ISSN: 2249 –4820

Chemistry & Biology Interface, 2012, 2, 1, 52-58

Chemistry & Biology Interface

An official Journal of ISCB, Journal homepage; www.cbijournal.com

Research Paper

An efficient synthesis of 2-*n*-butyl-5-nitrobenzofuran derivative, a key starting material for dronedarone hydrochloride

P. Raja Gopal,[1,3] M. Saravanan,[1] E.R.R. Chandrashekar,[1] B. Vijaya bhaskar,[1] Ch. Krishna rao [2] and P. Veera Somaiah[*3]

[1]*Research and Development, Dr. Reddy's Laboratories Ltd., IPDO, Hyderabad 500072, India.*
[2]*IPM, Dr. Reddy's Laboratories Ltd., IPDO, Hyderabad 500072, India.*
[3]*Department of Chemisty, Osmania University, Hyderabad 500007, India.*
Received 8 February 2011; Accepted 19 February 2012

Keywords: Dronedarone, rearrangement, cyclisation, benzofuran, acylation, demethylation.

Abstract: An efficient and alternative synthesis of (2-butyl-5-nitrobenzofuran-3-yl)(4-hydroxy phenyl)methanone (**2**) was achieved using inexpensive raw materials and reagents is described. The key steps involved in this synthesis are nucleophilic substitution of 1-bromo-4-nitrobenzene with hexan-2-one oxime (**3**) using NaOH and rearrangement of hexan-2-one O-(4-nitrophenyl) oxime (**4**) to 1-(2-hydroxy-5-nitrophenyl)hexan-2-one (**5**) using 1.8 N HCl in acetic acid.

Introduction

(2-Butyl-5-nitrobenzofuran-3-yl)(4-hydroxy phenyl)methanone (**2**) is a key intermediate for the synthesis of dronedarone hydrochloride **(1)** (Figure-1), which is an anti arrhythmic drug. Dronedarone is used for the treatment of atrial fibrillation and atrial flutter in patients whose hearts have either returned to normal rhythm or who undergo drug therapy or electric shock treatment to maintain normal rhythm. Although, several methods[1-10] are appeared in the literature for the synthesis of **2**, they are expensive. Cambrex karlskoga *et al*[11] reported the synthesis of benzofuran derivatives *via* oxime formation, which prompted us to develop an alternative and efficient synthesis of title compound. Herein we report an alternative process for **2**.

Corresponding Author* Email: rajagopal@drreddys.com
Tel: +91 9866497190; Fax: +91 40 44346285
DRL-IPM-Communication No. 00320

Results and Discussion

In our approach (Scheme-1), first step involved the condensation of hexan-2-one and hydroxylamine hydrochloride as per literature procedure [12-14] furnished hexan-2-one oxime (**3)** in 90% yield. The product **3** was resulted with a mixture of *syn* and *anti* configuration, which was being confirmed by NMR (^{1}H and ^{13}C).

Nucleophilic substitution of oxime **3** with 1-bromo-4-nitrobenzene using NaOH in the presence of DMSO at 50 - 55 ^{o}C afforded

ISSN: 2249 –4820

Chemistry & Biology Interface, 2012, 2, 1, 52-58

compound **4**. During feasibility studies, NaH[15] as base used to facilitate the conversion of **3** to **4**. Being NaH is explosive, its handling is very difficult at large scale use and hence it need to be replaced with a suitable base. Initially, we screened the reaction with Na_2CO_3 and K_2CO_3 as a base using different solvents such as DMF, DMSO and THF. In all the cases product formation was not observed even maintained the reaction for prolonged duration at room temperature to elevated temperature (Table 1, entries 1 - 3), where as around 30 - 40% product was formed by using NaOH as a base and DMF as a solvent (Table 1, entry 4). By selecting NaOH as a choice of base, we examined the reaction with different solvents such as THF and DMSO to achieve complete reaction conversion. Among these, DMSO is preferable solvent in terms of true reaction conversion (Table 1, entry 6). With a choice of base and solvent in hand, we studied the reaction at different temperature. The reaction was not initiated by performing the reaction below 30 ^oC (Table 1, entry 9), where as beyond 65 ^oC the resulted product undergo decomposition and gave decreasing trend of yield with respect to function of increase in temperature (Table 1, entries 6 and 8). Finally, excellent yield was achieved by conducting reaction at 50 - 55 ^oC for 6 - 7 h (Table 1, entry 7).

