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Phase transfer alkylation of arylacetonitriles revisited

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Abstract—Phase transfer alkylations of phenylacetonitrile derivatives carried out in the presence of 60–75% aqueous KOH, instead of the typical 50% NaOH, provide substantial improvements in the overall yields and purity of products. Reactions with simple secondary alkyl halides, as well as cycloalkylations with 1,2- and 1,3-dihaloalkanes proceed with good yields. Increasing the concentration of base diminishes the formation of by-products from competitive β-elimination processes.

Phase transfer catalysis (PTC) is now a well established method in organic synthesis applicable to reactions of inorganic and organic anions and other active species with organic compounds.[1] PTC reactions are carried out in two-phase systems of negligible mutual solubility—organic and aqueous. Reacting anions are continuously introduced into the non-polar organic phase as ion pairs with lipophilic cations—most often tetraalkylammonium cations—supplied by the catalyst. Further reactions of these ion pairs proceed in the organic phase. Of particular importance are processes in which carbanions are produced in situ in the presence of aqueous NaOH. Since the pioneering work of Mąkosza in the mid 1960s on the alkylation of phenylacetonitrile (**1**),[2] these reactions have been thoroughly studied, as many pharmaceuticals contain the arylacetic acid moiety.[3] This method was later extended, for example, for the generation and reactions of carbenes,[4] and for enantioselective synthesis[5] or co-catalytic processes.[6] High yields of products of monoalkylation of arylacetonitrile carbanions are as a rule obtained with primary alkyl bromides in the presence of 50% aqueous NaOH and a lipophilic quaternary ammonium salt catalyst.[7] However, this protocol has numerous drawbacks, namely, (a) yields of reactions with *sec*-alkyl bromides are usually moderate and seldom exceed 60%;[2b] (b) introduction of the second alkyl group to the 2-arylalkanenitriles proceeds with difficulty; (c) yields of 1-aryl-1-cyanocyclobutane derivatives in reactions with 1,3-dibromopropane are low;[2f] (d) cyclopropanation of **1** with 1,2-dichloro- or 1,2-dibromoethane does not proceed, but dehydrohalogenation of the dihaloalkane takes place instead. It was suggested that β-elimination is induced by the phenylacetonitrile carbanion in the organic phase and not by the hydroxide anion.[2f] On the other hand, reaction of **1** with 1-bromo-2-chloroethane under PTC conditions leads to the cyclopropane derivative **3** in 62% yield.[8,9]

In this letter, we present that exchanging 50% aqueous NaOH for 60–75% KOH solution overcomes all of the problems mentioned above. Since a saturated aqueous solution of potassium hydroxide at room temperature has a concentration close to 60%,[10,11] in some cases we can take advantage of the greater solubility of KOH at higher temperatures ($\leqslant$111 °C), where concentrations of solutions up to 75% are available.

Initially we investigated simple alkylations of **1** with moderately active secondary alkyl bromides.[12] Products **2a**–**c** were obtained in high yields and selectivity toward monosubstitution in the presence of 60% KOH and 2% mol tetrabutylammonium bromide (TBAB) as catalyst (Table 1).[13] Under slightly forced conditions, even the product of diisopropylation **2d** could be synthesized in high yield. It is worthy to note that the reaction with cyclohexyl bromide, carried out in the presence of 50% NaOH, resulted in dehydrobromination of the alkylating agent.[2b]

We next studied more challenging cycloalkylation processes and noticed that, contrary to the literature,[2f] the reaction of **1** with 1,2-dichloroethane (1:5 molar

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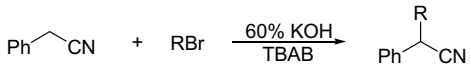
Table 1. Alkylation of **1** with *sec*-alkyl bromides in the presence of 60% KOH[13]



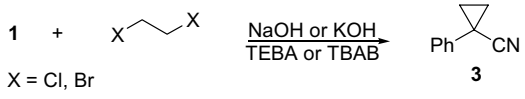
1 **2a-d**

R	**1**:RBr:KOH	Temp. (°C)	Time (h)	Yield (%)	Bp (°C/Torr)	Purity (%)[a]
i-Pr	1:1.1:5	45	3.5	**2a**, 93	114–115/7	98
sec-Bu	1:1.05:5	45	2.5	**2b**, 92	69–70/0.2	99
c-C_6H_{11}	1:2:7	70	2	**2c**, 84	106–110/0.2[b]	99
i-Pr	1:5:12	55–60	5	**2d**, 92[c]	82–84/0.3	99

