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A Selective and Practical Synthesis of Nitroolefins

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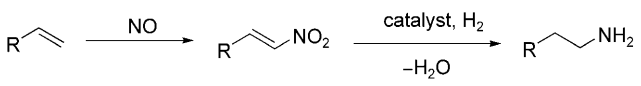
Abstract: A straightforward and general synthesis of nitroolefins from nitric oxide (NO) and olefins is presented. The direct nitration of aromatic olefins, allyl compounds, and acrylic acid derivatives proceeds smoothly at room temperature with high regioselectivity and good yields. The advantages of this novel procedure compared to established nitration procedures are demonstrated.

Keywords: nitration; nitric oxide (NO); nitroolefins; olefins

Nitro-substituted compounds are of significant importance for the bulk and fine chemical industry as building blocks for polymers, dyes, but also for the synthesis of pharmaceuticals and agrochemicals.[1] Most often they serve as valuable intermediates for the corresponding amines and carbonyl compounds, however, even some naturally occurring bio-active nitro derivatives are known.[2] For some time, we have been interested in the development of new and improved methods for the formation of carbon-nitrogen bonds. In this respect catalytic hydroamination,[3,4] and hydroaminomethylation[5] of olefins and alkynes as well as environmentally friendly alkylation of alcohols and amines[6] have been of special interest to us.

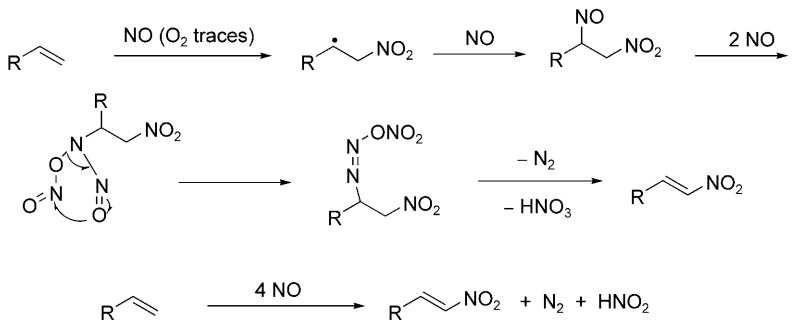
More recently, we became attracted by the possibility to form carbon-nitrogen bonds *via* nitration of olefins to form nitroolefins or nitroalkanes. The resulting products should be easily reduced to the corresponding amines (Scheme 1). Notably, such a reaction sequence offers a straightforward, atom-efficient access towards primary amines. Up to date a number of reagents such as $NaNO_2$,[7] $RONO_2$,[8] $C(NO_2)_4$,[9] $CeNH_4(NO_3)_4$,[10] N_2O_4,[11] NO_2,[12] and HNO_3[13] have been established for the nitration of olefins. However, most of these protocols produce at least stoichiometric amounts of waste and show little functional group tolerance. Surprisingly, direct nitrations with NO, which is an economic and easily available nitrogen source, have only been scarcely investigated.[14] Due to its biological action NO was termed sometime ago as "molecule of the year".[15] Nevertheless, up to date NO has attracted relatively little attention as nitration reagent.



Scheme 1. Envisoned synthesis of primary amines via nitration and hydrogenation.

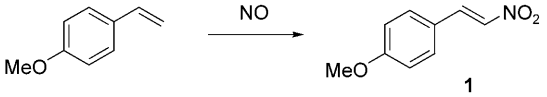
Formally, the nitration reaction constitutes a simple substitution of hydrogen by NO_2, however, in this oxidation process several radical reactions are known to be involved making the transformation more complicated.[16] In Scheme 2 the assumed mechanism is shown. The reaction is initiated by oxidation of NO to NO_2 with traces of oxygen present. NO_2 reacts with the olefinic double bond to form a carbon-centered radical. In this step the regioselectivity of the addition will be determined. Hence, the product with the most stable radical intermediate will be formed. Next, the radical is trapped by NO, which is further oxidized to the corresponding nitro derivative of a (nitrooxy)diazene. Subsequent elimination of nitrogen and HNO_3 leads to the nitroalkene. Once the process is initiated, NO_2 results from the reaction of NO with HNO_3.[17] The generation of N_2 and the formation of nitrous acid (HNO_2) and/or nitric acid (HNO_3) have been experimentally determined by chemical analysis of the products of the nitration reaction of olefins with NO.[14] The proposed equation of this reaction is shown in Scheme 2.

