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THE UNEQUIVOCAL SYNTHESES OF 2- AND 4-TRIFLUOROMETHYLCARBAZOLES VIA DIPHENYLS

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Abstract—4- and 6-Trifluoromethyl-1-phenylbenzotriazoles have been prepared by standard methods. They do not decompose to give carbazoles. 2-Nitro-4-trifluoromethyldiphenyl and 2′-nitro-2-trifluoromethyldiphenyl have been reduced to the amines which were diazotized and converted into azides. The former decomposes in ultra-violet light to give 2-trifluoromethylcarbazole, the latter decomposes on heating to give 4-trifluoromethylcarbazole.

WHEN the *m*-trifluoromethylphenylhydrazone of cyclohexanone was treated with a mixture of sulphuric acid and acetic acid, it yielded only one tetrahydro-carbazole, which was converted into the carbazole.[1] According to whether the cyclization of the hydrazone occurred *ortho* or *para* to the trifluoromethyl group this carbazole would be the 4- or 2-trifluoromethylcarbazole. Unequivocal syntheses of these two compounds has now shown that the original carbazole is in fact the 2-trifluoromethyl isomer. This means that the cyclization of the hydrazone occurs mainly *para* to the trifluoromethyl group (yield of tetrahydrocarbazole 70 per cent), which recalls the preferential formation of 7-trifluoromethylquinoline from *m*-trifluoromethylaniline in the Skraup reaction[2] (ratio of 7- to 5-trifluoromethyl isomers is 5 : 1). These results are probably determined by electronic rather than steric influences, for it is certain that the deactivating effect of the dipole associated with the trifluoromethyl group will be more strongly felt in the *ortho* position than in the *para* position. The formation of 4-trifluoromethylisatin (30 per cent: the other isomer was not detected) from *m*-trifluoromethylisonitroso acetanilide[3] remains anomolous.

We first attempted to prepare these carbazoles by the thermal decomposition of the requisite benzotriazoles. 1-Phenyl-4-trifluoromethylbenzotriazole (I) was made as follows. 3-Bromo-2-nitrotrifluoromethylbenzene was heated with an excess of aniline in the presence of cuprous bromide and potassium carbonate. 2-Nitro-3-trifluoromethyldiphenylamine was thereby obtained in no more than 19 per cent yield. This diphenylamine was better prepared by heating 3-amino-2-nitrotrifluoromethylbenzene with excess aniline under the same conditions as above when the yield was raised to 52 per cent. This difference in yield may be accounted for by considerations of the transition states of the two reactions. The former would receive a major contribution from the form (II) in which the NO_2 entity is planar to the benzene ring. Steric interaction with the trifluoromethyl group will however prevent its formation

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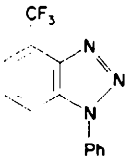
[1] Preceding paper: *Tetrahedron* **8**, 67 (1960).

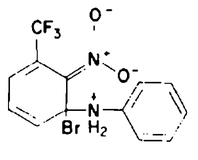
[2] H. Gilman and D. T. Blume, *J. Amer. Chem. Soc.* **65**, 2467 (1943); R. Belcher, M. Stacey, A. Sykes and J. C. Tatlow, *J. Chem. Soc.* 3846 (1954).

[3] B. R. Baker, R. E. Schaub, J. P. Joseph, F. J. McEvoy and J. H. Williams, *J. Org. Chem.* **17**, 164 (1952).

and so destabilize the transition state. Such considerations do not apply to the second reaction.



