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Note

Catalyst-free and solventless Hantzsch ester mediated reduction of nitroolefins at elevated temperature

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A catalyst-free and solventless protocol for the reduction of nitroolefins to the corresponding nitroalkanes at 100°C has been developed. Various nitroalkenes have been reduced in good to excellent yield with short reaction times.

Keywords: Catalyst-free, solventless, nitroolefins, nitro-alkanes, Hantzsch ester

Organic synthesis under solvent free conditions is imperative to develop benign chemical technologies. Among various alternatives such as use of water, ionic liquid, supercritical and liquid carbon dioxide, polyethylene and polypropylene glycol, the most convenient one is without using any solvent, so called 'solventless reaction'[1]. Catalyst free reactions also lead to new environmentally benign methodologies that save scarce resources. Solvent-free and catalyst free reactions possess additional advantages over conventional reactions as they not only reduce the load of effluents, but also eliminate the detrimental consequences that are inherited with them.

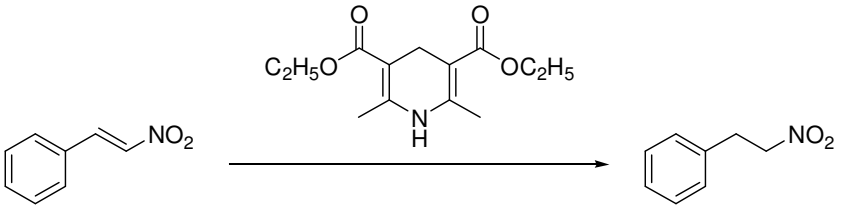
On the other hand, selective reduction of nitroolefinic double bond in preference to nitro group is of great interest due to the potential value of corresponding nitroalkanes as they can be converted into a diverse range of compounds of biological and industrial interest through the transformation of nitro functionality into carbonyl[2], amino[3], oxime[4] and substitution with hydrogen[5]. The reduction of unsaturated double bond in nitroalkenes was efficiently carried out by various reducing agents such as borohydride, metal hydride as well as metal halides[6]. These methods have the inherent limitation of employing toxic metals and metal ions. Another problem that is associated with these methods is of selectivity, as the reduction of nitro group simultaneously takes place along with the olefinic bond and in some cases polymerization has been reported to occur.

The natural electron transfer processes are mediated by various oxidoreductase enzymes[7]. These enzymes are often associated with cofactors like flavin adenine dinucleotide ($FADH_2$) and dihydropyridine based nucleotides such as nicotinamide adenine dinucleotide (NADH) for *in vivo* reduction processes[8]. These co-factors have been the motivating factor for the development of synthetic NADH models which have been used as reducing agents in organic synthesis. Hantzsch esters are the most widely studied biomimetic reducing agent due to their low cost and high stability. Recently, they have been used for asymmetric reduction as well as reductive amination in the reactions catalyzed by organocatalysts[9]. Hantzsch ester has been employed for reduction of nitroolefins in the presence of strong acids in toxic organic solvents[10]. In 2007, Zhang and Schreiner reported the organocatalytic biomimetic reduction of nitroolefins mediated by Hantzsch ester using thiourea as catalyst under reflux condition in dichloromethane[11]. The reported methods are often associated with harmful solvents, longer reaction duration, low yield of the product and the use of acidic catalysts that are difficult to remove from the reaction mixture, anhydrous reaction conditions and inert atmosphere. To eliminate these limitations and keeping in mind the environmental concern, Hantzsch ester mediated nitroolefin reduction in the absence of any catalyst and solvent has now been developed.

Results and Discussion

Initially, the reduction of *trans* β-nitrostyrene was performed with 1.1 equivalent of Hantzsch ester at 100°C without any solvent. The authors were delighted to find that the desired nitroalkane was formed with 98% conversion of nitrostyrene in 1.5 hr (**Table I,** entry 1). Using water as solvent no improvement in the reaction rate was observed (**Table I**, entry 2), while performing the reaction under refluxing condition in protic solvents resulted in 86% conversion (**Table I**, entry 4 and 5). Under neat conditions at 80°C 92% nitrostyrene was converted into the desired product after 3.5 hr (**Table I**, entry 7).

