

Organic Electrosyntheses. IX.* Condensation of 2-Aminophenylhydrazine with Ortho Esters

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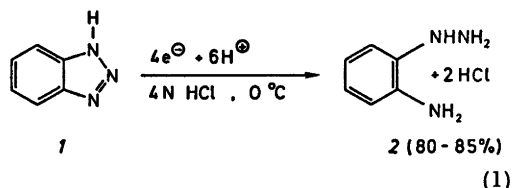
A procedure for the preparation of 2-aminophenylhydrazine (**2**) in high yield by large-scale cathodic reduction of benzotriazole (**1**) in acidic medium has been developed. With **2** as an easily available starting material a simple and efficient synthesis of 3-substituted benzo-1,2,4-triazines (**4**) by condensation with the corresponding ortho esters is presented. The optimum conditions for this reaction were found from kinetic measurements and variation of the reaction parameters, determining the product concentration by means of cathodic DC-polarography.

Benzo-1,2,4-triazines have been prepared by several methods,¹⁻¹² but few of these are both general and give satisfactory yields. Kwee and Lund¹¹ have briefly reported on the formation of 3-substituted benzo-1,2,4-triazines by condensation of electrochemically prepared 2-aminophenylhydrazine dihydrochloride (**2**) with carboxylic acid derivatives in rather low yields. In the present work we have scaled up the electrolytic reduction of benzotriazole (**1**) from a 1 g scale to about 50–100 g to make **2** an available starting material for synthetic purposes, and optimized the condensation of **2** with ortho esters to produce the corresponding

3-substituted benzo-1,2,4-triazines (**4**) in high yields (90–95 %).

RESULTS AND DISCUSSION

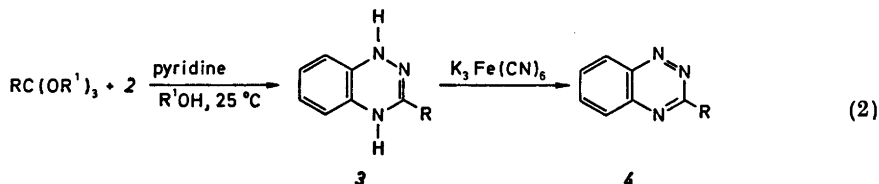
The procedure for the cathodic reduction of benzotriazole to **2** in acidic medium is similar to that of Lund and Kwee,¹¹ and details are to be found in the experimental section (eqn. 1).



The methyl and ethyl ortho esters of formic, acetic, propionic, and benzoic acid were found to react with **2** in the presence of a tertiary amine (eqn. 2). The intermediate dihydro derivative **3** has not been isolated, but could be detected by anodic polarography,¹¹ and was oxidized by excess potassium hexacyanoferrate(III) to **4** which was isolated by continuous extraction with benzene.

The formation of **4** could conveniently be followed by cathodic polarography in alkaline

* For Part VIII, see Ref. 14.



(90–95% overall yield)

Table 1. Yields, solvents, and second order rate constants (k_2) for the formation of 3-substituted benzo-1,2,4-triazines (4) from the condensation of ortho esters with 2-aminophenylhydrazine (2) in the presence of pyridine and subsequent oxidation with potassium hexacyanoferrate(III).

Ortho ester Case	RC(OR ¹) ₂		Sol- vent	Yields (%) of 4 (based on 2)			k_2 (25 °C) (dm ³ mol ⁻¹ min ⁻¹)
	R	R ¹		Anal.	Crude	Isol.	
aa	H	Me	MeOH	87	82	77	4.7 ± 0.2
ab	H	Et	EtOH	99	93	89	23.2 ± 1.9
ba	Me	Me	MeOH	98	94	88	4.0 ± 0.4
bb	Me	Et	EtOH	99	96	92	20.2 ± 1.7
ca	Et	Me	MeOH	97	93	93	2.6 ± 0.3
cb	Et	Et	EtOH	99	93	93	7.4 ± 0.8
da	Ph	Me	MeOH	95	90	84	1.0 ± 0.2
db	Ph	Et	EtOH	96	91	86	2.0 ± 0.2

