Synthesis of 4-methoxymethylbenzoic acid

Supplementary Material

This experiment was recently introduced on the list of classroom experiments and was tested by students of intermediate organic chemistry in which the concepts of radical halogenation and nucleophilic substitution were taught. Experimental procedure can be easily performed by first and second-years undergraduate students. Radical halogenation experiments are commonly avoided in a classroom due to the use of hazardous reactants. In this experiment, *N*-bromosuccinimide (NBS) is used as the bromine source for the radical halogenation, which is safer and easier to use than molecular bromine. The product obtained in the first step (4-bromomethylbenzoic acid) is not lachrymatory, unlike most benzyl halides. Most reactions involving NBS use carbon tetrachloride as a solvent, but in this work chlorobenzene was used instead. 4-Bromomethylbenzoic acid can also be used to synthesize 4-vinylbenzoic acid and can be found elsewhere in this book. The second step involves a nucleophilic substitution on a saturated carbon atom, allowing discusses the two possible mechanisms (SN_1 or SN_2). Several factors point out towards a SN_2[1,2] mechanism: the methanolic solution of KOH generates the methoxide nucleophile[3] and the substituent in the aromatic ring is an electron-withdrawing carboxylic group[4] favoring S_N2 mechanism by stabilization of transition state.

Additional notes on the preparation of 4-bromomethylbenzoic acid:

Benzoyl peroxide should be added carefully through a solid addition funnel, making sure that no solid residue adheres to the side of the flask, since this reactant is potentially explosive when heated in the solid state. For that reason, chlorobenzene is added after benzoyl peroxide to wash down any residue remaining on the flask sides. Reflux was performed with an oil bath instead of flame, to better reach the boiling point of chlorobenzene and also to allow the magnetic stirring of the reaction mixture,

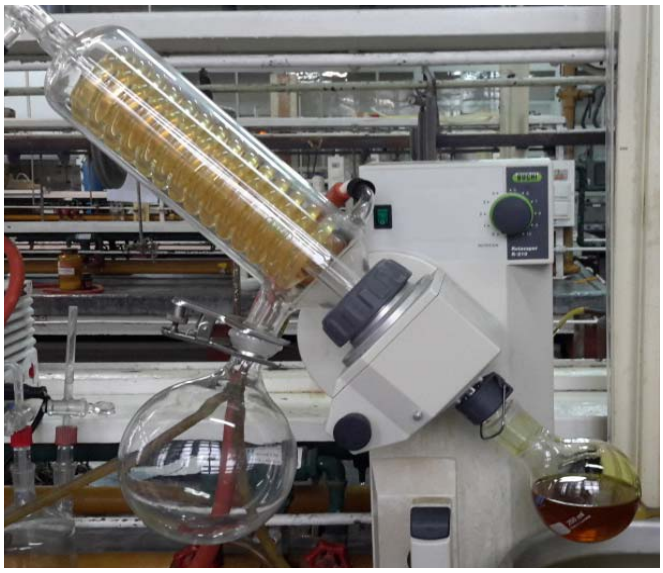
leading to a better yield[4] (Figure **SM 11.1.1**). Petroleum ether (bp 40-60ºC) can be substituted by hexane.

SM 11.1.1 – Reaction set-up apparatus for 4-bromomethylbenzoic acid

The obtained product can be used on the second step as it is and no further purification is needed. Yield varies between 50-60 % while the melting point is between 226 and 228ºC. The melting point range is never higher than 1ºC (literature: 227-229ºC[5]).

Additional notes on the preparation of 4-methoxymethylbenzoic acid:

Methanol removal on a rotary evaporator (Figure **SM 11.1.2**) should be performed with gentle warming in order to avoid bumping.

