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Novel three-component tandem reactions of cyclic mono ketones, isatin and sarcosine: formation of dispiropyrrolidines

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Abstract—One-pot, three-component tandem reactions of cyclic mono ketones, isatin and sarcosine affording dispiropyrrolidines stereoselectively are reported for the first time.

Tandem reactions are of paramount importance in the context of green chemistry as they offer a convenient strategy for the rapid, elegant and convergent construction of complex organic molecules without isolating and purifying the intermediates resulting in substantial minimisation of waste, labour, time and cost.[1] 1,3-Dipolar cycloaddition of azomethine ylides is a versatile protocol for the construction of highly functionalised five-membered ring heterocycles.[2] Azomethine ylides, generated in situ from isatin and sarcosine, add to α,β-unsaturated carbonyl compounds to afford spiropyrrolidines.[3] Some spiropyrrolidines are potential antileukemic and anticonvulsant agents[4] and possess antiviral[5] and local anaesthetic[6] activities. They are found in a number of biologically active compounds.[7] Isatin and its derivatives have interesting biological activities and are widely used as precursors for many natural products.[8] Spiropyrrolidinyloxindoles are also found in a number of alkaloids of biological importance.[9]

Nair et al.[10] recently reported the formation of novel spiropyrrolidines by the reaction of dicarbonyl compounds with azomethine ylides formed in situ from isatin and sarcosine via decarboxylation. As a part of our continuing interest in the construction of novel heterocycles,[11] we have investigated the reaction of simple cyclic mono ketones with isatin and sarcosine, which quite unexpectedly, led to the formation of spiropyrrolidines, presumably via a tandem sequence of reactions, and these results are reported in this Letter. To the best of our knowledge, this is the first report on the reaction of mono ketones with isatin and sarcosine.

In the present investigation, the reaction of a cyclic mono ketone, isatin and sarcosine in a molar ratio of 1:1:2 in methanol at reflux for 6–7.5 h (Scheme 1)[12] furnished novel dispiropyrrolidines in moderate yields (42–57%) (Table 1). The expected reaction, the dipolar cycloaddition of the azomethine ylide to the C=O functionality of the mono ketone to form oxazolidine **5**, did not occur (Scheme 2).

The reaction is diastereoselective as ketones **3a**–**g**, **3i** and **3j**, isatin and sarcosine afforded only one diastereomer of dispiropyrrolidines **4a**–**g**, **4i** and **4j** exclusively in all the cases, except in the case of enantiomerically pure **3h**, wherein a 1:0.8 mixture of two inseparable diastereomeric dispiropyrrolidines **4h** was obtained. In order to optimise the reaction conditions, this reaction was investigated in different solvents (Table 2). The yield of dispiropyrrolidine **4f** was lower and a longer reaction time was required in *i*-propanol, *t*-butanol, acetonitrile and dimethylformamide compared to methanol or ethanol. This can be ascribed to the diminished stabilisation of the polar transition states and/or intermediates involved in this reaction in *i*-propanol, *t*-butanol, acetonitrile and dimethylformamide. The reaction when performed with two moles of isatin and sarcosine per one mole of ketone (1-methyl-4-piperidone, **3f**) afforded only a slightly enhanced 60% yield of **4f** relative to the reaction with ketone **3f**, isatin and sarcosine in a molar ratio of 1:1:2. When conducted with different amounts of

