Ene Reactions of Arylmethylenedihydropyrazoles with 4-Phenyl-3*H*-1,2,4-triazole-3,5(4*H*)-dione

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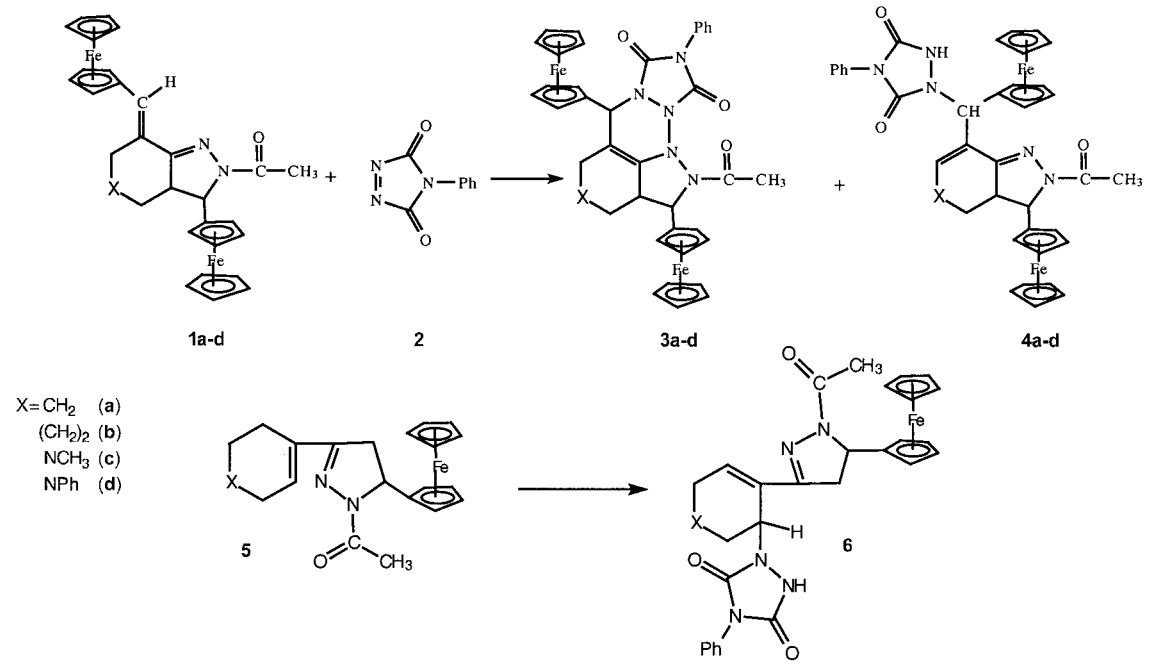
Abstract: 2-Acetyl-3-aryl-7-arylmethylene-3,4,5,6,7,9-hexahydro-2*H*-indazoles enter into the ene reaction with 4-phenyl-3*H*-1,2,4-triazole-3,5(4*H*)-dione to give the corresponding monoene adducts. Under analogous conditions, 3-aryl-7-arymethylene-2-methyl-3,4,5,6,7,9-hexahydro-2*H*-indazoles give mono- and polyaddition products. The structures of compounds obtained were established using UV, IR, ^{1}H and ^{13}C NMR spectroscopy and X-ray diffraction analysis.

Key words: chalcones, Diels–Alder reactions, ene reactions, dihydropyrazoles

α,β-Chalcones react with hydrazine to form unstable, 1-unsubstituted 4,5-dihydropyrazoles, which are converted into stable 1-acetyl derivatives by acetylation.[1–5] It is known that many biologically active compounds incorporate pyrazole fragments. Thus bicyclic acetyldihydropyrazoles synthesized from mono- and bis(arylmethylene)-cycloalkanones manifest rather high pharmacological activities.[6–8] Ferrocenyl substituted dihydropyrazoles also possess biological activities, as is exemplified in antiviral 4-acetyl-3-ferrocenyl-1,4,5- triazatricyclo[5.2.2.0^{2,6}]undec-5-ene.[9]

Introduction of additional nitrogen-containing fragments into dihydropyrazoles may be promising as regards broader spectrum of valuable biological properties in compounds to be synthesized.

In this respect, [4+2] cycloaddition and ene reaction products (compounds **3** and **4**, respectively, Scheme 1) recently prepared[10,11] from bi- and monocyclic ferrocenyldihydropyrazoles **3a–d** and *N*-phenylazodicarboximide **2** are of certain interest. The nitrogenous organic compounds **3a–d** possess antiviral activities.[11–15]



Scheme 1

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Poor solubilities of these compounds in different solvents is their major drawback. Thus, the development of the methods for the synthesis of this type of compounds with aryl or alkyl substituents and studies of their chemical and pharmacological properties is a topical problem. In the present work, we have studied the reactions of arylmethylene substituted dihydropyrazoles with 4-phenyl-3*H*-1,2,4-triazole-3,5(4*H*)-dione (**2**).

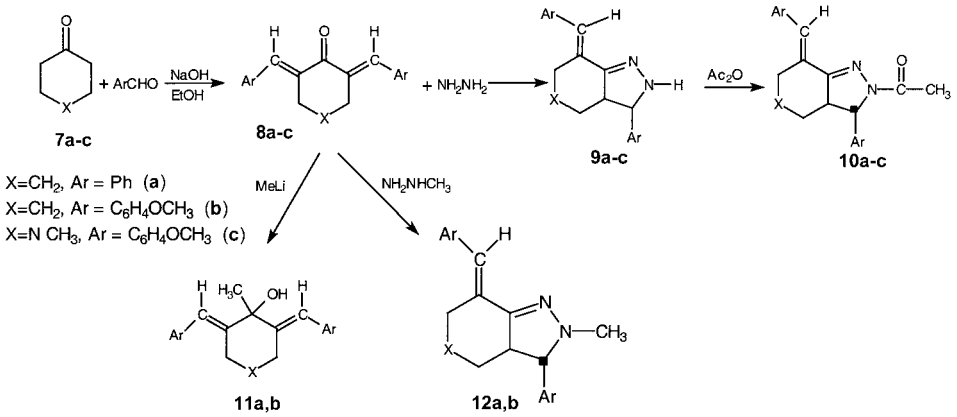
Chalcones **8a**–**c** prepared by the condensation of benzaldehyde or anisaldehyde with cyclohexanone **7a**,**b** or 1-methyl-4-piperidone (**7c**) in the presence of alkali in aqueous ethanol served as the starting compounds for the synthesis of pyrazoles **9** and **10** (Scheme 2).

