# Regio- and stereoselectivity in 1,3-dipolar cycloaddition reaction of 2-diazopropane with benzylidene-*N*-arylsuccinimide and benzylidene-*N*-arylmethylsuccinimide derivatives: synthesis of *gem*-dimethylcyclopropane

**Naoufel Ben Hamadi* and Moncef Msaddek**

*Laboratoire de Synthèse Hétérocyclique et substances naturelles, Département de Chimie, Faculté des Sciences 5000 Monastir, Tunisia*

1,3-dipolar cycloaddition of 2-diazopropane with (*E*)-benzylidene-*N*-arylsuccinimide and (*E*)-benzylidene-*N*-arylmethylsuccinimide derivatives is taking place regiospecifically to give a new spiro-pyrazolines. The reaction of 2-diazopropane with (*E*)-benzylidene-*N*-arylmethylsuccinimide derivatives is diastereospecific. Irradiation of the pyrazoline led to clean extruction of nitrogen to give the new spiro-cyclopropanes.

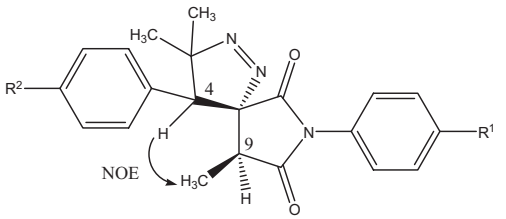
**Keywords:** 1,3-cycloaddition, spiro-pyrazolines, irradiation, spiro-cyclopropanes

Cyclopropane ring, a common motif among natural compounds, deserves high interest, in terms of access, synthetic potential, and bioactivities.[1] The *gem*-dimethyl-cyclopropane unit is a key structural of many valuable natural products[2,3] such as phorbol, aristolone and chrysanthemic acid.

## Results and discussion

(*E*)-Benzylidene-*N*-arylsuccinimide derivatives **2a–d** are obtained by condensation of aldehydes ArCHO with ylides, by the procedure reported in the literature.[4] Wittig reaction products **2e–h** between aldehydes and several ylides were carried out in refluxing 1,2-dichloroethane.[5] Addition of ethereal 2-diazopropane **1** to a solution of **2** in dichloromethane at –78°C until **2** was consumed followed by warming to room temperature gave a racemic monoadducts spiro-$\Delta^1$-pyrazolines **3** in good yield (Scheme 1). The spiro adducts **3a–h** were purified and characterised.

The 1,3-dipolar cycloaddition of 2-diazopropane is, in each case, regiospecific. The chemical shifts of $C_5$ ($^{13}$C NMR) are in excellent agreement with those usually obtained when this quaternary carbon is attached to nitrogen atom.[6] The cycloaddition to the (*E*)-benzylidene-*N*-arylmethyl-succinimide derivatives **2e–h** proceeded fully analogously. Also in this case the approach of the dipole occurs at the *anti*-face to the methyl substituent in the dipolarophile **2e–h**. The attack of the 1,3-dipole occurred from the less hindered face of the dipolarophile **2e–h** giving the isomer **3e–h**. The stereochemistry of this cycloaddition product was determined from a NOESY spectrum. The *trans* relationship between protons $H_4$ and $H_9$ was deduced from observation of an NOE effect between $H_4$ and the methyl protons (Fig. 1). The stereochemical pathway




**3e-h** **e**:$R_1$=H, $R_2$=H, $R_3$=$CH_3$
**f**:$R_1$=H, $R_2$=$OCH_3$, $R_3$=$CH_3$
**g**:$R_1$=$OCH_3$, $R_2$=H , $R_3$=$CH_3$
**h**:$R_1$=$OCH_3$, $R_2$=$OCH_3$, $R_3$=$CH_3$

**Fig. 1**

of cycloaddition of **1** to **2e–h** resembles that of reaction between 2-arylidene-3'-methylindan-1'-ones with diaryl-nitrilimines.[7]