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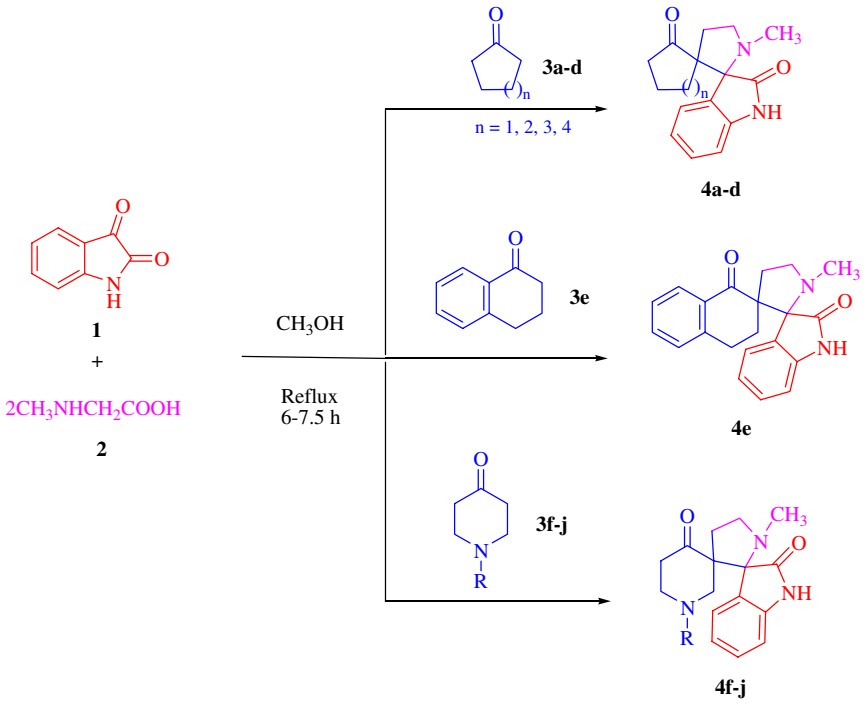
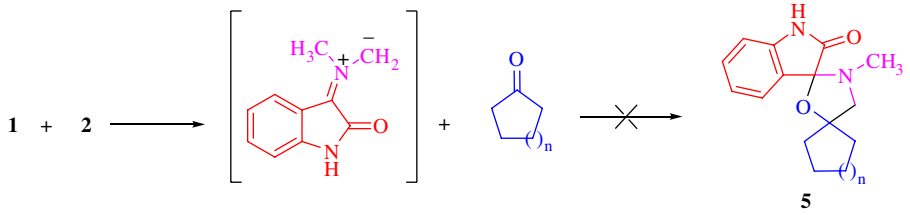


Scheme 1. Synthesis of dispiropyrrolidines.

Table 1. Synthesis of dispiropyrrolidines

Entry	Compound	*n*	R	Reaction time (h)	Yield (%)	Mp (°C)
1	**4a**	1	—	7.0	42	[a]
2	**4b**	2	—	6.0	45	124–125
3	**4c**	3	—	6.5	48	164–165
4	**4d**	4	—	6.0	46	175–176
5	**4e**	—	—	7.5	48	201–202
6	**4f**	—	CH_3	6.0	57	130–131
7	**4g**	—	CH_2Ph	6.5	48	133–134
8	**4h**	—	$CH_3(CH)Ph$	6.0	54	[b]
9	**4i**	—	$C(CH_3)_3$	7.0	44	117–118
10	**4j**	—	NO	10.0	42	176–177

[a] Viscous liquid.
[b] Viscous liquid comprising a mixture of diastereomers in 1:0.8 ratio.



Scheme 2.

sarcosine, namely, 0.5, 1, 1.5 and 2 mmol per 1 mmol of cyclic ketone **3f** and isatin the reaction afforded the dispiropyrrolidine **4f** in 18%, 42%, 56% and 57% yields, respectively, (Fig. 1) indicating that the optimum yield was obtained when the ratio of ketone, isatin and sarcosine was 1:1:1.5.

Structural elucidation of the dispiropyrrolidines was accomplished using 1D and 2D NMR spectroscopic data as described for **4f**.[13] The ^{1}H NMR spectrum of **4f** demonstrated a singlet at 2.07 ppm due to the N–CH_3 protons of the pyrrolidine ring, which showed a HMBC correlation with C-2 at 73.9 ppm and C-5 at 52.7 ppm (Fig. 2). From the C,H-COSY correlation, the multiplets at 3.03–3.11 and 3.22–3.30 ppm were assigned to the 5-CH_2 protons. The multiplets at 1.52–1.62 and 2.86–2.94 ppm were assigned to 4-CH_2 from their H,H-COSY correlation with 5-CH_2. A doublet of

Table 2. Influence of solvent on the yield of **4f**

Solvent	Time (h)	Yield of **4f** (%)
MeOH	6	57
EtOH	6	52
i-PrOH	10	47
t-BuOH	10	48
CH_3CN	13	43
DMF	10	40

