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Reactions of Aliphatic Diazo Compounds: V.* Reaction of Methyl Diazoacetate with Imides of Itaconic Acid**

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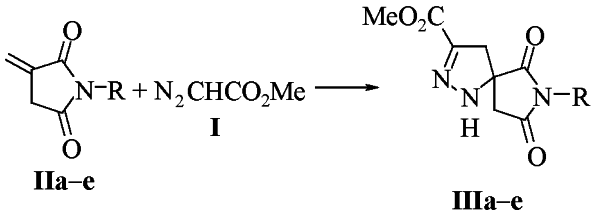
Abstract—Methyl diazoacetate regioselectively adds to N-substituted imides of itaconic acid to afford 2-pyrazolines, methyl 7-aryl-6,8-dioxo-1,2,7-triazaspiro[4.4]non-2-ene-3-carboxylates that in reaction with halogens (Cl_2, Br_2) yield methyl 5-aryl-1-halo-4,6-dioxo-5-azaspiro[2.4]heptane-1-carboxylates as a mixture of *syn*- and *anti$(2$)-isomers.*

We formerly established that reaction between esters of substituted 7-aryl-6,8-dioxo-2,3,7-triazabicyclo-[3.3.0]-oct-3-ene-4-carboxylic acids prepared from alkyl diazoacetates and N-substituted maleimides and halogens gave rise to alkyl 4-halo-2,3,7-triazabicyclo[3.3.0]oct-2-ene-4-carboxylates. The latter on heating in a vacuum eliminate nitrogen affording alkyl 6-halo-3-azabicyclo[3.1.0]hexane-6-carboxylates [2].

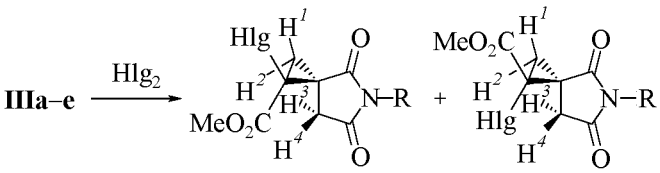
In this study we investigated the reaction of methyl diazoacetate (**I**) with a series of N-substituted imides of itaconic acid, and the reaction of the resulting products with halogens (Cl_2, Br_2).



II, III, R = C_6H_5 (**a**), 4-$CH_3C_6H_4$ (**b**), 3-Cl-4-$CH_3C_6H_3$ (**c**), 4-ClC_6H_4 (**d**), 4-BrC_6H_4 (**e**), 4-FC_6H_4 (**f**).

Reaction of methyl diazoacetate with imides **IIa–f** in benzene at room temperature furnished methyl 7-aryl-6,8-dioxo-1,2,7-triazaspiro[4.4]non-2-ene-3-carboxylates (**IIIa–f**). The composition and structure of esters **IIIa–f** were established from elemental analyses (Table 1) and spectral data (Table 2). In the IR spectra of compounds are observed absorption bands of C=O and NH groups in the regions 1700 and 3400 cm^{-1} respectively. In the ^1H NMR spectra of esters **IIIa–f** appear doublet signals from the methylene group protons in the imide ring at 3.4 and 2.9 ppm (J 18 Hz) and two doublets at 3.2 ppm (J 18 Hz) corresponding to methylene group protons of the pyrazoline ring, a signal from NH group in the region of 8.8 ppm, and also signals of aromatic protons and the protons of ester group. In the ^{13}C NMR spectrum of ester **IIId** the signal belonging to carbon in 5-position is present at 70 ppm indicating that it is adjacent to a heteroatom.

