

Reactions of terpene tosylates with sodium ethyl carbonate

Z. Rykowski and E. Drozd-Szczygiel
*The Chair of Organic Chemistry, Medical Academy,
pl. Nankiera 1, Wrocław, Poland*

For a long time [1] terpene compounds have been arousing a continuously growing interest of chemists, pharmacologists and pharmacists. This interest was only enhanced by their prevalence and frequent ample occurrence in easily accessible vegetable material.

They are widely applied mainly in perfume, cosmetic food and pharmaceutical industries. Chemical reactivity research of these combinations has contributed to theoretical knowledge and what is more important it facilitated the exploration of a number of stereochemistry principles.

P-toluenesulfonyl acid terpene alcohols esters, called tosylates, were of particular interest among terpenes derivatives. From the theoretical point of view they constitute an interesting group of combinations. Terpene tosylates reduced with lithium-aluminium hydride, unlike other esters which produce alcohols, afford hydrocarbons [2]. While reduced with lithium in ethyl amine [3] terpenes tosylates afford to obtain free alcohols both in the case of mono- and polyhydroxide alcohols.

Unlike other esters, terpene tosylates are not hydrolysed under the influence of alkalis. Strong bases in non-aqueous solutions result in eliminations. This is an easy way to obtain unsaturated hydrocarbons [4] with good efficiency. Polyhydroxide alcohol tosylates depending on their structure may form aldehydes [5], ketones [6] or epoxides [7].

The introduction of aprotic solvents terpenes to chemistry created new opportunities. In these conditions monohydroxide alcohols tosylates easily reacted in nucleophilic substitution producing azides or nitriles [8] with good effectiveness. The latter form useful substrates for the synthesis of new derivatives.

1. RESULTS AND DISCUSSION

In the research on terpene derivatives the fact that –neo series alcohols are far less accessible in comparison with elementary series alcohols attracted particular attention. We assumed that in the reaction of menthol tosylate SN_2 with carbonates it will be possible to obtain neomenthol carbonate, which after hydrolysis should afford not easily accessible neo-menthol. The experiment has shown that menthol tosylate does not react with sodium carbonate neither in protic nor aprotic solvents. The attempts with sodium hydrocarbonate yielded no result, either. We devoted particular attention to a common method of diethyl pyrocarbonate synthesis [9] where chlorine atom in ethyl chloroformate particle is substituted by ethylcarbonate radical derived from sodium ethylcarbonate. We expected that during the reaction of terpene tosylates with sodium ethylcarbonate (it should involve inversion at the attacked carbon atom) –neo series ethylcarbonate will be afforded. Unexpectedly we found out that the main products afforded in the reactions were ketones. They were accompanied by unsaturated hydrocarbons and their structure was of the type to be expected in an elimination reaction of tosyloxy group. Such experiment result, although it did not lead to achieving the adopted goal, encouraged us to examine the reaction on a few terpene systems. We have also decided to examine the response of –neo series alcohol tosylates. We carried out the reactions of sodium ethylcarbonate with dihydrocarveol tosylates (1), neo-dihydrocarveol (2), menthol (3), neo-menthol (4), carvomenthol (5) and neo-carvomenthol (6). Reactions were carried out in DMSO solution and in each of the examined cases the main product of the reaction was an appropriate ketone only sometimes accompanied by non-saturated carbohydrates. The formation of carbonic acid esters was not observed in any of the cases. When an aprotic solvent was substituted with an alcohol one (comparative concentration conditions, temperature and reaction forming time were maintained) we could not observe visible changes in the starting tosylate. The change of sodium ethylcarbonate to sodium hydrocarbonate also made it impossible to carry on the reaction. Just like in Kornblum's *inter alia* [10] research, we think that DMSO is the oxidising agent. However, in our experiment the applied conditions were much more lenient, as a result of terpene tosylates were not exposed to decomposition.

