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Reaction of CH Acids with 2-Arylidenecycloalkanones: Synthesis of β-Keto Acid Anilide Derivatives of Naphthalene, Indene, Fluorene, and Phenanthrene

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Summary. 2-Arylidene-cyclohexanone **1**, -cyclopentanone **2**, -1-indanone **3** and -1-tetralone **4** react with acetoacetanilide **5** yielding 2-oxo-4-aryl-3-carboxylic acid anilides derivatives of naphthalene **7**, indene **8**, fluorene **9** and phenanthrene **10**. Reaction of **1** and **3** with benzoylacetanilide **6** yields the corresponding Michael adducts **11** and **12**.

Keywords. 2-Arylidenecycloalkanones; β-keto acid anilides; Michael addition.

Reaktion von CH-Säuren mit 2-Arylidencycloalkanonen. Synthese von β-Ketosäureanilid-Derivaten von Naphthalin, Inden, Fluoren und Phenanthren

Zusammenfassung. 2-Arylidencyclohexanone **1**, -cyclopentanone **2**, -1-indanone **3** und -1-tetralone **4** reagieren mit Acetoacetanilid **5** unter Bildung von 2-Oxo-4-aryl-3-carbonsäureanilid-Derivaten von Naphthalin **7**, Inden **8**, Fluoren **9** und Phenanthren **10**. Die Reaktion von **1** und **3** mit Benzoylacetanilid **6** ergibt die entsprechenden Michael-Addukte **11** und **12**.

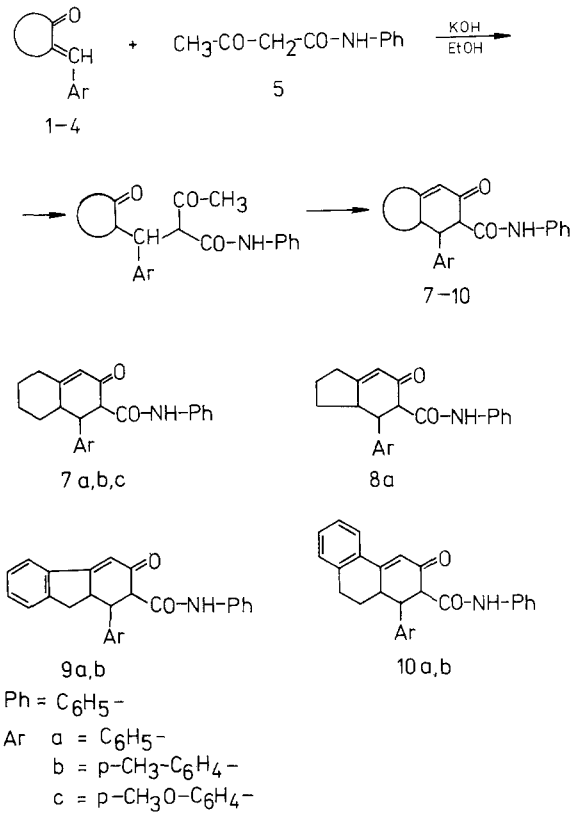
Introduction

Continuing our studies on the application of cyclic β-keto acid anilides in synthesis of heterocyclic compounds [1, 2] we focused our attention on the preparation of various 1,3-dicarbonyl derivatives containing fused carbocyclic and heterocyclic skeletons.

Our approach to the synthesis of these dicarbonyl compounds was based on the Robinson annulation [3, 4]. The Robinson annulation has been proven to the useful for the synthesis of a number of fused carbocyclic systems like steroids and some terpenes [5, 6]. In this work we report on the reaction of 2-arylidenecycloalkanones **1–4** with acetoacetanilide **5** and benzoylacetanilide **6**.

Results and Discussion

The reaction of 2-arylidenecycloalkanones **1–4** with acetoacetanilide **5** was carried out in ethanolic solution in the presence of catalytic amounts of potassium hydroxide. Compounds **7–10** were obtained in moderate to good yields (Scheme 1).



