane (PNC) process (Figure 1),[6] which enables oxime formation directly from cyclohexane in a single step without going through the related ketone, interest in photo-oximation[7] has grown considerably.

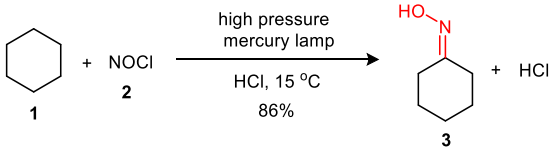

Figure 1 The Toray process towards Nylon-6 synthesis.

In 2019 Lebl *et al.*[8] reported a continuous version of the Toray process claiming 57% overall yield for the photochemical step and showing how the transformation could benefit from flow processing in terms of scaling-up, sustainability, reaction time and safety. Despite the power of this strategy it has several drawbacks, primarily amongst these is the need to generate the unstable nitrosyl chloride (**2**) and the highly corrosive character of its reaction by-product hydrochloric acid. Consequently, several others nitrosylating agents have been studied, with alkyl nitrites[9] showing good synthetic utility and being readily available especially *t*-butyl nitrite. The corresponding oxamination reaction (Figure 2), like the Toray process, also involves the photo-promoted dissociation of the nitrosylating agent **4**, the alkoxy radical formed then abstracts a hydrogen atom from the hydrocarbon generating a second radical which can react with the remaining nitroso radical leading to the desired product **3** after tautomerisation. However, it has been shown that the main product of the reaction is actually the *trans* configured dimer **5**[10] whilst the desired oxime **3** is obtained as a minor product; however the reaction shows good yields (81% varying ratios **3**:**5**).[11] As a result several batch methods have been devised to convert **5** into the synthetically more valuable oxime **3**.[12]

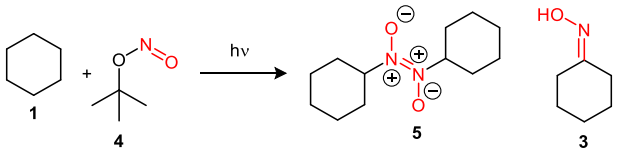

Figure 2 Nitrosation of cyclohexane with *t*-butyl nitrile.

Interested in the synthetic potential of being able to activate normally inert alkanes and the inherent benefits offered by conducting photochemical reactions in flow[13] we embarked upon a more in-depth study of this chemistry in flow.

For our study we utilised a commercial Vapourtec E-series flow reactor in combination with a UV 150 photochemical add-on allowing constant monitoring of temperature and application of external cooling if required.[14] The photoreactor was equipped with a set of 365 nm LEDs (9 W) providing irradiation to a 10 mL FEP coiled tube flow reactor (1 mm ID). The choice of the light source was influenced by the absorption spectra of the species involved in the transformation. The absorption band responsible for the homolytic breaking of *t*-BuONO lies between 320-430 nm but is partially overlapped, with the absorption band of the oxime **3** product and the dimer **5** which have a maximum at 300 nm but extends to around 360 nm. Wysocki *et al.*[15] has shown that activation is efficient using an emission between 365 and 405 therefore a set of 365 nm LED's were used. However, this does introduce some limitation regarding photon flux and can therefore lead to the requirement for longer reaction times.

To establish the flow process we used cyclohexane and screened several molar ratios of reagents, temperature and flow rates in order to find optimum conditions for the transformation. Wysocki *et al.*[15] in their study had determined that the addition of *t*-BuOH as an additive was highly beneficial to the reaction

progress in batch. We therefore additionally wished to validate this finding with respect to the flow process (Table 1).

