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A Green and Effective Approach of Two-step's 2,2',4,4',6,6'-Hexanitrostilbene Preparation and Its Industrial Scale Study

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ABSTRACT: An environmental friendly approach for two-step synthesis of hexanitrostilbene (HNS) has been studied here. In the first step from trinitrotoluene (TNT) to hexanitrobienzyl (HNBB), commercial NaClO was employed as oxidant in mixed solvent of ethyl acetate/ethanol (0.25mL/1.25mL per mmol of TNT) instead of benzene/ethanol. In the second step from HNBB to HNS, 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO)/FeCl₂ was used as an effective catalytic system with O₂ in DMSO solvent. A complex of metal ion and O₂ [M(n+1)OO⁻] was supposed to be the active agent, and TEMPO itself was difficult to initiate dehydrogenation of HNBB but could promote the catalytic cycle of complex M(n+1)OO⁻. Finally, we increased the scale from 30 g to 1000 g to investigate the feasibility of production. The total yield of two steps would be unprecedentedly as high as 70%.

KEYWORDS: hexanitrostilbene, oxidation, dehydrogenation, TEMPO/FeCl₂, scale-up

1. Introduction

2,2',4,4',6,6'-Hexanitrostilbene (HNS) is an excellent explosive known for its steady detonation performance under extreme conditions such as high pressure and wide temperature range (-193 °C to 280 °C).^{1,2} It has been applied in not only deep petroleum well perforating, aeronautic and astronautic areas but also heat-shock resistance systems in military ordnance. ^{3,4}

The synthetic route of HNS available for industrial process was firstly disclosed by Shipp and Kaplan^{5,6} as shown in Scheme 1. In tetrahydrofuran/methanol mixed solvent, 2,4,6trinitrobenzene was halogenated into trinitrobenzyl chloride (TNBCl), after which hexanitrobienzyl (HNBB) was generated through coupling followed by the final formation of HNS through dehydrogenation. Though this was a one-pot reaction, only 35-40% of yield was obtained. Moreover, the purity was about 90-95% and recrystallization was usually required to obtain product of high quality. Several modified approaches have been found in literatures and the yields were increased to about 50% with oxidative metal salts as catalysts. Considering that the dehydrogenation of HNBB was inefficient in Shipp's method, Kompothy⁷ separated the process into two steps and HNBB was dehydrogenated under another oxidative condition. In this case, about 60% and 80% yield could be achieved for HNBB in the first and second step, respectively. Later, with bromine as the dehydrogenating agent for benzyl, Lu improved the yield of second step up to 95%.⁸ The "two steps" method significantly improved the total yield to 55~60% with high purified HNS and thus had been industrialized in China.⁹ However, environmental issues relating to dangerous agents Br₂ and toxic solvents benzene/pyridine were also brought about. To solve this problem, an alternative method

 employing N-Hydroxyphthalimide (NHPI)/FeCl₂ as catalyst was investigated in our recent works to assist the dehydrogenation of HNBB to HNS, which was proved to be a better choice compared with the previous methods.^{10,11}

< Insert Scheme 1 here>

Based on that work, herein we reported a more environmental friendly and industrial applicable method. Oxygen gas was employed as green oxidant instead of high hazard bromine in the HNS preparation step with the help of 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO). Benzene and pyridine solvents of high toxicity were also replaced by ethyl acetate (EA) and dimethyl sulfoxide (DMSO). This procedure was further enlarged to middle-size, and several factors in scale-up were investigated with the purpose of obtaining an industrial available process scheme.

2. Experimental section

Step 1 Synthesis of HNBB: TNT (30/100/1000g) was added into the mixed solvent of ethyl acetate ($0.25mL/mmol \ of \ TNT$) and ethanol ($1.25mL/mmol \ TNT$). The system was kept in 50 °C for 60 min, followed by the addition of NaClO solution (effective Chlorine content of 5% and pH value of 13.45, n(NaClO): n(TNT) = 0.53: 1) within 1 min. Intermediate HNBB was collected by filtration and dried under vacuum.

