[Contribution from the Department of Industrial Chemistry, Faculty of Engineering, Kyôto University]

A NEW SYNTHESIS OF DIARYLACETONITRILES

KEIITI SISIDO, HITOSI NOZAKI, MITIO NOZAKI, AND KOITI OKANO

Received June 11, 1954

Most of the known preparations of diphenylacetonitrile can be classified into the following routes: (a) the dehydration of diphenylacetamide (1), (b) the reaction of diphenylmethyl halides with metal cyanides (2), (c) the α-cyanobenzylation of benzene with benzaldehyde cyanohydrin (3) or with α-bromophenylacetonitrile (4), and (d) others (5). The disadvantages of these methods consist in either the difficulties of the procedure or in the use of lachrymatory intermediates. We have discovered that the reaction of α-cyanobenzyl *p*-toluenesulfonate with benzene in the presence of aluminum chloride or a trace of concentrated sulfuric acid results in the formation of diphenylacetonitrile in good yields. In view of the remarkable use of diphenylacetonitrile as a starting material in the "Methadone" or "Amidone" synthesis (4b, 6) the results so far obtained are reported in this paper.

α-Cyanobenzyl *p*-toluenesulfonate was prepared from benzaldehyde, *p*-toluenesulfonyl chloride, and potassium cyanide according to the method of Dodson and Turner (7) for the preparation of α-cyanobenzyl benzenesulfonate. When various aromatic aldehydes were used in place of benzaldehyde under the similar conditions, the corresponding arylcyanomethyl sulfonates could not be isolated in a pure state, and accordingly the present reaction could be applied only to the cyanobenzyl ester. It should be added that α-cyanobenzyl *p*-toluenesulfonate is rather stable at room temperature and is not lachrymatory in contrast to α-bromophenylacetonitrile which has been used most frequently as a starting material.

Treatment of a solution of α-cyanobenzyl *p*-toluenesulfonate in a large excess of benzene with equimolar aluminum chloride at the boiling point of benzene for three hours gave diphenylacetonitrile in a 82.4% yield. This reaction could successfully be extended to other aromatic compounds which are feasible of the Friedel-Crafts alkylation. The corresponding diarylacetonitriles were obtained in slightly less yields under analogous conditions as above. Details of the experimental results have been summarized in Tables I and II.

When the condensation of the cyanobenzyl ester with benzene was carried out in the presence of 10 mole-% of aluminum chloride, the yield of diphenylacetonitrile was reduced to only 7.5% after three hours' refluxing. Prolonged heating of the reaction mixture, *i. e.*, 15 hours' refluxing, increased the yield up to 70%. It is safe to say that the use of equimolar aluminum chloride is profitable to secure high yields of the desired diphenylacetonitrile in this reaction. It should be noted that nitrobenzene proved to be a less satisfactory solvent in the present Friedel-Crafts reaction and that the use of a large excess of aromatic components as a diluent was found to be desirable.

Concentrated sulfuric acid may be used as a catalyst of this reaction in place

TABLE I

THE CONDENSATION OF α-CYANOBENZYL p-TOLUENESULFONATE WITH AROMATIC COMPOUNDS IN THE PRESENCE OF ALUMINUM CHLORIDE

Reactant	React. Conditions[a]		Products	Yield[b], %
	Temp., °C.	Time, hours		
Benzene	Reflux	4	Ph_2CHCN	82.4
Benzene[c]	Reflux	15	Ph_2CHCN	70.0
Toluene	Reflux	1.5	p-$MeC_6H_4CH(Ph)CN$	71.6
Bromobenzene	35–40	2.5	p-$BrC_6H_4CH(Ph)CN$	73.1
Bromobenzene	90	3	p-$BrC_6H_4CN(Ph)CN$	42.4
Chlorobenzene	35–40	4	p-$ClC_6H_4CH(Ph)CN$	63.0
Anisole	93–95	7	p-$MeOC_6H_4CH(Ph)CN$	60.5

[a] Unless otherwise stated the procedure is similar to the method (*a*) for preparing diphenylacetonitrile which is described in the experimental part. [b] The yields are based on purified products having constant melting points. [c] The condensation was carried out in this case in the presence of 10 mole-% of aluminum chloride.