Scheme 1

The reaction of **1–4** with **5** in alkaline solution leads in the first step to the Michael adduct, which in the second step undergoes condensation resulting in **7–10**. The structure of these products was confirmed by analytical and spectral data; e.g. the IR spectra of **7** displayed characteristic CO and NH absorptions at 1660 cm^{-1} and 3290 cm^{-1}, respectively. The ^1H NMR spectrum revealed a signal at 5.88 ppm corresponding to one vinylic proton at C-1. The MS data of **7–10** exhibited a fragmentation pattern typical for β-keto anilides [7]. All spectra showed molecular ions of moderate intensity. The main fragmentation pathway is connected with elimination of arylcarbamoyl and arylamine ions. Table 1 summarizes the analytical and spectral data of compounds **7–10**.

Reaction of **1a** and **4a** with **6** in boiling ethanolic solution in the presence of potassium hydroxide yielded the colourless products **11** and **12** (Scheme 2). Their analytical and spectral data showed that they were Michael adducts. The IR spectrum of **11** displayed broad bands at 3590 cm^{-1} and 3370 cm^{-1} for OH and NH groups, and at 1630 cm^{-1} and 1690 cm^{-1} corresponding to CO groups. The MS spectrum of compound **11** did not show a molecular ion peak (*m/z* 425). Fragmentation of **11** started with loss of a water molecule leading to an ion at *m/z* 407 of medium intensity. The most intensive peaks in the MS spectrum correspond to $C_6H_5CO^+$, $C_6H_5NHCO^+$ and $C_6H_5^+$ ions. A similar fragmentation pattern was observed in the mass spectrum on **12**. All attempts of cyclization of **11** to the appropriate 3-benzoyl chinolone **13** in *PPA* were unsuccessful. From the oily

Table 1. Yields, physical properties, elemental analysis and spectroscopic data of the compounds

No.	Yield [%]	M.p. °C	Empirical formula Mol. mass	Analysis calcd. (found)			IR [cm^{-1}]	^1H NMR [δ ppm]	MS *m/z*
				C	H	N			
7a	64	213–215	$C_{23}H_{23}NO_2$ 345.42	79.97 79.78	6.71 6.50	4.05 4.32	3290 3180 NH 1660 CO	1.18–2.41 m 8H CH_2, 1H CH 3.37 m 1H CH 3.48 m 1H CH 5.88 s 1H CH vinylic 7.18 m 10H arom. 7.75 s 1H NH	345 M^+ 253 $[M-C_6H_5NH]^+$ 225 $[M-C_6H_5NHCO]^+$ 148 $[M-C_6H_5NHCO, C_6H_5]^+$ 92 $[C_6H_5NH]^+$ 77 $[C_6H_5]^+$
7b	55	210–211	$C_{24}H_{25}NO_2$ 359.47	80.19 80.78	7.01 6.82	3.90 3.32	3300 3190 NH 1670 CO	1.97–2.42 m 8H CH_2, 1H CH 2.22 s 3H CH_3 3.37 m 1H CH 3.44 m 1H CH 5.91 m 1H CH vinylic 7.03 m 9H arom. 7.43 m 1H NH	359 M^+ 267 $[M-C_6H_5NH]^+$ 239 $[M-C_6H_5NHCO]^+$ 148 $[M-C_6H_5NHCO, C_6H_4CH_3]^+$ 120 $[C_6H_5NHCO]^+$ 92 $[C_6H_5NH]^+$ 77 $[C_6H_5]^+$
7c	32	215–217	$C_{24}H_{25}NO_3$ 375.46	76.77 77.19	6.71 7.08	3.73 3.72	3260 3073 NH 1650 CO	1.25–2.76 m 8H CH_2, 1H CH 3.60 m 1H CH 3.72 s 3H CH_3 4.04 m 1H CH 5.95 s 1H CH vinylic 7.04 m 9H arom. 7.63 s 1H NH	375 M 283 $[M-C_6H_5NH]^+$ 255 $[M-C_6H_5NHCO]^+$ 148 $[M-C_6H_5NHCO, CH_3OC_6H_4]^+$ 120 $[C_6H_5NHCO]^+$ 107 $[CH_3OC_6H_4]^+$ 92 $[C_6H_5NH]^+$ 77 $[C_6H_5]^+$