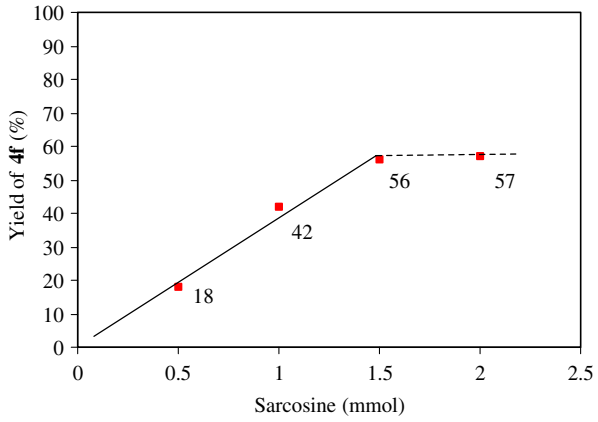


Figure 1. Effect of varying the amount of sarcosine (per 1 mmol of ketone and isatin) on the yield of **4f**.

doublets at 3.74 ($J = 12.0$, 2.6 Hz) and a doublet at 2.03 ($J = 12.0$ Hz) were assigned to 2″-H_{eq} and 2″-H_{ax}, respectively. The H,H-COSY correlation between 2″-H_{eq} and 6″-H_{eq} via a long range coupling was useful in assigning the multiplets at 2.13–2.17 and 2.65–2.70 ppm to 6″-H_{ax} and 6″-H_{eq}, respectively. The 5″-CH_2 protons appeared as multiplets at 1.52–1.62 and 1.97–2.02 ppm. The N–CH_3 protons of the piperidone ring and the NH proton of the oxindole ring occurred as singlets at 2.20 and 8.74 ppm, respectively, and the aromatic protons appeared as a multiplet at 6.85–7.24 ppm. The piperidone and the oxindole C=O group occured at 208.1 and 179.3 ppm, respectively. An X-ray crystallographic study of a single crystal of **4f** (Fig. 3)[14] confirmed the structure deduced from NMR spectroscopic studies. The structure of dispiropyrrodlidine **4d**

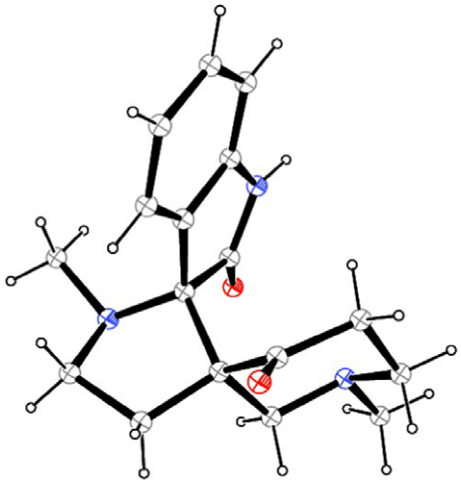


Figure 3. ORTEP diagram of **4f**.

was also determined by an X-ray crystallographic study (Fig. 4).[14]

Dispiropyrrolidines **4** are presumably formed by a multi-step tandem sequence of reactions (Scheme 3). The reaction of isatin and sarcosine is known to form azomethine ylide **11**.[3] Iminium carboxylic acid **5** presumably

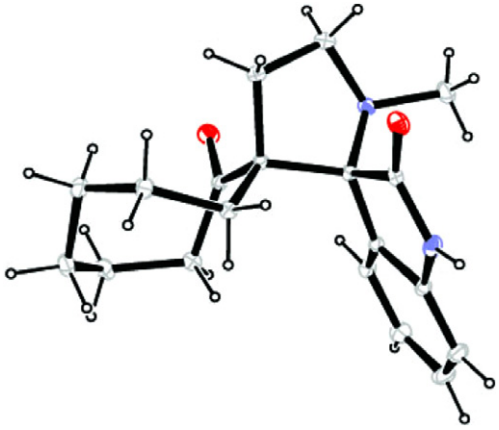


Figure 4. ORTEP diagram of **4d**.