Step 2 Synthesis of HNS: A 10 L reaction pot containing HNBB (40/100/1000 g), TEMPO, $FeCl_2 \cdot 7H_2O$ of certain amount and DMSO was kept under a constant temperature of 55 °C under stirring. Oxygen was inputted into the bottom of the solution.

After 10 h, crude product was obtained through filtration, washed four times with acetone and dried over 50 °C.

Step 3 Recycle of catalyst and solvent: (1) The filtrate in step 2 was poured into the reaction vessel, followed by the replenish of HNBB and recharge of DMSO, $FeCl_2 \cdot 4H_2O$, TEMPO respectively. The reaction was allowed to proceed at 55 °C under stirring. Oxygen was inputted into the bottom of the solution. After 10 h, crude product was obtained through filtration, washed fourth with acetone and dried under 50 °C. (2) Repeat (1) for 3 to 4 times.

3. Results and Discussion

3.1 Preparation of HNBB

3.1.1 Solvent effect

Presently, utilization of NaClO aqueous solution as oxidant was a good choice in the green preparation process for HNBB. The problem that still existed is to improve the solubility of TNT in aqueous system, so the option of co-solvent would directly affect the efficiency of NaClO and yield of oxidation process. Shipp developed a THF/methanol system with THF as co-solvent. The addition of methanol was to form a better homogeneous system, as reported by Shipp ⁶ and Burlinson ¹². If water was used together with THF instead of methanol, however, no products could be obtained. So methanol was supposed to participate in the reaction actually. Several solvent-co-solvent systems ¹³ were tested for the synthesis of HNBB as shown in Figure 1. With dielectric constant

used as the index of polarity, the relationship between polarity and yields were demonstrated.

< Insert Figure 1 here>

In terms of alcohol solvent, the yield of HNBB increased with the polarity. Bernasconi¹⁴ and Fyfe¹⁵ reported that TNT would form salt with alcohol (conjugate base of alcohol) under alkaline conditions generating Meisenheimer complex ^{16,17}. After which, TNT could react with NaClO to generate TNBCl and finally HNBB was formed, as shown in Figure 2. The higher polarity the alcohol, the stronger alkaline the salt was, which was beneficial for the formation of Meisenheimer complex. This mechanism could be confirmed to be reliable by analyzing the relationship between pH value of solution and yield of HNBB. As can be seen in Figure 3a, with different EA/EtOH ratios, highest yield of HNBB also tended to be different. Moreover, in our reaction condition with decreased EtOH ratio, high pH was required to obtain the best yield. In other words, when the alcohol concentration was low, stronger alkaline condition would be helpful to generate the RCH₂O⁻ intermediate ^{18,19}. The process agreed with the mechanism we mentioned above. This phenomenon was different from the one step reaction in which too strong alkaline condition would reduce the reactivity and was not suggested. In a word, alcohol not only played a role of solvent but also participated in the reaction.

< Insert Figure 2 here>

On the other hand, the choice of co-solvent gave the opposite case. Generally, cosolvent of high polarity was unfavorable for the generation of HNBB, as in polar solvents side reactions were easy to take place. ²⁰ In solvents of low polarity, side reactions were

significantly hindered, leading to high yield of HNBB. If solvents of too low dielectric constant were used, however, reactions would be difficult to proceed due to the poor solubility of TNT. So the ideal co-solvent was found to be ethyl acetate/ethanol (1:2), which owns a dielectric constant that close to but slightly higher than TNT to achieve good solubility and reduce side reactions at the same time.

