

Synthesis of Aryl- and Heteryl-Containing *gem*-Acylnitrocyclohexenes

R. I. Baichurin, N. I. Aboskalova, G. A. Berkova, and V. M. Berestovitskaya

Herzen Russian State Pedagogical University, St. Petersburg, 191186 Russia
e-mail: kohrgpu@yandex.ru

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Abstract—Reactions of 2-aryl(heteryl)-1-acetyl(benzoyl)-1-nitroethenes with 2,3-dimethyl-1,3-butadiene led to the formation of products of [4+2]-cycloaddition, 1-acyl-6-aryl(heteryl)-3,4-dimethyl-1-nitro-3-cyclohexenes. Their structure was proved by IR and ^1H NMR spectroscopy.

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Preparatively available *gem*-activated nitroethenes containing as the second electron-withdrawing group a carbonyl are highly reactive precursors for numerous chemical processes, among them especially important are cyclocondensation reactions. Proceeding from these compounds many heterocyclic structures were prepared, in particular, pyrimidines [1], triazoles [2, 3], pyrazoles [2, 4], dihydrofurans [5] etc.

The extensive application of nitroethenes as dienophiles in Diels–Alder reaction with acyclic and cyclic conjugated diene hydrocarbons resulted in the synthesis of a wide range of functionally substituted carbocyclic systems [6, 7]. However the information on involvement into the diene condensation of *gem*-acylnitroethenes is scarce [8–10]. For instance, *gem*-benzoylnitroethene obtained in situ [8] and β -benzoyl- β -nitrostyrene [10] were brought into reactions with cyclopentadiene.

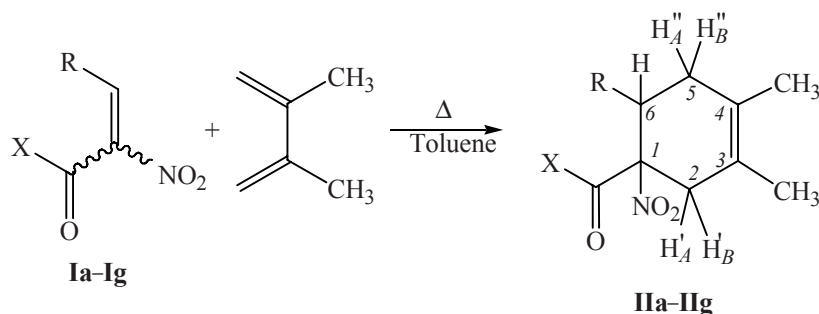
We investigated the reaction of β -acetyl-(benzoyl)- β -nitrostyrenes and their furan- and thiophene-containing

analogues **Ia–Ig** with a typical representative of linear dienes, 2,3-dimethyl-1,3-butadiene. These reactions successfully proceeded without catalyst at excess diene in anhydrous toluene at reflux within 11–48 h and led to the formation of acylnitrocyclohexenes **IIa–IIg** in up to 84% yields.

