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[A0065]

REARRANGEMENT OF HETEROCYCLES VIA-2-OXOKETENES

Synthesis and Rearrangement Reactions of Cross-Conjugated Mesomeric Pyridazino[2,3-*a*]pyrimidines [1]

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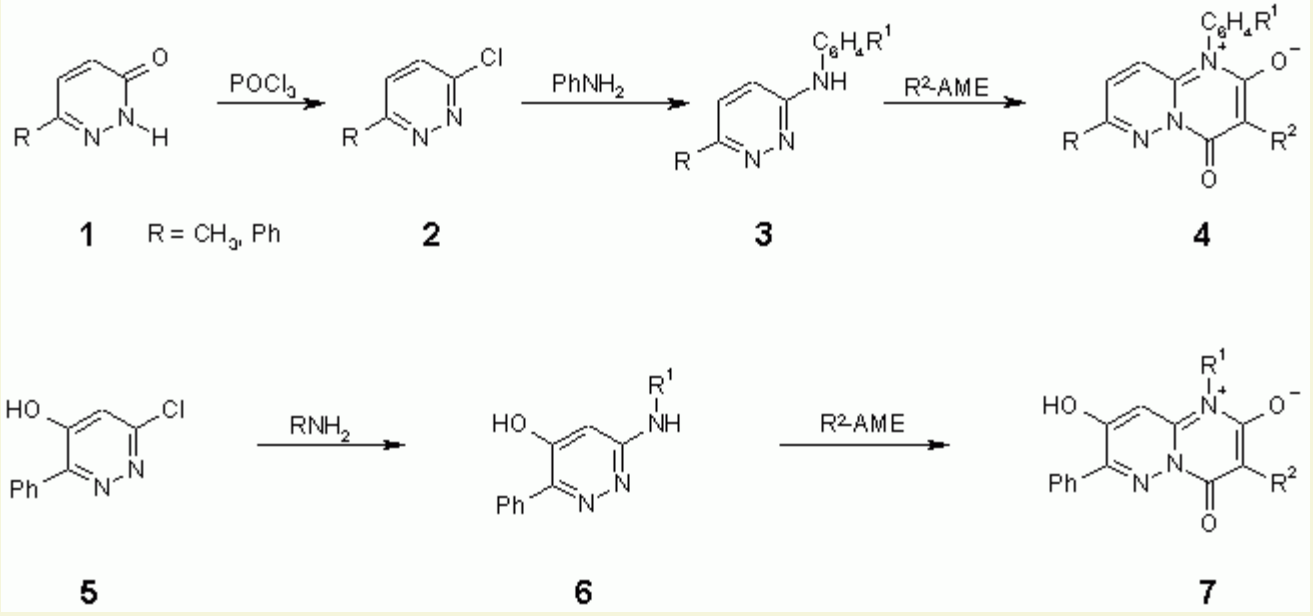
Cross-conjugated mesomeric betaines play an important role in heterocyclic synthesis. They can act as 1,4-dipoles in cycloaddition reactions or can be rearranged at higher temperatures to thermodynamically more stable compounds [2,3,4].

The rearrangement of cross-conjugated mesomeric pyrimidines has been extensively studied. When substituted on nitrogen with an aryl substitutent they can be rearranged to 2,3-disubstited 4-quinolones *via* unsaturated ?-lactame intermediates [2,3,5] (**type A rearrangements** [3])or *via* 2-oxoketenes to 4-hydroxy-2-quinolones (**type B rearrangements** [2]) [2,3,4,6]. In this paper we want to present **type B rearrangements** of pyridazino[2,3-a]pyrimidines in which the intermediate 2-oxoketene has two possibilities for ringclosure reactions to lead to thermodynamically more stable compounds. The thermolysis of pyrido[1,2-a]pyrimidines has been described before [6].

