C-Aroylations of imides and *N*-aroylations of β-keto amides with aromatic esters by means of sodium hydride to form β-keto imides[1]

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Aroylations at the methyl groups of *N*-acetylbenzamide and *p*-benzoylaminoacetophenone, and at a methylene position of succinimide with appropriate aromatic esters were effected by means of sodium hydride in refluxing monoglyme. Benzoylation at the amide group of α-benzoylacetamide and salicylamide were accomplished similarly. The yields of β-keto imides from these *C*- and *N*-aroylations by sodium hydride, with which intermediate dianions were evidently not formed, were generally much better than those obtained through dianions produced by means of an alkali amide in liquid ammonia. The synthetic utility of the sodium hydride method is discussed.

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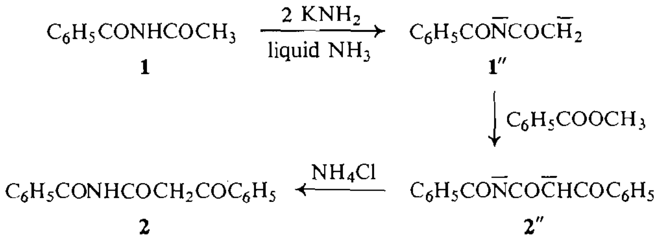
N-Acetylbenzamide (**1**) has previously (1) been benzoylated at its methyl group with methyl benzoate by means of two molecular equivalents of potassium amide in liquid ammonia to form β-keto imide **2**; dianions **1''** and **2''** were intermediates (Scheme 1). Similarly, vinylogous imide **3** has been benzoylated at its methyl group to form **4** (2) and imide **5** at a methylene group to give **6** (3) through corresponding dianions.



$$\begin{tikzcd}
\underset{\mathbf{1}}{C_6H_5CONHCOCH_3} \arrow[r, "2\ KNH_2", "\text{liquid } NH_3"'] & \underset{\mathbf{1''}}{C_6H_5CO\overset{-}{N}CO\overset{-}{C}H_2} \arrow[d, "C_6H_5COOCH_3"] \\
\underset{\mathbf{2}}{C_6H_5CONHCOCH_2COC_6H_5} & \underset{\mathbf{2''}}{C_6H_5CO\overset{-}{N}CO\overset{-}{C}HCOC_6H_5} \arrow[l, "NH_4Cl"']
\end{tikzcd}$$

SCHEME 1

Imides **1**, **3**, and **5** have now been benzoylated in better yields by means of sodium hydride in refluxing monoglyme, as summarized in Table I. For example, the yield of β-keto imide **2** from imide **1** with sodium hydride, eq. [1], was 85%, which is three times that (28%) obtained with potassium amide.

$$[1] \quad \mathbf{1} \xrightarrow[\text{NaH, monoglyme}]{C_6H_5COOCH_3} \mathbf{2''} \xrightarrow{\text{acid}} \mathbf{2}$$

Whereas in the alkali amide method the imide is first converted to the dianion (see Scheme 1), in the sodium hydride method a mixture of the imide and ester is added to the reagent. When imide **1** was first treated with sodium hydride and methyl benzoate then added, the yield of **2** was only fair (36%) and much benzamide was obtained; the latter product arose through cleavage of imide **1** by the sodium hydride (see Experimental).

Similarly, imide **1** was aroylated with methyl

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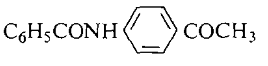

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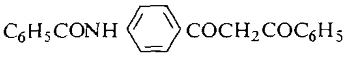

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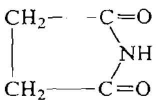

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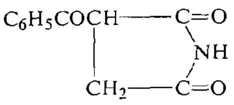

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TABLE I

Yields of benzoylation products of imides by the sodium hydride and alkali amide methods

Imide	Benzoylation product	Yield (%) NaH method	Yield (%) MNH_2 method
1	**2**	85	28*
3	**4**	88	52†
5	**6**	56	44‡

*Ref. 1.
†Ref. 2.
‡Ref. 3.