Chalcones **8a**–**c** were isolated exclusively as single diastereoisomer forms with *E*,*E*-configuration of the arylmethylene fragments. Crystals suitable for X-ray structural analysis of these chalcones could not be grown. However, indirect proof of their structures was obtained from X-ray structural analysis of single crystals of alcohols prepared by the addition of methyllithium, e.g., of 2,5-diarylmethylidene-1-methyl-cyclohexanols **11a** and **11b**.

The general view of the molecules **11a**,**b** are shown in Figure 1. As follows from X-ray structural data, the arylmethylene fragments in the alcohol possess *E*,*E*-configuration. One may state with high degree of confidence that the same configurations exist in the respective original chalcones **8a**–**c**.

N-Acetylated dihydropyrazoles **10a**–**c** were obtained by the addition of hydrazine to chalcones **8a**–**c** followed by acylation of the 2-unsubstituted bicyclic products **9a**–**c**. *N*-Methyldihydropyrazoles **12a**,**b** were prepared by the addition of methylhydrazine to chalcones **8a** and **8b**, respectively. Both unsubstituted and 2-substituted dihydropyrazoles were obtained in good yields. The formation of dihydropyrazoles **9a**–**c**, **10a**–**c** and **12a**,**b** occurs stereospecifically.[16,17] These compounds were isolated as only one diastereoisomeric form with *trans*-orientation of the hydrogen atoms H-3 and H-9 of the dihydropyrazole ring as evidenced from ^{1}H and ^{13}C NMR spectral data. Thus chemical shifts for the protons H-3 in **9a**–**c**, **10a**–**c**, **12a**, and **12b** are, δ = 4.35, 4.54, 5.59, 4.93, 4.86, 5.63, 3.65, and 3.58, and the spin-spin coupling constants $^{3}J_{\text{H-3, H-9}}$ are equal to 10.2, 10.3, 9.8, 9.3, 9.5, 11.2, 13.8, and 14.0, respectively, which is characteristic of *trans*-isomers. It has been shown that *cis*-isomers are characterized by smaller coupling constants ($^{3}J_{\text{H-3, H-9}}$ = 5.0–2.0 Hz).[18]

Dihydropyrazoles **10**, **12** contain a C=C double bond conjugated with the C=N bond of the dihydropyrazole ring. They can behave as *s*-*cis*-heterodienes in reactions with active dienophiles. The presence of allylic hydrogen atoms in compounds **10**, **12** makes it possible to perform ene synthesis as has been shown in the case of ferrocenyl substituted analogs.



Scheme 2

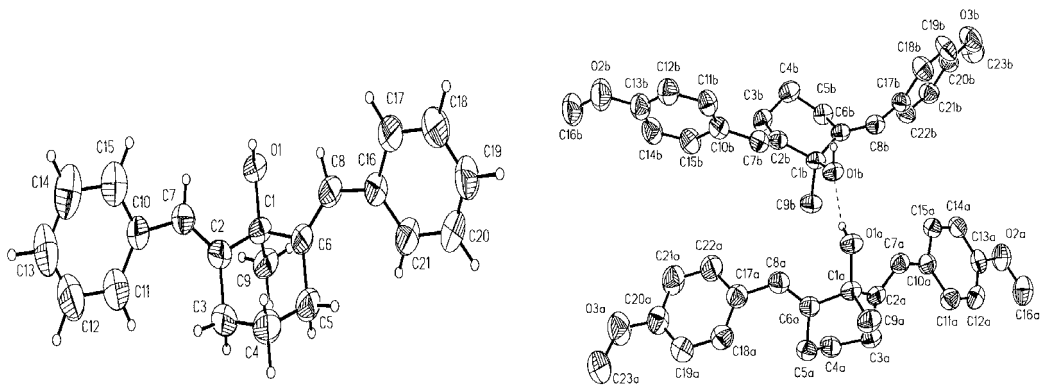
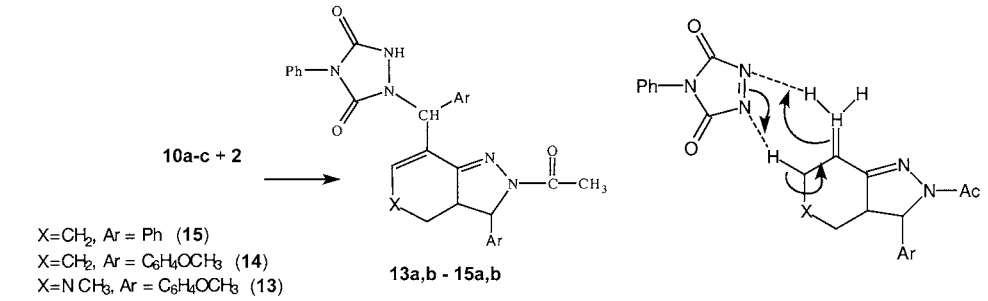


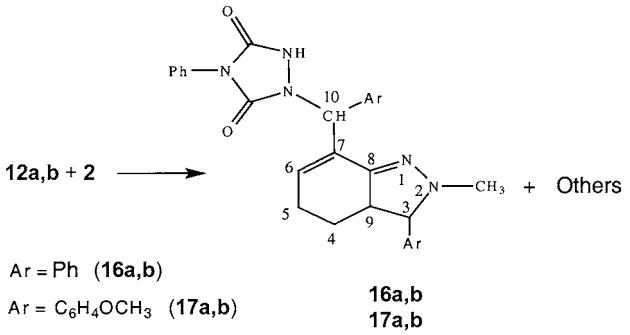
Figure 1 X-ray structure of compounds **11a** and **11b**.



Scheme 3 Ene addition to compounds **13**–**15** and one of the possible mechanisms of ene product formation[20,21]

However, dihydropyrazoles **10**, **12** do not enter into [4+2] cycloaddition with **2**, they rather give products of the ene addition. In the case of compounds **10a**–**c**, monoaddition products **13**–**15** are formed (Schemes 3 and 4), this could be due to the acceptor character of the substituents.

Unlike *N*-acetyl derivatives, *N*-methyl analogs **12a**,**b** were found to be able to add up to seven moles of the enophile per mole of the starting dihydropyrazole.



