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A greener approach for the synthesis of 1-*N*-methyl-(spiro[2.3′]oxindolespiro[3.2″]/spiro[2.3′]indan-1,3-dionespiro[2.2″])cyclopentanone-4-aryl pyrrolidines

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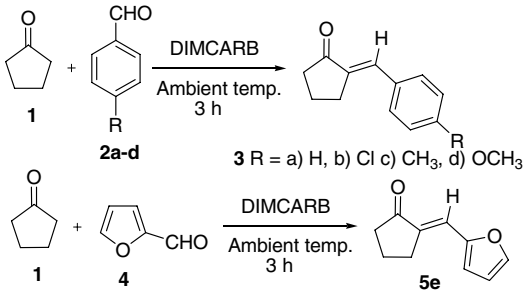
Abstract—*N*,*N*-Dimethylammonium *N*′,*N*′-dimethyl carbamate (DIMCARB), a reusable reaction medium, has been used in the synthesis of a number of monoarylidene cyclopentanones. These compounds are used as dipolarophiles in the 1,3-dipolar cycloaddition reaction of an azomethine ylide, generated in situ by the decarboxylation method for the synthesis of spiropyrrolidines by the application of microwave methodology.

Minimising the number of steps, simplicity, reduced wastage, energy usage, safety and whether the chemistry is environmentally acceptable[1,2] are the keywords of sustainable technology. Reducing the use of organic solvents can minimise the generation of waste which is one of the principles of green chemistry.[3] Alternative media to organic solvents include ionic liquids and supercritical CO_2, water (including at high temperature, under microwave irradiation[4]), polyethylene and polypropylene glycol. The use of microwave heating for chemical processes is also important. The main advantages of solvent-free reactions include the formation of high purity compounds, fast kinetics, lower energy usage, simplicity, low equipment cost, possible sequential reaction and a highly eco-friendly processing route. *N*,*N*-Dimethyl ammonium-*N*′,*N*′-dimethyl carbamate (DIMCARB) is a reusable reaction medium which can also act as the catalyst[5] in the Michael reaction of enolisable ketones. This solvent has been used in the synthesis of monoarylidene cyclopentanones which can serve as dipolarophiles in the 1,3-dipolar cycloaddition reaction with azomethine ylides generated in situ by decarboxylation.[6] The coupling of microwave irradiation with the use of mineral supports under solvent-free condition provides clean chemical processes.[7] In this paper, we highlight the application of microwave methodology in the synthesis of spiropyrrolidines.[8–10] Many spiro compounds are naturally occurring substances characterised by highly pronounced biological properties.[11,12] The enhancements in the rate of reaction and in yields are striking. The monoarylidene cyclopentanones were reported to possess the *E*-configuration on the basis of proton NMR analysis.[13,14]

Using DIMCARB, monoarylidene cyclopentanones were formed when a 1:1 ratio of aldehyde and ketone was used and the yields were moderate to excellent (Scheme 1). In other media (except water) these reactions frequently produce bis arylidene cyclopentanones.[15] The conventional method was able to provide reduced yields even after a longer reaction time (Table 1).



Scheme 1.

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Table 1. Percentage yields of **3a–d** and **5e** under two different conditions after 3 h

Entry	Product	DIMCARB method	Conventional method
1	**3a**	85	25
2	**3b**	91	20
3	**3c**	80	15
4	**3d**	78	15
5	**5e**	74	10

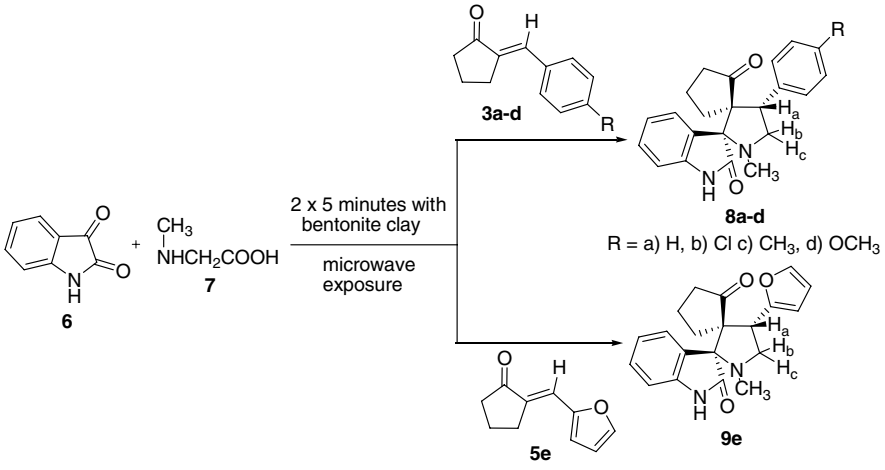
Table 2. Percentage yields of **8a–d** and **9e** under different conditions after 10 min

