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Synthesis of 3-Substituted Dialkyl 2-Aroyl-2-ethylcyclopropane-1,1-dicarboxylates by the Reformatsky Reaction

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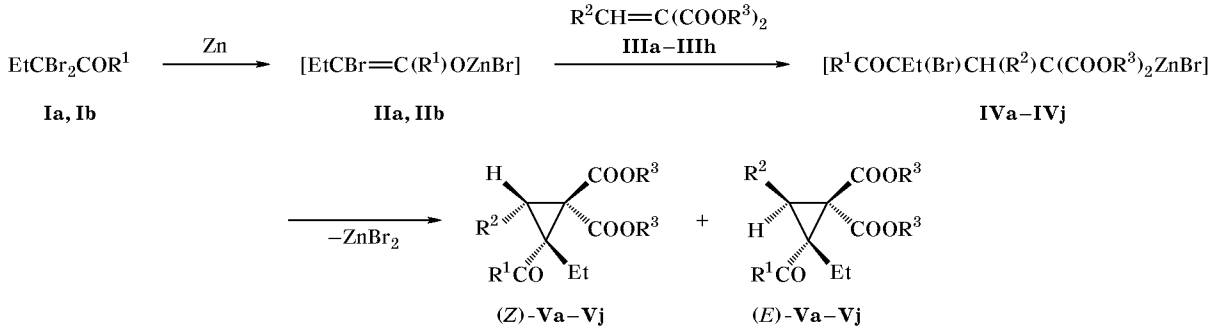
Abstract—1-Aryl-2,2-dibromobutan-1-ones react with zinc and dialkyl arylmethylene- or isobutylidenemalonates to give dialkyl 2-aroyl-3-phenyl(isopropyl)-2-ethylcyclopropane-1,1-dicarboxylates which are formed mainly as *Z* isomers.

One of the main procedures for synthesizing cyclopropane derivatives with an acyl substituent is based on the reaction of oxo carbenes with olefins [1]. However, the yields of the target products are very poor because of a large contribution of side processes. Cyclopropane compounds having alkoxycarbonyl groups are obtained by cyclization of bromo-substituted alkylidene derivatives of β-dicarbonyl compounds by the action of $NaBH_4$ [2]. Most methods for building up cyclopropane ring substituted by acyl and alkoxycarbonyl groups are based on the Michael addition of halogen-containing nucleophilic organometallic compounds derived from α-halo- and α,α-dihaloacetic or -malonic acid esters to activated double bond in α,β-unsaturated carbonyl compounds and subsequent cyclization of intermediate adducts [3–8].

Zinc enolates generated from α,α-dibromoketones were not involved in the above reactions. With the goal of obtaining substituted cyclopropane-1,1-dicarboxylic acid esters possessing an aroyl group in the ring we examined the reaction of 1-aryl-2,2-dibromobutan-1-ones **I** with zinc and dialkyl arylmethylene- or isobutylidenemalonates **III** (Scheme 1). In the first stage α,α-dibromoketone **I** react with zinc in ether–ethyl acetate (1 : 3) to give zinc enolate **II** which then reacts with dialkyl arylmethylenemalonates **IIIa**–**IIIf** or dialkyl isobutylidenemalonates **IIIg** and **IIIh**, yielding intermediate **IV**. The latter undergoes

Scheme 1.



I, **II**, R^1 = Ph (**a**), 4-MeC_6H_4 (**b**); **III**, R^3 = Me, R^2 = Ph (**a**), 4-ClC_6H_4 (**b**), 4-BrC_6H_4 (**c**), 3,4-$(MeO)_2C_6H_3$ (**d**), 3-$NO_2C_6H_4$ (**e**), 4-$NO_2C_6H_4$ (**f**), *i*-Pr (**g**); R^3 = Et, R^2 = *i*-Pr (**h**); **IV**, **V**, R^1 = Ph, R^3 = Me, R^2 = Ph (**a**), 4-ClC_6H_4 (**b**), 4-BrC_6H_4 (**c**), 3,4-$(MeO)_2C_6H_3$ (**d**), 3-$NO_2C_6H_4$ (**e**), 4-$NO_2C_6H_4$ (**f**); R^1 = 4-MeC_6H_4, R^2 = Ph, R^3 = Me (**g**); R^1 = Ph, R^2 = *i*-Pr, R^3 = Me (**h**), Et (**i**); R^1 = 4-MeC_6H_4, R^2 = *i*-Pr, R^3 = Et (**j**).

