Phase-Transfer Catalyzed Nucleophilic Addition of Arylalkanenitrile Carbanions to Substituted Propenylarenes[1]

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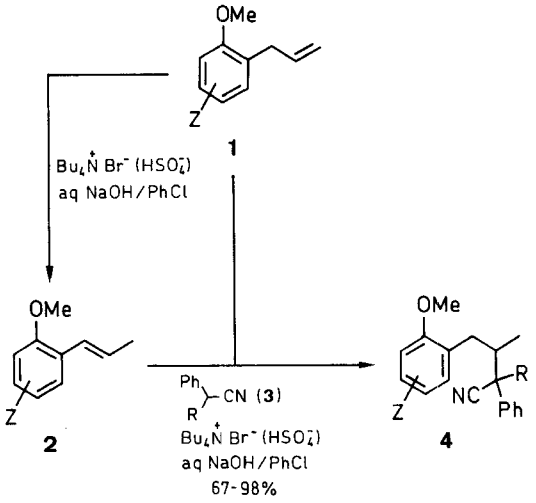
Dedicated to Professor E. V. Dehmlow on the occasion of his 60th birthday

Phenylacetonitrile and 2-phenylalkanenitriles react under phase transfer catalysis conditions with 2-propenylanisoles containing electron-withdrawing substituents (or their corresponding precursors, 2-allylanisoles) via the Michael addition pathway to give substituted 4-aryl-2-phenylbutyronitriles.

Phase-transfer catalysis is presently a general methodology for reactions of anionic species, particularly stabilized carbanions.[2] During the course of our studies on some mechanistic features of phase-transfer catalysis (PTC) we became interested in the base-catalyzed isomerization of allylarenes.[3] Although this process was already used for the isomerization of allylarenes,[4] in the present case we turned our attention to allylarenes, which could rearrange relatively easily; hence moderately electron-withdrawing substituents could be present in the aromatic ring. The simplest way of introducing an allyl group into the aromatic ring is by the Claisen rearrangement of allyl aryl ethers to *ortho*-allylphenols;[5] hence a series of the desired ethers were synthesised via *O*-allylation of substituted phenols. The ethers were thermally rearranged to *ortho*-allylphenols and the latter *O*-methylated to give the desired, substituted *ortho*-allylanisoles **1**.

Studies on the isomerization process catalyzed by the phenylacetonitrile carbanion generated in the PTC system showed that some propenylarenes – products of the isomerization – add subsequently the carbanion to produce 4-aryl-3-methyl-2-phenylbutyronitriles. On the other hand, the isomerization catalyzed by extracted OH^- anions proceeds without complication, giving the corresponding propenylanisoles, quantitatively.[3] On the basis of NMR spectra and GC analysis it was shown that all *o*-propenylanisoles are formed as the single *trans*-isomers. The ^1H NMR data of *o*-propenylanisoles **2a–e**, which were isolated[3] are given in Table 1 along with *o*-allylanisoles **1a–e**.

Since there are only a few examples of reactions, in which propenylarenes or unactivated alkenes act as Michael-type acceptors towards stabilized carbanions,[6] this process was studied extensively and was found to be general. Thus, not only phenylacetonitrile **(3a)** but also 2-phenylalkanenitriles **3b,c**, add to substituted *o*-propenylanisoles, giving the corresponding substituted 4-arylbutyronitriles **4** (Scheme). Since the educts in the addition process, substituted *o*-propenylanisoles **2**, are formed via the base-catalyzed isomerization of the *o*-allylanisoles **1** under essentially the same conditions, in the preparative experiments the former were used as the starting materials without affecting yields of the adducts. For the success of the reaction it is imperative to work under a strictly deoxygenated atmosphere, otherwise the tertiary nitrile carbanions are oxidized to the corresponding ketones.[7]