At the start of our investigation we studied the reaction of 4-methoxystyrene with NO as a model system for the nitration of olefins. Selected results of the preliminary screening of reaction conditions are shown in Table 1. In general, the reaction proceeds well already at a room temperature and low pressure (2 bar) of NO. Notably, the reaction is highly solvent-dependent, giving best results in 1,2-dichloroethane, THF and CCl_4 (Table 1, entries 3, 5 and 7). In these



Scheme 2. Proposed mechanism and full equation of the nitration of olefins with NO.

Table 1. Nitration of 4-methoxystyrene under different reaction conditions.[a]



1

Entry	Solvent	Pressure bar	Temp. [°C]	Additive	Time [h]	Conv.[b] [%]	Yield[b] [%]
1	CH_2Cl_2	2	22	–	3	57	52
2	1,2-dichloroethane	1	22	–	5	88	72
3	1,2-dichloroethane	2	22	–	3	97	92 (90)
4	1,2-dichloroethane	2	40	–	2	100	64
5	THF	2	22	–	3	95	92 (90)
6	EtOH	2	22	–	3	5	0
7	CCl_4	2	22	–	3	98	90
8	1,2-dichloroethane	2	22	HQ[c]	3	20	0
9	1,2-dichloroethane	2	22	TEMPO[c]	3	90	21
10	1,2-dichloroethane	2	22	N_2O[d]	3	64	63

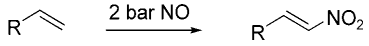
[a] *Reaction conditions:* 2.0 mmol 4-methoxystyrene in 20 mL of solvent.
[b] Conversion and yield determined by GC analysis with decane as internal standard; isolated yield is given in parenthesis.
[c] Concentration: 10 mol%.
[d] Partial pressure: 10 bar.

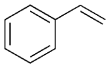
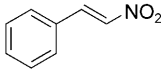
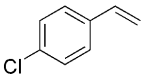
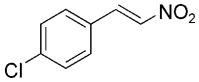
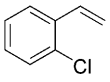
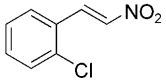
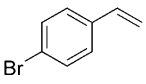
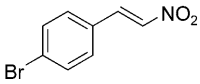
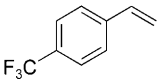
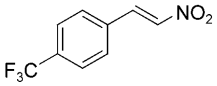
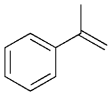
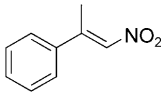
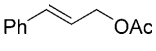
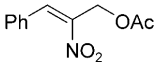
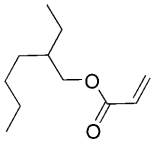
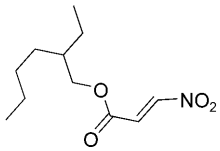
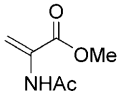
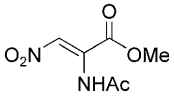
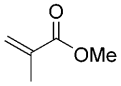
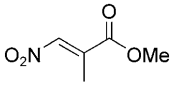
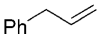
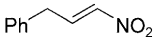
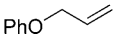
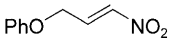
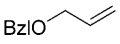
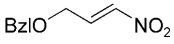
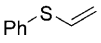
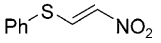
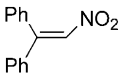
solvents, the reaction proceeds almost completely (conversion 95–98%) within 3 h at 2 bar NO and room temperature. Here, an excellent yield (90–92%) of the target product 1-methoxy-4-(2-nitrovinyl)-benzene (**1**) is obtained, which is formed as a mixture of *E/Z* isomers in a ~1:1-ratio. Increasing the temperature or lowering the pressure decreased the product yield significantly. Notably, in protic solvents, for example, EtOH, the reaction is strongly inhibited (Table 1, entry 6). Due to the increased stability of the benzyl radical, the nitration occurred fully regiospecific (>99%) giving the linear β-nitrostyrene. Under optimized conditions full conversion of the olefin and high chemoselectivity are achieved. In some reactions the addition product of water to the activated double bond (1-hydroxy-1-phenyl-2-nitroethane) could be obtained to a minor extent (<10% yield).

In order to verify the radical character of the reaction and also to improve of N-balance of the process, hydroquinone (HQ), TEMPO (2,2,6,6-tetramethylpiperidinyloxy), and N_2O have been added to different reactions (Table 1, entries 8–10). While HQ inhibited the nitration completely, in the presence of TEMPO the yield of the nitration product was much lower (21% instead 92%). Similarly, the addition of N_2O decreased the conversion of the starting material and the product yield.

