A New Route to cevimeline

Chinmoy Pramanik, Pradip Patil, Sandeep Kotharkar, Narendra K. Tripathy, Mukund K. Gurjar

PII: S0040-4039(13)00504-2
DOI: http://dx.doi.org/10.1016/j.tetlet.2013.03.090
Reference: TETL 42716

To appear in: *Tetrahedron Letters*

Received Date: 1 October 2012
Revised Date: 19 March 2013
Accepted Date: 22 March 2013

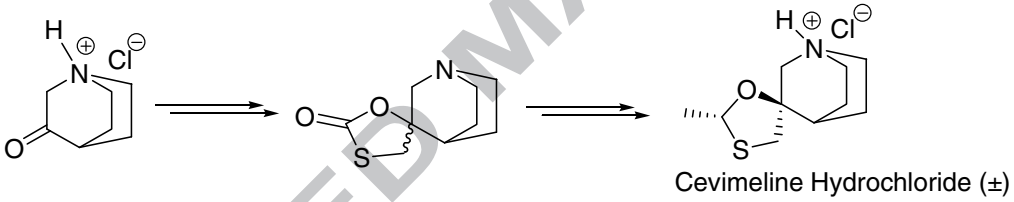
Please cite this article as: Pramanik, C., Patil, P., Kotharkar, S., Tripathy, N.K., Gurjar, M.K., A New Route to cevimeline, *Tetrahedron Letters* (2013), doi: http://dx.doi.org/10.1016/j.tetlet.2013.03.090

A New Route to cevimeline

ChinmoyPramanik*, PradipPatil, SandeepKotharkar, Narendra K. Tripathy, and Mukund K. Gurjar

API R&D Centre, Emcure Pharmaceuticals Ltd., ITBT Park, Phase-II, MIDC, Hinjwadi, Pune-411057, India

Fax: +91-20-39821445. E-mail: chinmoy.pramanik@emcure.co.in



Cevimeline Hydrochloride (±)

A New Route to cevimeline

Authors: ChinmoyPramanik*, PradipPatil, SandeepKotharkar, Narendra K. Tripathy, and Mukund K. Gurjar

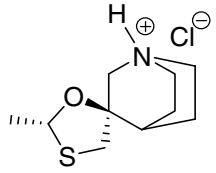
API R&D Centre, Emcure Pharmaceuticals Ltd., ITBT Park, Phase-II, MIDC, Hinjwadi, Pune-411057, India

Corresponding author: Fax: +91-20-39821445. E-mail: chinmoy.pramanik@emcure.co.in

Abstract: Thepresent work demonstrates a new route for the synthesis of cevimeline hydrochloride in which safe and odorless thioureais utilized as athiolating reagent.

*Keywords***:**Cevimeline hydrochloride, spirocyclic compound,Active Pharmaceutical Ingredients (API), muscarinic agent,thiourea, process development.

Cevimeline hydrochloride (**1**, Figure 1), chemically known as *cis*-2-methyspiro(1,3-oxathiolane-5,3)quinuclidine, exists as a racemic mixture,an oral muscarinic agent that has been recently approved for the treatment of xerostomia in the setting of Sjogren's syndrome.[1]Sjogren syndrome is a systemic chronic inflammatory disorder characterized by xerostomia, anhidrosis, and conjunctivitis sicca due to lymphocytic infiltration ofexocrine organs, such as salivary, sweat, and lacrimal glands. Cevimeline directly stimulates M_3 receptors in the salivary glands and increases salivary secretion and it lasts longer (5 h) than for pilocarpine (3 h).It is distributed under the brand name Evoxac(R) by Daiichi Sankyo (Tokyo, Japan) in the USA, Japan, and Taiwan. Common reported side effects of this drug includenausea, headache, rhinorrhea, diarrhea, abdominal pain, and diaphoresis.

