monohydrochloride in 100 ml of water was added dropwise a warm solution of 1.4 g (0.01 mole) of uracil-5-carboxaldehyde in 200 ml of water. The mixture was heated on a steam bath for 1 hr and stirred for an additional hour at room temperature. The white solid was collected by filtration and washed with ethanol and ether to give 1.4 g (quantitative yield) of the **azine of uracil-5-carboxaldehyde** (IV), mp >360°. An analytical sample was obtained by dissolving the product in dilute KOH, filtering, and acidifying the filtrate to pH 5 with dilute HCl: $\lambda_{max}^{pH\ 1}$ 229 (ε 20,200), 274 (ε 24,000), and 358 mμ (ε 3600); $\lambda_{max}^{pH\ 11}$ 280 (ε 13,500) and 357 mμ (ε 38,800).

Anal. Calcd for $C_{10}H_8N_6O_4$: C, 43.48; H, 2.92; N, 30.43. Found: C, 43.68; H, 2.96; N, 30.15.

Experiment B.—To a stirred solution of 1.28 g (0.04 mole) of 97% hydrazine in 50 ml of water and 0.6 g of acetic acid was added dropwise a warm solution of 2.8 g (0.02 mole) of uracil-5-carboxaldehyde in 180 ml of water. The resulting solution was heated with stirring on a steam bath for 1 hr. On cooling, a light yellow solid (2.0 g) was separated, which consisted of a mixture of azine (IV) and the rearranged product (**4-ureidomethylene-1H-5-pyrazolone**, IIIb). These were separated by recrystallizing the crude product from 800 ml of water. The azine IV, which was quite insoluble in water, was isolated first to yield 1 g (36%), mp >360°. The rearranged product IIIb was obtained from the concentrated filtrate to give 0.8 g (25% yield), mp 289–290° dec. Further recrystallization from water yielded an analytically pure sample as white needles: mp 290° dec; $\lambda_{max}^{pH\ 1}$ 231 mμ (ε 13,700); $\lambda_{max}^{pH\ 11}$ 234 mμ (ε 12,200). The product gave a yellow coloration with acidified *p*-dimethylaminobenzaldehyde (positive test for R-NHCONH$_2$[4,5]).

Anal. Calcd for $C_5H_6N_4O_2$: C, 38.96; H, 3.92; N, 36.35. Found: C, 38.87; H, 3.89; N, 36.03.

Experiment C.—To a solution of 1.6 g (0.05 mole) of 97% hydrazine in 100 ml of water was added a warm solution of 1.4 g (0.01 mole) of uracil-5-carboxaldehyde in 300 ml of water containing 0.2 g of acetic acid. The resulting mixture was heated on a steam bath for 1 hr. On cooling, 0.32 g (20.8% yield) of white solid, mp 280–282°, was collected (impure IIIb). The filtrate was concentrated to 30 ml under reduced pressure and a light orange solid separated. This was collected by filtration and washed with a small amount of ethanol and ether to give 0.5 g (32.4% yield) of the **hydrazone of uracil-5-carboxaldehyde** (IIb): mp 275–276°; $\lambda_{max}^{pH\ 1}$ 230 (ε 12,400), 274 mμ (ε 3400); $\lambda_{max}^{pH\ 11}$ 234 (ε 9700), 311 mμ (ε 3000).

Anal. Calcd for $C_5H_6N_4O_2$: C, 38.96; H, 3.92; N, 36.35. Found: C, 38.16; H, 3.49; N, 36.63.

Attempted further purification of this product from boiling water resulted in its conversion to IIIb.