(continued)

Table 1. (*continued*)

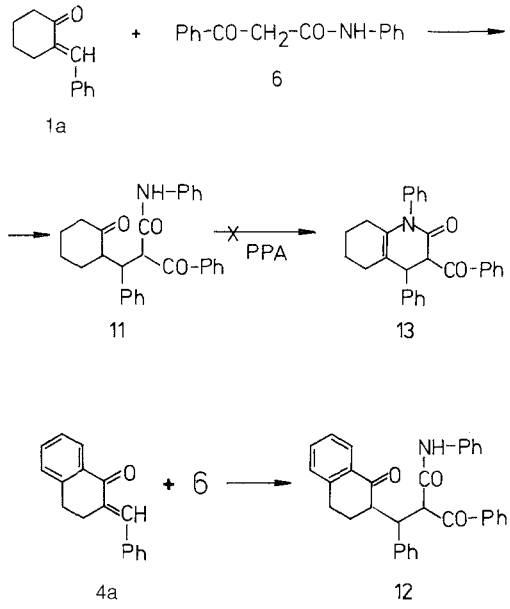
No.	Yield [%]	M.p. °C	Empirical formula Mol. mass	Analysis calcd. (found)			IR [cm^{-1}]	^1H NMR [δ ppm]	MS *m/z*
				C	H	N			
8a	64	188–190	$C_{22}H_{21}NO_2$ 331.42	79.73 80.21	6.39 6.17	4.23 4.13	3200 3160 NH 1640 CO	1.15–2.85 m 6H CH_2, 1H CH 3.29 m 1H CH 3.49 m 1H CH 6.04 s 1H CH vinylic 7.19 m 10H arom. 7.56 s 1H NH 9.93 s 1H NH	331 M^+ 21 $[M-C_6H_5NHCO]^+$ 134 $[M-C_6H_5NHCO, C_6H_5]^+$ 120 $[C_6H_5NHCO]^+$ 92 $[C_6H_5NH]^+$ 77 $[C_6H_5]^+$
9a	36	277–279	$C_{26}H_{21}NO_2$ 379.44	82.29 82.24	5.58 5.57	3.69 3.70	3290 NH 1670 CO	2.50 m 1H CH 3.05 m 1H CH 3.36 d 2H CH_2 4.04 d 1H CH 6.56 s 1H CH vinylic 7.65 m 14 H arom. 9.97 s 1H NH	379 M^+ 287 $[M-C_6H_5NH]^+$ 259 $[M-C_6H_5NHCO]^+$ 231 $[M-C_6H_5NHCO, CO]^+$ 120 $[C_6H_5NHCO]^+$ 92 $[C_6H_5NH]^+$ 77 $[C_6H_5]^+$
9b	32	236–237	$C_{27}H_{23}NO_2$ 393.46	82.42 81.99	5.89 5.77	3.56 3.97	3280 NH 1670 CO	2.29 s 3H CH_3 2.50 m 1H CH 3.02 m 1H CH 3.77 d 2H CH_2 4.03 d 1H CH 6.58 s 1H CH vinylic 7.43 m 13 H arom. 10.11 s 1H NH	393 M^+ 301 $[M-C_6H_5NH]^+$ 273 $[M-C_6H_5NHCO]^+$ 245 $[M-C_6H_5NHCO, CO]^+$ 120 $[C_6H_5NHCO]^+$ 92 $[C_6H_5NH]^+$ 77 $[C_5H_5]^+$