In reaction of esters **IIIa–f** with chlorine in 73–87% yield arise methyl 5-aryl-1-chloro-4,6-dioxo-5-azaspiro[2.4]heptane-1-carboxylates as a mixture of *syn*-isomers **IVa–f** and *anti*-isomers **Va–f**. The reaction was carried out by two procedures: in the first mode the dry chlorine was passed at 0°C through a solution of a pyrazoline in chloroform; in the second procedure the chlorine was passed at 75°C through a solution of pyrazoline in glacial acetic acid. The isomer ratio **IV : V** was in reaction carried out along first procedure 1 : 1.9 (**a**), 1 : 1.5 (**b**), 1 : 1.6 (**d**), 1 : 1.3 (**f**); along the second procedure 2.5 : 1 (**c**), 12 : 1 (**d**), 3.9 : 1 (**e**). The reaction in acetic acid at 75°C afforded prevailingly the thermodynamically



IV, V, Hlg = Cl, R = C_6H_5 (**a**), 4-$CH_3C_6H_4$ (**b**), 3-Cl-4-$CH_3C_6H_3$ (**c**), 4-ClC_6H_4 (**d**), 4-BrC_6H_4 (**e**), 4-FC_6H_4 (**f**); **VI, VII**, Hlg = Br, R = C_6H_5 (**a**), 4-$CH_3C_6H_4$ (**b**), 3-Cl-4-$CH_3C_6H_3$ (**c**), 4-ClC_6H_4 (**d**), 4-BrC_6H_4 (**e**), 4-FC_6H_4 (**f**).

* For communication IV see [1].

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Table 1. Yields, melting points, and elemental analyses of newly synthesized compounds

Compd. no.	Yield, %	mp, °C	Found, %			Formula	Calculated, %		
			C	H	N		C	H	N
IIIa	72	193–194[a]	58.51	4.60	14.51	$C_{14}H_{13}N_3O_4$	58.63	4.56	14.63
IIIb	69	172–174[a]	59.80	4.89	14.03	$C_{15}H_{15}N_3O_4$	59.80	5.02	13.95
IIIc	71	180–183[a]	61.01	5.32	13.39	$C_{16}H_{17}N_3O_4$	60.95	5.43	13.33
IIId	84	190–191[a]	52.14	3.92	13.27	$C_{14}H_{12}ClN_3O_4$	52.27	3.76	13.06
IIIe	82	180–182[a]	45.87	3.41	11.60	$C_{14}H_{12}BrN_3O_4$	45.92	3.30	11.48
IIIf	66	184–186[a]	54.93	4.07	13.90	$C_{14}H_{12}FN_3O_4$	55.08	3.96	13.77
IVa+Va	77	164–166	57.23	4.01	4.68	$C_{14}H_{12}ClNO_4$	57.25	4.12	4.77
IVb+Vb	75	105–108	58.53	4.63	4.49	$C_{15}H_{14}ClNO_4$	58.55	4.59	4.55
IVc+Vc	81	205–208	52.51	3.88	4.17	$C_{15}H_{13}Cl_2NO_4$	52.65	3.83	4.09
IVd+Vd	73	173–175	51.16	3.29	4.41	$C_{14}H_{11}Cl_2NO_4$	51.24	3.38	4.27
IVe+Ve	87	176–178	45.07	3.02	3.80	$C_{14}H_{11}BrClNO_4$	45.13	2.98	3.76
IVf+Vf	82	164–166	54.03	3.41	4.62	$C_{14}H_{11}ClFNO_4$	53.95	3.56	4.49
VIa+VIIa	71	173–176	49.59	3.61	4.28	$C_{14}H_{12}BrNO_4$	49.73	3.58	4.14
VIb	69	101–102	51.58	3.93	4.15	$C_{15}H_{14}BrNO_4$	51.16	4.01	3.98
VIc+VIIc	63	213–215	46.63	3.51	3.58	$C_{15}H_{13}BrClNO_4$	46.60	3.39	3.62
VId	65	181–183	45.15	3.07	3.93	$C_{14}H_{11}BrClNO_4$	45.13	2.98	3.76
VIe	73	190–192	40.51	3.07	3.51	$C_{14}H_{11}Br_2NO_4$	40.32	2.66	3.36
VIf+VIIf	64	206–209	47.27	3.24	3.90	$C_{14}H_{11}BrFNO_4$	47.21	3.11	3.93

[a] With decomposition.

