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Solvent-free microwave-assisted conversion of Baylis–Hillman adducts of ninhydrin into functionalized spiropyrrolidines/pyrrolizidines through 1,3-dipolar cycloaddition

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Abstract—Microwave-assisted synthesis of spiropyrrolidines/pyrrolizidines has been accomplished using the alkene unit of Baylis–Hillman adducts of ninhydrin with sarcosine/proline and various activated ketones through 1,3-dipolar cycloaddition.

1. Introduction

Microwave irradiation is a powerful technique which is being increasingly used to accelerate thermal organic reactions. Further, a solvent-free approach involving microwave (MW) exposure of neat reactants catalyzed by mineral supports, such as alumina, silica gel, clay or doped surfaces, is applicable to a wide range of organic reactions such as modern drug discovery processes,[1] and is proving quite successful in the formation of carbon–heteroatom and carbon–carbon bonds.[2]

As part of our efforts to synthesize novel spiropyrrolidines and pyrrolizidines,[3] we aimed to explore the olefin segment of the Baylis–Hillman adduct of ninhydrin in a 1,3-dipolar cycloaddition reaction. The results obtained are presented in this Letter.

2. Results and discussion

Methyl 2-(2,3-dihydro-2-hydroxy-1,3-dioxo-1*H*-inden-2-yl) acrylate, which was synthesized by the Baylis–Hillman reaction of ninhydrin and methyl acrylate in the presence of 0.1 equiv of DABCO as catalyst,[4] was utilized as a dipolarophile for the first time.

The azomethine ylides generated from various mono-, di- and tri-ketones, were reacted with the olefin segment of Baylis–Hillman adducts of ninhydrin under three different sets of conditions to afford a series of novel spiro adducts, **8**–**11** and **12**–**15**.

The reaction of **1** was carried out with the azomethine ylide generated in situ by the decarboxylative condensation of isatin **4** and sarcosine **2** in methanol at room temperature. The reaction afforded the novel spiro adduct **8** in a 51% yield with a high regioselectivity (Scheme 1).

The structure of **8** was determined by spectroscopic analysis. The ^{1}H NMR spectrum of **8** showed two doublets at δ 2.74 ($J = 10.8$ Hz) and 2.82 ($J = 10.8$ Hz) for the CH_2 protons of the pyrrolidine ring system. The NCH_2 protons of the pyrrolidine ring appeared as two doublets at δ 2.94 ($J = 12.4$ Hz) and 2.98 ($J = 12.4$ Hz). If the other regioisomer **8a** had been formed, multiplets for each of the CH_2 protons of the pyrrolidine ring system would have been observed. The ^{13}C NMR spectrum of **8** showed a signal at δ 66.3 for the spiro carbon, signals at δ 198.3 and 199.5 for the carbonyl carbons of the indane-1,3-dione unit and signals at δ 172.0 and δ 178.9 ppm for the ester and amide carbonyl carbons, respectively. Finally the structure of product **8** was confirmed by mass spectrometry, which showed a molecular ion at peak at m/z 420.21.

To improve the yield, we examined the reaction under three different sets of conditions. Thus, the reaction of **1**, and sarcosine with various activated ketones at 60 °C in methanol afforded spiro adducts **8**–**11** in 30–58% yields, but required longer reaction times.

