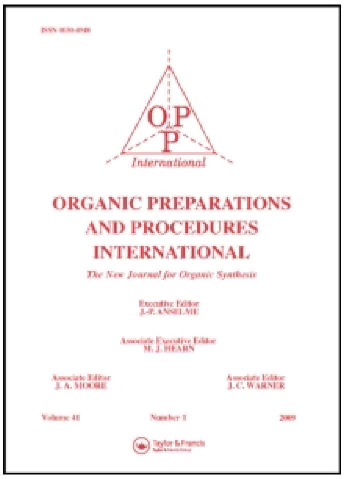

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SYNTHESIS OF 1-ARYLCYCLOPROPANECARBONITRILES UNDER PHASE-TRANSFER CATALYTIC CONDITIONS

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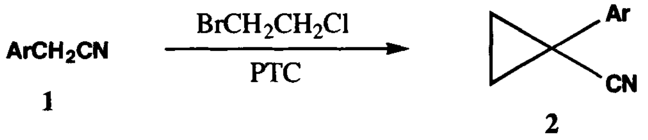
Previously it has been found that phenylacetonitrile (**1a**) can be efficiently cycloalkylated in the presence of conc. aq. NaOH solution and a quaternary ammonium salt as a catalyst (phase transfer catalysis, PTC),[1] with a variety of α,ω-dihaloalkanes. However, the carbanion of **1a** acts as a base toward 1,2-dibromo- or 1,2-dichloroethane[2] leading to the elimination of hydrogen halides with the formation of vinyl bromide or chloride, respectively. On the other hand, 1-phenylcyclopropanecarbonitrile (**2a**) was prepared in high yield from **1a** and 1,2-dibromoethane, under modified PTC conditions if equimolar amounts of **1a** and of the catalyst were used.[3] Application of the solid KOH/DMSO system for this reaction afforded **2a** as well, albeit in much lower yield.[4] Nitrile **2a** can be also synthesized by cyclopropanation of **1a** with a variety of 1,2-dihaloethanes or esters of ethylene glycol, when carried out in the presence of strong bases in strictly anhydrous aprotic solvents.[5-7] We have found that simple stirring of **1a** with 1-bromo-2-chloroethane (BCE), in the presence of 50% aq. NaOH and benzyltriethylammonium chloride (TEBAC) as a catalyst, at ambient temperature, afforded **2a** in 62% yield (Table 1). On the basis of the literature data,[2] we expected that anions more basic than that of **1a**, generated by PTC from the corresponding nitriles, would eliminate hydrogen halides from 1,2-dibromoethane, exclusively. However, our results have shown that this is not the case.



a) Ar = C_6H_5 b) Ar = p-$MeOC_6H_4$ c) Ar = 3,4-$(MeO)_2C_6H_3$
d) Ar = p-BrC_6H_4 e) Ar = p-MeC_6H_4 f) Ar = o-MeC_6H_4
g) Ar = p-FC_6H_4 h) Ar = m-ClC_6H_4

TABLE 1. Yields and Physical Constants of Cyclopropanecarbonitriles **2**

	Base	Ratio of 1/BCE/Base (mol/mol/mol)	Temp. (°C)	Time (hrs)	Yield (%)	bp. (°C/torr) or mp. (°C)	
						Found	Lit.
2a	50% NaOH	1/1.5/6	50	6	62	107-110/7	100-103/2[4]
2b	60% KOH	1/2/7	40-45	8	56	93-96/0.1	92-94/0.05[8]
2c	60% KOH	1/2.5/8.3	50	9	58	126-130/0.075 68-69	ca 130/0.1[9] 68-69
2d	50% NaOH	a	45	9 (5+4)	62 (47[b])	79-80	61-63[10]
2e	60% KOH	a	50	17 (7+10)	47	128-130/8	—
2f	50% NaOH	1/2/6	45-50	4	50 (39[b])	125-127/9	105-107/2[10]
2g	50% NaOH	1/2/7	45	6	65 (48[b])	116-118/8 23-24	155/4.5[10]
2h	50% NaOH	1/2/7	40	2.5	80 (76[b])	82-85/0.1 32-33	105-107/0.8[10]

a) See Experimental Section. b) Lit.[10] yield by PTC, using 1,2-dibromoethane.

