Synthesis and photolysis of hexahydropyrrolo[3,4-*c*]pyrazole derivatives

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The 1,3-dipolar cycloaddition of 2-diazopropane **1** with *N*-arylcitraconimides and *N*-arylmaleimides **2**, at –78°C, has led to monoadducts **3**. The same addition of 2-diazopropane with maleimide **4**, has led to a new and unexpected Δ^3-1,3,4-oxadiazoline **5**. Irradiation of the pyrazolines **3** led to clean extruction of nitrogen to give the cyclopropanes **6**.

Keywords: 1,3-cycloaddition, Δ^1-pyrazolines, oxadiazoline, cyclopropanes

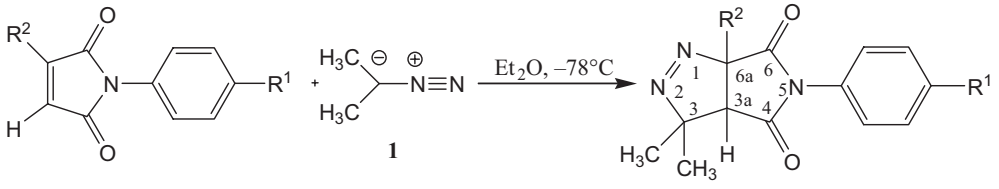
One of the most important reactions for the construction of five-membered heterocyclic rings is the 1,3-dipolar cycloaddition reaction.[1-4] The chemical reactivity of diazoalkanes according to alkenes,[5,6] as well as the regio- and the stereoselectivity of theses reactions have been thoroughly studied. Considerable attention has been focused on the synthesis of pyrazolines,[7] both for their high pharmacological and biological activities.[8-13] Cyclopropane ring, a common motif among natural compounds, deserves high interest, in terms of access, synthetic potential, and bioactivities.[14-16] In continuation to our work on the synthesis of heterocycles via 1,3-dipolar cycloaddition and evolution of cycloadducts,[17,18] we reported previously the development of 1,3-dipolar cycloaddition of 2-diazopropane. We now describe how these compounds can be converted to cyclopropanes.

Results and discussion

1,3-dipolar cycloaddition of ethereal 2-diazopropane **1** to a solution of *N*-arylcitraconimides **2** and *N*-arylmaleimides **2** in dichloromethane at –78°C leads to the corresponding Δ^1-pyrazolines **3** in good yield (Scheme 1).

The ^{1}H NMR spectra of the adducts are consistent with the structure assignments shown in Scheme 1, which are compatible with the direction of bond polarisation of both reactants. The *cis* relationship of the two rings in all adducts is supported by the coupling constant of 8.3 Hz observable between H_{3a} and H_{6a}. In all cases, only one regioisomeric pyrazolines was obtained, indicating high regioselectivity of the transformation. We now have to determine the addition mode of 2-diazopropane with *N*-arylcitraconimides. Unambiguous proofs for the obtained cycloadducts regiochemestry arised from their spectral data. However, regiochemical assignments of all adduct were deduced from their ^{13}C NMR spectra. Particularly the chemical shifts of C_{6a} (99.91–100.30 ppm) are in excellent agreement with those usually obtained when this quaternary carbon is attached to nitrogen atom.[19]

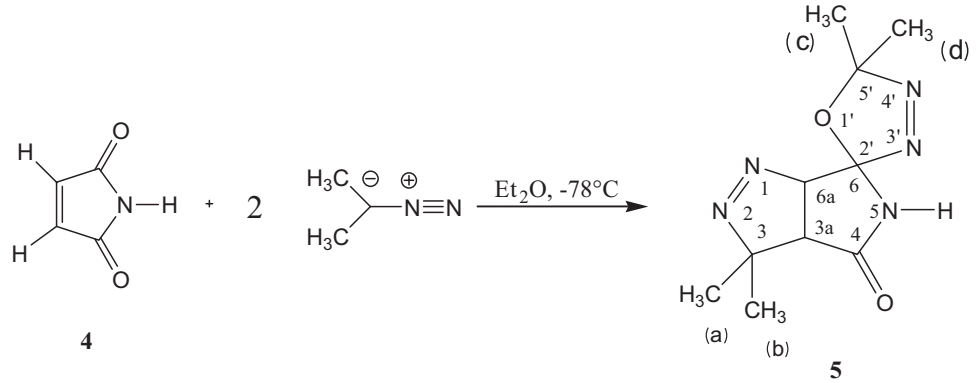
On the other hand, the same reaction is carried out under similar operating conditions with maleimide **4**, has led to a



