Preparation and Stereochemistry of 3-Phenacylidenephthalimidines

Robert K. Howe

Research Division, Monsanto Agricultural Products Company,
St. Louis, Missouri 63167

Received April 27, 1984

Yields of 3-phenacylidenephthalimidines are maximized and yields of phthalimide byproducts are minimized by use of acetic acid as the solvent in reactions of amines with 3-phenacylidenephthalides. The 3-phenacylidenephthalimidines are formed as *E, Z* mixtures, in which the *E* isomers predominate. A homonuclear NOE nmr experiment was employed to determined product stereochemistry.

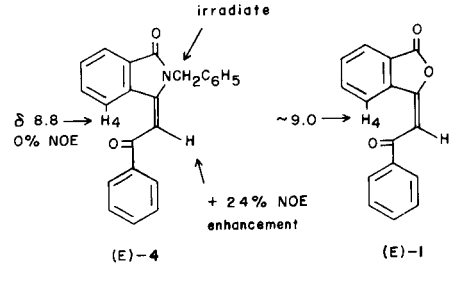
J. Heterocyclic Chem., **22**, 71 (1985).

In the course of other work, we required a sample of 2-benzyl-3-phenacylidenephthalimidine (**4**). Phenacylidenephthalimidines have been prepared by a few multistep procedures [1]. The shortest reported procedure [1] consists of heating amines with 3-phenacylidenephthalides in inert, high-boiling solvents such as 1,2-dichlorobenzene. In the present work, use of this latter procedure in an attempt to prepare **4** gave a mixture which contained **4** only as a minor component and in both *E* and *Z* forms. Our further investigations of this reaction have led to this report of an improved procedure for preparation of phenacylidenephthalimidines and of the stereochemistry of these products.

Reaction of benzylamine with 3-phenacylidenephthalide (**1**) in *o*-dichlorobenzene at reflux gave a 87:10:3 mixture of *N*-benzylphthalimide (**3**), *(E)*-**4**, and *(Z)*-**4** (Scheme 1). The phthalimide **3** results from loss of acetophenone from intermediate **2**. Since 3-hydroxy-3-phenacylphthalimidines such as **2** are known [1] to eliminate water under acid catalysis (*e.g.*, *p*-toluenesulfonic acid in ethanol) to form 3-phenacylidenephthalimidines, we thought that use of an acid in the reaction of **1** with benzylamine should result in less **3** and more **4** through promotion of loss of water from the intermediate **2**. We therefore employed acetic acid as the solvent for the reaction (at 90-95°) and obtained a 90:10 mixture of *(E)*-**4** and *(Z)*-**4**; less than 5% of **3** was formed. The ratio of *(E)*-**4** and *(Z)*-**4** did not change between 12 minutes and 4.5 hours; the reaction was 95% complete in 45 minutes. The intermediate **2** was not detected during the reaction (nmr analysis after 12 minutes when the reaction was already 75% complete). Pure *(E)*-**4** was obtained from the reaction mixture in 78% yield by simple crystallization.

To test the generality of the procedure, a relatively unreactive aniline was employed. Reaction of 3-trifluoromethylaniline with *(E)*-3-phenacylidenephthalide in acetic acid (at 90-95°) gave a mixture of *(E)*-**5** and *(Z)*-**5**, from which pure *(E)*-**5** was isolated in 50% yield (by crystallization) after a reaction time of 4.5 hours. This *E* isomer of **5** was identical with the 3-phenacylidene-2-(3-trifluoromethylphenyl)phthalimidine product previously reported [1] with undetermined stereochemistry. A substantial amount of the intermediate **6** was detected in the reaction mixture after 17 minutes *via* its methylene AB quartet, J = 17 Hz, centered at 1.7 ppm to lower field of the solvent methyl signal in the nmr spectrum; the ratio of *E* to *Z* products at that time was 80:20. After 4.5 hours, very litle of **6** was left. Essentially the same results were obtained on a larger scale starting with *(Z)*-3-phenacylidenephthalide, and all three products [*(E)*-**5**, *(Z)*-**5**, and **6**] were isolated and characterized. In a control experiment, *(Z)*-**1** was found to isomerize in substantial amount to *(E)*-**1** under the reaction conditions (43% conversion in 2 hours at 90-95° in acetic acid).

