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Synthesis of novel spiro-[3*H*-indole-3,3′-[1,2,4]triazolidine]-2-ones via azomethine imines

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Abstract—Novel spiroindoles **5** are prepared easily via a one-pot, 1,3-dipolar cycloaddition reaction of azomethine imines with isatin imines under thermal conditions.

Systematic investigation of spiroindoles is of great interest due to the fact that if the indole ring is joined to the other heterocyclic systems through a spiro carbon atom at C-3, the resulting compounds show an increased spectrum of biological activities.[1,2] Also, varied pharmacological properties are associated with 1,2,4-triazolidines.[3–5] Thus it is expected that production of a 1,2,4-triazolidine moiety at C-3 of the 2-indolinone system would enhance the biological activity significantly.

In continuation of our previous work on the synthesis of spiroindoles,[6] we report the facile synthesis of novel spiroindoles with the new skeleton **5** in fairly good yields under microwave irradiation and classical heating method.

Azomethine imines are important intermediates as 1,3-dipoles in cycloaddition reactions.[7] Spiro [3*H*-indole-3,3′-[1,2,4]triazolidine]-2-ones **5** were obtained by reaction of the corresponding imines of isatin **1**[8] with azomethine imine **4**, generated[9] in situ from 1-methyl-2-phenylacetyl hydrazine **2**[10] with paraformaldehyde **3**. By using microwave irradiation, the reaction time was reduced greatly from 9–14 hours to 6–8 min and the yield of the reaction was enhanced by 10–20% compared to the conventional heating method (Scheme 1).

The structures of compounds **5a–g** were assigned on the basis of their elemental analyses, ^{1}H NMR, ^{13}C NMR and mass spectral data, as well as the IR spectra,[11] which displayed $\nu_{C=O}$ of the oxindole at 1715–1745 cm^{-1}, $\nu_{C=O}$ of the acetyl at 1645–1670 cm^{-1} and ν_{N-H} at 3150–3250 cm^{-1}.

The assignment of the structure **5** to the product and exclusion of structure **5′** was supported by the ^{1}H and ^{13}C NMR spectra. The ^{1}H NMR spectra of **5a–g** at 25°C in acetone-d_6 showed resonances corresponding to the methylene of the triazolidine ring as an AB quartet at δ 4.7–5.1 ppm, the benzylic methylene as an AB quartet at δ 3.6–4 ppm, the methyl as two singlets at δ 2.6–2.75 ppm and the NH as a singlet at δ 8.6–8.7 ppm. The ^{13}C NMR spectra of **5a–g** at 25°C in acetone-d_6 showed resonances corresponding to the carbonyl signals at δ 169–175 ppm, the methylene of the triazolidine at δ 77–78 ppm, the benzylic methylene at δ 42–43 ppm, the methyl as two signals at δ 37–38 ppm and a signal at δ 96–97 ppm attributable to the spiro carbon atom. All of the mentioned chemical shifts are in complete agreement with the proposed structure **5**.

Due to inversion of the nitrogen atom, the methyl group attached to it in the ^{1}H NMR spectra of compounds **5a–g** at 25°C in DMSO-d_6 showed two singlets ($\Delta\nu = 18$ Hz) in an approximate ratio of 1:1. Raising the temperature causes rapid positional exchange, until at 85°C, the two signals coalesced. According to the Eyring equation, the free enthalpy of activation ($\Delta G^{\ddagger}$) at the coalescence temperature is equal to 18.45 kcal mol^{-1}. Similarly, in the ^{13}C NMR spectra the two signals of the methyl group ($\Delta\nu = 123$ Hz) coalesced at 105°C. The corresponding $\Delta G^{\ddagger}$ at the coalescence temperature is equal to 18.08 kcal mol^{-1}, which is in good agreement with the proton data.[12]

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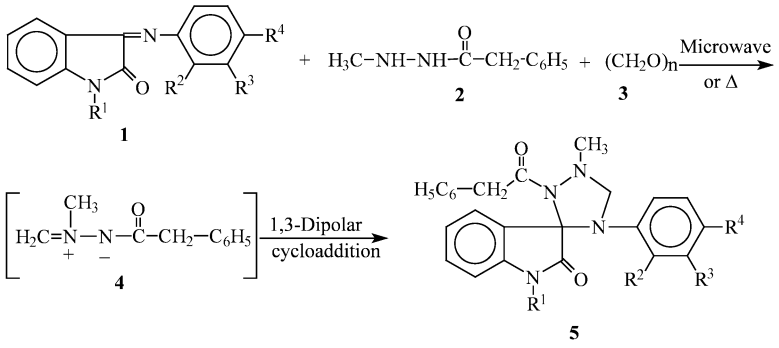
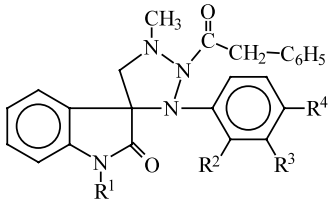