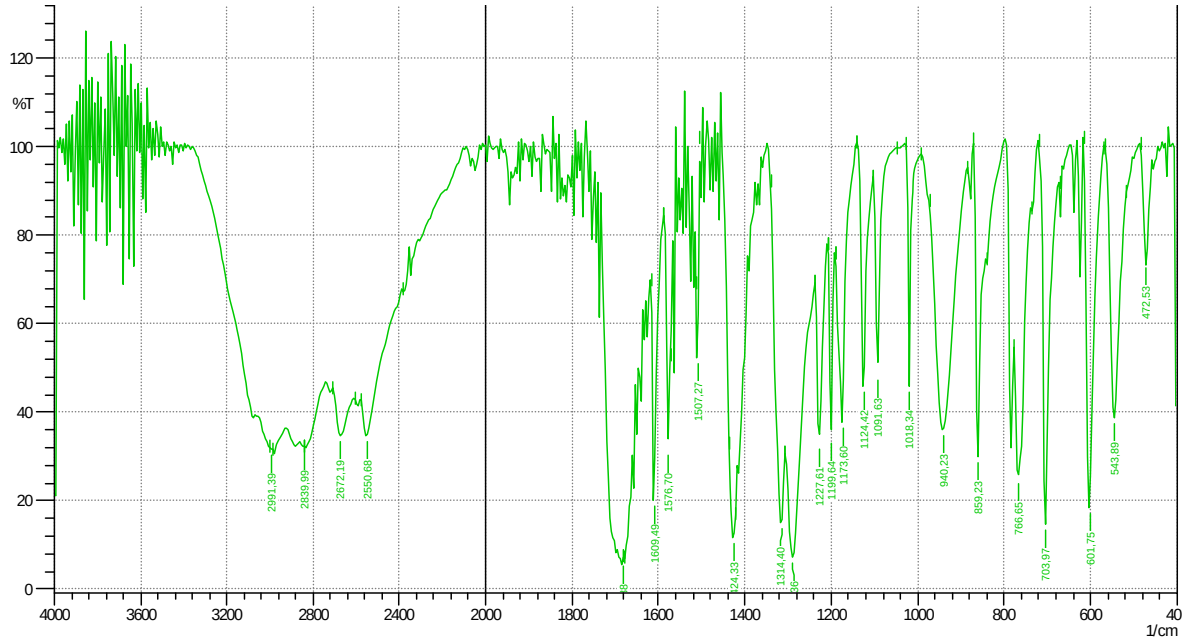


SM 11.1.2 – Rotary evaporator for methanol removal

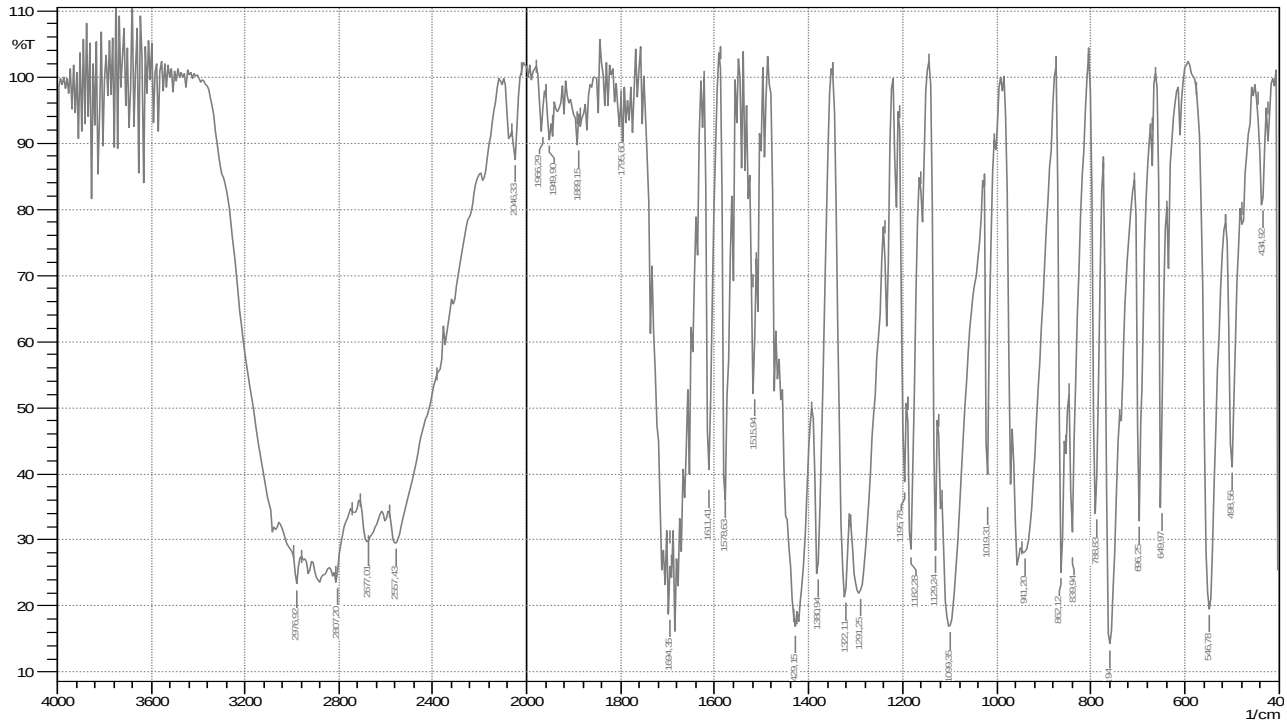
Yield of 4-methoxymethylbenzoic acid is 50-70 %. The melting point found is between 108 and 112ºC, with a melting point range never superior to 1ºC (literature: 111-113ºC[6]).

IR spectra:

Students easily identify a strong band due to C=O group at 1700 cm^{-1} for 4-bromomethylbenzoic acid. C-Br absorption can be observed at 703 cm^{-1} as well two intense bands at 1289 cm^{-1} and 1314 cm^{-1} due to C-H of CH_2Br group (Figure **SM 11.1.3**). For 4-methoxymethylbenzoic acid, the same strong band due to C=O group at 1700 cm^{-1} is observed. Characteristic absorption strong band for C-O-C bonds is observed at 1099 cm^{-1} (Figure **SM 11.1.4**). The IR spectrum for 4-bromomethylbenzoic acid can be found in SDBS under number 11103[7].



SM 11.1.3: IR (KBr) of 4-bromomethylbenzoic acid



SM 11.1.4: IR (KBr) of 4-methoxymethylbenzoic acid

NMR spectra:

The students analyzed the ^{1}H NMR ($CDCl_3$) spectrum of 4-bromomethylbenzoic acid available in *The Aldrich Library of NMR Spectra*[8]. They easily identify the aromatic protons, the protons of CH_2 group and O-H proton. ^{1}H NMR data for 4-methoxymethylbenzoic acid is available in literature[5].

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[1] J. March, *Advanced Organic Chemistry*, John Wiley & Sons, New York, 4th ed., 1992, 306.
[2] Clayden, Greeves, Warren and Wothers, Organic Chemistry, Oxford, 2001, 426.
[3] A. Y. Platanov, A. V. Kurzin, A. N. Evdokimov, *J. Solution Chem.*, 2010, **39**, 335.
[4] M. K. Priebat, L. Chauffe, *J. Am., Chem., Soc.,* 1976, **41**, 3914.
[5] E. S. Olson, *J. Chem. Educ.*, 1980, **57**, 157.
[6] D. L. Tuleen, B. A. Hess, *J. Chem. Educ.,* 1971, **48**, 476.
[7] http://sdbs.db.aist.go.jp/sdbs/cgi-bin/direct_frame_top.cgi, accessed in Oct 2015.
[8] C. Pouchert, *The Aldrich library of NMR spectra*, 2nd ed., **2**, 1983, 190.

Synthesis of benzopinacolone *via* benzophenone photoreduction followed by pinacol rearrangement

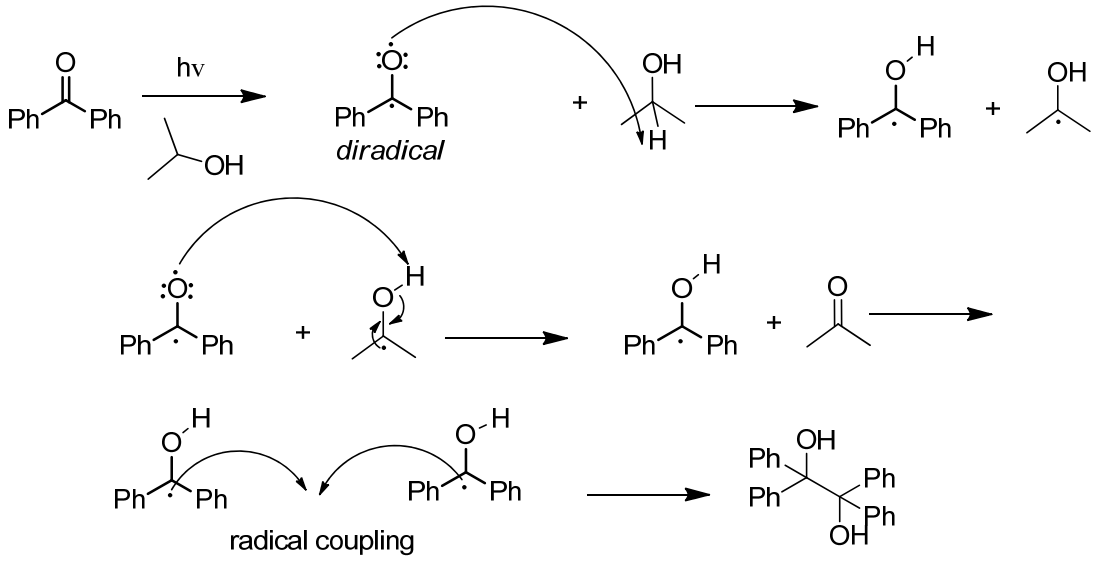
Supplementary Material

This experiment allows the study of the phototransformation of benzophenone to benzopinacol and the pinacol rearrangement. These two methodologies are easily performed, reproducible, in yields obtained by the students above 85% for each reaction, and with melting points in the range of literature, benzopinacol (171-173ºC, Aldrich), benzopinacolone (182-184ºC, Aldrich).[a]

Step 1: Synthesis of benzopinacol

The photoreduction of benzophenone to benzopinacol must be carried out in a sunny place. The benzophenone is dissolved in isopropanol that act as solvent and reagent.[b] Precipitation of the product, as a white solid is then observed.[c] A catalytic amount of acetic acid is added to ensure the removal of traces of alkali, which cause decomposition of the benzopinacol into benzophenone and benzohydrol. The phototransformation of benzophenone illustrates the photochemical characteristics of the carbonyl group, such as the radical coupling (Scheme SM 11.2.1). The reaction mechanism, shown in Scheme SM 11.2.1, involves the formation of a radical intermediate (diradical) by the benzophenone, which in the presence of isopropanol forms a more stable radical intermediate that, *via* radical coupling originates the benzopinacol product.

