JOTCS A
Journal of the Turkish Chemical Society
Section: A
Chemistry
TURKISH CHEMICAL SOCIETY

MODIFICATION OF NOVEL ISOXAZOLINES OF FULVENE DERIVATIVES WITH 1,3-DIPOLAR CYCLOADDITION REACTION

Omer T. Gunkara

Department of Chemistry, Faculty of Science and Arts, Yildiz Technical University, Davutpasa Campus, Istanbul, Turkey.

Abstract: In this work, 1,3-Dipolar cycloaddition reactions were studied to synthesize fulvene derivatives containing isoxazoline groups in good yields. 1,3-Dipolar cycloaddition reactions are among the most useful strategies for the preparation of organic compounds. All newly synthesized fulvene compounds were structurally characterized by FTIR, 1H, 13C NMR and GC/MS analyses.

Keywords: 1,3-Dipolar cycloaddition, Cycloaddition, Fulvenes, Heterocycles, Isoxazoles.

Submitted: November 19, 2018. **Accepted:** December 04, 2018.

Cite This: Gunkara OT. Modification of Novel Isoxalines of Fulvene Derivatives With 1,3-Dipolar Cycloaddition Reaction. 2018. 5(3):1351-60.

DOI: http://dx.doi.org/10.18596/jotcsa.484885.

***Corresponding author. E-mail:** gunkara@yildiz.edu.tr

INTRODUCTION

The 1,3-dipolar cycloaddition reaction is among the most outstanding method in organic chemistry field (1-3). It involves several dipoles and alkenes to prepare heterocycles in one step (4). The common application of 1,3-dipolar reactions in organic synthesis was first established by the systematic investigations by Huisgen (5). At the same time, the new notion of conservation of orbital symmetry, investigated by Woodward and Hoffmann, appeared in the literature (6, 7). Woodward and Hoffmann's paper was a cornerstone for the understanding of the mechanism of decided 1,3-dipolar cycloaddition chemistry. On the basis of the concept their work have further contributed to our comprehension and ability to foresee the reactivity and regioselectivity of 1,3-dipolar cycloaddition reactions (8-10).

Since their discovery in 1900, fulvenes and their analogues have collected considerable attention from scientists and industry because of their unusual features in the fields of organic chemistry, medicinal chemistry, and materials science (11-20). Fulvenes have found common use as building blocks in the preparation of natural products such as hinesol, capnellene, silphinene, hirsutene and viburtinal. They are traditionally prepared by the condensation reaction of cyclopentadienes with aldehyde or ketones, a preparation procedure which is typically limited by the availability of the cyclopentadienes, obtained from multistep reactions in which regio-selectivity and substituted group tolerance are often main difficulties.

Cycloadditions of fulvenes (e.g., [4+3], [2+2], [4+2], [2+4], [6+4], [6+2], [6+3] (21-23)) provide multiple and powerful procedures to

multifarious heterocyclic systems and natural products.

In our times, cancer has increasingly become the first reason of death over the world and seriously affecting the health of humans for a long time. All efforts have been made to find some drugs against cancer cell in the last decade as a result of research in molecular biology leading to the development of anticancer drugs capable of targeting the cancer cells with minimum side effects. Natural products have noticeably promoted to the development of a great number of potent anticancer agents. Nearly 50% of all anticancer drugs verified internationally are either natural products or natural product analogues and were prepared on the basis of the knowledge acquired from small or macromolecules existing in nature (24).

In the last decade, several azole analogues have attracted huge attention in the field of anticancer drug investigation (25, 26). Among them, isoxazoline derivatives are an important class of five membered heterocyclic rings that exhibited promising biological activities. The common chemical formula of isoxazoline ring is shown in Figure 1.

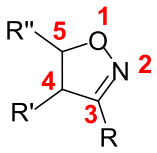


Figure 1: Chemical structure of isoxazoline.

There is too many biologically active isoxazoline derivative examples in the literature. For example, 3,5-diaryl-isoxazoline-attached 2,3-dihydroquinazolinone hybrid (27) 1 and arylisoxazoline containing anthranilic diamide derivatives 2 (28), (Figure 2) are natural products which have got anticancer agent potential.

