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1,6-Dialkoxy-3,4-diones **3** are easily accessible by acylation of enol ethers **1** with oxalyl chloride and subsequent elimination of hydrogen chloride using triethylamine. The open-chain 2,5-dimethyl derivative **3b** is converted with amidines **4a-c** and *S*-methylisothiourea (**4d**), respectively, to give 2,2'-disubstituted 5,5'-dimethyl-4,4'-bipyrimidines **5a-d**. The dihydrofuran and dihydropyran derivatives **3c** and **3d**, however, react with benzamidine (**4c**) in dimethylformamide only in the presence of calcium hydride as condensation agent yielding 5,5'-bis(2-hydroxyethyl)- and 5,5'-bis(3-hydroxypropyl)-2,2'-diphenyl-4,4'-bipyrimidine **6a** and **b**.

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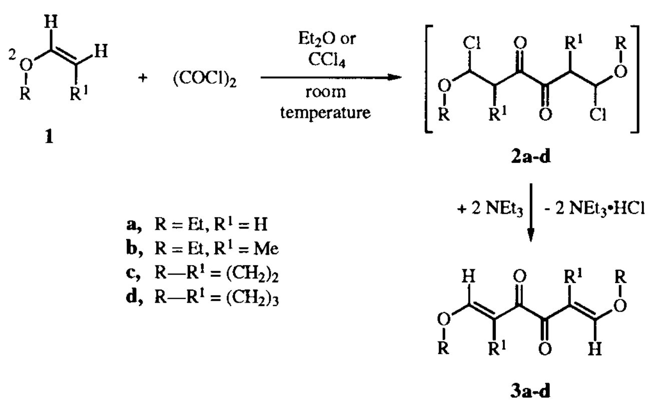
1,6-Diethoxy-1,5-hexadiene-3,4-dione (**3a**) is accessible in good yields by reaction of vinyl ethyl ether with oxalyl chloride and subsequent elimination of hydrogen chloride using a tertiary amine [3]. As a 1,3,4,6-tetracarbonyl compound, with two potential aldehyde functions in the 1,6 and two keto groups in 3,4 positions, **3a** is of particular interest as a starting compound for the preparation of heterocycles. Reactions of **3a** with amidines or thiourea and hydrazines as a twofold 1,3-dicarbonyl compound to give 4,4'-bipyrimidines and bipyrazoles, respectively, are reported [3]. As 1,6-dicarbonyl compound **3a** reacts with primary amines to give azepine-4,5-diones which are suitable starting compounds for the synthesis of fused heterocycles containing an azepine ring [1].

In the present paper we report on the extension of the synthetic potential of acylation products derived from various enol ethers and oxalyl chloride, particularly for the synthesis of 5,5'-disubstituted 4,4'-bipyrimidines.

Acylation of Enol Ethers with Oxalyl Chloride.

The acylation of vinyl ethyl ether (**1a**) and 3,4-dihydro-2*H*-pyran (**1d**) with oxalyl chloride is described [3]. As expected, also ethyl propenyl ether (**1b**) and 2,3-dihydrofuran (**1c**) react with oxalyl chloride yielding the addition products **2b** and **2c** which, however, were not isolated. By elimination of hydrogen chloride from **2b-d** using triethylamine 1,6-dialkoxy-3,4-diones **3b-d** are formed in good yields (Scheme 1, Table 1). The ^{1}H nmr spectroscopic studies of the dihydropyran intermediate **2d** indicate that a stereospecific *cis* addition of oxalyl chloride to **2d** occurs where the conformation with chlorine in the axial and the keto group in the equatorial position dominates [4]. Surprisingly, compounds **3c** and **3d** differ significantly in color: in contrast to the colorless dihydropyran derivative **3d** the dihydrofuran product **3c** is intensively yellow colored. It was shown by spectroscopic studies and by crystal structure determination that **3c** exists to a large extent in an antiperiplanar conformation whereas both chromophores in **3d** are twisted against each other [5].

Scheme 1



Synthesis of 2,2',5,5'-Tetrasubstituted 4,4'-Bipyrimidines **5**, **6**.

