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# Studies on the synthesis of spiroheterocycles and their derivatives using dimedone as synthetic precursor

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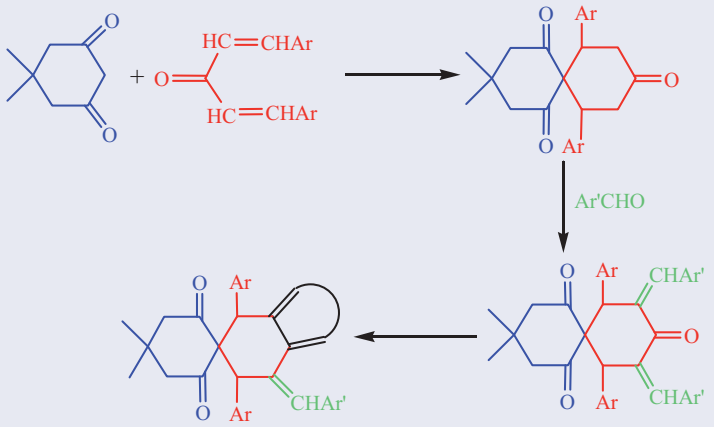
**ABSTRACT**

Diarylidene ketones **1a–c**, formed by the condensation of acetone with diverse appropriate aryl aldehydes undergo Micheal reaction with dimedone to afford the desired spiro compounds **2a–c**. The spirodiarylidene derivatives **3a–l** on cyclisation with hydrazine, phenyl hydrazine, hydroxyl amine, urea, thiourea and guanidine carbonate furnish the respective insitu oxidized pyrazole **4a–l**, phenylpyrazole **5a–l**, isoxazole **6a–l**, pyrimidine **7a–l**, aminopyrimidine **8a–l**. The antibacterial activities of the synthesized compounds have been investigated against the gram negative *Escherichia coli* and gram positive bacteria *Staphylococcus aureus*.

**GRAPHICAL ABSTRACT**




**Ar = $C_6H_5$, *p*- $MeOC_6H_4$, *p*-$ClC_6H_4$**
**Ar' = $C_6H_5$, *p*- $MeOC_6H_4$, *p*-$ClC_6H_4$ , *p*-$BrC_6H_4$**

Diarylidene ketone undergo Micheal rection with dimedone to afford the spiro compounds followed by cyclisation with some bidentate ligands to furnish the respective insitu oxidized pyrazole, phenylpyrazole, isoxazole, pyrimidine, aminopyrimidine derivatives and the synthesized compounds were screened for their antibacterial activities.

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**KEYWORDS**
Antibacterial activities; dimedone; isooxazole; pyrazole; pyrimidine; spiroheterocycles

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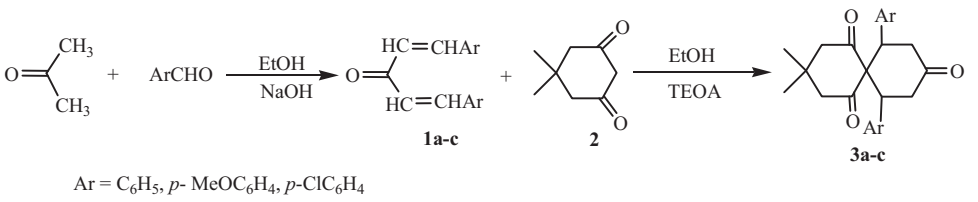



**Scheme 1.** Synthesis of spiro compounds **3a–c**.

## Introduction

Dimedone is an alicyclic compound having 1,3-dicarbonyl groups flanked by a methylene group and exists in a tautomeric trans-enolized form where intermolecular hydrogen bonding[1] does exist. It is an excellent synthetic precursor due to the presence of C-1, C-2, and C-3 reactive centres. In addition, dimedone is a unique compound for construction of partially hydrogenated fused heterocycles.[2] A wide range of practical applications of dimedone include their uses as versatile precursors for synthesis of numerous hetero and spirocyclic compounds,[3–5] xanthene derivatives[6] with their industrial[7] and synthetic[8] applications, photo-antiproliferative,[9] anticancer[10] agents and also as reagent for various analytical determinations.[11] Moreover, the fused heterocyclic ring systems are important scaffolds in medicinal chemistry and appear in several natural and synthetic compounds of significant pharmacological properties.[12] Spiroheterocycles are of considerable interest because of their conformational restriction associated to the structural rigidity which steers the biological activity.[13]