5	R^1	R^2	R^3	R^4	Yield / %	
					Thermal	Microwave
a	H	H	H	H	69	84
b	H	H	H	Br	74	89
c	H	H	H	OCH_3	68	82
d	H	H	CH_3	CH_3	66	80
e	H	OCH_3	H	OCH_3	61	78
f	H	H	NO_2	H	58	74
g	CH_3	H	H	H	71	87

Scheme 1. Reaction of isatin imines with azomethine imines.



The compounds **5a**–**g** were prepared via the following procedures:

A. Thermal: A mixture of isatin imine (5 mmol), 1-methyl-2-phenylacetylhydrazine (5 mmol) and paraformaldehyde (7 mmol) was refluxed in toluene (50 ml) in the presence of molecular sieves (type 4 Å, 1/16 inch beads) for 9–14 h. After completion of the reaction (monitored by TLC), the solvent was removed under reduced pressure and the crude product was purified by column chromatography (silica gel, pet. ether/ethyl acetate, 1:1.5).

B. Microwave: A mixture of isatin imine (5 mmol), 1-methyl-2-phenylacetylhydrazine (5 mmol) and paraformaldehyde (12 mmol) in *N*,*N*-dimethylacetamide (DMAC) (1 ml) was placed in an Erlenmeyer flask covered with a watch glass and irradiated in a microwave oven at 400 W in the presence of molecular sieves for 6–8 min. After completion of the reaction (monitored by TLC), ethanol (10 ml) and ice water (5 ml) were added to the reaction mixture and kept at room temperature. The crude product was purified by column chromatography (silica gel, pet. ether/ethyl acetate, 1:1.5).

References

1. Joshi, K. C.; Jain, R.; Chand, P. *Heterocycles* **1985**, *23*, 957–996.
2. Mogilaiah, K.; Babu Rao, R. *Indian J. Chem.* **1998**, *37B*, 894–898.
3. Maclauchlin, C.; Hall, I. H.; Izydore, R. A. *Arch. Pharm.* **1999**, *332*, 225–232.
4. Hall, I. H.; Wong, O. T.; Simlot, R.; Miller, M. C.; Izydore, R. A. *Anticancer Res.* **1992**, *12*, 1355–1361.
5. Shamsuzzaman, A. S.; Kishwar, S.; Mukhtar, A. K. *Indian J. Chem.* **1997**, *36B*, 617–619.
6. (a) Azizian, J.; Morady, A. V.; Jadidi, K.; Mehrdad, M.; Sarrafi, Y. *Synth. Commun.* **2000**, *30*, 537–542; (b) Azizian, J.; Soozangarzadeh, S.; Jadidi, K. *Synth. Commun.* **2001**, *31*, 99–103; (c) Azizian, J.; Asadi, A.; Jadidi, K. *Synth. Commun.* **2001**, *31*, 1–7; (d) Azizian, J.; Jadidi, K.; Mehrdad, M.; Sarrafi, Y. *Synth. Commun.* **2000**, *30*, 2309–2315; (e) Azizian, J.; Sarrafi, Y.; Mehrdad, M.; Jadidi, K. *Indian J. Chem.* **2000**, *39B*, 304–307.
7. Stanovnik, B.; Jelen, B.; Turk, C.; Zlicar, M.; Svete, J. *J. Heterocycl. Chem.* **1998**, *35*, 1187–1204.
8. Rajopadhye, M.; Popp, F. D. *J. Heterocycl. Chem.* **1985**, *22*, 93–96.
9. Oppolzer, W. *Tetrahedron Lett.* **1970**, *11*, 2199–2204.
10. Theuer, W. J.; Moore, J. A. *J. Org. Chem.* **1964**, *29*, 3734–3735.
11. **5b**: Yellow crystals, Yield 89% (thermal 74%), mp 194°C; ν_{max} (cm^{-1}) 3200 (N–H), 1725, 1667 (C=O); δ_H (300 MHz, acetone-d_6) 6.7–7.8 (13H, m, Ar), 8.7 (1H, s, NH), 4.8–5.1 (2H, AB q, $J=14.5$ Hz, NCH_2N), 3.6–3.9 (2H, AB q, $J=15$ Hz, $COCH_2$), 2.65, 2.71 (both 3H, s, CH_3); δ_C (300 MHz, acetone-d_6) 111.81–146.23 (aromatic carbons), 96.88 (spiro carbon), 170.03 (C=O), 174.91 (C=O), 77.70