1, 2	Z	3	R
a	4-Br	**a**	H
b	3,4,6-Cl_3	**b**	Me
c	4,6-Br_2	**c**	Et
d	4-CN		
e	4-Cl,5,6-(CH=CH)$_2$		

4	Z	R	4	Z	R
ba	3,4,6-Cl_3	H	**db**	4-CN	Me
ca	4,6-Br_2	H	**eb**	4-Cl,5,6-(CH=CH)$_2$	Me
da	4-CN	H	**cc**	4,6-Br_2	Et
ea	4-Cl,5,6-(CH=CH)$_2$	H	**dc**	4-CN	Et
ab	4-Br	Me			

Scheme

In all the adducts **4** prepared, there are two chiral carbon atoms, hence they can be formed as two diastereoisomers. In the reaction with phenylacetonitrile, configuration of one stereogenic center can be changed via base-catalyzed epimerization; stereochemical results of the addition of 2-phenylalkanenitriles are kinetically controlled. As shown in Table 2, usually the isomeric products were formed in a ratio of about 1:1 and were not separated. The ratio of diastereoisomeric products was estimated on the basis of NMR spectra.

^1H NMR spectra were recorded on a Gemini Varian 200 MHz spectrometer with TMS as internal standard. Accurate mass measurements were done on Intectra AMD-604 mass spectrometer, using

Table 1. Allyl- and Propenylanisoles **1** and **2** Prepared

Product[a]	mp (°C) or bp (°C)/Torr[b]	^{1}H NMR ($CDCl_3$/TMS) δ, J (Hz)
1a	60/0.01	3.35 (d, J = 6.6, 2H), 3.80 (s, 3H), 5.07 (dt, J = 17.7, 1.4, 1H), 5.09 (dt, J = 9.4, 1.4, 1H), 5.96 (qt, J = 17.7, 9.4, 6.6, 1H), 6.71 (d, J = 8.8, 1H), 7.25 (d, J = 2, 1H), 7.28 (dd, J = 8.8, 2.0, 1H)
1b	73/0.04	3.61 (dt, J = 6, 1.7, 2H), 3.84 (s, 3H), 5.01 (dq, J = 17.0, 1.5, 1.7, 1H), 5.08 (dq, J = 10.2, 1.5, 1.7, 1H), 5.93 (dq, J = 10.2, 17.0, 6, 1H), 7.41 (s, 1H)
1c	81/0.01	3.40 (dt, J = 6.5, 1.5, 2H), 3.79 (s, 3H), 5.08 (dq, J = 16.8, 1.5, 1.5, 1H), 5.13 (dq, J = 10.2, 1.5, 1.5, 1H), 5.91 (qt, J = 10.2, 16.8, 6.5, 1H), 7.25 (d, J = 2.3, 1H), 7.54 (d, J = 2.3, 1H)
1d	87/0.03	3.37 (d, J = 6.6, 2H), 3.89 (s, 3H), 5.07 (dq, J = 16.8, 1.7, 1.4, 1H), 5.11 (dq, J = 10.3, 1.7, 1.4, 1H), 5.93 (qt, J = 16.8, 10.3, 6.6, 1H), 6.89 (d, J = 8.5, 1H), 7.42 (d, J = 2.2, 1H), 7.52 (dd, J = 8.5, 2.2, 1H)
1e	107/0.15	3.60 (dt, J = 6.6, 1.4, 2H), 3.93 (s, 3H), 5.12 (dq, J = 10.1, 1.7, 1.4, 1H), 5.17 (dq, J = 17.0, 1.7, 1.4, 1H), 6.06 (qt, J = 17.0, 10.1, 6.6, 1H), 7.5 (s, 1H), 7.59–7.71 (m, 2H), 8.11–8.24 (m, 2H)
2a	69/0.01	1.89 (dd, J = 6.6, 1.7, 3H), 3.80 (s, 3H), 6.20 (dq, J = 16.0, 6.6, 1H), 6.62 (dq, J = 16.0, 1.7, 1H), 6.69 (d, J = 8.7, 1H), 7.24 (dd, J = 8.7, 2.6, 1H), 7.48 (d, J = 2.6, 1H)
2b	40	1.96 (d, $J \approx$ 4.9, 3H), 3.72 (s, 3H), 6.35–6.63 (m, $J \approx$ 15.9, 2H), 7.37 (s, 1H)[c,d]
2c	48	1.93 (dd, J = 6.6, 1.6, 3H), 3.77 (s, 3H), 6.27 (dq, J = 15.9, 6.6, 1H), 6.57 (dq, J = 15.9, 1.6, 1H), 7.50 (d, J = 2.4, 1H), 7.52 (d, J = 2.4, 1H)
2d	56	1.91 (dd, J = 6.6, 1.6, 3H), 3.90 (s, 3H), 6.26 (dq, J = 15.9, 6.6, 1H), 6.63 (dq, J = 15.9, 1.6, 1H), 6.88 (d, J = 8.6, 1H), 7.48 (dd, J = 8.6, 2.1, 1H), 7.64 (d, J = 2.1, 1H)
2e	103/0.01 mp 19	1.96 (dd, J = 6.6, 1.7, 3H), 3.88 (s, 3H), 6.63 (dq, J = 15.9, 6.6, 1H), 6.81 (dq, J = 15.9, 1.7, 1H), 7.38–7.65 (m, 2H), 7.68 (s, 1H), 8.03–8.23 (m, 2H)