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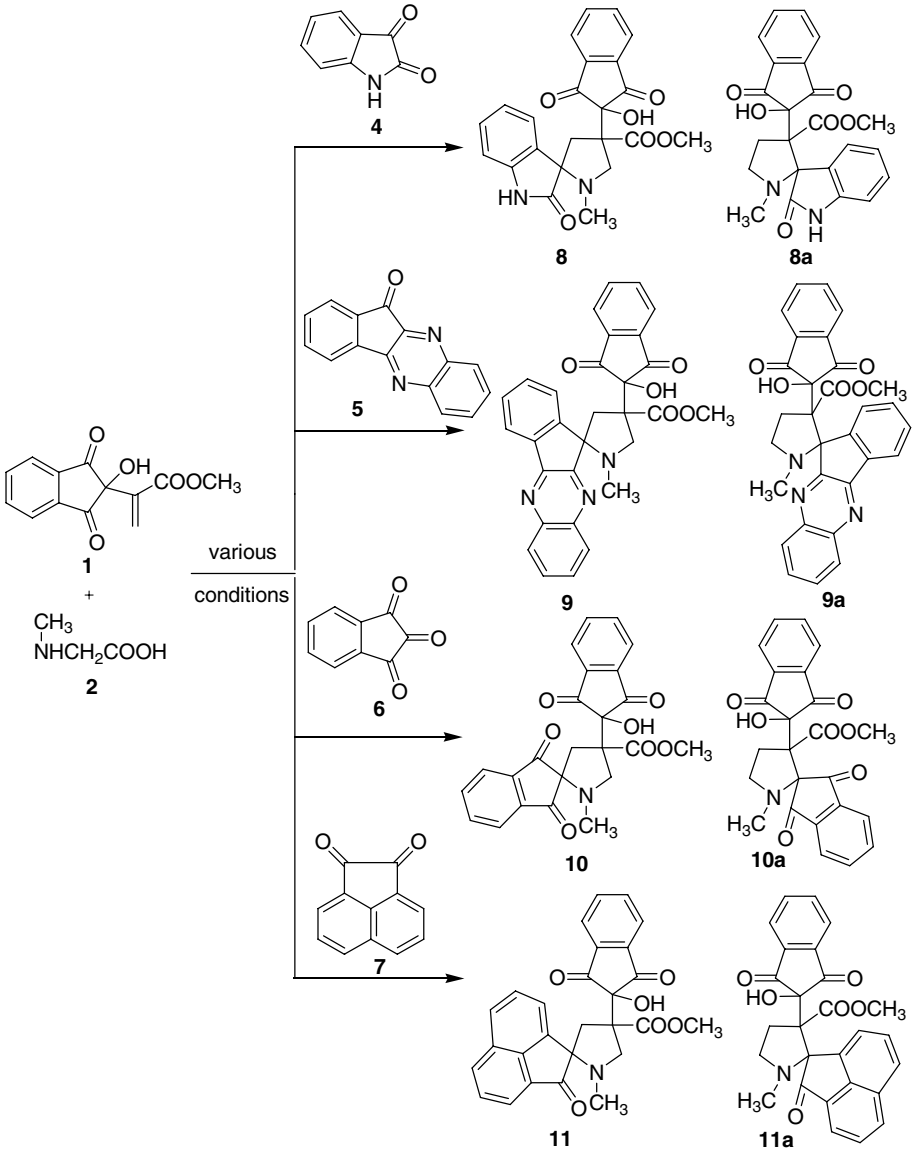


Scheme 1.

11*H*-Indeno[1,2-*b*]quinoxalin-11-one **5** also reacted under these conditions, but did not give satisfactory yields.

When the reaction was carried out under microwave irradiation in methanol, a slight improvement in yields was observed, but **5** again did not react satisfactorily.

