Asian Journal of Chemistry; Vol. 31, No. 10 (2019), 2257-2260

ASIAN JOURNAL OF CHEMISTRY

https://doi.org/10.14233/ajchem.2019.22059

A Concise and Efficient Synthesis of an Impurity, N-Desmethyl Alcaftadine from Alcaftadine: An H1 Antagonist

G. SRAVYA[1], GRIGORY V. ZYRYANOV[1,2], K. RAMASESHAIAH[3,4], G. MALLI KARJUNA REDDY[1], C. SURESH REDDY[5] and N. BAKTHAVATCHALA REDDY[1,*]

[1]Ural Federal University, Chemical Engineering Institute, Yekaterinburg 620002, Russia
[2]I. Ya. Postovskiy Institute of Organic Synthesis, Ural Division of the Russian Academy of Sciences, Yekaterinburg 620219, Russia
[3]Rajeev Gandhi Memorial College of Engineering and Technology (Autonomous), Nandyal-518501, India
[4]Department of Chemistry, Krishna University, Machilipatnam-521001, India
[5]Department of Chemistry, Sri Venkateswara University, Tirupati-517502, India

*Corresponding author: E-mail: drbvreddyn@gmail.com

Received: 6 March 2019; *Accepted*: 19 May 2019; *Published online*: 30 August 2019; AJC-19532

Herein, a simple approach for the synthesis of N-desmethyl alcaftadine, an H1 histamine antagonist in solid state and its structure is presented. The reactions were performed under mild and metal free conditions at reflux temperature within a range of 65-70 ºC and the desired product N-desmethyl alcaftadine was obtained in high purity with good yield (96.42 %). It was detected by ultra-high-performance liquid chromatography (UHPLC).

Keywords: Antihistamine, Alcaftadine, N-Desmethyl Alcaftadine.

INTRODUCTION

Histamine is an important mediator of immediate hypersensitivity reactions acting locally and causing smooth muscle contraction, vasodilation, increased vascular permeability, edema and inflammation. Histamine acts through specific cellular receptors which have been categorized into four types, H1 through H4. Antihistamines represent a class of medications that block the histamine type 1 (H1) receptors. It is important to note that the antihistamines do not block or decrease the release of histamine, but rather ameliorate its local actions. Agents that specially block other H2 receptors are generally referred to as H2 blockers rather than antihistamines.

The nitrogen-containing heterocyclic compounds are common constituents of natural products, agrochemicals, pharmaceuticals and are also useful intermediates in a number of microbial transformations and industrial processes [1,2]. Among nitrogen heterocyclic compounds, benzazepines are fine raw chemical materials and represent a privileged structure for its biological target. The benzazepines form a class of seven-membered aza-heterocycles fused with an aromatic ring, which is divided into the three distinct isomeric forms (1-, 2- and 3-benzazepines), depending on the relative position of nitrogen atom. A huge variety of nitrogen-containing bioactive molecules contains a benzazepine as an essential core, as proven by the scaffold of tolvaptan, galanthamine, esticarbazepine acetate and benazepril (Fig. 1). Numerous series of benzazepine derivatives have been marketed for their therapeutic applications as antidepressant, antihypertensive, anti-ischaemic and their rapid screening for pharmacological properties have been recently reviewed by various researchers [3-10].

Benzazepines rings are now coming of age and they are incorporated in a large number of well-known drugs, such as alcaftadine, used for the prevention of itching associated with allergic conjunctivitis [11]. Alcaftadine, an ophthalmic histamine H1 receptor antagonist, was approved by the FDA for the prevention of itching associated with allergic conjunctivitis and was launched under the trade name Lastacaft® in early 2011 [12]. Alcaftadine was discovered by Janssen Pharmaceuticals and marketed by Vistakon Pharmaceuticals, both subsidiaries of Johnson & Johnson. However, unlike other marketed drugs, the synthesis of alcaftadine was only mentioned in the patents

