Available online at http://www.journalcra.com

International Journal of Current Research
Vol. 10, Issue, 08, pp.72908-72910, August, 2018

INTERNATIONAL JOURNAL
OF CURRENT RESEARCH

ISSN: 0975-833X

RESEARCH ARTICLE

A MILD, SIMPLE, COST EFFICIENT, CHEMOSELECTIVE AND HIGH YIELDING PROCEDURE FOR THE ANTI-CANCER DRUG LETROZOLE KEY INTERMEDIATE 4-FLUOROBENZONITRILE

***[1]Shiva Rama Krishna Samala, [2]Kishore Gokavarapu, [2]Srinivasa Rao, B.,**
[3]Sarita Gokavarapu and [4]Sunil Gandhi

*[1]Research and Development Department – Helios Life Sciences Limited, 79 & 100,
Industrial Growth Center, Malanpur, Bhind, MP – 477117
[2]Production Department–Helios Life Sciences Limited, 79 and 100, Industrial Growth Center,
Malanpur, Bhind, MP – 477117
[3]QC and ADL Department–Helios Life Sciences Limited, 79 and 100, Industrial Growth Center,
Malanpur, Bhind, MP – 477117
[4]Chairman –Helios Life Sciences Limited, 79 and 100, Industrial Growth Center, Malanpur, Bhind, MP – 477117

ARTICLE INFO

Article History:
Received 14th May, 2018
Received in revised form
24th June, 2018
Accepted 27th July, 2018
Published online 31st August, 2018

Key Words:
Letrozole, Anticancer, Fluoro benzonitriles.

ABSTRACT

As we know Anti-cancer Drug have very tight and stringent specifications in final stage purity then only US FDA use to allow to keep that particular drug in to the market, especially in the preparation of Letrozole Drug one of the key Fluoro intermediate is 4-fluorobenzonitrile which is already available in market, using same difficult to generate desired specification at final stage of Letrozole Drug. So that, to avoid these issues we have worked on synthesizing this intermediate in our unit. In literature there are so many synthetic procedures are available but they are not industrial approach procedures almost all routes are involved costly key starting materials but in our research the starting material is 4-Fluorobenzaldehyde other key reagent is Hydroxylamine hydrochloride and solvents Dimethyl Suloxide (DMSO) and water.

Citation: Shiva Rama Krishna Samala, Kishore Gokavarapu, Srinivasa Rao, B., Sarita Gokavarapu and Sunil Gandhi. **2018.** "A mild, simple, cost efficient, chemoselective and high yielding procedure for the anti-cancer drug letrozole key intermediate 4-fluorobenzonitrile", *International Journal of Current Research*, 10, (08), 72908-72910.

INTRODUCTION

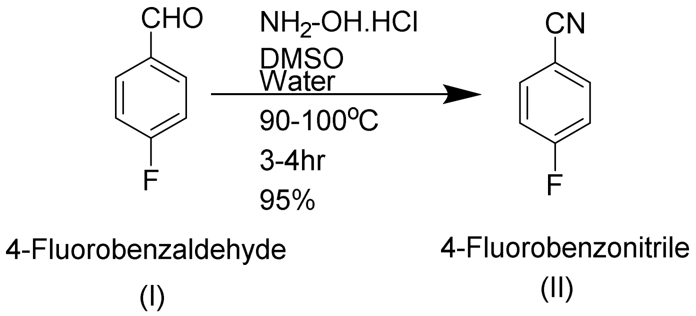
Organic nitriles are versatile synthetic intermediates that can easily be converted into a variety of other functional groups (Friedrich *et al*., 1970; Fatiadi 1983). Nitriles have been used in a variety of processes including the production of pharmaceuticals, agrochemicals, and biologically important compounds (Mathew, 1998; Chihiro *et al*., 1995; Serrano *et al*., 1995; Medwid *et al*., 1990). Thus, methods for preparing organic nitriles are highly desirable. One of the more widely used methods for preparing nitriles and one that has received much recent attention involves the dehydration of aldoximes. A number of dehydration agents have been employed including trichloromethyl carbonchloridate, (Mai, 1986) di-2-pyridyl sulfite, (Kim, 1986) thionylchloride, (Telvekar *et al*., 2004) dialkyl hydrogen phosphonates= triethylamine, (Surgie, 1969) diphosphoroustetraiodide, (Suzuki *et al*., 1978) 1, 10-dicarbonylbisimidazole, (Foley, 1973) chlorothionformate, (Clive, 1970) and triphenylphosphine=I2, (Narsaiah, 2006) to name a few. In addition, metals and metal complexes have been used including iron porphyrins, (Hart-Davis *et al*., 1998) titanium tetrachloride, (Lehnert, 1971) cetyltrimethylammonium dichromate. (Sahu *et al*., 2005) copper (II) acetate, (Attanasi, 1983) and certain ruthenium-based catalysts (Yang, 2001; Choi *et al*., 2002). Although these methods may be effective at dehydrating aldoxidmes, they have disadvantages too in that the reagents may be expensive, hazardous, or inconvenient to use. Recently, we demonstrated that aldoximes are readily dehydrated tonitriles with Raney nickel in refluxing 2-propanol (Zuidema *et al*., 2008) unfortunately we also found that the Raney nickel catalyst was poisoned in the reaction and could not be reused. During our systematic study directed at regenerating the catalyst and exploring other possible dehydrating metal catalysts, surprisingly we discovered that aldoximes readily dehydrate in dimethylsulfoxide (DMSO) solvent at 100°C. Knowing that aldoximes are readily prepared from aldehydes