Scheme 4

If the reaction was carried out at –5 to 0 °C with equimolar ratio of reactants, the ene adducts **16** and **17** were isolated in satisfactory yields. However, one could not suppress the formation of polyadducts, which were formed in 20–25% yields (TLC, ^{1}H NMR data). The monoaddition products **16**, **17** were separated from the products of the reaction by chromatography on alumina. Also observed were other compounds apparently mixtures of di-, tri-, and polyaddition (others) products; their isolation in the individual form and structural elucidation could not be accomplished so far because of their poor solubilities in organic solvents. ^{1}H NMR spectroscopic data suggest the presence of different diastereoisomers; attempts to separate them by TLC failed. Heavy overlap of signals in all the regions of the ^{1}H NMR spectra precluded their assignments. Data from NMR and mass spectrometry allowed only rough estimates of the number of the enophile molecules that reacted with one molecule of dihydropyrazole. Studies in this direction are in progress. It was convincingly established that the sequential mole-per-mole addition of the enophile to a solution of *N*-methyl dihydropyrazole results in the incorporation of 7 moles of the enophile per mole of the ene component.

The structures of compounds **13**–**17** were established on the basis of ^{1}H and ^{13}C NMR spectra. ^{1}H NMR spectral data suggest that these compounds were formed as mixtures of two diastereomers in ca. 2:1, 2.5:1, or 3:1 ratios the major diastereomeric form hereafter is denoted **a** and the minor **b**.

Characteristic signals in the ^{1}H NMR spectra include broad singlets for the NH protons (δ = ca. 9.5–9.9), singlets for the aliphatic methine protons, singlets of an olefinic protons of compounds **13a** and **13b** or triplets of analogous olefinic protons of compounds **14a**–**17a** and **14b**–**17b**.

Individual diastereomers of compound **15** were separated by PTLC on silica gel. The spatial structure of the adduct **15a** was established using X-ray diffraction analysis of single crystals grown from 96% aqueous methanol. X-Ray structural analysis of **15a** (Figure 2) has shown that the orthorhombic crystals of **15a** contain in their unit cell twin asymmetric molecules of the ene adducts corresponding to both diastereomers connected to each other through crystallized water molecules. The yields of compounds **8**–**10** and **12**–**17** are listed in Table 1.

The water molecules form hydrogen bonds with NH and C=O groups (5-oxo) of the 1-phenylurazolyl substituent. The general view of the molecule **15a** and packing of the molecules in a crystal are shown in Figure 2. The key element in the structure of **15a** is the central bicyclic framework. The six-membered ring is fused to the five-membered ring existing in a flattened envelope conformation. The phenyl substituent at C-7 is pseudo-equatorial. The hydrogen atoms H-3 at C-3 and H-9 at C-9 are *trans*-arranged. Data from the X-ray analysis show that the N-1–C-8 bond in the the dihydropyrazole ring is somewhat longer [d = 1.260(6) Å], while the N-1–N-2 bond is somewhat shorter [d = 1.408(5) Å] than the standard values (C=N bond length is 1.23 Å[18] and N–N bond length is 1.45 Å[19]). The geometrical parameters of the cyclohexene and phenyl moieties have standard values.

It was thus shown that reactions of arylmethylene substituted bicyclic dihydropyrazoles with active dieno- enophiles follow the ene pathway.[20,21] In the case of the acetyl substituent at N-2, mono-ene addition products are formed. Substitution of the donor methyl group for the acceptor acetyl group results in enhanced reactivities of the ene components which can add stepwise several enophile

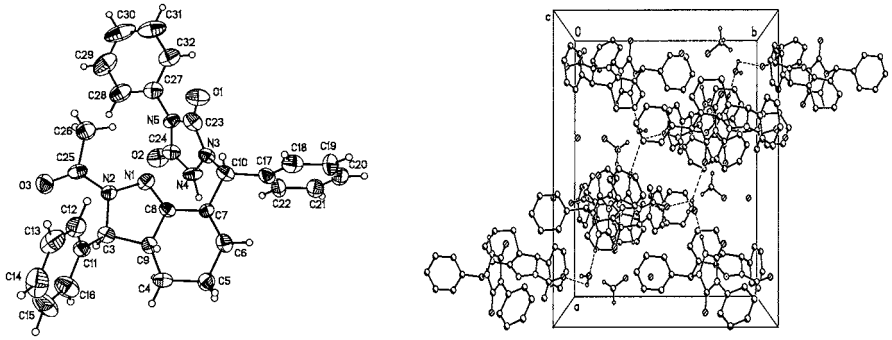


Figure 2 Molecular and Crystal packing of compound **15a**. The dihedral angles are C25 N2 C3 C11 –63.1 (7), N1 N2 C3 C11 136.2 (5), C25 N2 C3 C9 176.4 (5), N1 N2 C3 C9 15.7 (5), C9 C3 C11 C16 -85.9 (7), C25 N2 C3 C9 176.4 (5), N1 N2 C3 C9 15.7 (5), C7 C8 C9 C4 –42.2 (7), C7 C8 C9 C3 –167.9 (5), C5 C4 C9 C3 172.5 (4), C11 C3 C9 C8 -138.5 (5), C11 C3 C9 C4 99.4 (6), C9 C3 C11 C12 87.6 (8).

Table 1 Compounds **8**–**17** Prepared

Compound	Yield (%)	Compound	Yield (%)
8a	68	**13b**	24
8b	65	**14** (ca. 2:1),	65
8c	71	**14a**	43
9a	74	**14b**	22
9b	72	**15a** (ca. 2.5:1)	70
9c	67	**15a**	50
10a	73	**15b**	20
10b	71	**16** (ca. 2.5:1.	60
10c	69	**16a**	42
12a	72	**16b**	17
12b	69	**17**	58
13 (ca. 2:1)	73	**17a**	43
13a	48	**17b**	14

molecules depending on the number of the allylic hydrogen atoms formed upon each addition step. Studies of the effects of different factors on the features of the stepwise additions ene poly-addition and isolation of products of each step deserve special investigations.

UV spectra were recorded on a Specord UV-VIS spectrophotometer. IR spectra were obtained for pellets with KBr using a Specord 75-IR spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded on a Unity Inova Varian (300 and 75 MHz) spectrometer for solutions in $CDCl_3$ with Me_4Si as the internal standard. Mass spectra were obtained on a Varian MAT CH-6 (70 eV) instrument. Column chromatography was carried out on alumina (activity III according to Brockmann) and TLC was carried out on SiO_2. The parameters of the unit cell and the X-ray diffraction intensities were recorded on Siemens P4/PC spectrometer. The crystallographic data, parameters of the X-ray experiment, and refinements are listed in the legend to Figure 2. Structures of compounds **10** and **12a** were solved by the direct method and refined using the least-squares method in a full-matrix anisotropic approximation for non-hydrogen atoms.

