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Effective synthesis of 5-aryl-3-ethylidene-3*H*-pyrrol-2-ones

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Substituted 5-aryl-3-ethylidene-3*H*-pyrrol-2-ones were synthesized by the reaction of the corresponding 4-aryl-4-oxobutanoic acids with ketones in the presence of aminating agents. The conditions of this reaction were developed with the use of both the conventional condensation technique and microwave activation. The structures of the reaction products were confirmed by elemental analysis, IR spectroscopy, and ^{1}H NMR spectroscopy.

Key words: 4-aryl-4-oxoalkanoic acids, 5-aryl-3-ethylidene-3*H*-pyrrol-2-ones, ketones, tautomers, microwave activation.

Condensation of 3*H*-pyrrol-2-ones with carbonyl compounds has been studied for the reactions with aromatic aldehydes.[1,2] Earlier,[3] ammonolysis of O-heteroanalogs has been demonstrated to be the most facile procedure for the synthesis of 3-arylidene-3*H*-pyrrol-2-ones. Data on the use of alkyl aryl ketones of the unsubstituted pyrrol-2-one series as the carbonyl component are scarce and were reported only in the studies.[4—6]

We have synthesized *N*-unsubstituted 5-aryl-3*H*-pyrrol-2-ones by azaheterocyclization of 4-aryl-4-oxoalkanoic acids with ammonium acetate.[7]

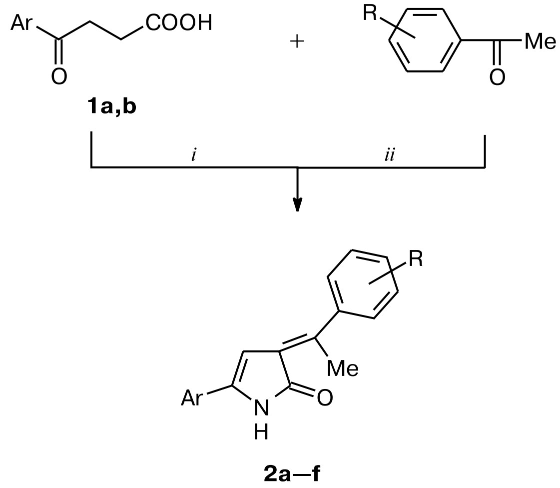
We used 5-aryl-3*H*-pyrrol-2-ones as the methylene component in the condensation with ketones. The reactions were carried out by refluxing the reagents in acetic anhydride in the presence of sodium acetate for 2 h. Attempts to synthesize the target compounds based on 3*H*-pyrrol-2-ones were unsuccessful because we failed to isolate the final products from the reaction mixture in preparative yields. Apparently, acylation at the nitrogen atom of the heterocycle is the major process under these conditions. In addition, alkyl aryl ketones are much less reactive as the carbonyl component compared to aldehydes used earlier.[3]

In the present study, we synthesized 5-aryl-3-(1-arylethylidene)-3*H*-pyrrol-2-ones from 4-aryl-4-oxobutanoic acids both in the presence of condensing agents and with the use of microwave heating as an efficient source of thermal activation.

Results and Discussion

The reactions were performed by heating a solution of an equimolar mixture of oxo acids **1a,b** and the carbonyl component in acetic anhydride in the presence of an aminating agent (ammonium acetate) for 1.5—2 h. Alkyl aryl (Scheme 1) and alicyclic ketones were used as the carbonyl component.

Scheme 1



	a	b	c	d	e	f
Ar	Ph	*p*-Tol	*p*-Tol	*p*-Tol	*p*-Tol	*p*-Tol
R	H	H	4-Cl	3-NO_2	4-NO_2	4-NH_2

Reagents and conditions: *i*. $AcONH_4$, Ac_2O; *ii*. $AcONH_4$, microwave irradiation.

