Phase Transfer Catalysis without Solvent. Synthesis of Cycloalkane-1,1-dicarbonitriles and Alkanetetracarbonitriles

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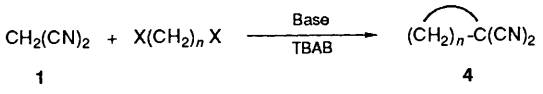
Cycloalkane-1,1-dicarbonitriles **4** and alkane α,α,ω,ω-tetracarbonitriles **5** have been selectively synthesized in the absence of solvent. Cycloalkane-1,1-dicarbonitriles have been prepared by reaction of malononitrile with α,ω-dihalogenoalkanes, while alkane tetracarbonitriles have been synthesized by reaction of malononitrile with (ω-bromoalkyl)malononitriles **2**, prepared by monoalkylation of malononitrile, or by reaction of monoalkylmalononitriles with α,ω-dibromoalkanes.

Phase transfer catalysis in the absence of solvent is a powerful method of anionic activation. This method is characterized, together with a simplification of the experimental procedure, by the selectivity achieved and the use of very mild conditions.[1] The absence of solvent permits the use of alkyl iodides with only catalytic amounts,[2] of the phase transfer agent; in the absence of organic solvents, other techniques such as microwaves[3] may be used.

In previous papers we have studied the influence of various factors on the alkylation of malononitrile[4,5] and selectively synthesized mono-and di-alkylmalononitriles.[6]

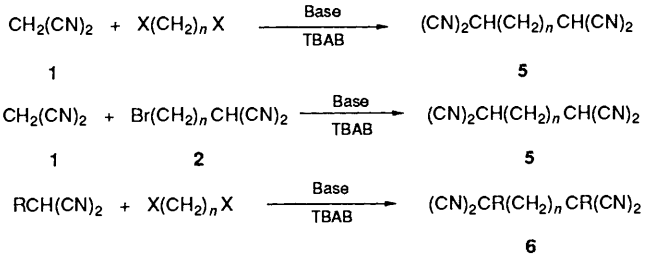
Results

In this paper we report the synthesis of cycloalkane-1,1-dicarbonitriles **4** and alkane α,α,ω,ω-tetracarbonitriles **5**. Cycloalkane-1,1-dicarbonitriles **4** were synthesized by reaction of malononitrile with α,ω-dihalogenoalkanes (Scheme 1).



Scheme 1

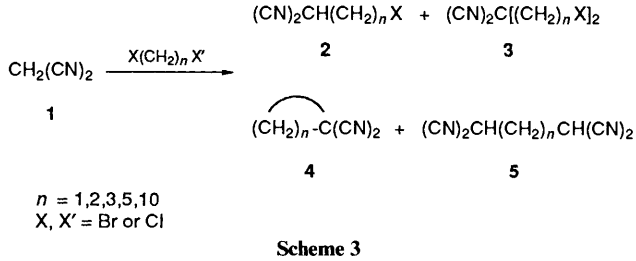
The synthesis of alkanetetracarbonitriles **5** was planned by three synthetic strategies: direct alkylation of malononitrile with α,ω-dihalogenoalkanes, alkylation of malononitrile with (ω-bromoalkyl)malononitriles and reaction of monoalkylmalononitriles with α,ω-dihalogenoalkanes (Scheme 2).



Scheme 2

Reaction with α,ω-Dihalogenoalkanes.—The presence of a second halogen in the alkylating agent permits *a priori* the synthesis of four products; monoalkylmalononitriles **2**, dialkylmalononitriles **3**, cycloalkane-1,1-dicarbonitriles **4** and alkanetetracarbonitrile **5** (Scheme 3).

The alkylation of malononitrile with α,ω-dihalogenoalkanes usually affords cycloalkane derivatives but in low yield. Reaction with 1,2-dibromoethane affords 1-cyanocyclopropanecarboxylic acid[7] or cyclopropane-1,1-dicarbonitrile,[8] and 1,5-dibromopentane affords cyclohexane-1,1-dicarbonitrile.[9] However, 1,8-dibromooctane behaves as a monohalogenoalkane and, in the alkylation of diethyl malonate, affords the corresponding diethyl dialkylmalonate.[10]



Scheme 3

The best results obtained are collected in Table 1.

