Heterocycl. Commun., Vol. 17(5-6), pp. 215–218, 2011 • Copyright © by Walter de Gruyter • Berlin • Boston. DOI 10.1515/HC.2011.034

Synthesis and chemistry of pyrazolines derived from diphenyldiazomethane

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Abstract

The reaction of diphenyldiazomethane with *N*-substituted maleimides produces Δ^1-pyrazolines. The photolysis of Δ^1-pyrazolines leads to cyclopropanes.

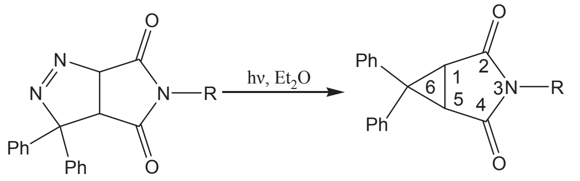
Keywords: cyclopropanes; 1,3-dipolar cycloaddition; irradiation; pyrazolines.

Introduction

The synthesis of pyrazoles and their derivatives remains of great interest owing to the wide application of such heterocycles in the pharmaceutical and agrochemical industry (Elguero, 1984, 1986). In particular, a 1,3-dipolar cycloaddition reaction of alkenes with diazoalkanes has been used to prepare pyrazolines (Huisgen, 1984; Padwa and Pearson, 2002). Many pyrazolines show antibacterial (Bilgin et al., 1992, 1993, 1994), antidepressant (Gokhan et al., 2003), anticonvulsant (Amr et al., 2003a), antiparkinsonian (Amr and Abou-Ghalia, 2004), and anti-inflammatory activities (Amr et al., 2003b). This paper describes the synthesis and reactivity of pyrazolines derived from diphenyldiazomethane (Richard et al., 1961a; Jaz and Millet, 1967; Millet, 1969; Dietrich-Bucheker and Frank-Neumann, 1977; Boukamcha et al., 1999).

Results and discussion

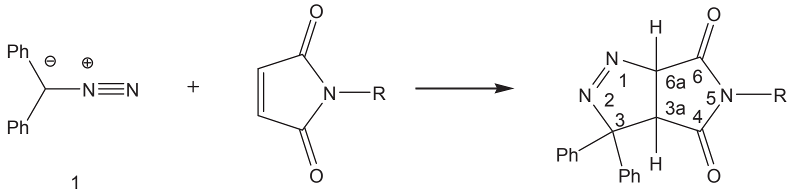
The 1,3-dipolar cycloaddition reaction of diphenyldiazomethane **1** with *N*-arylmaleimides **2** led to exclusive formation of pyrazolines **3** (Scheme 1).



3a-d

4a-d
4a: R=CH_3
4b: R=C_6H_5
4c: R=p-$CH_3OC_6H_4$
4d: R=p-$NO_2C_6H_4$

Scheme 2 The 1,3-dipolar cycloaddition of diphenyldiazomethane (**1**) with maleic anhydride (**5**), at 40°C, furnished a cyclopropane derivative **6** (Thomas et al., 1976). The lactone moiety of **6** was opened by the reaction with an amine yielding the product **7** (Scheme 3) (Richard et al., 1961b; Hibbs et al., 1997).