In continuation of our earlier work,[14] the present effort has been focused on spirolization of versatile dimedone precursor with diarylidene ketones and later the spiran formed underwent condensation with diverse arylaldehydes in the cyclohexanone moiety to form its diarylidene derivatives. Thereafter, the diarylidene intermediate has been the focal point for systematic installation of biologically active heterocyclic units such as pyrazole, isoxazole and pyrimidine onto the $\alpha,\beta$-unsaturated scaffold of spiro frame work. However, the findings of dimedone chemistry here is in contrast with our earlier piece of the research work.[15] The spirolization appears due to manipulation of reactivity of C-2 carbon.

## Results and discussion

The diarylideneacetones **1a–c** were prepared[16–18] by the condensation of aryl aldehydes and acetone in ethanolic NaOH. Subsequently, the reaction of diarylideneacetones **1a–c** with dimedone **2** was performed in presence of triethanolamine (TEOA) via Michael addition to afford spiro compounds **3a–c** (Scheme 1). The analytical and spectral data suggest the formation of spiro derivatives **3a–c**. The IR spectrum of **3a** ($Ar = C_6H_5$) furnishes two characteristic sharp peaks at 1714 and 1680 $cm^{-1}$ corresponding to carbonyl stretchings of dimedone and cyclohexanone rings, respectively.

The PMR spectrum of **3a** ($Ar = C_6H_5$) gives two separate singlets at $\delta = 1.60$ and 2.01 corresponding to six protons of gem dimethyl groups at C-3 and four methylene

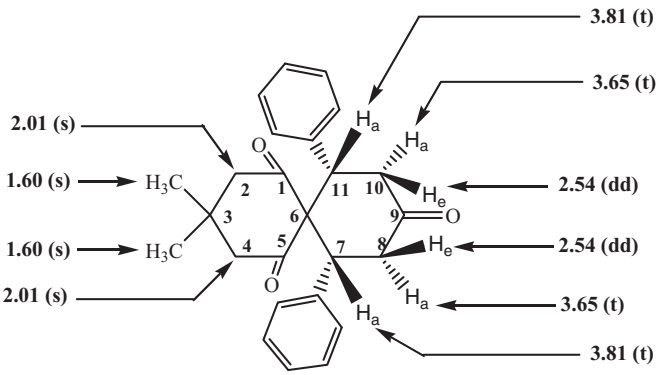


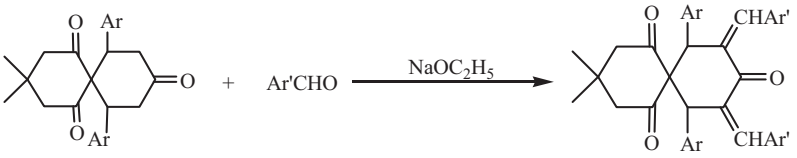

**Figure 1.** $^{1}$H NMR assignment of compound **3a**.

protons at C-2 and C-4 of dimedone ring, respectively. The equivalence of four protons at C-2 and C-4 may be accounted for planarity of dimedone ring due to presence of two carbonyl groups at C-1 and C-5. A doublet of doublet centred at $\delta = 2.54$ ($J_{H8-H'8} = 14.8$ Hz and $J_{H8-H7} = 3.6$ Hz) for the two equatorial protons at C-8 and C-10, a triplet at $\delta 3.65$ ($J_{H'8-H8} = J_{H'8-H7} = 14.8$ Hz) for the two axial protons at C-8 and C-10 and another doublet of doublet resonating at $\delta = 3.81$ ($J_{H8-H'8} = 14.8$ Hz and $J_{H8-H7} = 3.6$ Hz) for two axial protons at C-7 and C-11 are compatible to the proposed spiran **3a** (Fig. 1). It is supportive by a complex multiplet at $\delta = 7.07$–$7.29$ corresponding to 10 protons of two phenyl groups attached to C-7 and C-11. The axial protons at C-8 and C-10 experience down field shift as compared to their equatorial protons due to anisotropy effect of the carbonyl group.