---

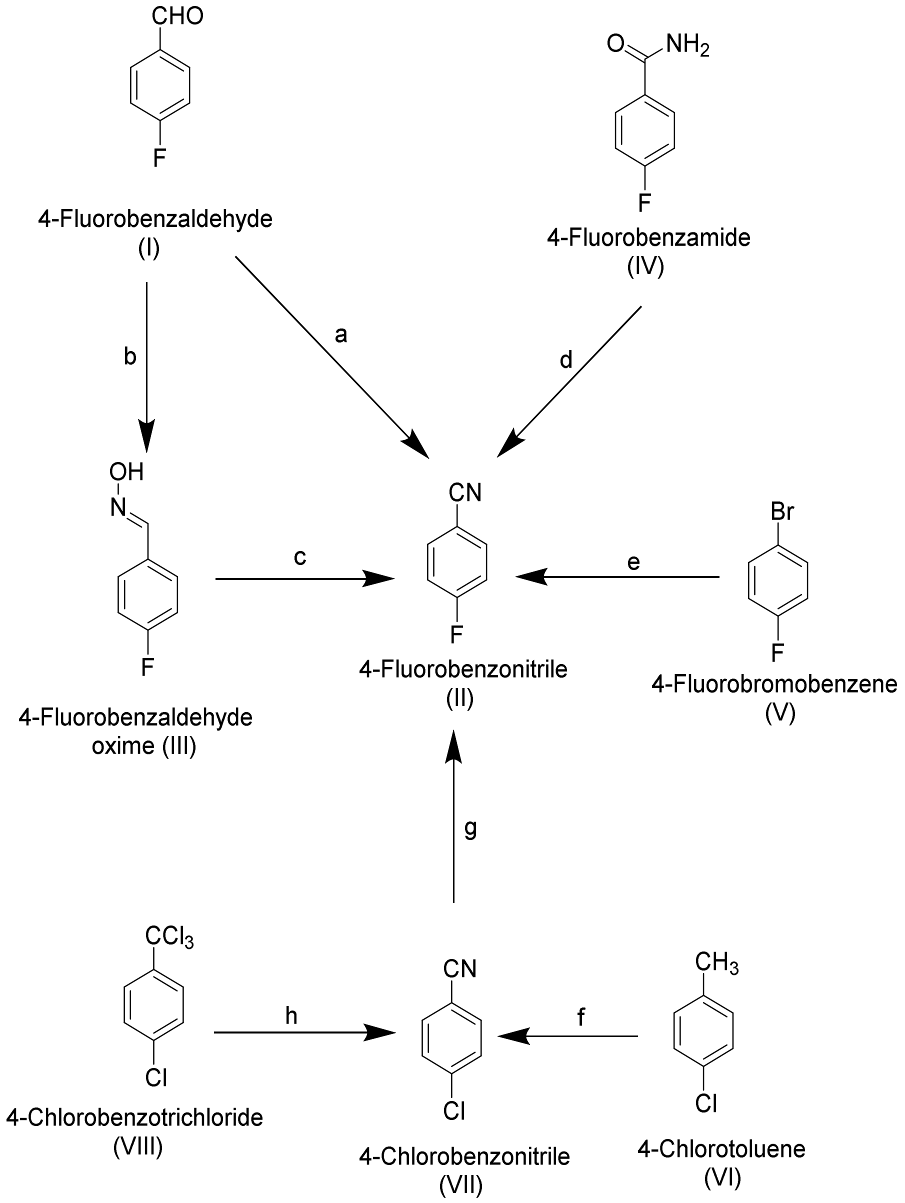
Corresponding author: **Shiva Rama Krishna Samala**
Research and Development Department – Helios Life Sciences Limited, 79 & 100, Industrial Growth Center, Malanpur, Bhind, MP – 477117.

