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Continuous Flow of Nitroso Diels-Alder Reaction

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Abstract

Our flow reaction systems have provided quantitative yields of nitroso Diels-Alder products with no byproducts in cases of cyclic dienes without temperature and pressure controls. Additionally, the reaction times were significantly shortened by using homogeneous catalyst (CuCl) or heterogeneous reagent (MnO₂) in comparison with batch reaction.

Nitroso Diels–Alder (NDA) reactions have long been a valuable synthetic operation for multistep syntheses of many natural products, since the introduction of the first NDA by Wichterle¹ and Arbuzov² in 1947. Being subsequent to the earlier studies by Kresze's³ and Kirby's group⁴ on the NDA reactions, many research groups have made significant contributions to this field.⁵ Among the various nitroso derivatives, acyl nitroso compounds are known to have exceedingly high reactivity, and the acyl group is easy to remove after the reaction. However, nitroso derivatives have a very short lifetime (~1 ms)⁶ and they require mostly *in situ* preparation in the system. Moreover, nitroso compounds are known to be poisonous (the LD₅₀ of *N*-nitrosodimethylamine for rats is 37 mg/kg (RTECS)), and they can also cause explosions in the production site. Nitroso derivatives can be smoothly prepared *in situ* by oxidizing hydroxylamine with ruthenium, iridium, copper, vanadium, or iron catalysts.⁷ Those catalysts are also reactive for the *in situ* oxidation of hydroxamic acid to the corresponding acyl nitroso dienophiles, which undergo a subsequent Diels-Alder reaction with dienes.⁸ Flow chemistry, especially that using microfluidic devices, allows reactions to be performed safely while controlling reaction times, obviating the need to handle reactive intermediates, and providing efficient heat and mass transfer.⁹ Recently, enormous attention has been drawn to the studies of the flow reaction using a column packed with heterogeneous catalyst, for example, Ley et al reported several flow reactions using column packed with environmentally-friendly catalyst, MnO₂, for hydration of nitriles to amides,¹⁰ cross-coupling reactions *via* diazo compounds¹¹ as well as the rapid synthesis of oxazolines and oxazoles.¹² Furthermore Kobayashi recently reported a multistep continuous-flow synthesis of (*R*) - and (*S*) - rolipram using columns packed with

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heterogeneous catalysts.¹³ Although using a single micro flow reactor can only synthesize chemicals in small quantities, it is easy to increase the production scale by employing several micro reactors in parallel.¹⁴ Furthermore, the parallel system can continuously provide products without halting the reactors or plant systems in the case of an emergency or cleaning. Thus, micro flow reactors are expected to significantly reduce the time and expense for upscaling in industry, and the advantages of parallel systems would include the prevention of explosion, downsizing of industrial plants, and reduction of maintenance loads and facilities costs.¹⁵ We envisage that the flow method would circumvent these problematic issues. For example, explosions which can occur in classic batch reactors, caused by either electrostatic ignition, local overheating or insufficient stirring, could be prevented by using micro flow reactors.

In this context we have studied two different systems of NDA reaction using CuCl/air¹⁶ and MnO₂¹⁷ as oxidants both in flask and flow reactions without temperature and pressure controls (Scheme 1). Stevens's group reported an excellent NDA reaction using a flow system.¹⁸ Unfortunately, the use of nitrosotoluene as a starting material requires several extra steps to achieve the non-protected amino derivative starting from the NDA products. They also tested acyl nitroso derivatives for this NDA reaction. However, their method relied on a periodate oxidation process, which will generate a significant amount of residue after oxidation. On the other hand, using our flow reaction systems, the NDA reactions provided products in quantitative yields in the cases of cyclic dienes, and the same yields were obtained when we used a single syringe-pump to run two micro flow reactors in parallel under the same conditions. Additionally, our methodology, especially the MnO₂ process, furnished a product in pure form at the output of the systems that is ready to be connected to the next reaction sequences.