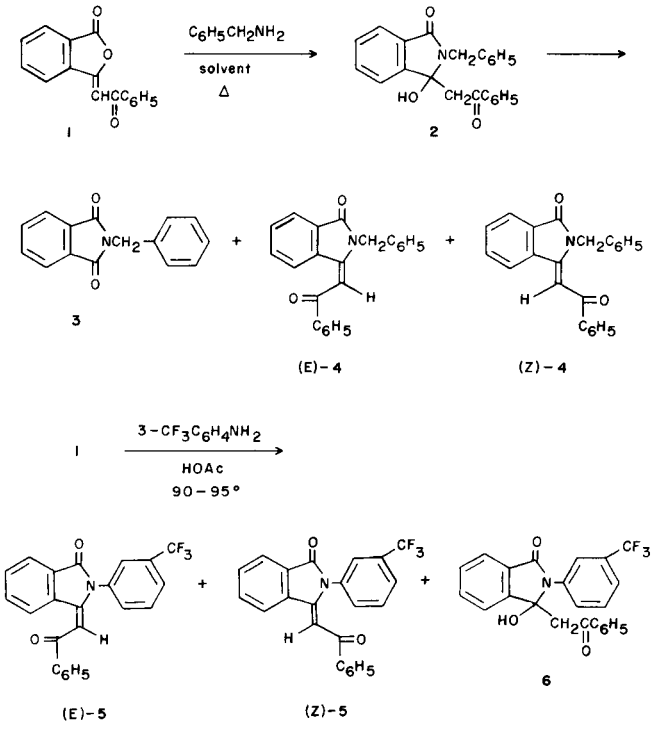
The configurational assignments for the phenacylidenephthalimidines were determined and confirmed by a homonuclear NOE nmr experiment on *(E)*-**4**. Irradiation of the NCH_2 protons gave a +24% NOE enhancement of the intensity of the vinyl proton and no effect on H_4, which appears at lower field (δ 8.8) than the other aromatic protons as a result of deshielding by the adjacent carbonyl group. The *E* isomer of phenacylidenephthalide similarly shows H_4 at δ 9.0 [2,3]; this low field shift of H_4 thus is diagnostic for the *E* isomers of both phenacylidenephthalides and phenacylidenephthalimidines.



Examination of Dreiding models of **2** revealed that for R ≠ H the steric interactions are considerably less in the **2** rotomer and the transition state that produces the *(E)*-3-phenacylidenephthalimidine product isomer (*trans* elimination of water) than in the **2** rotomer and the transition state that produces the *Z* product isomer. For R = H, steric interactions are less for the rotomer and the transition state that produces the *Z* product isomer. These steric effects thus appear to account for our observed results in de-

hydration of 3-hydroxy-3-phenacylphthalimidines, as well as for the reported results [4] of dehydration of 3-benzyl-3-hydroxyphthalimidines.

Scheme I



EXPERIMENTAL

Melting points are corrected. The nmr spectra were obtained on Varian T-60 nmr spectrometers at 60 MHz. The homonuclear NOE experiment, however, was performed at 100 MHz on a JEOL FX-100 nmr spectrometer.

Reaction of *N*-Benzylamine with *(E)*-3-Phenacylidenephthalide.

A solution of 9.35 g (0.0374 mole) of *(E)*-3-phenacylidenephthalide and 4.20 g (0.0392 mole) of *N*-benzylamine in 125 ml of *o*-dichlorobenzene was held at reflux for 3 hours and concentrated under oil pump vacuum to 10.18 g of solid residue which consisted of a 87:10:3 mixture of *N*-benzylphthalimide, *(E)*-**4**, and *(Z)*-**4** (nmr analysis). Crystallization of the solid from ethanol gave 5.8 g (65%) of pale yellow solid, mp 112-115°. This solid was recrystallized from ethanol to give 5.2 g of yellow needles, mp 115-117° (lit [5] mp 116°); ir spectra of this solid and of authentic *N*-benzylphthalimide were identical. The nmr (deuteriochloroform) showed the NCH_2 protons as a singlet at δ 4.80.

(E)-2-Benzyl-3-phenacylidenephthalimidine.

A solution of 25.0 g (0.10 mole) of 3-phenacylidenephthalide and 10.7 g (0.10 mole) of *N*-benzylamine in 300 ml of glacial acetic acid was heated in a steam bath for 5 hours. Water, 20 ml, was added, and the solution was cooled to 20°. Seed crystals were added. Crystallization of product occurred slowly giving 15.13 g of yellow needles, mp 121.5-123°; nmr (deuteriochloroform): δ 8.77 (m, 1), 7.82 (m, 1), 7.7-7.32 (m, 7), 7.28 (s, 5, $NCH_2C_6H_5$), 6.53 (s, 1, vinyl-H), 5.08 (s, 2, NCH_2). Addition of water to the filtrate resulted in an additional 11.33 g of product, mp 121-123° (total yield of 78%).

Anal. Calcd. for $C_{23}H_{17}NO_2$: C, 81.40; H, 5.05. Found: C, 81.38; H, 5.08.