Entry	Molar ratio **1**:*t*BuOH:**4**	Temp (°C)	tRes (min)	Total NMR Conv. (%)	Ratio of **5**:**3**
1	100:0:1	50	10	66	5.4:1
2	100:0:1	28	10	55	6.4:1
3	100:0:1	18	10	42	9.5:1
4	100:0:1	18	20	41	4.3:1
5	100:15:1	28	10	58	6.3:1
6	100:15:1	28	2.5	53	12.3:1
7	100:15:1	28	1.25	37	6.4:1
8	100:15:1	50	5	60	6.2:1
9	200:30:1	50	5	62	10.5:1
10	30:0:1	18	10	32	8.9:1
11	30:15:1	18	10	46	7.9:1
12	30:15:1	28	10	57	5.9:1
13	30:15:1	50	10	68	4.6:1
14	45:15:1	50	10	68	8.8:1
15	60:15:1	50	10	67	10.1:1
16	45:0:1	50	10	69	6.2:1
17	15:30:1	50	10	55	4.5:1
18	30:60:1	50	10	55	4.5:1

Table 1 Selected data for the evaluation of the molar ratio **1**:*t*BuOH:**4**; 10 mL flow coil; conversion vs an internal standard.

Several general observations can be made. Firstly, the reaction produces mainly the dimer **5** in accordance with previous literature reported batch results.[16] Furthermore and in validation of Wysocki's study[15] the addition of *t*-BuOH does have an impact on conversion (Table 1; cf. entries 3&5, 10&11) and also changes the ratio between **5** and **3** in favour of the desired monomer **3**; again in accordance with their report (albeit not as significantly). However, the influence of the *t*-BuOH seems limited (cf. entries 13&14, 17&18) and seemingly dilution (cf. entries 3&10) and more significantly temperature (cf. entries 1-3, 11-13) has a more pronounced effect on the reaction outcome with regards overall conversion and product composition. The fact that equitable results were obtained at higher reactor temperature (unregulated reactor temperature, higher temperatures failed to give better results) without the addition of the *t*-BuOH suggests under these conditions it does not play an important role behaving only as a diluent (entries 1,8,9 & 14,16). Finally, residence time indicates an optimal reaction window of between 5-10 min based upon this initial scoping.

Several of these observations can be rationalised. A high dilution of the *t*-butyl nitrite reduces competing termination and side reactions which are competitive when using non-activated reactants such as cyclohexane.[6-8] For example, it was noted that nitrocyclohexane was formed in small amounts (2-9%) as a by-product increasing proportionally with higher concentration of *t*-butyl nitrite (identified by GC-MS and ^{1}H NMR); consistent with studies of Mackor *et al.* when high nitric oxide concentrations were employed.[12] The impact of temperature is less clear but to discount a purely thermal fragmentation process the reaction was also conducted (Repeat of Table 1, entry 9) without irradiation which resulted in recovery of only unreacted starting materials. As higher temperatures yield higher compositions of the monomer **3** it may be the monomer is more stable than the dimer **5** to decomposition and hence this accounts for the improved conversions.

We have previously found value in screening a range of alkyl nitrites in other projects[17] therefore additional alkyl nitrite sources were evaluated (e.g. isoamyl nitrite, butyl nitrite) but all gave inferior results (conversion/purity) compared to *t*-butyl nitrite. This is consistent with other literature studies[12,15,17] explaining that non-tertiary alkyl nitrites undergo undesirable side reactions, such as the Barton reaction, when irradiated.

With good initial results from the direct reaction of *t*-butyl nitrite (**4**) and cyclohexane (**1**) (Table 1, entry 16, 48% isolated yield of **5** by recrystallisation from cyclohexane) we decided to target these conditions for further optimisation focusing on concentration and residence time (Table 2, Figure 3). Reviewing the data indicated we had already serendipitously identified the best conditions (Table 1 entry 16, Table 2 entry 5).

Entry	Molar ratio **1**:**4**	Product ratio **5**:**3**	Total NMR %conv.
1	10:1	8.1:1	35
2	20:1	7.2:1	57
3	30:1	6:5:1	59
4	40:1	6.4:1	65
5	**45:1**	**6.2:1**	**69**
6	50:1	6.1:1	64
7	60:1	7.0:1	64
8	70:1	7.0:1	64
9	80:1	6.9:1	63
10	90:1	7.0:1	64
11	100:1	5.4:1	66

Table 2 Molar ratio study. Flow rate of 1 mL/min; conversion vs an internal standard.

