A SIMPLE METHOD FOR OBTAINING TERBINAFINE HYDROCHLORIDE

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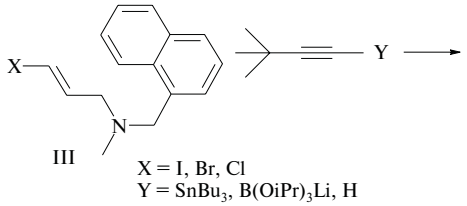
In recent decades, one of the most important achievements in pharmacology was undoubtedly the discovery of antimycotic agents in the series of allyl amines. Even quite recently, the treatment of mycotic diseases did not lead to complete recovery. Only the appearance of terbinafine (I) — a drug of a new generation of antimycotic agents — made possible such full recovery and significantly reduced the risk of side effects related with the use of other drugs [1].

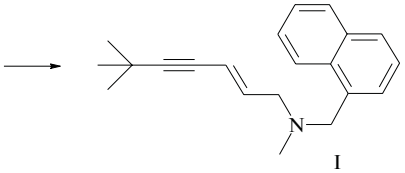
However, terbinafine is still among the very expensive drugs and not all patients, even in developed countries, can afford a complete course of terbinafine therapy. Since the discovery of terbinafine in 1984 [2, 3], the effort of many researchers was devoted to the development of effective methods for the synthesis of this drug. Stutz et al. [3 – 5] succeeded in obtaining terbinafine with a yield of up to 46% via reduction of N-(6,6-dimethyl-2,4-heptadiinyl)-N-methyl-(naphth-1-yl)methylamine by diisobutylaluminum hydride. According to the patented technology [3], terbinafine is synthesized by reductive amination of (*E*)-6,6-dimethyl-2-hepten-4-in-1-al with N-methyl(naphth-1-yl)methylamine. Recently patented technology [6] is based on dehydration of N-(6,6-dimethylhept-4-in-2-ol)-N-methyl(naphth-1-yl)methylamine, but this process leads predominantly to the formation of the inactive *Z*-isomer (II).

By means of condensation of N-methyl-N-(3-halogenprop-2-enyl)-naphth-1-ylmethylamine (III) with *tert*-butylethinyltributyltin, it is possible to obtain terbinafine with a yield of 87% [7]. Using lithium *tert*-butylethinyl(tri-isopropoxy)borate Oh and Jung [8] increased the yeld of terbinafine up to 98%. In the presence of unsubstituted *tert*-butylacetylene (Y = H), the yield of terbinafine falls within 89 – 93% [9 – 11]. However, all variants of this process require the use of expensive palladium catalysts.



III

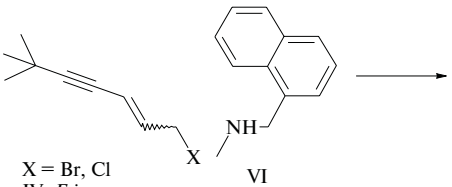
X = I, Br, Cl
Y = $SnBu_3$, $B(OiPr)_3Li$, H



I

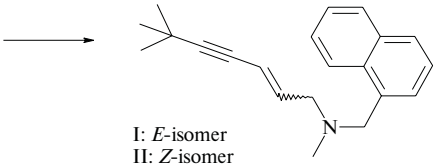
Alternatively, terbinafine can be obtained by alkylating (*E*)-N-(6,6-dimethyl-2-hepten-4-inyl)methylamine with 1-chloromethylnaphthalene. In order to provide for a high (up to 90%) yield of product I, the reaction has to be conducted in DMSO (use of isopropyl alcohol reduces the yield to 60%) [11, 12].

According to the aforementioned patent [3], terbinafine is obtained with a yield of 43.5% by alkylation of N-methyl-(naphth-1-yl)methylamine (VI) by a mixture of *Z*/*E*-isomers of 1-bromo-6,6-dimethyl-2-hepten-4-ine (IV, V) in DMF (*E* to *Z*-isomer ratio, 3 : 1).



X = Br, Cl
IV: *E*-isomer
V: *Z*-isomer

VI



I: *E*-isomer
II: *Z*-isomer

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TABLE 1. Solubility of Terbinafine Hydrochloride (I · HCl) in various Solvents at Room Temperature

Solvent	Solubility,* g/liter
Methylene chloride	220
Isopropyl alcohol	120
Isobutyl alcohol	21
Acetonitrile	9
Water	8
Toluene	6
Benzene	4
Ethyl acetate	1.7
Acetone	< 0.5
Diethyl ether	< 0.5

* Determined under the following conditions: ~ 0.5 g of I · HCl was boiled with 5 ml of solvent, kept for 24 h at room temperature, and filtered; solubility determined by the difference in sample weights.

