Short Communication

The synthesis and characterization of the two 2-(*tert*-butyl) cyclohexyl methanesulfonate compounds

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ABSTRACT

This short communication reports the synthesis and characterization of the mixture of two diastereoisomeric methanesulfonate compounds, 2-(*tert*-butyl) cyclohexyl methanesulfonate. Methanesulfonate group was introduced into the compounds due to its effectiveness as a protecting and good leaving group in nucleophilic substitution reactions. These intermediate compounds were prepared in an attempt to introduce fluorine at position two of the two target diastereoisomeric fluorinated compounds 1-(*tert*-butyl)-2-fluorocyclohexane which are important for studying the properties of hydrogen bond in fluorinated compounds. The two methanesulfonate compounds were formed as an inseparable mixture in 23% yield through alkylation with methanesulfonyl chloride and were characterized and identified by the ^{1}H NMR and ^{13}C NMR spectroscope. The compounds are reported as useful substrates in nucleophilic substitution reactions due to their effectiveness as leaving groups.

Keywords: Characterization; Cyclohexyl; Methanesulfonate; Mixture of diastereoisomers; Protecting and leaving groups; *tert*-Butyl

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INTRODUCTION

Methanesulfonate compounds are reported as the good leaving groups in nucleophilic substitution reactions due efficient delocalization of negative charge between the three oxygen atoms (Elgemeie and Mohamed-Ezzat, 2022; Avendaño and Menéndez, 2023). This robotic property has made these compounds potent and useful and is recognized as protecting groups for alcohols in organic synthesis (Ritter *et al.*, 2004; Sharma *et al.*, 2017). Their properties as good leaving groups identifies them as better

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option for nucleophilic substitution reactions such as fluorination. Studies show that selective fluorination of organic molecule improves metabolic stability, bioavailability, lipophicility and protein ligand interaction over a wide range of compounds that are essential pharmaceuticals (Ni *et al*., 2008). The importance of fluorine in life sciences is linked with the development of agrochemicals and pharmaceuticals (Ni and Hu, 2016). Reports show that about 30-40% of agrochemicals and 20% of pharmaceutical compounds contain at least one fluorine atom (Purser *et al*., 2008; O'Hagan, 2010; Belhomme *et al*., 2015; Zhou *et al*., 2016). Due to electronic effects that change the physicochemical properties of molecules, the presence of fluorine atoms in the molecule have a tendency of improving the bioavailability and thus, increasing potency of drugs (Chandra *et al*., 2023). These important functions of fluorine makes it the second heteroelement most used in life sciences investigations (Cottet *et al*., 2003; Jeschke *et al*., 2007; O'Hagan, 2008; Britton *et al*., 2021). Furthermore, when fluorine is added onto a molecule for medical purposes, it significantly improves the biological activities of the molecules compared to non-fluorinated complements (Al-Harthy *et al*., 2020).

The two compounds 2-(*tert*-butyl) cyclohexyl methanesulfonate 1 and 2 were synthesized in an attempt to produce the substrates for studying the properties of hydrogen bonding in fluorinated compounds. These two compounds were the intermediates towards making the two fluorinated compounds (1*R*,2*R*)-1-(*tert*-butyl)-2-fluorocyclohexane 3 and (1*R*,2*S*)-1-(*tert*-butyl)-2-fluorocyclohexane 4 as shown in Figure 1.

1 **2** **3** **4**

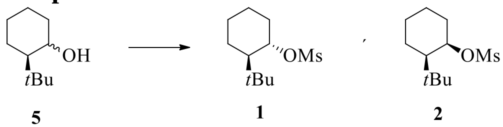
Figure 1. Target compounds

MATERIALS AND METHODS

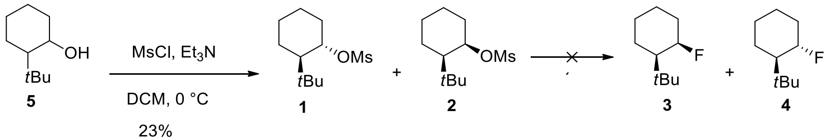
All the chemicals used in this experiment were of analytical/HPLC grade ≥ 98% purity and were purchased from Sigma Aldrich and Thermo Fisher Scientific Inc., and thus, were used directly without any need for purification. Glassware that had been thoroughly vacuum-dried and placed under nitrogen were used in all experiments. All solvents used in the reactions were distilled as follows: triethylamine over CaH_2, diethyl ether over benzophenone and dichloromethane over CaH_2.