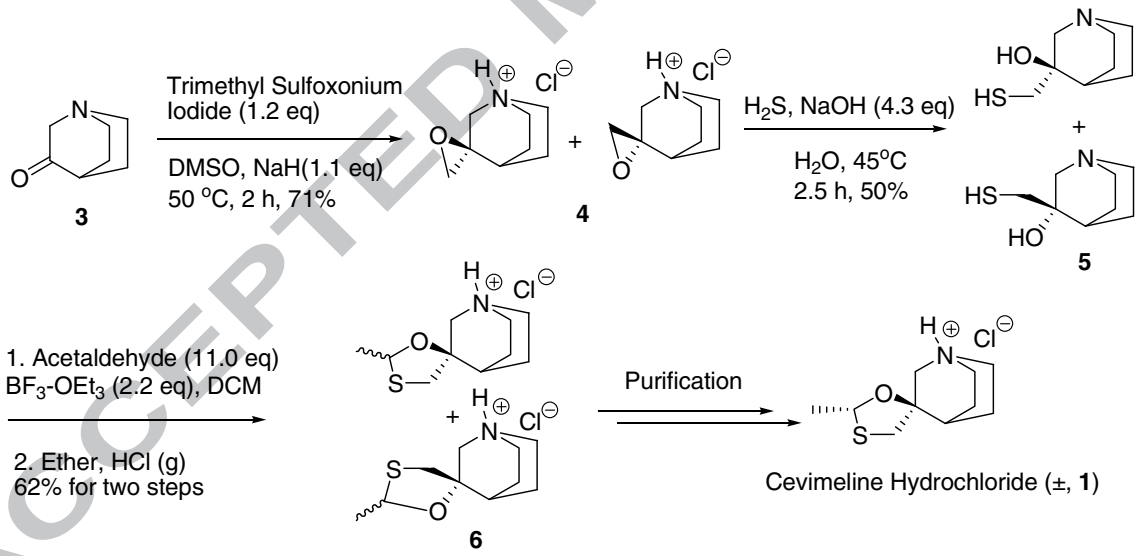


Cevimeline Hydrochloride (±, **1**)

Figure 1 (Cevimeline Hydrochloride)

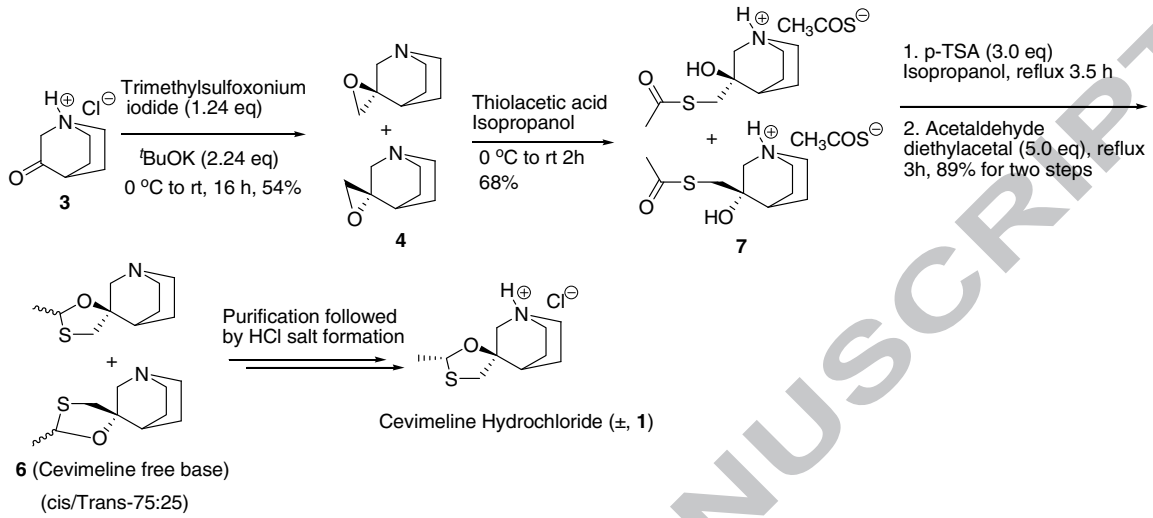
A detailed literature study revealed that there are two patent procedures available for the commercial manufacturing of cevimeline/cevimeline hydrochloride. Fisher *et. al.*[2] started the process with the ketone **3**(Scheme 1), which on epoxidation following the Corey-Chaykovsky conditions[3]produced the epoxide **4**. Compound **4** on treatment with hydrogen sulfide followed by cyclization of the resulting thiol**5** with acetaldehyde in presence of $BF_3.Et_2O$ produced **6** (1:1 cis:trans mixture). Cevimeline hydrochloride (**1**) (cis isomer) is resolved from the mixture by successive purifications.

