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Selectfluor and Alcohol Mediated Synthesis of Bicyclic Oxyfluorination Compounds by Wagner-Meerwein Rearrangement

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Abstract

Herein, we report the first environmentally friendly systematic fluoroalkoxylation reactions in bicyclic systems. New oxyfluorination products were obtained with excellent yields (up to 99%) via Wagner-Meerwein rearrangement using benzonorbornadiene and chiral natural compound (4)-camphene as bicyclic alkenes, selectfluor as an electrophilic fluorine source, and water and various alcohols as nucleophile sources. The structure of bicyclic oxy- and alkoxyfluorine compounds was determined by NMR and GC-MS analyses.

Keywords

bicyclic alkene; selectfluor; oxyfluorination; alkoxyfluorine compounds; Wagner-Meerwein rearrangement

Introduction

Organofluorines are of great importance in the pharmaceutical and agrochemical industries, as the presence of fluorine has a serious effect on the biological activities of organic compounds by changing their metabolic stability, hydrogen bonding ability, lipophilicity, solubility, bioavailability, conformation and general structure.[1-4] About 20% of commercially available drugs contain fluorine, and this ratio is estimated to increase further.[5, 6] Among organofluorines, oxyfluorines are an important subclass used as an active ingredient in many different drugs such as fludrocortisone (the first fluorine-containing commercial drug),[7, 8] sofosbuvir (antihepatitis C),[9] dexamethasone (to treat ashma, severe allergies),[10] Difluprednate (ocular anti-inflammatory)[11, 12] and many more (Figure 1). On the other hand, with unusual geometry and high reactivity norbornadiene and benzonorbornadiene derivative bicyclic compounds attract great attention by researchers with their use as building blocks in different application areas such as polymers, solar energy storage materials, supramolecular and bioactive compounds.[13-17] To the best of our knowledge, although the oxifluorination of various olefins with water and alcohols is known in the literature,[18-26] there is no systematic study on the oxifluorination of bicyclic alkenes. Herein, we synthesized bicyclic oxy- and alkoxyfluorine compounds using electrophilic fluorination reagent, water and various alcohols.

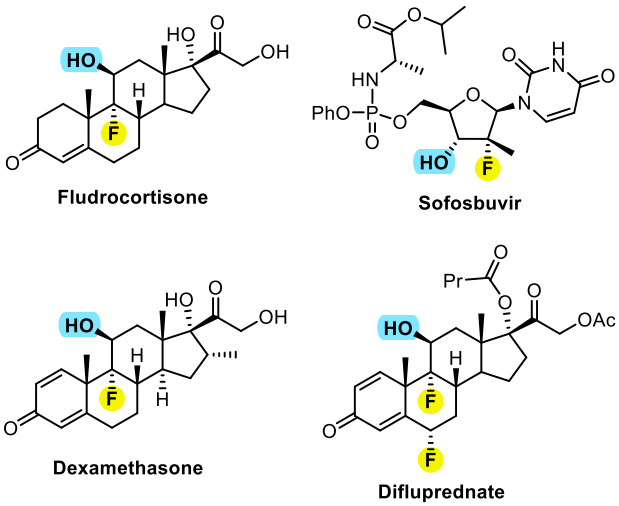


Figure 1. Organofluorine derived drugs

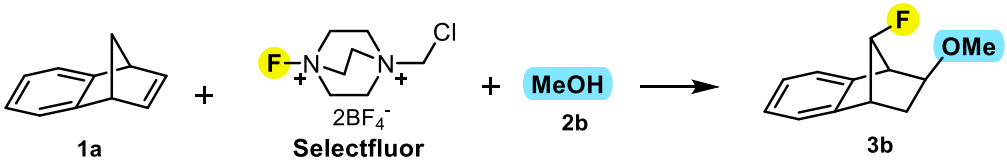
Results and Discussion

In this study, benzonorbornadiene (**1a**) and chiral natural product (+)-camphene (**1b**) were used as bicyclic alkenes. Safe, easily soluble, easy to use, stable solid, reactive and commercial available selectfluor**[18, 27, 28]** was selected for electrophilic fluorination source. Water and various alcohols were used as nucleophiles.