Thin Layer Chromatography (TLC) silica gel 60 F254 Merck KGaA, aluminium sheet from Darmstadt, Germany was used for column chromatography purifications. Purification of the extracts was achieved by using column chromatography with silica gel technical grade 60 with particle sizes between 40 and 63 µm.

The Synthesis of Compounds 1 and 2



The procedure in the synthesis of the desired compounds started with the introduction of the mesylate group onto compound 5 (Scheme 1).



Scheme 1. Synthesis of compounds 1- 4

Mesylate is a good leaving group that was expected to be easily replaced by a fluorine atom in an S_N2 mechanism. In this case, compound **5** was reacted with methanesulfonyl chloride and triethylamine (Adams and Duncton, 2001). The procedure for transformation of compound 5 into 1 and 2 was the same as the one used by Adams and Duncan (Adams and Duncton, 2001). The reaction involved dropwise addition of 3.1 mL methanesulfonyl chloride for about 30 minutes to a stirring solution of 5.0 g of compound 5 in 7.0 mL of Et_3N and 50 mL of DCM at 0 °C. The residue was separated into aqueous and organic layers and the extracts was washed with 50 mL of brine and dried with $MgSO_4$ to obtain the crude product. The crude product was then purified by column chromatography by using ethyl acetate/petroleum ether in the ratio 2:98 that also contained 0.5% Et_3N for basifying silica gel. This obtained 1.728 g, 23% of 1 and 2 as diastereoisomeric mixture.

RESULTS AND DISCUSSION

The desired methanesulfonate compounds were synthesized as a mixture of two diastereoisomers 1 and 2 in low yield of 23% probably due to steric hindrance by the neighbouring bulky *tert*-butyl group. Methanesulfonate compounds have been widely reported as good protecting and leaving group for phenols, hence their preference in this reaction (Ritter *et al.*, 2004). Attempts to separate the two diastereoisomers were not successful even on High Performance Liquid Chromatography (HPLC).

Attempts to fluorinate the diastereoisomers 1 and 2 to the fluorinated products 3 and 4 (Scheme 1) was not successful by using the two reagents tetrabutylammonium fluoride and tetrabutylammonium tetra *tert*-butanol coordinated fluoride. The reagent tetrabutylammonium tetra *tert*-butanol coordinated fluoride was prepared (73% yield) on gram scale following the procedure used by Kim *et al.* (Kim *et al*., 2008).

The development of appropriate and effective procedures for fluorinating organic compounds continues to pose a challenge in synthetic organic chemistry (Khandelwal *et al*., 2022). In this communication, nucleophilic fluorination reaction by using methanesulfonate compounds was expected to result in the desired products due to their effectiveness as good leaving group. However, this was not achieved probably due to steric reasons by the neighbouring bulky *tert*-butyl and methanesulfonate groups as shown in Figure 2. For the *cis*- isomer, all the possible sites of attack are sterically hindered by the large groups, *tert*-butyl and the methanesulfonate. The *trans*- isomer has one meagre possible site of attack where methanesulfonate is equatorial and thus the nucleophile could attack from the top even though it did not also give the desired product. This is probably due to orientation of the methanesulfonate group that continues to pose steric hindrance on the top side of the molecule.

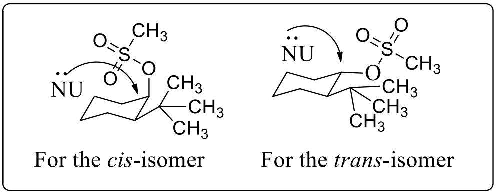


Figure 2. Steric hindrance towards attack by the nucleophile

The *tert*-butyl group in this case is the locking group that only prefers the equatorial position in the chair conformation. An axial *tert*-butyl group is really unfavourable and could rarely happen unless it gets twisted into a boat like conformation to adopt an equatorial position as shown in Figure 3.

