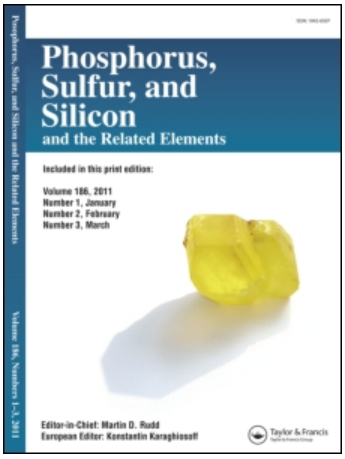

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STUDY OF THE ACYLATION REACTION OF 2(3H)-BENZOTHIAZOLONES IN THE MIXTURE OF $ZnCl_2$-DMF

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The use of polyphosphoric acid and the complex $AlCl_3$-DMF in 6-acylation of 2(3H)-benzothiazolones previously have been reported. Instead of the frequently used $AlCl_3$ as a catalyst in the Friedl-Crafts reactions, we conducted the acylation of 2(3H)-benzothiazones using zinc chloride as a catalyst in DMF as solvent and acid chlorides or anhydrides as acylating agents.

Keywords: $AlCl_3$-DMF; 2(3H)-benzothiazolone; 6-acyl-2(3H)-benzothizolones; acylation reaction; polyphosphoric acid; $ZinCl_2$-DMF

INTRODUCTION

The use of the complex of aluminum chloride-*N*,*N*-dimethylformamide in Friedl-Crafts reaction was previously reported.[1–4] This process was applied to the Haworth reaction of 2(3H)-benzoxazolones[2] and to the synthesis of various serotonin receptor ligands.[5,6] When the $AlCl_3$-DMF reagent was applied as a catalyst in the acylation reaction of 2(3H)-benzothiazolones using acid halides or anhydrides, the acylation products are obtained in good yields[7] (Scheme 1, Method b). The polyphosphoric acid[8] as solvent and catalyst was also applied using carboxylic acids or anhydrides (Scheme 1, Method a). However, the (PPA) method was not found as satisfactory as the $AlCl_3$-DMF complex in the case of halogeno or dicarboxylic acids.[7] The products were not formed or obtained only in low yields. The regioselectivity for position 6 of 2(3H)-benzothiazolones was observed and extended to other compounds by the use of high-field ^{1}H-NMR[7].

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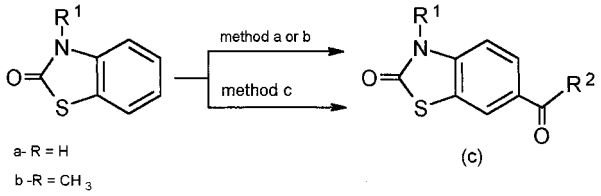
The 6-acyl-2(3H)-benzothiazolones such as the 6-acyl-benzoxazolones have interesting analgesic, anti-inflammatory, antiepileptic and antiviral properties.[9] Instead of the frequently used $AlCl_3$ as catalyst in Friedl-Crafts reactions, we conducted the acylation of 2(3H)-benzothiazolones using zinc chloride as catalyst in *N*,*N*-dimethylformamide as solvent[10] and acid chlorides or anhydrides as acylating agent (Scheme 1, Method c). With this method we obtained the corresponding 6-acyl-2(3H)-benzothiazolones in good yields and we optimized the conditions of their synthesis.



SCHEME 1

RESULTS AND DISCUSSION

The essential problem in the Friedl-Crafts acylation is the complexation of 2(3H)-benzothiazolone by Lewis acids such as $ZnCl_2$. The substrate became therefore highly deactivated in this electrophilic aromatic substitution process.[11] In view to this problem, the first study involved the determination of the zinc chloride/2(3H)-benzothiazolone ratio. The DMF/2(3H)-benzothiazolone ratio was kept constant at **3**. The acylation in the present case was found to proceed with a satisfactory rate and yield only, when this ratio was in the range of 8–10.

The treatment of 2(3H)-benzothiazolone at the temperatures used in the case of $AlCl_3$-DMF for the acid halides, and anhydrides,[7] gave a negative result. We have not observed any reactivety of zinc chloride in these temperatures. After these results, the second part was the optimisation of the temperatures in order to obtain the acylation products. The optimum was at 125–130°C for the aliphatic and at 140–145°C for the aromatic and heterocyclic chlorides. In the case of anhydrides we have study the succinic anhydride. The mixture was treated at 120–125°C for 6 h. Under these conditions we have isolated only the starting material and the corresponding acid was not formed. This failure is probably due to the degradation of succinic anhydride.

