Pergamon

Tetrahedron Letters 41 (2000) 3895–3898

TETRAHEDRON LETTERS

A stereoselective synthesis of (*E*)-1-halo-6,6-dimethyl-2-hepten-4-yne: a key intermediate for terbinafine

Shan-Yen Chou,* Chin-Lu Tseng and Shyh-Fong Chen

Development Center For Biotechnology, 102, Lane 169, Kang Ning St., Hsichih, Taipei Hsien, Taiwan, R.O.C.

Received 27 January 2000; revised 6 March 2000; accepted 24 March 2000

Abstract

A study of the stereoselective halogenation of 6,6-dimethyl-1-hepten-4-yn-3-ol (**1**) using a series of halogenating agents is described. Of the many agents investigated, boron trichloride is the most successful reagent for stereoselective halogenation (E:Z=9:1$_{max}$). The resulting (*E*)-1-halo-6,6-dimethyl-2-hepten-4-yne (**2**), a key intermediate for terbinafine, an antifungal agent, is obtained in good yield and stereoselectivity. Two structurally related enyne alcohols have been studied likewise and shown similar versatility.

Keywords: halogenation; terbinafine; boron trichloride; *trans* olefin.

In recent years research in the field of squalane epoxidase inhibitors has resulted in the discovery of a new class of antifungal agents.[1] Terbinafine (brand name: Lamisil), one of the orally active antifungal agents developed by Janssen Co., is a representative with excellent activity toward dermatological infections.[2] *trans* 1,2-Disubstituted olefin moiety is a common pharmacophore in terbinafine and related agents (Fig. 1).[2,3] Therefore, our effort is to find a highly stereoselective method to achieve a *trans*-ene-yne system.

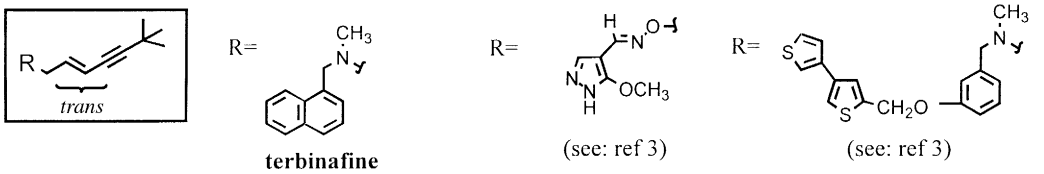


Fig. 1.

A previous study described the conversion of **1** to **2** by using aqueous HBr in 3:1 E:Z ratio.[2] This low stereoselectivity prohibited high recovery of terbinafine in subsequent steps. An independent method was then developed for the improvement of E:Z ratio, but it requires an expensive reagent and laborious

* Corresponding author.

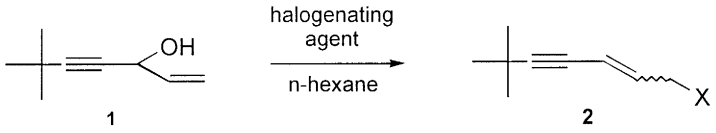
0040-4039/00/$ - see front matter
PII: S0040-4039(00)00511-6

procedures, although the *E*:*Z* ratio can be improved to 5:1.[2] Therefore, we intended to improve the stereoselectivity of the conversion of **1** to **2** by using alternate halogenating agents.

During the early stage of our study, magnesium bromide etherate was selected for conversion of **1** to **2** in benzene/*n*-hexane. It was found that the *E*:*Z* ratio of **2** increased progressively with the proportion of *n*-hexane in the mixed solvent. Other solvents, such as THF and *i*-Pr_2O are inappropriate for their chelating properties. Unexpectedly, the bromination does not work in *t*-BuOMe even under vigorous refluxing. Although these tests indicate that *n*-hexane is a promising solvent for controlling of stereochemistry, owing to the poor dispersing property of magnesium bromide in *n*-hexane, we have to search an alternative method.

