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RESEARCH ARTICLE

Selective Synthesis of Trispiropyrrolidine /Thiapyrrolizidines Using Green Deep Eutectic Solvent

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Abstract: A facile synthesis of trispiropyrrolidine/thiapyrrolizidine derivatives have been carried out by 1,3-dipolar cycloaddition reaction of azomethine ylides with a dipolarophile 8,10-bis[(*E*)arylidene]-3,3-dimethyl-1,5-dioxa-spiro[5.5]undecan-9-one using deep eutectic solvent

Keywords: 1,3-Dipolar cycloaddition, Spiro[5.5]undecanone, Azomethine ylide, Pyrrolidine, Thiapyrrolizidines, Deep eutectic solvents.

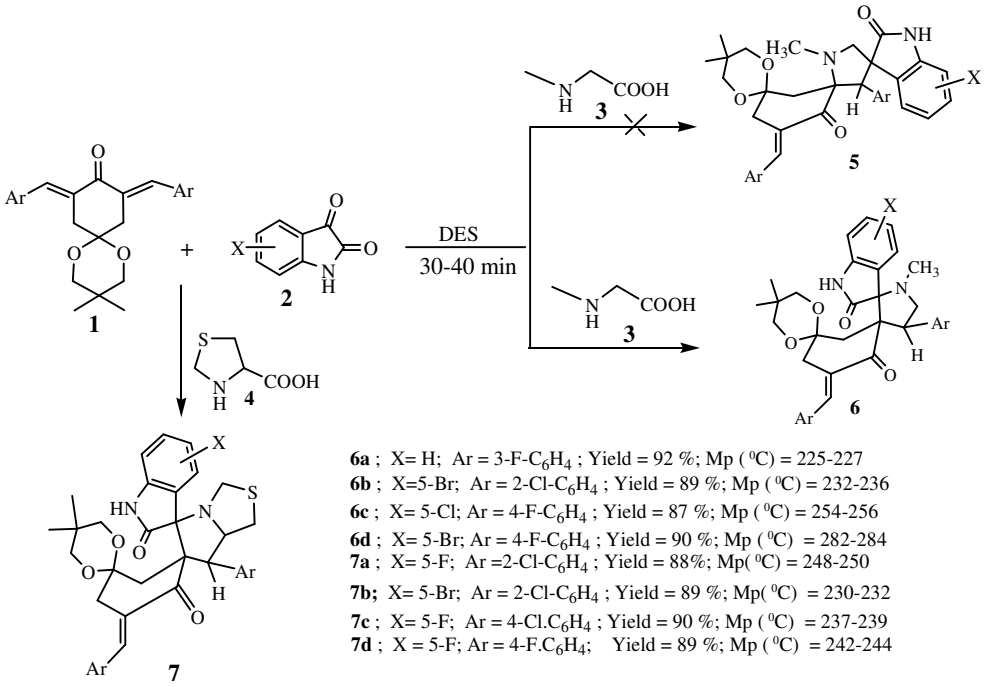
Introduction

Spiro-indole-pyrrolidines is a core structure in many natural occurring compounds and they exhibits a numerous biological activities *e.g*., coerulescine[1], the simplest spirooxindole-pyrrolidine hybrid found in nature, displays local anesthetic effect, pteropodine modulates the function of muscarinic serotonin receptors[2]. In recent years, the construction of spiropyrrolidines and thiapyrrolizidines by 1,3-dipolar cycloaddition reaction of azomethine ylides has been well developed with high regio- and stereoselectivity[3].

As a new flow in organic synthesis, deep eutectic solvents (DESs) have attracted much attention as advanced ionic liquids. They are perfect systems of solvents due to their comfortable availability, absence of purification problems, reusability, and biodegradability compared to hazardous organic solvents[4]. In continuation of our research programme toward synthesis of biologically active spiroheterocycles[5], we report herein the regio- and diastereselective synthesis of new trispiro-oxindoles **6** and **7** containing 1,5-dioxa-spiro[5.5]undecanone *via*, a facile catalyst-free, three-component 1,3-dipolar cycloaddition reaction of novel dipoarophile 8,10-bis[(*E*)arylidene]-1,5-dioxa-spiro[5,5]decane-9-ones **1**, isatins **2** and sarcosine **3** /1,3-thiazolane-4-carboxylic acid **4** using easiest deep eutectic solvents ChCl/Urea as a recoverable greener solvent (Scheme 1).