[a] This experiment was performed by students of different classes (aprox. 15 students/class) of organic chemistry.
[b] The benzophenone slowly dissolved in isopropanol at room temperature. Sometimes the dissolution was also achieved by gently heating.
[c] If the weather is not sunny, longer time is required (up to two weeks).



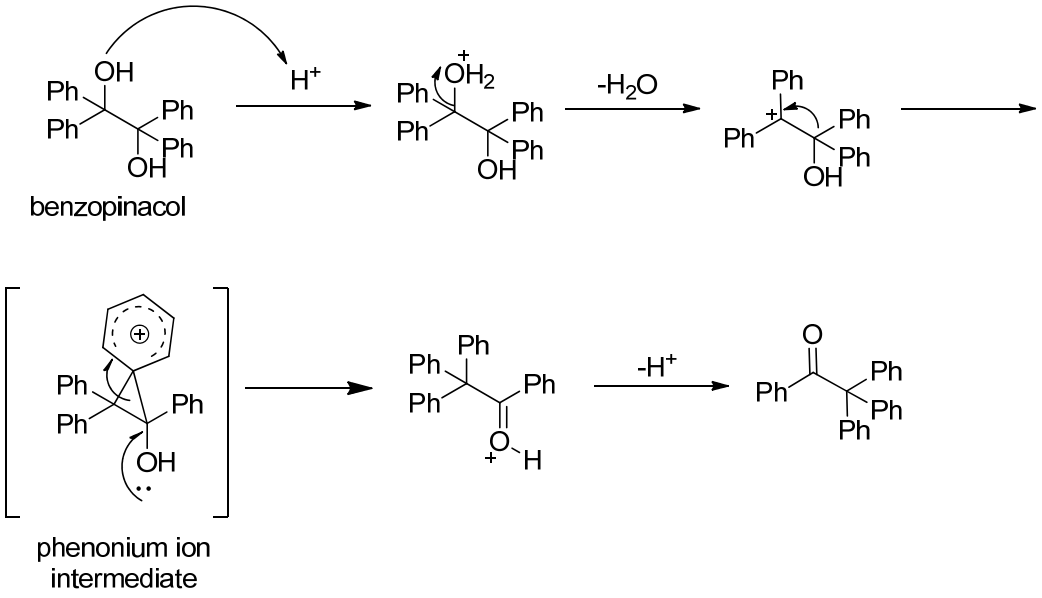
Scheme SM 11.2.1. Mechanism benzophenone-benzopinacol.

To enrich the mechanism discussion, comparative experiments can be carried out using different conditions, such as absence of sunlight, and presence of the radical inhibitor butylated hydroxytoluene (BHT). In the first case, no reaction occurs and, in the second case, reaction inhibition occurs during the first weeks and then the formation of a precipitate is observed, although in low quantity when compared with the reaction without BHT.

Step 2: Pinacol rearrangement

The pinacol rearrangement mechanism, involve the protonation of one hydroxyl group, water loss and formation of a relatively stable tertiary carbocation. A 1,2-methyl shift originate an even more stable carbocation, since the positive charge is delocalized by heteroatom resonance. In the end deprotonation occurs to give pinacolone. This transformation illustrates a carbocation rearrangement that is driven by the stability of the oxygen-substituted carbocation shown as the protonated carbonyl resonance form. It is also a demonstration of the strength of the carbon-oxygen double bond.[1]

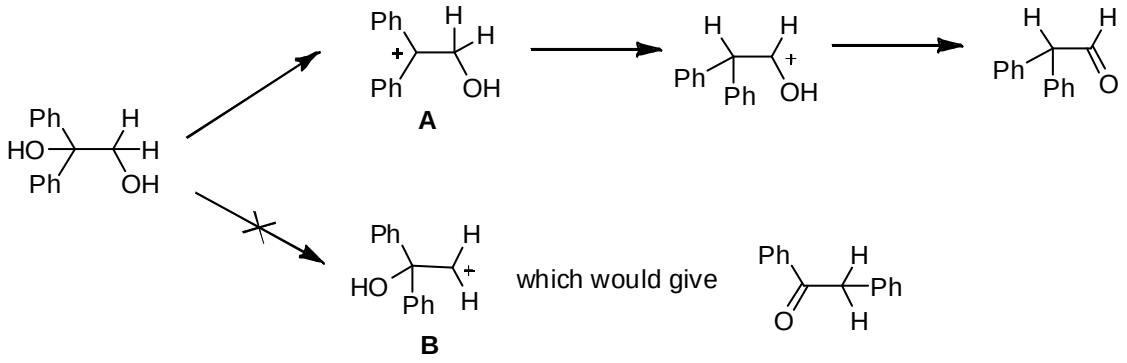
The mechanism of benzopinacol to benzopinacole represented in Scheme SM 11.2.2, is similar to the mechanism described for pinacol rearrangement, however the presence of phenyl-substituents suggest the formation of a phenonium ion as an intermediate. The iodine is considered as a mild acid catalyst. A catalytic amount of iodine is used for promote the hydroxyl group activation in order to facilitate the elimination of water.[2]



Scheme SM 11.2.2. Mechanism benzopinacol-benzopinacole.

In addition to the mechanistic discussion, the pinacol rearrangement provides the opportunity to study the carbocation rearrangement, including the relative migratory aptitudes, the carbocation stability, the reactivity of 1,2 diols with different substituents and the kinetics versus thermodynamic product. Examples are shown in Schemes SM 11.2.4 and SM 11.2.5.

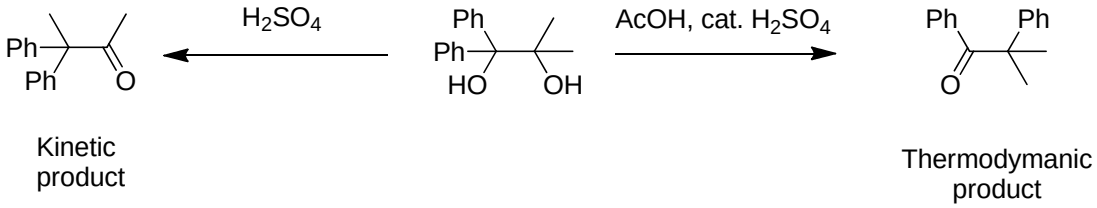
Scheme SM 11.2.3 shows the mechanism of exclusive transformation of 1,1-diphenylethanediol to diphenylacetaldehyde.



Scheme SM 11.2.3 Mechanism of the transformation of 1,1-diphenylethanediol to diphenylacetaldehyde.

The hydroxyl group that leaves is the one whose loss gives rise to the more stable carbocation. The carbocation A is more stable than carbocation B, since carbocation stability is enhanced by groups in the order aryl >alkyl >hydrogen.[1]

In Scheme SM 11.2.4 an example of the formation of kinetic or thermodynamic product, that can be driven by using different acidic conditions, is presented.[3]



Scheme SM 11.2.4 Kinetic and thermodynamic product formation.

The diol reacts under kinetic conditions with cold sulphuric acid, the more stable carbocation intermediate is formed followed by 1,2-methyl group migration to originate the kinetic product. On the other hand, under thermodynamic conditions, a less stable carbocation is formed and 1,2-phenyl group migrates to originate the thermodynamic product.