Next, we were interested in the scope and limitations of our novel procedure with different olefins (Table 2). For this purpose, we studied the reaction of NO with various olefins at room temperature in either 1,2-dichloroethane or THF. Besides 4-methoxystyrene also styrene and other 2- and 4-substituted styrene derivatives gave the corresponding nitroolefins (**2**–**6**) in 52–90% yield (Table 2, entries 1–5). In addition, substituents in both the α- and β-positions of the double bond are well tolerated giving the β-nitrostyrene derivatives **7** and **8** in good yield (Table 2, entries 6 and 7). The reaction of 2-ethylhexyl acrylate led to the novel β-nitroacrylate **9** (Table 2, entry 8). Even the sensitive methyl 2-acetamidoacrylate react-

Table 2. Reaction of various olefins with NO.[a]

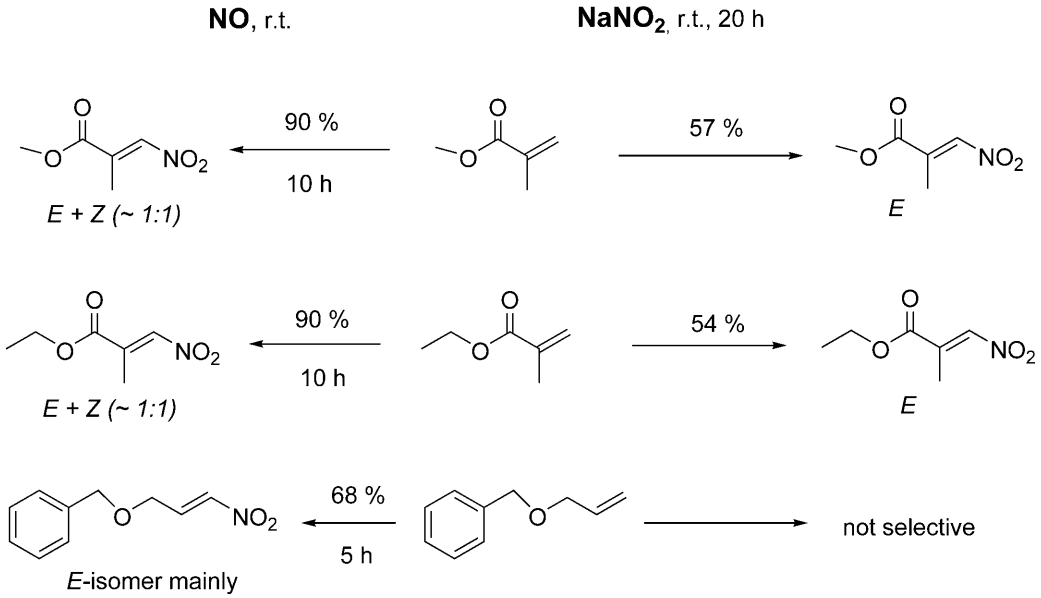


Entry	Olefin	Product	Time [h]	Conv.[b] [%]	Yield[c] [%]	*E/Z*
1			3	98	90	94:6
2			3	100	90	>99:1
3			4	92	57	92:8
4			4	90	83	94:6
5			20	95	52	>99:1
6			3	100	69	90:10
7			4	96	88	>99:1
8			17	82	30	>99:1
9			4	100	53	1:0.66
10			20	100	92	1:1
11			3	100	81	1:0.68
12			3.5	100	66	75:25
13			3.5	86	68	90:10
14			24	100	39	80:20
15			22	97	81	–

[a] *Reaction conditions:* 2.0 mmol olefin, in 20 mL 1,2-dichloroethane, at room temperature.
[b] Conversion was determined by GC analysis with decane as internal standard.
[c] Isolated yield is given.

ed to afford the 3-nitro-2-acetamidoacrylate **10** in acceptable yield (53%). To the best of our knowledge the latter reaction is the first example of the nitration of unsaturated α-amino acid derivatives. Methyl methacrylate led to the β-nitromethacylate **11** in high yield (92%; Table 2, entry 10). In addition, we did some reactions with allylic substrates, for example allylbenzene, allyl phenyl ether, and allyl benzyl ether. Again, the desired products are formed in high regioselectivity in 66–81% yields (Table 2, entries 11–13).

Moreover, phenyl vinyl sulfide and 1,1-diphenylethylene were reacted with NO (Table 2, entries 14 and 15). The resulting 1-nitro-2-thiophenylethylene is an interesting new building block which might be used for the otherwise difficult preparation of 1-thio-2-aminoalkanes.[18]



Scheme 3. Comparison of nitration of three olefins with NO and $NaNO_2$.

