Some 2,3-Diarylpropylamines

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Convenient and practical methods are offered for the preparation of 2,3-diarylacrylonitriles. Suitable reduction of the acrylonitriles ordinarily produces 2,3-diarylpropylamines. One example is described of a catalytic reduction employing Raney nickel, in which aromatic chlorine is retained.

THE 2,3-DIARYLPROPYLAMINES reported here were synthesized for the purpose of investigating their possible adrenal-inhibitory effects (*25*). The method of preparation consisted essentially of a two-step process, involving the base-catalyzed condensation of an aromatic aldehyde with an arylacetonitrile, followed by reduction of the resulting 2,3-diarylacrylonitrile, as indicated by the sequence below, in which Ar and Ar′ represent aromatic groups.

$$Ar{-}\overset{\overset{O}{\|}}{C}{-}H + Ar'{-}CH_2{-}CN \xrightarrow{base} Ar{-}CH{=}\underset{\underset{Ar'}{|}}{C}{-}CN \xrightarrow{reduction}$$

$$Ar{-}CH_2{-}\underset{\underset{Ar'}{|}}{CH}{-}CH_2NH_2$$

Most of the 2,3-diarylacrylonitriles were prepared by the condensation of an aromatic aldehyde and an arylacetonitrile in methanol solution containing 5 to 7% potassium hydroxide. Although the literature recommends the use of sodium ethoxide as the basic catalyst in such reactions (*24*), nevertheless, the use of potassium hydroxide in methanol gave products in very good yield and in high purity. In most instances, recrystallization of the crude materials produced no significant change in melting points. Since *p*-nitrophenylacetonitrile is sensitive to strong bases, condensations involving this reagent were accomplished with excellent results using a secondary amine, as suggested by other workers (*3*).

Table I lists the 2,3-diarylacrylonitriles which were prepared, along with yields and melting points. The literature melting points and the melting points found are in very close agreement. The Experimental section describes typical procedures. Infrared spectra of the compounds in chloroform solution showed the expected conjugated unsaturated nitrile peaks at about 2230 cm.$^{-1}$, 4.50 microns (*9*).

Catalytic reduction of the acrylonitriles was ordinarily accomplished using Raney nickel (No. 28) catalyst in methanol with added ammonia, in order to keep secondary amine formation at a minimum (*1*). However, similar procedures, when applied to compounds containing chlorine, have led to extensive hydrogenolysis of chlorine (*7*). For this reason, 2-(*p*-chlorophenyl)-3-(*m*-nitrophenyl)acrylonitrile was reduced, using Raney nickel in tetrahydrofuran without added ammonia. Reduction proceeded smoothly, with no detectable loss of chlorine. Attempts to reduce 3-(*o*-nitrophenyl)-2-phenylacrylonitrile to the corresponding propylamine were unsuccessful. Previous investigators (*16*) had found that the reduction of this acrylonitrile using tin and hydrochloric acid produced 2-amino-3-phenylquinoline, involving ring formation. It was suggested that catalytic reduction using Raney nickel in the presence of ammonia might avoid ring formation. However, such treatment led exclusively to 2-amino-3-phenylquinoline, which was identified through its melting point, infrared spectrum, and the melting point of its picrate derivative. Because compounds containing sulfur readily undergo desulfurization on treatment with Raney nickel (*5*), 2-phenyl-3-(*p*-thiomethoxyphenyl)acrylonitrile was reduced with lithium aluminum hydride, using a method similar to that of other workers (*14*). The reduction procedures also converted nitro substituents to amino substituents.

With but three exceptions, the 2,3-diarylpropylamines were obtained as oils. Infrared spectra of three solids and of the oils in chloroform solution were consistent with the structures assigned, particularly with regard to the presence of the primary amine functions (*21*). For purposes of purification and analysis, the oils were converted to salts, using hydrogen chloride or fumaric acid. In such cases, the over-all yields were reported, including the steps of reduction and salt formation. The preparation of 3-(*p*-aminophenyl)-2-phenylpropylamine involved the reduction