Scheme 1



Bratovanov *et al.*[4] (Scheme 2) used the same epoxide (**4**) but opened the ring with thioacetic acid which was followed by *p*-TSA catalyzed thioacetal formation in two steps. The reported routes suffer major disadvantage with respect to the thiolating agent. In both the cases, they have used highly hazardous, very foul smelling and difficult to handle reagents like hydrogen sulfide or thioacetic acid.

Scheme 2

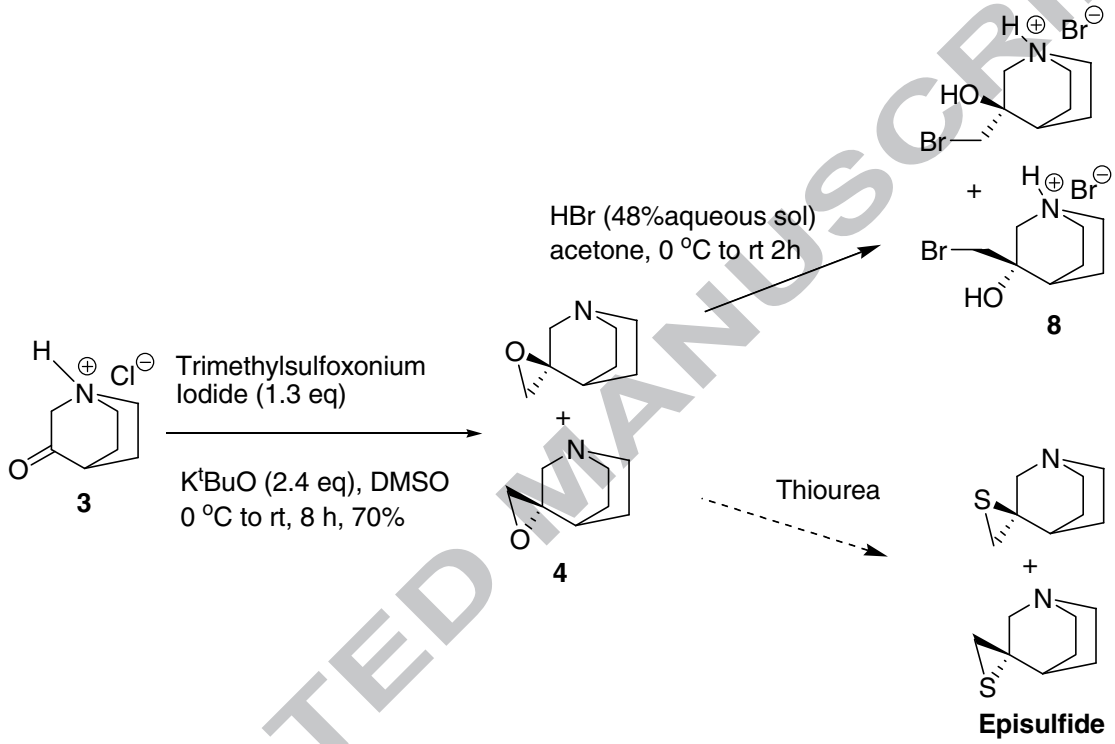


In our continuous efforts to develop improved processes for generic drugs of our interest, we decided to investigate an alternate route to cevimelinehydrochloride (**1**).In this case the basic premise would be to focus on the thiolating agents other than hazardous hydrogen sulfide or thioacetic acid.Herein we report a convenient, economical, much greener route (Scheme 3) for the synthesis of cevimeline hydrochloride (**1**) using nonhazardous and odorlessreagent thiourea as the thiolating reagent.