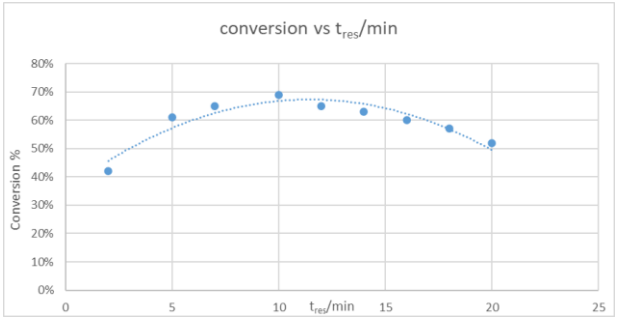

Figure 3 Residence time optimization, 10 mL FEP coil reactor using 45:1 of **1**:**4**; conversion vs an internal standard.

Our next consideration was the transformation of dimer **5** to the corresponding monomer **3**. Donaruma had reported[19] that isomerisation could be performed by dissolution and heating in MeOH, indeed 20 min reflux resulted in complete conversion (2 M, 50 mmol). As a note the solution changed from colourless to blue, indicating the formation of the monomer species. By comparison, testing t-BuOH gave only 15-18% conversion after 90 min (65 °C) indicating a much slower process. Interestingly, whilst performing melting point purity analysis on **5**, it was observed that when heated neat it readily interconverted to the corresponding oxime **3**. Thus when a purified sample of **3** was heated neat at 100 °C for 30 min a quantitative conversion to the monomer **3** was achieved.[20] However, when a sample of a crude reaction product (69% ^{1}H NMR conversion; 4.2:1 of **5**:**3**) a less clean transformation was observed and only 44% isolated yield of **3** was obtained following chromatographic purification. We found that dimer **5** can be easily isolated and recrystallized from cyclohexane which offers a simple processing sequence.

So, although it is trivial to batch collect the reactor output and remove the excess low boiling point cyclohexane leaving the products **5**/**3**; which in a second step can be heated to convert them to **3**, we wished to establish the principles of a more

continuous operation. To create a viable set-up we also had to consider some further reaction aspects: During our work we had found that prolong heating of oxime **3** neat (>45 min) led to its slow but progressive decomposition. This was nevertheless completely suppressed if a solvent such as cyclohexane with quantities of *t*-BuOH was present. However, the low solvent reflux temperature of cyclohexane resulted in the need for longer heating periods to effect full conversion **5**→**3**. Therefore, and to avoid any addition issues with needing to regulate the rate of a continuous distillation (not drying out the product), but allowing constant heating (conversion of **5**→**3**) we adopted a mixed flow and continuous distillation set-up (Figure 4).

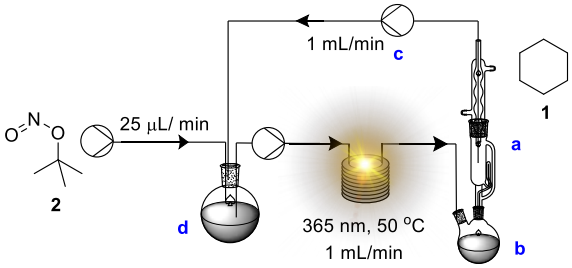

Figure 4 Continuous flow recycling process for cyclohexane.

An assembled Soxhlet extraction apparatus (**a**) functioned to separate the product solution (**b**) from unreacted cyclohexane (**a**) whilst converting the dimer **3** to oxime **4** (**b**) and simultaneously acting to regulate an essentially constant liquid level (**a**/**b**). Unreacted cyclohexane was continuously distilled and could be pumped from the top of the Soxhlet collection chamber (**a**, containing pure cyclohexane) to a stirred stock flask (**d**) where it was continuously refreshed with additional *t*-butyl nitrite at a flow rate commensurate to maintain the established 45:1 reagent ratio. The stock solution (**d**) was pumped through the photoreactor with an optimised residence time of 10 min and a theoretical throughput of 1.24 g/h.