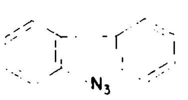
I



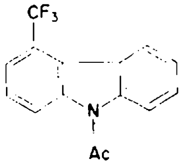
II

2-Nitro-3-trifluoromethyldiphenylamine was reduced catalytically to the amine, which was diazotized in the usual manner to afford the triazole (I), which when treated in a variety of ways, including heating to 300° with *m*-dinitrobenzene,[4] yielded no carbazole. The conditions either gave starting material or resulted in extensive decomposition. 2-Nitro-5-trifluoromethyldiphenylamine was prepared in good yield from 3-amino-4-nitrotrifluoromethylbenzene and bromobenzene. Its conversion into 1-phenyl-6-trifluoromethylbenzotriazole was analogous to the preparation of the 4-trifluoromethyl isomer from 3-trifluoromethyl-2-nitrodiphenyl. Under a variety of conditions, 1-phenyl-6-trifluoromethylbenzotriazole also failed to form a carbazole. The difficulty of obtaining carbazoles by this method when the triazole contains electro-withdrawing substituents has been noticed previously.[5]

A number of carbazoles have been prepared in good yield by decomposing *o*-azidodiphenyls (III) with heat or ultra-violet light.[6] When this method was applied to the preparation of the trifluoromethyl carbazoles it was successful. 2-Nitro-4-trifluoromethyldiphenyl was obtained by diazotizing 4-amino-3-nitrotrifluoromethylbenzene[7] and coupling the diazo-compound with benzene in the presence of sodium acetate. The nitrodiphenyl was reduced catalytically and the resulting 2-amino-4-trifluoromethyldiphenyl diazotized in the usual manner. When the diazo-solution was treated with sodium azide, 2-azido-4-trifluoromethyldiphenyl was obtained as an oil. Its dilute solution in tetralin was irradiated in a quartz vessel with ultra-violet light. After a brief induction period nitrogen was evolved steadily. 2-Trifluoromethylcarbazole was thereby produced in 45 per cent yield, and proved to be identical with the carbazole obtained by dehydrogenating the tetrahydrocarbazole obtained from the *m*-trifluoromethylphenylhydrazone of cyclohexanone.[1]



III



IV

4-Trifluoromethylcarbazole was made analogously. The diphenyl required for the preparation of this carbazole was obtained from *o*-iodotrifluoromethylbenzene (of which a sample was available) and *o*-nitrobromobenzene by the Ullmann procedure.

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[4] B. Starkova, A. Vystrcil and L. Starka, *Chem. Listy* 536 (1957).

[5] R. C. Elderfield, *Heterocyclic Compounds* p. 298. John Wiley, New York (1952).

[6] P. A. S. Smith and B. B. Brown, *J. Amer. Chem. Soc.* 73, 2435 (1951).

[7] M. R. Pettit and J. C. Tatlow, *J. Chem. Soc.* 3852 (1954).

Fractional crystallization of the reaction mixture served to separate 2,-2′-dinitrodiphenyl, and chromatography on alumina of the residue afforded 2-nitro-2′-trifluoromethyldiphenyl (14 per cent). This was converted into 2-azido-2′-trifluoromethyldiphenyl in the manner described for the other isomer. Again the azide was obtained as an oil, which was not purified. When a dilute solution of this azide in tetralin was irradiated with ultra-violet light nitrogen was evolved, but no carbazole could be isolated from the reaction mixture; indeed colour reactions failed to detect any carbazole in the product. When the decomposition of the azide was carried out thermally in decalin at 180–190°, the product did contain a carbazole as evidenced by the production of a stable blue-green colour when its solution in sulphuric acid was treated with sodium nitrite. The carbazole could not however be obtained pure, and was isolated from the mixture as its N-acetyl derivative (IV). Hydrolysis of the amide (IV) gave a gum which could not be induced to crystallize. Its ultra-violet spectrum and colour reactions were typical of a carbazole, and leave no doubt as to the correctness of structure (IV) for the acetyl compound.