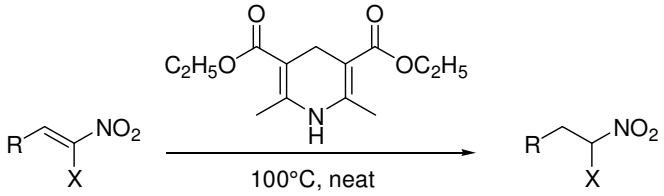
Table I — Reduction of *trans* β-nitrostyrene with Hantzsch ester under different conditions[a]

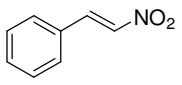
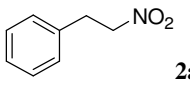
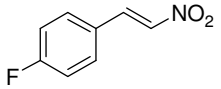
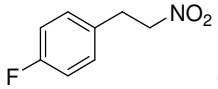
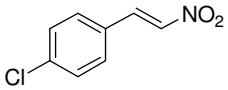
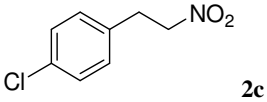
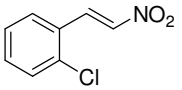
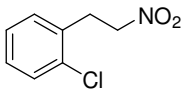
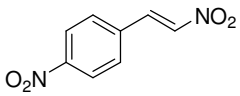
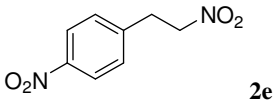
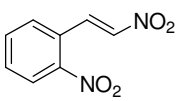
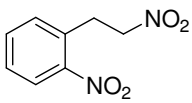
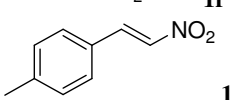
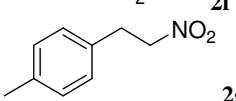


Entry	Solvent	Temp (°C)	Time (hr)	Conversion (%)[b]
1	-	100	1.5	98
2	Water	100	1.5	98
3	Water	80	3.5	93
4	MeOH	Reflux	3.5	85
5	EtOH	Reflux	3.5	86
6	EtOH	RT	24	15
7	-	80	3.5	92

[a]Reaction conditions: 1 mmole nitroalkenes and 1.1 mmole Hantzsch ester. [b]Conversion determined by gas chromatography of crude sample.

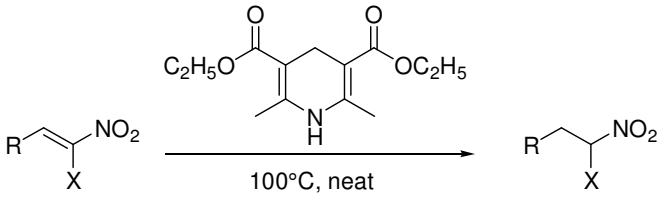
Table II — Reduction of different nitro-olefins at 100°C by Hantzsch ester[a] —*Contd*

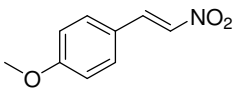
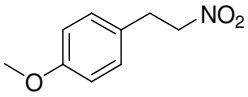
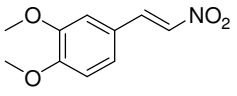
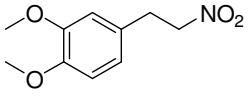
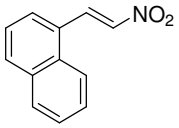
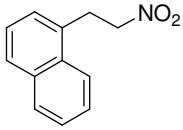
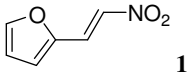
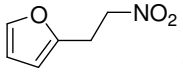
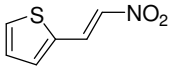
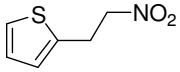
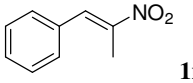
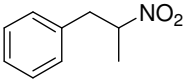
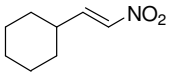
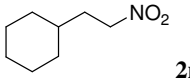
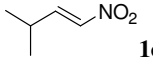
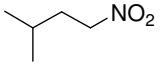


Entry	Nitroalkenes	Product	Time (hr)	Yield (%)[b]
1	 **1a**	 **2a**	2	96 (100)[c]
2	 **1b**	 **2b**	1.5	95
3	 **1c**	 **2c**	1.5	96
4	 **1d**	 **2d**	1	94
5	 **1e**	 **2e**	1	97
6	 **1f**	 **2f**	0.5	96
7	 **1g**	 **2g**	4	85

—*Contd*

Table II — Reduction of different nitro-olefins at 100°C by Hantzsch ester[a] —*Contd*