2,6-Bis(arylmethylidene)cyclohexanones 8a–c

These compounds were synthesized using a conventional procedure[5] from cyclohexanone and benzaldehyde or *p*-anisaldehyde in the presence of alkali in aq EtOH and purified by column chromatography on alumina (eluent, hexane–$CHCl_3$, 3:1).

8a

Pale yellow powder; yield: 68%; mp 120–121 °C (Lit.[5] mp 121–122 °C).

^{1}H NMR: δ = 1.77 (m, 2 H, CH_2), 2.91 (m, 4 H, CH_2), 7.31–7.48 (m, 10 H, C_6H_5), 7.80 (2 H, CH=, *J* = 2.0 Hz).

^{13}C NMR: δ = 22.9 (CH_2), 28.3 (2 CH_2), 128.2 (2 CH_2=), 128.5, 130.2, 136.8 (2 C_6H_5), 135.8,136.1 (2 C_{ipso}), 190.2 (C=O).

MS: *m*/*z* = 273 $[M]^+$.

8b

Pale yellow powder; yield: 65%; mp 153–154 °C (Lit.[5] mp 155 °C).

^{1}H NMR: δ = 1.79 (m, 2 H, CH_2), 2.91 (m, 4 H, CH_2), 3.84 (s, 6 H, 2 CH_3), 6.93 (d, 2 H, C_6H_4), 7.45 (d, 2 H, C_6H_4, *J* = 8.8 Hz), 7.76 (s, 2 H, CH=).

^{13}C NMR: δ = 22.9 (CH_2), 28.4 (2 CH_2), 55.2 (2 CH_3), 113.8 (2 CH=), 132.1, 136.4 (2 C_6H_4), 128.6 (2 C), 134.2 (2 C_{ipso}), 159.8 (2 C–O), 190.0 (C=O).

MS: *m*/*z* = 334 $[M]^+$.

8c

Pale yellow powder; yield: 71%; mp 210–211 °C.

IR: 1620, 1678, 2826, 3949 cm^{-1}.

^{1}H NMR: δ = 2.48 (s, 3 H, CH_3), 3.76 (d, 4 H, CH_2, *J* = 1.2 Hz), 3.84 (s, 6 H, CH_3), 6.95 (d, 4 H, C_6H_4, *J* = 9.0 Hz), 7.37 (d, 4 H, C_6H_4, *J* = 9.0 Hz), 7.77 (s, 2 H, CH=).

^{13}C NMR: δ = 45.8 (CH_3), 55.2 (CH_2), 57.1 (2 CH_3), 114.0 (2 CH=), 132.2, 135,9 (C_6H_4), 127.9 (2 C), 131.2 (2 C_{ipso}), 160.1 (2 C–O), 186.7 (C=O).

UV ($CHCl_3$): λ_{max} = 205, 356 nm.

Anal. Calcd for $C_{22}H_{23}NO_3$: C, 75.62; H, 6.63; N, 4.01. Found: C, 75.53; H, 6.75; N, 3.87.

Dihydropyrazoles 9a–c

These compounds were synthesized by a standard procedure[5] from the chalcones **8a–c** and hydrazine hydrate in EtOH. The precipitated dihydropyrazoles were filtered, washed with EtOH on a filter, and dried over P_2O_5.

9a

Colorless powder; yield: 74%; mp 84–86 °C (Lit.[5] mp 84–86 °C).

^{1}H NMR: δ = 1.43 (m, 1 H, CH_2), 1.57 (m, 1 H, CH_2), 1.80 (m, 1 H, CH_2), 1.98 (m, 1 H, CH_2), 2.48 (m, 1 H, CH_2), 2.88 (m, 1 H, CH_2), 3.00 (m, 1 H, CH, *J* = 10.2 Hz), 4.35 (d, 1 H, CH, *J* = 10.2 Hz), 7.19 (d, 1 H, CH, *J* = 1.8 Hz), 7.24–7.49 (m, 10 H, 2 C_6H_5).

MS: *m*/*z* = 228 $[M]^+$.

9b

Colorless powder; yield: 72%; mp 94–95 °C (Lit.[5] mp 93–95 °C).

^{1}H NMR: δ = 1.47 (m, 1 H, CH_2), 1.69 (m, 1 H, CH_2), 1.97 (m, 1 H, CH_2), 2.21 (m, 1 H, CH_2), 2.56 (m, 1 H, CH_2), 2.91 (m, 1 H,CH_2), 2.99 (m, 1 H, CH, *J* = 10.3 Hz),3.77 (s, 3 H, CH_3), 4.54 (d, CH, *J* = 10.3 Hz), 6.92 (m, 4 H, C_6H_5), 7.12 (d, 1 H, CH, *J* = 2.3), 7.21 (m, 4 H, C_6H_5), 8.61 (s, 1 H, NH).

MS: *m*/*z* = 316 $[M]^+$.

9c

Colorless crystals; yield: 67%; mp 169–171 °C.

^{1}H NMR: δ = 2.25 (s, 3 H, CH_3), 2.70 (dd, 1 H, CH_2, *J* = 5.7, 9.8 Hz), 2.88 (dd, 1 H, CH_2, *J* = 2.6, 9.8 Hz), 3.59 (m, 2 H, CH_2), 3.77 (s, 3 H, CH_3), 3.82 (s, 3 H, CH_3), 3.86 (d, 1 H, CH, *J* = 11.3 Hz), 5.59 (d, 1 H, CH, *J* = 11.3 Hz), 6.78–7.20 (m, 8 H, 2 C_6H_5), 7.33 (s, 1 H, CH=), 9.60 (s, 1 H, NH).

Anal. Calcd for $C_{22}H_{25}N_3O_2$: C, 72.70; H, 6.93; N, 11.56. Found: C, 72.58; H, 7.09; N, 11.43.

MS: *m*/*z* = 363 $[M]^+$.

***N*-Acetyldihydropyrazoles 10a–c**

These compounds were obtained by treatment of anhyd compounds **9a–c** with Ac_2O according to a standard procedure and purified by recrystallization from EtOH.

2-Acetyl-3-phenyl-7-phenylmethylidene-3,4,5,6,7,9-hexahydro-2*H*-indazole (10a)

Colorless crystals; yield: 73%; mp 168–169 °C (Lit.[5] mp 168–169 °C).

