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CYCLOPROPYL CARBANIONS DERIVED FROM ESTERS OF 2-PHENYLCYCLOPROPYLCARBOXYLIC ACIDS: CONFIGURATIONAL STABILITY AND REACTION WITH ELECTROPHILES

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Abstract—The base-catalyzed *cis–trans* isomerization of *cis* and *trans*-alkyl 2-phenylcyclopropylcarboxylates was studied in several aprotic solvents. It was found that contact ion-pairs of the derived carbanion lithium salts were configurationally more stable than the solvent-separated ones. Reaction of either the *cis* or the *trans* esters with MeI, and the reaction of the *cis* ester with $Ph_2C = O$, resulted in the corresponding 1-substituted derivatives having *cis* geometry only. This was explained as due to steric hindrance to electrophilic attack exerted by the 2-phenyl group in the case of the *trans* substrate. The *trans* esters did not react with $Ph_2C=O$. Inhibition of the *trans*-to-*cis* isomerization of the carbanion salt of the *trans* substrate in presence of $Ph_2C=O$ could lead to this result.

The configurational stability of cyclopropyl carbanions is higher than that of the analogous carbanions derived from saturated carbon acids. The calculated energy barriers for the inversion of methyl and cyclopropyl carbanions are 20.2 and 36.3 kcal. $mole^{-1}$ respectively.[1] The initial hybridization of the carbon and the constraint in a small ring are factors which affect the energy barrier for the racemization of the derived cyclopropyl carbanions. Thus, for example, a complete retention of configuration of the carbanion derived from 1-cyano-2, 2-diphenylcyclopropane was observed in a methanol-methoxide solution[2], while that derived from the acyclic compound 2-methyl-3, 3-diphenyl-propiononitrile racemized completely under these conditions.[3] The configurational stability of α-substituted cyclopropyl carbanion salts depends on the solvating properties of the reaction medium and on the type of the substituent—whether it is a delocalizing or a non-delocalizing one.[4]

The present work describes a case where other factors related to the electrophile, and to the mutual location of the substituents of a 1, 2-disubstituted cyclopropyl carbanion, affect the formation and the geometry of its reaction product with electrophiles.

RESULTS AND DISCUSSION

Cis-trans isomerization

The base-catalyzed isomerizations of methyl *trans*-2-phenylcyclopropylcarboxylate (*trans*-**1**) and ethyl *cis*-2-phenylcyclopropylcarboxylate (*cis*-**2**) were carried out in the presence of LDA at −78°. Two types of solvent were used as reaction medium: (a) a poor solvating medium–diethyl ether (DEE) and DEE–hexane (1:2) mixture, in which carbanion lithium salts exist mostly as contact ion-pairs[5]; (b) a relatively good solvating medium–THF and DEE containing an effective solvating agent (HMPT), in which these salts exist as separated ion pairs[5]. A solution of either *trans*-**1** or *cis*-**2** was added into a cooled LDA solution and the reaction mixture was quenched by dilute hydrochloric acid. The results are summarized in Table 1.

At relatively short reaction periods (5 min) the extent of the *cis*-to-*trans* isomerization of *cis*-**2** in the poorly-solvating medium was smaller (*ca* 35%) than in the better solvating medium (*ca* 65%). Similarly, the *trans* isomer (*trans*-**1**) which turned out to be the more stable, isomerized to some extent (15%) in THF and not at all in DEE. At longer reaction periods (60 min) the isomerization system equilibrated to a *cis*:*trans* ratio of about 35:65 regardless of the reaction medium and of the starting isomer.

The observed effect of the solvating properties of the reaction medium on the base-catalyzed isomerization of *cis*-**2** indicates that the configurational stability of the corresponding cyclopropyl carbanion lithium salt in aprotic solvents depends on its ion-pairing characteristics, the contact ion pair being configurationally more stable than the separated ion pair. The cyclopropyl carbanion salts studied had partial configurational stability in ethereal solvents. This in general was the behaviour in ethereal solvents of other α-substituted cyclopropyl carbanions having electronegative delocalizing substituents such as $-C \equiv N$,[6] $-C \equiv C - R$.[7] In contrast, complete retention of configuration was observed in most cases in protic solvents,[2] which could be due to the realtively short lifetime of the cyclopropyl carbanions in the protic solvents. Carbanions derived from α-substituted cyclopropanes having a non-delocalizing substituent such as $-CH_3$,[8] –F, –Cl, $-OCH_3$,[9] $-NC$[4], are configurationally stable in both protic and aprotic solvents.

