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A Facile Synthesis of Epinastine HCl via Dehydroepinastine Intermediate

Sang Won Park, Han Eol Kang, Wheesahng Yun, Sang Yeul Lee and Tae-gyu Nam*

Department of Pharmacy and Institute of Pharmaceutical Science and Technology, Hanyang University, Ansan, Gyeonggi-do 15588, Republic of Korea

*Corresponding author

Email: tnam@hanyang.ac.kr, Tel: +82-31-400-5807; Fax: +82-31-400-5958

Abstract

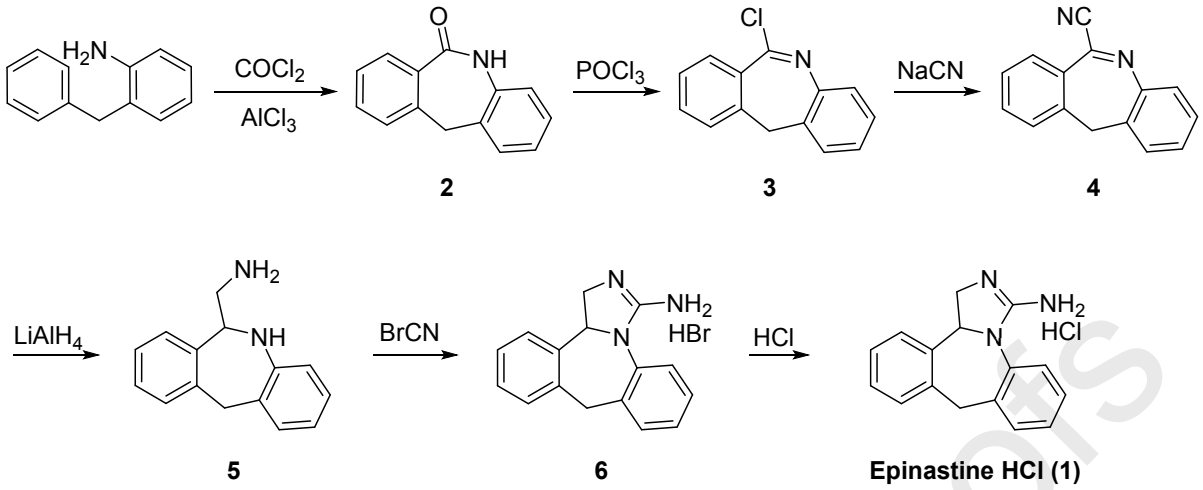
Epinastine is a second generation histamine H_1 receptor antagonist used as a non-sedative antiallergic drug. When given orally, epinastine poorly penetrates blood-brain barrier (BBB) and appears to be free of cardiac toxicity as compared to other antihistamine drugs. A couple of synthetic approaches for epinastine HCl have been reported so far. They hold several problems such as explosive, highly toxic or expensive reagents. Moreover, they usually do not offer concise synthetic steps. In our synthesis shown here, a commonly used starting material, 6-(chloromethyl)-11*H*-dibenzo[*b*,*e*]azepine is treated with cyanamide to afford dehydroepinastine (**14**) in significantly high yield, which is subsequently reduced in the presence of aqueous HCl to give epinastine HCl in only two steps (75% overall yield for two steps). The problems associated with the reported processes such as using toxic and dangerous chemicals, lengthy synthetic steps or low overall product yields can be overcome by utilizing this new route. We believe our synthetic scheme might provide a breakthrough to reduce the cost of the production of epinastine HCl.