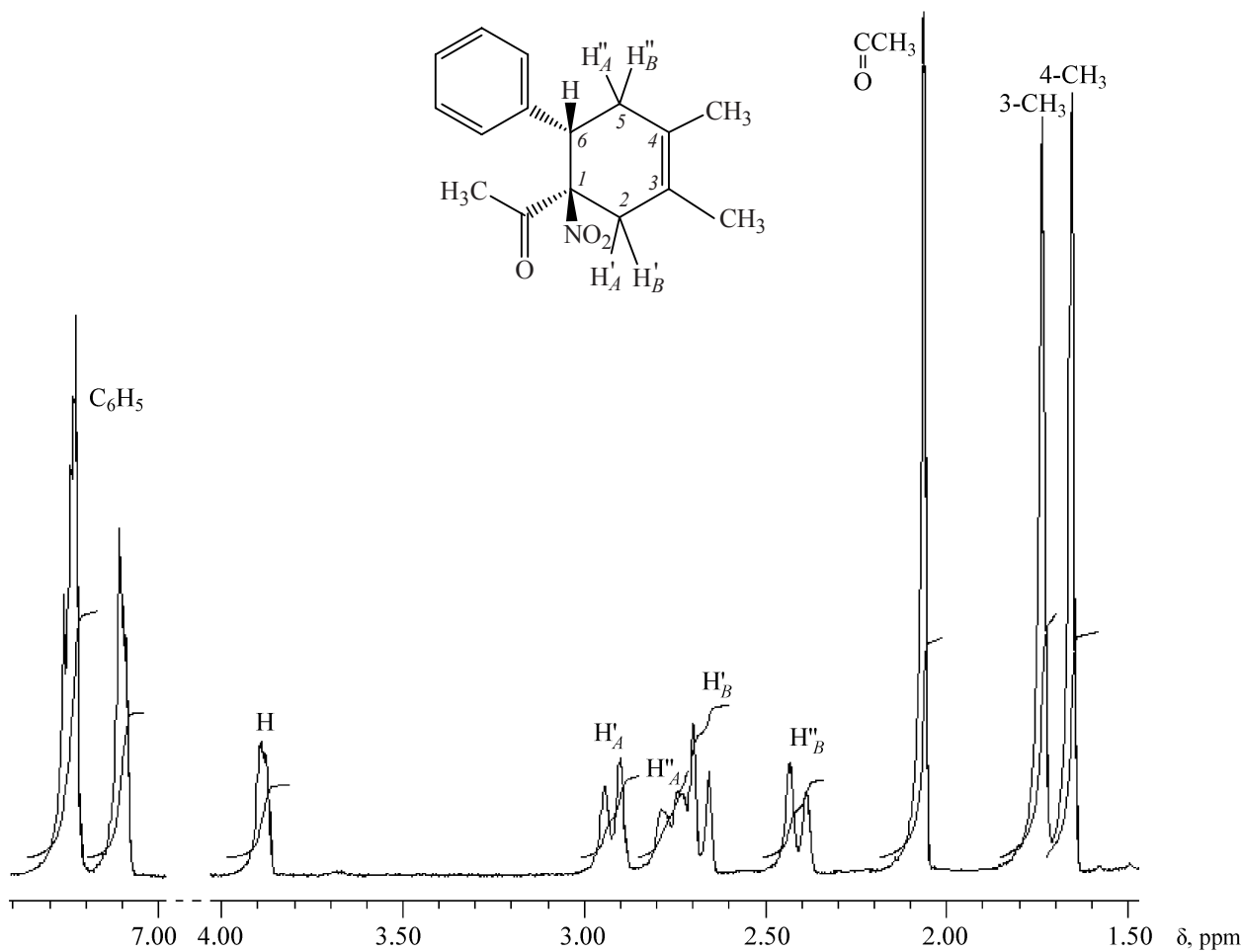
The composition and structure of obtained compounds **IIa–IIg** were confirmed by elemental analysis, IR and ^1H NMR spectroscopy.

In the IR spectra of these compounds strong absorption bands appeared of nonconjugated nitro- (1545–1550, 1355–1360 cm^{-1}) and carbonyl (1690–1735 cm^{-1}) groups.

^1H NMR spectra of *gem*-acylnitrocyclohexenes **IIa–IIg** contained the signals corresponding to all structural fragments of the molecules. For instance, in the ^1H NMR spectrum of compound **IIa** (see the figure) singlets are present originating from groups 3- CH_3 and 4- CH_3 at the double bond of the ring (1.74, 1.65 ppm) and from the acetyl group (2.06 ppm). Endocyclic methylene protons



X = Me, R = Ph (**a**), 4-MeOC₆H₄ (**b**), 2-furyl (**c**), 2-thienyl (**d**); X = Ph, R = Ph (**e**), 2-furyl (**f**), 2-thienyl (**g**).



^1H NMR spectrum of 1-acetyl-3,4-dimethyl-1-nitro-6-phenyl-3-cyclohexene (**IIa**) in CDCl_3 .