[a] According to GC.
[b] Mp 56–58 °C (MeOH).
[c] Diisopropylation product.

ratio), carried out in the presence of 50% NaOH and benzyltriethylammonium chloride (TEBA), gave 1-cyano-1-phenylcyclopropane (**3**) in 63% isolated yield and 98.5% purity (GC), although dehydrochlorination of the alkylating agent proceeded to some extent. The use of 1,2-dibromoethane gave a similar result (60% yield). Again the 75% aqueous KOH/TBAB system gave better results; with 1,2-dibromoethane the yield of **3** was 74%, while with 1-bromo-2-chloroethane the yield was 90% (Scheme 1).[14]

Next we investigated the synthesis of cyclobutane derivatives from arylacetonitriles and 1,3-dibromopropane, described previously as being unselective and yielding only 18% of **4a**.[2f] As cyclization to four-membered rings is usually much slower than to three-membered ones,[15] formation of polymeric side products of competitive intermolecular alkylations of intermediates was initially observed. To avoid this problem, we diluted the organic phase with toluene (135 mL for 0.05 mol of **1**), which favored the cyclization to cyclobutane derivatives. The influence of temperature on the reaction course was also apparent, since at

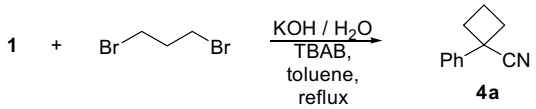


Scheme 1. Reaction of **1** with 1,2-dihaloethanes under PTC conditions.[14]

70 °C the yield of the product was lower than at reflux (about 110 °C). In reactions performed with 60% aqueous KOH, 1-aryl-1-cyanocyclobutanes were formed in moderate to good yields. However, under these conditions variable amounts of by-products of allylation and diallylation of the starting nitrile were formed, making isolation of the product difficult.[16] We observed that by increasing the concentration of potassium hydroxide above the 60% limit, formation of inseparable by-products of mono- and diallylation was substantially diminished. We systematically investigated this phenomenon on two model systems: with compound **1** (Table 2) and with 3,4-dimethoxyphenylacetonitrile (Table 3). In both cases we observed gradual changes in the amounts of inseparable contaminants in isolated products **4a** and **4b**, respectively.

This effect can be rationalized as follows. The β-elimination process is induced by hydroxide anions, but not by carbanions, as suggested in the literature.[2f] Hydroxide ions are generated and subsequently liberated in the organic phase by the reaction of a carbanion with a water molecule, which hydrate the ionic pair of carbanion with the quaternary ammonium salt. Thus, a higher concentration of potassium hydroxide reduces the accessibility of water[17] and prevents the residual hydration of ion pairs.[18] A second possible explanation involves a kinetic effect, since for more concentrated solutions of hydroxide, alkylation proceeds much faster and dominates over side reactions.

Table 2. Alkylations of phenylacetonitrile with 1,3-dibromopropane in the presence of KOH at different concentrations[10]

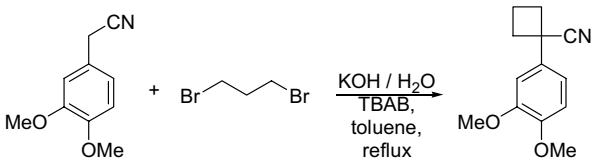


4a

Concentration of KOH (%)	Time (min)	Isolated yield (%)	Purity (%)[a]
75	80	61	98.5
70	80	63	98
65	120	64	96
60	220	61	92
55	250	61	86
70 (reaction at 70 °C)	105	50	98
60 (reaction at 70 °C)	120	46	96

[a] According to GC, the distillate contained mono- and diallylphenylacetonitrile as by-products.

Table 3. Alkylations of 3,4-dimethoxyphenylacetonitrile with 1,3-dibromopropane in the presence of KOH at different concentrations[10]

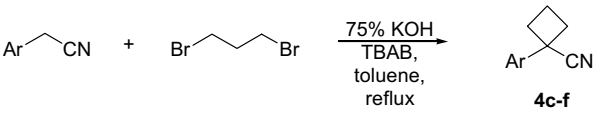


4b

Concentration of KOH (%)	Time (min)	Isolated yield (%)	Purity (%)[a]
75	105	60	98
70	180	59	96
65	420	55	92
60	300	61	82

[a] According to GC, the distillate contained α-allyl- and α,α-diallyl-3,4-dimethoxyphenylacetonitrile as by-products.