2 **1** **3**

a: R^1= H, R^2 = H
b: R^1= H, R^2 = CH_3
c: R^1= OCH_3, R^2 = H
d: R^1= OCH_3, R^2 = CH_3
e: R^1= NO_2, R^2 = H
f: R^1= NO_2, R^2 = CH_3

Scheme 1



4 **5**

Scheme 2

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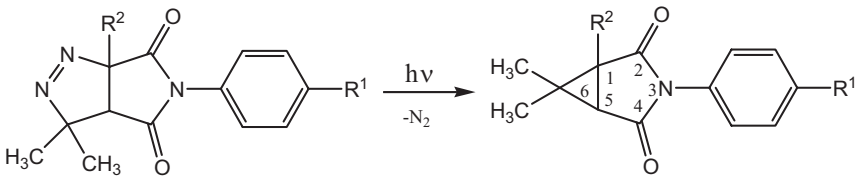

3 **6**

a: R^1= H, R^2= H
b: R^1= H, R^2= CH_3
c: R^1= OCH_3, R^2= H
d: R^1= OCH_3, R^2= CH_3
e: R^1= NO_2, R^2= H
f: R^1= NO_2, R^2= CH_3

Scheme 3

new and unexpected heterocyclic structure **5**. Microanalyses indicate that **5** result from addition of two DAP equivalent. On the other hand, ^{1}H NMR spectra of adduct **4** shows four methyl singlets (Scheme 2).

The chemoselectivity of the addition of 2-diazopropane with the carbonyl function was deduced from their HMBC 2D NMR spectra. The methyl protons H_a and H_b correlate with carbons atom C_{3a} (47.23 ppm), C_4 (172.41 ppm) via ^3J and ^4J coupling constants.

Regiochemistry of oxadiazoline **5** could be also established from their ^{13}C spectra. The high chemical shifts of C_6 (149.90 ppm) and $C_{5'}$ (130.16 ppm) indicate that each of these two carbons is linked to heteroatoms. The "inverse" regiochemical sense in cycloaddition of 2-diazopropane on the carbonyl function seems to be essentially conditioned by steric factors.

The photolysis of an ethereal solution of the Δ^1-pyrazolines **3** through Pyrex with a high pressure mercury arc lamp (Philips HPK 125 W) at 0–5°C led to exclusive formation of gem-dimethylcyclopropanes **6** (Scheme 3).[20]

This study demonstrates that the *gem*-dimethylcyclopropanes subunit which is often incorporated into biologically important natural products can easily be obtained in a two-step sequence from *N*-arylcitraconimides and *N*-arylmaleimides. During the 1,3-dipolar cycloaddition of 2-diazopropane with maleimide derivatives, both carbonyl and ethylenic double bond can be a priori, subjected to 1,3-dipolar attack.

Experimental

Generalities: IR spectra were recorder on Perkin-Elmer IR-197 IR spectrometer. Mass spectra were determined on a Nierjohnson MS80RF spectrometer. Melting points were determined on a Buchi-510 capillary melting point apparatus. Thin layer chromatography (TLC) was performed on silica gel 254 plates (Merck) with UV (254 nm) visualisation whereas chromatographic separations were conducted on silica gel Si-60-7734 Merck using water-Jacketed columns. ^{1}H NMR and ^{13}C NMR spectra recorded at 300 MHz and 75.47 MHz, respectively. Coupling constants are given in Hz. Elemental analyses were performed on a Perkin-Elmer 240B microanalyser. Diethyl ether was freshly distilled over sodium wire with a trace of benzophenone. Dichloromethane was distilled from calcium hydride.

