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Short Report

Influence of Different Protecting Groups on the Regioselectivity of the Hydrotelluration Reaction of Hydroxy Alkynes

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A influência de grupos protetores na síntese régio- e estereosseletiva de teluretos vinílicos preparados a partir de BuTeNa e álcoois propargílicos e homopropargílicos demonstrou que o eter de silício TIPS é útil como grupo régio-dirigente. A aplicação da metodologia na síntese de um fragmento do (±)-Seselidiol, um produto natural, demonstrou a aplicabilidade da metodologia desenvolvida.

The influence of protecting groups on the synthesis of regio- and stereodefined vinyl tellurides derived from the reaction of BuTeNa and propargylic- or homo-propargylic alcohols showed that TIPS silyl ether is useful as a regiodirecting group. The application of the methodology to the synthesis of a fragment of (±)-Seselidiol, a natural product, demonstrated the applicability of the new methodology.

Keywords: hydrotelluration, alkynes, seselidiol, regioselectivity

Introduction

The hydrometalation of alkynes is a common method for the preparation of functionalized alkenes. Usually, the reaction proceeds in a *syn* fashion to yield the corresponding *E*-alkene via a four-membered ring concerted mechanism.[1]

The hydrotelluration reaction differs from the other hydrometalations, since it proceeds by an *anti* addition leading to the corresponding *Z*-vinyl telluride, which is stereochemically stable, since no isomerization to the *E* isomer has been reported to date.[2] This characteristic makes the hydrotelluration reaction a very important method for the generation of *Z*-alkenes (starting from alkynes), which are not easily accessible by other methodologies.

Allylic alcohols containing a stereodefined double bond are important synthetic intermediates.[3] These compounds can be easily prepared when hydroxyl-alkynes are subjected to hydrotelluration conditions. The *Z*-isomer is usually obtained in good yields together with the corresponding regioisomer. These, can be separated by column chromatography. Early studies dealing with the influence of the structure of the hydroxyl alkyne on the regioselectivity of the reaction were performed and different regioisomeric ratios were obtained.[4] Later, Comasseto and co-workers[5] have studied the influence of some protective groups in the reaction.

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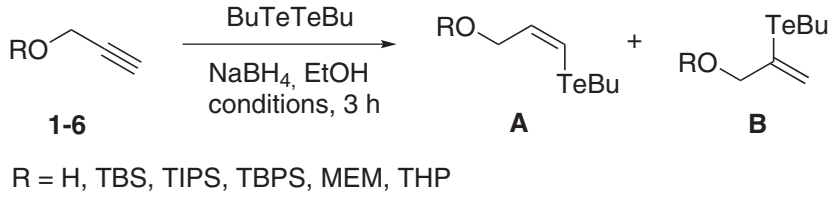
Results and Discussion

We describe herein the results obtained in the hydrotelluration reaction of protected propargylic and homo-propargylic alcohols. In an initial approach propargyl alcohol **1** was converted into its TBS,[6] **2**; TIPS,[7] **3**; TBPS,[8] **4**; MEM,[9] **5**; and THP,[10] **6** derivatives according to literature procedures. All compounds were obtained in good yields and purified by distillation. Compounds **1**-**6** were then subjected to hydrotelluration conditions[11] to yield the corresponding regioisomeric vinyl tellurides **A** and **B**.

The regioisomeric ratio was determined by ^{1}H NMR and confirmed by ^{125}Te NMR and gas chromatography as shown on Figure 1.

The obtained results are shown on Table 1. When **1** was used as the alkyne source an almost 1:1 mixture of regioisomers **A** and **B** was observed (Table 1, entry 1).



Scheme 1.