^{1}H, ^{13}C NMR spectra and IR spectrum of benzopinacol and benzopinacolone

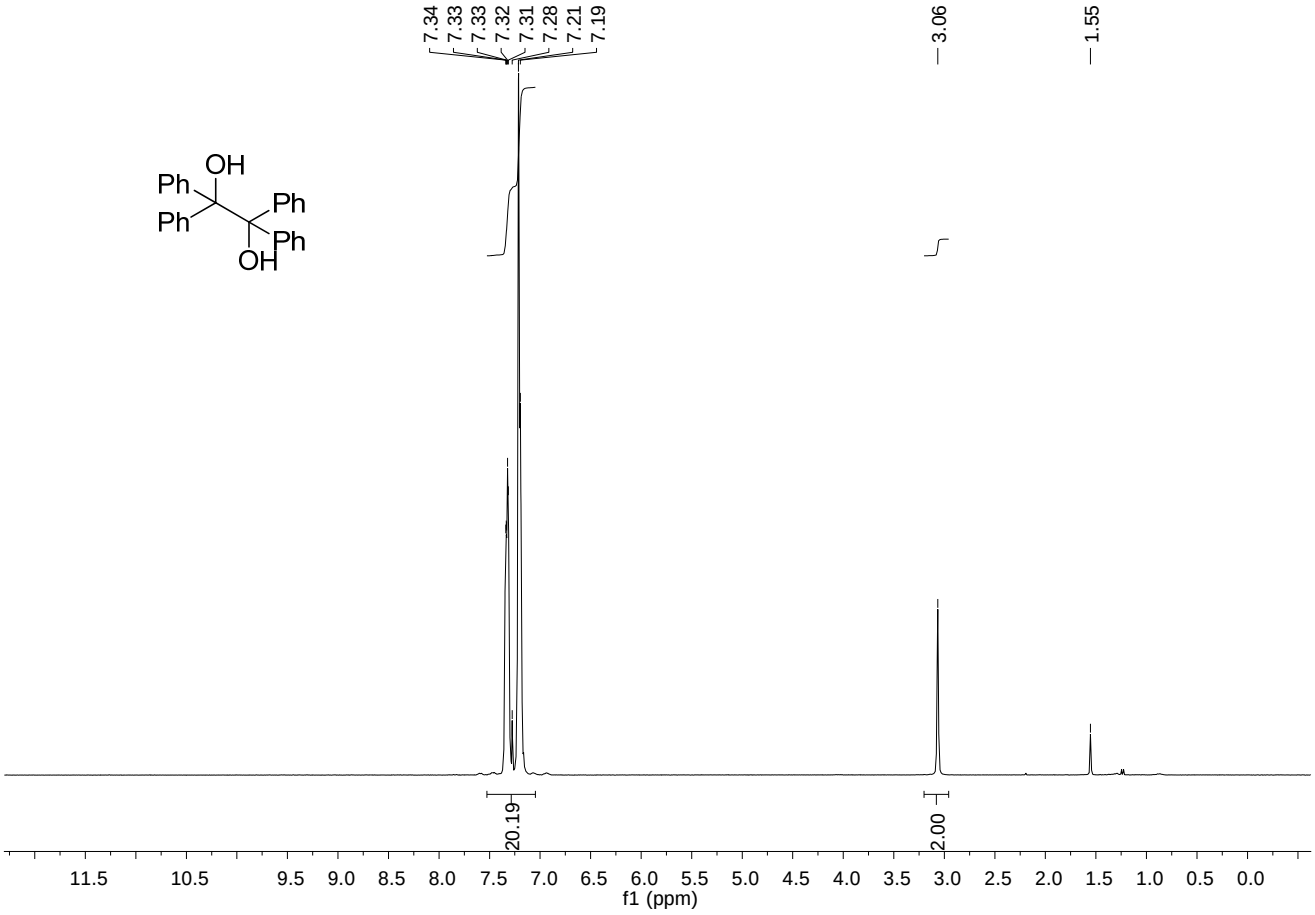


Figure SM 11.2.1. ^{1}H NMR spectrum (300 MHz, $CDCl_3$) of benzopinacol.

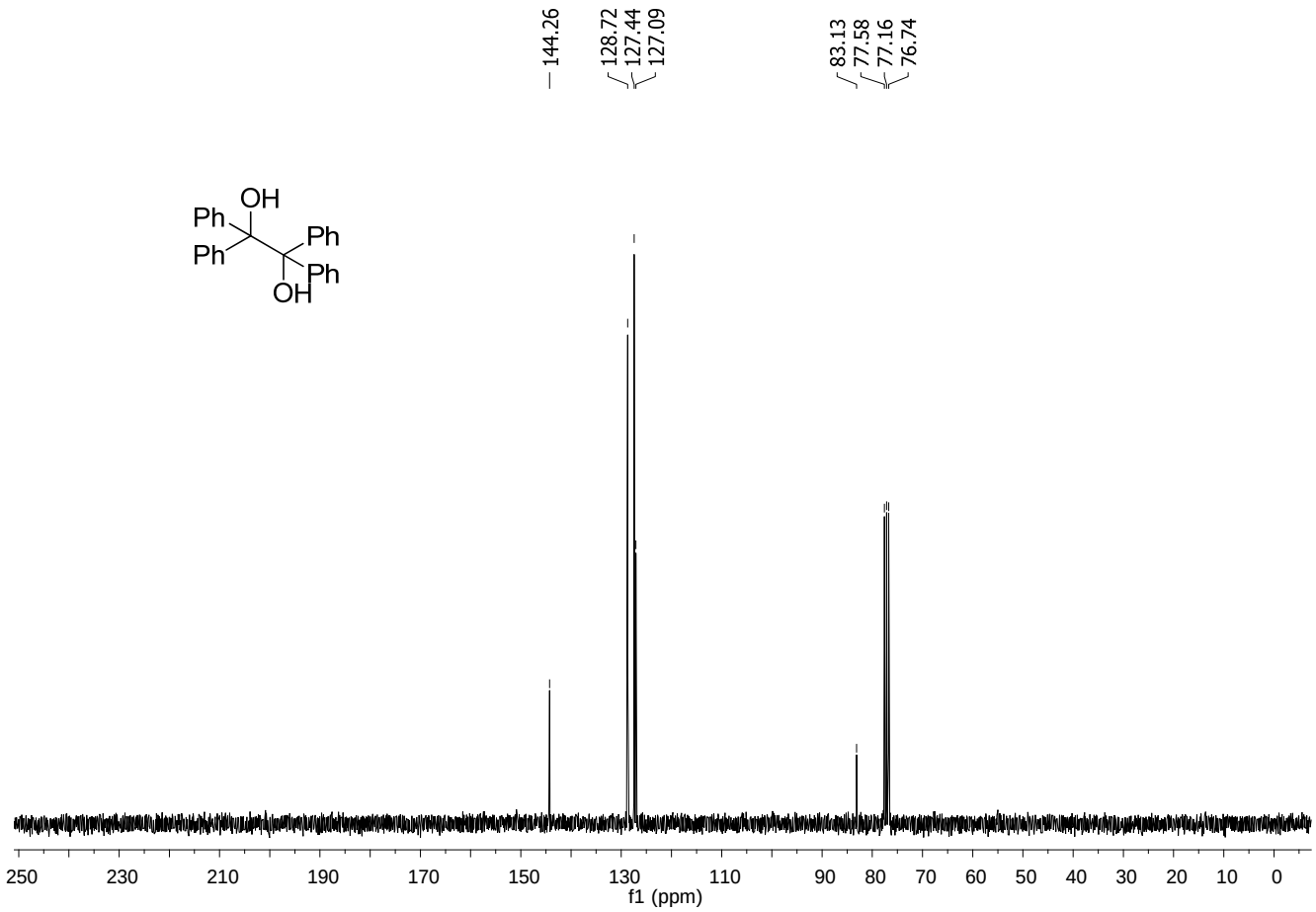


Figure SM 11.2.2. ^{13}C NMR spectrum (75 MHz, $CDCl_3$) of benzopinacol.