TABLE II

PROPERTIES OF DIPHENYLACETONITRILES PREPARED

Substituent	M.P., °C.		Ref.	Analyses			
				C		H	
	Found	Recorded		Calc'd	Found	Calc'd	Found
None	74–75	74–75	4b	87.01	87.46	5.74	6.06
p-Methyl-	57–58	62	4a	86.92	86.81	6.32	6.29
p-Bromo-	79–81	82–83	4e	61.78	61.94	3.70	3.56
p-Chloro-	75–76	75–76	4f	73.86	74.46	4.43	4.58
p-Methoxy-	130–131	127	4a	80.69	80.83	5.87	6.07

TABLE III

THE CONDENSATION OF α-CYANOBENZYL p-TOLUENESULFONATE WITH AROMATIC COMPOUNDS IN THE PRESENCE OF A TRACE OF CONCENTRATED SULFURIC ACID

Reactant	React. Conditions		Yield of Diarylacetonitriles,[a] %
	Temp., °C.	Time, hours	
Benzene[b, c]	Reflux	3.5	41.0
Toluene	82–90	1.5	56.2
Bromobenzene	140	13	21.0
Chlorobenzene	130	13	12.6
Anisole	75–80	1	42.0

[a] The yields are based on purified products having constant melting points. [b] When a catalytic amount of p-toluenesulfonate was used in place of concentrated sulfuric acid and the reaction mixture was refluxed for six hours, diphenylacetonitrile was obtained in a 37.3% yield. [c] When 70% sulfuric acid was used as a catalyst, a mixture of diphenylacetamide and diphenylacetic acid was obtained.

of aluminum chloride. Addition of a trace of concentrated sulfuric acid to the solution of α-cyanobenzyl *p*-toluenesulfonate in benzene or its derivatives followed by heating at 80–90° for several hours afforded the desired diarylacetonitriles. The results have been summarized in Table III. The yields realized in the presence of concentrated sulfuric acid are generally lower than those obtained by using aluminum chloride as a catalyst. A catalytic amount of *p*-toluenesulfonic acid was found to be also capable of initiating this condensation. It should, however, be added that heating the benzene solution of α-cyanobenzyl *p*-toluenesulfonate in the absence of these acidic catalysts resulted in a complete recovery of the unchanged starting materials.

EXPERIMENTAL

We are indebted to Mr. S. Wakimoto for assistance in some of the experiments herein described. All melting points are uncorrected.

α-Cyanobenzyl p-toluenesulfonate. The procedures are essentially the same as described by Dodson and Turner (7) for the preparation of α-cyanobenzyl benzenesulfonate. In a 500-cc. four-necked flask, fitted with a mechanical stirrer, a dropping-funnel, a reflux condenser, and a thermometer, were placed 53 g. (0.5 mole) of benzaldehyde and 95 g. (0.5 mole) of *p*-toluenesulfonyl chloride. The mixture was cooled with an ice-salt bath and a solution of 33 g. (0.5 mole) of potassium cyanide in 100 cc. of water was added dropwise with stirring at a rate sufficient to maintain the temperature below 5°. The mixture was allowed to stand for an hour at 0–5° with stirring. The solid was separated by filtration and then dissolved in 250 cc. of a cold mixture of acetone, alcohol, and ether (2:2:1). The undissolved material was separated from this solution by filtration. The addition of 150 g. of ice to the cold filtrate precipitated an oil which solidified on standing at 0°. The solid was separated by filtration and thus 53 g. of α-cyanobenzyl *p*-toluenesulfonate, m.p. 57–59°, was obtained. The lower layer of the filtrate was separated and concentrated at room temperature under reduced pressure. There was obtained an additional 48 g. of the *p*-toluenesulfonate, m.p. 56–58°. The total yield of α-cyanobenzyl *p*-toluenesulfonate was 101 g. (70.0%). It melted at 59° after recrystallizations from ethanol.