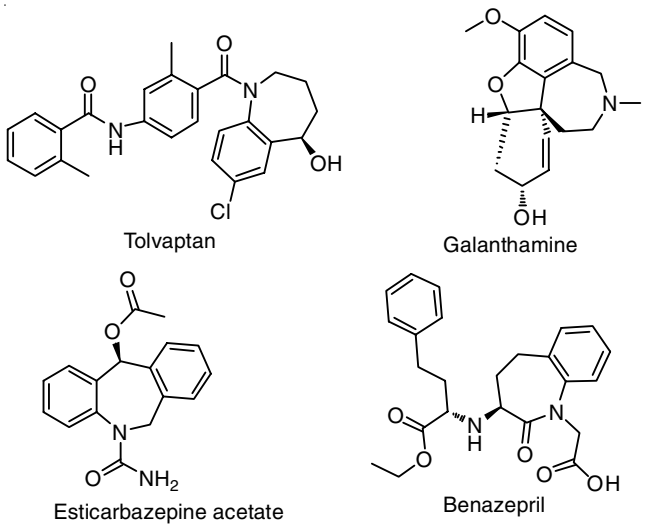


Fig. 1. Benzazepine containing drugs

filed by Janssen's scientists approximately 20 years ago. However, many scientific researchers are still encountering some problems to be solved in the synthesis of benzazepines based drug molecules, such as presence of high impurities and obtaining pure product with very low yields, that troubling the synthesis and application of benzazepines.

Pharmaceuticals impurities are the unwanted chemicals that remain with active pharmaceuticals ingredients, API or drug product formulations. The impurities observed in drug substances may arise during or may be derived from sources such as starting material, intermediates, reagents, solvents, catalysts and also reaction by products. Particularly, organic impurities may arise from racemization, conversion of an optically active substance into and optically inactive mixture of equal amounts of dextrorotatory and levorotatory or contamination of enantiomer form with another [13]. During drug development, impurities may be formed as a result of the intuitive stability of drug substances or may be due to incompatibility with added excipients or may appear as the result of interactions with packing materials.

Various regulatory authorities at International level such as ICH (International Conference on Harmonization), USFDA (United States Food and Drug Administration), EMA (European Medicine Agencies), CDHA (Canadian Drug and Health Sciences) and JPMDA (Japanese Pharmaceutical and Medical Devices Agency) are focusing on the control of impurities and also incorporating limits that restrict the impurity levels present in APIs as well as in drug formulations. The amount of various impurities found in drug substance will determine the ultimate safety of the final pharmaceutical product. Therefore, identification, quantitation, qualification and control of impurities are now a critical part of the drug development process.

Several methods have been applied to N-demethylation of tertiary amines. These include the von Braun reaction with cyanogen bromide [14] photochemical reactions [15,16] ruthenium catalyzed reactions with alkyl and hydrogen peroxides [17,18] oxidation with *m*-chloroperbenzoic acid [19,20] and reactions with chloroformates [21-25]. To best of our knowledge, we are the first to achieve N-desmethyl alcaftadine from alcaf-tadine through telescoping synthesis by using 1-chloroethyl chloroformate (ACE-Cl).

