Organic Syntheses

A Publication
of Reliable Methods
for the Preparation
of Organic Compounds

Working with Hazardous Chemicals

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These paragraphs were added in September 2014. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

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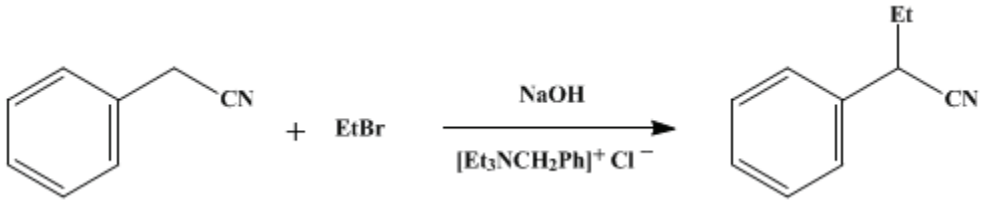
Organic Syntheses, Coll. Vol. 6, p.897 (1988); Vol. 55, p.91 (1976).

PHASE-TRANSFER ALKYLATION OF NITRILES: 2-PHENYLBUTYRONITRILE

[Benzeneacetonitrile, α-ethyl-]



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Checked by Harold W. Wagner and Richard E. Benson.

1. Procedure

Caution! Benzene has been identified as a carcinogen; OSHA has issued emergency standards on its use. All procedures involving benzene should be carried out in a well-ventilated hood, and glove protection is required.

A 3-l., four-necked, round-bottomed flask equipped with a mechanical stirrer, a dropping funnel, a thermometer, and an efficient reflux condenser is charged with 540 ml. of 50% aqueous sodium hydroxide, 257 g. (253 ml., 2.20 moles) of phenylacetonitrile (Note 1), and 5.0 g. (0.022 mole) of benzyltriethylammonium chloride (Note 2). Stirring is begun, and 218 g. (150 ml., 2.00 moles) of ethyl bromide (Note 3) is added dropwise over a period of approximately 100 minutes at 28–35°. If necessary, the flask may be cooled with a cold-water bath to keep the temperature of the mixture at 28–35°. After the addition of ethyl bromide is complete, stirring is continued for 2 hours, then the temperature is increased to 40° for an additional 30 minutes. The reaction mixture is cooled to 25°, 21.2 g. (20.3 ml., 0.200 mole) of benzaldehyde (Note 4) is added, and stirring is continued for 1 hour. The flask is immersed in a cold-water bath, and 750 ml. of water and 100 ml. of benzene are added. The layers are separated, and the aqueous phase is extracted with 200 ml. of benzene. The organic layers are combined and washed successively with 200 ml. of water, 200 ml. of dilute hydrochloric acid (Note 5), and 200 ml. of water. The organic layer is dried over anhydrous magnesium sulfate, and the solvent is removed by distillation under reduced pressure. The product is distilled through a Vigreux column, giving 225–242 g. (78–84%) of 2-phenylbutyronitrile, b.p. 102–104° (7 mm.), n_D^{25} 1.5065–1.5066 (Note 6),(Note 7),(Note 8).

2. Notes

1. The checkers used phenylacetonitrile obtained from Aldrich Chemical Company, Inc., and distilled it before use. It may also be purified according to the directions given in *Org. Synth.*, **Coll. Vol. 1**, 108 (1948).
2. Benzyltriethylammonium chloride is available from Fisher Scientific Company. The preparation of this reagent is described in *Org. Synth.*, **Coll. Vol. 6**, 232 (1988).
3. Ethyl bromide (available from Fisher Scientific Company) was distilled before use.
4. Benzaldehyde (available from Fisher Scientific Company) was distilled before use. It is added at this point to convert any unreacted phenylacetonitrile to the high-boiling α-phenylcinnamonitrile (Note 7).
5. The acid solution was prepared by adding 1 volume of acid to 5 volumes of water.
6. The checkers obtained a forerun of 7–12 g. of product having n_D^{25} 1.5065–1.5066.
7. The α-phenylcinnamonitrile (Note 4) present in the distillation flask can be recovered. The residue is broken up with 75 ml. of methanol, the mixture stirred and cooled, and the product recovered by filtration. Recrystallization from methanol gives 17–20 g. of crystalline material, m.p. 86–88°. The ^{1}H

NMR spectrum ($CDCl_3$) shows complex multiplets at δ 7.20–8.00.
8. GC analysis on a column packed with silicone gum nitrile on acid-washed Gas Chrome Red, 80–100 mesh and heated at 150°, shows that the product is about 97% pure. The material has the following spectral properties; IR (neat) $cm.^{-1}$: 2250 (C≡N), 1610, 1590 shoulder and 1500 (aromatic C≡C), 1385 (C-CH_3), and 760 and 697 (monosubstituted aromatic); ^1H NMR (CCl_4), δ (multiplicity, coupling constant *J* in Hz., number of protons, assignment): 0.99 (t, *J* = 7, 3H, C*H*$_3$), 1.82 (m, 2H, C*H*$_2$), 3.70 (t, *J* = 7, 1H, C*H*), 7.32 (s, 5H, C_6H_5).

