NEW COMPOUNDS

Acylation Reactions of Phenylhydrazines. Preparation and Properties of New Diacylphenylhydrazines

Michael J. Hearn,* Debra J. Magee, Randi Alhart, Marye Gleva, Susan Goldstein, Fiona Levy, Colette Muenzen, Isabel Neuringer, Mary Racin, Judith Rosenberg, Holly Silva, and Paula Williams

Department of Chemistry, Wellesley College, Wellesley, Massachusetts 02181

Anhydride acylation reactions of a variety of substituted arylhydrazines under mild conditions led to controlled formation of the acid phenylhydrazides I (Table I). The procedures were tailored to the particular state of the starting arylhydrazine. Second-stage acylation of phenylhydrazides conveniently produced the *N,N'*-diacylphenylhydrazines II (Table II), in which the acyl groups were the same or nonidentical. β acylation of phenylhydrazine resulted in significant changes in the ultraviolet spectrum (Table III); the ultraviolet spectra thus provide useful data in the determination of the extent and site of acylation.

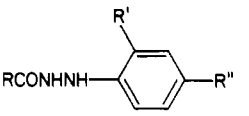
As one consequence of the lack of experimental work done on their controlled functionalization reactions, not much is known about the behavior of phenylhydrazines with mild acylating reagents (*1-14*). We now report new data on the preparation of acid phenylhydrazides and diacylphenylhydrazines, which have received scant mention in the literature.

Our results on the preparation of acid phenylhydrazides are summarized in Table I and in the representative procedures (methods A–D) given in the Experimental Section (vide infra). Selection of the appropriate method depends on the state of the starting arylhydrazines, occasionally available as the neutral liquids or solids but more commonly encountered in the form of the hydrochloride or dihydrochloride salts. The isolation of a pure product conveniently results from its crystallization and filtration from the reaction medium.

Table II describes the production of the diacylphenylhydrazines II. In a typical example (Table II, entry 6), 1-benzoyl-2-phenylhydrazine was reacted with propionic anhydride, resulting in the isolation of crystalline 2-benzoyl-1-propionyl-1-phenylhydrazine (77%) as a sharp melting solid. That the site of acylation was indeed the nitrogen atom bearing the phenyl group was confirmed by the substantial broadening of the NMR signal for the hydrogens α to the carbonyl group in the newly introduced acyl moiety and by separate control experiments.

It might well be anticipated that the general features of the ultraviolet spectra of the 1-acyl-2-phenylhydrazines (Ia–e, Table III, entries 4–8) should closely resemble those of phenylhydrazine itself (IV, entry 2), especially in view of the report (*15*) that β-acyl groups cause little change in the spectra of IV. Even so, we have now discerned two new distinct maxima (log ϵ ca. 3) in the spectra of the β-acyl compounds Ia–e, occurring near 263 and 269 nm, as well as the predicted maxima near 235 and 285 nm. Certain useful trends are evident. Both aniline (III, entry 1) and IV display characteristic absorption maxima near 235 and 285 nm. Acylation of III to give acetonitrile (V, entry 3) causes the latter maximum to disappear.

Table I. Acid Phenylhydrazides

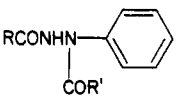


I

entry	compd	R	R'	R"	yield, %
1	Ia	Me	H	H	90[a]
2	Ib	Et	H	H	91[a]
3	Ic	Pr	H	H	73[a]
4	Id	*i*-Pr	H	H	86[a]
5	Ie	Ph	H	H	86[a]
6	If	Me	NO_2	NO_2	64[b]
7	Ig	Et	NO_2	NO_2	67[b]
8	Ih	Pr	NO_2	NO_2	57[b]
9	Ii	*i*-Pr	NO_2	NO_2	40[b]
10	Ij	Me	H	Cl	70[c]
11	Ik	Et	H	Cl	66[c]
12	Il	Et	H	Me	69[c]
13	Im	Pr	H	Cl	57[c]
14	In	*i*-Pr	H	Cl	oil[d]
15	Io	Ph	H	Cl	47[c]
16	Ip	Ph	H	Me	78[c]

[a] Method A. See Experimental Section. [b] Method B. See Experimental Section [c] Method C. See Experimental Section. [d] Method D. See Experimental Section. The crude yield was quantitative, and purification was accomplished by recrystallization.

Table II. Diacylphenylhydrazines



II

entry	compd	R	R'	yield, %
1	IIa	Me	Me	99
2	IIb	Et	Et	97
3	IIc	*i*-Pr	*i*-Pr	66
4	IId	*i*-Pr	Et	55
5	IIe	Ph	Me	97
6	IIf	Ph	Et	77
7	IIg	Ph	Pr	49
8	IIh	Ph	*i*-Pr	59

Acylation of IV to give Ia–e gives rise to the spectra with the four maxima noted. On the other hand, formation of the diacylphenylhydrazines (IIa,e–h, entries 9–13) dramatically simplifies the spectra, leaving them with the single maximum at 230 nm.