3.1.2 The effect of pH

As analyzed in section 1.1, pH is an important factor that affects the reaction. The reason lies in two aspects: 1) the formation of Meisenheimer complex; 2) the improved stability of NaClO as well as activity. As shown in Figure 3b, the reaction went on slowly under relatively low alkaline condition, which could be ascribed to low RCH_2O^{-1} concentration. Under high alkaline condition, TNT structure might be disrupted and NaClO activity was decreased obviously.^{21,22} In addition, different pH was required with different co-solvents. The optimized pH value was relatively low with co-solvents of high polarity. It was conjectured that co-solvents of high polarity gave better water-solubility, which promoted the reaction between OH⁻ in NaClO and TNT, so relatively low pH was required. As shown in Figure 2, TNBCl was an important intermediate in the oxidation process. This intermediate could be obtained only in THF solvent by adding HCl (TNT:HCl = 3:1) to stop the reaction.¹⁸ In Figure 3b, highest yield of curve a and curve b was obtained with completely the same pH value. The fact indicated that the pH mainly participate in the first half of reaction mechanism in Figure 2 and affect the formation of TNBC1.

< Insert Figure 3 here>

3.2 Preparation of HNS

The HNS preparation step was much more hazardous than that for HNBB because of the employment of high toxic oxidant bromine in industry. 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO) is commonly used as a radical catalyst for oxidation reactions due to its high efficiency and selectivity. But their application in dehydrogenation was seldom reported. In this work, HNS was prepared through aerobic dehydrogenation of HNBB in a TEMPO/metal salts system.

3.2.1 The influence of Solvent

Due to the importance of solvents, ²³ different solvents were tried and the results were listed in Table 1 for comparison. Almost no product was obtained in ethyl acetate or benzene as HNBB could not be dissolved. Acetonitrile was not applicable for the dehydrogenation of HNBB either, though it was usually used as solvent for oxidation of alcohols catalyzed by TEMPO.²⁴ The volatile acetone could not give a satisfactory result either due to its low boiling point. When amides (DMF and hexamethylphosphoramide) or amine (cyclohexylamine) were used as solvents, a great quantity of by-products was detected in HPLC with red viscous solid generated during experimental process. ^{25,26} So after screening, DMSO was determined as the best solvent for dehydrogenation of HNBB. The reasons were twofold. Firstly, DMSO could dissolve the substrate and catalyst completely; and more importantly, bonding was achieved through sulfur or oxygen atom with metal salts, which increased the activity of metal catalyst so as to accelerate the reaction. ^{27,28} To further confirm this conclusion, sulfolane was used instead of DMSO, giving almost no product.

< Insert Table 1 here>

Moreover, the influence of volume of DMSO was studied in detail. At least 5 mL of DMSO was required to dissolve the substrate. The yield of HNS increased with further addition of DMSO and a maximum yield was observed when 15 mL of DMSO was used. The reaction efficiency would drop down if the amount of DMSO further increased. To analyze the reason, crude products with DMSO of 10 mL and 25 mL were collected and applied to HPLC. It was found that the contents of TNT in these two situations were of 0.01% and 40% respectively. So it was suggested that excessive solvent hindered the contact between substrate and catalyst thus reduced the possibility of reaction.

3.2.2 Evaluation of different catalytic system

Based on the combination forms of various catalysts shown in Table 2, dehydrogenation process of HNBB was the result of both nitroxide radical and metal ions. Some conclusions could be found:

1) Without nitroxide radical catalyst, no products or only poor yield of 10% could be obtained with most metal salts under oxygen gas, except $Pt^{2+} Cu^+$ and Fe^{2+} . The addition of TEMPO could increase the yield to about 20%.

2) When alkali metal or transition metal ions with no multi-valance and low oxidation capacity (K^+ , Mg^{2+} and Zn^{2+} , entry 2 to 4) was used together with TEMPO, the yield remains 20%. It showed that these metal ions had little effect on the dehydrogenation of HNBB.

3) Entry 5 and 6 showed that some metal ions like Pb^{2+} and Mn^{2+} could abstract the secondary hydrogen -CH₂- of HNBB, but they were difficult to be oxidized by nitroxide radical catalyst, so the yield with or without TEMPO was similar or just increased a little.