DOI: https://doi.org/10.24941/ijcr.32211.08.2018

Graphical abstract:



Possible routes available in literature



and hydroxylamine hydrochloride (Bruice, 2007), the experimental procedure for the one-pot synthesis of nitriles is simple and straightforward and generally affords nitriles in good isolated yields. Aldehyde to nitrile conversion was quantitative as determined by gas chromatography, and 1H NMR showed that this study had a purity of >98%.

Experimental Section: In literature there are so many reports are there to prepare aromatic nitriles but specially Fluoro benzonitriles preparation is not that much easy because the main impurity in this desfluoro benzonitriles and these desfluoro benzonitriles separation is so difficult from the main compound. 4-fluorobenzonitrile is the key intermediate in Letrozole API (Oncology), while making final API of this Letrozole, if we use desfluoro contained benzonitrile not obtained the desired specification API at the end, to control this desfluoro impurity in 4-Fluorobenzonitrile we have conducted several experiments finally succeeded to control this.

This procedure already reported in literature but it is not giving the desired specification product, then we have designed few experiments changing equivalents of reagents, mode of addition and changing temperatures are controlled the desfluoro impurity, this was the great achievement in our process optimization and which was given desired specification material in Letrozole API synthesis.

Possible routes available in literature: Reagents and conditions: (a) $NH_2OH.HCl$, DMSO, Water 90-100^oC (b) $NH_2OH.HCl$, DCM, TEA (c) $SOCl_2$, DCM (d) $SOCl_2$, $CHCl_3$ (e) CuCN, DMF, reflux (f) Ammoxiation (g) KF, DMF, TBAB (h) NH_4Cl, reflux

Brief procedure: In a Clean and dry round bottom flask charged 4-fluorobenzaldehyde (1 mmol) followed by DMSO (2 volume) and water (1.5 volume) mixed thoroughly brought reaction mass temperature 80^oC then drop wise addition of hydroxylamine HCl in water to above reaction mass between 80-100oC maintain at same temperature around 1hr monitored the reaction conversion by GC poured reaction mass in to ice and cold water filtered obtained solid below 20^oC dried under vacuum.

Conclusion

In summary, a new and novel process of Letrozole key intermediate 4-fluorobenzonitrile process optimized using 4-fluorobenzaldehyde as starting material.

Acknowledgment

We would like to show our gratitude to the Mr. Sunil Gandhi chairman of Helios Life sciences Limited for sharing their pearls of wisdom with us during the course of this research.

REFERENCES

Attanasi, O., Palma, P., Serra-Zanetti, F. 1983. Effect of metal ions in organic synthesis, XVII:. Mild, easy, and high-yield conversion of aldoximes into nitriles under copper (II) acetate-catalysis. *Synthesis*, 741–742.

Bruice, P. Y. 2007. Organic Chemistry, 5th Ed., Pearson Prentice Hall: Upper Saddle River, NJ,; p. 811.

Chihiro, M., Nagamoto, H., Takemura, I., Kitano, K., Komatsu, H., Sekiguchi, K., Tabuse, F., Mori, T., Tominaga, M., Yabuuchi, Y. 1995. Novelthiazole derivatives as inhibitors of superoxide production by human neutrophils: Synthesis and structure-activity relationships. *J. Med. Chem.,* 38, 353–358.