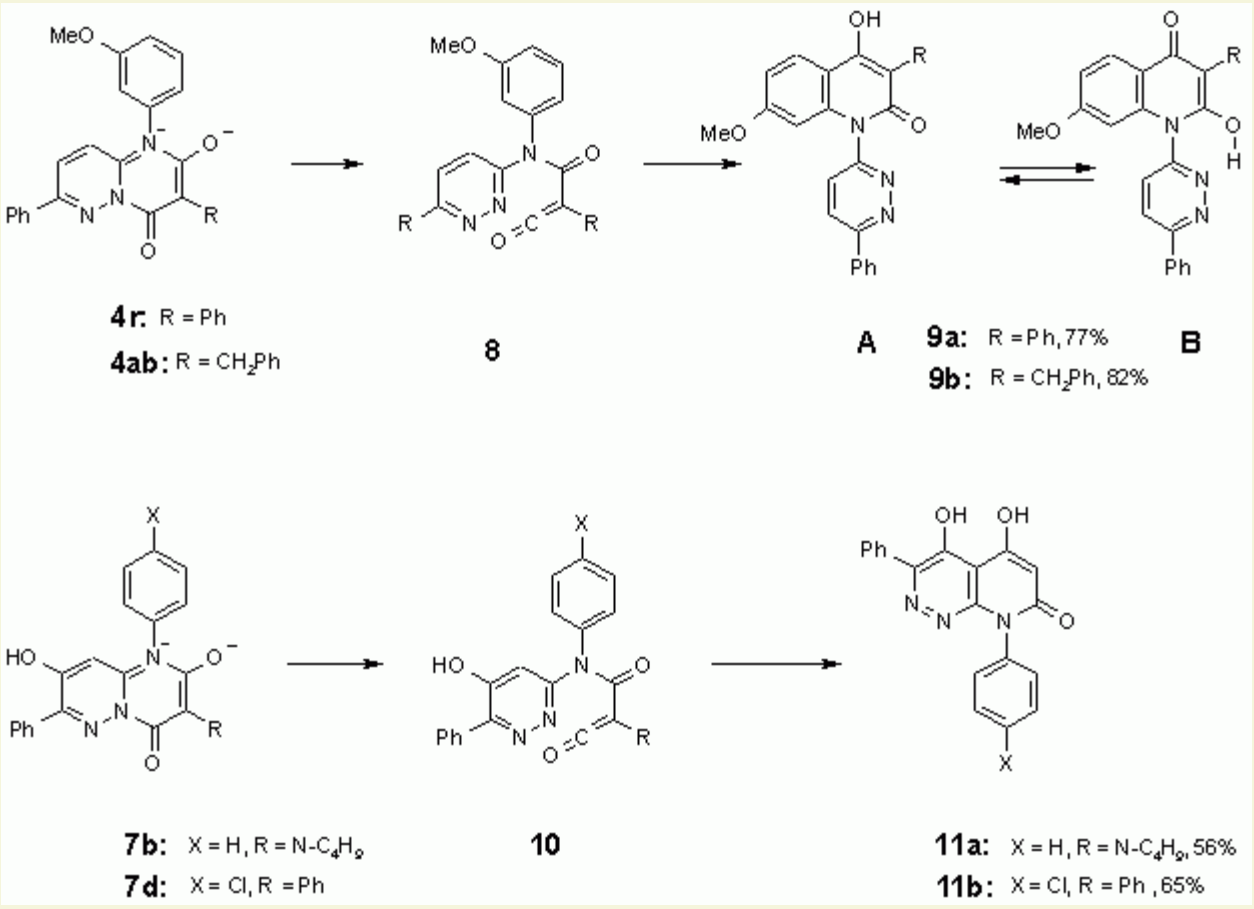
For this investigation two typs of pyridazino[2,3-a]pyrimidines were required. One with (the usual) electron-deficient pyridazine moiety (**4**) and one with with an electron rich pyridazine nucleus (**7**), i.e. with a high electron density at position 9 to allow an electrophilic attack of the expected ketene intermediate.