The required new dipolarophiles 8,10-bis[(*E*)arylidene]-3,3-dimethyl-1,5-dioxa-spiro[5.5]undecan-9-one **1** were prepared by Claisen-Schmidt condensation reaction of 1,5-dioxa-spiro[5.5]undecanone with various substituted benzaldehydes using mild base K_2CO_3.

The dipolarophile **1** is versatile synthone for the construction of more complex spiro-heterocycles owing to presence of diverse dipolarophile functions such as two C=C and one C=O. In effort to optimize the process first the three component reaction of bis arylidene-1,5-dioxa-spiro[5,5]decane **1**, isatin 2 and sarcosine **3** as a simple model substrate was investigated in different solvents such as ethanol, methanol, acetonitrile, 1,4-dioxane and toluene and it has been found that the present reaction occurred successfully in all investigated solvents and cycloadduct **6a** was obtained in good yield after refluxing the mixture for 7-8 h.

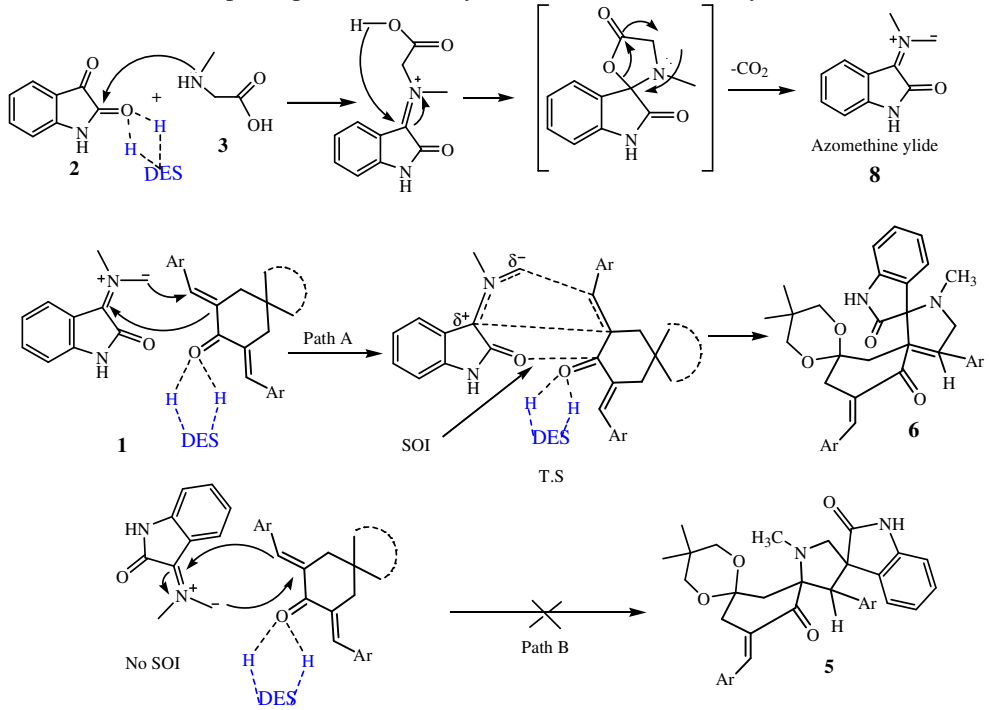


6a ; X= H; Ar = 3-F-C_6H_4 ; Yield = 92 %; Mp (^{0}C) = 225-227
6b ; X=5-Br; Ar = 2-Cl-C_6H_4 ; Yield = 89 %; Mp (^{0}C) = 232-236
6c ; X= 5-Cl; Ar = 4-F-C_6H_4 ; Yield = 87 %; Mp (^{0}C) = 254-256
6d ; X= 5-Br; Ar = 4-F-C_6H_4 ; Yield = 90 %; Mp (^{0}C) = 282-284
7a ; X= 5-F; Ar =2-Cl-C_6H_4 ; Yield = 88%; Mp(^{0}C) = 248-250
7b; X= 5-Br; Ar = 2-Cl-C_6H_4 ; Yield = 89 %; Mp(^{0}C) = 230-232
7c ; X= 5-F; Ar = 4-Cl.C_6H_4 ; Yield = 90 %; Mp (^{0}C) = 237-239
7d ; X = 5-F; Ar = 4-F.C_6H_4; Yield = 89 %; Mp (^{0}C) = 242-244

