Solid-Liquid Phase-Transfer Catalysis I. Benzylation of Malononitrile

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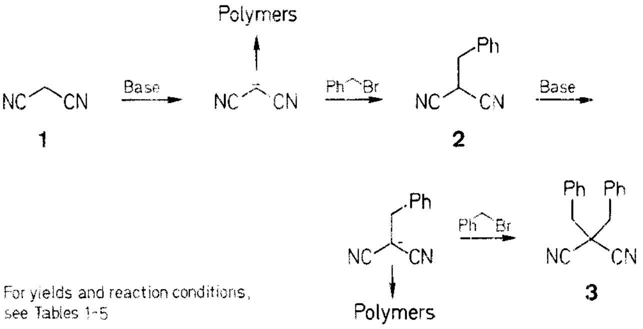
Benzylation of malononitrile has been carried out under solid-liquid phase-transfer catalysis conditions without solvent. The influence of different variables, such as type of base, addition of alumina, molar ratio of phase-transfer agent, temperature, time, and mole ratio of alkylating agent/anion on the final result has been studied carefully. In our hands, the use of potassium carbonate, a 10 mmol/mol ratio of tetra-*n*-butylammonium bromide, and a 1 : 2 benzyl bromide/malononitrile mole ratio at 20°C and 5 hours are the best conditions to effect the benzylation of malononitrile.

Malononitrile is a useful reagent in organic synthesis; to quote Fatiadi,[1] "the reagent has become a keystone for the synthesis of unique heterocyclic systems ..." Thus, monoalkylated malononitriles have been used to prepare *C*-alkylated heteroaromatic compounds,[2] but no general procedure to prepare monoalkylated derivatives has been reported. Alkylation of malononitrile affords disubstituted compounds under various reaction conditions: in liquid ammonia,[3] with sodium hydride in dimethyl sulfoxide,[4] by phase-transfer catalysis,[5] or using 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in dimethylformamide.[6] Normally, monoalkylated malononitriles are prepared by indirect methods: hydrogenation of alkylidenemalononitriles,[7] dehydration of malonoamides,[8] or intramolecular dehydration between alcohols and malononitrile.[9]

The application of solid-liquid phase-transfer catalysis without solvent to several substrates yields excellent results, in addition providing smooth and economic reaction conditions.[10] The aim of this work is the study of the benzylation of malononitrile by phase-transfer catalysis without solvent. The general scheme is illustrated below.



For yields and reaction conditions, see Tables 1-5

In order to get good yields and a high **2**/**3** product ratio, the influence of six effects has been evaluated: type of base, addition of alumina, temperature, reaction time, benzyl bromide/malononitrile mole ratio, and percentage of phase-transfer agent.

Table 1 summarizes the results obtained with different bases at room temperature. When weak bases are used, deprotonation is slow, and specially the deprotonation of benzylmalononitrile. Thus, only the monoalkylated product, **2**, is obtained with basic alumina or potassium fluoride (Table 1, entries 1 and 2) and only a small amount of **3** is formed with long reaction times (Table 1, entry 3). However, as the rate of formation of the anion is slow, yields are also very low.

The use of hydroxide or carbonate as base, which increases the rate of deprotonation, affords both mono and dialkylated malononitriles. Lithium hydroxide gives a lower amount of dialkylated product than potassium hydroxide (Table 1, entries 5 and 6) due to the minor activity of lithium salts. This fact has been explained considering the higher lattice energy in lithium salts than in potassium salts.[11]

Table 1. Effect of Different Bases on the Benzylation of Malononitrile

Entry	Base	BnBr/Base[a]	Time	Yield[b] (%)	2/3 (%)
1	basic alumina[c]	1/3	4 d	3	100/0
2	basic alumina/KF[d]	1/1	4 d	18	100/0
3	$KHCO_3$	1/1.5	7 d	24	89/11
4	K_2CO_3	1/2	5 h	96	79/21
5	LiOH	1/1	3 d	10	75/25
6	KOH	1/1	3 d	48	55/45
7	K_2CO_3/KOH[e]	1/2	10 min	84	70/30
8	KOBu-*t*	1/2	10 min	71	82/18
9	NaOMe	1/2	10 min	66	78/22

[a] mol/mol.
[b] Yield of isolated product mixture **2** + **3** (except entries 1 and 2). Except for entries 4, 7, 8, and 9, some benzyl bromide is also recovered in all other cases.
[c] Basic alumina (Merck).
[d] Basic alumina/KF (3 : 1).
[e] K_2CO_3/KOH (1 : 1).

