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New Aspects in the Reaction of Azomethines with Cyclic CH-Acidic Compounds

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Summary. Treatment of substituted benzylidene anilines **1a–f** with cyclic CH-acidic compounds **2a–m** in ethanol at room temperature yields in additon/elimination reactions the corresponding arylidene derivatives **4** and the 2:1 adducts **5**. The addition products **3**, which are formed as intermediates, could not be isolated in any case. The donor/acceptor effect of the substituents on the benzylidene moiety influences to a significant extent the reactivity towards the azomethine carbon.

Keywords. Azomethine; CH-Acidic compound; Addition/elimination reaction.

Neue Aspekte der Reaktion von Azomethinen mit cyclischen CH-aciden Verbindungen

Zusammenfassung. Bei der Umsetzung der substituierten Benzylidenaniline **1a–f** mit den cyclischen CH-aciden Verbindungen **2a–m** in Ethanol bei Raumtemperatur erhält man in Additions/Eliminierungsreaktionen die Arylidenderivate **4** und die 2:1-Addukte **5**. Die als Intermediat gebildeten Additionsprodukte **3** konnten in keinem Fall isoliert werden. Die Donor- bzw. Acceptorwirkung der Substituenten am Benzylidenrest beeinflußt maßgebend die Reaktivität am Azomethinkohlenstoff.

Introduction

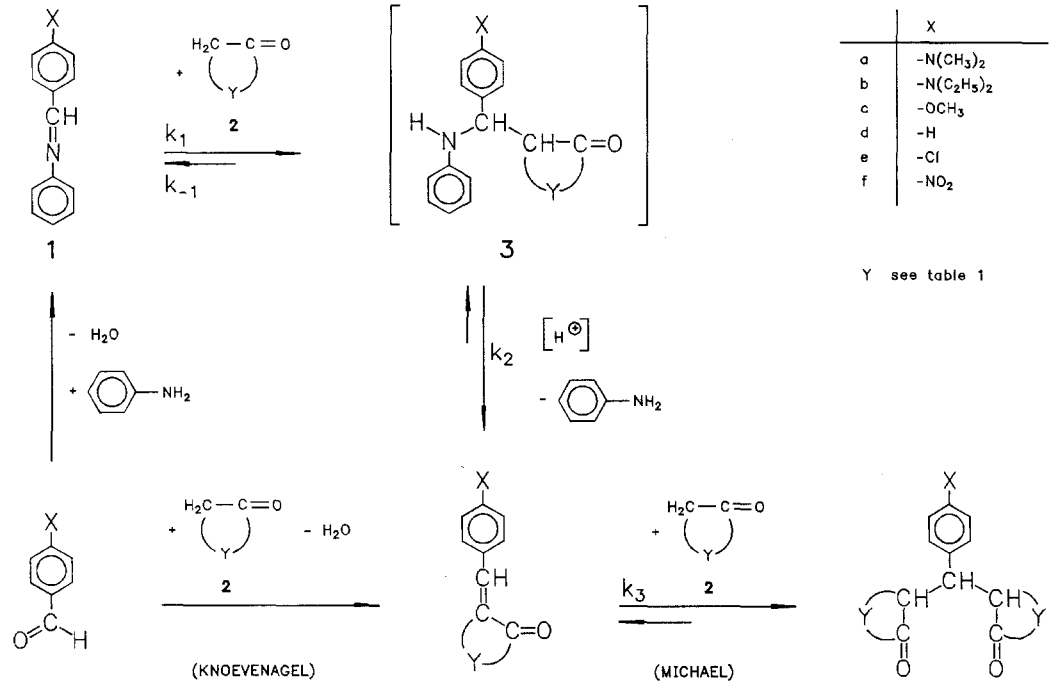
It is well known that the reaction of azomethines (Schiff bases) with CH-acidic compounds gives addition products in the first step. This addition to the C=N double bond is facilitated with increasing acidity of the reacting compound, and it is possible to catalyse the reaction with mineral acids [1]. The reactions of benzylidene aniline with ethyl acetoacetate (pK_a 10.5) [2, 3], malonic diester (pK_a 13.3) [4], α-naphthol (pK_a 9.8) [5] and indole (pK_a 17.0) [6] are examples of such additions.