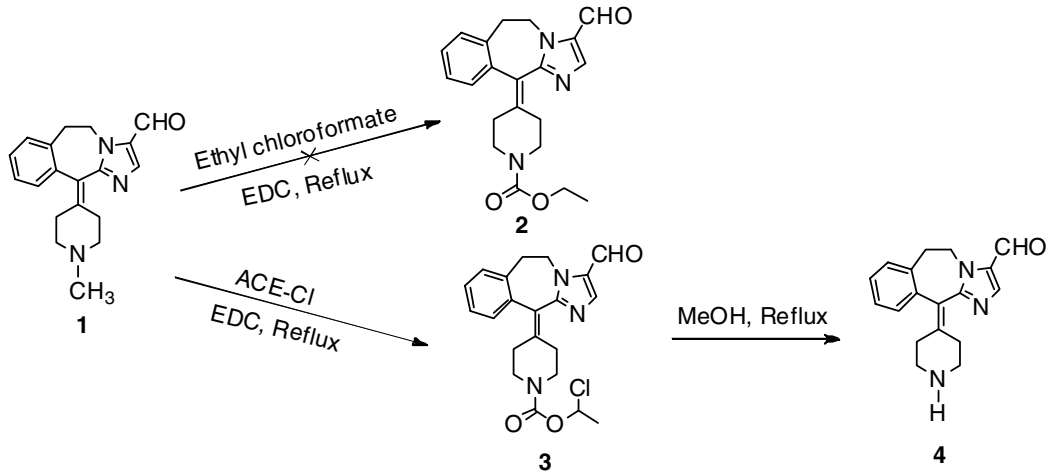
EXPERIMENTAL

All reagents were purchased from Sigma-Aldrich, and used without further purification. AscendTM Bruker 400 (Bruker, Fallanden, Switzerland) instrument and operating at 400 MHz for ^{1}H NMR and 100 MHz for ^{13}C NMR using DMSO-d_6 solvent and tetramethylsilane (TMS) as internal standard. The ^{1}H chemical shift values were reported on δ scale in ppm, relative to TMS (δ = 0.00 ppm) and in ^{13}C chemical shift values were reported relative to DMSO-d_6 (δ = 39.5 ppm). The infrared spectroscopy data recorded on a Shimadzu IR Affinity-I FT-IR spectrophotometer (Shimadzu Corporation, Kyoto, Japan) over the range of 4000-400 cm^{-1} by pressed pellet method using KBr. The spectra were acquired by accumulation of 42 scans with 4 cm^{-1} resolution. The ESI/MS experiment was performed on a Velos Pro ion trap mass spectrophotometer from Thermo Scientific (San Jose, CA, USA). Thermo X-Calibre, version 2.2 software from X-Caliber Technologies (Pune, India) was used for analysis of data. The chromatographic analysis was performed using a Shimadzu, Nexera-X2 UHPLC system (Shimadzu Corporation, Kyoto, Japan) equipped with a photodiode array detector (SPD 20A) and SPD M30 dual wavelength absorbance detector. Empower PDA software was utilized for process monitoring, data acquisition and system control.

General procedure for the synthesis of 11-(piperidin-4-ylidene)-6,11-dihydro-5*H*-benzo[*d*]imidazo[1,2-a]azepine-3-carbaldehyde: The procedure using ACE-Cl was based on the method of Olofson *et al*. [24]. The tertiary amine drug alcaftadine (20 mg) [26] was dissolved in dry 1,2-dichloroethane (4 mL). Four equivalents of ACE-Cl was added and the mixture was refluxed for 2 h under nitrogen. After completion of reaction, which was monitored by TLC (DCM:MeOH:TEA = 9.5:0.5:1). The solvent was evaporated and the residue was dissolved in methanol. The solution was kept at 65-70 ºC for 2 h to hydrolyze the intermediate ACE-alcaftadine (**3**) and then concentrated to a volume of 0.5 mL before the purification step. Later, it was purified by recrystallization from acetonitrile to furnish pure desired pale yellow solid as product **4** (**Scheme-I**).

RESULTS AND DISCUSSION

The new process is exemplified by the specific N-demethylation of alcaftadine (**1**) to give N-desmethyl alcaftadine (**4**) in 57.9 % yield with 96.42 % purity. In an initial endeavor, the reaction is performed by adding ACE-Cl to compound **1** in 1,2-dichloroethane (DCE) at room temperature slowly for 15-20 min followed by refluxing the reaction mixure for 1-2 h. The progress of the reaction was monitored by TLC and after completion of the reaction the solvent was evaporated and the residue was purified by using 60-120 mesh silicagel column chromatography using ethylacetate:hexane (1:1) as mobile phase to afford the intermediate ACE-alcaftadine (**3**) as oily mass at 94.8 % yield. Later, it was dissolved in methanol and the solution was stirred at 65-70 ºC for 2 h to hydrolyze the intermediate and then concentrated, purified by recrystallization from acetonitrile to get the desired pure product **4**. All the spectral data IR, mass, ^{1}H NMR and ^{13}C NMR were in good agreement with the proposed structure. The selective synthesis of N-desmethyl alcaftadine impurity (**4**), and the optimized reaction conditions are summarized in Table-1. The reaction was conducted in



Scheme-I: Synthesis of N-desmethyl alcaftadine from alcaftadine

TABLE-1
REACTION CONDITIONS OF N-DESMETHYL ALCAFTADINE IMPURITY (**4**)[a]

Entry	Bases	Solvents	Reagent	Temp. (°C)	Yield (%)[b]
1	NaOH	^{i}PrOH	Ethylchloroformate	50-60	NR[c]
2	NaOH	^{i}PrOH	1-Chloroethylchloroformate	83-86	NR[c]
3	KOH	^{i}PrOH	Ethylchloroformate	60-70	NR[c]
4	KOH	^{i}PrOH	1-Chloroethylchloroformate	83-86	NR[c]
5	–	MeOH	Ethylchloroformate	50-60	NR[c]
6	–	MeOH	1-Chloroethylchloroformate	65-70	57.9

[a]Reaction condition: **1** (1.0 equiv.), 1-Chloroethylchloroformate (ACE-Cl) (4.0 equiv.), MeOH (20 mL) stirred for 1-2 h at specified temperature. [b]Isolated product of **4** after recrystallization. [c]NR means no reaction.