Scheme 1. Synthesis of trispiropyrrolidine/ thiapyrrolizidine derivatives

Further, to check the role of DESs in this cycloaddition reaction, we have also study the present reaction in deep eutectic solvent (Urea:ChCl) and we obtained very good yield of desire product **6a** in reduce time (2 h.). With these optimized conditions in hand, we examined the scope of this new domino 1,3-dipolar cycloaddition reaction using various substituted isatins and dipolarophiles. Further, in order to extend the scope of this reaction another azomethine ylide generated *in situ* by the reaction of isatin **2** and 1,3-thiazolane-4-carboxylic acid **4** was also explored and corresponding thiapyrrolizidine derivatives **7a-d** were obtained in good yield in shorter reaction time. The ^{1}H NMR spectra of all the products confirmed the formation of single regio- and stereoisomer. Only one C=C bond of **1** is involved in the cycloaddition reaction, ascribable to steric hindrance encountered for the second cycloaddition resulting in chemoselectivity. The IR spectrum of compound **6a** showed two intense absorption bands at 1722, 1684 cm^{-1} due to two carbonyl functionalities. The ^{1}H NMR spectrum of product **6a** showed a sharp singlet at δ 2.18 and two triplets at δ 3.52 (J = 9.1 Hz) and 3.83 (J = 9.1 Hz) for pyrrolidine N–CH_3 and N–CH_2 protons, respectively. The pyrrolidinyl methine proton also appeared as a triplet at δ 4.98 (J = 9.6 Hz) clearly demonstrating the regiochemistry of the cycloaddition reaction. In the other regioisomer **5**

formed, the pyrrolidinyl ethane proton would have appeared as a singlet in the ^{1}H NMR spectrum. A reasonable mechanism for the formation of the trispiro-cycloadduct **6** is planned in Scheme **2**. Azomethine ylide **8** formed *in situ* by the decarboxylative condensation of isatin **2** with sarcosine **3** and subsequently react with dipolarophile to give cycloadduct **6**. Stronger hydrogen-bonding capabilities of DES increase the electrophilicity of carbonyl carbons of the isatins **2** as well as dipolarophile **1** and catalyses the reaction sufficiently.



Scheme 2. Plausible mechanism for the formation of the trispiroadducts

The regiochemistry in the product formation can be explained by considering secondary orbital interaction (SOI)[6] of the carbonyl group of dipolarophile 1a with those of the ylide 8 as shown in Scheme 2. Accordingly, the observed regioisomer **6** via path A is more favourable due to the presence of SOI which is not possible in path B. Hence, only one regioisomer **6** was obtained in the reaction. The spiro-pyrrolidinyl oxindoles were also formed with complete stereoselectivity, affording one diastereomer exclusively, even with the presence of three newly formed stereocenters in the product.

Experimental

The deep eutectic solvent used in the present work was easily prepared from choline chloride (1 eq) and urea (2 eq) at 80 °C by a previously reported method.[7]

General procedure for the synthesis of trispiro-pyrrolidine/thiapyrrolizidines

An equimolar mixture of appropriate 8,10-bis[(*E*)arylidene]-3,3-dimethyl-1,5-dioxa-spiro[5.5]undecan-9-one **1** (1 mmol), isatin **2** and sarcosine **3 /** 1,3-thiazolane-4-carboxylic acid **4** (1 mmol) in DES (10 ml) were taken in a round bottom flask and stirrer the mixture at 80 ^{o}C for 1-2 h. After completion of the reaction as indicated by (TLC), the reaction mixture

was cooled to room temperature. Then, it was extracted using ethyl acetate. The ethyl acetate phase was separated from undissolved DES and the organic layer was separated, dried, filtered, and concentrated in vacuum. The crude solid residue that remained was then crystallized from ethanol. Similarly, the other compounds of the series were prepared. Synthesized compounds were well characterized on the basis of ^{1}H NMR and Mass spectra.

Results and Discussion

1-N-Methyl-spiro[2.3']oxindole-spiro[3.8'']-10''-(3-fluorophenylmethylidene)-3'',3''-dimethyl-1'',5''-dioxa-spiro[5.5]undecan-4-(3-fluorophenyl)-pyrrolidine-2',9''-dione ***(6a)***

White solid; mp 225-227 ^{o}C; IR (KBr, ν): 2965, 1720, 1685 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.69 (s, 3H, CH_3), 0.89 (s, 3H, CH_3), 2.16 (s, 3H, *N*–CH_3), 2.58 (d, 1H, CH_2, *J* = 11.2 Hz), 2.61 (d, 1H, CH_2, *J* = 12.84 Hz), 2.86 (m, 2H, CH_2), 3.07-3.22 (m, 4H, $(OCH_2)_2$), 3.52 (t, 1H, CH, *J* = 9.1 Hz), 3.83 (t, 1H, CH, *J* = 9.1 Hz), 4.98 (t, 1H, CH, *J* = 9.6 Hz), 6.71-7.83 (m, 13H, Ar–H and =CH–Ar), 10.54 (s, 1H, NH) ppm; MS (ESI, m/z, M^+): 584.

