Synthesis and Antifungal Activity of Spiro[cyclopropane-1,4'-pyrazol-3-one] Derivatives

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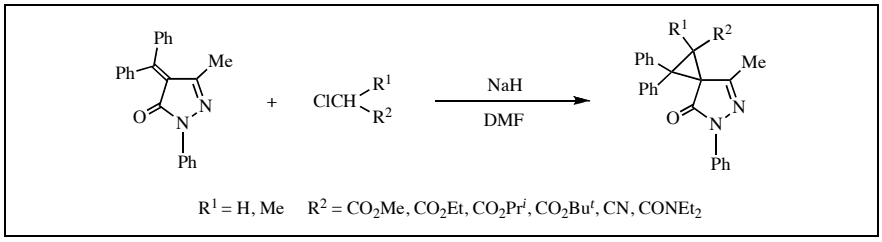

A series of new spiro[cyclopropane-1,4'-pyrazol-3-one] derivatives **3a–h** were synthesized by the reaction of 4-arylidene-3*H*-pyrazol-3-one **1** with secondary and tertiary carbanions derived from a methylene and methine group bearing both a leaving group and electron-withdrawing group, *e.g.* methyl chloroacetate, ethyl chloroacetate, isopropyl chloroacetate, *tert*-butyl chloroacetate, chloroacetonitrile, 2-chloro-*N*,*N*-diethylacetamide, methyl 2-chloropropionate and 2-chloropropionitrile, in the presence of sodium hydride. All the synthesized compounds **3a–h** were active against *Candida albicans* with MIC ≥ 25 μg/mL *in vitro*.

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INTRODUCTION

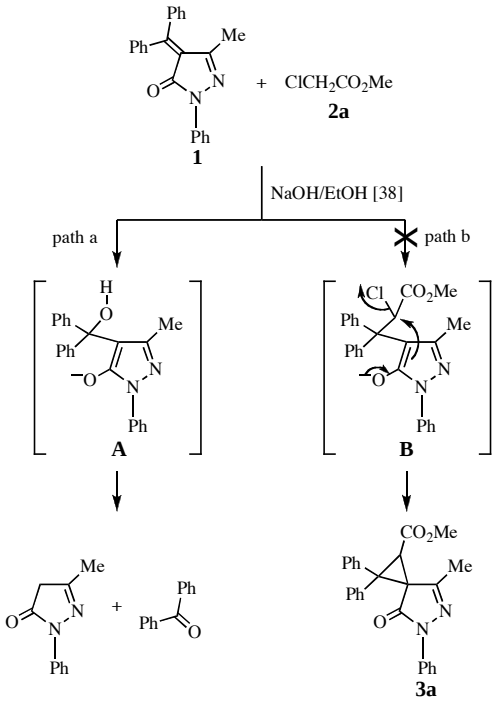
Pyrazoles are key substructures in a large variety of compounds of therapeutic importance [1–3]. Compounds containing this ring system are known to display diverse pharmacological activities such as analgesic, antidepressant, antibacterial, plant growth regulatory, anti-inflammatory and antihyperglycemic activities [4–9]. Thus, it seems likely that the biological activities of pyrazoles depend on the nature of the substituents. In this context, the synthesis [10–17] of pyrazole derivatives continues to attract attention and provides an interesting challenge. In our previous paper [18], we discussed the synthesis of 1-acyl-1,2-dihydro-3*H*-pyrazol-3-ones through Lewis acid-mediated rearrangement of 3-acyl-oxypyrazoles.

Spiro compounds are well known to possess varied pharmacological activities [19–26] and hence their synthesis has always been a challenge and of attraction to organic chemists [27–31]. To the best of our knowledge there are relatively few methods in the literature describing the preparation of spiro-cyclopropanepyrazoles [32–37], even though they also have biological activity [38]. For these reasons, we have been interested in the development of the methods for the synthesis of spiro-cyclopropanepyrazoles. Thus, we herein wish to report an efficient method for preparing new spiro[cyclopropane-1,4'-pyrazol-3-one] derivatives with antifungal activity.

