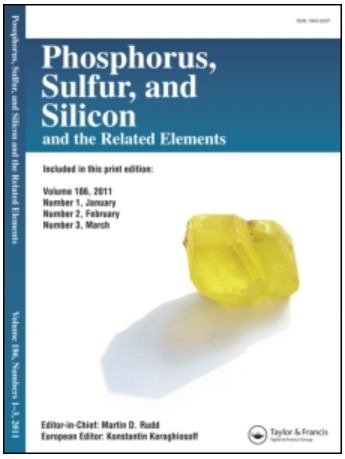

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Application of the "Fries Like" Rearrangement Using ZnCl 2 for the Synthesis of 6-Acyl-2(3H)-benzothiazolones

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APPLICATION OF THE "FRIES LIKE" REARRANGEMENT USING $ZnCL_2$ FOR THE SYNTHESIS OF 6-ACYL-2(3H)-BENZOTHIAZOLONES

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In this work we report another method of acylation on the 6-position of the 2(3H)-benzothiazolone ring with Fries-like rearrangement catalyzed by zinc chloride instead of aluminium chloride and 3-acyl-2(3H)-benzothiazolones derivatives as starting materials. This method is advantagous in regard to other acylation methods as it requires only three equivalents of $ZnCl_2$ to produce 6-acyl-derivatives with yields of 82–94%.

Keywords: 2(3H)-Benzothiazolone; 3-acyl-2(3H)-benzothiazolones; 6-acyl-2(3H)-benzothiazolones; Fries-like rearrangement; $ZnCl_2$; $ZnCl_2$-DMF

It is known that the major problem in the use of Lewis acids in the Friedl-Crafts acylation of electron-rich aromatic compounds is the complexation of these substrates by Lewis acids. These substrates become highly deactived in this electrophylic aromatic substitution.[1] This problem can be alleviated to some extent by using the complex ($AlCl_3$-DMF) as a catalyst.[2] This reagent was reported in a series of recent papers.[3–6] The application of these conditions in the case of 2(3H)-benzothiazolone was previously reported.[7]

Recently,[8,9] the use of zinc chloride as a catalyst instead of aluminium chloride in dimethylformamide as complexing agent,[10] in the acylation reaction of 2(3H)-benzothiazolone using activated forms of carboxylic acids (acid halides or anhydrides), 6-acyl-2(3H)-benzothiazolones were formed in satisfactory yields.[9] The disadvantage of the use of these complexes is the important consumption of $AlCl_3$ and $ZnCl_2$ necessary to accomplish the reaction in high yields. The acylation in the present case was found to proceed with satisfactory rate and yields only when

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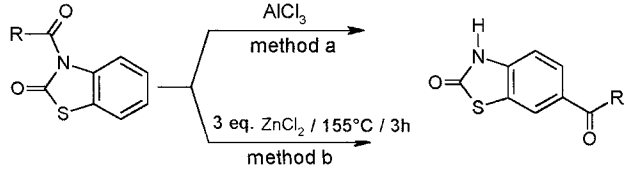
the ratio of $AlCl_3$/substrate was in the range of 7–11[7] and in the range of 8–10[9] in the case of $ZnCl_2$/substrate ratio.

The alternative synthetic method which employs "Fries-like" rearrangement catalyzed by $AlCl_3$ and 3-acyl-2(3H)-benzothiazolones as starting materials, permits the preparation of 6-acyl-derivatives in high yields[11] (Scheme 1 method a). This method presented an advantage with regard to other acylation methods.[7,9,12] It requires only 2,5 equivalents of $AlCl_3$ to perform the reaction in good yields.[11]

6-Acyl-2(3H)-benzothiazolones derivatives have particularly interesting anti-inflammatory, antiepileptic, antiviral, analgesic, and anticonvulsant properties.[11] In view of the interest of these compounds, an optimization of their synthesis was performed.

In this work, the 6-acyl-2(3H)-benzothiazolones were obtained by the use of Fries-like rearrangement with zinc chloride as a catalyst instead of aluminium chloride and the 3-acyl-2(3H)-benzothiazolones were the preferred starting materials for the synthesis of these derivatives (Scheme 1, method b). This method yielded the 6-acyl derivatives in high yield and excellent purity.



SCHEME 1

RESULTS AND DISCUSSION

According to the synthesis shown in Figure 1, 2(3H)-benzothiazolone was used as starting material to prepare the tragect 6-acyl-2(3H)-benzothiazolones with 3-acyl-(2H)-benzothiazolones as intermidiates.