medium where the hexacyanoferrate(III) ion is not reducible. The wave-height was found to be independent of the concentrations of $K_3Fe(CN)_6$, $K_4Fe(CN)_6$, KOH, and added amine up to 10 times that of the concentrations used in any of the samples investigated. This facilitated kinetic measurements (Fig. 1) which showed that the reaction is first order in both 2-aminophenylhydrazine and ortho ester. Results are given in Table 1 and some of the properties of 4 in Table 2. The procedure described seems to be the method of choice for the preparation of 4, provided the automatic equipment for the electrochemical reduction of 1 into 2 is available. The most reliable other procedures are probably those of Kwee and Lund¹¹ or Adgar *et al.*¹²

Compound 2 has been prepared by reduction of 2-nitrophenylhydrazine with tin and hydrochloric acid,¹³ but is difficult to obtain pure in a reasonable yield. The yield of 2 from cathodic reduction of 1 is probably nearly quantitative, but certain losses are inevitable during longtime electrolysis and work-up due to the very easy oxidation of 2 even in acidic media as described in the experimental section.

The optimum conditions for the formation of 4 were investigated by changing variables such as amount of oxidant, temperature, added base, reaction time, and solvent, the yields being determined by cathodic DC-polarography.

It was unnecessary to use excess of $K_3Fe(CN)_6$ in the oxidation step (*cf.* Fig. 1), but reaction times could of course be shortened. Some experiments were made using air as the oxidating agent, by passing a stream of air through the reaction mixture. Though it was possible

to get relatively high yields of 4 by this method, it extended the duration of the oxidation step by a factor of at least 10–15.

The temperature had a significant influence on the pathway of the reaction, most pronounced in the case of the formation of 4a where the yield was nearly halved by increasing the temperature from 25 to 65 °C (case aa) or to 78 °C (case ab, see Table 1). At these temperatures about 15% of benzimidazole was also isolated. In the case of formation of 4b or 4c, the yields decreased by about 25% under identical conditions, and about 5% of 2-methylbenzimidazole was isolated together with 4b. The formation of 4d seemed to be insensitive to variations of temperature. In none of these cases were the yields increased by lowering the temperature to 0 °C.

Using Et_3N or Na_2CO_3 as base in equivalent amounts had no significant effect on the yields of 4. These yields seemed to be independent of the type of base used, as long as this was not used in too large an excess. In the limiting case where pyridine was used both as a solvent and a base, the yields decreased by 40–60%.

From a preparative point of view it is preferable to use the triethyl ortho esters, both because the reaction time is shorter which can be seen from the rate constants given in Table 1, and because the yields of 4 are generally higher, especially for the cases aa and ab where an increase in the yield of 12% was found by using triethyl orthoformate instead of trimethyl orthoformate (Table 1).

Fig. 1 shows the results from typical kinetic runs for the oxidation step on a 0.0256 mol scale of 2 with equivalent amounts of pyridine,

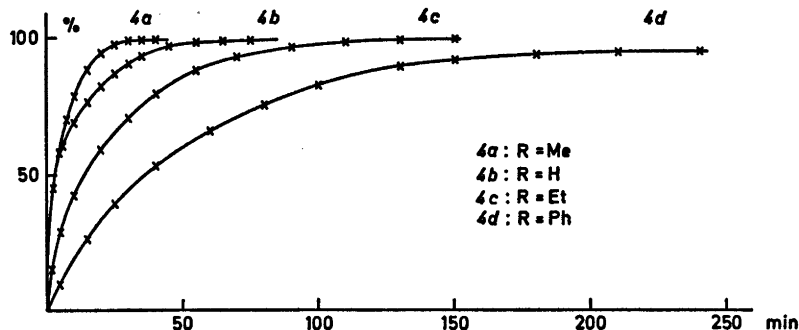


Fig. 1. Results from typical kinetic runs of the oxidation step of the reaction (2) with equivalent amounts of 2-aminophenylhydrazine, ortho ester, pyridine, and potassium hexacyanoferrate(III) (for details see the experimental section).

ortho ester, and $K_3Fe(CN)_6$. It is seen that the reaction requires an oxidation time between 40 min and 4 h which was much less than with air oxidation where at least 24 h were required for the full conversion of 3. As expected, the duration of the oxidation step was independent of whether trimethyl or triethyl ortho esters were used.

