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Using Homoenolate Annulated Products for Synthesis of Indole Embedded Derivatives

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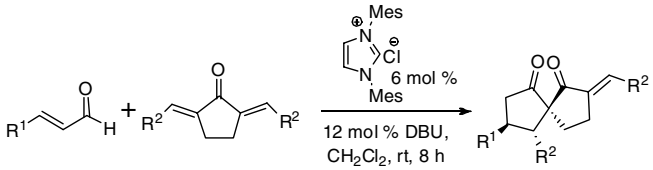
The facile transformation of the functionalized spiro-cyclopentanones obtained by *N*-heterocyclic carbenes (NHC) catalyzed homoenolate annulation strategy, leading to the synthesis of indole embedded compounds is described.

Keywords: Homoenolate, Spiro cyclopentanone, Indole derivatives.

INTRODUCTION

Organo-catalysis can be defined as the acceleration of chemical reactions by the addition of a substoichiometric quantity of an organic compound, which does not contain an inorganic element [1-9]. Between the extremes of transition metal catalysis and enzymatic transformations, organo-catalysis has several advantages and currently this is an interesting and fast growing area of research. The catalysts are usually robust, inexpensive and readily available. In this scenario, *N*-heterocyclic carbenes (NHCs) have been studied for their ability to catalyze organic reactions [10-15]. In recent years, NHCs have assumed importance due to the progress made in generating homoenolates. Homoenolates, a species containing anionic β-carbon to a carbonyl group has been introduced by Nickon and Lambert [16]. The potential utility of this homoenolate equivalent in carbon-carbon bond formation was first described by Nakamura and Kuwajima [17] in their report on the addition of cyclopropanone ketal to a carbonyl compound in the presence of $TiCl_4$ delivering γ-lactones in high yield. Other notable accomplishments on the use of homoenolate equivalents include the use of β-propionate anion equivalent [18-21]. The difficulty in generating homoenolates directly, limited to an extent the application of homoenolates in organic synthesis in contrast to the wide-ranging use of enolates. A conceptually new approach for the generation of homoenolate from enal using nucleophilic NHC was introduced independently and simultaneously by Bode *et al*. [22] and Burstein & Glorius [23] based on on the mechanistic pathways available to the Breslow intermediate. They speculated that just as the addition of NHC to aldehyde would generate an enol/enaminol (Breslow intermediate), the addition of NHC to an α,β-unsaturated aldehyde can, in principle, generate a conjugated acyl anion (extended Breslow intermediate), more appropriately called homoenolate [24,25]. Work from different research groups revealed that the versatility and usefulness of NHC-bound homoenolate annulation with various electrophiles leading to δ-lactones [26,27], pyrazolidinones [28], pyridazininones [29], lactams [30-33], spiro cyclopentanones [34-37] and cyclopentenes [38-42]. Homoenolates have also been shown to add efficiently to nitrostyrenes [43] and sulfonimines [29] leading to precursors for novel γ-aminobutyric acid (GABA) derivatives.

The last decade witnessed the development of NHC catalyzed homoenolate reactions as an effective strategy in the generation of synthetically challenging organic compounds [34]. To our surprise, the synthetic utility of the products obtained from homoenolate reactions have not been taken forward to its further possibilities. On a closer study of these reactions, the spiro-cyclopentanones which are produced by the homoenolate annulation of α,β-unsaturated aldehydes with dibenzylidene cycopentanones caught our attention (**Scheme-I**). The ambient reaction conditions as well as the easy access to the reagents



Scheme-I: Homoenolate annulation of α,β-unsaturated aldehydes with dibenzylidene cycopentanones

added to our interest in exploring the further utility of homoenolate annulated product [44-47].