Systematic studies of conversion of **1** to **2** were performed to examine a number of reaction variables such as the type of halogenating agent, the stoichiometry of the halogenating agent with the substrate, the reaction time and the concentration for probing the stereoselectivity of halogenation. A series of halogenating agents were employed for the reaction in *n*-hexane and the results are summarized in Table 1. Most conventional halogenating agents are not suitable due to their low yields and/or stereoselectivity. Under some circumstances (entries 1, 2, and 4), a large amount of unrearranged halides and intractable tars were also generated. In contrast, the high yields obtained from the boron trichloride mediated halogenation prompted us to optimize the reaction condition (see entries 6–13). In comparing with that in the literature,[2] the *E*:*Z* ratio has been improved from 3:1 to $9{:}1_{max}$. To our knowledge, no systematic study of boron trichloride mediated chlorinating of alcohols has been reported.[4]

Table 1



1 **2**

X=Cl, Br

Entries[a]	Substrate **1** (mmol)	Molar ratio of halogenating agent to substrate **1**	Reaction time	Reaction temperature	Isolated Yield (%)	E/Z ratio
1	12	$POCl_3$, (1.25)	3h	25°C	28	6/1
2	12	PCl_3, (1.25)	3h	25°C	30	6/1
3	12	PBr_3, (1.25)	30 min	25°C	95	3/1
4	12	$SOCl_2$, (1.25)	4h	25°C	50	5/1
5	12	BBr_3, (1.25)	10 min	25°C	60	5/1
6	12	BCl_3, (0.42)	10 min	25°C	55	3/1
7	12	BCl_3, (0.84)	10 min	25°C	90	5.5/1
8	12	BCl_3, (1.25)	10 min	25°C	95	9/1
9	12	BCl_3, (1.25)	10 min	reflux	95	9/1
10	32	BCl_3, (1.31)	10 min	25°C	95	3/1
11	21	BCl_3, (1.28)	10 min	25°C	95	6/1
12	12	BCl_3, (1.25)	20 h	25°C	95	1.1/1
13	380	BCl_3, (1.25)	10 min	25°C	95	9/1

a. The halogenation were carried out by using 0.12 M of **1** in n-hexane for entries 1-9 and 12-13, and 0.32 M of **1**, 0.21 M of **1** for entries 10 and 11 respectively.

As shown in entries 6–8, Table 1, the stoichiometry of the halogenating agent with the substrate is an important factor for enhancement of *E*:*Z* ratio. When we used less than 100 mole% of boron trichloride, the *E*:*Z* ratio decreased drastically (see entries 6 and 7). It indicates that coordination between boron trichloride and hydroxyl group is essential for controlling of stereochemistry. In comparing entries 8, 10, and 11, the effect of dilution on the halogenating of **1** was studied by varying the BCl_3 concentration in *n*-hexane. The *E*:*Z* ratio of **2** increased progressively with dilution. It indicated that intramolecular

chloride attack is more competitive than that of intermolecular chloride attack and favorable for *E* form formation. As shown in entry 12, Table 1, a long period of stirring results in equilibrium of *E* and *Z* form, although a short period of refluxing is tolerable (see entry 9). The boron trichloride mediated reaction was performed on scales as large as 50 g without changing isolated yield and stereoselectivity (see entry 13). In comparing with those of conventional halogenating agents, both the stereoselectivity and isolated yield are good. The worked-up and purification procedures are not laborious because no tarry compounds or unrearranged halide were observed.

