ISSN 1070-4280, Russian Journal of Organic Chemistry, 2008, Vol. 44, No. 12, pp. 1776–1779. © Pleiades Publishing, Ltd., 2008.
Original Russian Text © A.A. Afon'kin, M.L. Kostrikin, A.E. Shumeiko, A.F. Popov, 2008, published in Zhurnal Organicheskoi Khimii, 2008, Vol. 44, No. 12, pp. 1802–1806.

Synthesis of Some Electron-Rich Aryl(hetaryl)oxiranes under Phase-Transfer and Homogeneous Conditions

A. A. Afon'kin, M. L. Kostrikin, A. E. Shumeiko, and A. F. Popov

Litvinenko Institute of Physical Organic and Coal Chemistry, National Academy of Sciences of Ukraine, ul. R. Luksemburg 70, Donetsk, 83114 Ukraine
e-mail: AAAfonkin@newmail.ru

Received December 31, 2007

Abstract—Reactions of mono-, di-, and trimethoxybenzaldehydes with trimethylsulfonium methyl sulfate readily occur under mild homogeneous and heterogeneous phase-transfer conditions to give the corresponding aryloxiranes whose yields are comparable with those typical of severe Corey–Chaykovsky reaction conditions. The phase-transfer version ensures better purity of the epoxy derivatives and is the only possible way of preparing 1-methyl-3-(oxiran-2-yl)-1*H*-indole.

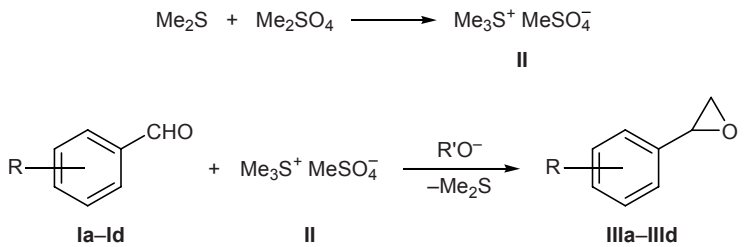
DOI: 10.1134/S1070428008120099

Aryl- and hetaryloxiranes having electron-donating substituents in the aromatic ring are widely used in the synthesis of biologically active compounds. In particular, products of their regioselective aminolysis are structurally related to catecholamine neuromediators, and they act as α(β)-adrenergic blockers (Labetalol, Tibalosine, Butoxamine) and α(β)-adrenergic stimulators (Norphenylephrine, Izadrin, Midodrine, Mezaton, Methoxamine, etc. [1]. In addition, such β-hydroxyphenethylamines are key starting materials in the synthesis of alkaloid-like isoquinoline compounds [2], including completely aromatic ones, and some psychotropic benzoazepines [3].

Methoxy-substituted phenyloxiranes are typical representatives of the above series of compounds; they can be obtained by dehydrohalogenation of the corresponding vicinal arylhalohydrins, oxidation of fairly rare substituted styrenes with peroxy acids, or addition of a methylene fragment to the carbonyl group of more accessible benzaldehydes according to Corey–Chaykovsky [4]. In the latter reaction, the source of methylene unit may be sulfur ylides (selenium and arsenic ylides are used more seldom [5]) which are generated from trialkylsulfonium (sulfoxonium) salts by the action of strong bases (NaH [6], *t*-BuOK, BuLi [5], $MeSOCH_2^-\cdot Na^+$ [4]) in anhydrous solvents (DMSO, THF). On the other hand, it is known that carbonyl compounds can be converted into oxirane derivatives under milder conditions, under which sulfur methylides are generated using alkoxide ions in acetonitrile [7] or hydroxide ions in two-phase liquid–liquid systems [8]. However, published data on such syntheses are very scanty, and they do not allow us to predict the results for alkoxy-substituted benzaldehydes whose conversion into epoxy derivatives in the classical version of the Corey–Chaykovsky reaction is lower [6].

The goal of the present work was to develop a mild and readily scalable procedure for the transformation

Scheme 1.



