102. *1,2,4-Triazoles. Part II.*[1] *3-Alkyl-5-aryl-1,2,4-triazoles.**

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Several triazoles of the above type have been synthesised by the fusion of aromatic cyanides with hydrazide benzenesulphonates of aliphatic acids. Diaryltriazoles are also formed, mainly when acethydrazide benzenesulphonate is used, and evidence is presented to account for these products. This synthesis is restricted to the use of aromatic cyanides and hydrazide benzenesulphonates of aliphatic or aromatic acids.

In a previous communication[1] the fusion of a benzene-, *p*-nitrobenzene-, or toluene-*p*-sulphonic acid salt of an arylhydrazide with an aromatic cyanide was shown to yield a 3,5-diaryl-1,2,4-triazole. This paper describes the preparation of 3-alkyl-5-aryl-1,2,4-triazoles * from aromatic cyanides and hydrazide benzenesulphonates of aliphatic acids, and shows that the method is not satisfactory for the preparation of 3,5-dialkyl-1,2,4-triazoles.

The condensation is effected by heating together equimolar quantities of the reactants at 200° for 1—2 hours. A 3,5-diaryltriazole is sometimes found associated with the 3-alkyl-5-aryltriazole, with the aryl groups corresponding to that of the aromatic cyanide used. The diaryltriazole must be formed either by reaction of the aromatic cyanide with some intermediate product or by a similar condensation between products derived from the initial reactants in some way. Evidence suggests that triazole formation occurs through the intermediate hydrazidinium salt (I). This would immediately undergo ring closure with elimination of water,[2] rather than further reaction with unchanged cyanide. That the diaryltriazole is actually formed in a similar condensation was verified for the reaction of *o*-tolyl cyanide with hydrazide benzenesulphonates of aliphatic acids. From several of these reactions *o*-toluamide was isolated. This must arise by hydration of the *o*-tolyl cyanide, the necessary water coming from the ring closure that occurs simultaneously. Under these reaction conditions cyanides are known[3] to give amides very readily. The amide formed is then available to take part in a transamination: $R'{\cdot}CO{\cdot}NH_2 + R{\cdot}CO{\cdot}NH{\cdot}NH_2 \rightleftharpoons R'{\cdot}CO{\cdot}NH{\cdot}NH_2 + R{\cdot}CO{\cdot}NH_2$. Similar transaminations under related

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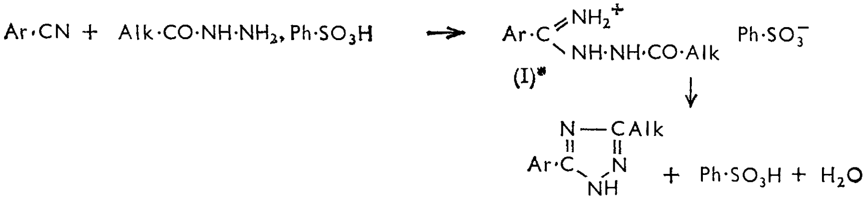
* As the position of the imino-hydrogen is unknown, these may also be regarded as 5-alkyl-3-aryl-1,2,4-triazoles.

[1] Part I, Potts, *J.*, 1954, 3461.

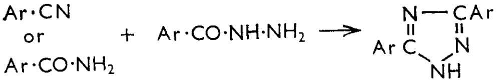
[2] (*a*) Atkinson and Polya, *J.*, 1954, 3323; (*b*) Atkinson and Polya, *J. Amer. Chem. Soc.*, 1953, **75**, 1471; (*c*) Pinner, *Ber.*, 1894, **27**, 997.

[3] Kilpatrick, *J. Amer. Chem. Soc.*, 1947, **69**, 42; DeBenneville, Levesque, Exner, and Hertz, *J. Org. Chem.*, 1956, **21**, 1072.

conditions have been noted previously,[4,5] and recent investigations have shown [6] that at temperatures of 180—200° the equilibrium in the fusion of an aliphatic amide, particularly a substituted acetamide, and an amine salt is shifted completely to the right in 15 min. In the Pellizzari synthesis involving fusion of an amide and a hydrazide at 200—280°, mixtures of triazoles are nearly always obtained, particularly when acethydrazide is used; [4] *e.g.*, from benzamide and acethydrazide a mixture of 3,5-diphenyl-, and 3-methyl-5-phenyl-1,2,4-triazole is obtained; [2a] this side reaction is the main disadvantage of the Pellizzari method.[7] It has now been shown that in the fusion of benzamide and acethydrazide benzenesulphonate the equilibrium in the initial transamination is shifted completely to the right, so that only 3,5-diphenyl-1,2,4-triazole is isolated from the reaction. These results suggest that after formation in the transamination the arylhydrazide can condense in two ways, the over-all result being the same. The first involves reaction with unchanged cyanide,[1] and the second a Pellizzari-type reaction with the aromatic amide. As all these species are present in the melt at the same time the two reactions probably occur concurrently.



