An Anomalous Neber Reaction. A General Method for the Preparation of 3-Carboxy-1-naphthylamines

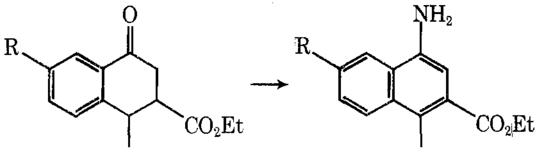
Michael E. Garst, Daniel D. Cox, Richard W. Harper,
and D. S. Kemp*

Department of Chemistry,
Massachusetts Institute of Technology,
Cambridge, Massachusetts 02139

Received November 19, 1974

A need for 4-amino-1,6-dialkyl-2-naphthoate esters, to be used as intermediates in the synthesis of unsymmetrical 2,6-disubstituted naphthalene cyclophanes, and the ready availability of 3-carboalkoxy-1-tetralones[1,2] focused our attention on means of effecting the conversion of tetralone to naphthylamine (Scheme I).

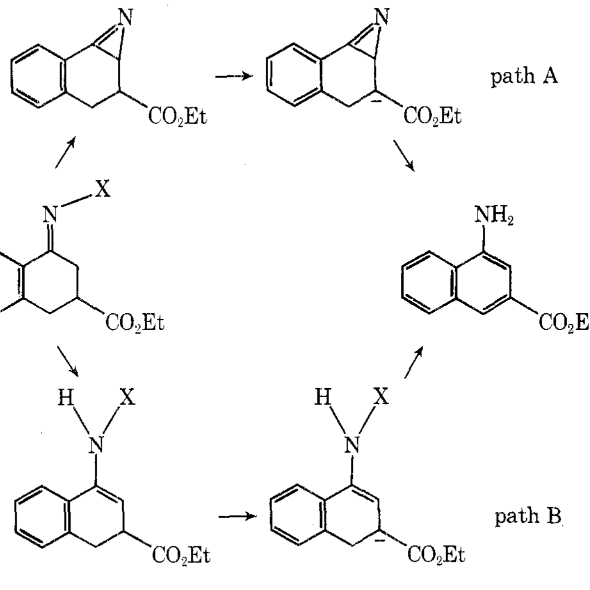
Scheme I



After a variety of more conventional approaches to this conversion had been examined with limited success, attempts were made to utilize the known acid-catalyzed transformation of tetralone oxime[3] or hydrazone derivatives[4] to naphthylamines, despite the low yields reported for most of these conversions. Perhaps because of the electron-withdrawing effect of the carboethoxy group, yields in our systems never exceeded 30% under all conditions tried with these reactions.

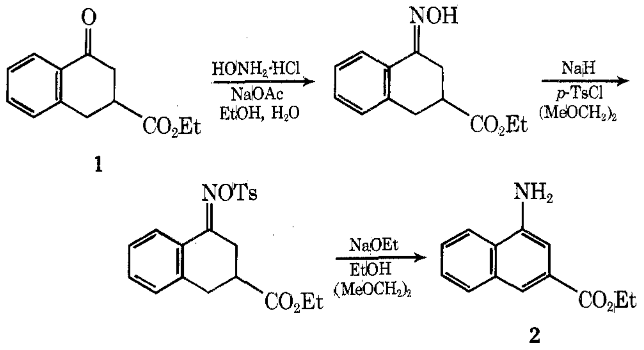
To our knowledge, a base-catalyzed conversion of 1-tetralone to 1-naphthylamine has not been reported, and indeed the Neber reaction of tetralone oxime tosylates is known to yield products other than naphthylamines under these basic conditions.[7] Nevertheless, the presence of the carboethoxy group seemed to offer potential activation for production of naphthylamine by one of the routes shown in Scheme II. We now report an effective base-catalyzed conversion of tetralone to naphthylamine.