4) Metal ions with multi-valance but not strong oxidation capacity (Cr^{3+} , Co^{2+} , Ni^{2+} , Cu^{+} and Fe^{2+} , entry 7 to 11) exhibited catalytic performance together with TEMPO. Comparing the performance with and without Cr^{3+} , Co^{2+} and Ni^{2+} , yields increased from trace to 30~40%. It meant that Cr^{3+} , Co^{2+} and Ni^{2+} could not be oxidized by oxygen directly and TEMPO was essential in this process. While for Cu^{+} and Fe^{2+} , they could be oxidized by oxygen even though their catalytic efficiency was low, and the addition of TEMPO could significantly improve the efficiency.

5) If another nitroxide radical catalyst NHPI was used instead of TEMPO (entry 11 and 12), the catalytic efficiency decreased slightly with conversion still remained over 60%. The different catalytic activity was supposed to be the reason for different catalytic performance.

6) As for ions of high valance such as Fe^{3+} and Cu^{2+} (entry 13 and 14), however, almost no catalytic performance was exhibited. The results suggested that it was their oxides in the form of M(III)OO- that participated in the reaction instead of metal ion themselves. The conclusion was further confirmed by the experimental results with N₂ replacing O₂ as shown in Figure 4.

< Insert Table 2 here>

The details of experiment in Figure 4 were designed according to the catalytic mechanism study about TEMPO²⁹⁻³² and results were shown as follow:

1) TEMPO was used as the oxidizing agent under N_2 gas, and three situations with no (R1), catalytic amount (R2) and 1 equivalent amount (R3) of FeCl₂ were tested. In all cases, only 10% yield of HNS could be obtained. The results showed that O_2 was the oxidizing agent and source of O through the whole reaction.

2) The dehydrogenation ability of TEMPO itself was limited in either N_2 or O_2 atmosphere (R1 and R5), while Fe²⁺ in N_2 or O_2 gas (R4 and R6) exhibited significantly different performance. Combining 1) and 2), TEMPO was not the catalytic agent that directly reacted with HNBB.

3) In R3, without O_2 , TEMPO/Fe²⁺ (or accurately Fe³⁺ formed) could not catalyzed the reaction even equivalent amount of catalyst was added. It agreed with the result and conclusions mentioned in Table 2 for entry 12 and 13. Fe³⁺ was also not the catalytic agent in dehydrogenation.

4) The most possible mechanism was described in Figure 5. Fe^{2+} was first oxidized into Fe(III)OO- by O₂³³, followed by the interaction with HNBB to generate HNS through dehydrogenation. During this process, Fe(III)OO- was reduced into Fe(II)OOH, which would be activated again into Fe(III)OO- by TEMPO. The role of O₂ was to oxidize TEMPOH to obtain TEMPO as active nitroxide radical.

< Insert Figure 4 and 5 here>

3.3 Enlargement and recycle of catalyst and solvent

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The main procedures for kilogram-leveled scaling up were shown in Scheme 2. Several points could be generalized and shown as follows:

1) Stirred batch reactor was employed in both steps. In the first step, due to the high reaction rate and short reaction time, kenics static mixer was reported to be a good choice and 40% HNS could be generated directly in this step. ^{34,35} Its advantage was continuous flow and well mixed, however, low yield of HNS and difficulty and high cost in kg- or ton-size scale-up limited its industrial application.

2) In the second step, pipe was used to introduce O_2 into reaction solution. As the dehydrogenation rate of HNBB was slow, the diffusion rate of O_2 gas in solution was faster than the reaction rate with the help of stirring, so there was no particular requirement for gas dispersity.

3) All the solvent could be recovered by distillation, which would be discussed in detail in the following part, and the residues were to be burned directly.

< Insert Scheme 2 here>

To provide reliable variation trend for larger scale production, two key points should be considered during this process: mass-transfer effect and the recovery of solvent containing catalyst.