Table 2. IR and ^{1}H NMR spectra of compounds **IIIa–f, IVa–f, Va–f, VIa–f, VIIa, c, f** [a]

Compd. no.	IR spectrum, cm^{-1}	^{1}H NMR spectrum, δ, ppm (*J*, Hz)
IIIa	890, 1050, 1130, 1220, 1380 s, 1450, 1510, 1580, 1720 v.s, 3050, 3390	2.94 d (1H, 18), 3.19 d (1H, 18), 3.22 d (1H, 18), 3.41 d (1H, 18), 3.73 s (3H), 7.29–7.54 (5H), 8.85 s (1H)
IIIb	880, 1060, 1130, 1240, 1380 s, 1450, 1520, 1590, 1720 v.s, 3050, 3380	2.35 s (3H), 2.92 d (1H, 18), 3.17 d (1H, 18), 3.20 d (1H, 18), 3.36 d (1H, 18), 3.72 s (3H), 7.18 d (2H, 8), 7.31 d (2H, 8), 8.84 s (1H)
IIIc	880, 1060, 1140, 1200, 1380 s, 1450, 1500, 1580, 1720 v.s, 3050, 3370	2.38 s (3H), 2.94 d (1H, 18), 3.18 d (1H, 18), 3.20 d (1H, 18), 3.38 d (1H, 18), 3.73 s (3H), 7.21 d (1H, 8), 7.41 s (1H), 7.51 d (1H, 8), 8.78 s (1H)
IIId[b,c]	980, 1080, 1130, 1240, 1380 s, 1450, 1500, 1590, 1720 v.s, 3050, 3380	2.94 d (1H, 18), 3.18 d (1H, 18), 3.20 d (1H, 18), 3.39 d (1H, 18), 3.73 © (3H), 7.35 d (2H, 9), 7.60 d (2H, 9), 8.80 s (1H)
IIIe	870, 1020, 1070, 1110, 1130, 1230, 1380 s, 1450, 1490, 1590, 1720 v.s, 3050, 3380	2.94 d (2H, 18), 3.18 d (1H, 18), 3.20 (1H, 18), 3.38 d (1H, 18), 3.73 s (3H), 7.29 d (2H, 9), 7.73 d (2H, 9), 8.80 s (1H)
IIIf	890, 1030, 1080, 1140, 1230, 1380 s, 1450, 1480, 1590, 1720 v.s, 3050, 3390	2.95 d (1H, 18), 3.18 d (1H, 18), 3.20 d (1H, 18), 3.39 d (1H, 18), 3.76 s (3H), 7.36 m (4H), 8.83 s (1H)
IVa[d]	980, 1110, 1170, 1290, 1390 s, 1500, 1600, 1720 v.s, 3050	2.33 d (1H, 6), 2.37 d (1H, 6), 2.94 d (1H, 19), 3.04 d (1H, 19), 3.92 s (3H), 7.28–7.51 (5H)
IVb	980, 1110, 1170, 1290, 1390 s 1520, 1720 v.s, 3050	2.32 d (1H, 6), 2.36 d (1H, 6), 2.40 s (3H), 2.92 d (1H, 19), 3.03 d (1H, 19), 3.92 s (3H), 7.15–7.27 (4H)
IVc	880, 980, 1060, 1110, 1170, 1290, 1390 s, 1510, 1720 v.s, 3050	2.32 d (1H, 6), 2.36 d (1H, 6), 2.42 s (3H), 2.93 d (1H, 19), 3.03 d (1H, 19), 3.92 s (3H), 7.11–7.38 (3H)
IVd	980, 1020, 1100, 1160, 1290, 1390 s, 1500, 1720 v.s, 3050	2.32 d (1H, 6), 2.37 d (1H, 6), 2.94 d (1H, 19), 3.03 d (1H, 19), 3.92 s (3H), 7.26–7.49 (4H)

Table 2. (Contd.)