General procedure for trapping of 2-diazopropane with N-arylmaleimides and N-arylcitraconimides

To a stirred solution containing 5.34 mmol of **2** or **4** in 50 ml of anhydrous dichloromethane at –78°C was added in small fractions a 2.6M ethereal solution prepared at –78°C. The progress of the reaction was monitored by TLC control (60–40 hexane-ethyl acetate elution) and the reaction was discontinued when **2** or **4** had totally reacted. The solution was allowed to react 6 h at 0°C and the solvent was evaporated under reduced pressure. Recrystallisation from ethanol.

3,3-dimethyl-5-phenyl-3,3a,4,5,6,6a-hexahydropyrrolo[3,4-c] pyrazole (**3a**): White crystals (1.16 g, 90%), m.p. 136°C (dichloromethane–ether of petrol). MS, *m/z* (%): [$M^{+\cdot}$-N_2, 215], 215 (100%). Anal. Calcd. for $C_{13}H_{13}N_3O_2$: C, 64.19; H, 5.39; N, 17.27%; Found: C, 65.10; H, 5.35; N, 17.17%; IR ν_{cm}^{-1}; 1518 (N=N); 1680, 1670 (C=O). ^{1}H NMR (300 MHz; $CDCl_3$) δ_{ppm}: 1.58 (s, 3H, CH_3), 1.64 (s, 3H, CH_3), 3,00 (d, 1H, H_{3a}), 5.99 (d, 1H, H_{6a}): AX patt. $J_{H3a\text{-}H6a}$ = 8.3 Hz, 7.21–7.51 (m, 5H, H_{arom}). ^{13}C NMR (75 MHz; $CDCl_3$) δ_{ppm}: 22.94 (CH_3), 28.25 (CH_3), 47.40 (C_{3a}), 94.24 (C_3), 95.39 (C_{6a}), 125.18–131.23 (C_{arom}), 168.77 (C_4), 173.21 (C_6).

3,3,6a-trimethyl-5-phenyl-3,3a,4,5,6,6a-hexahydropyrrolo[3,4-c] pyrazole (**3b**): White crystals (1.25 g, 91%), m.p. 98°C, MS, *m/z* (%): [$M^{+\cdot}$-N_2, 229], 229 (100%). Anal. Calcd. For $C_{14}H_{15}N_3O_2$: C, 65.34; H, 5.89; N, 16.33%; Found: C, 65.50; H, 5.80; N, 16.45%; IR (KBr) ν_{cm}^{-1}; 1510 (N=N); 1725, 1730 (C=O). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.52 (s, 6H, CH_3), 1.83 (s, 3H, CH_3), 2.58 (s, 1H, H_{3a}), 7.14–7.41 (m, 5H, H_{arom}); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 20.88 and 23.19 (CH_3), 29.06 (CH_3), 53.34 (C_{3a}), 95.45 (C_3), 100.30 (C_{6a}), 126.61–131.41 (C_{arom}), 172.15 (C_4), 172.84 (C_6).

3,3-dimethyl-5-(4-methoxyphenyl)-3,3a,4,5,6,6a-hexahydro-pyrrolo[3,4-c]pyrazole (**3c**): White crystals (1.17 g, 80%), m.p. 103°C (dichloromethane–ether of petrole). MS, *m/z* (%): [$M^{+\cdot}$-N_2, 245], 96 (100%). Anal. Calcd. For $C_{14}H_{15}N_3O_3$: C, 61.52; H, 5.54; N, 15.37%; Found: C, 62.01; H, 5.45; N, 13.41%; IR ν_{cm}^{-1}; 1526 (N=N); 1695, 1700 (C=O). ^{1}H NMR (300 MHz; $CDCl_3$) δ_{ppm}: 1.57 (s, 3H, CH_3), 1.62 (s, 3H, CH_3), 2.98 (d, 1H, H_{3a}), 5.97 (d, 1H, H_{6a}): AX patt. $J_{H3a\text{-}H6a}$ = 8.3 Hz, 3.83 (s, 3H, OCH_3), 6.96 (d, 2H) and 7.11 (d, 2H): AA'BB' patt. J = 8.4 Hz; ^{13}C NMR (75 MHz; $CDCl_3$) δ_{ppm}: 22.94 (CH_3), 28.24 (CH_3), 47.34 (C_{3a}), 55.93 (OCH_3), 94.22 (C_3), 95.25 (C_{6a}), 115.00–160.19 (C_{arom}), 169.04 (C_4), 173.47 (C_6).

