Silylation and characterization of piroxicam with some silylating reagents

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Abstract:

In this work, we synthesized some organosilicon derivatives of piroxicam. Due to the some properties of organosilicon compounds, including increased lipophilicity and thermal stabilization and prodrug for drugs, some silyl ethers of this drug were synthesized and characterized. Increasing of the lipophilic properties of this drug can be very important in the rate of absorption and its effectiveness.

Graphic abstract:

Keywords: Piroxicam, Silyl ether, Organosilicon, Drug delivery, Lipophilic
1. Introduction:

Piroxicam is a painkiller and its main use is to reduce or stop pain. In osteoarthritis, this drug has anti-inflammatory effects. This drug is used to treat many diseases such as headache and toothache, leg pain and piroxicam reduces the production of prostaglandins by controlling cyclooxygenase, thus showing its effectiveness in reducing and eliminating pain.

It is also used to relieve joint, bone and muscle pain. It is even used to control gout and menstrual cramps. It binds to a large amount of protein and is metabolized in the liver and then excreted in the urine.

For long-term storage of piroxicam, it is recommended that it be stored at -20 °C, which should be stable for at least two years [1, 2].

In recent years, after 2001, the application of silicon in biotechnology has received much attention and many studies on the development of biocatalytic products from silicon polymers, release systems for enzymes, strong biosynthetic systems and Enzyme has been formed in the formation of silicon-carbon bonds [3].

Carbohydrates are one of the most numerous compounds in the biosphere that play a major role in cellulose synthesis. The use of silicon and silicon-based protecting groups in the synthesis of carbohydrates was first proposed in 1970 [4, 5, 6].

Silyl ethers are among the most widely used protecting groups for the alcohol functionally because the rate of deprotection can be modulated by simply altering the substituents on the silicon atom. As a result, the synthesis of small-molecule silyl ether have been explored using a variety of acid sensitive silane attachments including trimethyl silyl ether (TMS), triethyl silyl ether (TES), and triisopropyl silyl ether (TIPS). Three types of silyl ether prodrugs a) small molecule
monofunctional silyl ether, b) polymeric monofunctional silyl ether prodrug, and c) polymeric asymmetric bifunctional silyl ether prodrug were used [7,8,9].

Piroxicam is a phenolic drug. These drugs are difficult to pass through the lipid barrier, and the presence of lipophilic groups, such as organosilicon, will increase this property, that is, increase the property of the drug, so the introduction of these groups will modify the property of the drug. For this reason, we did this work with various silyl groups.

2. Experimental

2.1. Measurements and Materials

The IR spectra were recorded on a Bruker PS-15 spectrometer. The melting points were measured on an Electrothermal Melting Point Apparatus Model 9100-2. All starting materials and reactants were commercially available and were purchased from Merck. The commercial reagents were used without prior prepurification. All reactions were done in the argon atmosphere.

2.2.1. Synthesis of trimethylsiloxypiroxicam (1)

First, 1.5 mmol (0.5 g) of piroxicam, 0.2 ml of trimethylchlorosilane and 0.30 ml of triethylamine as base in 20 ml of dry THF were mixed for 40 hours under argon atmosphere, then it was stirred at ambient temperature with a stirrer and the progress of the reaction was monitored by TLC. After 40 hours the product was subjected to thin layer chromatography using n-Hexane and ethyl acetate system with ratios of 7:3. The product was evaporated under vacuum to obtain a pure yellow solid.
FT-IR (KBr) ($V$/cm$^{-1}$): 3392 ($N-H$ stretch), 2924, 2853 ($C-H$ stretch), 1745 ($C=O$ stretch), 1181 ($SO_2$ bend), 1576 ($C=C$ stretch), 1261 ($Si-C$ stretch), 1094 ($Si-O$ stretch), 801 ($Si-C$ bend).

2.2.2. Synthesis of triethylsiloxypiroxicam (2)

The process is similar to the previous, the time is 45 hours and the purification system is similar to the previous reaction.

FT-IR (KBr) ($V$/cm$^{-1}$): 3393, (NH stretch), 2854, 2918, (C-H stretch), 1708, (C=O stretch), 1181 (SO$_2$ bend), 1577 (C=C stretch), 1260 (Si-C stretch), 1094 (Si-O stretch), 803 ($Si-C$ bend).

