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A MICROWAVE ASSISTED ONE – POT SYNTHESIS OF TICLOPIDINE HYDROCHLORIDE THROUGH 4,5,6,7-TETRAHYDRO (3,2-C) THIENO PYRIDINE HYDROCHLORIDE

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ABSTRACT

The microwave assisted Pictet Spengler reaction of thiophene ethyl amine and formaldehyde afforded 4,5,6,7-tetrahydro (3,2-c) thieno pyridine hydrochloride (**I**), which was then subjected to alkylation with 2-chloro benzyl chloride under microwave conditions to afford Ticlopidine Hydrochloride, thus making it one-pot, efficient and economical approach.

KEY WORDS: Ticlopidine Hydrochloride, Pictet-Spengler, Schiff base, Alkylation, Microwave.

INTRODUCTION

Pictet-Spengler reaction was achieved first in 1934 by Schöpf and Bayerle, since then numerous applications have been recorded. The Pictet-Spengler type reaction[(1-2)] can be achieved by heating the amine with a slight excess of aldehyde and excess of 20–30% hydrochloric acid at suitable temperature. Similarly there is plethora of examples in literature suggesting N-alkylation of secondary amine. Based on rate of reaction the time factor for the sequence individually may vary from 30 min –10 hr[(3)]. As per the literature both the above explained steps are very efficiently carried out under microwave condition in presence of base in aqueous medium[(2 – 11)]. The microwave assisted approach will have a great impact on the synthesis of life saving drugs. In view of these observations from literature, we envisioned and selected Ticlopidine hydrochloride (**II**) [(12-13)] (**Figure 1**) synthesis through 4,5,6,7-tetrahydro (3,2-c) thieno pyridine hydrochloride (**I**) (**Figure 1**), an advanced precursor under microwave condition.

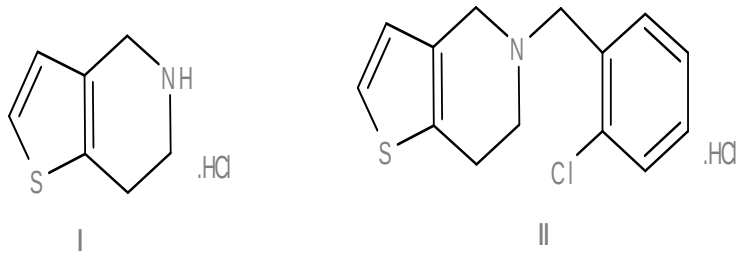
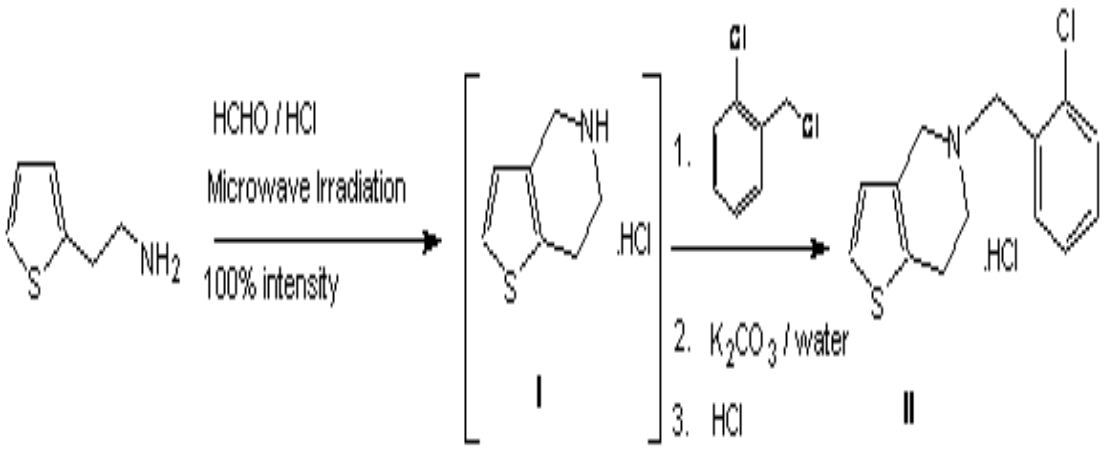


Fig 1. 4,5,6,7-tetrahydro (3,2-c) thieno pyridine hydrochloride (I), Ticlopidine Hydrochloride (II).

Ticlopidine Hydrochloride (**II**) is antithrombotic drug patented by Sanofi (France) [12-13]. It is marketed worldwide in more than 110 countries. Generic versions of the drug have already hit the market. Major pharmaceutical giants are coming with innovative manufacturing route to compete and capture generic market[2-22], but none of them have given a thought for the molar efficiency of the reaction so that the impact of waste generated on the environment is minimized. To improve the rate of reaction and molar efficiency of the final drug, it was thought worthwhile to carry out the reaction in a much simpler, eco-friendly and convenient way. This could be possible under microwave condition to get compound **II** as depicted in **Scheme 1**. It was observed that reaction of thiophene -2- ethyl amine and formaldehyde requires more than 8 hrs to afford compound **I.** Similarly alkylation of the compound **I** in presence of base takes more than 8 hrs. Under microwave condition compound **I** and **II** are not reported, though microwave assisted Pictet-Spengler Reaction and alkylation of secondary amines is reported in literature [1 - 11].



Scheme 1. One-pot approach of compound II under microwave irradiation.