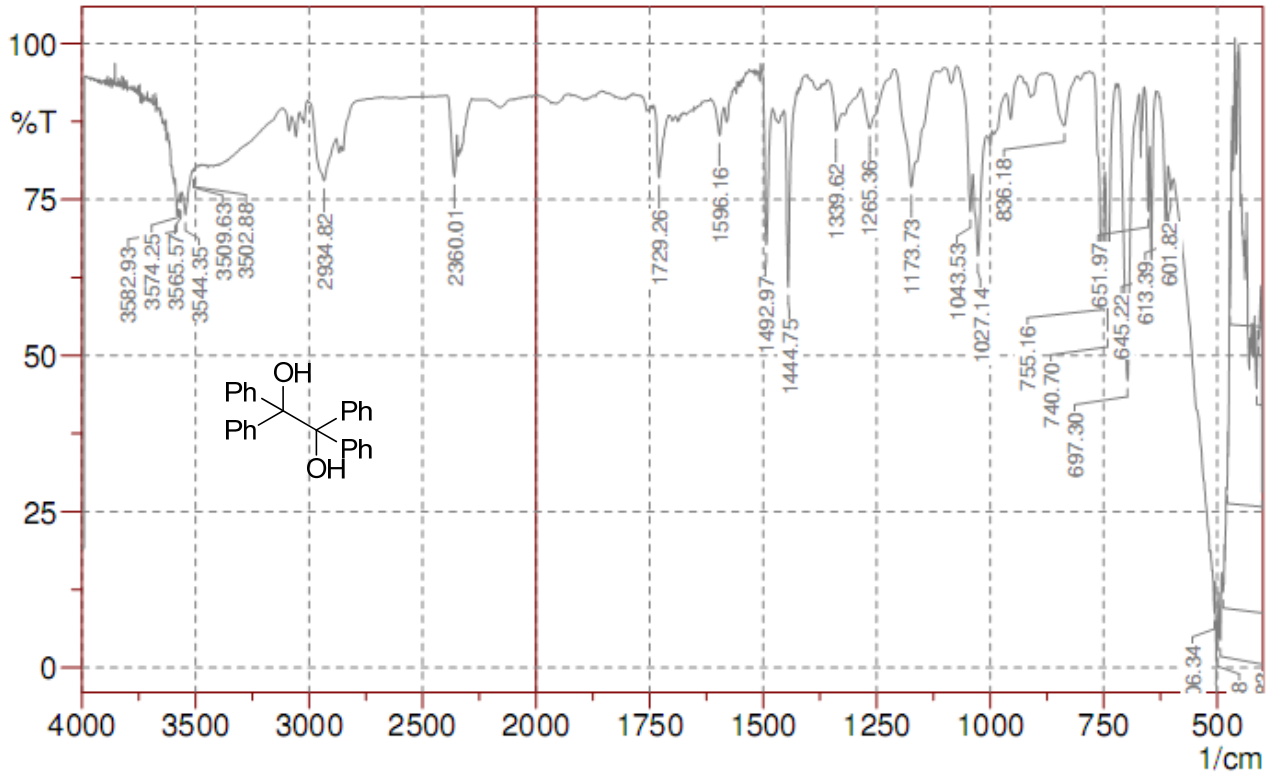


Figure SM 11.2.3. IR spectrum of benzopinacol.

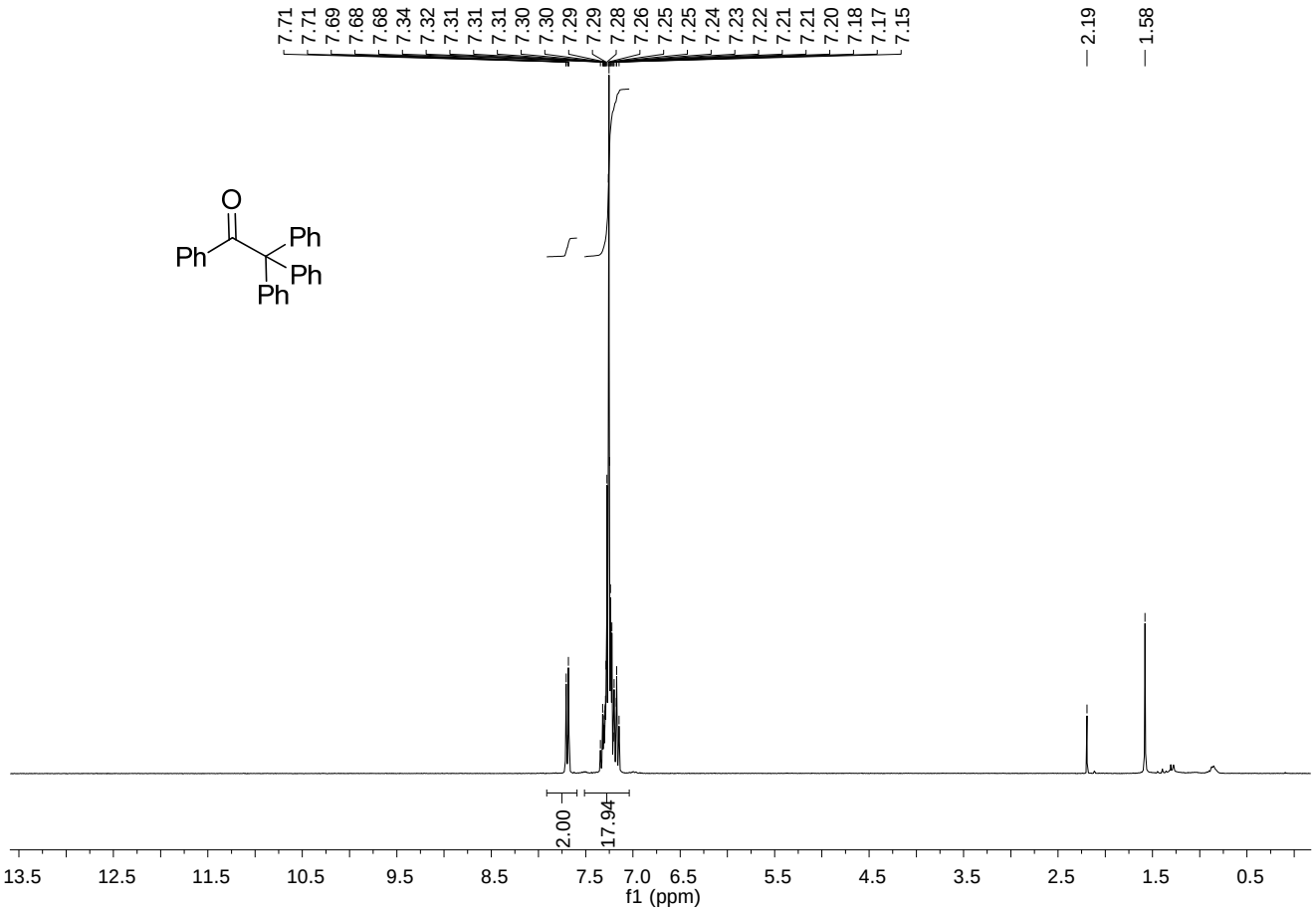


Figure SM 11.2.4. ^{1}H NMR spectrum (300 MHz, $CDCl_3$) of benzopinacolone.