Investigations with methylene active ketones of low acidity, e. g., cyclopentanone (pK_a 16.5) or acetophenone (pK_a 19.1) gave conflicting results concerning the preparative aspects [7]. The addition products can decompose in acidic medium or at higher temperature by deamination with formation of benzal compounds, which cause more consecutive reactions [8–10]. Thus, the course of the reaction is not unitary and the yields of the remaining addition and addition-elimination products are normally low.

Only few results of reactions of azomethines with cyclic carbonyl compounds of high acidity are known yet.

Results and Discussion

We have investigated the reaction of several substituted arylidene anilines **1a–f** and a series of methylene active compounds **2a–m** with pK_a values in the range from 4 to 8 (Table 1, Scheme 1).



Scheme 1

Simple treatment of ethanolic solutions of *p*-dimethylaminobenzylidene aniline (**1a**) and cyclic β-dicarbonyl compounds **2a–f** or heteroanalogous compounds **2g** and **2h** in equimolar quantities at room temperature affords the corresponding 4-N,N-dimethylaminobenzylidene derivatives **4** with yields between 80 and 95%. These "exchange products" crystallize from the reaction mixture as coloured compounds mostly in a few minutes.

In the reaction of the β-dicarbonyl compounds **2i–m** with **1a** the formation of considerable amounts of 2:1 condensation products **5** besides the benzal derivatives can be observed even when using equimolar quantities of **1a**. Hence, in these cases the deamination of the addition products (k_2) and the subsequent Michael addition (k_3) of reactant **2**, which is still available, on the α,β-unsaturated compounds **4** are faster than the addition equilibrium (k_1/k_{-1}). An excess of **2** leads to a complete conversion into **5**. Table 2 gives a survey on the prepared benzal compounds **4** and the 2:1 adducts **5**.

In contrast to **4k, l, m** compounds **4a–i** are not enolizable ketones or lactames. Such circumstance will obviously retard the further reaction to **5**. Moreover, **4a–h** easily crystallize from the reaction mixture. In the case of compound **1i** one has to consider that this compound is very little soluble in ethanol.

Table 1. Cyclic methylene active compounds

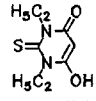
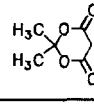
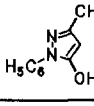
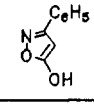
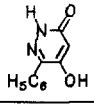
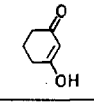
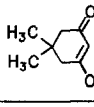
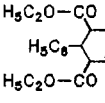
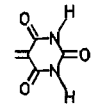
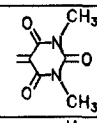
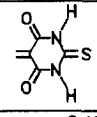
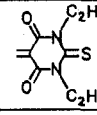
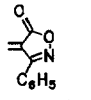
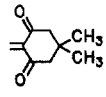
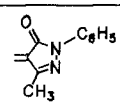
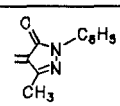
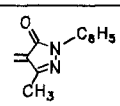
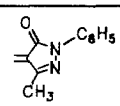
	Compound $H_2C-C=O \rightleftharpoons HC=C-OH$	m.p. [°C]	Portion of carbonyl tautomers	pK_a (75 vol% dioxane/H_2O; 25°C)	^{1}H-NMR δ-CH=	^{1}H-NMR δ-CH_2-
2a		129-132	>95%(DMSO) >95%($CDCl_3$)	5,3		3,33(DMSO) 3,22($CDCl_3$)
2b		248-252	>95%(DMSO)	5,8		3,55(DMSO)
2c		124-126	>95%(DMSO) >95%($CDCl_3$)	4,7		3,70(DMSO) 3,67($CDCl_3$)
2d		>300	<10%(DMSO)	4,1	5,04(DMSO)	
2e		109-112	<10%(DMSO) >95%($CDCl_3$)	4,2	5,90(DMSO)	3,70($CDCl_3$)
2f		94-96	>90%(DMSO)	4,8	5,50(DMSO)	4,00(DMSO) 4,60($CDCl_3$)
2g		129-130	<5%(DMSO) >95%($CDCl_3$)	8,9	5,34(DMSO)	3,40($CDCl_3$)
2h		150-152	~40%(DMSO) >95%($CDCl_3$)	5,7	5,70(DMSO)	4,31(DMSO) 3,79($CDCl_3$)
2i		328-334 [11]	<5%(DMSO)	7,1	6,11(DMSO)	
2k		103-105	~25%(DMSO) >95%($CDCl_3$)	5,3 [12]	5,50(DMSO)	3,42($CDCl_3$)
2l		149-151	~15%(DMSO) >95%($CDCl_3$)	5,2 [12]	5,18(DMSO)	3,36($CDCl_3$)
2m	 (cis-trans isomers)	177-180	~30%(DMSO) >95%($CDCl_3$)	5,6	5,39(DMSO)	3,73($CDCl_3$)