The *N*-acylate reaction of 2(3H)-benzothiazolone was performed by allowing it to interact with acid anhydrides in refluxing[11] solvent (Scheme 2, method c) or with acid halides in the presence of

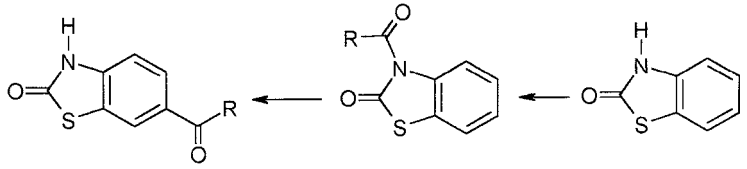
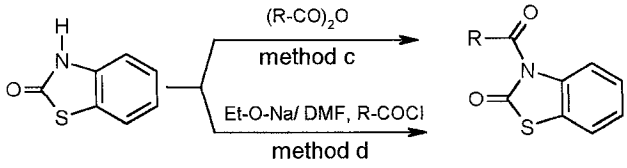


FIGURE 1

sodium ethylate in dimethyl sulfoxyde.[13] In our work we have used the dimethylformamide as solvent (Scheme 2, method d). This method gave the corresponding 3-acyl-2(3H)-benzothiazolones (**2a–f**) in excellent yields (Table I).



1 **(2a-f)**

SCHEME 2

The migration of the acyl groupe from the *N*-position to the 6-position of this heterocycle was also obtained by the reaction shown in Scheme 1, method b.

Treatment of 3-acyl-2(3H)-benzothiazolones (**2a–f**) employing 3 equivalents of zinc chloride at the temperature of 155°C, gave the desired 6-acyl-2(3H)benzothiazolones in high yields in the range of (82–94%) (Table I). The 6-acyl derivatives were the only products isolated from the reaction medium. Their structures were confirmed by IR, ^{1}H-NMR spectroscopy, and elemental analysis. They were compatible with the products obtained with $AlCl_3$ and are in accordance with published data.[7,11,14]

The mechanism of the rearrangement is intramolecular. The investigation of this mechanism was previously study by reaction of 3-benzoyl-2(3H)-benzothiazolone in the presence of 2(3H)-benzothiazolone.[11] No product was detected under these conditions.

As already mentioned above, the major problem of the use of ($ZnCl_2$-DMF) reagent such as in the case of ($AlCl_3$-DMF) is the important

TABLE I Yields of 3-Acyl-2(3H)-benzothiazolone (**2a–f**) and 6-Acyl-2(3H)-benzothiazolone (**3a–f**) Derivatives

No.	R	Yields (%)	No.	Yields (%)	m.p. (°C)
2a	CH_3	97[a]	**3a**	87	190–191
2b	CH_2CH_3	94[a]	**3b**	82	203–205
2c	C_6H_5	98[b]	**3c**	94	216–217
2d	C_6H_4(Cl-p)	96[b]	**3d**	86	275–277
2e	$C_6H_4(NO_2$-p	97[b]	**3e**	84	254–265
2f	C_6H_4(F-p)	97[b]	**3f**	85	235–237

[a]Method c.
[b]Method d.

TABLE II Comparative Yields of 6-Acyl-derivatives Obtained by ($ZnCl_2$-DMF) and Fries-like Methods

		Condions of ($Zncl_2$-DMF) method				
No.	R	$ZnCl_2$ equi	Temp (°C)	Reaction time (h)	Yields (%)	Fries-like yield (%)
3a	CH_3	9	130	1,30	67	87
3b	CH_2CH_3	9	130	1,40	63	82
3c	C_6H_5	9	140	2	81	94
3d	C_6H_4(Cl-p)	9	145	2	68	86
3e	$C_6H_4(NO_2$-p)	9	145	2	64	84
3f	C_6H_4(F-p)	9	145	2	25	83

consumption of $ZnCl_2$. The present method requires only 3 equivalents of this catalyst to performed the reaction in good yields. To investigate this method, we have caused to react 2(3H)-benzothiazolone with the corresponding acid halides in the presence of the condition of Friedl-Crafts using the complex ($ZnCl_2$-DMF).[11,12] However, under these conditions, the yields (Table II) of the corresponding 6-acyl-derivatives were lower than those of the present method. The comparative yields obtained by the zinc chloride-*N*,*N*-dimethylformamide method and Fries-like reaction using zinc chloride for similar compounds are summarized in Table II.

CONCLUSION

The rearrangement of 3-acyl-2(3H)-benzothiazolones to the 6-position of the heterocycle catalyzed by $ZinCl_2$ appears to be parallel to that with $AlCl_3$. In Fries-like rearrangement, the 3-acyl-2(3H)-benzothiazolones at the temperature of 155°C in the presence of 3 equivalents of zinc chloride as a catalyst gave the 6-acyl-2(3H)-benzothiazolones in high yields (82–94%). The 6-acyl-derivatives can be obtained by the reaction of 2(3H)-benzothiazolone with acid halides and the complex of ($ZnCl_2$-DMF). However, the yields in these conditions are lower than that in the present method. From these results, it appears that this method can be an alternative to the former acylation procedures of 2(3H)-benzothiazolone.