10a	42	261–263	$C_{27}H_{23}NO_2$ 393.46	82.42 82.96	5.89 5.83	3.56 3.38	3250 NH 1670 CO	1.25–1.75 m 2H CH_2 2.50–3.25 m 2H 2CH 3.43–3.67 t 2H CH_2 4.02 d 1H CH 6.91 s 1H CH vinylic 7.51 m 14H arom. 9.93 s 1H MH	393 M^+ 301 $[M-C_6H_5NH]^+$ 273 $[M-C_6H_5NHCO]^+$ 245 $[C_6H_5NHCO, CO]^+$ 120 $[C_6H_5NHCO]^+$ 92 $[C_6H_5NH]^+$ 77 $[C_6H_5]^+$
10b	44	255–257	$C_{28}H_{25}NO_2$ 407.49	82.53 82.73	6.18 6.35	3.44 3.87	3290 NH 1670 CO	1.25–1.75 m 2H CH_2 2.28 s 3H CH_3 2.50–3.25 m 2H 2CH 3.49 t 2H CH_2 4.05 d 1H CH 6.89 s 1H CH vinylic 7.51 m 13 H arom. 9.93 s 1H NH	407 M^+ 315 $[M-C_6H_5NH]^+$ 287 $[M-C_6H_5NHCO]^+$ 259 $[M-C_6H_5NHCO, CO]^+$ 120 $[C_6H_5NHCO]^+$ 92 $[C_6H_5NH]^+$ 77 $[C_6H_5]^+$
11	57	200–202	$C_{28}H_{27}NO_3$ 425.53	79.03 79.11	6.40 6.46	3.29 3.14	3590 OH 3520 3370 NH 1690 CO 1640	1.25–1.56 m 8H CH_2 2.33 m 1H CH 3.50 d 1H CH 4.40 d 1H CH 4.49 s 1H NH 7.34–7.82 m 15H arom.	407 $[M-H_2O]^+$ 330 $[M-H_2O, C_6H_5]^+$ 302 $[M-H_2O, C_6H_5CO]^+$ 105 $[C_6H_5CO]^+$ 92 $[C_6H_5NH]$ 77 $[C_6H_5]^+$
12	48	218–220	$C_{32}H_{27}NO_3$ 473.54	81.58 81.13	5.74 5.68	2.96 2.91	3420 3280 NH 1660 CO	2.52 m 2H CH_2 2.94 m 2H CH_2 4.97 d 1H CH 5.30 d 1H CH 7.21–7.49 m 19 H arom. 8.42 s 1H NH	455 $[M-H_2O]^+$ 378 $[M-H_2O, C_6H_5]^+$ 120 $[C_6H_5NHCO]^+$ 105 $[C_6H_5CO]^+$ 77 $[C_6H_5]^+$

(*continued*)

Table 1. (*continued*)

No.	Yield [%]	M.p. °C	Empirical formula Mol. mass	Analysis calcd. (found)			IR [cm^{-1}]	^1H NMR [δ ppm]	MS *m/z*
				C	H	N			
14	36	232–234	$C_{23}H_{26}N_2O_2$ 362.75	76.21 76.53	7.23 7.01	7.72 7.54	3350 3100 NH 1630 CO	1.07–1.54 m 8H CH_2, 1H CH 2.26–3.31 m 4H CH 6.82–7.19 m 10H arom. 1H NH 7.80 2H NH_2	362 M^+ 306 $[M-C_4H_8]^+$ 270 $[M-C_6H_5NH]^+$ 242 $[M-C_6H_5NHCO]^+$ 226 $[M-C_6H_5NHCO, NH_2]^+$ 120 $[C_6H_5NHCO]^+$ 92 $[C_6H_5NH]^+$ 77 $[C_6H_5]^+$
15	89	249–250	$C_{23}H_{25}NO_2$ 347.46	79.51 79.60	7.25 7.31	4.03 3.93	3550 OH 3240 NH	1.89–2.70 m 12H $CH_2$1H CH 4.75 d 1H CH 5.40 s 1H vinylic. 7.19–7.79 m 9H arom. 1H NH	329 $[M-H_2O]^+$ 237 $[M-H_2O, C_6H_5NH]^+$ 209 $[M-H_2O, C_6H_5NHCO]^+$ 132 $[M-H_2O, C_6H_5NHCO, C_6H_5]^+$ 120 $[C_6H_5NHCO]^+$ 92 $[C_6H_5NH]^+$ 77 $[C_6H_5]^+$
16	77	315–318	$C_{17}H_{20}N_2O_2$ 284.36	71.81 72.43	7.09 7.48	9.85 9.90	3150– NH –2860 OH	1.00–2.00 m 8H CH_2 3.27 m 4H CH_2, 1H CH 4.08 s 1H OH 7.17 m 5H arom. 10.0 s 1H NH	284 M^+ 266 $[M-H_2O]^+$



