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Straightforward hetero Diels–Alder reactions of nitroso dienophiles by microreactor technology

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ABSTRACT

The hetero Diels–Alder reactions of 2-nitrosotoluene and some representative acylnitrosodienophiles with a selected set of 1,3-dienes were studied under microflow conditions. The main assets of the technology, that is, an accurate control of the reaction parameters and continuous operating, led to an increased efficiency of this reaction.

The hetero Diels–Alder (HDA) reactions of nitroso dienophiles have gained a considerable attention in the last decade.[1] At present, it becomes a privileged tool in heterocyclic organic synthesis. This reaction leads to polyfunctional 3,6-dihydro-1,2-oxazine scaffolds (Fig. 1) comprising of at least three different entries for selective chemical modifications.[2] Among these, oxidation reactions, ring opening or ring contraction of 1,2-oxazines have been used in numerous total syntheses of nitrogen-containing bioactive natural products or synthetic analogs.[3]

Two main classes of nitroso compounds are predominantly used, namely aryl- (**1**) and acylnitroso (**3**) dienophiles (Fig. 1), although some studies emphasized the synthetic utility of vinylnitroso,[4] α-chloro-[5] and α-acyloxynitroso dienophiles.[2b] 2-Nitrosotoluene (**1**) is generated from its stable commercial dimer by solvation. Acylnitrosodienophiles (**3a–c**) are generated in situ in the presence of the guest diene from stable precursors, mainly hydroxamic acids (**2a–c**) under oxidative conditions.[6] On the other hand, some recent improvements in acylnitroso generation were reported, using metal catalysts; however under environmentally unfriendly conditions.[7]

These cycloaddition reactions are exothermic and stoichiometry-sensitive, hence demanding accurate thermal and stoichiometric control to avoid side-reactions. Indeed, a local excess of hydroxamic acid under oxidative conditions can lead to acylnitroso dimerization and degradation according to Kirby.[8] The main assets of the microreactor technology, namely efficient heat-exchange and strictly controlled local stoichiometry, therefore look attractive for further optimization of such a HDA reaction. Commercial microreactor systems are being increasingly and successfully used to improve organic synthesis, due to the above-mentioned and other benefits such as an easy control of reaction and operating parameters, adequate mixing, efficient processing of unstable intermediates, the possibility of continuous processing without time delays characteristic for batch conditions, and the use of dangerous reagents, etc.[9] Even though some recent reports are dedicated to continuous Diels–Alder reactions,[10] to the best of our knowledge there is no record of flow nitroso DA reactions. As a part of our ongoing research in flow chemistry, the microreactor technology has been investigated to continuously produce 1,2-oxazine synthons from a selected set of available dienes. In this Letter, we report the flow synthesis of 1,2-oxazines derived from nitrosotoluene (**1**) or acylnitroso derivatives (**3a–c**) and a set of dienes (**4**) (Table 1).

The CPC College System from Cytos[11a] (47 mL total volume) and the X-Cube from ThalesNano[11b] (6 mL total volume) were used for this project. Experiments requiring higher pressures have been carried out using the X-Cube microsystem. The cycloaddition reactions of 2-nitrosotoluene (**1**) were first investigated using a microreactor setup A as described in Figure 1. A temperature ranging from 0 to 95 °C, a pressure ranging from 1 to 100 bar, and flow rates ranging from 0.2 to 1 mL min^{-1} were considered for equimolar solutions (0.15 N). Several solvents were investigated: acetone, methanol,