$^1$H-NMR (400MHz, DMSO) ($\delta$/ppm): 0.4-0.5 (m, CH$_2$, 6H), 0.85-1.25 (t, CH$_3$, 9H), 2.85 (s, N-CH$_3$, 3H), 7.2-8.4 (m, C-H, aromatic ring, 8H), 12 (s, N-H, 1H).

2.2.3. Synthesis of dimethyl-t-Bu-siloxypiroxicam (3)

The process is similar to the previous, the time, after 45 hours the product was subjected to thin layer chromatography using n-Hexane and ethyl acetate system with ratios of 7:1. The product was evaporated under vacuum to obtain a pure yellow solid.

FT-IR (KBr) ($V$/cm$^{-1}$): 3338 ($N-H$ stretch), 2958, 2918 ($C=O$ stretch), 1181 ($SO_2$ bend), 1576 ($C=C$ stretch), 1260 ($Si-C$ stretch), 1096 ($Si-O$ stretch), 802 ($Si-C$ bend).
1H-NMR (400MHz, DMSO) (δ / ppm): 0.82 (s, (CH$_3$)$_2$, 6H), 1.25 (s, t-Bu, 9H), 2.85(s, N−CH$_3$, 3H), 7.2-8.4 (m, aromatic ring, 8H), 12 (s, N−H, 1H).

2.2.4. Synthesis of dimethylvinylsiloxypiroxicam (4)

The process is similar to the previous. After 45 hours the product was subjected to thin layer chromatography using n-Hexane and ethyl acetate system with ratios of 7: 1. The product was evaporated under vacuum to obtain a pure yellow solid.

FT-IR (KBr) (ν /cm$^{-1}$): 3390 (N−H stretch), 3010, 2950 (C-H stretch), 1745 (C=O stretch), 1181 (SO$_2$ bend), 1570 (C=C stretch), 1260 (Si−C stretch), 1090 (Si−O stretch), 830 (Si−C bend).

2.3. Synthesis of copolymers

2.3.1. Synthesis of co-poly-ethylene-vinyl-siloxy-piroxicam with Methacrylic acid (5)

(MAA)

10 mg (0.024 mmol) of resulting vinyl dimethyl siloxypiroxicam monomer, 0.56 ml of methacrylic acid (ratio of 1:3), 0.03 g of AIBN radical initiator and 30 ml of dry THF as solvent were mixed in round bottom flask, and was heated in 70°C for 72h. After cooling the product and washing with cooled methanol for three times, the resulting was evaporated to obtained white product.

This reaction was repeated with ratio of 1:5 of monomers (5-a).

2.3.2. Synthesis of co-poly-ethylene-vinyl-siloxy-piroxicam with Syrene (6)
10 mg (0.024 mmol) of resulting vinyl dimethyl siloxypiroxicam monomer 0.072 ml of styrene(ratio of 1:3), 0.03 g of AIBN radical initiator and 30 ml of dry THF as solvent were mixed in round bottom flask, and was heated in 70°C for 24h. After cooling the product and washing with cooled methanol for three times, the resulting was evaporated to obtained white product. This reaction was repeated with ratio of 1:5 of monomers(6-a).

3. Results and Discussions

As mentioned in previous section piroxicam is one of the important drug, but this drug is one of compoundshave hydrophilic property. The enhanced lipophilicity afforded to these compounds by the addition of silicon containing groups is expected to improve some properties. Increasing the lipophilicity of the drug causes the drug to pass quickly through the lipid barrier, thus multiplying the properties and effects of the drug. Cleavage of the silicon-drug bond is effected by chemical hydrolysis, a process less prone to interpatient variability than the metabolic process required for activation of conventional prod rugs. [10]. In other works neurotropic and antitumor activities of pyridyl-substituted 5-Si- soxazolines have been investigated, and these compounds have more potency in protection against hypoxia than their analogues [11]. Also silatranes are intracomplex organosilicon tris(2-hydroxy-alkyl) amine esters that have exhibited a broad spectrum of biological activity 12 – 14]. In ddition to these compounds other organosilicion compounds were synthesized and their biological activities were studied [15, 16]. Because of this, we synthesizes some silyl ethers of pyroxicam, and some network polymers of it. Incorporation of silyl ether into piroxicam not only increases its effectiveness but also causes a long-term effect as a prodrug.

3.1. Synthesis of trialkylsiloxypiroxicam
This derivative can be prepared by simple method, i.e. coupling chlorotrialkylsilanes in the presence of triethylamine as base, and in solvent such as THF, DMSO, and Deep Eutectic Solvent (DES)[17]. We used THF as solvent for our reactions. The method used is shown in Scheme 1.