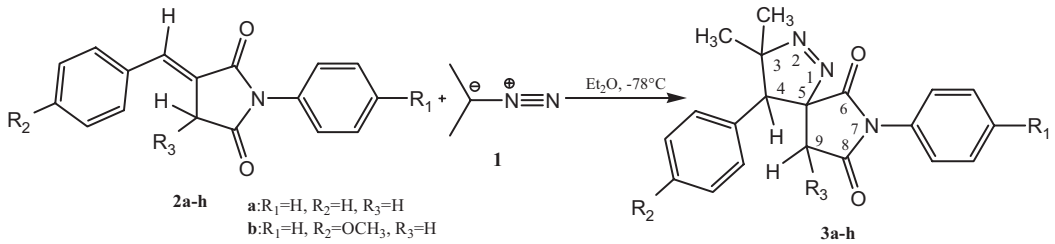
Irradiation of an ethereal solution of the $\Delta^1$-pyrazolines **3** through Pyrex with a high-pressure mercury arc lamp (Philips HPK 125 W) at 0–5°C led to exclusive formation of *gem*-dimethylcyclopropanes[8] **4** (Scheme 2). Its spectroscopic data (NMR) fit perfectly with those of product **4a–d**.

## Conclusion

The reaction of 2-diazopropane with (*E*)-benzylidene-*N*-arylmethylsuccinimide derivatives is regio- and diastereo-specific. Photolysis of the initially formed $\Delta^1$-pyrazoline **3a–d** derivatives afforded *gem*-dimethylcyclopropanes **4a–d**. The biological evaluation of this compound is in progress.

## Experimental

IR spectra were recorded on a Perkin-Elmer IR-197 spectrometer. NMR spectra were obtained on a bruker AC 300 spectrometer



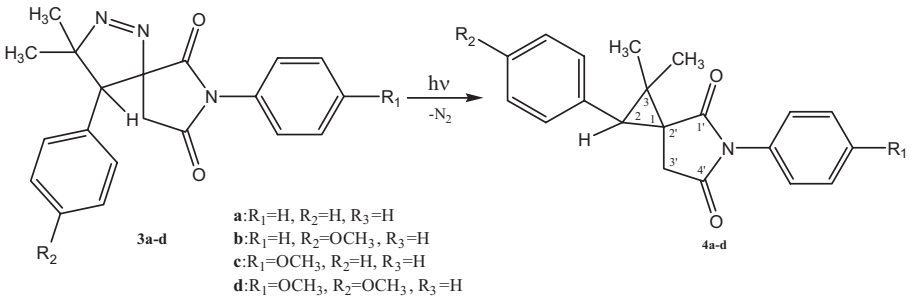

**2a-h** **a**:$R_1$=H, $R_2$=H, $R_3$=H
**b**:$R_1$=H, $R_2$=$OCH_3$, $R_3$=H
**c**:$R_1$=$OCH_3$, $R_2$=H, $R_3$=H
**d**:$R_1$=$OCH_3$, $R_2$=$OCH_3$, $R_3$=H
**e**:$R_1$=H, $R_2$=H, $R_3$=$CH_3$
**f**:$R_1$=H, $R_2$=$OCH_3$, $R_3$=$CH_3$
**g**:$R_1$=$OCH_3$, $R_2$=H , $R_3$=$CH_3$
**h**:$R_1$=$OCH_3$, $R_2$=$OCH_3$, $R_3$=$CH_3$

**1**

**3a-h**

**Scheme 1**

* Correspondent. E-mail: bh_ naoufel@yahoo.fr




**Scheme 2**

operating at 300 MHz for $^1$H and at 75.64 MHz for $^{13}$C. Melting points were determined on a BUCHI-510 capillary melting point apparatus. All reagents were of commercial quality or purified by standard procedures. 2-diazopropane **1** was prepared according to the literature procedure[9] and conserved in ethereal solution at –78°C.

*General procedure for trapping of 2-diazopropane* **1** *with alkenes* **2**
A stirred solution of **2** (5 mmol) in dry dichloromethane (150 ml) was cooled to –78°C and treated with an ethereal solution of 2-diazopropane. The mixture was monitored by thin-layer chromatography (TLC) and the addition of 2-diazopropane was ceased when no starting materiel was present. The mixture was allowed to warm to room temperature 3 hours and concentrated to give the crude reaction product. Recrystallisation from ethanol.