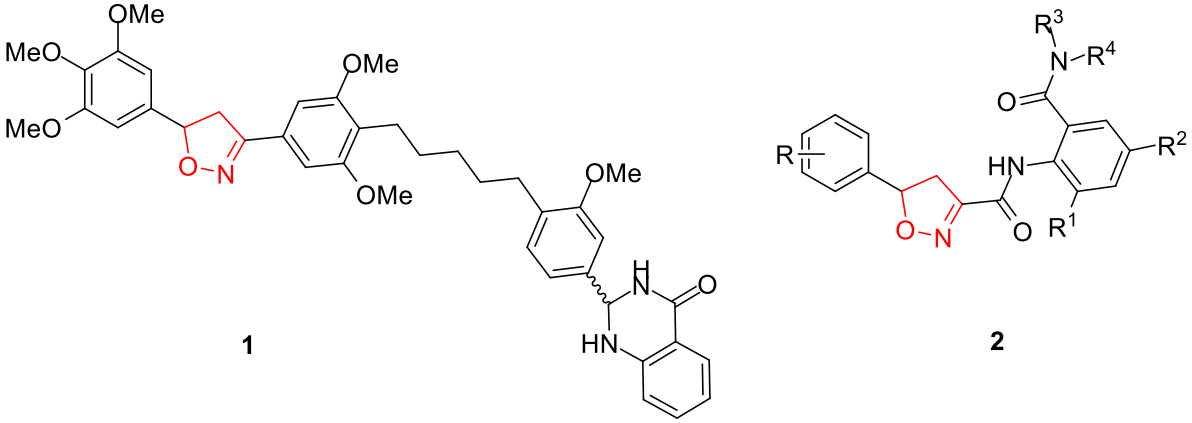
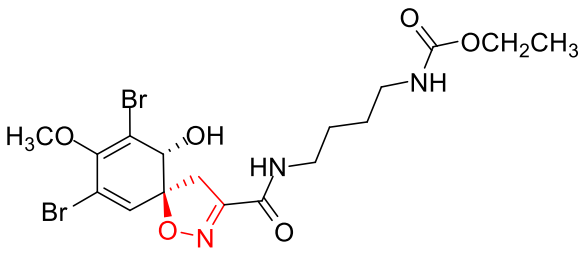


Figure 2: Chemical structures of 2,3-dihydroquinazolinone hybrid 1 and anthranilic diamide derivatives 2.

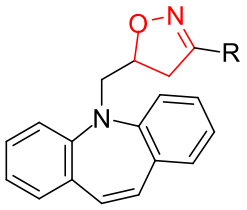
And also the other example of isoxazoline derivative is (+)-subereamolline A 3. It shows inhibition to the migration and invasion of metastatic human breast cancer cells at the minimum dosage level (29) (Figure 3).



3

Figure 3: Chemical structures of (+)-subereamolline A.

Dibenzo[b,f]azepine-tethered isoxazoline analogues 4 (30) that show anticancer activity with an improved pharmacokinetics profile (Figure 4).



4

Figure 4: Chemical structures of dibenzo[b,f]azepinetethered isoxazoline analogues.

Because of these reasons, the preparation of isoxazoline heterocycles continues to attract the considerable attention of synthetic organic and medicinal scientists. Viewing the importance of natural products as well as isoxazoline containing pharmacophore in the field of cancer research, I am focused on synthesis fulvene derivatives which have got isoxazoline heterocycles showing anticancer activity.

EXPERIMENTAL

Materials and Methods

All reactants and reagents were commercially available and used without further purification. Thin-layer chromatography (TLC) on silica gel GF 254 was used to control reaction progress. A Gallenkamp digital thermometer was used to determine melting points of all solid compounds. IR spectra were recorded on a Perkin Elmer FT-IR spectrometer. ^{1}H and ^{13}C NMR spectra were obtained with a Bruker Avance III-500 MHz NMR system. Chemical shifts were reported in parts per million (ppm) with respect to internal standard TMS. Peak multiplicities are designated by the following abbreviations: s, singlet; d, doublet; dd, double doublet; t, triplet; dt, double triplet; m, multiplet; br, broad. Mass spectral studies were performed on an Agilent 6890N/5973 GC/IMSD system.