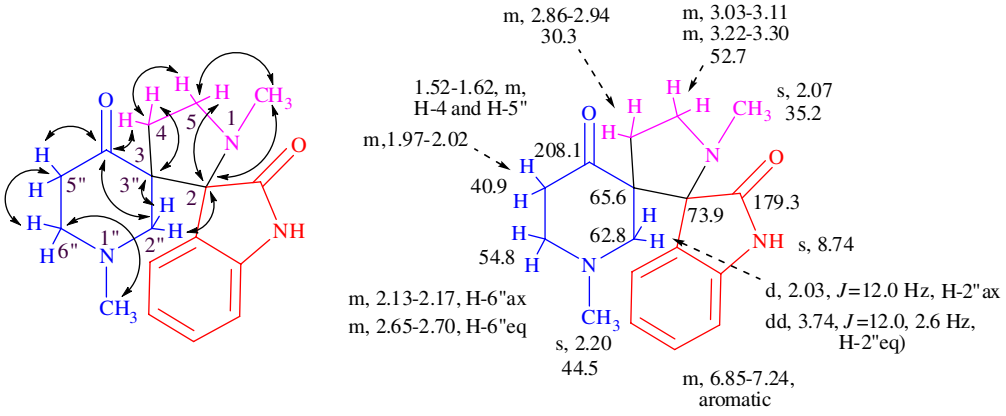
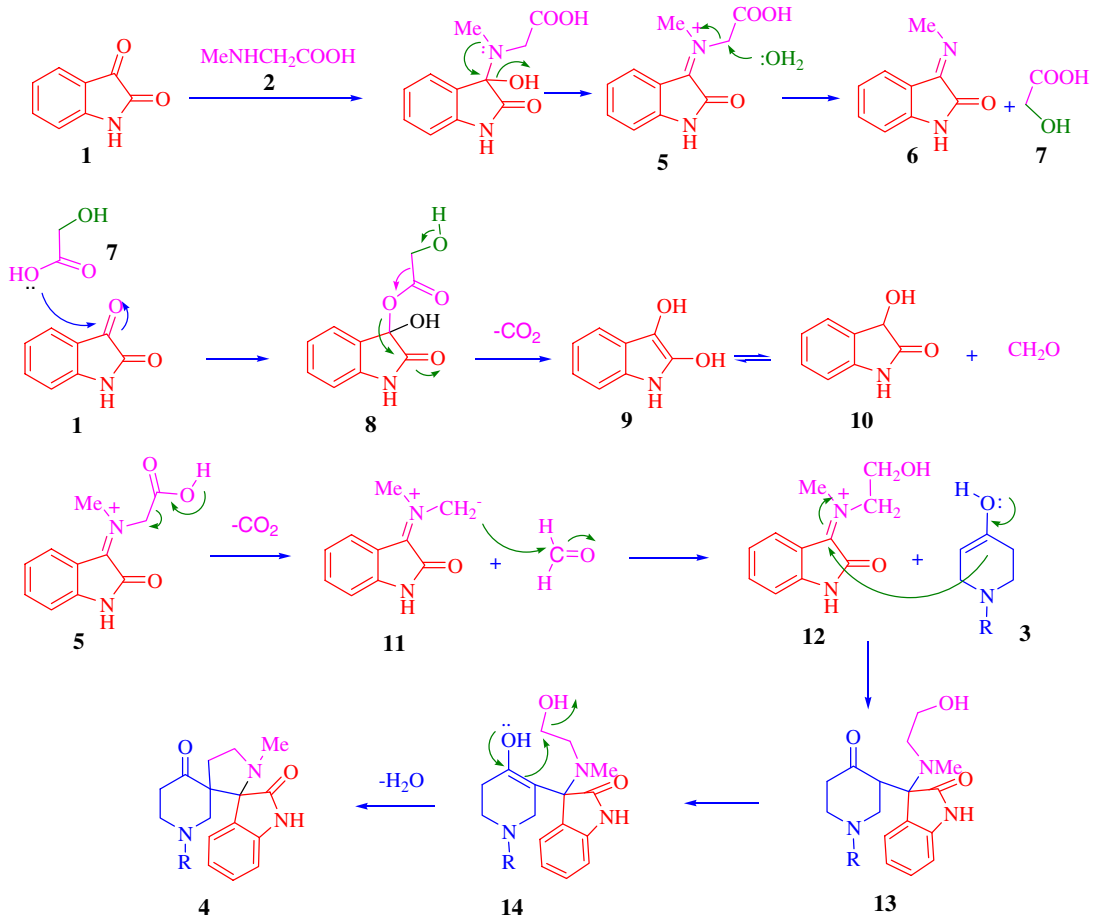