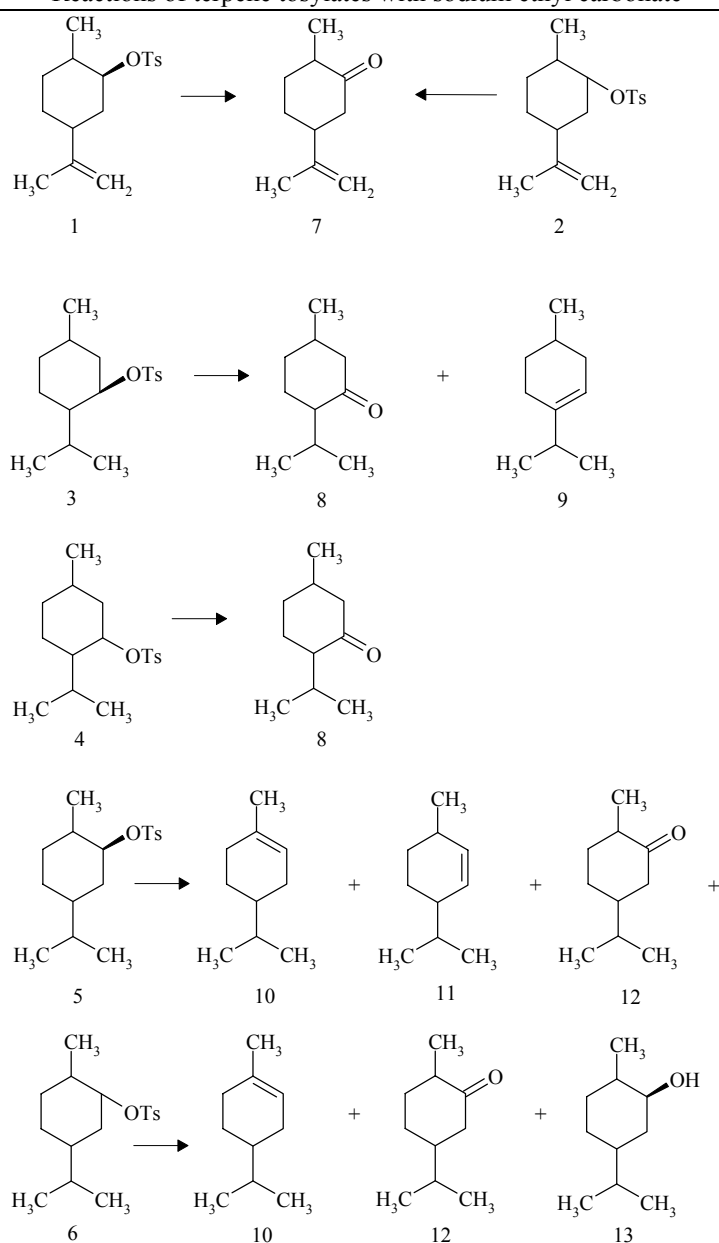


Fig. 1. 1. Dihydrocarveol tosylate 8. Menthone
 2. Neo-dihydrocarveol tosylate 9. Ment-3-en
 3. Menthol tosylate 10. Ment-1-en
 4. Neo-menthol tosylate 11. trans-p-Ment-2-n
 5. Carvomenthol tosylate 12. Carvomenthone
 6. Neo-carvomenthol tosylate 13. Carvomenthol
 7. Dihydrocarvon

Sodium ethylcarbonate acts as a basic agent which is more active than sodium carbonate used by Kornblum [10], thanks to that terpene tosylates react at the temperature of 80°C avoiding the danger of thermal decomposition.

Finally we would like to stress that the described reactions, carried out in lenient conditions, may be applied as a convenient method to obtain terpene ketones especially in the case when the release of pure alcohol for the purpose of its oxidation is difficult. Alcohol tosylates are released in pure state much more easily and may be transformed into ketones.

2. EXPERIMENTAL

General considerations. Melting points were determined in a Koffler block and were uncorrected. ¹HNMR spectra were performed on Tesla BS/478 (80 MHz) apparatus with TMS as an internal standard. GLC was performed on Elpo N/501 apparatus, column 2m long, stationary phase 10% Reoplex on Celite 545, carrier – nitrogen, column temperature 140°C. TLC was carried out on Merc silica gel.