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cyclization to cyclopropane-1,1-dicarboxylic acid ester **V** which can be formed as *Z* and *E* isomers. After recrystallization from hexane or methanol, dimethyl 2-aroyl-3-aryl-2-ethylcyclopropane-1,1-dicarboxylates **Va**–**Vg** were isolated in 32–65% yield as a single stereoisomer. The structure of products **Va**–**Vg** was established on on the basis of analytical data and IR and ^{1}H NMR spectra.

The IR spectra of **Va**–**Vg** contained characteristic absorption bands belonging to the ketone (1680 and 1690 cm^{-1}) and ester carbonyl groups (~1720 and 1740 cm^{-1}). In the ^{1}H NMR spectra recorded in $CDCl_3$ or DMSO-d_6 signals in the regions δ 1.18–1.29, 2.15–2.23, 3.31–3.36, 3.91–4.03, and 3.10–3.33 ppm were present due to methylene protons of the CH_2CH_3 group, methyl protons of the ester moieties, and CH proton (ArCH), respectively.

It was impossible to unambiguously assign the structure of **Va**–**Vg** to *Z* or *E* isomer on the basis of spectral data. According to the X-ray diffraction data for compound **Va**, its major isomer has *Z* configuration with *cis* arrangement of the phenyl and benzoyl substituents [9]. The similarity of the ^{1}H NMR spectra of **Va** and compounds **Vb**–**Vg** led us to conclude that the latter are also *Z* isomers. After vacuum distillation, compound **Va** showed in the ^{1}H NMR spectrum signals belonging to the major *Z* isomer and a number of weak signals, in particular at δ 3.30 and 3.70 ppm ($COOCH_3$). These signals are likely to arise from the corresponding *E* isomer whose fraction was estimated at ~10%. We failed to isolate the pure *E* isomer of **Va** and rigorously prove its structure.

The ^{1}H NMR spectra of some esters (compounds **Vh**–**Vj**), recorded after vacuum distillation, showed a different isomer ratio, (60–80):(40–20). Obviously, triple recrystallization from methanol yields the major isomer which crystallizes better. By recrystallization of diethyl 2-benzoyl-2-ethyl-3-isopropylcyclopropane-1,1-dicarboxylate (**Vi**) from hexane we obtained a mixture of isomers at a ratio of 4:1. We succeeded in separating them by column chromatography on silica gel with benzene as eluent, and the pure isomers were examined by ^{1}H and ^{13}C NMR spectroscopy using ^{1}H–^{1}H and ^{1}H–^{13}C two-dimensional techniques. The ^{1}H NMR spectrum of the major isomer of **Vi** is given in table. The spectrum of the minor isomer contains the following signals ($CDCl_3$), δ, ppm: 0.88 t (3H, $CH_2C\mathbf{H}_3$), 0.96 t and 1.40 t (6H, $OCH_2C\mathbf{H}_3$), 1.22 d and 1.24 d [6H, $CH(C\mathbf{H}_3)_2$], 1.56 m and 2.36 m (2H, $C\mathbf{H}_2CH_3$), 1.73 m [1H, $C\mathbf{H}(CH_3)_2$], 2.14 d (1H, CH), 3.86 m and 4.35 q (4H, $OC\mathbf{H}_2CH_3$), 7.42–7.58 m and 8.20 m (5H, C_6H_5). The steric structure of the minor isomer was determined from the NOE data. Irradiation of one proton of the methylene group in the 2-ethyl substituent (δ 2.36 ppm) gave a response at the CH signal of the isopropyl group (δ 1.73 ppm). This is possible only when both ethyl and isopropyl groups are located at one side of the cyclopropane ring. Hence the minor isomer **Vi** has *E* configuration, and the major isomer (like the major isomers of **Vh** and **Vj** showing similar ^{1}H NMR spectra) has *Z* configuration. The ^{13}C NMR spectra of both isomers of **Vi** are given in Experimental.

