Reactions of Organic Anions. LXVII[1]. Catalytic Synthesis of Cyclopropane Derivatives in Aqueous Medium

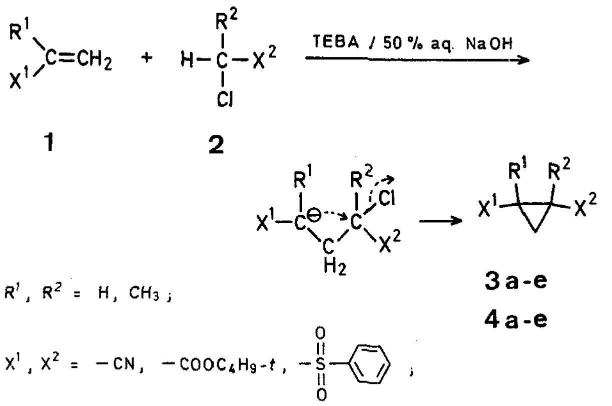
Andrzej Jończyk, Mieczysław Mąkosza*

Institute of Organic Chemistry and Technology, Technical University (Politechnika), 00-662 Warsaw, Koszykowa 75, Poland

Among the numerous routes employed for the synthesis of a substituted cyclopropane ring, the most versatile method seems to be a condensation of electrophilic alkenes with α-halocarbanions[2,3]. Many electrophilic alkenes (e.g. acrylonitrile, ethyl acrylate etc.) and α-haloesters, ketones, and nitriles are reported to enter this condensation. Usually the reaction was carried out in the presence of sodium hydride, sodium ethoxide, or potassium *t*-butoxide under strictly anhydrous conditions[2,3]. Some copper(I)-isonitrile complexes have been also used as catalysts for this reactions[4]. Although yields of cyclopropane derivatives were reported to be only moderate to good, the availability and simplicity of the starting materials makes this route practically attractive.

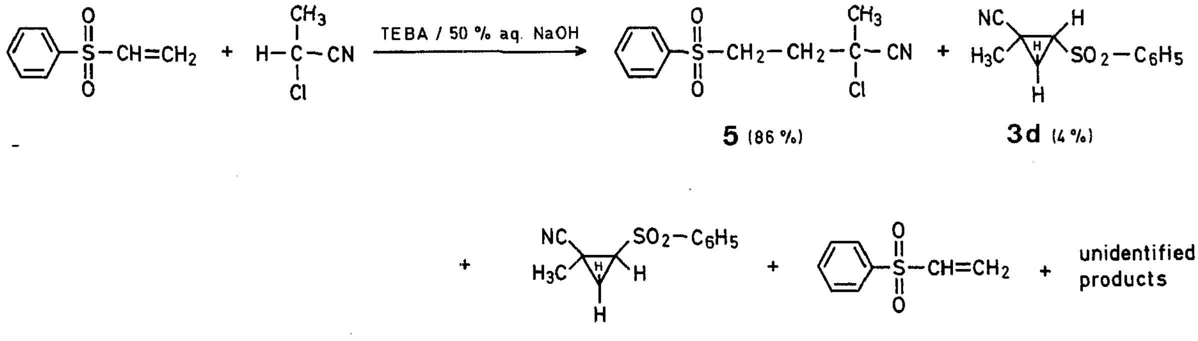
It was recently found that many reactions of carbanions and halocarbenes can be successfully performed in two-phase systems using as base concentrated aqueous sodium hydroxide solution in the presence of a catalytic amount of some tetraalkylammonium halides[5,6,7]. The system was also used for the generation of carbanions from α-halonitriles[8], α-haloesters[9], or halomethyl sulfones[10] and their reaction with carbonyl compounds (Darzens type condensation). Merz and Märkl[11] have applied these conditions in synthesis of some cyclopropylphenyl ketones via sulfoxonium ylids.

Now we would like to report that 50% aqueous sodium hydroxide solution with catalytic quantities of benzyltriethylammonium chloride (TEBA) is very convenient for the synthesis of substituted cyclopropane derivatives via addition of α-halocarbanions to electrophilic alkenes.



