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Facile Synthesis of 2-Alkoxy-2-aryloxiranes

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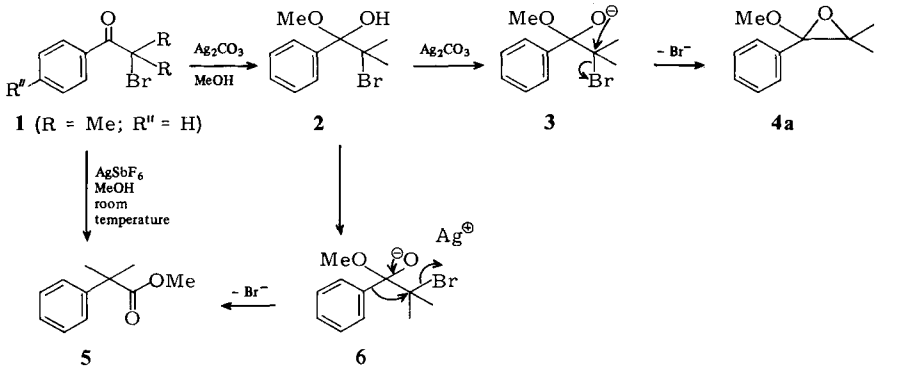
Tertiary α-bromoalkyl aryl ketones **1** were converted into 2-alkoxy-2-aryloxiranes **4** exclusively by reaction with excess potassium carbonate in the corresponding dry alcohol. Silver carbonate in a dry alcohol with these α-bromo ketones yielded competitively formation of 2-alkoxyoxiranes and semi-benzilic *Favorskii* rearrangement (→**5**), while silver hexafluoroantimonate in the same medium afforded the latter rearrangement reaction exclusively.

Eine einfache Darstellung von 2-Alkoxy-2-aryloxiranen

Tertiäre (α-Bromalkyl)arylketone **1** reagierten mit überschüssigem Kaliumcarbonat in trockenem Alkohol ausschließlich zu den entsprechenden 2-Alkoxy-2-aryloxiranen **4**. Silbercarbonat in trockenem Alkohol führte in einer Konkurrenzreaktion zur Bildung von **4** und zu einer semibenzilischen *Favorskii*-Umlagerung (→**5**). Dagegen trat mit Silber-hexafluoroantimonat ausschließlich die letztere Umlagerungsreaktion ein.

In the course of our recent investigations in the field of α-acylcarbenium ions[2] and α-imidoylcarbenium ions[3], we came across the reaction of 2-bromoisobutyrophenone **1** (R = CH_3; R″ = H) with silver carbonate in dry methanol at room temperature, leading to two competitive reactions, namely semi-benzilic *Favorskii* rearrangement (63%) and 2-methoxy-2-phenyloxirane formation (33%). The *Favorskii*-type rearrangement gave rise to methyl 2-methyl-2-phenylpropionate (**5**) according to a mechanism by which the methanol adduct **2** undergoes a silver-assisted ionization of the carbon-halogen bond with migration of the phenyl group. Whether or not α-acylcarbenium



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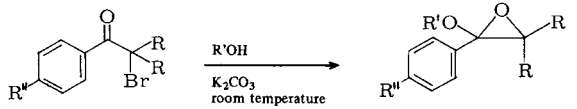
ions are involved in such reactions is still a point of discussion[4]. Not only the silver ion-promoted reaction took place but hemi-acetal **2** was also deprotonated by the base (silver carbonate) to afford anion **3**, which yielded intramolecular nucleophilic substitution with formation of 2-methoxyoxirane **4a**. The reasoning behind this dual reactivity, as outlined in the scheme, implicates that a less basic silver reagent, e.g. silver hexafluoroantimonate, would give rise to the *Favorskii*-type rearrangement, exclusively, and that the semi-benzilic rearrangement could be eliminated by using a basic non-silver reagent, bearing in mind that the reagent should be compatible with the rather labile nature of the final 2-alkoxyoxiranes **4** thus formed.

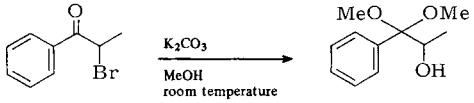
In fact, 2-bromoisobutyrophenone **1** (R = CH_3, R'' = H) reacted with silver hexafluoroantimonate in methanol at room temperature to afford methyl 2-methyl-2-phenylpropionate (**5**), exclusively, a result which is in complete accordance with an analogous experiment with 1-bromocyclohexyl phenyl ketone which afforded methyl 1-phenylcyclohexanecarboxylate[4]. Similar conversions of 2-bromoisobutyrophenone-type compounds to the carboxylic acids with silver nitrate have been described previously[5,6].

The second idea in our hypothesis, put forward above, proved to open a successful route to 2-alkoxy-2-aryloxiranes **4**. The reaction was performed in a dry alcohol (methanol, ethanol) in the presence of a five molar excess of dry potassium carbonate (room temperature; 1 – 5 hours). Non-aqueous work-up provides 2-alkoxy-2-aryloxiranes as colorless liquids as the sole products (80 – 92%). Results of this synthesis of α-functionalized epoxides, together with their ^1H NMR data are presented in Table 1, while the ^{13}C NMR data of compounds **4** are compiled in Table 2.