Table 2. Effect of Alumina on the Base-Catalyzed Benzylation of Malononitrile

Entry	Base	Al_2O_3[a]/Base	Time	Yield (%)	2/3
1	$NaHCO_3$	–	7 d	24	89/11
2	$NaHCO_3$	3/1	3 d	28	95/5
3	K_2CO_3	–	15 min	81	79/21
4	K_2CO_3	3/1	15 min	47	80/20
5	KOH	–	3 d	48	55/45
6	KOH	3/1	2 d	41	76/24
7	K_2CO_3/KOH	–	10 min	84	70/30
8	K_2CO_3/KOH	3/1	10 min	60	72/28
9	KOBu-*t*	–	10 min	71	82/18
10	KOBu-*t*	3/1	10 min	65	80/20

[a] Neutral alumina (Merck).

The differences observed between weak and intermediate bases, or between lithium and potassium hydroxide indicate that an increase in the deprotonation rate provides a major amount of dibenzylmalononitrile and higher yield of the reaction.

When strong bases, such as alkoxides and a 1 : 1 mixture of potassium carbonate and potassium hydroxide, are used (Table 1, entries 7–9), the reaction time is reduced. Deprotonation rates are higher, thus the malononitrile anion is available in shorter time. When the alkylation is more rapid than the second deprotonation, then benzylmalononitrile is almost consumed in the first alkylation avoiding dibenzylation to a great extent. Yields are higher, but due to side reactions, no more than 84 % of alkylated products are obtained. No significant differences between methoxide and *tert*-butoxide have been detected. In these cases neither benzyl bromide nor malononitrile are recovered.

However, the best result is obtained with potassium carbonate, an intermediate, and a non-nucleophilic base. The use of this base avoids dibenzylation to a great extent because the second deprotonation is very slow and provides high yields (96 %), because the low nucleophilic character of potassium carbonate avoids side reactions.

Table 2 summarizes our results on the benzylation of malononitrile carried out with and without addition of alumina at room temperature.

Alumina has been used as a solid support for many type of reactions,[12] including in dry medium,[13] as an activating agent for bases, especially fluorides.[14]

With sodium hydrogen carbonate and potassium hydroxide (Table 2, entries 1, 2, 5, and 6), the monoalkylation reaction is improved. This activation permits the use of shorter reaction times with the subsequent improvement of the monobenzyl/dibenzylmalononitrile ratio. However, with potassium carbonate (Table 2, entries 3 and 4), the addition of alumina produces only a low conversion. A bad adsorption of the base in alumina may be the reason of this anomalous result.

When potassium *tert*-butoxide or a 1 : 1 mixture of potassium carbonate and potassium hydroxide is used, no activation is observed due to the very short time used. Only an increase of side reactions is detected because monobenzyl and dibenzylmalononitrile can react further and polymerization takes place.

Table 3 shows the effect of temperature and time on yield and on the monobenzyl/dibenzylmalononitrile product ratio. Any change that increase the reaction rate affords better yield, but also favors dibenzylation. This effect has been observed when the temperature is increased.

Table 3. Influence of Temperature and Time on the Benzylation of Malononitrile

Entry	Base	Temp. (°C)	Time	Yield (%)	**2/3**
1	$NaHCO_3$	r.t.	7 d	24	89/11
2	$NaHCO_3$	60	1 d	58	69/31
3	KF/Al_2O_3[a]	r.t.	1 d	16	100/0
4	KF/Al_2O_3[a]	60	1 d	25	85/15
5	$NaHCO_3$	60	3 h	10	100/0
6	$NaHCO_3$	60	6 h	25	93/7
7	$NaHCO_3$	60	24 h	58	69/31
8	K_2CO_3	r.t.	15 min	81	80/20
9	K_2CO_3	r.t.	5 h	96	79/21

[a] Basic alumina (Merck); KF/Al_2O_3 (1 : 3).

A similar effect has been observed using long reaction times, in these cases as the second deprotonation is consecutive, the probability of this reaction increases with longer reaction times.

Table 4 shows the results obtained when the ratio alkylating agent/malononitrile is modified. An increase in the malononitrile ratio should improve yields and the monobenzyl/dibenzylmalononitrile ratio.