^{1}H NMR: δ = 1.50 (m, 1 H, CH_2), 2.38 (s, 3 H, CH_3), 3.05 (m, 1 H, CH, *J* = 9.3 Hz), 4.93(d, 1 H, CH, *J* = 9.3 Hz), 7.18 (d, 1 H, CH, *J* = 2.0 Hz), 7.24–7.40 (m, 10 H, 2 C_6H_5).

^{13}C NMR: δ = 22.2 (CH_3), 24.3, 29.0, 30.7 (3 CH_2), 57.2, 57.7 (2 CH), 125.5 (CH=), 127.3 (C), 127.5, 127.9, 128.2, 128.7, 129.5, 130.6 (C_6H_5), 135.9, 141.8 (2 C_{ipso}), 158.6 (C=N), 170.1 (C=O).

MS: *m*/*z* = 330 $[M]^+$.

2-Acetyl-3-(4-methoxyphenyl)-7-(4-methoxyphenyl)methylidene-3,4,5,6,7,9-hexahydro-2*H*-indazole (10b)

Colorless crystals; yield: 71%; mp 162–163 °C (Lit.[5] mp 162–163 °C).

^{1}H NMR: δ = 1.49 (m, 1 H, CH_2), 1.63 (m, 1 H, CH_2), 1.93 (m, 1 H, CH_2), 2.16 (m, 1 H, CH_2), 2.42 (m, 1 H, CH_2), 2.97 (m, 1 H, CH_2), 2.35 (s, 3 H, CH_3), 3.04 (m, 1 H, CH, *J* = 9.5 Hz), 3.78 (s, 3 H, CH_3), 3.83 (s, 3 H, CH_3), 4.86 (d, 1 H, CH, *J* = 9.5 Hz), 6.89 (m, 4 H, C_6H_4), 7.14 (d, 1 H, CH, *J* = 2.6 Hz), 7.22 (m, 4 H, C_6H_5).

^{13}C NMR: δ = 22.2 (CH_3), 24.3, 29.0, 30.0 (3 CH_2), 55.2 (2 CH), 57.2, 67.3 (2 CH), 126.9 (CH=), 127.6 (C), 113.7, 114.2, 131.1 (2 C_6H_5), 128.8, 144.1 (2 C_{ipso}), 158.8 (2 C–O), 159.1 (C=N), 170.29 (C=O).

MS: *m*/*z* = 390 $[M]^+$.

2-Acetyl-3-(4-methoxyphenyl)-7-(4-methoxyphenyl)methylidene-5-methyl-5-aza-3,4,5,6,7,9-hexahydro-2*H*-indazole (10c)

Colorless crystals; yield: 69%; mp 232–233 °C.

^{1}H NMR: δ = 2.27 (s, 3 H, CH_3), 2.42 (s, 3 H, CH_3), 2.74 (dd, 1 H, CH_2, *J* = 6.0, 10.2 Hz), 2.86 (dd, 1 H, CH_2, *J* = 2.54, 10.2 Hz), 3.64 (m, 2 H, CH_2, *J* = 1.5 Hz), 3.78 (s, 3 H, CH_3), 3.83 (s, 3 H, CH_3), 3.90 (dm, 1 H, CH, *J* = 11.2 Hz), 5.63 (d, 1 H, CH, *J* = 11.2 Hz), 6.82–7.25 (m, 8 H, 2 C_6H_4), 7.34 (br, 1 H,CH=).

IR: 1024, 1150, 1609, 1628, 1679, 2846, 2894 cm^{-1}.

UV ($CHCl_3$): λ_{max} = 313 nm.

MS: *m*/*z* = 405 $[M]^+$.

Anal. Calcd for $C_{24}H_{27}N_3O_3$: C, 71.09; H, 6.71; N 10.36. Found: C, 70.93; H, 6.89; N, 10.47.

Methylidenecyclohexanols 11a,b

These compounds were prepared according to the standard procedure by reacting the ketones **8a–c** with MeLi in Et_2O.

1-Methyl-2,6-bis(phenylmethylidene)cyclohexanol (11a)

Pale yellow powder; yield: 68%; mp 120–121 °C (Lit.[5] mp 121–122 °C).

^{1}H NMR: δ = 1.27–1.60 (m, 1 H, CH_2), 1.64 (m, 3 H, CH_3), 1.72–1.88 (m, 1 H, CH_2), 1.88 (s, 1 H, OH), 2.15–2.31 (m, 2 H, CH_3), 2.90–3.02 (m, 2 H, CH_2), 7.16–7.36 (m, 10 H, C_6H_5), 7.79 (2 H,CH=).

^{13}C NMR: δ = 18.5 (CH_3), 22.9 (CH_2), 28.3 (2 CH_2). 128.2 (2 CH=), 128.5, 130.2, 136.8 (2 C_6H_5), 135.8, 136.10 (2 C_{ipso}), 141.3 (C–O).

1-Methyl-2,6-bis(4-methoxyphenyl)methylidenecyclohexanol (11b)

Pale yellow powder; yield 65%; mp 153–154 °C (Lit.[5] mp 155 °C).

^{1}H NMR: δ = 1.72–1.85 (m, 2 H, CH_2), 1.61 (m, 3 H, CH_3), 1.73–1.84 (m, 1 H, CH_2), 2.15–2.33 (m, 2 H, CH_3), 2.61 (s, 1 H, OH), 7.26–7.48 (m, 10 H, C_6H_5), 7.79 (2 H, CH=).

^{13}C NMR: δ = 19.6 (CH_3), 22.9 (CH_2), 28.9 (2 CH_2), 50.6 (2 CH_3), 113.8 (2 CH=), 132.1, 136.4 (2 C_6H_4), 128.6 (2 C), 134.2 (2 C_{ipso}), 137.8 (2 C–O).

***N*-Methyl Substituted Dihydropyrazoles 12a,b; General Procedure**

A mixture of a chalcone **8a** or **8b** (5 mmol) and methylhydrazine (2 mL) was boiled in MeOH (30 mL) with stirring for 1 h and cooled to 0 °C. The crystals formed were filtered, washed with aq MeOH, and purified by recrystallization from MeOH.

2-Methyl-3-phenyl-7-phenylmethylidene-3,4,5,6,7,9-hexahydro-2*H*-indazole (12a)

Yellow crystals; yield: 72%; mp 120–121 °C.

