The Reaction of *N*-Aminophthalimide With Isothiocyanates [1]

Michael J. Hearn* and Laura E. Lucas

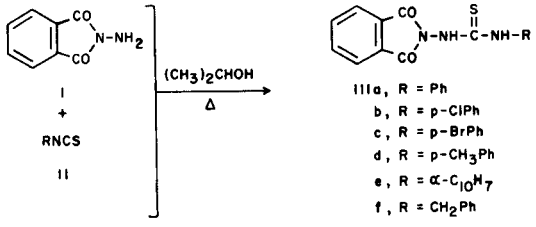
Department of Chemistry, Wellesley College,
Wellesley, Massachusetts 02181

Received August 1, 1983

N-Aminophthalimide (I) reacted in refluxing isopropyl alcohol with a number of isothiocyanates to give the related 1:1 addition products, *N*-(3-substitutedthioureido)phthalimides III. On the other hand, heating I directly with an excess of neat arylisothiocyanates produced the *N*-arylphthalimides IV. As shown for IIIa, the 1:1 addition products are conveniently deblocked by the Ing-Manske procedure to yield the 4-substituted thiosemicarbazide.

J. Heterocyclic Chem., **21**, 615 (1984).

We would like to report our observations on a new reaction of the 1:1 addition products of *N*-aminophthalimide (I) to isothiocyanates II. We have found that these addition products (III, *N*-(3-arylthioureido)phthalimides) are subject to heat-induced transformation to the corresponding *N*-arylphthalimides IV. Our observations were gathered in the course of the development of means by which I may serve as a hydrazine synthon in a controlled and selective process leading to the formation of the 4-substituted thiosemicarbazide [2,3,4]. Thus we found that phenylisothiocyanate (IIa) reacted with I (0.96 equivalents) in dry refluxing 2-propanol for three hours to produce a white solid IIIa, 83%, ir (potassium bromide): 3310, 3200, 3015, 1794 (w), 1733 (s), 1592, 1535 and 1497 cm^{-1}; nmr (90 Mc, DMSO-d_6): δ 7.94 (s, 4H) and 7.34 (m, 5H); mp 190-191° [5]. Deblocking of the phthalide moiety took place without complication in 64% aqueous hydrazine hydrate (8.04 equivalents) in refluxing 95% ethanol for two hours. Filtration of the voluminous precipitate of phthalhydrazide and evaporation of the filtrate gave 4-phenylthiosemicarbazide (69%) [6].

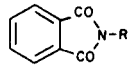


In sharp contrast to the reaction which we noted in 2-propanol, treatment of I with an excess of the isothiocyanate as the neat liquid led exclusively to the isolation of a different product. Compound I was heated with phenylisothiocyanate (5.39 equivalents) at reflux for 30 minutes. The mixture was taken up in hot 95% ethanol, concentrated to approximately half volume and cooled in ice to induce crystallization. The solid was filtered off and recrystallized from 95% ethanol to give light yellow needles, mp 205.5-206°; ir (potassium bromide): 3040, 1780 (sh), 1750 (sh), 1705 (s), 1605 and 1510 cm^{-1}; nmr (90 Mc, DMSO-d_6): δ 8.05 (m, 5H) and 7.50 (s, 4H). High resolution mass spectrometry was consistent with elemental composition $C_{14}H_9NO_2$ (Calcd. 223.06333. Found 223.06347). *Anal.* Calcd. for $C_{14}H_9NO_2$: C, 75.33; H, 4.06; N, 6.27. Found: C, 75.19; H, 4.16; N, 6.32. These data led us to the conclusion that the product of the neat reaction was *N*-phenylphthalimide (IVa, 40% yield based on I), which corresponds, in a formal sense, to loss of the elements of thioformaldehyde [7] and molecular nitrogen from IIIa. In a separate control experiment, IIIa was isolated as outlined above for the reaction in 2-propanol, then subjected to treatment with an excess of hot neat phenylisothiocyanate and the usual work-up. This procedure also gave formation of *N*-phenylphthalimide (IVa, 42%) suggesting the possible intermediacy of IIIa in the rearrangement process.

Table

N-(3-Substitutedthioureido)phthalimides

Entry	Compound	Mp °C	% Yield
1	IIIa	190-191	83
2	IIIb	178-179	94
3	IIIc	183-185	93
4	IIId	192.5-194	94
5	IIIe	126-127	31
6	IIIf	181-182	74



IV

Our results on the formation of the 1:1 adducts are summarized in the Table, and representative procedures are given below for their preparation, as well as for the direct one-pot conversion of I to compounds IV in neat isothiocyanates (*vide infra*). We note that although the formation of the benzylic compound IIIf took place with ease employing the usual procedure in isopropyl alcohol, this material did not experience change to the protected amine IVf under the conditions examined.

