Reactions of *N*-Aminophthalimide With Electrophiles. II. Preparation and Properties of Araldehyde Hydrazones

Michael J. Hearn* and Elena R. Lucero

Department of Chemistry, Wellesley College, Wellesley, Massachusetts 02181

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N-Aminophthalimide (I) reacted with a variety of aromatic aldehydes to give the related arylideneaminophthalimides (III-X), although typical ketones such as acetone and benzophenone did not under the specific conditions employed. Catalytic reduction of benzylideneaminophthalimide (III) led to *N*-benzylaminophthalimide (XI), a stable acid-free precursor of benzylhydrazine.

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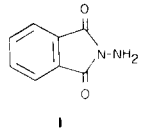
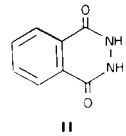
Despite the fact that its characterization and synthesis on a preparative scale were carried out by Drew and Hatt some time ago (1), not a great deal is known about the reactions of *N*-aminophthalimide (I). Possessing one nitrogen atom protected within the phthalide moiety and another more immediately available for reactions with electrophilic reagents, the compound is potentially suitable as a hydrazine synthon in transformations requiring regiospecific functionalization. In view of the unique steric and electronic environments of the free amino group, the molecule might well be expected to exhibit a degree of chemospecificity. In this way, I has lately received attention as an equivalent of hydrazine in the formation of heterocyclic systems bearing *N*-amino groups, including pyrroles (2) and aziridines (3), approaches which have had in common the recovery of the protected nitrogen atom in a deblocking stage subsequent to the assembly of the heterocycle. Since I is known to suffer conversion to phthalhydrazide (II) under appropriate conditions (1,4,5) any assessment of its reactions must take into consideration the possibility of this skeletal rearrangement.



I



II

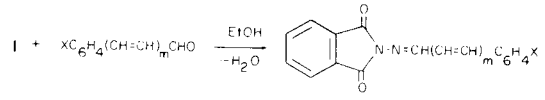
We recently found that I underwent ready monoacylation with aliphatic anhydrides, maintaining configurational integrity of the phthalide structure (4). Nonetheless I remained inert toward even very reactive esters, under conditions normally conducive to substitution in simple hydrazines. We now report on the reactions of *N*-aminophthalimide with aldehydes and ketones and remark on the dramatic selectivity observed between the two. Thus under reflux in neutral ethanolic solution for 2.25 hours, I remained virtually unreacted with benzophenone (6). Prolonged reflux with acetone similarly returned starting materials. On the other hand, I conveniently formed hydrazones III-X with a variety of aldehydes under similar conditions. For example, when *p*-nitrobenzaldehyde was reacted with *N*-aminophthalimide in refluxing 95% ethanol for a little more than two hours, the corresponding hydrazone VIII was obtained in good yield as a sharp melting crystalline solid, analyzing satisfactorily for $C_{15}H_9N_3O_4$ and displaying infrared bands consistent with the formation of an arylideneaminopthalimide at 1770 (m), 1720 (s), 1680 (sh) and 1650 (sh) cm^{-1}. Our results are summarized in the Table. We believe that the hydrazones have one stereochemistry, as evidenced from the appearance of a single 1H singlet in the nmr spectrum near δ 9.3 ppm downfield from TMS and attribute this to the *anti*-isomer.

Table

Araldehyde Hydrazones

Entry	Compound	Mp° C	% Yield	Analysis % Calculated (Found) C	H	N
1.	III	166-167 (a)	90	—	—	—
2.	IV	206-209	98	63.28 (63.09)	3.19 (3.18)	9.84 (9.65)
3.	V	180	88	63.28 (63.37)	3.19 (3.39)	9.84 (9.84)
4.	VI	201-202	96	63.28 (63.49)	3.19 (3.13)	9.84 (9.85)
5.	VII	189-191 (b)	92	—	—	—
6.	VIII	301-305	100	61.02 (60.87)	3.07 (3.20)	14.23 (13.98)
7.	IX	199-200 (c)	78	—	—	—

(a) Lit (1) mp 166-167°. (b) Lit (1) mp 189-191°. (c) Lit (1) mp 199-200°. All hydrazones could be recrystallized from 95% ethanol.



III, X = H, m = 0
IV, X = 4-Cl, m = 0
V, X = 3-Cl, m = 0
VI, X = 2-Cl, m = 0
VII, X = 4-OCH_3, m = 0
VIII, X = 4-NO_2, m = 0
IX, X = H, m = 1
X, X = 4-CHO, m = 0

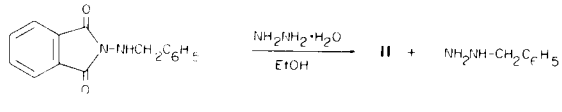
Treatment of I (133% molar excess) with terephthalaldehyde under the usual conditions for 3 hours occasioned a very ready reaction leading to the occlusion of the solvent in a pasty mass of product. The dialdehyde was completely consumed. Filtration of the solid, followed by recrystallization from 95% ethanol provided the monohydrazone X, mp 320-323° dec; ir (mull): 1765 (m), 1720 (s), 1685 (s) and 1650 (sh) cm^{-1}.