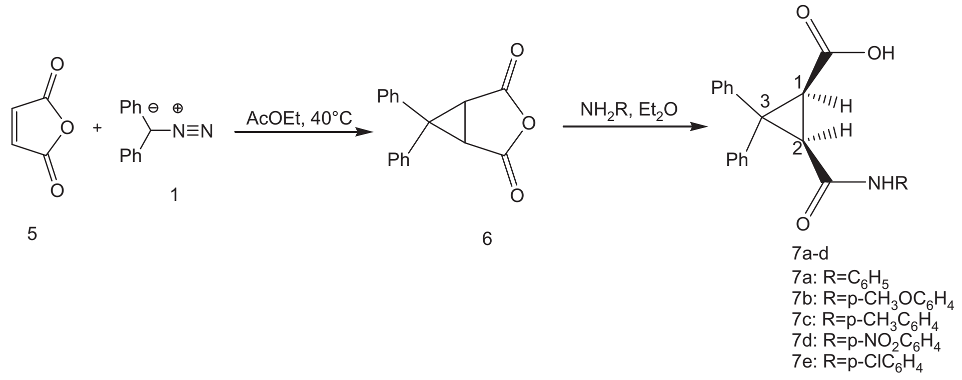


1

2a-d

3a-d
3a: R=CH_3
3b: R=C_6H_5
3c: R=p-$CH_3OC_6H_4$
3d: R=p-$NO_2C_6H_4$

Scheme 1 The photolysis of an ethereal solution of the Δ^1-pyrazolines **3** at 0–5°C led to exclusive formation of *gem*-diphenylcyclopropanes **4** (Scheme 2) (Nesrine et al., 2011).



Scheme 3 The suggested *cis* substitution of the cyclopropane moiety of **7** is consistent with the coupling constant $J_{H1,H3}$=8.7 Hz for derivatives **7a–d** and 9.0 Hz for **7e**.

Experimental section

General

Infrared spectra were recorded on a Perkin-Elmer IR-197 spectrophotometer. Mass spectra were determined on a Nierjohnson MS80RF spectrometer. Melting points were determined on a BuchI-510 capillary melting point apparatus and were not corrected. Thin layer chromatography (TLC) was performed on silica gel 254 plates (Merck) with UV (254 nm) visualisation, and preparative chromatographic separations were conducted on silica gel Si-60-7734 (Merck). The ^{1}H-NMR and ^{13}C-NMR spectra were recorded at 300 MHz and 75 MHz, respectively. 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.

Reaction of diphenyldiazomethane (1b) with *N*-arylmaleimides (2)

To a solution of **2** (5 mmol) in ethyl acetate (20 ml), diphenyldiazomethane (6 mmol) was added and the resulting solution was heated under an argon atmosphere at 40°C for 2 h, after which time the mixture was cooled to ambient temperature and concentrated under reduced pressure. Products **3a–d** were crystallised from ethanol.

5-Methyl-3,3-diphenyl-3,3a,4,5,6,6a-hexahydropyrrolo[3,4-*c*]-pyrazole (3a) Yield 1.06 g (70%); white solid; mp 120°C; IR: ν 1530, 1670, 1675 cm^{-1}; ^{1}H-NMR (CDCl$_3$; 300 MHz): δ 2.64 (s, 3H, CH$_3$), 3.88 and 5.99 (2H, H$_{3a}$, H$_{6a}$, J=8.4 Hz), 6.71–7.75 (m, 10H, H$_{arom}$); ^{13}C-NMR (CDCl$_3$): δ 24.9 (CH$_3$), 47.7 (C$_{3a}$), 94.9 (C$_{6a}$), 106.1 (C$_3$), 126.9–139.5 (C$_{arom}$), 169.4 (C$_4$), 172.6 (C$_6$). Anal. calcd. for $C_{18}H_{15}N_3O_2$: C, 70.81; H, 4.95; N, 13.76. Found: C, 70.89; H, 4.98; N, 13.67.

3,3-Diphenyl-5-phenyl-3,3a,4,5,6,6a-hexahydropyrrolo[3,4-*c*]-pyrazole (3b) Yield 1.10 g (60%); white solid; mp 150°C; IR: ν 1530, 1670, 1675; ^{1}H-NMR (DMSO-d_6): δ 4.17 and 6.22 (2H, H$_{3a}$, H$_{6a}$, J=8.4 Hz), 6.46–7.70 (m, 15H, H$_{arom}$); ^{13}C-NMR (DMSO-d_6) δ: 47.7 (C$_{3a}$), 96.3 (C$_{6a}$), 105.3 (C$_3$), 126.9–141.6 (C$_{arom}$), 169.4 (C$_4$), 172.7 (C$_6$). Anal. calcd. for $C_{23}H_{17}N_3O_2$: C, 75.19; H, 4.66; N, 11.44. Found: C, 75.26; H, 4.70; N, 11.45.