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 1310 spectrophotometer as potassium bromide pellets. Nuclear magnetic resonance spectra were obtained on a Perkin-Elmer R-32 90 Mc spectrometer with tetramethylsilane as the internal standard. *N*-Aminophthalimide was used as received from Fluka A.-G. or conveniently prepared by the standard method of Drew and Hatt [8]. Reagent grade solvents were purchased from Baker. Isothiocyanates from Fluka, Aldrich or Eastman Organic Chemicals were used without further purification.

N-(3-Phenylthioureido)phthalimide (IIIa).

Compound I (4.16 g, 25.6 mmoles) was weighed into a flask, and dry 2-propanol (25 ml) was added. Phenylisothiocyanate (3.20 ml, 27.0 mmoles) was added from a graduated pipet, and the mixture was heated at reflux for three hours to produce a white solid. The mixture was cooled, then added to 50% aqueous ethanol and allowed to stir at ambient temperature for one hour. The white solid (IIIa, 83%) was isolated by filtration *in vacuo*; mp 190-191°; ir (potassium bromide): 3310, 3200, 3105, 1794 (w), 1733 (s), 1592, 1535 and 1497 cm^{-1}; nmr (DMSO-d_6): δ 7.94 (s, 4H) and 7.34 (m, 5H) [5]. The following compounds were prepared in a similar manner.

N-(3-*p*-Chlorophenylthioureido)phthalimide (IIIb).

This reactive compound was prepared in 94% yield, mp 178-179°; ir: 3340, 3220, 1796, 1725, 1610, 1550 and 1513 cm^{-1}; nmr (acetone-d_6): δ 7.89 (s, 4H), 7.54 (m, 2H) and 7.35 (m, 2H). Owing to its thermal lability, recrystallization of this compound from hot ethanol did not lead to improvement of purity (*Anal.* Calcd. for $C_{15}H_{10}ClN_3SO_2$: C, 54.30; H, 3.04; N, 13.67. Found: C, 54.11; H, 3.20; N, 12.54), and further verification of structure was obtained from the high resolution mass spectrum: m/z Calcd. (m/z observed) 168.9753 (168.9782), 162.0429 (162.0438) and 152.0141 (152.0156).

N-(3-*p*-Bromophenylthioureido)phthalimide (IIIc).

The material was prepared in 93% yield, mp 183-185°; ir: 3340, 3225, 1793, 1720, 1608, 1550 and 1515 cm^{-1}; nmr (acetone-d_6): δ 7.92 (s, 4H) and 7.41 (m, 4H).

Anal. Calcd. for $C_{15}H_{10}BrN_3SO_2$: C, 47.89; H, 2.68; N, 11.17. Found: C, 48.01; H, 2.79; N, 10.99.

N-(3-*p*-Tolylthioureido)phthalimide (IIId).

This product was obtained in 94% yield, mp 192.5-194°; ir: 3305, 3195, 2950, 1790, 1732, 1587 and 1533 cm^{-1}; nmr (DMSO-d_6): δ 10.25 (s, 1H), 9.97 (s, 1H), 7.82 (s, 4H), 7.07 (m, 4H) and 2.24 (s, 3H).

Anal. Calcd. for $C_{16}H_{13}N_3SO_2$: C, 61.72; H, 4.21; N, 13.50. Found: C, 61.83; H, 4.35; N, 13.58.

N-(3-α-Naphthylthioureido)phthalimide (IIIe).

The product was prepared in 31% yield, mp 126-127°; ir: 3250, 3150, 1793, 1728, 1594 and 1485 cm^{-1}; nmr (DMSO-d_6): δ 10.59 (br s, 1H), 10.26 (br s, 1H), 7.81 (m, 6H), 7.67 (s, 2H) and 7.46 (m, 3H). The purity of this thermally labile compound was not improved upon attempted recrystallizations from hot ethanol (*Anal.* Calcd. for $C_{19}H_{13}N_3SO_2$: C, 65.69; H, 3.77; N, 12.10. Found: C, 64.93; H, 4.09; N, 11.98), and further verification of structure was obtained from the high resolution mass spectrum: m/z Calcd. (m/z observed) 185.0299 (185.0313), 168.0688 (168.0630) and 162.0429 (162.0428).

N-(3-Benzylthioureido)phthalimide (IIIf).