3.3.1 The test of mass-transfer effect

During the scale up experiments of four magnitudes of 30, 100, 500 and 1000 grams as shown in Table 3 to 6, no obvious heating-up was found when HNBB and HNS were

feeding, which suggested that thermal effect was relatively weak during the mixing period. Besides, there was neither sudden cold nor fever observed during the reaction process, so the two-step reaction is not violently exothermic or endothermic. Due to the fast reaction rate for HNBB generation, ³⁶ scaling up process would be influenced obviously by diffusion effect. Extending reaction time was needed to obtain the same yield. In contrast, the reaction rate was much lower for HNS and 10 hours were required to complete the reaction. So it was almost free from the influence of diffusion effect.

3.3.2 The recovery of solvent containing catalyst

Ethyl acetate and alcohol were used as solvents for the synthesis of HNBB. More than 95% solvents could be recovered through distillation and reused without further treatment. During the distillation process, small amount of water was also recovered together as azeotrope. The water had little effect on the yield after a comparative test with dehydrated solvent.

The solvent DMSO used for the preparation of HNS could not be distillated containing the catalyst. So direct recycling was tried firstly. As shown in Table 6, the total yield after 5 times' recycling was over 85.9% while it decreased to lower than 85% for the sixth recycling, and the declining rate was growing. After analyzing of the solvent reused for several times through HPLC, dozens of compounds were identified which may originated from impurities in substrates and accumulation of by-products during the recycling process. Considering the purity of product and rational use of raw materials, recycling for 5 times gave the best result. At this point, the recovery rate of DMSO was approximately 80%.

An interesting phenomenon was observed that, after direct recycling of DMSO solvent containing catalyst, the yield of HNS was much higher than 68% (Table 1 entry 10). It was because the product HNS was partly dissolvable in DMSO. In the first cycle some of the HNS product would stay in the DMSO solvent and form a saturated solution, which showed a relative "low" yield. This saturated solution of HNS, which was reused directly in later cycles, would dissolve no more HNS, and thus gave a real and high yield.

During the 5 times' recycling, small amount of TEMPO and FeCl₂ would be washed away or lost their catalytic activity. If they were not supplemented after each recycling, the yield would deceased much more quickly, and less than 60% yield were obtained in this situation (in Table $s_1 \sim s_4$ in supporting information).

< Insert Table 3,4,5 and 6 here>

4. Conclusion

In this paper, we reported a green approach for two-step synthesis of hexanitrostilbene (HNS) and extended it by using a larger mixer, enabling the scale to be increased from 30 g to 1000 g of trinitrotoluene (TNT). In the intermediate hexanitrobienzyl (HNBB) preparation step, mixed solvent ethyl acetate/ethanol (0.25mL/1.25mL per mmol of TNT) was used instead of more expensive and toxic solvents THF/ethanol or benzene/ethanol with pH controlled commercial NaClO as oxidant, giving the optimized yield over 80%. Further investigation showed that polarity of mixed solvent and pH were two main factors affecting the yield.

In HNS preparation step, an effective catalytic system 2,2,6,6-tetramethylpiperidine-1oxyl (TEMPO)/FeCl₂ was used with oxygen in DMSO solvent. A complex of metal ion and O_2 , donated as M(n+1)OO·, was supposed to be the active agent that took part in the reaction after analysis. TEMPO itself was difficult for the dehydrogenation of HNBB, but could promote the formation of M(n+1)OO· and assist the catalytic cycle.

In order to investigate the feasibility of production, we increased the scale to kg-size under the same mixing condition. The yield of HNBB in the first step maintained over 80% during the scale-up process. In the second step, the total yields of pure HNS were more than 85% after 5 times repeating before recovering the solvent and catalysts. The total yield of the two steps would be more than 68%, and no other literatures had reported such high yield. Besides, the avoiding of hazardous agents and recovery of catalysts and solvent made this procedure extremely valuable for industry.