The $^{13}$C NMR spectrum of this compound gives signals at $\delta = 213.0$, 211.5, 208.5, 69.5, 56.09, 54.10, 50.7, 43.70, 28.67 and 28.5 corresponding to two carbonyl functions of dimedone ring(C-1 and C-5), carbonyl group of cyclohexanone moiety (C-9), spiro carbon (C-6), methylene carbon (C-8 and C-10), quarternary carbon (C-3), methylene carbon (C-2 and C-4), methane carbon (C-7 and C-11) and methyl carbon, respectively. The signals for the quarternary carbon atom of the phenyl groups linked to C-7 and C-11, meta carbons, ortho carbons and para carbon appear at $\delta = 138.6$, 128.9, 128.6 and 127.9, respectively which are compatible with the proposed structure **3a**. The supplementary evidence in support of the formation of the spiran was obtained from its EI-MS spectrum which gave [M + 1] peak at *m*/*z* 375.

The spirans **3a–c** were refluxed with different aryl aldehydes in presence of EtONa in 2:1 molar ratio to afford the spiro diarylidene derivatives **4a–l** (Scheme 2).

The IR spectrum of the spiro dibenzylidene **4a** ($Ar = Ar' = C_6H_6$) gives two sharp peaks at 1707 and 1656 cm$^{-1}$ corresponding to two carbonyl functions at two different structural environment. The shift for the carbonyl stretching of cyclohexanone ring from 1680 to 1656 cm$^{-1}$ may be attributed to conjugation of two exocyclic double bonds and almost no appreciable change in the other carbonyl absorption ensures the formation of the dibenzylidene derivatives. The PMR spectrum of dibenzylidene derivatives **4a** shows a sharp singlet at $\delta = 4.01$ in lieu of a doublet of doublet for the two axial protons at C-7 and C-11. The disappearance of doublet of doublet and the triplet of **3a** ($Ar = C_6H_6$) corresponding to four protons at C-8 and C-10 ascertains the condensation of two ketomethylene groups with benzaldehyde at the aforesaid positions. On the




Ar = $C_6H_5$, *p*- $MeOC_6H_4$, *p*-$ClC_6H_4$;
Ar' = $C_6H_5$, *p*- $MeOC_6H_4$, *p*-$ClC_6H_4$ , *p*-$BrC_6H_4$