* Or an equivalent formulation.



In agreement with earlier observations [4] it was found that propionhydrazide only underwent transamination to a small extent, and butyrhydrazide appeared not to react at all.

Attempts to prepare these triazoles by the alternative route, the fusion of alkyl cyanides with the hydrazide benzenesulphonate of an aromatic acid, were unsuccessful. From the attempted condensation of methyl cyanide or ethyl cyanide with benzhydrazide benzenesulphonate at 200° the same compound was isolated, and shown to be 4-benzamido-3,5-diphenyl-1,2,4-triazole (II; R = Bz). This can only result by self-condensation of benzhydrazide in some way. It is known that fusion of benzhydrazide [8,9] or its benzenesulphonate at 260° readily yields 4-amino-3,5-diphenyl-1,2,4-triazole (II; R = H); and, when benzhydrazide is heated under reflux for short periods with a small amount of benzenesulphonic acid in an ionising solvent such as dimethylformamide, dibenzoylhydrazine is one of the products formed. This suggests that in the above reaction the alkyl cyanide merely acts as an ionising solvent and the intermediate dibenzoylhydrazine condenses with unchanged benzhydrazide to form the triazole (II; R = Bz). This compound has previously been obtained in a related reaction by condensation of benzhydrazide and di-(α-chlorobenzylidene)hydrazine.[10] Methyl cyanide with aniline hydrochloride forms a mixture of *N*-phenyl- and *NN*-diphenyl-acetamidine [11] and on enhancement of its

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[4] Pellizzari, *Gazzetta*, 1911, **41**, 20.

[5] Hoggarth, *J.*, 1949, 1164.

[6] Gerchuk, Lifshits, and Taits, *J. Gen. Chem.* (*U.S.S.R.*), 1950, **20**, 924; Ridel and Gerchuk, *ibid.*, 1958, **28**, 1365.

[7] Potts, *Chem. Rev.*, 1960, in the press.

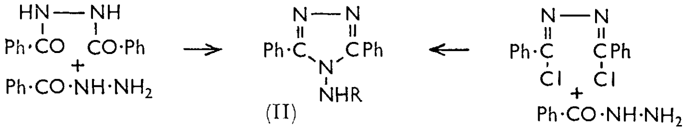
[8] Stolle, *J. prakt. Chem.*, 1903, **68**, 464.

[9] Silberrad, *J.*, 1900, **77**, 1190.

[10] Stolle and Thomä, *J. prakt. Chem.*, 1906, **73**, 295.

[11] Bernthsen, *Annalen*, 1877, **184**, 290.

activity by combination with a catalyst such as aluminium chloride [12] it reacts with aniline itself, forming the same amidines. In trichloromethyl cyanide [13] the inductive effect of the polar substituents so increases the positive character of the α-carbon atom that amidine formation occurs very readily. Indeed, with nitromethyl cyanide, salts and not amidines are formed.[14] Thus it appears that benzenesulphonic acid is not a sufficiently strongly cationoid catalyst to effect the condensation of an alkyl cyanide and a hydrazide.



(II)

Reaction of methyl cyanide with acethydrazide benzenesulphonate also did not give the expected triazole. No homogeneous product, apart from hydrazine dibenzenesulphonate, which is probably formed in the working up of the reaction mixture, was isolated.

The opportunity is taken to record some incidental observations. Heating an equimolar mixture of cyanide, hydrazide, and benzenesulphonic acid affords the triazole in yields similar to those obtained when the benzenesulphonate salt is used. No increase in yield occurs from reaction in sealed tubes. Methyl cyanide does not react with the hydrazide benzenesulphonate under these conditions. Replacement of the hydrazide salt with an acylarylhydrazine salt should give rise to a 1,3,5-trisubstituted 1,2,4-triazole. However, benzenesulphonate salts of these substituted hydrazides could not be obtained; in all the instances investigated the acyl group was either eliminated and the benzenesulphonate salt of the arylhydrazine obtained or the material was recovered unchanged. The alternative method, heating of the three components together, was not successful, no identifiable products being isolated.

EXPERIMENTAL

Evaporation of solvents was under reduced pressure on a water-bath. Light petroleum refers to the fraction of b. p. 60—80°.

