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SIMPLE PHASE TRANSFER CATALYTIC METHOD FOR α-METHOXYLATION OF STERICALLY HINDERED KETONES

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Abstract. Reactions of sterically hindered ketones of ArylCOCHR^{1}R^2 type (R^1, R^2 = Me, Et, Ph) with carbon tetrachloride and methyl iodide in the presence of solid KOH and 18-crown-6 afford the corresponding α-methoxyketones [ArylCOC(OMe)R^{1}R^2] in one-pot process in 30-67% yields.

Some of α-alkoxycarbonyl compounds are of interest as photoactive substances and intermediates for the synthesis of biologically active compounds. Oxidative methods are considered the main for the preparation of α-hydroxy- and α-alkoxyketones[1]. Enantioselective phase transfer catalyzed molecular oxygen mediated α-hydroxylation of ketones also has been described[2].

Carbon tetrachloride reacts with carbaniones generated from ketones in two phase system, chlorination[3,4] with the subsequent transformations being the main reaction. For example, aryl methyl or aryl ethyl ketones

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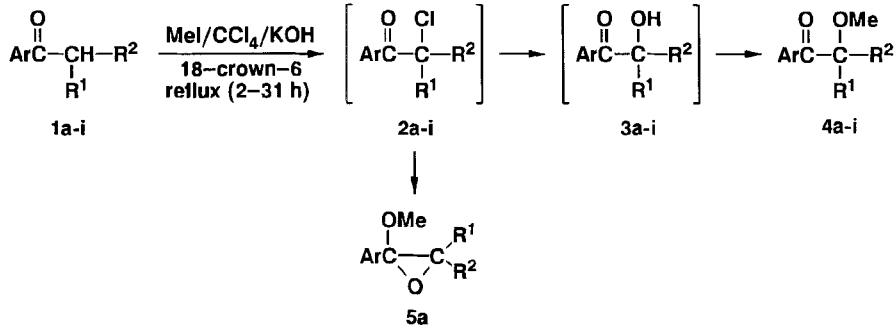
undergo cyclization into epoxides[3-5]. In cases of the sterically hindered ketones ($ArCOCHR_2$, R = Me, Et) the corresponding α-hydroxyketones[5-6] were obtained as main products. The present work was performed in the continuation of our previos studies of phase transfer catalyzed (PTC) reactions of alkyl hetaryl ketones with CCl_4[5].

The reactions of sterically hindered ketones (**1a-i**) were carried out in carbon tetrachloride/solid KOH system in the presence of methyl iodide and 18-crown-6 (the molar ratio **1**:MeI:KOH:18-crown-6 = 1 : 2 : 4 : 0.1) at elevated temperature to give the corresponding α-methoxy ketones (**4a-i**) in 30-67% yields (Table 1).



According to the GC and GC/MS data, the reactions proceed through α-chloroketones (**2**), which undergo the rapid nucleophilic substitution to give readily detectable intermediates - the corresponding α-hydroxy ketones (**3**). Obviously, due to the rapid changes the α-chloroketones assigned by mass spectra only in some cases (for example, m/z 216 (M^+) for compound **2h**). Compounds **3a-i** undergo slow subsequent PTC alkylation with methyl iodide to afford the corresponding α-methoxy ketones (**4a-i**) as main products. α-Haloketones are well known to undergo the cyclization into the corresponding epoxides in the presence of alkali metal alcoholates[7]. The formation of similar epoxides **5** in two-phase solid/liquid catalytic system was detected only in the reaction of phenyl isopropyl ketone (**1a**) with KOH/CCl_4. In this case reaction mixture after reaction completion besides the main product **4a** (79%) contains also ~21% of 2-methoxy-2-phenyl-3,3-dimethyloxirane (**5a**) (GC and GC/MS data), resulting from the

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Table 1. PTC α-methoxylation of ketones **1a-i**

Start. ketone	Ar	R^1	R^2	React. time (h)	Product	Yield[a] (%)	B.p. (°C/ mmHg) or m.p. (°C)	Mol.form.[b] or liter. mp
1a	Ph	Me	Me	21	**4a**	66	111-114/10	-[c]
1b	Ph	Me	Ph	2	**4b**	40	126-130/0.5	35-36[d]
1c	Ph	Me	Et	5	**4c**	67	87/2.5	$C_{12}H_{16}O_2$ (192.3)
1d	Ph	Et	Et	31	**4d**	39	107-109/3.5	$C_{13}H_{18}O_2$ (206.3)
1e	2-furyl	Me	Me	11	**4e**	37	64-65	$C_9H_{12}O_3$ (168.2)
1f	2-thienyl	Me	Me	11	**4f**	53	112-114/10 66	$C_9H_{12}O_2S$ (184.3)
1g	2-thienyl	Me	Ph	2	**4g**	31	124-126/1.5	$C_{14}H_{14}O_2S$ (246.3)
1h	2-thienyl	Et	Et	22	**4h**	30	89-91/1	$C_{11}H_{16}O_2S$ (212.3)
1i	5-bromo-2-thienyl	Me	Me	5	**4i**	64	95-96/2	$C_9H_{11}BrO_2S$ (263.2)