The nature of the dihalogenoalkane determines the nature and proportion of the final products. Different selectivities are obtained with various alkyl halides, using the same malononitrile:dihalogenoalkane:base mole ratio (Table 1, entries 1, 3, 5 and 7).

The reaction with the dihalogenomethanes, dichloro-, dibromo- or diiodo-methane afforded none of the expected products, probably because of α-elimination in the dihalogenomethane or side reactions of the halogenomethylmalononitrile such as β-elimination or reaction with the base.[11]

When 1,2-dihalogenoethanes are used, only cyclopropane-1,1-dicarbonitrile **4a** is obtained in moderate yield either with 1,2-dibromoethane or with 1-bromo-2-chloroethane, in accordance with the similar rate of cyclization of diethyl 2-chloroethyl- and 2-bromoethyl-malonate.[12] In the reaction with 1,2-dichloroethane starting material was recovered.

No butane-1,1,4,4-tetracarbonitrile **5a** was obtained even when malononitrile was allowed to react in the absence of solvent with cyclopropane-1,1-dicarbonitrile **4a** under phase transfer catalytic conditions. Only decomposition took place.

The selectivity of the alkylation with 1,3-dibromopropane (Table 1, entries 3 and 4) depends on the strength of the base. Use of a mild base, such as potassium carbonate, afforded mainly (3-bromopropyl)malononitrile **2b** while the stronger potassium carbonate:potassium hydroxide (1:1) mixture produced cyclobutane-1,1-dicarbonitrile **4b** as the main product. Use of potassium *tert*-butoxide eliminated hydrogen bromide and afforded a complex mixture in which allylmalononitrile was detected.

With a malononitrile:dihalogenoalkane:base mole ratio of (1:1:2) selective alkylation with 1,5-dibromopentane (Table 1, entries 5 and 6), gives cyclohexane-1,1-dicarbonitrile **4c**

Table 1 Reaction of malononitrile, **1**, with α,ω-dihalogenoalkanes[a]

Entry	Dihalogenoalkane	Base	Mole ratio[b]	Time	**2**:**3**:**4**:**5**[c]	Yield[d]
1	$BrCH_2CH_2Br$	K_2CO_3	2:1:1	4 h	—:—:100:—	52
2	$ClCH_2CH_2Br$	K_2CO_3	2:1:1	4 h	—:—:100:—	60
3	$Br(CH_2)_3Br$	K_2CO_3	2:1:1	4 h	90:—:10:—	34
4	$Br(CH_2)_3Br$	K_2CO_3:KOH	2:1:1	4 h	20:—:80:—	18
5	$Br(CH_2)_5Br$	KBu^{t}O	2:1:1	10 min	41:—:32:27	92
6	$Br(CH_2)_5Br$	KBu^{t}O	1:1:2	5 h	—:—:100:—	42
7	$Br(CH_2)_{10}Br$	KBu^{t}O	2:1:1	5 h	100:—:—:—	21
8[e]	$Br(CH_2)_{10}Br$	KBu^{t}O	1:2.2:2.2	5 h	—:100:—:—	29

[a] Room temperature and 4% of TBAB. [b] Malononitrile:dihalogenoalkane:base. [c] 2:3:4:5 mol percent. [d] Total yield%. [e] 48% of polymeric products.

Table 2 Reaction with (5-bromopentyl)malononitrile[a]

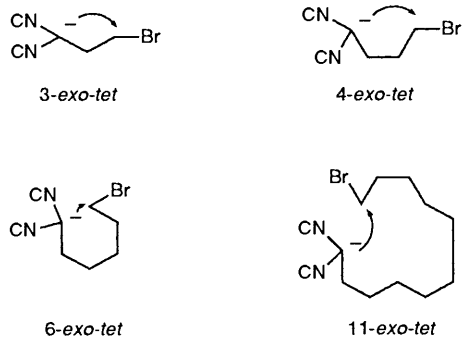
Entry	Base	Mole ratio[b]	Time	**4c**:**5c**[c]	Yield
1	K_2CO_3	2:1:1	5 h	57:43	47
2	KBu^{t}O	2:1:1	10 min	56:44	68

[a] Room temperature and 4% of TBAB. [b] Malononitrile:(5-bromopentyl)-malononitrile:base. [c] **4c**:**5c** mol percent. [d] Total yield %.

exclusively whilst a mol ratio of 2:1:1 gives a mixture of (5-bromopentyl)malononitrile **2c**, cyclohexane-1,1-dicarbonitrile **4c** and heptane-1,1,7,7-tetracarbonitrile **5c**.