Table I. 2,3-Diarylacrylonitriles

$$Ar{-}CH{=}\underset{\underset{Ar'}{|}}{C}{-}CN$$

Ar	Ar′	Yield, %	M.P., °C.[a]	Lit. M.P., °C.	
C_6H_5	C_6H_5	92	85–7	86–8	(*24*)
4-$CH_3OC_6H_4$	C_6H_5	90	93–5	93	(*6*)
4-$(CH_3)_2NC_6H_4$	C_6H_5	93	134–6	136	(*8*)
4-$CH_3SC_6H_4$	C_6H_5	88	95–7[b]		
4-$CH_3CONHC_6H_4$	C_6H_5	87	221–3[c]		
3,4-$(CH_3O)_2C_6H_3$	C_6H_5	77	86–8	88	(*4*)
3-$O_2NC_6H_4$	C_6H_5	67	133–5	133	(*2*)
2-$O_2NC_6H_4$	C_6H_5	85	128–30	127–8	(*6*)
C_6H_5	4-$O_2NC_6H_4$	96	177–9	175–6	(*17*)
4-$(CH_3)_2NC_6H_4$	4-$O_2NC_6H_4$	72	245–7	245	(*18*)
4-$CH_3OC_6H_4$	4-$O_2NC_6H_4$	100	162–3	165–6	(*17*)
4-$(CH_3)_2NC_6H_4$	4-$CH_3OC_6H_4$	75	149–51	149	(*13*)
3-$O_2NC_6H_4$	4-$CH_3OC_6H_4$	80	160–1	159	(*13*)
3-$O_2NC_6H_4$	4-ClC_6H_4	99	191–3	191	(*23*)
4-C_5H_4N[d]	C_6H_5	63	129–31	126–8	(*10*)

[a] Melting points were determined using a copper block and are uncorrected. [b] Recrystallized from methanol. Analyses calculated for $C_{16}H_{13}NS$: C, 76.45; H, 5.21. Found: C, 76.45; H, 5.50. [c] Recrystallized from ethanol. Analyses calculated for $C_{17}H_{14}N_2O$: C, 77.84; H, 5.38; N, 10.68. Found: C, 77.61; H, 5.32; N, 10.52. [d] This is the 4-pyridyl group.

of 3-(*p*-acetamidophenyl)-2-phenylacrylonitrile, followed by hydrolysis of the acetamido group by a well-known method (22).

Table II lists the 2,3-diarylpropylamines which were synthesized, along with other pertinent information. The hydrochloride salt of 3-(*p*-methoxyphenyl)-2-phenylpropylamine, a known compound, was analyzed because the melting point found was about 10° C. higher than the value reported in the literature.

EXPERIMENTAL

2-Phenyl-3-(*p*-thiomethoxyphenyl)acrylonitrile. To a solution of 20.0 grams of potassium hydroxide (assay, 85%) in 300 ml. of methanol at room temperature were added, with stirring, 28.0 grams (0.24 mole) of phenylacetonitrile and 30.4 grams (0.20 mole) of *p*-thiomethoxybenzaldehyde. The reaction mixture was allowed to stand for one hour, and was then placed in a refrigerator for two hours. Filtration of the reaction mixture, followed by washing with 80% methanol and drying under vacuum, gave 44.0 grams, 88% yield, of 2-phenyl-3-(*p*-thiomethoxyphenyl)acrylonitrile as a colorless solid, m.p. 95–7° C. Recrystallization from methanol produced no change in the melting point. The infrared spectrum of the product, in chloroform solution, showed a significant absorption peak at 2240 cm.$^{-1}$ (4.48 microns), indicative of a conjugated unsaturated nitrile group (*9*).

3-(*p*-Methoxyphenyl)-2-(*p*-nitrophenyl)acrylonitrile. To a solution of 27.2 grams (0.20 mole) of *p*-methoxybenzaldehyde and 37.3 grams (0.23 mole) of *p*-nitrophenylacetonitrile in 600 ml. of methanol, at room temperature, was added 10 ml. of diethylamine. The reaction mixture was warmed at about 40° C. for one-half hour, and was then allowed to stand overnight. Filtration of the reaction mixture, followed by washing with 95% methanol and drying under vacuum, gave 56.1 grams, 100% yield, of 3-(*p*-methoxyphenyl)-2-(*p*-nitrophenyl)acrylonitrile as a yellow solid, m.p. 162–3° C. Recrystallization from methanol produced yellow needles, with no change in the melting point. The infrared spectrum of the product, in chloroform solution, showed the typical conjugated unsaturated nitrile band (*9*) at 2219 cm.$^{-1}$ (4.52 microns), nitro bands (*15*) at 1558 cm.$^{-1}$ (6.43 microns) and 1340 cm.$^{-1}$ (7.47 microns), and a band at 1258 cm.$^{-1}$ (7.96 microns), which may be ascribed to an aromatic methyl ether group (*20*).

