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A method for catalytic synthesis of convenient thioxanthone crown ethers using Wells-Dawson, $H_6[P_2W_{18}O_{62}]$ and Preyssler $H_{14}[NaP_5W_{30}O_{110}]$, heteropolyacid catalysts

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Heteropolyacids (HPAs) were used as an effective catalyst for the synthesis of thioxanthone crown ethers from the reaction of thiosalicylic acid and benzocrown ethers. This reaction was carried out subsequently via intramolecular electrophilic cyclization. The reaction was in mild and clean conditions, and has high selectivity with good yields.

Keywords: Heteropolyacid; Wells-Dawson; Preyssler; Thioxanthone; Crown ether; Catalyst

INTRODUCTION

The reactions, catalyzed by heteropolyacids (HPAs) and polyoxometalates (POMs) in both heterogeneous and homogeneous systems, have been reviewed by various authors [1]. HPAs have several advantages as catalysts, which make them economical and environmentally attractive in both academic and industrial points. They have a very strong Brønsted acidity, approaching the super-acid region. They have significantly higher catalytic activity than that of strong mineral or organic acids, such as H_2SO_4, HCl, HNO_3, TsOH, TfOH, $MeSO_3H$, and conventional catalysts, such as alumina, silica gel, zeolites, clay, and acidic Amberlyst-15 [2]. Heteropolyacids (HPAs) are strong Brønsted acids composed of heteropolyanions and protons as the counter cations and promising solid acids to replace environmentally harmful liquid acid catalysts [3-5]. Among HPAs, the Keggin-type HPAs have attracted much interest since they possess strong acidity, while a few studies have been published on the use of Preyssler's anion heteropolyacids. Even, in some cases there have been reports of no catalytic activity [6]. The important advantages of this polyanion, in comparison to the Keggin heteropolyacids are: a) more thermal stability, b) more hydrolytic stability (pH=0–12), and c) larger number of protons. These properties are very important in catalytic processes especially in synthesis of drugs. Crown ethers have enjoyed widespread use in various areas of science and technology [7] ever since the first preparation of the ligands by Pedersen [8]. Thioxanthone derivatives are potential anti-cancer drugs and they are an important class of molecules and are a common heterocyclic scaffold in biologically active and medicinally significant compounds. Thioxanthone ring is the core structure of a wide variety of naturally occurring and synthetic compounds that exhibit extraordinary anti-tumor activity [9] and methods for the synthesis of thioxanthones are used in concentrated sulfuric acid at room or high temperature [9].

RESULTS AND DISCUSSION

We wish to report a catalytic convenient synthesis of thioxanthone crown ether with reaction of thiosalicylic acid and benzo-15-Crown-5 (**2c**) in the presence of Wells-Dawson, various heteropolyacids, HY-zeolit, H_3PO_4, $C_6H_5SO_3H$ and H_2SO_4 at room temperature (Scheme 1 and 2).

In the synthesis of thioxanthone crown ether, the results were compared with the yields of other catalysts types at room temperature (Table 1).