EXPERIMENTAL

3-*Bromo-2-nitrotrifluoromethylbenzene*

A warm solution of 3-amino-2-nitrotrifluoromethylbenzene (10 g) in conc H_2SO_4 (40 cc) and water (36 cc) was cooled rapidly with vigorous stirring. The fine suspension of amine sulphate so produced was treated with a solution of sodium nitrite (4·0 g) in water (10 cc) at 0°. After being stirred for 20 min the diazo-solution was poured into a cold mixture of cuprous bromide (7·0 g) and 48% hydrobromic acid (10·0 cc). After 15 min, the mixture was boiled for 5 min and then steam distilled. From the distillate 3-*bromo-2-nitrotrifluoromethylbenzene* was isolated as a pale-yellow solid (8·5 g, 70%), m.p. 29–30°, b.p. 138–140°/14 mm (Found: C, 31·3; H, 1·3. $C_7H_3O_2NF_3Br$ requires: C, 31·1; H, 1·1%).

2-*Nitro-3-trifluoromethyldiphenylamine*

(a) A mixture of 3-bromo-2-nitrotrifluoromethylbenzene (1·0 g), freshly-distilled aniline (3·0 g), anhydrous potassium carbonate (1·0 g) and a trace of cuprous bromide was heated under reflux at 200–210° for 20 hr. After removing excess aniline in steam, the residue was extracted several times with ether. The combined extracts were dried and evaporated to yield a solid, which crystallized from aqueous ethanol. 2-*Nitro-3-trifluoromethyldiphenylamine* was thereby obtained in lustrous orange-red needles (0·2 g, 19%), m.p. 100–101° (Found; C, 55·0; H, 3·1; F, 20·4. $C_{13}H_9O_2NF_3$ requires: C, 55·3; H, 3·2; F, 20·2%).

(b) A mixture of 3-amino-2-nitrotrifluoromethylbenzene (9·0 g), bromobenzene (30 cc), anhydrous potassium carbonate (2·0 g) and cuprous iodide (0·5 g) was heated under reflux with stirring for 18 hr. Excess bromobenzene was distilled off in steam, and the residue was poured into water. The precipitate was collected and extracted with boiling ethanol. A little water was added to the extract, which on cooling afforded long red needles (6·3 g, 52%), m.p. 101–102° undepressed on admixture with a sample prepared by method (a).

2-*Amino-3-trifluoromethyldiphenylamine*

A solution of 2-nitro-3-trifluoromethyldiphenylamine (0·75 g) in ethanol (15·0 cc) was hydrogenated at room temp and press using Raney nickel catalyst (ca. 0·5 g). When the uptake of hydrogen was complete (ca. 1·5 hr), the solution was filtered and evaporated under reduced pressure. The residual solid was recrystallized from aqueous ethanol to give long colourless needles of 2-*amino-3-trifluoromethyldiphenylamine* (0·62 g, 92%), m.p. 79–80° (Found: C, 61·7; H, 3·8. $C_{13}H_{11}N_2F_3$ requires: C, 61·9; H, 4·3%).

1-*Phenyl-4-trifluoromethylbenzotriazole*

A fine suspension of 2-amino-3-trifluoromethyldiphenylamine hydrochloride (from 0·34 g amine) in 2 N HCl (12 cc) was stirred and treated with a solution of sodium nitrite (0·065 g) in water (2 cc), the mixture being kept below 5°. After the mixture had been stirred for a further 15 min, the solid was collected and recrystallized from aqueous ethanol. 1-*Phenyl-4-trifluoromethylbenzotriazole* (0·28 g, 79%) was thereby obtained in colourless plates, m.p. 152–153° (Found: C, 59·0; H, 2·8; F, 21·5. $C_{13}H_8N_3F_3$ requires: C, 59·3; H, 3·0; F, 21·7%).

The decomposition of 1-*phenyl*-4-*trifluoromethylbenzotriazole*

An intimate mixture of the triazole (0·5 g) and *m*-dinitrobenzene (0·5 g) was heated in an oil-bath for 1 hr at 300°. From the dark reaction mixture starting material (0·4 g) was recovered.

When equal weights of the triazole and either copper bronze or calcium oxide were heated together at 350° for 15 min extensive decomposition occurred. No triazole or carbazole was isolated from the reaction.