Addition of more water to the last filtrate gave 3.9 g of 75:25 solid mixture of *E* and *Z* product isomers, mp 100-115°. The nmr peaks (deuteriochloroform) attributable to the *Z* isomer include δ 6.85 (s, 5, $NCH_2C_6H_5$), 6.54 (s, 1, vinyl-H; located at 0.013 ppm lower field than in the *E* isomer), 5.3 (s, 2, NCH_2).

(E)- and *(Z)*-3-Phenacylidene-2-(3-trifluoromethylphenyl)phthalimidine (**5**).

A. A solution of 0.19 g (0.76 mmole) of *(E)*-3-phenacylidenephthalide and 0.12 g (0.75 mmole) of 3-(trifluoromethyl)aniline in 2.0 ml of acetic acid was heated on a steam bath for 2 hours and then was allowed to cool. The resultant solid was collected and washed with 1 ml of acetic acid to give 0.15 g (50%) of yellow solid product, mp 179-180.5° (lit [1] 174°).

B. A mixture of 6.22 g (0.0249 mole) of *(Z)*-3-phenacylidenephthalide and 4.01 g (0.0249 mole) of 3-(trifluoromethyl)aniline in 60 ml of acetic acid was heated on a steam bath for 2 hours and then was allowed to cool. The resultant solid was collected and washed with 10 ml of acetic acid to give 5.60 g (57%) of yellow solid *E* product, mp 179.5-181°; ir (Nujol): 1720 cm^{-1}; nmr (deuteriochloroform): δ 8.90 (m, 1), 8.03-7.27 (m, 12), 6.50 (s, 1).

Addition of water to the acetic acid filtrate gave 3.6 g of yellow solid, mp 165-192°, that was a 30:70 mixture of *E* and *Z* product isomers plus the intermediate 3-hydroxy compound **6** (nmr and tlc analyses). This solid was heated with 25 ml of 1,2-dichloroethane, the mixture was cooled, and the resultant solid was collected to give 0.65 g of *Z* product, mp 198-201°. Recrystallization of this *Z* product from acetonitrile gave 0.45 g of pale yellow crystals, mp 209-210°; ir (Nujol): 1718, 1642 cm^{-1}; nmr (deuteriochloroform): δ 8.05-7.13 (m, 13), 6.63 (s, 1, vinyl-H).

Anal. Calcd. for $C_{23}H_{14}F_3NO_2$: C, 70.23; H, 3.59. Found: C, 70.05; H, 4.10.

The 1,2-dichloroethane filtrate gave four spots (one at origin) upon tlc on silica gel with 1,2-dichloroethane. This filtrate was subjected to hplc on a LOBAR C silca gel column with elution at 23 ml/minute with 1,2-dichloroethane. The first material off the column consisted of 0.8 g of *E* product isomer, mp 178.5-180°. The next fraction consisted of 0.9 g of *Z* product isomer, mp 190-192 + ° (ir, nmr analyses). Further elution with 5% ethyl acetate in 1,2-dichloroethane gave 0.7 g of 3-hydroxy compound **6**, mp 144-148°. Crystallization of this latter material from toluene gave 0.35 g of white solid, mp 157.5-158.5°; ir (Nujol): 3260 (s), 1680 (s) cm^{-1}; nmr (deuteriochloroform + dimethylsulfoxide-d_6): δ 8.0-7.1 (m, 13), 6.97 (s, 1, OH; exchanges with deuterium oxide), 3.67 (q, 2, J = 17 Hz, $CH_2C(O)C_6H_5$). Facile thermal reactions of **6** led to deviations from theoretical values in elemental analyses.

Anal. Calcd. for $C_{23}H_{16}F_3NO_3$: C, 67.15; H, 3.92. Found; C, 67.64; H, 4.27.

REFERENCES AND NOTES

[1] U. S. Patent 4,129,729; *Chem. Abstr.*, **90**, 13764a (1979).

[2] P. A. Chopard, R. F. Hudson and R. J. G. Searle, *Tetrahedron Letters*, 2357 (1965).

[3] C. F. Ingham, R. A. Massy-Westropp, G. D. Reynolds, and W. D. Thorpe, *Aust. J. Chem.*, **28**, 2499 (1975).

[4] A. Marsili and V. Scartoni [*Gazz. Chim. Ital.*, **102**, 806 (1972)] reported that acid catalyzed dehydration of 2,3-dibenzyl-3-hydroxyphthalimidine gave a 90:10 *E*:*Z* mixture of 2-benzyl-3-benzylidenephthalimidines and that 3-benzyl-3-hydroxyphthalimidine gave predominantly *(Z)*-3-benzylidenephthalimidine.

[5] CRC Handbook, 50th Ed, p C431 (1969-1970).