Compd. no.	IR spectrum, cm^{-1}	^1H NMR spectrum, δ, ppm (*J*, Hz)
IVe	980, 1020, 1080, 1100, 1160, 1290, 1390 s, 1490, 1720 v.s, 3050	2.32 d (1H, 6), 2.37 d (1H, 6), 2.94 d (1H, 19), 3.04 d (1H, 19), 3.92 s (3H), 7.26 d (2H, 8), 7.63 d (2H, 8)
IVf	980, 1110, 1160, 1290, 1390 s, 1510, 1600, 1720 v.s, 3050	2.32 d (1H, 6), 2.37 d (1H, 6), 2.94 d (1H, 19), 3.04 d (1H, 19), 3.92 s (3H), 7.14–7.32 (4H)
Va[e]		1.71 d (1H, 7), 2.68 d (1H, 7), 2.92 d (1H, 19), 3.44 d (1H, 19), 3.82 s (3H), 7.28–7.51 (5H)
Vb		1.70 d (1H, 7), 2.39 s (3H), 2.67 d (1H, 7), 2.91 d (1H, 19), 3.42 d (1H, 19), 3.81 s (3H), 7.15–7.27 (4H)
Vc		1.71 d (1H, 7), 2.42 s (3H), 2.67 d (1H, 7), 2.91 d (1H, 19), 3.43 d (1H, 19), 3.82 s (3H), 7.11–7.38 (3H)
Vd		1.72 d (1H, 7), 2.67 d (1H, 7), 2.92 d (1H, 19), 3.44 d (1H, 19), 3.82 s (3H), 7.26–7.49 (4H)
Ve		1.72 d (1H, 7), 2.68 d (1H, 7), 2.92 d (1H, 19), 3.44 d (1H, 19), 3.82 s (3H), 7.21 d (2H, 8), 7.63 d (2H, 8)
Vf		1.71 d (1H, 7), 2.68 d (1H, 7), 2.92 d (1H, 19), 3.43 d (1H, 19), 3.82 s (3H), 7.14–7.32 (4H)
VIa	980, 1100, 1160, 1290, 1390 s, 1510, 1600, 1720 v.s, 3050	2.26 d (1H, 6), 2.43 d (1H, 6), 2.89 d (1H, 19), 3.04 d (1H, 19), 3.91 s (3H), 7.28–7.53 (5H)
VIb[f]	980, 1100, 1160, 1290, 1390 c, 1520, 1720 v.s, 3050	2.26 d (1H, 6), 2.41 m (4H), 2.87 d (1H, 19), 3.02 d (1H, 19), 3.90 s (3H), 7.22 d (2H, 8), 7.30 d (2H, 8)
VIc	870, 970, 1060, 1100, 1160, 1290, 1380 s, 1500, 1720 v.s, 3050	2.26 d (1H, 6), 2.43 m (4H), 2.88 d (1H, 19), 3.02 d (1H, 19), 3.91 s (3H), 7.16–7.39 (3H)
VId	970, 1020, 1090, 1160, 1290, 1380 s, 1500, 1720 v.s, 3050	2.26 d (1H, 6), 2.42 d (1H, 6), 2.89 d (1H, 19), 3.03 d (1H, 19), 3.91 s (3H), 7.31 d (2H, 8), 7.48 d (2H, 8), 7.31 d (2H, 8)
VIe	970, 1020, 1080, 1160, 1290, 1380 s 1490, 1720 v.s, 3050	2.27 d (1H, 6), 2.43 d (1H, 6), 2.89 d (1H, 19), 3.04 d (1H, 19), 3.90 s (3H), 7.26 d (2H, 8) 7.63 d (2H, 8)
VIf	840, 970, 1100, 1160, 1290, 1390 s, 1520, 1720 v.s, 3050	2.27 d (1H, 6), 2.43 d (1H, 6), 2.89 d (1H, 19), 3.03 d (1H, 19), 3.91 s (3H), 7.17–7.37 (4H)
VIIa		1.73 d (1H, 7), 2.72 d (1H, 7), 2.96 d (1H, 19), 3.46 d (1H, 19), 3.81 s (3H), 7.28–7.53 (5H)
VIIc		1.73 d (1H, 7), 2.71 d (1H, 7), 3.45 d (1H, 19), 3.81 s (3H), 7.16–7.39 (3H)
VIIf		1.74 d (1H, 7), 2.72 d (1H, 7), 2.96 d (1H, 19), 3.45 d (1H, 19), 3.81 s (3H), 7.17–7.37 (4H)

[a] ^1H NMR spectra of compounds **IIIa**–**f** were registered in DMSO-d_6, of the other compounds in $CDCl_3$.

[b] ^1H NMR spectrum, $(CD_3)_2CO$, δ, ppm (*J*, Hz): 3.16 d (1H, 19), 3.31 d (1H, 18), 3.33 d (1H, 19), 3.61 d (1H, 18), 3.78 ©(3H), 7.39 d (1H, 9), 7.62 d (1H, 9), 8.18 © (1H).