*4,7-diphenyl-3,3-dimethyl-1,2,7-triazaspiro[4.4]non-1-ene-6,8-dione* **3a**: By the above method, phenylidene-*N*-phenylsuccinimide (1.31 g, 5 mmol) to give a white solid (1.33 g, 80%), m.p. 129°C. IR (KBr) $\nu_{cm}^{-1}$; 1515 (N=N). $^1$H NMR ($CDCl_3$) δ: 1.27 (s, 3H, $CH_3$), 1.75 (s, 3H, $CH_3$), 2.85 (d, 1H, $J$ = 18.3 Hz, $H_9$), 3.19 (d, 1H, $J$ = 18.3 Hz, $H_9$), 3.58 (s, 1H, $H_4$), 6.92–7.51 (m, 10H, $H_{arom}$), $^{13}$C NMR ($CDCl_3$) δ: 24.19 and 28.29 ($CH_3$), 37.47 ($C_9$), 52.80 ($C_4$), 97.38 ($C_3$), 99.41 ($C_5$), 126.42–135.45 ($C_{arom}$), 173.08 and 173.20 ($C_{6,8}$). Anal. Calcd. For $C_{20}H_{19}N_3O_2$: C, 72.05; H, 5.74; N, 12.60%; Found: C, 72.14; H, 5.80; N, 12.45%.

*4-anisyl-7-phenyl-3,3-dimethyl-1,2,7-triazaspiro[4.4]non-1-ene-6,8-dione* **3b**: By the above method, anisylidene-*N*-phenylsuccinimide (1.46 g, 5 mmol) to give a white solid (1.27 g, 70%), m.p. 106°C. IR (KBr) $\nu_{cm}^{-1}$; 1520 (N=N). $^1$H NMR ($CDCl_3$) δ: 1.26 (s, 3H, $CH_3$), 1.72 (s, 3H, $CH_3$), 2.86 (d, 1H, $J$ = 18.3 Hz, $H_9$), 3.15 (d, 1H, $J$ = 18.3 Hz, $H_9$), 3.21 (s, 1H, $H_4$), 3.81 (s, 3H, $OCH_3$), 6.86–7.51 (m, 9H, $H_{arom}$), $^{13}$C NMR ($CDCl_3$) δ: 24.11 and 28.14 ($CH_3$), 37.28 ($C_9$), 52.12 ($C_4$), 55.39 ($OCH_3$), 96.99 ($C_3$), 99.16 ($C_5$), 114.20–159.21 ($C_{arom}$), 173.13 and 173.31 ($C_{6,8}$). Anal. Calcd. For $C_{21}H_{21}N_3O_3$: C, 69.41; H, 5.82; N, 11.56%; Found: C, 69.43; H, 5.90; N, 11.44%.

*7-anisyl-4-phenyl-3,3-dimethyl-1,2,7-triazaspiro[4.4]non-1-ene-6,8-dione* **3c**: By the above method, phenylidene-*N*-anisylsuccinimide (1.46 g, 5 mmol) to give a yellow solid (1.36 g, 75%), m.p. 110°C. IR (KBr) $\nu_{cm}^{-1}$; 1520 (N=N). $^1$H NMR ($CDCl_3$) δ: 1.28 (s, 3H, $CH_3$), 1.76 (s, 3H, $CH_3$), 2.84 (d, 1H, $J$ = 18.3 Hz, $H_9$), 3.18 (d, 1H, $J$ = 18.3 Hz, $H_9$), 3.59 (s, 1H, $H_4$), 3.84 (s, 3H, $OCH_3$), 6.93–7.37 (m, 9H, $H_{arom}$), $^{13}$C NMR ($CDCl_3$) δ: 23.53 and 28.63 ($CH_3$), 37.75 ($C_9$), 53.14 ($C_4$), 55.93 ($OCH_3$), 97.66 ($C_3$), 99.69 ($C_5$), 114.94–160.13 ($C_{arom}$), 173.71 and 173.77 ($C_{6,8}$). Anal. Calcd. For $C_{21}H_{21}N_3O_3$: C, 69.41; H, 5.82; N, 11.56%; Found: C, 69.33; H, 5.93; N, 11.62%.