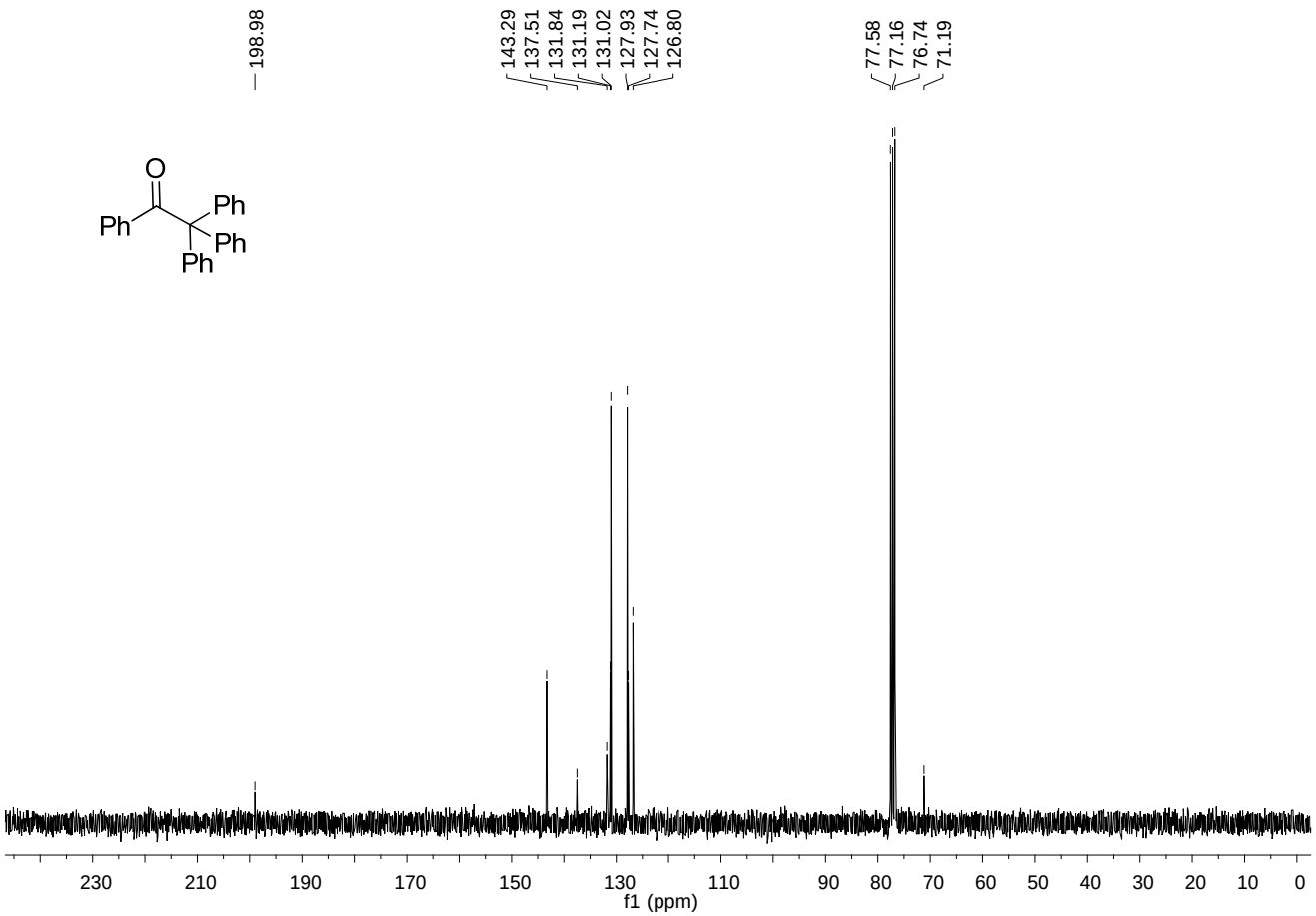


Figure SM 11.2.5. ^{13}C NMR spectrum (75 MHz, $CDCl_3$) of benzopinacolone.

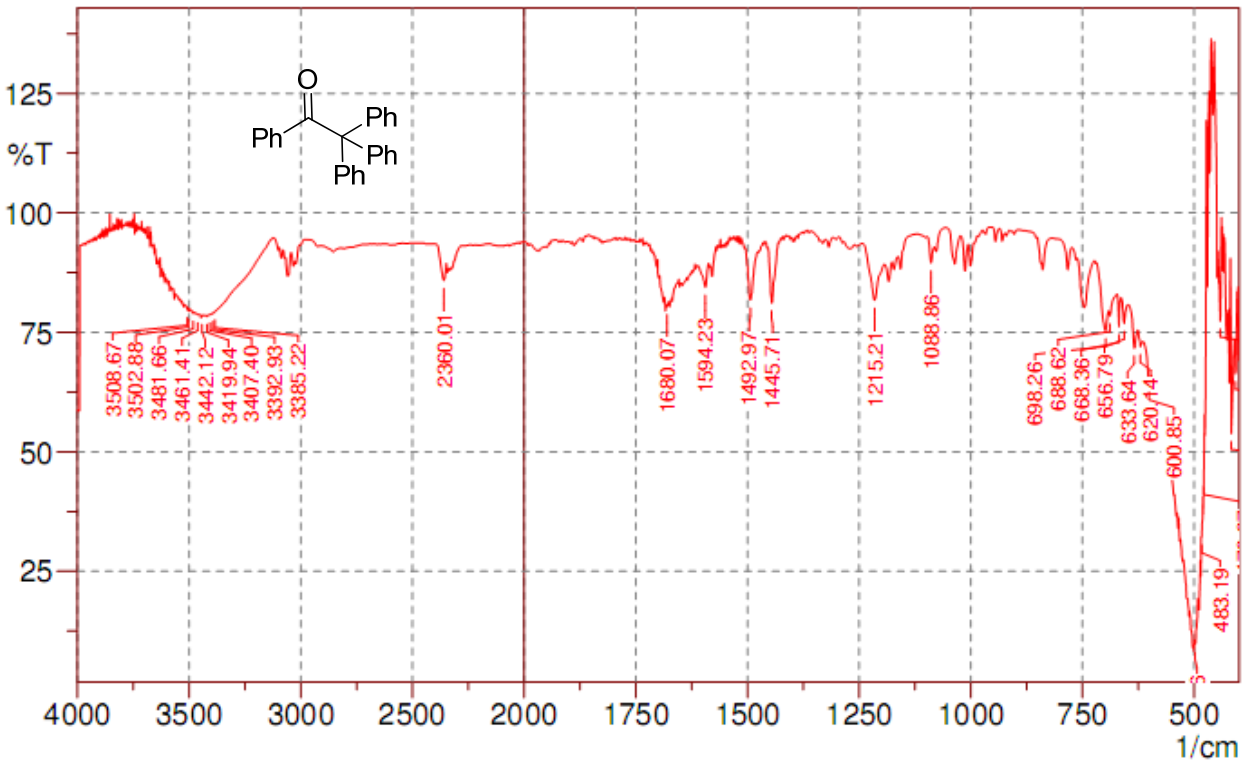


Figure SM 11.2.6. IR spectrum of benzopinacolone.