In recent years 4,4'-bipyrimidines have gained increasing interest as complexing agents for various metal ions [6,7], and they are also discussed as products of the irradiation of nucleic acids [8]. 4,4'-Bipyrimidines have been prepared mainly *via* coupling reactions of two pyrimidine moieties which are also used for the preparation of biaryls. Besides the classical Ullmann reaction [9] nickel and palladium catalyzed [10] coupling reactions are described. The oxidation of the dihydro intermediates derived from the addition of metalated pyrimidines to pyrimidines affords also 4,4'-bipyrimidines [11]. Unsymmetrical 4,4'-bipyrimidines are obtained from pyrimidines, containing a substituent with a β-dicarbonyl function in the 4 position, *via* a condensation reaction with guanidine or urea [12]. We have already shown that 2,2'-disubstituted 4,4'-bipyrimidines are easily accessible starting from compound **3a** with amidines and thiourea, respectively [3]. A comparable synthesis of 6,6'-diethoxy-2,2'-diphenyl-4,4'-bipyrimidines starting from the acylation product of a ketene acetal with oxalyl chloride was described by H.-D. Stachel [13].

With the newly synthesized tetracarbonyl compounds **3b-d** we have now investigated the synthesis of 5,5'-disubstituted 4,4'-bipyrimidines. Of particular interest is the steric influence of the substituents in the 5 and 5' positions

Table 1

Acylation of Enol Ethers **1** with Oxalyl Chloride at Room Temperature to Open-chain and Cyclic Bis(β-alkoxyvinylketones) **3**, Respectively

	Enol Ethers 1					Bis(alkoxyvinylketones) 3		
1	R=	R[1]=	Reaction Time (h)	Solvent	**3**	Yield (%)	mp (°C)	Ref
a	Et	H	19 (1)	Et_2O	**a**	75 (1)	53-54	[1,3]
b	Et	Me	27.5	Et_2O	**b**	53	123	
c	—$(CH_2)_2$—		25.5	CCl_4	**c**	86	155.5-156	
d	—$(CH_2)_3$—		25.0	CCl_4	**d**	56	114	[3,4]

on the conformation of 4,4'-bipyrimidines and the therefore resulting change of complex stability with metal ions [7]. As described for **3a** [3] the 2,5-dimethyl derivative **3b**, which differs only slightly in structure, can easily be converted with the amidines **4a-c** and *S*-methylisothiourea (**4d**) yielding the 2,2'-disubstituted 5,5'-dimethyl-4,4'-bipyrimidines **5a-d** (Scheme 2, Table 2). The reactions of the dihydrofuran and dihydropyran derivatives **3c** and **3d** with amidines, however, are much more complicated. Therefore we have optimized the reaction parameters for the condensation of **3d** with benzamidine (**4c**). The best conditions for this condensation are the following: dimethylformamide as solvent, addition of calcium hydride for removing the water formed during the condensation in the reaction medium, a reaction temperature of 70° and addition of sodium methanolate in the molar ratio **3d**:**4c**:sodium methanolate = 1:3:0.4. By applying the optimized reaction conditions we obtained the bipyrimidines **6a** and **6b** in satisfactory yields (Scheme 3). In the reaction of **3d** with **4c** we have also isolated and characterized the 1:1 reaction product **7** (Scheme 3). The formation of by-products in the synthesis of **6** can be referred predominantly to hydrolysis reactions. Compound **7** can react with water resulting from the condensation reaction. By elimination of water with calcium hydride the formation of by-products is suppressed. The condensation reaction of **3c** and **3d** with benzamidine (**4c**) should be applicable without difficulties also to other amidines or *S*-methylisothiourea (**4d**).