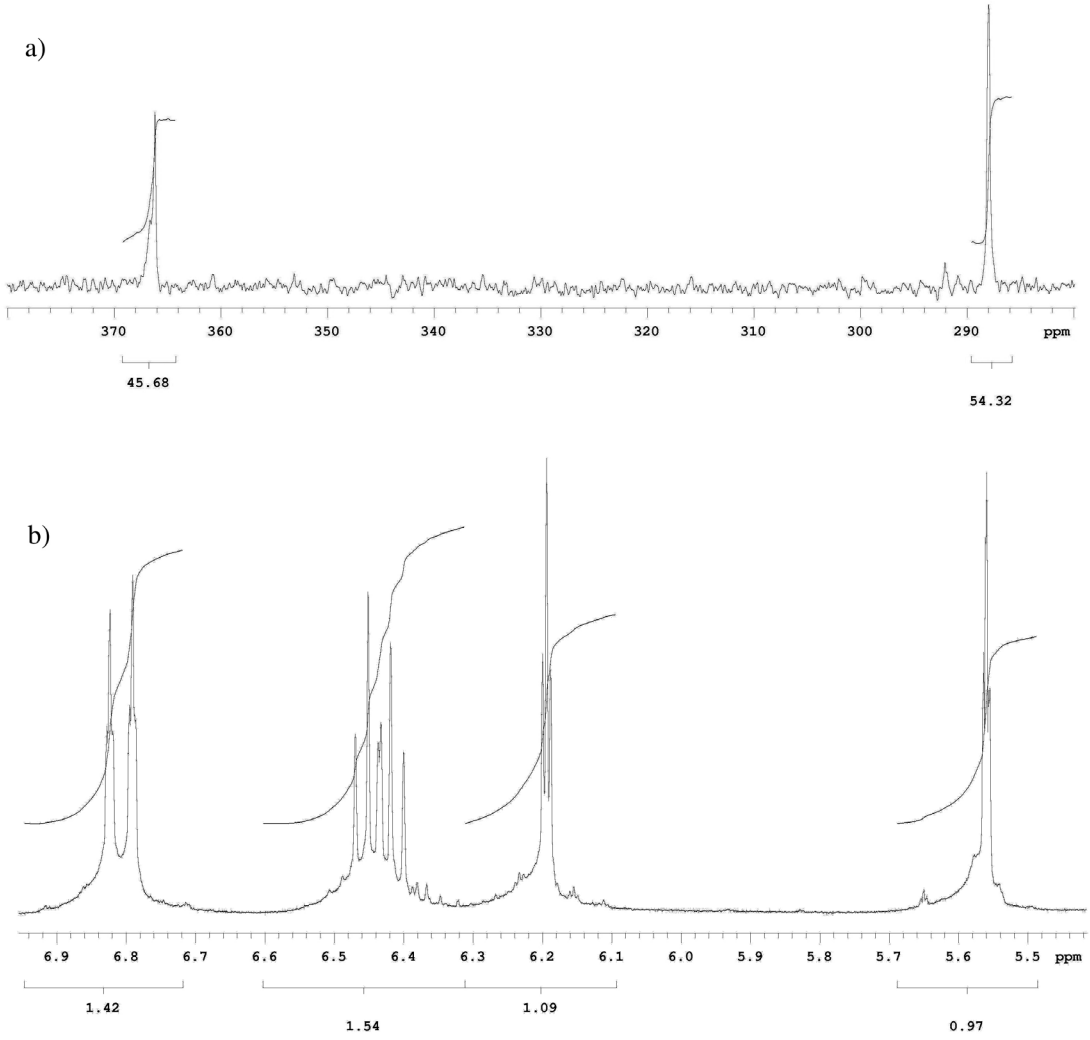


Figure 1. Vinyl telluride **1** (a) ^{1}H NMR (300 MHz, $CDCl_3$, parts) and (b) ^{125}Te NMR (94.6 MHz, $CDCl_3$) prepared according to Scheme 1. The ratio of regioisomers **A** and **B** in both spectra is the same.