Synthesis and Characterization

Procedure for the synthesis of (Cyclopenta-2,4-dienylidenemethylene)dibenzene 1(31): NaOMe (540 mg, 10 mmol), ethanol (10 mL), and benzophenone (1.86 g, 10 mmol) were added to a reaction flask. Cyclopentadiene (1.6 mL, 20 mmol) was added to the reaction flask, giving a red solution. After stirring for 7 days, the orange crude solid was filtered and rinsed with 5 mL of ethanol. The crude product was refluxed in 10 mL of methanol for 1 h. After cooling to the room temperature, the solid was filtered, rinsed with 7,5 mL of methanol, and dried in under reduced pressure for 24 h to give the product as an range solid 136.18 g (86.2%). MS (GC-MS): $C_{18}H_{14}$, m/z 230.3 (M^{+}).

Procedure for the synthesis of 2-(cyclopenta-2,4-dien-1-ylidenemethyl)-1,4-dimethoxybenzene 2 (32): 0.330 g (5 mmol) of freshly distilled cyclopentadiene was dissolved 5 mL of methanol, then 0.213 g (3 mmol) of pyrrolidine was added to the reaction mixture. Then, 0.332 g of (2 mmol) 2,5-dimethoxybenzaldehyde was added slowly to the reaction flask. The solution was stirred under nitrogen atmosphere at room temperature for 6 h. 0.18 g of glacial acetic acid was added to the reaction mixture. The mixture was diluted with 20 mL of diethyl ether, the layers were separated, and the organic layer was washed

with water (2 x 15 mL). The organic phase was dried over Na_2SO_4, filtered and concentrated. The red oil was obtained after purification with column chromatography on silica gel. Yield: %78. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.81 (s, 3OCH_3), 3.83 (s, 3OCH_3), 6.38-6.35 (m, 1=CH), 6.54-6.51 (m, 1=CH), 6.66-6.65 (t, J=3.19, 2=CH), 6.93-6.82 (m, 2CH), 7.18-7.14 (d, J= 2.87, 1CH), 7.53 (s, 1CH) ppm. MS (GC-MS): $C_{14}H_{14}O_2$ m/z 214 (M^+).

General procedure for the synthesis of oxime derivatives 3-5: Oxime derivatives were prepared with an aldehyde, hydroxylamine hydrochloride, and sodium carbonate in ethyl alcohol at room temperature with the known procedure (50-51). A solution of hydroxylamine hydrochloride (0.417 g, 6 mmol) in water (0.5 mL) and a solution of Na_2CO_3 in water (1.5 mL) were added drop wise to the solution of an aldehyde (2 mmol) in EtOH (1.5 mL), respectively. Resulting solid was filtered and purified by recrystallization from alcohol. Oxime derivatives (3-5) were obtained in almost quantitative yields.

4-Chlorobenzaldehyde oxime 3 (33): White solid, yield 100%, m.p. 92-94ºC, Rf: 0.52 (1:2 ethyl acetate/n-hexane), FT-IR (ATR) 3301 (OH), 1589 (C=N), 1496 (C-N), 971 (C-H), 694 (C-Cl) cm^{-1}, GC-MS (EI), m/z (%): 155 (M^+·, 99), 139 (100), 136 (82), 111 (73), 75 (70).

4-Bromobenzaldehyde oxime 4 (33): Yellow solid, yield 100%, m.p. 106-108ºC Rf: 0.45 (1:2 ethyl acetate/n-hexane), FT-IR (ATR) 3310 (OH), 1590 (C=N), 1470 (C-N), 960 (C-H), cm^{-1}, GC-MS (EI), m/z (%): 200 (M^+·, 70), 185 (30), 92 (40), 155 (70), 74 (100).

2,4-Dimethoxybenzaldehyde oxime 5 (34): White solid, Yield 94%, m.p. 103-105ºC, FT-IR (KBr pellet) 2944, 1610, 1504, 1466, 1414, 1270, 1206, 1112, 1026, 922, 832 cm^{-1}, ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.73 (1H, s, CH=N-OH), 7.0 (1H, d, J = 8.5 Hz, Ar-H), 6.03 (1H, s Ar-H), 6.06 (1H, d, J = 8.5 Hz, Ar-H), 3.6 (6H, s, 2xOCH3) ppm, calcd for [$C_9H_{11}NO_3$] C 59.66 H 6.11 N 7.70%, found C 60.01 H 6.19%.