Figure 1. Synthesis of HNBB in different solvent/co-solvent systems. Reaction condition when changing cosolvent: TNT 4.4 mmol, NaClO (pH=13.5) 6.5 mL, ethanol 10.0 mL, 40 °C, 1 h; Reaction condition when changing solvent: TNT 4.4 mmol, NaClO (pH=13.5) 6.5 mL, ethyl acetate 5.0 mL, 40 °C, 1 h.



Figure 2. Oxidation mechanism of TNT in alcohol solvent.



Figure 3. The influence of pH of NaClO to HNBB preparation in different solvent. Reaction condition in (a): TNT 4.4mmol, NaClO(pH=12.4~13.9) 6.5mL, 40°C, 30min; 4: 6, 4: 7 and 4: 8 stand for EA : EtOH = 4mL: 6mL, 4mL: 7 mL and 4mL: 8mL. Reaction condition in (b): TNT 4.4mmol, Na ClO(pH=12.4-13.9) 6.5mL, 40°C, 30min. a) THF 20mL, EtOH 10mL; b) THF 20mL, EtOH 10mL, 1% w.t. HCl 200mL was added after 1min of reacting; c) EA 4mL, EtOH 8mL; d) Benzene 2mL, EtOH 8mL.

80-	R1	R2	R3	R4	R5	R6	R7
N 60-							
⊥ 40-							
eld -							
TEMPO ^a	1:1	1:1	י 1:1		ו 2:3	1 	2:3
FeCl		1:10	1:1	1:1		2:3	2:3
Gas	N_2	N ₂	N_2	N_2	0 ₂	0 ₂	0 ₂

Figure 4. Evaluation the role of each element in catalytic system. Reaction condition: HNBB 2.2mmol, DMSO 10 mL, 55°C, 8 h, gas 1 atm. a) TEMPO: HNBB (mmol: mmol); b) FeCl₂: HNBB (mmol: mmol).



Figure 5. Dehydrogenation mechanism of HNBB with TEMPO/Fe²⁺/O₂.

SCHEMES



Scheme 1. Preparation method of HNS reported in previous works.





Scheme 2. Process of HNS preparation from TNT in scale-up production.

TABLES.

Table 1. The influence of solvents in dehydrogenation of HNBB^a

Entry	Solvent	Volume (mL)	Yield of HNS (%)
1	Ethyl acetate	20	
2	Benzene/ethanol	15/15	
3	DMF	15	
4	[(CH ₃)2N] ₃ PO ^b	20	trace
5	$(CH_2)_4SO_2$ ^c	20	
6	$C_6H_{11}NH_2\ ^d$	20	
7	acetone	15	12.3
8	Acetonitrile	20	17.9
9	DMSO	5	43.2
10	DMSO	15	68.7
11	DMSO	25	49.4

a) Reaction condition: HNBB 2.2mmol, TEMPO 0.13mmol, $FeCl_2 \cdot 7H_2O$ 0.14mmol, $55^{\circ}C$, 8 h, O_2 1 atm. b) Hexamethylphosphoramide; c) Tetramethylene sulfone; d) Cyclohexylamine

Table 2. The influence of different metal salts on HNS preparation with/without TEMPO.

Entry	Metal salts	Yield of H	NS (%)
		With TEMPO ^a	Without TEMPO ^b
1		21.4	trace
2	Na ₂ CO ₃	21.0	9.1
3	MgSO ₄ ·H ₂ O	24.9	10.9
4	ZnCl ₂ ·7H ₂ O	21.8	11.9
5	Pb(CH ₃ COO) ₂ ·3H ₂ O	22.9	21.0

