Benzoin Condensation Reactions of 5-Membered Heterocyclic Compounds Catalyzed by Thiazolium Salts

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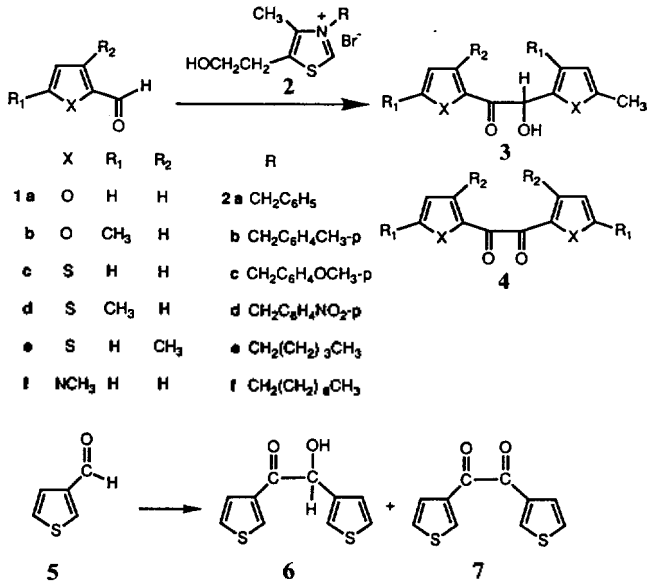
Benzoin condensation reactions of furfurals and thiophenecarboxaldehydes in the presence of substituted benzyl and alkyl thiazolium salts were examined in order to improve the yield of the reaction and to examine the effect of the electronic nature of the catalysts. Thiophene derivatives gave thenils as the major products in low yields while furan derivatives gave only furoins in moderate to high yields.

Introduction

Benzoin condensation reactions of heterocyclic aromatic compounds have been done mostly to compare the reactivity of 5-membered heterocyclic aldehydes with that of benzaldehyde.[1] Unlike to benzaldehyde which forms benzoin in 92% yield under the presence of KCN furoin and thenoin are formed in 38%[1] and 32%[2] yields from furfural and 2-thiophenecarboxaldehyde, respectively. The yield of furoin was improved up to 66% by adding 18-crown-6 or dibenzo-18-crown-6.[3]

Several catalysts have been prepared and used for benzoin condensation reactions to improve the yield as well as to make the work-up process easy. They include derivatives of quaternary ammonium salts of thiazoles,[4] thiadiazoles,[5] and polymer-supported quaternary ammonium cyanides.[6] The most widely examined thiazolium salt was 3-alkyl-5-(2'-hydroxyethyl)-4-methylthiazolium chloride which had structural analogy to thiaminepyrophosphate (TPP).[4] By reacting with chloromethylated polystyrene the thiazole could be bound to the polymer so that the catalyst could be easily recovered for reuse and the yields were reached to quantitative amounts for benzoin and furoin.[7].

Although furfural has been used as a substrate for the benzoin condensation reaction with the thiazolium catalysts, reactions with 2-thiophenecarboxaldehyde under similar conditions are rare. In the course of our effort of preparing α-hydroxyketones we came to prepare furoins and thenoins from furfurals and thiophenecarboxaldehydes, respectively. One of the notable observations was the low reactivity of thiophenes (**1c-e**). The starting materials were always recovered in 50-80%. In addition, the major reaction products were the thenils (**4c-e**) instead of the thenoins (**3c-e**) when KCN or CN-resin was used as a catalyst.[8] Here we report our extensive examination on the benzoin condensation reactions of 5-membered heterocyclic aromatic compounds in the presence of various substituted thiazolium salt catalysts (**2a-f**).

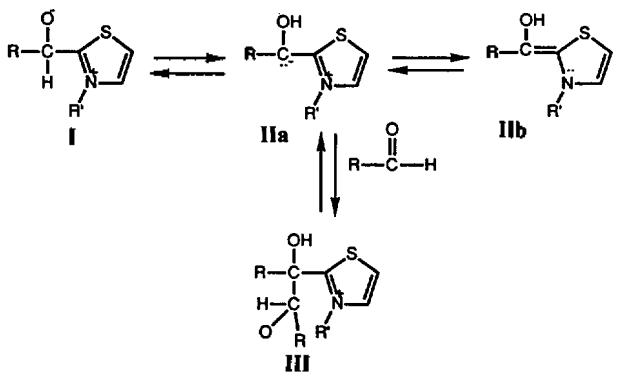


	X	R_1	R_2	R
1a	O	H	H	2a $CH_2C_6H_5$
b	O	CH_3	H	b $CH_2C_6H_4CH_3$-p
c	S	H	H	c $CH_2C_6H_4OCH_3$-p
d	S	CH_3	H	d $CH_2C_6H_4NO_2$-p
e	S	H	CH_3	e $CH_2(CH_2)_3CH_3$
f	NCH_3	H	H	f $CH_2(CH_2)_6CH_3$