I, **III**, R = 4-MeO (**a**), 2,5-$(MeO)_2$ (**b**), 3,4-$(MeO)_2$ (**c**), 3,4,5-$(MeO)_3$ (**d**); R′ = Me, H.

of electron-rich carbonyl compounds **I** into the corresponding phenyloxiranes **III**. As source of methylene unit we used trimethylsulfonium methyl sulfate (**II**) which, unlike its sulfoxonium analog, is characterized by higher reactivity [4, 8] and selectivity [3, 4] toward carbonyl compounds.

The reactions were carried out (1) under homogeneous conditions in anhydrous acetonitrile in the presence of sodium methoxide as base and trimethylsulfonium methyl sulfate (**II**) generated *in situ* by treatment of dimethyl sulfide with dimethyl sulfate and (2) in heterogeneous two-phase system 50% aqueous sodium hydroxide–methylene chloride (1 : 1, by volume) using benzyl(dimethyl)(phenyl)ammonium chloride or tetrabutylammonium bromide as phase-transfer catalyst and preliminarily prepared trimethylsulfonium methyl sulfate (**II**).

In both cases, the conversions of methoxybenzaldehydes into the corresponding epoxy derivatives were similar (~75%, see table) and comparable with those attained in the classical version of the Corey–Chaykovsky reaction. Increase in the number of methoxy groups in the aromatic ring of initial benzaldehyde was not accompanied by reduction of the yield of aryloxiranes, in contrast to the reactions carried out under severe conditions as described in [6].

In the homogeneous system, more than 1.5-fold excess of trimethylsulfonium salt **II** with respect to carbonyl substrate **I** was necessary to effect deprotonation. As a result, final products **III** purified by fractional distillation contained ~3–5% of sulfonium salt **II** which was difficult to separate. The yield of aryloxiranes **III** depended on the state of the base: the use of solid sodium methoxide ensured higher yield (by 10–12%) as compared to a solution of sodium methoxide in excess methanol with the same concentration.

The heterogeneous phase-transfer reaction required 1.2 equiv of trimethylsulfonium methyl sulfate (**II**) to attain the same conversion of the initial carbonyl compound, and the isolated oxirane contained no impurity of sulfonium salt **II**. The lipophilicity and concentration of phase-transfer catalyst were not crucial factors, for reagent **II** itself is capable of being extracted into the organic phase [8, 9] and hence acting as carrier of methylene fragment generated at the phase boundary. Moreover, it is known [8] that more hydrophilic quaternary ammonium or tertiary sulfonium salts having short-chain alkyl (phenyl, benzyl) groups are extracted more readily into concentrated alkali solution as compared to lipophilic analogs; therefore, such salts are preferred as phase-transfer catalysts in processes like the examined one.

Corey–Chaykovsky reactions of aldehydes **Ia**–**Id** and **IV** with trimethylsulfonium salts under homogeneous and phase-transfer conditions

Initial aldehyde no.	Yield of the corresponding oxirane,[a] %		
	DMSO–NaH	MeCN–MeONa	CH_2Cl_2–50% aq. NaOH
Benzaldehyde	75 [4]	83 [7]	92 [8]
Ia	75 [6]	87 [7], 56[b], 68[c]	75
Ib	60 [6]	72	76
Ic	–	–	77
Id	–	–	75
IV	–	–	~50

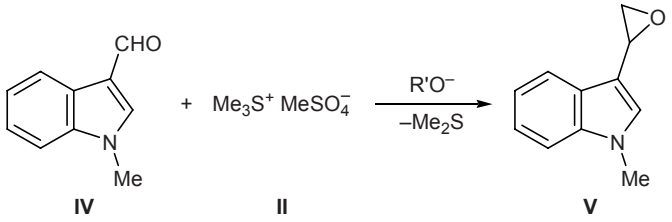
[a] Yields of the isolated products are given except for compound **V**.
[b] A solution of sodium methoxide in methanol was used.
[e] Solid sodium methoxide was used.