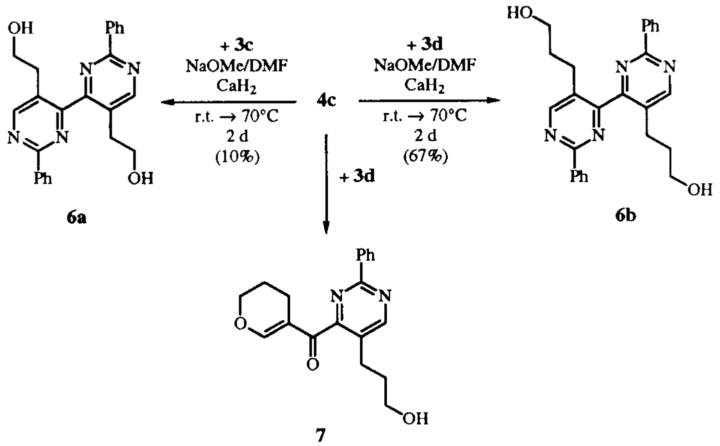
5,5'-Disubstituted 4,4'-bipyrimidines **5** are now easily accessible in a two-step reaction starting from enol ethers **1** *via* the acylation products **3** with oxalyl chloride. With the cyclic enol ethers dihydrofuran (**1c**) and dihydropyran (**1d**), substituents with a primary alcohol function are introduced in 5 position of the bipyrimidines **6**, which are of great interest for further functionalization of the 5 positions in the bipyrimidines **6**.

Table 2

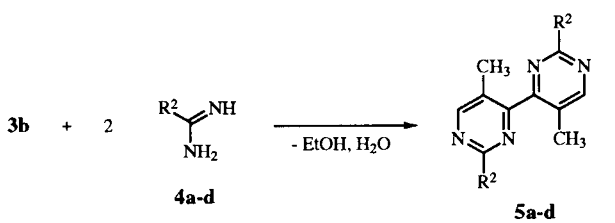
Conversion of 1,6-Diethoxy-2,5-dimethyl-1,5-hexadiene-3,4-dione (**3b**) with Amidines **4a-c** and *S*-Methylisothiourea (**4d**) to 2,2'-Disubstituted 5,5'-Dimethyl-4,4'-bipyrimidines **5a-d**

	Amidines 4	Reaction Conditions			4,4'-Bipyrimidines 5	
4	R[2] =	Time (d)	Temp (°C)	**5**	Yield (%)	mp (°C)
a	H	4.5	-10	**a**	48	147-147.5
b	CH_3	5	-20	**b**	40	147
c	C_6H_5	4	-10	**c**	65	197
d	SCH_3	6	-20	**d**	23	169.5-170 dec

Scheme 3



Scheme 2



4, 5	R[2]
a	H
b	Me
c	Ph
d	SMe

EXPERIMENTAL

All melting points are determined on a Büchi SMP 20 and are uncorrected. The ^1H nmr spectra are recorded on a Bruker HX 90 and CXP 300 at 90 and 300 MHz with tetramethylsilane (TMS) as the internal standard. For column chromatography glass columns with different volumes are used; silica gel 60, size 0.040-0.063 mm from Macherey and Nagel, basic aluminium oxide Alumina Woelm B Super I from Woelm. The mplc was performed using the system developed by Glatz [14]. All solvents are purified and dried as described in the literature.

General Procedure for the Preparation of **3b** and **c**.

At room temperature **1** (150 mmoles of **1b** or 30 mmoles of **1c**) was added dropwise with stirring within 30-50 minutes to a solution of oxalyl chloride (50 mmoles for **3b** or 10 mmoles for **3c**) in diethyl ether (150 ml) or carbon tetrachloride (20 ml), and the reaction mixture was stirred for additional 5.5 (**3b**) or 2.5 hours (**3c**). Then triethylamine (150 mmoles for **3b** or 30 mmoles for **3c**) was added dropwise within 80 (**3b**) or 35 minutes (**3c**) and the reaction mixture stirred for additional 20-22 hours. Triethylamine hydrochloride was filtered off, the filtrate was concentrated *in vacuo* and filtered off. The combined solids were washed with sodium bicarbonate solution and water to remove triethylamine hydrochloride. The remaining solid was dried *in vacuo* and chromatographed to give **3b** or **3c**.

1,6-Diethoxy-2,5-dimethyl-1,5-hexadiene-3,4-dione (**3b**).

This compound was chromatographed on aluminium oxide with ethyl acetate and obtained as colorless needles; ^{1}H nmr (deuteriochloroform): δ 1.34 (t, 6H, CH_2CH_3, J = 7.1 Hz), 1.77 (d, 6H, CH_3, ^{4}J = 1.1 Hz), 4.10 (q, 4H, CH_2CH_3), 7.17 (q, 2H, CH).