[a] Satisfactory microanalyses obtained: C ± 0.28, H ± 0.27, N ± 0.27, Cl ± 0.40, Br ± 0.09 or HRMS ± 0.0002 amu.
[b] Kugelrohr distillation.
[c] On the basis of this approximation of the first order spectrum a programme of the LAOCOON-type was used for the strongly coupled spectrum to calculate the true parameters of the propenyl system: H_α, δ = 6.426, J = 15.89 Hz; H_β, δ = 6.512, J = 6.26 Hz; H_γ, δ = 1.963, $J \approx$ 0 Hz.
[d] Spectrum shows the presence of the *cis*-isomer (ratio: *trans*/*cis* ≈ 9 : 1).

Table 2. Substituted 4-Arylbutyronitriles **4** Prepared

Product	Method	Reaction Time (min)	Yield (%)	Ratio of Isomers	^{1}H NMR ($CDCl_3$/TMS)[a] δ, J (Hz)
4ba	A	180	92	1.5 : 1	major: 0.98 (d, J = 6.8, 3H), 3.83 (s, 3H), 7.63 (s, 1H)[b] minor: 0.96 (d, J = 6.8, 3H), 3.67 (s, 3H), 7.59 (s, 1H)[b]
4ca	A	60	98	one isomer	0.97 (d, J = 6.2, 3H), 2.39 (m, 1H), 2.36 (d, J = 9.8, 1H), 2.84 (d, J = 9.8, 1H), 3.51 (s, 3H), 3.87 (d, J = 5.3, 1H), 7.16 (d, J = 2.3, 1H), 7.45 (m, 6H)
4da	B	165	84	1.4 : 1	major: 0.96 (d, J = 6.6, 3H), 3.90 (s, 3H), 6.93 (d, J = 8.6, 1H), 7.38 (d, J = 2.1, 1H), 7.56 (dd, J = 8.6, J = 2.1, 1H) minor: 0.95 (d, J = 6.2, 3H), 3.77 (s, 3H), 6.83 (d, J = 8.6, 1H), 7.43 (d, J = 2.2, 1H), 7.50 (dd, J = 8.6, J = 2.2, 1H)
4ea	B	165	80	1.3 : 1	major: 0.97 (d, J = 6.5, 3H), 3.69 (s, 3H), 7.29 (s, 1H) minor: 1.03 (d, J = 6.8, 3H), 3.90 (s, 3H), 7.25 (s, 1H)
4ab	B	480	72	1.1 : 1	major: 0.97 (d, J = 6.6, 3H), 1.69 (s, 3H), 3.66 (s, 3H)[c] minor: 0.66 (d, J = 6.0, 3H), 1.80 (s, 3H), 3.77 (s, 3H)[c]
4db	B	280	67	1.1 : 1	major: 1.03 (d, J = 5.9, 3H), 1.74 (s, 3H), 3.76 (s, 3H), 6.80 (d, J = 8.6, 1H), 7.34 (d, J = 2.3, 1H) minor: 0.72 (d, J = 6.4, 3H), 1.84 (s, 3H), 3.87 (s, 3H), 6.88 (d, J = 8.6, 1H), 7.21 (d, J = 2.1, 1H)
4eb	B	180	73	1.0 : 1	major: 0.78 (d, J = 6.6, 3H), 1.90 (s, 3H), 3.58 (s, 3H) minor: 1.06 (d, J = 6.0, 3H), 1.77 (s, 3H), 3.86 (s, 3H)
	A	570	88	1.2 : 1	major: 0.78 (d, J = 6.6, 3H), 1.90 (s, 3H), 3.58 (s, 3H) minor: 1.06 (d, J = 6.0, 3H), 1.77 (s, 3H), 3.86 (s, 3H)
4cc	A	120	96	1.3 : 1	major: 0.79 (t, J = 7.3, 3H), 1.07 (d, J = 6.6, 3H), 3.37 (s, 3H) minor: 0.64 (d, J = 6.0, 3H), 0.89 (t, J = 7.3, 3H), 3.83 (s, 3H)