1-N-Methyl-spiro[2.3']-5'-bromooxindole-spiro[3.8'']-10''-(2-chlorophenylmethylidene)-3'',3''-dimethyl-1'',5''-dioxaspiro[5.5]undecan-4-(2-chlorophenyl)-pyrrolidine-2',9''-dione ***(6b)***

White solid; mp 232-236 ^{o}C; IR (KBr, ν): 2963, 1722, 1685 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.67 (s, 3H, CH_3), 0.88 (s, 3H, CH_3), 2.17 (s, 3H, *N*–CH_3), 2.59 (d, 1H, CH_2, *J* = 11.1 Hz), 2.63 (d, 1H, CH_2, *J* = 12.83 Hz), 2.84 (m, 2H, CH_2), 3.07-3.26 (m, 4H, $(OCH_2)_2$), 3.46 (t, 1H, CH, *J* = 9.2 Hz), 3.84 (t, 1H, CH, *J* = 9.2 Hz), 4.91 (t, 1H, CH, *J* = 9.6 Hz), 6.71-7.83 (m, 12H, Ar–H and =CH–Ar), 10.55 (s, 1H, NH) ppm.

1-N-Methyl-spiro[2.3']-5'-chlorooxindole-spiro[3.8'']-10''-(4-fluorophenylmethylidene)-3'',3''-dimethyl-1'',5''-dioxa-spiro[5.5]undecan-4-(4-fluorophenyl)-pyrrolidine-2',9''-dione ***(6c)***

White solid; mp 254-256 ^{o}C; IR (KBr, ν): 2965, 1723, 1684 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.69 (s, 3H, CH_3), 0.91 (s, 3H, CH_3), 2.19 (s, 3H, *N*–CH_3), 2.60(d, 1H, CH_2, *J* = 11.1 Hz), 2.62 (d, 1H, CH_2, *J* = 12.82 Hz), 2.89 (m, 2H, CH_2), 3.13-3.35 (m, 4H, $(OCH_2)_2$), 3.51 (t, 1H, CH, *J* = 9.1 Hz), 3.86 (t, 1H, CH, *J* = 9.1 Hz), 4.93 (t, 1H, CH, *J* = 9.5 Hz), 6.73-7.85 (m, 12H, Ar–H and =CH–Ar), 10.57 (s, 1H, NH) ppm.

1-N-Methyl-spiro[2.3']-5'-bromooxindole-spiro[3.8'']-10''-(4-fluorophenylmethylidene)-3'',3''-dimethyl-1'',5''-dioxa-spiro[5.5]undecan-4-(4-fluorophenyl)-pyrrolidine-2',9''-dione ***(6d)***

White solid 282-284 ^{o}C; IR (KBr, ν): 2966, 1720, 1686 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.72 (s, 3H, CH_3), 0.95 (s, 3H, CH_3), 2.22 (s, 3H, *N*–CH_3), 2.63(d, 1H, CH_2, *J* = 11.1 Hz), 2.65 (d, 1H, CH_2, *J* = 12.82 Hz), 2.93(m, 2H, CH_2), 3.15-3.37 (m, 4H, $(OCH_2)_2$), 3.54 (t, 1H, CH, *J* = 9.1 Hz), 3.89 (t, 1H, CH, *J* = 9.1 Hz), 4.95 (t, 1H, CH, *J* = 9.5 Hz), 6.75-7.87 (m, 12H, Ar–H and =CH–Ar), 10.58 (s, 1H, NH) ppm.

Spiro[5.3']5'-fluorooxindole-spiro[6.8'']-10''-(2-chlorophenylmethylidene)-3'',3''-dimethyl-1'',5''-dioxaspiro[5.5]undecan-7-(2-chlorophenyl)-1H-pyrrolo[1,2-c][1,3]-thiazole-2',9''-dione ***(7a)***

Yellow solid; mp 248-250 ^{o}C; IR (KBr, ν): 2965, 1705, 1678 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.78 (s, 3H, CH_3), 0.89 (s, 3H, CH_3), 1.87 (d, 1H, CH_2, *J* = 11.6 Hz), 2.50-2.53

(m,1H, CH_2), 2.92-3.02 (m, 2H, CH_2), 3.20-3.40 (m, 4H, $(OCH_2)_2$, 3.44 (d, 1H, CH, *J* = 8.4 Hz), 3.97(d, 1H, CH, *J* = 10.0 Hz), 4.45(d, 1H, CH, *J* = 10.8 Hz), 4.71-4.74 (m, 1H, CH), 6.26-7.87 (m, 12H, Ar–H and =CH–Ar), 9.22 (s, 1H. NH) ppm.