RESULTS AND DISCUSSION

The starting material, 2,4-dihydro-5-methyl-2-phenyl-4-(diphenylmethylene)-3*H*-pyrazol-3-one (**1**), was prepared by treatment of 2,4-dihydro-5-methyl-2-phenyl-3*H*-pyrazol-3-one and benzophenone as originally reported by Du *et al.* [39,40]. An initial attempt to react compound **1** with methyl chloroacetate (**2a**) using the method of Westöö [38] failed and the expected spiro compound **3a** was not observed at all (Scheme 1). In this reaction, a retro-Aldol case probably occurs (path a). This reaction appears to proceed by a stepwise mechanism involving first conjugate addition of the hydroxide ion to compound **1**, giving the intermediate conjugate addition product **A**. This addition is then followed by tautomerization and elimination to afford the intact 2,4-dihydro-5-methyl-2-phenyl-3*H*-pyrazol-3-one and benzophenone. This result indicates that this type of straightforward preparation of spiro compounds is not easy. In order to achieve an efficient synthesis of spiro compounds, we hypothesized if a carbanion could be derived from a methylene group of **2a** and Michael adduct **B** would then be produced readily by the conjugate addition typical of an α,β-unsaturated carbonyl compound as **1** under appropriate conditions, the synthesis of the spiro-compound **3a** would be possible (path b).

Scheme 1

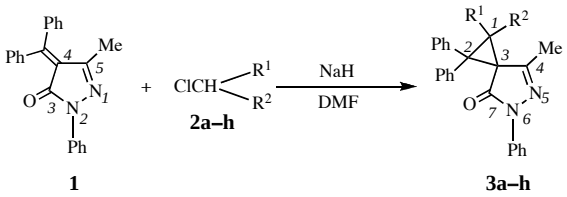


After some optimization, the best result was obtained when **1a** was treated with **2a** in *N,N*-dimethylformamide in the presence of sodium hydride, and the expected spiro compound **3a** was isolated in 63% yield (Table 1). Although we tested the reactions under a variety of other conditions such as a potassium *tert*-butoxide/*N,N*-dimethylformamide and sodium hydride/tetrahydrofuran system, those attempts were not successful. It makes us believe that the conjugate addition reaction of carbanions and spiro-cyclization of the intermediate Michael adduct can only be promoted by using sodium hydride/*N,N*-dimethylformamide. The ir spectrum of **3a** displays two carbonyl bands at 1751 and 1711 cm^{-1}. The ^1H nmr spectrum of **3a** exhibits a three-proton singlet at δ 3.85 attributable to the methyl protons of a methoxy group. The ^{13}C nmr spectrum of **3a** shows a signal at δ 52.6 due to the methyl carbon of a methoxy group, three signals at δ 42.4, 46.5 and 56.7 due to the spiro-cyclopropane carbons, and two signals at δ 167.3 and 168.3 due to the two carbonyl carbons. Elemental analysis and spectral data of **3a** are consistent with the proposed structure (see experimental section).

Based on these results, we carried out the reactions of **1** with **2b–h** by use of a sodium hydride/*N,N*-dimethylformamide system. Indeed, when a mixture of **1** with **2b–h** in the presence of sodium hydride in *N,N*-dimethylformamide was stirred at 0–5 °C for 2 hours or at room temperature for 6 hours, the expected spiro compounds **3b–h** were obtained in moderate to good yields. The results are listed in Table 1. In the case of the preparation of **3g,h**, the reaction was carried out at room temperature because the conversion was not completed at the lower reaction temperature (entries **7** and **8**). By comparison of nmr, mass spectra and elemental analyses of **3b–h** it seems that the structural assignments given to these compounds are correct.

Table 1

Synthesis of Spiro Compounds **3a–h** by the Reaction of **1** with **2a–h**



Entry	Reagent	R^1	R^2	Product	Yield (%)
1	**2a**	H	CO_2Me	**3a**	63 [a]
2	**2b**	H	CO_2Et	**3b**	60 [a]
3	**2c**	H	CO_2Pr^i	**3c**	65 [a]
4	**2d**	H	CO_2Bu^t	**3d**	81 [a]
5	**2e**	H	CN	**3e**	33 [a]
6	**2f**	H	$CONEt_2$	**3f**	59 [a]
7	**2g**	Me	CO_2Me	**3g**	57 [b]
8	**2h**	Me	CN	**3h**	88 [b]

[a] 0-5 °C, 2 hours. [b] r.t., 6 hours.

