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Synthesis of Efavirenz by an innovative cost effective cyclisation process

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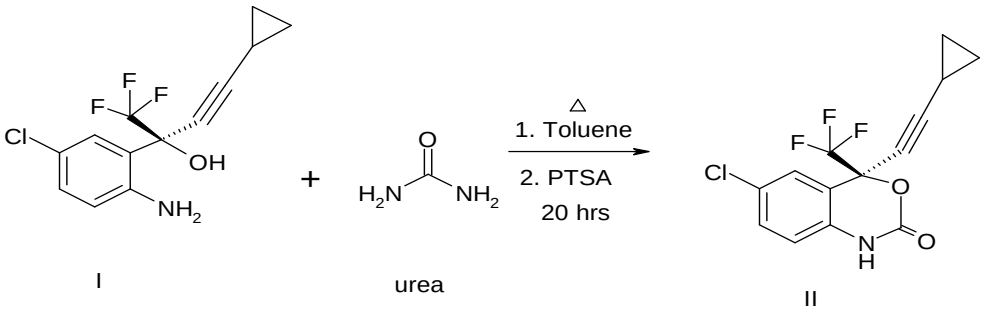
ABSTRACT

The present invention relates to a novel process for the preparation of (4S)-6-chloro-4-(cyclopropylethynyl)-1, 4-dihydro-4-(trifluoromethyl)-2H-3, 1-benzoxazin-2-one (Efavirenz) of Formula I with simple and commercially available urea.



Key words: Benzoxazinones**,** Efavirenz, Urea, Cyclisation

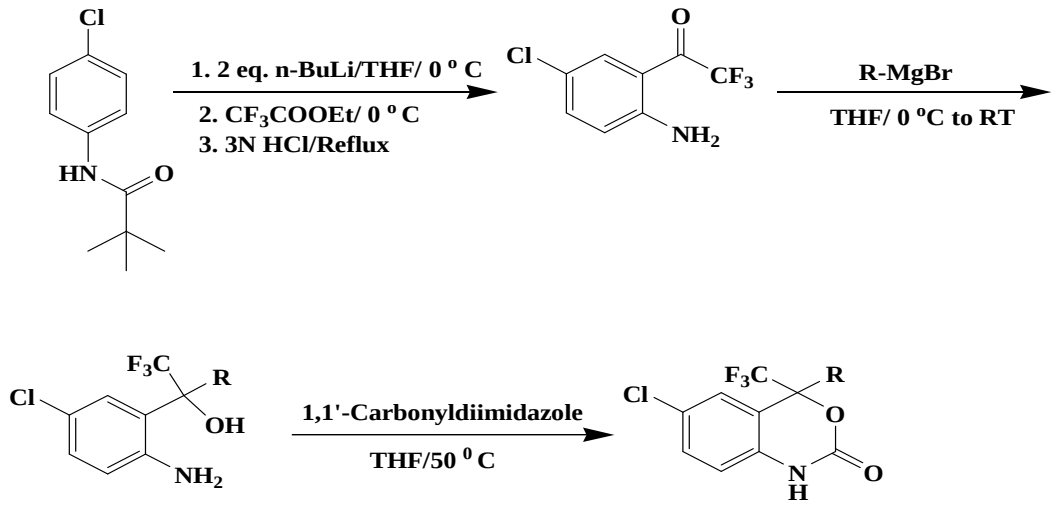
INTRODUCTION

Human immunodeficiency virus type -1 (HIV-1) is the causative agent for the transmission and development of the acquired immunodeficiency syndrome (AIDS).

Efavirenz **(II)** a potent NNRTI, is a significant component of a very effective (protease sparing) regimen when co administered with AZT and 3TC [1].

Importance of Efavirenz led to the development of several strategies for its synthesis, the world great potential drug Efavirenz still inaccessible to millions of people because of its atom economy and toxic[2] process involvement. During the course of drug development most of the world pharmaceutical companies attempt well in the handling of environment friendly Efavirenz development especially Merck [3] (scheme-I) and Lonza [4] developed toxic free process by using CDI and recently Peter H. Seeberger etal developed one development and optimization of the copper-catalyzed N-arylcarbamate formation and Cyclisation in a batch process [5][6][7][8][9]. But none of the method employed a best cost effective process, so that we became interested in designing a more economic and environmental toxic free Cyclisation process (Scheme-III) by using simple urea instead of using toxic phosgene, triphosgene and costly carbodiimidazole.