3,3,6a-trimethyl-5-(4-methoxyphenyl)-3,3a,4,5,6,6a-hexahydropyrrolo[3,4-c]pyrazole (**3d**): White crystals (1.23 g, 80%), m.p. 140°C, MS, *m/z* (%): [$M^{+\cdot}$-N_2, 259], 134 (100%). Anal. Calcd. For $C_{15}H_{17}N_3O_3$: C, 62.69; H, 5.97; N, 14.63%; Found: C, 62.73; H, 5.99; N, 14.49%; IR (KBr) ν_{cm}^{-1}; 1516 (N=N), 1720, 1738 (C=O). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.51 (s, 6H, CH_3), 1.82 (s, 3H, CH_3), 2.61 (s, 1H, H_{3a}), 3.75 (s, 3H, OCH_3), 6.87 (d, 2H) and 7.05 (d, 2H): AA'BB' patt. J = 9 Hz; ^{13}C NMR (75 MHz, $CDCl_3$) δ: 20.88 and 23.18 (CH_3), 29.04 (CH_3), 53.27 (C_{3a}), 55.91 (OCH_3), 95.32 (C_3), 100.27 (C_{6a}), 114.94–160.13 (C_{arom}), 172.38 (C_4), 173.09 (C_6).

3,3-dimethyl-5-(4-nitrophenyl)-3,3a,4,5,6,6a-hexahydro-pyrrolo[3,4-c]pyrazole (**3e**): Yellow crystals (1.08 g, 70%), m.p. 130°C, MS, *m/z* (%): [$M^{+\cdot}$-N_2, 260], 260 (100%). Anal. Calcd. For $C_{13}H_{12}N_4O_4$: C, 54.17; H, 4.20; N, 19.44%; Found: C, 54.62; H, 4.25; N, 19.45%; IR (KBr) ν_{cm}^{-1}; 1520 (N=N), 1689, 1695 (C=O). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.63 (s, 6H, CH_3), 2,90 (d, 1H, H_{3a}), 6.01 (d, 1H, H_{6a}), AX patt. $J_{H3a\text{-}H6a}$ = 8.3 Hz, 7.56 (d, 2H) and 8.42 (d, 2H): AA'BB' patt. J = 9 Hz; ^{13}C NMR (75 MHz, $CDCl_3$) δ: 21.45 and 22.87 (CH_3), 54.62 (C_{3a}), 94.35 (C_3), 95.98 (C_{6a}), 123.47–146.10 (C_{arom}), 172.16 (C_4), 173.02 (C_6).

3,3,6a-trimethyl-5-(4-nitrophenyl)-3,3a,4,5,6,6a-hexahydro-pyrrolo[3,4-c]pyrazole (**3f**): Yellow crystals (1.52 g, 94%), m.p. 147°C, MS, *m/z* (%): [$M^{+\cdot}$-N_2, 274], 274 (100%). Anal. Calcd. For $C_{14}H_{14}N_4O_4$: C, 55.65; H, 4.67; N, 18.52%; Found: C, 55.45; H, 4.62; N, 18.65%; IR (KBr) ν_{cm}^{-1}; 1520 (N=N), 1718, 1735 (C=O). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.60 (s, 6H, CH_3), 1.92 (s, 3H, CH_3), 2.71 (s, 1H, H_{3a}), 7.53 (d, 2H) and 8.31 (d, 2H): AA'BB' patt. J = 9 Hz; ^{13}C NMR (75 MHz, $CDCl_3$) δ: 20.45 and 22.86 (CH_3), 28.65 (CH_3), 52.92 (C_{3a}), 95.67 (C_3), 99.91 (C_{6a}), 124.53–147.00 (C_{arom}), 171.06 (C_4), 171.07 (C_6).