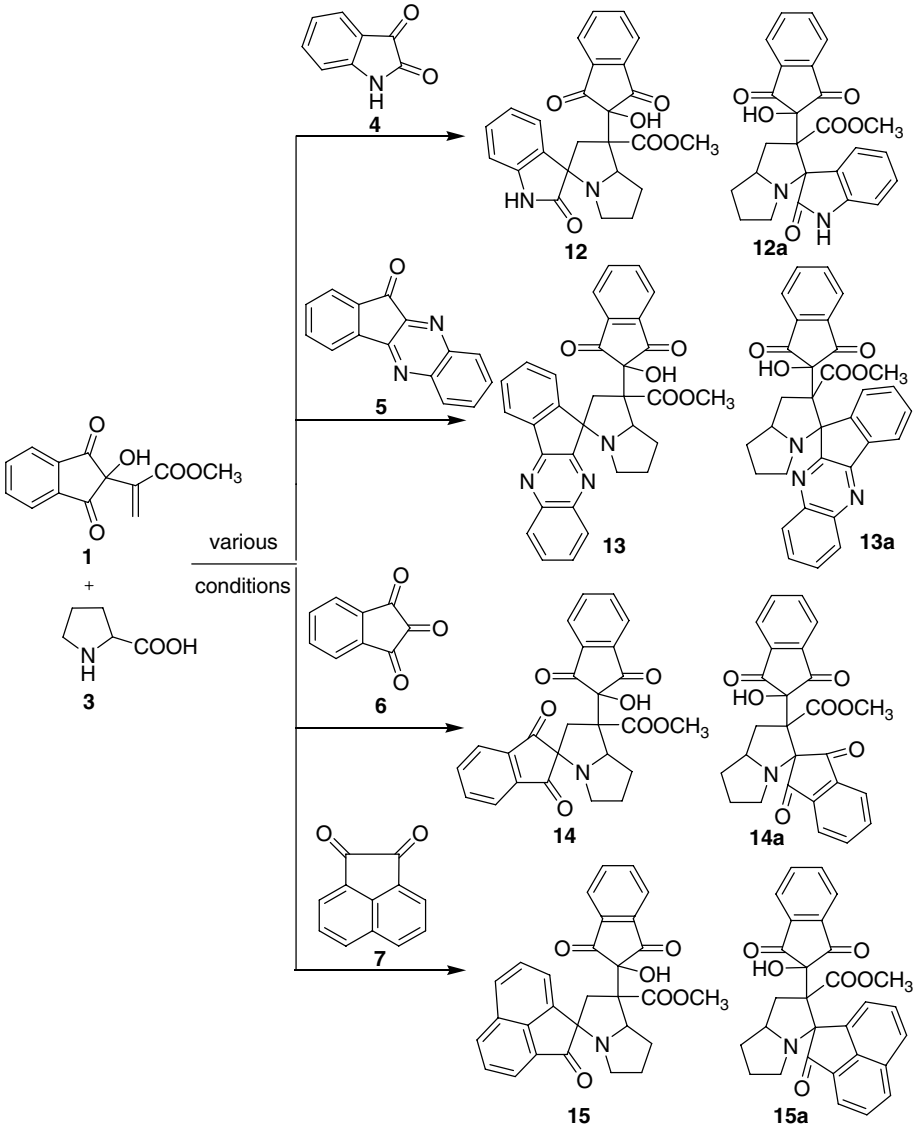
In the next series of experiments, we carried out the multicomponent reaction under solvent-free conditions, simply by gentle grinding of the three components with Montmorillonite K-10 clay, then microwave irradiation of the mixture. Under these conditions, cycloadducts were obtained in good yields with high regio- and stereoselectivity, and **5** also reacted to give the anticipated cycloadduct in a good yield (70%). We found that the yields of all products increased from modest to excellent (30–58% to 78–88%) in changing from Method A to Method C. The results are summarized in Table 1.

To enhance the scope of the above methodology, we reacted Baylis–Hillman adduct **1** with the azomethine ylide generated from activated ketones, **4**–**7** with the secondary amino acid, proline. The reaction yielded novel spiropyrrolizidine derivatives **12**–**15** via one-pot three-component reactions (Scheme 2). The ^{1}H NMR spectrum of **12** showed multiplets in the region δ 1.32–2.97 for the pyrrolizidine ring protons. The CH_2 protons of the pyrrolizidine ring appeared as two doublets at δ 3.35 ($J = 15.4$ Hz) and 3.57 ($J = 15.4$ Hz). The ring junction proton appeared as a triplet at δ 4.99 ($J = 6.8$ Hz). If the other regioisomer **12a** had been formed, multiplets for each of the CH_2 protons of the pyrrolizidine ring system would have been observed. The ^{13}C NMR spectrum of **12** showed a signal at δ 68.4 for the spiro carbon, signals at δ 199.4 and 198.4 for the carbonyl carbons of the indane-1,3-dione unit and signals at δ 173.9 and δ 182.9 ppm for the amide and ester carbonyl carbons, respectively. Finally, the structure of product **12** was confirmed by mass

