SYNTHESIS AND SPECTRAL CHARACTERIZATION OF SOME NEW SUBSTITUTED BIS-SPIROCYCLOHEXANONES DERIVED FROM ACETONE

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ABSTRACT:
Diarylidene acetones (DAA) (1-5) had been prepared by the condensation of acetone with substituted benzaldehydes via Claisen-Schmidt reaction, DAA’s brought to condense with anthrone to afford the title compounds (6-10) through Michael addition. The structures of the products were suggested in the light of spectral data (UV, IR, 1H&13C-NMR).

KEYWORDS: Anthrone, spirocyclohexanones, Michael addition.

1. INTRODUCTION
Baeyer in 1900 was first used the name (Spirocycle) (Rios, 2012). The quaternary carbon center and the presence of two fused rings cause a complexity of these ring structures. Natural Compounds that isolated from different plant sources are found to contain many Spiro cyclic structures (Smith and Baxendale, 2015). Spiro compounds have generated considerable interest in recent years due to their pharmacological activities (Ghandi et al., 2009; Raj and Raghathan, 2003). Many Spiro compounds have been found to show anticancer, narcotic, anti-inflammatory and analgesic properties (Dandia et al, 2006; Sebahar and Williams, 2000; Ma and Hecht, 2004; Kang et al, 2002; Ding et al, 2005). Spiro compounds can be prepared by various methods (Jayashankaran et al, 2005; Khan et al, 2003; Marti and Carreira, 2005; Pearson, 2002; Ungureanu et al, 2001). But the reaction of dibenzalacetone with a compound having active methylene group yielding double Michael adduct would be an interesting subject of investigation. Aggarwal and co-worker carried out the reaction of dibenzylidene acetone and N,N-dimethyl barbituric acid in ethylene glycol (Aggarwal and Vij, 2014).

The reaction of dibenzylidene acetone and N,N-sub. barbituric acid.

Treatment of barbituric acid with dibenzylidene acetone in presence of ammonium acetate as a basic medium afforded a mixture of products (Assy et al, 2015).

Wang and co-worker have developed a methodology for the construction of spiro[cyclohexanone-oxindoles] through cascade [5+1] Michael/Michael addition reactions between divinyl ketones and N-protected oxindoles catalyzed by combinations of cinchona-based chiral primary amines and α-amino acid derivatives. The final products were obtained with good diastereoselectivities and enantioselectivities (Wu et al, 2012).

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The reaction between divinyl ketones and N-unprotected oxindoles catalyzed by combinations of cinchona-based chiral primary amines and ω-amo acid derivatives.

It had been witnessed in the last decade a growth of RCM (Rearranged Claisen-Michael) reaction as one of the powerful synthetic tools in organic synthesis (Grubbs and O’Leary, 2015). Its use in the synthesis of Spiro systems, however, was under-exploitation. It was found that there are very few reports on the synthesis of Spiro cyclic compounds based on RCM reaction. It was conceived that a combination of Claisen rearrangement and RCM reaction-based methodology developed (Srikrishna and Vasantha Lakshmi, 2005). In the present work a new class of Spiro compounds, bis-spiro-cyclohexane with different substituted aryl group, are prepared by Michael reaction of diaryldiene acetones with active methylene compound (Anthrone). The products of these reactions are of interest in terms of their stereochemistry and as starting materials for the synthesis of compounds with expected biological activity.

2. EXPERIMENTAL

2.1 Materials

Melting points were measured on Gallenkamp and uncorrected. UV-spectra were displayed using UV-visible spectrophotometer (1650-PC). IR spectra were recorded on FT-IR-600 Fourier-Transform infrared spectrophotometer. $^1$H-NMR spectra were recorded by Bruker spectrometer (400 MHz), using TMS as an internal standard and CDCl$_3$ / D$_2$O-DMSO as solvents. $^{13}$C-NMR spectra were taken on Bruker spectrometer (75.5 MHz).

Condensation of acetone with benzaldehyde and substituted benzaldehydes

The steps of the original procedure had been followed to get diaryldiene acetones compared with the authentic samples showing a good agreement of their physical properties and spectral data. m.p. =38-40 °C, UV (CHCl$_3$, $\lambda_{max}$= 292nm), IR(KBr, $\nu$ cm$^{-1}$): 1666(C=O), 1612 (C=C), 1450 (C==O).

Condensation of diaryldiene acetones with different benzaldehydes (Al-Hamdany et al, 2014).

