Organic Process Research & Development

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An Improved and Impurity-Free Large-Scale Synthesis of Venlafaxine Hydrochloride†

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ABSTRACT: An improved and impurity-free synthetic method for large-scale synthesis of venlafaxine hydrochloride was developed using inexpensive reagents. The overall yield obtained from this newly developed process is 55% in a highly pure state with >99.9% purity by HPLC.

INTRODUCTION

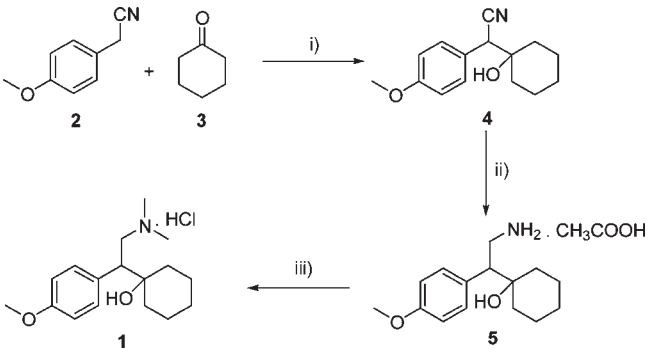
Venlafaxine,[1−3] (*RS*)-1-[2-(Dimethylamino)-1-(4-methoxyphenyl)ethyl]cyclohexanol hydrochloride (**1**), is a member of the cycloalkanol ethylamine scaffold and was the first dual-acting serotonin and norepinephrine reuptake inhibitor (SNRI), used for the treatment of depression and anxiety disorders. It was developed by Wyeth laboratories and is currently being marketed under the trade name Effexor.

RESULTS AND DISCUSSION

Venlafaxine was first synthesized by Yardley and co-workers[1] and then by different groups by various methods. The first reported[1] and most common approach for large-scale synthesis involves neucleophilic addition of 4-methoxyphenyl acetonitrile (**2**) with cyclohexanone (**3**) using LDA at −78 °C to afford (*RS*)-1-[cyano-(4-methoxyphenyl)methyl]cyclohexanol (**4**). Catalytic hydrogenation of **4** over rhodium on alumina in ethanolic ammonia to provide (*RS*)-1-[2-amino-1-(4-methoxypheny) ethyl]-cyclohexanol (**5**) then dimethylation of **5** using Eschweiler−Clarke procedure and isolation of the resulting venlafaxine as hydrochloride salt **1** are further stages in this synthesis with an overall yield <25%. When we have explored this reported synthetic process for the preparation of **1**, it was realized that this method suffered from disadvantages such as: (i) Reaction is at very low temperature −78 °C, and is particularly unattainable at tropical conditions. (ii) Usage of pyrophoric reagents such as *n*-BuLi and LDA made the process industrially unattractive. (iii) Excessive load of expensive Rh/alumina catalyst for catalytic hydrogenation of **4** rendered the process economically nonviable. (iv) Amine compound **5** was found to be unstable at ambient temperature and needed to be processed to the next stage immediately. (v) Final product **1** was associated with several impurities and required several purifications. (vi) Overall yield of this process is less than 30%. Although a few other syntheses have been reported in the literature,[4−8] they were either expensive or involved tedious workup procedures to isolate the product.

Herein, we report an improved, efficient, cost-effective, and impurity-free synthesis of venlafaxine with an overall yield of 55%, which has been accomplished by modifying the original process to one suitable for the large-scale synthesis by addressing the aforementioned limitations.

Scheme 1[a]



[a] Reagents and conditions: (i) MeOH, NaOMe, 5 °C, 4 h; (ii) AcOH, Kalcat C-8030-type Raney-Ni, H_2, 10−12 bar, 50 °C, 3 h; (iii) water, 37% HCHO, HCOOH, 100 °C, 20 h, toluene, 10% HCl in isopropanol.