4dc	A	1140	79	1.2 : 1	major: 0.64 (d, J = 6.4, 3H), 0.81 (t, J = 7.3, 3H), 3.75 (s, 3H), 6.79 (d, J = 8.5, 1H) minor: 0.88 (t, J = 7.3, 3H), 1.08 (d, J = 6, 3H), 3.91 (s, 3H), 6.90 (d, J = 8.5, 1H)

[a] Only well separated signals of diagnostic value are reported. Signals of protons bound at 2-, 3- and 4-positions of the aliphatic chain, as well as those bound to aromatic rings form overlapping multiplets which are difficult to analyse.
[b] Solvent: acetone-d_6.
[c] Solvent: CD_3OD.

double-focusing at a resolving power 10.000 and perfluorokerosene (PFK) as the reference. All melting points are uncorrected. Capillary GC analyses were performed on Shimadzu GC-14 A gas chromatograph, using Macherey-Nagel SE-52-Permabond column (25 m × 0.32 mm ID × 0.25 μ) at 2 mL/min N_2 flow, split about 1:40. Column chromatography was done using Merck Kieselgel 60 (100–200 mesh). All phenols are commercial products with purity more than 95% and were used without further purification. Anhydr. K_2CO_3 and solid NaOH were analytical grade reagents. Commercial pure benzyl cyanide was distilled before use and was of 99% purity (GC). Alkylated derivatives of benzyl cyanide were prepared according to the procedure described[8] and had a purity of around 98%. All solvents, quaternary ammonium catalysts and alkylating agents are commercial products with purity of at least 97% and were used without further purification.

All allylarenes were synthesized from the corresponding phenols via allylation, the Claisen rearrangement and methylation reactions.

Allylation of Substituted Phenols; General Procedure:
A solution of the appropriate substituted phenol (0.1 mol), allyl bromide (14.52 g, 0.12 mol) and Bu_4NBr (1.61 g, 5 mmol) in MeCN (50 mL) was added to anhydr. K_2CO_3 (20 g, 0.2 mol) and the suspension was stirred at r.t. under Ar until the substrate had disappeared (GC control). When the reaction was complete, the mixture was diluted with water to dissolve all solids, the organic product was extracted with EtOAc, the extract washed twice with water, dried ($MgSO_4$) and the solvent evaporated; yields: > 96%.