Table 2

In Vitro Antifungal Activity of Compounds **3a–h** Against *C. albicans* and *S. cerevisiae*

Compound	MIC (μg/mL)	
	C. albicans [a]	*S. cerevisiae* [b]
3a	25 [c]	50 [d]
3b	25 [c]	50 [d]
3c	25 [c]	50 [d]
3d	25 [c]	50 [d]
3e	25 [c]	50 [d]
3f	25 [c]	50 [d]
3g	25 [c]	50 [d]
3h	25 [c]	50 [d]
Miconazole	2 [e]	0.5 [f]
Itraconazole	2 [e]	4 [g]
DMSO	>12.5%	>6.25%
EtOH	>12.5%	>6.25%

[a] RPMI1640 medium, 37 °C. [b] YM medium, 25 °C. [c] containing 0.2% DMSO. [d] containing 0.39% DMSO. [e] containing 0.015% DMSO. [f] containing 0.04% DMSO. [g] containing 0.03% DMSO.

Eight of the newly synthesized spiro-cyclopropane-pyrazoles **3a–h** were tested for their *in vitro* antifungal activity against *Candida albicans* and *Saccharomyces cerevisiae*. *In vitro* susceptibility tests were performed to evaluate MICs and minimal fungicidal concentrations (MFCs) using the method described in the guidelines of NCCLS M27-A2 [41]. Miconazole and Itraconazole were

used as standard drugs for comparison of the antifungal activity. The results obtained are summarized in Table 2. All spiro compounds **3a–h** were active against *Candida* with MIC ≥ 25 μg/mL and *Saccharomyces* with MIC ≥ 50 μg/mL. It is worth noting that none of the test compounds **3a–h** showed superior activity to the standard drugs Miconazole and Itraconazole. Preliminary bioassay results indicated that all synthesized compounds **3a–h** display moderate or week antifungal activity against *Candida* and *Saccharomyces*.

In conclusion, we have developed a convenient straightforward method for the construction of spiro[cyclopropane-1,4'-pyrazol-3-one] derivatives **3a–h** by the reaction of 2,4-dihydro-5-methyl-2-phenyl-4-(diphenylmethylene)-3*H*-pyrazol-3-one with secondary and tertiary carbanions derived from a methylene and methine group bearing both a leaving group and electron-withdrawing group in the presence of sodium hydride. This methodology offers significant advantages with regard to the supply of spirocyclopropanepyrazoles, which may exhibit biological activities such as antifungal and antimicrobial activities. In this present work, we showed that spiro compounds **3a–h** have antifungal activity *in vitro*. Our results suggest that **3a–h** would play a role *in vivo*. Additional studies are needed to elucidate the exact mechanisms for the spiro compounds-mediated pathogenesis of several diseases. Functionalized pyrazoles are important building blocks in organic synthesis and for the preparation of biologically active compounds with interest in medicinal chemistry.

EXPERIMENTAL

All melting points are uncorrected. The ir spectra were recorded on a JASCO FT/IR-230 spectrometer. The ^{1}H and ^{13}C nmr spectra were recorded on a JEOL JNM-A500 spectrometer at 500 and 125 MHz, respectively. The ^{1}H and ^{13}C chemical shifts (δ) are reported in parts per million (ppm) relative to tetramethylsilane as internal standard. The positive FAB mass spectra were obtained on a JEOL JMS-700T spectrometer. The elemental analyses were performed on a YANACO MT-6 CHN analyzer.

General Procedure for the Preparation of Spiro Compounds 3a–h from 1 and 2a–h. To an ice-cooled and stirred solution of **1** [39,40] (1.69 g, 5 mmoles) and **2a** (2.17 g, 20 mmoles), **2b** (2.45 g, 20 mmoles), **2c** (2.73 g, 20 mmoles), **2d** (3.01 g, 20 mmoles), **2e** (1.52 g, 20 mmoles), **2f** (2.99 g, 20 mmoles), **2g** (2.45 g, 20 mmoles) or **2h** (1.79 g, 20 mmoles) in *N*,*N*-dimethylformamide (20 mL) was added 60% sodium hydride (0.60 g, 15 mmoles). After the mixture was stirred at 0-5 °C for 2 hours (in the case of the preparation of **3a–f**) or room temperature for 6 hours (in the case of the preparation of **3g,h**), cold water was added to the reaction mixture. The resulting mixture was extracted with chloroform (60 mL). The extract was dried over anhydrous sodium sulfate and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel with chloroform as the eluent to afford **3a–h**.