Key Words: Epinastine, Dehydroepinastine, Cyanamide, Antihistamine

Introduction

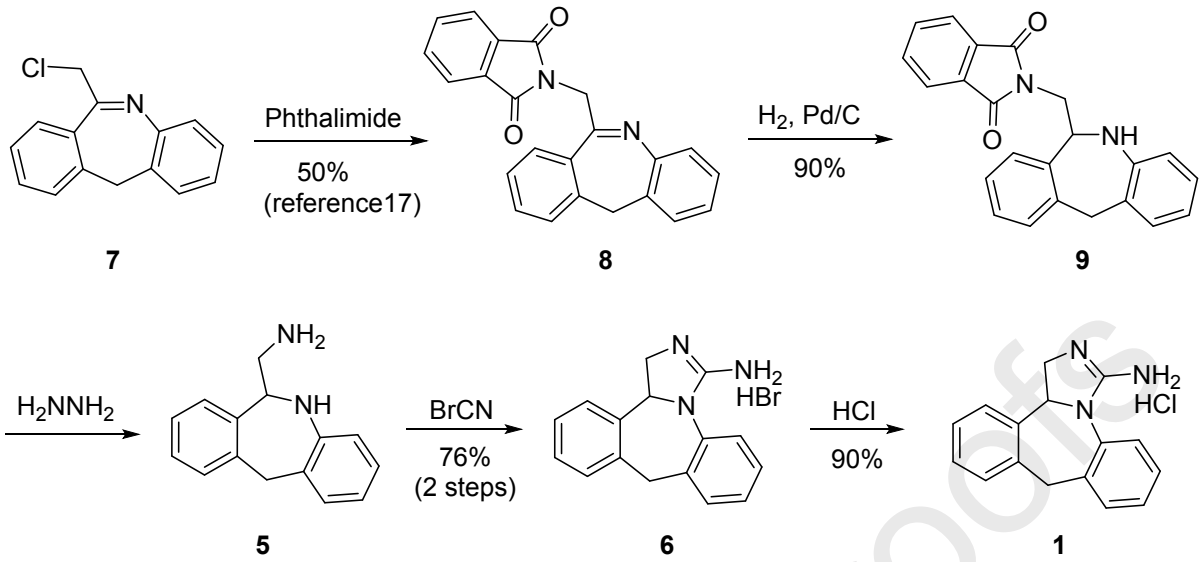
Epinastine is a second generation histamine H_1 receptor antagonist used as a non-sedative antiallergic drug. Epinastine hydrochloride has been used as tablets for the treatment of bronchial asthma, allergic rhinitis and skin diseases with pruritus in adult patients and as topical ophthalmic solution for allergic conjunctivitis.[1-3] When given orally, epinastine poorly penetrates the blood-brain barrier (BBB) and appears to be free of cardiac toxicity as compared to other antihistamine drugs such as astemizole and terfenadine.[4,5]

As a successful active pharmaceutical ingredient (API), a couple of synthetic approaches for epinastine HCl have been reported so far. The original synthetic scheme began with the treatment of a commercially available 2-benzylaniline with phosgene to form an isocyanate intermediate that was converted to 6-morphanthridone or 5,11-dihydro-6H-dibenzo[b,e]azepin-6-one **2** by an intramolecular Friedel-Crafts acylation (Scheme 1).[6] Exposing **2** to phosphorus oxychloride afforded 6-chloromorphanthridine **3**, which was allowed to react with sodium cyanide to give 6-cyanomorphanthridine **4**. Both nitrile and imine functional groups on **4** were simultaneously reduced by lithium aluminum hydride to produce 6-aminomethyl-5,6-dihydromorphanthridine **5**. The primary amine on compound **5** reacted with cyanogen bromide to form *N*-((5,6-dihydromorphanthridine-6-yl)methyl)cyanamide that was spontaneously cyclized to provide epinastine HBr salt (**6**) from which desired epinastine HCl (**1**) was afforded via a salt exchange. However, this scheme has several problems in especially large scale synthesis: a notorious phosgene gas should be avoided in the large scale synthesis, cyanogen bromide is also a highly volatile and toxic substance, every synthetic step requires purification, and overall product yield was low.



Scheme 1. The original synthetic route for Epinastine HCl (**1**).