Interval sampling and ^{1}H NMR analysis of the photoreactor output indicated that the sum (69% ±1.8 total conversion) and ratio **5**:**3** (1:4.2 ±0.08) remained essentially constant (4 h run). However, the resulting isolated yield of 45% was rather disappointing when compared to previous reported batch processes (53-82%).[12c,15] However, it should be noted that these previous batch experiments typical involved prolonged irradiation times of >16 h. Wysocki[15] had noted that in batch after 180 min irradiation (high power 365 nm NVSU233A LED diodes from Nichia Corp) conversion reached a maximum considering the sum of **5**/**3** (with **3** only being detected at >45 min), whereas, it took an additional 13 h of irradiation to completely convert the dimeric species to oxime **4**. The conversion of dimer **5** to the corresponding monomer **4** is therefore also photochemically induced. Indeed, we also demonstrated that reducing the flow rate (1→0.5 mL/min) led to a higher proportion of the monomer (3.1:1 v's 4.3:1 **5**:**3**) in the photoreactor output but this was associated with a reduced overall conversion (69→60%; Figure 3). Fortunately, our continuous distillation system should due to the longer processing times overcome this need for additional irradiation, due to the thermally conducted splitting of the dimer.

The Soxhlet system (Figure 4) was therefore run in continuous mode for an extended 20 h and generated after recrystallisation from cyclohexane 14.72 g of pure product **3** (59%) demonstrating the scalability achievable with this simple system. We also believe it should also be possible to couple multiple photoreactors to a single Soxhlet system to drastically increase throughput, currently the photoreactor is the limiting component.

Having determined the feasibility of the process we next explored the scope of the transformation in terms of other viable substrates. First, we considered the value of introducing unsaturation to the reactant, namely testing cyclohexene, as the product would offer value as an aniline precursor via the Semmler–Wolff reaction.[21] In addition the alkene should make cyclohexene a better substrate by assisting the proton abstraction step due to the lower bond dissociation energy of the allylic hydrogen compared with the purely alkyl bond (85 vs 96 kcal mol^{-1}).[22]

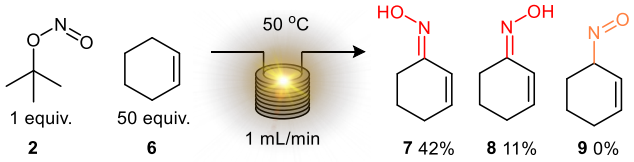

Figure 5 Photo-promoted oximation of cyclohexene.

When the reaction was run in flow it produced predominantly compound **7** (Figure 5) which exists in equilibrium with **8** (3.8:1). This was proven by the partial conversion of a pure solution of **7** back to a 3.8:1 mixture of **7**:**8** (24 h in $CDCl_3$). The preference for the *anti*-isomer **7** can be rationalised by a 1,4-interaction between the hydroxyl group and the vinyl proton in **8** (Figure 6).

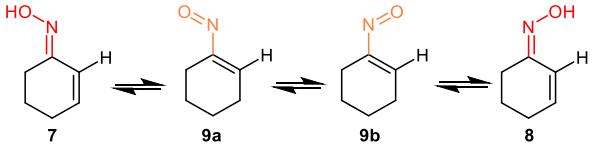

Figure 6 Interconversion of 2-cyclohexenone oxime isomers.

As the reagent ratio had been an important parameter in the reaction of the cyclohexane (**1**) a rapid screening was performed finding again that a large excess of cyclohexene was advantageous (See SI). A substrate to nitrite ratio of 100:1 gave the best results again at 50 °C. For this substrate the rate of the reaction was much faster, with higher conversions being achieved at increased flow rates, ultimately, 2 mL/min was deemed optimal (83% conv. 61:22 **7**+**8**:**9**). Also it was noted that under shorter residence times higher proportions of compound **9** was observed which tautomerised slowly upon standing but was shown to be rapidly interconverted upon further irradiation presumably by a photochemical [1,3]-sigmatropic hydride shift.