Methyl 5,6-diaza-4-methyl-7-oxo-2,2,6-triphenylspiro[2.4]-hept-4-ene-1-carboxylate (3a). This compound was obtained as colorless prisms (1.29 g, 63%), mp 174–176 °C (acetone-petroleum ether); ir (potassium bromide): ν 1751, 1711 cm^{-1} (C=O); ^{1}H nmr (deuteriochloroform): δ 1.83 (s, 3H, 4-Me), 3.63 (s, 1H, 1-H), 3.85 (s, 3H, CO_2*Me*), 7.12–7.30 (m, 7H, Ph-H), 7.34–7.38 (m, 6H, Ph-H), 7.89–7.91 ppm (m, 2H, Ph-H); ^{13}C nmr (deuteriochloroform): δ 18.8 (4-Me), 42.4 (C-1), 46.5 (C-3), 52.6 (CO_2*Me*), 56.7 (C-2), 118.6, 124.9, 127.7, 128.1, 128.2, 128.7, 128.8, 129.3, 136.6, 138.4, 140.1 (Ph-C), 156.5 (C-4), 167.3, 168.3 ppm (C=O); ms: m/z 411 [M+H]$^+$. *Anal.* Calcd. for $C_{26}H_{22}N_2O_3$: C, 76.08; H, 5.40; N, 6.82. Found: C, 76.10; H, 5.40; N, 6.78.

Ethyl 5,6-diaza-4-methyl-7-oxo-2,2,6-triphenylspiro[2.4]-hept-4-ene-1-carboxylate (3b). This compound was obtained as colorless prisms (1.27 g, 60%), mp 143–145 °C (acetone-petroleum ether); ir (potassium bromide): ν 1753, 1711 cm^{-1} (C=O); ^{1}H nmr (deuteriochloroform): δ 1.37 (t, J = 7.0 Hz, 3H, $CO_2CH_2CH_3$), 1.83 (s, 3H, 4-Me), 3.62 (s, 1H, 1-H), 4.30 (q, J = 7.0 Hz, 2H, $CO_2CH_2CH_3$), 7.14–7.30 (m, 7H, Ph-H), 7.34–7.40 (m, 6H, Ph-H), 7.89–7.91 ppm (m, 2H, Ph-H); ^{13}C nmr (deuteriochloroform): δ 14.2 ($CO_2CH_2CH_3$), 18.9 (4-Me), 42.7 (C-1), 46.5 (C-3), 55.7 (C-2), 61.8 ($CO_2CH_2CH_3$), 118.6, 124.8, 127.6, 128.1, 128.3, 128.7, 128.8, 129.4, 136.7, 138.4, 140.2 (Ph-C), 156.6 (C-4), 166.8, 168.4 ppm (C=O); ms: m/z 425 [M+H]$^+$. *Anal.* Calcd. for $C_{27}H_{24}N_2O_3$: C, 76.39; H, 5.70; N, 6.60. Found: C, 76.40; H, 5.81; N, 6.51.