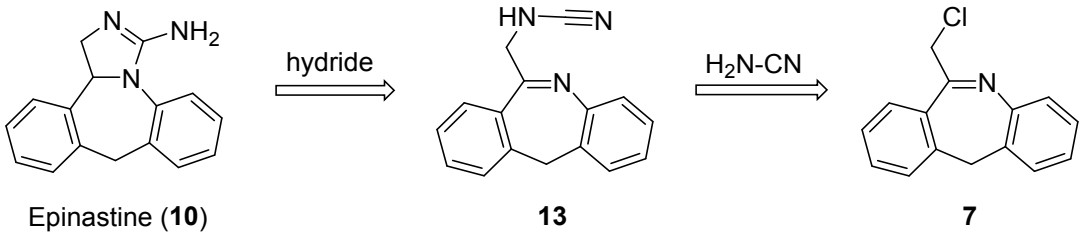
In order to address the issues associated with the original scheme, scientists at Boehringer-Ingelheim developed an improved synthetic route for the key intermediate **5** starting from a known compound **7** (Scheme 2).[7] They prepared a chloro compound **7** according to the literature procedure and converted it to compound **8** through Gabriel synthesis protocol. The imino group on **8** was reduced under hydrogenation in presence of formic acid to provide a secondary anime **9**, and the hydrazinolysis of the phthalimide of **9** afforded **5**, which can be merged to the original synthetic pathway for epinastine. However, this scheme also has some problems in that removal of the phthalyl hydrazide byproduct can be troublesome and that toxic hydrazine is not an ideal reagent in mass production. Besides, treating hydrobromide requires a special equipment adding an extra cost for synthesis especially in production scale. Since then, a number of synthetic routes for epinastine have been reported.[8-16] Those routes consist of preparation of compound **5** or *N*-substituted **5**, followed by conversion to *N*-cyanylation, and subsequent cyclization to afford epinastine or its *N*-substituted analogue, and the final treatment of hydrochloric acid to provide epinastine HCl (**1**).



Scheme 2. Synthetic route in reference 7

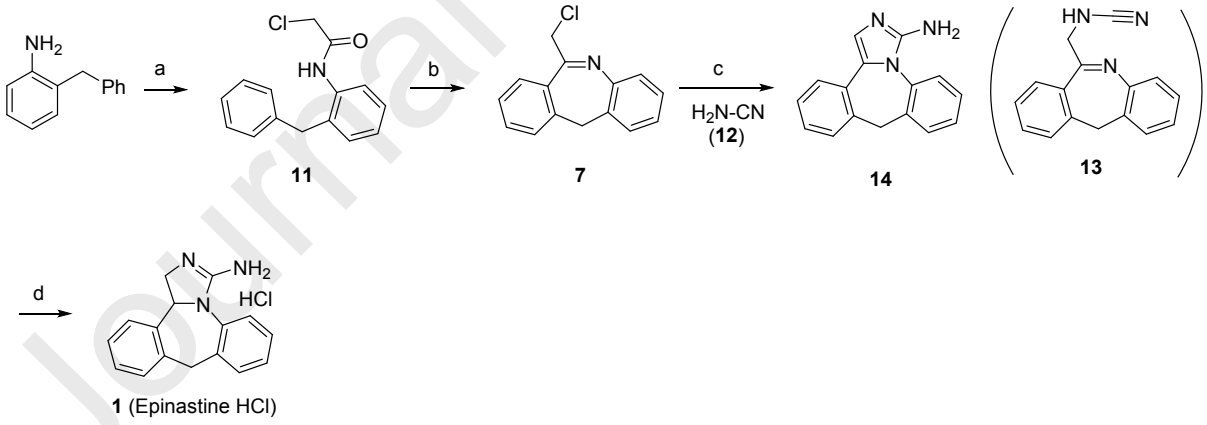
Results and Discussion

After a careful examination of reported synthetic routes, we designed a new synthetic scheme, which might reduce the number of synthetic steps and improve overall yield (Scheme 3). In a new scheme, we predicted that the chloride on compound **7** undergo S_N2 displacement by cyanamide **12** to produce a cyanoamine **13** and the imine functionality on the compound **13** is selectively reduced by a hydride reagent to form a secondary amine intermediate. It is spontaneously cyclized to an imidazolidin-2-imine that can undergo a tautomerization to provide epinastine free base **10**. Epinastine **10** could be easily converted to its HCl salt (**1**). Cyanamide is the key reagent in the new scheme and has desirable features in that it is not only readily available but also very affordable. A kilogram quantity is available from a common commercial source for only $97.6 according to SciFinder database.