Anal. Calcd. for $C_{12}H_{18}O_4$: C, 63.70; H, 8.02. Found: C, 63.62; H, 8.00.

1,2-Bis(4,5-dihydrofuran-3-yl)ethane-1,2-dione (**3c**).

This compound was chromatographed on silica gel with ethyl acetate and obtained as yellow crystals; ^{1}H nmr (deuteriochloroform): δ 2.93 (t, 4H, OCH_2CH_2, J = 10.0 Hz), 4.63 (t, 4H, OCH_2CH_2), 7.93 (s, 2H, CH).

Anal. Calcd. for $C_{10}H_{10}O_4$: C, 61.85; H, 5.19. Found: C, 61.63; H, 5.14.

General Procedure for the Preparation of 2,2'-Substituted 5,5'-Dimethyl-4,4'-bipyrimidines **5a-d**.

At 0 to -10° a solution of sodium ethanolate in ethanol was slowly added dropwise to a stirred solution of amidine acetate (**4a**), amidine hydrochloride (**4b,c**) or amidine sulfate (**4d**) and after 1-2 hours the precipitated corresponding sodium salt was filtered off. To the filtrate a solution of **3b** (1.13 g, 5 mmoles) in 70 ml of methanol or 60 ml of ethanol/50 ml of methanol (**5b**) was added dropwise with stirring at the given temperature (Table 3). After standing at the given temperature and time (Table 2) the precipitate was filtered off, the filtrate concentrated and filtered. The combined precipitates were washed with small amounts of ethanol.

5,5'-Bis(2-hydroxyethyl)-2,2'-diphenyl-4,4'-bipyrimidine (**6a**).

To a stirred suspension of sodium methanolate (10.8 mg, 0.2 mmole) in 2 ml of dimethylformamide (DMF) at room temperature a solution of **4c** (180.2 mg, 1.2 mmoles) in 6 ml of DMF was added followed by addition of calcium hydride (84.2 mg, 2.0 mmoles) and a solution of **3c** (97.1 mg, 0.5 mmole) in 9 ml of DMF. After stirring at 70° for 2 days the reaction mixture was neutralized (*p*H 6) with methanolic hydrogen chloride, filtered through a silica gel column with methanol and the eluate evaporated *in vacuo*. The residue was mixed with dichloromethane, filtered off, and the filtrate was concentrated and chromatographed on silica gel with ethyl acetate and ethyl acetate/acetone (7:3). The resulting yellow solid was purified by digesting with 4 ml of ethyl acetate/petroleum ether (1:1), filtration and digesting with acetone to give **6a** as a colorless solid, 20.0 mg (10%), mp 169.5°; ^{1}H nmr (DMSO-d_6): δ 2.80 (t, 4H, pyrimidine-CH_2, J = 6.5 Hz), 3.61 (m, 4H, CH_2OH), 4.75 (t, 2H, OH, J = 5.0 Hz), 7.56 (m, 6H, *m*-, *p*-Ph), 8.40 (m, 4H, *o*-Ph), 9.05 (s, 2H, pyrimidine).

5,5'-Bis(3-hydroxypropyl)-2,2'-diphenyl-4,4'-bipyrimidine (**6b**).

A solution of **4c** (90.1 mg, 0.57 mmole) in 3 ml of DMF and sodium methanolate (5.4 mg, 0.1 mmole) in 1 ml of DMF was added at room temperature to calcium hydride (42.1 mg, 1.0 mmole). Then a solution of **3d** (55.1 mg, 0.25 mmole) in 3 ml of DMF was added dropwise with stirring and the reaction mixture was heated to 70° for 2 days. The reaction mixture was neutralized (*p*H 5-6) with methanolic hydrogen chloride and filtered through a silica gel column with ethyl acetate. The filtrate was evaporated *in vacuo* and the residue recrystallized from 350 ml water to give **6b**, 71.7 mg (67%), mp 124.5-125.5°; ^{1}H nmr (deuteriochloroform): δ 1.82 (m, 4H, $CH_2CH_2CH_2$), 2.20 (broad s, 2H, OH), 2.75 (t, 4H, pyrimidine-CH_2, J = 7.5 Hz), 3.52 (t, 4H, CH_2OH, J = 6.0 Hz), 7.47 (m, 6H, *m*-, *p*-Ph), 8.42 (m, 4H, *o*-Ph), 8.86 (s, 2H, pyrimidine).