References:

[1]M. Smith; *March's Advanced Organic Chemistry: Reactions, Mechanisms, and Structure,* Wiley, 7th Edition*,* 2013, pag. 1329-1330.

[2.] G. Stavber, M. Zupanand, S. Stavber, *Tetrahedron Letters*, 2006, **47**, 8463. Hibbert, H. *J. Am. Chem. Soc.,* 1915, **37**, 1748. M. Jereb, D. Vrazi, M. Zupan, *Tetrahedron*, 2011, **67**, 1355.

[3] A. R. Katritzky, O. Meth-Cohn, S.M. Roberts, C. W. Rees, *Comprehensive Organic Functional Group Transformations*, Pergamon, Volume 1, 1995, pag. 384-386.

Iodosulfonylation-Dehydroiodination of Styrene: Synthesis of (*E*)-β-tosylstyrene

Supplementary Material[1]

Radical processes are not currently used in a demonstrating laboratory because they required expensive devices to be performed, the toxicity of reagents and products is notable, and the risk of explosion is high. In this experiment the radical mild preparation of β-tosylstyrene from the correspondent alkene and sodium *p*-toluenesulfinate followed by a β-elimination is described. The initial white suspension formed by sodium *p*-toluenesulfinate and styrene in methanol was turning yellow-orange as iodine was slowly added. The reaction was turning white and a new amount of iodine was added. This gave information about the consumption of this reagent upon addition onto styrene. At this point, sunlight was beneficial but it was of pivotal importance that vigorous stirring is used along the process for the improvement of the chemical yield of the first step. The radical mechanism was emphasized in order to show the students that this methodology can be used without the presence of expensive and sophisticated reactors or lamps. The second stage represented a β-elimination of hydrogen iodide promoted by an inexpensive base like potassium hydroxide. The final sulfone could be purified by crystallization in warm 95% ethanol, filtered (Buchner funnel) and dried (placed in a glass vial, under vacuum using a membrane pump at room temperature for 15 min) without any special precaution due to its high stability. The final purity could be checked by gas chromatography.
The reproducibility of the experiment was assessed by its repetitive execution by second year undergraduate students and also by last year graduated students (range of chemical yield 78-83%, mp. 120-121) of the University of Alicante.

The white-colorless prisms were immediately analyzed and characterized:

Mp.: 120-121 ºC from 95% ethanol [Lit.[2] mp. 120-121 ºC from 95% ethanol].

R_f = 0.40 (silica gel, hexane/ethyl acetate: 4/1).

Analysis of the purity by GC (Figure **SM.11.3.***1).*

GC (Figure **SM.11.3.**1, HP-3390A, WWCOT column, OV-101 stationary phase)

T_0 = 100 ºC (3 min), 15 ºC/min, T_f = 250 ºC.

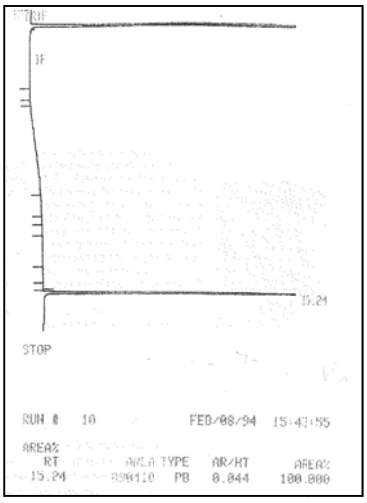


Figure SM.11.3.1. GC chromatogram.

FTIR (Figure **SM.11.3.***2, ATR for solids) 3042, 1614, 973 (C=C), 1314, 1303, 1141 (SO_2).*

FT-IR 4100LE (JASCO) using PIKE MIRacle ATR device.

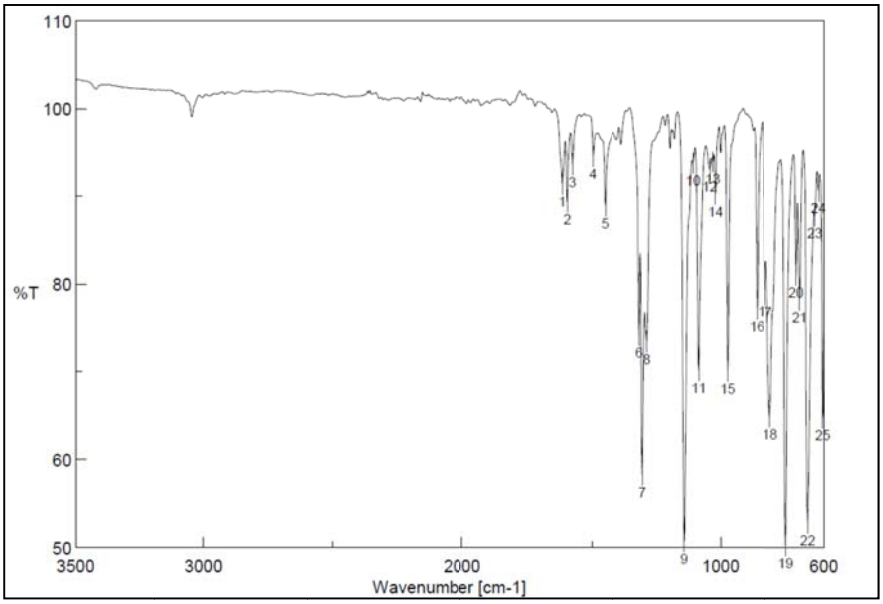


Figure SM.11.3.2. FTIR spectra.

^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.42 (s, 3H, Me), 6.86, 7.66 (2 d, J = 15.5 Hz, 2H, CH=CH), 7.32-7.48 (m with a d at 7.34, J = 8.2 Hz, 7H, Ph and 2H pTol-H) and 7.83 (d, J = 8.2 Hz, 2H, pTol-H).
Bruker AC-300 by using $CDCl_3$ as solvent and TMS as the internal standard.