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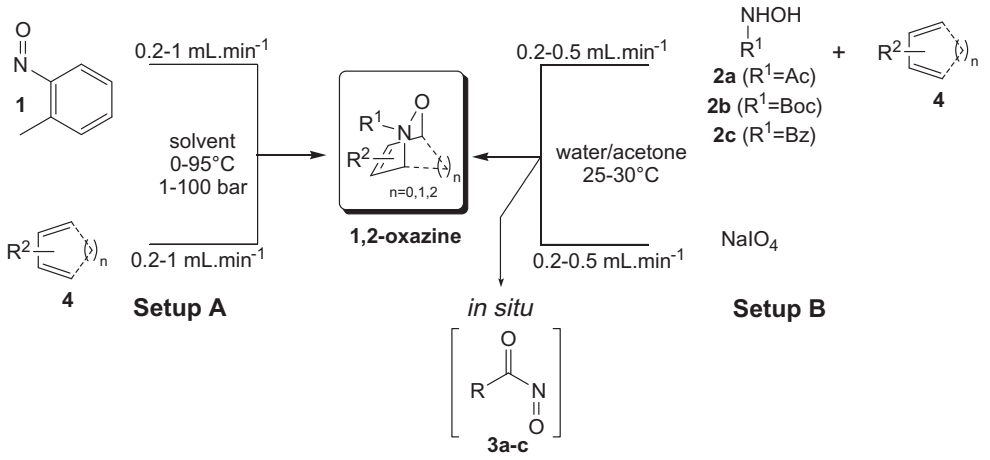
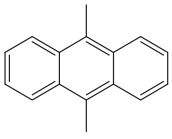
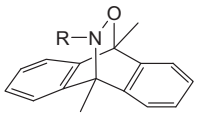
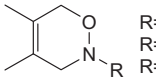
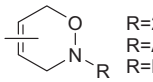
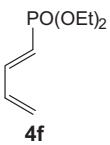
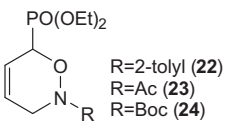
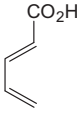
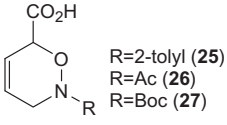


Figure 1. Setups A–B of the microreactor and HDA reactions of nitrosodienophiles.

Table 1
Cycloadditions of nitroso dienophiles 1, **3a–c** with dienes **4a–g** under microflow conditions (standard pressure conditions)[12]

Entry	Dienophiles	Diene	Adduct	Microflow conditions			Batch
				rt[a] (min)	Scale (g h−1)	Yield[b] (%)	Yield (%)
1	**1**	 **4a**	 R=2-tolyl (**5**) R=Ac (**6**) R=Boc (**7**)	47	0.90	92	67[3e]
2	**3a**			117.5	0.19	94	57[3h]
3	**3c**			117.5	0.25	87	93[3i]
4	**1**	 **4b**	 R=2-tolyl (**8**) R=Ac (**9**) R=Boc (**10**) R=Bz (**11**)	/	/	0	0
5	**3a**			117.5	0.33	85	84–99[3g]
6	**3b**			117.5	0.47	72	78[7a]
7	**3c**			117.5	0.48	70	68[3h]
8	**1**	 **4c**	 R=2-tolyl (**12**) R=Ac (**13**) R=Boc (**14**) R=Bz (**15**)	/	/	0	0
9	**3a**			117.5	0.33	90	90[3j]
10	**3b**			117.5	0.40	92	72[8d]
11	**3c**			117.5	0.41	81	82[3h]
12	**1**	 **4d**	 R=2-tolyl (**16**) R=Ac (**17**) R=Boc (**18**)	47	0.91	96	92
13	**3a**			117.5	0.19	87	82
14	**3c**			117.5	0.26	85	76[7a]
15	**1**	 **4e**	 R=2-tolyl (**19**) R=Ac (**20**) R=Boc (**21**)	47	0.85	91[c]	89
16	**3a**			117.5	0.17	72[d]	75
17	**3c**			117.5	0.23	65[e]	65[7a]
18	**1**	 **4f**	 R=2-tolyl (**22**) R=Ac (**23**) R=Boc (**24**)	117.5	0.56	89	95[7a]
19	**3a**			/	/	0	0
20	**3c**			/	/	0	0
21	**1**	 **4g**	 R=2-tolyl (**25**) R=Ac (**26**) R=Boc (**27**)	47	1.0	75	80
22	**3a**			/	/	0	0
23	**3c**			/	/	0	0

[a] Residence time.
[b] Isolated.
[c] 1/4 mixture of regioisomers.
[d] 1/8 mixture of regioisomers.
[e] 1/1 mixture of regioisomers.