Deuteration experiments were also carried out for most of the points of Table 1 (entries 1, 2, 5–10) to determine the extent of D-incorporation. The isomerization reaction mixtures were each quenched with

Table 1. The effect of solvent on the base-catalyzed *cis–trans* isomerization of ethyl *cis*-2-phenylcyclopropylcarboxylate (*cis*-**2**) and methyl *trans*-2-phenylcyclopropylcarboxylate (*trans*-**1**)[a,b]

Entry	Substrate	Solvent	Time (min)	Products *cis*	(%) *trans*
1	*cis*-**2**	THF	5	35	65
2	*cis*-**2**	DEE	5	65	35
3	*cis*-**2**	DEE-hexane (1:2)	5	63	37
4	*cis*-**2**	DEE[c]	5	33	67
5	*cis*-**2**	THF	60	37	63
6	*cis*-**2**	DEE	60	38	62
7	*trans*-**1**	THF	5	15	85
8	*trans*-**1**	DEE	5	0	100
9	*trans*-**1**	THF	60	38	62
10	*trans*-**1**	DEE	60	35	65

[a]See Experimental Section for the experimental conditions.
[b]Deuteration experiments were carried out for entries, 1, 2, 5–10.
[c]HMPA (2.5 mmole) was used.

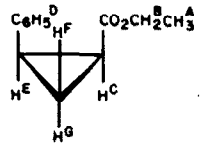
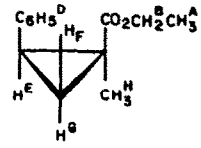
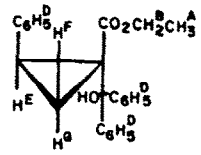
dilute DCl–D_2O. The extents of the isomerization in these experiments were practically the same as in Table 1, but incorporation of deuterium at C_1 was very low ($\leq$ 3–4%) as was evident from the ^{1}H-NMR spectrum of the isolated mixture of isomers of each of the isomerization experiments. This indicates that the equilibrium concentrations of the corresponding cyclopropyl carbanion lithium salts are very low in a poorly solvating medium. Similar cases have been previously reported for other carbanion lithium salts: an optically pure enantiomer of the chiral compound 1-phenyl-1-isocyanopropane racemised in THF (at −70°), but no incorporation of deuterium was observed after quenching the reaction mixture with D_2O.[4] Similarly, in the *trans*-PhCh=CH–CO_2Et–LDA–Ph_2C=O reaction mixture (in THF at −78°), high yields of the corresponding β-diphenyl carbinol derivative (derived from $PhC^-(Li^+)$=CH–CO_2Et) were obtained, whereas quenching of the reaction mixture with D_2O or MeOD did not result in any detectable incorporation of deuterium.[10] An irreversible formation of the reaction product could lead to the high yields in spite of a very low equilibrium constant of the carbon acid-base reaction. The observed lack of deuterium incorporation therefore suggests that the two-step process of the *cis–trans* isomerization, that is, formation of the cyclopropyl carbanion salt and then its isomerization, is to be explained in terms of the second stage and not in terms of a slow anion formation.