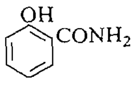
anisate, methyl *p*-chlorobenzoate, and ethyl nicotinate to form the new β-keto imides 7*a*–*c* in yields of 79, 93, and 78%, respectively. Structural assignments for these products were supported by analyses and absorption spectra (see Experimental).

$C_6H_5CONHCOCH_2COAr$
7*a*, Ar = $C_6H_4OCH_3$-*p*
7*b*, Ar = C_6H_4Cl-*p*
7*c*, Ar = 3-Pyridyl

Next, β-keto amide **8** was benzoylated by the sodium hydride method to form the *N*-benzoyl derivative **2** in 91% yield, eq. [2]. This *N*-benzoylation represents an alternate route for the preparation of **2**, the other route involving *C*-benzoylation of imide **1**, see eq. [1].

$$[2] \quad \underset{\mathbf{8}}{C_6H_5COCH_2CONH_2} \xrightarrow[\text{NaH method}]{C_6H_5COOCH_3} \mathbf{2}$$

Similarly, salicylamide (**9**), which may be regarded as an enolized β-keto amide, was benzoylated by the sodium hydride method to give the *N*-benzoyl derivative **10** in 90% yield.



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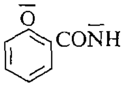
10

In contrast to sodium hydride, sodium amide was observed to effect the *N*-benzoylation of β-keto amide **8** through its dianion **8″** in only 14% yield, and none of the *N*-benzoyl derivative of **9** was obtained with sodium amide through dianion **9″**. That dianions **8″** and **9″** were formed initially was indicated by lack of stilbene formation on treatment with benzyl chloride (see Experimental).

$C_6H_5CO\bar{C}HCO\bar{N}H$

8″



9″

Finally, attempts were made to effect benzoylations at the methyl group of β-keto imide **11** and the phenolic imide **12** by the sodium hydride method. However, instead of *C*-benzoylation, cleavage of the respective acetyl groups occurred to form the β-keto amides **8** and **9** (or their anions), which underwent *N*-benzoylation to give the β-keto imides **2** and **10**, respectively.

$C_6H_5COCH_2CONHCOCH_3$

11

12

Discussion

These results show that sodium hydride in refluxing monoglyme is preferable to an alkali amide in liquid ammonia for *C*-aroylations of imides **1**, **3**, and **5** and especially, for *N*-aroylation of β-keto amides **8** and **9**. Presumably the sodium hydride method could be extended, not only to other aromatic esters, but also to other imides and β-keto amides, thereby leading to the syntheses of many new products. In certain cases, the same product may be prepared by either *C*-aroylation of an imide or *N*-aroylation of a β-keto amide as illustrated above for **2** by eqs. [1] and [2],

$$RCONHCOCH_3 \xrightarrow[\text{NaH}]{R'COOCH_3} \underset{\mathbf{13}}{RCONHCOCH_2COR'} \xleftarrow[\text{NaH}]{RCOOCH_3} R'COCH_2CONH_2$$

SCHEME 2

respectively. These complementary courses of reaction may be generalized by Scheme 2 in which R and R′ are appropriate aroyl groups of symmetrical or unsymmetrical β-keto imides of type **13**.

Interestingly, as in previously reported aroylations of β-diketones (4) by means of sodium hydride, the present aroylations of imides and β-keto amides by this reagent evidently do not involve the intermediate formation of dianions, for example **1**′′, which is the reactive intermediate in an aroylation by an alkali amide (see Scheme 1). Instead, only the imide monoanion such as **1**′ (see Scheme 3), seems to be formed, at least until the ester is added. This was indicated by evolution of only about one molecular equivalent of hydrogen on addition of imide **1** or **5** to five molecular equivalents of sodium hydride in refluxing monoglyme (see Table II); yet the expected three molecular equivalents of hydrogen were evolved on addition of a mixture of the imide and methyl benzoate to the reagent in accordance with Scheme 3 (see Table III). Although somewhat more than one equivalent of hydrogen was evolved with imide **3** alone (see Table II), only the anticipated three equivalents of hydrogen were formed with a mixture of **3** and ester (see Table III).