^{1}H NMR: δ = 1.40 (m, 1 H, CH_2), 1.52 (m, 1 H, CH_2), 1.88 (m, 1 H, CH_2), 2.02 (m, 1 H, CH_2), 2.40 (m, 1 H, CH_2), 2.86 (m, 1 H, CH_2), 2.80 (s, 3 H, CH_3), 3.01 (dd, 1 H, CH, *J* = 13.8 Hz), 3.65 (d, 1 H, CH, *J* = 13.8 Hz), 7.20 (d, 1 H, CH=, *J* = 1.8 Hz), 7.22–7.46 (m, 10 H, C_6H_5).

^{13}C NMR: δ = 24.3 (CH_2), 26.7 (2 CH_2), 42.0 (CH_3), 55.2, 81.4 (2 CH), 127.0 (CH=), 127.1 (C), 127.3, 127.7, 128.0, 128.6, 128.6 (2 C_6H_5), 130.9, 136.6 (2 C_{ipso}), 155.2 (C=N).

Anal. Calcd for $C_{21}H_{22}N_2$: C, 83.41; H, 7.33; N, 9.26. Found: C, 84.53; H, 7.21; N, 9.33.

3-(4-Methoxyphenyl)-7-(4-methoxyphenyl)methylidene-2-methyl-3,4,5,6,7,9-hexahydro-2*H*-indazole (12b)

Yellow crystals; yield: 69%; mp 105–106 °C.

^{1}H NMR: δ = 1.48 (m, 1 H, CH_2), 1.88 (m, 1 H, CH_2), 1.98 (m, 1 H, CH_2), 2.39 (m, 1 H, CH_2), 2.83 (m, 1 H, CH_2), 2.87 (m, 1 H, CH_2), 2.77 (s, 3 H, CH_3), 2.99 (dm, 1 H, CH, *J* = 14.0 Hz), 3.58 (d, 1 H, CH, *J* = 14.0 Hz), 3.81 (s, 3 H, CH_3), 3.82 (s, 3 H, CH_3), 7.15 (d, 1

H, CH=, *J* = 1.8 Hz), 6.85–6.94 (m, 4 H, C_6H_4), 7.27–7.38 (m, 4 H, C_6H_4).

^{13}C NMR: δ = 24.2, 28.5, 28.6 (3 CH_2), 41.9, 55.1, 55.2 (3 CH_3), 54.9, 80.9 (2 CH), 128.5 (CH=), 129.9 (C), 113.7, 114.2, 130.1 (2 C_6H_4), 130.4, 130.5 (2 C_{ipso}), 156.0 (C=N), 158.6, 159.2 (2 C–O).

Anal. Calcd for $C_{23}H_{26}N_2O_2$: C, 76.21; H, 7.23; N, 7.73. Found: C, 76.38; H, 7.09; N, 7.84.

Reaction of Dihydropyrazoles 10a–c and 12a,b with 4-Phenyl-3*H*-1,2,4-triazole-3,5(4*H*)-dione (2); General Procedure

A: Imide **2** (0.175 g, 1 mmol) was added to a stirred solution of dihydropyrazoles **10a–c** or **12a**,**b** (1 mmol) in $CHCl_3$ (20 mL) at 20 °C. Disappearance of bright red coloration of the solution (ca. 5 min) indicated that the reaction was over. The solvent was removed in vacuo and the residue was chromatographed on alumina (benzene–EtOAc, 4:1).

2-Acetyl-3-(4-methoxyphenyl)-7-[4-methoxyphenyl-(4-phenyl-1-urazolyl)methyl]-5-methyl-5-aza-3,4,5,9-tetrahydro-2*H*-indazole (13)

Mixture of two diastereomers **13a** and **13**b (ca. 2:1); pale yellow powder; yield: 0.42 g (73%).

MS: *m*/*z* = 580 $[M]^+$.

Anal. Calcd for $C_{32}H_{32}N_6O_5$: C, 66.20; H, 5.55; N, 14.77. Found: C, 66.08; H, 5.71; N, 14.63.

Isomer 13a

^{1}H NMR: δ = 2.24 (s, 3 H, CH_3), 2.89 (s, 3 H, CH_3), 3.34 (m, 2 H, CH_2), 3.52 (td, 1 H, CH, *J* = 6.5, 11.7 Hz), 3.77 (s, 3 H, CH_3), 3.78 (s, 3 H, CH_3), 4.84 (d, 1 H, CH, *J* = 11.7 Hz), 6.15 (s, 1 H, CH), 6.59 (s, 1 H, CH=), 6.84–7.84 (m, 13 H, 3 ArH), 9.87 (br, 1 H, NH).

Isomer 13b

^{1}H NMR: 2.39 (s, 3 H, CH_3), 2.89 (s, 3 H, CH_3), 3.16 (m, 2 H, CH_2), 3.55 (td, 1 H, CH, *J* = 6.0, 12.1 Hz), 3.82 (s, 3 H, CH_3), 3.83 (s, 3 H, CH_3), 4.88 (d, 1 H, CH, *J* = 12.1 Hz), 6.21 (s, 1 H, CH), 6.39 (s, 1 H, CH=), 6.84–7.67 (m, 13 H, 3 ArH), 9.80 (br, 1 H, NH).

2-Acetyl-3-(4-methoxyphenyl)-7-[4-methoxyphenyl-(4-phenyl-1-urazolyl)methyl]-3,4,5,9-tetrahydro-2*H*-indazole (14)

Mixture of isomers **14a** and **14b** (ca. 2:1); pale yellow powder; 65%; yield: 0.32 g.

IR: 1230, 1426, 1599, 1463, 1700, 2900, 3063, 3460 cm^{-1}.

UV ($CHCl_3$): λ_{max} = 210 nm.

Anal. Calcd for $C_{30}H_{27}N_5O_3$: C, 71.27; H, 5.38; N, 13.85. Found: C, 71.38; H, 5.22; N, 13.94.

Isomer 14a

^{1}H NMR: δ = 1.77 (m, 1 H, CH_2), 2.07 (m, 1 H, CH_2), 2.36 (m, 1 H, CH_2), 2.91 (m, 1 H, CH_2), 2.20 (s, 3 H, CH_3), 3.18 (m, 1 H, CH, *J* = 9.6 Hz), 3.78 (s, 3 H, CH_3), 3.82 (s, 3 H, CH_3), 4.78 (d, 1 H, CH, *J* = 9.6 Hz), 6.31 (t, 1 H, CH=, *J* = 4.6 Hz), 6.40 (s, 1 H, CH), 6.78–6.83 (m, 4 H, C_6H_4), 7.16–7.25 (m, 4 H, C_6H_4), 7.29–7.40 (m, 5 H, C_6H_5), 9.20 (br, 1 H, NH).