The synthesis of the mesoionic compounds **4** and **7** requires the 2-amino-pyridazines **3** and **6**. These compounds are readily available from the chloropyridazines **2** and **5** with the appropriate amine in boiling 1-propanol [7] or by heating in the amine itself without solvent [8], see Table 1. Compounds **2** (R=Me, Ph) were obtained from the corresponding lactams **1** in refluxing phosphorus oxychloride [7], while 3-chloro-5-hydroxy-6-phenyl-pyridazine **5** (which is an intermediate in the commercial synthesis of the herbicide PYRIDATE®) was provided by CHEMIE LINZ AG [9].

Scheme 1



The mesomeric betaines **4** and **7** were prepared from the amines **3** and **6** with the help of substituted bis-(2,4,6-trichlorophenyl)-malonates (AME?s, magic malonates) [10] by standard procedures. In order to prevent early thermal rearrangement we have choosen refluxing chlorobenzene (b.p. 132 °C) as reaction solvent. We have prepared 30 compounds of type **4** and 6 compounds of type **7** (see Table 2).



For preliminary testing of the rearrangement behavior of these mesoions we have selected two compounds of each series (Scheme 2). From the first series we have selected two compounds (**4r,ab**) both with a meta-methoxy

group in the N1-phenyl substituent in order to facilitate an electrophilic attack of the intermediate ketene at the para-position at the phenyl group. As expected, heating of **4r,ab** in boiling diphenyl ether (b.p. 250°) lead to the 4-hydroxy-2-quinolones **9a,b** (A) in 77% and 82% yield, respectively. The spectroscopic data suggest that compounds **9** exist (due to the formation of a hydrogen bridge between the OH group and a pyridazine nitrogen atom) predominatly in their tautomeric 2-hydroxy-4-quinolone form B. The outcome of the reaction is in complete analogy to the rearrangement of mesomeric pyrido[1,2-a]pyrimidines leading to N-pyridyl substituted 4-hydroxy-2-quinolones as describend by Lube [6]. Preliminary experiments (**DSC**) have shown that the presence of a methoxy group in para-position of the intermediate 2-oxo-ketene **8** seems not to be essential for the reaction pathway.

Quite different results are obtained in the thermolysis reaction of 8-hydroxy-pyridazino[2,3-a]pyrimidines **7b,d** . Under identical reaction conditions (boiling diphenyl ether) the pyrido[2,3-c]pyridazines **11a,b** are formed. The presence of the enol moiety in the intermediate ketene **10** makes the pyridazine nucleus more favorable for an electrophilic attack than the phenyl substituent at N, regardless if unsubstituted or bearing a chloro substituent. The structural formulas of the 2-oxo-ketenes **8** and **10** present the situation just after ringopening. However, they can existist in several rotameric or tautomeric (e.g. **10**) forms which are for instance required for the electrophilc ringclosure reactions. For more information on 2-oxo-ketenes see the review by C. Wentrup [4]. It should be mentioned that formula **11** represents only one structure of potential tautomeric isomers. The outcome of this reaction was not surprising since we have shown earlier [9,11] that at N1 unsubstituted pyridazino[2,3-*a*]pyrimidines rearrange also at 250° to pyrido[2,3-*a*]pyridazines. In this case there is no other other nucleophilic postion available. The results obtained demonstrate that mesomeric pyridazino[2,3-*a*]pyrimidines undergo ringopening at temperatures above 200° to 2-oxo-ketenes and that stabilization of these intermediates is directed by the nucleophilicity of the available C-atoms.

EXPERIMENTAL

3-Chlor-6-methylpyridazine 2a

A mixture of 50 mmol of the pyridazone **1a** and 20mL phosphorus oxychloride was heated for 30 min under reflux. After cooling the phosporoxychloride was removed by destillation and the residue poored into ice-water. The solution was made alkaline and a yellow precipitate was filtered by suction. The filtrate was extracted twice with diethylether , dried with sodium sulfate and evaporated to dryness to yield 34% of **2a**.