Scheme II



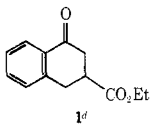
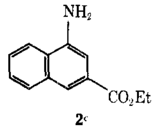
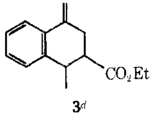
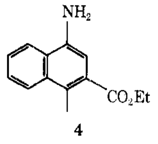
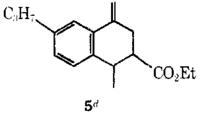
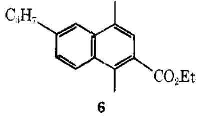
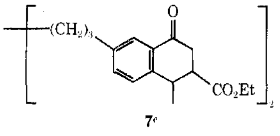
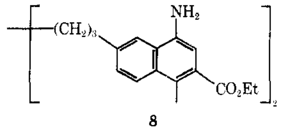
The conversion of 3-carboethoxy-1-tetralones, e.g., **1**, to the corresponding oxime proceeded in excellent yield. The oxime tosylate was then prepared in anhydrous dimethoxyethane from the oxime, sodium hydride, and *p*-toluenesulfonyl chloride. Dilution of the crude tosylate solution with 2–3 equiv of sodium ethoxide in ethanol produced the aminonaphthoate **2** in good yield (Scheme III). A variety of 4-amino-2-naphthoates were thus prepared (Table I). Naphthylamines **2**, **4**, and **6** were consistently prepared in 70% yields. The yield of **8** is lower both because of its bifunctional nature and because of the impurity of tetralone **7**.

Scheme III



Optimization of conditions received some attention by an examination of oxime leaving group, base, and solvent. The *O*-tosyl group proved to be better than the *O*-methyl, *O*-acetyl, or *O*-trifyl leaving group. Aromatization of the *O*-methyl or *O*-acetyl oxime of **5** was possible in 30–50% yield utilizing lithium 2,2,6,6-tetramethylpiperidide[8] in large excess. The *O*-triflate rearranged prior to the addition of base. Of the bases examined, ethoxide or methoxide gave higher yields of naphthylamines than more highly hindered alkoxides, amine anion bases, or dimsyl anion. Ethoxide was chosen to minimize transesterification. Less basic tertiary amines were unreactive. Ethanol as solvent was superior to isopropyl alcohol, *tert*-butyl alcohol, *tert*-amyl alcohol, or dimethyl sulfoxide. Ethanol was also better than tetrahydrofuran–ethanol or ether–ethanol mixtures; however, a dimethoxyethane–ethanol (2:1 v/v) solvent mixture

Table I

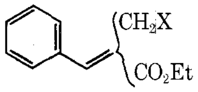
Tetralone	Amine[a]	% yield[b]
 **1**[d]	 **2**[c]	72
 **3**[d]	 **4**	72
 **5**[d]	 **6**	70
 **7**[e]	 **8**	20

[a] All amines are completely characterized spectroscopically and analytically. [b] Isolated yield. [c] Converted to amino acid, mp 205-207° (lit.[5] mp 204-206°). [d] Distilled tetralone. [e] Crude material.

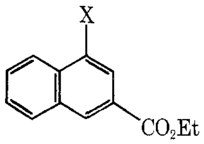
increased yields by 10–20%. Although some cooling is desirable for the mildly exothermic reaction, low temperature (−70°) offered no advantages. Finally, it was noticed that the rigorous exclusion of oxygen afforded a cleaner product.

The question of mechanism has not been studied in detail, and no firm conclusions can be drawn. The formation of **6** from **5** methoxyoxime and lithium 2,2,6,6-tetramethylpiperidide and mechanistic studies of the Neber reaction[6] suggest path B in Scheme II. Nevertheless, it is intriguing that optimum conditions for this reaction are very similar to those found for the closely related Neber conversion. A point which apparently has not been given prior attention is whether naphthylamines are formed from simple tetralone oxime tosylates under Neber conditions.[7] We have found that in fact 5–10% of 1-aminonaphthalene is formed from 1-tetralone oxime tosylate with sodium ethoxide in dimethoxyethane–ethanol. Clearly the carboethoxy group facilitates but does not induce the pathway to naphthylamines. Thus several different mechanisms may be involved in the naphthylamine formation.[9]