EXPERIMENTAL

The ^{1}H and ^{13}C NMR spectra of **Va** and the ^{1}H NMR spectra of **Vh** and **Vi** were recorded on an INOVA-300 Cunmr I instrument (300 MHz) in $CDCl_3$. The ^{1}H NMR spectra of **Vb**–**Vg** and **Vj** were obtained on a Bruker AM-300 (300 MHz) spectrometer from solutions in DMSO-d_6. Tetramethylsilane was used as internal reference. The IR spectra were measured on a UR-20 spectrophotometer from neat substances.

Dialkyl 2-aroyl-2-ethylcyclopropane-1,1-dicarboxylates Ia–Ij. *a. Compounds **Va**–**Vc** and **Vg**.* A mixture of 0.05 mol of α,α-dibromoketone **Ia** or **Ib** and 0.05 mol of dialkyl arylmethylene(or isobutylidene)malonate in 15 ml of diethyl ether and 15 ml of ethyl acetate was added dropwise with stirring to a mixture of 10 g of zinc (prepared as fine turnings), 5 ml of diethyl ether, and 15 ml of ethyl acetate. The mixture was heated to initiate the process, and the reaction then occurred spontaneously. When the reaction was over, the mixture was heated for 30 min on a water bath, cooled, neutralized with 5% hydrochloric acid, and extracted with ether. The extract was dried over Na_2SO_4, the solvent was distilled off, and the residue was recrystallized from hexane or methanol.

*b. Compounds **Vd**–**Vf** and **Vh**–**Vj**.* A solution of 0.15 mol of α,α-dibromoketone in 15 ml of ethyl acetate was added dropwise with stirring to a mixture of 20 g of zinc (prepared as fine turnings), 15 ml of diethyl ether, and 15 ml of ethyl acetate. The mixture was heated to initiate the process, and the reaction then occurred spontaneously. When the reaction was over, the mixture was heated for 15 min on a water bath and cooled, and the liquid part was separated from zinc and transferred into another flask. A solution of 0.05 mol of dialkyl arylmethylene(or isobutylidene)malonate in 15 ml of ethyl acetate was added, and the subsequent procedure was the same as described above in *a*. The yields, melting points, ^{1}H NMR spectra, and analytical data of the products are given in table (for samples recrystallized from methanol).

Yields, melting points, ^{1}H NMR spectra, and elemental analyses of dialkyl (*Z*)-3-R-2-aroyl-2-ethylcyclopropane-1,1-dicarboxylates **Va**–**Vj**

Compound no.	Yield, %	mp, °C	Found, %		Formula	Calculated, %	
			C	H		C	H
Va	65	133–134	69.98	5.96	$C_{22}H_{22}O_5$	72.12	6.05
Vb	57	105–106	65.92	5.10	$C_{22}H_{21}ClO_5$	66.08	5.29
Vc	63	120–121	59.11	4.61	$C_{22}H_{21}BrO_5$	59.34	4.75
Vd[a]	32	154–155	67.40	6.02	$C_{24}H_{26}O_7$	67.59	6.15
Ve[a]	52	122–123	64.02	5.03	$C_{22}H_{21}NO_7$	64.23	5.15
Vf[a]	58	161–162	64.00	5.05	$C_{22}H_{21}NO_7$	64.23	5.15
Vg	64	138–139	72.38	6.26	$C_{23}H_{24}O_5$	72.61	6.36
Vh[a]	67[b]	114–116	68.44	7.16	$C_{19}H_{24}O_5$	68.66	7.28
Vi[a]	71[b]	93–95	70.18	7.10	$C_{21}H_{28}O_5$	70.37	7.31
Vj[a]	69[b]	92–94	70.20	7.95	$C_{22}H_{30}O_5$	70.56	8.08

