218. *Nitrogeneous By-products in the Cadiot–Chodkiewicz Reaction.*

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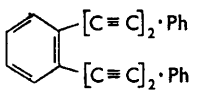
The cuprous-catalysed coupling reaction between 1-bromoacetylenes and terminal acetylenes in the presence of primary amines has been shown to produce amidoxime and amidine by-products in certain circumstances.

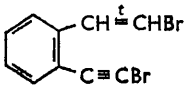
The widely-used Cadiot–Chodkiewicz coupling reaction leading to diacetylenes can be summarised as follows [1]

$$RC{\equiv}CH + BrC{\equiv}CR' \xrightarrow{Cu^+,\ R''NH_2} RC{\equiv}C{\cdot}C{\equiv}CR' + HBr$$

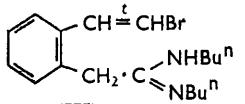
Typically, aqueous ethylamine is employed as the base and the reaction carried out with cuprous chloride in solvents such as ethanol, tetrahydrofuran, and dimethylformamide; small quantities of hydroxylamine or hydrazine hydrochlorides are added as necessary to maintain the cuprous state of the copper catalyst. This procedure when applied to *o*-diethynylbenzene [2] as one of the coupling components gave a highly-insoluble yellow copper complex which appeared unreactive towards the bromoacetylene component. This difficulty was overcome by changing to an anhydrous medium comprising n-butylamine–ethanol (4 : 1). Coupling of *o*-diethynylbenzene and two mols. of 1-bromo-2-phenylacetylene in this medium proceeded smoothly to give a 60% yield of the desired tetrayne (I).



(I)



(II)



(III)

Extension of this coupling to the more complicated bromoacetylene component (II) [3] produced none of the expected tetrayne. The suspicion that an unwanted side-reaction was removing (II) before the desired coupling was confirmed by subjecting (II) alone to the reaction conditions; it was then found to be converted in fair yield into a crystalline hydrochloride, $C_{18}H_{27}N_2Br,HCl$. This molecular formula, coupled with the i.r. and u.v. spectral characteristics of the hydrochloride and the free base, strongly indicated the amidine structure (III) for the base. To see whether this side-reaction could be induced in simpler cases, 1-bromo-2-phenylacetylene was subjected to the same conditions. With this component two nitrogen-containing products were isolated. The first was the expected amidine (IV), isolated as the hydrochloride; this assigned structure was confirmed by hydrolysis to *N*-n-butylphenylacetamide and by a synthesis of (IV) by treatment of *N*-n-butylphenylacetamide with phosphorus pentachloride and n-butylamine.

$PhCH_2{\cdot}C(NHBu^n){=}NBu^n$ (IV)

$PhCH_2{\cdot}C(NH{\cdot}OH){=}NBu^n$ (V)

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[1] Chodkiewicz, *Ann. Chim.* (*France*), 1957, **2**, 819; Eglinton and McCrae, "Advances in Organic Chemistry," Vol. 4, Wiley-Interscience, New York, 1963.
[2] Behr, Eglinton, Galbraith, and Raphael, *J.*, 1960, 3614.
[3] Eglinton and McCrae, *J.*, 1963, 2295.

The second product was isolated as a hydrochloride $C_{12}H_{18}N_2O$,HCl which was identified as the salt of the amidoxime (V) by a synthesis involving interaction of *N*-n-butylphenylthioacetamide and hydroxylamine. When hydrazine was used in place of hydroxylamine in the reaction medium only the amidine (IV) was obtained.

Normally these side-reactions do not occur to any extent in Cadiot–Chodkiewicz couplings because of the great speed of this process and the fact that relatively small amounts of reactive amine and of hydroxylamine hydrochloride are employed. However, it is clear such complications should be borne in mind whenever a sluggish bromoacetylene component is being used or modified reaction conditions employed. Related conversions of ethoxyacetylene [4] and of bromopropiolic acid [5] into amidines have been reported, while more recently, 1-bromo-2-phenylacetylene has been found to give 2,2-bisdiethylaminostyrene on treatment with diethylamine.[6] It is evident from these results, the present work, and from very recent studies,[7] that 1-bromoacetylenes are not so inert to nucleophilic substitution as had been believed.