1,10-Dibromodecane behaves as a monohalogenoalkane (Table 1, entries 7 and 8). (10-Bromodecyl)malononitrile **2d** or bis(10-bromodecyl)malononitrile **3d** were obtained by using the 'standard' conditions for the selective mono- or di-alkylation of malononitrile.[6] Under the latter conditions a certain degree of polymerization took place.

The selectivity observed is explained by considering that the alkylation reaction is usually kinetically controlled. Considering Baldwin's rules,[13] the cyclizations are favoured *exo-tet* processes. Baldwin's rules consider the stereochemical requirements in the transition state of the cyclization process and they are related to kinetic control. However, when competitive reactions are possible, the selectivity observed depends on the probability that the intermediate adopts the appropriate conformation for the cyclization and the distance between the reactive centres in this conformation (Scheme 4).



Scheme 4

Considering these facts and the influence of the halogen in the (ω-halogenoalkyl)malononitrile, three-membered and five-membered ring formation are kinetically favourable while four-membered and eleven-membered ring formation are kinetically unfavourable.[14]

The reaction of malononitrile with α,ω-dihalogenoalkanes by phase transfer catalysis in the absence of solvent leads to the effective synthesis of medium or small ring cycloalkane-1,1-dicarbonitriles **4**. (ω-Halogenoalkyl)malononitriles **2** are obtained exclusively with 1,10-dibromodecane and selectively with 1,3-dibromopropane and 1,5-dibromopentane. The procedure is not, however, effective for the synthesis of alkane-α,α,ω,ω-tetracarbonitriles.

Reaction with ω-Halogenoalkylmalononitriles.—The preparation of (ω-halogenoalkyl)malononitriles permits the use of these products as alkylation agents in a second strategy for the synthesis of alkane-α,α,ω,ω-tetracarbonitriles. Thus, malononitrile is alkylated with (5-bromopentyl)malononitrile **2c** and (10-bromodecyl)malononitrile **2d** by phase transfer catalysis in the absence of solvent.

This stategy eliminates the possibility of dialkylation but the cyclization may still be an important competitive reaction. In fact, the reaction with (5-bromopentyl)malononitrile **2c** under the 'standard' conditions for monoalkylation afforded a mixture of cyclohexane-1,1-dicarbonitrile **4c** and heptane-1,1,7,7-tetracarbonitrile **5c** (Table 2) either with potassium carbonate or potassium *tert*-butoxide because the formation of a six-membered ring is a highly favoured process. The fact that (5-bromopentyl)malononitrile can react intramolecularly proves again that the second alkylation is disfavoured[6] with respect to the favourable ring formation.

However, due to the low probability of cyclization, the reaction with (10-bromodecyl)malononitrile **2d** is a highly selective process. The alkylation using potassium *tert*-butoxide in a 2:1:1 mole ratio afforded exclusively the dodecane-1,1,12,12-tetracarbonitrile **5d** in good yield.

Reaction of Monoalkylmalononitriles with Dihalogenoalkanes.—In order to avoid the possibility of intramolecular cyclization we alkylated monoalkylmalononitriles with α,ω-dihaloalkanes by phase transfer catalysis in the absence of solvent.

We chose the reaction of benzylmalononitrile with 1,5-dibromopentane, but the conditions designed can be used with other monoalkylmalononitriles or dihalogenoalkanes.

The reaction using a benzylmalononitrile:1,5-dibromopentane:potassium *tert*-butoxide 2:1:2 mole ratio gave 1,9-diphenylnonane-2,2,8,8-tetracarbonitrile **6** in 97% yield.

Conclusion

Phase transfer catalysis in the absence of solvent permits the selective synthesis of alkane-α,α,ω,ω-tetracarbonitriles. The exclusive preparation of long chain alkanetetracarbonitriles **5** in good yield is performed by alkylation of malononitrile with (ω-bromoalkyl)malononitriles **2** while disubstituted alkanetetracarbonitriles **6** are prepared in excellent yield by alkylation of monoalkylmalononitriles with α,ω-dihaloalkanes.