The revelation that various biological activities are shown by tetrahydro cyclopenta[*b*]indole alkaloids bearing a quaternary carbon center facilitated our intrerest in this direction. Bruceolline J, emindole SB, paspaline and penitrem A, having those cores already proved to exhibit antimalarial, analgesic, antiinflammatory, anti-Alzheimer and potassium channel inhibiting effects [48-51]. Inspite of the high demand of these scaffolds, synthetic protocols developed were albeit less [52-54]. The synthetic protocols developed either involved metal catalysts [52] or complex steps towards the starting material synthesis [55,56]. In this line, the easy access to the starting materials *viz.*, spiro cyclopentanones and the simple protocol employed makes this strategy stand apart from others. The procedure involves the addition of DBU (12 mol %) to a suspension of carbene precursor (6 mol%), cinnamaldehyde (1.0 mmol) and dienone (0.5 mmol) in dry dichloromethane under argon atmosphere. This solution was stirred for 12 h at room temperature. Removal of solvent followed by column chromatography afforded the spiro cyclopentanone derivative as a white crystalline solid, which was used as the starting material for the reaction [44-47].

Naturally, the spiroketones appeared to be interesting from the point of view of their transformation to complex spiro cyclic systems [57-59]. In particular, the presence of two carbonyl groups, one involving a conjugation along with the spirocentre makes these spiroketones, unique substrates for further modifications. Therefore, we set out to explore such possibilities.

EXPERIMENTAL

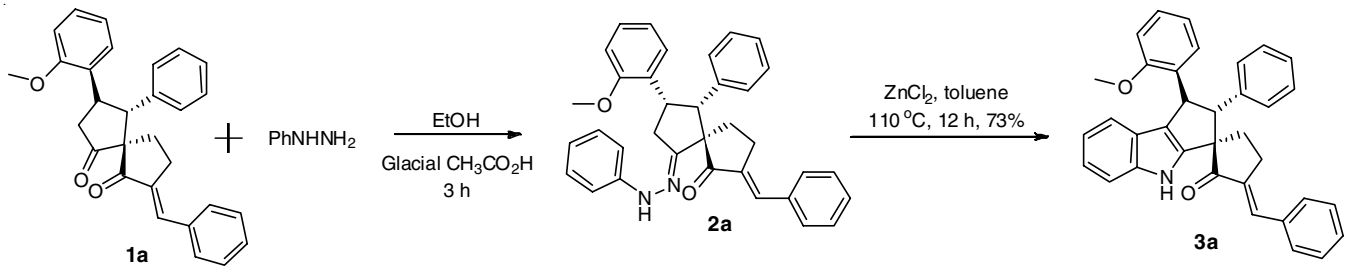
Melting points were recorded on a Büchi melting point apparatus and are uncorrected. NMR spectra were recorded at 500 (^{1}H) and 126 (^{13}C) MHz respectively on a Bruker DPX-500 MHz NMR spectrometer. Chemical shifts (δ) are reported relative to TMS (^{1}H) and $CDCl_3$ (^{13}C) as the internal standards. Coupling constant (*J*) is reported in Hertz (Hz). Mass spectra were recorded under FAB on a JEOL JMS 600H mass spectrometer. IR spectra were recorded on a Bruker Alpha-T FT-IR spectrophotometer. Gravity column chromatography was performed using 100-200 mesh silica gel and mixtures of hexane-ethyl acetate were used for elution.

General procedure for the synthesis of hydrazones: A mixture of spiro cyclopentanone (0.83 mmol) and phenylhydrazine (1.6 mmol) were taken in a round bottom flask. To this 5 mL of ethanol was added and stirred. Then two drops of glacial acetic acid was also added and the stirring was continued to 2-3 h. The cold reaction mixture was filtered and the solid residue was washed with dil. HCl followed by cold rectified spirit and the spiroketone hydrazone (**2a**) was obtained in good yield. IR (film, ν_{max}, cm^{-1}): 3267, 1693, 1492, 1247; ^{1}H NMR (500 MHz, $CDCl_3$): δ ppm 7.50-7.55 (m, 3H), 7.34-7.42 (m, 4H), 7.09-7.16 (m, 9H), 6.69-6.86 (m, 5H), 4.46 (d, *J* = 13.2, 1H), 4.15-4.25 (m, 1H), 3.91 (s, 3H), 3.05-3.30 (m, 2H), 2.49-2.57 (m, 1H), 2.30-2.39 (m, 1H), 2.16-2.23 (m, 1H), 1.66-1.76 (m, 1H) ^{13}CNMR (125 MHz, $CDCl_3$): δ 200.9, 157.7, 155.6, 146.7, 143.9, 139.1, 135.6, 135.2, 129.5, 128.6, 128.5, 127.9, 126.9, 125.9, 123.1, 122.4, 120.8, 119.5, 113.9, 69.0, 56.1, 47.7, 37.4, 22.2, 19.8. LRMS-FAB $(M+H)^+$ calculated: 513.25; found: 513.63.