Hydrazide Benzenesulphonates.—General method. The hydrazide, dissolved in the minimum amount of warm ethanol, was treated with a 10% excess of benzenesulphonic acid, added in small portions, with occasional cooling. The salt was precipitated by the addition of an equal volume of dry ether, collected, and dried (yield usually >90%). *Acethydrazide benzenesulphonate* crystallised from ethanol–ether as needles, m. p. 175—176° (Found: C, 41·4; H, 4·9. $C_8H_{12}N_2O_4S$ requires C, 41·4; H, 5·2%), and *propionhydrazide benzenesulphonate* as plates, m. p. 149—150° (Found: C, 43·8; H, 5·6. $C_9H_{14}N_2O_4S$ requires C, 43·9; H, 5·7%). *Butyrhydrazide benzenesulphonate* crystallised as needles, m. p. 161—162°, from ethanol (Found: C, 46·4; H, 6·2. $C_{10}H_{16}N_2O_4S$ requires C, 46·2; H, 6·2%). In the preparation of those salts, particularly benzhydrazide benzenesulphonate, where boiling alcohol is required to effect dissolution of the hydrazide, a small quantity of a white, insoluble product soon appears after addition of the benzenesulphonic acid. This was identified as hydrazine dibenzenesulphonate by direct comparison (m. p., infrared and ultraviolet spectra) with a specimen prepared from hydrazine and two mols. of benzenesulphonic acid. It crystallised from a large volume of ethanol as plates, m. p. 284—285° (decomp.) [15] (*vacuo*) (Found: C, 41·8; H, 4·7; N, 8·0; S, 18·4. Calc. for $C_{12}H_{16}N_2O_6S_2$: C, 41·4; H, 4·6; N, 8·0; S, 18·4%).

3-*Alkyl*-5-*aryl*-1,2,4-*triazoles.—General method.* The hydrazide benzenesulphonate (0·05 mole) and the aromatic cyanide (0·05 mole) were heated together in a vapour-bath at 200° for

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[12] Oxley, Partridge, and Short, *J.*, 1947, 1110.

[13] G.P. 671,785; *Chem. Abs.*, 1939, **33**, 6345; Oxley, Partridge, and Short, *J.*, 1948, 303; Grivas and Taurins, *Canad. J. Chem.*, 1958, **36**, 771.

[14] Grivas and Taurins, *Canad. J. Chem.*, 1959, **37**, 1266.

[15] Curtius and Lorenzen, *J. prakt. Chem.*, 1903, **58**, 177.

1—2 hr. Effervescence usually occurred for about 45 min. and water formed on the walls of the tube. An equal volume of water was added to the cooled melt and the solution brought to pH ~7 with sodium hydroxide or carbonate. Any solid that separated (usually only 3,5-diphenyltriazole) was removed and the solution extracted with ether. After working up of the ether extract in the usual way, the partly crystalline residue was purified by one of two methods. In condensations involving the use of phenyl cyanide, the 3-alkyl-5-phenyltriazole was extracted from the more insoluble 3,5-diphenyltriazole with light petroleum. Purification was then by recrystallisation or by distillation followed by recrystallisation. With *o*-tolyl cyanide purification was slightly more difficult owing to the presence of a three-component mixture. The crude material was separated into two fractions by distillation *in vacuo*. The low-boiling fraction was mainly *o*-toluamide, contaminated with the 3-alkyl-5-*o*-tolyltriazole which was removed by extraction with light petroleum. After several recrystallisations from benzene, the *o*-toluamide separated as needles, m. p. 140—141° alone or on admixture with an authentic specimen that had an identical infrared spectrum (Found: C, 71·4; H, 6·7. Calc. for C_8H_9NO: C, 71·1; H, 6·7%). The high-boiling fraction was purified by recrystallisation or, if this was insufficient, by chromatography in benzene on neutral alumina (activity 1). A small amount of *o*-toluamide was eluted first. The 3-alkyl-5-*o*-tolyltriazole was recrystallised or further purified by sublimation *in vacuo*. From the recrystallisation mother-liquors a small amount of 3,5-di-*o*-tolyltriazole was isolated as the picrate.

The *products* obtained are recorded in the Table.

Triazoles prepared by the reaction of aromatic cyanides with hydrazide benzenesulphonates of aliphatic acids.