Uracil-5-carboxaldehyde Formylhydrazone.—To 5.0 g (0.08 mole) of formylhydrazine in 400 ml of water was added dropwise, with stirring, a warm (60–70°) solution of 5.7 g (0.04 mole) of uracil-5-carboxaldehyde in 1 l. of water and 2 ml of acetic acid. The mixture was heated on a steam bath for 1 hr and cooled. The resulting white solid was collected by filtration and recrystallized from dimethylformamide to give 7.2 g (97% yield) of the formylhydrazone, which darkened at 350° and decomposed at 360°: $\lambda_{max}^{pH\ 1}$ 231 (ε 9500) and 268 mμ (ε 11,800); $\lambda_{max}^{pH\ 11}$ 272 (ε 14,000) and 320 mμ (ε 19,000).

Anal. Calcd for $C_6H_6N_4O_3$: C, 39.56; H, 3.32; N, 30.76. Found: C, 39.51; H, 3.28; N, 30.55.

The following derivatives of I were prepared in a similar fashion. **Uracil-5-carboxaldehyde phenylhydrazone** showed mp 309–310° (lit.[3] mp 298–300°) and ultraviolet bands were at λ_{max}^{EtOH} 290 (ε 16,300) and 365 mμ (ε 14,000). **Uracil-5-carboxaldehyde oxime** had mp 290° dec (lit.[3] mp 260° dec) and ultraviolet bands were at $\lambda_{max}^{pH\ 1}$ 238 (ε 10,700) and 281 mμ (ε 9400) and $\lambda_{max}^{pH\ 11}$ 257 (ε 11,400) and 307 mμ (ε 11,200). **Uracil-5-carboxaldehyde thiosemicarbazone** had mp >360° (lit.[7] mp 320° dec) and ultraviolet bands were at $\lambda_{max}^{pH\ 1}$ 270 (ε 17,200) and 315 mμ (ε 22,900) and $\lambda_{max}^{pH\ 11}$ 283 (ε 17,000) and 328 mμ (ε 31,000).

Registry No.—I, 1195-08-0; IIa, 15352-84-8; IIb, 15352-85-9; IIIa, 15352-86-0; IIIb, 15352-87-1; IV, 14684-66-3; hydrazine, 302-01-2; methylhydrazine, 60-34-4; uracil-5-carboxaldehyde formylhydrazone, 15352-89-3; uracil-5-carboxaldehyde phenylhydrazone, 14859-92-8; uracil-5-carboxaldehyde oxime, 14859-93-9; uracil-5-carboxaldehyde thiosemicarbazone, 13545-08-9.

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Twofold Aroylations of Certain Amides by Means of Sodium Hydride[1]

JAMES F. WOLFE AND GEORGE B. TRIMITSIS

Department of Chemistry, Virginia Polytechnic Institute, Blacksburg, Virginia 24061

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Recent publications[2,3] describing 1,3-diaroylations of acetone and dimethyl sulfone with aromatic esters by means of sodium hydride prompt us to report the results of a study in which acetamide and certain other primary amides were found to undergo related twofold aroylations in the presence of these reagents.

Treatment of acetamide with excess sodium hydride and 2.5 mol equiv of the appropriate aromatic ester in refluxing 1,2-dimethoxyethane (monoglyme) afforded β-keto imides **1a–c** in yields of 62–100% (eq 1). Simi-

$$CH_3CONH_2 \xrightarrow[2.\ \text{acid}]{1.\ \text{ArCOOR, NaH}} \text{ArCOCH}_2\text{CONHCOAr} \quad (1)$$

1a, Ar = C_6H_5
b, Ar = $C_6H_4OCH_3$-*p*
c, Ar = C_6H_4Cl-*p*

larly, phenylacetamide gave the products **2a–d** in yields of 27–92%. That the method was general for higher primary amides was demonstrated by twofold benzoylation of butyramide and hexanamide to produce **3a** and **3b** in yields of 68 and 65%, respectively. The results of these experiments are summarized in Table I.