Table 4. Influence of the Molar Ratio of Benzyl Bromide/Malononitrile on the Benzylation of Malononitrile

Entry	Base	Ratio[a]	Time	Yield (%)	**2/3**
1	$NaHCO_3$	1/1	7 d	24	89/11
2	$NaHCO_3$	1/2	4 d	37	92/8
3	KOBu-*t*	1/1	10 min	65	67/33
4	KOBu-*t*	1/2	10 min	71	82/18
5	KOBu-*t*	1/3	10 min	61	86/14
6	KOBu-*t*	1/4	10 min	27	84/16
7	NaOMe	1/2	10 min	66	78/22
8	NaOMe	1/3	10 min	39	85/15

[a] Benzyl bromide/malononitrile molar ratio.

Yields and the **2/3** product ratio rise when the benzyl bromide/malononitrile mole ratio changes from 1 : 1 to 1 : 2 (Table 4, entries 1–2 and 3–4), but yields decrease with higher malononitrile ratios (Table 4, entries 4–6 and 7–8). A large increase in the concentration of malononitrile rises the rate of alkylation, but specially the rate of condensation of malononitrile with its anion, decreasing the yield of benzylation.[15]

Table 5 summarizes the results obtained when the percentage of phase-transfer agent is modified. In all cases a reaction time of 10 minutes is used. Addition of 10 mmol/mol of tetra-*n*-butylammonium bromide (TBAB) as phase-transfer agent has an important influence on the yield. Deprotonation may be more rapid, but no significant differences on the **2/3** product ratio are observed. Further addition of phase-transfer agent does not improve the catalytic effect.[16]

Table 5. Effect of Phase-Transfer Agent TBAB[a] on the Benzylation of Malononitrile

Entry[b]	Base	TBAB	Yield (%)	**2/3**
1	KOBu-*t*	–	61	79/21
2	KOBu-*t*	10	71	82/18
3	KOBu-*t*	40	72	80/20

[a] Tetra-*n*-butylammonium bromide (mmol/mol).
[b] Reaction time = 10 min.

The type of base is the factor that influences most on the yield and on the 2/3 product ratio. Two strategies seem to be possible, the use of a strong bases such as potassium *tert*-butoxide in order to get the malononitrile anion within a very short time, or the use of an intermediate base, such as potassium carbonate, in order to slow down the second deprotonation.

All reagents were of commercial quality from freshly opened containers. Benzyl bromide and malononitrile were purchased from Merck. Column chromatography was performed on silica gel Merck 70–230 mesh. ^1H-NMR spectra were obtained using a Bruker AW 80 spectrometer.

In all experiments 25 mmol of malononitrile and 40 mmol/mol of TBAB, unless otherwise is stated, are used. For other reaction conditions see Tables 1–5.

Benzylation of Malononitrile; General Procedures:

1. *Using $NaHCO_3$ or LiOH as Base:* $NaHCO_3$ or LiOH is added to malononitrile at 40 °C with stirring, and the stirring is continued at 40 °C for 30 min. TBAB and benzyl bromide are added at the desired temperature and the stirring is continued for the desired time (Tables 1–4). Extraction with CH_2Cl_2 (250 mL), removal of the solvent, and column chromatography on silica gel (toluene) affords monobenzylmalononitrile: mp 90.5–91.5 °C (EtOH) (Lit.[17] mp 91 °C) and dibenzylmalononitrile: mp 130–131 °C (EtOH) (Lit.[6] mp 132 °C).

2. *Using K_2CO_3, KOH, or KOBu-t as Base:* Benzyl bromide and TBAB are added to malononitrile with stirring, and the stirring is continued for 30 min. The base is then added at the desired temperature, and the stirring is continued for the desired time (Tables 1–5). Work-up is performed as given above in procedure 1.

3. *Using Alumina Supported Bases:* At room temperature, the corresponding base adsorbed on dried alumina is added to a stirred mixture of benzyl bromide, malononitrile, and TBAB. The stirring is continued at room temperature, for the desired time (Tables 1–3), and work-up is performed as in procedure 1.

We gratefully acknowledge Prof. G. Bram, Université de Paris-Sud, for helpful discussions, and Junta de Castilla-La Mancha for a grant to A. M.

Received: 14 September 1988; revised: 7 December 1988

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