The Claisen Rearrangement of Substituted Allyl Phenols; General Procedure:
Allyl aryl ethers prepared as above were heated under Ar with stirring at controlled temperature till completion of the rearrangement (GC analysis). The mixture was cooled and the product isolated and purified via distillation, recrystallization or column chromatography. Temperatures for the rearrangement: allyl *p*-bromophenyl ether: 223–230 °C; allyl 2,4,5-trichlorophenyl ether: 219–228 °C; allyl 2,4-dibromophenyl ether: 195–206 °C; allyl *p*-cyanophenyl ether: 221–227 °C and allyl 4-chloronaphthyl ether: 148–152 °C. In the latter case, the ether was rearranged as a solution in an equal volume of *N,N*-dimethylaniline in order to prevent decomposition; yields: 59–85%.

Methylation of *o*-Allylphenols; General Procedure:
A solution of the appropriate *o*-allylphenol obtained via the Claisen rearrangement (0.05 mol), MeI (0.06 mol) and Bu_4NBr (0.97 g, 3 mmol) in MeCN (50 mL) was added to anhydr. K_2CO_3 (10 g, 0.1 mol) and the suspension was stirred under Ar at r.t. until the substrate had disappeared (GC control). After workup as described for the allylation of phenols, the crude product was purified by vacuum distillation; yields: > 90%.

Addition of Phenylalkanenitriles 3 to the Propenylarenes 2 Formed in situ from the Allylarenes 1; General Procedure:
A solution of the appropriate nitrile **3** (2 mmol), allylarene **1** (1 mmol) and Bu_4NBr (0.3 mmol) (Method A) or Bu_4NHSO_4 (1 mmol) (Method B) in chlorobenzene was carefully deoxygenated by a few vacuum-nitrogen cycles. To this was added a solution of aq NaOH (3.5 mL, 68 mmol) using a syringe with a thick needle and the mixture magnetically stirred under N_2 at r.t. till the reaction was complete (GC analysis). The mixture was diluted with water, and the product extracted with CH_2Cl_2. The combined extracts were washed with H_2O, dried (Na_2SO_4) and the solvent evaporated. All the products **4** were purified via column chromatography on silica gel, using toluene or cyclohexane/Et_2O (3:1) mixture as eluents.

(1) Reactions of Organic Anions, Part 199. Part 198: Mąkosza, M.; Sypniewski, M. *Phosphorus, Sulphur and Silicon*, submitted.
(2) Dehmlow, E.V.; Dehmlow, S.S. *Phase-Transfer Catalysis*; 2nd Ed., Verlag Chemie: Weinheim, 1983.
Mąkosza, M. *Pure Appl. Chem.* **1975**, *43*, 439.
Mąkosza, M.; Fedoryński, M. *Adv. Catal.* **1987**, *35*, 375.
(3) Lasek, W.; Mąkosza, M. *J. Phys. Org. Chem.*, submitted.
(4) Halpern, M.; Sasson, Y.; Rabinovitz, M. *J. Org. Chem.* **1983**, *48*, 1022.
(5) Rhoads, S.J.; Raulins, N.R. *Org. React.* **1975**, *22*, 1.
(6) Arseniyadis, S.; Kyler, K.S.; Watt, D.S. *Org. React.* **1984**, *34*, 1.
Farr, R.A.; Dolfini, J.E.; Carr, A.A. *J. Org. Chem.* **1981**, *46*, 1212.
Bernasconi, C.F. *Tetrahedron* **1989**, *45*, 4017.
Fava, A.; Bongini, A.; Cere, V.; Paolucci, C.; Pollicino, S. Sandri, E. *Pure Appl. Chem.* **1987**, *53*, 995.
(7) Donetti, A.; Boniardi, O.; Ezhaya, A. *Synthesis* **1980**, 1009.
(8) Mąkosza, M.; Jończyk, A. *Synthesis* **1976**, *55*, 91.