The first step of our synthesis (Scheme 1) commences with condensation of **2** with **3** in the presence of sodium methoxide using methanol as solvent to afford **4** in 91% yield with 99.0% purity. The selection of methanol as a solvent and sodium methoxide as a base facilitates the carbanion generation from the benzylic position of **2** at 0−5 °C, and thereby addition of **3** allowed reaction completion in 4 h. Simple addition of water to the reaction mass assisted the precipitation of **4** as a white, crystalline solid and thus avoided the use of cryogenic reaction conditions as well as pyrophoric reagents such as *n*-BuLi and LDA.

On the basis of our previous experience in process development of the catalytic hydrogenation of **4**[9] and the available literature,[10−18] we were very certain that catalytic hydrogenation of **4** to **5** coupled with a workup procedure which minimizes the process impurities is crucial to the success of the synthesis of **1** as per regulatory requirements.[19] Among the available reducing agents[15] for reduction of **4** to **5**, Kalcat C 8030-type Raney Ni[20] was found to be an attractive choice (Table 1, entries 10 and 11) in view of its low cost and scope for its recovery and reuse in up to three reaction cycles.

Subsequently, we investigated the effect of different solvents on the hydrogenation by carrying out the reaction in the following solvents: methanol, isopropyl alcohol, methanolic ammonia, acetic acid, and aqueous ammonia−methanol using Kalcat C

Received: August 15, 2011
Published: October 20, 2011

Table 1. Hydrogenation of 4 using different reducing agents

entry	reducing agent (% of load)	solvent	H_2 (bar)	temp (°C)	time (h)	% yield[a]
1	LAH	THF	–	25	14	55
2	Pd/C (10%)	methanolic ammonia	10−12	50	9	47
3	wet Pd/C (10%)	acetic acid	10−12	50	7	45
4	Rh-Al_2O_3 (25%)	methanolic ammonia	6−8	25	6	68
5	Raney Ni-type B (50%)	methanolic ammonia	8−10	50	24	43
6	Raney Ni-type F (50%)	methanolic ammonia	8−10	50	11	25
7	Raney Ni-type CORM III (75%)	methanolic ammonia	8−10	25	9	67
8	Raney Ni-type CORM III (75%)	acetic acid	8−10	45	9	52
9	Raney Ni-type CORM III (25%)	acetic acid	8−10	45	14	48
10	Raney Ni-type C 8030 (10%)	methanolic ammonia	10−12	45	11	76
11	Raney Ni-type C 8030 (10%)	acetic acid	10−12	45	3	81

[a] isolated yield.

Table 2. Solvent screening for hydrogenation of 4

entry	solvent	4[a]	6[a]	7[a]	8[a]	9[a]	% yield[b]
1	methanol	12	1.62	2.57	8.6	0.02	64
2	isopropyl alcohol	14	1.07	1.23	10.1	0.07	63
3	methanolic ammonia	10	1.40	0.78	6.4	0.06	72
4	acetic acid	0.4	0.33	0.14	0.7	0.07	83
5	aq NH_3-methanol	17	1.93	0.96	4.8	0.02	59

[a] Result reported on basis of HPLC area %. [b] Isolated yield.

Table 3. Optimization of Kalcat C 8030-type Raney Ni quantity for hydrogenation of 4

entry	Raney Ni (% w/w)	time (h)	4[a]	6[a]	7[a]	8[a]	9[a]	% yield[b]
1	7	7.0	5.21	0.24	0.32	4.3	0.02	73
2	9	4.0	0.40	0.23	0.19	2.1	0.07	78
3	10	3.0	0.47	0.14	0.13	1.8	0.06	82
4	11	3.0	0.21	0.12	0.12	1.5	0.07	81
5	12	2.5	0.32	0.17	0.10	3.5	0.02	79
6	18	1.0	0.15	0.32	0.22	10.2	0.02	69

[a] Result reported on the basis of HPLC area %. [b] Isolated yield.

