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Journal of Fluorine Chemistry 126 (2005) 1425–1431
JOURNAL OF FLUORINE CHEMISTRY
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Synthesis and structure-activity relationship (SAR) of novel perfluoroalkyl-containing quaternary ammonium salts

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Received 5 June 2005; received in revised form 21 July 2005; accepted 6 August 2005
Available online 15 September 2005

Abstract

A new series of perfluoroalkyl-containing quaternary ammonium compounds were prepared and examined for their antibacterial activities. The perfluoroalkyl-containing quaternary ammonium salts mainly exhibited excellent antibacterial activity for the Gram-positive strain such as *Staphylococcus aureus*, the MIC (minimal inhibitory concentration) values was between 2.5 and 10 μg/mL and the MBC (minimal bactericidal concentration) values were 20 μg/mL. They all showed weak activity against the Gram-negative strain such as *Escherichia coli*, and against fungi such as *Candida albicans*, the MIC values and MBC values were about 100 μg/mL. Moreover, the relationship between their antimicrobial activities and structures were further discussed.

Keywords: Perfluoroalkyl-containing compounds; Quaternary ammonium salt; Antibacterial activity

1. Introduction

In daily life, people inevitably get in touch with many kinds of microorganisms such as bacteria, fungi (yeasts, molds, mildew) and algae, some of which can bring about unpleasant odor, stain, and discoloration to fabric. One important reason is that textiles are excellent medium for the growth of microbes, which will be easily impregnated if the suitable moisture and enough time are given. Thus, they unassailably pose a threat to human health via breeding on textiles. As the increasing demand for healthy living, it is urgent to develop materials capable of killing harmful microorganisms [1]. Recently, antibacterial finishing has received more and more attention owing to their antibacterial properties, and various antibacterial agents (such as antiobiotics, silver ions, iodine and quarternary ammonium compounds et al.) have been applied to the textiles [2–8]. The long-chain quaternary ammonium salt surfactants were firstly discovered to have marked antimicrobial activity in 1935 [9], which directly caused its wide research and utilization in the past 70 years.

The antibacterial activity of quaternary ammonium compounds is supposed to be due to their surface activity properties. Recently, the perfluoroalkyl-containing compounds and fluoropolymers have been shown to be effective in application as repellent agents in textile finishing, which worked by reducing the critical surface energy of fabrics [10]. In addition, some fluoroalkyl end-capped compounds with cationic segments such as trimethylammonium, pyridinium [11,12], allylammonium [13,14], and diallylammonium groups, were also reported to be valid in reducing the surface tension of water and oil with the cationic surfactants. These fluorinated compounds also exhibited antibacterial activity to some extent [11–14].

Our research group has recently reported on the synthesis and antimicrobial activity of the perfluoroalkyl-containing compound **1** (Fig. 1), which has good antibacterial activity for Gram-positive strain (*Staphylococcus aureus* ATCC 6538) and Gram-negative strain (*Escherichia coli* 8099)

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doi:10.1016/j.jfluchem.2005.08.004

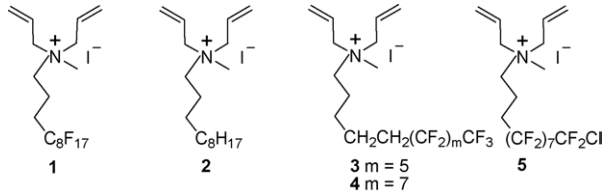


Fig. 1. Structures of compounds **1**–**5**.

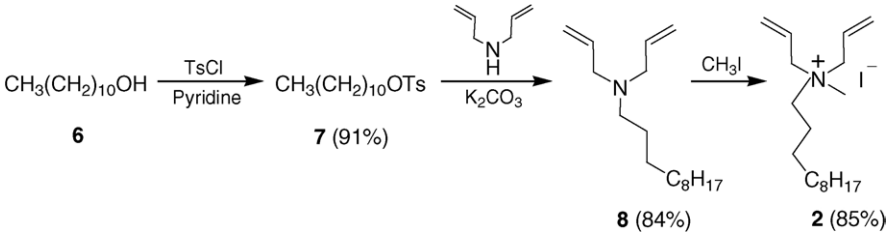
[15]. In connection with our ongoing project about textile finishing, we need to further investigate the structure-activity relationship about some analogues of compound **1**. Here reported is our synthesis and antibacterial activity test of a novel series of perfluoroalkyl-containing quaternary ammonium salts **2**–**5**, all of which are the analogues of our reported compound **1**. We have a preliminary comprehension about the impact of chain-length, halogen atoms and nonfluoroalkyl chain on the antibacterial activity.