*4,7-dianisyl-3,3-dimethyl-1,2,7-triazaspiro[4.4]non-1-ene-6,8-dione* **3d**: By the above method, anisylidene-*N*-anisylsuccinimide (1.61 g, 5 mmol) to give a white solid (1.18 g, 60%), m.p. 85°C. IR (KBr) $\nu_{cm}^{-1}$; 1510 (N=N). $^1$H NMR ($CDCl_3$) δ: 1.28 (s, 3H, $CH_3$), 1.74 (s, 3H, $CH_3$), 2.86 (d, 1H, $J$ = 18.3 Hz, $H_9$), 3.14 (d, 1H, $J$ = 18.3 Hz, $H_9$), 3.54 (s, 1H, $H_4$), 3.83 (s, 3H, $OCH_3$), 3.84 (s, 3H, $OCH_3$), 6.88–7.28 (m, 8H, $H_{arom}$), $^{13}$C NMR ($CDCl_3$) δ: 24.45 and 28.48 ($CH_3$), 37.56 ($C_9$), 52.46 ($C_4$), 55.72 ($OCH_3$), 55.92 ($OCH_3$), 97.27 ($C_3$), 99.45 ($C_5$), 114.52–160.111 ($C_{arom}$), 173.76 and 173.87 ($C_{6,8}$). Anal. Calcd. For $C_{22}H_{23}N_3O_4$: C, 67.16; H, 5.89; N, 10.68%; Found: C, 67.19; H, 5.86; N, 10.75%.

*4,7-diphenyl-3,3,9-trimethyl-1,2,7-triazaspiro[4.4]non-1-ene-6,8-dione* **3e**: By the above method, phenylidene-*N*-phenylmethylsuccinimide (1.39 g, 5 mmol) to give a yellow solid (0.96 g, 55%), m.p. 151°C. IR (KBr) $\nu_{cm}^{-1}$; 1520 (N=N). $^1$H NMR ($CDCl_3$) δ: 0.57 (d, 3H, $J$ = 6.9 Hz, $CH_3$), 1.20 (s, 3H, $CH_3$), 1.65 (s, 3H, $CH_3$), 3.26 (q, 1H, $J$ = 6.9 Hz, $H_9$), 3.48 (s, 1H, $H_4$), 6.94–7.49 (m, 10H, $H_{arom}$), $^{13}$C NMR ($CDCl_3$) δ: 15.04, 24.01 and 26.46 ($CH_3$), 47.46 ($C_9$), 50.10 ($C_4$), 97.02 ($C_3$), 99.11 ($C_5$), 127.02–136.05 ($C_{arom}$), 173.18 and 177.23 ($C_{6,8}$). Anal. Calcd. For $C_{21}H_{21}N_3O_2$: C, 72.60; H, 6.09; N, 12.10%; Found: C, 72.51; H, 6.21; N, 12.19%.

*4-anisyl-7-phenyl-3,3,9-trimethyl-1,2,7-triazaspiro[4.4]non-1-ene-6,8-dione* **3f**: By the above method, anisylidene-*N*-phenylmethylsuccinimide (1.54 g, 5 mmol) to give a white solid (0.85 g, 45%), m.p. 116°C. IR (KBr) $\nu_{cm}^{-1}$; 1515 (N=N). $^1$H NMR ($CDCl_3$) δ: 0.59 (d, 3H, $J$ = 6.9 Hz, $CH_3$), 1.18 (s, 3H, $CH_3$), 1.62 (s, 3H, $CH_3$), 3.21 (q, 1H, $J$ = 6.9 Hz, $H_9$), 3.49 (s, 1H, $H_4$), 3.79 (s, 3H, $OCH_3$), 6.78–7.49 (m, 9H, $H_{arom}$), $^{13}$C NMR ($CDCl_3$) δ: 15.06, 23.99 and 27.56 ($CH_3$), 47.01 ($C_9$), 50.01 ($C_4$), 55.67 ($OCH_3$), 96.01 ($C_3$), 99.06 ($C_5$), 114.25–159.88 ($C_{arom}$), 173.23 and 178.46 ($C_{6,8}$). Anal. Calcd. For $C_{22}H_{23}N_3O_3$: C, 70.01; H, 6.14; N, 11.13%; Found: C, 70.02; H, 5.99; N, 11.20%.

