High-pressure-assisted addition of (methoxyphenyl)maleic anhydrides to dienes. Synthesis of 3a-aryltetrahydroisoindole-1,3-diones

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A new synthesis of (2- and 4-methoxyphenyl)maleic anhydrides was accomplished, the reactions of which with cyclopentadiene and 3-sulfolene, serving as a 1,3-butadiene equivalent, furnished the [4+2]-cycloadducts. The latter were converted into imides of 2-aryl-bicyclo[2.2.1]hept-5-ene-2,3-dicarboxylic and 1-arylcyclohex-4-ene-1,2-dicarboxylic acids respectively.

Key words: Diels—Alder reaction, Heck reaction, fumaric acid, maleic anhydrides, tetrahydro-2-benzofuran-1,3-diones, tetrahydroisoindole-1,3-diones, sulfolene, cyclopenta-diene, high pressure, imides.

By now, only a limited number of 3a-aryl derivatives of tetrahydroisoindole-1,3-dione 1, 2 (see Refs 1, 2) and hexahydroisoindole 3 (see Ref. 3) was described in the chemical literature. Compound 1 was found to have a soporific effect,¹ compounds of type 3, an analgesic or analgesic antagonists activity,³ and compound 2 was predicted by PASS⁴ program to have the immunomodulating activity with 0.94 probability.



3a-Aryltetrahydroisoindole-1,3-diones as imides of cyclohex-4-ene-1,2-dicarboxylic acid can be synthesized from the corresponding anhydrides. The latter can be obtained, for example, by [4+2]-cycloaddition of dienes and arylmaleic anhydrides. However, synthesis of arylmaleic anhydrides often turns out to be labourous (the representative example is described in Ref. 5: four stages and 39% yield) and their activity as dienophiles in Diels—Alder reaction is relatively low.

In the present work, a convenient method for the synthesis of arylmaleic anhydrides based on the palladiumcatalyzed reaction of arylhalides with olefins (the Heck reaction) is proposed. Its stereochemical outcome consists in primary formation of arylfumaric acid esters from maleic acid esters and formation of arylmaleic acid esters from fumaric acid esters.⁶ The aq. DMF-K₂CO₃ system is used in modern version of this reaction, which enables one to accelerate the process and, for example, to carry out arylation of acrylic acid rather than its ester.^{7,8} Application of these conditions enabled us for the first time to involve fumaric acid in the Heck reaction: 2-arylmaleic acids were obtained from 2-iodoanisole and 4-iodoanisole (Scheme 1). The latter by heating *in vacuo* easily form the corresponding (methoxyphenyl)maleic anhydrides **4a** and **4b**. The yields of the anhydrides (60–80%) in our case proved to be much higher than in Meerwein synthesis^{9,10} (~30%).

Further we studied the influence of pressure on addition of anhydrides 4a and 4b to cyclopentadiene (Table 1). At room temperature and atmospheric pressure anhydride 4a reacts smoothly but too slowly to give adduct 5a (entry 1). The increase in the pressure up to 6-10 kbar enables one to accelerate the reaction approximately by the order of magnitude (entries 2 and 3), with the highest yield of adduct 5a being 89%. Anhydride 4b reacts with cyclopentadiene somewhat faster than 4a (entry 9; cf. with the data in Ref. 5), and the reaction is also considerably accelerated with the pressure increase (entry 10). In this case, a 5.5:1 mixture of endo-adduct 5b and its exo-stereoisomer (as NMR data suggest) is formed irrespective of pressure. The endo-configuration of the anhydride bridge in adduct 5b is confirmed by the presence in its ¹H NMR spectrum of a doublet ($\delta_{\rm H} = 3.84$, Table 2) with the spin-spin coupling constant value of 4.6 Hz, which is characteristic of exo-protons in norbornene system. The similar doublet presents in the spectrum of adduct 5a, as well as in the spectrum of endo-anhydride with R = H described in the literature² (see also earlier references cited in Ref. 11).