Table 4. Alkylations of arylacetonitriles with 1,3-dibromopropane in the presence of 75% KOH[19]



4c-f

Ar	Isolated yield (%)	Bp (°C/Torr)	Purity (%)[a]
4-MeO–C_6H_4	**4c**, 55	117–119/0.3	95
4-Me–C_6H_4	**4d**, 64	92–93/0.3	96
4-Cl–C_6H_4	**4e**, 72	110–112/0.5	98.5
4-F–C_6H_4	**4f**, 71	148–150/20	98

[a] According to GC.

Finally, we applied our optimized conditions[19] to the synthesis of other 1-aryl-1-cyanocyclobutane derivatives **4c–f** (Table 4).

In conclusion we have substantially improved the procedure for alkylation of phenylacetonitrile derivatives under PTC conditions. The use of concentrated aqueous solutions of potassium hydroxide allows the alkylations with moderately active secondary bromides to proceed in good yields. Also, the synthesis of 1-phenyl-1-cyanocyclopropane **3** and 1-aryl-1-cyanocyclobutanes (**4a–f**), described previously as ineffective,[2f] was successfully realized. Additionally, higher concentrations of KOH (>60%), available under elevated temperatures, diminished the amounts of inseparable side products from the competitive β-elimination process in the reactions of **1** and its derivatives with 1,3-dibromopropane.

Acknowledgements

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References and notes

1. For reviews see: (a) Dehmlow, E. V.; Dehmlow, S. S. *Phase Transfer Catalysis*, 3rd ed.; VCH: Weinheim, 1993; (b) Starks, C. M.; Liotta, C. L.; Halpern, M. *Phase Transfer Catalysis. Fundamentals, Applications and Industrial Perspectives*; Chapman & Hall: New York, 1994; (c) *Handbook of Phase Transfer Catalysis*; Sasson, Y., Neumann, R., Eds.; Blackie Academic & Professional, 1998; (d) Mąkosza, M.; Fedoryński, M. Phase Transfer Catalysis. In *Interfacial Catalysis*; Volkov, A. G., Ed.; Marcel Dekker, 2002; pp 159–193; reprinted in: *Catal. Rev.* **2003**, *45*, 321–367; (e) Mąkosza, M.; Fedoryński, M. *Pol. J. Chem.* **1996**, *70*, 1093–1110; (f) Jones, R. A. *Quaternary Ammonium Salts: Their Use in Phase Transfer Catalysis*; Academic Press, 2001.
2. (a) Mąkosza, M.; Serafinowa, B. *Roczn. Chem.* **1965**, *39*, 1223–1231; *Chem. Abstr.* **1966**, *64*, 12595h; (b) Mąkosza, M.; Serafinowa, B. *Roczn. Chem.* **1965**, *39*, 1401–1408; *Chem. Abstr.* **1966**, *64*, 17474g; (c) Mąkosza, M.; Serafinowa, B. *Roczn. Chem.* **1965**, *39*, 1595–1602; *Chem. Abstr.* **1966**, *64*, 17475c; (d) Mąkosza, M.; Serafinowa, B. *Roczn. Chem.* **1965**, *39*, 1799–1803; *Chem. Abstr.* **1966**, *64*, 17475e; (e) Mąkosza, M.; Serafinowa, B. *Roczn. Chem.* **1965**, *39*, 1805–1810; *Chem. Abstr.* **1966**, *64*, 17475g; (f) Mąkosza, M.; Serafinowa, B. *Roczn. Chem.* **1966**, *40*, 1647–1655; *Chem. Abstr.* **1967**, *66*, 94792x; (g) Mąkosza, M.; Serafinowa, B. *Roczn. Chem.* **1966**, *40*, 1839–1848; *Chem. Abstr.* **1967**, *66*, 115435a.