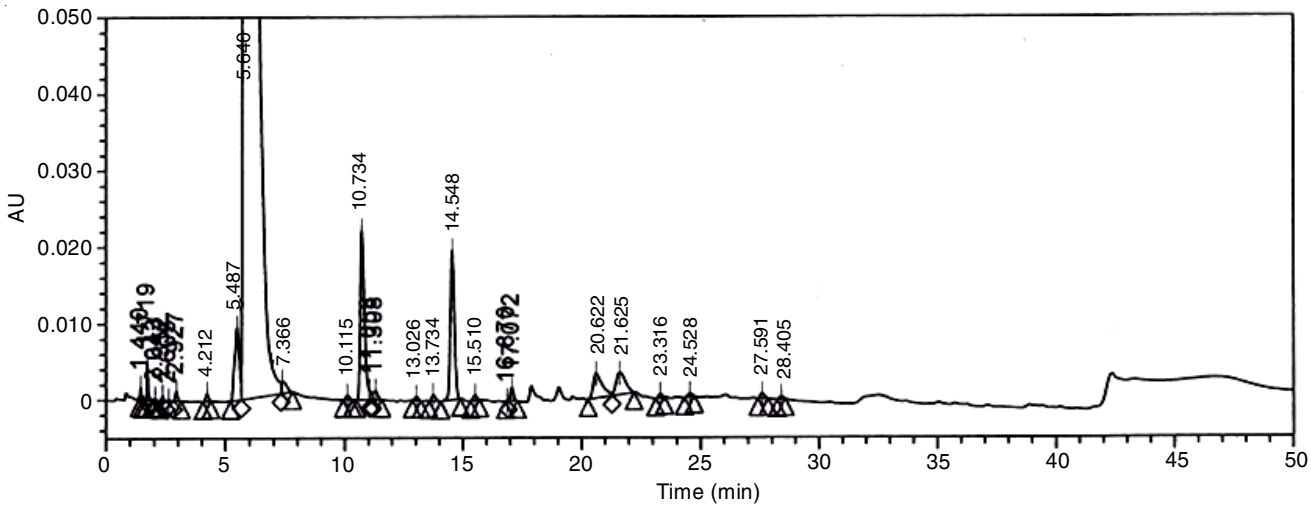


Fig. 2. UHPLC chromatogram of compound **4**

presence of different bases and solvents, such as NaOH, KOH and iPrOH but noteworthy reaction did not occur with protecting groups ethylchloroformate and 1-chloroethyl chloroformate (Table-1, entries 1-4). We attempted the reaction in the absence of base at 65-70 ºC, in the presence of MeOH and 1-chloroethyl chloroformate which was proved to be favorable conditions for formation of compound (**4**) (Table-1, entry 6).

Identification of peaks by ultra performance liquid chromatography (UHPLC): Peak resolution is a requirement for sensitive, accurate chromatographic analysis. Literature survey revealed that for the alcaftadine assay there were no methods available for the estimation of related impurity N-desmethyl alcaftadine. So, we would like to execute the UHPLC analytical technique for the determination of the impurity by comparing the retention times (RT) of both commercial as well our synthesized products. Initially we injected commercially purchased alcaftadine along with its constituent impurities, and followed by our synthesized impurity N-desmethyl alcaftadine. From the UHPLC chromatogram, it clearly demonstrates that present synthesized product was exactly matching with the commercially available product and yielding highest assay of 96.42 % at RT 5.84 min (Fig. 2).

Conclusion

A faster and more accurate UHPLC approach, a specialized chromatographic technique was used to identify N-desmethyl

alcaftadine that was synthesized from alcaftadine. We employed this particular technology to prove that UHPLC is an appropriate technique to overcome the struggles in detecting the presence of performance-enhancing or diminishing moieties in drugs. Using simple and neat reaction conditions place ACE-Cl method in a superior position.

ACKNOWLEDGEMENTS

One of the authors, C. Suresh Reddy, being an associate member of Institute of Food Security and Sustainable Agriculture, University Malaysia Kelantan, Jeli Campus, Malaysia expresses his sincere thanks to University Malaysia Kelantan for their timely encouragement in the present research work.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