1 **4**

The reaction described in this paper is limited to tertiary α-bromo ketones **1**. Secondary α-bromo ketones, e.g. 2-bromopropiophenone (**7**), afforded α-hydroxyacetal **8**, exclusively, on reaction with potassium carbonate in methanol at room temperature (2 hours). This reaction product resulted from ring-opening of the intermediate α-methoxyepoxide in the methanolic medium. The same reaction with phenacyl bromide **1** (R = R'' = H) only produced tars.



7 **8**

The reaction of α-bromo ketones **1** to afford 2-alkoxy-2-aryloxiranes **4** is a simple high-yield alternative to previously published syntheses, which employed equimolecular amounts of sodium methoxide in alcoholic[7-10,20] or ethereal[11-16] medium. By appropriate choice of the reagents, α-bromoalkyl aryl ketones **1** can be converted into either

2-alkoxy-2-aryloxiranes **4** or rearranged esters, e.g. **5**, or into a mixture of both compounds **4** and **5**. The title compounds have been previously shown to be versatile synthons for a variety of heterocyclic compounds, among others 2-oxazolines[17], 2-oxazolidinones[18,19,23], and 1,3-dioxolanes[21], while their aminolysis is a convenient route to otherwise difficultly accessible α-(*N*-alkyl)aminoketones[10,20,22,24].

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Experimental Part

Infrared spectra: Perkin Elmer model 1310 spectrophotometer. – ^{1}H NMR spectra: Varian T-60 NMR spectrometer. – ^{13}C NMR spectra: Varian FT-80 NMR spectrometer.

α-Bromoalkyl aryl ketones **1** were prepared by a standard bromination procedure, involving reaction of the parent ketone with 1.05 molar equivalents of bromine in dichloromethane (ambient temperature), after which (≈15 min) the reaction mixture was poured into water, extracted with dichloromethane, the combined organic phases being washed with aqueous sodium hydrogensulfite and brine; after drying ($MgSO_4$) and filtration, the solvent was removed in vacuo and the remaining oil was distilled in vacuo to afford α-bromo ketones **1** as oils.

Physical data and yields: 2-bromo-2-methylpropiophenone: b.p. 85–89°C/0.3 torr (94%); 2-bromo-4'-chloro-2-methylpropiophenone: b.p. 78–84°C/0.01 torr (92%); 2-bromo-4'-fluoro-2-methylpropiophenone: b.p. 70–72°C/0.01 torr (89%); 2-bromo-2-ethylbutyrophenone: b.p. 90–100°C/0.01 torr (86%).

2-Alkoxy-2-aryloxiranes **4**: A solution of 0.05 mol of α-bromo ketone **1** in 20 ml of dry alcohol (methanol or ethanol) was stirred at ambient temperature with 0.25 mol of dry potassium carbonate. After being stirred for the time indicated in Table 1 (1–5 h) the reaction mixture was stirred with 50 ml of dry diethyl ether and filtered, the solid being washed with dry ether. The combined filtrates were evaporated under vacuo to leave a slurry which was again treated as above, i.e. trituration with ether (50 ml), filtration, and evaporation. This procedure is repeated another time, if necessary, in order to obtain a clear oil (colorless in most cases). The remaining oil (shown to be pure 2-alkoxy-2-aryloxirane **4** by ^{1}H NMR) was distilled in vacuo to afford compounds **4**. Yields and physical data are given in Table 1 while ^{13}C NMR data are compiled in Table 2. The infrared spectra of **4** (NaCl; liquid film) did not show characteristic absorptions.

Reaction of 2-bromoisobutyrophenone with silver carbonate in methanol: A solution of 2.27 g (0.01 mol) of 2-bromoisobutyrophenone (**1**, R = CH_3; R″ = H) in 20 ml of dry methanol was treated with 2.76 g (0.01 mol) of silver carbonate. The suspension was stirred for 18 h at ambient temperature and subsequently treated with 50 ml of dichloromethane, filtered and the precipitate washed with dichloromethane. The combined filtrates were evaporated to afford a clear oil which was analyzed by gas chromatography (SE 30 column) and spectrometric methods. The reaction mixture was shown to consist of 63% of *methyl 2-methyl-2-phenylpropionate* (**5**) and 33% of *2-methoxy-3,3-dimethyl-2-phenyloxirane* (**4a**).

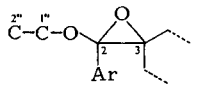
Reaction of 2-bromoisobutyrophenone with silver hexafluoroantimonate in methanol: A solution of 0.22 g (1.00 mmol) of 2-bromoisobutyrophenone (**1**, R = CH_3; R″ = H) in 3 ml of dry methanol was stirred with 0.51 g (1.5 mmol) of silver hexafluoroantimonate at room temperature for 2 h. The suspension was poured into water and extracted with ether. The combined ether extracts were dried ($MgSO_4$) and evaporated to leave 90% of *methyl 2-methyl-2-phenylpropionate* (**5**) as a colorless liquid.