First, optimization experiments were carried out for fluoroalkoxy reactions with benzonorbornadiene (**1a**) (Table 1). As a result of experiments conducted in six different solvents at room temperature with 1.0 equivalent of selectflor and 1.0 equivalent of methanol, it was observed that there was a 12% conversion with CH_3CN and a 10% conversion with nitromethane, while no conversion occurred with the other solvents including, CH_2Cl_2, EtOAc, 1,2-dioxane and DMF (Table 1, entries 1–6). To see the effect of reactant ratios on yields, when reactants were gradually increased at room temperature, the best result was obtained with 1.2 equivalents of selectflor and 2.4 equivalents of methanol, yielding 21% (Table 1, entry 7). There was no significant change at higher equivalents. At 50°C, 30% yield was achieved with 1.2 equivalents of selectflor and 2.4 equivalents of methanol for one hour, while at 90°C, a 67% yield

was obtained (Table 1, entries 8 and 9). Finally, when the reaction time was increased to two hours at 90 °C, a product was obtained with a 98% conversion (Table 1, entry 10).

Table 1. Optimizing the Conditions for the Oxyfluorination of Bicyclic Alkenes[a]



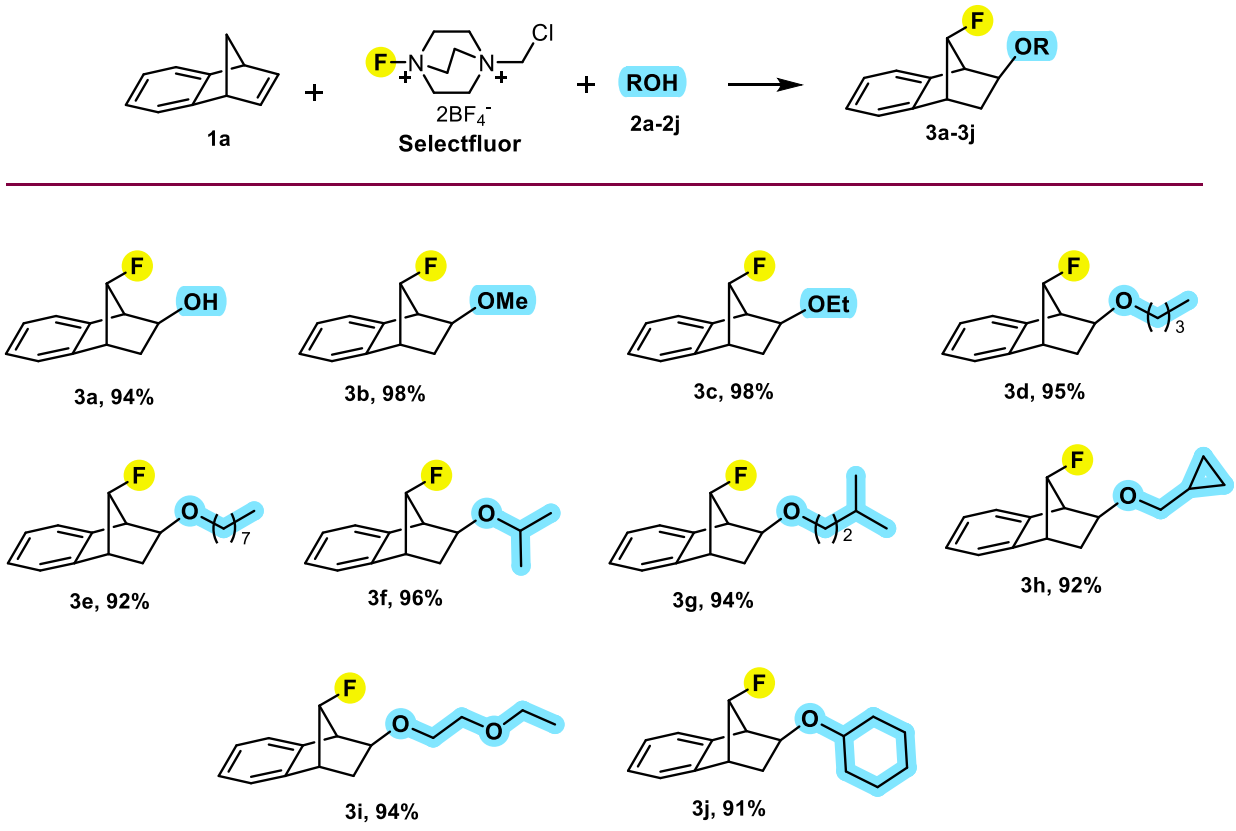
1a Selectfluor 2b 3b

Entry	Solvent	Selektflor (equiv.)	CH_3OH (equiv.)	Temperature (°C)	Time	Yield (%)
1	CH_3CN	1	1	rt	1 h	12
2	CH_2Cl_2	1	1	rt	1 h	-
3	EtOAc	1	1	rt	1h	-
4	1,4-dioxane	1	1	rt	1h	-
5	DMF	1	1	rt	1h	-
6	CH_3NO_2	1	1	rt	1h	10
7	CH_3CN	1.2	2.4	rt	1h	21
8	CH_3CN	1.2	2.4	50 °C	1h	30
9	CH_3CN	1.2	2.4	90 °C	1 h	67
10	**CH_3CN**	**1.2**	**2.4**	**90 °C**	**2 h**	**98**