Further, to check the efficiency of process, we examined the reaction with fluoro and chloro substituted nitrobenzene (Table 2) and found similar results with respect to yield and quality.

Rearrangement of compound **4** in 1.8 N HCl[15,16] in acetic acid followed by the resulted *in-situ* intermediate imine was hydrolysed with water at room temperature provided 1-(2-hydroxy-5-nitrophenyl)hexan-2-one (**5**) in 70% yield**.** Dehydration of **5** using zinc chloride[16] in acetic acid at 25 - 30 ^oC gave benzofuran **6** in 70 - 75% yield. Friedel-Crafts acylation[17-19] of **6** with 4-methoxybenzoyl chloride in the presence of $AlCl_3$ and subsequent isolation of the product from IPA afforded **7** in 80% yield**.** Finally, demethylation of **7** with $AlCl_3$[17] in chlorobenzene media at 80 - 85 ^oC afforded off-white colored target key starting material **2** with 80% yield and 98% purity by HPLC. Attempts made to prepare **2** by using aqueous HCl and aqueous HBr at different conditions were ended up with incomplete reaction. As synthesis of **7** and **2** are $AlCl_3$ mediated reaction, we targeted to telescope both the reaction in one pot, and found the reaction did not go for completion even using excess equiv of $AlCl_3$.

Conclusion

In conclusion, we have developed an alternative process using inexpensive and commercially available raw materials for the preparation of (2-butyl-5-nitrobenzofuran-3-yl)(4-hydroxy phenyl)methanone, a key and intermediate of dronedarone HCl.

Acknowledgements

The authors wish to thank the management of the Dr. Reddy's Laboratories Ltd., for supporting this work.

Experimental Section

The ^{1}H-NMR spectra were recorded in $CDCl_3$ and DMSO-d_6 on a Varian Gemini-2000 at 400 & 500 MHz FT NMR spectrometer, the chemical shifts are reported in δ ppm relative to TMS. The FT-IR spectra were recorded in the solid state as KBr dispersion medium using Perkin Elimer 1650 FT-IR spectrophotometer. The mass analysis was performed on HP-5989A LC/MS spectrometer. The solvents and

ISSN: 2249 –4820

Chemistry & Biology Interface, 2012, 2, 1, 52-58

reagents were used without further purification.

Hexan-2-one oxime (3)

To a stirred solution of hexan-2-one **(**20.0 g, 0.199 mol) and hydroxylamine hydrochloride (27.75 g, 0.3994 mol), was added $FeCl_3.6H_2O$ (10.8 g, 0.0399 mol) at 25 - 30 ^oC and maintained for 5 h. After completion of reaction, was added water (100 mL) and stirred for 15 min. The product was extracted into DCM (2 x 100 mL) and the resulted organic layer was washed with water (100 mL), followed by 5% aqueous $NaHCO_3$ solution (40 mL). The resultant organic layer was distilled at 35 ^oC under vacuum afforded **3** as syrup in 90% yield**.** MS : *m/z* 116 (M^++1); FT-IR (cm^{-1}) : 1466.6 (C=N stretching), 3246 (O-H stretching); ^{1}H-NMR (400 MHz, $CDCl_3$): δ 0.9 (t, *J* = 6.8Hz, 3H), 1.3 (m, 2H), 1.5 (m, 2H), 1.8 (s, 1H), 2.2 (m, 2H), 8.2 (s, 1H); ^{13}C NMR (400 MHz, $CDCl_3$) : δ 13.0, 13.5, 22.0, 28.2, 35.1, 158.2 ;

Hexan-2-one O-(4-nitrophenyl) oxime (4)