The anionic part of sulfonium salt **II** could affect to a considerable extent the transformation of aldehydes into epoxy compounds under heterogeneous conditions. As shown in [9], phase-transfer epoxidation of β-ionone with sulfonium fluorides is accompanied by strong exothermic effect, the reaction in the presence of iodides is characterized by poor yields, and the best results were obtained using the corresponding chlorides.* Therefore, phase-transfer catalyst must be selected with account taken of possible anion exchange between the ammonium and sulfonium cations of the catalyst and reagent, respectively; otherwise, the reagent could be converted into a weakly reactive form. The optimal version is that where the anions in both salts are characterized by comparable hydrophilicities (e.g., chlorides, bromides, or methyl sulfates [8]) and ensure sufficiently high rate of epoxidation under phase-transfer conditions.

Of particular interest was the transformation of indole-3-carbaldehyde **IV** into 3-oxiranylindole **V**. The latter compound is a promising starting material for the preparation of hydroxy gramines, hydroxy tryptamines, hydroxy tryptophols, etc. Though the reactions with sulfonium salt **II** under homogeneous conditions in the presence of solid sodium methoxide successfully afforded methoxy-substituted phenyloxiranes, epoxida-

* Epoxidation of unsubstituted benzaldehyde is less sensitive to the counterion of sulfonium salt and is successful both with sulfonium iodides and ammonium iodides as phase-transfer catalyst [8].

Scheme 2.



R = Me, H.

tion of compound **IV** under analogous conditions resulted in strong tarring.

Unlike various benzofuran- and benzothiophenecarbaldehydes, which gave rise to 60–88% of the corresponding epoxy derivatives in the heterogeneous Corey–Chaykovsky reaction [3], the yield of epoxy compound **V** from indolecarbaldehyde **IV** did not exceed 50% (Scheme 2). We failed to improve the yield of **V** by prolonging the reaction time, increasing the amount of catalyst [$Me_2(PhCH_2)PhN^+$ Cl^-] by a factor of 3, reducinng the temperature to 25°C, increasing the amount of reagent **II** to 1.9 equiv, using more lipophilic phase-transfer catalyst (Bu_4N^+ Br^-), or adding sulfonium salt **II** to the two-phase system in portions. According to the TLC data, the yield of 1-methyl-3-(oxiran-2-yl)-1*H*-indole (**V**) reached its maximal value in 25 h and then insignificantly decreased. Here, the amount of epoxy derivative **V** was comparable with that of unreacted indolecarbaldehyde **IV**; insofar as the boiling points of **IV** and **V** are similar, isolation of the latter by distillation is strongly difficult, and preparative chromatography is necessary.

On the whole, the heterogeneous version of the Corey–Chaykovsky reaction seems to be preferred, for it ensures preparation of the target products with higher purity under as mild conditions as in the homogeneous version and is readily scalable (up to 1 mol of the initial aldehyde may be involved).

EXPERIMENTAL

The ^1H NMR spectra were recorded on a Varian Gemini-200 spectrometer (200 MHz) from solutions in chloroform-*d* using tetramethylsilane as internal reference. The melting points were determined on a Boetius melting point apparatus. Analytical thin-layer chromatography was performed on Silufol plates (Chemapol, Czechia) using chloroform–methanol (99.5 : 0.5) as eluent. Spots were visualized by heating the chromatograms at 100–120°C for 1–2 min.

Commercial 4-methoxybenzaldehyde (**Ia**) and 2,5-dimethoxybenzaldehyde (**Ib**) (from Merck) were purified by vacuum distillation. 3,4-Dimethoxybenzaldehyde (**Ic**) was synthesized by methylation of vanillin with dimethyl sulfate according to the procedure described in [10], mp 42–43°C; published data [10]: mp 42.5–43.5°C. 3,4,5-Trimethoxybenzaldehyde (**Id**) was prepared by bromination of vanillin, followed by methanolysis [11] and methylation with dimethyl sulfate [10], mp 74–75°C; published data [11]: mp 74–76°C. 1-Methyl-1*H*-indole-3-carbaldehyde (**IV**) was synthesized by formylation of indole [12] and subsequent methylation of 1*H*-indole-3-carbaldehyde with dimethyl sulfate [13], mp 69–70°C [13].