Table 1. Cycloadditions of the Baylis–Hillman adduct of ninhydrin with sarcosine and various activated ketones under three different sets of conditions

Ketones	Product	Method A		Method B		Method C	
		Time (h)	Yield (%)	Time (min)	Yield (%)	Time (min)	Yield (%)
4	**8**	3.0	51	20	62	5	84
5	**9**	5.5	30	30	40	10	70
6	**10**	2.0	58	10	70	2	88
7	**11**	2.5	40	25	65	3	78

Method A: conventional methanol reflux.
Method B: methanol/MW.
Method C: K-10 Montmorillonite clay/MW.



Scheme 2.

spectrometry, which showed a molecular ion peak at *m*/*z* 446.15.

The stereochemistry of compound **14** was assigned by X-ray crystal structure analysis and is shown in Figure 1.[5]

As observed in the earlier cases, the yields of [3+2] cycloaddition reactions of **1**, **5** and proline were not satisfactory using Methods A and B. However, when the reaction was carried out under solvent-free conditions, by irradiating the reactants with microwaves (Kenstar, 600 W) in the presence of K-10 Montmorillonite clay,

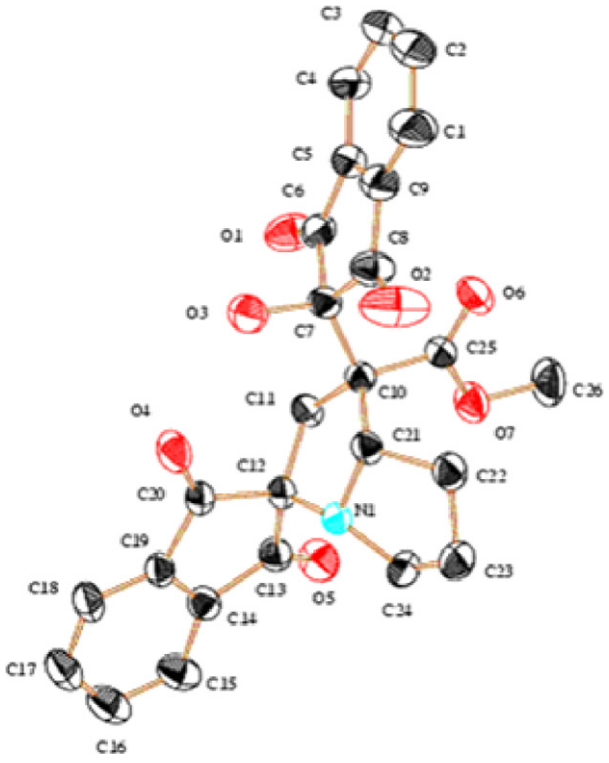


Figure 1. ORTEP diagram of **14**.

the products were obtained in excellent yields with high regioselectivity in a short time. Similarly, we found that the yields of all the products increased from 32–78% to 77–87% when we used Method C. The results are summarized in Table 2.

3. Conclusion

In conclusion, we have described a solvent-free microwave multicomponent reaction which provides an easy entry into a number of spiropyrrolidine/pyrrolizidine derivatives using the Baylis–Hillman adduct of ninhydrin as the dipolarophile.

4. Experimental

4.1. Representative procedure for the synthesis of spiro pyrrolidines/pyrolizidines

4.1.1. Method A. A solution of the Baylis–Hillman adduct of ninhydrin (1 mmol), sarcosine/proline (1 mmol) and mono/di/tri-ketones (1 mmol) in methanol was refluxed. Completion of the reaction was evidenced by TLC analysis. The solvent was removed in vacuum. The crude product was subjected to column chromatography on silica gel (100–200 mesh) using petroleum ether–ethyl acetate (7:3) as the eluent.

4.1.2. Method B. A solution of the Baylis–Hillman adduct of ninhydrin (1 mmol), sarcosine/proline (1 mmol) and mono/di/tri-ketones (1 mmol) in methanol was irradiated under microwave conditions (Kenstar, 600 W). After completion of the reaction, the solvent was evaporated and the crude product was subjected to column chromatography on silica gel (100–200 mesh) using petroleum ether–ethyl acetate (7:3) as the eluent.