Entry	Product	Microwave exposure	Conventional refluxing
1	**8a**	90	40
2	**8b**	92	45
3	**8c**	80	42
4	**8d**	85	45
5	**9e**	50	20

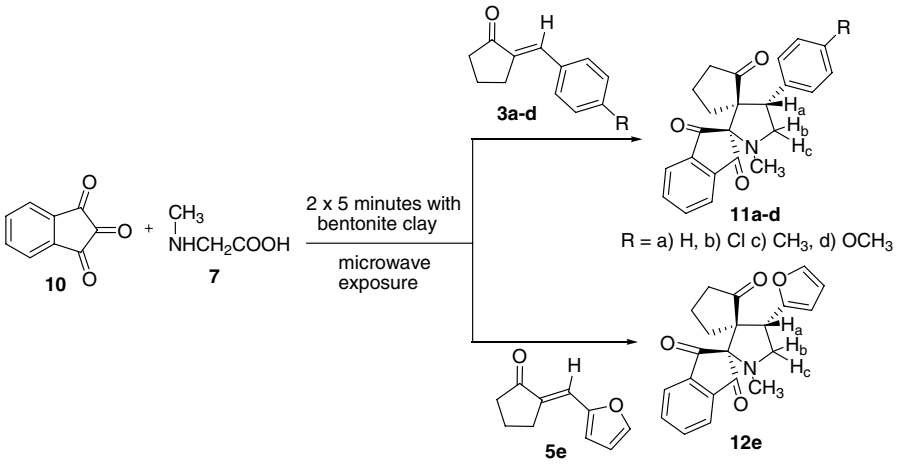
Using our method,[16] we have carried out a range of dipolar cycloaddition reactions in solvent-free conditions via combination of supported reagents and microwave irradiation in a domestic microwave oven.[17] 2-Arylidene-1-cyclopentanones **3a–d** and **5e** readily underwent 1,3-dipolar cycloaddition reactions with the non-stabilised ylide generated in situ by the decarboxylative condensation of isatin **6** and sarcosine **7** to afford dispiropyrrolidinyl oxindole derivatives **8a–d** and **9e** in a highly regioselective manner (Scheme 2). The reactions were carried out in a microwave oven for a period of 10 min under neat conditions. The results were compared with those obtained from the conventional method of refluxing with aqueous methanol (Table 2).