2-*Nitro-5-trifluoromethyldiphenylamine*

A mixture of 3-amino-4-nitrotrifluoromethylbenzene (4·5 g), bromobenzene (15 cc), potassium carbonate (1·0 g) and cuprous iodide (0·5 g) was stirred and boiled under reflux for 15 hr. Excess bromobenzene was removed by steam distillation, and the residue was cooled and diluted with water. The precipitate was collected at the pump, washed with water, dried *in vacuo* and extracted with boiling ethanol (15 cc). The extract was filtered, and the hot filtrate was diluted with water. On cooling the mixture afforded orange-yellow needles (4·3 g, 67%) of 2-*nitro-5-trifluoromethyldiphenylamine* m.p. 79° (Found: C, 55·8; H, 3·4; F, 20·0. $C_{13}H_9O_2N_2F_3$ requires: C, 55·3; H, 3·2; F, 20·2%).

2-*Amino-5-trifluoromethyldiphenylamine*

A solution of 2-nitro-5-trifluoromethyldiphenylamine (5·0 g) in ethanol (45 cc) was shaken under hydrogen at room temp and press with Raney nickel (ca. 2·5 g). When hydrogen uptake was complete (ca. 1·5 hr) the solution was filtered and evaporated. The residue, which soon solidified, was taken up in light petroleum (b.p. 60–80°). On cooling the solution deposited colourless needles (4·0 g) of 2-*amino-5-trifluoromethyldiphenylamine* m.p. 59° (Found: C, 61·8; H, 4·3; F, 22·3. $C_{13}H_{11}N_2F_3$ requires: C, 61·9; H, 4·3; F, 22·6%).

1-*Phenyl-6-trifluoromethylbenzotriazole*

A fine suspension of 2-amino-5-trifluoromethyldiphenylamine hydrochloride (from 0·34 g amine) in a mixture of 2 N HCl (6 cc) and glacial acetic acid (5 cc) was treated at 0–5° with a solution of sodium nitrite (0·065 g) in water (2 cc) with stirring. After being stirred for a further 15 min at 0°, the mixture was diluted with water (10 cc) and filtered. The solid was dried *in vacuo* and recrystallized from light petroleum (b.p. 60–80°). 1-*Phenyl-6-trifluoromethylbenzotriazole* was thereby obtained in colourless prisms (0.18 g 58%), m.p. 92–93° (Found: C, 59·3; H, 3·3. $C_{13}H_8N_3F_3$ requires: C, 59·3; H, 3·0%).

The decomposition of the triazole was attempted under the same conditions as for the 4-trifluoromethyl isomer. The results were essentially the same as those for that isomer.

2-*Nitro-4-trifluoromethyldiphenyl*

A mixture of 4-amino-3-nitrotrifluoromethylbenzene[7] (12·0 g), conc H_2SO_4 (12 cc) and water (10 cc) was vigorously stirred at 0° and treated with a solution of sodium nitrite (4·7 g) in water (10 cc). Stirring was continued for a further 30 min at 0°. The diazo-solution was then filtered and mixed with benzene (150 cc). A solution of hydrated sodium acetate (75 g) in water (170 cc) was then added dropwise to the vigorously stirred mixture whilst the temp was kept below 5°. After the mixture had been stirred for a further 2 hr at this temp, it was shaken for 96 hr. The benzene layer was then separated and the aqueous layer extracted with ether (2 × 125 cc). The combined organic layers were dried and distilled to yield a liquid (4·2 g), b.p. 144–146°/5 mm, which was dissolved in light petroleum (b.p. 60–80°) and chromatographed on neutral alumina (3 × 30 mm). Elution with the same solvent afforded the first fraction as a yellow oil (3·45 g), b.p. 125–127°/0·5 mm, which solidified. Recrystallization from aqueous ethanol afforded 2-*nitro-4-trifluoromethyldiphenyl* (3·4 g, 22%) in long yellow needles, m.p. 45–46° (Found: C, 58·4; H, 3·2; F, 21·3. $C_{13}H_8O_2NF_3$ requires: C, 58·4; H, 3·0; F, 21·3%).