3. For the application of 1-(4-chlorophenyl)-1-cyanocyclobutane in the synthesis of pharmacologically active metabolites of the anti-obesity drug—sibutramine, see: (a) Krishnamurthy, D.; Han, Z.; Wald, S. A.; Senanayake, Ch. H. *Tetrahedron Lett.* **2002**, *43*, 2331–2333; (b) Lu, Z.-H.; Bhongle, N.; Su, X.; Ribe, S.; Senanayake, Ch. H. *Tetrahedron Lett.* **2002**, *43*, 8617–8620.
4. Mąkosza, M.; Wawrzyniewicz, M. *Tetrahedron Lett.* **1969**, 4659–4662.
5. For reviews see: (a) O'Donnel, M. J. *Acc. Chem. Res.* **2004**, *37*, 506–517; (b) Lygo, B.; Andrews, B. I. *Acc. Chem. Res.* **2004**, *37*, 518–525.
6. For a review see: Mąkosza, M.; Fedoryński, M. *Arkivoc* **2006**, *iv*, 7–17.
7. Mąkosza, M.; Jończyk, A. *Org. Synth.* **1976**, *55*, 91–95.
8. Fedoryński, M.; Jończyk, A. *Org. Prep. Proc. Int.* **1995**, *27*, 355–359.
9. For the synthesis of **3** under similar conditions see: (a) Sychkova, L. D.; Shabarov, Yu. S. *J. Org. Chem. USSR (Engl. Transl.)* **1980**, *16*, 1775–1779; *Zh. Org. Chim.* **1980**, *16*, 2086–2091 (stoichiometric amount of quaternary ammonium salt); (b) Singh R. K., U.S. Patent 4,859,232 (**1989**); *Chem. Abstr.* **1990**, *112*, P 32155b.
10. The concentration of saturated KOH in water at room temperature is about 60%, based on the mass of commercial reagent. This value is smaller for a pure substance which is free of water. Since we always used commercial material (standard ~85% KOH) without any purification, the reported values correspond to 'practical concentrations' based on the masses of ingredients used.
11. For concentrations of saturated aqueous solutions of NaOH and KOH as a function of temperature see: *Ullmann's Encyclopedia of Industrial Chemistry*; Elvers, B., Ed.; VCH, 1993; Vol. A22, p 94.
12. Studies on PTC alkylation of *p*-chlorophenylacetonitrile with *i*-propyl bromide in solid–liquid systems were described in: Yadav, G. D.; Jadhav, Y. B. *Org. Process Res. Dev.* **2003**, *7*, 588–598.
13. *Typical procedure for the alkylation* of **1** with *sec*-halides. To a vigorously stirred mixture of phenylacetonitrile (11.7 g, 0.1 mol), cyclohexyl bromide (32.6 g, 0.2 mol) and TBAB (0.64 g, 2.0 mmol), 60% aqueous KOH (65.5 g, 0.7 mol) was added dropwise and the temperature was kept at 50 °C and stirring was continued at this temperature for 2 h. After