3,3,5',5'-tetramethyl-3a,4,5,6a-tetrahydro-3H,5'H-spiro[pyrrolo [3,4-c]pyrazole-6,2'-[1,3,4]oxadiazole]-4-one (**5**): White solid

(0.82 g, 65%), m.p. 114°C, MS, *m/z* (%): [$M^{+\cdot}$, 237], 209 (100%). Anal. Calcd. For $C_{10}H_{15}N_5O_2$: C, 50.62; H, 6.37; N, 29.52%; Found: C, 50.49; H, 6.31; N, 29.43%; IR (KBr) ν_{cm}^{-1}; 1540 (N=N), 1720, (C=O). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.45; 1.59 (s, 3H, $CH_{3(a,b)}$), 2.02; 2.14 (s, 3H, $CH_{3(c,d)}$), 2.76 (s, 1H, H_{3a}), 5.91 (s, 1H, H_{6a}), AX patt. $J_{H3a\text{-}H6a}$ = 8.4 Hz, 8.93 (s, 1H, NH); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 18.72, 22.36, 25.22 and 22.86 (CH_3), 27.77 (CH_3), 47.23 (C_{3a}), 91.67 (C_3), 93.82 (C_{6a}), 130.16 ($C_{5'}$), 149.90 (C_6), 172.41 (C_4).

*General procedure for the irradiation of the Δ^1-pyrazolines (**3**)*

All irradiation were carried out using similar conditions. The derivative was dissolved in ether (pre-treated by stirring with solid ($NaCO_3$), filtering and flushing with argon) and irradiation at 5°C for a total of 2 hours or until the starting materiel was consumed (TLC). After this period the solvent was removed in a vacuum without heating to give brown oil, which was subjected to rapid silica filtration. Recrystallisation from light petroleum.

6,6-dimethyl-3-phenyl-3-azabicyclo[3.1.0]hexane-2,4-dione (**6a**): A solution of **3a** (500 mg, 1.95 mmol) in ether (200 ml) was irradiated as previously described to give a white solid. Yield 50%, m.p. = 123°C, MS, *m/z* (%): [$M^{+\cdot}$, 215], 215 (100%). Anal. Calcd. For $C_{13}H_{13}NO_2$: C, 72.52; H, 6.10; N, 6.51%; Found: C, 72.60; H, 6.02; N, 6.39%; ^{1}H NMR (300 MHz; $CDCl_3$) δ: 1.30 (s, 3H, CH_3), 1.41 (s, 3H, CH_3), 2.48 (s, 2H, $H_{1,5}$), 7.24–7.46 (m, 5H, H_{arom}); ^{13}C NMR (75 MHz; $CDCl_3$) δ: 16.01 (CH_3), 25.74 (CH_3), 33.70 ($C_{1,5}$), 35.39 (C_6), 126.28–131.54 (C_{arom}), 172.92 ($C_{2,4}$).

1,6,6-trimethyl-3-phenyl-3-azabicyclo[3.1.0]hexane-2,4-dione (**6b**): A solution of **3b** (500 mg, 1.95 mmol) in ether (200 ml) was irradiated as previously described to give a white solid. Yield 70%, m.p. = 118°C, MS, *m/z* (%): [$M^{+\cdot}$, 229], 110 (100%). Anal. Calcd. For $C_{14}H_{15}NO_2$: C, 73.36; H, 6.60; N, 6.10%; Found: C, 73.60; H, 6.39; N, 6.30%; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.30 (s, 3H, CH_3), 1.38 (s, 3H, CH_3), 1.56 (s, 3H, CH_3), 2.16 (s, 1H, H_5), 7.28–7.47 (s, 5H, H_{arom}); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 10.28 and 17.18 (CH_3), 23.05 (CH_3), 36.77 (C_1), 37.62 ($C_{5,6}$), 126.18–131.64 (C_{arom}), 173.53 (C_4), 176.35 (C_2).