Isopropyl 5,6-diaza-4-methyl-7-oxo-2,2,6-triphenylspiro-[2.4]hept-4-ene-1-carboxylate (3c). This compound was obtained as colorless prisms (1.43 g, 65%), mp 136–138 °C (acetone-petroleum ether); ir (potassium bromide): ν 1751, 1712 cm^{-1} (C=O); ^{1}H nmr (deuteriochloroform): δ 1.31 [d, J = 6.1 Hz, 3H, $CO_2CH(CH_3)_2$], 1.41 [d, J = 6.1 Hz, 3H, $CO_2CH(CH_3)_2$], 1.84 (s, 3H, 4-Me), 3.60 (s, 1H, 1-H), 5.14 [sep, J = 6.1 Hz, 1H, $CO_2CH(CH_3)_2$], 7.14–7.29 (m, 7H, Ph-H), 7.33–7.41 (m, 6H, Ph-H), 7.89–7.91 ppm (m, 2H, Ph-H); ^{13}C nmr (deuteriochloroform): δ 19.0 (4-Me), 21.8 [$CO_2CH(CH_3)_2$], 43.1 (C-1), 46.5 (C-3), 55.7 (C-2), 69.8 [$CO_2CH(CH_3)_2$], 118.6, 124.8, 127.6, 128.1, 128.2, 128.6, 128.8, 129.5, 136.7, 138.4, 140.2 (Ph-C), 156.6 (C-4), 166.3, 168.5 ppm (C=O); ms: m/z 439 [M+H]$^+$. *Anal.* Calcd. for $C_{28}H_{26}N_2O_3$: C, 76.69; H, 5.98; N, 6.39. Found: C, 76.70; H, 6.05; N, 6.38.

***tert*-Butyl 5,6-diaza-4-methyl-7-oxo-2,2,6-triphenylspiro-[2.4]hept-4-ene-1-carboxylate (3d).** This compound was obtained as colorless needles (1.84 g, 81%), mp 170–172 °C (acetone-petroleum ether); ir (potassium bromide): ν 1750, 1712 cm^{-1} (C=O); ^{1}H nmr (deuteriochloroform): δ 1.56 [s, 9H, $CO_2C(CH_3)_3$], 1.83 (s, 3H, 4-Me), 3.56 (s, 1H, 1-H), 7.13–7.38 (m, 7H, Ph-H), 7.33–7.38 (m, 4H, Ph-H), 7.43–7.45 (m, 2H, Ph-H), 7.89–7.91 ppm (m, 2H, Ph-H); ^{13}C nmr (deuterio-chloroform): δ 19.0 (4-Me), 28.1 [$CO_2C(CH_3)_3$], 44.1 (C-1), 46.5 (C-3), 55.7 (C-2), 82.9 [$CO_2C(CH_3)_3$], 118.6, 124.8, 127.6, 128.1, 128.3, 128.5, 128.6, 128.8, 129.6, 136.9, 138.5, 140.5 (Ph-C), 156.8 (C-4), 165.7, 168.7 ppm (C=O); ms: m/z 453 [M+H]$^+$. *Anal.* Calcd. for $C_{29}H_{28}N_2O_3$: C, 76.97; H, 6.24; N, 6.19. Found: C, 77.07; H, 6.37; N, 6.14.

5,6-Diaza-4-methyl-7-oxo-2,2,6-triphenylspiro[2.4]hept-4-ene-1-carbonitrile (3e). This compound was obtained as colorless needles (0.63 g, 33%), mp 174–176 °C (acetone-petroleum ether); ir (potassium bromide): ν 2246 (C≡N), 1714 cm^{-1} (C=O); ^{1}H nmr (deuteriochloroform): δ 1.78 (s, 3H, 4-Me), 3.35 (s, 1H, 1-H), 7.17–7.40 (m, 11H, Ph-H), 7.53–7.55 (m, 2H,

Ph-H), 7.86–7.88 ppm (m, 2H, Ph-H); ^{13}C nmr (deuteriochloroform): δ 16.9 (4-Me), 24.2 (C-1), 45.3 (C-3), 53.9 (C-2), 115.1 (C≡N), 118.6, 125.3, 128.1, 128.3, 128.9, 129.1, 129.4, 135.5, 137.4, 138.1 (Ph-C), 154.8 (C-4), 166.8 ppm (C=O); ms: m/z 378 $[M+H]^+$. *Anal.* Calcd. for $C_{25}H_{19}N_3O$: C, 79.55; H, 5.07; N, 11.13. Found: C, 79.78; H, 5.21; N, 11.10.