Table 1. Influence of temperature on the formation of vinyl tellurides **A** and **B** prepared via Scheme 1

Entry	Alkyne	**A**:**B**		δ (ppm) ^{125}Te NMR ($CDCl_3$)		Yield (%)[a]
		25 °C	78 °C	**A**	**B**	
1	**1**, R = H	56:44	56:44	287.9	366.1	72 (78)
2	**2**, R = TBS	70:30	85:15	292.9	378.6	89 (90)
3	**3**, R = TIPS	82:18	88:12	298.6	387.7	88 (87)
4	**4**, R = TBDPS	-[b]	86:14	308.1	394.3	0 (80)
5	**5**, R = MEM	64:36	79:21	301.4	402.2	88 (80)
6	**6**, R = THP	55:45	76:24	305.9	400.1	85 (87)

[a]Chromatographic yields (the yield between parenthesis corresponds to the reaction at 78 °C); [b]Products not observed at this temperature.

The influence of the protective group is remarkable. When bulky groups such as TBS and TIPS were used (Table 1, entries 2 and 3) better regioselectivities were observed. The THP and MEM ethers gave lower regioselectivities when compared with the silyl groups (Table 1, entries 4 and 5).

In spite of the widespread use of bulky groups in organic chemistry, there are few attempts at quantifying the intuitive concept of bulkiness.[12] The screening action of a bulky group on an atom could be described by an angle.[13] This concept of cone angle was applied to silyl groups and the cone angles found for TIPS, $\theta = 160°$, and TBS, $\theta = 139°$.[14] In other words, the bulkiness of TIPS seems to be of the correct magnitude as to exhibit a good compromise between useful steric effects (rather than electronic factors) to give the desired regioisomer.

The influence of the temperature on the reaction was also studied. When the hydrotelluration reaction was performed at 0 °C the formation of the corresponding vinyl tellurides **A** and **B** was not observed for all substrates. This fact might be due to the lower reactivity of the involved species at this temperature. When the reaction was performed at 25 °C, under controlled conditions, the observed regioselectivities were lower if compared with the results obtained under reflux conditions.

The two regioisomeric tellurides **A** and **B** were obtained under different conditions, with vinyl telluride **A** predominating at higher temperature. This fact should indicate that the telluride **A** might be the thermodynamic product. Therefore, vinyl telluride **B** would be the kinetic product (or the product of kinetic control) since it should be formed faster at lower temperatures. To test this hypothesis, a 55:45 mixture of tellurides **A** and **B** were stirred in EtOH under reflux during 2 h. No change in the ratio of the products was observed, even when an additional amount of sodium borohydride was added.

The effect of the distance of the hydroxyl moiety from the triple bond, as well as the influence of a substituted propargylic alcohol on the ratio of the products were also studied (Scheme 2). The results are depicted in Table 2.

Lower regioselectivities were observed for the unprotected alcohols (Table 2, entries 1 and 2). However, better regioselectivities were observed when TIPS was used (Table 2, entries 3 and 4). It is interesting to note that when **9** was used as the alkyne source; only one regioisomer was obtained (Table 2, entry 3).

The methodology was then applied for the diastereoselective synthesis of the double bond present in (±)-Seselidiol (Figure 1) a natural product isolated in 0.0085% yield from the roots of *Seseli mairei* Wolff (Umbelliferae) and used as herbal remedies for human inflammation, swelling, rheumatism, pain, and common cold in folk Chinese medicine.[15] It also showed significant cytotoxicity in KB, P-388, and L-1210 tumor cells ($ED50 < 10\ \mu g\ mL^{-1}$).[16] The absolute stereochemistry of the stereogenic centers in Seselidiol is not known, and to date no total synthesis of the natural product has been attempted.