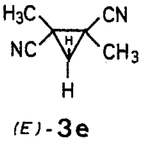
The reaction is carried out by simply stirring the starting materials and the catalyst with aqueous sodium hydroxide solution for about 1 h. The expected cyclopropane derivatives are formed in good yield (Table).

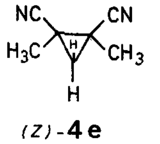
Michael type adducts of α-halocarbanions with electrophilic olefins cannot be isolated because cyclization of the intermediate carbanions is usually very fast. However, phenyl vinyl sulfone and α-chloropropionitrile react with the formation of 3-cyano-3-chlorobutyl phenyl sulfone (**5**) as the main product (yield 81%):



The chlorosulfone **5** was then cyclized under more drastic conditions to give both isomers of the cyclopropane. In this particular case, the reaction is probably difficult due to the low acidity of the sulfone **5**.

In all cases, both geometrical isomers **3** and **4** were formed (Table). They were separated by a fractional distillation, recrystallization, or a combination of these methods. Identification of the pure isomers was based on their ^{1}H-N.M.R. spectra. Thus, in the spectrum of isomer **3e** (m.p. 44–46°) only two singlets were present ($\delta = 1.38$ ppm and $\delta = 1.65$ ppm) in a 1:3 ratio. This is obviously the (*E*)-isomer (both methyl groups and cyclopropane ring protons are in equal surrounding). The ^{1}H-N.M.R. spectrum of the second isomer **4e** (m.p. 99–100°) consists of a singlet at $\delta = 1.48$ ppm and two doublets centered at $\delta = 1.07$ ppm ($J = 6$ Hz) and $\delta = 1.87$ ppm ($J = 6$ Hz) in a 6:1:1 ratio. The doublet at lower field is due to the ring proton located on the same side of a cyclopropane ring as the cyano groups, whereas that at higher field to the ring proton on the opposite side. Thus, this is obviously the (*Z*)-isomer.

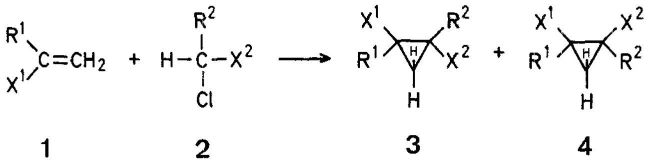

(*E*)-**3e**


(*Z*)-**4e**

These conclusions are also supported by the value of chemical shifts for the protons of the methyl groups. Those in **3e**, being on the same side of the ring as the cyano group, absorb at lower field (*E* configuration) than the protons of the methyl groups in the (*Z*)-isomer **4e**. Similar considerations allowed us to ascribe the (*Z*)- and (*E*)-structures to the other cyclopropane derivatives. They also agree well with the literature data[12,13].

The reported procedure seems to be the simplest one leading to substituted cyclopropane derivatives. Results of a detailed stereochemical and synthetic study will be published elsewhere.

Table. Preparation of Cyclopropanes



	R^1	R^2	X^1	X^2	Configuration	Total yield (%)	Ratio (*E*): (*Z*)[a]	b.p./torr of mixture	Method of separation	b.p./torr or m.p.[b]	Crystallization solvent
3a **4a**	H	H	CN	$COOC_4H_9$-*t*	*E* *Z*	45	71:29	104–140°/10	distillation crystallization	106°/9; 54–56° 68–70°	aqueous CH_3OH hexane
3b **4b**	H	CH_3	CN	CN	*E* *Z*	75	54:46	109–160°/12	frac. dist. frac. dist.	111–112°/14 152–154°/13	– –
3c **4c**	H	CH_3	$COOC_4H_9$-*t*	CN	*E* *Z*	67	76:24	110–130°/16	frac. dist. crystallization	108–109°/15 63–65°	– hexane
3d **4d**	H	CH_3	$SO_2C_6H_5$	CN	*E* *Z*	7[c]	68:32	–	frac. cryst.[d] crystallization[d]	77–79° 146–148°	hexane CH_3OH
3e **4e**	CH_3	CH_3	CN	CN	*E* *Z*	75	55:45	105–165°/16	distillation crystallization	90–91°/10; 44–46°[e] 99–100°	hexane CCl_4

[a] Determined by G.L.C. on distilled (except for compounds **3d** and **4d**) reaction mixtures.