To a stirred solution of NaOH (2.4 g, 0.06 mol.) and DMSO (35 mL), was added compound **3** (6.4 g, 0.055 mol) followed by 1-bromo-4-nitrobenzene (11.2 g, 0.05 mol) and heated at 55 ^oC for 7 h. After completion of the reaction, poured the reaction mass into water (100 mL) and stirred for 15 min. The product was extracted with toluene (3 x 50 mL) and washed the combined toluene layers with water (3 x 75 mL), finally distillation of resultant organic layer at 50 ^oC under vacuum afforded **4** in 94% yield. MS : *m/z* 236 (M^+-1); FT-IR (cm^{-1}) : 1159.8 (C-O-C stretching), 1339.2, 1590.9 (-NO_2 stretching), 1467.2 (C=N stretching); ^{1}H-NMR (400 MHz, $CDCl_3$): δ 0.9 (m, 3H), 1.4 (m, 2H), 1.6 (m, 2H), 2.1 (s, 3H), 2.3 (m, 2H), 7.2 (m, 4H); ^{13}C NMR (400 MHz, $CDCl_3$) : δ 13.4, 14.6, 22.0, 27.8, 35.1, 113.9, 125.3, 132.3, 141.6, 164.0.

1-(2-Hydroxy-5-nitrophenyl)hexan-2-one (5):

Compound **4** was dissolved **(**18.0 g, 0.076 mol) in 1.8 N HCl in acetic acid (72 mL) at 25-30^oC and the aliquot was kept at same temperature for 12 h without stirring. After completion of reaction, the reaction mass was poured into water (150 mL) and stirred for 30 min. The product was extracted with toluene (2 x 90 mL) and combined toluene layer was washed with water (50 mL), followed by 5% aqueous $NaHCO_3$ solution (90 mL) and finally with water (90 mL). Separated toluene layer was distilled off at 55 ^oC under vacuum afforded **5** in 70% yield. MS : *m/z* 238 (M^+-1); FT-IR (cm^{-1}) : 1340.1,1592.1 (NO_2 stretching), 1704.6 (C=O stretching), 3226.0 (O-H stretching); ^{1}H-NMR (400 MHz, $CDCl_3$): δ 0.9 (m, 3H), 1.3 (m, 2H), 1.6 (m, 2H), 2.3 (m, 2H), 2.7 (m, 2H), 6.9 (m, (1H), 8.1 (m, 2H); ^{13}C NMR (400 MHz, $CDCl_3$) : δ 13.7, 22.0, 25.4, 43.2, 45.2, 117.3, 121.6, 125.2, 126.9, 141.0, 161.4, 212.6.

2-Butyl-5-nitrobenzofuran (6):

To a stirred solution of compound **5** (10 g, 0.042 mol) in acetic acid (50 mL), was added $ZnCl_2$ (8.6 g, 0.063 mol.) at 25 – 30 ^oC and maintained at 25 – 30 ^oC for 4 h. After completion of reaction, the reaction mass was poured into water (50 mL) and extracted the product with hexane (2 x 50 mL). The combined organic layer was washed with water (50 mL), followed by 5% aqueous $NaHCO_3$ solution (50 mL) and water (50 mL). The organic layer was distilled off at 45 ^oC under vacuum afforded **6** with 74% yield. MS: *m/z* 218 (M^+-H); FT-IR cm^{-1}: 1064.5 (aromatic-O-CH ether

ISSN: 2249 –4820

Chemistry & Biology Interface, 2012, 2, 1, 52-58

stretching), 1345.8, 1592.4 (-NO_2 stretching), ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.94 (t, *J* = 7.2 Hz, 3H), 1.40 (m, 2H), 1.70 (m, 2H), 2.77 (t, *J* = 7.6 Hz, 2H), 6.49 (d, *J* = 8.0 Hz, 1H), 7.42 (d, *J* = 8.8 Hz, 1H), 8.10 (dd, *J* = 8.8 Hz, *J* = 2.0 Hz, 1H), 8.36 (d, *J* = 2.4 Hz, 1H) ; ^{13}C NMR (400 MHz, $CDCl_3$): δ 13.6, 22.1, 28.0, 29.3, 102.4, 110.7, 116.4, 118.9, 129.3, 143.7, 157.4, 163.3.