usual work-up, the product was isolated by vacuum distillation (see Table 1). Physicochemical data of products **2a–d** were consistent with the literature.

14. *Typical procedure for the synthesis of 1-cyano-1-phenylcyclopropane* (**3**). To a mixture of solid KOH (9.54 g, 0.12 mol), 60% aqueous KOH (16.8 g, 0.18 mol), phenylacetonitrile (5.86 g, 0.05 mol) and TBAB (0.16 g, 0.5 mmol), 1-bromo-2-chloroethane (14.3 g, 0.1 mol) was added dropwise. A strong exothermic effect was observed and the temperature was kept at 50 °C (external cooling). After the addition stirring was continued at this temperature for 30 min. After usual work-up the product was isolated by vacuum distillation at 72–74 °C/0.35 Torr (lit.[20] 65–74 °C/0.4 Torr) to give 1-cyano-1-phenylcyclopropane (6.44 g, 90%) as a colorless liquid.
15. See, for example: (a) Nakagaki, R.; Sakuragi, H.; Mutai, K. *J. Phys. Org. Chem.* **1989**, *2*, 187; (b) Mandolini, L. *Adv. Phys. Org. Chem.* **1986**, *22*, 1; (c) Winnik, M. A. *Chem. Rev.* **1981**, *81*, 491.
16. The products of allylation and diallylation of arylacetonitriles may be formed in two possible ways: (1) β-elimination of 1,3-dibromopropane and subsequent allylation of carbanions with allyl bromide, or (2) β-elimination of intermediate 1-aryl-1-cyano-4-bromobutane and its derivatives. Independent of which of these ways is in fact realized, we observed that the amounts of these products decreased with C–H acidity of arylacetonitrile, giving support to the hypothesis that β-elimination is dependent on the carbanion, the basicity of which correlates well with the amount of elimination products: Fedoryński, M.; Marciniak, K., unpublished results.
17. We observed the gradual dependence of the boiling (reflux) temperature of reaction mixtures as a function of concentration of base in both of the series investigated (from 103 °C for 55% KOH to 111 °C for 75% KOH, at the beginning of reaction). One may assume that this effect is related to the amount of water 'accessible' in this system and the boiling points of 'effective azeotropic mixtures' above the liquids.
18. For a similar interpretation see: (a) Landini, D.; Maia, A. M.; Montanari, F. *J. Chem. Soc., Chem. Commun.* **1975**, 950–951; (b) Landini, D.; Maia, A. M.; Montanari, F. *J. Am. Chem. Soc.* **1978**, *100*, 2796–2801; (c) Landini, D.; Maia, A. M.; Rampoldi, A. *Gazz. Chim. Ital.* **1989**, *119*, 513–517.
19. *Typical procedure for the synthesis of 1-cyano-1-phenylcyclobutane* (**4a**). A mixture of solid KOH (22.4 g, 0.4 mol), water (7.5 g), phenylacetonitrile (5.86 g, 0.05 mol), 1,3-dibromopropane (10.1 g, 0.05 mol), TBAB (0.16 g, 0.5 mmol) and toluene (135 mL) was heated to ~100 °C with only occasional slow stirring to facilitate liquification of the inorganic phase. Heating was removed and the mixture was vigorously stirred (see Ref. 21). A water bath was used at the beginning to avoid overboiling (CAUTION! exothermic effect, reaction vessel should be at least double the volume as compared to the reactants). Then the mixture was refluxed with continuous vigorous stirring for 1 h. After work-up the product was isolated by vacuum distillation at 83–85 °C/0.3 Torr (lit.[2f] 107 °C/8 Torr) to give 1-cyano-1-phenylcyclobutane (4.80 g, 61%) as a colorless liquid. Physicochemical data of products **4c–e** were consistent with the literature. For characterization data of compounds **4b** and **4f** see Ref. 22.
20. Küntzel, H.; Wolf, H.; Schaffner, H. *Helv. Chim. Acta.* **1971**, *54*, 868–897.
21. Vigorous mechanical stirring of mixtures is crucial to reproduce all of the presented results (especially yields and amounts of by-products in the syntheses of cyclobutanes).
22. *Characterization data for new compounds:* Compound **4b**: Oil, bp = 156–159 °C/1.4 Torr. ^{1}H NMR ($CDCl_3$, 200 MHz): δ 6.82–6.98 (m, 3H), 3.90 (s, 3H), 3.88 (s, 3H), 2.70–2.88 (m, 2H), 2.27–2.69 (m, 3H), 1.94–2.14 (m, 1H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 149.2, 148.6, 132.2, 124.5, 117.7, 111.1, 108.9, 55.9 (overlapped), 39.9, 34.7, 16.9. MS (EI, relative intensity) $m/z = 217$ (M^+, 26), 202 (4), 189 (100), 186 (23), 174 (31), 119 (33). IR (neat): 2953, 2837, 2228, 1591, 1519, 1465, 1413, 1258, 1172, 1142, 1027, 809, 765, 643, 622 cm^{-1}. Anal. Calcd for $C_{13}H_{15}NO_2$: C 71.87, H 6.96, N 6.45. Found C 71.59, H 7.07, N 6.35. Compound **4f**: Oil, bp = 148–150 °C/20 Torr. ^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.29–7.46 (m, 2H), 7.00–7.15 (m, 2H), 2.70–2.92 (m, 2H), 2.30–2.69 (m, 3H), 1.96–2.20 (m, 1H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 162.1 (d, $^1J_{C-F} =$ 246 Hz), 135.6, 127.3 (d, $^3J_{C-F} = 8.4$ Hz), 124.1, 115.7 (d, $^2J_{C-F} = 22$ Hz), 39.6, 34.7, 17.0. MS (EI, relative intensity) $m/z = 175$ (M^+, 8), 160 (1), 147 (100), 133 (5), 120 (15). IR (neat): 2998, 2954, 2231, 1602, 1511, 1233, 1163, 1102, 1014, 833, 596, 549, 622 cm^{-1}. Anal. Calcd for $C_{11}H_{10}NF$: C 75.41, H 5.75, N 7.99. Found C 75.52, H 5.71, N 8.05.