5,6-Diaza-*N*,*N*-diethyl-4-methyl-7-oxo-2,2,6-triphenylspiro[2.4]hept-4-ene-1-carboxamide (3f). This compound was obtained as colorless needles (1.33 g, 59%), mp 134–136 °C (acetone-petroleum ether); ir (potassium bromide): ν 1703, 1656 cm^{-1} (C=O); ^{1}H nmr (deuteriochloroform): δ 1.17 [t, J = 7.0 Hz, 3H, $N(CH_2CH_3)_2$], 1.24 [t, J = 7.0 Hz, 3H, $N(CH_2CH_3)_2$], 1.78 (s, 3H, 4-Me), 3.39–3.47 and 3.57–3.63 [m, 4H, $N(CH_2CH_3)_2$], 3.57 (s, 1H, 1-H), 7.14–7.36 (m, 9H, Ph-H), 7.37–7.39 (m, 2H, Ph-H), 7.44–7.46 (m, 2H, Ph-H), 7.91–7.94 ppm (m, 2H, Ph-H); ^{13}C nmr (deuteriochloroform): δ 12.8 and 14.1 (2xNCH_2CH_3), 18.3 (4-Me), 40.4 and 42.4 (2xNCH_2CH_3), 42.3 (C-1), 47.1 (C-3), 56.7 (C-2), 118.6, 124.8, 127.4, 127.7, 128.0, 128.4, 128.6, 128.8, 130.3, 136.5, 138.5, 140.9 (Ph-C), 157.5 (C-4), 164.6, 169.0 ppm (C=O); ms: m/z 452 $[M+H]^+$. *Anal.* Calcd. for $C_{29}H_{29}N_3O_2$: C, 77.14; H, 6.47; N, 9.31. Found: C, 77.17; H, 6.53; N, 9.24.

Methyl 5,6-diaza-1,4-dimethyl-7-oxo-2,2,6-triphenylspiro-[2.4]hept-4-ene-1-carboxylate (3g). This compound was obtained as pale orange prisms (1.21 g, 57%), mp 166–168 °C (acetone-petroleum ether); ir (potassium bromide): ν 1737, 1710 cm^{-1} (C=O); ^{1}H nmr (deuteriochloroform): δ 1.45 (s, 3H, 4-Me), 1.86 (s, 3H, 1-Me), 3.75 (s, 3H, CO_2Me), 7.13–7.27 (m, 10H, Ph-H), 7.38–7.56 (m, 3H, Ph-H), 7.99–8.02 ppm (m, 2H, Ph-H); ^{13}C nmr (deuteriochloroform): δ 16.8 (1-Me), 18.2 (4-Me), 46.3 (C-3), 48.0 (C-1), 52.4 (CO_2Me), 57.6 (C-2), 118.8, 124.8, 127.1, 127.5, 128.3, 128.4, 128.8, 129.3, 129.9, 137.1, 138.6, 139.1 (Ph-C), 156.6 (C-4), 167.9, 169.8 ppm (C=O); ms: m/z 425 $[M+H]^+$. *Anal.* Calcd. for $C_{27}H_{24}N_2O_3$: C, 76.39; H, 5.70; N, 6.60. Found: C, 76.42; H, 5.74; N, 6.60.

5,6-Diaza-1,4-dimethyl-7-oxo-2,2,6-triphenylspiro[2.4]-hept-4-ene-1-carbonitrile (3h). This compound was obtained as colorless needles (1.72 g, 88%), mp 196–198 °C dec. (chloroform-petroleum ether); ir (potassium bromide): ν 2238 (C≡N), 1708 cm^{-1} (C=O); ^{1}H nmr (deuteriochloroform): δ 1.77 (s, 3H, 4-Me), 1.96 (s, 3H, 1-Me), 7.15–7.29 (m, 8H, Ph-H), 7.30–7.39 (m, 2H, Ph-H), 7.40–7.50 (m, 3H, Ph-H), 7.94–7.97 ppm (m, 2H, Ph-H); ^{13}C nmr (deuteriochloroform): δ 15.5 (1-Me), 17.7 (4-Me), 31.3 (C-1), 46.1 (C-3), 56.2 (C-2), 118.9 (Ph-C), 119.0 (C≡N), 125.3, 127.9, 128.5, 128.7, 128.9, 129.1, 129.2, 134.7, 138.0, 138.2 (Ph-C), 155.3 (C-4), 166.2 ppm (C=O); ms: m/z 392 $[M+H]^+$. *Anal.* Calcd. for $C_{26}H_{21}N_3O$: C, 79.77; H, 5.41; N, 10.73. Found: C, 79.77; H, 5.58; N, 10.66.

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