As performed previous, we investigated the reaction of cyclohexene (**6**) in the integrated Soxhlet-Flow reactor which allowed easy scaling of the reaction and isolation of 21.98 g of a mixture of **7**/**8** (3.8:1) in 77% isolated yield from a 22 h run.

Given these encouraging results we decided to pursue a small expansion of the reaction scope by investigating several other alkanes (Figure 7). The new substrates selected were by comparison all non-volatile therefore removal of unreacted starting material was no longer achievable by simple evaporation requiring all crude products to be separated by chromatographic purification. To enact the flow process a standard stock solution comprising substrate:*t*-BuOH:*t*-BuONO

20:20:1 (10 mmol *t*-BuONO scale) was prepared and pumped through the photoreactor at 1 mL/min and 50 °C (no optimisation was performed). The reactor output was collected and the solvent evaporated before the products separation.

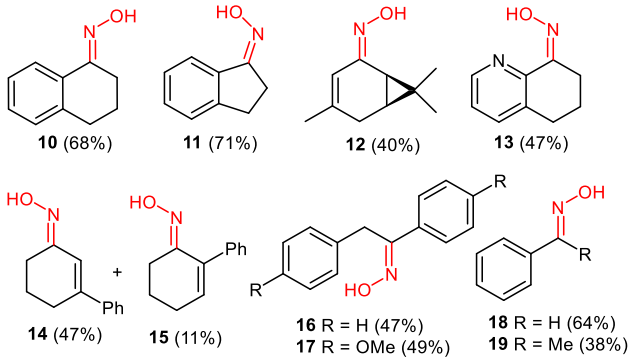

Figure 7 Expansion of substrate scope.

Compounds **10** and **11** were obtained starting from tetraline and indane as single regio and diastereoisomers (confirmed by single crystal x-ray determination; see SI) in 68% and 71% yield, respectively. The regiospecificity for the benzylic proton abstraction arises from the lower bond dissociation energy (83 vs 96 kcal abstraction mol^{-1}).[23] The associated diastereoselectivity is accounted for by conformational preference arising from the varying interactions between the hydroxy group and the α-geminal protons v's the α-*peri*-interaction with the aromatic proton (Figure 8, **20**-**21**).

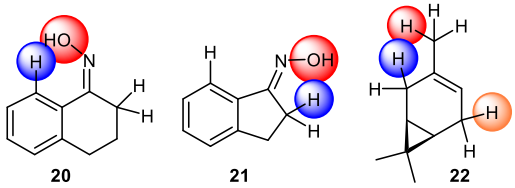

Figure 8 Disfavoured interactions conformational interactions.

Compound **12** was obtained from the (1*R*,6*S*)-3-carene. Again, excellent regio and stereoselectivity were observed arising from the steric hindrance between the allylic positions (orange favoured abstraction site) on the cyclohexene ring and the methyl group (Figure 8, **22**). Interestingly no oximation was observed on the allylic methyl arguably because the primary radical obtained is less stable compare with the alternative secondary positions. In order to test the reaction on a heterocyclic core, tetrahydroquinoline was processed. Of the two possible kinetic regioisomeric products only compound **13** forms as a single stereoisomer probably due to the presence of stabilising hydrogen bonding between the hydroxyl proton and the pyridine nitrogen. Starting from 1-phenylcyclohexene a 4.3:1 regioisomeric mixture of compounds **14** and **15** were obtained with preference for abstraction at the less hindered allylic proton. Finally, oximes **16** and **17** were generated from their symmetrical precursor alkanes and similarly the systems **18** and **19**, could be prepared from toluene and ethyl benzene respectively.

In conclusion, we have reported the photoflow oximation of several alkanes using *t*-butyl nitrite. The flow process allows for a considerable reduction in the reaction time and enables easy scale up of the transformation. An integrated continuous distillation process was also investigated in order to gauge the possibility of recycling the volatile unreacted starting materials.

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Supporting Information

YES (this text will be updated with links prior to publication)

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