Experimental

General.—Melting points were determined on a Kofler block and are uncorrected. Ultraviolet and infrared spectral survey data were recorded with Unicam S.P. 500 and Perkin-Elmer 137 spectrophotometers, respectively. Gas–liquid chromatographic measurements were made with a Pye " Argon " chromatograph, equipped with a strontium-90 detector and a column (46 in. × 0·2 in.) packed with Celite (100—120 mesh) coated with Apiezon " L " (5% by weight) as stationary phase. The alumina for column chromatography was acid-washed, neutralised, and standardised (Grade I) according to Brockmann's method. Light petroleum was of b. p. 40—60° unless otherwise stated. Thin layer chromatography (t.l.c.) was carried out with kieselgel G silica support.

o-Di-(4-phenylbuta-1,3-diynyl)benzene (I).—Hydroxylamine hydrochloride (1·04 g.) and freshly prepared cuprous chloride (21 mg.) were dissolved under nitrogen in a mixture of n-butylamine (17 ml.) and ethanol (4 ml.) to form a colourless solution. *o*-Diethynylbenzene [2] (630 mg.) was added, whereupon the solution became pale yellow and a small amount of solid was precipitated. A solution of 1-bromo-2-phenylacetylene (2·0 g.) in *n*-butylamine (15 ml.) and ethanol (3 ml.) was added very slowly to the mixture with vigorous stirring and ice cooling, the temperature being held between 14 and 18°. After 2 hr., an aliquot part was extracted from the mixture, and found to show strong ethynyl absorption in the infrared spectra. More bromoacetylene (300 mg.) was therefore added, and, after being stirred for a further 30 min., examination of a second portion showed negligible ethynyl absorption. Potassium cyanide (*ca.* 1 g.), was added, the solvents were evaporated under reduced pressure, and the residue extracted with ether. The neutral fraction, a brown gum, was chromatographed on alumina (grade H, 150 g.). Elution with light petroleum (300 ml.) yielded unchanged bromoacetylene, but further elution with benzene–light petroleum (1 : 4) gave a yellow oily solid, recrystallisation of which gave the *tetrayne* (I; 1·05 g., 64%) as almost colourless needles, m. p. 130—132° (from benzene–light petroleum) (Found: C, 95·5; H, 4·7. $C_{26}H_{14}$ requires C, 95·7; H, 4·3%); $\nu_{max.}$ (in CS_2) 3080, 3062, 3032, 3020, 2211, 1492, 1481, 1444, 1111, 1071, 1030, 945, and 913 cm.$^{-1}$; (as KCl disc) 760, 751, and 683 cm.$^{-1}$; $\lambda_{max.}$ (in cyclohexane) 349, 327, 304, 286, 271, 263, 250, 243, and 232 mμ (log ε 4·36, 4·44, 4·57, 4·46, 4·54, 4·65, 4·68, 4·67, and 4,69); $\lambda_{min.}$ 342, 314, 292, 278, 258, and 238 mμ (log ε 4·31, 4·37, 4·38, 4·42, 4·60, and 4·65).

Catalytic reduction (10% palladium–charcoal) in ethyl acetate provided substantially pure o-*di*-(4-*phenylbutyl*)*benzene* as a pale yellow oil, b. p. 165°(block)/10^{-4} mm. (Found: C, 90·6; H, 8·95. $C_{26}H_{30}$ requires C, 91·1; H, 8·85%); $\nu_{max.}$ (film) 3010, 2930, 2850, 1600, 1490, 1450, 1080, 1034, 747, and 698 cm.$^{-1}$; $\lambda_{max.}$ (in cyclohexane) 269, 265·5, and 262·5 mμ (log ε 2·98, 3·00, and 3·04); $\lambda_{min.}$ 242 mμ (log ε 2·73). G.l.c. indicated that the oil was a single substance. Reduction with sodium in liquid ammonia of the tetrayne (I) dissolved in tetrahydrofuran resulted in partial reduction, the product being an oil, absorbing in the i.r. spectrum at 1605

[4] Arens and Rix, *Proc. k. ned. Akad Wetenschap.*, 1954, *B***57**, 275.
[5] Mabery and Kraus, *Ber.*, 1889, **22**, 3305.
[6] Wolf and Block, *Annalen*, 1960, **637**, 121.
[7] Ziegler, Weldi, Orzech, Kikkawa, and Miller, *J. Amer. Chem. Soc.*, 1963, **85**, 1648.

and 970 cm.$^{-1}$ (film). Further reduction with palladium–charcoal (10%) in ethyl acetate gave an oil, no longer absorbing near 950 cm.$^{-1}$, which was shown by chromatography over alumina and by g.l.c. to contain at least two hydrocarbons in addition to the *o*-diphenylbutylbenzene. The chromatographic fraction containing these two hydrocarbons (as detected by g.l.c.) had b. p. 170° (block)/10^{-4} mm. (Found: C, 91·5; H, 8·4. $C_{26}H_{28}$ requires C, 91·7; H, 8·3%); $\lambda_{max.}$ (in hexane) 273, 266, and 261 mμ (log ε 3·01, 3·10, and 3·07). These data suggest that the hydrocarbons concerned are transannular hydrogenation products (cf. refs. 2 and 8).