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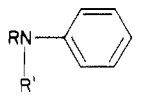
Table III. Ultraviolet Absorption Maxima[a]



entry	compd	R	R′	maxima, nm			
1	III	H	H	235			285
2	IV	NH_2	H	241			283
3	V	MeCO	H	240			
4	Ia	MeCONH	H	236	263	268	283
5	Ib	EtCONH	H	235	262	269	284
6	Ic	PrCONH	H	236	263	269	286
7	Id	*i*-PrCONH	H	235	262	265	283
8	Ie	PhCONH	H	230	263	269	283
9	IIe	PhCONH	MeCO	230			
10	IIf	PhCONH	EtCO	230			
11	IIg	PhCONH	PrCO	229			
12	IIh	PhCONH	*i*-PrCO	230			
13	IIa	MeCONH	MeCO	230			

[a] We obtained the data for entries 1–13 as solutions of approximately 1 mg (100 mL of 95% ethanol). See Experimental Section.

Experimental Section

Satisfactory elemental analyses were obtained for all new compounds and were submitted for review. Elemental analyses were performed by Galbraith Laboratories, Knoxville, TN. Melting points were taken in open capillary tubes by using a Mel-Temp apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer Model 727 or 1310 spectrophotometer as noted. A GCA-McPherson 707 vis/UV/near-IR spectrometer was employed in obtaining the ultraviolet spectra, run at concentrations of 1 mg/(100 mL of 95% ethanol). NMR spectra were obtained on a Perkin-Elmer R-32 90 Mc spectrometer in the solvents listed, using tetramethylsilane as an internal standard. Aliphatic coupling constants were 6 Hz, unless otherwise noted. Hydrazines and carboxylic acid anhydrides were used as received from Aldrich Chemical Co., Fluka A.-G., or Eastman Co.

Preparation of Acid Phenylhydrazides. Method A. This method is appropriate for the preparation of acid phenylhydrazides from basic arylhydrazines which are very soluble in typical organic solvents. Representative procedures and characterization data for compounds Ia–e have been provided (*1*).

Method B. This procedure is suitable for the preparation of acid phenylhydrazides from basic arylhydrazines which are insoluble in typical organic solvents. Representative procedures and characterization data have been given for compounds If–i (*4*).

Method C. This method was developed for the reaction of arylhydrazine hydrochlorides or dihydrochlorides with the appropriate anhydrides. In routine checks of the stoichiometry of the salts, samples were titrated against standardized sodium hydroxide solution in an aqueous medium, phenolphthalein being used as an indicator.

1-Acetyl-2-(4-chlorophenyl)hydrazine (Ij). 4-Chlorophenylhydrazine hydrochloride (0.522 g) was suspended in 5 mL of ethanol, and 10% aqueous sodium bicarbonate (4 mL) was added in several portions, accompanied by mild effervescence. After several minutes, the mixture was homogeneous and had attained a deep yellow coloration. The solution was warmed to boiling, and acetic anhydride (0.5 mL) was added dropwise over 5 min, causing the reaction mixture to reflux more rapidly. After 20 min of refluxing, the solution had become a distinctly lighter shade of yellow. Chilling the solution occasioned the immediate precipitation of Ij, which was collected by vacuum filtration and recrystallized from ethanol (70%): mp 150–152 °C; IR (KBr) 3250, 3060, 1615 cm^{-1}; NMR (acetone-d_6) δ 7.1 (aromatic pseudoquartet, 4 H, J = 8 Hz), 3.0 (s, 2 H), 2.2 (s, 3 H). In a similar manner, the following compounds were prepared:

1-Propionyl-2-(4-chlorophenyl)hydrazine (Ik). Mp 168.5–169 °C; IR (mull) 3300, 1670–1640 cm^{-1}; NMR (acetone-d_6) δ 7.1 (pseudoquartet, 4 H, J = 8 Hz), 2.8 (s, 2 H), 2.3 (q, 2 H), 1.1 (t, 3 H).

1-Propionyl-2-(4-methylphenyl)hydrazine (Il). Mp 173–175 °C [lit. (*16*) mp 170 °C]; IR (KBr) 3300, 1630 cm^{-1}; NMR (acetone-d_6) δ 6.94 (pseudoquartet, J = 8 Hz), 2.91 (s, 2 H), 2.28 (q, 2 H), 1.11 (t, 3 H).

1-Butyryl-2-(4-chlorophenyl)hydrazine (Im). Mp 126.5–127 °C; IR (KBr) 3290, 1650 cm^{-1}; NMR (acetone-d_6) δ 7.05 (pseudoquartet, 4 H, J = 8 Hz), 2.91 (s, 2 H), 2.28 (t, 2 H, J = 8 Hz), 1.69 (sextet, 2 H, J = 8 Hz), 0.95 (t, 3 H, J = 8 Hz).