To a cold stirred mixture of the substituted benzaldehydes (0.03 mole) and diaryldiene acetone (0.03 mole) in 50 ml absolute ethanol, 1 gm of potassium hydroxide was added in small portion to the mixture in a period of 15 min. The stirring was continued for additional 1 h. at room temperature. The resulting precipitate was then filtered off, washed with a little amount of cold ethanol and recrystallized from ethanol to get a solid product (1,3-dibenzyldiene acetone). Some physical properties and spectral data were illustrated in Tables (I, III, IV and V).

Table 1. Some physical properties of 1,3-diaryldiene acetones

| Comp. No. | X | Y | Name of compound | Color | m.p. (°C) | Yield (%) |
|-----------|---|---|------------------|-------|-----------|-----------|
| 1 | H | H | 1,5-diphenyl|penta-1,4-dien-3-one | Yellow | 99-100 | 50 |
| 2 | Cl | 4-Br | 1-(4-bromophenyl)-5(2-chlorophenyl) penta-1,4-dien-3-one | Pale Yellow | 174-175 | 25 |
| 3 | 4-Br | 4-MeO | 1-(4-methoxyphenyl)-5(4-bromophenyl) penta-1,4-dien-3-one | Yellow | 178-180 | 50 |
| 4 | H | 3-NO$_2$ | 1-(3-nitrophenyl)-5-phenylpenta-1,4-dien-3-one | Pale Yellow | 130-132 | 90 |
| 5 | 4-Br | 4-Br | 1,5-bis(4-bromophenyl) penta-1,4-dien-3-one | Pale Yellow | 180-181 | 50 |

Condensation of Anthrone with DAA (Hussein, 2016).

A mixture of DAA (0.01 mole) and anthrone (0.01 mole) was magnetically stirred in the presence of 3ml of 50% NaOH in absolute ethanol. The stirring was continued for 2 hrs. at 50 °C in 10 ml DMSO. Some physical properties and spectral data were illustrated in Tables (II, VI, VII, and VIII).
The acidic protons of acetone had been used to get a condensation product by the addition of one mole of benzaldehyde or substituted benaldehydes to afford arylidene acetone as shown below (Fig. 8):

The condensation of Acetone with Benzaldehyde.

The condensation of arylidene acetones with another mole of the same or different substituted benzaldehydes gave diarylidene acetones DAA(1-5) as shown on (Fig. 9):

The condensation of Arylidene Acetones with Benzaldehydes.

The spectral data (FTIR, U.V., ¹H-NMR and ¹³C-NMR) of DAA compounds, which prepared from the condensation between Arylidene Acetones with Benzaldehydes, were consistent with the structures of (1-5), Tables (III, IV and V).

### Table 2. Some physical properties of spirocyclohexanones

| Comp No. | X  | Y   | Name of compound                        | Color    | m.p. (°C) | Yield (%) |
|----------|----|-----|-----------------------------------------|----------|-----------|-----------|
| 6        | H  | H   | 3,5-Diaryl/cyclohexane spiro [4,9'] anthrone | Pale paige | 143-146   | 60        |
| 7        | 2-Cl | 4-Br | 3-(4-Bromophenyl)-5-(2-chlorophenyl) cyclohexanone [4][Spiro[9] anthrone | Pale orange | 133-134 | 40        |
| 8        | 4-Br | 4-MeO | 3-(4-bromophenyl)-5-(4-methoxyphenyl) cyclohexanone [4][Spiro[9] anthrone | Dark paige | 166-167 | 11        |
| 9        | H   | 3-Nitro | 3-(phenyl)-5-(3-nitrophenyl)cyclohexanone [4][Spiro[9] anthrone | Brown   | 170-172 | 75        |
| 10       | 4-Br | 4-Br | 3,5-Di-(4-bromophenyl)cyclohexanone Spiro[4,9'] anthrone | Paige | 137-139 | 14        |

### Table 3. Spectral data (FTIR, U.V.) of 1,3-diarylidene acetones

| Comp. No. | U.V. CHCl₃ nm | FTIR (KBr) cm⁻¹ |
|-----------|---------------|-----------------|
|           | C=O | C=C | C=O |
| 1         | 320 | 1651 | 1446 | 1626 |
| 2         | 340 | 1653 | 1490 | 1618 |
| 3         | 336 | 1650 | 1510 | 1593 |
| 4         | 318 | 1668 | 1589 | 1624 |
| 5         | 334 | 1649 | 1487 | 1624 |