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Scheme 1



R = 2-OMe (a), 4-OMe (b)

Reagents and conditions: *a*. PdCl₂(MeCN)₂ (0.5 mol.%), Ph₃P, K₂CO₃, DMF-H₂O, ~120 °C, 4–12 h; *b*. 300–350 °C, 2 Torr; *c*. THF, 18 °C; *d*. CH₂Cl₂, 145 °C; *e*. NH₄OAc, THF, 10 kbar, 145 °C, 5 h.

In addition, we have studied the reaction of anhydride **4a** with 3-sulfolene (2,5-dihydrothiophene-1,1-dioxide), which is normally used as an equivalent of 1,3-butadiene in Diels—Alder reactions.¹² We failed to isolate adduct **6a** in the reaction at 145 °C and atmospheric pressure (*cf.* data in Ref. 13), whereas it forms in considerable amounts when the reaction was carried out in a sealed ampoule at moderate pressure (see Table 1, entry 4). Although the increased pressure shifts the equilibrium of the first stage

Table	1.	Pressure	influence	on	the	reactions	of	(methoxy-
pheny	l)m	aleic anhy	drides with	ı cy	clope	entadiene a	ınd	3-sulfolene

Entry	P/kbar	<i>T</i> /°C	<i>t</i> /h	Yield ^a (%)				
$4a + C_5H_6$ (1 : 1.2, in THF)								
1	0.001	18	192	79				
2	10	18	24	78				
3	6.5	18	72^{b}	89				
4a + sulfolene (1 : 1.15, in CH ₂ Cl ₂)								
4	0.8	145	8	58				
5	2.5	145	8	69				
6	7.5	145	8	77				
7	11	145	8	84				
8	6	145	18	86				
$4b + C_5H_6$ (1 : 1.2, in THF)								
9	0.001	18	120^{b}	66 (80)				
10	6	18	24^{b}	66 (80)				
4b + sulfolene $(1 : 1.15, \text{ in } CH_2Cl_2)$								
11	2.5	145	8^b	(91)				

^{*a*} The yield of isolated product with acceptable melting point; in parentheses, the yield based on ¹H NMR spectroscopic data. ^{*b*} The complete conversion of starting anhydride (TLC or NMR).

of the reaction (the dissociation of sulfolene into 1,3-butadiene and SO₂) to the left, the overall process is slightly accelerated (entries 5–7), with the highest yield of compound **3a** being 86% (entry 8). Anhydride **4b** reacts with 3-sulfolene easier than its isomer **4a** (entry 11, cf. with entry 5).

The melting points of 2-methoxyphenyl derivatives **5a** and **6a** are higher than those of 4-methoxyphenyl isomers **5b** and **6b**, as well as of their analogs with R = H (see Refs 1 and 2), by 50 °C or more (Table 3). Considerable differences are also observed in NMR signals of aliphatic protons located near the aryl group: for some protons the changes of δ_H values in different directions may be as large as 0.5 (see Table 2). It can be supposed that these anomalies occur due to the structure reasons: the 2-methoxy group should hinder the rotation of the benzene ring around Ar—C bond resulting in its "freezing" in position of the minimum sterical repulsion.

The sterical factor causes chemical inertness of anhydride **5a**. Thus the effort to obtain imide **7** by fusion of anhydride **5a** with urea at 150 °C gave the recovered anhydride **5a** only. Its reaction with NH₃ solution in CHCl₃ at room temperature after 24 h reaches 30% conversion only. However, we succeeded in obtaining of imide **7** in 90% yield by reaction of compound **5a** with a small excess of NH₄OAc at 10 kbar and 145 °C. Anhydride **6a** smoothly forms imide **8** under the same conditions.

In conclusion, application of the Heck reaction with the subsequent diene synthesis under high pressure enables one to perform an effective synthesis of 3a-aryl derivatives of tetrahydro-2-benzofuran-1,3-dione and tetrahydroisoindole-1,3-dione.

