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Heterocycles LXXI. *Sommelet* and *Kröhnke* Reactions in the Series of 2,4′-Bisthiazoles

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Summary. The synthesis of some 4-formyl-2′-aryl-2,4′-bisthiazoles by the methods of *Sommelet* and *Kröhnke* is described. The *Sommelet* reaction attacks position 4 of the thiazolic ring.

Keywords. 2,4′-Bisthiazoles; *Kröhnke*; *Sommelet*; Nitrones.

Heterocyclen, 71. Mitt. Anwendung der *Sommelet*- und *Kröhnke*-Reaktionen auf 2,4′-Bisthiazole

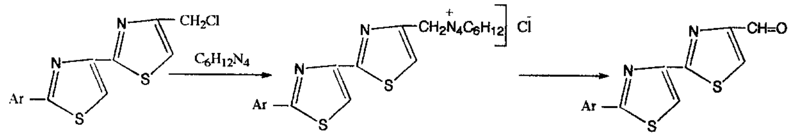
Zusammenfassung. Die Synthese einiger 4-Formyl-2′-aryl-2,4′-bisthiazole wird beschrieben. Die *Sommelet*-Reaktion greift die Position 4 des Thiazolrings an.

Introduction

Our previous studies were concerned with the application of the *Sommelet* [1–3] and *Kröhnke* [4] reactions in the field of heteroaromatic compounds and with the formylation of the corresponding halomethyl derivates [5–10]. The *Sommelet* reaction may be used only for heteroarenes with the halomethyl group attached to a carbon atom having an electron density similar to that of the carbon atoms of the benzene ring, whereas the *Kröhnke* reaction may be applied to carbon atoms with electron deficiency, for instance for position 2 of 1,3,4-thiadiazole [11]. This paper presents comparative studies of the two related reactions, concerning the possibility of their application to reactions at position 4 of the 2′-aryl-4-chloromethyl-2,4′-bisthiazolic system.

Results and Discussions

In a previous paper [12], we reported the synthesis of some 2′-aryl-4-chloromethyl-2,4′-bisthiazoles with substituents with different electronic effects in *para* position of the phenyl ring (**1**). The *Sommelet* reaction allowed the synthesis of 4-formyl-2′-aryl-2,4′-bisthiazoles (**3**) with 50–60% yields (Scheme 1). The urotropinium salts **2** were obtained by treating the chloromethyl-bisthiazoles **1** with urotropine in warm chloroform. Hydrolysis of the urotropinium salts was performed with 50% acetic acid.

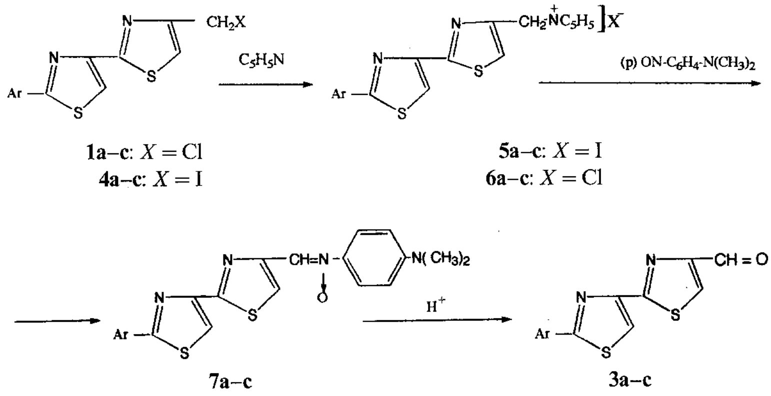


1a–f 2a–f 3a–f

1, 2, 3	a	b	c	d	e	f
Ar	C_6H_5	p-$C_6H_4CH_3$	p-C_6H_4Cl	p-C_6H_4Br	p-$C_6H_4CF_3$	p-$C_6H_4OCH_3$