$$\begin{tikzcd}
\mathbf{1} \arrow[r, "\text{NaH}", "\text{(excess)}"'] & \underset{\mathbf{1'}}{C_6H_5CO\overline{N}COCH_3} + H_2 \arrow[d, "\text{NaH}"', "C_6H_5COOCH_3"] \\
H_2 + \mathbf{2''} & C_6H_5CO\overline{N}COCH_2COC_6H_5 + H_2 \arrow[l, "\text{NaH}"']
\end{tikzcd}$$

SCHEME 3

Although a total of only three molecular equivalents of hydrogen were evolved when a mixture of β-keto amide **8** or **9** and methyl benzoate was added to the sodium hydride reagent (see Table III), prolonged treatment of **8** and **9** alone with excess reagent produced considerably more than one molecular equivalent of hydrogen (see Table II); this indicated that **8** and **9** were slowly converted to dianions **8**′′ and **9**′′, respectively. However, formation of these dianions appears to be much too slow to account for the rate at which the benzoylations were realized in the presence of methyl benzoate (see Table III). Therefore dianions **8**′′ and **9**′′ seem not to be the reactive intermediates in these aroylations.

Several possible mechanisms for the related aroylations of β-diketones have previously been considered (4), and analogous mechanisms might also be possible for the present aroylations of imides and β-keto amides.

Experimental

Melting points were taken on a Thomas–Hoover melting point apparatus in open capillary tubes and are corrected. Analyses were performed by Galbraith Laboratories, Knoxville, Tennessee. Infrared (i.r.) spectra were taken on a Beckman IR-5A spectrophotometer using the potassium bromide pellet method. Nuclear magnetic resonance (n.m.r.) spectra were obtained on a Varian Associates A-60 spectrometer using deuteriodimethyl sulfoxide as solvent and tetramethylsilane as external standard. Chemical shifts are measured to the center of a singlet or multiplet. Thin-layer chromatograms (t.l.c.) were carried out with an Eastman Chromagram apparatus using Chromagram Sheets Type 1301R (silica gel) with fluorescent indicator and toluene–ethanol (3:1) as the developing solvent. Spots were detected with ultraviolet light. Monoglyme was distilled from sodium ribbon immediately before use. Sodium hydride was used as obtained from Metal Hydrides, Inc., Beverly, Massachusetts. Unless otherwise specified, chemicals were commercial reagent grade, and were used without further purification. All hydrogen evolution values are corrected for temperature, pressure, and water vapor pressure.

Benzoylations of Imides

In Table III are presented hydrogen evolution data accompanying these reactions. Additional details are given below.

(a) Of Imide 1

This reaction, as well as each of the subsequently described aroylations, was carried out in a 1 l three-necked flask equipped with a heating mantle, a pressure-equalizing addition funnel, and a high-efficiency reflux condenser, which was connected through a cold trap (Dry Ice–Acetone) to a Precision Scientific Co. wet-test meter filled with water. The center neck of the flask was tightly stoppered and the reaction mixture was stirred magnetically. The flask was charged with 250 ml of monoglyme and 0.25 mole of sodium hydride as an approximately 50% dispersion in mineral oil. A solution of 8.15 g (0.05 mole) of **1** (5) and 10.89 g (0.08 mole) of methyl benzoate in 100 ml of dry monoglyme was placed in the addition funnel. The system was then flushed with dry nitrogen and closed to the atmosphere. The sodium hydride – monoglyme slurry was brought to reflux, and when thermal equilibrium had been established, an initial reading was

TABLE II

Evolution of hydrogen from imides and β-keto amides with sodium hydride

	H_2 from addition of active hydrogen compound			
Imide or β-keto amide	Calculated for 1 mole equivalent (ml)	Found (ml)	% of theory	Reaction period (h)
1	1120	1220	109	6*
3	1120	1500	123	10.5
5	1120	1096	98	4.5*
8	560†	797	142	12
9	1120	1990	178	58

*Hydrogen evolution did not increase significantly with longer reaction periods.
†In this experiment 0.025 mole of **8** to 0.125 mole of sodium hydride was used; in all other experiments 0.05 mole of active hydrogen compound to 0.25 mole of sodium hydride was employed.