Scheme 2

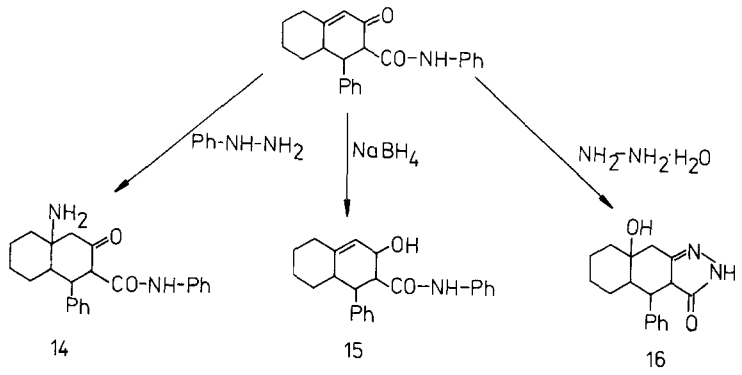
reaction mixture only a small amount of benzoylacetanilide could be isolated by chromatography.

To use β-keto anilides **7–10** in the synthesis of pyridine derivatives, we reacted cyclic β-keto acid anilides with malononitrile [8]. Reaction of **7a** with malononitrile in various solvents and with various catalysts, such as piperidine, sodium ethoxide, ammonium acetate, and piperidinium acetate failed. This non-reactivity of the carbonyl groups may be attributed to their conjugation with the C=C bond. Recently [9] the condensation of malonic ester with compounds containing a carbonyl group conjugated with two C=C bonds was reported. According to [9], reaction of **7** with malononitrile in the presence of anhydrous ammonium acetate was carried out at 160–170 °C. The dark orange product was insoluble in organic solvents and did not melt up to 360 °C. Thus it could not be identified.

When **7a** was heated with an excess of phenylhydrazine in acetic acid, compound **14** was isolated (Scheme 3). The analytical and spectral data suggested that **14** was formed by addition of one ammonia molecule to the double bond of **7a**. This was confirmed by its ^{1}H NMR spectrum which did not reveal the signal of a vinyl proton. Moreover, its molecular mass (*m/z* 362) was higher by 17 mass units than that determined for **7a**. To explain this we assumed that the reaction of **7a** with phenylhydrazine involves the formation of an adduct as intermediate which under the reaction conditions may undergo hydrogenation affording **14**.

Reaction of **7a** with sodium borohydride led to compound **15**. Its IR spectrum revealed a broad band at 3240–3550 cm^{-1} characteristic for an OH group. The MS spectrum of **15** did not exhibit the molecular ion peak. The peak of the highest value *m/z* 329 resulted from the elimination of a water molecule from the molecular ion of **15**.