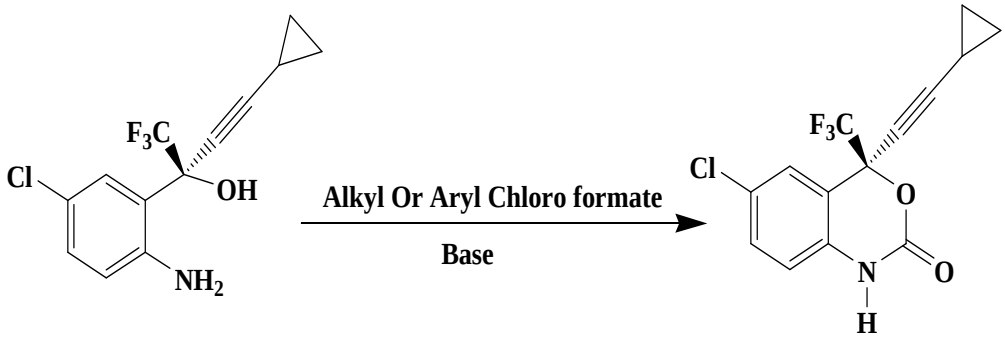
Scheme-I (Merck)



This general method teaches,
(1) Metallation of the pivalamide of parachloroaniline with n-butyl lithium followed by nucleophillic substitution with an ester to form a ketone,
(2) Synthesis of a tertiary carbinol by Grignard addition to the ketone and
(3) Cyclization of unprotected amine with the carbinol by addition of large excess of condensing agent to form a benzoxazinone.

Additionally the literature discloses the preparation of Efavirenz comprising cyclization of an amino alcohol using alkyl or aryl chloroformates and base. The process is depicted in the following scheme-**II**

Scheme-II



The main disadvantage of the above process is the use of aryl chloroformates[6, 7, 8, 9]which upon heating, decomposes into phosgene and if it comes in contact with water it produces toxic, corrosive fumes. The main advantage of this invention is the Cyclisation of an amino alcohol with urea which is a cheap source and non-hazardous in nature.

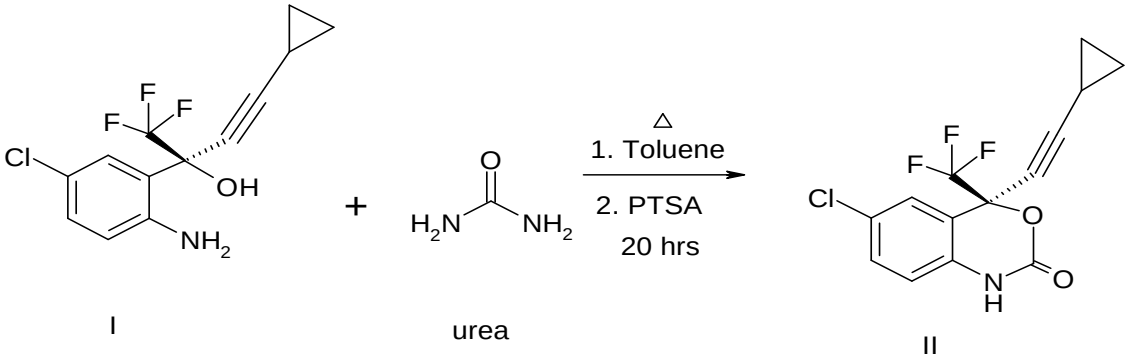
RESULTS AND DISCUSSION

We have surprisingly found that compound of Efavirenz can be prepared in good yield and high purity by Cyclisation of compound of (S)-2-(2-amino-5-chlorophenyl)-4-cyclopropyl-1,1,1-trifluorobut-3-yn-2-ol with urea as shown in the below scheme.

This cyclization of compound of (S)-2-(2-amino-5-chlorophenyl)-4-cyclopropyl-1, 1, 1-trifluorobut-3-yn-2-ol is effected in a suitable reaction media which includes aromatic hydro carbons, aqueous alcohols, ketones and ethers

etc., more preferably toluene.Optionally, the above Cyclisation is conducted in presence of an acid. The suitable acids may include mineral acids for example hydrochloric acid, sulfuric acids etc. organic acids like *p*-toluenesulphonic acid, acetic acid and trifluoro acetic acid etc. The cyclization is conveniently affected at elevated temperatures, most conveniently at reflux temperature of the reaction mixture. The reaction may be conveniently carried out under an inert gas atmosphere like nitrogen.

Scheme-III:



MATERIALS AND METHODS

General procedure- ^{1}H NMR spectra were recorded on a Gemini 300 MHz FT NMR spectrometer; the chemical shifts are reported in δ ppm relative to TMS. The IR spectra were recorded in the solid state as KBr dispersion using Perkin Elmer Spectrophotometer. The mass spectra were recorded on Shimadzu LCMS-QP8000, LC-MS and AB-4000 Q-trap LC-MS/MS.

