The Chemistry of 2*H*-3,1-Benzoxazine-2,4(1*H*)-dione (Isatoic Anhydride). **19** [1]. Direct Formation of 2-Aminobenzyl Alcohols from the Reduction of *N*-Substituted Isatoic Anhydrides

Gary M. Coppola

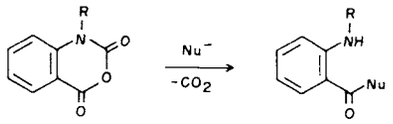
Sandoz Research Institute, Sandoz, Inc., Chemistry Research Department, Route 10, East Hanover, New Jersey 07936

Received August 15, 1985

Isatoic anhydrides **1** are easily reduced with sodium borohydride to *o*-(substituted-amino)benzyl alcohols **3** in good yield. Sequential reduction of *N*-(2-nitrobenzyl)isatoic anhydride (**5**) with sodium borohydride followed by catalytic hydrogenation of the nitro group affords the naturally occurring 2-(2'-aminobenzylamino)-benzyl alcohol (**4**) in 72% yield.

J. Heterocyclic Chem., **23**, 223 (1986).

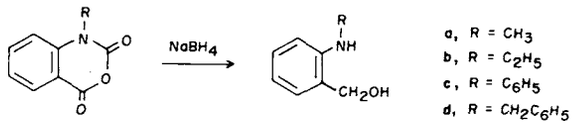
Isatoic anhydrides **1** are amazingly versatile molecules due to the susceptibility of the C-4 carbonyl towards nucleophilic attack. Reactions at this position occur over a wide choice of temperatures ranging from greater than +100° to −78° [2,3,4]. Nucleophiles such as alcohols, mercaptans, amines, and carbanions add with equal facility to provide adducts of general structure **2** in high yields. Surprisingly, no one has attempted the reaction of **1** with the simplest of all nulceophiles, the hydride ion. The purpose of this paper is to report the results of our investigation into the reduction of isatoic anhydride derivatives with hydrides.



1 2

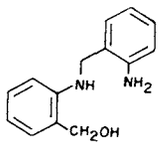
The first objective is to choose a hydride reagent with mild reducing capabilities in order to preclude secondary reductions of potentially susceptible functionalities which may be attached to the periphery of the isatoic anhydride nucleus. Sodium borohydride fits this reactivity profile. It easily reduces cyclic anhydrides [5,6] while being relatively inert to most other functional groups (with the exception of aldehydes and ketones).

When various *N*-substituted isatoic anhydrides **1** are treated with an equimolar amount of sodium borohydride in tetrahydrofuran at room temperature, a slow gaseous effervesence is observed and within a period of 2-4 hours, all of **1** is consumed. Spectral analysis of the product indicates that complete reduction had occurred affording 2-aminobenzyl alcohol **3** in good yield. No 2-aminobenzaldehyde could be detected. Even when the reaction is performed with a deficiency of sodium borohydride (0.5 equivalents), the only product formed is **3**. The remainder of the mixture is composed of unreacted **1**. Other boron reducing agents such as diborane or diisobutylaluminum hydride have no appreciable affect on the isatoic anhydride nucleus as observed by lack of reaction at room temperature even after 48 hours.



1 3

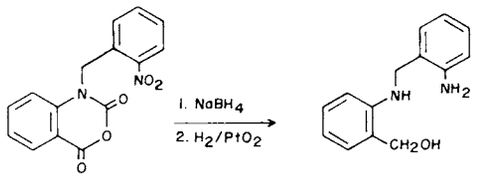
The sodium borohydride reduction of the isatoic anhydride nucleus can be exploited to gain entrance to interesting naturally occurring amines. From the extracts of the leaves of *Justicia gendarussa*, which is known for its medicinal properties, have been isolated four relatively simple *o*-disubstituted aromatic amines [7]. One of them has been characterized as **4** and its structure verified by an independent synthesis requiring five steps which gives the product in less than 2% overall yield.