TABLE III

Evolution of hydrogen when a mixture of an imide or β-keto amide and methyl benzoate was added to excess sodium hydride

	H_2 from addition of active hydrogen compound and ester			
Imide or β-keto amide	Calculated for 3 mole equivalent (ml)	Found (ml)	% of theory	Reaction period (h)*
1	3360	3560	106	11
3	3360	3330	99	23
5	3360	3260	97	44
8	3360	3360	100	1
9	3360	3340	99	4

*Hydrogen evolution did not increase significantly with longer reaction periods.

taken on the test meter. The solution of imide and ester was added over a period of 25 min, the resulting reaction mixture was allowed to reflux until hydrogen evolution had ceased, and a final reading was taken on the test meter (see Table III). Most of the monoglyme was removed under reduced pressure and the remaining pasty residue was cooled to 0 °C in an ice–water bath. The residue was then treated with 150 ml of ether followed, after a few minutes, by 20 ml of cold water; initially, the water was added dropwise until the excess sodium hydride had been destroyed. The solid which separated between the layers was collected by filtration, treated with excess cold 6 *N* HCl, washed with 5% sodium bicarbonate solution, and recrystallized from 95% ethanol to afford 11.33 g (85%) of *N*,α-dibenzoylacetamide (**2**), m.p. 170–171 °C. A mixture melting point determination with an authentic sample of **2** (1) showed no depression; the i.r. spectra of the two samples were identical.

In one experiment, imide **1** (0.025 mole) was added to 0.125 mole of sodium hydride in 150 ml of monoglyme and the reaction mixture was allowed to reflux for 2 h during which time one molecular equivalent of hydrogen was evolved. Methyl benzoate (0.04 mole) was then added and refluxing was continued for 5 h; slightly less than two additional equivalents of hydrogen were evolved during this period. The reaction mixture was processed in the usual manner to afford 2.46 g (36%) of β-keto imide **2**. Thin-layer chromatography (t.l.c.) of the residues obtained by concentration of both the ethereal and aqueous layers revealed that they consisted primarily of benzamide.

In another experiment, imide **1** (0.025 mole) was treated with 0.125 mole of sodium hydride in refluxing monoglyme for 6 h but methyl benzoate was excluded. The reaction mixture was processed as usual to afford a crude semisolid which consisted predominately of benzamide as shown by t.l.c. In order to establish that **1** was not hydrolyzed to benzamide during the basic work-up of the reaction, a 1 g sample of **1** was treated with 100 ml of 5% aqueous sodium hydroxide solution for 30 min. The basic solution was acidified with cold 12 *N* hydrochloric acid and extracted with ether. The extracts were dried (Na_2SO_4) and concentrated to afford 0.8 g (80%) of recovered **1**.

(*b*) *Of Imide 3*

A mixture of 11.96 g (0.05 mole) of **3** (2) and 10.89 g (0.08 mole) of methyl benzoate in 100 ml of monoglyme, was added to 0.25 mole of sodium hydride in 250 ml of refluxing monoglyme. The reaction mixture was heated at reflux for 23 h. The solvent was removed under reduced pressure and the residue was treated as described above to yield 17.39 g of crude product. This was further purified through its copper chelate (2) to give 15.14 g (88%) of **4**, m.p. 183–185 °C, (lit. (2) m.p. 184.5–186 °C), mixture m.p. 183–185 °C.