The chlorinating process could be explained by our envisaged mechanism. As shown in Fig. 2, two possible conformers, **A** and **B**, are in equilibrium. The predominant conformer **A** exists in major form, since the quasi gauche and 1,3-diaxial interactions exists in conformer **B** rather in **A**. The vacant orbital of boron atom of BCl_3 is suitable for the formation of a six-membered transition state to act as either donor or acceptor of electron pairs. Owing to the outer-shell and the number of outer-shell electrons of the coordinated boron atom (i.e. boride ion) are similar to those of carbon atom, the high efficiency for controlling of stereochemistry might be attributed to such a low-strained cyclohexane-like transition state.[5]

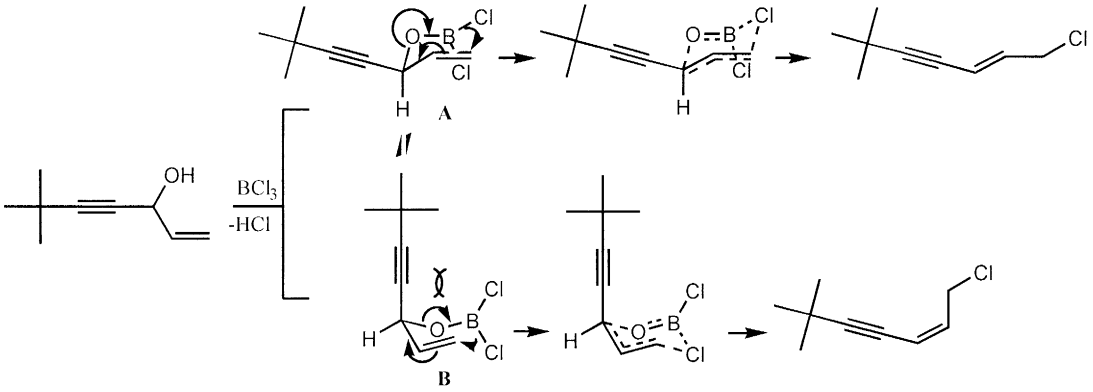


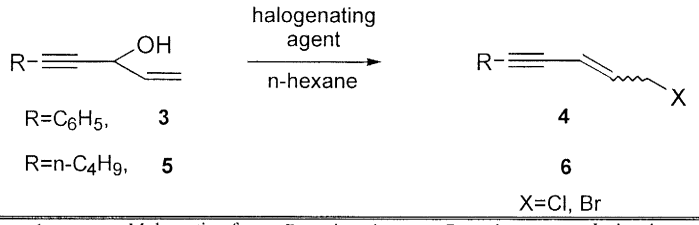
Fig. 2.

For comparison purposes, two structurally related alcohols (**3**, **5**) were prepared and subjected to the halogenation conditions,[6] As shown in Table 2, the boron trichloride mediated chlorinating remains superior in terms of stereoselectivity and chemoselectivity.[7] It should be noted that the *E*:*Z* ratios increased progressively with the steric hindrance of the substituent *R* (comparing entry 8, Table 1 and entries 1 and 2, Table 2).

A typical procedure for preparing of (*E*)-1-chloro-6,6-dimethyl-2-hepten-4-yne (**2**) using boron trichloride is as follows: Compound **1** (53 g, 0.38 mol) in 2800 mL of *n*-hexane was cooled to 10–15°C. Boron trichloride (1 M in hexane, 480 mL, 0.48 mol) was added to the mixture at 15–20°C over a 10 min period. After 10 min of stirring at 20°C, the mixture was quenched with 1000 mL of water and stirred for 10 min. The separated organic phase was washed with 20% NaCl, dried ($MgSO_4$), and evaporated to afford the title compound **2** (57.1 g, 95%) in 9:1 *E*:*Z* ratio.[8] Other tests in Table 1 were accomplished in a similar method.

In conclusion, a boron trichloride mediated synthesis of (*E*)-1-chloro-6,6-dimethyl-2-hepten-4-yne (**2**) from the enyne alcohol **1** has been developed. By judicious choice of the reaction conditions, the chloride can be obtained in excellent stereoselectivity and isolated yield. The obtained $E{:}Z_{max}$ (9:1) is the maximum value among those reported.[2,3] Furthermore, we have demonstrated that both the