4

A much more simple strategy for the preparation of **4** begins with the known *N*-(2-nitrobenzyl)isatoic anhydride (**5**) [8] which contains all the requisite atoms correctly positioned on its skeleton. By a facile two-step manipulation, **5** is easily transformed directly to **4** in good yield.

The initial step, a sodium borohydride reduction of the anhydride ring, proceeds smoothly at room temperature and is complete within 4 hours. The intermediate nitro alcohol is not isolated but is catalytically hydrogenated in the presence of platinum oxide to furnish **4** in 72% overall yield (after purification). All physical data is in full accord with that of the natural product.



5 4

EXPERIMENTAL

Melting points were determined on a Thomas-Hoover Unimelt apparatus and are uncorrected. The infrared spectra were recorded on either Perkin-Elmer Model 257 and 457, or Analect FX-6200 spectrophotomers. Absorption frequencies are quoted in reciprocal centimeters. The proton NMR spectra were recorded on EM-360 and Jeol FX-90-Q spectrometers using TMS as an internal reference. Chemical shifts are quoted in parts per million (s = single, d = doublet, t = triplet, q = quartet, m = multiplet). The mass spectra were determined on a Finnegan 4600 spectrometer either in EI or CI modes. No attempt has been made to optimize the yields of the described reactions.

General Procedure for the Reduction of Isatoic Anhydrides with Sodium Borohydride.

To a suspension of 0.38 g (0.01 mole) of sodium borohydride in 20 ml of tetrahydrofuran at 0° was added dropwise a solution of 0.01 mole of an appropriate isatoic anhydride derivative **1** in 50 ml of tetrahydrofuran. After the addition was complete the reaction was stirred at room temperature until **1** was consumed (2-4 hours). Saturated aqueous ammonium chloride solution (4.0 ml) was added dropwise and, after 30 minutes the mixture was diluted with 100 ml of methylene chloride. After drying over sodium sulfate, the solvent was removed under reduced pressure to give the product.

2-Methylaminobenzyl Alcohol (**3a**).

Obtained from **1a** according to the general procedure and purified by flash chromatography using 5% ethyl acetate/methylene chloride to elute the product. Compound **3a** was isolated as an oil in 55% yield, lit [9] bp (0.3 mm) 83-85°; ir (chloroform); 3599, 3421, 3018, 2933, 2867, 1600, 1514 cm^{-1}; nmr (deuteriochloroform): δ 7.30-6.90 (m, 2H), 6.71-6.50 (m, 2H), 4.58 (s, 2H), 3.37-2.74 (m, broad, 2H, OH and NH), 2.82 (s, 3H).

2-Ethylaminobenzyl Alcohol (**3b**).

Obtained from **1b** according to the general procedure and purified by distillation to give **3b** as an oil in 76% yield, bp (0.3 mm) 90-95° lit [10] bp (2 mm) 122-125°; ir (neat): 3395, 2970, 2872, 1606, 1514 cm^{-1}; nmr (deuteriochloroform): δ 7.31-6.92 (m, 2H), 6.73-6.50 (m, 2H), 4.63 (s, 2H), 3.29 (s, broad, 2H), 3.16 (q, 2H), 1.29 (t, 3H).

2-Phenylaminobenzyl Alcohol (**3c**).

Obtained from **1c** according to the general procedure and purified by flash chromatography using methylene chloride to elute the product, **3c**, in 74% yield. An analytical sample was triturated with pentane, mp 59-62°; ir (film): 3384, 3045, 2900, 2877, 1593, 1509, 1300 cm^{-1}; nmr (deuteriochloroform): δ 7.40-6.72 (m, 11H), 4.68 (s, 2H).

Anal. Calcd. for $C_{13}H_{13}NO$: C, 78.36; H, 6.58; N, 7.03. Found: C, 78.48; H, 6.85; N, 6.79.

2-Benzylaminobenzyl Alcohol (**3d**).