**Scheme 2.** Synthesis of spiro diarylidene derivatives **4a–l**.

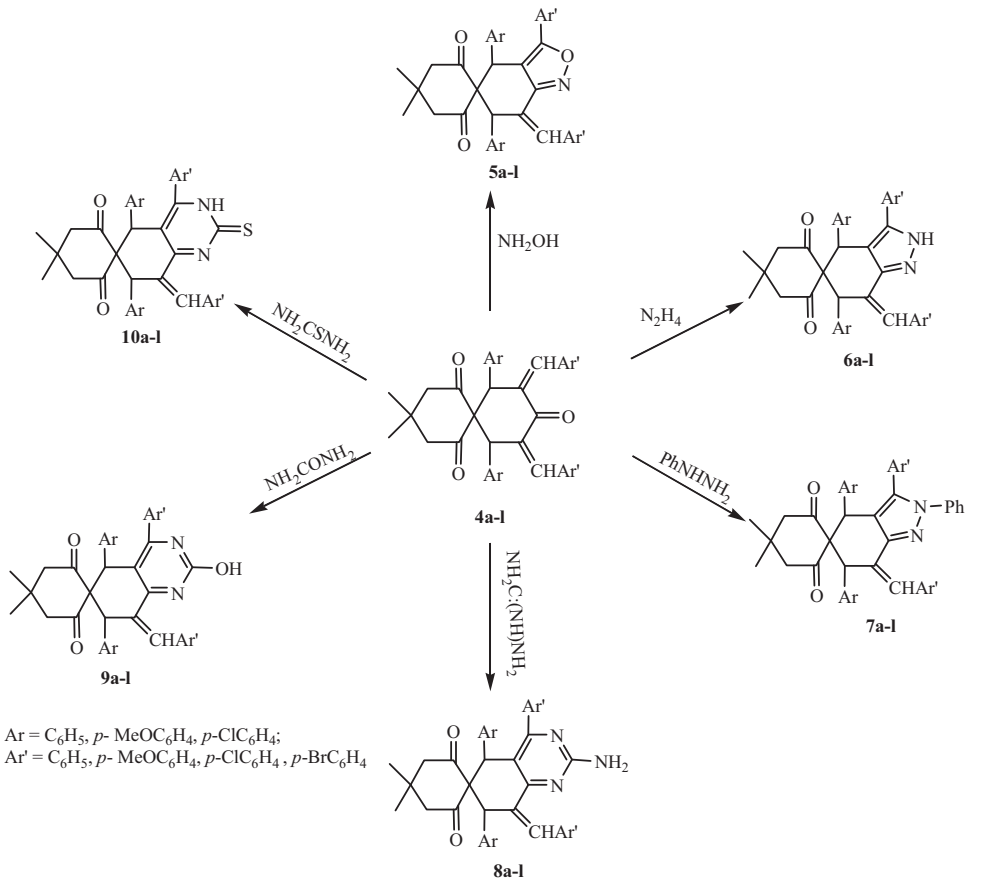
contrary, three separate multiplets centred at $\delta = 6.93$–$6.98$, 7.21–7.30 and 7.43–7.48 each corresponds to four, eight and eight phenyl protons. In addition, a sharp singlet at $\delta = 8.30$ is attributed to two exo-olefinic protons. $^{13}C$ NMR spectrum of this compound shows characteristic signals at $\delta = 154$, 122.15, 115.06, 63.06, 55.7, 52.0, 46.20 and 31.0 corresponding to carbonyl carbons, exomethylene $sp^2$ carbons, carbons adjacent to carbonyl carbon at C-8 and C-10, $sp^3$ spiro carbon, methylene carbon at C-2 and C-4, quarternary carbon at C-3 methine carbons at C-7 and C-11 and methyl carbons, respectively. The two signals at $\delta = 141.0$ and 138.0 corresponding to quarternary carbon of the phenyl rings linked to exomethylene carbon and cyclohexanone ring besides the closely spaced six signals in the range of $\delta = 126.7$–$132.65$ for other carbon atoms of the phenyl rings. The formation of diarylidene compound is also evident from its EI-MS spectrum with the molecular ion peak (M + 1) at *m*/*z* 551.

The diarylidene derivatives **4a–l** on Michael addition and subsequent dehydrative cyclization with hydroxylamine, hydrazine, phenyl hydrazine, guanidine carbonate, urea and thiourea afforded their respective in situ oxidized products **5a–l–10a–l** (Scheme 3).

The driving force for this *in situ* oxidation is the aromatization of the newly build heterocyclic rings similar to the results reported earlier.[16] In the IR spectra of **5a–l, 6a–l, 7a–l, 8a–l, 9a–l** and **10a–l**, the carbonyl stretching frequencies at 1656 $cm^{-1}$ disappear.

The PMR spectra of all these compounds **5a–l–10a–l** display a complex multiplet appearing in the range of $\delta = 6.46$–$7.80$ due to presence of large number of aromatic protons and a multiplet at $\delta = 8.02$–$8.37$ for one exo-olefinic proton. In addition, four separate singlets appear in the range of $\delta = 1.0$–$1.16$, 2.20–2.50, 3.87–4.25 and 4.17–4.45 corresponding to methyl proton, methylene protons at C-2 and C-4 and each methine protons at C-7 and C-11, respectively. However, the PMR spectrum of **6a** (Ar = Ar′=$C_6H_5$) shows an additional broad singlet at $\delta = 10.43$ for –NH proton which underwent exchange with $D_2O$. Similarly, another broad singlet at $\delta = 10.05$ was observed for phenolic –OH protons in the PMR spectrum of the compound **9a** (Ar = Ar′=$C_6H_6$) whereas a singlet at $\delta = 6.05$ in the PMR spectrum of **8a** (Ar = Ar′=$C_6H_6$) has been attributed for $-NH_2$ protons.