(2-Butyl-5-nitrobenzofuran-3yl)(4-methoxyphenyl)methanone (7)

To a stirred solution of $AlCl_3$ (6.7 g, 0.05 mol) in DCM (100 mL), was added 4-methoxybenzoyl chloride (10.1 g, 0.068 mol) over a period of 20 min at 0 - 5 ^{o}C and maintained for 30 min. To the above contents added drop wise 2-butyl-5-nitrobenzofuran **6** (10 g, 0.045 mol) over a period of 15 min and allowed the reaction mass to room temperature and stirred for 4 h. After completion of reaction, the reaction mass mass poured into chilled 5% aq.HCl solution (100 mL) and stirred for 15 min. The organic layer was separated and washed with 5% aqueous $NaHCO_3$ solution (50 mL) followed by water (50 mL) and distilled off to afford residue. The residue thus obtained was dissolved in *i*-PrOH (30 mL), cooled to 0 - 5 ^{o}C and maintained for 1 h. The separated solid was filtered, washed with chilled *i*-PrOH (5 mL) to afford **7** in 80% yield. MS: *m/z* 354.1 (M^++H); FT-IR (KBr) cm^{-1}: 1023 (O-CH_3 stretching), 1165.2 (C-O-C stretching), 1600.8 (-NO_2 stretching), 1640.6 (-C=O keto stretching); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.87 (t, *J* = 7.2 Hz, 2H), 1.30 (m, *J* = 7.2 Hz, 2H), 1.72 (m, *J* = 7.2 Hz, 2H), 2.90 (t, *J* = 7.2 Hz, 2H), 3.91 (s, 3H), 6.97 (m, 2H), 7.55 (d, *J* = 8.8 Hz, 1H), 7.81 (m, 2H), 8.20 (dd, *J* = 8.8 Hz, *J* = 2.4 Hz,1H), 8.34 (d, *J* = 2.4 Hz, 1H); ^{13}C NMR (400 MHz, $CDCl_3$): δ 13.5, 22.2, 27.8, 29.8, 55.4, 111.2, 113.9, 117.1, 117.5, 120.1, 127.8, 130.8, 131.5, 144.5, 156.2, 163.9, 167.0, 188.9.

(2-Butyl-5-nitrobenzofuran-3-yl)(4-hydroxy phenyl)methanone (2)

To a stirred solution of $AlCl_3$ (6.7 g, 0.051 mol) in chlorobenzene (42 mL), was added drop wise a solution (2-butyl-5-nitrobenzofuran-3yl)(4-methoxyphenyl)methanone **7** (6.0 g, 0.016 mol) in chlorobenzene(12 mL) over a period of 10 min at room temperature. The reaction mixture was heated to 75^{o}C and maintained for 5 h. After completion of reaction, the reaction mass was poured into chilled 5% aqueous HCl solution (60 mL) and DCM (24 mL). The layers were separated and extracted the aqueous layer with DCM (12 mL). The combined organic layer was washed with water (15 mL), followed by 5% aqueous $NaHCO_3$ solution (15 mL) and water (15 mL). The resulted organic layer was concentrated under vacuum followed by the residue thus obtained was dissolved in chlorobenzene (12 mL) and heated at 75 - 80 ^{o}C for 15 min, then cooled to 0 - 5 ^{o}C and stirred for 1 h. The separated solid was filtered, washed with chlorobenzene (3 mL) afforded **2** in 70% yield. MS: *m/z* 338 (M^+-H); FT-IR (KBr) cm^{-1}: 1166.3 (C-O-C stretching); 1577.1(-C=O stretching), 1599.8 (-NO_2 stretching), 3216.9 (O-H stretching), ^{1}H NMR ($CDCl_3$): δ 0.87 (t, *J* = 7.2 Hz, 3H), 1.30 (m, *J* = 7.2 Hz, 2H), 1.72 (m, *J* = 7.6 Hz, 2H), 2.90 (t, *J* = 7.6 Hz, 2H), 6.43 (s, 1H), 6.93 (m, 2H), 7.55 (d, *J* = 9.2 Hz, 1H), 7.77 (m, 2H), 8.20 (dd, *J* = 8.8 Hz, *J* = 2.0 Hz, 1H), 8.34 (d, *J* = 2.0 Hz, 1H); ^{13}C NMR (400 MHz, $CDCl_3$): δ 13.5, 22.2, 27.9, 29.7, 111.4, 115.8, 117.1, 117.5, 120.2, 127.7, 130.3, 132.1, 144.5, 156.3, 161.6, 167.6, 190.3.