Table 2. Benzal compounds **4** and 2:1 aducts **5**

	x	z	X-C6H4-CH=Z (4) Fp [°C] (yield)	δ_{CH} (DMSO)	Lit.	X-C6H4-CH(ZH)2 (5) Fp	δ_{CH} (DMSO)	Lit.
a	$N(CH_3)_2$		206 - 208 (92 %)	7,58	[13]	—	—	—
b	$N(CH_3)_2$		268 - 270 (88 %)	8,14	[14]	—	—	—
c	$N(CH_3)_2$		236 - 238 (89 %)	8,43		—	—	—
d	$N(CH_3)_2$		259 - 261 (85 %)	8,16	[15]	—	—	—
e	$N(CH_3)_2$		214 - 216 (91 %)	8,43	[16]	—	—	—
f	$N(CH_3)_2$		176 - 177 (81 %)	8,30	[17]	—	—	—
g	$N(CH_3)_2$		200 - 202 (94 %)	7,09	[18]	—	—	—
h	$N(CH_3)_2$		184 - 186 (86 %)	7,38	[19]	—	—	—
i	$N(CH_3)_2$		ca 182 - 188 yellow compound	8,51	—	248 - 254 colourless compound	6,15	—
k	$N(CH_3)_2$		red compound	—	—	150 - 155 colourless compound	5,38	[20]
l	$N(CH_3)_2$		red compound	—	—	194 - 195 pale yellow compound	5,74	[21]
m	$N(CH_3)_2$		red compound	—	—	167 - 168 pale yellow compound	6,22	—

a

	X	Z	X-C6H4-CH=Z (4) Fp [°C] (yield)	δ_{CH} (DMSO)	Lit.	X-C6H4-CH(ZH)2 (5) Fp	δ_{CH} (DMSO)	Lit.
n	$N(C_2H_5)_2$		156 - 158 (83 %)	7,83	[10]	—	—	—
o	OCH_3		156 - 157 (91 %)	7,81	[13] [24]	—	—	—
p	H		151 - 153 (83 %)	7,88	[22] [24]	—	—	—
q	Cl		179 - 180 (92 %)	7,80	[23]	—	—	—
r	NO_2		232 - 234 (87 %)	7,88	[13] [24]	—	—	—
s	NO_2		181 - 183 (75 %)	*	[25]	225 - 227	—	[26]
t	NO_2(ortho)		161 - 164 (75 %)	*	[27]	231 - 232	—	[28]
u	OCH_3		128 - 131 (84 %)	*	[29]	174 - 176	—	[30]
v	H		106 - 108 (73 %)	*	[31]	164 - 166	—	[32]