Reaction with electrophiles

The *cis* and *trans* alkyl esters of 2-phenylcyclopropyl carboxylic acid were reacted in THF at −78°, in presence of LDA, with each of the electrophiles methyl iodide and benzophenone. The reactions of *cis*-**2** afforded the corresponding 1-substituted derivatives **3** and **4** with retention of the *cis* geometry (Table 2). The corresponding *trans* products were not detected at all. This retention of the *cis* geometry was unexpected because the isomerization of the (*cis*-**2**)$^-$Li$^+$ salt in THF and formation of a (*cis*-**2**)$^-$Li$^+$ – (*trans*-**2**)$^-$Li$^+$ mixture was quite fast (Table 1). It might be argued that formation of the *cis* product only (compound **4**, Table 2) in the *cis*-**2**–LDA–Ph_2C=O reaction system results from a greater rate of trapping of the *cis*-**2** carbanion (by Ph_2C=O) as compared to its isomerization to (*trans*-**2**)$^-$, thus preventing the (*cis*-**2**)$^-$ ⇄ (*trans*-**2**)$^-$ pre-equilibrium formation. However, comparing the rates of the isomerization of (*cis*-**2**)$^-$ to (*trans*-**2**)$^-$ (65% within 5 min, entry 1, Table 1) and that of formation of **4** (see Experimental) reveals that the rate of trapping of the (*cis*-**2**)$^-$ by the electrophile is smaller (or at the most, of the same order) than the rate of isomerization to (*trans*-**2**)$^-$. In addition, an experiment of a prior formation of a *cis–trans* carbanion mixture, followed by addition of the electrophilic trapping agent Ph_2C=O, was not expected to change the observed situation of the sole formation of the *cis* product **4**. This was evident from the fact that a 1-diphenylcarbinol derivative was not formed at all in the *trans*-**1**–LDA–PH_2C=O reaction system. It might therefore be reasonably assumed that the electrophiles used react preferentially with the carbanion derived from *cis*-**2**, thus shifting the (*cis*-**2**)$^-$Li$^+$ and (*trans*-**2**)$^-$Li$^+$ equilibrium towards the formation of the *cis* products **3** and **4**.

The result obtained in the *trans*-**1**-LDA-MeI (THF −78°) reaction system, in which MeI was added to a preformed (*trans*-**1**)$^-$–(*cis*-**1**)$^-$ mixture, seems to clarify and support the above assumption. The 1-methyl derivative of *cis*-**1** (**5**) was obtained (30% yield) but none of the corresponding *trans* isomer. The rest of the unreacted reactant was recovered. The formation of **5** from *trans*-**1** indicated that both (*trans*-**1**)$^-$Li$^+$ and (*cis*-**1**)$^-$Li$^+$ were present in the reaction mixture. The exclusive formation of the *cis* product **5** (in spite of the facile *cis*-to-*trans* isomerization) paralleled the formation of the *cis* products **3** and **4**. The combined results of the isomerization experiments and the *cis* geometry of products **3**–**5** clearly indicates that the *cis* geometry of compounds **3**, **4** and **5** is not due to a relatively high configurational stability of the corresponding *cis*-cyclopropyl carbanions, but rather to some interference to an attack of the electrophile on the negatively charged C_1 atom of the *trans*-**2** (or the *trans*-**1**) carbanion. We suggest that the phenyl group at C_2 exerts steric hindrance to the approach of an electrophile to the negatively charged C_1 of the *trans* and not of the *cis* carbanion, resulting in substitution products having a *cis* geometry only. Protonation, because

Table 2. ^{1}H-NMR data[a] of the ethyl *cis*-2-phenylcyclopropylcarboxylate derivatives

Compound		H^A	H^B	H^C	H^D	H^E	H^F	H^G	H^H
cis-2		0.96	3.85	2.07	7.25	2.62	1.70	1.31	
		t	q	mc	bs	dd	mc	mc	
		3H	2H	1H	5H	1H	1H	1H	
3		0.80[b]	3.74		7.21	2.34	1.95	1.07	1.49
		t	q		bs	dd	dd	dd	s
		3H	2H		5H	1H	1H	1H	3H
4		0.67	3.60		7.30	2.17-2.57		1.15	
		t			mc	mc		dd	
		3H	2H		15H	2H		1H	

[a] 60 MHz spectrum in $CDCl_3$, TMS used as internal standard, δ units.