^{13}C NMR: δ = 21.7, 54.6, 54.9 (3 CH_3), 26.0, 26.6 (2 CH_2), 59.5, 65.8, 66.2 (3 CH), 125.3 (CH=), 127.0 (C), 114.3, 114.6, 127.6, 128.0, 128.8, 129.0 (3 C_6H_5), 130.4, 132.9, 140.4 (3 C_{ipso}), 151.6, 152.7 (2 C–O), 158.9 (C=N), 168.0, 169.1, 169.2 (2 C=O).

Isomer 14b

^{1}H NMR: δ = 1.79 (m, 1 H, CH_2), 2.11 (m, 1 H, CH_2), 2.34 (m, 1 H, CH_2), 2.75 (m, 1 H, CH_2), 2.18 (s, 3 H, CH_3), 3.20 (m, 1 H, CH, *J* = 9.6 Hz), 3.77 (s, 3 H, CH_3), 3.83 (s, 3 H, CH_3), 4.80 (d, 1 H, CH, *J* = 9.6 Hz), 6.22 (t, 1 H, CH=, *J* = 5.1 Hz), 6.34 (s, 1 H, CH), 6.83–6.93 (m, 4 H, C_6H_4), 7.14–7.23 (m, 4 H, C_6H_4), 7.41–7.49 (m, 5 H, C_6H_5), 9.48 (br, 1 H, NH).

^{13}C NMR: δ = 21.6, 55.3, 55.3 (3 CH_3), 26.0, 26.9 (2 CH_2), 59.5, 65.4, 66.6 (3 CH), 125.3 (CH=), 127.1 (C), 114.2, 114.3, 127.6, 128.0, 128.8, 129.2 (3 C_6H_5), 131.2, 133.3, 141.5 (3 C_{ipso}), 152.9, 154.5 (2 C–O), 159.5 (C=N), 169.9 (2 C=O), 170.0 (1 C=O).

2-Acetyl-3-phenyl-7-[phenyl-(4-phenyl-1-urazolyl)methyl]-3,4,5,9-tetrahydro-2*H*-indazole (15)

Mixture of two diastereomers **15a** and **15b** (ca. 2.5:1); pale yellow powder; yield: 0.4 g (70%).

IR: 1284,1377,1559, 1656, 1699, 2830, 3226, 3331 cm^{-1}.

MS: *m*/*z* = 565 $[M]^+$.

UV($CHCl_3$): λ_{max} =208 nm.

Anal. Calcd for $C_{32}H_{31}N_5O_5$: C, 67.95; H, 5.53; N, 12.38. Found: C, 68.03; H, 5.37; N, 12.51.

15a

Isolated by repeated recrystallization from MeOH; mp 192–193 °C.

^{1}H NMR: δ = 1.38 (m, 1 H, CH_2), 1.87 (m, 1 H, CH_2), 2.43 (m, 1 H, CH_2), 3.13 (m, 1 H, CH_2), 2.19 (s, 3 H, CH_3), 3.19 (m, 1 H, CH, *J* = 10.5 Hz), 4.85 (d, 1 H, CH, *J* = 10.5 Hz), 6.38 (t, 1 H, CH=, *J* = 4.8 Hz), 6.45 (s, 1 H, CH), 7.27–7.56 (m, 15 H, 3 C_6H_5), 8.60 (br, 1 H, NH).

^{13}C NMR: δ = 22.4 (CH_3), 26.1, 26.6, (2 CH_2), 55.1, 60.3, 67.2 (3 CH), 125.3 (CH=), 125.6 (C), 127.8, 128.1, 128.5, 128.6, 128.8, 128.9, 128.9, 129.1, 129.1 (3 C_6H_5), 131.4, 136.0, 140.8 (C_{ipso}) 141.8 (C=N), 152.6, 154.6 (3 C=O).

IR: 1227, 1423, 1601, 1640, 1707, 1771, 3061, 3430 cm^{-1}.

UV ($CHCl_3$): λ_{max} = 210 nm.

Anal. Calcd for $C_{30}H_{27}N_5O_3$: C, 71.27; H, 5.38; N, 13.85. Found: C, 71.20; H, 5.41; N, 13.76.

15b

^{1}H NMR: δ = 1.25 (m, 1 H, CH_2), 1.87 (m, 1 H, CH_2), 2.41 (m, 1 H, CH_2), 3.10 (m, 1 H, CH_2), 2.35 (s, 3 H, CH_3), 3.16 (m, 1 H, CH, *J* = 9.6 Hz), 4.60 (d, 1 H, CH, *J* = 9.6 Hz), 6.33 (t, 1 H, CH=, *J* = 4.5 Hz), 6.40 (s, 1 H, CH), 7.16–7.55 (m, 15 H, 3 C_6H_5), 8.50–8.60 (br, 1 H, NH).

^{13}C NMR: δ = 22.3 (CH_3), 26.1, 26.9 (2 CH_2), 54.9, 60.3, 67.0 (3 CH), 125.7 (CH=), 127.4 (C), 127.6, 127.8, 128.1, 128.5, 128.6, 128.92, 129.1, 129.4 (3 C_6H_5), 131.2, 134.8, 140.8 (C_{ipso}) 142.2 (C=N), 153.1, 154.2 (3 C=O).

2-Methyl-3-phenyl-7-[phenyl-(4-phenyl-1-urazolyl)methyl]-3,4,5,9-tetrahydro-2*H*-indazole (16)

Yield: 0.29 g (60%) and polyadducts related **16** (0.10 g). The product **16** was a mixture of two diastereomers

16a and **16b** (ca. 2.5:1); pale yellow powder.

IR: 1284, 1357, 1423, 1601, 1656, 1699, 3206, 3364 cm^{-1}.

MS: *m*/*z* = 477 $[M]^+$.

UV ($CHCl_3$): λ_{max} = 213 nm.

Anal. Calcd for $C_{29}H_{27}N_5O_2$: C, 72.95; H, 5.70; N, 14.65. Found: C, 73.03; H, 5.93; N, 14.39.

Polyadduct related to **16** was a colorless powder; mp ca. 250 °C (dec.).

MS: *m*/*z* = 625, 827, 1050 $[M]^+$.