REFERENCES

1. H.X. Ding, K.K.C. Liu, S.M. Sakya, A.C. Flick and C.J. O'Donnell, *Bioorg. Med. Chem.*, **21**, 2795 (2013); https://doi.org/10.1016/j.bmc.2013.02.061.
2. I.A. Parshikov, A.I. Netrusov and J.B. Sutherland, *Appl. Microbiol. Biotechnol.*, **95**, 871 (2012); https://doi.org/10.1007/s00253-012-4220-z.
3. J.H. Shah, R.M. Hindupur and H.N. Pati, *Curr. Bioact. Compd.*, **11**, 170 (2015); https://doi.org/10.2174/1573407211666150910202200.
4. H.-C. Lin, G. Chiou, Y.-H. Chooi, T.C. McMahon, W. Xu, N.K. Garg and Y. Tang, *Angew. Chem. Int. Ed.*, **54**, 3004 (2015); https://doi.org/10.1002/anie.201411297.
5. T. Gozler, B. Gozler, I. Weiss, A.J. Freyer and M. Shamma, *J. Am. Chem. Soc.*, **106**, 6101 (1984); https://doi.org/10.1021/ja00332a069.
6. H. Li, Y. Wen, F. Wang, P. Wu and X. Wei, *Tetrahedron Lett.*, **56**, 5735 (2015); https://doi.org/10.1016/j.tetlet.2015.08.071.
7. H.S. Chung, P.M. Hon, G. Lin, P.P. But and H. Dong, *Planta Med.*, **69**, 914 (2003); https://doi.org/10.1055/s-2003-45100.
8. H.R. Howard, *Expert Opin. Therap. Patents*, **15**, 1811 (2005); https://doi.org/10.1517/13543776.15.12.1811.
9. J.P. Hieble, Method of Treating Benign Prostatic Hypertrophy, U.S. Patent 4755507 (2010).
10. D.M. Wilson, J. Apps, N. Bailey, M.J. Bamford, I.J. Beresford, M.A. Briggs, A.R. Calver, B. Crook, R.P. Davis, S. Davis, D.K. Dean, L. Harris, T.D. Heightman, T. Panchal, C.A. Parr, N. Quashie, J.G.A. Steadman, J. Schogger, S.S. Sehmi, T.O. Stean, A.K. Takle, B.K. Trail, T. White, J. Witherington, A. Worby and A.D. Medhurst, *Bioorg. Med. Chem. Lett.*, **23**, 6897 (2013); https://doi.org/10.1016/j.bmcl.2013.09.089.
11. S.J. Ono and M.B. Abelson, *J. Allergy Clin. Immunol.*, **115**, 118 (2005); https://doi.org/10.1016/j.jaci.2004.10.042.
12. A.I. Graul, E. Cruces, C. Dulsat, E. Arias and M. Stringer, *Drugs Today*, **48**, 33 (2012); https://doi.org/10.1358/dot.2012.48.1.1769676.
13. S. Yusuf, F. Zhao, S.R. Mehta, S. Chrolavicius, G. Tognoni and K.K. Fox, *N. Engl. J. Med.*, **345**, 494 (2001); https://doi.org/10.1056/NEJMoa010746.
14. H.A. Hageman, Organic Reactions, John Wiley & Sons: New York, vol. 7, Chap. 4 (1953).
15. J. Santamaria, R. Ouchabane and J. Rigaudy, *Tetrahedron Lett.*, **30**, 2927 (1989); https://doi.org/10.1016/S0040-4039(00)99160-3.
16. J. Santamaria, R. Ouchabane and J. Rigaudy, *Tetrahedron Lett.*, **30**, 3977 (1989); https://doi.org/10.1016/S0040-4039(00)99299-2.
17. S.I. Murahashi, T. Naota, N. Miyaguchi and T. Nakato, *Tetrahedron Lett.*, **33**, 6991 (1992); https://doi.org/10.1016/S0040-4039(00)60914-0.
18. S.I. Murahashi, T. Naota and K. Yonemura, *J. Am. Chem. Soc.*, **110**, 8256 (1988); https://doi.org/10.1021/ja00232a060.
19. I. Monkovic, H. Wong and C. Bachand, *Synthesis*, 770 (1985); https://doi.org/10.1055/s-1985-31342.
20. H.Y.P. Choo, Y.O. Shin and J. Park, *J. Anal. Toxicol.*, **14**, 116 (1990); https://doi.org/10.1093/jat/14.2.116.
21. K.C. Rice, *J. Org. Chem.*, **40**, 1850 (1975); https://doi.org/10.1021/jo00900a044.
22. S.W. Baldwin, P.W. Jeffs and S. Natarajan, *Synth. Commun.*, **7**, 79 (1977); https://doi.org/10.1080/00397917709410059.
23. T.A. Montzka, J.D. Matiskella and R.A. Partyka, *Tetrahedron Lett.*, **14**, 1325 (1974); https://doi.org/10.1016/S0040-4039(01)82479-5.
24. R.A. Olofson, J.T. Martz, J.P. Senet, M. Piteau and T. Malfroot, *J. Org. Chem.*, **49**, 2081 (1984); https://doi.org/10.1021/jo00185a072.
25. R.A. Olofson, *Pure Appl. Chem.*, **60**, 1715 (1988); https://doi.org/10.1351/pac198860111715.
26. F.E. Janssens, G.S.M. Diels and J.E. Leenaerts, Imidazo[2,1-*b*]benzazepine Derivatives, Compositions and Method of Use, U.S. Patent US5468743 A (1995).