Other approaches to the formation of 4-amino-2-naphthoate esters were explored with very limited success. The dimethylenamine[10a] or pyrrolidine enamine[10b] of **5** could be prepared in low yield only with difficulty, and preliminary dehydrogenation experiments were not encouraging. The benzylamine Schiff base of **3** or **5** provided **4** or **6** in moderate yield (40–50%) after treatment with 10% palladium on carbon in refluxing mesitylene;[11] but under similar conditions the benzylamine Schiff base of **7** gave **8** in only 5% yield. Other attempts to aromatize the Schiff base of **3**, as well as **3** itself, failed to provide adequate yields of the corresponding aminonaphthalene or naphthol.[12] Despite a variety of precedents, direct cyclization of **9** to **10**[13] or of **11–14** to the corresponding naphthylamine[14,15] failed with one exception. Amide **14** capriciously provided up to 30% of amine **15** after treatment with phosphorus oxychloride.[15]



9, X = CO$_2$H
11, X = CN
12, X = CONH$_2$
13, X = CONHMe
14, X = CONMe$_2$



10, X = OAc
15, X = NMe$_2$

Experimental Section

General Procedure.[16] Ethyl 4-Amino-1-methyl-2-naphthoate (4). A solution of 0.350 g (1.50 mmol) of 3-carboethoxy-1-tetralone **3**, 0.115 g (1.1 equiv) of hydroxylamine hydrochloride, 0.132 g (1.1 equiv) of sodium acetate, and 10 ml of 80% ethanol was refluxed for 1 hr. The solution was partitioned between ether and water (25 ml each), and the layers separated. The aqueous layer was washed with additional ether (3 × 25 ml). The combined ether layers were then washed with saturated sodium chloride solution, dried over anhydrous sodium sulfate, and condensed to provide a quantitative yield of the oily oxime: ir (film) 3400 and 1730 cm^{-1}. This crude oxime and 0.306 g (1.60 mmol) of *p*-tosyl chloride were dissolved in 20 ml of dry dimethoxyethane and treated with 0.090 g (1.87 mmol) of sodium hydride mineral oil dispersion.[17] The mixture was stirred under nitrogen for 17 hr, cooled to 0°, and treated with 10 ml of 0.6 *N* sodium ethoxide in ethanol.[18] The solution was stirred at 0° under nitrogen for an additional 2 hr and then subjected to the ether–water extractive work-up described above to provide crude oily amine. Purification by elution with 1:9 ethyl acetate–pentane from alumina provided 0.248 g (72%) of **4**: mp 73–74°; ir ($CHCl_3$) 3490, 3400, and 1720 cm^{-1}; NMR ($CDCl_3$) δ 1.34 (t, 3 H), 2.77 (s, 3 H), 4.00 (s, 2 H), 4.37 (q, 2 H), 7.05 (s, 1 H), and 7.1–8.2 ppm (m, 4 H).

The hydrochloride salt was prepared by crystallization of **4** from ethanolic hydrochloric acid: mp 243–246°.

Anal. Calcd for $C_{14}H_{16}NO_2Cl$: C, 63.28; H, 6.07; N, 5.27. Found: C, 63.02; H, 6.08; N, 5.24.

Acknowledgment. Financial support from the National Science Foundation through Research Grant GP 33265X is gratefully acknowledged.

Registry No.—**1**, 22743-00-6; **2**, 54143-46-3; **3**, 54143-47-4; **4**, 54143-48-5; **4** HCl, 54143-49-6; **5**, 54143-50-9; **6**, 54143-51-0; **7**, 54307-68-5; **8**, 54143-53-2.