1-Benzoyl-2-(4-chlorophenyl)hydrazine (Io). The solvent employed for this reaction was isopropyl alcohol, and the reflux time was 60 min: mp 153 °C [lit. (*17*) mp 153 °C].

1-Benzoyl-2-(4-methylphenyl)hydrazine (Ip). The solvent employed for this reaction was isopropyl alcohol, and the reflux time was 80 min: mp 135 °C; IR (KBr) 3290, 1630 cm^{-1}.

Method D. The arylhydrazine hydrochloride was acylated in an unbuffered mixture of water and ethanol.

1-Isobutyryl-2-(4-chlorophenyl)hydrazine (In). 4-Chlorophenylhydrazine hydrochloride (2 mmol) was mixed with water (5 mL) and brought to reflux. A mixture of 95% ethanol (15 mL) and isobutyric anhydride (10 mL) was added, and the refluxing was continued for a further 25 min, during which time the mixture took on a deep yellow color. The solution was then evaporated to give an approximately quantitative yield of a yellow product, the melting point of which (131–137 °C) indicated that recrystallization would be necessary. The material was recrystallized from 75% aqueous ethanol to give In: mp 133–135 °C; IR (KBr) 3290, 3250, 1630 cm^{-1}.

Preparation of Diacylphenylhydrazines. Representative Procedure. 2-Benzoyl-1-propionyl-1-phenylhydrazine (IIf). 1-Benzoyl-2-phenylhydrazine (Ie, 0.500 g, 2.35 mmol, prepared as noted above) was mixed with propionic anhydride (8 mL), and the mixture was heated on a boiling water bath for 25 min. The solution was permitted to cool to room temperature and then plunged into an ice–water bath. The resulting crystals were filtered at the pump, washed sparingly with chilled propionic anhydride, and allowed to air dry (77%): mp 192–192.5 °C; IR (KBr) 3250, 2975, 1650, 1590 cm^{-1}; NMR ($CDCl_3$) δ 9.38 (s, 1 H), 7.76 (m, 2 H), 7.37 (m, 8 H), 2.35 (q, 2 H), 1.13 (t, 3 H). In a similar manner the following compounds were also prepared:

1,2-Diacetyl-1-phenylhydrazine (IIa). Mp 113–114 °C [lit. (*18*) mp 107–108 °C]; IR (KBr) 3200, 3000, 1650, 1590 cm^{-1}.

1,2-Dipropionyl-1-phenylhydrazine (IIb). Mp 77–77.5 °C; IR (KBr) 3230, 2975, 1680, 1600 cm^{-1}; NMR ($CDCl_3$) δ 7.1 (s, 5 H), 2.0 (m, 4 H), 0.90 (m, 6 H).

1,2-Diisobutyryl-1-phenylhydrazine (IIc). Mp 159–159.5 °C; IR (KBr) 3220, 2990, 1675, 1590 cm^{-1}; NMR ($CDCl_3$) δ 7.90 (s, 1 H), 7.32 (m, 5 H), 2.50 (m, 2 H), 1.15 (overlapping doublets, 12 H).

2-Isobutyryl-1-propionyl-1-phenylhydrazine (IId). Mp 102–102.5 °C; IR (KBr) 3210, 2990, 1650, 1595 cm^{-1}; NMR ($CDCl_3$) δ 7.13 (s, 5 H), 2.75 (m, 3 H), 0.95 (m, 9 H). Similar treatment of 1-propionyl-2-phenylhydrazine with isobutyric anhydride led to an entirely different result (difficultly recrystallized syrup: mp 165–168 °C; NMR ($CDCl_3$) δ 7.60 (s, 5 H), 2.95 (m, 1 H), 2.53 (q, 2 H), 1.45 (m, 9 H)), a result which is consistent only with acylation at the anilino nitrogen.

2-Benzoyl-1-acetyl-1-phenylhydrazine (IIe). Mp 113–113.5 °C; IR (KBr) 3270, 3005, 1680, 1650, 1590 cm^{-1};

NMR ($CDCl_3$) δ 9.75 (s, 1 H), 7.78 (m, 2 H), 7.42 (m, 8 H), 2.10 (br, s, 3 H).

***2-Benzoyl-1-butyryl-1-phenylhydrazine* (*IIg*).** Mp 173.5–174 °C; IR (KBr) 3275, 2975, 1670, 1600 cm^{-1}; NMR ($CDCl_3$) δ 7.72 (m, 2 H), 7.32 (m, 8 H), 2.32 (br, t, 2 H), 1.70 (q, 2 H).