2-*Amino-4-trifluoromethyldiphenyl*

A solution of 2-nitro-4-trifluoromethyldiphenyl (1·0 g) in methanol (20 cc) was shaken under hydrogen at room temp and press with Raney nickel (ca. 0·5 g). When hydrogen uptake was complete (ca. 1 hr), the solution was filtered and evaporated to dryness. The solid residue was recrystallized from aqueous ethanol to afford 2-*amino-4-trifluoromethyldiphenyl* in colourless leaflets (0·8 g), m.p. 48–49° (Found: C, 65·9; H, 4·3; F, 23·8. $C_{13}H_{10}NF_3$ requires: C, 65·8; H, 4·2; F, 24·0%.)

2-*Trifluoromethylcarbazole*

A stirred solution of 2-amino-4-trifluoromethyldiphenyl (0·3 g) in glacial acetic acid (1 cc) and conc H_2SO_4 (2 cc) was kept at 5° during the dropwise addition of the solution of sodium nitrite (0·1 g) in water (2 cc). The solution was stirred for a further 20 min, filtered and treated with urea. The diazo-solution was then diluted with water (40 cc), cooled in ice and treated with a solution of sodium azide (0·1 g) in water (5 cc). The turbid mixture was stirred for a further 30 min at 0° and then set aside overnight. Next morning the mixture was neutralized with N-potassium carbonate and extracted with ether (2 × 25 cc). The combined extracts were dried and evaporated to give 2-azido-4-trifluoromethyldiphenyl (0·3 g, 90%) as an oil, which was not purified further.

A solution of the azide (0·2 g) in pure tetralin (10 cc) was irradiated in a quartz vessel with a mercury vapour lamp. After a short induction period nitrogen was evolved. When the evolution of nitrogen had ceased (ca. 2·5 hr) the solution was evaporated at 70°/3 mm to ca. 3 cc. The residue, when treated at 0° with light petroleum-benzene mixture, afforded a colourless solid which was collected and washed with light petroleum. It crystallized from benzene to afford colourless leaflets of 2-trifluoromethylcarbazole (0·08 g, 45%), m.p. 209–210°, undepressed on admixture with a sample prepared by the Fischer–indole method. The infra-red spectrum of the two samples were identical.

2-*Nitro-2′-trifluoromethyldiphenyl*

Activated copper bronze (15 g) was added in small portions with stirring to a mixture of *o*-iodotrifluoromethylbenzene[8] (14 g) and *o*-bromonitrobenzene (10 g) at 150°. A condenser was then attached to the flask and the temp was raised successively to 220° for 30 min and to 270° for 30 min. The cooled mixture was pulverized and extracted with boiling ether (2 × 150 cc). The combined extracts were treated with charcoal and evaporated to afford a gum, which was taken up in boiling light petroleum, (b.p. 60–80). On cooling the solution deposited a solid which, on recrystallization from ethanol, afforded yellow needles (1·4 g) of 2,2′-dinitrodiphenyl, m.p. 122–123°.

The ethanolic filtrate was evaporated to a solid residue, which, on boiling with light petroleum, afforded an undissolved residue of 2,2′-dinitrodiphenyl (0·8 g). When the solution was evaporated to dryness it afforded a solid residue 'A' (0·4 g), m.p. 74–76°.

When the first light petroleum filtrate was evaporated to ca. 10 cc and kept overnight it afforded a solid which after recrystallization from ethanol was obtained as yellow needles, 'B', (1·8 g), m.p. 76–78°.

Solids 'A' and 'B' were combined, dissolved in a mixture of benzene–light petroleum (b.p. 60–80°) (4 : 1) and chromatographed on alumina (2 × 10 cm). Elution with the same solvent (200 cc) afforded a solid which crystallized from aqueous ethanol. 2-*Nitro-2-trifluoromethyldiphenyl* was thereby obtained in long pale-yellow needles (1·7 g, 14%), m.p. 73–74° (Found: C, 58·3; H, 2·9. $C_{13}H_8O_2NF_3$ requires: C, 58·4; H, 3·0%).