Initially, we studied the scope of the NDA reaction of acyl nitroso derivative with several dienes in a flask (Table 1). The NDA reactions of the nitroso precursor *tert*-butyl *N*-hydroxycarbamate (1 equiv., BocNHOH) with various dienes (1.2 equiv.) in the presence of CuCl (0.2 equiv.) and pyridine (0.05 equiv.) in 0.095M of THF were stirred at room temperature in a flask (Method 1).¹⁶ Most reactions gave the corresponding cycloadducts in excellent yields (Table 1, Entries 1–3 and 5–7), while in the case of 1,3-cyclooctadiene (**1d**) and 1,4-diphenyl-1,3-butadiene (**1h**), only moderate yields were achieved (Table 1, Entries 5 and 8). Additionally, the reactions of BocNHOH (1 equiv.) with various dienes (1.2 equiv.) in the presence of MnO₂ (3 equiv.) in 0.095M of DCM were performed at room temperature in a flask (Method 2). The reactions of cyclic dienes gave the products in excellent yields (Table 1, Entries 1–4), while in the other cases, the products were obtained in moderate to high yields (Table 1, Entries 5–8). Generally, the NDA reactions using CuCl and air proceeded rather quickly and excellent yields were achieved, typically with cyclic dienes as substrates. On the other hand, NDA reaction using MnO₂ proceeded relatively slowly, but excellent yields were obtained with 1,3-cyclooctadiene using 3 equiv. of MnO₂.

With these results in hand, we then tested the flow reaction with these two oxidants under the optimum conditions used for flask reactions. We also examined the reactions with different ratios of BocNHOH to dienes; these were 2:1, 1:1, 1:2 in both cases (Table 2). Table 2 shows the results for the flow reaction in a T-type reactor using CuCl and air as

oxidant (Method 3). Quantitative yields were obtained in the cases with 1,3-cyclopentadiene (**1a**), 1,3-cyclohexadiene (**1b**) and 1,3-cycloheptadiene (**1c**) as substrates (Table 2, Entries 1–3, Method 3). When 1,3-cyclooctadiene (**1d**), isoprene (**1f**), and 1,4-diphenyl-1,3-butadiene (**1h**) were employed as starting materials, the reactions gave similar results to the corresponding flask reactions (Table 2, Entries 4, Entries 6, Entries 8, Method 3). In the case of isoprene (**1f**), higher diene/BocNHOH ratios resulted in better yields (Table 2, Entry 6, Method 3). On the contrary, in the case of 9,10-dimethylantracene (**1g**), the reaction afforded a product with higher efficiency when excessive BocNHOH was employed (Table 2, Entry 7, Method 3).

Further on, the results are shown for the flow reaction using a column reactor filled with MnO₂ in Table 2 (Method 4a, b). Excellent results were achieved in the cases with 1,3-cyclopentadiene (**1a**), 1,3-cyclohexadiene (**1b**) and 1,3-cycloheptadiene (**1c**) as substrates (Table 2, Entries 1–3, Method 4a, b). In the case of isoprene (**1f**) and 9,10-dimethylantracene (**1g**), higher yields were obtained in comparison to those in the flask reactions (Table 2, Entries 6 and 7, Method 4b). Furthermore, it turned out that, in the case in the cases of 1,3-cyclooctadiene (**1d**), 2,3-dimethyl-1,3-butadiene (**1e**), and isoprene (**1f**), increasing the diene/BocNHOH ratios benefited the yields from the cycloaddition reactions (Table 2, Entries 4–6, Method 4a, b). Again, in the case of 9,10-dimethylantracene (**1g**), the reaction afforded a product with higher efficiency when excessive BocNHOH was employed (Table 2, Entry 7, Method 4a, b). It is noteworthy that the cycloadducts **2a** and **2b** required no further purification after the flow reactions, because MnO₂ was retained in the column reactor. The products **2d** was obtained in >99% NMR yield and ~94% isolated yield (Table 2, Entries 2, Method 4a). Our single reactor was successfully scaled up to 1.2 mmol and in this way 1.1 g of total adduct was achieved by running five of the single reactors in parallel in 9 hours (Table 2, Entry 2, Method 4a). Therefore, these results have potential advantages over CuCl/air for further direct connection to another flow reaction to achieve acyl group and/or N-O bonding cleavage.

