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A CONVENIENT AND SIMPLIFIED PREPARATION OF BOTH ENANTIOMERS OF α-TERPINYL CHLORIDE

Marcio C. S. de Mattos* and Antonio Manzolillo Sanseverino

Instituto de Química, Departamento de Química Orgânica, Universidade Federal do Rio de Janeiro, 21949-900, Rio de Janeiro, Brazil

ABSTRACT: Several methodologies to produce α -terpinyl chloride from "hydrochlorination" of limonene were studied and the best results were obtained by reaction with 0.5 mol equiv. SOCl₂ in SiO₂ / CH₂Cl₂. Using this methodology (*R*)- and (*S*)- α -terpinyl chloride can easily be prepared in good yields from (*R*)- and (*S*)-limonene, respectively.

 α -Terpinyl chloride [4-(1-chloro-1-methylethyl)-1-methylcyclohexene], which is known for more than a century for the work of Riban,¹ is an interesting intermediate and precursor of diverse 8-substituted *p*menthenes.² It is generally prepared in moderate yields (36 - 55 %) by hydrochlorination of limonene, by performing a slow and laborious addition of dry gaseous HCl to dry limonene with³ or without^{2b} solvent in the absence of moisture, at low temperature and long (6 - 24 h) reaction time (Scheme 1).

^{*}to whom correspondence should be addressed; e-mail: mmattos@iq.ufrj.br



In general, hydrohalogenation is only effective if the alkene is activated by a structural or electronic feature.⁴ Hence, alternate methodologies for performing hydrohalogenation of alkenes are the subject of study in different laboratories.^{5,6}

As part of our continuing interest in chemo- and regiospecific functionalization of the 8,9-double bond of limonene,⁷ we decided to study the 'hydrochlorination' of this substrate.

RESULTS

The reaction of (R)-(+)-limonene (10 mmol) with 0.5 mol equiv. SOCl₂ at room temperature in the heterogeneous media⁴ SiO₂/CH₂Cl₂ produced (R)-(+)- α -terpinyl chloride in 83 % crude yield after only 15 min. In an attempt to test the methodology for producing α -terpinyl chloride on a multigram-scale, the reaction was performed with 50 mmol of limonene and the product was obtained in 81 % crude yield (54 % after distillation). (R)-(+)- α -Terpinyl chloride was characterized by spectroscopic methods and by comparison of its physical data with that previously reported.^{2b}

The above reaction when performed on a 10 mmol-scale with 2 mol equiv. H₂O in the absence of SiO₂ produced (*R*)-(+)- α -terpinyl chloride in

similar yield and longer reaction time (45 min). However, the scaled up reaction (50 mmol) didn't prove effective, being incomplete after several hours and α -terpinyl chloride was obtained along with unreacted limonene. Unfortunately, reaction without solvent failed too and (*R*)-limonene was recovered unchanged.

Other methodologies for hydrochlorination of alkenes when applied to limonene led to disappointing results, as only insignificant amounts of α -terpinyl chloride were produced [determined by HRGC (high-resolution gas chromatography)]. The methodologies tested were reactions with aqueous HCl in different solvents (CH₂Cl₂ and THF) or with Me₃SiCl/H₂O⁶ and in all cases the substrate was recovered. On the other hand, the reaction of limonene with Me₃SiCl/SiO₂ in CH₂Cl₂ produced the chloride along with unreacted substrate. All results are summarized in Scheme 2 and Table 1.

Chiral-HRGC of the (R)-(+)- α -terpinyl chloride purified by reduced-pressure distillation showed > 84 % *ee*. As the (R)-(+)-limonene employed was > 99 % *ee* (determined by chiral-HRGC), we concluded a little racemization (< 7 %) occurred during the reaction. Curiously, some workers diation the optical purity^{2b,c} of the product or obtained it racemic from chiral limonene.^{3a} Furthermore, in contrast to the literature that describes partial racemization⁸ and easy polymerization^{2e} of (R)-(+)- α -terpinyl chloride, in our hands the product was stable for 24 h on



entry	i	time (h)	yield ^a (%)
16	SOCl ₂ / SiO ₂ / CH ₂ Cl ₂	0.25	83
2 ^{<i>c</i>}	SOCl ₂ / SiO ₂ / CH ₂ Cl ₂	0.75	$81(54^d)$
3°	SOCl ₂ / H ₂ O / CH ₂ Cl ₂	0.75	84
4 ^{<i>c</i>}	SOCl ₂ / H ₂ O / CH ₂ Cl ₂	1.5	68 ^e
5 ^c	SOCl ₂ / H ₂ O / CH ₂ Cl ₂	50	75 ^e
6	SOCl ₂ / H ₂ O	24	-
7 ⁸	aq. HCl / CH ₂ Cl ₂	24	_
8 ^b	aq. HCl / THF	22	-
96	Me ₃ SiCl / H ₂ O	24	-
10 ^b	Me ₃ SiCl / SiO ₂ / CH ₂ Cl ₂	0.25	68 ^e

TABLE 1: results of 'hydrochlorination' of (R)-(+)-limonene.

^acrude yield; ^b10 mmol limonene used; ^c50 mmol limonene used; ^dafter distillation at reduced pressure; ^cincompleted reaction.

standing at room temperature or at least one month if stored in a freezer (analysis by polarimetry showed no loss of optical activity).

The same reactions applied to (S)-(-)-limonene produced (S)-(-)- α terpinyl chloride in nearly the same yields on both reduced and larger scale. Chiral-HRGC of product indicated > 60 % *ee*, but this low value is because our (S)-(-)-limonene was initially of low enantiomeric purity (> 80 %).