Scheme 1

The synthesis of aldehydes **3a**–**c** was performed by means of the *Kröhnke* reaction (Scheme 2), starting from 2′-aryl-4-chloromethyl-2,4′-bisthiazoles **1** or from 2′-aryl-4-iodomethyl-2,4′-bisthiazoles **4**. The pyridinium salts **5** and **6** were obtained from compounds **1** and **4** with pyridine, affording better results in chloroform than in anhydrous ethanol. The pyridinium salts were then transformed to nitrones **7** with *p*-nitrosodimethylaniline. Acidic hydrolysis of the nitrones resulted in 4-formyl-bisthiazoles **3**; their reaction with 2,4-dinitrophenylhydrazine gave 2,4-dinitrophenylhydrazones **9a**–**c**, corresponding to aldehydes **3**. This last reaction may be used for the identification of the nitrones.



1a–c: $X = Cl$
4a–c: $X = I$

5a–c: $X = I$
6a–c: $X = Cl$

7a–c 3a–c

1, 4, 5, 6, 7	a	b	c
Ar	C_6H_5	p-$C_6H_4CH_3$	p-C_6H_4Cl

Scheme 2

In order to characterize the bisthiazolic aldehydes **3**, the corresponding oximes **8a**–**c** were prepared. The characterization of the aldehydes and nitrones was performed by means of IR and UV spectroscopy. In the IR spectra, the characteristic frequencies of the C=O group appear between 1670–1700 cm^{-1}, a values which is influenced by *R* in accordance with the values of 2-aryl-4-formyl-thiazoles [5].

The application of the *Sommelet* and *Kröhnke* reactions in the series of 2′-aryl-4-halomethyl-2,4′-bisthiazoles illustrates the possibility of the introduction of a formyl group in position 4 of the 2,4'-bisthiazolic ring. It appears that, contrary to a previous statement [13], the *Sommelet* reaction may be applied for reactions at position 4 (α with respect to the nitrogen atom) of the thiazolic system. Comparing the result obtained by the two types of reactions, it is obvious that the use of the *Sommelet* reaction results in both higher yields and purities.

Experimental

Melting points are uncorrected. IR spectra were run on a FT-IR NICOLET 205 instrument, UV spectra on a UV-VIZ-ULTROSPEC III instrument.

4-Hexamethylenetetramonium-2'-aryl-2,4'-bisthiazole chlorides (**2a**–**f**)

0.005 moles of **1a**–**f** dissolved in the minimum amount of chloroform and 0.006 moles of hexamethylenetetramin were refluxed for 1 hour. After cooling, the compounds were filtered and washed with ether.

2a: Ar = C_6H_5; m.p.: 189–192 °C; $C_{19}H_{21}ClN_6S_2$ (432.99)[1]; **2b**: Ar = *p*-$C_6H_4CH_3$; M.p.: 212–213 °C; $C_{20}H_{23}ClN_6S_2$ (447.02); **2c**: Ar = *p*-C_6H_4Cl; M.p.: 199–201 °C; $C_{19}H_{20}Cl_2N_6S_2$ (467.43); **2d**: Ar = *p*-C_6H_4Br; M.p.: 202–205 °C; $C_{19}H_{20}BrClN_6S_2$ (511.88); **2e**: Ar = *p*-$C_6H_4CF_3$; M.p.: 193–195 °C; $C_{20}H_{20}ClF_3N_6S_2$ (501); **2f**: Ar = $C_6H_4OCH_3$; M.p.: 185–189 °C; $C_{20}H_{23}ClN_6OS_2$ (436.01).

4-Formyl-2'-aryl-2,4'-bisthiazoles (**3a**–**f**)

1 g **2a**–**f** and 1 g hexamethylenetetramin were boiled for 1 h in 20 ml of 50% acetic acid. After cooling, the compounds were filtered and recrystallized.

