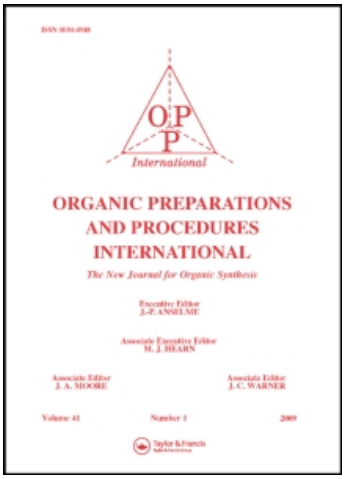

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SIMPLE PHASE-TRANSFER ALKYLATION OF O-(TETRAHYDROPYRAN-2-YL) ARYLALDEHYDE CYANOHYDRINS

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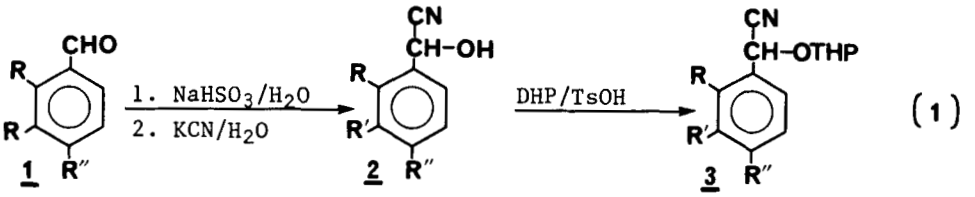
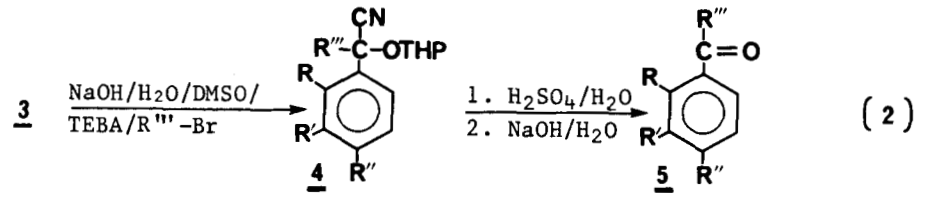
The alkylation of protected cyanohydrins anions constitutes an excellent method for ketones synthesis.[1] Generally, the anions are generated from aliphatic or aromatic aldehyde protected cyanohydrins with lithium diisopropylamide or sodium hydride in anhydrous tetrahydrofuran or dimethoxyethane under nitrogen at -78°. The addition of an alkyl halide produces the protected ketone cyanohydrin. The carbonyl group is then liberated by successive treatment with dilute acid and dilute aqueous base.



a) R = R'= R"=H ; b) R= OMe, R'= R"=H ; c) R =H, R'=R"= OMe



a) R=R'=R"=H, R"'=nBu ; b) R=R'=R"=H, R"'= C_6H_{11}; c) R=OMe, R'=R"=H R"'=nBu ; d) R=OMe, R'=R"=H, R"'=C_6H_{11}; e) R=H, R'=R"=OMe, R"'=nBu ; f) R=H, R'=R"=OMe, R"'=C_6H_{11}

Recently, it was reported a simple general method for the preparation of aromatic ketones[2] based on the phase-transfer catalyzed alkylation of benzaldehyde cyanohydrins (Eq. 1). We now report a complement to this procedure for the synthesis of aromatic ketones 5 by alkylation of the O-(tetrahydropyran-2-yl) arylaldehyde cyanohydrins 3 under similar reaction conditions (Eq. 2).

The method consists in the generation of the protected cyanohydrin carbanion from 3 with aqueous sodium hydroxide in dimethyl sulfoxide and a catalytic amount of triethylbenzylammonium chloride followed by the addition of an alkyl bromide in dimethyl sulfoxide. The mixture is vigorously stirred for 1-24 hrs at room temperature to produce the protected cyanohydrin 4 which can be purified or hydrolyzed directly to give 5.

Arylaldehyde cyanohydrins 2 were made following the general method described to prepare mandelonitrile[3] and were protected by the tetrahydropyranyl group[4] to produce 3 in high yields (Table 1) using p-toluenesulfonic acid as catalyst[5] in order to avoid volatile catalysts and to simplify work-up of the reaction mixture.