(NCH_2N), 42.26 (CO-$^{13}CH_2$), 37.08, 37.48 (CH_3); MS (m/z, %) 477 (M^+, 7), 462 (M^+–CH_3, 61), 176 (M^+–$C_{14}H_9BrN_2O$, 83) (Found: C, 60.2; H, 4.5; N,11.6, $C_{24}H_{21}BrN_4O_2$ requires C, 60.38; H, 4.43; N, 11.74%). **5c**: Yellow crystals, Yield 82% (thermal 68%), mp 191°C; ν_{max} (cm^{-1}) 3245 (N–H), 1731, 1668 (C=O); δ_H (300 MHz, acetone-d_6) 6.8–7.7 (13H, m, Ar), 8.7 (1H, s, NH), 4.8–5.1 (2H, AB q, $J=15$ Hz, NCH_2N), 3.7–4.0 (2H, AB q, $J=15$ Hz, $COCH_2$), 3.7 (3H, s, OCH_3), 2.67, 2.73 (both 3H, s, CH_3); δ_C (300 MHz, acetone-d_6) 111.49–147.33 (aromatic carbons), 96.24 (spiro carbon), 169.91 (C=O), 173.78 (C=O), 78.02 (NCH_2N), 42.94 (CO-$^{13}CH_2$), 55.90 (OCH_3), 37.12, 37.53 (CH_3); MS (m/z, %) 428 (M^+, 9), 413 (M^+–CH_3, 53), 176 (M^+–$C_{15}H_{12}N_2O_2$, 91) (Found: C, 70.1; H, 5.8; N, 13.1, $C_{25}H_{24}N_4O_3$ requires C, 70.08; H, 5.65; N, 13.08%). **5d**: Yellow crystals, Yield 80% (thermal 66%), mp 178°C; ν_{max} (cm^{-1}) 3251 (N–H), 1715, 1655 (C=O); δ_H (300 MHz, acetone-d_6) 6.7–7.6 (12H, m, Ar), 8.6 (1H, s, NH), 4.7–5.0 (2H, AB q, $J=14.5$ Hz, NCH_2N), 3.6–3.9 (2H, AB q, $J=15$ Hz, $COCH_2$), 2.28 (3H, s, CH_3), 2.33 (3H, s, CH_3), 2.64, 2.70 (both 3H, s, NCH_3); δ_C (300 MHz, acetone-d_6) 111.87–147.49 (aromatic carbons), 96.41 (spiro carbon), 170.11 (C=O), 175.09 (C=O), 77.82 (NCH_2N), 42.76 (CO-$^{13}CH_2$), 20.03 (CH_3), 20.48 (CH_3), 37.46, 37.86 (NCH_3); MS (m/z, %) 426 (M^+,12), 411 (M^+–CH_3, 36), 176 (M^+–$C_{16}H_{14}N_2O$, 84) (Found: C, 73.4; H, 6.2; N, 13.0, $C_{26}H_{26}N_4O_2$ requires C, 73.22; H, 6.14; N, 13.14%). **5e**: Yellow crystals, Yield 78% (thermal 61%), mp 169°C; ν_{max} (cm^{-1}) 3250 (N–H), 1733, 1660 (C=O); δ_H (300 MHz, acetone-d_6) 6.7–7.7 (12H, m, Ar), 8.7 (1H, s, NH), 4.8–5.1 (2H, AB q, $J=15$ Hz, NCH_2N), 3.7–4.0 (2H, AB q, $J=14.5$ Hz, $COCH_2$), 3.65 (3H, s, OCH_3), 3.70 (3H, s, OCH_3), 2.66, 2.73 (both 3H, s, CH_3); δ_C (300 MHz, acetone-d_6) 111.08–147.69 (aromatic carbons), 97.04 (spiro carbon), 170.09 (C=O), 174.87 (C=O), 77.90 (NCH_2N), 42.22 (CO-$^{13}CH_2$), 55.31 (OCH_3), 55.70 (OCH_3), 37.21, 37.62 (CH_3); MS (m/z, %) 458 (M^+, 7), 443 (M^+–CH_3, 47), 176 (M^+–$C_{16}H_{14}N_2O_3$, 81) (Found: C, 68.0; H, 5.7; N, 12.3, $C_{26}H_{26}N_4O_4$ requires C, 68.11; H, 5.72; N, 12.22%). **5f**: Yellow crystals, Yield 74% (thermal 58%), mp 206°C; ν_{max} (cm^{-1}) 3180 (N–H), 1741, 1655 (C=O); δ_H (300 MHz, acetone-d_6) 6.6–7.8 (13H, m, Ar), 8.7 (1H, s, NH), 4.7–5.0 (2H, AB q, $J=14.5$ Hz, NCH_2N), 3.7–4.0 (2H, AB q, $J=15$ Hz, $COCH_2$), 2.69, 2.75 (both 3H, s, CH_3); δ_C (300 MHz, acetone-d_6) 111.46–148.69 (aromatic carbons), 96.48 (spiro carbon), 169.36 (C=O), 173.82 (C=O), 77.18 (NCH_2N), 43.09 (CO-$^{13}CH_2$), 37.13, 37.55 (CH_3); MS (m/z, %) 443 (M^+, 5), 428 (M^+–CH_3, 66), 176 (M^+–$C_{14}H_9N_3O_3$, 79) (Found: C, 65.1; H, 4.8; N, 15.6, $C_{24}H_{21}N_5O_4$ requires C, 65.00; H, 4.77; N, 15.79%). **5g**: Yellow crystals, Yield 87% (thermal 71%), mp 197°C; ν_{max} (cm^{-1}) 1726, 1645 (C=O); δ_H (300 MHz, acetone-d_6) 6.7–7.5 (14H, m, Ar), 4.7–5.0 (2H, AB q, $J=15$ Hz, NCH_2N), 3.6–3.9 (2H, AB q, $J=14.5$ Hz, $COCH_2$), 3.0 (3H, s, $CONCH_3$), 2.61, 2.67 (both 3H, s, NCH_3); δ_C (300 MHz, acetone-d_6) 111.27–150.06 (aromatic carbons), 96.14 (spiro carbon), 170.56 (C=O), 174.10 (C=O), 77.29 (NCH_2N), 42.38 (CO-$^{13}CH_2$), 26.53 (CON-$^{13}CH_3$), 37.47, 37.87 (NCH_3); MS (m/z, %) 412 (M^+, 10), 397 (M^+–CH_3, 58), 176 (M^+–$C_{15}H_{12}N_2O$, 87) (Found: C, 72.7; H, 5.9; N, 13.7, $C_{25}H_{24}N_4O_2$ requires C, 72.80; H, 5.86; N, 13.58%).