Com-	δ (<i>J</i> /Hz)						
pound	CH ₂	СН	OCH ₃ (s)	=СН	Ar—H	NH (s)	
4a	_	_	3.98	7.38 (s)	7.00 -7.15 (m, 2 H); 7.52 (t, 1 H, $J = 7.9$); 8.34 (dd, 1 H, J = 7.9, $J = 1.3$)	_	
4b	_	_	3.90	6.83 (s)	7.01, 7.98 (both d, 2 H each, $J = 8.9$)		
5a	1.88, 1.93 (both d, 1 H each, <i>J</i> = 9.0)	3.35 (d, 1 H, J = 4.6); 3.47, 3.86 (both m, 1 H each)	3.81	6.42, 6.49 (both dd, 1 H each, <i>J</i> = 5.7, <i>J</i> = 3.0)	6.92 (d, 1 H, <i>J</i> = 8.5); 7.05 (t, 1 H, <i>J</i> = 7.6); 7.32–7.41 (m, 2 H)	_	
5b	1.73, 1.82 (both d, 1 H each, <i>J</i> = 9.2)	3.59 (m, 2 H); 3.84 (d, 1 H, J = 4.6)	3.82	6.43, 6.51 (both dd, 1 H each, J = 5.7, J = 3.0)	6.95, 7.45 (both d, 2 H each, <i>J</i> = 9.2)	—	
6a	2.24 (dd, 1 H, $J = 16.4$, J = 5.9); 2.71 (ddd, 1 H, $J = 16.4$, $J = 5.7$, J = 2.0); 2.75–2.80 (m, 2 H)	3.44 (dd, 1 H, J = 7.6, J = 2.4)	3.82	6.03, 6.12 (both m, 1 H each)	6.94 (d, 1 H, <i>J</i> = 7.9); 7.02 (td, 1 H, <i>J</i> = 7.7, <i>J</i> = 1.1); 7.33-7.36 (m, 2 H)		
6b	2.40–2.52, 2.78–2.95 (both m, 2 H each)	3.55 (dd, 1 H, J = 7.9, J = 2.6)	3.82	6.03 (m, 2 H)	6.92, 7.32 (both d, 2 H each, $J = 9.2$)	_	
7**	1.63, 1.72 (both d, 1 H each, <i>J</i> = 8.2)	3.07 (d, 1 H, $J =$ 4.9); 3.22, 3.74 (both m, 1 H each)	3.70	6.23, 6.32 (both m, 1 H each); 7.47 (d, 1 H, J = 7.3)	6.98–7.04 (m, 2 H); 7.31 (t, 1 H, <i>J</i> = 7.6)	10.80	
8**	2.17 (m, 1 H); 2.39–2.47 (m, 2 H); 2.66 (br.d, 1 H, <i>J</i> = 15.3)	3.05 (dd, 1 H, J = 7.3, J = 2.4)	3.75	5.92, 6.04 (both m, 1 H each)	6.97 (t, 1 H, <i>J</i> = 7.6); 7.06 (d, 1 H, <i>J</i> = 8.6); 7.28–7.33 (m, 2 H)	11.22	

Table 2. ¹ H NMR spectra (CDCl ₃) of co	ompounds synthesized*
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* Operating frequency 250 MHz, for spectrum of **3a**, 500 MHz. ** In DMSO-d₆.

 Table 3. Elemental analysis data and melting points of compounds synthesized

Com- pound	Yield (%)	M.p. /°C	<u>Fou</u> Cale	nd culated	Molecular formula	
			С	Н	N	
5a	89	133—	<u>71.33</u>	<u>5.32</u>	_	$C_{16}H_{14}O_4$
5b	66	-135 85-86	71.10 <u>71.31</u>	5.22 <u>5.50</u>	_	C ₁₆ H ₁₄ O ₄
6a	86	124.5—	71.10 70.11	5.22 5.79	_	$C_{15}H_{14}O_{4}$
		-125.5	69.76	5.46		15 14 4
6b	91	Oil		—	—	$C_{15}H_{14}O_4^*$
7	90	237	<u>70.88</u>	<u>6.00</u>	<u>5.22</u>	$C_{16}H_{15}NO_{3}$
			71.36	5.61	5.20	
8	68	203.5 -	<u>69.96</u>	<u>6.07</u>	<u>5.40</u>	C ₁₅ H ₁₅ NO ₃
		-204.5	70.02	5.88	5.44	

* FT MS, found: m/z 259.09641, $[M + H]^+$, $C_{15}H_{15}O_4$; calculated: $[M + H]^+$ 259.09649 Da.