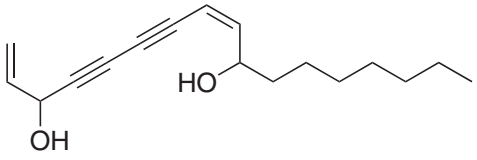
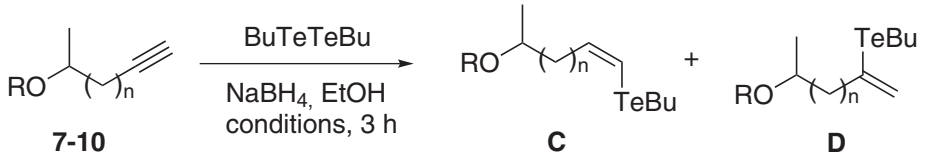


Figure 2. (±)-Seselidiol

Our approach for the synthesis of Seselidiol started with 1-octanol **11** which was oxidized into the corresponding

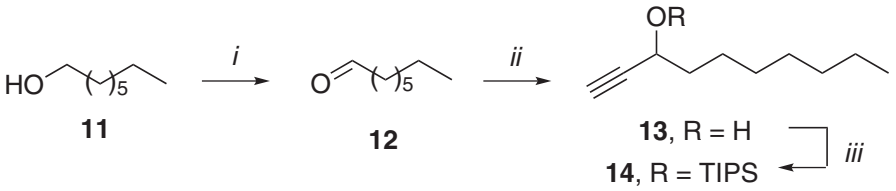


Scheme 2.

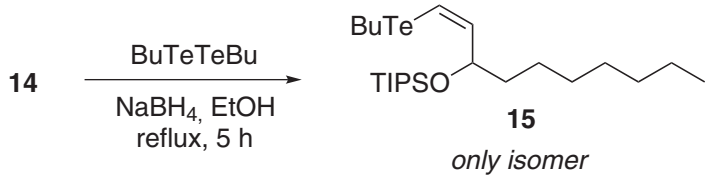
Table 2. Influence of temperature on the formation of vinyl tellurides prepared via Scheme 2

Entry	Alkyne	n	**C**:**D**		δ (ppm) ^{125}Te NMR ($CDCl_3$)		Yield (%)[a]
			25 °C	78 °C	**C**	**D**	
1	**7**, R = H	0	-[b]	77:23	301.9	338.3	0 (70)
2	**8**, R = H	1	-[b]	58:42	357.6	274.1	0 (65)
3	**9**, R = TIPS	0	85:15	100:0	279.1	-	65 (80)
4	**10**, R = TIPS	1	63:37	82:18	358.8	286.9	62 (78)

[a]Chromatographic yields (the yield between parenthesis corresponds to the reaction at 78°C); [b]Products not observed at this temperature.



Scheme 3. (i) PCC, CH_2Cl_2, 3 h, 0 °C (55%); (ii) ethynylmagnesium bromide, THF, 25 °C, 12 h (50%); (iii) TIPSCl, imidazole, DMF, 25 °C, 12 h (85%).



Scheme 4.

aldehyde **12** using PCC.[17] Addition of ethynylmagnesium bromide to **12** at room temperature[18] gave alcohol **13** which was converted into its TIPS ether derivative **14** (Scheme 3).

Hydrotelluration of **14** using the developed methodology gave the corresponding *Z*-vinyl telluride **15** as a single isomer determined by ^{1}H, and confirmed by ^{125}Te NMR and gas chromatography in 90% yield (Scheme 4).

It is noteworthy that when the hydrotelluration reaction was performed without TIPS as the protective group a mixture of 78:22 of the two regioisomers were observed.

Conclusions

In summary, the methodology presented is shown to be useful for the synthesis of regio- and stereo-defined vinyl tellurides, the TIPS group being successfully used as a regio-directing group. The application of the methodology to the synthesis of a natural product was performed in order to demonstrate its applicability. Finally, the methodology offers future possibilities in the development of new organometallic approaches to the compounds containing *Z*-double bonds. The completion of the synthesis of (±)-Seselidiol and its asymmetric version are ongoing in our laboratory and will be reported in a due course.

Acknowledgments

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Supplementary Information

Supplementary information, with extra experimental and characterization data, is available free of charge at http://jbcs.sbq.org.br, as PDF file.

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