

# Photochemical Flow Oximation of Alkanes

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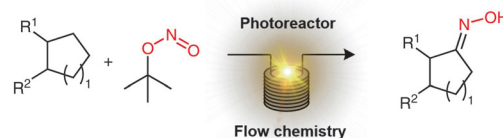
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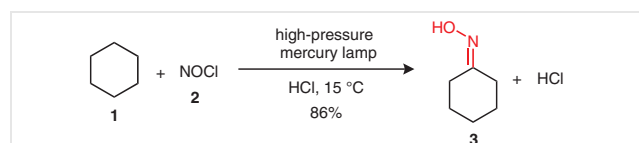
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**Abstract** The nitrosation of several alkanes using *tert*-butyl nitrite has been performed in flow showing a remarkable reduction in the reaction time compared with batch processing. Due to the necessity for large excesses of the alkane component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

**Key words** nitrosation, oximes, flow chemistry, Toray process, photochemistry

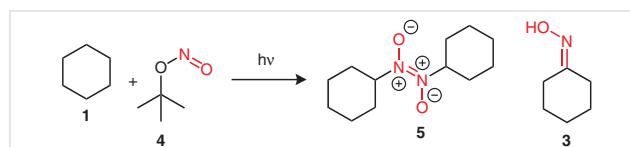
Oximes are an important class of molecules that have found numerous applications in many different fields such as coordination chemistry,<sup>1</sup> material science,<sup>2</sup> and medicinal chemistry.<sup>3</sup> The further importance of these molecules is also highlighted by the large number of important biologically active compounds possessing this chemical moiety.<sup>4</sup> 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.<sup>5</sup>

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 (Scheme 1),<sup>6</sup> which enables oxime formation directly from cyclohexane in a single step without going through the related ketone, interest in photo-oximation<sup>7</sup> has grown considerably.



**Scheme 1** The Toray process towards nylon-6 synthesis

In 2019 Lebl *et al.*<sup>8</sup> 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 byproduct hydrochloric acid. Consequently, several other nitrosylating agents have been studied, with alkyl nitrites<sup>9</sup> showing good synthetic utility and being readily available especially *tert*-butyl nitrite. The corresponding oximation reaction (Scheme 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 tautomerization. However, it has been shown that the main product of the reaction is actually the *trans*-configured dimer **5**<sup>10</sup> whilst the desired oxime **3** is obtained as only a minor product; however, the reaction shows good yields (>80% varying ratios **3/5**).<sup>11</sup> As a result several batch methods have been devised to convert **5** into the synthetically more valuable oxime **3**.<sup>12</sup>



**Scheme 2** Nitrosation of cyclohexane with *tert*-butyl nitrite

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

For our study we utilized a commercial Vapourtec E-series flow reactor in combination with a UV 150 photochem-

ical add-on allowing constant monitoring of temperature and application of external cooling if required.<sup>14</sup> The photo-reactor 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 product **3** and the dimer **5** which have a maximum at 300 nm but extends to around 360 nm. Wysocki *et al.*<sup>15</sup> has shown that efficient activation of *t*-BuONO can be achieved using an emission between 365 and 405 nm and therefore a set of 365 nm LEDs were used. However, this does introduce some limitation regarding photon flux and can therefore lead to the requirement for longer reaction times to ensure high conversions.

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. In their study, Wysocki *et al.*<sup>15</sup> 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).

Several general observations can be made. Firstly, the reaction produces mainly the dimer **5** in accordance with previous-literature-reported batch results.<sup>16</sup> Furthermore and in validation of Wysocki's study<sup>15</sup> the addition of *t*-BuOH does have an impact on conversion (Table 1; cf. entries 3 and 5, 10 and 11) and also changes the ratio between **5** and **3** in favor 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 and 14, 17 and 18) and seemingly dilution (cf. entries 3 and 10) and more significantly temperature (cf. entries 1–3, 11–13) has a more pronounced effect on the reaction outcome with regards to overall conversion and product composition. The fact that equitable results were obtained at higher reactor temperature (higher temperatures failed to give better results) without the addition of the *t*-BuOH suggests that under these conditions it does not play an important role behaving only as a diluent (entries 1, 8, 9, 14, and 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 rationalized. A high dilution of the *tert*-butyl nitrite reduces competing termination and side reactions which are competitive when using non-activated reactants such as cyclohexane.<sup>6–8</sup> For example, it was noted that nitrocyclohexane was formed in small amounts (2–9%) as a byproduct increasing proportionally with higher concentration of *tert*-butyl nitrite (identified by GC–MS and <sup>1</sup>H NMR spectroscopy); consis-

**Table 1** Selected Data for the Evaluation of the Molar Ratio 1/*t*-BuOH/4<sup>a</sup>

Entry	Molar ratio 1/ <i>t</i> -BuOH/4	Temp (°C)	<i>t<sub>r</sub></i> (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

<sup>a</sup> 10 mL flow coil; conversion vs an internal standard.

tent with studies of Mackor *et al.* when high nitric oxide concentrations were employed.<sup>12</sup> 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.