Thus, the nitriles **1b,c**, which are weaker C-H acids than **1a** (their anions should be more basic), can be cyclopropanated with 1,2-dibromoethane, albeit in rather low yields. The use of BCE in place of 1,2-dibromoethane afforded **2b,c** under comparable conditions in better yields (Table 1). Furthermore, we have found that the reactions of arylacetonitriles **1d-h** with BCE, under PTC conditions, resulted in the formation of the corresponding cyclopropanes **2d-h**. In the majority of cases, the yields were higher than those obtained under PTC conditions by the use of 1,2-dibromoethane (Table 1).[10] GC analyses revealed that the rate of cyclopropanation of nitriles **1d, e** was rather slow. In these cases, the mixtures were diluted with water, the phases were separated, and the reactions were carried out with a fresh portion of BCE, TEBAC and a base. In this manner, the yields of **2d, e** increased to some extent. Such an exchange of water phase have been previously applied in the cases of autoinhibited PTC reactions.[11] The unreacted nitriles were transformed into high boiling benzylidene derivatives which remained in the distillation flask, thus facilitating the separation of the products **2**.

Of two cycloalkylation reactions which might occur in the case of dinitrile **1i**, only *bis*-cyclopropanation was observed. Dilution of the organic phase of two phase system with benzene, stopped cyclopropanation completely, and **1i** was regenerated unchanged.

The ^1H NMR spectra of the products **2** showed two symmetrical multiplets corresponding to the cyclopropane ring protons; the signal of methylene protons which is present in **1** disappeared (Table 2).

TABLE 2. ^1H NMR of Cyclopropanecarbonitriles **2**

Cmpd	^1H NMR ($CDCl_3$, δ) two sym m, 4H, CH_2CH_2	other signals	m, ArH
2a	1.37-1.44 and 1.69-1.76	—	7.27-7.38 (5H)
2b	1.22-1.43 and 1.54-1.75	3.79 (s, 3H, OCH_3)	6.82-6.90 and 7.18-7.26 (two m, 4H)
2c	1.22-1.44 and 1.55-1.77	3.86 (s, 3H, OCH_3) 3.89 (s, 3H, OCH_3)	6.80-6.86 (3H)
2d	1.27-1.48 and 1.63-1.84	—	7.11-7.18 and 7.42-7.49 (two m, 4H)
2e	1.27-1.47 and 1.58-1.78	2.34 (s, 3H, CH_3)	7.12-7.20 (4H)
2f	1.20-1.42 and 1.58-1.80	2.57 (s, 3H, CH_3)	7.13-7.34 (4H)
2g	1.25-1.46 and 1.60-1.81	—	6.96-7.08 and 7.22-7.33 (two m, 4H)
2h	1.31-1.52 and 1.64-1.85	—	7.20-7.30 (4H)
2i	1.60-1.87 (sym m, 8H)	—	7.32-7.45 (4H)

We have shown that BCE is superior to 1,2-dibromoethane in the cyclopropanation of phenylacetonitrile, under PTC conditions. It is also recommended for the cyclopropanation of other arylacetonitriles, as it affords higher yields of 1-arylcyclopropanecarbonitriles.

EXPERIMENTAL SECTION

All boiling points and melting points are uncorrected. ^1H NMR spectra were recorded on a Varian Gemini 200 spectrometer at 200 MHz, using $CDCl_3$ as solvent. Chemical shifts are reported in ppm downfield from TMS (δ 0.00). The gas chromatography (GC) analyses were carried out on a GCHF 18.3 chromatograph, OV-17 (5%) on Chromosorb W-HP (80-100 mesh) column. The nitriles **1** and BCE were commercial products (Aldrich).