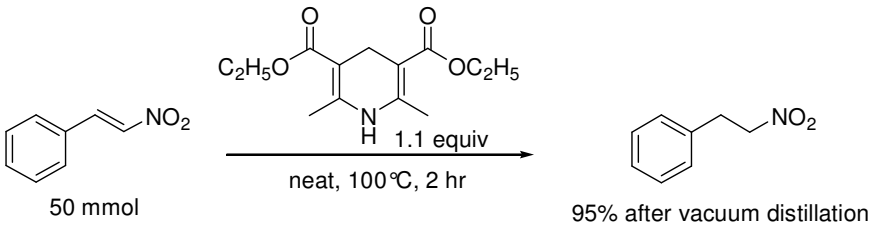
Entry	Nitroalkenes	Product	Time (hr)	Yield (%)[b]
8	 **1h**	 **2h**	5	87
9	 **1i**	 **2i**	24	78
10	 **1j**	 **2j**	2	93
11	 **1k**	 **2k**	3	79
12	 **1l**	 **2l**	3	83
13	 **1m**	 **2m**	12	84
14	 **1n**	 **2n**	12	90
15	 **1o**	 **2o**	5	89

[a]Reaction conditions: 1 mmol nitroalkenes and 1.1 mmol Hantzsch ester at 100°C. [b]yield refers to the isolated yield after column chromatography. [c]Yield on the basis of conversion.

The progress of reaction was found to be very slow at RT when performed in ethanol (**Table I**, entry 6).

The different nitroolefins were screened using 1.1 equivalent of Hantzsch ester as reducing agent at 100°C under neat conditions[12]. The *trans* β-nitrostyrene was reduced to the corresponding nitroalkane in 96% yield in 2 hr with 100% conversion (**Table II**, entry 1). It was found that the reaction rate was dependent on the substituents on the phenyl ring of the nitrostyrene. The nitroalkenes bearing electron-withdrawing groups on the phenyl ring such as fluoro, chloro and nitro reacted faster in comparison to *trans* β-nitrostyrene (**Table II**, entry 2-6). With electron releasing groups such as methyl and methoxy the reaction rate was comparably low (**Table II**, entry 7-9). The nitroolefin derived from 1-naphthaldehyde also reacts in 2 hr with high yield of the product (**Table II**, entry 10). When hetero-aromatic nitroalkenes such as 2-(2-nitrovinyl)furan and 2-(2-nitrovinyl)thiophene were employed, the target product was obtained in acceptable yield under the same reaction conditions (**Table II**, entry 11 and 12). The nitroalkene substituted with methyl group at β-position was also reduced with good yield in 12 hr (**Table II**, entry 13). Also, the nitroalkenes derived from alicyclic and aliphatic aldehydes were efficiently reduced under these reaction conditions (**Table II,** entry 14 and 15).

To demonstrate preparative utility, the reaction was performed at gram scale using 50 mmol of *trans* β-



Scheme I — Gram scale reduction of *trans* β-nitrostyrene mediated by Hantzsch ester

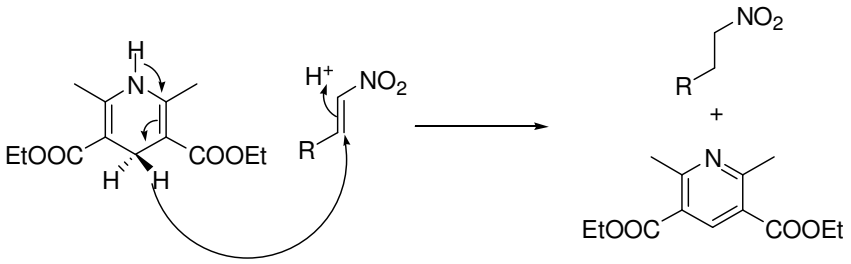
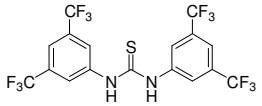


Figure 1 — Proposed mechanism

Table III — Comparison of the present methodology with previously reported methods for reduction of *trans*-β nitrostyrene

Entry	Catalyst	Solvent	Temp (°C)	Time (hr)	Yield (%)[a]
1	-	-	100	2	96 (100)[b]
2 (Ref 10a)	Silica gel	Benzene	60	20	96 (100)[b]
3 (Ref 10b & 10d)	Silica gel	Benzene	Reflux	5	84
4 (Ref 10c)	AcOH	Benzene	80	15	- (100)[b]
5 (Ref 11)		Dichloromethane	Reflux	20	89

[a]Yield refers to the isolated yield. [b]Yield determined on the basis of conversion.

nitrostyrene and 1.1 equivalent of Hantzsch ester. The product was isolated by vacuum distillation after 2 hr in 95% yield (**Scheme I**).