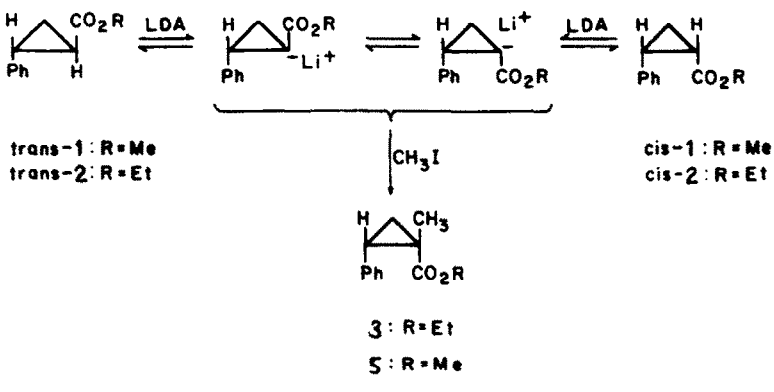
[b] ^{1}H-NMR data of methyl *cis*-2-phenyl-1-methylcyclocarboxylate: [12] δ 7.08 (s, 5H, Ph); 3.17 (s, 3H, Me of ester); 2.42–1.68 (m, 2H cyclopropyl and benzylic); 1.42 (s, 1H, Me); 1.01 (dd, 1H, cyclopropyl). ^{1}H-NMR data of methyl *trans*-2-phenyl-1-methylcyclopropylcarboxylate. [12] δ 7.13 (s, 5H, Ph); 3.63 (s, 3H, Me); 3.75 (dd, 1H, benzylic); 1.62 (dd, 1H, cyclopropyl); 1.21–0.88 (m, 4H, cyclopropyl and methyl).

of the small size of the electrophile, takes place with both the *cis* and the *trans* carbanions (Table 1). The proposed mechanism of formation of the 1-methyl derivatives **3** and **5** is shown in Scheme 1.

As mentioned, the 1-diphenylcarbinol derivative was not obtained in the *trans*-1-LDA-$Ph_2C{=}O$ reaction system, but rather in the corresponding *cis*-**2** system. It was an unexpected result in view of the formation of **5** and **3** in the *trans*-1-LDA-MeI and in the *cis*-**2**-LDA-MeI reactions systems, respectively. This might suggest that the equilibrium conversion of the *trans*-**1** carbanion salt to the *cis*-**1** carbanion salt, which is the one capable of reacting with the electrophile, cannot take place in the presence of $Ph_2C{=}O$. A possible existence of relatively stable (*trans*-**1**)$^-Li^+$. $Ph_2C{=}O$ adduct might be responsible for this observation.

The suggestion of steric hindrance exerted by the C_2 phenyl group at the spatial vicinity of C_1 is further supported by another observation in the literature. In the basic hydrolysis of a mixture of the *cis* and *trans* isomers of ethyl 2-phenylcyclopropylcarboxylate the *trans* ester only is selectively hydrolyzed to the corresponding *trans* acid.[11] It seems that the nucleophilic attack of the OH^- ion on the ester group is effectively hindered by the C_2-phenyl group in the case of the *cis* ester.

^{1}H-NMR data of the methyl esters of the *cis* and *trans* isomers of 1-methyl-2-phenylcyclopropylcarboxylic acids have been given.[12] It was confirmed, by comparing the ^{1}H-NMR data, that **3** and **5** were the 1-methyl derivatives of *cis*-**2** and *cis*-**1**, respectively. The *cis* geometry of **4** was clearly confirmed by performing an X-ray diffraction analysis (Fig. 1). Intensity data were collected using CuK_α radiation on a CAD 4 automatic diffractometer. Crystal data obtained were: Monoclinic, $P2_1/c$, $a = 11.935(1)$, $b = 6.243(3)$, c 27.837(4) Å, $\beta = 101.82(1)°$, $Z = 4$.



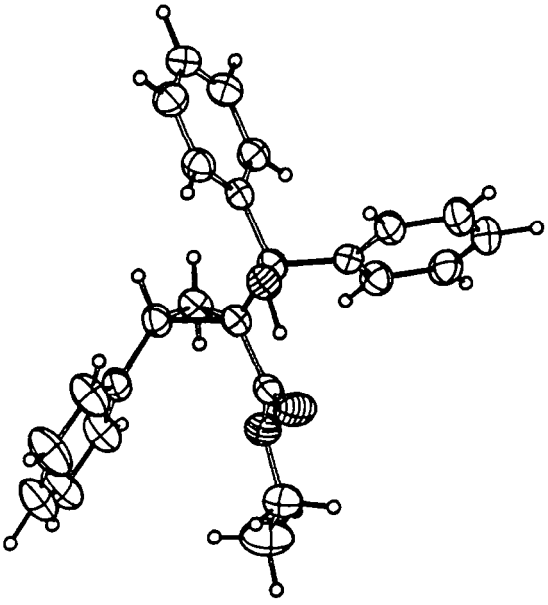


Fig. 1. ORTEP drawing of compound 1.