* CH signal is hidden by aromatic absorptions

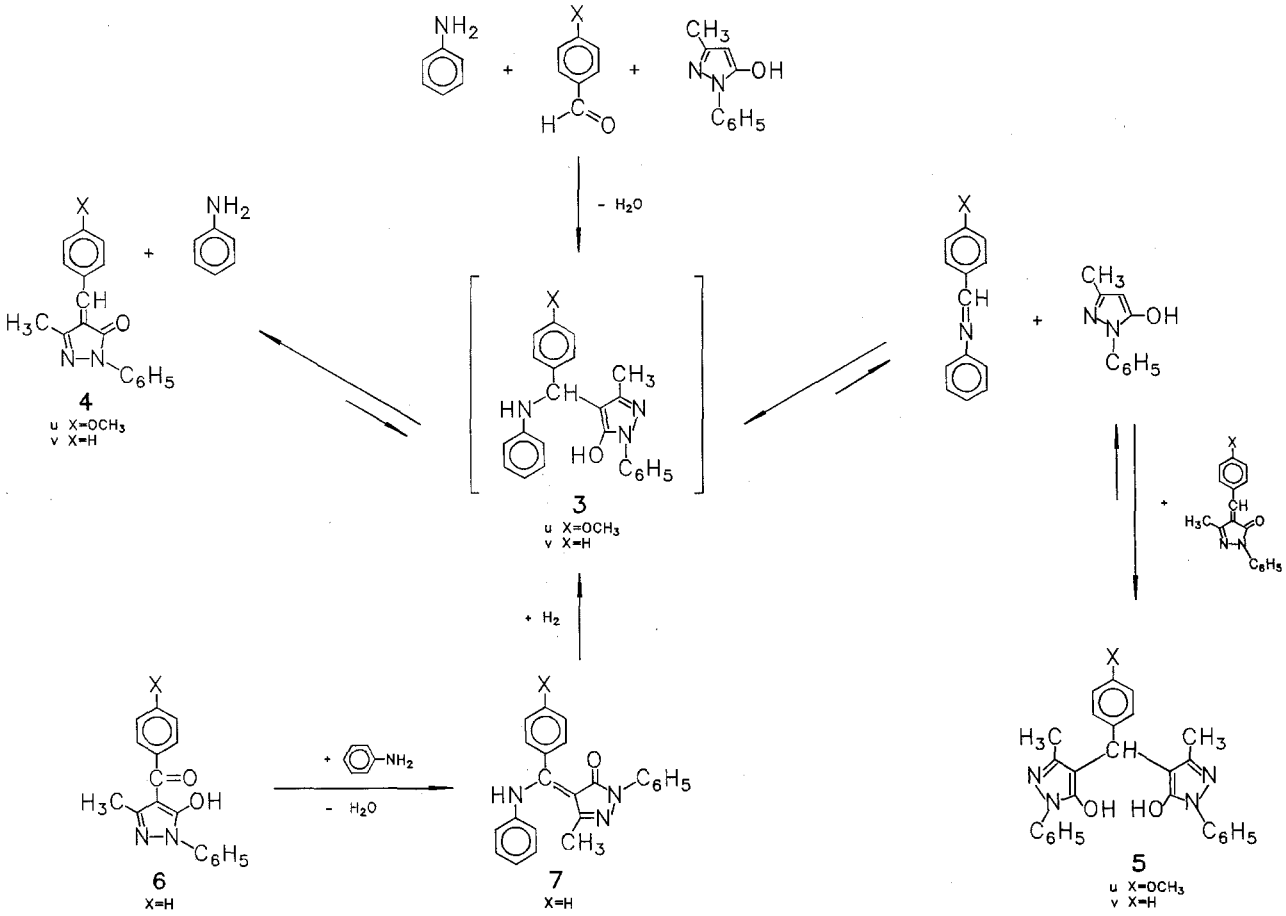
b

In the case of indanedione (**2a**) the addition-elimination products **4** are also obtained in very good yields if the donor substituted benzylidene anilines **1a–c** are replaced by the unsubstituted benzylidene aniline **1d** or the acceptor substituted compounds **1e** and **1f**. The resulting products **4n–r** are compiled in Table 2. The synthesis of **4a** and **4n–r** from indanedione and benzylidene anilines is more convenient than that from indanedione and the corresponding aldehydes by catalysis with polymeric fluorides [24].