Anal. Calcd. for $C_{16}H_{10}N_2O_3$: C, 69.06; H, 3.62; N, 10.06. Found: C, 68.97; H, 3.80; N, 10.16.

Catalytic hydrogenation of III proceeded smoothly at 50 psi in dimethylformamide containing palladium on charcoal, leading to the diacylhydrazine XI, 82%, flakes from ethanol, mp 108.5-110°; ir (mull): 3280 (m), 1770 (m), 1705 (s) cm^{-1}; nmr (DMSO-d_6): δ 7.86 (m, 4H), 7.59-7.26 (m, 5H), 6.19 (t, 1H, J = 6 cps), 4.22 (d, 2H, J = 6 cps).

Anal. Calcd. for $C_{15}H_{12}N_2O_2$: C, 71.42; H, 4.79; N, 11.10. Found: C, 71.32;, H, 4.89; N, 11.10.

The resistance of this compound to hydrogenolytic cleavage of the nitrogen-nitrogen single bond under these conditions (*vide infra*) is in line with previous findings on acylated hydrazines (7). We found XI to be a highly stable material, which did not decompose over significant time on the shelf.



XI XII

Reaction of reduction product XI with 64% aqueous hydrazine hydrate (3.2 equivalents) was effected in refluxing ethanol over 2.5 hours and led after work-up to the formation of benzylhydrazine (XII, 98% based on obtained phthalhydrazide, 65% in hand) identified by comparison (ir, gc) with an authentic sample. We are exploring further the utility of compounds such as XI as acid-free precursors of aralkylhydrazines.

EXPERIMENTAL

Elemental analyses were performed by Galbraith Laboratories, Knoxville, Tennessee. Melting points were taken in open capillary tubes using a Mel-Temp apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer 727 spectrophotometer as Nujol mulls. Nuclear magnetic resonance spectra were obtained on a Perkin-Elmer R-32 90 Mc spectrometer in dimethylsulfoxide-d_6 with internal tetramethylsilane as the standard. Gas chromatography was performed on a Varian Aerograph 1400 instrument using a 5' × 0.125" 5% SE-30 column packed on Chromosorb W at a column temperature of 70°C and a helium flow rate of 60 ml/minute. *N*-Aminophthalimide was prepared by the known method (reference 1) or was purchased from Fluka A.-G. Aldehydes were those commercially available from Aldrich or Eastman Chemical Companies and were used as received. Catalytic hydrogenations were carried out in a Parr shaker apparatus, using 5% palladium on charcoal catalyst purchased from Engelhard Industries.

Preparation of Araldehyde Hydrazones. 2-(3-Chlorobenzylimino)-1*H*-isoindole-1,3(2*H*)-dione (V).

N-Aminophthalimide (1.00 g, 6.17 mmoles) was mixed with 95% ethanol (25 ml) and *m*-chlorobenzaldehyde (1.40 g, 9.93 mmoles). The reaction mixture was brought to reflux, which was accompanied by the formation of a yellow solution, although complete homogeneity was not attained. Heating was continued for 2.5 hours, the solution was allowed to cool to room temperature and to stand over night. Filtration under vacuum gave the product V (88%). The material thus in hand was suitable for further transformations without purification, but could be recrystallized if desired from 95% ethanol. The application of an analogous procedure to benzophenone did not lead to a hydrazone product in useful quantities; refluxing I with acetone similarly gave back starting materials.

Hydrogenation of Hydrazones. 2-Benzylamino-1*H*-isoindole-1,3(2*H*)-dione (XI).

Compound III (0.500 g, 2.00 mmoles, obtained in the above manner) was reacted with hydrogen at 50 psi in dimethylformamide (10 ml) containing 5% palladium on charcoal catalyst (0.15 g) for 20 hours. The contents of the pressure bottle were initially heterogenous but clarified somewhat as the reaction took place. Filtration of the mixture through a pad of Celite to remove the catalyst was followed by pouring into distilled water (70 ml). The product XI crystallized from the aqueous portion upon standing for several hours in iridescent flakes (82%), which could be recrystallized from 95% ethanol.

Hydrozinolysis. Benzylhydrazine.

When XI (0.524 g, 2.08 mmoles) was refluxed with 64% aqueous hydrazine hydrate (Eastman, 0.50 g, 3.2 equivalents) in 95% ethanol (10 ml) for 2.5 hours, a voluminous white precipitate was formed. The mixture was allowed to stand over night and the precipitate (98%) was filtered off and identified as II by comparison with an authentic sample (Aldrich Chemical Company). The filtrate was concentrated *in vacuo*, taken up in ether (10 ml) and dried over anhydrous magnesium sulfate. Filtration and evaporation of the ether gave benzylhydrazine XII (65%), identified on the basis of comparison (ir, gc coinjection) with an authentic sample prepared by basification of benzylhydrazine dihydrochloride (Aldrich Chemical Company). Similar sequences led to *p*-anisylhydrazine from VII (hydrogenation 79%, hydrazinolysis 65%) and to 3-phenylprophylhydrazine from IX (81%, 66%).

Acknowledgments.

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