Attempted Cadiot–Chodkiewicz Coupling of o-*Diethynylbenzene with* 1-(trans-2-*Bromovinyl*)-2-(2-*bromoethynyl*)*benzene* (II).—(*a*) When *o*-diethynylbenzene and the bromoacetylene (II) [3] were mixed under the conditions already described for the preparation of the tetrayne (I) no product of unsymmetrical coupling could be detected though the ether-soluble fraction did show i.r. absorptions attributable to C≡CH, C≡CBr, and CH=CHBr groupings. Variations in temperature, −10 to 30°, and time (1 to 3 hr.) were to no avail.

(*b*) A solution of the bromoacetylene (II; 84 mg.) in ether (1 ml.) was added under nitrogen to the modified Cadiot–Chodkiewicz reagent [5 ml.; a mixture of n-butylamine–ethanol (4 : 1) containing a trace of cuprous chloride and sufficient hydroxylamine hydrochloride to render it colourless]. After 90 min. the reaction mixture was poured into water and acidified with dilute hydrochloric acid, whereupon a crystalline solid appeared in the ether layer. The hydrochloride of *o*-trans-2′-*bromovinyl*-NN′-*di-n-butylphenylacetamidine* (50 mg.) after recrystallisation from hot water, was obtained as needles, m. p. 154—155° (Found: C, 55·3; H, 6·8; N, 7·2; O, 0·6. $C_{18}H_{27}N_2Br$,HCl requires C, 55·7; H, 7·3; N, 7·3%); $\nu_{max.}$ (Nujol) 1645 cm.$^{-1}$ (C=N); $\lambda_{max.}$ (in EtOH) 250 mμ (log ε 4·13).

Treatment of the hydrochloride with saturated sodium carbonate solution yielded the base (III) as an oil (from which the hydrochloride could be regenerated); $\nu_{max.}$ (in CCl_4) 3400 (NH), 1645 (C=N), 950, and 935 cm.$^{-1}$ (*trans*-CH=CHBr).

NN′-*Di-n-butylphenylacetamidine* (IV).—(*a*) A solution of 1-bromo-2-phenylacetylene (906 mg.) in ether (4 ml.) was added to the modified Cadiot–Chodkiewicz reagent [21 ml.; a mixture of n-butylamine–ethanol (4 : 1), containing cuprous chloride (10 mg.), and hydrazine hydrochloride (41 mg.) instead of hydroxylamine hydrochloride] and the reaction mixture stirred at 0° for 90 min., with the occasional addition of hydrazine hydrochloride to maintain the pale yellow coloration. After evaporation at 0° under reduced pressure the residue was treated with dilute hydrochloric acid (6N), and the aqueous layer washed well with ether. The aqueous layer was brought to neutrality, again washed with ether, and then thoroughly extracted with chloroform. Evaporation of the chloroform extracts furnished an oil (870 mg.) which solidified on trituration with benzene and light petroleum (60—80°). The crude hydrochloride of the amidine was purified by liberation of the free base followed by re-extraction with hydrochloric acid and chloroform. The pure hydrochloride separated from ethanol–ether at −80° as microprisms, m. p. 86—87° (Found: C, 67·8; H, 9·7; N, 10·1. $C_{16}H_{26}N_2$,HCl requires C, 67·9; H, 9·6; N, 9·9%); $\nu_{max.}$ (solid) 3000 region (broad; NH_2^+ etc.) 1645 (C=N); $\lambda_{max.}$ (in EtOH) 264, 258, and 252 mμ (log ε 2·07, 2·19, and 2·05).

Treatment of the hydrochloride with sodium carbonate solution, and isolation with ether followed by distillation, gave the free *amidine base*, b. p. 118°/0·15 mm., n_D^{20} 1·5180 (Found: C, 77·6; H, 10·4; N, 11·1. $C_{16}H_{26}N_2$ requires C, 77·9; H, 10·7; N, 11·4%); $\nu_{max.}$ (in CCl_4) 3400 (free NH) and 1650 (C=H) cm.$^{-1}$.

The amidine hydrochloride was also a major product when the reaction was conducted in the presence of small quantities of hydroxylamine hydrochloride instead of the hydrazine hydrochloride (see below), and when *n*-butylamine alone was mixed with the bromoacetylene. In this last case the reaction was slow but was greatly accelerated by the addition of traces of cupric acetate. The elimination of bromide ion was followed quantitatively by titration with silver nitrate–potassium thiocyanate, a ferric alum indicator being used. Attempts to extend the reaction by employing other bases, *e.g.*, aniline and *o*-phenylenediamine, were unsuccessful.