$\text{C}^2\text{H}'_A$ and $\text{C}^2\text{H}'_B$ give rise to an *AB* system and appear as doublets at 2.93 and 2.68 ppm. Protons $\text{C}^5\text{H}''_A$, $\text{C}^5\text{H}''_B$, and C^6H of the three-spin system *ABX* are present as multiplets at 2.75, 2.40, and 3.88 ppm respectively. The phenyl ring protons are seen as a multiplet in the region 7.10–7.25 ppm.

Thus the reaction of *gem*-acylnitroethenes with 2,3-dimethyl-1,3-butadiene can be used as a convenient preparative method for the synthesis of acylnitrocyclohexenes.

The obtained new functionally substituted cyclohexenes combining in the ring a nitro and a carbonyl groups are of an applied interest for they can be used as synthetic intermediate in the preparation of pharmacologically active substances. A considerable part of naturally occurring structures (alkaloids, hormones), of drugs and other practically significant compounds is known to be substituted cyclohexanes [6, 7]. A special importance have *gem*-acylnitrocyclohexenes containing in the molecules pharmacophore structures of furan or

thiophene since a lot of derivatives of these heterocycles are widely used in the medicine (nitrofurazone, furazolidone, furazidin, furosemide, ketof, bifantrel etc. [11])

EXPERIMENTAL

IR spectra were recorded on a Fourier spectrophotometer InfraLYuM FT-02 from solutions in chloroform (C 40 mg ml^{-1}). ^1H NMR spectra were registered on spectrometers Bruker WM-400 (400 MHz) and Jeol JNM-ECX400A (400 MHz) from solutions in deuteriochloroform. Chemical shifts were measured relative to TMS. Mass spectra were obtained on an instrument MKh 1321 with a direct admission of the sample into the ion source, ionizing voltage 70 V, the temperature in the ionization chamber 180°C.

2,3-Dimethyl-1,3-butadiene was obtained by procedure [12], *gem*-acylnitroethenes **Ia–Ig**, by methods [5, 13, 14].

1-Acetyl-3,4-dimethyl-1-nitro-6-phenyl-3-cyclohexene (IIa). To a dispersion of 0.764 g (4 mmol) of reagent **Ia** in 10 ml of anhydrous toluene was added 1.312 g (16 mmol) of 2,3-dimethyl-1,3-butadiene, 0.1 g of hydroquinone, and the reaction mixture was boiled for 15 h. After removing the solvent on a rotary evaporator the residue was treated with ethanol. Yield 0.675 g (62%), colorless crystals, mp 139–141°C (ethanol). IR spectrum, ν , cm^{-1} : 1545, 1355 (NO_2), 1730 ($\text{C}=\text{O}$). ^1H NMR spectrum, δ , ppm: 1.65 s (4- CH_3), 1.74 s (3- CH_3), 2.06 s (COCH_3), 2.40 d.d ($\text{C}^5\text{H}_B''$, $^3J_{A''B''}$ 18.38, $^3J_{\text{HB}''}$ 2.80 Hz), 2.68 d ($\text{C}^2\text{H}_B'$, $^3J_{A'B'}$ 17.65 Hz), 2.75 d.d ($\text{C}^5\text{H}_A''$, $^3J_{A''B''}$ 18.38, $^3J_{\text{HA}''}$ 5.88 Hz), 2.93 d ($\text{C}^2\text{H}_A'$, $^3J_{A'B'}$ 17.65 Hz), 3.88 d.d (C^6H , $^3J_{\text{HA}''}$ 5.88, $^3J_{\text{HB}''}$ 2.80 Hz), 7.10–7.25 m (5H_{arom}). Found, %: N 5.16. $\text{C}_{16}\text{H}_{19}\text{NO}_3$. Calculated, %: N 5.13.

Compounds **IIb–IIg** were similarly prepared.