ArCOCHCONHCOAr
|
C_6H_5

2a, Ar = C_6H_5
b, Ar = $C_6H_4OCH_3$-*p*
c, Ar = C_6H_4Cl-*p*
d, Ar = 3-pyridyl

$C_6H_5COCHCONHCOC_6H_5$
|
R

3a, R = C_2H_5
b, R = *n*-C_4H_9

The identity of **1a** was established by comparison with an authentic sample, which was prepared from dipotassio N-acetylbenzamide.[4] The structural assignments for **1b**, **1c**, **2a–d**, **3a**, and **3b**, all of which appear to be new compounds, were based on analyses and nmr spectra (Table II). Further confirmation of structures **2a** and **2b** was provided by their acid-catalyzed hydrolysis to form, in the case of **2a**, benzoic acid and deoxybenzoin, and in the case of **2b**, anisic acid and 2-phenyl-4′-methoxyacetophenone. Acidic hydrolysis of **3a** afforded benzoic acid and butyrophenone, while that of **3b** gave benzoic acid and caprophenone. β-

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TABLE I

TWOFOLD AROYLATIONS OF AMIDES WITH AROMATIC ESTERS BY MEANS OF SODIUM HYDRIDE IN REFLUXING MONOGLYME

Starting amide	Methyl ester	Product	Reaction period, hr	Yield, %	Mp, °C
Acetamide	Benzoate	N,α-Dibenzoylacetamide (**1a**)	19	100	170–171[b,c]
Acetamide	Anisate	N,α-Dianisoylacetamide (**1b**)	20	62	165–166[b]
Acetamide	*p*-Chlorobenzoate	N,α-Di(*p*-chlorobenzoyl)acetamide (**1c**)	20	70	198.5–199[b]
Phenylacetamide	Benzoate	N,α-Dibenzoylphenylacetamide (**2a**)	18	92	208–210[b]
Phenylacetamide	Anisate	N,α-Dianisoylphenylacetamide (**2b**)	9	60	219.5–220.5[b]
Phenylacetamide	*p*-Chlorobenzoate	N,α-Di(*p*-chlorobenzoyl)phenylacetamide (**2c**)	9.5	68	222–223[b]
Phenylacetamide	Nicotinate[a]	N,α-Dinicotinoylphenylacetamide (**2d**)	9	27	191–192[d]
Butyramide	Benzoate	N,α-Dibenzoylbutyramide (**3a**)	9	68	155.5–156.5[b]
Hexanamide	Benzoate	N,α-Dibenzoylhexanamide (**3b**)	9	65	140.5–141.5[b]

[a] Ethyl ester. [b] Recrystallized from absolute ethanol. [c] Lit.[4] mp 168–169°. [d] Recrystallized from 95% ethanol.

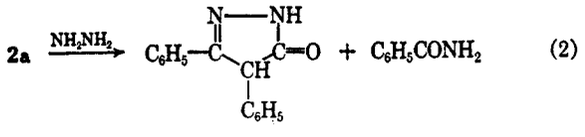
TABLE II

NMR[a] AND ANALYTICAL DATA FOR NEW β-KETO IMIDES

Compd	Types of hydrogen and chemical shift, δ (ppm)[b] Aromatic	Methinyl	Other	Formula	Calcd, % C	H	N	Found, % C	H	N
1b[c]	7.50[e]		4.43,[f,g] 3.70[f,h]	$C_{18}H_{17}NO_5$	66.05	5.24	4.28	66.14	5.40	4.38
1c[c]	7.63[e]		4.60[f,g]	$C_{16}H_{11}Cl_2NO_3$[l]	57.16	3.30	4.12	57.00	3.35	3.94
2a[d]	7.22[e]	6.23[f]		$C_{22}H_{17}NO_3$	76.95	4.99	4.08	77.09	5.09	3.89
2b[d]	7.55[e]	6.68[f]	3.75[e,h]	$C_{24}H_{21}NO_5$	71.45	5.25	3.47	71.56	5.27	3.41
2c[c]	7.55[e]	6.66[f]		$C_{22}H_{15}Cl_2NO_3$[m]	64.09	3.67	3.40	64.03	3.68	3.28
2d[c]	8.30[e]	6.90[f]		$C_{20}H_{15}N_3O_3$	69.55	4.37	12.16	69.60	4.54	12.10
3a[c]	7.86[e]	5.35[e]	1.83,[e,g] 0.96[i,j]	$C_{18}H_{17}NO_3$	73.20	5.80	4.74	73.43	5.73	4.81
3b[d]	7.68[e]	5.10[e]	0.80[e,k]	$C_{20}H_{21}NO_3$	74.28	6.54	4.33	74.41	6.65	4.32