Experimental

Melting points were determined using an electrothermal melting point apparatus and are uncorrected. The IR spectra were recorded on a

spectrometer Shimadzu Chart 200-91538 and the ^{1}H-NMR spectra were recorded on a Bruker AC 250 spectrometer (250 MHz) using Me_2SO-d_6. Chemical shifts (δ) are reported in ppm with tetramethylsilane as internal standard. Elemental analysis were performed by the Ecole Nationale Supérieure de Chimie Montpellier. France. The compounds were pure in T.L.C. (Merck silica gel. 60_{254}. ethylacetate/cyclohexane, 3/2, v/v).

Procedures for the Synthesis of 3-Acyl-2(3H)-benzothiazolones (2a–f)

Method C (2a–b). A solution of 2(3H)-benzothiazolone (0.0145 mmol) in acetic or propionic anhydride (20 ml) was refluxed for 3 h. After cooling, the resulting solution was evaporated in the vacuum and the residue recrystallized from ethanol. The physical properties (mp, IR, ^{1}H-NMR) are in accordance with published data.[11]

Method D (2c–f). To a solution of (0.015 mmol) 2(3H)-benzothiazolne in 30 ml of dimethylformamide was added sodium ethylate (0.017 mmol). Then added dropwise a solution of acid halides dissolved in a minimum of dimethylformamide. The reaction mixture was heated at the temperature of 75°C under stirring during a period of 4 h. After cooling, ice water was added and the muxture stirred for 1 h. Then filtered and washed with a solution of 10% of ($NaHCO_3$), finally washed with water and dried. Recrystallized from ethanol. The following examples demonstrate the procedure.

3-(4-Chloro)-benzoyl-2(3H)-benzothiazolone (2d). m.p. 108–110°C, IR (KBr): 1660 cm^{-1}, (C=O. lactan), 1630 cm^{-1}, (C=O); ^{1}H-NMR. (250 MHz, DMSO-D_6): 7,29 (2H, m), 7,46 (3H, m), 7,60 (dd, 1H, J = 1,6, 8,4 Hz), 7,81 (2H, dd, J = 1,6, 8,4 Hz).

3-(4-Nitro)-benzoyl-2(3H)-benzothiazolone (2e). m.p. 160–161°C, IR (KBr): 1665 cm^{-1}, (C=O. lactan), 1630 cm^{-1}, (C=O); ^{1}H-NMR. (250 MHz, DMSO-D_6): 7,40 (2H, m), 7,77 (1H, d, J = 8,6 Hz), 7,86 (1H, d, J = 8,6 Hz), 8,10 (2H, d, J = 8,4 Hz), 8,30 (2H, m).

General Procedure for the Reaction of 3-Acyl-2(3H)-benzothiazolones by Fries-like Rearrangement Using Zinc Chloride

Zinc chloride (0.111 mmol, 15,127 g) and (0.037 mmol) of 3-acyl-2(3H)-benzothiazolone (**2a–f**) were placed in a three necked round bottom flask (100 ml) with a reflux condenser and a $CaCl_2$ tube. The reaction medium was heated for 3 h at 155°C under stirring. After cooling,

the dark complex was decomposed by addition of water and 2 ml of 1N HCl. The resulting precipitate was stirred for 30 min, filtered, washed with water, dried, and recrystallized from ethanol. The following examples demonstrate the procedure.

6-Acetyl-2(3H)-benzothiazolone (3a). IR (KBr): 3160 cm^{-1} (NH), 1700 cm^{-1}, (C═O. lactan), 1660 cm^{-1}, (C═O); ^{1}H-NMR. (250 MHz, DMSO-D_6): 2.57 (3H, s), 719 (1H, d, J = 8.4 Hz), 7.88 (1H, dd, J = 1,6, 8,4 Hz), 8,23 (1H, d, J = 1,6 Hz), 12.18 (1H, s, broad). Anal: Calcul: C, 55,94, H, 3,64, N, 7.25. Found: C, 55,76, H, 3,64, N, 7,28.

6-Benzoyl-2(3H)-benzothiazolone (3c). IR (KBr, ν cm^{-1}); 3220 cm^{-1}, (NH), 1680 cm^{-1}, 1630 cm^{-1}, (C═O); ^{1}H-NMR (250 MHz, DMSO-D_6): 7,23 (d, 1H, J = 8,4 Hz), 7,58 (m, 6H), 8,00 (d, 1H, J = 1,6 Hz), 12 (s, 1H, NH). Anal: Calcul: C, 65,87, H, 3,54, N, 5,48. Found: C, 65,69, H, 3,60, N, 5,39.

6-(4-Chloro)-benzoyl-2(3H)-benzothiazolone (3d). IR (KBr, ν cm^{-1}); 3160 cm^{-1}, (—NH), 1680 cm^{-1}, 1630 cm^{-1}, (C═O); ^{1}H-NMR (250 MHz, DMSO-D_6): 7,24 (d, 1H, J = 8,4 Hz), 7,58 (m, 2H), 7,68 (dd, 1H, J = 1,6 Hz), 7,74 (m, 2H), 8,01 (d, 1H, J = 1,6 Hz), 12 (s, 1H, NH). Anal: Calcul: C, 58,03, H, 2,78, N, 4,83. Found: C, 57,84, H, 2,81, N, 4,99.

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