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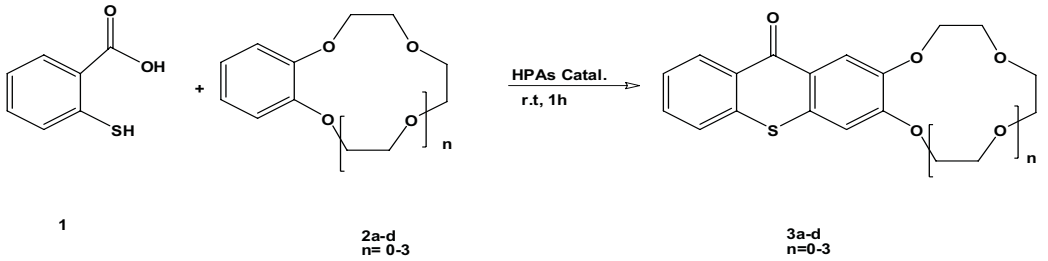
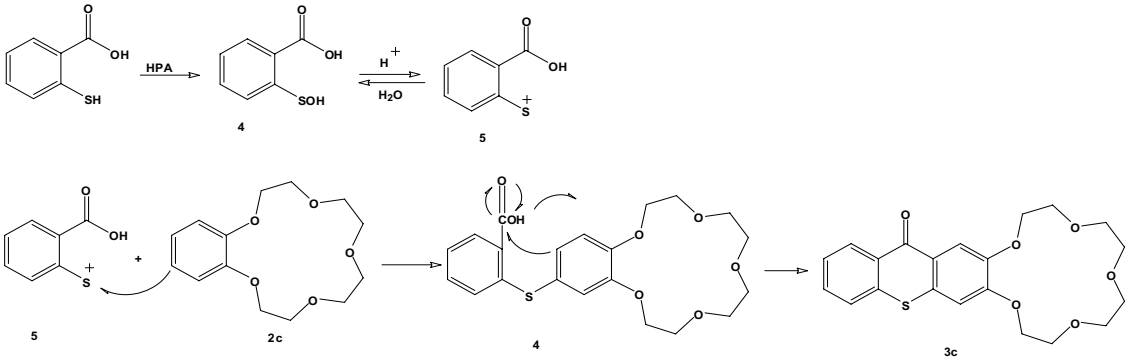
We developed our researches in this synthesis and used various crown ethers with the same conditions in the synthetic reaction, and obtained the corresponding thioxanthone crown ethers in good yields (Scheme 2) (Table 2).



Scheme 1. Synthesis of convenient thioxanthone crown ethers.



Scheme 2. The mechanism and the synthesis of convenient thioxanthone crown ethers using Wells-Dawson, $H_6[P_2W_{18}O_{62}]$ and Preyssler $H_{14}[NaP_5W_{30}O_{110}]$ heteropolyacids catalysts.

Table 1. The yields of **3a-d** (5 mmol) in the presence of Preyssler catalyst $H_{14}[NaP_5W_{30}O_{110}]$,(H_{14}–P_5).

Entry	n (Substrate)	Time (h)	[a]Yield [%]
1	0	1.5	94
2	1	1.5	91
3	2	1.5	77.5
4	3	1.5	72

[a] Isolated yield

Table 2. The yields of **3a** (5 mmol) in the presence of various catalysts.

Entry	Catalyst	Time (h)	[a]Yield [%]
1	$H_3[PMo_{12}O_{40}]$	2	74
2	$H_3[PW_{12}O_{40}]$	2	82
3	$H_4[SiW_{12}O_{40}]$	2	79
4	$H_6[P_2W_{18}O_{62}]$	1.5	86
5	$H_4[SiMo_{12}O_{40}]$	2	71.5
6	HY-zeolite	3	71
7	H_3PO_4	2	55
8	H_2SO_4	2	69
9	$C_6H_5SO_3H$	2	67

[a] Yields are analyzed by GC and products isolated.

The Wells-Dawson heteropolyacid and various heteropolyacid catalysts have very straight acidic and oxidation properties because the thiosalicylic acid **1** is oxidized to sulfenic acid by heteropolyacid and this compound decomposes to sulfenium ion 2,3,5,6–Tetrahydro-14*H*-thioxantheno[2,3-*b*] [1,4,7]trioxonin-14-one (3a), [10] and when using electrophilic substitution of sulfenium ion with the benzo-15-crown-5 (**2c**) gave intermediate thioether, and then with the cyclization of thioether gave the thioxanthone-15-crown-5 ether (**3c**) (Scheme 2). The results in Table 1 showed that the yields of the products (**3a-d**) were good and so the yields of the products with n=0, 1 (**3a** and **3b**) were higher than other products (entry 1, 2).