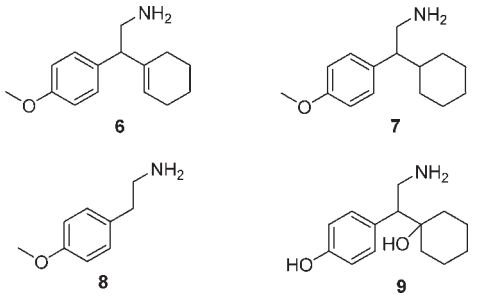


Figure 1. Structure of impurities **6**−**9**.

8030-type Raney Ni at 45−55 °C under 10−12 bar hydrogen gas pressure. Among these, acetic acid was found to be the best solvent of choice in terms of conversion and yield (Table 2, entry 4).

Further, the impact of catalyst load on yield and quality of the product was studied. At a low load of catalyst (Table 3, entry 1), it took a longer time for reaction completion and led to the formation of significant amounts of impurities during the longer reaction time, resulting in lower yield of the product. When the catalyst load was high, though the reaction was completed in 1 h, impurity levels were substantially higher, and product yield was only moderate (Table 3, entry 6) due to reverse aldol reaction. When catalytic hydrogenation was carried out with 10−12% w/w catalyst load based on weight of **4**, the product was formed in excellent yield (Table 3, entries 3−5). Finally, using acetic acid as solvent and Kalcat C 8030-type Raney Ni as catalyst, a systematic screening of one variable at a time (reaction temperature, reaction time, hydrogen gas pressure) was carried out, and the optimum conditions were identified as 55 ± 2.5 °C, 3.5 ± 0.5 h, 10−12 bar hydrogen gas.

After the completion of reaction, the catalyst was filtered, and the filtrate was concentrated under reduced pressure to get crude **5** as a thick syrup. The crude **5** contains **6**, **7**, **8**, and **9** as major impurities (Figure 1). Since these impurities have a free amino functional group, all these impurities can participate in the subsequent stage of the venlafaxine synthesis (**5** to **1**, Eschweiler−Clarke reaction) leading to the formation of corresponding **10**, **11**, **12**, and **13** impurities in the final drug substance **1** (Figure 2).[21] To remove these impurities, crude **5** was dissolved in water and washed with various antisolvents such as toluene, ethyl acetate, and dichloromethane. Among them, toluene was identified as the ideal solvent to eliminate these impurities very effectively without losing the desired product. Finally, the product was extracted into ethyl acetate after basifying with aqueous ammonia, and the organic layer was concentrated to provide the free base of **5**. To isolate pure **5** (substantially free from **6**−**9**) in the form of solid, the free base of **5** was treated with acetic acid in different solvents such as toluene, methanol, ethyl acetate, and dichloromethane. Among them, ethyl acetate was found to be an appropriate solvent to enhance the purity to >99.3%. An important parameter was observed during establishment of the isolation procedure, wherein 1.5 mol equiv of acetic acid is essential to achieve the excellent yield and purity of **5**. The acetate salt thus obtained was found to be stable for more than one year at room temperature, and it can be conveniently converted into venlafaxine HCl without incorporating any purification. The optimized process has been validated at kilo scale, and the results of the batches are reported in Table 4 along with the content of impurities. Thus, removal of expensive catalyst and achievement of desired purity, yield, and excellent stability were addressed.

dx.doi.org/10.1021/op200221y |*Org. Process Res. Dev.* 2011, 15, 1392–1395

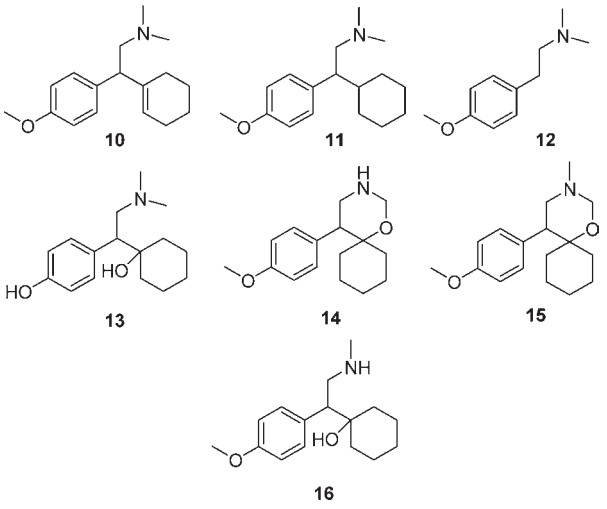


Figure 2. Structures of impurities **10**−**16**.