When **7a** was heated with an excess of hydrazine hydrate in the presence of sodium acetate, compound **16** was formed. The analytical and spectral data



Scheme 3

suggested a napthopyrazolone structure outlined in Scheme 3. The IR spectrum of **16** revealed a broad band of bonded OH and NH groups at 3150–2860 cm^{-1}. The ^1H NMR spectrum showed a singlet at $\delta = 4.08$ ppm corresponding to OH and a broad signal at $\delta = 10.0$ ppm for the NH group. Since the spectrum did not reveal the signal of a vinyl proton it suggested that the reaction of **7a** with hydrazine hydrate involved addition of a water molecule to C=C of **7a**, followed by condensation with hydrazine and cyclization accompanied by elimination of aniline. The molecular weight of **16** *m/z* 284 was consistent with this structure. The fragmentation of **16** started with elimination of a water molecule giving the ion at 266. This fragmentation pathway is typical for alcohols.

Experimental Part

Melting points were determined on a Boetius apparatus and are corrected. The IR spectra were obtained in Nujol and in HCB mulls on a Specord IR-75 spectrometer. The ^1H NMR spectra were measured in $CDCl_3$ solutions with a Tesla BS-587A 100 MHz spectrometer. The chemical shifts are expressed on δ/ppm downfield from internal *TMS*. The mass spectra were measured on a LKB 20918 instrument at 70 eV ionizing energy.

The 2-Arylidenecycloalkanones **1–4** were prepared according to the methods described in literature [10–14].

Reaction of 2-Arylidenecycloalkanones **1–4** *with Acetoacetanilide* **5**
Synthesis of Compounds **7–10**

A mixture of the appropriate 2-arylidencycloalkanone **1-4** (0.05 mol), acetoacetanilide (0.05 mol) and potassium hydroxide (0.5 g) was refluxed in ethanol (100 ml) for 4–5 h. After cooling, the precipitate was separated and washed with ethanol. The crude products were crystallized from ethanol (**7**, **8**) or from *DMF* (**9**, **10**).

Reaction of 2-Arylidenecycloalkanones **1** *and* **4** *with Benzoylacetanilide* **6**
Synthesis of Adducts **11** *and* **12**

A mixture of **1** (1.86 g, 0.01 mol), **6** (2.39 g, 0.01 mol) and potassium hydroxide (0.2 g) was refluxed in 50 ml of ethanol for 2.5 h. The precipitate was filtered off and washed with ethanol. Colourless prisms were obtained from acetonitrile or ethanol.

Adduct **12** was prepared in a similar way as colourless needles from acetonitrile.

4a-Amino-3-oxo-1-phenyl-1,2,3,4,4a,5,6,7,8,8a-decahydronaphthalene-2-carboxylic Acid Anilide (**14**)

A mixture of 2.1 g (0.006 mol) of **7a**, 1 g (0.01 mol) of phenylhydrazine and 30 ml of acetic acid was refluxed for 3 h. After cooling the precipitate was separated, washed with methanol and recrystallized from methanol.

2-Hydroxy-4-phenyl-2,3,4,4a,5,6,7,8-octahydronaphthalene-3-carboxylic Acid Anilide (**15**)

To the stirred methanolic solution (100 ml) of **7a** (1.9 g, 0.005 mol) the alkaline aqueous solution of sodium borohydride (0.6 g $NaBH_4$, 1 ml 2*N* NaOH, 8 ml H_2O) was added dropwise. The temperature was maintained at 25 °C and the mixture was stirred for 30 min. After evaporation of solvent, the residue was triturated with a diluted solution of hydrochloric acid. The precipitate was filtered off, washed with water and recrystallized from methanol.

8a-Hydroxy-2H,3,3a,4,4a,5,6,7,8,8a,9-decahydro-4-phenyl-naphtho[2,3-c]pyrrazol-3-on (**16**)

To the ethanolic solution (100 ml) of **7a** (1.7 g, 0.005 mol) hydrazine hydrate (0.6 g, 40%) was added. The mixture was refluxed for 3 h. After cooling the precipitate was separated and crystallized as colourless prisms from acetic acid.

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