1-Arylcyclopropanecarbonitriles (2a-c, f-h).- To a stirred mixture of the nitrile (**1a-c, f-h**, 50 mmol), TEBAC (0.23 g, 1 mmol) and BCE (Table 1), 50% aq. NaOH or 60% aq. KOH (Table 1) was added dropwise at the specified temperature in Table 1 (exotherm). After addition, the reaction was continued at the temperature and for the time given in Table 1. The mixtures were analyzed by GC to show unreacted nitriles **1** (in the case of **2g** and **2h**, the starting nitriles were not detected). Benzaldehyde (in amounts corresponding to unreacted **1**, as evaluated by GC) was added at 30°, and the mixture was stirred at ca 35° for 45 min. The reaction mixture was diluted with water (ca 50 mL), the organic products were extracted with benzene or dichloromethane (2 x 20 mL), the combined organic phase was washed with 5% aq. HCl (ca 25 mL), and water (ca 25 mL), then dried over $MgSO_4$. The solvent was evaporated, and the cyclopropanecarbonitriles **2a-c**, **f-h** were isolated by vacuum distillation (Table 1).

1-Arylcyclopropanecarbonitriles (2d, e).- The reaction of nitrile **1d** (9.8 g, 50 mmol) or **1e** (6.6 g, 50 mmol) with BCE (14.34 g, 100 mmol), TEBAC (0.23 g, 1 mmol) and 50% aq. NaOH (24.0 g, 300 mmol) (in the case of **1d**) or 60% aq. KOH (31.3 g, 335 mmol) (in the case of **1e**) was carried out as described above. GC analyses indicated that **2d,e** were produced in low yield. The mixtures were diluted with water (ca 40 mL), the water phases were separated and extracted with BCE (7.2 g, 50 mmol, in the case of **1d**; 10.8 g, 75 mmol, in the case of **1e**). The extract and TEBAC (0.23 g, 1 mmol) were combined with the organic phase. The mixture was stirred while 50% aq. NaOH (40 g, 500 mmol) (in the case of **1d**) or 60% aq. KOH (46.8 g, 500 mmol) (in the case of **1e**) was added dropwise, and the reactions were carried out at the temperature and for the time given in Table 1. The mixtures were analyzed by GC, the unreacted nitriles **1d, e** were allowed to react with benzaldehyde, and the reactions were carried out and worked up as described above. In the case of **2d**, the residue after evaporation of the solvent was crystallized from EtOH to give the product, mp. 79-80°, lit.[10] mp. 61-63°.

Anal. Calcd for $C_{10}H_8BrN$: C, 54.08; H, 3.63; N, 6.31. Found: C, 54.08; H, 3.72; N, 6.43

Product **2e** was isolated by vacuum distillation (Table 1).

Anal. Calcd for $C_{11}H_{11}N$: C, 84.04; H, 7.05; N, 8.91. Found: C, 84.15; H, 7.11; N, 8.91

***bis*-Cyclopropanecarbonitrile 2i.** - Dinitrile **1i** (7.8 g, 50 mmol), BCE (28.7 g, 200 mmol) and TEBAC (0.23 g, 1 mmol) were stirred while 50% aq. NaOH (40 g, 26.7 mL, 500 mmol) was added dropwise at 50° (exotherm). The reaction was carried out at 50° for 4 hrs (after 0.5 hr of stirring, 20 mL benzene was added, due to a very thick reaction mixture). The dark mixture was diluted with water (50 mL), filtered through Celite, the filter cake was washed with benzene (20 mL), and the phases were separated. The combined organic phase was successively washed with 5% aq. HCl (30 mL), and water (30 mL) then dried ($MgSO_4$). The solvent was evaporated, the residue was distilled using a Kugelrohr apparatus (bp. 164-212°/0.5 torr) and the distillate solidified and was crystallized (EtOH) to give 3.7 g (47%) of **2i**, mp. 90-92°.

Anal. Calcd for $C_{14}H_{12}N_2$: C, 80.74; H, 5.81; N, 13.45. Found: C, 80.52; H, 5.67; N, 13.44.

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