Representative procedure for the preparation of Efavirenz

A solution of (S)-5-chloro-α-(cyclopropylethynyl)-2-amino-α-(trifluoroethyl)benzene methanol **(I)** (10 gm, 0.034 mole) and urea (2.48 gm, 0.0414 mole in toluene are refluxed in the presence of *para*-tolunesulphonic acid (PTSA) (0.31 gm, 0.0006 mole) for 20 hrs. After completion of the reaction as monitored by Thin Layer Chromatorgraphy (TLC), the reaction mixture was cooled to room temperature and then 30 ml of water was added. The obtained aqueous layer was extracted with toluene. The combined toluene layers were concentrated under reduced pressure. The obtained residue was cooled to room temperature and 30 ml of methanol was added and stirred. Methanol was distilled of to remove the toluene traces. Again methanol was added to the residue and cooled to 10-15 ºC. To this residue water was added at 10-15 ºC and stirred for 3 hrs. The obtained white solid was re-crystallized in toluene and heptane mixture to get 9.2gms of (4S)-6-chloro-4-(cyclopropylethynyl)-1,4-dihydro-4-(trifluoromethyl)-2H-3,1-benzoxazin-2-one **(II)** (Efavirenz). **^{1}H NMR (300MHz in DMCO-d_6):** δ 0.782-0.815 (m, 2H), 0.908-0.956 (m, 2H), 1.557-1.646 (m, 1H, cyclopropyl), 6.98-7.013(d, 1H), 7.45(s, 1H), 7.55-7.58 (dd, 1H), 11.11(s, 1H). **MASS** m/z; 314.2, in negative ion mode. Yield: 85 %, MR: 136-139°C, SOR -92.8°(c 0.3 in MeOH)

CONCLUSION

In conclusion, we have described a novel synthesis for the preparation of Efavirenz employing simple reaction condition and simple substrate. The synthesis is economically viable and is capable of Industrial production.

REFERENCES

[1] Access Campaign, Medicines Sans Frontieres, **July 2014** "Untangling the web of Antiretroviral price reductions", 17th edn.,

[2] **a**) R. C. Rizzo, M. Udier-Blagovic, D.-P. Wang, E. K. Watkins, M. B. Kroeger Smith, R. H. Smith, J. Triado-Rives, W. L. Jorgensen, *J. Med. Chem*., **2002**, 45, 2970; **b)** J.W. Corbett, S. S. Ko, J. D. Rodgers, L. A. Gearhart, N. A. Magnus, L. T. Bacheler, S. Diamond, S. Jeffrey, R. M. Klabe, B. C. Cordova, S. Garber, K. Logue, G. Trainor, P. S. Anderson, S. K. Erickson-Vittanen, *J. Med. Chem*., **2000,** 43, 2019.

[3] **a)** L. A. Radesca, Y. S. Lo, J. R. Moore, M. E. Pierce, **1997**, *Synth. Commun*. 27, 4373; b) M. E. Pierce et al., J. Org. Chem. **1998,** 63, 8536; c) A. Choudhury, J. R. Moore, M. E. Pierce, J. M. Fortunak, I. Valvis, P. N. Confalone, *Org. Process Res. Dev*., **2003**, 7, 324.
[4] **a)** D. Dai, X. Long, B. Luo, A. Kulesza, J. Reichwagen, Y. Guo (Lonza Ltd), PCT Int. Appl. WO2012097510, **2012.** 136, 12245; **b)** J.-I. Yoshida, Chem. Rec. **2010**, 10, 332; c) H. Usutani, Y. Tomida, A. Nagaki, H. Okamoto, T. Nokami, J.-I. Yoshida, *J. Am. Chem. Soc*., **2007** 129, 3046. D. L. Browne, J. C. Pastre, C. Butters, D. Guthrie, S. V. Ley, *Org. Process Res. Dev*. **2013**, 17, 1192.
[5] Peter H. Seeberger, *Angew. Chem. Int. Ed*. **2015**, 54, 1–5
[6] Lisa F. Frey, Somerset; Edward J. J 'Grabowski; Richard D. Tillyer, United states Patent, **1999**, 006114569A.
[7] Uchida M., *Chem. & Pharm. Bull*., **1990**, 38(6), 1575-1586.
[8] Gouilleu X, L., *Tetrahedron Letters*, **1996**, 39(37), 7031-7034.
[9] Radesca, L. A., *Synthetic Communications*, **1997**, 27(24), 4373-4384.