General procedure for the synthesis of indole derivatives (3a): The spiroketone hydrazone (0.37 mmol) and zinc chloride (3.7 mmol) were taken in a round bottom flask. Then 5 mL of toluene was added to the reaction mixture and was refluxed in an oil bath for 12 h. The crude reaction mixture was purified by column chromatography on silica gel (100-200 mesh) using hexane-ethyl acetate (95:5) as eluent and the product was obtained as yellow crystalline solid (**Scheme-II**).

(*E*)-3'-Benzylidene-2-(2-methoxyphenyl)-1-phenyl-2,4-dihydro-1*H*-spiro[cyclopenta[*b*]indole-3,1'-cyclopentan]-2'-one (3a): m.p.: 214-216 ºC; IR (film, cm^{-1}): 3444, 2935, 1697, 1616, 1454, 1246; ^{1}H NMR (500 MHz, $CDCl_3$): δ ppm 7.71 (s, 1H), 7.40-7.44 (m, 2H), 7.29-7.40 (m, 8H), 7.19-7.7.25 (m, 3H), 7.07-7.14 (m, 4H), 6.97-6.98 (m, 1H), 6.85-6.86 (m, H), 5.34 (d, 1H, *J* = Hz), 4.30 (d, 1H, *J* = 8 Hz), 3.56 (s, 3H), 2.73-2.77 (1H, m), 2.06-2.14 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ ppm 206.8, 157.2, 142.4, 139.9, 137.3, 134.3, 133.7, 133.2, 129.7, 128.5, 128.3, 127.7, 127.6, 127.2, 126.9, 126.1, 122.9, 120.4, 118.8, 118, 112.6, 110.8, 67.5, 60.6, 53.9, 47.4, 29.1, 25.4; LRMS-FAB $(M+H)^+$calculated for $C_{35}H_{29}NO_2$: 496.22; found: 496.95, CCDC number: 1966911.

(*E*)-2-(2-Methoxyphenyl)-3′-(4-methylbenzylidene)-1-*p*-tolyl-2,4-dihydro-1*H*-spiro[cyclopenta[*b*]indole-3,1′-cyclopentan]-2′-one (3b): m.p.: 70-74 ºC; IR (film, ν_{max}, cm^{-1}): 3444, 1618, 2921, 1957, 1459 and 1242; ^{1}H NMR (500 MHz,



Scheme-II: Reactions of the functionalized spiro-cyclopentanones

$CDCl_3$): δ 7.70 (S, 1H), 7.29 (S, 1H), 7.29-7.36 (m, 4H), 7.12-7.23 (m, 4H), 6.92-7.09 (m, 5H), 6.76-6.86 (m, 3H), 5.30 (d, *J* = 7.5 Hz, 1H), 4.25 (d, *J* = 7.5 Hz, 1H), 3.59 (s, 3H), 2.68-2.79 (m, 2H), 2.36 (s, 3H), 2.29 (s, 3H), 1.90-2.07 (m, 2H) ^{13}C NMR (125 MHz, $CDCl_3$): δ ppm 207.9, 157.3, 143.9, 141.0, 139.8, 136.7, 136.3, 136.1, 134.8, 134.5, 134.4, 134.1, 132.6, 131.7, 130.8, 129.4, 129.1, 128.9, 128.6, 127.6, 127.2, 124.1, 121.9, 121.3, 120.9, 119.7, 119, 111.8, 110.3, 67.1, 61.6, 55.1, 41.9, 29.9, 26.9, 21.5, 21.4 LRMS-FAB (M+H)$^+$calculated for $C_{37}H_{33}NO_2$: 524.25; Found: 524.41.