Table 2



Entries[a]	Substrate **1** (mmol)	Molar ratio of halogenating agent to substrate	Reaction time	Reaction temperature	Isolated Yield (%)	E/Z ratio
1	**3**,(12)	BCl_3,(1.25)	10 min	25℃	95	6/1
2	**5**,(12)	BCl_3,(1.25)	10 min	25℃	95	5/1
3	**3**,(12)	$SOCl_2$,(1.25)	4 h	25℃	50	5/1
4	**5**,(12)	$SOCl_2$,(1.25)	4 h	25℃	45	4/1
5	**3**,(12)	$POCl_3$,(1.25)	20 min	25℃	54	5/1
6	**5**,(12)	$POCl_3$,(1.25)	20 min	25℃	43	3/1
7	**3**,(12)	BBr_3,(1.25)	10 min	25℃	45	3/1
8	**5**,(12)	BBr_3,(1.25)	10 min	25℃	44	2/1
9	**3**,(12)	PBr_3,(1.25)	30 min	25℃	95	3/1
10	**5**,(12)	PBr_3,(1.25)	30 min	25℃	90	1.7/1

a. The halogenation were carried out by using 0.12 M of **3** or **5** in n-hexane.

stoichiometric coordination of the enyne alcohol **1** with boron trichloride and intramolecular substitution via cyclohexane-like transition state are important factors for controlling *trans* olefin selectivity.

Acknowledgements

Financial support from the Ministry of Economic Affairs, R.O.C. is gratefully acknowledged.

References

1. Petranyi, G.; Ryder, N. S.; Stutz, A. *Science* **1984**, *224*, 1239.
2. (a) Stutz, A. Eur. Pat. Appl. 24,587, 1981. (b) Stutz, A.; Granitzer, W.; Roth, S. *Tetrahedron* **1985**, *41*, 5685. (c) Stutz. A.; Petranyi, G. *J. Med. Chem.* **1984**, *27*, 1539.
3. (a) Meki, N.; Nishida, K. U.S. Patent 5,021,446, 1991. (b) Meki, N.; Nishda, K. U.S. Patent 5,036,158, 1991.
4. (a) Miyaura, N. In *Encyclopedia of Reagents for Organic Synthesis*; Paquette, L. A., Ed.; John Wiley & Sons Inc.: New York, 1995; Vol. 1; pp. 648–651 and references cited therein. (b) Larock, R. C. *Comprehensive Organic Transformations*; VCH Publishers Press: New York, 1989; pp. 353–363.
5. March, J. *Advanced Organic Chemistry*, 3rd ed.; John Wiley & Sons Inc.: New York, 1985; p.128 and references cited therein.
6. The alcohol (**3**, **5**) was prepared from phenylacetylene or 1-hexyne with acrolein under a similar reaction condition of **1** as described in literature.[2] Satisfactory spectra were collected for **3**–**6**.
7. Characteristic peaks of allylic CH_2 in *E*:*Z* mixture appeared at δ 3.99 (dd, J=4.4, 1.1 Hz) and δ 4.21 (d, J=8.1 Hz) for **4** (x=Br), or δ 4.17 (dd, J=3.5, 1.3 Hz) and δ 4.40 (d, J=7.5 Hz) for **4** (x=Cl), or 3.97 (dd, J=3.9, 0.97 Hz) and δ 4.16 (d, J=8.1 Hz) for **6** (x=Br), or δ 4.08 (dd, J=3.4, 0.89 Hz), and δ 4.29 (d, J=7.5 Hz) for **6** (x=Cl).
8. Compound **2** (x=Cl), ^{1}H NMR ($CDCl_3$, 500 MHz) 6.08 (m, 0.9H), 5.92 (m, 0.1H), 5.75 (d, J=15.6 Hz, 0.9H), 5.60 (d, J=10.5 Hz, 0.1H), 4.25 (d, J=7.2 Hz, 0.2H), 4.05 (dd, J=3.6, 1.2 Hz, 1.8H), 1.23 (s, 9H). HPLC was carried out with a Si60 Lichrospher (4.0 mm×25 cm), eluent, hexane isocratic at 1 mL/min, detector, UV at 225 nm, room temperature.