Anal. Calcd. for $C_{26}H_{26}N_4O_2$: C, 73.22; H, 6.14; N, 13.14.

Table 3

Conversion of **3b** with **4a-d** to 2,2'-Disubstituted 5,5'-Dimethyl-4,4'-bipyrimidines **5a-d** and Physical Data

4	g (mmoles)	Na (g)/ EtOH (ml)	Reaction Temp (°C)	5	Yield g	Molecular Formula	Analysis (%) Calcd./Found C	H	N	S
a	3.12	0.69/	-10 → -20	a	0.45	$C_{10}H_{10}N_4$	64.50	5.41	30.09	
	(30.0)	12.5				(186.2)	64.52	5.51	29.96	
b	1.42	0.35/	-20 → -30	b	0.43	$C_{12}H_{14}N_4$	67.27	6.59	26.15	
	(15.0)	7.5				(214.3)	67.11	6.65	25.87	
c	2.35	0.35/	-10 → -20	c	1.10	$C_{22}H_{18}N_4$	78.08	5.36	16.56	
	(15.0)	15.0				(338.4)	78.01	5.25	16.40	
d	2.78	0.46/	0 → -20	d	0.32	$C_{12}H_{14}N_4S_2$	51.77	5.07	20.13	23.03
	(10.0)	16.0				(278.4)	51.82	5.23	20.03	22.53

^{1}H NMR (in $CDCl_3$) ppm

5a	2.28 (s, 6H, 5,5'-CH_3), 8.83 (s, 2H, 6,6'-H), 9.25 (s, 2H, 2,2'-H)
5b	2.17 (s, 6H, 5,5'-CH_3), 2.77 (s, 6H, 2,2'-CH_3), 8.52 (s, 2H, 6,6'-H)
5c	2.40 (s, 6H, 5,5'-CH_3), 7.54 (m, 6H, *m*-, *p*-Ph), 8.56 (m, 4H, *o*-Ph), 8.93 (s, 2H, 6,6'-H)
5d	2.20 (s, 6H, 5,5'-CH_3), 2.57 (s, 6H, SCH_3), 8.47 (s, 2H, 6,6'-H)

Found: C, 73.08; H, 6.10; N, 12.95.

(3,4-Dihydro-2*H*-pyran-5-yl) [5-(3-Hydroxypropyl)-2-phenylpyrimidin-4-yl] Ketone (**7**).

A solution of sodium (0.35 g, 15 mmoles) in 15 ml of ethanol was added dropwise at -10° to a stirred solution of **3d** (1.11 g, 5 mmoles) and **4c** (2.35 g, 15 mmoles) in 80 ml of ethanol. After stirring at -10° for 2 days the reaction mixture was filtered off and the filtrate concentrated. The residue, crystallized during drying *in vacuo*, was purified by mplc with acetone and acetone/ethyl acetate as eluents to give besides **6b**, compound **7** as colorless crystals, mp 105.5-107.5°; ^{1}H nmr (deuteriochloroform): δ 1.93 (m, 4H, 2 $CH_2CH_2CH_2$), 2.48 (t, 2H, CH_2), 2.73 (t, 3H, pyrimidine-CH_2, OH), 3.62 (t, 2H, CH_2OH, J = 6.0 Hz), 4.18 (t, 2H, CH_2OC, J = 5.0 Hz), 7.45 (m, 4H, *m*-, *p*-Ph, OCH), 8.41 (m, 2H, *o*-Ph), 8.76 (s, 1H, pyrimidine); ^{13}C nmr (deuteriochloroform): δ 61.0 (CH_2OH), 67.8 (CH_2OC), 192.9 (CO).

Anal. Calcd. for $C_{19}H_{20}N_2O_3$: C, 70.35; H, 6.21; N, 8.64. Found: C, 70.28; H, 6.28; N, 8.57.

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