[a] Nmr spectra were obtained on a Varian Associates A-60 spectrometer. [b] Chemical shifts, relative to tetramethylsilane as external standard, are measured to the center of a singlet or multiplet. Peak areas were consistent with the assignments given above. [c] Deuteriodimethyl sulfoxide was used as the nmr solvent. [d] Trifluoroacetic acid was used as the nmr solvent. [e] Multiplet. [f] Singlet. [g] Methylene. [h] *p*-OCH_3. [i] Triplet. [j] Methyl. [k] *n*-C_4H_9. [l] Calcd: Cl, 21.09. Found: Cl, 21.01. [m] Calcd: Cl, 17.20. Found: Cl, 17.32.

Keto imide **2a** also underwent cyclization with hydrazine[4] to form pyrazolone **4** and benzamide (eq 2).

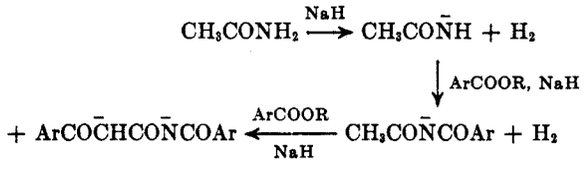


(2)

4

The present twofold aroylations of acetamide appear to follow the course outlined in Scheme I, in which

SCHEME I



initial ionization of an NH hydrogen of the amide is followed by N-aroylation and subsequent loss of the imide hydrogen to form the monoanion of the appropriate N-aroylacetamide. Removal of a methyl hydrogen from this monoanion, as the condensation with a second ester molecule proceeds, produces the monoanion of the final product which is then converted, by loss of a methylene hydrogen, to its dianion. This sequence was supported by the observation that the diaroylations of acetamide were accompanied by evolution of 4 mol equiv of hydrogen. In addition, treatment of acetamide with 1 mol equiv of methyl benzoate in the presence of sodium hydride resulted in liberation of 2 mol equiv of hydrogen and formation of N-acetylbenzamide, along with its cleavage product benzamide; α-benzoylacetamide, which would have been produced by initial C-benzoylation of acetamide, could not be detected. Although the twofold aroylations of phenylacetamide were also accompanied by the evolution of 4 mol equiv of hydrogen, these reactions appear to follow a somewhat different pathway. Thus, treatment of phenylacetamide with 1 mol equiv of methyl benzoate and sodium hydride produced a mixture of α-benzoyl- and N-benzoylphenylacetamides. Apparently both of these compounds are converted, through the appropriate sodio salts, to the final diaroyl derivative when the reaction is carried out in the presence of excess ester.

The present twofold aroylations provide a convenient one-step route to a variety of β-keto imides which would ordinarily be available only through less direct synthetic procedures.[4]

Experimental Section[5]

Twofold Aroylations of Amides.—In a 500-ml, two-necked flask equipped with a pressure-equalizing addition funnel, a magnetic stirring bar, and a reflux condenser, connected at its upper end through a cold trap (Dry Ice–acetone) to a Precision Scientific wet-test meter filled with water, was placed 250 ml of

(5) Melting points were taken on a Thomas–Hoover "Uni-Melt" apparatus in open capillary tubes, and are corrected. Analyses were performed by Galbraith Laboratories, Knoxville, Tenn., and by Q. H. Tan using an F & M Model 185 C, H, and N analyzer. Infrared spectra were taken on a Beckman IR-5A infrared spectrophotometer using the potassium bromide pellet method. Thin layer chromatograms were carried out with an Eastman Chromagram apparatus using Chromagram sheets Type K301R (silica gel) with fluorescent indicator and toluene–ethanol (3:1) as the developing solvent. Spots were detected with ultraviolet light.