2-(*p*-Aminophenyl) - 3 - (*p*-dimethylaminophenyl)propylamine. A 300-ml. hydrogenation vessel was charged with 15.0 grams (0.051 mole) of 3-(*p*-dimethylaminophenyl)-2-(*p*-nitrophenyl)acrylonitrile, 140 ml. of methanol, about 10 grams of liquid ammonia, approximately 10 ml. of a Raney nickel (No. 28)–methanol slurry, and hydrogen at an initial pressure of 2000 p.s.i.g. The reaction vessel was then heated with rocking at 100° C. for about one hour. After cooling, the mixture was filtered, and the solution was evaporated under vacuum. There was obtained 11.4 grams, 83% yield, of 2-(*p*-aminophenyl)-3-(*p*-dimethylaminophenyl)propylamine as a yellow solid, 116–20° C. Recrystallization from benzene–petroleum ether (b.p. 60–71° C.) produced yellow crystals, m.p. 122–4° C. The infrared spectrum of the product, in chloroform solution, showed a primary amine doublet at 3550 cm.$^{-1}$ (2.82 microns) and 3400 cm.$^{-1}$ (2.95 microns) (*21*).

2-Amino-3-phenylquinoline. Using a similar procedure, 15.0 grams (0.060 mole) of 3-(*o*-nitrophenyl)-2-phenylacrylonitrile, 125 ml. of methanol, approximately 10 grams of liquid ammonia, about 10 ml. of a Raney nickel (No. 28)–methanol slurry, and hydrogen under an initial pressure of 2300 p.s.i.g. produced 13.1 grams, 99% yield of 2-amino-3-phenylquinoline, m.p. 145–52° C. Recrystallization from methanol gave colorless needles, m.p. 156–8° C., lit. m.p. 155° C. (*16*). The infrared spectrum of the product, in chloroform solution, showed a typical primary amine doublet at 3520 cm.$^{-1}$ (2.85 microns) and 3340 cm.$^{-1}$ (3.00 microns) (*21*). Using an established procedure (*19*), the known picrate derivative of this 2-amino-3-phenylquinoline was prepared; m.p. 235–7° C., lit. m.p. 234° C. (*16*).

3-(*m*-Aminophenyl)-2-(*p*-chlorophenyl)propylamine Monofumarate. In like manner, 15.0 grams (0.053 mole) of 2-(*p*-chlorophenyl)-3-(*m*-nitrophenyl)acrylonitrile, 135 ml. of tetrahydrofuran, about 10 ml. of a Raney nickel (No. 28)–tetrahydrofuran slurry, which had been prepared by washing the Raney nickel three times with methanol, three times with tetrahydrofuran, and then storing under tetrahydrofuran, and hydrogen under an initial pressure of 2020 p.s.i.g. produced 14.5 grams of a faintly yellow oil. The infrared spectrum of the oil, in chloroform solution, showed a peak at 3340 cm.$^{-1}$ (3.0 microns) with a shoulder at 3455 cm.$^{-1}$ (2.90 microns), indicative of the primary amine groups (*21*).

A solution of 13.0 grams of the oil in 50 ml. of anhydrous ether was added with stirring to a solution of 14.0 grams (0.12 mole) of fumaric acid in 250 ml. of tetrahydrofuran. After allowing the mixture to stand for two hours, filtration, followed by washing with ether-tetrahydrofuran, and then drying under vacuum, gave 16.0 grams, 93% over-all yield, of the monofumarate salt of 3-(*m*-aminophenyl)-2-(*p*-chlorophenyl)propylamine, m.p. 149–52° C. Purification by recrystallization from methanol-benzene produced a colorless solid melting at 152–4° C.

2-Phenyl-3-(*p*-thiomethoxyphenyl)propylamine Hydrochloride. A solution of 15.0 grams (0.06 mole) of 2-phenyl-3-(*p*-thiomethoxyphenyl)acrylonitrile in 40 ml. of anhydrous ether and 40 ml. of tetrahydrofuran was added dropwise to a stirred slurry of 10.0 grams (0.264 mole) of lithium aluminum hydride in 360 ml. of anhydrous ether in a well-vented hood. The reaction mixture was stirred for three-fourths of an hour after the addition was complete, was mounted on an ice bath, and 30 ml. of distilled water was added dropwise (*cautiously!*) with stirring. Then 500 ml. of a 20% sodium potassium tartrate solution was added with vigorous stirring. The organic layer was removed,

Table II.[a] 2,3-Diarylpropylamines

$$\mathrm{Ar{-}CH_2{-}\underset{\displaystyle Ar'}{\underset{|}{CH}}{-}CH_2{-}NH_2}$$