Table 4. Results of scaled-up batches of 5

		HPLC purity (%)						
entry	input **4** (kg)	**5**[a]	**6**[a]	**7**[a]	**8**[a]	**9**[a]	**4**[a]	% yield[b]
1	60	99.42	0.04	0.19	0.02	0.003	ND	73.1
2	60	99.33	0.03	0.16	0.04	ND	ND	68.6
3	60	99.35	0.05	0.12	0.04	ND	ND	71.7

[a] Result reported on the basis of HPLC area %. [b] Isolated yield; ND = not detected.

Table 5. Results of scaled-up batches of 1

	HPLC purity (%)								
input **5** (kg)	**1**[a]	**10**[a]	**11**[a]	**12**[a]	**13**[a]	**14**[a]	**15**[a]	**16**[a]	% yield[b]
60	99.94	ND	ND	0.01	ND	ND	ND	0.002	76.5
60	99.91	ND	ND	ND	ND	ND	ND	ND	81.6
60	99.92	ND	ND	0.01	ND	ND	0.002	ND	78.2

[a] Result reported on the basis of HPLC area %. [b] Isolated yield; ND = not detected.

The isolated acetate salt **5** is then treated with 6.1 equiv of formic acid and 3 equiv of 37−40% aqueous formaldehyde in the presence of water as the reaction medium at near reflux temperature for 22 h. HPLC analysis of reaction mass indicated that product **1** was associated with about 0.5−2.0% of **14**, **15** and **16** as major impurities (Figure 2), which are intermediates in the conversion of **5** to **1**. Since these impurities have a nitrogen atom, all these impurities can form the corresponding HCl salt while making the HCl salt of free base **1** and lead to unacceptable levels of impurities in the final API **1**. Hence, these impurities need to be removed to a negligible amount before treating with the HCl source. To remove these impurities, efforts were made to wash the aqueous reaction mass with various solvents such as toluene, ethyl acetate, dichloromethane, and ethers. Among them, dichloromethane was identified as the best solvent to eliminate the impurities **14**, **15**, and **16**. Finally, the product was extracted into toluene after basifying the reaction mass to pH 9−10 with 20% NaOH solution. The toluene layer was dried over anhydrous sodium sulfate to remove water, since the product **1** is highly soluble in water, then treated with 10% HCl in isopropyl alcohol solution followed by recrystallizing the product from isopropyl alcohol to get 82% of **1** as a highly pure (Tables 5 and 6), white crystalline compound with purity >99.9% (by a validated HPLC method).

Table 6. Organic volatile impurities results of 1

	content of residual solvent in **1**[a] in ppm						
entry	MeOH	IPA	DCM	EtOAc	toluene	AcOH	HCOOH
1	ND	25	ND	ND	ND	ND	ND
2	ND	88	ND	ND	ND	ND	ND
3	ND	75	ND	ND	15	ND	ND

[a] Residual solvent limits in ppm: MeOH NMT 2000, IPA NMT 3000, DCM NMT 600, toluene NMT 300, AcOH NMT 1500, HCOOH NMT 1500, NMT = not more than.

CONCLUSION

In conclusion, we have provided an improved, impurity-free, cost-effective, and scalable process for the production of venlafaxine HCl with an overall yield of 55% in a highly pure state (>99.9% purity by HPLC) by switching to cheaply available Kalcat C8030-type Raney Ni in place of expensive Rh/alumina for hydrogenation and sodium methoxide in place of LDA.