Experimental

M.p.s were determined on a Gallenkamp apparatus and are

uncorrected. B.p.s were determined by ball-to-ball distillation on a Büchi GKR-51 apparatus. IR spectra were recorded on a Philips PV 9500 spectrometer and NMR spectra on a Bruker AW80 at 80 MHz in $CDCl_3$ solution and using tetramethylsilane (TMS) as internal standard. *J* Values are in Hz. Microanalyses were performed at the Faculty of Pharmacy, University of Navarra.

Reaction of Malononitrile with α,ω-Dihalogenoalkanes.—General procedure. Malononitrile (25 mmol) and the appropriate proportions of dihalogenoalkane and TBAB (4%) were introduced into a two-necked flask provided with a reflux condenser. The base was added at once using a Schlenk tube and the mixture was stirred at room temperature for the time indicated in Table 1.

The crude mixture was extracted with dichloromethane (200 ml). Removal of the solvent and column chromatography on silica gel (Merck, 70–230 mesh) to remove the excess of malononitrile afforded the products.

Reaction with 1,2-*dibromoethane.* (Table 1, entry 1). Elution with dichloromethane afforded cyclopropane-1,1-dicarbonitrile **4a** (52%); b.p. 100 °C/27 mbar (lit.,[15] 103 °C/27 mbar); ν_{max}/cm^{-1} 2255 (CN); δ_H 1.82 (4 H, s, CH_2).

Reaction with 1,3-*dibromopropane.* (Table 1, entry 3). Elution with dichloromethane afforded a mixture of (3-bromopropyl)-malononitrile **2b** and cyclobutane-1,1-dicarbonitrile **4b** which was rechromatographed on silica gel. Elution with light petroleum (b.p. 50–70 °C)–ethyl acetate (9:1) afforded cyclobutane-1,1-dicarbonitrile **4b** (3%). M.p. 36 °C (distillation 85 °C/33 mbar) (lit.,[16] 37 °C); ν_{max}/cm^{-1} 2250 (CN); δ_H 2.84 (4 H, t, *J* 7.2, CH_2C), 2.40 (2 H, m, CH_2CH_2), followed by (3-bromopropyl)malononitrile **2b** (31%); b.p. 140 °C/0.01 mbar; ν_{max}/cm^{-1} 2260 (CN) and 650 (CBr); δ_H 3.80 (1 H, m, CH), 3.46 (2 H, m, CH_2Br) and 2.20 (4 H, m, CH_2) (Found: C, 38.8; H, 3.8; N, 14.7. $C_6H_7BrN_2$ requires C, 38.5; H, 3.8; N, 15.0%).

Reaction with 1,5-*dibromopentane.* (Table 1, entry 5). Elution with dichloromethane afforded a mixture of (5-bromopentyl)-malononitrile **2c**, cyclohexane-1,1-dicarbonitrile **4c** and heptane-1,1,7,7-tetracarbonitrile **5c** which was rechromatographed on silica gel. Elution with light petroleum–ethyl acetate (9:1) afforded cyclohexane-1,1-dicarbonitrile **4c** (29%); m.p. 64–65 °C (from light petroleum) (lit.,[17] 66 °C); ν_{max}/cm^{-1} 2250; δ_H 2.08 (4 H, m, CH_2C) and 2.0–1.3 (6 H, m, CH_2); followed by (5-bromopentyl)malononitrile **2c** (38%); b.p. 180 °C/0.03 mbar; ν_{max}/cm^{-1} 2260 (CN) and 640 (CBr); δ_H 3.72 (1 H, t, *J* 6.4, CH), 3.41 (2 H, t, *J* 6.4, CH_2Br) and 2.3–1.4 (8 H, m, CH_2) (Found: C, 44.7; H, 5.3; N, 12.7. $C_8H_{11}BrN_2$ requires C, 44.7; H, 5.2; N, 13.0%), and finally heptane-1,1,7,7-tetracarbonitrile **5c** (25%); m.p. 65–66 °C (from light petroleum–ethyl acetate); ν_{max}/cm^{-1} 2260 (CN); δ_H 3.73 (2 H, t, *J* 6.6, CH) and 2.3–1.5 (10 H, m, CH_2) (Found: C, 65.9; H, 6.2; N, 27.9. $C_{11}H_{12}N_4$ requires C, 66.0; H, 6.0; N, 28.0%).