[b] Satisfactory elemental analysis were obtained for new compounds (C ±0.30%, H ±0.20%).

[c] 3-Cyano-3-chlorobutyl phenyl sulfone (yield 81%) was the main component of this mixture.

[d] Separated from the mixture after cyclization of 3-cyano-3-chlorobutyl phenyl sulfone (**5**).

[e] Lit.[14] m.p. 46–48°; author did not ascribe a steric structure for this compound.

G.L.C. analyses were performed on a Chrom 4 instrument, 1.20 m column, 8% silicone oil XE-60 on Kieselguhr silanized with trimethylchlorosilane. ^{1}H-N.M.R. spectra were measured at 100 MHz on a Jeol JNM-MH-100 spectrometer with TMS as internal standard. Fractional distillations were done on an "Abegg" spinning band column (Büchi).

Condensation of Vinyl Cyanides and *t*-Butyl Acrylate (1) with α-Chloronitriles and α-Chloroester (2); General Procedure:
To stirred mixture 50% aqueous sodium hydroxide (20 ml) and benzyltriethylammonium chloride (0.4 g), a solution of the α-chloro compound (**2**; 0.10 mol) and the electrophilic olefin (**1**; 0.12 mol) was added dropwise at 35–40° (exothermic reaction). Addition of the mixture of *t*-butyl chloroacetate and acrylonitrile was done at 8–10°. After the addition was completed, stirring was continued for 1 h at about 25°. The mixture was diluted with water, extracted with benzene, the extracts washed with aqueous sodium chloride, dried with magnesium sulfate, and distilled in vacuo. The distillate was analyzed by G.L.C. and the (*E*)- and (*Z*)-isomers separated by reported methods (Table).

Condensation of Phenyl Vinyl Sulfone with α-Chloropropionitrile:
Phenyl vinyl sulfone (2.10 g, 0.0125 mol), α-chloropropionitrile (1.35 g, 0.0150 mol), benzyltriethylammonium chloride (0.06 g) and 50% aqueous sodium hydroxide (2.5 ml) were stirred for 1 h at 26–28°. The mixture was diluted with water, the solid products filtered, thoroughly washed with water, and dried in vacuo over phosphorus pentoxide. The composition of the products (3.05 g) was determined by G.L.C.: 3-cyano-3-chlorobutyl phenyl sulfone (**5**), 86% (yield: 81%); (*E*)-1-methyl-1-cyano-2-phenylsulfonylcyclopropane (**3d**) 4%; (*Z*)-1-methyl-1-cyano-2-phenylsulfonylcyclopropane (**4d**) 2%; phenyl vinyl sulfone –4%; and unidentified products 4%. The mixture was crystallized from methanol giving 3-chloro-3-cyanobutyl phenyl sulfone; yield: 1.80 g (56%); m.p. 96–98°. After two crystallizations analytically pure product was obtained; m.p. 99–101°.

^{1}H-N.M.R. ($CDCl_3$): $\delta = 1.92$ (s, 3H), 2.44 (t, 2H, $J \simeq 7$ Hz), 3.41 (t, 2H, $J \simeq 7$ Hz), 7.47–8.09 ppm (m, 5H).

The crude products prepared as above (2.0 g), acetonitrile (10 ml), benzyltriethylammonium chloride (0.04 g), dimethyl sulfoxide (2 ml), and 50% aqueous sodium hydroxide (6 ml) were stirred at 36–40° for about 2 h. The progress of the reaction was followed by G.L.C. After this time practically all of the chlorosulfone **5** was consumed (G.L.C. analysis) and two geometrical isomers **3d** and **4d** were formed in a ratio of about 1.4:1, accompanied by some unidentified products. The mixture was worked up as reported in the general procedure, passed through a column filled with silica gel (40 g, elution with chloroform), and the isomers were separated by crystallization (Table); yields: (**3d**) 0.27 g (18%); (**4d**) 0.30 g (20%).

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