[a] Yield of isolated products.
[b] Satisfactory microanalysis obtained.
[c] Compound **4a** was identified comparing its ^{1}H NMR and mass spectrum with those described in literature[7].
[d] Compound **4b** was identified comparing its ^{1}H NMR spectra with those described in literature[8].

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cyclization of intermediate **2a**. α-Methoxyketone **4a** can be separated by distillation. The interaction of ketones **1a** and **1f** with less hard electrophile than MeI, i.e. EtI, under similar PTC conditions at prolonged refluxing (9-21 h) in the presence of two-fold excess of ethyl iodide in all cases leads to the mixture of the corresponding α-hydroxy and α-ethoxyketones. Reaction between 2-pyridyl and 3-pyridyl isopropyl ketones and CCl_4/ MeI occured under PTC, too. The reaction mixture after the reaction completion contains some products in low yields: corresponding α-hydroxy, α-

Table 2. Spectral data of synthesized α-methoxyketones **4c-i**

Comp.	^{1}H NMR ($CDCl_3$/TMS)[a]; δ (ppm), J (Hz)	MS(70 eV), m/z[b]
4c	0.84(t, 3H, $CH_2C\underline{H}_3$), 1.44(s, 3H, CH_3), 1.93 (q, 2H, $C\underline{H}_2CH_3$), 3.18(s, 3H, OCH_3), 7.3-7.6 and 8.2-8.3(m, 5H, C_6H_5)	177(M^+-Me, 0.5), 163 (2), 105 (13), 87(100), 77(16), 55(35), 43(13), 28(14)
4d	0.78(t, 6H, J = 7.4, $CH_2C\underline{H}_3$), 1.96(q, 4H, J = 7.4, $C\underline{H}_2CH_3$), 3.15(s, 3H, OCH_3), 7.2-7.6 and 8.1-8.3(m, 5H, C_6H_5)	177(M^+-Et, 2) 101 (100), 77 (24), 59(29), 45(48), 29(20)
4e	1.47(s, 6H, CH_3), 3.22(s, 3H, OCH_3), 6.53 (dd, 1H, $J_{3,4}$ = 3.6, $J_{4,5}$ = 1.8, H-4), 7.53 (dd, 1H, $J_{3,4}$ = 3.6, $J_{3,5}$ = 0.6, H-3), 7.60 (dd, $J_{4,5}$ = 1.8, $J_{3,5}$ = 0.6, H-5)	168(M^+, 0.3), 153(1), 117(5), 95(9), 73(100), 43(28), 28(12)
4f	1.33(s, 6H, CH_3), 3.11(s, 3H, OCH_3), 6.96 (dd, 1H, $J_{4,5}$ = 4.8, $J_{3,4}$ = 3.8, H-4), 7.44 (dd, 1H, $J_{4,5}$ = 4.8, $J_{3,5}$ = 1.4, H-5), 7.96 (dd, 1H, $J_{3,4}$ = 3.8, $J_{3,5}$ = 1.4, H-3)	184(M^+, < 0.1), 119(4), 111(15), 83(4), 73(100), 59(37), 43(23), 39(24)
4g	1.73(s, 3H, CH_3), 3.36(s, 3H, OCH_3), 6.91 (dd, 1H, $J_{4,5}$ = 4.8, $J_{3,4}$ = 3.8, H-4), 7.0-7.6 (m, 5H, C_6H_5), 7.48(dd, 1H, $J_{4,5}$ = 4.8, $J_{3,5}$ = 1.4, H-5), 7.82(dd, 1H, $J_{3,4}$ = 3.8, $J_{3,5}$ = 1.4, H-3)	237(M^+-Me, 0.1), 135(100), 105 (7), 77(20), 51(10), 43(63)
4h	0.82(t, 6H, J = 8.0, $CH_2C\underline{H}_3$), 1.93 (q, 4H, J = 8.0, $C\underline{H}_2CH_3$), 3.22(s, 3H, OCH_3), 7.11 (dd, 1H, $J_{4,5}$ = 5.0, $J_{3,4}$ = 3.8, H-4), 7.60(dd, 1H, $J_{4,5}$ = 5.0, $J_{3,5}$ = 1.4, H-5), 8.11(dd, 1H, $J_{3,4}$ = 3.8, $J_{3,5}$ = 1.4, H-3)	212(M^+, < 0.1), 111(22), 101 (100), 78(7), 69(13), 59(28), 45 (48), 39(20), 29(18)
4i	1.44(s, 6H, CH_3), 3.22(s, 3H, OCH_3), 7.07 (d, 1H, J = 4.0, H-4), 7.80(d, 1H, J = 4.0, H-3)	262(M^+, 0.5), 189(4), 117(4), 82 (7), 73(100), 43(10), 28(30)

[a] Recorded on a Bruker WH-90 spectrometer.
[b] Recorded on a Kratos MS-25 apparatus.