Scheme 3. Envisioned synthetic scheme.

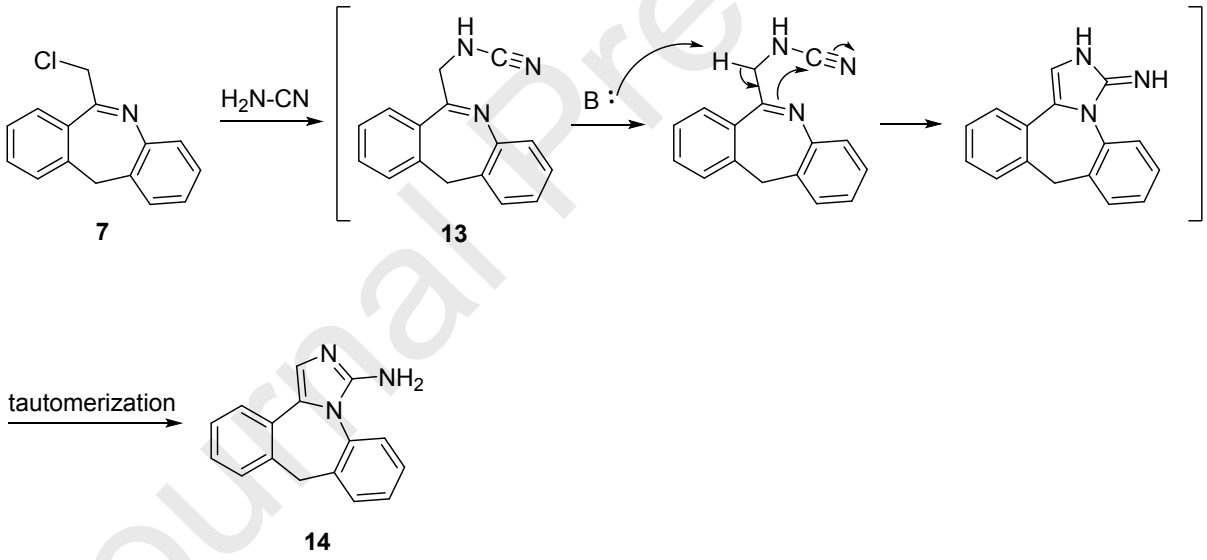
In our synthesis, 2-benzylaniline was treated with chloroacetyl chloride to provide an amide **11** in 85% yield.[18] Compound **11** was warmed at 120 °C in the presence of polyphosphoric acid and phosphorus oxychloride to provide **7** in 75% yield. When **7** was allowed to react with cyanamide **12**, however, to afford **13** was unsuccessful. As shown in scheme 4, dehydroepinastine **14** was unexpectedly obtained without giving the expected product **13** or other cyclized compounds.



Scheme 4. Synthesis of epinastine HCl via dehydroepinastine **14** using cyanamide.

reagents and conditions a) Chloroacetyl chloride, pyridine, toluene, 0 °C → r.t., 1.5 h, 85%; b) polyphosphoric acid, $POCl_3$, 120 °C, 2 h, 90%; c) H_2N-CN, conditions (see table 1), 0% ~ 85%; (d) Pd/C, H_2, MeOH, 6 N HCl, 87%

The proposed mechanism for **14** would be that the initial S_N2 reaction product **13** might be formed and experience a base-promoted intramolecular cyclization proceeding to give an imino intermediate that tautomerizes to result in dehydroepinastine **14** (Scheme 5). It is interesting that HCl salt of **14** is indicated as one of the major impurities of epinastine HCl in pharmacopeia (impurity A).[19] Many pharmaceutical impurities are usually formed in small amount but hard to remove, still causing costly damage to the purity of API. It will be a significantly interesting approach to utilize an impurity as a key intermediate for the synthesis, not trying to minimize its formation.