Drawing 1

Results and Discussion

The mechanism of the benzoin condensation has been known to involve preequilibrium formation of cyanide-added carbanion which will attack a carbonyl carbon of the other aldehyde molecule in the rate determining step.[9] A similar mechanism has been proposed with a thiazolium salt without kinetic investigation.[4] Apparently, the enhanced yields of acyloins with the thiazolium catalyst seem to be due to easy formation of **IIa** which should be stabilized by resonance



Drawing 2

Table 1. Acyloin Condensation of **1a-e** and **5** in the Presence of Various Thiazolium Salts (**2a-f**)

		2a	2b	2c	2d	2e	2f
1a	Ratio,[a] h[b]	20 : 1, 1	20 : 3, 1	20 : 3, 2	15 : 1, 7	15 : 1, 2	5 : 1, 2
	Product (%)	3a (90)	3a (60)	3a (86)	4a (24)	3a (68)	3a (40)
1b	Ratio,[a] h[b]	20 : 1, 1	6: 1, 3	30 : 4, 9	15 : 1, 20	15 : 1, 20	6 : 1, 20
	Product (%)	3b (90)	3b (68)	3b (55)	4b (5)	3b (51)	3b (32)
1c	Ratio,[a] h[b]	20 : 1, 1	6 : 1, 10	5 : 1, 4	15 : 1, 12	15 : 1, 20	5 : 1, 20
	Product (%)	4c (35)	4c (20)	4c (10)	4c (trace)	4c (56)	4c (14)
1d	Ratio,[a] h[b]	20 : 1, 1	6 : 1, 10	5 : 1, 4	15 ; 1, 12	15 : 1, 20	5 : 1, 20
	Product (%)	4d (15)	4d (14)	4d (14)	4d (trace)	4d (25)	4d (10)
1e	Raito,[a] h[b]	20 : 1, 1	5 : 1, 5	4 : 1, 10	15 : 1, 24	10 :1, 20	5 : 1, 20
	Product (%)	4e (13)	4e (12)	4e (47)	4e (trace)	4e (20)	4e (15)
5	Ratio,[a] h[b]	20 : 1, 1	30 : 4, 3	30 : 4, 3	15 : 1, 5	30 : 4, 3	5 : 1, 20
	Product (%)	6 (90)	6 (60)	6 (86)	6 (24)	6 (68)	6 (40)

[a]Molar ratio of 1 : 2. [b]Hour of reflux.

Table 2. ^{1}H-NMR Data of the Thiazolium Salts **2**, δ

Compd	2-H	4-CH_3 (s)	CH_2O (t)	5-CH_2 (t)	N-CH_2	others
thiazole[a]	8.60	2.37	3.83	3.00	–	–
2a	9.28	2.52	3.90	3.18	5.73 (s)	7.45 (s)
2b	9.95	2.60	4.00	3.28	5.80 (s)	7.47 (s, C_6H_4), 2.43 (CH_3)
2c	9.90	2.63	3.93	3.27	5.77 (s)	7.17 and 7.57 (AB, C_6H_4), 3.93 (OCH_3)
2d	10.07	2.53	4.00	3.27	6.02 (s)	7.63 and 8.38 (AB, C_6H_4)
2e	9.91	2.60	3.93	3.20	4.53 (t)	1.1-1.6 (6 H), 0.92 (t, CH_3)
2f	10.07	2.60	3.92	3.22	4.65 (t)	1.1-1.6 (16 H), 0.85 (t, CH_3)

[a]In deuterated chloroform.

structures such as **IIb**. Our attempt was not to figure out the correct mechanism of the reaction. Instead we hoped to improve the yields of acyloins by employing various catalysts and to compare the reactivities of furan, pyrrole, and thiophene under the similar conditions.

The results of the benzoin condensation reactions of **1a-e** catalyzed by various thiazolium salts (**2a-f**) are listed in Table 1. Various efforts to enhance the yield of **3c** from **1c** while minimizing the formation of **4c** by modifying the reaction conditions such as temperature and ratio of solvents or catalyst all failed. One of the contrasts between the furan (**1a, b**) and the thiophene (**1c-e**) compounds is the formation of the furoins (**3a, b**) and the thenils (**4c-e**), respectively. The conversion of the thiophene compounds to the thenoins and thenils, however, was usually smaller than that of furans to furoins. On the other hand, 3-thiophenecarboxaldehyde (**5**) gave only **6** and the thenil **7** was not detected in the reaction mixture. As reported in the literature with KCN,[10] 1-methyl-2-pyrrolecarboxaldehyde (**1f**) did not undergo benzoin condensation in the presence of all the thiazolium salts employed in this research.