ISSN: 2249 –4820

Chemistry & Biology Interface, 2012, 2, 1, 52-58

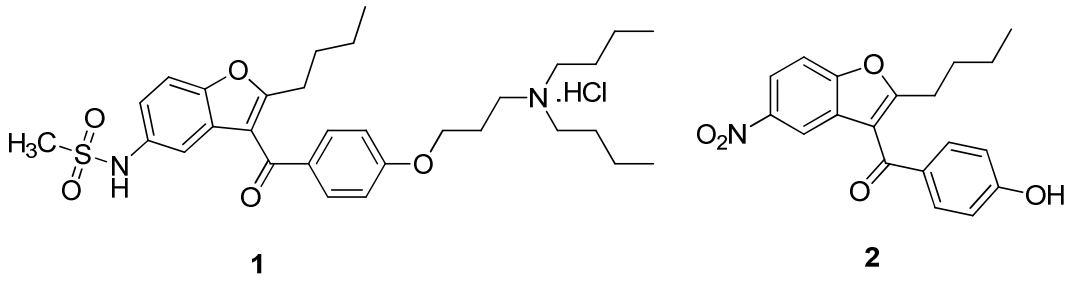
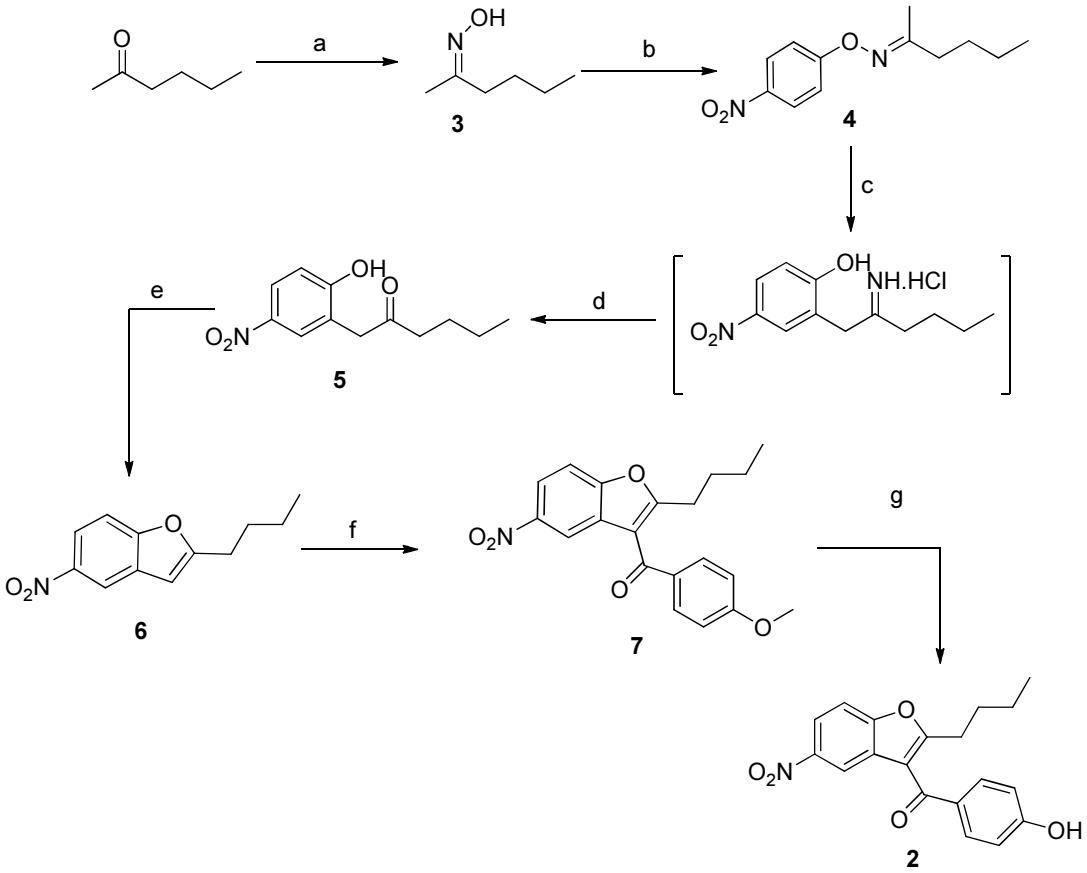