THF, acetonitrile, and dimethylformamide. The optimized conditions and results obtained under standard pressure are listed in Table 1 (entries 1, 4, 8, 12, 15, 18, and 21).[12]

The cycloaddition of **1** was relatively insensitive toward solvent polarity. For example, using cyclohexadiene (**4a**) at 55 °C and 1 mL min^{-1} total flow (i.e., 47 min residence time), the conversion was complete in THF, acetonitrile, and methanol. In DMF, under the same flow conditions, total conversion was reached at 95 °C (92% yield). Doubling of the flow rate (i.e., shortening the reaction time by a factor two) led to 85% conversion. Using the X-Cube microsystem with a backpressure of 100 bar led to a significant reduction in residence time (15 min) leading to 95% conversion. For the reaction of **1** and **4b**,[13] the dimerization of cyclopentadiene was the major phenomenon observed. At 0 °C and with a 0.4 mL min^{-1} total flow, no reaction occurred. As expected, no cycloaddition was observed for 9,10-dimethylanthracene (**4c**) and 2-nitrosotoluene.[14] 2,3-Dimethylbutadiene (**4d**) gave its corresponding *N*-2-tolyl-1,2-oxazine cycloadduct **16** in 96% yield (after extraction) in DMF at 95 °C and 1 mL min^{-1} total flow.[15] At lower temperatures, the conversion of **4d** was lower than for cyclohexadiene (**4a**), even with lower flow rates. The reaction of isoprene (**4e**) and **1** gave a 1:4 (LC) mixture of regioisomers in 91% yield. No modification of the regioselectivity is observed in comparison to batch conditions. Next, the cycloadditions of functionalized dienes **4f** and **4g** with **1** led to the corresponding cycloadducts **22** and **25**, respectively, in moderate to good yields after extraction. In both cases, the regioselectivity is total. The longer residence time needed to complete the reaction of **1** and **4f** emphasizes the lower reactivity of diene **4f**.[16] These results can be interpreted within the electrophilicity scale as introduced by Domingo.[17] Nitrosotoluene has a high electrophilicity power (ω = 2.82 eV) and will consequently react through polar Diels–Alder reaction toward electron rich dienes (i.e., nucleophilic ones). For instance, the relatively low ω values ranging from 0.83 to 1 eV for dienes **4a,b,** and **4d–e** emphasize their higher nucleophilic nature. For 9,10-dimethylanthracene (**4c**), the computed ω equals 1.61 eV. This, combined with the high reversibility of its Diels–Alder reaction with nitroso dienophiles, explains the lack of reactivity observed. The presence of electron-withdrawing substituents onto the butadienyl moiety (dienes **4f**–**g**) increases their relative electrophilicity (and thus reduces their intrinsic nucleophilicity), as showed by their higher electrophilicity power (ω**4f**$_g$ = 1.58 and 1.89 eV, respectively) in agreement with the observed lower conversions.

Further on, the cycloaddition reactions of acylnitroso dienophiles (**3a–c**) were studied. The transient acylnitroso species were generated in situ in the mixing unit of the reactor by pumping separately the oxidant and the hydroxamic acids (**2a–c**) (Setup B, Fig. 1). Sodium metaperiodate is preferred over tetrabutylammonium periodate, as the latter led to the formation of significant amounts of solid byproducts that clogged the micrometric channel of the reactor. Several solvent mixtures were investigated, the best results being realized with a 3/1 water/acetone mixture, and the optimum temperature being 30 °C (except for 9,10-dimethylanthracene (**4c**), which reacted best in DMF at 65 °C). By using the ThalesNano X-Cube (total flow rates ranging from 0.2 to 1 mL min^{-1}), no beneficial effect of the increased pressure has been observed. Several attempts were performed using the ThalesNano X-Cube using catalyst cartridges filled with supported $NaIO_4$ to convert in situ the hydroxamic acid into the nitroso derivative in order to avoid the extraction step; however these experiments gave poor results. Flow rates ranged from 0.2 to 0.5 mL min^{-1} with the CPC College System from Cytos for 0.1 N equimolar solutions of diene/hydroxamic acid (in a 1/1 water/acetone mixture) and sodium periodate (in water). The optimized conditions and results are listed below (Table 1).