The course of the reactions was monitored by TLC. Target products **2a—f** were isolated in yields of up to 66%. It was found that the reactions with alicyclic ketones do not proceed in the conditions under consideration. The

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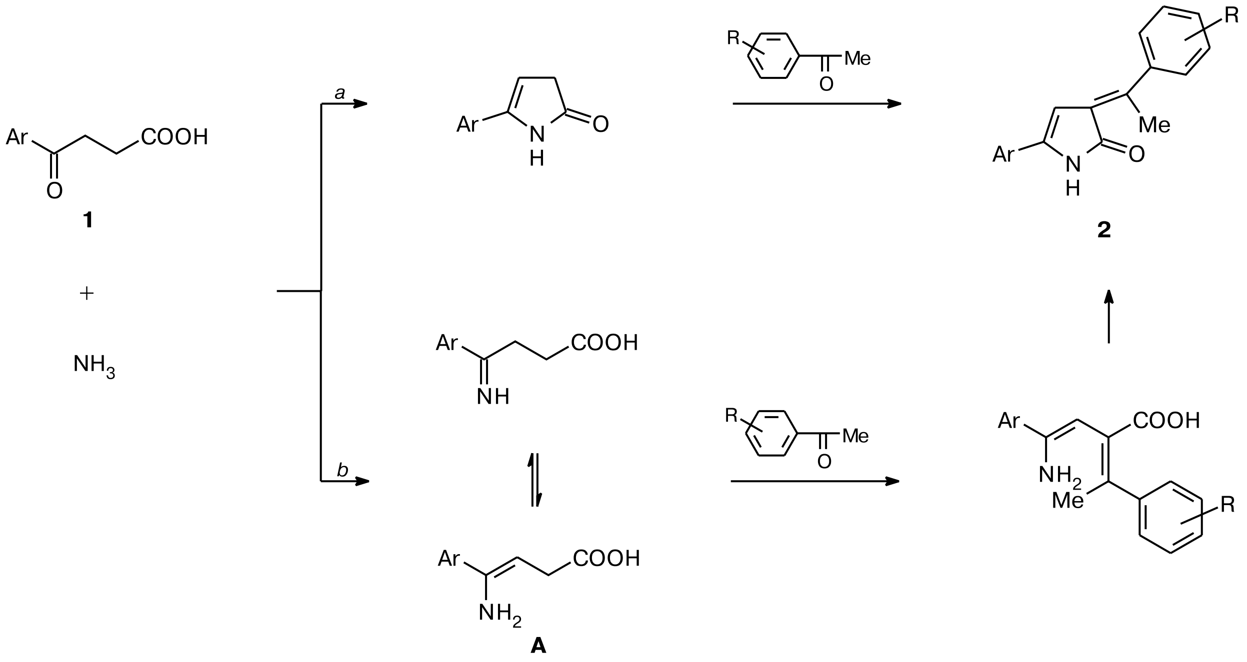
Scheme 2



yields of the condensation products in the reactions with alkyl aryl ketones depend on the nature of the substituent in the phenyl ring of the starting ketone and the synthesis conditions.

The possible scheme of the synthesis of final products **2a—f** can be represented (Scheme 2) as the initial formation of pyrrol-2-ones followed by condensation of ketones at the methylene unit of the heterocycle (path *a*). The possibility of generation of the intermediate **A**, which can exist as two tautomeric forms, *viz.*, enamine and imine, was not ruled out (path *b*).

According to quantum chemical calculations by the PM3 method, the enamine structure is thermodynamically more stable due to conjugation of the aromatic ring, the C=C bond, and the electron pair of the nitrogen atom. The intermediate **A** is involved in further condensation followed by azaheterocyclization to give compounds **2a—f**.

With the aim of increasing the yield of products **2a—f**, we changed the reaction conditions. We used aromatic hydrocarbons (toluene or xylene) as the solvent. However, these conditions appeared to be unacceptable due, apparently, to low polarity of the solvent.

The compositions and structures of compounds **2a—f** were confirmed by elemental analysis, IR spectroscopy, and ^{1}H NMR spectroscopy (Table 1).

The IR spectra of compounds **2a—f** show absorption bands of the amide carbonyl group (amide I) at 1757 cm^{-1}, amide II at 1580—1560 cm^{-1}, and N—H at 3310 cm^{-1}.

The ^{1}H NMR spectra of compounds **2a—f** show signals for the vinyl protons at the C(4) atom at δ 6.98, a singlet for the protons of the methyl group at δ 2.35, a multiplet for the protons of the aryl substituent at δ 7.27—7.98, and a broadened signal for the proton at the nitrogen atom at δ 8.12. The numbers, positions, and multiplicities of the signals correspond to the proposed structures.