EXPERIMENTAL SECTION

All the solvents and reagents were used as received without further purification. The ^{1}H NMR spectra were recorded on a Varian Mercury plus 400 MHz FT NMR spectrometer, the chemical shifts are reported in δ (ppm) relative to TMS. The ^{13}C NMR spectra were recorded on a Varian Mercury plus 200 MHz FT NMR spectrometer, the chemical shifts are reported in δ (ppm) relative to $CDCl_3$. The IR spectra were recorded in the solid state as a KBr dispersion using a Perkin-Elmer FT-IR spectrometer. The mass spectra were recorded on a Shimadzu LCMS-QP8000 and Micromass LCT Premier XE mass spectrometer. Elemental analysis for CHN was performed on a Perkin-Elmer model 2400 CHNS/O analyzer.

Synthesis of 1-(Cyano-(4-methoxyphenyl)methyl)cyclohexanol (4). To a solution of sodium methoxide powder (45.9 kg, 0.850 kmol) in methanol (250.0 L) was added 4-methoxyphenyl acetonitrile (**2**, 50.0 kg, 0.340 kmol) at 5 °C, and the resultant suspension was stirred at 0−5 °C for 2 h. Cyclohexanone (**3**, 43.3 kg, 0.442 kmol) was added and stirred at 0−5 °C for 4 h. Water (500.0 L) was added while maintaining the temperature below 10 °C and stirred for 1 h. The separated solid was filtered and washed with water (75.0 L). The resulting wet compound was taken in toluene (500.0 L) and heated at 65 ± 3 °C, followed by washing the toluene layer twice with water (2 × 125 L). The reaction mass was cooled to 5−10 °C and maintained at 5−10 °C for 2 h. The separated solid was filtered, washed with toluene (25 L), and dried at 45 ± 2.5 °C to afford **4** as a white crystalline solid. Yield: 75.8 kg (91%); HPLC purity: 99.1%; MS: m/z 246 ($M^+ + 1$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.21 (d, 2H, Ar−H); 6.85 (d, 2H, Ar−H), 3.74 (s, 3H, OCH_3), 3.66 (s, 1H,

CH−CN), 1.0−1.6 (m, 10H, cyclohexyl); ^{13}C NMR (200 MHz, $CDCl_3$): δ 21.4, 21.5, 25.1, 34.7, 34.8, 49.2, 55.2, 72.6, 114.0, 119.8, 123.6, 130.5, 159.6.

Synthesis of [*RS*]-1-[2-Amino-1-(4-ethoxypheny)ethyl]cyclohexanol Acetic Acid (5). A mixture of **4** (60.0 kg, 0.24 kmol) and acetic acid (360.0 L) was placed in an autoclave equipped with hydrogen gas induction system. Kalcat C 8030-type Raney-Ni (9.0 kg, 15% w/w based on **4**) was added (*CAUTION! The catalyst is extremely pyrophoric when exposed to the air in a dry condition; it should be kept with solvent at all times!*), and the reaction mixture was flushed twice with 2 bar hydrogen gas pressure. The reaction was maintained at 55 ± 2.5 °C with 10−12 bar hydrogen gas pressure for 3 h and then cooled to 25 °C. The catalyst was filtered (*CAUTION! Fire hazard!* See above precaution.), and then the filtrate was concentrated under reduced pressure below 60 °C. The residual mass was dissolved in water (300.0 L) and then washed with toluene (120.0 L). The product was extracted into ethyl acetate (360.0 L) by adjusting the pH 7.5−8.0 using 25% aqueous ammonia (60.0 L). The organic layer was then concentrated under reduced pressure to dryness and then dissolved in ethyl acetate (300.0 L). Acetic acid (22 kg, 0.36 kmol) was added, heated at 75 °C for 15 min, and then stirred at 20−25 °C for 2 h. The separated solid was filtered, washed with ethyl acetate (30.0 L), and dried at 70 °C to afford **5** as a white crystalline solid. Yield: 54.3 kg (71.7%); HPLC purity: 99.3%; MS: *m*/*z* 250.3 (M^+ + 1); ^{1}H NMR (400 MHz, CD_3OD): δ 7.2 (d, 2H, Ar−H); 6.9 (d, 2H, Ar−H), 3.8 (s, 3H, OCH_3), 3.5 (dd, 1H, Ar−CH−CH_2), 3.3 (m, 2H, CH_2−NH_2), 1.9 (s, 3H, AcOH), 0.9−1.5 (m, 10H, cyclohexyl); ^{13}C NMR (200 MHz, $CDCl_3$): δ 20.9, 21.1, 22.4, 25.3, 33.0, 36.5, 54.5, 54.9, 71.8, 112.9, 130.0, 131.7, 157.6, 173.2; Anal. Calcd for $C_{17}H_{27}NO_4$: C, 65.99; H, 8.80; N, 4.53. Found: C, 65.91; H, 8.75; N, 4.49.