monoglyme[6] and 0.5 mole of sodium hydride.[7] A solution of the appropriate amide (0.05 mole) and ester (0.125 mole)[8] in 125 ml of monoglyme was placed in the addition funnel and the system was purged with dry nitrogen, then closed to the atmosphere. The monoglyme in the reaction flask was heated to reflux and when thermal equilibrium had been established, an initial reading was taken on the gas meter. The solution of ester and amide was then added over a period of 20 min, and the resulting suspension was refluxed until hydrogen evolution had ceased[9] (Table I). The solvent was removed under reduced pressure, and the remaining pasty residue was cooled to 0°. Addition of ether (125 ml) was followed after several minutes by the cautious addition of 30 ml of water. The sodio salts of the products, which separated between the layers, were collected, and stirred with a mixture of 50 ml of concentrated hydrochloric acid and 300 g of crushed ice. The resulting solids were collected by filtration, washed with 5% sodium bicarbonate solution,[10] and recrystallized from appropriate solvents (Table I).

In the aroylation of phenylacetamide with ethyl nicotinate to form **2d**, the sodio salts, which separated between the layers, were collected by filtration and dissolved in 500 ml of cold 25% hydrochloric acid. The acidic solution was neutralized (pH 8) with solid sodium bicarbonate to precipitate β-keto imide **2d** which was then recrystallized.

Yields of β-keto imides prepared in the above manner are given in Table I. Analytical data and principal nmr absorptions for new products **1b**, **1c**, **2a–d**, **3a**, and **3b** are given in Table II. All of these compounds had infrared absorption at 3.10–3.40 (NH) and 5.80–6.00 μ (C=O).

Hydrolysis of β-Keto Imides 2a, 2b, 3a, and 3b.—A 2.0-g sample of **2a** was refluxed with 200 ml of 12 *N* hydrochloric acid for 24 hr. The hydrolysis mixture was extracted with ether, and the ethereal extracts were washed with 5% sodium bicarbonate solution. The combined bicarbonate extracts were acidified with 12 *N* hydrochloric acid to precipitate 0.69 g (97%) of benzoic acid. The ethereal extracts were dried ($MgSO_4$) and concentrated to afford 0.95 g (83%) of deoxybenzoin, mp 54–56° (lit.[11] mp 55–56°). The infrared spectrum was identical with that of an authentic sample of deoxybenzoin.

Similarly, **3a** gave nearly quantitative yields of benzoic acid and butyrophenone, and **3b** afforded caprophenone and benzoic acid.

A 1.5-g sample of **2b**, which was resistant to hydrochloric acid hydrolysis, was refluxed with a mixture of 10 ml of concentrated sulfuric acid, 10 ml of water, and 30 ml of acetic acid for 18 hr. The reaction mixture was processed as described above to yield 0.20 g (35%) of anisic acid, mp 182–184°, and 0.33 g (40%) of 2-phenyl-4′-methoxyacetophenone, mp 73°, (lit.[12] mp 76°) which was identified by comparison of its infrared spectrum with that of an authentic sample.

Cyclization of 2a with Hydrazine to Form Pyrazolone 4.—A solution of 2.0 g of **2a** and 20 drops of 95% hydrazine in 100 ml of 95% ethanol was refluxed for 1.5 hr. The reaction mixture was diluted with 100 ml of water and a few drops of 3 *N* hydrochloric acid were added. The volume was then reduced to 130 ml, and the solution was cooled to precipitate 0.50 g (37%) of 3,4-diphenylpyrazolone-5 (**4**), mp 234–236° (lit.[13] mp 234–235°). A mixture melting point determination with an authentic sample showed no depression. The infrared spectra of the two samples were identical. The aqueous solution was further reduced in volume to precipitate 0.25 g (35%) of benzamide, mp 125.5–127°.