6	MnSO ₄ ·H ₂ O	39.8	21.0
7	CrCl ₃ ·4H ₂ O	37.8	trace
8	$Co(acac)_2$ ^c	39.8	trace
9	NiCl ₂ ·6H ₂ O	32.9	trace
10	CuCl	62.7	34.9
11	FeCl ₂ ·7H ₂ O	81.0	20.6
12	FeCl ₂ ·7H ₂ O	60.1 ^d	20.9
13	CuCl ₂ ·H ₂ O	trace	trace
14	FeCl ₃	9.9	9.0

a) Reaction condition: HNBB 2.2mmol, metal salts 0.14 mmol, TEMPO 0.13mmol, DMSO 10 mL, 55°C, 8 h, O_2 1 atm. b) TEMPO was not added in these reactions. c) $Co(acac)_2$ was short for Cobalt(II) acetylacetonate. d) NHPI was used instead of TEMPO with the same moles.

Table 3. Scaled result of HNBB synthesis.

Entry	TNT / g	HNBB / g	Yield / %	m. p. / °C	Purity / % a
1	30	24.3	81.3	216~218	99.9
2	100	79.3	80.8	216~218	99.9
3	500	392.9	80.2	215~217	99.8
4	1000	818.7	81.5	216~218	99.9

a: determined by HPLC with both UV and differential refractometer detector.

Table	4. Recycle	of catalyst and	solvent in	100g HNS	synthesis
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Entry	DMSO / mL	TEMPO / g	FeCl ₂ / g	HNS / g	m. p. / °C	Purity / % ^a
1	1000	2.5	4.5	52.2	316~317.5	99.8

2	40	0.5	3.5	115.2	316~317.5	99.9
3	45	0.5	2.5	93.9	315.5~317.5	99.8
4	70	0.5	2.5	89.7	315.5~317.5	99.6
5	70	0.5	2.5	87.6	315~317	99.5
6	75	0.5	2.5	80.0	315~317	99.5
		Total yield: 86.	1% (5 recy	cles); 85.2% ((6 recycles).	

a: determined by HPLC with both UV and differential refractometer detector.

a. determined by Th EC with both 6 v and differential reflacionicies detector

Table 5. Recycle of catalyst and solvent in 500g HNS synthesis

Entry	DMSO / mL	TEMPO / g	FeCl ₂ / g	HNS / g	m. p. / °C	Purity / % ^a
1	4500	10.0	15.0	256.7	316~317.5	99.8
2	280	2.0	10.0	496.1	316~317.5	99.8
3	260	2.0	10.0	389.9	316~317.5	99.7
4	500	2.0	10.0	340.0	315~317	99.6
5	450	2.0	10.0	332.1	315~317	99.5
6	400	2.0	10.0	312.1	315~317	99.5
	Τ-4	-1	(5	. 01 20/ (C		

Total yield: 85.1% (5 recycles); 84.3% (6 recycles).

a: determined by HPLC with both UV and differential refractometer detector.

Table 6. Recycle of catalyst and solvent in 1000g HNS synthesis

Entry	DMSO / mL	TEMPO / g	FeCl ₂ / g	HNS / g	m. p. / °C	Purity / % ^a
1	8000	20.0	35.0	655.9	316~317.5	99.8
2	900	5.0	25.0	936.0	316~317.5	99.8
3	500	5.0	25.0	763.1	315~317	99.6

4	700	5.0	25.0	694.3	315~317	99.6
5	720	5.0	25.0	688.8	315~317	99.5
6	690	5.0	25.0	637.8	314~316.5	99.3
		Total yield: 8	5.9% (5 recycle	es); 84.8% (6	recycles).	
a: d	etermined by	HPLC with both	UV and differe	ential refracto	ometer detector.	
ASSC	OCIATED C	ONTENT				
Supp	orting Infor	mation.				
Exper	rimental data	of recovery of so	olvent and catal	ysts in scale-u	ip was listed in	Table s1,
s2, s3	and s4.					
AUTI	HOR INFOR	MATION				
AUTI Corre	HOR INFOR	MATION				
AUTI Corre	HOR INFOR	MATION	00504015000	E	00504015000	
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