As expected the yields decreased rapidly when the water content of the reaction medium was raised. Using water as solvent gave about 3–10 % of 4, and using 96 % EtOH decreased the yields by 20–60 %.

Condensation of 1 with formic acid, acetic acid, propionic acid, benzoic acid, acetic anhydride, propionic anhydride, methyl acetate, ethyl acetate, and methyl benzoate gave yields of 4 only in the range 5–20 % using the optimum conditions given in the experimental section. Raising the temperature also decreased these yields.

Instead of using a large scale procedure for the preparation of 2 (which included a purification step, details are to be found in the experimental section), a one-step procedure involving the reduction of 1 on a 5 g scale was worked out in which the resulting crude 2 was used without further purification before the condensation reaction with triethyl ortho acetate under the optimum conditions found. The overall analytical, crude, and recrystallized yields of 4b (based on 1) were 96, 93, and 90 %, respectively. This result further indicated that the electrochemical reduction of benzotriazole is an almost quantitative reaction.

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Attempts to condense 2 with carbonyl compounds using *in situ* technique¹⁴ with electrolytic reduction of 1 in an aqueous acetate buffer of pH 5 in the presence of excess acetaldehyde or acetone were not very promising, as no cyclized product could be found after consumption of 4F/mol. However, a rather fast condensation reaction must have taken place during the electrolysis, as azomethine bonds were detected spectroscopically in the isolated product mixture which was not further separated and characterized.

Preliminary experiments to condense 2 with biacetyl to form 3,4-dimethylbenzo-1,2,5-triazepine using conditions similar to the ortho ester reaction gave complicated reaction mixtures which were difficult to work up, and this possibility was not further explored. However, yields of up to 60 % 2,3-dimethylquinoxaline were isolated.

EXPERIMENTAL

Apparatus. An H-type 3-electrode cell of conventional design¹⁵ was used in combination with a JUUL Electronic 40V/25A potentiostat. The cell was cooled by means of a HETOFRIG CB122 cryostat. Spectra were recorded on a Varian A60 NMR spectrometer, a Perkin-Elmer Infracord or a Beckmann IR 18-A IR spectrophotometer, a Perkin-Elmer 402 UV spectrophotometer, and a CEC 21-104 mass spectrometer. DC-polarograms were recorded on a Radiometer PO4 polarograph. Melting and boiling points are uncorrected. GLC purity checks were performed on a Hewlett-Packard 5711A gas chromatograph in combina-

tion with a Hewlett-Packard 3370B integrator using 15 % SE 30 on Chromosorb WAW (80–100 mesh) on a 2 m SS-column. Coulometric measurements were done by means of an LK 5A electromechanical integrator.

Materials. Benzotriazole (*1*) was a commercial product. Ortho esters were either commercial products (cases aa, ab, ba, bb, ca, db, see Table 1) or prepared according to published procedures.¹⁸ The commercial products were used as received (checked by GLC). Our yields of triethyl ortho-propionate b.p. 43–44 °C/12 mmHg, n_D^{25} 1.3941 and trimethyl orthobenzoate b.p. 69–71 °C/12 mmHg, n_D^{25} 1.4900 were 49 and 16 %, respectively (purity checked by GLC).