3a: Ar = C_6H_5; M.p.: 153–155 °C (ethanol); $C_{13}H_8N_2OS_2$ (272.35); IR (KBr): $\nu(C{=}O) = 1689\,cm^{-1}$; UV ($CH_3OH$): $\lambda_{max} = 309$ nm; **3b**: Ar = *p*-$C_6H_4CH_3$; M.p.: 128–130 °C (ethanol); $C_{14}H_{10}N_2OS_2$ (286.4); IR (KBr): $\nu(C{=}O) = 1670\,cm^{-1}$; UV ($CH_3OH$): $\lambda_{max} = 323.5$ nm; **3c**: Ar = *p*-C_6H_4Cl. M.p.: 190 °C (ethanol); $C_{13}H_7ClN_2OS_2$ (306.79); IR (KBr): $\nu(C{=}O) = 1693\,cm^{-1}$; UV ($CH_3OH$): $\lambda_{max} = 335$ nm; **3d**: Ar = *p*-C_6H_4Br; M.p.: 210 °C (ethanol); $C_{13}H_7BrN_2OS_2$ (351.24); IR (KBr): $\nu(C{=}O) = 1698\,cm^{-1}$; UV ($CH_3OH$): $\lambda_{max} = 332$ nm; **3e**: Ar = *p*-$C_6H_4CF_3$; M.p. 195 °C (ethanol); $C_{14}H_7F_3N_2OS_2$ (340.33) IR (KBr): $\nu(C{=}O)$ $1700\,cm^{-1}$; UV (CH_3OH): $\lambda_{max} = 327$ nm; **3f**: Ar = *p*-$C_6H_4OCH_3$; M.p.: 175–178 °C (ethanol); $C_{14}H_{10}N_2O_2S_2$ (302.4); IR (KBr): $\nu(C{=}O) = 1677\,cm^{-1}$; UV ($CH_3OH$): $\lambda_{max} = 322$ nm.

4-Pyridinium-methyl-2'-aryl-2,4'-bisthiazole iodides (**5a**–**c**) *and chlorides* (**6a**–**c**)

5a–**c**: 0.001 moles of **4a**–**c** in 10 ml chloroform were refluxed for 1 h with 0.1 ml pyridine. After cooling, the compounds were filtered and washed with ether.

6a–**c**: 0.001 moles of **1a**–**c** in 10 ml chloroform were refluxed for 3 h with 0.1 ml pyridine. After cooling, the compounds were filtered and washed with ether.

5a: Ar = C_6H_5; M.p.: 216 °C; $C_{18}H_{14}IN_3S_2$ (463.36);
5b: Ar = *p*-$C_6H_4CH_3$; M.p.: 210 °C; $C_{19}H_{16}IN_3S_2$ (477.38);
5c: Ar = *p*-C_6H_4Cl; M.p.: 240 °C; $C_{18}H_{13}ClIN_3S_2$ (497.8);
6a: Ar = C_6H_5; M.p.: 210 °C; $C_{18}H_{14}ClN_3S_2$ (371.91);
6b: Ar = *p*-$C_6H_4CH_3$; M.p.: 202–204 °C; $C_{19}H_{16}ClN_3S_2$ (385.9);
6c: Ar = *p*-C_6H_4Cl; M.p.: 213–215 °C; $C_{18}H_{13}Cl_2N_3S_2$ (406.35).

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[1] All compounds gave satisfactory elemental analyses (C, H, N).

4-(N-(p-dimethylanilino)-N-oxoiminomethylen)-2′-aryl-2,4′-bisthiazoles (**7a–c**)

0.001 moles of **5a**–**c** or **6a**–**c** dissolved in 10 ml anhydrous ethanol, 0.1 ml of pyridine, and 0.0012 moles of *p*-nitrosodimethylaniline dissolved in 2 ml anhydrous ethanol were boiled for 2 h. After cooling, the compounds were filtered and recrystallized.