Trimethylsulfonium methyl sulfate (II). Freshly distilled dimethyl sulfate, 130.6 g (1.03 mol), was added under stirring to a solution of 62 g (1 mol) of dimethyl sulfide (Acros) in 75 ml of anhydrous acetonitrile on cooling with an ice bath during the first hour. The mixture was left overnight, and the solvent was distilled off on a rotary evaporator. The solid residue was washed with anhydrous diethyl ether (3 × 150 ml), and the residual diethyl ether was removed by distillation on a rotary evaporator under reduced pressure (5–7 mm). The solid product (yield quantitative) was additionally dried in a vacuum desiccator over P_2O_5. Its physical constants were consistent with those reported in [14].

General procedure for the synthesis of compounds III and V under homogeneous conditions. Finely cut metallic sodium, 0.335 mol, was dissolved under stirring in 100 ml of anhydrous methanol. The solution was evaporated to dryness (in some cases, 50–60 ml of methanol was distilled off on a rotary evaporator, and the remaining sodium methoxide solution in excess methanol was used to generate sulfonium ylide). A mixture of 0.33 mol of dimethyl sulfide and 0.32 mol of dimethyl sulfate in 120 ml of anhydrous acetonitrile (preliminarily kept overnight) was added under stirring to the solid sodium methoxide residue

(epoxidation of compound **IV** under homogeneous and heterogeneous conditions was performed under argon). A solution of 0.18 mol of aldehyde **Ia**–**Id** or **IV** in 70 ml of anhydrous acetonitrile was added dropwise over a period of 30 min, and the mixture was stirred for 2 h. When the reaction was complete, the solvent was distilled off, the residue was dissolved in 100 ml of water, the solution was extracted with methylene chloride (3 × 100 ml), the combined extracts were washed with water and dried over potassium carbonate, the solvent was distilled off, and the viscous residue was subjected to fractional distillation under reduced pressure.

General procedure for the synthesis of compounds III and V under heterogeneous conditions. A mixture of 100 ml of methylene chloride, 100 ml of 50% aqueous sodium hydroxide, 0.18 mol of aldehyde **Ia**–**Id** or **IV**, 0.21 mol of trimethylsulfonium methyl sulfate (**II**), and 1 mmol of phase-transfer catalyst was stirred for 22–25 h at 50°C. When the reaction was complete, the organic phase was separated, and the aqueous phase was extracted with 100 ml of methylene chloride. The extract was combined with the organic phase, washed with water (2 × 200 ml), and dried over potassium carbonate, the solvent was distilled off, and the residue was subjected to fractional distillation under reduced pressure.

In the synthesis of compound **V**, the dry extract was applied to a column charged with basic Al_2O_3 (silica gel promoted decomposition of the product). The tar-containing fraction was discarded, the fraction containing compound **V** and unreacted aldehyde **IV** was evaporated, the residue was dissolved in 50 ml of methanol, and the solution was added dropwise under stirring to 100 ml of a saturated aqueous solution of sodium bisulfite. The mixture was stirred for 5–6 h, diluted with 100 ml of water, and extracted with methylene chloride (2 × 100 ml). The combined extracts were dried and evaporated, and fractional distillation of the residue under reduced pressure gave compound **V** with a satisfactory purity.

2-(4-Methoxyphenyl)oxirane (IIIa). bp 117–119°C (7–8 mm); the boiling point given in [6], bp 120°C (0.25 mm), is invalid. ^{1}H NMR spectrum, δ, ppm: 2.80 m (1H, CH_2), 3.10 m (1H, CH_2), 3.80 s (3H, OCH_3), 3.82 m (1H, CH), 6.85 d (2H, H_{arom}), 7.20 d (2H, H_{arom}).