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methoxyketones and also side chain chlorination products (GC and GC/MS data). Thus, PTC α-methoxylation is a simple method for the synthesis of sterically hindered α-methoxyketones which otherwise are difficult to obtain.

EXPERIMENTAL

GC analysis was performed on a Chrom-5 instrument equipped with a flame-ionization detector using glass column packed with 5% OV-17/Chromosorb W-HP (80-100 mesh) (1.2 m • 3mm). 2-Acetylfuran, 2-acetylthiophene, 2-bromothiophene, 2-methyl-1-phenyl-1-propanone (**1a**) and 18-crown-6 were Fluka products. 5-Bromo-2-acetylthiophene was obtained by Friedel-Crafts acylation of 2-bromothiophene with acetyl chloride[9]. 2-Phenyl-1-(2-thienyl)-1-propanone and 1,2-diphenyl-1-propanone were prepared similarly from phenylacetic chloride and thiophene or benzene, correspondingly. 2-Methyl-1,2-diphenyl-1-propanone (**1b**), 2-methyl-1-(2-furyl)-1-propanone (**1e**), 2-methyl-1-(2-thienyl)-1-propanone (**1f**), 2-methyl-2-phenyl-1-(2-thienyl)-1-propanone (**1g**) and 2-methyl-1-(5-bromo-2- thienyl)-1-propanone (**1i**) were obtained by PTC methylation of 1,2-diphenyl-1-propanone, 2-acetylfuran, 2-acetylthiophene, 2-phenyl-1-(2-thienyl)-1-propanone or 5-bromo-2-acetylthiophene, correspondingly[10]. 2-Methyl-1-phenyl-1-butanone (**1c**), 1-phenyl-2-ethyl-1-butanone (**1d**) and 2-ethyl-1-(2-thienyl)-1-butanone (**1h**) were obtained by PTC alkylation of the corresponding 1-phenyl-1-propanone, acetophenone or 2-acetylthiophene with EtI[10].

General procedure for α-methoxylation of ketones **1a-i.** Finely powdered KOH (2.24 g, 40 mmol) was added to a solution of ketone (**1a-i**; 10 mmol), methyl iodide (1.25 ml, 20 mmol) and 18-crown-6 (0.26 g, 1mmol) in 20 ml of carbon tetrachloride. The mixture was refluxed for 2-31 h (see Table 1) to achieve the complete disappearance of the starting ketones **1a-i** and intermediates **2a-i** and **3a-i** from the solution (GC control: 180-250°C). The resulting mixture was filtered over Al_2O_3, the excess of MeI and CCl_4 were removed at reduced pressure and the residue was distilled in vacuo to give α-methoxyketones (**4a-i**) (see Tables 1, 2).

REFERENCES

1. Brian Jones A. in "Comprehensive Organic Synthesis", Trost, B.M., Flemming, I., Eds, vol. 7, Pergamon Press, Oxford, 1991, pp. 151-191.

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2. Masui, M., Ando, A., Shioiri, T., Tetr. Lett., 1988, 29, 2835.
3. Preston Reeves, W., Creswell, M.W., Synth. Commun., 1983, 13, 945.
4. Makosza, M., Kvast, A., Kwast, E., Jonczyk, A., J. Org. Chem., 1985 , 50, 3722.
5. Abele, E., Rubina, K., Popelis, J., Goldberg, Y., Shymanska, M., Chem. Heterocycl. Comp., 1994, N 3, 312.
6. Koehler, M., Roemer, M., Herz, C.P. Ger. Pat. 3,512,541 (Merck Patent GMBH) 1985; CA 1987, 107, 32575q.
7. House, H.O., Prabhu, A.V., Wilkins, J.M., Lee, L.F., J.Org.Chem., 1976, 41, 3067.
8. Heine, H.G., Liebigs Ann. Chem., 1970, 735, 56.
9. Organic Synthesis, vol. 12. John Willey & Sons. New York, 1932, p. 62.
10. Abele, E., Goldberg, Yu., Popelis, J., Shymanska, M., Zh. Org. Khim., 1990, 26, 1784.

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