Reaction with 1,10-*dibromodecane.* First experiment (Table 1, entry 7). Elution with dichloromethane afforded a mixture which was rechromatographed on silica gel. Elution with light petroleum–ethyl acetate (9:1) afforded (10-bromodecyl)malononitrile **2d**; b.p. 200 °C/0.01 mbar; ν_{max}/cm^{-1} 2260 (CN) and 640 (CBr); δ_H 3.68 (1 H, t, *J* 6.6, CH), 3.40 (2 H, t, *J* 6.6, CH_2Br), 2.3–1.1 (18 H, m, CH_2) (Found: C, 54.8; H, 7.7; N, 9.6. $C_{13}H_{21}BrN_2$ requires C, 54.7; H, 7.4; N, 9.8%).

Second experiment (Table 1 entry 8). Elution with dichloromethane afforded a mixture which was rechromatographed on silica gel. Elution with light petroleum afforded 1,10-dibromodecane. Elution with light petroleum–ethyl acetate (9:1) afforded bis(10-bromodecyl)malononitrile **3d** (29%) as an undistillable oil; b.p. >250 °C/0.01 mbar; ν_{max}/cm^{-1} 2250 (CN) and 640 (CBr); δ_H 3.39 (4 H, t, *J* 6.8, CH_2Br) and 2.1–1.2 (36 H, m, CH_2) (Found: C, 54.5; H, 7.9; N, 5.4. $C_{23}H_{40}Br_2N_2$ requires C, 54.8; H, 8.0; N, 5.6%). Further elution afforded some uncharacterized polymeric products.

Reaction of Malononitrile with (ω-Bromoalkyl)malononitriles **2**.—*General procedure.* Malononitrile (25 mmol) and the appropriate proportions of the corresponding ω-bromoalkyl-malononitrile **2** and TBAB (4%) were introduced into a two-necked flask provided with a reflux condenser. The mixture was stirred at room temperature for 30 min. At 0 °C, potassium *tert*-butoxide was added at once with a Schlenk tube and the mixture was stirred at room temperature for the time indicated in Table 2.

The crude mixture was extracted with dichloromethane (200 ml). Removal of the solvent and column chromatography on silica gel using dichloromethane removed the excess of malononitrile and afforded the product.

Reaction with 10-bromodecylmalononitrile **2d** afforded dodecane-1,1,12,12-tetracarbonitrile **5d** (56%); m.p. 67–68 °C (dry ethanol); ν_{max}/cm^{-1} 2260 (CN); δ_H 3.69 (2 H, t, *J* 6.6) and 2.3–1.2 (20 H, m, CH_2) (Found: C, 71.1; H, 8.2; N, 20.7. $C_{16}H_{22}N_4$ requires C, 71.1; H, 8.2; N, 20.7%).

Reaction of Benzylmalononitrile with 1,5-*Dibromopentane.*—Benzylmalononitrile (1.88 g, 12 mmol), 1,5-dibromopentane (0.81 ml, 6 mmol) and TBAB (4%) were introduced into a two-necked flask provided with a reflux condenser. The mixture was stirred at room temperature for 30 min. At 0 °C, potassium *tert*-butoxide (1.35, 12 mmol) was added with a Schlenk tube and the mixture was stirred at room temperature for 4 h.

The crude mixture was extracted with dichloromethane (100 ml). Removal of the solvent and column chromatography on silica gel (40 g) using dichloromethane afforded 1,9-diphenylnonane-2,2,8,8-tetracarbonitrile **6** (97%); m.p. 164–165 °C (ethanol); ν_{max}/cm^{-1} 2250 (CN); δ_H 7.36 (10 H, s, Ph), 3.20 (4 H, s, CH_2Ph) and 2.2–1.4 (10 H, m, CH_2) (Found: C, 78.8; H, 6.5; N, 14.6. $C_{25}H_{24}N_4$ requires C, 78.9; H, 6.4; N, 14.7%).

Acknowledgements

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