3. Discussion

This reaction is illustrative of a general procedure for the tetraalkylammonium salt-catalyzed alkylation of active methylene functions in the presence of concentrated aqueous alkali. This catalytic method has been used to alkylate arylacetonitriles with monohaloalkanes,[2] dihaloalkanes,[3] α-chloroethers,[4] chloronitriles,[5] haloacetic acid esters,[6] and halonitro aromatic compounds.[7] It has also been used to alkylate ketones,[8] 1*H*-indene,[9] 9*H*-fluorene,[10] and the Reissert compound.[11] The reaction is inhibited by alcohols and iodide ion.[2]

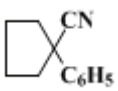
Methods for the alkylation of nitriles have been reviewed.[12] These procedures, as well as those applied to other active methylenes, generally involve the use of dangerous and expensive condensing agents (sodium amide, metal hydrides, triphenylmethide, potassium *tert*-butoxide, etc.) and strictly anhydrous organic solvents (ether, benzene, *N,N*-dimethylformamide, dimethyl sulfoxide, etc.) or liquid ammonia. The catalytic method is much simpler and generally gives good yields of purer products. Because of its high selectivity[13] it is particularly adapted to the synthesis of pure monoalkyl derivatives of phenylacetonitrile which have also been obtained by alkylation of ethyl cyanophenylacetate[14] or cyanophenylacetic acid,[15] followed by elimination of the ethoxycarbonyl or carboxyl groups.

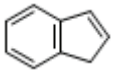
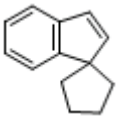
The catalytic conditions (aqueous concentrated sodium hydroxide and tetraälkylammonium catalyst) are very useful in generating dihalocarbenes from the corresponding haloforms. Dichlorocarbene thus generated reacts with alkenes, giving high yields of dichlorocyclopropane derivatives,[16] even in cases where other methods have failed,[17] and with some hydrocarbons, yielding dichloromethyl derivatives.[18] Similar conditions are suited for the formation and reactions of dibromocarbene,[19] bromofluoro- and chlorofluorocarbene,[20] and chlorothiophenoxy carbene,[21] as well as the Michael addition of trichloromethyl carbanion to unsaturated nitriles, esters, and sulfones.[22]

This method exemplifies a broad class of processes that proceed *via* transfer of reacting species between two liquid phases. Such processes may require a catalyst that can combine with species present in one phase and effect their transfer in this form to the second phase where the main reaction occurs. Starks[23] has termed such a process "phase-transfer catalysis" and has demonstrated its utility in reactions involving inorganic anions. For example, he has shown that the rates of some displacement, oxidation, and hydrolysis reactions conducted in two-phase systems are dramatically enhanced by the presence of ammonium and phosphonium salts. However, in reactions involving weakly active methylenes, the catalyst seems to be more than a simple transfer agent; it is necessary for carbanion formation.

The versatility of this method for the alkylation of compounds containing active methylene groups is illustrated by Table I. Review articles have recently appeared,[24] and the application to the Hofmann carbylamine reaction is described in *Org. Synth.*, **Coll. Vol. 6**, 232 (1988).

TABLE I
ALKYLATIONS IN AQUEOUS MEDIUM

Compound	Alkylation Agent	Product	(%) Yield	Reference
$C_6H_5CH_2CN$	$(C_6H_5)_2CHCl$	$(C_6H_5)_2CHCH(C_6H_5)CN$	94	2
$C_6H_5CH_2CN$	$Br(CH_2)_4Br$		88	3

$C_6H_5CH(C_2H_5)CN$	$C_6H_5CH_2Cl$	$C_6H_5CH_2C(C_6H_5)(C_2H_5)CN$	94	2
$(C_6H_5)_2CHCN$	$BrCH_2CH_2Br$	$(C_6H_5)_2C(CH_2CH_2Br)CN$	91	3
$C_6H_5CH(CH_3)CN$	$ClCH_2OCH_3$	$C_6H_5C(CH_2OCH_3)(CH_3)CN$	68	4
$C_6H_5CH(CH_3)CN$	$4\text{-}ClC_6H_4NO_2$	$C_6H_5C(4\text{-}NO_2C_6H_4)(CH_3)CN$	82	11
$C_6H_5CH(C_2H_5)CN$	$ClCH_2COOC_4H_9\text{-}tert$	$C_6H_5C(CH_2COOC_4H_9\text{-}tert)(C_2H_5)CN$	77	6
$C_6H_5CH_2COCH_3$	$BrCH_2CH_2Br$		54	8
	$Br(CH_2)_4Br$		64	9

This preparation is referenced from:

- Org. Syn. Coll. Vol. 6, 232
- Org. Syn. Coll. Vol. 6, 940
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Appendix
Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

triphenylmethide

hydrochloric acid (7647-01-0)

ammonia (7664-41-7)

Benzene (71-43-2)

methanol (67-56-1)

ether (60-29-7)

sodium hydroxide (1310-73-2)

Ethyl bromide (74-96-4)

benzaldehyde (100-52-7)

phenylacetonitrile (140-29-4)

magnesium sulfate (7487-88-9)

1H-Indene (95-13-6)

9H-fluorene (86-73-7)

sodium amide (7782-92-5)

N,N-dimethylformamide (68-12-2)

α-Phenylcinnamonitrile (2510-95-4)

dimethyl sulfoxide (67-68-5)

ethyl cyanophenylacetate (4553-07-5)

dichlorocarbene

benzyltriethylammonium chloride (56-37-1)

2-Phenylbutyronitrile,
Benzeneacetonitrile, α-ethyl- (769-68-6)

cyanophenylacetic acid

dibromocarbene (4371-77-1)

chlorofluorocarbene

chlorothiophenoxy carbene

potassium tert-butoxide (865-47-4)