Scheme 1. Reactions of organosilicon compounds with piroxicam

3.2. Identification of silyl groups in piroxicam

We identified all compound by spectroscopic methods.

3.2.1. FT-IR Spectroscopy

Incorporation of silyl groups in all products were confirmed by FT-IR These groups in our silyl ethers (R$_3$Si-) are: R$_3$=Me$_3$, Et$_3$, Me$_2$-t-Bu, Me$_2$-vinyl.Absorption in 1261 is related to C-Si stretching vibrations, peak in 1090-1100 is related to Si-O stretching vibrations, and in 820-830 is related to C-Si stretching vibrations. These data conform the silyl groups in all of product. We, also showed the presence of piroxicam link in product. Absorptions of 3340 and
3393 are related to N-H stretching vibrations, adsorptions in 2958, 2918 are related to aliphatic C-H stretching vibrations. Absorption in 1708 is related to C =O stretching vibrations, peak in 1180 is related to SO2 stretching vibration. These data also conform presence of piroxicam. In all products we can investigate and conform structures. A typical figure of FT-IR spectrum was shown in Fig.1.

![FT-IR spectrum](image)

**Fig.1.** FT-IR spectrum of dimethyl vinyl siloxy piroxicam

### 3.2.2 ¹H-NMR Spectroscopy

As we showed in previous section, all of groups in silyl ethers were investigated and approved. Also all of protons in piroxicam for example protons of aromatic ring were identified. Typical spectrum were shown in Fig.2, and Fig.3.
Fig.2. $^1$H-NMR spectrum of dimethyl vinyl siloxy piroxicam
Silyl ethers are among the most widely used protecting groups for the alcohol functionally because the rate of deprotection can be modulated by simply altering the substituents on the silicon atom. As a result, the synthesis of small-molecule silyl ether prodrugs have been explored using a variety of acid sensitive silane attachments including trimethyl silyl ether (TMS), triethyl silyl ether (TES), and triisopropyl silyl ether (TIPS). Although these materials are labile in vivo they are typically fastidious because of their vulnerability to acidic workups [18]. This limitation can be alleviated by incorporating silyl ether prodrugs within a polymeric drug delivery system. The combination of a small molecule drug with high molecular weight polymer provides protection for the therapeutic, and reduces the rate of degradation. Previously, polybutadiene and polyamine polymers have been functionalized with monofunctional (silyl ether prodrugs) of antiulcer
prostaglandins [19, 20], which were designed to degrade under the harsh acidic environment found in the stomach.

3.3. Synthesis of polymers

3.3.1. Synthesis of copolymers of vinyl siloxy piroxicam with methacrylic acid (MAA)

In the next step of work, some network polymer of vinyl siloxy piroxicam derivatives were synthesized. Due to the fact that methacrylic acid has several applications in various fields, including in drug delivery systems, we prepared the copolymer of this monomer with vinyl .siloxy piroxicam with ratio of 1:1, 1:3 and 1:5 in the presence of AIBN as radical catalyst. All of polymers were identified with FT-IR spectroscopy, peaks of functional groups of monomer, and MAA, also silyl groups are seen. This evidence confirms the existence of vinyl siloxy piroxicam MAA, and silyl group in network polymers. Also, silyl group was identified by EDX spectroscopy, as shown in some of the spectra in Fig 4-8.

TGA of all polymers shows that increasing of thermal stability of piroxicam. This modifications can be very important in this drug, i.e. increasing of thermal stability can be used in drug life and storage time.
Scheme 2. Copolymerization vinyl siloxy piroxicam with methacrylic acid (MAA)

Scheme 3. Copolymerization of vinyl siloxy piroxicam with styrene
Fig. 5. FT-IR of Poly-Methacrylic acid - silyl monomer

Fig. 6. TGA Poly-Methacrylic acid - silyl monomer with various ratio
Fig. 7. FT-IR of Poly-Styrene-silyl monomer

Fig. 8. TGA of PolyStyrene - silyl monomer with various ratio

Table 1. shows the silyl ether and copolymers.
Conclusion

In this work, we synthesized silyl ether of piroxicam for improving of some properties of this drug. This work can be used in drug delivery system, such as improving thermal stability, storage time, and lipophilicity of phenolic drug, especially for piroxicam ointment. By increasing the lipophilicity of the drug, it easily passes through the lipid barrier and its effectiveness is significantly increased.

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