7a: Yellow crystals; Ar = C_6H_5; M.p.: 202–204 °C (ethanol); $C_{21}H_{18}N_4OS_2$ (406.53); IR (KBr): ν(C=N) = 1649 cm^{-1}, UV (CH_3OH): λ_{max} = 381 nm; **7b**: yellow crystals; Ar = *p*-$C_6H_4CH_3$; M.p.: 228–230 °C (ethanol); $C_{22}H_{20}N_4OS_2$ (420.56); IR (KBr): ν(C=N) = 1645 cm^{-1}; UV (CH_3OH): λ_{max} = 384 nm; **7c**: yellow crystals; Ar = *p*-C_6H_4Cl; M.p.: 273 °C (ethanol); $C_{21}H_{17}ClN_4OS_2$ (440.97); IR: ν(C=N) = 1651 cm^{-1}; UV (CH_3OH): λ_{max} = 389 nm.

4-Formyl-2′-aryl-2,4′-bisthiazoles (**3a**–**c**)

0.2 g of **7a**–**c** with 1 ml conc. hydrochloric acid were refluxed for 5 min. After cooling and dilution with 1 ml water, the compounds were filtered and recrystallized.

3a: Ar = C_6H_5; M.p.: 153 °C (ethanol); $C_{13}H_8N_2OS_2$ (272.35); IR (KBr): 1688 cm^{-1}; UV (CH_3OH): λ_{max} = 310 nm; **3b**: Ar = *p*-$C_6H_4CH_3$; M.p.: 130–132 °C (ethanol); $C_{14}H_{10}N_2OS_2$ (286.4); IR (KBr): 1672 cm^{-1}; UV (CH_3OH): λ_{max} = 325.5 nm; **3c**: Ar = *p*-C_6H_4Cl; M.p.: 190 °C (ethanol); $C_{13}H_7ClN_2OS_2$ (306.79); IR (KBr): 1693 cm^{-1}; UV (CH_3OH): λ_{max} = 331 nm.

4-Formyl-2′-aryl-2,4′-bisthiazolic oximes (**8a**–**c**)

0.001 moles of **3a**–**c** dissolved in 3 ml ethanol, 0.0015 moles of hydroxylamine hydrochloride, and 0.0015 moles of sodium acetate dissolved in 2 ml water were warmed for 10 minutes and then poured in water. The compounds were filtered and recrystallized.

8a: Ar = C_6H_5; M.p.: 198–200 °C (ethanol); $C_{13}H_9N_3OS_2$ (287.36); IR (KBr): ν(C=N) = 1630 cm^{-1}; UV (CH_3OH): λ_{max} = 330 nm; **8b**: Ar = *p*-$C_6H_4CH_3$; M.p.: 193–195 °C (ethanol); $C_{14}H_{11}N_3OS_2$ (301.37); IR (KBr): ν(C=N) = 1633 cm^{-1}; UV (CH_3OH): λ_{max} = 333.4 nm; **8c**: Ar = *p*-C_6H_4Cl; M.p.: 204 °C (ethanol); $C_{13}H_8ClN_3OS_2$ (321.8); IR (KBr): ν(C=N) = 1640 cm^{-1}; UV (CH_3OH): λ_{max} = 337 nm.

2,4-Dinitrophenylhydrazones of 4-Formyl-2′-aryl-2,4′-bisthiazoles (**9a**–**c**)

0.001 moles of **3a**–**c** were dissolved in 5 ml cooled ethanol. 0.001 moles of 2,4-dinitrophenylhydrazone dissolved in a mixture of 1 ml conc. sulfuric acid, and 4 ml ethanol were added. After 1 hour, the precipitates were filtered and recrystallized.

9a: Ar = C_6H_5; M.p.: 263 °C (acetic acid); $C_{19}H_{12}N_6O_4S_2$ (452.47); **9b**: Ar = *p*-$C_6H_4CH_3$; M.p.: 241 °C (acetic acid); $C_{20}H_{14}N_6O_4S_2$ (466.48); **9c**: Ar = *p*-C_6H_4Cl; M.p.: 241 °C (acetic acid); $C_{18}H_{11}ClN_6O_4S_2$(486.9).

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