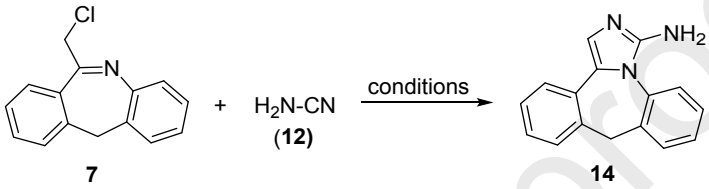


Scheme 5. Proposed mechanism for compound **14**.

Synthetically useful routes for epinastine HCl utilizing the impurity, dehydroepinastine, have been reported, we envisioned that the olefinic double bond on imidazole ring of **14** could be selectively reduced to afford desired epinastine and decided to utilize **14** as the precursor of epinastine in our new synthetic scheme. Accordingly, the

optimization study for **14** was performed (Table 1). While a few recent reports exist[19,20] on the synthesis of dehydroepinastine **14**, they introduced an oxidative preparation of **14** from epinastine in order to use it as a standard material for analytical purpose and therefore are not synthetically useful.

Table 1. Optimization study for **14**



Entry	Conditions					Results
	12 (eq.)	**Base (**eq.**)**	**Solvent** [a]	**Temp.** [b]	**Time**	
1	2.0	-	DMF	130 °C	18 h	decomp.[c]
2	2.0	K_2CO_3 (1.5)	DMF	90 °C	8 h	decomp.[d]
3	2.0	DIPEA (1.5)	DMF	90 °C	8 h	10%
4	2.0,	NaO^{t}Bu (1.5)	DMF	90 °C	18 h	17%
5	2.0	NaO^{t}Bu (1.5)	THF	reflux	18 h	15%
6	2.0	NaO^{t}Bu (1.5)	MeCN	reflux	18 h	32%
7	3.0	NaO^{t}Bu (1.5)	MeCN	reflux	12 h	86%
8	2.0	NaO^{t}Bu (1.5)	DMF	*MW*, 120 °C	30 min.	20%
9	2.0	NaO^{t}Bu (1.5)	DMF	*MW*, 160 °C	30 min.	29%
10	2.0	NaO^{t}Bu (1.5)	DCE	*MW*, 120 °C	50 min.	Trace
11	2.0	NaO^{t}Bu (1.5)	THF	*MW*, 120 °C	50 min.	Trace
12	2.0	NaO^{t}Bu (1.5)	DMSO	*MW*, 200 °C	30 min.	38%

13	2.0	NaO^{t}Bu (1.5)	DMSO	*MW*, 120 ^{o}C	30 min.	55%
14	2.0	NaO^{t}Bu (1.5)	MeCN	*MW*, 120 ^{o}C	30 min.	63%
15	2.0	NaO^{t}Bu (2.0)	MeCN	*MW*, 120 ^{o}C	30 min.	56%
16	3.0	NaO^{t}Bu (1.5)	MeCN	*MW*, 120 ^{o}C	30 min.	66%
17	2.0	KO^{t}Bu (2.0)	MeCN	*MW*, 120 ^{o}C	30 min.	38%
18	2.0	Na_2CO_3,(2.0)	MeCN	*MW*, 120 ^{o}C	50 min.	5%
19	2.0	K_2CO_3,(2.0)	MeCN	*MW*, 120 ^{o}C	50 min.	51%
20	2.0	Cs_2CO_3,(2.0)	MeCN	*MW*, 120 ^{o}C	50 min.	13%
21	2.0	$KHCO_3$ (2.0)	MeCN	*MW*, 120 ^{o}C	50 min.	N. R.[e]
22	2.0	NaOH (2.0)	MeCN	*MW*, 120 ^{o}C	50 min.	29%
23	2.0	DIPEA (3.0)	MeCN	*MW*, 120 ^{o}C	50 min.	10%
24	2.0	NaI (1.0)	MeCN	*MW*, 120 ^{o}C	50 min.	decomp.[d]
25	3.0	NaI(1.0)/NaOtBu(1.5)	MeCN	reflux	18 h	28%
26	5.0	NaI(3.0)/NaOtBu(1.5)	MeCN	reflux	18 h	28%