(*E*)-3′-Benzylidene-2-(4-methoxyphenyl)-1-phenyl-2,4-dihydro-1*H*-spiro[cyclopenta[*b*]indole-3,1′-cyclopentan]-2′-one (3c): m.p.: 210-212 ºC; IR (film, cm^{-1}): 3452, 2985, 1707, 1421, 1249; ^{1}H NMR (500 MHz, $CDCl_3$): δ ppm 7.82 (s, 1H), 7.41 (m, 4H), 7.32-7.33 (m, 2H), 7.25-7.30 (m, 3H), 7.15-7.21 (m, 6H), 7.08-7.11 (m, 2H), 6.99-7.03 (m, 2H), 6.88-6.91 (m, 1H), 6.65-6.67 (m, 2H), 4.74 (d, 1H, *J* = 8.5 Hz), 4.20 (d, 1H, *J* = 8.5 Hz), 3.66 (s, 3H), 2.62-2.68 (m, 1H), 1.90-2.08 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ ppm 207.4, 157.4, 143.5, 139.7, 134.2, 133.9, 132.1, 129.9, 128.3, 127.9, 127.5, 126.9, 126.7, 126.6, 126.1, 122.8, 121.4, 120.3, 119, 118.9, 116.5, 115.2, 113.5, 112.6, 111.9, 111, 110.4, 68.3, 65.5, 62.1, 55.9, 49.4, 25.4; LRMS-FAB (M-H)$^+$ calculated for $C_{35}H_{29}NO_2$: 494.22; Found: 494.74.

(*E*)-2-(4-Methoxyphenyl)-3′-(4-methylbenzylidene)-1-*p*-tolyl-2,4-dihydro-1*H*-spiro[cyclopenta[*b*]indole-3,1′-cyclopentan]-2′-one (3d): m.p.: 250-252 °C; IR (film, cm^{-1}): 3347, 2957, 1703, 1604, 1244; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.77 (s, 1H), 7.46 (s, 1H), 7.33-7.35 (m, 1H), 7.25-7.28 (m, 2H), 7.15-7.18 (m, 6H), 7.05-7.10 (m, 4H), 6.95-6.98 (1H), 6.72-6.74 (m, 2H), 4.78 (d, 1H, *J* = 8.5 Hz), 4.25 (d, 1H, *J* = 8.5 Hz), 3.74 (s, 3H), 2.38 (s, 3H), 2.31 (s, 3H), 2.71-2.79 (m, 1H), 2.05-2.13 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 207.7, 158.2, 143.7, 140.9, 140, 136.6, 135.4, 135, 134.38, 134.31, 132.5, 130.9, 130.8, 129.5, 129.3, 129, 128.8, 124, 121.5, 119.9, 119.1, 113.6, 111.8, 68, 61.6, 55, 53.2, 48.5, 30.2, 21.5, 14.1; LRMS-FAB (M+H)$^+$ calculated for $C_{37}H_{33}NO_2$:524.25; Found: 524.81.

(*E*)-3′-Benzylidene-1,2-diphenyl-2,4-dihydro-1*H*-spiro[cyclopenta[*b*]indole-3,1′-cyclopentan]-2'-one (3e): m.p.: 84-86 ºC; IR (film, cm^{-1}): 3353, 2956, 1703, 1620, 1375; ^{1}HNMR (500 MHz, $CDCl_3$): δ ppm 7.80 (s, 1H), 7.47-7.49 (m, 1H), 7.42 (s, 1H), 7.34-7.36 (m, 4H), 7.18-7.21 (m, 9H), 7.09-7.15 (m, 4H), 6.90-6.91 (m, 1H), 4.80 (d, 1H, *J* = 8.5), 4.27 (d, 1H, *J* = 8.5), 2.67-2.72 (m, 1H), 1.95-2.07 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ ppm 203.6, 156.6, 155.2, 153.0, 152.9, 152.4, 151.7, 150.2, 149.4, 148.6, 148, 147.7, 146.4, 145.9, 144.6, 143.6, 144, 142.4, 141.5, 140.8, 140.2, 139.8, 138.6, 135.3, 128.4, 126.4, 124.1; LRMS-FAB (M+H)$^+$ calculated for $C_{34}H_{27}NO$: 466.21; Found: 466.17.