The dispiroheterocyclic ring structures of products **8a–d** and **9e** were confirmed by IR, ^{1}H, ^{13}C NMR and mass spectral studies. The IR spectrum of **8d** revealed the presence of a carbonyl stretching vibration band at 1750 cm^{-1}, showing an increase of 42 cm^{-1} from the normal value of 1708 cm^{-1} for 2-arylidene-1-cyclopentanones indicating the loss of conjugation. A peak at 1712 cm^{-1} corresponding to the carbonyl group of the oxindole and a peak at 3348 cm^{-1} which corresponds to the –NH group of the oxindole ring were also observed. The ^{1}H NMR, spectrum of **8d** revealed one sharp singlet at δ 2.16 due to the *N*-methyl protons. The benzylic proton H_a exhibited a doublet of doublets at δ 4.11 ($J = 9.8$, 8.5 Hz). H_c of the *N*-CH_2 proton appeared as a doublet of doublets at δ 3.51 ($J = 12.6$, 8.5 Hz). A doublet of doublets was also observed at δ 3.88 ($J = 12.6$, 8.0 Hz) for the H_b proton. The aromatic protons appeared as a multiplet in the region δ 6.84–7.43 and there was a broad singlet at δ 8.51 for the NH proton of the oxindole. The regiochemistry of the product **8d** was confirmed by its ^{1}H NMR spectrum. If the other isomer had been formed one would expect a singlet instead of doublet of doublets for the benzylic proton. The regiochemistry of the product **8d** was also confirmed by its ^{13}C NMR spectrum. The off resonance decoupled ^{13}C NMR spectrum of **8d** exhibited signals at δ 65.78 ppm due to the spiro carbon C3 of the pyrrolidine ring and at δ 76.59 ppm due to the C2 spiro carbon of the pyrrolidine ring. The resonances at δ 178.26 ppm and 214.08 ppm were due to the oxindole carbonyl and keto carbonyl carbons, respectively. Signals at δ 37.64 ppm due to *N*-CH_3 and at δ 55.18 ppm due to *N*-CH_2 carbons were also observed. The mass spectrum of **8d** showed a molecular ion peak at *m*/*z* 375 (M^+), which further confirmed the formation of the cycloadduct[18] by the single crystal X-ray structural analysis.[19] Similar results were recorded for the other such derivatives.

With a view to explore the potential of the cycloaddition reaction of azomethine ylides for the synthesis of novel dispiro heterocycles, we extended the same protocol using the triketone, ninhydrin **10**, with sarcosine **7** and 2-arylidene-1-cyclopentanones (Scheme 3). **11a–d** and **12e** were characterised by IR, mass, ^{1}H NMR and ^{13}C NMR. The mass spectrum of **11a** demonstrated a molecular ion peak at *m*/*z* 359. The IR spectrum of **11a** displayed the absorptions at 1738 cm^{-1} for indan-1,3-dione and at 1747 cm^{-1} for the cyclopentanone carbonyls. The ^{1}H NMR showed the following characteristic peaks. A sharp singlet was noticed at δ



Scheme 2.



Scheme 3.

Table 3. Percentage yields of **11a–d** and **12e** under different conditions after 10 min

Entry	Product	Microwave exposure	Conventional refluxing
1	**11a**	90	20
2	**11b**	70	13
3	**11c**	50	10
4	**11d**	40	10
5	**12e**	40	8

2.33 which was indicating the presence of N-CH_3 protons. The H_c proton resonated as a doublet of doublets at δ 2.49 with $J = 7.8$, 6.8 Hz. A doublet of doublets at δ 2.71 ($J = 7.8$, 10.6 Hz) was for the H_b proton. The H_a proton exhibited a doublet of doublets at δ 3.47 ($J = 6.8$, 10.6 Hz) and the aromatic protons were found to resonate at δ 7.03–7.90 as a multiplet. The off resonance decoupled ^{13}C NMR spectrum added a conclusive support. The cyclopentanone ring carbonyl carbon was found to resonate at δ 204.78 ppm and indan-1,3-dione ring carbonyl carbon appeared at δ 200.8 ppm. There were 11 aromatic ring carbon signals. The spiro carbon (C2) of pyrrolidine ring was observed at δ 76.71 ppm. A signal at 64.51 ppm indicated the presence of C3 spiro carbon of pyrrolidine ring system. The N-CH_2 carbon showed a signal at δ 52.29 ppm and N-CH_3 carbon exhibited a signal at δ 35.85 ppm.[20] Comparable results were found for other derivatives (Table 3).

Thus a green synthesis for dispiropyrrolidines was achieved. The present synthetic protocol for the synthesis of spiropyrrolidines is advantageous over the previous method: (i) the reaction could be performed with environmentally benign catalysts; (ii) provides good yields of products and (iii) the reaction occurs more rapidly. The high regioselectivity might be of potential interest in the construction of various alkaloids.

Acknowledgements

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17. An unaltered domestic Kenstar microwave oven operating at 230 V and 50 Hz with a consumption of 800 W and microwave frequency of 2.4 GHz was used for the irradiation in this work.