[a)] Reaction concentration was 0.1 M [b)] MW = microwave reaction [c)] decomposition of **7**. [d)] dechlorinated compound of **7** was observed. [e)] N.R. = no reaction

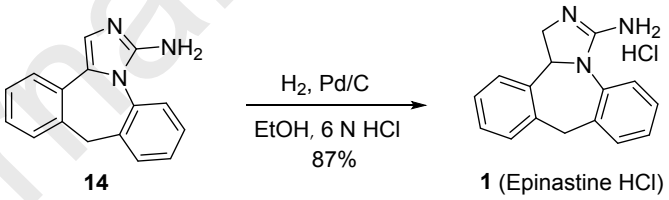
At first, compound **7** was treated with 2.0 eq. of **12** in DMF with various conditions (entries 1–4). When the reaction mixtures were warmed at 90 ^{o}C without a base or in presence of 1.5 eq. K_2CO_3, only decomposition of **7** was observed (entries 1–2). Addition of mild base DIPEA to the reaction mixture produced small amount of **14** (10% yield, entry 3). When NaO^{t}Bu was used as a base, **14** was obtained in 17% yield at 90 ^{o}C (entry 4), however, the

starting material was almost decomposed when the temperature was raised to 130 °C (data not shown). Other solvents, such as THF and MeCN, were also tested (entries 5 and 6). While running the reaction in THF provided a similar result to DMF, the reaction in MeCN afforded a promising yield (32%). Finally, use of 3.0 eq. of **12** in refluxing MeCN afforded **14** in 85% yield (entry 7).

In search of alternative reaction conditions, microwave-assisted syntheses were tested. Microwave reactions generally resulted in better product yields along with cleaner reaction profiles than thermal counterparts. To find an optimal solvent, compound **7** was treated with 2.0 eq. of **12** and 1.5 eq. of NaO^{t}Bu and exposed to microwave reaction conditions in different solvents (entries 8-14). When running the reaction at 120 °C in DMF (normal abs, 30 min), the result was similar to that of the thermal condition (20%, entry 8), while producing enhanced yield of 29% at higher temperature (160 °C) (entry 9). Reactions in DCE and THF produced only a trace amount of **14** (entries 10–11). However, reactions in DMSO displayed significant improvements (38% at 200 °C and 55% at 120 °C) with inverse dependency on temperature (entries 12–13). Switching the solvent to MeCN even increased yield to 63% (entry 14). Doubling of reaction concentration of entry 14 to 0.2 M resulted in ~10% reduction in yield (data not shown). Varying the amount of the base always resulted in decrease in yield. More than 1.5 eq. of NaO^{t}Bu decreased the yield to 56% (entry 15) and less equivalent decreased the yield to a greater extent (data not shown). Addition of one more equivalent of cyanamide **12** slightly improved the reaction to afford 66% yield (entry 16) but change of base generally resulted in poorer yields than NaO^{t}Bu except for K_2CO_3 that afforded 51% yield (entries 17-23). Finkelstein protocol was also tried, but desired **14** was not formed, but small amount of dechlorinated compound of **7** was observed. Addition of NaO^{t}Bu improved the yields which were not more than 30% (entry 24-26). With above optimization study, it was evident that

reaction time was dramatically reduced through microwave conditions however the best yield was obtained under refluxing condition. (entry 7).