(*E*)-3′-(4-Methylbenzylidene)-2-phenyl-1-*p*-tolyl-2,4-dihydro-1*H*-spiro[cyclopeanta[*b*]indole-3,1′-cyclopentan]-2′-one (3f): m.p.: 205-207 ºC; IR (film, cm^{-1}): 3338, 2923, 1706, 1453, 1262; ^{1}H NMR (500 MHz, $CDCl_3$): δ ppm 7.74 (s, 1H), 7.48 (s, 1H), 7.35-7.37 (m, 2H), 7.30-7.54 (m, 2H), 7.14-7.21 (m, 7H), 7.05-7.11 (m, 5H), 6.96-6.98 (m, 1H), 4.83 (d, 1H, *J* = 8.5), 4.32 (d, 1H, *J* = 8.5), 2.70-2.78 (m, H), 2.03-2.1 (m, 3H), 2.38 (s, 3H), 2.32 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$); δ ppm 207.7, 142.8, 141.8, 139.8, 138.9, 135.5, 134.3, 133.29, 133.20, 131.5, 129.8, 128.4, 128.3, 128.2, 128, 127.9, 127.7, 127.1, 126.8, 126.7, 125.3, 122.9, 120.4, 120.2, 118.8, 118.0, 110.71, 66.7, 60.5, 48.2, 30.87, 29.2, 25.5, 21.6; LRMS-FAB (M+H)$^+$ calculated for $C_{36}H_{31}NO$: 494.24; Found: 494.98.

(*E*)-2-(2-Methoxyphenyl)-1-(thiophen-2-yl)-3′-(thiophen-2-ylmethylene)-2,4-dihydro-1*H*-spiro[cyclopenta[*b*]indole-3, 1′-cyclopentan]-2′-one (3g): m.p.: 208-210 ºC; IR (film, cm^{-1}): 3334, 2926, 1693, 1450, 1242; ^{1}H NMR (500 MHz, $CDCl_3$): δ7.90 (s, 1H), 7.70 (s, 1H), 7.51-7.52 (m, 1H), 7.31-7.34 (m, 2H), 7.20-7.22 (m, 1H), 7.10-7.17 (m, 3H), 7.01-7.04 (m, 1H), 6.96-6.98 (m, 1H), 6.89-6.92 (m, 2H), 6.82-6.86 (m, 3H), 5.29 (d, 1H, *J* = 8.5), 4.67 (d, 1H, *J* = 8.5), 3.71 (s, 3H), 2.71-2.78 (m, 1H), 2.12-2.24 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ ppm 206.9, 157.5, 143.3, 142.3, 140.7, 139.8, 133.3, 133.1, 130.7, 130.6, 130.5, 128.9, 128.8, 128.1, 127.5, 126.9, 126.4, 126.1, 124.1, 123.8, 121.7, 121.4, 120.8, 119.9, 118.9, 118.8, 111.8, 62.4, 61.7, 55.8, 55.3, 54.8; LRMS-FAB (M+H)$^+$ calculated for $C_{31}H_{25}NO_2S_2$:507.13; found 507.51.

RESULTS AND DISCUSSION

Initially, our attention was focussed on the introduction of an indole ring since this was deemed a demanding and fascinating problem [60,61]. Indole chemistry owing its origin to the study of the dye indigo, attained recognition being core of alkaloids, amino acid tryptophan and auxins, a scaffold capable of providing useful ligands for diverse receptors [62-65]. Nevertheless the presence of indole moiety in natural and unnatural molecules with biological activity [66-69] made us to explore the possibility of subjecting the homoenolate annulated spiro-ketone to the Fischer indole protocol [70-72].