The product was obtained in 74% yield, mp 181-182°; ir: 3300, 3240, 3020, 1800, 1740, 1604 and 1550 cm^{-1}; nmr (DMSO-d_6): δ 7.80 (s, 4H), 7.15 (s, 5H) and 4.66 (s, 2H).

Anal. Calcd. for $C_{16}H_{13}N_3SO_2$: C, 61.72; H, 4.21; N, 13.50. Found: C, 61.54; H, 4.34; N, 13.47.

4-Phenylthiosemicarbazide.

Compound IIIa (0.261 g, 0.750 mmoles), 64% hydrazine hydrate (Eastman, 0.529 g, 7.04 mmoles) and 95% ethanol (10 ml) were mixed at once and brought to reflux. When warmed, the mixture became homogeneous. Heating was continued for two hours, and during the course of the reaction a voluminous white precipitate formed on the sides of the flask. The reaction mixture was allowed to cool, and the precipitate was filtered off. The mother liquor was warmed to reduce its volume, then evaporated on a watchglass, forming white needles, of the thiosemicarbazide (69%), identified by comparison of its infrared spectrum with that of the authentic material available in the literature [6], mp 137-138°, lit [9] mp 140°.

N-Phenylphthalimide.

Compound I (0.502 g, 3.10 mmoles) and phenylisothiocyanate (2.00 ml dispensed from a graduated pipet, 16.7 mmoles) were mixed without solvent and refluxed for 30 minutes, taking on a yellow color as they heated. The mixture was taken up in hot 95% ethanol, the solution was concentrated to half volume, and upon cooling in ice a precipitate developed, which was filtered off under vacuum and recrystallized from 95% ethanol to give IVa as light yellow needles (40%); mp 205.5-206°; ir (potassium bromide): 3040, 1780 (sh), 1750 (sh), 1705 (s), 1605 and 1510 cm^{-1}; nmr (DMSO-d_6): δ 8.05 (m, 5H) and 7.50 (s, 4H). High resolution mass spectrum, Calcd. for $C_{14}H_9NO_2$: 223.06333. Found: C, 223.06347).

Anal. Calcd. for $C_{14}H_9NO_2$: C, 75.33; H, 4.06; N, 6.27. Found: C, 75.19; H, 4.16; N, 6.32.

In a similar manner direct conversions were observed for I to *N*-*p*-chlorophenylphthalimide (34%), *N*-*p*-tolylphthalimide (50%) and *N*-α-naphthylphthalimide (10%).

Compound IIIa (0.501 g, 1.68 mmoles) was isolated as noted above and treated with an excess of phenylisothiocyanate for 45 minutes at reflux. As the solution cooled to room temperature, a light yellow precipitate formed. The material was filtered off and recrystallized from 95% ethanol to give IVa (42%), the infrared spectrum of which was identical to that of the material obtained from the neat reaction of I with phenylisothiocyanate.

Acknowledgments.

This work was supported by grants from the Merck Foundation and the American Philosophical Society. We are grateful to Dr. C. Costello of the Massachusetts Institute of Technology for the determination of mass spectra.

REFERENCES AND NOTES

[1] Reactions of *N*-Aminophthalimide with Electrophiles. III. For Part II, see reference [4].

[2] L. Drobnica, P. Kristian and J. Augustin, in "The Chemistry of Cyanates and Their Derivatives", S. Patai, ed, John Wiley and Sons, New York, 1977, pp 1109ff.

[3] M. J. Hearn and S. B. Prisch, *Org. Prep. Proced. Int.*, **13**, 421 (1981).

[4] M. J. Hearn and E. R. Lucero, *J. Heterocyclic Chem.*, **19**, 1537 (1982).

[5] N. Patel and J. Rutter, US Patent 4,264,502, April 28, 1981; *Chem. Abstr.*, **94**, 121314e (1981).

[6] Aldrich Library of Infrared Spectra, **2**, 965F. Isolated yields of the phthalhydrazide from the Ing-Manske procedure are virtually quantitative, *cf.* reference [4].

[7] In an experiment directed at the trapping of any thioformaldehyde which may have been formed in the transformation of IIIa to IVa, *N*-(3-phenylthioureido)phthalimide was refluxed in xylenes with an excess of the butadiene precursor 3-sulfolene; although IVa was obtained in 66% yield in very pure form, we did not observe formation of thiacyclohexene.

[8] H. Drew and H. Hatt, *J. Chem. Soc.*, 16 (1937).

[9] "Handbook of Chemistry and Physics", 61st Edition, R. Weast, ed, CRC Press, Cleveland, 1980, p C-498.