In this reaction which is used from Preyssler heteropolyacid catalyst at room temperature, and with acidic protons [11] has more straight acidic properties than other heteropolyacids and catalysts, and when Preyssler catalyst was used in this reaction, its time was 1.5 h, but when H_2SO_4, H_3PO_4, HY-zeolit, $C_6H_5SO_3H$ and Keggin heteropolyacids were used in the reaction, the reaction times were 2 and 3 h (Table 2, entries 1–3, 5–9) and the yield of the product (**3a**) was lower than when using Wells-Dawson heteropolyacid and Preyssler catalysts (Table 1, entry 1, Table 2, entry 4). There is a

proposed mechanism, an electrophilic substitution of sulfenium ion with the benzo-15-crown-5 (**2c**) would then give intermediate thioether and the cyclization of thioether gives the thioxanthone-15-crown-5 ether (**3c**) (Scheme 4). Thioxanthone crown ether yields depended directly upon the sulfuric acid concentration because sulfonation of **2c** competes with the generation of sulfenium ion (**5**) and subsequent electrophilic substitution [12]. The spectral data for the compounds **3a-3d** are presented in Table 3.

Table 3. Spectral data of the compounds (**3a-3d**).

Compound	Spectral data
2,3,5,6-Tetrahydro-14*H* thioxantheno [2,3-*b*][1,4,7]trioxonin-14-one (3a)	IR, $\tilde{\nu}$ /cm^{-1}: 2900 (s), 1630 (s), 1590 (s), 1490 (s), 1300 (s), 1125 (s), 1045 (s), 870 (s), 740 (s) ^{1}H NMR (DMSO-d_6), δ: 3.92(m, 4H), 4.31 (m, 2H), 4.70 (m, 2H), 7.07 (s, 1H), 7.52 (m, 3H), 8.25 (s, 1H), 8.55 (d, 1H, J=7.4 Hz) MS, *m*/*z* (I_r/%): 314 (M+)
2,3,5,6,8,9-Hexahydro-17*H*-thioxantheno[2,3-*b*][1,4,7,10] tetraoxacyclododecin-17-one (3b)	IR, $\tilde{\nu}$ /cm^{-1}: 2873 (s), 1635 (s), 1593 (s), 1505 (s), 1440 (s), 1292(s), 1269 (s), 1254 (s), 1149 (s), 1115 (s) 745 (s) ^{1}H NMR (DMSO-d_6), δ: 3.78 (s,4H), 3.85 (m, 4H), 3.94 (m, 2H), 4.30 (s, 2H), 7.06 (s, 3H),7.46 (t, 1H, J=7.2 Hz), 7.58 (m, 2H), 8.20 (s, 1H), 8.59 (d, 1H J=7.4 Hz) MS, *m*/*z* (I_r/%): 358 (M+)
2,3,5,6,8,9,11,12-Octahydro-20*H*-thioxantheno[2,3-*b*] [1,4,7,10,13] pentaoxacyclopentadecin-20-one (3c)	IR, $\tilde{\nu}$ /cm^{-1}: 2875 (s), 1595 (s) ,1505 (s), 1446 (s), 1409 (s), 1261 (s), 1210 (s), 1135 (s), 1085 (s), 935 (s) 740 (s) ^{1}H NMR (DMSO-d_6), δ: 3.35 (s, 8H), 3.63 (s, 4H), 3.81 (s, 2H), 4.20 (s, 2H), 7.35 (s, 3H), 7.57 (t, 1H, J=7.5 Hz), 7.74 (t, 1H, J=7.5. Hz), 7.82 (d, 1H, J=7.9. Hz), 7.86 (s, 1H), 8.55 (d, 1H, J=7.9. Hz) MS, *m*/*z* (I_r/%): 402 (M+)
2,3,5,6,8,9,11,12,14,15-Decahydro-23*H*-thioxantheno[2,3-*b*] [1,4,7,10,13,16]hexaoxacyclooctadecin-23-one (3d)	IR, $\tilde{\nu}$ /cm^{-1}: 2925(s), 2860 (s), 1685 (s), 1589 (s), 1505 (s), 1415 (s), 1260 (s), 1120 (s), 950 (s), 740 (s) ^{1}H NMR (DMSO-d_6), δ: 3.75 (s, 8H), 3.97 (s, 2H), 4.28 (s, 2H), 6.92 (s, 1H), 7.50 (m, 2H), 7.56 (s, 1H), 8.02 (s, 1H), 8.60 (d, 1H, J=7.5. Hz MS, *m*/*z* (I_r/%): 446 (M+)