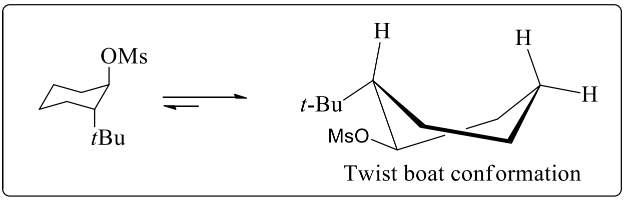


Figure 3**.** The *t*-Bu group avoiding an axial position

Compound characterization for 1 and 2

All NMR experiments were performed at room temperature by using the solvent, $CDCl_3$. The coupling coefficients and the chemical shifts were measured in Hertz and ppm, respectively. The ^{1}H NMR signals were typically designated as singlet (s), doublet (d), triplet (t), quintet (q) and multiplet (m).

Mw for ($C_{11}H_{22}O_3S$): 234.36; Rf in EtOAc/hexane 07:93: 0.33; ^{13}C NMR data for major diastereoisomer (75 MHz, $CDCl_3$) ppm: δ 84.50, 51.00, 40.20, 34.30, 32.90, 28.89 (3C), 26.70, 25.30, 21.80; data for the minor diastereoisomer: δ 80.80, 52.50, 39.80, 32.50, 28.90 (3C), 28.10, 26.20, 24.30, 20.00. ^{1}H NMR data of a mixture of 1 and 2 (300 MHz, $CDCl_3$) ppm: δ 4.72 (1H, td, *J* 10.00, 4.30 Hz, $H1_{ax}$), 3.68 (1H, br. s, $H1_{eq}$), 3.00 (6H, s, CH_3), 2.22–2.39 (2H, m, H2), 1.04–1.97 (16H, m, H3,4,5,6), 1.00 (18H, s, *t*Bu). These spectra data for the diasteriomeric mixture of 1 and 2 have not been reported in the journal media. The ^{13}C NMR and ^{1}H NMR spectrum are presented in Figure 4 and 5 in the support information section.

The ^{13}C NMR and ^{1}H NMR spectrum presented in Figure 4 and 5, respectively in the supplementary information section, have a profound indication for the formation of the two diastereoisomers as the mixture. The ^{13}C NMR and ^{1}H NMR of the mixture have a total of 22 carbons and 44 protons while a single diastereoisomer could have 11 carbons and 22 protons. This in part reveals the presence of the two diastereoisomers in a mixture. From the ^{13}C NMR spectrum, the major and minor diastereoisomer could be clearly identified by the differences in their peak intensities and have been reported separately as major and minor diastereoisomers. For the ^{1}H NMR due to complexity of the multiplet, their separation into major and minor isomers has not been clear and hence reported as a mixture.

CONCLUSIONS

The synthesis, identification and characterization of the mixture of the two diastereoisomeric methanesulfonate compounds, 2-(*tert*-butyl)cyclohexyl methanesulfonate were successfully achieved. However, the products were formed in low yield (23%) probably due to steric hindrance by the bulky neighbouring group, the *tert*-butyl. The spectra provide a good reference for students and scientist when describing the structures of different compounds by the nuclear magnetic resonance. The introduction of fluorine atom at C1 is still important for further studies on the influence of fluorine on bioactive compounds. This study recommends more attempts towards introduction of fluorine into the diastereoisomers and characterization by using specialised NMR experiments for the two 2-(*tert*-butyl)cyclohexyl methanesulfonate compounds.

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Declarations

Consent for publication: The author hereby give permission to publish research findings including identifiable details, such as figures and scheme.

Competing interests: There are no conflicts of interest to declare.