Finally, we compared the novel protocol with the most common nitration reaction applying $NaNO_2$ similar to a literature protocol.[19] Methyl and ethyl methacrylate as well as benzyl allyl ether were taken as olefinic starting materials. As shown in Scheme 3 in all cases the yield of nitro products was significantly improved by using NO as nitration reagent. However, in case of acrylates and methacrylates a mixture of *E/Z* isomers is obtained. On the other hand using benzyl allyl ether the selectivity is considerably improved applying NO.

In conclusion, we have developed a convenient protocol for the synthesis of various nitroolefins. Starting from easily available substrates a range of interesting building blocks are obtained selectively under mild conditions.

Experimental Section

General Procedure for the Nitration with NO

In an autoclave under an argon atmosphere the corresponding olefin (2 mmol) was dissolved in 1,2-dichloroethane (20 mL). Autoclave was filled with NO gas under pressure 2 bar, and the mixture was stirred at room temperature for the respective time (see Table 2). The solvent was removed under vacuum, and the crude product was purified by column chromatography (eluents: hexane/ethyl acetate in different ratio).

All the products (Table 1 and Table 2) have been identified by ^1H, ^{13}C NMR and mass spectrometry. The spectral data obtained for known compounds **1–8, 11–12, 14–16** are agreement with the data published in the literature.[20–32]

General Procedure for the Nitration with $NaNO_2$

A stirred solution of olefin in benzene (50 mmol in 10 mL) was treated with acetic acid:water (3:2, 20 mL) and the mixture was cooled to 0 °C. Sodium nitrite (5 g, 70 mmol) was gradually introduced over a period of 15 min. Then, the reaction mixture was stirred at room temperature for 20 h. The layers were separated, the organic layer was washed with water and dried under $MgSO_4$, and solvents were evaporated. The products were isolated after purification by column chromatography (silica gel 60, eluted by hexane/ethyl acetate 2:1).

(*E*)-2-Ethylhexyl 3-nitroacrylate (9): ^1H NMR ($CDCl_3$): $\delta = 0.75$–0.90 (m, 6H, 2 CH_3), 1.2–1.4 (m, 8H, 4 CH_2), 1.58 (m, 1H, CH), 4.11 (m, 2H, OCH_2), 7.02 (d, $J = 13.5$ Hz, 1H, =CHCO), 7.59 (d, $J = 13.5$ Hz, 1H, =$CHNO_2$); ^{13}C NMR ($CDCl_3$): $\delta = 10.9$, 14.0, 22.9, 23.7, 28.9, 30.3, 38.7, 68.8, 127.7, 148.9, 162.8; MS (70 eV, EI): *m/z* (%) = 129 (2.74), 112 (7.90), 90 (3.22), 84 (8.06), 83 (17.74), 71 (56.45), 70 (43.55), 69 (22.58), 62 (9.68), 57 (100), 56 (16.13), 55 (37.10), 43 (53.22), 41 (38.71).

(*E*)-Methyl 2-acetamido-3-nitroacrylate (10): ^1H NMR ($CDCl_3$): $\delta = 2.21$ (s, 3H, CH_3CO), 3.83 (s, 3H, CH_3O), 6.71 (s, 1H, =$CHNO_2$), 10.18 (s, 1H, NH); ^{13}C NMR ($CDCl_3$): $\delta = 23.7$, 53.9, 121.7, 137.8, 162.0, 168.1; MS (70 eV, EI): *m/z* (%) = 188 (M^+, 1.34), 157 (8.41), 146 (75.06), 130 (11.62), 116 (10.04), 114 (19.08), 87 (14.58), 43 (100); HR-MS (EI): *m/z* = 188.04908, calcd. for $C_6H_8N_2O_5$: 188.04277; yellow crystals, mp 81 °C.

(*E*)-(3-Nitroallyloxy)benzene (13): ^1H NMR ($CDCl_3$): $\delta =$ 4.83 (dd, $J = 1.5$, 2.9 Hz, 2H, CH_2), 6.96–7.14 (m, 3H, Arom.), 7.34–7.45 (m, 4H, arom + HC=CH); ^{13}C NMR ($CDCl_3$): $\delta = 63.7$, 114.6, 122.1, 129.8, 137.0, 140.2, 157.5; MS (70 eV, EI): *m/z* (%) = 179 (M^+, 0.73), 134 (9.61), 105 (57.70), 103 (12.63), 91 (5.29), 79 (14.75), 77 (80.83), 65 (6.57), 51 (25.84), 39 (11.59); HRMS (EI): *m/z* = 179.057506, calcd. for $C_9H_9NO_3$: 179.05769.

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