TABLE 2. Synthesis of Terbinafine Hydrochloride under Various Conditions

Charged per 20 mmole of IV			Temperature, °C	Reaction time, h	Yield, %
VI, mmole	HCl acceptor, mmole	organic solvent, ml			
41	…	Benzene, 15	80	10	60(82)[b]
18	Solid K_2CO_3, 40	Benzene, 15	80	10	57(78)[b]
18	50 % K_2CO_3, 20.5	Benzene, 15	80	10	61(83)[b]
18	20 % K_2CO_3, 30	–	25	20	56[c]
23	10 % NaOH, 30	–	25	15	65(81)[c]
30	15 % NaOH, 30	–	60	7.5	73(91)[c]
23	15 % NaOH, 24	–	70	5	81(92)[d]

Notes: [a] Values in parentheses indicate yield by HPLC data. Isolation conditions; [b] organic layer treated with concentrated HCl, filtered, and recrystallized from 2-propanol; [c] mixture diluted with ether, organic layer separated and processed as in (b); [d] mixture treated with concentrated HCl and processed as in (b).

The same reaction conducted in toluene with an aqueous solution of potassium carbonate in the presence of tetrabutylammonium bromide leads to the formation of a mixture of *cis* (II) and *trans* (I) isomers of terbinafine with a yield of 92% [13].

It should be emphasized that all the aforementioned methods stipulate chromatographic purification of terbinafine. These processes employ expensive precursors and catalysts and involve stages carried out at negative temperatures (on the Celsius scale).

The method proposed in this study is based on the alkylation of N-methyl(naphth-1-yl)methylamine (VI) by (*E*)-1-chloro-6,6-dimethyl-2-hepten-4-ine (IV, X = Cl). It was established that this reaction proceeds without changing the isomer composition. Therefore, using pure (*E*)-isomer of compound IV, it is possible to simplify isolation of the target product and, hence, increase the yield of terbinafine (I). We used the initial 1-chloro-6,6-dimethyl-2-hepten-4-ine with an (*E*)-isomer content of not less than 95% obtained as described in [14].

The solvent for the synthesis of terbinafine was selected so as to provide conditions for isolating (*E*)-N-(6,6-dimethyl-2-hepten-4-inyl)-N-methyl(naphth-1-yl)methylamine hydrochloride (I · HCl) directly from the reaction mixture, without preliminary isolation of amine I in the base form. For this purpose, we have studied the solubility of I · HCl in various solvents (Table 1). It was found that the presence of even a small amount of moisture in solvents miscible with water significantly increases the solubility of terbinafine hydrochloride in reaction mixtures. For this reason, solvents such as acetonitrile, acetone, propanol, and butanol were rejected because of considerable difficulties involved in isolation of the target product.

We have established that the nature of solvents (ether, benzene, methylene chloride) does not significantly influence the synthesis of terbinafine. Nor does the product yield depend on the nature of hydrogen chloride acceptor. For the process conducted for 6 – 8 h in benzene at 80°C in the presence of various HCl acceptors — excess of initial amine or potassium carbonate (anhydrous or hydrated — the yield of terbinafine was about 60% irrespective of the nature of base (see Table 2). It was also shown that (*E*)-1-chloro-6,6-dimethyl-2-hepten-4-ine (IV, X = Cl) is stable with respect to hydrolysis: no products of hydrolysis were detected for 16 h at 80°C in the presence of an aqueous solution of potassium carbonate.

Rejection of organic solvents in favor of an aqueous solution of potassium carbonate or sodium hydroxide allows the duration of synthesis at room temperature to be significantly reduced (to 15 – 20 h) without decreasing the yield. Moreover, in the absence of organic solvents, the process can be additionally accelerated by increasing the temperature (to 60 – 70°C) also without decreasing the yield. As can be seen from the data presented in Table 2, the losses predominantly take place during isolation of the target compound.

We suggest converting terbinafine base into hydrochloride by adding hydrochloric acid to the reaction mixture. Under the proposed reaction conditions, we obtained (*E*)-N-(6,6-dimethyl-2-hepten-4-inyl)-N-methyl(naphth-1-yl)methylamine hydrochloride (I · HCl) containing about 92% of the *trans* isomer. After recrystallization, the yield of I · HCl amounted to 81%, at a relative content of the target compound in excess of 99%.

Thus, we have developed a simple method readily applicable under commercial conditions for the synthesis of terbinafine.

EXPERIMENTAL PART

The melting points were determined using a Mettler FP-5 device. The ^{1}H NMR spectra were recorded on a Bruker AM-370 spectrometer operating at a working frequency of 360.13 MHz. The reaction mixtures and target products were analyzed by HPLC. The measurements were performed on a Milichrom-1 chromatograph equipped with a 200 × 2 mm column. The column was filled with Silasorb C18 (5 μm) and eluted with a mixture of distilled water, acetonitrile, and trifluoroacetic acid (30 : 20 : 0.2, *v*/*v*) at a flow rate of 100 μl/min. The system was equipped with a spectrophotometric detector tuned to 260 nm. The quantitative HPLC analyses were performed using the internal calibration technique.