### Table 4. Spectral data (¹³C-NMR) of 1,3-diarylidene acetones

| Comp. No. | C-2, C-4 | C-1, C-5 | C=O | Ar-C ppm |
|-----------|----------|----------|-----|----------|
| 1         | 131      | 152      | 188 | 127-129  |
| 2         | 130      | 151      | 188 | 127-132  |
| 3         | 130      | 152      | 188 | 115-132  |
| 4         | 132      | 153      | 188 | 126-130  |
| 5         | 131      | 151      | 188 | 122      |

### Table 5. Spectral data (¹H-NMR) of 1,3-diarylidene acetones

| Comp. No. | H-2 | H-4 | H-1 | H-5 | H-8 ppm |
|-----------|-----|-----|-----|-----|---------|
| 1         | 6.7d (1H) | 7.1d (1H) | 7.9d (1H) | 7.7d (1H) | 7.2-7.4m (1H) |
| 2         | 6.7d (1H) | 7.1d (1H) | 8.1d (1H) | 7.8d (1H) | 7.2-7.4m (8H) |
| 3         | 7.1d (2H) | 7.7d (2H) | 6.8-7.5m (8H) |
| 4         | 7.1d (1H) | 7.4d (1H) | 7.7d (1H) | 7.8d (1H) | 7.2-8.3m (8H) |
Michael Condensation of Anthron with DAA.

The FT-IR spectrum of products (spiro cyclohexanone 6-10) manifests a strong absorption band at (1715 cm⁻¹) corresponds to stretching vibration of carbonyl group compared with corresponding 1,3-diaryliden acetones compounds (1653 cm⁻¹) (Table III). This difference may be attributed to the absence of the conjugation and cyclization. Another absorption band appeared at (1606 cm⁻¹) related to the stretching vibration of aromatic ring. The U.V. spectra showed wavelengths at maximum absorption (λmax) 332-386 nm (Table VI).

The ¹H-NMR for compound 6 as a representative model for the series showed a doublet signal for 4H resonates at δ 2.7 ppm for H-2 & H-6, while a triplet signal displayed at δ 3.6 attributed to 2H of H-3 and H-5. The aromatic 18H seemed as a multiplet signal at 7.13 - 7.87. ¹³C-NMR showed a signal at δ 45 for C-2 and C-6, δ 40 for C-3 and C-5, δ 56 for C-4, but a signal at δ 190 related to C=O of anthrone, finally δ 212 belongs to C=O of C-1, Tables (VII and VIII).

Table 5. spectral data (flr, uv) of spirocyclohexanones

| Comp. No. | U.V. CHCl₃ nm | FTIR (KBr) cm⁻¹ | C=O | C=C
|-----------|---------------|-----------------|------|------|
| 6         | 332           | 1639            | 1601 |      |
| 7         | 386           | 1715            | 1606 |      |
| 8         | 340           | 1637,1710       | 1616 |      |
| 9         | 344           | 1637            | 1616 |      |
| 10        | 382           | 1637,1710       | 1618 |      |

Table 6. spectral data (¹³C-NMR) of spirocyclohexanones

| Comp. No. | C-2, C-6 | C-3, C-5 | C-4 | C=O of Anthrone | C=O of Cyclohexanone |
|-----------|----------|----------|-----|-----------------|---------------------|
| 6         | 45, 40   | 56       | 190 | 212             |                     |
| 7         | 44, 46   | 41, 36   | 58  | 191             | 213                 |
| 8         | 44, 40   | 54       | 188 | 210             |                     |
| 9         | 44, 39   | 56       | 192 | 211             |                     |
| 10        | 45, 41   | 57       | 190 | 212             |                     |

The suggested mechanism for the reaction of (DAA) and anthrone to produce the expected final spiro product.

The prepared DAA’s (1-5) had been condensed with anthrone in a strong basic medium to afford the title compounds (6-10) as shown in Fig. 10. below:

![Structure of the first anion.](image)

Structure of the first anion.

The anion may attack the β-carbon via Michael addition to afford M1, which may lose another acidic proton under the strong basic conditions to afford the second anion, fig. 12, which in turn may attack the β’-carbon via intramolecular Michael addition to produce the expected final spiro product.
4. CONCLUSION

The two acidic protons of anthrone were the basis of the reaction, i.e. under strong basic conditions these protons will be abstracted to afford the corresponding carbanions which act as nucleophiles added as intermolecular Michael addition to DAA’s to give the Spiro products.