Electrolytic reduction of benzotriazole (1). Electrolyses were performed in an H-type cell of about 400 ml catholyte volume and 65 cm² of mercury surface immersed in a methanol bath thermostated around 0 °C by means of a magnetic valve and a contact thermometer in the cathode compartment. *1* (50–75 g) was reduced in 4 N aqueous hydrochloric acid at –1.2 V (*vs.* Ag/AgCl in 4 N HCl) under nitrogen which was purified by passing over a BASF R3-11 catalyst at 120–150 °C. The hydrochloride of *1* precipitated by cooling, thus making magnetic stirring difficult and limiting the amount of *1* which could be used in the beginning. More *1* could be added after 5–6 h of electrolysis at a relatively low current (0.8–1.2 A), the total electrolysis time being 2–3 days with consumption of 4 F/mol. Efficient cooling and temperature control was indispensable, as a much more impure product was obtained from electrolysis at 10 °C, and below 0 °C magnetic stirring was virtually impossible due to the high viscosity of the semisolid catholyte mixture. In practice it is very difficult to avoid the formation of deep reddish coloured by-products, probably caused by the presence of trace amounts of oxygen in the catholyte, as seen by the pink colour developed in the neighbourhood of the mercury surface shortly after the current had been switched on. It was *not* due to oxidation by compounds formed at the anode, as the red colour diffused through the glass frit into the middle compartment from the cathode side. The anolyte was a 1:1 4 N hydrochloric acid/ethanol mixture as earlier reported.¹⁷

After electrolysis the clear, reddish catholyte was thoroughly evaporated *in vacuo* (1 mmHg) at a bath temperature not exceeding 40 °C. The pink residue was purified by heating (5–10 min) in deaerated methanol to dissolve unreduced *1* (hydrochloride) and strongly coloured impurities, cooled to –20 °C, rapidly filtered, washed with cold deaerated methanol, and dried to constant weight *in vacuo* over silica gel. *2* was isolated in 80–85 % yield (based on *1*) as a pinkish material, identified by IR,¹⁸ showing an anodic polarographic wave and assayed by potentiometric titration with standard silver nitrate solution, giving mol.wt.

196.0 ± 1.5 (normally 195.5). The compound was unstable against air and must be stored *in vacuo* or under nitrogen. A direct DC-polarographic determination¹⁹ of the concentration of *2* in an aliquot of the catholyte was not attempted due to the difficulties in obtaining a standard sample of known purity. Probably the formation of *2* by electrolytic reduction of *1* is nearly quantitative, but some losses must be envisaged due to air oxidation during work-up and a finite solubility of *2* in methanol.

General procedure for the preparation of benzo-1,2,4-triazines (4). *2* (0.025 mol) was added to a deaerated mixture of the ortho ester (0.025 mol) and pyridine (0.060 mol) in 50 ml of the corresponding alcohol (methanol or abs. ethanol) at room temperature under nitrogen. After an appropriate time (usually 2–18 h, *cf.* Table 1) the reaction mixture was poured into 100 ml of an aqueous solution of potassium hexacyanoferrate(III) (0.090 mol) and left for 1–4 h at room temperature. The benzo-1,2,4-triazine (*4*) was extracted continuously by benzene (175 ml) for 16 h. After drying over anhydrous potassium carbonate the benzene solution was evaporated *in vacuo* (12 mmHg) at a bath temperature not exceeding 40 °C in order to avoid sublimation (distillation). The residue was either recrystallized from light petroleum (b.p. < 50 °C), or chromatographed on alumina with a 1:1 mixture of chloroform and redistilled light petroleum, or fractionated *in vacuo*. Usually the crude products *4* were very pure (as checked by TLC) so that chromatographic purification was unnecessary before recrystallization (or sublimation), except if a trace impurity of some strongly yellowish material should be removed. The yields of *4* (Table 1) are based on purified *2*, assuming the material to be the pure dihydrochloride, mol.wt. 196. Identification of *4* was done by comparison with spectroscopic data for authentic samples except for the 3-ethylbenzo-1,2,4-triazine (*4c*), which has not been reported in the literature. Some properties of *4* are indicated in Table 2. It should be noticed that compounds *4a*, *4b*, and *4d* easily sublime at reduced pressures which could also be used for their purification.

One-step procedure for the preparation of benzo-1,2,4-triazines (4). *1* (4.65 g, 0.0378 mol) was reduced during 8 h according to the above procedure at –1.1 V (*vs.* Ag/AgCl) with the H-cell (catholyte volume about 175 ml) immersed in an ice-water bath. After evaporation to dryness *in vacuo* (1 mmHg) the pink residue was dissolved in 60 ml of deaerated ethanol, poured into a solution of triethyl orthoacetate (0.0378 mol) and pyridine (0.0756 mol) in 40 ml of ethanol at room temperature under nitrogen. After 2 h of magnetic stirring the reaction mixture was poured into 100 ml of an aqueous solution of potassium hexacyanoferrate(III) (0.0756 mol) and left for 1 h. The

Table 2. Properties of 3-substituted benzo-1,2,4-triazines (4). (No ¹H NMR, IR, or MS data have been stated in the literature).