The mechanism of reduction of nitroolefins may be visualized as involving one step hydride transfer from Hantzsch ester to the β-carbon of nitroolefin as illustrated in **Figure 1**. Similar mechanism has also been reported with supporting evidence in the reduction of aldehydes, ketones and activated double bonds[12].

A comparison of the present methodology with the methods known in literature for the reduction of *trans* β-nitrostyrene with Hantzsch ester shows that the present method (**Table III**, entry 1) is faster and environmentally benign. The *trans* β-nitrostyrene undergoes reduction efficiently in less time with higher yield without use of either acidic catalysts or harmful organic solvents.

Experimental Section

Typical Procedure: To a preheated 10 mL round bottom flask 1 mmole of nitroolefin and 1.1 mmole of Hantzsch ester were added. The reaction mixture was stirred at 100°C and progress of the reaction was monitored with TLC/GC [Varian WCOT fused silica 30 M × 0.32 mm CP SIL SCB DF = 0.25 µm column; column oven = 90°C; FID 270°C; injector 250°C; T_r = 15.50 min (product); T_r = 17.29 min (nitrostyrene)] until the nitroolefin was consumed. After completion of the reaction the product was purified by vacuum distillation or column chromatography.

1-(2-Nitroethyl)benzene[11], **2a**. Yield 96%; oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.29 (t, *J* = 7.5 Hz, 2H, CH_2), 4.56 (t, *J* = 7.5 Hz, 2H, CH_2), 6.15-7.33 (m, 5H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 33.4, 76.3, 127.4, 128.6, 129.2, 135.7.

1-Fluoro-4-(2-nitroethyl)benzene, **2b**. Yield 95%; oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.27 (t, *J* = 7.2 Hz, 2H, CH_2), 4.51-4.66 (m, 2H, CH_2), 6.93-7.14 (m, 2H, ArH), 7.15-7.25 (m, 2H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 32.4, 76.2, 115.6, 115.9, 130.0, 130.1, 131.4, 160.4, 163.6.

1-Chloro-4-(2-nitroethyl)benzene[13], **2c**. Yield 96%; oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.29 (t, *J* = 7.2 Hz, 2H, CH_2), 4.57-4.64(m, 2H, CH_2), 7.12-7.16 (m, 2H, ArH), 7.27-7.30 (m, 2H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 32.7, 75.9 129.1, 129.9, 133.4, 134.1.

1-Chloro-2-(2-nitroethyl)benzene[14], **2d**. Yield 94%; oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.44 (t, *J* = 7.5 Hz, 2H, CH_2), 3.63 (t, *J* = 7.2 Hz, 2H, CH_2), 7.18-7.26 (m, 3H, ArH) 7.35-7.41 (m, 1H ArH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 33.3. 77.1, 127.3, 129.0, 12.8, 131.0, 133.3, 133.9.

1-Nitro-4-(2-nitroethyl)benzene[13], **2e**. Yield, 97%; oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.44 (t, *J* = 7.5 Hz, 2H, CH_2), 4.67-4.76 (m, 2H, CH_2), 7.41 (d, *J* = 8.7 Hz, 2H, ArH), 8.18 (d, *J* = 8.7 Hz, 2H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 32.8, 75.2, 124.1, 129.5, 143.2, 147.3.

1-Nitro-2-(2-nitroethyl)benzene[15], **2f**. Yield 96%; oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.61 (t, *J* = 6.9 Hz, 2H, CH_2), 4.75-4.80 (m, 2H, CH_2), 7.38-7.41 (m, 1H, ArH), 7.45-7.51 (m, 1H, ArH), 7.57 -7.63 (m, 1H, ArH), 8.06-8.09 (m, 1H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 31.5, 75.2, 123.1, 125.5, 128.9, 131.2, 132.8, 133.9.