16a

^{1}H NMR: δ = 1.80–2.21 (m, 2 H, CH_2), 2.43 (m, 2 H, CH_2), 2.75 (s, 3 H, CH_3), 3.10 (td, 1 H, CH, *J* = 7.18 Hz), 7.32–7.60 (m, 15 H, 3 C_6H_5), 9.99 (br, 1 H, NH).

^{13}C NMR: δ = 25.6 (2 CH_2), 41.7 (CH_3), 54.4, 61.7, 79.6 (3 CH), 125.6 (CH=), 127.4 (C), 127.3, 127.8, 128.1, 128.2, 128.5, 128.8, 128.9, 129.0, (3 C_6H_5), 136.6, 138.4, 138.56 (3 C_{ipso}), 139.4, (C=N), 151.9, 152.1 (3 C=O).

16b

^{1}H NMR: δ = 1.58–2.08 (m, 2 H, CH_2), 2.35 (m, 2 H, CH_2), 2.77 (s, 3 H, CH_3), 2.95 (td, 1 H, CH, *J* = 5.8, 13.6 Hz), 3.65 (d, 1 H, CH, *J* = 13.6 Hz), 6.32 (s, 1 H,CH), 7.09 (t, 1 H, CH=, *J* = 7.02 Hz), 7.20–7.60 (m, 15 H, 3 C_6H_5), 9.59 (br, 1 H, NH).

^{13}C NMR: δ = 25.4 (2 CH_2), 41.5 (CH_3), 53.9, 61.1, 79.9 (3 CH), 125.5 (CH=), 126.2 (C), 127.4, 127.8, 127.8, 127.9, 128.2, 128.3, 128.6, 128.8, 129.0, 129.1 (3 C_6H_5), 131.6, 132.4, 136.1 (3 C_{ipso}), 140.2 (C=N), 151.8, 152.2 (3 C=O).

3-(4-Methoxyphenyl)-7-[4-methoxyphenyl-(4-phenyl-1-urasolyl)methyl]-2-methyl-3,4,5,9-tetrahydro-2*H*-indazole (17)

Yield: 0.31 g (58%) and polyadducts-related **17** (0.13 g). The product **17** was a mixture of two diastereomers **17a** and **17b** (ca. 3:1); pale yellow powder.

IR: 1269, 1382, 1562, 1670, 1701,2827, 3219, 3341 cm^{-1}.

MS: *m*/*z* = 537 $[M]^+$.

UV ($CHCl_3$): λ_{max} = 209 nm.

Anal. Calcd for $C_{31}H_{31}N_5O_4$: C, 69.26; H, 5.81; N, 13.02. Found: C, 69.38; H, 5.74; N, 12.94.

The polyadducts-related **17** was a colorless powder.

MS: *m*/*z* = 702, 887, 1063 $[M]^+$.

17a

^{1}H NMR: δ = 1.76–2.00 (m, 2 H, CH_2), 2.40 (m, 2 H, CH_2), 2.74 (s, 3 H, CH_3), 3.06 (td, 1 H, CH, *J* = 5.1, 13.8 Hz), 3.65 (d, 1 H, CH, *J* = 13.8 Hz), 3.82 (s, 3 H, CH_3), 3.83 (s, 3 H, CH_3), 6.29 (s, 1 H, CH), 6.79 (t, 1 H, CH=, *J* = 7.6 Hz), 6.88 (d, 2 H, C_6H_4, *J* = 8.7 Hz), 6.93 (d, 2 H, C_6H_4, *J* = 8.7 Hz), 7.35 (d, 2 H, C_6H_4, *J* = 8.7 Hz), 7.35 (d, 2 H, C_6H_4, *J* = 8.7 Hz), 7.54 (d, 2 H, C_6H_4, *J* = 8.7 Hz), 7.38–7.50 (m, 5 H, 3 C_6H_5), 9.99 (br, 1 H, NH).

^{13}C NMR: δ = 25.5, 25.6 (2 CH_2), 41.6, 55.2, 55.3 (3 CH_3), 54.2, 61.5, 79.1 (3 CH), 125.6 (CH=), 126.2 (C), 113.9, 114.1, 127.8, 128.4, 128.9, 129.0, 129.1 (3 C_6H_5), 131.6, 138.2, 139.1 (3 C_{ipso}), 151.9, 152.3 (2 C–O), 159.1, (C=N), 159.3, 159.5, 159.7 (3 C=O).

17b

^{1}H NMR: δ = 1.56–1.78 (m, 2 H, CH_2), 2.06 (m, 2 H, CH_2), 2.75 (s, 3 H, CH_3), 2.93 (td, 1 H, CH, *J* = 5.1,14.4 Hz), 3.62 (d, 1 H, CH, *J* = 14.4 Hz), 3.81 (s, 3 H, CH_3), 3.82 (s, 3 H, CH_3), 6.31 (s, 1 H, CH), 6.76 (t, 1 H, CH=, *J* = 8.0 Hz), 6.86 (d, 2 H, C_6H_4, *J* = 8.4 Hz), 6.91 (d, 2 H, C_6H_4, *J* = 8.4 Hz), 7.44 (d, 2 H, C_6H_4, *J* = 8.4 Hz), 7.70 (d, 2 H, C_6H_4, *J* = 8.4 Hz), 7.22–7.35 (m, 5 H, 3 C_6H_5), 10.12 (br, 1 H, NH).

^{13}C NMR: δ = 25.4, 25.4 (2 CH_2), 41.3, 55.2, 55.3 (3 CH_3), 53.7, 61.0, 79.4 (3 CH), 125.5 (CH=), 125.6 (C), 114.0, 114.1, 127.9, 128.1, 128.7, 128.7, 129.0 (3 C_6H_5), 131.5, 138.2, 139.9 (3 C_{ipso}), 151.7, 152.2 (2 C–O), 159.0, (C=N), 159.7, 159.9, 160.2 (3 C=O).

B: Ene Polyaddition of the Imide 2 to the Dihydropyrazole 12a

N-Phenylimide **2** was added in 17.5-mg portions with stirring at 20 °C to a solution of compound **12a** (30 mg) in $CHCl_3$ (20 mL) after discoloration of the reaction mixture. Discoloration occurred virtually instantaneously after addition of the first two portions and retarded with each subsequent portion of the enophile. The addition of the seventh molar equivalent took ca. 3 h. The mixture was diluted with Et_2O (100 mL), the colorless precipitate was filtered and washed with Et_2O.

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