*7-anisyl-4-phenyl-3,3,9-trimethyl-1,2,7-triazaspiro[4.4]non-1-ene-6,8-dione* **3g**: By the above method, phenylidene-*N*-anisylmethylsuccinimide (1.54 g, 5 mmol) to give a yellow solid (1.22 g, 65%), m.p. 123°C. IR (KBr) $\nu_{cm}^{-1}$; 1510 (N=N). $^1$H NMR ($CDCl_3$) δ: 0.56 (d, 3H, $J$ = 6.9 Hz, $CH_3$), 1.19 (s, 3H, $CH_3$), 1.61 (s, 3H, $CH_3$), 3.28 (q, 1H, $J$ = 6.9 Hz, $H_9$), 3.52 (d, 1H, $H_4$), 3.75 (s, 3H, $OCH_3$), 6.78–7.23 (m, 9H, $H_{arom}$), $^{13}$C NMR ($CDCl_3$) δ: 14.96, 24.92 and 28.96 ($CH_3$), 45.50 ($C_9$), 49.56 ($C_4$), 55.94 ($OCH_3$), 89.82 ($C_3$), 99.02 ($C_5$), 114.75–160.08 ($C_{arom}$), 172.46 and 178.74 ($C_{6,8}$). Anal. Calcd. For $C_{22}H_{23}N_3O_3$: C, 70.01; H, 6.14; N, 11.13%; Found: C, 69.89; H, 6.03; N, 11.22%.

*4,7-dianisyl-3,3,9-trimethyl-1,2,7-triazaspiro[4.4]non-1-ene-6,8-dione* **3h**: By the above method, anisylidene-*N*-anisylmethylsuccinimide (1.68 g, 5 mmol) to give a yellow solid (0.81 g, 40%), m.p. 170°C. IR (KBr) $\nu_{cm}^{-1}$; 1510 (N=N). $^1$H NMR ($CDCl_3$) δ: 0.61 (d, 3H, $J$ = 6.9 Hz, $CH_3$), 1.20 (s, 3H, $CH_3$), 1.64 (s, 3H, $CH_3$), 3.25 (q, 1H, $J$ = 6.9 Hz, $H_9$), 3.51 (s, 1H, $H_4$), 3.78 (s, 3H, $OCH_3$), 3.81 (s, 3H, $OCH_3$), 6.77–7.31 (m, 8H, $H_{arom}$), $^{13}$C NMR ($CDCl_3$) δ: 15.01, 23.99 and 27.86 ($CH_3$), 46.43 ($C_9$), 49.57 ($C_4$), 55.82 ($OCH_3$), 55.96 ($OCH_3$), 99.00 ($C_3$), 99.05 ($C_5$), 114.63–161.10 ($C_{arom}$), 172.99 and 177.89 ($C_{6,8}$). Anal. Calcd. For $C_{23}H_{25}N_3O_4$: C, 67.80; H, 6.18; N, 10.31%; Found: C, 67.69; H, 6.05; N, 10.51%.

*General procedure for the irradiation of the* $\Delta^2$*-pyrazolines* **3a–d**
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 1 h 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 dichloromethane/light petroleum.

*2,5-diphenyl-1,1-dimethyl-5-azaspiro[2.4]heptane-4,6-dione* **4a**: A solution of **3a** (666 mg, 2 mmol) in ether (150 ml) was irradiated as previously described to give a white solid. Yield 45%, m.p. = 188°C. $^1$H NMR ($CDCl_3$) δ: 1.19 (s, 3H, $CH_3$), 1.64 (s, 3H, $CH_3$), 2.65 (d, 1H, $J$ = 19.2 Hz, $H_7$), 2.81 (d, 1H, $J$ = 19.2 Hz, $H_7$), 3.05 (s, 1H, $H_2$), 7.14–7.53 (m, 10H, $H_{arom}$), $^{13}$C NMR ($CDCl_3$) δ: 20.74 and 20.86 ($CH_3$), 31.30 ($C_7$), 31.87 ($C_1$), 34.04 ($C_3$), 40.28 ($C_2$), 126.63–134.32($C_{arom}$), 175.17 and 177.54 ($C_{4,6}$). Anal. Calcd. For $C_{20}H_{19}NO_2$: C, 78.66; H, 6.27; N, 4.59%; Found: C, 78.45; H, 6.23; N, 4.55%.