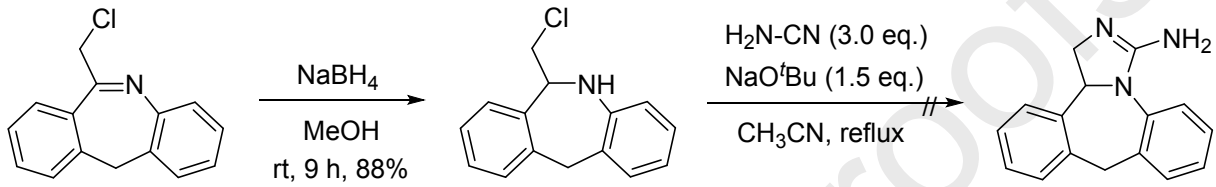
Once the robust protocol for epinastine precursor **14** was established, a selective reduction procedure for the C-C double bond on **14** in presence of an imine moiety was investigated. Metal hydrides such as $NaBH_4$, $LiBH_4$, DIBAL-H and $LiAlH_4$ did not proceed the reduction and majority of starting material **14** was recovered. Next, compound **14** was exposed to hydrogenation condition in various solvents. Attempts for hydrogenation of **14** in MeOH, EtOH, EtOAc, DMF and THF all produced epinastine in quite low yield (<10%). It was speculated that the primary amine on **14** might be the culprit for the unsuccessful reduction by poisoning the catalyst. We decided to protonate the amine functional group and hydrogenation in a mixture of EtOH and aqueous 6 N HCl as a co-solvent afforded the final compound epinastine HCl. This hydrogenation protocol is beneficial not only for high yield up to 87% but also for a facile synthesis; it does not require final salt formation or salt exchange step (Scheme 6).



Scheme 6. Final hydrogenation step toward epinastine HCl (1)

Then, we have explored an alternative route to get to epinastine **10** without association of palladium-catalyzed reduction (Scheme 7). In this scheme, we hoped to form epinastine **10** in two step from compound **7** by a reaction of cyanamide with compound **15** as a key step. Imine group of compound **7** was successfully reduced using $NaBH_4$ to give **15** in 88% yield. However,

all attempts including a simple S_N2 reaction of **15** with cyanamide **12** and Finkelstein protocol did not afford epinastine **10** even under refluxing condition. It is probably due to the different reactivity of methylene group in **7** and **15**; a very reactive α-chloroimine group in **7** *vs.* a much less reactive primary alkyl chloride in **15**.



7 **15** **10**

Scheme 7. Alternative route for epinastine **10** starting from compound **7**

In conclusion, a facile and cost-effective synthetic route for epinastine HCl was developed. From known compound **7**, epinastine HCl was prepared in just two synthesis steps. The problems associated with the reported processes such as using toxic and dangerous chemicals, long synthetic steps or low overall product yields can be overcome by utilizing this new route. Selective hydrogenation of an olefin moiety on 2-amino imidazole was achieved by adding aqueous HCl. Our synthesis scheme might give rise an opportunity to reduce the cost in mass production of epinastine HCl.

Acknowledgement

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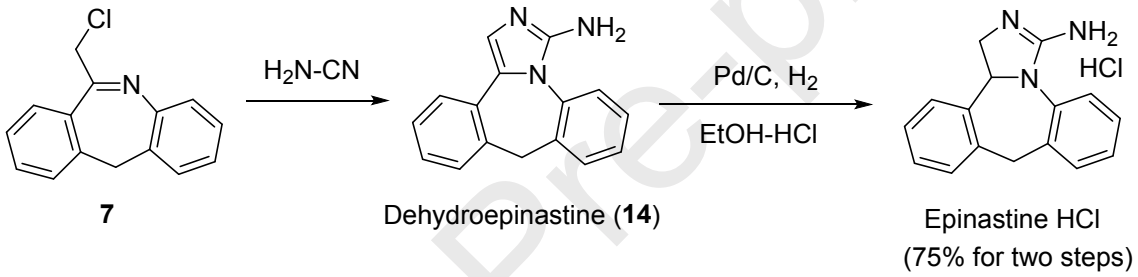
Graphical Abstract



Highlights

Epinastine, an antiallergic drug, was synthesized efficiently via dehydroepinastine.

Dehydroepinastine was synthesized using cyanamide in high yield.

Epinastine HCl was synthesized in 75% yield in two steps from available intermediate

Declaration of Interest

Authors declare no conflict of interest.