Chromatograms were developed in a hexane system: ethanol (10:1) and visualised in iodine vapours. Dihydrocarveol boiling point 84–86°C/4mmHg, $n_D^{20} = 1.4820$ was prepared according to Wallach [11]. Dihydrocarveol tosylate boiling point 61.8–62.9°C was prepared according to Kozina and Danilov [12].

Neo-dihydrocarveol boiling point 93–95.5°C/10mmHg, $n_D^{20} = 1.4700$ was prepared according to Johnston and Read [13] and neo-dihydrocarveol tosylate melting point 38.5–40°C was prepared according to Chabudziński, Rykowski and Orszańska [14].

Neo-menthol boiling point 84–85°C/5mmHg $n_D^{20} = 1.4605$ was prepared from menthol [15] according to Grubba and Read [16], neo-menthol tosylate melting point 62.8–63°C was prepared according to Huckel and Tappe [17]. Commercial menthol melting point 42–43°C and menthol tosylate melting point 97°C, $[\alpha]_D^{20} = -67^\circ \text{C}$ (CHCl₃, c=5) was prepared according to Hilditch [18].

Carvomenthol boiling point 81°/3mmHg, $n_D^{20} = 1.4624$, $\alpha_D^{20} = -25.2^\circ$ was prepared according to Chabudziński, Rykowski and Kuczyński [19], carvomenthol tosylate melting point 55–56°C, $[\alpha]_D^{20} = +58.2^\circ$ (CHCl₃, c=1.9) was prepared according to Chabudziński and Kuduk [20].

Neo-carvomenthol boiling point 72°C/4mmHg, $n_D^{20} = 1.4644$, $\alpha_D^{20} = +42.4^\circ$ was prepared according to Read and Johnston [21].

Sodium ethylcarbonate preparation (according to Faurholt and Gjaldbach) [9]. The amount of 500 ml of absolute ethanol was placed in a flask with a reflux condenser. Small portions of sodium, 40g (0.357 mol) were inserted into the flask. The whole was heated in a water bath until sodium dissolved completely. Solid carbon dioxide was inserted to the thus afforded sodium

ethylate under constant stirring. The product was filtered from excess ethanol and next dried. The reaction afforded 115g of sodium ethylcarbonate.

Dihydrocarveol tosylate (1) reaction with sodium ethylcarbonate in DMSO.

To a solution containing 15.5 g (0.0503 mol) of dihydrocarveol tosylate in 150 ccm of anhydrous DMSO 8.5g (0.0759 mol) of sodium ethylcarbonate was added. The whole was heated at 85 °C for 8 h. The cooled reaction mixture was diluted with fivefold volume of water (750 ml) and extracted with hexane (5 x 50ccm). Hexane extracts were dried over anhydrous MgSO₄, concentrated and distilled under reduced pressure affording 4.5 g of product boiling point 74–83 °C/5mmHg, $n_D^{20} = -16.93^\circ$. TLC chromatography showed the presence of dihydrocarvon (7) in 60% yield. The obtained compound formed semicarbazone melting point 184.4–185.9 °C, 2,4-dinitrophenylhydrazon melting point 128–130 °C, so the properties were in accordance with literature [22].

Neo-dihydrocarveol tosylate (2) reaction with sodium ethylcarbonate in DMSO.

To a solution containing 5.4g (0.0175 mol) of neo-dihydrocarveol tosylate in 53 ccm of anhydrous DMSO 3 g (0.0268 mol) of sodium ethylcarbonate was added and heated at 85 °C for 8 h. The cooled reaction mixture was diluted with fivefold volume of water (270 ccm) and extracted with hexane (4 x 25 ccm). Hexane extracts were dried over anhydrous MgSO₄, concentrated and distilled under reduced pressure. The obtained compound 1.4 g boiling point 68–74 °C/3mmHg, $n_D^{20} = 1.4700$, $\alpha_D^{20} = 16.94^\circ$.