(*c*) *Of Imide 5*

A solution of **5** (4.95 g, 0.05 mole) and methyl benzoate (10.89 g, 0.08 mole) was treated with 0.50 mole of sodium hydride in refluxing monoglyme for 44 h. The reaction mixture was processed in the usual manner to afford, after one crystallization of the crude product from absolute ethanol, 5.71 g (56%) of pure **6**, m.p. 138–140 °C, (lit. (3) m.p. 137.5–138 °C), mixture m.p. 138–140 °C. The i.r.

spectrum of this compound was identical with that of an authentic sample of **6** prepared by the potassium amide method (3).

*Aroylations of Imide **1** with other Aromatic Esters*

The general procedure for these aroylations was essentially the same as for the benzoylations described above. In all cases a mixture of 0.05 mole of **1**, 0.08 mole of the appropriate ester, and 0.25 mole of sodium hydride was refluxed in 350 ml of monoglyme, and the resulting mixture was processed in the usual manner. Additional details are given below.

(a) With Methyl Anisate

The reaction mixture was refluxed for 9 h. The crude product was recrystallized from absolute ethanol to afford 11.2 g (79%) of *N-benzoyl-α-(p-methoxybenzoyl)-acetamide* (*7a*), m.p. 177–178 °C; n.m.r. peaks at δ 7.7 (m, 9, aromatic), at 4.56 (s, 2, $COCH_2CO$), and at 3.82 p.p.m. (s, 3, CH_3O); and i.r. absorption at 3400 (NH) and 1690 cm^{-1} (C═O).

Anal. Calcd. for $C_{17}H_{15}NO_4$: C, 68.67; H, 5.08; N, 4.71. Found: C, 68.44; H, 5.12; N, 4.85.

(b) With Methyl p-Chlorobenzoate

The crude produce obtained after 6.5 h of refluxing was recrystallized from absolute ethanol to give 14.0 g (93%) of *N-benzoyl-α-(p-chlorobenzoyl)acetamide* (*7b*), m.p. 168–169 °C; n.m.r. peaks at δ 7.85 (m, 9, aromatic), and at 4.60 p.p.m. (s, 2, $COCH_2CO$); and i.r. absorption at 3400 (NH) and 1695 cm^{-1} (C═O).

Anal. Calcd. for $C_{16}H_{12}ClNO_3$: C, 63.69; H, 4.01; Cl, 11.75; N, 4.64. Found: C, 63.49; H, 3.87; Cl, 11.93; N, 4.52.

(c) With Ethyl Nicotinate

The reaction mixture was allowed to reflux for 6 h. The monoglyme was removed and the residue was treated with ether and water. The solid which separated between the layers was collected by filtration and dissolved in 300 ml of cold 3 *N* hydrochloric acid. The acidic solution was neutralized with solid sodium bicarbonate. The crude yellow solid which precipitated from the neutral solution was recrystallized from tetrahydrofuran to afford 10.47 (78%) of *N-benzoyl-α-nicotinoylacetamide* (*7c*), m.p. 166–167 °C; n.m.r. peaks at δ 7.80 (m, 9, aromatic) and at 5.76 p.p.m. (s, 2, $COCH_2CO$); and i.r. peaks at 3400 (NH) and at 1600 cm^{-1} (C═O).

Anal. Calcd. for $C_{15}H_{12}N_2O_3$: C, 67.16; H, 4.51; N, 10.44. Found: C, 67.45; H, 4.67; N, 10.26.

*Benzoylations of β-Keto Amides **8** and **9** by Means of Sodium Hydride*

Hydrogen evolution data for these reactions are presented in Table III.

*(a) Of β-Keto Amide **8***

A mixture of 8.15 g (0.05 mole) of **8** (6) and 0.08 mole of methyl benzoate was treated with 0.25 mole of sodium hydride in 350 ml of refluxing monoglyme for 1 h. The reaction mixture was processed as described above for the aroylations of imides to afford 12.5 g (91%) of the *N*-benzoyl derivative **2**, which was identical in all respects with the product obtained from the benzoylation of imide **1**.