Com- pound	R	M.p. (°C) or b.p./mmHg	60 MHz ¹ H NMR δ (CDCl ₃)	UV (96 % ethanol) λ_{\max} (nm)	log ϵ	IR (CHCl ₃) cm ⁻¹ ^a	MS (m/e) ^a
4a	H	71–72	9.98 (s)	241	3.80	940 (v), 965 (v), 1095 (m), 1105 (v)	131 (M ⁺), 103 (M ⁺ –N ₂)
				306	3.55	1125 (m), 1170 (v), 1280 (m), 1375 (m), 1435 (v), 1480 (m), 1570 (m), 1620 (v), 3000 (m), 3400 (b)	1210 (b), 1435 (v), 1620 (v)
4b	Me	90–91	3.18 (s)	243	3.93	880 (m), 955 (m), 1000 (v), 1065 (s), 1130 (v)	145 (M ⁺), 117 (M ⁺ –N ₂)
				305	3.56	1175 (m), 1210 (b), 1300 (s), 1370 (m), 1395 (m)	1300 (s)
				330	3.42	1455 (m), 1520 (s), 1620 (v), 3000 (m), 3400 (b)	1570 (m), 3400 (b)
4c	Et	101/1 ($n_D^{20} = 1.5920$)	1.69 (t, J=8) 3.45 (q, J=8)	304	3.87	960 (m), 1000 (v), 1040 (m), 1080 (m), 1125 (v)	159 (M ⁺), 131 (M ⁺ –N ₂)
				328	3.36	1210 (b), 1280 (v), 1325 (v), 1390 (v), 1460 (m)	1325 (v)
				341	3.50	1520 (s), 1570 (v), 3000 (m), 3400 (b)	1620 (v)
4d	Ph	122–123	7.30– 8.35 (m)	219	3.70	705 (s), 925 (v), 960 (m), 1015 (s), 1070 (v)	179 (M ⁺ –N ₂)
				269	4.12	1100 (m), 1125 (v), 1210 (b), 1270 (v)	1175 (m)
				254	3.38	1325 (s), 1395 (v), 1510 (s), 1570 (v), 3000 (m), 3400 (b)	1445 (m), 1615 (v)

^a Only main peaks are given.

work-up procedure was as above, and the analytical yield of *4b* (based on *1*) was 96 %, the crude yield 93 %, and the yield after recrystallization 90 %.

Kinetic measurements. Determination of the oxidation time. Reactions were performed with equivalent amounts of *2*, ortho ester and pyridine (0.0256 mol scale) in 60 ml of the appropriate alcohol according to the above procedure (reaction time 24 h). The reaction mixture was poured into 150 ml of an aqueous solution of potassium hexacyanoferrate(III) (0.0256 mol), diluted by water to a total volume of 250.0 ml and shaken. Periodically 1.0 ml samples of the solution were withdrawn and added to 24.0 ml of an alkaline sulfite solution¹⁹ (9 g of KOH and 20 g of Na₂SO₃ per l of water), and the analytical yield was determined by DC-polarography by means of a standard curve. The analytical results are depicted in Fig. 1 from which the time of oxidation was determined.

Determination of the reaction time. 2-Amino-phenylhydrazine dihydrochloride (*2*) was added to a deaerated mixture of the ortho ester and pyridine in equivalent amounts (0.0513 mol scale) in the appropriate alcohol (total volume of the reaction mixture: 250.0 ml). Periodically 1.0 ml samples were withdrawn, added to 24.0 ml of an aqueous solution of potassium hexacyanoferrate(III) (0.00041 mol) and the mixture polarographed as above.

Acknowledgement. Financial support (to P.E.I.) from the Danish Natural Science Research Council to purchase the HETO cryostat and the JUUL potentiostat is hereby gratefully acknowledged.

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Received May 24, 1976.