Treatment of Acetamide and Phenylacetamide with 1 Mol Equiv of Methyl Benzoate and Sodium Hydride.—To a suspension of 0.105 mole of sodium hydride in 200 ml of refluxing monoglyme contained in the apparatus described above, was added over a period of 15 min, a solution of 0.05 mole of acetamide and 0.05 mole of methyl benzoate. The reaction mixture was allowed to reflux for 3 hr, at the end of which time 2 mol equiv of hydrogen had been evolved. The solvent was removed under reduced pressure, and the resulting residue was processed in the usual manner except that enough water was added to completely dissolve the sodio salts. The aqueous layer was acidified with cold dilute hydrochloric acid, and the acidic solution was extracted with 500 ml of ether–ethyl acetate (1:1). The extracts were dried (Na_2SO_4) and concentrated to afford a thick oil which was shown by thin layer chromatography (tlc) to consist of N-acetylbenzamide and benzamide. Concentration of the ethereal layer afforded benzamide. α-Benzoylacetamide[14] which was shown to be well-resolved from N-acetylbenzamide and benzamide by tlc on a known mixture, could not be detected.

Phenylacetamide (0.05 mole) was treated with methyl benzoate (0.05 mole) and 0.105 mole of sodium hydride in 200 ml of refluxing monoglyme for 4 hr, at the end of which time 2 mol equiv of hydrogen had been liberated. The reaction mixture was processed as described above for the reaction with acetamide. Acidification of the aqueous layer followed by extraction with ether–ethyl acetate (1:1) and concentration of the extracts afforded a light yellow oil. Tlc of this material showed the presence of two components which were identified as N-benzoylphenylacetamide[15] and α-benzoylphenylacetamide[16] by comparison of their R_f values with those of authentic samples.

Registry No.—Sodium hydride, 7646-69-7; **1a**, 15231-17-1; **1b**, 15231-18-2; **1c**, 15231-10-4; **2a**, 14072-63-0; **2b**, 15231-12-6; **2c**, 15231-13-7; **2d**, 15231-14-8; **3a**, 15231-15-9; **3b**, 15231-16-0.

(6) The monoglyme was distilled from sodium ribbon immediately before use.

(7) This reagent was used as a 55% dispersion in mineral oil as obtained from Metal Hydrides, Inc., Beverly, Mass.

(8) Although only 2 mol equiv of ester and 4 mol equiv of sodium hydride are apparently needed to effect the dicondensation reactions, consistently higher yields and purer products were obtained with the above proportions of reactants.

(9) In all cases the total volume of gas, which was corrected for temperature, pressure, and water vapor pressure, was consistent with the production of 4 mol equiv of hydrogen.

(10) Acidification of the bicarbonate washings usually produced some of the acid corresponding to the ester which was used in the aroylation.

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Novel Formation of 11-Ketoindeno[1,2-c]isocoumarin

S. WAWZONEK AND J. K. STOWELL[1]

Department of Chemistry, University of Iowa, Iowa City, Iowa

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The recent paper[2] which demonstrated that the structure of the compound reported earlier[3] as dibenzo[*a*,*e*]cyclooctanetrione was actually 11-ketoindeno[1,2-*c*]isocoumarin (I) suggested a report on our work which arrived at the same conclusion. Our structure assignment was based on reactions, spectra, and synthesis.

Treatment of the isocoumarin I with alkali followed by acidification gave an acid which was identical with 2-(2-carboxyphenyl)-1,3-indandione[4] (II). This acid is oxidized in basic medium by bromine to 2,2′-benzil dicarboxylic acid and upon melting or refluxing with hydrochloric acid regenerates the isocoumarin I.

Oxidation of the isocoumarin I with chromic acid gave the same lactone that is formed when the isocoumarin is treated with nitric acid.[5] This compound

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