[c] ^{13}C NMR spectrum, δ, ppm: 42.0 (C^9), 43.7 (C^4), 52.5 (CH_3æ), 69.4 (C^5), 129.6, 129.9, 131.9, 133.8 (C arom), 138.9 (C^3), 162.9, 174.3, 177.3 (C=æ).

[d] ^{13}C NMR spectrum, δ, ppm: 28.2 (C^2), 32.9 (C^3), 35.9 (C^7), 49.0 (C^1), 54.9 (CH_3æ), 126.7, 126.8, 129.2, 132.1 (C arom), 162.9, 173.5, 174.2 (C=æ).

[e] ^{13}C NMR spectrum, δ, ppm: 26.6 (C^2), 32.9 (C^3), 34.8 (C^7), 49.0 (C^1), 54.0 (CH_3æ), 126.7, 126.8, 129.2, 129.6, 132.1 (C arom), 162.9, 173.5, 174.2 (C=æ).

[f] ^{13}C NMR spectrum, δ, ppm: 21.6 (CH_3), 28.2 (C^2), 33.6 (C^3), 34.7 (C^1), 35.4 (C^7), 54.7 (CH_3), 126.5, 129.8, 130.2, 139.6 (C arom), 167.8, 172.5, 173.9 (C=æ).

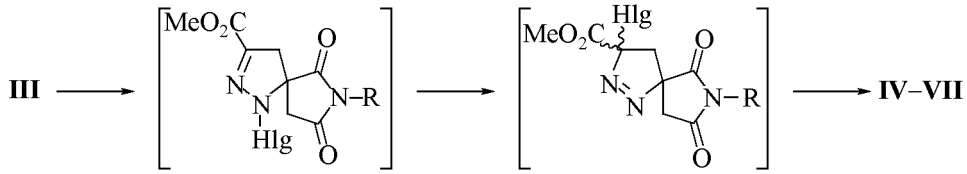
more stable isomer. Mixture of isomers **IVa** and **Va** was also obtained on treating pyrazoline **IIIa** with ICl. The structure and composition of compounds obtained were established from elemental analyses and spectral data.

In the IR spectra of esters **IVa–f**, **Va–f** is present an absorption band in the region of 1720 cm^{-1}. In the ^1H NMR spectra the signals from the methylene group proton of cyclopropane ring in *cis*-position to ester group (H^2 in **IVa–f** at 2.4 ppm, and H^1 in **Va–f**

at 2.7 ppm) appear downfield with respect to signals of protons (H^1 in **IVa–f** at 2.3 ppm and H^2 in **Va–f**) at 1.7 ppm) located *cis* to chlorine atom. The signals from the methylene group proton of the imide ring H^4 [**IVa–f**, 3.1 ppm (d, *J* 19 Hz), **Va–f**, 3.4 ppm (d, *J* 19 Hz)] are present downfield with respect to signals from H^3 proton [**IVa–f**, 2.93 ppm (d, *J* 19 Hz), **Va–f**, 2.91 ppm (d, *J* 19 Hz)] due to the through-space influence of the *syn*-located electron-withdrawing substituent at the cyclopropane ring (chlorine atom in the *anti*-isomer, methoxycarbonyl group in the *syn*-isomer). The stronger deshielding effect of the ester group results in larger downfield shift of signal from proton H^4–C^7 in *anti*-isomers **Va–f** compared to the signal of similar proton of the *syn*-isomers **IVa–f**.