Anal. Calc'd for $C_{15}H_{13}NO_3S$: C, 62.70; H, 4.56.
Found: C, 62.69; H, 4.65.

Diphenylacetonitrile. (*a*) *Condensation in the presence of aluminum chloride.* A dry 500-cc. four-necked flask, equipped with a mechanical-stirrer, a dropping-funnel, a reflux condenser, and a thermometer was mounted on a steam-bath. In the flask were placed 30 g. (0.39 mole) of dry, thiophene-free benzene and 20.0 g. (0.15 mole) of powdered anhydrous aluminum chloride. The stirring was started and the mixture was heated to refluxing. A solution of 43.1 g. (0.15 mole) of α-cyanobenzyl *p*-toluenesulfonate in 40 g. (0.51 mole) of dry, thiophene-free benzene was added to the boiling mixture over a period of two hours in small portions. After the addition was completed, the reaction mixture was refluxed for an additional two hours. The product was poured into a mixture of 200 g. of crushed ice and 20 cc. of concentrated hydrochloric acid. The benzene layer was separated and the aqueous layer was extracted with ether. The ether and benzene solutions were combined and washed successively with water, saturated sodium bicarbonate solution, and water. After drying over sodium sulfate the solvents were removed on a water-bath, the last trace of benzene being distilled off under reduced pressure. The residue crystallized on standing. The crystals were collected and weighed 27.7 g. (95.5%), m.p. 68–73°. After recrystallization from isopropyl alcohol or methanol, 23.8 g. (82.4%) of diphenylacetonitrile, melting at 74–75° was obtained and a mixture melting point with an authentic specimen showed no depression.

(*b*) *Condensation in the presence of concentrated sulfuric acid.* In a three-necked flask fitted with a mechanical stirrer, a reflux condenser and a thermometer were placed 20 g. (0.07 mole) of α-cyanobenzyl *p*-toluenesulfonate and 30 g. (0.3 mole) of dry, thiophene-free benzene. The stirring was started and three drops of concentrated sulfuric acid were added. The reaction mixture was refluxed on a water-bath for three hours. After cooling the product was washed with water, saturated sodium bicarbonate solution, and water, and dried over sodium sulfate. The solvent was removed on a water-bath and the last trace of benzene was distilled under reduced pressure. The residue crystallized on standing. The crystals were collected and weighed 8 g. (59.7%), m.p. 62–72°. After recrystallization from ethanol it melted at 74–75° and was not depressed on admixture with the authentic specimen.

α-(p-Methoxyphenyl)-α-phenylacetonitrile. (*a*). In a four-necked flask were placed 30 g. (0.1 mole) of α-cyanobenzyl *p*-toluenesulfonate and 53 g. (0.49 mole) of anisole. The stirring was started and the mixture was cooled in an ice-bath. Then 16 g. (0.12 mole) of powdered anhydrous aluminum chloride was added at 5–10° in small portions and the mixture was heated at 93–95° for seven hours. After cooling the product was poured into a mixture of 100 g. of crushed ice and 10 cc. of concentrated hydrochloric acid. The aqueous layer was extracted with benzene and the organic layers were combined, washed with water, saturated sodium bicarbonate solution, and water, and subjected to steam-distillation. The residue was extracted with benzene and the benzene solution was dried over sodium sulfate. The solvents were distilled under reduced pressure and the residue crystallized on standing. The crystals were collected and weighed 17.5 g. (70.6%), m.p. 118–125°. After recrystallization from ethanol 15 g. (60.5%) of α-(*p*-methoxyphenyl)-α-phenylacetonitrile, melting at 130–131°, was obtained.