TABLE 1. O-(Tetrahydropyran-2-yl)arylaldehyde Cyanohydrins 3

Product	Yields[a] [%]	^{1}H-NMR ($CDCl_3$) δ Ar-CH-CN[ppm]
3a	98	5.10 and 5.40[b]
3b	82	5.90
3c	83	5.35 and 5.50[b]

a) Based on 2 b) Mixture of diasteroisomers.

Alkylation proceeds smoothly with primary (n-butyl) or secondary (cyclohexyl) bromides in yields comparable to those reported[1] (Tables 2 and 3). However, the procedure used here has the advantage of being easy to perform, employs rather inexpensive reagents thus making it useful for large-scale preparations and does not require anhydrous conditions or purification of

TABLE 2. Microanalytical Data for Aromatic Ketones 5

Compd No	Molecular Formula	Elemental Analysis Calc (Found) C	H
5a	$C_{11}H_{14}O$	81.44 (81.30)	8.70 (8.79)
5b	$C_{13}H_{16}O$	82.93 (83.09)	8.57 (8.68)
5c	$C_{12}H_{16}O_2$	74.97 (75.17)	8.39 (8.20)
5d	$C_{14}H_{18}O_2$	77.03 (76.92)	8.31 (8.48)
5e	$C_{13}H_{18}O_3$	70.24 (70.18)	8.16 (8.03)
5f	$C_{15}H_{20}O_3$	72.55 (72.66)	8.12 (7.92)

the intermediates 2 and 4.

While the method has proved to be efficient for the alkylation of protected aromatic cyanohydrins, it is unsuitable for protected cyanohydrins derived from aliphatic aldehydes. The O-tetrahydropyranyl cyanohydrin of acetaldehyde could not be alkylated under these conditions, possibly because , the catalytic generation of the carbanion fails to proceed with insufficiently activated protected cyanohydrins.

EXPERIMENTAL SECTION

Column chromatography was carried out by using Merck silica gel 60 (0.063-0.2 mm). The preparative TLC plates were of Merck silica gel 60 F-254 (20 x 20 x 0.2 cm). In order to follow the progress of the reactions or the purity of the compounds, Merck F-254 thin-layer plates 250 (μm) cut into small slides (5 x 2.5 cm) were used. The products were visualized by UV absorption or I_2 vapor. ^{1}H-NMR spectra were obtained in $CDCl_3$ on Varian FT-80A spectrometer with Me_4Si, as an internal reference, and are expressed as δ values. Mass spectra were recorded on a Hewlett Packard 5985-B spectrometer at 70eV.

α-[Tetrahydro-2H-pyran-2-yl)oxy]-2-methoxybenzeneacetonitrile (3b). Typical Procedure.- A solution of cyanohydrin 2b (21 g, 0.13 mol), dry dihydro-4H-pyran (16.2 g, 0.19 mol) and 10 mg of p-toluenesulfonic acid was heated to reflux for 1.5 hr. The cooled mixture was treated with anhydrous potassium carbonate (0.1 g) and stirred for 1 hr. After the addition of dry ether (70 ml), the salts were removed by filtration and the resulting solution was concentrated in vacuo. The residue was chromatographed over silica gel

TABLE 3. Aromatic Ketones 5.

Product[a]	Reaction Time (hr)	Yield[b] [%]	^{1}H-NMR ($CDCl_3$) δ[ppm]	MS (70 eV) m/z (%)
5a[7]	1	94	0.95 (t, 3H, J = 6 Hz); 1.15-1.95 (m, 4H); 2.95 (t, 2H, J = 7 Hz); 7.25-7.60 (m, 3H); 7.80-8.05 (m, 2H).	162(M^+, 15), 120(72), 105 (100), 77(74), 51(16).
5b[7]	24	72	1.00-2.25 (m, 10H); 3.00-3.50 (m, 1H); 7.25-7.65 (m, 3H); 7.75-8.05 (m, 2H).	188(M^+, 23), 105(84), 77 (100), 55(30), 51(30).
5c[6]	1	91	See typical procedure	See typical procedure
5d	24	65	1.10-2.10 (m, 10H); 2.95-3.35 (m, 1H); 3.86 (s, 3H); 6.90 (dd, 1H, J = 8, 2 Hz); 6.96 (td, 1H, J = 8,2 Hz); 7.40 (td, 1H, J = 8,2 Hz); 7.45 (dd, J = 8, 2 Hz).	218(M^+,7), 136(9), 135 (100), 77(14).
5e[8]	1	92	0.95 (t, 3H, J = 6 Hz); 1.15-1.90 (m, 4H); 2.80 (t, 2H, J = 7 Hz); 3.92 (s, 6H); 6.84 (dd, 1H, J = 9,1 Hz); 7.50 (d, 1H, J = 2 Hz); 7.55 (dd, 1H, J = 9,2 Hz).	222(M^+,20), 180(66), 166 (15), 165 (100), 77(12).
5f[9]	24	53	1.10-2.00 (m, 10H); 3.00-3.40 (m, 1H); 3.93 (s, 6H); 6.85 (dd, 1H, J = 9, 1 Hz); 7.51 (d, 1H, J = 2 Hz); 7.57 (dd, 1H, J = 9, 2 Hz).	248 (M^+,12), 166(11), 165 (100), 79(9), 77(8).