[a]Reaction conditions: Benzonorbornadiene (**1a**) (0.5 mmol), Selectfluor (215 mg, 0.6 mmol) and MeOH (1.2 mmol), 2 mL of CH_3CN, 2 h and 90 °C. Conversions were calculated by ^1H NMR with 1,3-dinitrobenzene as an internal standard.

After obtaining the optimum fluoroalkoxylation conditions from benzonorbornadiene (**1a**), the reactions of benzonorbornadiene (**1a**) with with selechlorofluor and 10 different alcohol derivatives were examined (Scheme 1). Under optimum conditions, fluoroalkoxy **3a-3j** were obtained in excellent yields (92%-98%) by the reaction of benzoboronbornadiene (**1a**) with selechlorofluor and alcohols (Scheme 1). Additionally, (+)-Camphene (**1b**), a chiral natural product, was used as another alkene for fluoroalkoxy reactions. From (+)-camphene(**1b**), fluoroalkoxy **4a-4j** was also

obtained in very good yields (93%-99%) (Scheme 2). Since exo-selective fluoronium formation followed by Wagner-Meerwein rearrangement does not cause racemization or diastromeric mixture and preserves the initial enantiomeric excess in the obtained products, no additional analysis was needed for determining the enantiomeric excess of (+)-camphene's fluoroalkoxy derivatives (Scheme 4).



Scheme 1. Oxyfluorination of Benzonorbornadien (**1a**) with Selectfluor and Alcohols[a]. [a]All reactions were carried out using 0.5 mmol of Benzonorbornadiene (**1a**), 0.6 mmol of Selectfluor, and 1.2 mmol alcohol in 2 mL of CH_3CN at 90°C for 2 h. Conversions were calculated by ^1H NMR with 1,3-dinitrobenzene as an internal standard.