***2-Benzoyl-1-isobutyryl-1-phenylhydrazine* (*IIh*).** Mp 192 °C; IR (KBr) 3260, 2960, 1680, 1615 cm^{-1}; NMR ($CDCl_3$) δ 7.63 (m, 2 H), 7.35 (m, 8 H), 2.72 (m, 1 H), 1.15 (d, 6 H).

Acknowledgment

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Registry No. Ia, 114-83-0; Ib, 20730-02-3; Ic, 20730-03-4; Id, 5461-50-7; Ie, 532-96-7; If, 2719-07-5; Ig, 6561-63-3; Ih, 6561-60-0; Ii, 7461-93-0; Ij, 6947-29-1; Ik, 79984-65-9; Il, 92186-54-4; Im, 22207-29-0; In, 22207-30-3; Io, 17473-76-6; Ip, 65763-66-8; IIa, 38604-74-9; IIb, 92186-55-5; IIc, 92186-56-6; IId, 92186-57-7; IIe, 23459-55-4; IIf, 67491-56-9; IIg, 92186-58-8; IIh, 92186-59-9; $PhNHNH_2$, 100-63-0; $2,4-(NO_2)_2C_6H_3NHNH_2$, 119-26-6; $4-ClC_6H_4NHNH_2 \cdot HCl$, 1073-70-7; $4-MeC_6H_4NHNH_2 \cdot HCl$, 637-60-5; $(MeCO)_2O$, 106-24-7; $(EtCO)_2O$, 123-62-6; $(PrCO)_2O$, 106-31-0; $(i\text{-}PrCO)_2O$, 97-72-3; $(PhCO)_2O$, 93-97-0.

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Synthesis of *O*-Carbanilinobenzamidoximes

Maryone Borba Brito[†] and Rajendra M. Srivastava*

Departamento de Química Aplicada, Universidade Federal de Pernambuco, 50.000 Recife, PE, Brazil

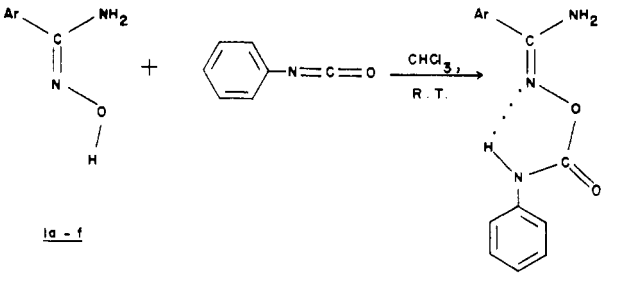
Preparation of six *O*-carbanilinobenzamidoximes, 2a–f, starting from benzamidoximes, 1a–f, is described. Spectroscopic results are in accord with the structure assignment. Compounds 2a–f were tested against bacteria and fungi. Only two, viz., *O*-carbanilinobenzamidoxime, 2a, and *O*-carbanilino-*o*-toluamidoxime, 2b, showed activity. The former inhibited the growth of *Escherichia coli* and *Neurospora crassa* whereas the latter stopped the growth of *N. crassa* only.

Introduction

So far, two publications (*1*, *2*) have appeared regarding the reaction of phenyl isocyanate with benzamidoxime. In the first report (*1*), *N*-carbanilinobenzamidoxime was proposed for the reaction product, while in the second one (*2*) the structure was assigned as *O*-carbanilinobenzamidoxime based on the infrared absorption results. Recently, the configuration and conformation of **2a** have also been studied (*3*). Reaction of *p*-toluamidoxime and phenyl isocyanate was reported (*4*) to yield *N*-carbanilino-*p*-toluamidoxime. Since, only two compounds, **2a** and **2b**, are known in this series and no other work except infrared spectroscopy (for **2a**) has been done, we thought it to be interesting to prepare some ring-substituted *O*-carbanilinobenzamidoximes and test their physiological activity. This paper reports the synthesis of six such compounds, **2a–f**, from **1a–f**

[†]Taken in part from the M.S. thesis of Maryone Borba Brito, Universidade Federal de Pernambuco, Recife, PE, 1982.

Scheme I



1a - f

2a - f

a : Ar = Ph
b : Ar = o-Tolyl
c : Ar = m-Tolyl
d : Ar = p-Tolyl
e : Ar = p-Chlorophenyl
f : Ar = p-Bromophenyl

(Scheme I) and their preliminary test for pharmacological activity.

Results and Discussion

Benzamidoximes, **1a–f** were allowed to react with phenyl isocyanate in alcohol-free chloroform at room temperature for an extended period of time. After purification, compounds **2a–f** were obtained in crystalline forms.

The infrared spectra of all *O*-carbanilinobenzamidoximes displayed strong absorption at 1715–1740 cm^{-1} (ν(–O–CO–)). Since no other product was detected on TLC, it is obvious that these are single compounds.

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