1-Acetyl-3,4-dimethyl-6-(4-methoxyphenyl)-1-nitro-3-cyclohexene (IIb). Yield 58%, colorless crystals, mp 78–79°C (ethanol). IR spectrum, ν , cm^{-1} : 1545, 1360 (NO_2), 1735 ($\text{C}=\text{O}$). ^1H NMR spectrum, δ , ppm: 1.66 s (4- CH_3), 1.74 s (3- CH_3), 2.07 s (COCH_3), 2.40 d.d ($\text{C}^5\text{H}_B''$, $^3J_{A''B''}$ 17.65, $^3J_{\text{HB}''}$ 2.88 Hz), 2.70 d ($\text{C}^2\text{H}_B'$, $^3J_{A'B'}$ 16.91 Hz), 2.75 d.d ($\text{C}^5\text{H}_A''$, $^3J_{A''B''}$ 17.65, $^3J_{\text{HA}''}$ 5.76 Hz), 2.90 d ($\text{C}^2\text{H}_A'$, $^3J_{A'B'}$ 16.91 Hz), 3.76 s (OCH_3), 3.85 d.d (C^6H , $^3J_{\text{HA}''}$ 5.76, $^3J_{\text{HB}''}$ 2.88 Hz), 6.75–7.15 m (4H_{arom}). Found, %: C 67.39; H 6.77; N 4.69. $\text{C}_{17}\text{H}_{21}\text{NO}_4$. Calculated, %: C 67.33; H 6.93; N 4.62.

1-Acetyl-3,4-dimethyl-1-nitro-6-(2-furyl)-3-cyclohexene (IIc). Yield 78%, light-brown crystals, mp 88–90°C (ethanol). IR spectrum, ν , cm^{-1} : 1550, 1360 (NO_2), 1730 ($\text{C}=\text{O}$). ^1H NMR spectrum, δ , ppm: 1.63 s (4- CH_3), 1.68 s (3- CH_3), 2.12 s (COCH_3), 2.47 d.d ($\text{C}^5\text{H}_B''$, $^3J_{A''B''}$ 16.38, $^3J_{\text{HB}''}$ 5.38 Hz), 2.54 d.d ($\text{C}^5\text{H}_A''$, $^3J_{A''B''}$ 16.38, $^3J_{\text{HA}''}$ 6.60 Hz), 2.78 d ($\text{C}^2\text{H}_B'$, $^3J_{A'B'}$ 17.64 Hz), 2.90 d ($\text{C}^2\text{H}_A'$, $^3J_{A'B'}$ 17.64 Hz), 3.95 d.d (C^6H , $^3J_{\text{HA}''}$ 6.60, $^3J_{\text{HB}''}$ 5.38 Hz), 6.10–6.40, 7.27 (3H_{furan}). Found, %: C 63.99; H 6.29. $\text{C}_{14}\text{H}_{17}\text{NO}_4$. Calculated, %: C 63.88; H 6.46.

1-Acetyl-3,4-dimethyl-1-nitro-6-(2-thienyl)-3-cyclohexene (IIId). Yield 74%, colorless crystals, mp 90–92°C (ethanol). IR spectrum, ν , cm^{-1} : 1545, 1360 (NO_2), 1730 ($\text{C}=\text{O}$). ^1H NMR spectrum, δ , ppm: 1.64 s (4- CH_3), 1.72 s (3- CH_3), 2.12 s (COCH_3), 2.46 d.d ($\text{C}^5\text{H}_B''$, $^3J_{A''B''}$ 17.65, $^3J_{\text{HB}''}$ 3.00 Hz), 2.70 d.d ($\text{C}^5\text{H}_A''$, $^3J_{A''B''}$ 17.65, $^3J_{\text{HA}''}$ 5.60 Hz), 2.83 d ($\text{C}^2\text{H}_B'$, $^3J_{A'B'}$ 17.65 Hz), 2.98 d ($\text{C}^2\text{H}_A'$, $^3J_{A'B'}$ 17.65 Hz), 4.23 d.d (C^6H , $^3J_{\text{HA}''}$ 5.60, $^3J_{\text{HB}''}$ 3.00 Hz), 6.75–7.00, 7.10–7.30 ($3\text{H}_{\text{thiophene}}$). Found M^+ 279. $\text{C}_{14}\text{H}_{17}\text{NO}_3\text{S}$. Calculated M 279.