MATERIALS AND METHODS

General Method

All solvents were obtained from commercial sources and dried or purified by standard procedures before use. Melting points were measured on Gallenkamp melting point apparatus and are uncorrected. IR spectra were recorded on Shimadzu FTIR-IR-4200 spectrophotometer in KBr discs. ^{1}H NMR was recorded on BRUKER FT-300 spectrophotometer with TMS as an internal standard, microwave reactions were carried out in Startsynth Microwave Synthesis Labstation.

One-pot microwave enhanced Pictet-Spengler and N-alkylation reaction : Formation of Ticlopidine Hydrochloride (II) [19 – 22].

Formaldehyde (0.15gm, 0,005mole) was added to 2-thiophene-(2-ethylamine) (0.635gm, 0.005mole) taken in 100ml round bottom flask. The mixture was irradiated in a microwave oven at 100% intensity for a period of 50 seconds. After this period the reaction mixture was taken out of microwave oven and allowed to cool. 1ml of concentrated hydrochloric acid was added to the mixture and then irradiated in a microwave oven at 100% intensity for a period of 2 minutes. After this period the reaction mixture was taken out of microwave oven and allowed to cool. The reaction mixture was quenched in 15ml water. To this potassium carbonate (3.801gm, 0.0275mole) and 2-chloro benzyl chloride (0.805gm, 0.005mole) were added in single lot, and again irradiated in a microwave oven at 100% intensity for a period of 12 minutes. TLC was checked for the absence of compound **I**. The reaction on completion was extracted with dichloromethane (3 x 10ml). The combined organic layer was dried over anhydrous sodium sulfate, and filtered. The clear filtrate on evaporation of solvent under vacuum afforded thick viscous pale yellow oil. The yellow oil on neutralization with conc. hydrochloric acid in ethanol afforded white crystals of Ticlopidine Hydrochloride, yield : 1.013gm (67.48%) m.p.184 - 186^{o}C, (lit[12, 13,19 - 22] m.p.186 - 187^{o}C). IR and ^{1}HNMR spectral data was also consistent with the reported data[12, 13,19 – 22].

RESULTS AND DISCUSSION

Pictet-Spengler type reaction is facilitated by formation of Schiff Base followed by increased electron density at the point of ring closure. The Schiff base formed can be isolated and then can be cyclized to get compound **I**, if required compound **I** can be isolated. To save time, energy and solvent usage Schiff base and 4,5,6,7-tetrahydro (3,2-c) thieno pyridine

hydrochloride (**I**) were not isolated. It was directly taken for alkylation to afford compound **II** making it one-pot synthesis.

CONCLUSION

Thus we were successful in carrying out one-pot synthesis of Ticlopidine Hydrochloride (**II**) for the first time under microwave irradiation in single step, with very good chemical yield, purity and in very short reaction time. It's a new, efficient and simple approach for an anti-thrombotic drug.

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REFERENCES

1. Whaley WM, Tuticorin R. Govindachari : The Pictet-Spengler Synthesis of Tetrahydroisoquinolines and Related Compounds : Organic Reaction Vol 4. John Wiley and Sons Publication, 15 March 2011.
2. Satyanarayana VSV, Sreevani P, Vijayakumar V : *Arkivoc*, 2008; xvii : 221 – 223.
3. March J : Advanced Organic Chemistry : Reaction Mechanism and Structure, 4th Edition, John Wiley and Sons Publication, 2010; 411 - 413
4. Mohamed S, Mohamed SA, Shalofh S, Fhid O : *J. Chem. Pharm. Res*, 2012; 4(5) : 2512 - 2516.
5. Chakraborty M, Baweja S, Bhagat S, Singh T : *Int. J. Chem. Reactor Eng.*2012; 10 : 6580 -2973.
6. Mohan S, Ananthan S : *Int. J. Chem. Research*, 2011; 2(3) : 37 - 41.
7. Naik B, Desai KR : *Indian J. Chem.* 2006; 45B : 267 -271.
8. Adimurthy S, Joshi G : *Indian J. Chem*. 2010; 49B : 771 -775.
9. Moore JL, Taylor SM, Soloshonok VA : *Arkivoc*, 2005; vi : 287 – 292.
10. Singh CB, Kavala V, Samal AK, Patel BK : *Eur. J. Org. Chem.* 2007; 1369 -1377.
11. Aillaud I, Haurena C, Gall EL, Marteus T, Ricci G : *Molecules*, 2010; 8144 – 8155.
12. Andre B, Andre M. Sanofi Socieye Anonyme – Fr, *FR Pat. 2769313*, 1997.
13. Aubert D, Touch PD, Fenand C, Saint-Agne R, Maffarand JP. Sanofi France, *US Pat. 4529596*, 1985.
14. Maria B, Tiborne B, Zsolt D, Katalin G, Attila S. Sanofi-Synthelabo, France, *WO 0027840*, 2000.

15. Maria B, Marianna CN, Leventene M, Antal G, Edit A. Sanofi, France, *WO 9851689*, 1998.
16. Maria B, Marianna CN, Zotten M, Piroska J, Tiborne B. Sanofi, France, *WO 9851681*, 1998.
17. Maria B, Marianna CN, Antal G, Edit A, Molnar E. Sanofi, France, *US Pat. 6180793*, 2001.
18. Andre B, Braye E. Parcor, Paris, France, *US Pat. 4174448*, 1979.
19. Descamps, *C.A.* 1963, *59*, 1605 – 1607.
20. Maffrand JP, Eloys F. *Eur. J. Med. Chem*. 1974, *9*, 483 - 486.
21. Maffrand JP, Eloys F. *J. Hetrocyclic Chem*. 1976, *13*, 1347 – 1349.
22. Castigne ARJ. Centre d' Etudes pour I' Industrie Pharmaceutique, France, *US Pat. 4051141*, **1977**.