3-anisyl-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2,4-dione (**6c**): A solution of **3c** (500 mg, 1.95 mmol) in ether (200 ml) was irradiated as previously described to give a white solid. Yield 60%, m.p. = 113°C, MS, *m/z* (%): [$M^{+\cdot}$, 215], 215 (100%). Anal. Calcd. For $C_{14}H_{15}NO_3$: C, 68.56; H, 6.16; N, 5.71%; Found: C, 68.63; H, 6.20; N, 5.79%; ^{1}H NMR (300 MHz; $CDCl_3$) δ: 1.29 (s, 3H, CH_3), 1.36 (s, 3H, CH_3), 2.44 (s, 2H, $H_{1,5}$), 3.84 (s, 3H, OCH_3), 6.88 (d, 2H) and 7.17 (d, 2H): AA'BB' patt. J = 8.4 Hz; ^{13}C NMR (75 MHz; $CDCl_3$) δ: 16.31 (CH_3), 25.54 (CH_3), 32.71 ($C_{1,5}$), 36.31 (C_6), 56.03 (OCH_3), 115.10–161.09 (C_{arom}), 171.82 ($C_{2,4}$).

3-anisyl-1,6,6-trimethyl-3-azabicyclo[3.1.0]hexane-2,4-dione (**6d**): A solution of **3d** (500 mg, 1.74 mmol) in ether (200 ml) was irradiated as previously described to give a yellow solid. Yield 65%, m.p. = 138°C, MS, *m/z* (%):[$M^{+\cdot}$, 259], 67 (100%). Anal. Calcd. For $C_{15}H_{17}NO_3$: C, 69.46; H, 6.62; N, 5.40%; Found: C, 69.37; H, 6.80; N, 5.29%; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.29 (s, 3H, CH_3), 1.37 (s, 3H, CH_3), 1.55 (s, 3H, CH_3), 2.13 (s, 1H, H_5), 3.80 (s, 3H, OCH_3), 6.93 (d, 2H) and 7.16 (d, 2H): AA'BB' patt. J = 9 Hz; ^{13}C NMR (75 MHz, $CDCl_3$) δ: 10.28 and 17.18 (CH_3), 23.04 (CH_3), 36.69 (C_1), 37.55 (C_5), 37.61 (C_6), 55.53 (OCH_3), 114.46–159.27 (C_{arom}), 173.84 (C_4), 176.62 (C_2).

6,6-dimethyl-3-(p-nitrophenyl)-3-azabicyclo[3.1.0]hexane-2,4-dione (**6e**): A solution of **3e** (500 mg, 1.65 mmol) in ether (200 ml) was irradiated as previously described to give a yellow solid. Yield 75%, m.p. = 147°C, MS, *m/z* (%): [$M^{+\cdot}$, 274], 274 (100%). Anal. Calcd. For $C_{13}H_{12}N_2O_4$: C, 60.00; H, 4.65; N, 10.76%; Found: C, 60.05; H, 4.70; N, 10.62%; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.14 (s, 3H, CH_3), 1.23 (s, 3H, CH_3), 2.35 (s, 2H, $H_{1,5}$), 7.39 (d, 2H) and 8.09 (d, 2H): AA'BB' patt. J = 9 Hz; ^{13}C NMR (75 MHz, $CDCl_3$) δ: 9.31 and 17.18 (CH_3), 36.13 (C_1), 36.70 (C_5), 36.81 (C_6), 122.42–146.38 (C_{arom}), 171.47 (C_4), 173.99 (C_2).

1,6,6-trimethyl-3-(p-nitrophenyl)-3-azabicyclo[3.1.0]hexane-2,4-dione (**6f**): A solution of **3f** (500 mg, 1.65 mmol) in ether (200 ml) was irradiated as previously described to give a yellow solid. Yield 75%, m.p. = 158°C, MS, *m/z* (%): [$M^{+\cdot}$, 274], 274 (100%). Anal. Calcd. For $C_{14}H_{14}N_2O_4$: C, 61.31; H, 5.14; N, 10.21%; Found: C, 61.19; H, 5.40; N, 10.31%; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.27 (s, 3H, CH_3), 1.29 (s, 3H, CH_3), 1.52 (s, 3H, CH_3), 2.15 (s, 1H, H_5), 7.49 (d, 2H) and 8.22 (d, 2H): AA'BB' patt. J = 9 Hz; ^{13}C NMR (75 MHz, $CDCl_3$) δ: 9.19 and 16.17 (CH_3), 21.97 (CH_3), 36.03 (C_1), 36.69 (C_5), 36.79 (C_6), 123.32–145.52 (C_{arom}), 171.51 (C_4), 174.51 (C_2).

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