The isomer composition of 1-chloro-6,6-dimethyl-2-hepten-4-ine (IV, V) was determined by gas chromatography. The measurements were performed on an LKhM-80M chromatograph (Russia) equipped with a DTP detector and a 1-m column filled with a 5% SE-30 sorbent on AW-DMCS; evaporator temperature, 200°C; detector temperature, 150°C. The system was operated in a programmed mode: initial temperature, 80°C; isothermal regime, 2 min; heating at 25 K/min up to 140°C.

TLC analyses were performed on Merck Silicagel-60 F_{254} plates eluted in a hexane – diethyl ether – isopropyl alcohol – 25% aqueous ammonia (150 : 25 : 10 : 1) solvent system. The spots were developed by exposure to UV radiation or by treatment with a 1% ninhydrin solution in a methanol – carbon tetrachloride (1 : 10) mixture.

Chromatographic purification was performed on a 300 × 50 mm column filled with Merck Silicagel 60 (0.040 – 0.063 mm) and eluted at an eluent pressure of 200 – 300 kPa.

N-Methyl(naphth-1-yl)methylamine (VI) was obtained as described previously [15].

(*E*)-1-chloro-6,6-dimethyl-2-hepten-4-ine (IV) was synthesized using a method described in [14].

Standard samples of (I) (*E*)- and (II) (*Z*)-N-(6,6-dimethyl-2-hepten-4-inyl)-N-methyl(naphth-1-yl)methylamine for chromatography were obtained according to [4]. Compounds I and II were isolated by chromatography on a column eluted with a hexane – diethyl ether (3 : 1) mixture. Pure *trans* isomer I (TLC, R_f = 0.77) is followed by *cis* isomer II (TLC, R_f = 0.62).

Compound I. ^{1}H NMR spectrum in $CDCl_3$ (δ, ppm): 1.32 (s, 9H, $C(CH_3)_3$), 2.29 (s, 3H, CH_3N), 3.2 (dd, 2H, J 6.4 and 1.5 Hz, $NC\underline{H}_2CH$=), 3.96 (s, 2H, $NC\underline{H}_2C_{10}H_7$), 5.76 (dt, 1H, J 15.8 and 1.5 Hz, CH=C$\underline{H}$–C≡), 6.23 (dt, 1H, J 15.8 and 6.4 Hz, CH_2–C$\underline{H}$=CH), 7.44 – 7.61 (m, 4H, arom. H), 7.83 – 7.91 (m, 2H, arom. H), 8.33 – 8.36 (m, 1H, arom. H); hydrochloride: m.p, 205°C (isopropyl alcohol).

Compound II. ^{1}H NMR spectrum in $CDCl_3$ (δ, ppm): 1.34 (s, 9H, $C(CH_3)_3$), 2.34 (s, 3H, CH_3N), 3.45 (dd, 2H, J 7.3 and 1.5 Hz, $NC\underline{H}_2CH$=), 4.00 (s, 2H, $NC\underline{H}_2C_{10}H_7$), 5.76 (dt, 1H, J 10.8 and 1.5 Hz, CH=C$\underline{H}$–C≡), 6.11 (dt, 1H, J 10.8 and 7.3 Hz, CH_2–C$\underline{H}$=CH), 7.45 – 7.61 (m, 4H, arom. H), 7.82 – 7.92 (m, 2H, arom. H), 8.35 – 8.38 (m, 1H, arom. H); hydrochloride: m.p, 135°C (ethyl acetate).

(*E*)-N-(6,6-dimethyl-2-hepten-4-inyl)-N-methyl(naphth-1-yl)methylamine hydrochloride (I · HCl). A mixture of 20 ml (23.3 g, 0.087 mole) of 15% aqueous solution of sodium hydroxide, 14.4 g (0.084 mole) of N-methyl(naphth-1-yl)methylamine (VI), and 11.0 g (0.07 mole) of (*E*)-1-chloro-6,6-dimethyl-2-hepten-4-ine (IV) (contains 5% of *Z*- isomer) was stirred for 5 h at 70 ± 5°C until complete conversion of IV (HPLC monitoring). To this mixture was added dropwise on cooling with water 4.0 ml of hydrochloric acid. The product was separated by filteration, washed with water, and dried to obtain 22.5 g of a pale-creamy substance (HPLC data: 92% I + 6% II). Recrystallization from 2-propanol yields 18.6 g of compound I · HCl (81%) containing more than 99% of *trans* isomer; m.p., 205°C.

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