Since the reactions performed under reflux in acetic anhydride afforded the final products in low yields, we developed the conditions for condensation with the use of microwave heating as an efficient source of thermal activation. The synthesis performed with microwave heating made it possible to obviate the need for solvents. In this case, the temperature of the reaction mixture is not limited by the boiling point of the solvent and the reaction proceeds much faster. This is an evident advantage of microwave heating over the conventional way of heat supplying from an external source.

We performed the microwave synthesis with the use of 4-aryl-4-oxobutanoic acids **1a,b** in a mixture with ketones in the presence of ammonium acetate. The reaction mixture was wetted with ethanol before being placed in a microwave oven (Scheme 3).

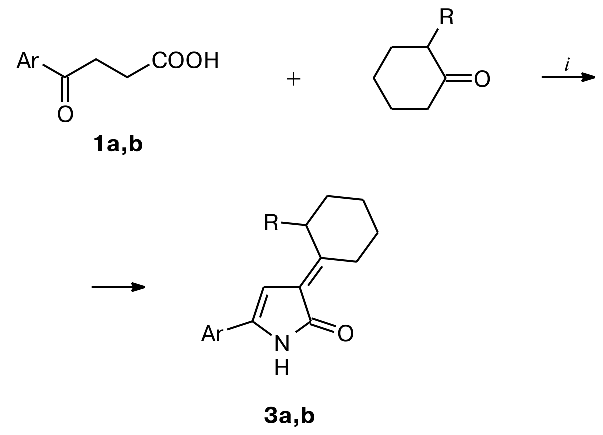
We chose ethanol as the solvent because the rate of absorption of microwave radiation energy linearly increases with increasing dielectric permeability of the solvent.[9] The solvent was used also to homogenize the reagents.

The synthesis performed in a microwave oven makes it possible to decrease the reaction time by a factor of 10—15 compared to the conventional reaction in an acetic anhydride solution (Table 2).

Table 1. Physicochemical characteristics of compounds **2a—f** and **3a,b**

Compound	M.p. /°C	Found/Calculated (%) C	H	N	Molecular formula	IR, ν/cm^{-1}	^{1}H NMR, δ
2a	123—125	82.54 82.73	5.92 5.79	5.32 5.36	$C_{18}H_{15}NO$	3310 (NH); 2950 (Me); 1757 (C=O); 1624 (C=C—Ph); 1583 (amide II); 1394 (=CH)	2.55 (s, 3 H, Me); 6.98 (s, 1 H, =CH);7.35—7.54 (m, 10 H, Ar); 8.12 (s, 1 H, NH)
2b	193—195	82.57 82.88	6.02 6.22	5.11 5.09	$C_{19}H_{17}NO$	3310 (NH); 2950 (Me); 1757 (C=O); 1624 (C=C—Ph); 1583 (amide II); 1394 (=CH)	2.35, 2.55 (both s, 3 H each, Me); 6.98 (s, 1 H, =CH); 7.27—7.54 (m, 9 H, Ar); 8.12 (s, 1 H, NH)
2c	153—155	73.12 73.66	5.20 5.21	4.44 4.52	$C_{19}H_{16}ClNO$	3310 (NH); 2950 (Me); 1757 (C=O); 1624 (C=C—Ph); 1583 (amide II); 1394 (=CH)	2.35, 2.55 (both s, 3 H each, Me); 6.98 (s, 1 H, =CH); 7.27—7.62 (m, 8 H, Ar); 8.12 (s, 1 H, NH)
2d	95—96	71.24 71.25	4.98 5.03	7.56 7.74	$C_{19}H_{16}N_2O_3$	3310 (NH); 2950 (Me); 1757 (C=O); 1624 (C=C—Ph); 1583 (amide II); 1394 (=CH); 1491, 1321 (Ar—NO$_2$)	2.35, 2.55 (both s, 3 H each, Me); 6.98 (s, 1 H, =CH); 7.27—7.98 (m, 8 H, Ar); 8.12 (s, 1 H, NH)
2e	98—99	71.11 71.24	4.81 5.03	7.73 7.74	$C_{19}H_{16}N_2O_3$	3310 (NH); 2950 (Me); 1757 (C=O); 1624 (C=C—Ph); 1583 (amide II); 1394 (=CH); 1491, 1321 (Ar—NO$_2$)	2.35, 2.55 (both s, 3 H each, Me); 6.98 (s, 1 H, =CH); 7.27—7.78 (m, 8 H, Ar); 8.12 (s, 1 H, NH)
2f	110—112	78.11 78.59	6.11 6.25	9.54 9.65	$C_{19}H_{18}N_2O$	3310 (NH); 2950 (Me); 1757 (C=O); 1624 (C=C—Ph); 1583 (amide II); 1394 (=CH)	2.35, 2.55 (both s, 3 H each, Me); 6.98 (s, 1 H, =CH); 7.05—7.54 (m, 8 H, Ar); 8.12 (s, 1 H, NH)
3a	78—79	77.52 77.60	6.32 6.56	5.02 5.23	$C_{17}H_{19}NO$	3310 (NH); 2950 (Me); 2927 (CH$_2$); 1757 (C=O); 1624 (C=C—Ph); 1583 (amide II); 1394 (=CH)	1.75—2.14 (m, 10 H, CH$_2$); 2.35 (s, 3 H, Me); 6.98 (s, 1 H, =CH); 7.27—7.43 (m, 4 H, Ar); 8.12 (s, 1 H, NH)
3b	82—84	79.53 79.86	7.53 7.82	4.98 5.14	$C_{18}H_{21}NO$	3310 (NH); 2950 (Me); 2927 (CH$_2$); 1757 (C=O); 1624 (C=C—Ph); 1583 (amide II); 1394 (=CH)	1.47—2.14 (m, 12 H, CH$_2$); 2.35 (s, H, Me); 6.98 (s, 1 H, =CH); 7.27—7.43 (m, 4 H, Ar); 8.12 (s, 1 H, NH)