Synthesis of [*RS*]-1-[2-Dimethylamino-1-(4-methoxyphenyl)-ethyl]cyclohexanol Hydrochloride (1). To a stirred solution of **5** (60.0 kg, 0.194 kmol) in water (300.0 L) was added 37−40% formaldehyde (96.0 kg, 1.18 kmol) and formic acid (26.8 kg, 0.582 kmol), and the reaction mixture was heated at 100 °C for 22 h. The reaction mixture was cooled to 25 °C and then washed with dichloromethane (300.0 L). The product was extracted into toluene (540.0 L) after basifying the reaction mass pH 8.0−9.0 using 20% NaOH solution. The organic layer was washed with water (180.0 L) followed by drying with sodium sulfate. The pH of the organic layer was adjusted to 3.0−4.5 using 8−10% IPA.HCl and stirred at 0−5 °C for 2 h. The separated solid was filtered and washed with toluene (25.0 mL). The resulting wet product was taken in isopropyl alcohol (360.0 L) and heated to reflux for 15−30 min. The reaction mass was cooled to 0−5 °C and maintained at 0−5 °C for 1−2 h. The separated product was filtered, washed with chilled isopropyl alcohol (60.0 L), and dried at 70 °C in a cone vacuum drier to afford **1** as a white crystalline solid. Yield: 47.4 kg (78%); HPLC purity: 99.93%; MS: *m*/*z* 278 (M^+ + 1); ^{1}H NMR (400 MHz, CD_3OD): δ 7.22 (d, 2H, *J* = 8.6 Hz, Ar−H); 6.96 (d, 2H, *J* = 7.8 Hz, Ar−H), 3.79 (s, 3H, OCH_3), 3.60−3.72 (m, 2H, CH_2−$N(CH_3)_2$), 3.03 (dd, 1H, Ar−CH− CH_2), 2.82 (s, 6H, $N(CH_3)_2$), 0.9−1.5 (m, 10H, cyclohexyl); ^{13}C NMR (200 MHz, $CDCl_3$): δ 21.0, 21.4, 25.2, 31.2, 36.5, 42.5, 44.9, 52.3, 55.1, 60.1, 73.4, 113.9, 130.0, 131.2, 158.7; Anal. Calcd for $C_{17}H_{28}ClNO_2$: C, 65.05; H, 8.99; N, 4.46. Found: C, 65.11; H, 8.96; N, 4.47.

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Notes

[†]IPDO-IPM Communication No. 00165

ACKNOWLEDGMENT

We are thankful to the management of Dr. Reddy's Laboratories Limited and the colleagues of Research and Development (R&D) for their constant encouragement and excellent cooperation.

REFERENCES

(1) (a) Morris Husbands, G. E.; Yardley, J. P.; Mills, G.; Muth, E. A. U.S. Patent 4,535,186, 1985. (b) Yardley, J. P.; Morris Husbands, G. E.; Stack, G.; Butch, J.; Bicksler, J.; Moyer, J. A.; Muth, E. A.; Andree, T.; Fletcher, H., III; James, N. G.; Sielecki, A. R. *J. Med. Chem.* **1990**, *33*, 2899–2905.