Table 1. Physical and spectrometric data of 2-alkoxy-2-aryloxiranes **4**

	R	OR′	R″	Reaction Time	Yield (%)	b.p. °C/torr	^{1}H NMR (δ)[a]
4a	Me	OMe	H	2 h RT	86	22–23/0.01[b]	δ($CDCl_3$): 1.00 (3H, s, *trans* CH_3); 1.53 (3H, s, *cis* CH_3); 3.20 (3H, s, OCH_3); 7.2–7.5 (5H, m, C_6H_5)
4b	Me	OMe	Cl	2 h RT	88	37–38/0.01	δ(CCl_4): 0.96 (3H, s, *trans* CH_3); 1.46 (3H, s, *cis* CH_3); 3.14 (3H, s, OCH_3); 7.33 (4H, s, C_6H_4)
4c	Me	OMe	F	1 h RT	92[c]	–	δ(CCl_4): 0.95 (3H, s, *trans* CH_3); 1.46 (3H, s, *cis* CH_3); 3.15 (3H, s, OCH_3); 6.9–7.6 (4H, m, C_6H_4)
4d	Me	OEt	H	4 h RT	83[d]	28–29/0.01	δ(CCl_4): 0.93 (3H, s, *trans* CH_3); 1.48 (3H, s, *cis* CH_3); 1.10 (3H, t, J = 7 Hz, O–C–CH_3); 3.1–3.7 (2H, m, OCH_2); 7.2–7.6 (5H, m, C_6H_5)
4e	Me	OEt	Cl	2.5 h RT	89	54–56/0.01	δ(CCl_4): 0.94 (3H, s, *trans* CH_3); 1.47 (3H, s, *cis* CH_3); 3.1–3.7 (2H, m, OCH_2); 1.12 (3H, t, J = 7 Hz, O–C–CH_3); 7.37 (4H, s, C_6H_4)
4f	Me	OEt	F	5 h RT	86	30–31/0.01	δ(CCl_4): 0.92 (3H, s, *trans* CH_3); 1.45 (3H, s, *cis* CH_3); 1.10 (3H, t, J = 7 Hz, O–C–CH_3); 3.1–3.7 (2H, m, OCH_2); 6.8–7.6 (4H, m, C_6H_4)
4g	Et	OMe	H	1 h RT	80	43–47/0.01[e]	δ(CCl_4): 0.75 (3H, t, *trans* CH_3); 0.9–1.5 (5H, m, overlap, *cis* CH_3 + *trans* CH_2); 1.6–2.1 (2H, m, *cis* CH_2); 7.1–7.5 (5H, m, C_6H_5); 3.10 (3H, s, OCH_3)

[a] The terms *cis* and *trans* in this column denote positions *cis* and *trans* with respect to the alkoxy substituent. – [b] Lit.[14] b.p. 85–85.5 °C/9.5 torr; Lit.[20] b.p. 55–60 °C/0.5 torr. – [c] Crude yield (without distillation); purity >95%. – [d] Lit.[22] b.p. 73–74 °C/1 torr. – [e] Lit.[16] b.p. 81–82 °C/2.7 torr.

Table 2. ^{13}C NMR data of 2-alkoxy-2-aryloxiranes **4**[a]



	C-2	C-3	O–C-1''	O–C-2''	R	Aromatic Carbons C-1'	C-2'	C-3'	C-4'
4a	91.33	66.92	52.37	–	20.05 19.82	134.97	128.07[b]	128.12[b]	128.41
4b	90.85	67.17	52.40	–	19.95 19.77	134.51[c]	128.44[b]	129.50[b]	133.60[c]
4c	91.02	67.17	52.30	–	19.99 19.83	131.08 (d) (J = 3.24 Hz)	130.02 (d) (J = 8.26 Hz)	115.23 (d) (J = 21.66 Hz)	163.59 (d) (J = 247.25 Hz)
4d	90.86	66.49	60.92	15.30	20.02 19.89	135.66	127.95[b]	128.04[b]	128.26
4e	90.39	66.69	61.00	15.29	19.91 19.84	134.37	128.41[b]	129.41[b]	–[d]
4f	90.52	66.69	60.93	15.31	19.95 19.88	131.70 (d) (J = 3.21 Hz)	129.82 (d) (J = 8.27 Hz)	115.10 (d) (J = 21.71 Hz)	162.94 (d) (J = 247.00 Hz)
4g	91.92	73.43	52.20	–	9.29 (CH_3) 8.61 (CH_3) 22.57 (CH_2) 22.78 (CH_2)	135.36	128.09	128.09	128.35

[a] Noise decoupled spectra ($CDCl_3$); appropriate multiplicities (not indicated) were observed under SFORD conditions. – [b] Chemical shifts for the *ortho* and *meta* carbons may be inverted. – [c] Or vice versa. – [d] Invisible (presumably overlap with signal at 134.37).

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