3,3-Diphenyl-5-(4-methoxyphenyl)-3,3a,4,5,6,6a-hexahydropyrrolo[3,4-*c*]pyrazole (3c) Yield 1.59 g (80%); white solid; mp 134°C; IR: ν 1535, 1695, 1705; ^{1}H-NMR (CDCl$_3$): δ 3.72 (s, 3H, OCH$_3$), 4.12 and 6.49 (2H, H$_{3a}$, H$_{6a}$, J=8.4 Hz), 6.67–7.73 (m, 14H, H$_{arom}$); ^{13}C-NMR (CDCl$_3$): δ 47.9 (C$_{3a}$), 55.9 (OCH$_3$), 96.3 (C$_{6a}$), 105.1 (C$_3$), 114.6–159.6 (C$_{arom}$), 169.5 (C$_4$), 172.6 (C$_6$). Anal. calcd. for $C_{24}H_{19}N_3O_3$: C, 72.53; H, 4.82; N, 10.57. Found: C, 72.51; H, 4.85; N, 10.53.

3,3-Diphenyl-5-(4-nitrophenyl)-3,3a,4,5,6,6a-hexahydropyrrolo[3,4-c]pyrazole (3d) Yield 1.03 g (50%); white crystals; mp 142°C; IR: ν 1530, 1675, 1680; ^{1}H-NMR (CDCl$_3$): δ 4.15 and 6.20 (2H, H$_{3a}$, H$_{6a}$, J=8.4 Hz), 6.26–8.10 (m, 14H, H$_{arom}$); ^{13}C-NMR (CDCl$_3$): δ 47.6 (C$_{3a}$), 97.0 (C$_{6a}$), 104.9 (C$_3$), 124.9–136.3 (C$_{arom}$), 169.4 (C$_4$), 172.6 (C$_6$). Anal. calcd. for $C_{23}H_{16}N_4O_4$: C, 66.99; H, 3.91; N, 13.59. Found: C, 66.93; H, 3.89; N, 13.35.

Synthesis of cyclopropane derivatives 4

A solution of substrate **3** (5 mmol) in ether was irradiated using a mercury lamp emitting at 254 nm at 5°C until the starting material was consumed (TLC). Then the solvent was removed on a rotary evaporator without heating to give brown oil that was purified by chromatography eluting with ethyl acetate/petroleum ether (1:4). Products **4a–d** were crystallised from ethanol.

3-Methyl-6,6-diphenyl-3-azabicyclo[3.1.0]hexane-2,4-dione (4a) Yield 0.69 g (50%); white crystals; mp 150°C; ^{1}H-NMR (CDCl$_3$): δ 2.28 (s, 3H, CH$_3$), 3.10 (s, 2H, H$_{1,5}$), 7.13–7.35 (m, 10H, H$_{arom}$); ^{13}C-NMR (CDCl$_3$): δ 24.11 (CH$_3$), 34.3 (C$_{1,5}$), 50.7 (C$_6$), 127.3–141.5 (C$_{arom}$), 173.6 (C$_{2,4}$). Anal. calcd. for $C_{18}H_{15}NO_2$: C, 77.96; H, 5.45; N, 5.05. Found: C, 77.80; H, 5.37; N, 5.09.

3,6,6-Triphenyl-3-azabicyclo[3.1.0]hexane-2,4-dione (4b) Yield 1.27 g (75%); white solid; mp 172°C; IR: ν 1530; 1670, 1675; ^{1}H-NMR (CDCl$_3$): δ 3.16 (s, 2H, H$_{1,5}$), 6.76–7.78 (m, 15H, H$_{arom}$); ^{13}C-NMR (CDCl$_3$): δ 35.1 (C$_{1,5}$), 51.3 (C$_6$), 126.9–139.5 (C$_{arom}$), 173.7 (C$_{2,4}$). Anal. calcd. for $C_{23}H_{17}N_3O_2$: C, 81.40; H, 5.05; N, 4.13. Found: C, 81.20; H, 5.00; N, 4.25.