In summary, α -terpinyl chloride can easily and quickly be prepared by the reaction of limonene with SOCl₂/SiO₂/CH₂Cl₂ without extensive racemization. The reaction conditions employed here are much simpler and the results are excellent compared with previous work using dry HCl and rigorous exclusion of moisture.^{2b,3} Moreover, this route is an alternative to the method of 'solvomercuration-demercuration' of limonene to form 8-substituted *p*-menthenes.⁹

EXPERIMENTAL

General. (R)-(+)-Limonene {Dierberger, $[\alpha]_{D}^{28}$ +118.7 (neat), lit.¹⁰ $[\alpha]_{D}^{20}$ +125.6 (neat)} [99 % (polarimetry), 95 % ee (chiral-HRGC)] was distilled at 177 °C (lit.¹⁰ 178 °C) prior to use. (S)-(-)-Limonene {Aldrich, $[\alpha]_D^{28}$ – 103.4 (neat), lit.¹⁰ $[\alpha]_D^{20}$ -122.1 (neat)} [85 % (polarimetry), 80 % ee (chiral-HRGC)] was used without further purification. SiO₂ (Aldrich, 270-70 MESH, 60 Å), SOCl₂ (Grupo Química), and other chemicals were used as received. ¹H NMR and ¹³C NMR were acquired on a Brucker AC-200 (200 MHz and 50 MHz, respectively) spectrometer in CDCl₃ solutions with TMS as internal standard. IR spectra were recorded on a Perkin-Elmer 1600 FT-IR spectrometer (KBr film). Polarimetric analysis was done on a Jasco DIP 370 polarimeter. MS were obtained on a Hewlett-Packard HP5896-A HRGC-MS using electron impact (70 eV). Chiral-HRGC analyses were performed on a Varian Star 3400CX (analysis of limonene) or on a Hewlett-Packard HP5890 (analysis of α -terpinyl chloride) chromatograph with FID. The conditions for the resolution of both enantiomers of limonene and α -terpinyl chloride are shown in Table 2.

(R)-(+)- α -Terpinyl chloride. To a stirred suspension of (R)-(+)-limonene (6.80 g) and SiO₂ (10 g) in CH₂Cl₂ (50 mL), a solution of SOCl₂ (3.0 g) in CH₂Cl₂ (10 mL) was added for 15 min at room temperature. After addition, the suspension was stirred for 25 min and then filtered. The SiO₂ was washed with CH₂Cl₂ (15 mL), the combined liquid was washed with 10 % NaHCO₃ (until no more gas was liberated), brine (2 x 25 mL) and the organic extract was dried (MgSO₄). The solvent was removed and the light yellow residue distilled in a short path at 66-69 °C / 3 Torr Downloaded by [La Trobe University] at 14:46 17 June 2016

TABLE 2: Chiral-HRGC conditions for resolution of both enantiomers of limonene and α -terpinyl chloride.

		· · · ·	
t, (min)	21.6 (S) 22.2 (R)	12.3 (S) 12.4 (R)	
Detector temp. (°C)	220	280	
Injector temp. (°C)	220	260	
Oven temp.	60 °C (isotherm)	70 °C, then 3 °C/min to 130 °C	
Phase thickness (µm)	0.25	0.3	
(nn) UI	0.25	0.3	
(m)	30	21	
Column	CYCLODEXB ⁴	DIMETBCD / SE-54 ^b	

^acarrier gas: He (40 cm/s); ^bcarrier gas: H₂ (50 cm/s)

(literature^{2b} 62-64 $^{\circ}$ C / 1-2 Torr) to give a colorless viscous liquid (4.68 g, 54 %).

¹H NMR: δ 1.54 (s, 3H), 1.59 (s, 3H), 1.66 (s, 3H), 1.73-2.13 (m, 7H), 5.38 (br s, 1H) ppm.

¹³C NMR: δ 23.2, 24.8, 27.4, 29.7, 30.7, 30.9, 46.5, 74.6, 120.1, 133.9 ppm.

IR: v 2969, 2928, 2854, 1455, 1439, 1369, 1117, 916, 801, 784 cm⁻¹.

MS: m / z (%) 172 (M^+ , 20), 174 (M^+ +2, 5), 136 (53), 121 (100), 93 (97), 67 (53).

 $[\alpha]_{0}^{26}$ +62.3 (neat)¹¹

Chiral-HRGC: tr 12.4 min (84 % ee)

(S)-(-)- α -Terpinyl chloride. Same as above, (S)-(-)-limonene used instead of (R)-(+)-limonene, 5.11 g (60 %) obtained after distillation (52-57 °C / 2 Torr).

 $[\alpha]_{D}^{26}$ -44.1 (neat)¹⁴

Chiral-HRGC: tr 12.3 min (60 % ee)

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- 11. The literature values of $[\alpha]$ for (R)-(+)- α -terpinyl chloride vary considerably $(0,^{3a} + 39.5,^{8} + 75^{12})$ and it should be mentioned that chiral analysis for determination of *ee* was not developed until recently. Our value of $[\alpha]$ for 84 % *ee* of (R)-(+)- α -terpinyl chloride would correspond to an absolute rotation¹³ of $[\alpha]_{max}$ +74.2.
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14. Our value of $[\alpha]$ for 60 % *ee* of (S)-(-)- α -terpinyl chloride would correspond to an absolute rotation¹³ of $[\alpha]_{max}$ -73.5.

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