The residue and filtrates which presumably contained 2,2′-bistrifluoromethyldiphenyl were not examined further.

2-*Amino-2′-trifluoromethyldiphenyl*

2-Trifluoromethyl-2′-nitrodiphenyl (0·2 g) in ethanol (15 cc) was hydrogenated at room temp and press with 7% palladized charcoal (0·1 g) as catalyst. When hydrogen uptake was completed (ca. 30 min) the solution was filtered and evaporated to dryness. The residual solid was recrystallized from light petroleum (b.p. 40–60°) to give 2-*amino-2′-trifluoromethyldiphenyl* as colourless needles (0·17 g), m.p. 47–48° (Found: C, 66·0; H, 4·3; F, 24·0. $C_{13}H_{10}NF_3$ requires: C, 65·8; H, 4·2; F, 24·0%).

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[8] R. G. Jones, *J. Amer. Chem. Soc.* **69**, 2346 (1947).

N-*Acetyl-4-trifluoromethylcarbazole*

A cold solution of sodium nitrite (0·1 g) in water (2 cc) was added dropwise with stirring to a solution of 2-amino-2′-trifluoromethyl-diphenyl (0·3 g) in glacial acetic acid (1 cc) and conc H_2SO_4 (2 cc). Stirring was continued for a further 30 min, when the diazo-solution was filtered, treated with urea and diluted with water (40 cc). A solution of sodium azide (0·15 g) in water (2 cc), was then added to the diazo-solution at 0°. After 2 hr at room temp the mixture was extracted with ether (2 × 50 cc). The combined ethereal extracts were dried and evaporated to give 2-azido-2′-trifluoromethyldiphenyl as a gum (0·2 g, 60%) which was not purified further.

When the azide was decomposed by ultra-violet light in the manner described for the other isomer nitrogen was evolved. No carbazole could be isolated from the product and colour reactions failed to detect any carbazole in the product.

A solution of the azide (0·2 g) in pure decalin (5 cc) was added dropwise to decalin (25 cc) at 180–190° (internal temp). A vigorous evolution of nitrogen ensued and heating was continued 2–3 min after the addition was complete. Removal of the solvent under reduced press afforded a gum which could not be obtained solid, but which gave a bluish-green colour when its solution in conc H_2SO_4 was treated with HNO_3. A solution of the gum in acetic anhydride (4 cc) and 60% perchloric acid (1 drop) was maintained at 75° for 1 hr and then poured into water. The mixture was extracted with ether (2 × 25 cc) and the combined extracts were dried. Removal of the solvent afforded a gum which was taken up in a mixture of benzene and light petroleum (b.p. 60–80°) (20 : 1) and chromatographed on alumina (1 × 12 cm). Elution with the same solvent gave a solid which crystallized from aqueous ethanol in colourless leaflets of N-*acetyl-4-trifluoromethylcarbazole* (0·03 g, 17%), m.p. 94–95° (Found: C, 64·6; H, 3·9; F, 20·4. $C_{15}H_{10}ONF_3$ requires: C, 65·0; H, 3·6; F, 20·6%). Light absorption: λ_{max} 261, 292 and 320 mμ; log ϵ_{max} 4·09, 4·16 and 3·78.

When the N-acetyl compound was heated at 70° for 1 hr with aqueous ethanolic potassium hydroxide, it afforded a gum which could not be obtained crystalline. Its solution in conc H_2SO_4 gave a deep bluish-green colour when treated with a trace of conc HNO_3. Light absorption in ethanol: λ_{max} 235, 245, 260, 300, 320 and 330 mμ; log ϵ_{max} 3·60, 3·57, 3·56, 3·5, 3·41 and 3·41 respectively.

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