Authors' contributions: The mentioned author has fully contributed to the planning of experiment, analysis and interpretation of data and writing of the manuscript.

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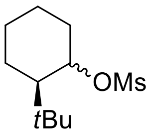
Supplementary materials

Spectrum for a Mixture of Compound 1 and 2



^{13}C NMR (75 MHz, $CDCl_3$)

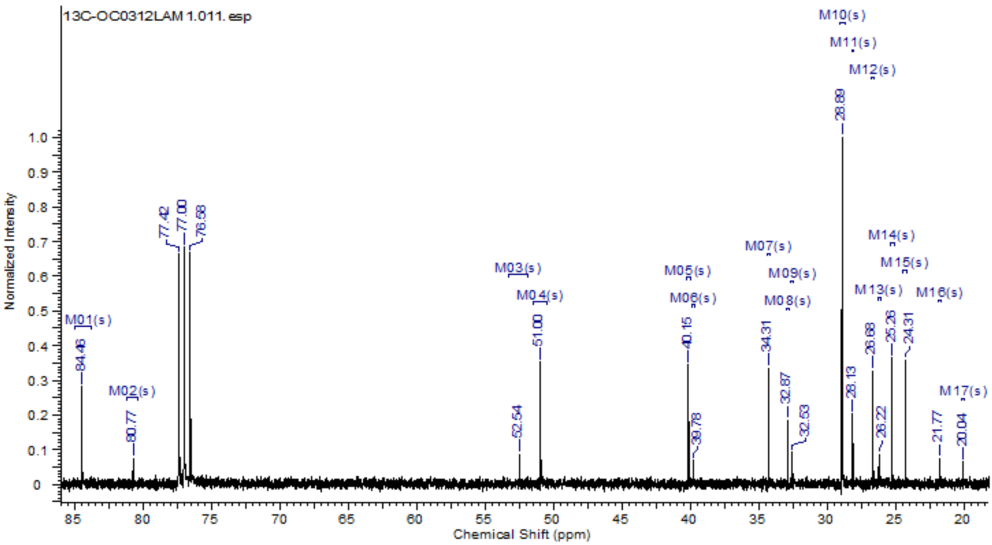


Figure 4. ^{13}C NMR spectrum

¹H NMR (300 MHz, $CDCl_3$)

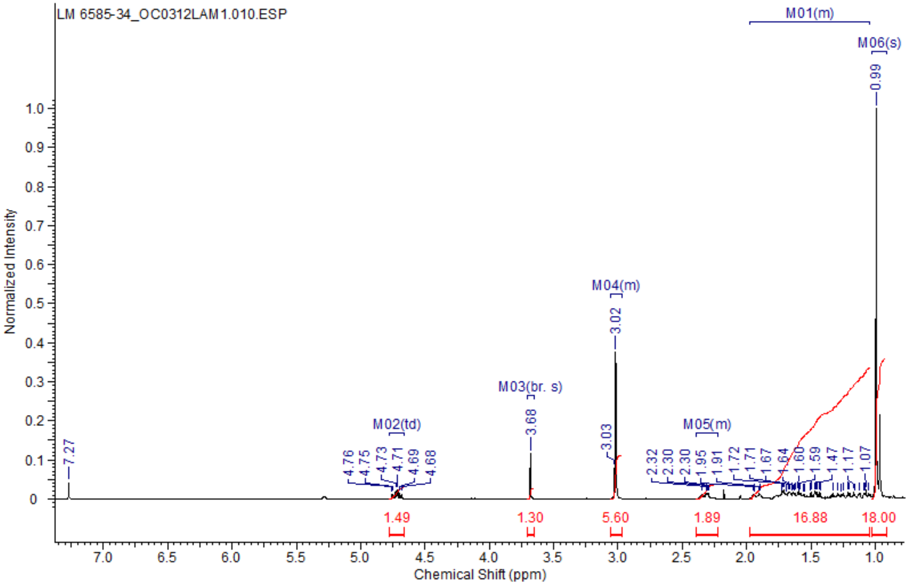


Figure 5. ¹H NMR spectrum