Experimental

Melting points (corrected) of the products synthesized were determined with the Boetius heating stage. ¹H NMR spectra were recorded on a Bruker WM-250 spectrometer (operating frequency 250.13 MHz) and on a Bruker WXR-500 spectrometer (operating frequency 500.13 MHz), ¹³C NMR spectra were recorded on a Bruker WXR-500 spectrometer (operating frequency 125.76 MHz). Elemental analysis was performed on a Perkin—Elmer 2400 apparatus. FT MS spectrum (Fourier transform ionic cyclotronic resonance) was registered on a Finnigan LTQ FT instrument.

Cyclopentadiene was obtained by thermal decomposition of the commercially available dicyclopentadiene immediately before use. THF was distilled over KOH and then over CaH_2 , all the other reagents and solvents (pure grade or pure for analysis grade) were used without further purification.

Reactions under high pressure were carried out on a Barostat¹⁴ setup of a cylinder—plunger type in a 1- or 4-mL Teflon ampoules.

(2-Methoxyphenyl)maleic anhydride (4a). A mixture of 2-iodoanisole (46.8 g, 0.2 mol), fumaric acid (23.2 g, 0.2 mol),

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 K_2CO_3 (55.2 g, 0.4 mol), $PdCl_2(MeCN)_2$ (0.26 g, 1 mmol, 0.5 mol.%), Ph_3P (0.52 g, 2 mmol, 1 mol.%), DMF (200 mL), and water (150 mL) was gently refluxed with stirring for 12 h under argon, during which the yellow solution with little precipitate was formed. The reaction mixture was concentrated *in vacuo*, the solid residue was washed with EtOAc, dissolved in minimum water, and acidified with HCl to the pH value of 1. The precipitate of (2-methoxyphenyl)maleic acid that liberated was filtered off, washed with a small amount of water, and dried in the open air. The crude acid was placed into a sublimation apparatus and slowly heated up to $300-350 \,^{\circ}C$ *in vacuo* (2 Torr). Anhydride **4a** was condensed as yellow crystals, the yield was 23.8 g (58%), m.p. 134–136 $^{\circ}C$ (toluene—hexane) (*cf.* Ref. 10: m.p. 135–136 $^{\circ}C$).

(4-Methoxyphenyl)maleic anhydride (4b) was obtained similarly from 4-iodoanisole, the duration of heating was 4 h, the yield was 79%. Yellow crystals, m.p. 145 °C (from toluene; with partial subl.) (*cf.* Refs 5 and 10: m.p. 142–143.5 °C).

Investigation of reactions of arylmaleic anhydrides 4a,b with cyclopentadiene and sulfolene under high pressure. A solution of anhydride 4a or 4b (0.12 g, 0.6 mmol) and cyclopentadiene (0.06 mL, 0.72 mmol) or sulfolene (0.08 g, 0.68 mmol) in THF or CH₂Cl₂ (0.8 mL) was kept under listed in Table 1 conditions. The presence of the unreacted anhydride was controlled by TLC (Silufol, acetone—hexane (1 : 3)). The work-up methods of the reaction mixtures are given below while describing syntheses of adducts 5a,b and 6a,b, their yields are summarized in Table 1.

(1*R**,2*S**,3*R**,4*S**)-2-(2-Methoxyphenyl)bicyclo[2.2.1]hept-5-ene-2,3-dicarboxylic acid anhydride (5a). A solution of anhydride 4a (0.45 g, 2.2 mmol) and freshly distilled cyclopentadiene (0.22 mL, 2.67 mmol) in anhydrous THF (3.5 mL) was kept under pressure of 6.5 kbar and 18 °C for 72 h. The solvent was evaporated and Et₂O (2 mL) was added to the residue. The formed colorless crystals of the adduct were washed with Et₂O—hexane mixture and dried *in vacuo*. The yield was 0.50 g (84% calculated from anhydride 4a); concentrating the mother liquor gave additional crop of the product 5a (0.03 g, 5%), m.p. 133–135 °C (Et₂O).