REFERENCES

A. A. Raj, and R. Raghathan, “Synthesis of spiropyrrolidine via formal [3,2]cycloaddition of unusual enones and cis 3-benzo 1-1-cyclohexy 1-2- phenylaziridine,” Tetrahedron, vol. 59, pp. 2907-2911, 2003.

A. Dandia, R. Singh, S. Khaturia, C. Merienne, G. Morgant, and A. Loupy, “Efficient microwave enhanced regioselective synthesis of a series of benzimidazolyl/triazolyl spiro[indole-hiazolidinones] as potent antifungal agents and crystal structure of spiro[3H-indole-3,2'-thiazolidine]-3'(1,2,4-triazol-3-yl)-2,4'(1H)-dione,” Bioorg. Med. Chem., vol. 14, pp. 2409–2417, 2006.

A. J. Al-Hamdany, M. S. Al-Jawady, R. A. Saeed, “Synthesis and Spectral Characterization of Some Pyrimidinones,” Raf. J. Sci., vol. 25(3), pp. 16-23, 2014.

A. Scala, M. Cordaro, G. Grassi, A. Piperno, and G. Barberi, “Direct synthesis of C3-mono-functionalized oxindoles from N- unprotected 2-oxindole and their antileishmanial activity,” Bioorg. & Med. Chem., vol. 22, pp.1063–1069,2014.

A. Srikrishna and B. Vasantha Lakshmi, “Construction of vicinal quaternary carbon atoms by Ireland ester Claisen rearrangement: total synthesis of (±)-herbertenolide, (±)-herberteneacetal, (±)-herbertene-1,14-diol and (±)-herbertene-1,15-diol,” Tetrahedron Lett., vol. 46, pp. 4879 , 2005.

B. Wu, J. Chen, M. Li, J. Zhang, and X. Wang, “Highly Enantioselective Synthesis of Spirocyclohexane-one-oxindoles and Spirocyclohexanolone-pyrazolones by Asymmetric Cascade [5+1] Double Michael Reactions,” Eur. J. Org. Chem., pp.1318–1327, 2012.

Ch. Marti and E. Carreira, “Total Synthesis of (±)-Spirotryprostatin B: Synthesis and Related Studies,” J. Am. Chem. Soc., vol. 127, pp.11505-11515, 2005.

I. Ungureanu, Ph. Klotz, A. Schoenfelder and A. Mann,” 2-Phenyl-N-tosylazetidine as a formal 1,4 dipole precursor,” Chem. Commun., pp. 958-959, 2001.

J. Jayashankanran, R. D. R. S Manian, and R. Raghathan, “A facile entry into a novel class of dispiroheterocycles through 1,3dipolar cycloaddition,” Arkivoc, vol. 11, pp. 32-39, 2005.

J. Ma, and S.M. Hecht, “Javaniside, a novel DNA cleavage agent from Alangium javanicum having a unusual oxindole skeleton,” Chem. Commun., pp. 1190–1191, 2004.

K. Aggarwal, and K. Vij, “An efficient catalyst free synthesis of nitrogen containing spiro heterocycles via [5 + 1] double Michael addition reaction,” RSC Adv., vol. 4, pp. 13313, 2014.

K. Ding, Y. Lu, N.Z. Coleska, S. Qiu, and Y. Ding, “Structure-Based Design of Potent Non-Peptide MDMZ Inhibitors” J. Am. Chem. Soc., vol. 127, pp. 10130–10131, 2005.

L. K. Smith, and I. R. Baxendale, “Total syntheses of natural products containing spirocarbocycles,” Org. Biomol. Chem., vol. 13, pp. 9907, 2015.

M. G. Assy, E. K. Mohamed, and A. S. Mohamed, “Heterocyclization of barbituric acid: Synthesis of novel condensed pyrimidines Reda A. Haggam,” Inter. J. of Adv. Res., vol. 3, pp. 692-698, 2015.

M. Ghandi, A. Yari, S. Jamal, and A. Taheri, “Synthesis of novel spiropyrrolidine through 1,3-dipolar cycloaddition,” Tetrahedron Lett., vol. 50, pp. 4724-472, 2009.

M. S. Hussein, “Synthesis, Characterization and Antibacterial Evaluation of Some Substituted Pyrrolidines,” Chem. Sci. Intern. J., vol 17(2), pp. 1-8, 2016.