In an initial experiment, (5R,8R,9R,*E*)-2-benzylidene-8-(2-methoxyphenyl)-9-phenylspiro[4.4]nonane-1,6-dione (**1a**) which was obtained by the homoenolate annulation of 2-methoxy cinnamaldehyde and dibenzylidene acetone was treated with phenylhydrazine in ethanol with a few drops of glacial acetic acid for about 3 h and the corresponding hydrazone was obtained. It was then refluxed with zinc chloride in toluene for about 12 h. The crude reaction mixture on column chromatography yielded the product as (*E*)-3′-benzylidene-2-(2-methoxyphenyl)-1-phenyl-2,4-dihydro-1*H*-spiro[cyclopenta[*b*]indole-3,1′-cyclopentan]-2′-one (**3a**) in 73% yield.

The structure of the product was elucidated by spectroscopic methods. The IR spectrum showed two characteristic bands at 3444 and 1697 cm^{-1} corresponding to N-H stretching and keto carbonyl stretching. In the ^{1}H NMR spectrum, the signals due to aromatic protons appeared between δ 7.49 and δ 6.86 and a singlet due to -OCH_3 proton appeared at δ 3.56. The methine protons appeared as doublet at δ 4.30 and δ 5.34 ppm. The ^{13}C showed keto carbonyl at δ 206.8 and methoxy carbon at δ 53.94. The structure and relative stereochemistry was unambiguously established by single crystal X-ray analysis (Fig. 1) [73].

Mechanistically the reaction of phenyl hydrazine with the preferred carbonyl group in **4** initially forms the corresponding phenyl hydrazone **5**, which isomerizes to the respective enamine (ene hydrazine) **6** on protonation. Then a cyclic[3,3]sigma-

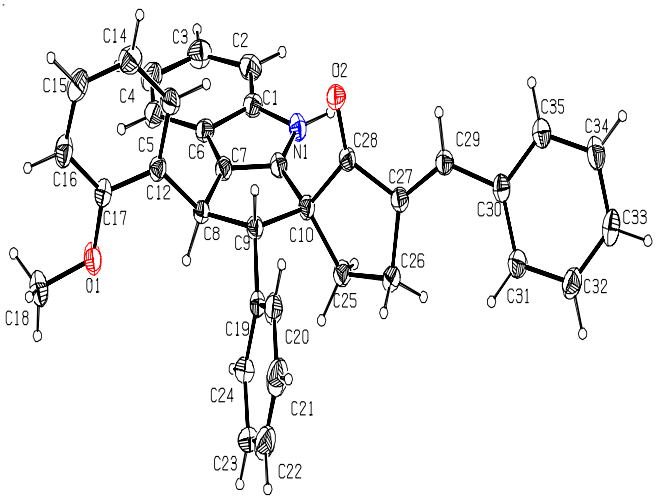
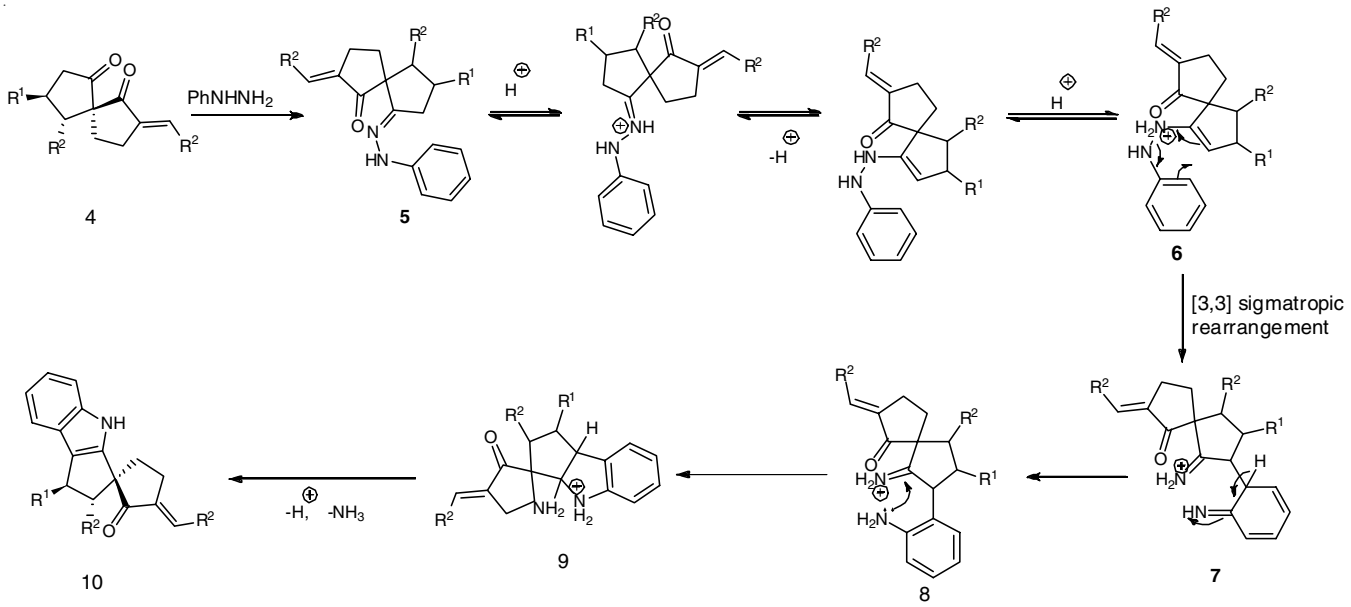