Scheme 3



	3a	3b
Ar	*p*-Tol	*p*-Tol
R	H	Me

Reagents and conditions: *i*. AcONH$_4$, microwave irradiation.

The physicochemical characteristics of compounds **2a—f**, which were prepared in an acetic anhydride solution, are completely identical with those synthesized in a microwave oven (see Table 1).

Microwave activation allows one to carry out the reactions in the absence of a toxic solvent, substantially decrease the reaction time, and, in addition, perform the reaction with alicyclic ketones.

Experimental

Microwave syntheses were carried out in a Daewoo-KOR 6167 domestic microwave oven (the power output was 800 W, the operating frequency was 2450 MHz).

The IR spectra were recorded on a Specord M-80 spectrometer in Nujol mulls and hexachlorobutadiene (a thin layer). The ^{1}H NMR spectra were measured on a Varian Unity Inova spectrometer (600 MHz, Me$_4$Si as the internal standard, CDCl$_3$ as the solvent). The yields and physicochemical characteristics of the reaction products are given in Tables 1 and 2.

Table 2. Yields of condensation products under different conditions*

Compound	Reaction in Ac_2O		Reaction in a microwave oven		Decrease in τ
	Yield (%)	τ/min	Yield (%)	τ/min	
2a	61	120	56	12	by a factor of 10
2b	60	120	59	12	by a factor of 10
2c	52	150	50	10	by a factor of 15
2d	55	120	62	12	by a factor of 10
2e	69	120	62	12	by a factor of 10
2f	66	90	63	7	by a factor of 13
3a	—	150	58	9	—
3b	—	150	56	9	—

* τ is the reaction time.

4-Oxoalkanoic acids **1a,b** were synthesized according to a known procedure.[10]

5-Aryl-3-(1-arylethylidene)pyrrol-2-ones 2a—f (general procedure). *A.* Azaheterocyclization of 4-oxo acids in acetic anhydride. 4-Oxobutanoic acid **1a,b** (0.01 mol), the corresponding ketone (0.01 mol), and ammonium acetate (0.025 mol) were placed in a 100-mL round-bottom flask equipped with a reflux condenser. Then acetic anhydride (15 mL) was added. The reaction mixture was heated for 2 h and poured into water. The crystals that formed were filtered off and recrystallized from hexane.

***B.* Condensation of 4-aryl-4-oxobutanoic acids with alkyl aryl ketones under microwave irradiation.** 4-Oxobutanoic acid **1a,b** (0.01 mol), ketone (0.01 mol), and ammonium acetate (0.025 mol) were thoroughly stirred in a heat-resistant bottle. The reaction mixture was wetted with ethanol and the bottle was placed in a microwave oven. The resulting crystals were recrystallized from hexane.

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