2. Results and discussion

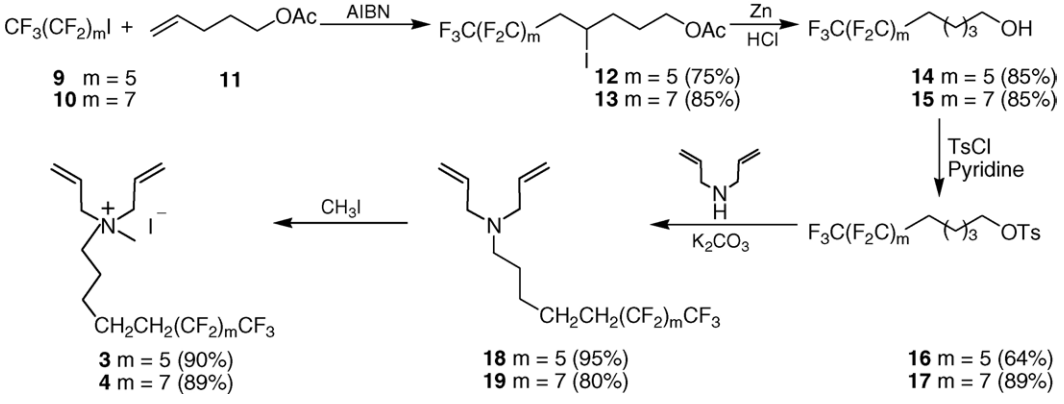
We firstly synthesized out designed target molecules **2**–**5**. The alkyl-containing quaternary ammonium compound **2** was prepared as shown in Scheme 1. Treatment of alcohol **6** with TsCl in the presence of pyridine afforded tosylate **7** in 91% yield. Then, alkylation of diallylamine with **7** in the presence of K_2CO_3 provided the desired compound **8** in 94% yield, which was finally transformed to the desired molecule **2** as ammonium salts in 85% yield.

Syntheses of compounds **3** and **4** started from perfluoroalkylated iodides **9** and **10**, respectively (Scheme 2). The first step proceeded by a free radical addition [16–18] of **9** and **10** to alkene **11** in the initiation of AIBN to provide the fluoroalkylated iodides **12** and **13** in good yield, respectively. Treatment of **12** and **13** with Zn dust and HCl gas [19] resulted in one-step removal of iodine and acetyl group and the desired alcohols **14** and **15** were furnished in 85% yield, respectively. Tosylation of compounds **14** and **15** smoothly gave the products **16** and **17**, which further reacted with diallylamine to produce the tertiary amines **18** and **19** in 95 and 80% yields. Finally, quaternary ammonium compounds **3** and **4** were obtained from the reaction of **18** and **19** with CH_3I in anhydrous CH_3CN in 90 and 89% yields, respectively.

As to the synthesis of target compound **5**, we firstly attempted to prepare the key intermediate **25** from chlorofluoroalkylated iodide **20** and allylic alcohol **21** (Scheme 3). However, treatment of compound **24** with Bu_3SnH/AIBN could not provide the alcohol **25**. The reaction was very complicated and in our opinion, reaction failure was attributed to the existence of chlorine atom, which involved in the free radical reaction. In addition, attempt to remove iodine in **25** via $LiAlH_4$ reduction [20] only gave the desired product **25** in 10% yield. In view of failure and low yield of above reactions, we decided to construct the requisite hydroxyl group in **25** via hydroboration-oxidation of corresponding alkene. Thus, reaction of chlorofluoroalkylated iodide **20** and allyl acetate **22** afforded adduct **24**, which was then converted into desired alkene **26**



Scheme 1.



Scheme 2.