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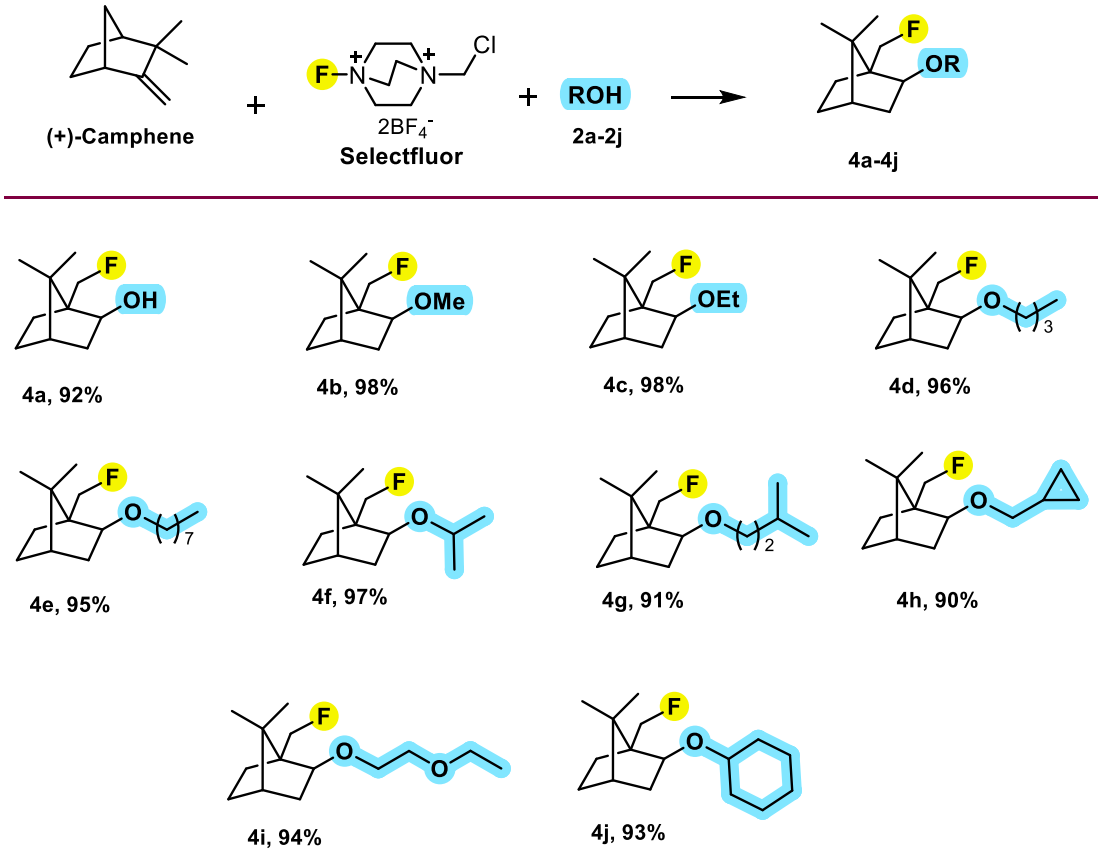
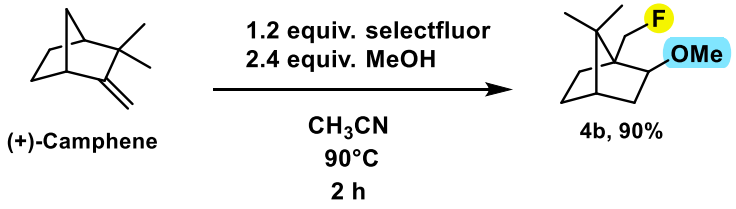