1-Methyl-4-(2-nitroethyl)benzene[11], **2g**. Yield, 85%; oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.32 (s, 1H, CH_3), 3.27 (t, *J* = 7.5 Hz, 2H, CH_2), 4.55-4.60 (m, 2H, CH_2), 7.07-7.24 (m, 4H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.0, 33.1, 77.4, 128.4, 129.6, 132.5, 137.1.

1-Methoxy-4-(2-nitroethyl)benzene[11], **2h**. Yield 87%; oil; ^{1}H NMR (300 MHz $CDCl_3$): δ 3.26 (t, *J* = 7.5 Hz, 2H, CH_2), 3.79 (s, 1H, CH_3), 4.54-4.59 (m, 2H, CH_2), 6.83-6.88(m, 2H, ArH), 7.10-7.26 (m, 2H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 32.7, 55.2, 77.4, 114.3, 127.4, 129.6, 158.9.

1,2-Dimethoxy-4-(2-nitroethyl)benzene[13], **2i**. Yield 78%; oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.26 (t, *J* = 7.5 Hz, 2H, CH_2), 3.87 (s, 2 × CH_3), 4.56-4.61 (m, 2H, CH_2), 6.70-6.83 (m, 3H, ArH), 7.10-7.26 (m, 2H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 32.7, 55.2, 77.4, 114.3, 127.4, 129.6, 158.9.

1-(2-Nitroethyl)naphthalene[13], **2j**. Yield 93%; oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.43 (t, *J* = 7.5 Hz, 2H, CH_2), 4.56-4.61 (m, 2H, CH_2), 6.70-6.83 (m, 3H, ArH), 7.10-7.26 (m, 2H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 32.7, 55.2, 77.4, 114.3, 127.4, 129.6, 158.9.

2-(2-Nitroethyl)furan[11], **2k**. Yield 79%; oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.42-3.51 (m, 2H, CH_2), 4.50-4.61 (m, 2H, CH_2), 6.78-6.90 (m, 2H, 2 × CH), 7.09-7.19 (m, 1H, CH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 26.0, 73.4, 107.4, 110.1, 143.8, 149.4.

2-(2-Nitroethyl)thiophene[13], **2l**. Yield 83%; oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.48-3.55 (m, 2H, CH_2), 4.56-4.66 (m, 2H, CH_2), 6.87-6.95 (m, 2H, 2 × CH), 7.15-7.25 (m, 1H, CH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 27.4, 75.9, 124.8, 126.2, 127.2, 137.3.

1-(2-Nitropropyl)benzene[13], **2m**. Yield 84%; oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.55 (d, *J* = 5.7 Hz, 3H, CH_3) 2.96-3.03 (m, 1H, CH_2), 3.45-3.27 (m, 1H, CH_2), 4.71-4.83 (m, 1H, CH), 7.12-7.33 (m, 4H, ArH), 7.39-7.44 (m, 1H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 18.7, 41.1, 84.4, 127.3, 128.8, 129.9, 133.5, 135.5.

(2-Nitroethyl)cyclohexane[11], **2n**. Yield 90%; oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.89-1.01 (m, 2H), 1.09-1.39 (m, 4H), 1.65-1.79 (m, 5H), 1.84-1.94 (m, 2H, CH_2), 4.38 (t, *J* = 7.5 Hz, 2H, CH_2); ^{13}C NMR (75 MHz, $CDCl_3$): δ 25.9, 26.2, 32.7, 34.6, 34.9, 73.8.

3-Methyl-1-nitrobutane[11], **2o**. Yield 89%; oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.89 (d, *J* = 6.6 Hz, 6H, 2 × CH_3), 1.18-1.66 (m, 1H, CH), 1.85 (q, *J* = 7.2 Hz, 2H, CH_2), 4.34 (t, *J* = 7.5 Hz, 2H, CH_2); ^{13}C NMR (75 MHz, $CDCl_3$): δ 22.0, 25.6, 36.0, 74.3.

Conclusion

In conclusion, an improved protocol for the Hantzsch ester mediated reduction of nitro-olefins to the corresponding nitroalkanes in higher yields and shorter reaction time under solventless condition without using any catalyst has been developed. The method is quite general with respect to the nitroolefins as the different nitroolefins such as aromatic, heteroaromatic as well as aliphatic nitroalkenes are reduced efficiently under these reaction conditions. The reaction can be performed on a large scale without the loss of reactivity and the product can be purified without using column chromatography.

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