Fig. 1. ORTEP diagram of **3a**

tropic rearrangement occurs producing an imine **7**. The resulting imine forms a cyclic amino acetal (aminal), which in the presence of $ZnCl_2$ eliminates ammonia resulting in indole **10** (**Scheme-III**). The reaction was extended to a number of spiroketones and the results are given in Table-1.

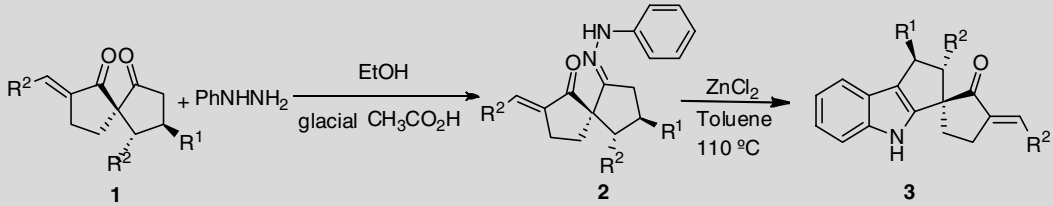
Conclusion

In conclusion, the synthetic utility of the NHC catalyzed homoenolate annulation strategy is successfully demonstrated particularly by studying the reactivity of highly functionalized spiro-cyclopentanones. The formation of indole embedded complex compounds, which may be of potential value suggest that the homoenolate annulated product may be amenable to further transformations. In particular, synthesized indoles may be further transformed to more complex polycyclic systems, endowed with interesting biological activities by virtue of the presence of enone functionality.



Scheme-III: Mechanism of the reaction

TABLE-1
SCOPE OF THE REACTION



Entry[a]	R^1	R^2	Product	Yield (%)[b]
1	2-Methoxy phenyl	Phenyl	**3a**	73
2	2-Methoxy phenyl	4-Methylphenyl	**3b**	62
3	4-Methoxy phenyl	Phenyl	**3c**	70
4	4-Methoxy phenyl	4-Methylphenyl	**3d**	60
5	Phenyl	Phenyl	**3e**	66
6	Phenyl	4-Methylphenyl	**3f**	71
7	2-Methoxyphenyl	Thienyl	**3g**	80

[a]Standard conditions: Spiroketone hydrazine **2** (0.37 mmol), zinc chloride (3.7 mmol), ethanol (5 mL), glacial acetic acid (2 drops).
[b]Yield of the isolated product after column chromatography.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

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73. CCDC 1966911 (**3a**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.