TLC chromatography showed the presence of 40% dihydrocarvon (7). The obtained semicarbazone melting point 186.4/188 °C had properties in accordance with literature [22].

Menthol tosylate (3) reaction with sodium ethylcarbonate in DMSO.

To a solution of 26 g (0.0839 mol) of menthol tosylate in 150 ccm of anhydrous DMSO 15g (0.1339 mol) of sodium ethylcarbonate was added. The whole was cooled down at 85 °C for 8 h. The cooled reaction mixture was diluted with fivefold volume of water (750 ccm) and extracted with hexane (4 x 50 ccm). Hexane extracts were dried over anhydrous MgSO₄. Next they were concentrated and distilled under reduced pressure and afforded 7.7g of the product boiling point 65–67 °C/4mmHg. $n_D^{20} = 1.4500$, $\alpha_D^{20} = -30^\circ$. TLC chromatography showed the presence of menthone (8) in 65% yield and menthene –3 (9) in 20% yield. The obtained semicarbazone melting point 181–183 °C, $[\alpha]_D^{20} = -49^\circ$, (EtOH, c=0.5) had properties in accordance with literature [23]. Semicarbazone obtained from standard menthone did not afford depression of melting point after mixing with the above one.

Neo-menthol tosylate (4) reaction with sodium ethylcarbonate in DMSO.

To a solution of 5.2 g (0.0168 mol) of neo-menthol tosylate in 55 ccm of anhydrous DMSO 3g (0.0268 mol) of sodium ethylcarbonate was added. The whole was heated at 85 °C for 8 h. The cooled reaction mixture was diluted with fivefold volume of water (275 ccm) and extracted with hexane (4 x 20 ccm). Hexane extracts were dried over anhydrous MgSO₄, next concentrated and distilled under reduced pressure.

The obtained product 0.950g, boiling point 70–73 °C/5mmHg, $n_D^{20} = 1.4508$, $\alpha_D^{20} = -25.60^\circ$. TLC chromatography showed the presence of menthone (8) in 35% yield. Semicarbazone melting point 183–184 °C, obtained from the reaction product, had properties in accordance with literature [23].

Carvomenthol tosylate (5) reaction with sodium ethylcarbonate in DMSO.

To a solution of 15 g (0.0484 mol) of carvomenthol tosylate in 150 ccm of anhydrous DMSO 8.1g (0.0725 mol) of sodium ethylcarbonate was added. The whole was heated at 85 °C for 8 h. The cooled reaction mixture was diluted with fivefold volume of water (750 ccm) and extracted with hexane (5 x 50 ccm). Hexane extracts were dried over anhydrous MgSO₄, concentrated and distilled under reduced pressure affording 4.07g (55%) of the product boiling point 91–92 °C/10mmHg, $n_D^{20} = 1,4555$, $\alpha_D^{20} = -25^\circ$. TLC chromatography showed the presence of four main signals (23:24:31:9) which were amplified after the addition of menthene-1 (10), trans-p-menthene-2 (11), carvomenthone (12) and carvomenthol (13), respectively. Semicarbazone obtained from the reaction product melting point of 192°C (ethanol crystallization) which is in accordance with literature for semicarbazone [24].

Neo-carvomenthol tosylate (6) reaction with sodium ethylcarbonate in DMSO.

To a solution of 15 g (0.0484 mol) of neo-carvomenthol tosylate in 150 ccm of anhydrous DMSO 8.1g (0.0725 mol) of sodium ethylcarbonate was added. The whole was heated at 85 °C for 8 h. The cooled reaction mixture was diluted with fivefold amount of water (750 ccm) and extracted with hexane (5 x 50 ml). Hexane extracts were dried over anhydrous MgSO₄, concentrated and distilled under reduced pressure affording 3.2g (43%) of the product boiling point 90–93 °C/10mmHg, $n_D^{20} = 1.4551$, $\alpha_D^{20} = -24.2^\circ$.