General procedure for the synthesis of **3a–d** *and* **3e** *by DIMCARB method*. To a stirred mixture of aldehyde (9.4 mmol) and DIMCARB (10 mL) kept at 50 °C, cyclopentanone was added. After completion of the reaction, DIMCARB was recovered by distillation at 60 °C under high vacuum and the residue was acidified with 0.5 M H_2SO_4 and extracted with ethyl acetate. The solvent was removed in vacuum and the product was purified through column chromatography using petroleum ether ethyl acetate mixture (9:1).

General procedure for the solvent-free microwave promoted cycloaddition reactions of the azomethine ylide generated from isatin **6**, *sarcosine* **7** *with 2-arylidene-1-cyclopentanones* **3a–d** *and* **5e**. A mixture of isatin **6** (1 mmol), sarcosine **7** (1 mmol), 2-monoarylidene cyclopentanones **3a–d**, **5e** (1 mmol) and 1 g of Bentonite clay was thoroughly mixed in a boiling tube which was loosely closed and immersed in a silica gel bath in a beaker and irradiated in microwave oven for about 10 min at the maximum microwave power level (600 W) for two 5 min durations with intermittent cooling. The temperature during irradiation rose to a maximum of about 158 °C as determined by measuring the maximum temperature of the silica gel bath immediately after irradiation was over by gently stirring the silica gel with the thermometer. After the completion, the reaction mixture was cooled and added to water (5 mL) and extracted with diethyl ether (5 mL). After filtering, the etheral layer was washed with water and dried with anhydrous sodium sulfate. The solvent was then removed under vacuum. The crude product was chromatographed on silica gel using hexane–ethyl acetate (5:1) as eluant to give **8a–d** and **9e**.

18. *1-N-Methyl-spiro[2.3′]oxindolespiro[3.2″]cyclopentanone 4-(4-methoxyphenyl) pyrrolidine* **8d**. 0.19 g, 85%, pale yellow coloured solid, mp: 200 °C; IR (KBr): 1712, 1750, 3348 cm^{-1}, ^1H NMR: δ 1.14–2.05 (m, 6H), 2.16 (s, 3H), 3.51 (dd, $J = 12.6$, 8.5 Hz, $1H_c$), 3.85 (s, 3H), 3.88 (dd, $J = 12.6$, 9.8 Hz, $1H_b$), 4.11 (dd, $J = 9.8$, 8.5 Hz, $1H_a$), 6.84–7.43 (m, 8H, ArH), 8.51 (br s, 1H); ^{13}C NMR: 18.55, 32.85, 34.84, 37.64, 55.18, 60.02, 65.78, 76.59, 109.57, 113.63, 123.12, 126.30, 127.10, 129.48, 131.26, 131.34, 141.67, 158.44, 178.26, 214.08; MS *m*/*z*: 376 (M^+); Anal. Calcd for $C_{23}H_{24}N_2O_3$: C, 76.67; H, 6.67; N, 7.78. Found: C, 76.49; H, 6.59; N, 7.67.

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20. *1-N-Methyl-spiro[2.2′]indan-1,3-dionespiro[3.2″] cyclopentanone-4-phenyl pyrrolidine* **11a**: 0.20 g, 90%, pale yellow powder, mp: 220 °C; IR (KBr): 1738, 1747 cm^{-1}, ^1H NMR: δ 1.93–2.40 (m, 6H), 2.33 (s, 3H), 2.49 (dd, $J = 7.8$, 6.8 Hz, $1H_c$), 2.71 (dd, $J = 10.6$, 7.8 Hz, $1H_b$), 3.47 (dd, $J = 10.6$, 6.8 Hz, $1H_a$), 7.03–7.90 (m, 9H, ArH); ^{13}C NMR: 26.24, 30.26, 34.79, 35.85, 52.29, 64.51, 76.71, 122.75, 128.70, 128.72, 129.72, 130.67, 134.38, 134.50, 135.04, 135.48, 136.74, 141.07, 141.90, 200.87, 204.78; MS *m*/*z*: 359 (M^+); Anal. Calcd for $C_{23}H_{21}NO_3$: C, 76.88; H, 5.85; N, 3.90. Found: C, 76.99; H, 5.98; N, 4.05.