3-(4-Methoxyphenyl)-6,6-diphenyl-3-azabicyclo[3.1.0]hexane-2,4-dione (4c) Yield 1.48 g (80%); white solid; mp 129°C; ^{1}H-NMR (CDCl$_3$): δ 3.32 (s, 2H, H$_{1,5}$), 3.73 (s, 3H, OCH$_3$), 6.20 and

6.72 (d, 4H, H_{arom}, J=9 Hz), 7.23–7.56 (m, 10H, H_{arom}); ^{13}C-NMR (CDCl$_3$) δ: 33.8 ($C_{1,5}$), 50.1 (C_6), 55.4 (OCH$_3$), 114.4–159.5 (C_{arom}), 172.6 ($C_{2,4}$). Anal. calcd. for $C_{24}H_{19}NO_3$: C, 78.03; H, 5.18; N, 3.79. Found: C, 78.10; H, 5.12; N, 3.63.

3-(4-Nitrophenyl)-6,6-diphenyl-3-azabicyclo[3.1.0]hexane-2,4-dione (4d) Yield 1.15 g (60%); white solid; mp 131°C; ^{1}H-NMR (CDCl$_3$): δ 3.38 (s, 2H, $H_{1,5}$), 6.28 and 8.08 (d, 4H, H_{arom}, J=8.7 Hz), 6.96–7.53 (m, 10H, H_{arom}); ^{13}C-NMR (CDCl$_3$): δ 34.1 ($C_{1,5}$), 50.1 (C_6), 124.2–136.7 (C_{arom}), 171.3 ($C_{2,4}$). Anal. calcd. for $C_{23}H_{16}N_2O_4$: C, 71.87; H, 4.20; N, 7.29. Found: C, 71.67; H, 4.31; N, 7.18.

6,6-Diphenyl-3-oxabicyclo[3.1.0]hexane-2,4-dione 6

This compound was prepared as described for the synthesis of adducts **3**: Yield 0.44 g (80%); yellow solid; mp 148°C; ^{1}H-NMR (CDCl$_3$): δ 3.46 (s, 2H, $H_{1,5}$), 7.16–7.48 (m, 10H, H_{arom}); ^{13}C-NMR (CDCl$_3$): δ 35.78 ($C_{1,5}$), 47.7 (C_6), 126.8–139.7 (C_{arom}), 166.5 ($C_{2,4}$). Anal. calcd. for $C_{17}H_{12}O_3$: C, 77.26; H, 4.58; N, 3.92. Found: C, 77.30; H, 4.55; N, 3.99.

Synthesis of cyclopropane derivatives 7

A solution of lactone **6** (10 mmol) in dry CH$_2$Cl$_2$ was stirred at -30°C under an argon atmosphere and treated dropwise with an amine RNH$_2$ (15 mmol). The resultant solid product **7** was filtered.

***cis*-3,3-Diphenyl-2-(phenylcarbamoyl)-1-cyclopropanecarboxylic acid (7a)** Yield 1.07 g (60%); yellow solid; mp 215°C; IR: ν 3330 cm^{-1}; ^{1}H-NMR (DMSO): δ 2.83; 2.94 (AX, H_1, H_3, J_{AX}=8.7 Hz), 7.09–7.51 (m, 16H, H_{arom}, NH), 11.12 (s, 1H, CO$_2$H); ^{13}C-NMR (DMSO-d_6): δ 34.7 and 35.8 ($C_{1,2}$), 43.6 (C_3), 120.7–145.7 (C_{arom}), 169.5 and 170.3 (C_{car}). Anal. calcd. for $C_{23}H_{19}NO_3$: C, 77.29; H, 5.36. Found: C, 77.30; H, 5.31.