Ar	Ar′	Derivative	Yield, %[b]	M.P., °C.[b,c]
C_6H_5	C_6H_5	HCl	89	193–5[d]
4-$CH_3OC_6H_4$	C_6H_5	HCl	76	173–4[e]
4-$(CH_3)_2NC_6H_4$	C_6H_5	2HCl	73	231–3[f]
4-$CH_3SC_6H_4$	C_6H_5	HCl	61	197–9[g]
4-$H_2NC_6H_4$	C_6H_5	1½ $C_4H_4O_4$[h]	79	152–4[g]
3,4-$(CH_3O)_2C_6H_3$	C_6H_5	$C_4H_4O_4$[h]	96	141–3[g]
3-$H_2NC_6H_4$	C_6H_5	$C_4H_4O_4$[h]	98	179–80[i]
C_6H_5	4-$H_2NC_6H_4$	2HCl	88	239–41[f]
4-$(CH_3)_2NC_6H_4$	4-$H_2NC_6H_4$	...	83[j]	122–4[j,k]
4-$CH_3OC_6H_4$	4-$H_2NC_6H_4$	...	85[j]	108–10[j,k]
4-$(CH_3)_2NC_6H_4$	4-$CH_3OC_6H_4$	...	93[j]	73–5[j,k]
3-$H_2NC_6H_4$	4-$CH_3OC_6H_4$	2HCl	87	249–50[i]
3-$H_2NC_6H_4$	4-ClC_6H_4	$C_4H_4O_4$[h]	93	152–4[g]
4-C_5H_4N[m]	C_6H_5	1¼ $C_4H_4O_4$[h]	62	138–40[f]

[a] Complete table, including elemental analyses may be obtained from ASIS. [b] Refers to the derivative of the 2,3-diarylpropylamine unless otherwise noted. [c] Melting points were determined using a copper block and are uncorrected. [d] Lit. (*12*) 194.7–5.2° C. [e] Lit. (*11*) 164° C. [f] Recrystallized from ethanol–ethyl acetate. [g] Recrystallized from methanol-benzene. [h] Salt with fumaric acid. [i] Recrystallized from tetrahydrofuran. [j] Compound was isolated as the free base. [k] Recrystallized from benzene–petroleum ether (b.p. 60–71° C.). [l] Recrystallized from methanol-tetrahydrofuran. [m] This is the 4-pyridyl group.

and the aqueous layer was extracted twice with 200 ml. of ether. The combined ether solutions were dried over anhydrous sodium sulfate, filtered, and the solvents were removed under vacuum, leaving 15.0 grams of a colorless oil. The infrared spectrum of this oil, in chloroform solution, showed a peak at 3270 $cm.^{-1}$ (3.06 microns) with a shoulder at 3480 $cm.^{-1}$ (2.88 microns), indicative of a primary amine group (*21*).

A solution of 14.0 grams of the oil in 50 ml. of anhydrous ether was added with stirring to a solution of 5.0 grams (0.12 mole) of hydrogen chloride in 150 ml. of anhydrous ether. After two hours, the resulting precipitate was removed by filtration, washed with anhydrous ether, and dried under vacuum. There was obtained 10.0 grams, 61% over-all yield, of 2-phenyl-3-(*p*-thiomethoxyphenyl)propylamine hydrochloride, m.p. 152–5° C. Recrystallization from methanol-benzene gave a light yellow solid, m.p. 197–9° C.

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An Improved Preparation of 5-Dimethylamino-1-naphthalenesulfonyl Chloride

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An improved synthesis is described for 5-dimethylamino-1-naphthalenesulfonyl chloride, formed by the reaction of 5-dimethylamino-1-naphthalenesulfonic acid with phosphorus pentachloride in phosphorus oxychloride.

THE IMPORTANCE of 5-dimethylamino-1-naphthalenesulfonyl chloride (dansyl chloride) as an extrinsic fluorescent chromophore in the field of protein chemistry is well documented (*1, 4*). The need for a reasonable amount of pure dansyl chloride prompted a better synthesis, since even the poor yields (25 to 40%) reported by Weber (*5*) have not been realized in this laboratory. Furthermore, commercial preparations are of variable purity. In this improved preparation, the yield has been increased to 85%. The earlier inconvenience of tediously grinding to a melt the precursor, 5-dimethylamino-1-naphthalenesulfonic acid, with phosphorus pentachloride has been avoided by conducting the reaction in phosphorus oxychloride. Simple one-day, room-temperature stirring of this solution followed by a routine processing of the reaction mixture afforded the desired product.

EXPERIMENTAL

Melting points were taken with a Thomas Hoover capillary melting point apparatus and are uncorrected. Infrared spectra were taken with Perkin Elmer Models 21 and 137 spectrophotometers. Thin-layer chromatography was performed on silica gel (E. Merck, grade GF_{254}). Column adsorption chromatography was conducted on silica gel (Davison grade 923, 100–200 mesh, air-deactivated), and alumina (Bio-Rad acid alumina AG4, 100–200 mesh).

Preparation of 5-Dimethylamino-1-naphthalenesulfonyl Chloride. A 500-ml., 2-necked flask containing a Teflon-coated magnetic stirring bar, air-cooled condenser, and Drierite-containing drying tube was charged with 25.1 grams (0.1 mole) of 5-dimethylamino-1-naphthalenesulfonic acid (*2, 3*) and 75 ml. (125.6 grams, 0.82 mole)