Under these conditions, the 6-acyl-derivatives were obtained in excellent yields in the range of 53–87% (Table I). The structures of

TABLE I Yields and Mp of the Compounds **c**

R^1	R^2	Time (h)	Cryst. solvent	Yields (%)	m.p. (°C)
H	CH_3	1,30	Ethanol	68	189–191
CH_3	CH_3	1,30	Ethanol	73	145–146
H	CH_2CH_3	1,40	Ethanol	63	204–205
CH_3	CH_2CH_3	1,40	Propanol	66	177–178
H	C_6H_5	2	Toliol	82	216–218
CH_3	C_6H_5	2	Ethanol	87	147–148
H	2-C_4H_3S	2	Ethanol	53	223–224
CH_3	2-C_4H_3S	2	Ethanol	58	223–225
CH_3	3-C_5H_4N	18	Ethanol	63	176–178
CH_3	CH_2—H_2—COOH	6	/	0	/

6-acyl-2(3H)-benzothiazolones were confirmed by IR, and ^{1}H-NMR spectroscopy and were compatible with the products obtained with $AlCl_3$-DMF. The precise position of acylation was unequivocally confirmed by x-ray single-crystal diffraction in the case of 6-benzoyl-2(3H)-benzothiazolone,[12] and was extended to other compounds by use of high field ^{1}H-NMR[7].

The reactivity of 2(3H)-benzothiazolones in this reaction appears to be parallel to that in the mixture $AlCl_3$-DMF at different temperatures and the $ZnCl_2$-DMF method (Scheme 1, Method c), provides good yields with aliphatic, aromatic, and heterocyclic chlorides. The comparative yields obtained by the aluminum chloride-*N*,*N*-dimethylformamide (B) and zinc chloride-*N*,*N*-dimethylformamide (c) methods, for similar compounds are summarized in Table II.

TABLE II Comparative Yields Obtained by the $AlCl_3$-DMF and $ZnCl_2$-DMF Method

Method		$AlCl_3$-DMF			$ZnCl_2$-DMF		
R^1	R^2	Temp (°C)	Time (h)	Yields (%)	Temp (°C)	Time (h)	Yields (%)
H	CH_3	75–80	3,30	61	125–130	1,30	68
H	CH_2CH_3	75–80	3	60	125–130	1,40	63
H	C_6H_5	95–100	4,30	83	140	2	82
H	2-C_4H_3S	95–100	4,30	57	140–145	2	53
CH_3	2-C_4H_3S	95–100	4,30	62	140–145	2	58
CH_3	3-C_5H_4N	85–90	28	71	140–145	18	63
CH_3	CH_2—CH_2—COOH	90–95	6	59	120–125	6	0

CONCLUSION

The results of this study indicate that the reactivity of 2(3H)-benzothiazolones in zinc chloride-*N*,*N*-dimethylformamide is parallel to that in aluminium chloride-*N*,*N*-dimethylformamide. At different temperatures, 2(3H)-benzothiazolones react with acids chlorides in the presence of a large excess of zinc chloride (8–10 equi) to give 6-acyl-2(3H)-benzothiazolones in excellent yields (53–87%).

EXPERIMENTAL

Melting points were determined using an Electrothermal melting point apparatus and are uncorrected. The IR spectra were recorded on a Shimadzu 40 (KBr pellets). H-NMR spectra were recorded using a Bruker 80 MHz spectometer with TMS as internal standard. The compounds were pure according to TLC (ethylacetate-cyclohexane, 3/2, v/v). The following examples demonstrate the procedure.

General Procedure for the Reaction of 2(3H)-Benzothiazolones with Aliphatic Acids Chlorides

Method (C)

Dimethyl formamide (0.039 mmol, 2.8 ml), was added to zinc chloride (0.117 mmol, 16 g). The mixture was stirred and maintained at 75°C, and 2(3H)-benzothiazolones (0.013 mmol), and acid chlorides (0.02 mmol) were added. The reaction mixture was warmed at 125–130°C for 1 h 40 min. After cooling the complex was decomposed by addition of ice water and 5 ml of 0.1N HCl. The resulting mixture was stirred for 1 h, filtered, and the filtrate washed with water and recrystallized.

6-Acetyl-2(3H)-benzothiazolone. IR (KBr, ν cm^{-1}); 3160, (–NH), 1695, 1660, (C=O); ^{1}H-NMR (80 MHz, DMSO D_6, δ in ppm); 2.55 (s, 3H), 7.19 (d, 1H, J = 8.4 Hz), 7.88 (dd, 1H, J = 1.6, 8.4 Hz), 8.23 (s, 1H), 12.20 (s, 1H, NH).

6-Propanoyl-2(3H)-benzothiazolone. IR (KBr, ν cm^{-1}); 3160, (–NH), 1685, 1655, (C=O); ^{1}H-NMR (80 MHz, DMSO D_6, δ in ppm); 1.08 (t, 3H), 3.01 (q, 2H), 7.18 (d, 1H, J = 8.4 Hz), 7.86 (d, 1H, J = 8.4 Hz), 8.20 (d, 1H, J = 1.6 Hz), 12.24 (s, 1H, NH).