Moreover, the substrate **4a–l** having a –C = C–CO– (α,β unsaturated carbonyl) is an ambient electrophile where the carbonyl carbon is hard and β-carbon is the soft centre.[19] The conjugation of the double bonds with the phenyl ring reduces the extent its conjugation with the carbonyl group. Since hydrazine and phenylhydrazine are hard nucleophiles and their $-NH_2$ group attacks the hard centre of the carbonyl carbon




**Scheme 3.** Reaction of diarylidene derivatives **4a–l** with different bidentate ligands.

giving rise to hydrazones which subsequently underwent cyclization and in situ oxidation to form compound **6a–l** and not the alternate structure. In case of hydroxylamine, the nucleophilicity of nitrogen is increased due to adjacent oxygen atom, thus making it a harder nucleophile[20] ($\alpha$-effect). Hence the attack of $-NH_2$ at carbonyl occurs first forming the isoxazole **5a–l** and not the alternate structure. On the basis of elemental analyses, IR and PMR spectra of the compounds **5a–l–10a–l** suggest the installation of isoxazole, pyrazole, phenylpyrazole, aminopyrimidine, hydroxypyrimidine and pyrimidinethione moieties, respectively in **4a–l.**[14,21]

## *Antimicrobial study*

All the synthesized compounds were screened for their antibacterial activity *in vitro* against gram negative bacteria *Escherichia coli* and gram positive bacteria *Staphylococcus aureus* using penicilin-G, erythromycin, ampicilin, cephalothin, clindamycin, co-trimoxazole and kanamycin as standard using Disk diffusion method. Most of the compounds showed moderate to good activities towards the aforesaid bacteria chosen by using 400 $\mu$g/ml (w/v) in DMSO. Chloro and methoxy substituents usually enhance the activities so much so that they are even comparable to standard drugs used in these

experiments. Compounds such as **6h**, **6j**, **6k**, **7c**, **7e, 7f** and **8g** showed good activities as compared to the standard drugs used.

## Conclusion

The fascinating art of synthetic design for annulations of cyclohexanone with pyrazole, isoxazole and pyrimidine has been successfully explored through Michael addition of spiro diarylidene derivatives with various ambient nucleophiles. In fact, the synthetic precursor for building of the aforesaid heterocycles has been achieved in good yield by successive spirolization of dimedone and diarylidene ketone and subsequent incorporation of exocyclic double bond on cyclohexanone moiety of the spiro hydrocarbon intermediate. All the synthesized compounds have been screened for their antibacterial activity *in vitro* against gram negative bacteria *E. coli* and gram positive bacteria *S. aureus* and some of them exhibit moderate to good activity.

## Experimental

Dibenzalacetone **1a**, 4,4′-dianisalacetone **1b**, 4,4′-dichlorobenzalacetone **1c**, were prepared according to the reported procedures.[16–18]

### *3,3-Dimethyl-7,11-diphenyl spiro[5,5] undecane-1,5,9-trione (3a–c)*

To a solution of dimedone (0.01 mol) and dibenzalacetone (0.01 mol) in rectified spirit, 10 drops of triethanol amine were added. It was refluxed with stirring for 7 h. The reaction mixture was concentrated and cooled. Solids thus separated were filtered, washed with rectified spirit, dried and crystallized from rectified spirit.

### *8,10-Dibenzylidene-3,3-dimethyl-7,11-diphenyl spiro[5,5]undecane-1,5,9-trione (4a–l)*

A mixture of **3a–c** (0.001 mol), benzaldehyde (0.002 mol) and sodium ethoxide (0.002 mol) in ethanol was refluxed for 16 h. The reaction mixture was filtered, while hot and acidified with dil. HCl after cooling it. The solid thus separated was filtered, washed with water, dried and crystallized from ethanol.

### *Synthesis of spiro isoxazolo (5a–l)/spiro pyrazolo (6a–l, 7a–l) [3,4–b] cyclohexane derivatives*

To a mixture of **4a–l** (0.001 mol) and hydroxylamine hydrochloride/hydrazine hydrate/phenylhydrazine (0.001 mol) in ethanol, few drops of KOH/piperidine was added and refluxed for 15–19 h. The reaction mixture was concentrated, cooled and poured into ice cold water. The solid thus separated out was filtered, washed and recrystallized from ethanol.

### *Synthesis of spiro pyrimido[5,6-b] cyclohexane derivatives (8a–l, 9a–l, 10a–l)*

To a refluxing solution of **4a–l** (0.001 mol) and guanidine carbonate/urea/thiourea (0.001 mol) in ethanol (10 mL), few drops of NaOH solution were added and refluxed for 16–18 h. The reaction mixture was cooled and neutralized. The solid product was filtered, washed several times with water and crystallized.

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