Obtained from **1d** according to the general procedure and purified by flash chromatography using 5% methyl *t*-butyl ether/methylene chloride to elute the product, **3d** in 73% yield. An analytical sample was crystallized from petroleum ether, mp 53-56°, lit [11] mp 55°; ir (chloroform): 3599, 3426, 3005, 2931, 2880, 2819, 1601, 1516 cm^{-1}; nmr (deuteriochloroform): δ 7.43-6.94 (m, 7H), 6.72-6.50 (m, 2H), 4.64 (s, 2H), 4.35 (s, 2H), NH and OH are seen as a broadening of the base line.

2-(2'-Aminobenzylamino)benzyl Alcohol (**4**).

To a suspension of 0.4 g (0.0105 mole) of sodium borohydride in 20 ml of tetrahydrofuran at 0° was added dropwise a solution of 3.22 g (0.01 mole) of **5** [8] in 80 ml of tetrahydrofuran. After stirring at room temperature for 4 hours, 4.0 ml of saturated aqueous ammonium chloride solution was added dropwise and stirring was continued for 30 minutes. The mixture was diluted with 100 ml of methylene chloride and was dried over sodium sulfate. The solvent was removed under reduced pressure and the residual yellow oil was dissolved in 50 ml of ethyl acetate. This solution was hydrogenated at one atmosphere in the presence of platinum oxide until the theoretical amount of hydrogen was absorbed (1 hour). The catalyst was filtered and the solvent was removed under reduced pressure. The resulting oil was purified by flash chromatography using 2% methanol/methylene chloride to give 1.65 g (72%) of **4**. An analytical sample was crystallized from chloroform, mp 129-131°, lit [7] mp 131°; ir (potassium bromide): 3407, 3395, 3196, 2885, 2843, 1606, 1511, 1459, 1319 cm^{-1}; nmr (deuteriochloroform): δ 7.35-6.60 (m, 8H), 4.60 (s, 2H), 4.23 (s, 2H), exchangeables seen as a broadening of the base line; ms (70 ev): m/z 228 (M^+).

Acknowledgement.

The author wishes to thank Sue Dicataldo for running the nmr spectra, Mrs. Frances McCrink for running the ir spectra, Jackie Misuro for performing the microanalyses, Mrs. Bertha Owens and Dr. Emil Fu for running the mass spectra, and Linda Hinchman for the hplc separation on the Waters Prep-500 apparatus.

REFERENCES AND NOTES

[1] Part 18: G. M. Coppola, *J. Heterocyclic Chem.*, **22**, 1087 (1985).

[2] G. M. Coppola, *Synthesis*, 505 (1980).

[3] T. Kappe and W. Stadlbauer, "Advances in Heterocyclic Chemistry", Vol 28, Academic Press, New York, 1981, p 127.

[4] G. M. Coppola, *J. Heterocyclic Chem.*, **22**, 491 (1985).

[5] D. M. Bailey and R. E. Johnson, *J. Org. Chem.*, **35**, 3574 (1970).

[6] D. E. Burke and P. W. LeQuesne, *J. Org. Chem.*, **36**, 2397 (1971).

[7] A. K. Chakravarty, P. P. G. Dastidar,and S. C. Pakrashi, *Tetrahedron*, **38**, 1797 (1982).

[8] G. E. Hardtmann, G. Koletar, and O. R. Pfister, *J. Heterocyclic Chem.*, **12**, 565 (1975).

[9] M. Lora-Tamayo, R. Madronero, and G. G. Munoz, *Chem. Ber.*, **94**, 208 (1961).

[10] E. Testa and L. Fontanella, *Farmaco Ed. Sci.*, **20**, 323 (1965); *Chem. Abstr.*, **63**, 18088h (1965).

[11] J. O. Jilek, J. Pomykacek, E. Svatek, V. Seidlova, M. Raisner, K. Pelz. B. Hoch, and M. Protiva, *Collect. Czech, Chem. Commun.*, **30**, 445 (1965); *Chem. Abstr.*, **63**, 4258h (1965).