The literature procedure[4]was modified to generate the epoxide intermediate **4**starting from commercially available3-quiniclidinone hydrochloride (**3**). For example, instead of adding the epoxidation reagent in one lot, we observed that sequential addition of trimethylsulfoxonium iodide and potassium tert-butoxide to a suspension of 3-quiniclidinone hydrochloride (**3**) in dimethylsulfoxide gave better quality product and improved yield. Our next concern was the insertion of "sulfur" atom. It is known[5] in the literature that direct opening of epoxide with thiourea preferably gives the three-membered 'episulfide' derivative (Scheme 3) which for our endeavor is an undesired intermediate.

Hence, we diverted our attention to the indirect route of 'sulfur' insertion *via* the corresponding halide intermediate.[6]The epoxide **4**wastreated with aqueous HBr in acetone to give the desired bromohydrinprecursor (**8**) in good yield (scheme 3).[7] The structure of **8** was substantiated by spectroscopic methods.

Scheme 3



We envisaged that under classical conditions[8] of bromide replacement with thiourea, compound **8** would give rise to the isothiourenium intermediate (**9,** Figure 2) which on simple hydrolysis with a base should provide the thiol derivative (**5**).

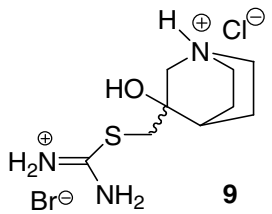


Figure 2 (Isothiourenium Intermediate)

As it turned out, the bromo replacement with thiourea was not a simple proposition and in fact failed under the reported conditions[8]even after using high boiling alcohols at elevated temperature. After several attempts, we concluded that the reaction of the bromo compound (**8)** with thiourea could best be achieved in water at reflux temperature for 2 h (Scheme 4). It is pertinent to mention that all the intermediates in this synthetic sequence were difficult to monitor by conventional TLC or HPLC techniques due to the lack of uvchromophores in the structures. Also, monitoring the transformations by using iodine or staining of the TLC was not satisfactory. We then resorted to monitoring the progress of the reaction by mass spectral analysis and obtained some interesting results. For instance, the major observed molecular ion peak after 2 h was at m/z 200 with a small peak at 174 which corresponds to the desired thiol intermediate (**5**). Interestingly no peak was detected for the isothiourenium intermediate **9** expected at m/z 215. After 10 h, the reaction mixture showed almost complete vanishing of the peak at m/z 200 and at the same time the peak localized at m/z 174 corresponding to the thiol**5**became hugely prominent (Figure-3), along with several additional peaks which could be attributed to the degradation products.

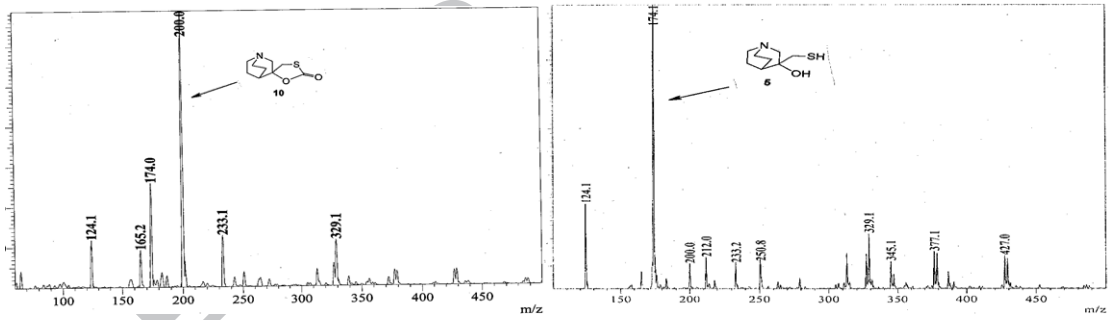
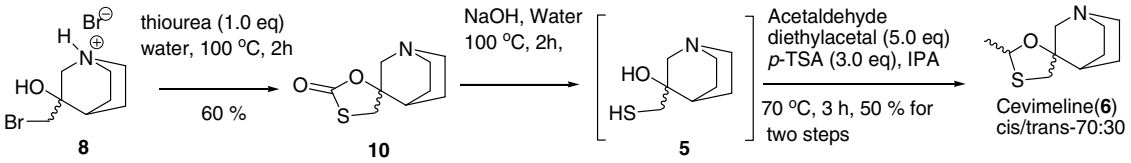