The reaction between pyrazolines **IIIa–f** with bromine in acetic acid at 75°C afforded methyl 1-bromo-4,6-dioxo-5-azaspiro[2.4]heptane-1-carboxylates as mixtures of syn-isomers **VIa–f** and anti-isomers **VIIa, c, f** in a ratio 1.5 : 1 (**a**), 7.8 : 1 (**c**), 1.4 : 1 (**f**). Isomers **VIb, d**, and **e** were isolated as the only reaction products. The composition and structure of compounds obtained were established from elemental analyses and spectral data. In the ^{1}H NMR spectra of esters **VI, VII** are observed the signals from methylene group protons of cyclopropane ring H^2 [**VIa–f**, 2.4 ppm (*d*, *J* 6 Hz), **VIIa, c, f**, 1.7 ppm (*d*, *J* 7 Hz)] and H^1 [**VIa–f**, 2.3 ppm (*d*, *J* 6 Hz), **VIIa, c, f**, 2.7 ppm (*d*, *J* 7 Hz)]; from methylene group protons of imide ring H^4 [**VIa–f**, 3.05 ppm (*d*, *J* 19 Hz), (**VIIa, c, f**, 3.4 ppm (*d*, *J* 19 Hz)] and H^3 [**VIa–f**, 2.9 ppm (*d*, *J* 19 Hz), (**VIIa, c, f**, 3.0 ppm (*d*, *J* 19 Hz)], and also signals of protons belonging to aromatic fragment and to ester group.

The scheme of halocyclopropanes formation includes electrophilic substitution at nitrogen giving rise to pyrazoline **VIII** followed by rearrangement into 1-pyrazoline **IX** that eliminates nitrogen yielding cyclopropanes **IV–VII**.



EXPERIMENTAL

IR spectra were recorded on spectrophotometer UR-20 from 2% solutions of compounds in chloroform. ^{1}H NMR spectra were registered on spectrometer Bruker DPX-300 (300 MHz) from 2% solutions in $CDCl_3$ or DMSO-d_6.

Methyl 6,8-dioxo-7-phenyl-1,2,7-triazaspiro-[4.4]non-2-ene-3-carboxylate (IIIa). To a solution of 0.5 g (2.6 mmol) of itaconic acid *N*-phenylimide (**IIa**) in 10 ml of anhydrous benzene was added 0.5 g (5 mmol) of methyl diazoacetate (**I**). The mixture was kept at room temperature till separated a precipitate (72 h). The precipitate was filtered off and recrystallized from methanol. Yield of pyrazoline **IIIa** 0.54 g (72%). Esters **IIIb–f** were obtained similarly.

Methyl 4,6-dioxo-5-phenyl-1-chloro-5-azaspiro-[2.4]heptane-3-carboxylate (IVa + Va). (a) Through a solution of 0.4 g (1.4 mmol) of pyrazoline **IIIa** in 15 ml of anhydrous chloroform at 0°C was passed a flow of dry chlorine to saturation (1 min). The chloroform was evaporated, the residue was recrystallized from methanol. Yield of ester **IVa + Va** 0.32 g (77%). Esters **IVb, d, f** and **Vb, d, f** were prepared in the same way.

(b) To a solution of 0.2 g (0.7 mmol) of pyrazoline **IIIa** in 10 ml of anhydrous chloroform was added 0.34 g (2.1 mmol of ICl. The mixture was stirred for 2 h at room temperature, washed with $Na_2S_2O_3$ solution, and dried with $MgSO_4$. The solvent was evaporated, the residue was recrystallized from methanol. Yield of ester **IVa + Va** 0.15 g (71%).

Methyl 4,6-dioxo-1-chloro-5-(4-chlorophenyl)-5-azaspiro[2.4]heptane-3-carboxylate (IVd + Vd). Through a solution of 0.3 g (0.9 mmol) of pyrazoline **IIIe** in 10 ml of glacial acetic acid was passed a flow of dry chlorine for 1 min. The solvent was distilled off in a vacuum, the residue was recrystallized from methanol. Yield of ester (**IVd + Vd**) 0.22 g (73%). Similarly were obtained esters **IVb, e** and **Vc, e**.

Methyl 1-bromo-4,6-dioxo-5-(4-tolyl)-5-azaspiro-[2.4]heptane-3-carboxylate VIb. A mixture of 0.24 g (0.8 mmol) of pyrazoline **IIIb** and 0.15 ml of bromine

in 10 ml of glacial acetic acid was heated for 30 min to 80°C. The solvent and excess bromine were distilled off in a vacuum, to the residue was added methanol, and the solvent was placed into refrigerator till separated a precipitate. The precipitate was filtered off and recrystallized from methanol. Yield of ester **VIb** 0.19 g (69%). Esters **VIa, c–f,** and **VIIa, c, f** were prepared in analogous way.

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