a) Isolated by chromatography on silica gel. All ketones 5, except 5d, are known (reference number are those given in the references) and their identity and purity were confirmed by microanalysis, IR, ^{1}H-NMR and mass spectral data b) Based on 3.

using hexane-ethyl acetate (75:25) as eluent to produce 26.3 g (82%) of 3b as a colorless oil.

2'-Methoxyvalerophenone (5c). Typical Procedure.- To a mixture of 3b (1.3 g, 5.25 mmol), 50% aqueous sodium hydroxide solution (0.8 g, 10 mmol) and benzyltriethylammonium chloride (0.16 g, 0.7 mmol) in 20 ml of dimethyl sulfoxide, a solution of 1-bromobutane (0.715 g, 5.25 mmol) in 5 ml of dimethyl sulfoxide was added. The mixture was vigorously stirred at room temperature for 1 hr. After the addition of water (25 ml), the mixture was extracted with ethyl acetate (3 x 25 ml), washed with saturated sodium chloride solution (3 x 25 ml), dried over sodium sulfate and evaporated to produce 1.5 g (94%) of 4c. To this crude product in 7 ml of methanol was added 5% aqueous sulfuric acid (1 ml) and the mixture was stirred at room temperature for 10 min. The solvent was evaporated and the residue extracted with ether (3 x 15 ml). The ethereal solution was shaken with 20 ml of 0.5 N aqueous sodium hydroxide for 10 min, separated, washed with water (2 x 25 ml), dried over sodium sulfate and evaporated. The crude product was purified by preparative TLC with hexane/ethyl acetate (70:30) as the eluent to give 0.92 g (91% based on 3b) of 2'-methoxyvalerophenone[6] (5c) as a yellow oil.

IR (neat): ν_{max} 1675 cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ 0.92 (t, 1H, J = 6 Hz), 1.10-1.85 (m, 4H), 2.95 (t, 2H, J = 7 Hz), 3.89 (s, 3H), 6.88 (dd, 1H, J = 8, 2 Hz), 6.95 (td, 1H, J = 8, 2 Hz), 7.40 (td, 1H, J = 8, 2 Hz), 7.57 (dd, 1H, J = 8, 2 Hz). MS (70 eV): m/z (%) 192 (M^+, 2), 150 (14), 135 (100), 92 (15), 77 (30).

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REFERENCES

1. G. Stork and L. Maldonado, J. Am. Chem. Soc., 93. 5286 (1971).
2. M. Makosza and T. Goetzen, Org. Prep. Proced. Int., 5, 203 (1973).
3. B. B. Corson, R. A. Dodge, S. A. Harris and J. S. Yeaw, Org. Synth., Coll. Vol. 1, 336 (1941).
4. E. Aufderhaar, J. E. Baldwin, D. H. R. Barton, D. J. Faulkner and M. Slaytor, J. Chem. Soc., (C), 2175 (1971).
5. P. De Ruggieri and C. Ferrari, J. Am. Chem. Soc., 81, 5725 (1959).
6. A. I. Meyers and R. Gabel., J. Org. Chem., 43, 1372 (1978).
7. K. Deuchert, V. Hertenstein, S. Hunig and G. Wehner, Chem. Ber., 112, 2045 (1979).
8. R. R. Hautala and R. H. Hastings, J. Am. Chem. Soc., 100, 648 (1978).
9. D. Berney, Helv. Chim. Acta, 61, 1110 (1978).

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