Spiro[5.3']5'-bromooxindole-spiro[6.8'']-10''-(2-chlorophenylmethylidene)-3'',3''-dimethyl-1'',5''-dioxaspiro[5.5]undecan-7-(2-chlorophenyl)-1H-pyrrolo[1,2-c][1,3]-thiazole-2',9''-dione ***(7b)***

Yellow solid; mp 230-232 ^oC; IR (KBr, ν): 2962, 1710, 1683 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 0.86 (s, 3H, CH_3), 0.96 (s, 3H, CH_3), 1.88 (d, 1H, CH_2, *J* = 11.6 Hz), 2.49-2.52 (m, 1H, CH_2), 2.94-3.04 (m, 2H, CH_2), 3.23-3.44 (m, 4H, $(OCH_2)_2$, 3.45 (d, 1H, CH, *J* = 8.5 Hz), 3.99(d, 1H, CH, *J* = 10.0 Hz), 4.47(d, 1H, CH, *J* = 10.8 Hz), 4.73-4.76 (m, 1H, CH), 6.23-7.92 (m, 12H, Ar–H and =CH–Ar), 9.28 (s, 1H. NH) ppm.

Spiro[5.3']5'-fluorooxindole-spiro[6.8'']-10''-(4-chlorophenylmethylidene)-3'',3''-dimethyl-1'',5''-dioxaspiro[5.5]undecan-7-(4-chloroxyphenyl)-1H-pyrrolo[1,2-c][1,3]-thiazole-2',9''-dione ***(7c)***

Yellow solid; mp 237-239 ^oC; IR (KBr, ν): 2964, 1712, 1685 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 0.85 (s, 3H, CH_3), 0.97 (s, 3H, CH_3), 1.96 (d, 1H, CH_2, *J* = 11.5 Hz), 2.51-2.54 (m, 1H, CH_2), 2.95-3.05 (m, 2H, CH_2), 3.22-3.43 (m, 4H, $(OCH_2)_2$), 3.47 (d, 1H, CH, *J* = 8.3 Hz), 3.99(d, 1H, CH, *J* = 9.8 Hz), 4.43(d, 1H, CH, *J* = 10.8 Hz), 4.71-4.75 (m, 1H, CH), 6.28-7.89 (m, 12H, Ar–H and =CH–Ar), 9.29 (s, 1H. NH) ppm.

Spiro[5.3']5'-fluorooxindole-spiro[6.8'']-10''-(4-fluorophenylmethylidene)-3'',3''-dimethyl-1'',5''-dioxaspiro[5.5]undecan-7-(4-fluorophenyl)-1H-pyrrolo[1,2-c][1,3]-thiazole-2',9''-dione ***(7d)***

Yellow solid; mp 242-244 ^oC; IR (KBr, ν): 2968, 1710, 1685 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 0.84 (s, 3H, CH_3), 0.96 (s, 3H, CH_3), 1.94 (d, 1H, CH_2, *J* = 11.6 Hz), 2.54-2.59 (m, 1H, CH_2), 2.95-3.08 (m, 2H, CH_2), 3.22-3.41 (m, 4H, $(OCH_2)_2$, 3.46 (d, 1H, CH, *J* = 8.4 Hz), 3.98 (d, 1H, CH, *J* = 10.0 Hz), 4.48 (d, 1H, CH, *J* = 10.8 Hz), 4.73-4.76(m, 1H, CH), 6.26-7.87 (m, 12H, Ar–H and =CH–Ar), 9.31 (s, 1H. NH) ppm.

Conclusions

We have developed an efficient protocol for the synthesis of new spirooxindoles containing pyrrolidine/thiapyrrolizidines by 1,3-cycloaddition reaction of azomethine ylide with 1,5-dioxa-spiro[5,5]undecan-9-one containing exocyclic double bond with high regio and stereoselectivity This methodology offers several advantages including mild reaction conditions, no requirement for metal catalysts or additional solvent and short reaction times.

Acknowledgements

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