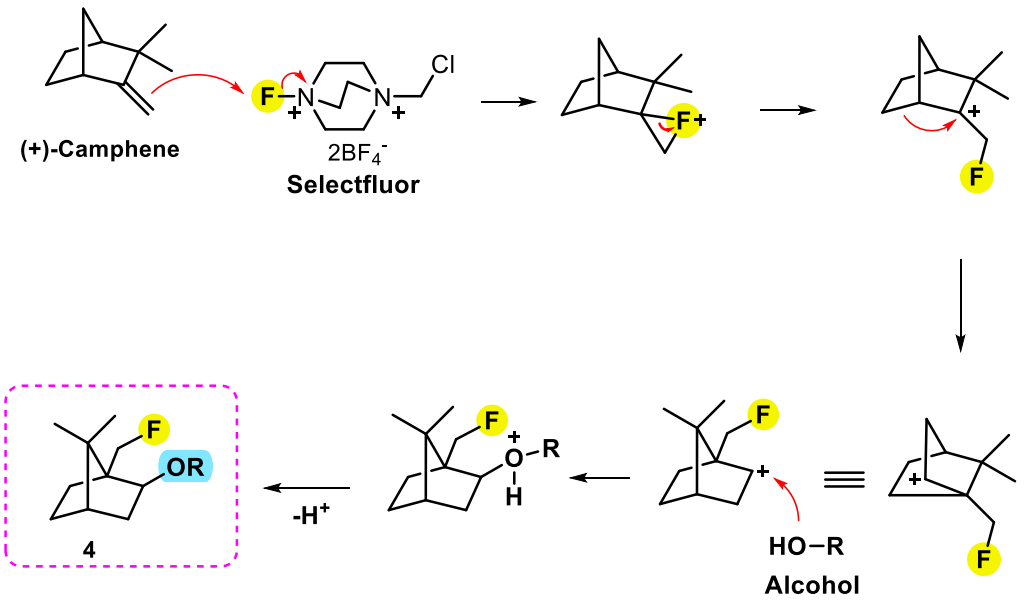
Scheme 2. Oxyfluorination of (+)-Camphene (**1b**) with Selectfluor and Alcohols[a]. [a]All reactions were carried out using 0.5 mmol of (+)-Camphene, 0.6 mmol of Selectfluor, and 1.2 mmol alcohol in 2 mL of CH_3CN at 90°C for 2 h. Conversions were calculated by ^1H NMR with 1,3-dinitrobenzene as an internal standard.

In order to demonstrate the gram-scale applicability of fluoro alkoxylation reactions in bicyclic systems using optimized reaction conditions with (+)-camphene (**1b**) (1 g, 7.34 mmol), scale-up experiments were conducted. The isolated yield of **4b** (1.26 g, 90% yield) is quite satisfactory, as can be seen from Scheme 3.



Scheme 3. Scale-Up Experiments[a]. [a]Reaction conditions: (+)-Camphene (**1b**) (1g, 7.34 mmol), Selectfluor (3.12 g, 8.81 mmol), MeOH (17.62 mmol), CH_3CN (20 mL), 90 °C, 2 h.

For the fluoroalkoxylation, we propose the mechanism given in Scheme 4. In this mechanism, first the double bond in (+)-camphene attacks the fluorine in the selectfluor and exo-selective fluorium is formed. Subsequently, fluoroalkoxy **4** is formed by Wagner-Meerving rearrangement followed by alcohol addition and deprotonation.



Scheme 4. Proposed Mechanism for Fluoroalkoxylation of (+)-Camphene by Wagner–Meerwein Rearrangement

Conclusion

New bicyclic fluoroalkoxy compounds were synthesized by a molecular fluorine-free and metal-free methodology. An environmentally friendly approach was pursued by using safe, easily soluble, easy to use, stable, solid and reactive Selectfluor as an electrophilic fluorination reagent, and water and various alcohols as a nucleophile source. Besides being novel, the presented oxyfluorination protocol provides distinct advantageous such as *(i)* the methodology does not require the presence of any metal moities, *(ii)* enables the synthesis of corresponding oxyfluorinated analogues with high yields and selectivity, *(iii)* allows derivatization of natural chiral molecules, *(iv)* uses a safe solvent in mild reaction parameters. We hope that these potentially biologically active bicyclic fluoroalkoxy compounds will find a place in various application areas in biological systems.

Supporting Information

Supporting Information File 1:

Experimental procedures, copies of ^{1}H NMR, ^{13}C NMR, and HRMS(Q-TOF) spectra

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