4.1.3. Method C. A mixture of the Baylis–Hillman adduct of ninhydrin (1 mmol), sarcosine/proline (1 mmol) with various ketones (1 mmol) were ground with K-10 Montmorillonite clay using a pestle for ca. 5 min. The homogenized mixture was placed in a microwave oven (Kenstar, 600 W) and irradiated for 2 min. The contents were cooled to room temperature and dissolved in $CHCl_3$. The solid inorganic material was filtered off, the products extracted with $CHCl_3$, the solvent removed in vacuo and crystallized from methanol to give pure crystalline solids.

4.2. Representative spectral data of the products

4.2.1. Oxindole spiro-(2.2′)-4′-methoxycarbonyl-4′-(2-hydroxy-indane-1,3-dione)-1-*N*-methyl pyrrolidine 8. Yellow solid, mp: 168–170 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.07 (s, 3H, NCH_3), 2.74 (d, $J = 10.8$ Hz, 1H, CH_2), 2.82 (d, $J = 10.7$ Hz, 1H, CH_2), 2.94 (d, $J = 12.4$ Hz, 1H, NCH_2), 2.98 (d, $J = 12.4$ Hz, 1H, NCH_2), 3.27 (br s, 1H), 3.60 (s, 3H, COOCH_3), 6.43–7.52 (m, 8H), 8.01 (s, 1*H*, N*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ 36.6, 38.7, 50.8, 51.8, 66.3, 111.4, 121.0, 123.2, 125.2, 128.4, 128.7, 128.9, 130.5, 132.6, 139.4, 141.3, 141.5, 172.0, 178.9, 198.3, 199.5. MS (EI, 70 eV) *m*/*z*: 420.41 (M^+). Anal. Calcd for $C_{23}H_{20}N_2O_6$: C, 65.71; H, 4.91; N, 6.66. Found: C, 65.81; H, 4.79; N, 6.68.

4.2.2. Oxindole spiro-(2.2′)-4′-methoxycarbonyl-4′-(2-hydroxy-indane-1,3-dione)-1-pyrrolizidine 12. Yellow solid, mp: 176–178 °C ^{1}H NMR (400 MHz, $CDCl_3$): 1.32–2.97 (m, 6H), 3.47 (s, 3H, COOCH_3), 3.35 (d, $J = 15.4$ Hz, 1H, CH_2), 3.57 (d, $J = 15.4$ Hz, 1H, CH_2), 4.99 (t, $J = 6.8$ Hz, 1H, –C*H*–), 6.71 (br s, 1H, –O*H*), 6.90–8.06 (m, 8H), 8.15 (br s, 1H, N*H*), ^{13}C

Table 2. Cycloadditions of the Baylis–Hillman adduct of ninhydrin and proline with various activated ketones under three different sets of conditions

Ketones	Product	Method A		Method B		Method C	
		Time (h)	Yield (%)	Time (min)	Yield (%)	Time (min)	Yield (%)
4	**12**	2.0	56	15	66	5	87
5	**13**	3.5	32	40	55	10	77
6	**14**	1.0	60	10	78	2	92
7	**15**	1.5	43	20	71	3	83

Method A: conventional methanol reflux.
Method B: methanol/MW.
Method C: K-10 Montmorillonite clay/MW.

NMR (100 MHz, $CDCl_3$): 25.9, 27.2, 42.3, 45.4, 52.1, 60.7, 67.7, 68.4, 73.5, 110.5, 123.3, 123.7, 125.5, 128.9, 129.6, 135.2, 135.7, 140.6, 140.8, 141.8, 173.9, 182.9, 198.4, 199.4. MS (EI, 70 eV) *m*/*z*: 446.15. Anal. Calcd for $C_{25}H_{22}N_2O_6$: C, 67.26; H, 4.97; N, 6.27. Found: C, 67.40; H, 5.02; N, 6.36.

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