12. **5a**: Yellow crystals, Yield 84% (thermal 69%), mp 187°C; ν_{max} (cm^{-1}) 3150 (N–H), 1745, 1665 (C=O); δ_H (300 MHz, acetone-d_6) 6.7–7.7 (14H, m, Ar), 8.6 (1H, s, NH), 4.7–5.0 (2H, AB q, $J=15$ Hz, NCH_2N), 3.6–3.9 (2H, AB q, $J=15$ Hz, $COCH_2$), 2.66, 2.72 (both 3H, s, CH_3); δ_C (300 MHz, acetone-d_6) 111.35–148.07 (aromatic carbons), 96.46 (spiro carbon), 169.12 (C=O), 174.42 (C=O), 77.36 (NCH_2N), 42.51 (CO-$^{13}CH_2$), 37.27, 37.68 (CH_3); MS (m/z, %) 398 (M^+, 11), 383 (M^+–CH_3, 46), 176 (M^+–$C_{14}H_{10}N_2O$, 89) (found: C, 72.2; H, 5.5; N, 14.1, $C_{24}H_{22}N_4O_2$ requires C, 72.34; H, 5.56; N, 14.06%). ^1H NMR spectra in DMSO-d_6 at 25°C revealed the methyl group as two singlets at δ 2.66 and 2.72, that coalesced to a singlet at δ 2.69 at about 85°C. ^{13}C NMR spectra in DMSO-d_6 at 25°C revealed the methyl group as two signals at δ 37.27 and 37.68, that coalesced to a singlet at δ 37.48 at about 105°C.