Choi, E., Lee, C., Na, Y., Chang, S. 2002. [RuCl2 (p-cymene)] 2on carbon: An efficient, selective, reusable, and environmentally versatile heterogeneous catalyst. Org. Lett., 4, 2369–2371.

Clive, D. L. 1970. A new method for conversion of aldoximes into nitriles: Use of chlorothionformate. *J. Chem. Soc., Chem. Commun.,* 1014.

Fatiadi, A. J. 1983. Preparation and Synthetic Applications of Cyano Compounds; Wiley: New York.

Foley, H. G., Dalton, D. R. 1973. Neutral conversion of aldoximes into nitriles at low temperature. *J. Chem. Soc., Chem. Commun.,* 628.

Friedrich, K., Waaensfesl, K. 1970. The Chemistry of the Cyano Group; Wiley-Interscience: New York.

Hart-Davis, J., Battioni, P., Boucher, J.L., Mansuy, D. 1998. New catalytic properties of iron porphyrins: Model systems for cytochrome P450-catalyzed dehydration of aldoxime. *J. Am. Chem. Soc.,* 120, 12524–12530.

Kim, S., Kyu, Y. Y. 1986. Di-2-pyridyl sulfite. A new useful reagent for the preparation of N-sylfinylamines, nitriles, isocyanides, and carbodiimides under mild conditions. Tetrahedron Lett. 27, 1925–1928.

Lehnert, W. 1971. Nitriles from oximes with TiCl4=pyridine under mild conditions. *Tetrahedron Lett*., 6, 559–560.

Mai, K., Patil, G. 1986. Trichloromethyl carbonchloridate: A dehydrating reagent for the preparation of nitriles from aldoximes. Synthesis, 12, 1037–1038.

Mathew, C. T., Su, H., Wu, B. 1998. Preparation of organic nitriles from aldoximes. WO Patent 9805630 A.

Medwid, J., Paul, R., Baker, J., Brockman, J., Du, M., Hallet, W., Hanifin, J., Hardy, R., Tarrant, M. 1990. Preparation of triazolo [1, 5] pyrimidines as potential antiasthama agents. *J. Med. Chem*., 33, 1230–1241.

Narsaiah, A. V., Sreenu, D., Nagaiah, K. 2006. Triphenylphosphine-iodine: An efficient reagent system for the synthesis of nitriles from aldoximes. *Synth. Commun.,* 36, 137–143.

Sahu, S., Patel, P., Mishra, B. K. 2005. Selective oxidation of arylaldoximes by cetyltrimethylammonium dichromate to arylaldehydes and arylnitriles. *Synth. Commun.,* 35, 3123–3126.

Serrano, J., Sierra, T., Gonzalez, Y., Bolm, C., Weickhardt, K., Magnus, A., Moli, G. 1995. Improving FLC properties: Simplicity, planarity, and rigidity in new chiral oxazoline derivatives. *J. Am. Chem. Soc.,* 117, 8312–8321.

Surgie, A. S. Converting aldehydes to nitriles under mild conditions: Reaction of dialkyl hydrogen phosphonates with oximes. J. Org. Chem. 1969, 34, 2805–2806.

Suzuki, H., Fuchita, T., Iwasa, A., Mishina, T. 1978. Diphosphorous tetrachloride as a reagent for converting epoxides into olefins and aldoximes into nitriles under mild conditions. Synthesis, 4, 905–908.

Telvekar, V. N., Akamanchi, K. G. 2004. A simple system for preparation of protected glycosidic carbohydrate nitriles from corresponding oximes. Synth. Commun., 34, 2331.

Yang, S. H., Chang, S. 2001. Highly efficient and catalytic conversion of aldoximes to nitriles. *Org. Lett.* 3, 4209–4211.

Zuidema, D. R., Dennison, A. L., Park, E. Y., Mebane, R. C. 2008. Conversion of aldoximes in to nitriles with Raney nickel in refluxing 2-propanol. *Synth. Commun.*, 38, 3810–3815.

****