***cis*-2-[(4-Methoxyphenyl)carbamoyl]-3,3-diphenyl-1-cyclopropanecarboxylic acid (7b)** Yield 1.23 g (64%); white solid; mp 213°C; IR: ν 3330 cm^{-1}; ^{1}H-NMR (DMSO-d_6): δ 2.83 and 2.92 (d, 2H, H_1, H_3, J=8.7 Hz), 3.72 (s, 3H, OCH$_3$), 6.91–7.43 (m, 15H, H_{arom}, NH), 11.13 (s, 1H, CO$_2$H); ^{13}C-NMR (DMSO-d_6): δ 34.6 and 36.3 ($C_{1,2}$), 43.5 (C_3), 55.7 (OCH$_3$), 114.5–156.7 (C_{arom}), 169.6 and 170.3 (C_{car}). Anal. calcd. for $C_{24}H_{21}NO_4$: C, 74.40; H, 5.46; N, 3.62. Found: C, 74.40; H, 5.45 N, 3.60.

***cis*-2-[(4-Methylphenyl)carbamoyl]-3,3-diphenyl-1-cyclopropanecarboxylic acid (7c)** Yield 1.39 g (75%); white solid; mp 170°C; IR: ν 3330; ^{1}H-NMR (DMSO-d_6): δ 2.32 (s, 3H, CH$_3$), 2.80 and 2.82 (d, 2H, H_1, H_3, J=8.7 Hz), 6.87–7.45 (m, 15H, H_{arom}, NH), 11.15 (s, 1H, CO$_2$H); ^{13}C-NMR (DMSO-d_6): δ 28.3 (CH$_3$), 34.5 and 37.0 ($C_{1,2}$), 42.9 (C_3), 126.5–136.6 (C_{arom}), 168.5 and 171.4 (C_{car}). Anal. calcd. for $C_{24}H_{21}NO_3$: C, 77.61; H, 5.70; N, 3.77. Found: C, 77.57; H, 5.65; N, 3.80.

***cis*-2-[(4-Nitrophenyl)carbamoyl]-3,3-diphenyl-1-cyclopropanecarboxylic acid (7d)** Yield 0.80 g (40%); white solid; mp 151°C; IR: ν 3330; ^{1}H-NMR (DMSO-d_6) δ: 2.73 and 2.80 (d, 2H, H_1, H_3, J=8.7 Hz), 6.29–8.09 (m, 15H, H_{arom}, NH), 11.08 (s, 1H, CO$_2$H); ^{13}C-NMR (DMSO-d_6): δ 34.5 and 35.9 ($C_{1,2}$), 44.1 (C_3), 123.6–137.6 (C_{arom}), 169.6 and 172.0 (C_{car}). Anal. calcd. for $C_{23}H_{18}N_2O_5$: C, 68.65; H, 4.51; N, 6.96. Found: C, 68.62; H, 4.55; N, 7.00.

***cis*-2-[(4-Chlorophenyl)carbamoyl]-3,3-diphenyl-1-cyclopropanecarboxylic acid (7e)** Yield 1.36 g (70%); white solid; mp 203°C; IR: ν 3330 cm^{-1}; ^{1}H-NMR (DMSO-d_6): δ 2.78 and 2.85 (d, 2H, H_1, H_3, J=9 Hz), 7.15–7.51 (m, 15H, H_{arom}, NH), 11.59 (s, 1H, CO$_2$H); ^{13}C-NMR (DMSO-d_6): δ 35.2 and 35.9 ($C_{1,2}$), 43.4 (C_3), 121.9–146.1 (C_{arom}), 169.2 and 170.8 (C_{car}). Anal. calcd. for $C_{23}H_{18}ClNO_3$: C, 70.50; H, 4.63; N, 3.57. Found: C, 70.47; H, 4.60; N, 3.53.

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Received July 19, 2011; accepted August 25, 2011; previously published online September 22, 2011