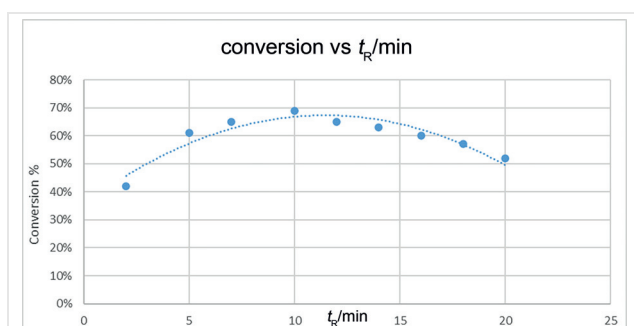
We have previously found value in screening a range of alkyl nitrites in other projects,<sup>17</sup> therefore additional alkyl nitrite sources were evaluated (e.g. isoamyl nitrite, butyl nitrite) but all gave inferior results (conversion/purity) compared to *tert*-butyl nitrite. This is consistent with other literature studies<sup>12,15,18</sup> 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 *tert*-butyl nitrite (**4**) and cyclohexane (**1**, Table 1, entry 16, 48% isolated yield of **5** by recrystallization from cyclohexane) we decided to target these conditions for further optimization focusing on concentration and residence time (Table 2, Figure 1). Reviewing the data indicated we had already serendipitously identified the best conditions (Table 1 entry 16, Table 2 entry 5).

**Table 2** Molar Ratio Study<sup>a</sup>

Entry	Molar ratio <b>1/4</b>	Product ratio <b>5/3</b>	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

<sup>a</sup> Flow rate of 1 mL/min; conversion vs an internal standard.

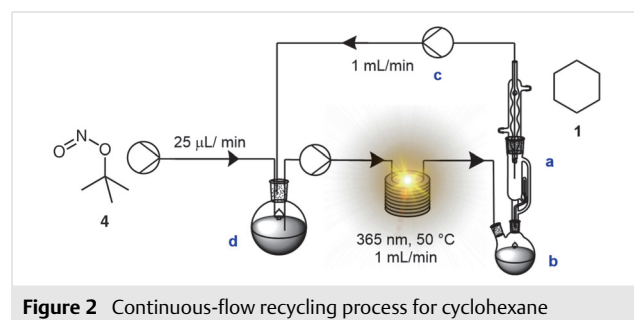


**Figure 1** Residence time optimization, 10 mL FEP coil reactor using 45:1 of **1/4**; conversion vs an internal standard

Our next consideration was the transformation of dimer **5** to the corresponding monomer **3**. Donaruma had reported<sup>18</sup> that isomerization 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 into the corresponding oxime **3**. Thus when a purified sample of **3** was heated neat at 100 °C for 30 min a quantitative conversion into the monomer **3** was achieved.<sup>20</sup> However, when a sample of a crude reaction product (69% <sup>1</sup>H NMR conversion; 4.2:1 of **5/3**) was heated similarly a less clean transformation was observed and only 44% isolated yield of **3** was obtained following chromatographic purification. We later 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 into **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 of **5** into **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** into **3**), we adopted a mixed flow and continuous distillation set-up (Figure 2).



**Figure 2** Continuous-flow recycling process for cyclohexane

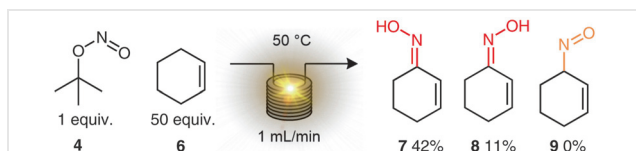
An assembled Soxhlet extraction apparatus (**a**) functioned to separate the product solution (**b**) from unreacted cyclohexane (**a**) whilst converting the dimer **5** into oxime **3** (**b**) and simultaneously acting to regulate an essentially constant liquid level (**a/b**). Unreacted cyclohexane 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 *tert*-butyl nitrite at a flow rate commensurate to maintain the established 45:1 reagent ratio. The stock solution (**d**) was pumped through the photo-reactor with an optimized residence time of 10 min and a theoretical throughput of 1.24 g/h.