3-Chlor-6-phenylpyridazine 2b

A mixture of 1 mol ofthe pyridazone **1b** and 400 mL phosphorus oxychloride was heated for 1 hour under reflux. After cooling the solution was carefully poured into ice-water. The precipitate was filtered off and washed sometimes with water until the motherlique becomes neutral. The yield was 97%.

General procedure for the synthesis of 3,6-substituted pyridazinones 3

A mixture of 10 mmol of the 3-chloropyridazinons **2a,b** and 10 mmol of the corresponding aniline was heated in 30 mL of 1-propanol for 2-7 hours under reflux. After cooling the mixture was evaporated to dryness and the residue was trituated with diluted Na_2CO_3-solution. The precipitate was filtered by suction , washed with water and recrystallized.

General procedure for the synthesis of 3,6-substituted 5-hydroxy-pyridazinones 6

A mixture of 10 mmol of the 3-chloro-5-hydroxy-6-phenyl-pyridazinone **5** and 20 mmol of the corresponding aniline was heated in 60 mL of 1-propanol for 2-20 hours under reflux. After cooling the precipitated product was filtered by suction.

Table 1

Experimental and Physical Data for Compounds **3** and **6**

No.	R	R^1	React.time	Yield	Mp.°C	Recry.
3a	CH_3	H	4h	86	167	toluene
3b	CH_3	4-Cl	6h	84	187-190	toluene
3c	CH_3	3-OCH_3	6h	89	170-172	toluene
3d	CH_3	4-CH_3	5h	93	189-193	toluene
3e	CH_3	3-CH_3	5h	84	143-146	toluene
3f	Ph	H	2h	85	198-200	toluene
3g	Ph	4-Cl	7h	99	226-229	toluene
3h	Ph	3-OCH_3	5h	95	164-165	toluene
3i	Ph	4-CH_3	6h	92	215-218	toluene
3j	Ph	3-CH_3	6h	88	147-150	toluene
3k	Ph	2-CH_3	12h	48	162-165	ethanol/H_2O
6a	--	CH_2Ph	25 min [a]	81	284-286	acetic acid
6b	--	C_6H_5	2h[a]	98	324-325	DMF
6c	--	4-Cl-C_6H_4	17h	97	350-352	DMF
6d	--	4-CH_3-C_6H_4	20h	42	310-315	ethanol
6e	--	3-CH_3-C_6H_4	20h	38	250-258	ethanol

[a]without solvent; after cooling trituation with methanol

General procedure for the synthesis of pyridazino[2,3-a]pyrimidin-1-ium-2-olates 4 and 7

A mixture of the 3,6-substitued pyridazinone **3** or the 3,6-substiuted 5-hydroxypyridazinone **6** and 12 mmol bzw. 20 mmol (for compounds 6) of the corresponding bis–2,4,6-trichlorophenylmalonate was heated in 50 mL of chlorobenzene for 1-5 hours under reflux. After cooling the solution was trituated with petrolether . The precipitate was filtered off and recrystallized.

Table 2

Experimental and Physical Data for Compounds **4** and **7**

No.	R	R^1	R^2	Reac.Time	Yield	Mp.°C	Recry.	Color
4a	CH_3	H	C_6H_5	3h	85	268-272	toluene	ochre
4b	CH_3	4-Cl	C_6H_5	2h	85	287-290	ethanol	red
4c	CH_3	OCH_3	C_6H_5	2h	83	236-239	toluene	orange
4d	CH_3	4-CH_3	C_6H_5	2h	82	277-280	ethanol	orange