Compound no.	^{1}H NMR spectrum,[c] δ, ppm			
	R^1, R^2	R^3	Et	CH
Va	7.22–7.55 m, 8.17–8.23 m (10H, C_6H_5)	3.33 s, 4.03 s (6H, CH_3)	1.13 t (3H, CH_3), 1.22 m, 2.32 m (2H, CH_2)	3.21 s
Vb	7.45–7.63 m, 8.05 d (5H, C_6H_5), 7.34 s (4H, 4-ClC_6H_4)	3.31 s, 3.92 s (6H, CH_3)	0.97 t (3H, CH_3), 1.20 m, 2.16 m (2H, CH_2)	3.20 s
Vc	7.40–7.63 m, 8.02 d (5H, C_6H_5), 7.30 d, 7.47 d (4H, 4-BrC_6H_4)	3.32 s, 3.91 s (6H, CH_3)	0.97 t (3H, CH_3), 1.20 m, 2.15 m (2H, CH_2)	3.18 s
Vd	7.46–7.60 m, 8.06 d (5H, C_6H_5), 3.65 d (6H, CH_3O), 6.81 d, 6.88 d, 7.00 s (3H, C_6H_3)	3.31 s, 3.93 s (6H, CH_3)	1.00 t (3H, CH_3), 1.20 m, 2.15 m (2H, CH_2)	3.10 s
Ve	7.50–7.65 m, 8.07 d (5H, C_6H_5), 7.62 t, 7.80 d, 8.12 d, 8.24 s (4H, 3-$NO_2C_6H_4$)	3.35 s, 3.96 s (6H, CH_3)	1.05 t (3H, CH_3), 1.29 m, 2.23 m (2H, CH_2)	3.33 s
Vf	7.48–7.63 m, 8.04 d (5H, C_6H_5), 7.62 d, 8.15 d (4H, 4-$NO_2C_6H_4$)	3.36 s, 3.97 s (6H, CH_3)	1.04 t (3H, CH_3), 1.28 m, 2.23 m (2H, CH_2)	3.32 s
Vg	2.40 s, 7.18–7.43 m, 7.95 d (12H, C_6H_5, 4-$CH_3C_6H_4$)	3.32 s, 3.92 s (6H, CH_3)	1.00 t (3H, CH_3), 1.18 m, 2.16 m (2H, CH_2)	3.15 s
Vh	0.87 d, 1.33 d, 2.02 m, [7H, $(CH_3)_2CH$], 7.43–7.60 m, 8.21 d (5H, C_6H_5)	3.42 s, 3.82 s (6H, CH_3)	0.86 t (3H, CH_3), 0.98 m, 2.06 m (2H, CH_2)	1.54 d
Vi	0.94 d, 1.38 d, 2.06 m, [7H, $(CH_3)_2CH$], 7.42–7.58 m, 8.20 d (5H, C_6H_5)	1.05 t, 1.44 t (6H, CH_3), 3.98 m, 4.40 q (4H, CH_2)	0.90 t (3H, CH_3), 1.02 m, 2.18 m (2H, CH_2)	1.56 d
Vj	0.85 d, 1.30 d, 1.90 m [7H, $(CH_3)_2CH$], 2.40 s, 7.28 d, 7.97 d (7H, 4-$CH_3C_6H_4$)	1.05 t, 1.35 t (6H, CH_3), 3.93 m, 4.30 q (4H, CH_2)	0.80 t (3H, CH_3), 0.95 m, 2.04 m (2H, CH_2)	1.45 d

[a] Synthesized by procedure *b* (see Experimental).

[b] Mixture of *Z* and *E* isomers.

[c] The spectra of compounds **Va**, **Vh**, and **Vi** were recorded in $CDCl_3$, and of the others, in DMSO-d_6.

Diethyl 2-benzoyl-2-ethyl-3-isopropylcyclopropane-1,1-dicarboxylate (Vi). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: *Z* isomer: 11.28 ($CH_2\mathbf{C}H_3$); 13.66, 14.18 ($OCH_2\mathbf{C}H3$); 21.85, 22.96 [$CH(\mathbf{C}H_3)_2$]; 23.86 (CH); 28.54 ($\mathbf{C}H_2CH_3$); 43.13 (C^3); 44.92, 45.36 (C^1, C^2); 61.36, 61.88 ($O\mathbf{C}H_2CH_3$); 128.37, 128.62, 132.68, 136.23 (Ph, COPh); 167.74, 167.09 (COO); 194.58 (CO); *E* isomer: 7.34 ($CH_2\mathbf{C}H_3$); 9.07, 9.51 ($OCH_2\mathbf{C}H_3$); 17.78 ($\mathbf{C}H_2CH_3$); 18.07, 18.17 [$CH(\mathbf{C}H_3)_2$]; 20.64 (CH); 37.00 (C^3); 37.93, 41.88 (C^1, C^2); 56.02, 56.86 ($O\mathbf{C}H_2CH_3$); 123.95, 124.22, 128.37, 131.15 (Ph, COPh); 161.74, 164.12 (COO); 191.78 (CO).

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