Interval sampling and <sup>1</sup>H NMR analysis of the photo-reactor 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 **3** was 45% (via recrystallisation) rather disappointing when compared to previous reported batch processes (53–82%).<sup>12c,15</sup> However, it should be noted that these previous batch experiments typical involved prolonged irradiation times of >16 h. Wysocki<sup>15</sup> 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 into oxime **3**. The

conversion of dimer **5** into the corresponding monomer **3** 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 vs 4.3:1 **5/3**) in the photoreactor output but this was associated with a reduced overall conversion (69 → 60%; Figure 1). 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.

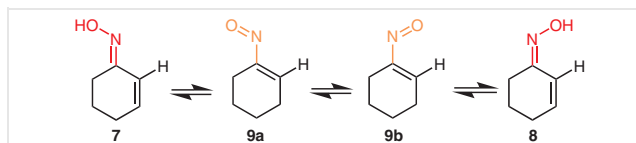
The Soxhlet system (Figure 2) was therefore run in continuous mode for an extended 20 h and generated after recrystallisation from cyclohexane 14.72 g of pure product **3** (59%) demonstrating the scalability achievable with this simple system. We also believe it should be possible to couple multiple photoreactors to a single Soxhlet system to drastically increase throughput, currently the photoreactor is the limiting processing component in this set-up.

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.<sup>21</sup> 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<sup>-1</sup>).<sup>22</sup>



**Scheme 3** Photopromoted oximation of cyclohexene

When the reaction was run in flow it produced predominantly compound **7** (Scheme 3) which exists in equilibrium with **8** (3.8:1). This was proven by the partial conversion of a pure solution of **7** back into a 3.8:1 mixture of **7/8** (24 h in CDCl<sub>3</sub>). The preference for the *anti*-isomer **7** can be rationalized by a 1,4-interaction between the hydroxyl group and the vinyl proton in **8** (Scheme 4).



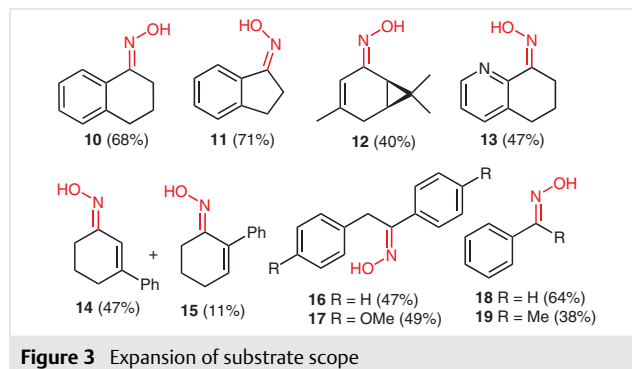
**Scheme 4** Interconversion of 2-cyclohexenone oxime isomers

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 the Supporting Information). 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 tautomerized 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.

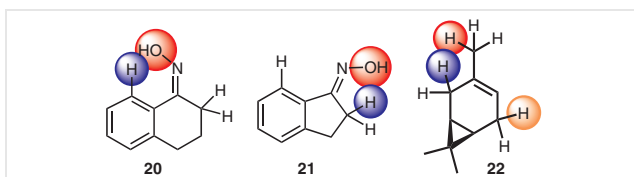
Given these encouraging results we decided to pursue a small expansion of the reaction scope by investigating several other alkanes (Figure 3). The new substrates selected were by comparison all non-volatile therefore removal of unreacted starting material was no longer achievable by simple evaporation 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 optimization was performed). The reactor output was collected, and the solvent evaporated before the products were isolated via chromatography.



**Figure 3** 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 the Supporting Information) in 68% and 71% yield, respectively. The regioselectivity for the benzylic proton abstraction arises from the lower bond dissociation energy (83 vs 96 kcal abstraction per mol).<sup>23</sup> The associated diastereoselectivity is accounted for by conformational preference arising from the varying interactions between the hydroxy group and the  $\alpha$ -geminal protons vs the  $\alpha$ -*peri*-interaction with the aromatic proton (Figure 4, **20** and **21**).





**Figure 4** Disfavored 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 favored abstraction site) on the cyclohexene ring and the methyl group (Figure 4, **22**). Interestingly no oximation was observed on the allylic methyl arguably because the primary radical obtained is less stable compared 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 stabilizing 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 *tert*-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

Supporting information for this article is available online at <https://doi.org/10.1055/s-0040-1707281>.

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