1-Benzoyl-3,4-dimethyl-1-nitro-6-phenyl-3-cyclohexene (IIe). Yield 71%, colorless crystals, mp 120–121°C (ethanol). IR spectrum, ν , cm^{-1} : 1545, 1355 (NO_2), 1690 ($\text{C}=\text{O}$). ^1H NMR spectrum, δ , ppm: 1.69 s (3- CH_3 , 4- CH_3), 2.41 d ($\text{C}^5\text{H}_B''$, $^3J_{A''B''}$ 17.77, $^3J_{\text{HB}''}$ 0 Hz), 2.88 d ($\text{C}^2\text{H}_B'$, $^3J_{A'B'}$ 18.48 Hz), 3.13 d ($\text{C}^2\text{H}_A'$, $^3J_{A'B'}$ 18.48 Hz), 3.13 d.d ($\text{C}^5\text{H}_A''$, $^3J_{A''B''}$ 17.77, $^3J_{\text{HA}''}$ 5.72 Hz), 4.29 d (C^6H , $^3J_{\text{HA}''}$ 5.72, $^3J_{\text{HB}''}$ 0 Hz), 6.95–7.60 (10H_{arom}). Found, %: C 75.50; H 6.57; N 4.33. $\text{C}_{21}\text{H}_{21}\text{NO}_3$. Calculated, %: C 75.22; H 6.27; N 4.18.

1-Benzoyl-3,4-dimethyl-1-nitro-6-(2-furyl)-3-cyclohexene (IIIf). Yield 50%, colorless crystals, mp 70–72°C (ethanol). IR spectrum, ν , cm^{-1} : 1545, 1355 (NO_2), 1695 ($\text{C}=\text{O}$). ^1H NMR spectrum, δ , ppm: 1.69 s (3- CH_3 , 4- CH_3), 2.47 d.d ($\text{C}^5\text{H}_B''$, $^3J_{A''B''}$ 18.50, $^3J_{\text{HB}''}$ 2.84 Hz), 3.01 d.d ($\text{C}^5\text{H}_A''$, $^3J_{A''B''}$ 18.50, $^3J_{\text{HA}''}$ 5.81 Hz), 3.08 d ($\text{C}^2\text{H}_B'$, $^3J_{A'B'}$ 18.68 Hz), 3.17 d ($\text{C}^2\text{H}_A'$, $^3J_{A'B'}$ 18.68 Hz), 4.58 d.d (C^6H , $^3J_{\text{HA}''}$ 5.81, $^3J_{\text{HB}''}$ 2.84 Hz), 6.64, 6.78, 7.10 (3H_{furan}), 7.41, 7.53, 7.61 (5H_{arom}). Found, %: C 69.86; H 6.07; N 4.18. $\text{C}_{19}\text{H}_{19}\text{NO}_4$. Calculated, %: C 70.14; H 5.89; N 4.31.

1-Benzoyl-3,4-dimethyl-1-nitro-6-(2-thienyl)-3-cyclohexene (IIg). Yield 84%, colorless crystals, mp 104–106°C (ethanol). IR spectrum, ν , cm^{-1} : 1545, 1355 (NO_2), 1690 ($\text{C}=\text{O}$). ^1H NMR spectrum, δ , ppm: 1.68 s (3- CH_3 , 4- CH_3), 2.45 d.d ($\text{C}^5\text{H}_B''$, $^3J_{A''B''}$ 17.27, $^3J_{\text{HB}''}$ 1.41 Hz), 2.90 d.d ($\text{C}^5\text{H}_A''$, $^3J_{A''B''}$ 17.27, $^3J_{\text{HA}''}$ 5.49 Hz), 2.95 d ($\text{C}^2\text{H}_B'$, $^3J_{A'B'}$ 17.27 Hz), 3.08 d ($\text{C}^2\text{H}_A'$, $^3J_{A'B'}$ 17.27 Hz), 4.42 d.d (C^6H , $^3J_{\text{HA}''}$ 5.49, $^3J_{\text{HB}''}$ 1.41 Hz), 6.03, 6.22, 7.16 ($3\text{H}_{\text{thiophene}}$), 7.38, 7.53, 7.65 (5H_{arom}). Found, %: N 4.00. $\text{C}_{19}\text{H}_{19}\text{NO}_3\text{S}$. Calculated, %: N 4.10.

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