2-(2,5-Dimethoxyphenyl)oxirane (IIIb). bp 140–143°C (8–9 mm); the boiling point given in [6], bp 175°C (0.25 mm), is invalid. ^{1}H NMR spectrum, δ, ppm: 2.65 m (1H, CH_2), 3.15 m (1H, CH_2), 3.75 s (3H, OCH_3), 3.85 s (3H, OCH_3), 4.20 m (1H, CH), 6.75 d (1H, H_{arom}), 6.80 d (1H, H_{arom}), 6.83 s (1H, H_{arom}).

2-(3,4-Dimethoxyphenyl)oxirane (IIIc). bp 142–143°C (6–7 mm), mp 37–38°C. ^{1}H NMR spectrum, δ, ppm: 2.80 m (1H, CH_2), 3.15 m (1H, CH_2), 3.85 m (1H, CH), 3.90 s (3H, OCH_3), 6.75 s (1H, H_{arom}), 6.85 m (2H, H_{arom}).

2-(3,4,5-Trimethoxyphenyl)oxirane (IIId). bp 127–129°C (4–5 mm), mp 54–55°C. ^{1}H NMR spectrum, δ, ppm: 2.75 m (1H, CH_2), 3.10 m (1H, CH_2), 3.80 m (1H, CH), 3.82 s (3H, 4-OCH_3), 3.88 s (6H, 3-OCH_3, 5-OCH_3), 6.52 s (2H, H_{arom}).

1-Methyl-3-(oxiran-2-yl)-1*H*-indole (V). bp 186–189°C (3–4 mm). ^{1}H NMR spectrum, δ, ppm: 2.55 m (1H, CH_2), 2.75 m (1H, CH_2), 3.20 m (1H, CH), 3.70 s (3H, CH_3), 6.90 s (1H, 2-H), 7.20–7.40 m (4H, 4-H, 5-H, 6-H, 7-H).

REFERENCES

1. Avakyan, O.M., *Farmakologicheskaya regulyatsiya funktsii adrenoretseptorov* (Pharmacological Regulation of Adrenoreceptors), Moscow: Meditsina, 1988.
2. Von Kleemann, A. and Engel, J., *Pharmazeutische Wirkstoffe. Synthesen. Patente. Anwendungen*, Stuttgart: Georg Thieme, 1982, 2nd. ed.
3. Bermand, C., Comel, A., and Kirsch, G., *Arkivoc*, 2000, part (i), p. 128.
4. Corey, E.J. and Chaykovsky, M., *J. Am. Chem. Soc*., 1965, vol. 87, p. 1353.
5. Rao, A.S., Paknikar, S.K., and Kirtane, J.G., *Tetrahedron*, 1983, vol. 39, p. 2323.
6. Guy, A., Doussot, J., Ferroud, C., Garreau, R., and Godefroy-Falgueres, A., *Synthesis*, 1992, p. 821.
7. Kutsuma, T., Nagayama, I., Okazaki, T., Sakamoto, T., and Akaboshi, S., *Heterocycles*, 1977, vol. 8, p. 397.
8. Dehmlow, E.V. and Dehmlow, S.S., *Phase-Transfer Catalysis*, Weinheim: Chemie, 1983, 2nd ed.
9. Rosenberger, M., Jackson, W., and Saucy, G., *Helv. Chim. Acta*, 1980, vol. 63, p. 1665.
10. *Organic Syntheses*, Blatt, A.H., Ed., New York: Wiley, 1943, collect. vol. 2, p. 619.
11. Rao, D.V. and Stuber, F.A., *Synthesis*, 1983, p. 308.
12. *Organic Syntheses*, Rabjohn, N., Ed., New York: Wiley, 1963, collect. vol. 4, p. 539.
13. Zhungietu, G.I., Budylin, V.A., and Kost, A.N., *Preparativnaya khimiya indola* (Preparative Chemistry of Indole), Kishinev: Shtinitsa, 1975, p. 83.
14. Colichman, E.L. and Love, D.L., *J. Org. Chem*., 1953, vol. 18, p. 40.