Figure-1: Structure of dronedarone hydrochloride (1) and key starting material (2).



***Scheme-1*:** Synthetic scheme for preparation of **2**

Reagents and condition: (a) $NH_2OH.HCl/FeCl_3.6H_2O$, 25 - 30 ^oC, 5 - 6 h; (b) 1-bromo-4-nitrobenzene, NaOH, DMSO, 50 - 55 ^oC, 6 - 7 h ; (c) 1.8N HCl in AcOH, 25 - 30 ^oC, 12 h ; (d) Water, 25 - 30 ^oC, 30 min; (e) $ZnCl_2$, AcOH, 25 - 30 ^oC, 4 h; (f) 4-methoxy-benzoyl chloride, $AlCl_3$, DCM, 25 - 30 ^oC, 4 h; (g) $AlCl_3$, chlorobenzene, 75 - 80 ^oC, 3 - 4 h.

ISSN: 2249 –4820

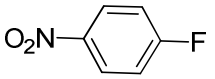
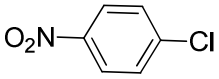
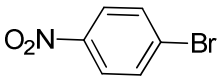
Chemistry & Biology Interface, 2012, 2, 1, 52-58

***Table 1*:** Screening of the base and solvent for reaction of 1-bromo-4-nitrobenzene and **3.**

Entry	Base	Equiv	Solvent	Temp (^oC)	Yield (%)[a]
1	K_2CO_3	3.0	DMF	90	-
2	Na_2CO_3	3.0	THF	55	-
3	Na_2CO_3	3.0	DMSO	55	-
4	NaOH	2.0	DMF	90	25
5	NaOH	2.0	THF	55	18
6	NaOH	2.0	DMSO	80	75
7	NaOH	1.1	DMSO	50	94
8	NaOH	1.1	DMSO	100	45
9	NaOH	1.1	DMSO	30	2

[a] Isolated syrup yield.

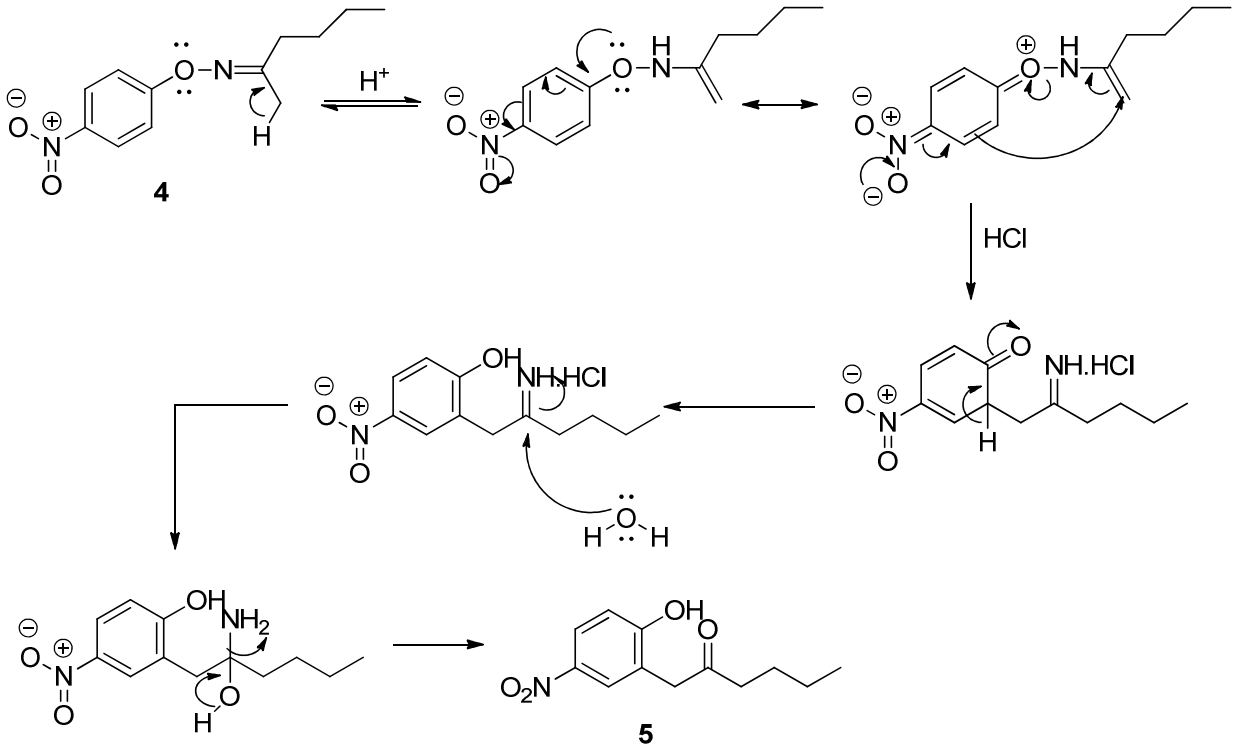
Table 2: Reaction of substituted nitrobenzene with **3**