The reaction of dimedone (**2l**) with azomethines allows the study of the equilibrium between **4** and **5**. The biscompound **5l** obtained from **1a** and **2l** is a pale

yellow substance with m. p. 194 – 195°C [21], which is gradually transformed into the red compound **41** with elimination of dimedone, either by warming in xylene or thin layer chromatography on silicagel. Compound **41** can in turn react again with dimedone to form the 2 : 1 adduct.

The preparation of ylidene compounds **4** from azomethines and CH-acids via addition and subsequent elimination of amine in the case of non-enolizable compounds is an advantageous synthetic method due to the mild reaction conditions, high yields, and purity of the products, in contrast to the Knoevenagel reaction of these CH-acids with aldehydes. In this case any excess of methylene active compound or even unreacted amounts of it will add again to the formed benzal compound and the 2 : 1 condensation products are obtained. E. g., the synthesis of compound **4t** from the corresponding *ortho*-substituted benzaldehyde has been described with poor reproducibility and in moderate yields only [27], while **4t** is obtained from the azomethine and pyrazolinone in 75% yield. Apparently, the deamination of adduct **3t** (k_2) is the rate determining step. Thus, less unreacted pyrazolinone is available for the Michael addition. For that reason biscompound **5t** is a by-product only (approximately 30%) in the reaction of pyrazolinone with *o*-nitrobenzylidene aniline.



Scheme 2

The isolation of pure addition products **3** could not be achieved in any case. The addition product **3u** from the reaction of pyrazolinone **2g** with methoxybenzylidene aniline **1c** has been reported [33]. However, all attempts to reproduce these results were unsuccessful.

The reaction was repeated and modified under different conditions with the following results:

(i) Treatment of equimolar quantities of **2g** and **1c** in ethanol at room temperature led immediately to the precipitation of 4-(4-methoxybenzylidene)-3-methyl-1-phenyl-2-pyrazolin-5-one (**4u**), which could be isolated in 77% yield.

(ii) If equimolar quantities of **2g** and **1c** were refluxed in ethanol the methoxybenzylidene pyrazolinone **4u** precipitated in 56% yield. In this case it was possible to isolate the bispyrazolinone **5u** in 36% yield from the remaining solution after standing for a few hours.

(iii) If equimolar amounts of **2g** and **1c** were mixed in ethanol at room temperature, after some time the separation of the intensively coloured methoxybenzylidene compound **4u** could be observed, which after standing overnight completely turned into the bispyrazolinone **5u**. The presence of aniline in the remaining solution was detected by gas chromatography (Scheme 2).

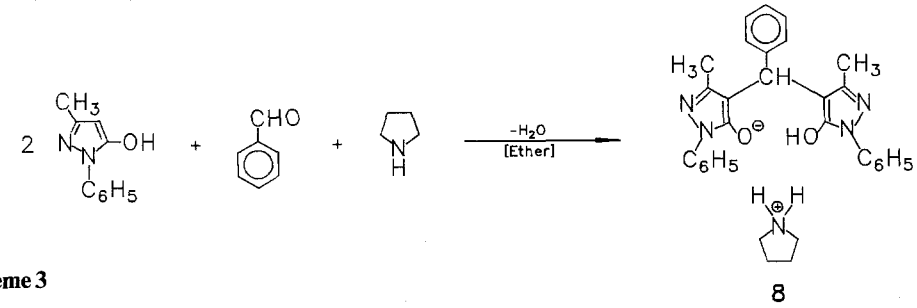
Attempts towards the preparation of addition products from anilines and benzylidene pyrazolinones analogously to Mustafa's procedure [34] were also unsuccessful. If the 4-methoxybenzylidene compound **4u** was treated with an equimolar quantity of aniline in ethanol at room temperature no reaction took place, while in the corresponding reaction between benzylidene pyrazolinone **4v** and *p*-anisidine decolourization of the reaction mixture was observed and bispyrazolinone **5v** was formed in high yield.