(1*R**,2*S**,3*R**,4*S**)-2-(4-Methoxyphenyl)bicyclo[2.2.1]hept-5-ene-2,3-dicarboxylic acid anhydride (5b). An oil was obtained in experiments 9 and 10 (see Table 1) after evaporating the solvent, which contained 80% of the main product (¹H NMR data). The only considerable impurity (15%) is characterized by ¹H NMR signals at δ : 6.03, 6.31 (both dd, =CH—, J = 5.6 Hz, J = 3.3 Hz), 6.88, 7.25 (both d, J = 9.2 Hz, Ar), which enables us to propose a structure of *exo*-stereoisomer for it (see also Ref. 11). The prolong storage of the oil in a vacuum desiccator caused crystallization. Ether was added to this mass, after a few hours the mother liquor was decanted, and the solid residue was recrystallized from benzene—hexane mixture. The yield was 66%, colorless shining crystals, m.p. 85—86 °C (benzene—hexane).

(1*R**,2*S**)-1-(2-Methoxyphenyl)cyclohex-4-ene-1,2-dicarboxylic acid anhydride (6a). A solution of anhydride 4a (1.03 g, 5.0 mmol) and 3-sulfolene (0.68 g, 5.75 mmol) in CH₂Cl₂ (3 mL) was kept under pressure of 6 kbar and 145 °C for 18 h. The solvent was evaporated and Et₂O (3 mL) was added to the residue. The formed colorless crystals of the adduct were washed with Et₂O—hexane mixture and dried *in vacuo*. The yield was 1.11 g (86% calculated from anhydride 4a), m.p. 122–124 °C (crude), m.p. 124.5–125.5 °C (benzene—hexane). ¹³C NMR (CDCl₃), δ : 23.59, 28.89 (CH₂); 47.16 (OC-<u>C</u>H-Ar); 50.67 (OC-<u>C</u>-Ar); 55.36 (OMe); 111.51, 121.11, 126.35, 126.95, 127.55, 128.05, 129.64 (C_{Ar}, =CH); 156.21 (<u>C_{Ar}</u>-OMe); 174.20, 175.91 (C=O).

(1*R**,2*S**)-1-(4-Methoxyphenyl)cyclohex-4-ene-1,2-dicarboxylic acid anhydride (6b). Yellow oil was obtained under conditions of experiment *11* (see Table 1) after evaporation of the solvent, which contained ~90% of the main product (¹H NMR data). The prolong storage in the open air transforms the oil-like anhydride into the corresponding acid, causing its solidification. MS (electrospray, MeCN-HCO₂H (0.5%), 2.6 kV, 1.5 μ L min⁻¹), found: *m*/*z* 277.10718, [M + H₂O + H]⁺, C₁₅H₁₇O₅; 259.09641 [M + H]⁺, C₁₅H₁₅O₄. Calculated: [M + H₂O + H]⁺, 277.10705 Da; [M + H]⁺ 259.09649 Da.

 $(1R^*, 2S^*, 3R^*, 4S^*)$ -2-(2-Methoxyphenyl)bicyclo[2.2.1]hept-5-ene-2,3-dicarboxylic acid imide (7). A mixture of anhydride 5a (0.20 g, 0.74 mmol), NH₄OAc (0.07 g, 0.91 mmol), and THF (0.8 mL) was kept under pressure of 10 kbar and 145 °C for 5 h. The solvent was evaporated, the residue was recrystallized from AcOH-H₂O. The yield was 0.18 g (90%), m.p. 237 °C (EtOAc-PrⁱOH).

 $(1R^*, 2S^*)$ -1-(2-Methoxyphenyl)cyclohex-4-ene-1,2-dicarboxylic acid imide (8) was obtained similarly from anhydride 6a in 68% yield, m.p. 203.5–204.5 °C (AcOH–H₂O (or EtOAc)).

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