Hydrolysis of the amidine hydrochloride with concentrated hydrochloric acid in a sealed tube at 220° for 6 hr. gave an almost quantitative yield of phenylacetic acid, m. p. and mixed m. p. 76—77°. Hydrolysis with 50% aqueous ethanol containing 2% sodium hydroxide by

[8] Friedel and Orchin, "Ultraviolet Spectra of Aromatic Compounds," Chapman and Hall, Ltd., London, 1951.

weight at 20° for 18 hr. resulted in a high yield of N-n-*butylphenylacetamide*, m. p. and mixed m. p. 55—56° (Found: C, 75·55; H, 9·0; N, 7·6. $C_{12}H_{17}NO$ requires C, 75·35; H, 8·95; N, 7·3%).

(*b*) *N*-*n*-Butylphenylacetamide (380 mg.) was added to a solution of phosphorus pentachloride (450 mg.) in benzene (30 ml.) which had been previously refluxed until the evolution of hydrochloric acid gas had ceased (cf. ref. 9). *n*-Butylamine (146 mg.), dissolved in benzene (5 ml.), was then added and the solution heated under reflux for 3 hr. The solvent was removed by evaporation, ammonia solution (0·88) added, and the product extracted with ether. Passage of hydrochloric acid gas then furnished the crude hydrochloride as an oily solid, which separated from ethanol–ether at −80° as microcrystals (57 mg.; 20%), m. p. 84—85°. This product was identical in every way with that isolated under (*a*).

Both the amide and the thioamide were recovered unchanged after treatment [10] with n-butylamine.

N-n-*Butylphenylacetamidoxime* (V).—(*a*) A solution of 1-bromo-2-phenylacetylene (815 mg.) in ether (8 ml.) was added to the modified Cadiot–Chodkiewicz reagent [21 ml.; a mixture of n-butylamine–ethanol (4 : 1), containing cuprous chloride (10 mg.) and sufficient hydroxylamine hydrochloride to render it colourless] at −10°. Further quantities of hydroxylamine hydrochloride were added to the stirred mixture during 30 min.; whereupon the mixture was poured into water and acidified with dilute hydrochloric acid. The aqueous layer was washed with ether and basified with solid sodium carbonate, and the basic product isolated by ether extraction. When the ether extract was treated with hydrochloric acid (6N), crystals (320 mg.) appeared in the ether layer and were collected by centrifugation. After recrystallisation from ethanol the pure *amidoxime hydrochloride* was obtained as plates, m. p. 182—184° with sublimation (Found: C, 59·3; H, 7·6; N, 11·6; Cl, 14·4. $C_{12}H_{18}N_2O$,HCl requires C, 59·6; H, 7·9; N, 11·6; Cl, 14·6%); $\nu_{max.}$ (Nujol) 3000br (=NH_2^+, OH, etc.) and 1460 (C=N); $\lambda_{max.}$ (in EtOH) 264, 258, and 251 mμ (log ε 2·18, 2·31, and 2·34).

Treatment of the hydrochloride with aqueous sodium carbonate followed by ether extraction and distillation gave the crude amidoxime (V); $\nu_{max.}$ (in CCl_4) 3600 (OH, free), 3400 (NH, free), 3200br (OH and NH, bonded), and 1645 $cm.^{-1}$ (C=N). Dilution studies in carbon tetrachloride revealed that the 3200 band was due to intermolecular hydrogen bonding.

A similar yield of the amidoxime hydrochloride resulted when a large excess of hydroxylamine hydrochloride was used in the *absence* of cuprous chloride but a considerable quantity of unchanged bromoacetylene was recovered after reaction for 4 hr. The amidine (IV) is also formed but was not isolated (*b*) To a solution in ethanol (25 ml.) of *N*-n-butylphenylthioacetamide (1·47 g.), prepared [11] from *N*-n-butylphenylacetamide (2·0 g.) and phosphorus pentasulphide (1·8 g.) in xylene (25 ml.), was added hydroxylamine hydrochloride (690 mg.) and sodium carbonate (497 mg.), and the mixture heated under reflux for 14 hr. Isolation as under (*a*) with hydrochloric acid and ether furnished the amidoxime hydrochloride as plates, m. p. 181—182°, from ethanol. It was identical in every respect with that already described under (*a*).

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[9] Hill and Cox, *J. Amer. Chem. Soc.*, 1926, **48**, 3214.
[10] Bernthsen, *Annalen*, 1878, **192**, 1; Wallach, *Ber.*, 1882, **15**, 210.
[11] Rivier and Schneider, *Helv. Chim. Acta*, 1920, **3**, 115.