Entry	Substituted nitro benzene	Base	Equiv	Time (h)	Temp (^oC)	Yield (%)[a]
1		NaOH	1.1	6-7	50 - 55	93
2		NaOH	1.1	6-7	50 - 55	92
3		NaOH	1.1	6-7	50 - 55	94

[a] Isolated syrup yield.

ISSN: 2249 –4820

Chemistry & Biology Interface, 2012, 2, 1, 52-58



Proposed mechanism for rearrangement of **4** to **5**

References

[1] Li, Yen. CN 102174032, **2011.**
[2] Li, Yen. CN 101948455, **2011.**
[3] Lonza. EP 224631, **2010.**
[4] G. Kretzschmar, V. Kraft, K. Rossen, J. Graser. WO 2010/136502, **2010**
[5] O. Hansson, A. Bergh, L. Elkund. WO 2010/116140, **2010.**
[6] A. Wellig, J. P. Roduit, D. Dai, R. Chen. WO 2010/040261, **2010.**
[7] L. Elkund. WO 2010/038029, **2010**.
[8] O. Diouf, T. Durand, S. Lemeune, J. F. Marcoux, N. Frison, L. Larquetoux, B. Folleas. WO 2008/139057, **2008.**
[9] D. Bourgeois, J. Turconi, J. Vastra. US 2008/0154049, **2008.**
[10] A. Schouteenten, F. Bleger, F. Mordacq, J. Piron. US 2007/0155831, **2007.**
[11] L. Elkund. WO 2009/044143, **2009.**
[12] H. Eshghi, A. Hassankhani. *Org. Prep. Proced. Int.*, **2005,** *37*, 575-579.
[13] K. Grela, L. Konopski. *Tetrahedron*. **2010**, *66*, 3614–3622.
[14] D. S. Brown, P.T. Gallagher, A.P. Lightfoot, C. J. Moody, A. M. Z. Slawin and E. Swann. *Tetrahedron.* **1995,** *51*, 11473 -11488.
[15] J. E. Arrowsmith, P. E. Cross, G. N. Thomas. US 5,158,964, **1992.**
[16] A. Mooradian, P. E. Dupont. US 3,547,997, **1970.**
[17] A. Gutman, G. Nisnevich, L. Yudovitch. US 7,312,345 B2, **2007**.
[18] McDonald, G. Matthew, A. Rettie. *Chem. Res. Toxicol*. **2007**, *20*, 1833 -1842.
[19] F. W. Michael, J. Promsuk, Q. Bettina, J. I. Timothy, M. F. Morin, R. R. Ian, J. R. Peter, A. Naohiko, E. Hitoshi. *J. Med. Chem*. **2011**, *54*, 2701 – 2713.