Generally, the flow reactions provided similar or better yields than the flask reactions. The flow reaction system demonstrated not only high efficiency, but also a shorter reaction time than that in the flask reactions. For example, in the case of 1,3-cyclohexadiene (**1b**) using CuCl/air, quantitative yields were achieved and the reaction was accelerated 9-fold (Scheme 2 (a)). The MnO₂ system with 1,3-cyclohexadiene (**1b**) gave quantitative yields and the reaction was accelerated 20-fold (Scheme 2 (b)). The NDA reaction using MnO₂ in a flask proceeded relatively slowly, but the flow system seems to be more efficient without the requirement of any purifications.

Conclusions

We developed flow system that provided good to quantitative yields of cycloadducts without any byproducts. Notably, with our parallel oxidation flow system, the flow reaction did not require the control of temperature and pressure, thereby overcoming various issues found with classic batch reactors for industrial-scale production. It can successfully be scale up to gram scale. Additionally, the flow system using MnO₂ as an oxidant did not require any

separation of the product from the oxidant. This context demonstrated a distinct advantage of applying flow chemistry to problematic oxidation reactions.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Scheme 1.

Nitroso Diels-Alder reaction of *in situ* generation of dienophile (1) with CuCl/air in flask, (2) with MnO₂ in flask, (3) with CuCl/air using T-reactor in flow, (4) with MnO₂ using column reactor in flow.

Scheme 2.

Comparison of flask and flow conditions for *in situ* generation of dienophile using (a) CuCl/air, (b) MnO₂.

Table 1 Nitroso Diels-Alder reaction of *in situ* generation of dienophile in flask.

BocNHOH + Diene		$\xrightarrow[\text{pyridine (0.05 equiv.)}]{\text{CuCl (0.2 equiv.)}}$ THF (0.095 M) RT, air, 3 h	Product(s)	Method 1
1	1		2	
BocNHOH + Diene		$\xrightarrow[\text{DCM (0.095 M)}]{\text{MnO}_2 \text{ (3 equiv.)}}$ RT, N ₂ , 10 h	Product(s)	Method 2
1	1		2	

Entry	Diene	Products	Yield [%] ^[a]	
			Method 1	Method 2
1			>99	>99
	1a	2a		
2			>99	>99
	1b	2b		
3			>99	>99
	1c	2c		
4			51	96
	1d	2d		
5			92	83
	1e	2e		
6		 	95	33
	1f	2f 2f'		

Table 2

Products and corresponding yields for the *in situ* generation of dienophile using CuCl/air and MnO₂ in flow conditions.

Entry	Diene	Products	Method ^[a]	Yield [%] ^[b]			
				BocNHOH : Diene			
				2:1	1:1	1:1.2	1:2
1			3	86	>99	>99	>99
		4a	4a	>99	>99	>99	>99
		4b	4b	>99	>99	>99	>99
2			3	90	>99	>99	>99
		4a	4a	79	>99	>99	>99 (94 ^[c])
		4b	4b	89	>99	>99	>99
3			3	89	>99	>99	>99
		4a	4a	90	94	93	97
		4b	4b	80	92	94	97
4			3	30	33	57	50
		4a	4a	10	31	34	45
		4b	4b	14	28	33	44

Entry	Diene	Products	Method ^[a]	Yield [%] ^[b]			
				BocNHOH : Diene			
				2:1	1:1	1:1.2	1:2
5			3	77	67	69	77
			4a	40	43	51	64
			4b	38	44	60	59
6			3	44	65	69	86
			4a	15	26	24	45
			4b	18	37	40	60
7			3	65	57	56	44
			4a	45	43	34	24
			4b	63	49	34	32
8			3	11	16	16	14
			4a	8	7	5	7
			4b	8	8	6	5

^[a] Method 4a using MnO₂ 3 equiv. and Method 4b using MnO₂ 5 equiv.

^[b] In the case of volatile dienes, NMR yields were based on BocNHOH; in the case of non-volatile dienes, NMR yields were based on dienes.

^[c] Isolate yield.