*2-anisyl-5-phenyl-1,1-dimethyl-5-azaspiro[2.4]heptane-4,6-dione* **4b**: A solution of **3b** (726 mg, 2 mmol) in ether (150 ml) was irradiated as previously described to give a white solid. Yield 65%, m.p. = 143°C. $^1$H NMR ($CDCl_3$) δ: 1.20 (s, 3H, $CH_3$), 1.64 (s, 3H, $CH_3$), 2.65 (d, 1H, $J$ = 19.2 Hz, $H_7$), 2.81 (d, 1H, $J$ = 19.2 Hz, $H_7$), 3.05 (s, 1H, $H_2$), 3.86 (s, 3H, $OCH_3$), 7.01–7.41 (m, 9H, $H_{arom}$), $^{13}$C NMR ($CDCl_3$) δ: 21.08 and 21.20 ($CH_3$), 31.59 ($C_7$), 32.12 ($C_1$), 34.33 ($C_3$), 40.54 ($C_2$), 55.92 ($OCH_3$), 114.81–159.74 ($C_{arom}$), 175.86 and 178.17 ($C_{4,6}$). Anal. Calcd. For $C_{21}H_{21}NO_3$: C, 75.20; H, 6.31; N, 4.18%; Found: C, 75.27; H, 6.40; N, 4.10%.

*5-anisyl-2-phenyl-1,1-dimethyl-5-azaspiro[2.4]heptane-4,6-dione* **4c**: A solution of **3c** (726 mg, 2 mmol) in ether (150 ml) was irradiated as previously described to give a yellow solid. Yield 75%, m.p. = 150°C. $^1$H NMR ($CDCl_3$) δ: 1.18 (s, 3H, $CH_3$), 1.62 (s, 3H, $CH_3$), 2.63 (d, 1H, $J$ = 19.2 Hz, $H_7$), 2.79 (d, 1H, $J$ = 19.2 Hz, $H_7$), 3.03 (s, 1H, $H_2$), 3.84 (s, 3H, $OCH_3$), 6.99–7.39 (m, 9H, $H_{arom}$), $^{13}$C NMR ($CDCl_3$) δ: 20.75 and 20.86 ($CH_3$), 31.25 ($C_7$), 31.79 ($C_1$), 33.98 ($C_3$), 40.20 ($C_2$), 55.59 ($OCH_3$), 114.47–159.39($C_{arom}$), 175.56 and 177.84 ($C_{4,6}$). Anal. Calcd. For $C_{21}H_{21}NO_3$: C, 75.20; H, 6.31; N, 4.18%; Found: C, 75.01; H, 6.21; N, 4.09%.

*2,5-dianisyl-1,1-dimethyl-5-azaspiro[2.4]heptane-4,6-dione* **4d**: A solution of **3d** (786 mg, 2 mmol) in ether (150 ml) was irradiated as previously described to give a yellow solid. Yield 60%, m.p. = 162°C. $^1$H NMR ($CDCl_3$) δ: 1.17 (s, 3H, $CH_3$), 1.61 (s, 3H, $CH_3$), 2.61 (d, 1H, $J$ = 19.2 Hz, $H_7$), 2.76 (d, 1H, $J$ = 19.2 Hz, $H_7$), 2.96 (s, 1H, $H_2$), 3.81 (s, 3H, $OCH_3$), 3.84 (s, 3H, $OCH_3$), 6.87–8.04 (m, 8H, $H_{arom}$), $^{13}$C NMR ($CDCl_3$) δ: 20.70 and 20.86 ($CH_3$), 31.24 ($C_7$), 31.88 ($C_1$), 33.99 ($C_3$), 39.68 ($C_2$), 55.36 ($OCH_3$), 55.58 ($OCH_3$), 113.79–159.37 ($C_{arom}$), 175.61 and 177.90 ($C_{4,6}$). Anal. Calcd. For $C_{22}H_{23}NO_4$: C, 72.31; H, 6.34; N, 3.83%; Found: C, 72.18; H, 6.45; N, 3.91%.

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