Figure 3: a) Mass spectrum of the reaction mixture after 2h. b) Mass spectrum of the reaction mixture after 10 h.

Hence, to avoid the degradation of the reaction mixture on prolonged heating (10 h), we decided to terminate the reaction after 2 h and isolate the intermediate with m/z 200. Based on spectral data,[9] the thiolactone structure (**10**) was assigned to this new intermediate having m/z 200.

Scheme 4



Thiolactone-intermediate **10** on treatment with NaOH in water under reflux underwent hydrolysis and afforded the thiol intermediate (**5**) in 2 h which was taken forward without isolation and treated with acetaldehyde diethyl acetal following literature procedures[4] to obtain the desired cyclized compound **6** (cevimeline-free base with 70:30, *cis:trans* ratio as seen in the ^{1}H NMR).

The present route can be useful for the development of commercial manufacturing of cevimeline hydrochloride.

In conclusion, we have developed a new route to cevimeline using much greener thiolating agent "thiourea" compared to hydrogen sulfide and thioacetic acid. Another advantage in this new route is the *insitu* conversion of the thiol intermediate (**5**) (which has a very bad smell) to cevimeline.

Acknowledgment

The authors wish to thank Mr. Samit Mehta, our management andARD group of Emcure Pharmaceuticals Ltd. for their willing support and constant encouragements.

Supplementary data

Supplementary data (general procedures and spectral data)associated with this article can be found, in the online version, athttp://dx.doi.org

Reference:

1. Weber, J.; Keating, G. M.*Drugs***2008**, *68(12),* 1691–1698. b) Ninomiya, I. Y.; Fukui, K.*Arthritis Rheum.* **1998**, *41*, S329. c) Fife, R. S.; Chase, W. F.; Dore, R. K.; Wiesenhutter, C. W.; Lockhart, P. B.; Tindall, E.; Suen, J. Y. *Arch Intern*

Med. **2002,***162,*1293-1300.d) Iga, Y.Arisawa, H.Ogane, N.*Jpn J Pharmacol.* **1998**, *78*, 373-380.

2. Fisher, A.; Karton, I.; Heldman, E.; Levy, A.; Grunfeld, Y. *US 4855290*, **1989**.
3. Corey, E. J.; Chaykovski, M. *J. Am. Chem. Soc.* **1965**, *87*, 1353–1364.
4. Bratovanov, S. S.; Benjan, E.; Wang, Z. X.; Horn, S. E. *US 0249312* A1, **2008**.
5. Baltork, I. M.; Khosropour, A. R. *Molecules* **2001**, *6*, 996-1000
6. Eccles, K. S.;Elcoate,C. J.; Lawrence,S. E.; Maguire, A. R. *ARKIVOC* **2010**, *(ix)*, 216-228.
7. Bordwell, F. G.; Frame, R. R.; Strong, J. G. *J. Org. Chem.***1968,** *33,* 3385-3388.
8. Styskala, J.; Cankar, P.; Soural, M.; Bednar, P.; Lemr, K. *ARKVOC* **2007**, *(XV)* 171-180.
9. NMR data is given in the Supplementary data section.