References and Notes

(1) W. S. Johnson, *Org. React.*, **2**, 114–177 (1944).
(2) W. S. Johnson and G. H. Daub, *Org. React.*, **6**, 1–73 (1951).
(3) M. S. Newman and W. M. Hung, *J. Org. Chem.*, **38**, 4073 (1973), and references cited therein.
(4) Aromatization of 1-tetralone azine gave only 15% 1-aminonaphthalene: E. C. Horning et al., *J. Am. Chem. Soc.*, **70**, 288 (1948).
(5) C. Butler and F. A. Royle, *J. Chem. Soc.*, 1649 (1923).
(6) D. J. Cram and M. Hatch, *J. Am. Chem. Soc.*, **75**, 33, 38 (1953); C. O'Brien, *Chem. Rev.*, **64**, 81 (1964).
(7) G. Drefahl and D. Martin, *Chem. Ber.*, **93**, 2497 (1960); R. B. Woodward et al., *J. Am. Chem. Soc.*, **78**, 3087 (1956); P. Neber et al., *Justus Liebigs, Ann. Chem.*, **526**, 277 (1936); J. G. Cannon et al., *J. Med. Chem.*, **15**, 348 (1972).
(8) R. A. Olofson and C. M. Dougherty, *J. Am. Chem. Soc.*, **95**, 582 (1973).
(9) Another mechanistic possibility is suggested by the rearrangement of *N*-acetoxy-*N*-methyliminium salts to 2-acetoxyimines: H. O. House and F. A. Richey, Jr., *J. Org. Chem.*, **34**, 1430 (1969).
(10) (a) W. H. White and H. Weingarten, *J. Org. Chem.*, **32**, 213 (1967); (b) U. K. Pandit et al., *Recl. Trav. Chim. Pays-Bas*, **89**, 1258 (1970).
(11) Cf. G. Schroeter, *Ber.*, **63**, 1308 (1930); E. C. Horning et al., *J. Am. Chem. Soc.*, **70**, 288 (1948); K. Yagi, *Chem. Abstr.*, **53**, 303*e* (1959).
(12) (a) Halogenation–dehydrohalogenation: A. W. Fort, *J. Org. Chem.*, **26**, 765 (1961). (b) Quinones: D. Walker and J. D. Hiebert, *Chem. Rev.*, **67**, 153 (1967).
(13) S. M. Abdel-Wahab and L. S. El-Assal, *J. Indian Chem. Soc.*, **46**, 927 (1969).
(14) (a) Trimethyloxonium fluoroborate: F. Johnson et al., *J. Org. Chem.*, **39**, 1434 (1974), and references cited therein. (b) Sulfuric acid: C. K. Bradsher et al., *J. Am. Chem. Soc.*, **78**, 2153 (1956). (c) Polyphosphoric acid: cf. L. F. Fieser and M. Fieser, "Reagents for Organic Synthesis", Vol. 1. Wiley, New York, N.Y., 1968, p 899. (d) Polyphosphate ester: ibid., p 892; Vol. 2, p 333. (e) Phosphorus pentachloride: W. M. Whaley and T. R. Govindachari, *Org. React.*, **6**, 74–150 (1951). (f) Phosphorus pentachloride then aluminum chloride: D. H. Hey and J. M. Williams, *J. Chem. Soc.*, 1527 (1951).
(15) See ref 14e.
(16) This procedure is typical of those used for preparation of amines **2**, **4**, **6**, and **8** and provides comparable yields on a 0.1-mol scale. Nuclear magnetic resonance (NMR) spectra were recorded on a Varian T-60 spectrometer at 60 MHz using tetramethylsilane as an internal standard. Infrared (ir) spectra were determined with a Perkin-Elmer 567 spectrometer. Melting points are uncorrected. Analyses were completed by Midwest Microlab, Ltd., Indianapolis, Ind. All new compounds have been adequately characterized. Reagent aluminum oxide for chromatography was purchased from Merck Chemical Division, Rahway, N.J.
(17) The sodium hydride was purchased from Alpha Ventron, Beverly, Mass., and washed with pentane after weighing, immediately prior to use.
(18) The reaction is relatively insensitive to concentration. During 0.1-mol scale reactions the tosylate and ethoxide concentrations were ten times greater. A volume ratio of 2:1 dimethoxyethane to ethanol is optimal.

Electrophilic Addition of $RPX_2/AlCl_3$ to Olefins. The Possibility of Phosphiranes

Phillip Crews

Thimann Laboratories, University of California,
Santa Cruz, California 95064

Received December 28, 1973

Small-ring heterocycles containing nitrogen, oxygen, or sulfur atom centers are rather common, whereas phosphorous analogs are obtainable only under special or awkward circumstances.[1,2,8] Phosphiranes are usually prepared by coupling vicinal dihalides with phosphides, while an unusual coupling reaction between $RPX_2/AlCl_3$ complexes and branched monoenes yields phosphetanes. Equation 1 summarizes this latter reaction and shows the breadth of ole-