General Procedure for the Reaction of 2(3H)-Benzothiazolones with Aromatic Acids Chlorides

Method (B)

Dimethyl formamide (0.039 mmol, 2.8 ml), was slowly added to aluminium chloride (0.117 mmol). The mixture was stirred and maintained at 45°C, and 2(3H)-benzothiazolones (0.013 mmol) and acids chlorides (0.0195 mmol) were added. The reaction mixture was warmed at 95–100°C for 4 h 30 min. After cooling, it was poured into ice water. The resulting mixture was stirred for 1 h, filtered and the filtrate washed with water and recrystallized.

Method (C)

Dimethyl formamide (0.037 mmol, 2.8 ml), was added to zinc chloride (0.117 mmol, 16 g). The mixture was stirred and maintained at 75°C, and 2(3H)-benzothiazolone or 3-methyl-2(3H)-benzoxazolone (0.013 mmol), and acids chlorides (0.02 mmol) were added. The reaction mixture was warmed at 140–145°C for 2 h. After cooling the complex was decomposed by addition of ice water and 5 ml of 0.1 N HCl. The resulting mixture was stirred for 1 h, filtered, and the filtrate washed with water and recrystallized.

6-Benzoyl-2(3H)-benzothiazolone. IR (KBr, ν cm^{-1}); 3190, (–NH), 1680, 1635, (C=O); ^{1}H-NMR (80 MHz, DMSO-D_6, δ in ppm); 7.23 (d, 1H, J = 8.4 Hz), 7.58 (m, 6H), 8.00 (d, 1H, J = 1.6 Hz), 12 (s, 1H, NH).

6-(2-Thinoyl)-2(3H)-benzothiazolone. IR (KBr, ν cm^{-1}); 3140, (–NH), 1735, 1620, (C=O); ^{1}H-NMR (80 MHz, DMSO-D_6, δ in ppm); 7.29 (m, 2H), 7.82 (m, 2H), 8.02 (m, 2H), 12 (s, 1H, NH).

3-Methyl-6-(2-thinoyl)-2(3H)-benzothiazolone. IR (KBr, ν cm^{-1}); 1660, 1620, (C=O); ^{1}H-NMR (80 MHz, DMSO-D_6, δ in ppm); 3.50 (s, 3H), 7.30 (d, 1H, J = 8.28 Hz), 7.40 (dd, 1H, J = 5, 3.6 Hz), 7.70 (d, 1H, J = 3.6 Hz), 7.88 (dd, 1H, J = 8.28, 1.5 Hz), 8.06 (d, 1H, J = 5 Hz) 8.18 (d, 1H, J = 1.5 Hz).

3-Methyl-6-nicotinoyl-2(3H)-benzothiazolone (Method C). Dimethyl formamide (0.039 mmol, 2.8 ml), was added to zinc chloride (0.117 mmol, 16 g). The mixture was stirred and maintained at 75°C, and 3-methyl-2(3H)-benzothiazolone (0.013 mmol, 2, 16 g), and nicotinoyl chloride hydrochloride (0.02 mmol) were added. The reaction mixture was warmed at 140–145°C for 18 h. After cooling the complex was decomposed by addition of ice water. The resulting mixture was stirred for 1 h, filtered, and the filtrate washed with water and recrystallized

from ethanol. IR (KBr, ν cm^{-1}); 1670, 1635, (C=O); ^{1}H-NMR (80 MHz, DMSO-D_6, δ in ppm); 3.49 (s, 3H), 7.40 (d, 1H, J = 8.2 Hz), 7.60 (m, 1H), 7.80 (m, 1H), 8.10 (m, 2H), 8.80 (m, 1H), 8.87 (d, 1H, J = 1.6 Hz).

4-Oxo-4-(3-methyl-2(3H)-benzothiazolon-6yl) butyric acid (Method B). Dimethyl formamide (0.039 mmol, 2.8 ml), was slowly added to aluminium chloride (0.2 mmol). The mixture was stirred and maintained at 45°C, and 3-methyl-2(3H)-benzothiazolone, and succinic anhydride (0.02 mmol) were added. The reaction mixture was warmed at 90–95°C for 6 h. After cooling the complex was decomposed by addition of ice water. The resulting mixture was stirred for 1 h, filtered, and the filtrate washed with water and recrystallized from ethanol. M.p. = 226–227°C: IR (KBr, ν cm^{-1}); 3290 (OH), 1730, 1680, 1660, (C=O); ^{1}H-NMR (80 MHz, (DMSO-D_6, δ in ppm); 2.54 (t, 2H), 3.25 (t, 2H), 3.48 (s, 3H), 7.33 (d, 1H, J = 8.4 Hz), 7.89 (d, 1H, J = 1.6 Hz), 8.32 (dd, 1H, J = 8.4, 1.6 Hz), 12.19 (s, 1H, OH).

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