All compounds were characterized by mass, IR and ^{1}H NMR spectra.

EXPRIMENTAL

The chemical materials were purchased commercially.^{1}H NMR spectra were recorded in $CDCl_3$ on a FT NMR Bruker 100 M Hz Aspect 3000 spectrometer. IR spectra were obtained with a Brucker 500 scientific spectrometer. The mass spectra were scanned on a Varian Mat. CH–7 at 70 ev.

Preparation of Preyssler catalyst, $H_{14}[NaP_5W_{30}O_{110}]$ (H_{14}–P_5)

H_{14}-P_5 was prepared by passage of a solution of the potassium salt in water through a column (50 cm×1 cm) of Dowex50W×8 in the H^+ form and evaporation of the elute to dryness under vacuum [13].

Preparation of Wells-Dawson species $H_6[P_2W_{18}O_{62}]$

The Wells-Dawson species $H_6[P_2W_{18}O_{62}]$ was prepared as described elsewhere [11], from an aqueous solution of α/β $K_6P_2W_{18}O_{62}\cdot 10H_2O$ salt which was treated with ether and concentrated (37%) HCl solution.

General procedure for the synthesis of thioxanthone crown ethers

A mixture of thiosalicylic acid (1 mmol), the appropriate crown ether (5 mmol) and catalyst (0.05 mmol) was added to a round-bottomed

flask, then this mixture was stirred and refluxed at room temperature for one hour. The reaction progress was monitored by TLC. After completion of the reaction, the mixture was poured onto ice and the product was filtered, washed with water and then washed with a saturated aqueous solution of sodium hydrogen carbonate until alkali-free and dried under vacuum over night at room temperature to yield product as shown in Table 2.

2,3,5,6-tetrahydro-1,4,7-benzotrioxonine (**2a**) was provided in accordance to the literature [14] and this product was known and characterized by comparison of their physical and ^{1}HNMR, IR and mass spectral data with those reported. The preparation of the benzo-9-crown-3 used as precursors has been described in accordance to the literature [15].

CONCLUSION

In summary, we have developed a novel, ecofriendly, and efficient method for the synthesis of thioxanthone crown ethers using HPAs as an inexpensive, green, and reusable catalyst. The advantages of the present method are simplicity of workup, high yields, short reaction times, recyclability of the catalyst.

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МЕТОД ЗА СИНТЕЗИРАНЕ НА ПОДХОДЯЩИ ТИОКСАНТОННИ КРАУН-ЕТЕРИ ПРИ ИЗПОЛЗВАНЕ НА УЕЛС-ДОУСЪН'ОВИ $H_6[P_2W_{18}O_{62}]$ И ПРАЙСЛЕР'ОВИ ХЕТЕРО-ПОЛИКИСЕЛИНИ $H_{14}[NAP_5W_{30}O_{110}]$ КАТО КАТАЛИЗАТОРИ

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(Резюме)

Хетеро-поликиселините са използвани като ефикасен катализатор за синтезата на тиоксантонови краун-етери чрез реакция между тио-салицилова киселина и бензо-краун-етери. Реакцията се извършва чрез вътрешно-молекулна циклизация и протича при меки условия, с висока селективност и добри добиви.