(*b*) To a mixture of 20 g. (0.07 mole) of α-cyanobenzyl *p*-toluenesulfonate and 20 g. (0.19 mole) of anisole two drops of concentrated sulfuric acid were added. The mixture was heated at 75–80° for one hour on a water-bath. After cooling the resulting mixture was treated with 5 g. of sodium bicarbonate and 2 g. of sodium acetate. This solution was steam-distilled under reduced pressure and the residue was extracted with benzene. The benzene layer was washed with water and alkali solution and after drying over sodium sulfate the solvent was distilled off under reduced pressure. The residue crystallized on standing. The solid (10.5 g.) was recrystallized from ethanol, m.p. 129–130°, yield 6.5 g. (42.0%).

SUMMARY

The condensation of α-cyanobenzyl *p*-toluenesulfonate with benzene and its derivatives in the presence of aluminum chloride gave the corresponding diarylacetonitrile in good yields. This reaction could also be effected by means of such acidic catalysts as concentrated sulfuric acid or *p*-toluenesulfonic acid, although the yields were less satisfactory.

KYÔTO, JAPAN

REFERENCES

(1) (a) REID AND HUNTER, *J. Am. Chem. Soc.*, **70**, 3515 (1948); (b) NEURE, *Ann.*, **250**, 140 (1889); (c) NORRIS AND KLEMKA, *J. Am. Chem. Soc.*, **62**, 1432 (1940); (d) HELLERMAN, COHN, AND HOEN, *J. Am. Chem. Soc.*, **50**, 1716 (1928); (e) FREEMAN, RINGK, AND SPOERRI, *J. Am. Chem. Soc.*, **69**, 858 (1947); (f) WILSON, *J. Chem. Soc.*, 2173 (1950); (g) ZINSSER, *Ber.*, **24**, 3556 (1891); (h) WEISS, CORDASCS, AND REINER, *J. Am. Chem. Soc.*, **71**, 2650 (1949).

(2) (a) ANSCHÜTZ AND ROMIG, *Ann.*, **233**, 327 (1886); (b) FRIEDEL AND BALSOHN, *Bull. soc. chim.*, [2] **33**, 590 (1880); (c) LOCK AND RIEGER, *Ber.*, **86**, 74 (1953).

(3) (a) HOMEYER AND SPLITTER, U. S. Patent 2,443,246 (June 15, 1948) [*Chem. Abstr.*, **42**, 7338a (1948)]; (b) MILLS, U. S. Patent 2,447,419 (Aug. 17, 1948) [*Chem. Abstr.*, **43**, 6666b (1949)]; (c) LILLY AND Co., British Patent 622,559 (May 4, 1949) [*Chem. Abstr.*, **43**, 7954d (1949)].

(4) (a) HOCH, *Compt. rend.*, **197,** 770 (1933); (b) SCHULTZ, ROBB, AND SPRAGUE, *J. Am. Chem. Soc.*, **69,** 2454 (1947); (c) ROBB AND SCHULTZ, *Org. Syntheses*, **28,** 55 (1948); (d) GINSBURG AND BAIZER, *J. Am. Chem. Soc.*, **71,** 2254 (1949); (e) SHAPIRO, *J. Org. Chem.*, **14,** 839 (1949); (f) SPEETER, CHENEY, AND BINKLEY, *J. Am. Chem. Soc.*, **72,** 1659 (1950).

(5) (a) DIXON, U. S. Patent 2,553,404 (May 15, 1951) [*Chem. Abstr.*, **45,** 9081d (1951)]; (b) FREUND AND IMMERWAHR, *Ber.*, **23,** 2845 (1890); (c) WITTIG AND HOPF, *Ber.*, **65,** 760 (1932); (d) LIPP, *Ann.*, **449,** 15 (1926); (e) BERGSTROM AND AGOSTINHO, *J. Am. Chem. Soc.*, **67,** 2152 (1945); (f) NERESHEIMER AND RUPPEL, German Patent 603,622 (Oct. 11, 1934) [*Chem. Abstr.*, **29,** 817^3 (1935)]; (g) BURR AND CIERESZKO, *J. Am. Chem. Soc.*, **74,** 5426 (1952).

(6) BOCKMÜHL AND EHRHART, *Ann.*, **561,** 52 (1949).

(7) DODSON AND TURNER, *J. Am. Chem. Soc.*, **73,** 4517 (1951).