Chromatography showed the presence of three main signals (60:30:10) which were amplified after the addition of menthene-1 (10), carvomenthone (12) and carvomenthol (13). Semicarbazone obtained from the reaction product melting point 191.5–193 °C – in accordance with literature for carvomenthone derivative [24].

REFERENCES

- [1] a) Simonsen J.L., *The Terpenes. Cambridge*, Vol. 1 and 2 (1957).
b) Wawrzęńczyk C., Lochyński S., *Monatsh.*, **116**, 99 (1985).
c) Łukasiak J., Świetlicki M., Zawisłak T., Glinka R., Falkiewicz B., *Pol. J. Cosmetol.*, **109** (1999).
- [2] a) Miligen B., Jefferies P.R., *Chemistry and Industry*, **22**, 487 (1956).
b) Schmid H., Karrer P., *Helv. Chim. Acta*, **32**, 1371 (1949).
c) Strating J., Backer H.J., *Recu. Trav. Chim.*, **69**, 909 (1950).
- [3] a) Wrzesień J., Rykowski Z., *Polish J. Chem.*, **55**, 2629 (1981)
b) Gubrynowicz O., Rykowski Z., Wrzesień J., *Polish J. Chem.*, **57**, 1237 (1983).
- [4] Rykowski Z., Orszańska H., Chabudziński Z., *Bull. Acad. Polon. Sci. Ser. Sci. Chim.*, **24**, 681 (1976).
- [5] Chabudziński Z., Lipnicka U., Rykowski Z., *Rocz. Chem.*, **44**, 2181 (1970).
- [6] Chabudziński Z., Rykowski Z., *Rocz. Chem.*, **43**, 235 (1969).
- [7] Chabudziński Z., Rykowski Z., *Bull. Acad. Polon. Sci. Ser. Sci. Chim.*, **15**, 95 (1967).
- [8] a) Chabudziński Z., Rykowski Z., Orszańska H., *Polish J. Chem.*, **52**, 767 (1978).
b) Rykowski Z., *Polish J. Chem.*, **55**, 2271 (1981).
c) Kubica Z., Piątkowski K., *Polish J. Chem.*, **57**, 1197 (1983).
- [9] Faurholt C., Gjaldbach J., *Danst. Tids. Pharm.*, **19**, 255 (1945).
- [10] Kornblum N., Jones W., Anderson G. J., *J. Am. Chem. Soc.*, **81**, 4113 (1959).
- [11] Wallach O., *Ann.*, **275**, 111 (1893).
- [12] Kozhina I.S., Danilowa A.S., *Zhurn. Obshch. Kim.*, **31**, 3783 (1961).
- [13] Johnston R.G., Read J., *J. Chem. Soc.*, 237 (1934).
- [14] Chabudziński Z., Rykowski Z., Orszańska H., *Polish J. Chem.*, **52**, 767 (1978).
- [15] Brown H.C., Garg C.P., *ibid.*, *J. Am. Chem. Soc.*, **83**, 2951 (1969).
- [16] Grubb W.J., Read J., *J. Soc. Chem. Ind.*, **53**, 237 (1934).
- [17] Huckel W., Tappe W., *Ann.*, **537**, 129 (1939).
- [18] Hilditch T., *J. Chem. Soc.*, **99**, 238 (1911).
- [19] Chabudziński Z., Rykowski Z., Kuczyński Z., *Rocz. Chem.*, **37**, 1571 (1963).
- [20] Chabudziński Z., Kuduk J., *Rocz. Chem.*, **39**, 1037 (1965).
- [21] Read J., Johnston G.R., *J. Chem. Soc.*, 229 (1934).
- [22] Johnston R.G., Read J., *Chem. Soc.*, 237 (1937).
- [23] Zeitschel O., Schmidt H., *Ber.*, **59**, 2298 (1926).
- [24] Johnston R.G., Read J., *J. Chem. Soc.*, 1139 (1935).