(2) Harvey, A. T.; Rudolph, R. L.; Preskorn, S. H. *Arch. Gen. Psychiatry* **2000**, *57*, 503–509.

(3) Montgomery, S. A. *Int. Clin. Psychopharmacol.* **1999**, *14*, 21–27.

(4) Chavan, S. P.; Kamat, S. K.; Sivadasan, L.; Balakrishnan, K.; Khobragade, D. A.; Ravindranathan, T.; Gurjar, M. K.; 5. Kalkote, U. R. *Tetrahedron Lett.* **2004**, *45*, 7291–7295.

(5) Chavan, S. P.; Khobragade, D. A.; Thakkar, M.; Kalkote *Synth. Commun.* **2007**, *37*, 3901–3906.

(6) Basappa, C. V.; Kavitha; Rangappa, K. S. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 3279–3281.

(7) Burgos, A.; Tonnel, J.; Dambrin, V.; Lucet, D.; Poirier, P. U.S. Patent 7,462,742 B2, 2008.

(8) Dhiraj, M. R.; Srinivasan, R.; Milind, M. G.; Nishant, M. P.; Mandar, M. D. U.S. Patent 6,756,502 B2, 2004.

(9) Buchi Reddy, R.; Rajasekher, K.; Srinivas Reddy, G.; Babu, I. U.S. Patent 2005/0033088 A1, 2005.

(10) Yoon, N. M.; Brown, H. C. *J. Am. Chem. Soc.* **1968**, *90*, 2927–2938.

(11) Brown, H. C.; Heim, P.; Yoon., N. M. *J. Am. Chem. Soc.* **1970**, *92* (6), 1637–1646.

(12) Xiaoqi, Yu.; Jun, Y.; Wenwu, Li.; Peng, Li.; Yong, W.; Ye, P. C. N. Patent 101503,365 A, 2009.

(13) Poorna, C. T.; Deepthi, S. K.; Kalyan, C. A.; Mahesh, R. G. *Asian J. Chem.* **2007**, *19* (7), 5157–5160.

(14) Suhas, S. V.; Baldey, P. N.; Pinky, P.; Srinivasan, R. I.N. Patent 189623 A1, 2003.

(15) Jagdish, C. S.; Rajender P. G.; Vilas, V. P.; Anand, J. D.; Vinodrai, M.; Shrikant, H. R. U.S. Patent 7,026,513 B2, 2006.

(16) Viswanathan, N.; Rhoit, C.; Baiju, S.; Sivaling, R. T.; Kumar, S. Y.; Kundik, P. Y. WO /2006/067808 A1, 2006.

(17) Kim, K.-s.; Kim, K.-i.; Chai, K.-b. U.S. Patent 2004/181093 A1, 2004.

(18) Barkoczy, J.; Kotay Nagy, P.; Gregor, T.; Simig, G.; Vereczkeyne, D. G.; Nagy, K.; Beck, I.; Nemeth, N.; Szabo, T. H.U. Patent 2000/04868 A2, 2003.

(19) ICH Guideline Q3A (R), Impurities in New Drug Substances, 7 February, 2002. *ICH Q3A Impurities in New Drug Substances*, R; February 2002 http://www.fda.gov/RegulatoryInformation/Guidances/ucm127942.htm.

(20) Activated alloy catalyst Kalcat C-8030 Raney Ni is a fine black powder suspended in water, and its pH is between 9 to 11. This catalyst, having 84−88% nickel content, nitrobenzene activity 40−60 mL of H_2/g/min, and bulk density between 0.60 to 0.85 g/cm^3, is procured from Monarch Catalyst Private Ltd., A-94 MIDC phase I, Dombivli, Thane - 421203, India.

(21) Saravanan, M.; Suresh Kumar, K.; Pratap Reddy, P.; Satyanarayana, B. *Synth. Commun.* **2010**, *40*, 1880–1886.