Other notable result is the ineffectiveness of the substituents in **2** on the yields of **3** or **4**. The observation is in contrast to the distinctive effect of long alkyl chain when N-alkylthiazolium bromide was used.[11] The observed yields of **3a, b** and **4c-e** were higher with *N*-n-pentyl (**2e**) than those with *N*-n-decyl (**2f**) salts. Although we used the thiazole having 4-methyl and 5-(2'-hydroxyethyl) substitutents we expected some electronic influence of the N-benzyl substituents if the suggested mechanism was operating indeed. The observed yields which do not show any correlation with the nature of the substitutents may be explained as a result of the reversibility of the benzoin condensation reaction. The reverse reaction, that is, the cleavage of the benzoins to aldehydes may well be catalyzed by the thiazolium salts, too. Therefore, the isolated yields of the products may vary depending on the extent of the equilibrium.

p-Nitrobenzylthiazolium salt (**2d**) turned out to be the poorest catalyst among the examined ones. Furthermore, it gave furils (**4a, b**) as the major products from **1a** and **1b** while other catalysts gave only furoins (**3a, b**). Apparently, the nitro group seems to cause the oxidation of the furoins, but we are not certain if the nitro group is reduced to either nitroso or amino group. We tried to prove the oxidation reaction of benzoin to benzil by nitrobenzene unsuccessfully. However, similar oxidation took place with furoin (**3a**) indicating that the nitro group may facilitate the air oxidation.

The substituents on the nitrogen atom seem to cause change in acidity of the C-2 proton of the thiazole ring which will eventually affect the formation of the zwitterion II. The chemical shift values of the protons in **2a-f** (Table 2) are marginally different. It is interesting to know that the values for **2d** (*p*-nitrobenzyl) and **2f** (decyl) are the same. Considering the extremely low yields of the condensation products with these catalysts the reaction is much complicated than one can rationalize based on the proposed mechanism.

Experimental Section

Melting points were determined on a Fisher Mel-Temp apparatus and were uncorrected. Infrared (IR) spectra were recorded on a Perkin-Elmer Model 1430 spectrophotometer. Nuclear magnetic resonance (NMR) spectra were recorded on a Varian EM-390 spectrometer and a Bruker 300 MHz FT-NMR spectrometer with TMS as an internal standard.

Starting Materials. Furfurals (**1a, b**) and thiophenecarboxaldehydes (**1c-e** and **5**) were commercial products which were distilled prior to use. 5-(2′-Hydroxyethyl)-4-methylthiazole and substituted benzyl bromides were purchased from the Aldrich Chemical Co. and used without further purification. Ethanol was distilled over calcium oxide and triethylamine was distilled over potassium hydroxide prior to use.

General Procedure for Preparation of the Thiazolium Salt (2). A mixture of benzyl bromide (30.0 mmol) and 5-(2′-hydroxyethyl)-4-methylthiazole (30.0 mmol) was heated at 100℃ for 6 h. Upon cooling it became a solid mass, which was dissolved in warm absolute ethanol (10 m*l*). The ethanol solution was filtered and diethyl ether (5 m*l*) was added to the filtrate. As the solution was cooled down, the solid precipitated slowly. The solids were collected by filtration and dried. There were instances of which no precipitate formed. Only gelly masses formed in cases of **2b**, **2c**, **2e**, and **2f**. The mp, yields, and infrared spectral data for each salt are as follows:

2a: 90%, mp. 108℃ (lit.[8] 109-110℃).

2b: 70%, gel, IR (neat) cm^{-1} 3330 (vs), 2940 (s), 1605 (w), 1580 (m), 1510 (m), 1460 (m), 1445 (s), 1410 (m), 1300 (m), 1065 (s), 800 (ms), 750 (m).

2c: 70%, gel, IR (neat) cm^{-1} 3350 (broad s), 1608 (m), 1582 (m), 1510 (s), 1460 (w), 1448 (m), 1300 (w), 1248 (s), 1178 (m), 1065 (m), 1022 (m), 818 (w).

2d: 97%, mp 139-141℃, IR (KBr) cm^{-1} 3380 (broad s), 3030 (s), 2925 (s), 2880 (w), 1601 (m), 1590 (m), 1512 (s, NO_2), 1494 (m), 1452 (ms), 1350 (s, NO_2), 1285 (m), 1210 (m), 1085 (ms), 1065 (s), 1015 (m), 1000 (m), 865 (ms), 850 (m).

2e: 60%, gel, IR (neat) cm^{-1} 3350 (broad s), 2940 (s), 2920 (m), 2860 (m), 1580 (m), 1450 (m), 1060 (s).

2f: 60%, gel, IR (neat) cm^{-1} 3300 (broad s), 2900 (s), 2830 (s), 1575 (w), 1455 (m), 1445 (s), 1410 (m), 1060 (s).

General Procedure for Benzoin Condensation Reaction. The procedure is a modified one from the literature[4] due to the extremely low yield, otherwise. To a solution of **2** (4 mmol) in absolute ethanol (10 m*l*) were added triethylamine (5 m*l*) and the aldehyde compound **1** (20 mmol). The resulting solution was heated at reflux under N_2 for 1-24 h (see Table 1). Upon cooling and standing in a refrigerator overnight, the product was precipitated. In case of no precipitation separation of the mixture was done by column chromatography (silica gel) eluting with benzene.

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