4e	CH_3	3-CH_3	C_6H_5	2h	74	224-226	ethanol	red
4f	CH_3	H	C_4H_9	3h	60	253-256	toluene	ochre
4g	CH_3	4-Cl	C_4H_9	2h	77	214-217	ethanol/H_2O	orange
4h	CH_3	OCH_3	C_4H_9	1h	59	245-248	toluene	yellow
4i	CH_3	4-CH_3	C_4H_9	2h	45	260-264	toluene	brown
4j	CH_3	3-CH_3	C_4H_9	2h	67	251-254	toluene	yellow
4k	CH_3	H	$CH_2C_6H_5$	0.5h	58	297-299	methanol	orange
4l	CH_3	4-Cl	$CH_2C_6H_5$	1h	86	245-250	ethanol	ochre
4m	CH_3	OCH_3	$CH_2C_6H_5$	2h	76	222-225	toluene	yellow
4n	CH_3	4-CH_3	$CH_2C_6H_5$	5h	78	268-271	ethanol	orange
4o	CH_3	3-CH_3	$CH_2C_6H_5$	5h	82	236-240	toluene	yellow
4p	Ph	H	C_6H_5	0.5h	78	295	toluene	red
4q	Ph	4-Cl	C_6H_5	0.5h	89	286-189	ethanol	red
4r	Ph	OCH_3	C_6H_5	1h	85	248-252	toluene	orange
4s	Ph	4-CH_3	C_6H_5	0.5h	84	295-297	toluene	red
4t	Ph	3-CH_3	C_6H_5	2h	62	288-292	toluene	red
4u	Ph	H	C_4H_9	2h	76	248-252	toluene	yellow
4v	Ph	4-Cl	C_4H_9	3h	79	265-269	toluene	orange
4w	Ph	OCH_3	C_4H_9	2h	66	272-276	toluene	yellow
4x	Ph	4-CH_3	C_4H_9	0.5h	54	281-284	toluene	yellow
4y	Ph	3-CH_3	C_4H_9	2h	68	266-269	toluene	yellow
4z	Ph	H	$CH_2C_6H_5$	2h	89	281-283	ethanol	orange
4aa	Ph	4-Cl	$CH_2C_6H_5$	4h	59	236-239	ethanol	red
4ab	Ph	OCH_3	$CH_2C_6H_5$	5h	85	268-271	toluene	yellow
4ac	Ph	4-CH_3	$CH_2C_6H_5$	3h	83	252-256	toluene	orange
4ad	Ph	3-CH_3	$CH_2C_6H_5$	5h	84	266-269	ethanol	yellow
7a	--	$CH_2C_6H_5$	C_6H_5	3h	74	223-226	ethanol	yellow
7b	--	4-Cl-C6H_4	C_6H_5	5h	67	260-264	ethanol	yellow
7c	--	$CH_2C_6H_5$	C_4H_9	5h	70	202-206	ethanol	yellow
7d	--	C_6H_5	C_4H_9	4h	82	243-246	ethanol	yellow
7e	--	$CH_2C_6H_5$	$CH_2C_6H_5$	5h	65	240-243	ethanol	yellow
7f	--	C_6H_5	$CH_2C_6H_5$	5h	84	213-217	ethanol	yellow

General Procedure for the synthesis of the rearranged pyridazino[2,3-a]pyrimidin-1-ium-2-olates 9 and 11

2 mmol of the pyridazino[2,3-a]pyrimidin-1-im-2-olate was heated in diphenylether for 1 hour under reflux. After cooling to about 40-50°C the solution was trituated with petrolether.The precipitate was filtered by suction and recrystallized.

Table 3

Experimental and Physical Data for Compounds **9** and **11**

No.	R	X	Yield	Mp. °C	Recry.	Color
9a	Ph	--	77	250-253	ethanol	white
9b	CH_2-C_6H_5	--	82	178-182	toluene	beige
11a	Cl	C_6H_5	65	195-200	toluene	yellow
11b	H	C_4H_9	56	222-225	toluene	yellow

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