Substituents		M. p.	Crystn. solvent[f]	Yield (%)	Found (%)			Formula	Required (%)		
					C	H	N		C	H	N
Me	Ph	166°[2a]	C_6H_6	25	67·9	5·4	—	$C_9H_9N_3$	67·9	5·7	—
Et	Ph	103—104	,,	18	69·4	6·3	24·0	$C_{10}H_{11}N_3$	69·3	6·4	24·3
Pr	Ph	71—72	Aq. EtOH	31	67·3	7·3	21·0	$C_{11}H_{13}N_3,0·5H_2O$[a]	67·4	7·1	21·4
Me	*o*-Tolyl	140—141	C_6H_6–Pet	50	69·6	6·4	23·9	$C_{10}H_{11}N_3$	69·3	6·4	24·3
Et	,,	87	,,	50	70·6	6·9	22·5	$C_{11}H_{13}N_3$[e]	70·6	7·0	22·5
Pr	,,	124—126	C_6H_6	40	72·0	7·6	20·8	$C_{12}H_{15}N_3$	71·6	7·5	20·9
Et	CH_2Ph	230—240/ 0·1 mm.[b]	—	—	70·1	6·9	—	$C_{11}H_{13}N_3$	70·6	7·0	—
Ph	Ph	189—190[1]	Pet	14	—	—	—	$C_{14}H_{11}N_3$	—	—	—
o-Tolyl	*o*-Tolyl	190—191	EtOH	—	55·3	3·9	17·4	$C_{22}H_{20}N_6O_7$[d]	55·0	4·2	17·5

[a] *Picrate*, prisms (from benzene), m. p. 129—130° (Found: C, 49·2; H, 3·9; N, 20·1. $C_{17}H_{16}N_6O_7$ requires C, 49·1; H, 3·9; N, 20·2%). [b] B. p. [c] Identity established by comparison of infrared spectrum with that of authentic specimen. [d] Isolated as picrate containing $1H_2O$. [e] *Picrate*, needles (from benzene), m. p. 138° (Found: C, 52·1; H, 4·1; N, 19·0. $C_{17}H_{16}N_6O_7,0·3C_6H_6$ requires C, 51·6; H, 4·1; N, 19·0%). Pet = light petroleum.

Attempted Condensation of Methyl Cyanide with Benzhydrazide Benzenesulphonate.—4-*Benzamido*-3,5-*diphenyl*-1,2,4-*triazole*. A mixture of methyl cyanide (1·6 g., 0·04 mole) and benzhydrazide benzenesulphonate (12·9 g., 0·044 mole) was heated under reflux at 200° for 2 hr., benzhydrazide subliming. The cooled melt was dissolved in sodium hydroxide solution, treated with charcoal, and acidified with concentrated hydrochloric acid. The sticky, grey precipitate crystallised, and separated from ethanol as prisms, m. p. 244—245° (lit.,[10] m. p. 240°) (Found: C, 74·2; H, 4·7; N, 16·6. Calc. for $C_{21}H_{16}N_4O$: C, 74·1; H, 4·7; N, 16·5%).

4-*Amino*-3,5-*diphenyl*-1,2,4-*triazole*.—Benzhydrazide benzenesulphonate (8·8 g., 0·03 mole) was heated at 200° for 2 hr. Water was evolved and a small amount of benzhydrazide sublimed. 4-Amino-3,5-diphenyl-1,2,4-triazole (1·1 g., 32%) was isolated by chloroform-extraction of the cooled melt rendered alkaline with sodium hydroxide solution. It crystallised from ethanol as plates, m. p. 259—260° (lit.,[8,16] m. p. 263°, 258°), and formed a picrate, plates (from benzene), m. p. 156—157° (lit.,[16] m. p. 154°).

Fusion of Acethydrazide Benzenesulphonate and Benzamide.—Acethydrazide benzenesulphonate (1·2 g., 0·005 mole) and benzamide (0·6 g., 0·005 mole) were heated together at 200° for 2 hr. A small amount of benzhydrazide sublimed. Water (10 ml.) was added to the cooled melt, this solution neutralised with sodium carbonate, and by ether-extraction and working up in the usual way an oil was obtained that crystallised slowly. After crystallisation from ethanol and then light petroleum (b. p. 60—80°) needles of 3,5-diphenyl-1,2,4-triazole, m. p.

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[16] Franzen and Kraft, *J. prakt. Chem.*, 1911, **84**, 129.

187°, were obtained. The m. p. was not depressed on admixture with an authentic specimen whose infrared spectrum was identical with that of the above product.

Microanalyses were carried out by the C.S.I.R.O. Microanalytical Laboratory, University of Melbourne. D. R. L. thanks the C.S.I.R.O. for the award of a junior postgraduate studentship.

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