The structure was solved by direct methods and refined anisotropically by a full-matrix least-squares using 2558 reflections with $I \geq 3\sigma(I)$. The final discrepancy index of convergence is $R = 0.045$. Bond distances within the cyclopropane ring are CH_2–$C(C_6H_5)$ 1.486Å, CH_2–C(COOEt) 1.502 Å and $C(C_2H_5)$–C(COOEt) 1.538 Å. Position and thermal parameters are available as supplementary material on request.

EXPERIMENTAL

Materials

The methyl and ethyl esters of *cis*-2-phenylcyclopropylcarboxylic acid (*cis*-1 and *cis*-2) and of *trans*-2-phenylcyclopropylcarboxylic acid (*trans*-1 and *trans*-2, respectively) were prepared by reaction of the corresponding alkyl diazoacetates with styrene.[11] THF was kept as a solution with sodium naphthalene. Absolute hexane and diethyl ether (DEE) were kept over Na. The required amounts of solvent were directly distilled from these stock solutions into the reaction apparatus. Solutions of LDA were prepared by adding an equimolar amount of BuLi in hexane to a stirred cooled (−78°) solution of diisopropylamide in the required solvent. All manipulations and reactions were carried out under nitrogen and anhydrous conditions.

Cis–trans isomerization of cis-2 *and* trans-1 (*see Table* 1)

A solution of either *cis*-2 or *trans*-1 (0.475 g, 2.5 mmole) in the required solvent (10 ml) was added dropwise over 5 min into a cooled (−78°) solution of LDA (7.5 mmole) in the same solvent. The mixture was further stirred for 5 min or 60 min at −78° and then quenched by dilute HCl solution. In the deuteration experiments, quenching was done by dilute DCl–D_2O. The residue recovered from the organic layer was subjected to column chromatography and the composition of the mixture of the corresponding *cis* and *trans* isomers was determined by both glc and ^{1}H-NMR.

*The reaction of cis-*2 *and* trans-1 *with* MeI *in presence of* LDA

A solution of MeI (1.42 g, 10 mmole) in THF (10 ml) was added dropwise during 5 min into a cooled (−78°) solution of LDA (7.5 mmole) and *cis*-2 (0.475 g, 2.5 mmole) in THF (30 ml). The mixture was stirred 20 min at −78°, quenched with a dilute HCl, and the residue recovered from the organic layer was separated by column chromatography. Ethyl *cis*-2-phenyl-1-methylcyclopropylcarboxylate (3) was obtained (0.36 g, 70%), *m/e* − 204 (M^+); its ^{1}H-NMR data are given in Table 2. A similar reaction was carried out using *trans*-1. A mixture of the starting material (0.338, 70%) and methyl *cis*-2-phenyl-1-methylcyclopropylcarboxylate (5) (0.15 g, 30%), which was not separated by column chromatography, was obtained. The composition of the mixture was determined by VPC and ^{1}H-NMR.

Ethyl cis-1-(*hydroxydiphenylmethyl*)-2-*phenylcyclopropylcarboxylate* (4)

A solution of benzophenone (0.546 g, 3.0 mmole) and *cis*-2 (0.475 g, 2.5 mmole) in THF (10 ml) was added dropwise during 10 min into a cooled (−78°) solution of LDA (7.5 mmole) in THF (30 ml). The cooled reaction mixture was further stirred for 60 min and quenched as described. After solvent removal, the oily residue solidified on addition of petroleum ether. The solid was filtered off and recrystallized to give 4 (0.80 g, 86%) m.p. 125–127° (from EA-PE). (Anal: Found: C, 80.6; H, 6.5. $C_{25}H_{24}O_3$ requires C, 80.65; H, 6.45.) IR (nujol): 1600, 1740, 3000, 3450 cm^{-1}; MS *m/e* 372 (M^+), 354 ($M^+ - H_2O$).

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