This different behaviour is caused by the donor effect of the methoxy group. In the first case this methoxy group reduces the electrophilicity of the carbon atom in the benzylidene moiety, rendering the nucleophilic attack of the aniline more difficult. In the second case the methoxy group increases the nucleophilicity of the aniline nitrogen atom, facilitating the nucleophilic attack. The formation of bispyrazolinone **5v** during the reaction implies either the cleavage of the intermediate addition compound **3** with formation of the unsubstituted pyrazolinone or hydrolysis of the benzylidene product [30].

Two independent ways towards the synthesis of the addition products **3** were also unsuccessful.

(i) 4-Benzoyl-5-hydroxy-pyrazole **6** was reacted with aniline almost quantitatively to form the condensation product **7** [35]. Subsequent hydrogenation of **7** led to the benzylidene compound **4v** by hydrogenolytic elimination of aniline. Amine elimination of this type already has been described in the case of 4-N,N-dimethylaminomethylene-3-methyl-1-phenyl-2-pyrazolin-5-one with sodium borohydride [36].

(ii) Mannich type reaction between pyrazolinone, benzaldehyde and aniline preferentially gave the benzylidene compound **4v** besides remaining starting material, whereas the reaction between pyrazolinone, benzaldehyde and pyrrolidine according to Chhabra's procedure [37] yielded the salt **8** [38] (Scheme 3).



Scheme 3

8

Experimental Part

Melting points were determined using a Boetius melting point apparatus. Elemental analyses were carried out with a "CHN-O-Rapid" (Heraeus) apparatus. Analytical data were within ±0.4% of the calculated values. NMR spectra were determined using a Tesla BS 487 C (80 MHz) and a Bruker MSL 300 (300 MHz), respectively, with $CDCl_3$ or *DMSO-d_6* as solvent (chemical shifts in δ, ppm).

General Procedure for Arylidene Compounds **4** *and 2 : 1-Adducts* **5**

A saturated ethanolic solution of 0.01 mol arylidene aniline **1** was treated with stirring with a saturated ethanolic solution of methylene active compound **2** at room temperature. Coloured crystals of **4** separated after a few minutes. The bisproducts **5** could be isolated after a few hours from the remaining solution. The products were collected, dried and recrystallized from ethanol. The purity of the substances was checked by TLC (toluene/ethyl acetate 3 : 1 or 1 : 1, Silufol).

The reaction of **1a** with **2k–m** led directly to **5k–m**, inclusively when treated in 1 : 1 portions. However, compounds **4k–m** were detected in TLC experiments. The thin layer chromatograms of **5k–m** showed in addition to their signals the spot corresponding to the coloured 1 : 1-adducts **4k–m** and the eliminated CH-acids **2k–m**. Two dimensional TLC equally showed that the signals of **5k–m** again eliminate the methylene active compounds, rendering **4k–m**.

Preparation of Salt **8**

Pyrazolinone **2g** (609 mg, 3.5 mmol) in dry ether (10 ml) was stirred for 5 min in a salt-ice bath under nitrogen. To this dry pyrrolidine (0.3 ml, 3.5 mmol) was added, followed by dropwise addition of freshly destilled benzaldehyde (427 mg, 3.5 mmol). After 10 min at the same temperature the reaction product was filtered off and washed with cold dry ether, yielding 550 mg of salt **8**. M. p. decomposition above 165°C. ^{1}H-NMR ($CDCl_3$): 1.34 s (broad) (-CH_2-, 4H), 2.20 s (CH_3, 6 H), 2.22 s (broad) (-CH_2-,4 H), 4.84 s (CH, 1 H), 7.03–7.32 (m) and 7.58 (d) (arom. H, 15 H), 10,01 (s, OH, 1 H)

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