*(b) Of Amide **9***

Treatment of 6.86 g (0.05 mole) of **9** with 0.08 mole of methyl benzoate and 0.25 mole of sodium hydride in 350 ml of refluxing monoglyme for 4 h produced 13.50 g (90%) of *N*-benzoylsalicylamide (**10**), m.p. 203–204 °C (lit. (7) m.p. 201 °C). The infrared spectrum of **10** was identical with that of an authentic sample.

*Results of Amides **8** and **9** with Sodium Amide*

To 0.10 mole of sodium amide prepared from 0.10 g-atom of sodium in 500 ml of commercial anhydrous liquid ammonia (8) was added 0.05 mole of **8**. The resulting suspension was allowed to stir for 30 min then 0.05 mole of methyl benzoate in 100 ml of anhydrous ether was added and stirring was continued for 1.5 h. The ammonia was evaporated (steam bath) as an equal volume of ether was added. The ethereal suspension was added to 300 ml of cold 3 *N* hydrochloric acid to precipitate 1.84 g (14%) of the *N*-benzoyl derivative **2**.

In a second experiment 0.025 mole of **8** was treated with 0.063 mole of sodium amide in liquid ammonia followed after 45 min by 0.05 mole of benzyl chloride[3] in 50 ml of anhydrous ether. After 3 h the reaction mixture was processed as described above. The ethereal layer was dried (Na_2SO_4) and concentrated to afford a crude solid which was shown by t.l.c. to consist primarily of unchanged **8**.

Treatment of a 0.05 mole sample of **9** with sodium amide (0.10 mole) in liquid ammonia followed by addition of methyl benzoate produced none of the desired *N*-benzoyl derivative **10**. Similarly, treatment of **9** with sodium amide and benzyl chloride gave a nearly quantitative recovery of starting material; no stilbene was detected.

*Attempted Benzoylations of Imides **11** and **12***

*(a) Of Imide **11***

To a suspension of 0.25 mole of sodium hydride in 250 ml of refluxing monoglyme was added a solution of 10.25 g (0.05 mole) of **11** (10) and 10.89 g (0.08 mole) of methyl benzoate in 350 ml of monoglyme. The reaction mixture was allowed to reflux for 18 h before being processed in the normal fashion. The solid residue which separated between the layers was collected by filtration, treated with hydrochloric acid, washed with sodium bicarbonate solution, and recrystallized from absolute ethanol to afford 12.7 g (95%) of **2**, m.p. 170–171 °C, mixture m.p. 170–171 °C. The i.r. spectrum of this material was identical with that of a sample of **2** prepared as described above.

*(b) Of Imide **12***

A mixture of 8.96 g (0.05 mole) of **12**, 0.08 mole of methyl benzoate, and 0.25 mole of sodium hydride in 250 ml of monoglyme was refluxed for 8 h. The reaction was processed in the manner described in section (*a*) above to afford, after one recrystallization of the crude product from 95% ethanol, 8.53 g (71%) of *N*-benzoylsalicylamide **10**, m.p. 201–202 °C, mixture m.p. 201–202 °C.

Measurements of Evolution of Hydrogen from Imides and Keto Amides with Sodium Hydride

In order to determine the extent of ionization of these active hydrogen compounds by sodium hydride, a 0.025–0.05 mole sample of the appropriate imide or amide in

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[3] Addition of the benzyl chloride was not accompanied by the transient purple color associated with stilbene formation and no stilbene was isolated. Thus, the two molecular equivalents of sodium amide were apparently consumed in the twofold ionization of **8** to form **8″**. See ref. 9.

100 ml of monoglyme, contained in the addition funnel of the apparatus described above, was added over a 15 min period to 0.125–0.25 mole of sodium hydride in refluxing monoglyme. The resulting mixture was allowed to reflux as periodic readings were taken on the test meter. When hydrogen evolution was essentially complete, the reaction time and total volume of hydrogen were noted. These values are presented in Table II.

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