Figure 2. Selected HMBC correlations and ^1H and ^{13}C chemical shifts of **4f**.



Scheme 3. Proposed mechanism for the formation of dispiropyrrolidines.

undergoes two reactions: (i) decarboxylation to afford azomethine ylide **11** and (ii) nucleophilic substitution to afford glycolic acid **7**, which in turn, undergoes decarboxylation upon reaction with isatin presumably to afford formaldehyde. Presumably, **11** reacts with formaldehyde to afford iminium alcohol **12**, which reacts with the enol of ketone **3** to furnish **13**, which undergoes cyclisation to afford **4**. The mechanism in Scheme 3 suggests that the stoichiometry of the reaction should be 1:2:2 (ketone:isatin:sarcosine), which indicates that the yield of the reaction should not exceed 50% when the molar ratio of the reactants (ketone:isatin:sarcosine) is 1:1:2. The observed yield of 42–57% from the reaction of cyclic mono ketone, isatin and sarcosine in a molar ratio of 1:1:2 suggests that either isatin is regenerated from dihydroisatin **10** via air oxidation or the dispiropyrrolidine is also be formed by alternative pathways.

A facile one-pot tandem protocol leading to the synthesis of new dispiropyrrolidines has been described. This methodology is more advantageous than the hitherto known methods, which require two steps: (i) conversion of the cyclic mono ketones to α-methyleneketones and, (ii) the dipolar cycloaddition of the α-methyleneketones with azomethine ylides. The versatility and scope of this one-pot tandem methodology employing diverse cyclic and acyclic ketones is being explored currently in our laboratory.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.07.197.

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12. *Experimental procedure for the synthesis of* **4f**: A mixture of isatin (0.390 g, 2.7 mmol), sarcosine (0.472 g, 5.4 mmol) and 1-methyltetrahydro-4(1*H*)-pyridinone (0.3 g, 2.7 mmol) in methanol (20 mL) was refluxed on a water bath for 6 h. After completion of the reaction (TLC), the excess solvent was removed under vacuum and the residue was subjected to flash column chromatography using petroleum ether/ethyl acetate mixture (4:1 v/v) as eluent.
13. *1-Methylspiro[2.3′]oxindolespiro[3.3″]-1″-methyltetrahydro-4″(1H)-pyridinone pyrrolidine* **4f**: Colourless solid, Anal. Calcd for $C_{17}H_{21}N_3O_2$: C, 68.20; H, 7.07; N, 14.04. Found: C, 68.16; H, 7.10; N, 14.09. IR (KBr): 1704, 1737, 3207 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ_H 1.52–1.62 (m, 2H, H-4 and H-5″), 1.97–2.02 (m, 1H, H-5″), 2.03 (d, 1H, $J = 12.0$ Hz, H-2″$_{ax}$), 2.07 (s, 3H, 1-N–CH_3), 2.13–2.17 (m, 1H, H-6″$_{ax}$), 2.20 (s, 3H, 1″-N–CH_3), 2.65–2.70 (m, 1H, H-6″$_{eq}$), 2.86–2.94 (m, 1H, H-4), 3.03–3.11 (m, 1H, H-5), 3.22–3.30 (m, 1H, H-5), 3.74 (dd, 1H, 12.0, 2.6 Hz, H-2″$_{eq}$), 6.85–7.24 (m, 4H, aromatic), 8.74 (s, 1H, NH). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 30.3, 35.2, 40.9, 44.5, 52.7, 54.8, 62.8, 65.6, 73.9, 109.8, 121.8, 126.8, 127.0, 128.9, 141.5, 179.3, 208.1.
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