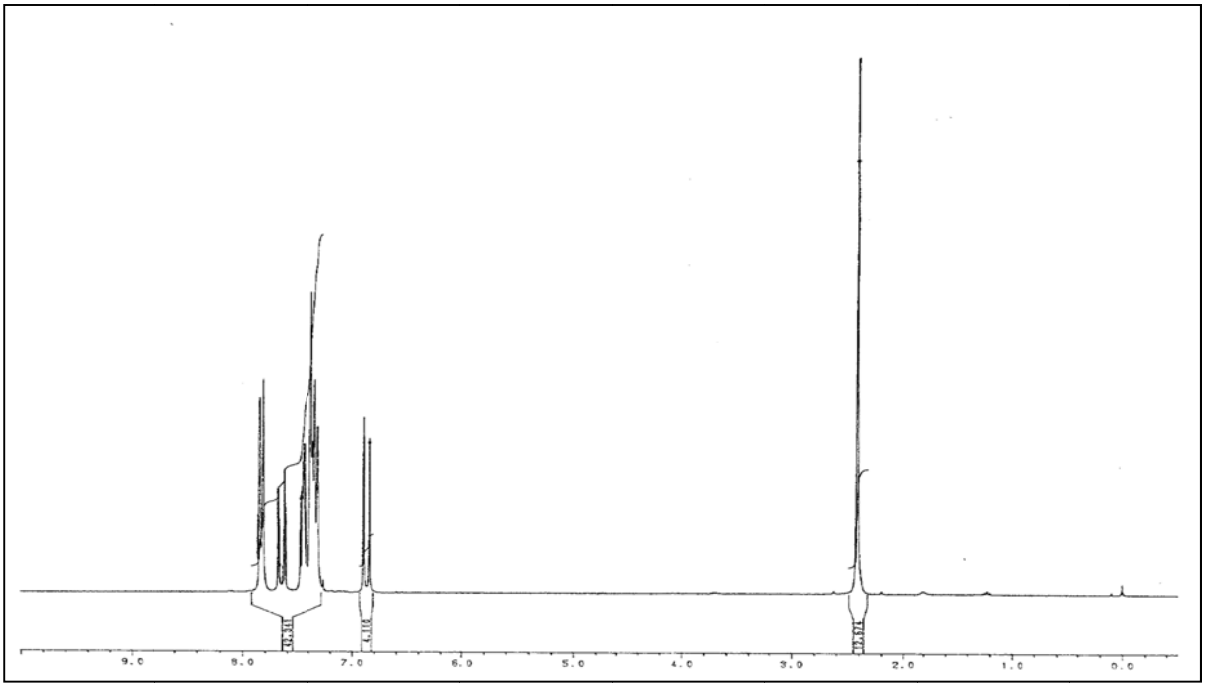


Figure SM.11.3.3. ^{1}H NMR spectra.

^{13}C NMR (75 MHz, $CDCl_3$) δ: 21.5 (Me), 127.5, 127.6, 128. 5, 129.0, 129.9, 131.0, 132.4, 137.7, 141.9, and 144.3 (ArC, and C=C).

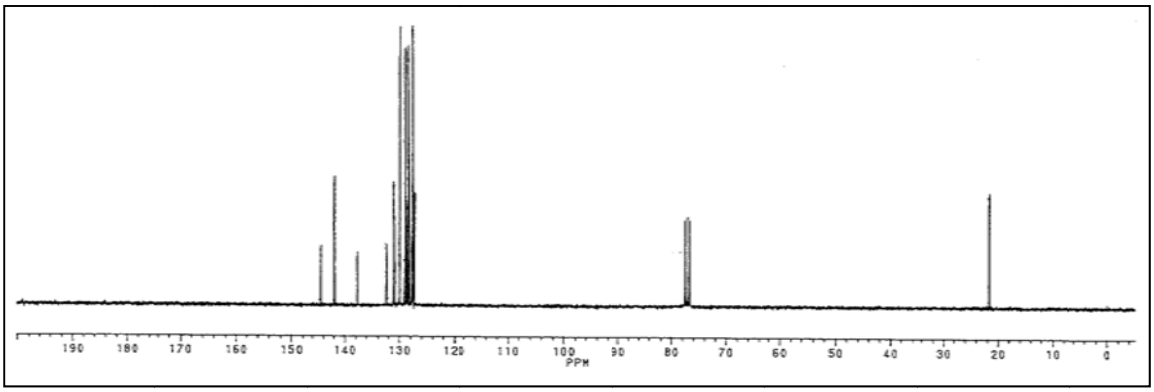


Figure SM.11.3.4. ^{13}C NMR spectra.

Proposed Mechanism.

In the first step, the generation of tosyl iodide, followed by light-promoted homolytic cleavage, trigger the radical process (first step). The intermediate β-iodosulfone **A** undergoes the β-elimination upon treatment with sodium hydroxide (Figure **SM.11.3.**5).

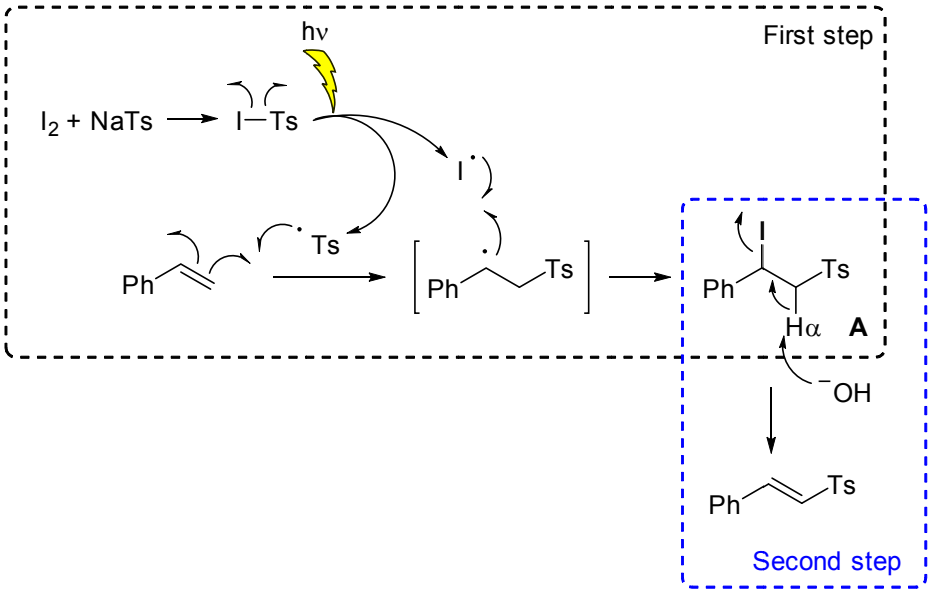


Figure SM.11.3.5. Two-step radical-β-elimination mechanism.

Conformational analysis using Newman's Projections.

This observed relative configuration can be explained through the following conformational analysis of the β-elimination of the intermediate β-iodosulfone **A** (Figure **SM.11.3.**6). More stable conformer **A'** gives the experimentally observed relative configuration of the product.

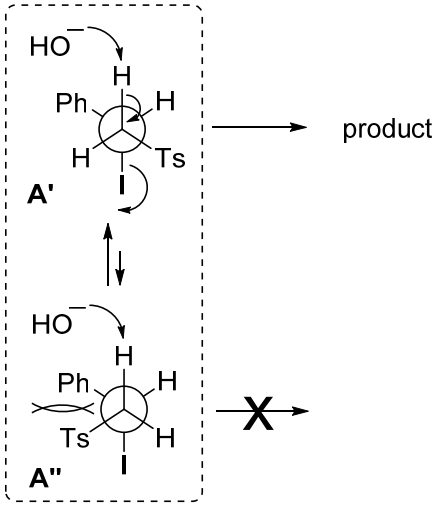


Figure SM.11.3.6. Conformational analysis of the reaction course.

References and notes

1 Reprinted (adapted) with permission from *J. Chem. Educ.*, 1995, 72 (7), pp 664–665. Copyright (1995) American Chemical Society.

2 L. K. Liu, Y. Chi, K. Y. Jen, *J. Org. Chem.* 1980, **45**, 406.