The cycloaddition of cyclohexadiene (**4a**) with acetyl- and *tert*-butoxycarbonylnitroso dienophiles (**3a** and **3b**) proceeded very well with total conversion of the diene and excellent yields (87–94%) with a residence time of 117.5 min (0.4 mL min^{-1} total flow rate). The use of shorter residence times (i.e., higher flows) significantly decreased the conversion. Under similar operating conditions, cyclopentadiene (**4b**) underwent cycloaddition with Ac-, Boc-, and Bz-nitroso derivatives (**3a–c**) in moderate to good yields (70–85%, after extraction). No dimerization of the diene was observed. Total conversion was observed for the cycloadditions of 9,10-dimethylanthracene (**4c**) with **3a–c** within 117.5 min of residence time. The instability of the corresponding cycloadducts lowers the yield and prevents any purification on silica gel column. Similarly to the results obtained in the cyclic series, 2,3-dimethylbutadiene (**4d**) reacted under flow conditions with acylnitroso dienophiles **3a** and **3b** yielding 1,2-oxazines **17**[18] and **18** in 85% and 87%, respectively. Isoprene (**4e**) led to a 1/8 and 1/1 mixtures of regioisomers with dienophiles **3a** and **3b**, respectively.[19] The yields were moderate (65–72%). No cycloadditions are observed for dienes **4f** and **4g**, even under 100 bar (X-Cube) and using an excess of hydroxamic acid.[20]

In conclusion, the cycloadditions of a selected set of dienes with representative nitrosodienophiles have been successfully conducted under microflow conditions, leading to the first example of a continuous lab-scale production of 1,2-oxazines (0.2–1 g h^{-1}). Using equimolar solutions of reagents, similar and in several cases higher yields to the corresponding batch reactions were obtained. The continuous process however offers a range of advantages over batch reactions, namely the efficient heat exchange, the easy control of the reaction stoichiometry and shorter residence (reaction) times. Moreover, no metal catalysts or specific additives were necessary to achieve good yields.

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12. The conversion is based on the ^{1}H NMR analysis of the crude reaction mixture and is relative to the diene. The yield is calculated after extraction. The regioisomer ratio is determined by analytical HPLC. The physical characterizations of all obtained products were in agreement with the reported data in the literature. See for example Ref. 7a and: Monbaliu, J.-C.; Marchand-Brynaert, J. *Tetrahedron Lett.* **2008**, *49*, 1839–1842.
13. Cyclopentadiene is freshly prepared before each run by thermal cracking of its dimer.
14. Monbaliu, J.-C.; Marchand-Brynaert, J.; Peeters, D. *Tetrahedron Lett.* **2009**, *50*, 2555–2558.
15. *Typical procedure of setup A*: freshly prepared equimolar 0.15 N solutions of 2,3-dimethylbutadiene and 2-nitrosotoluene in DMF are injected with a 0.5 mL min^{-1} flow each through the CPC microsystem (setup A). After 75 min stabilization at 95 °C, the outlet is connected to a continuous liquid–liquid extractor (ethyl acetate/water). Compound **16**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.23–7.01 (m, 4H), 4.24 (s, 2H), 3.47 (s, 2H), 2.29 (s, 3H), 1.66 (s, 3H), 1.58 (s, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.27, 133.04, 131.01, 126.52, 125.37, 124.87, 123.21, 118.22, 72.30, 56.19, 18.50, 16.18, 13.81 ppm.
16. Monbaliu, J.-C.; Dive, G.; Marchand-Brynaert, J.; Peeters, D. *J. Mol. Struct.: Theochem.*, submitted for publication.
17. See for example: (a) Domingo, L. R.; Sàez, J. A. *Org. Biomol. Chem.* **2009**, *7*, 3576–3583; (b) Domingo, L. R.; Saéz, J. A.; Zaragozà, R. J.; Arnò, M. *J. Org. Chem.* **2008**, *73*, 8791–8799. and references cited therein.
18. *Typical procedure of setup B*: freshly prepared equimolar 0.1 N solutions of 2,3-dimethylbutadiene/acetohydroxamic acid (in acetone/water 1/1) and sodium metaperiodate (in water) are injected with a 0.2 mL min^{-1} flow each through the CPC microsystem (setup B). After 188 min stabilization at 30 °C, the outlet is connected to a continuous extractor (ethyl acetate/water). Compound **17**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.15 (s, 2H), 3.96 (s, 2H), 2.07 (s, 3H), 1.61 (s, 3H), 1.53 (s, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.54, 122.63, 122.13, 72.92, 44.93, 19.88, 15.43, 13.91 ppm.
19. The same regioisomeric ratio was reported in the literature.[7a]
20. Under similar conditions, no cycloadditions are observed in batch either.