General procedure for the synthesis of compound 6-9: The (cyclopenta-2,4-dienylidenemethylene)dibenzene 1 (0.203 g, 1 mmol) and compound 3-4 (p-chlorobenzaldehyde oxime or p-bromobenzaldehyde oxime, respectively) (1 mmol) were dissolved in CH_2Cl_2 (8 mL). A solution of NaOCl (1.2 mL) was added slowly to the reaction mixture at 0 °C. The reaction mixture was stirred at 0 °C overnight. The progress of the reaction was monitored using TLC. After completion of the reaction, the mixture was extracted with CH_2Cl_2 (3x10 mL). The organic phase was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography.

3-(4-Chlorophenyl)-6-(diphenylmethylene)-6,6a-dihydro-3aH-cyclopenta[d]isoxazole 6: White solid, Yield 52%, m.p. 204-207 ºC, FT-IR (ATR) 3055 (Aromatic CH), 2952 (Aliphatic CH), 1595 (Aromatic C=C), 1179 (C-O), 1090 (C-N), 828, 827, 700, 677. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.64 (d, J= 6.8 Hz, 2H, Ar-H), 7.42 (d, J= 6.8 Hz, 2H, Ar-H), 7.34 (d, J= 8.8 Hz, 2H, Ar-H), 7.23-7.31 (m, 6H, Ar-H), 7.15 (d, J= 8.8 Hz, 2H, Ar-H), 6.37 (dd, J= 5.8; 1.9 Hz, 1H, =CH), 6.00 (dd, J= 5.8; 1.9 Hz, 1H =CH), 5.33 (d, J= 7.8 Hz, 1H, CH), 4.62 (dt, J= 7.8; 4.8 Hz, 1H, CH) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz) δ 155.7 (Cq), 141.9 (Cq), 141.5 (Cq), 140.8 (2xCq), 136.3 (2xCq), 134.5 (2xCAr), 131.3 (2xCAr), 130.3 (2xCAr), 130.2 (CAr), 129.4 (CAr), 128.3 (CAr), 128.20 (2xCAr), 128.18 (CAr), 128.11 (2xCAr), 128.07 (CAr), 127.8 (CAr), 86.2 (O-CH), 58.9 (C-CH) ppm. MS (GC-MS): $C_{25}H_{18}ClNO$, m/z 383 (M^+).

3-(4-Chlorophenyl)-4-(diphenylmethylene)-4,6a-dihydro-3aH-cyclopenta[d]isoxazole 7: White solid, Yield 24%, m.p. 160-162ºC, FT-IR (ATR) 3071 and 3021 (Aromatic CH), 2938 and 2850 (Aliphatic CH), 1583 (Aromatic C=C), 1488, 1442, 1287 (C-O), 1087 (C-N), 828, 830, 698, 680. ^{1}H NMR ($CDCl_3$, 500 MHz) 7.15-7.23 (m, 6H, Ar-H), 6.87-6.93 (m, 6H, Ar-H), 6.70 (d, J= 8.8 Hz, 2H, Ar-H), 6.49 (d, J= 5.8 Hz, 1H, =CH), 6.05 (dd, J= 5.8; 1.9 Hz, 1H, =CH), 5.84 (dd, J= 7.8; 1.9 Hz, 1H CH), 5.31 (d, J= 7.8 Hz, 1H, CH) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz) δ 157.0 (Cq), 141.2 (Cq), 140.8 (Cq), 140.7 (Cq), 137.9 (Cq), 137.5 (2xCq), 135.4 (2xCAr), 133.8 (2xCAr), 133.5 (2xCAr), 129.1 (2xCAr), 128.8 (CAr), 127.8 (2xCAr), 127.4 (CAr), 127.3 (CAr), 127.1 (CAr), 126.9 (CAr), 126.5 (CAr), 87.1 (O-CH), 52.8 (C-CH) ppm. MS (GC-MS): $C_{25}H_{18}ClNO$, m/z 383 (M^+).

3-(4-Bromophenyl)-6-(diphenylmethylene)-6,6a-dihydro-3aH-cyclopenta[d]isoxazole 8: White solid, Yield 53%, m.p. 124-128ºC, FT-IR (ATR) 3050 and 3021 (Aromatic CH), 2962 (Aliphatic CH), 1595 (Aromatic C=C), 1158 (C-O), 1088 (C-N), 830, 825, 700, 675. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.62 (d, J= 6.9 Hz, 2H, Ar-H), 7.45 (d, J= 6.9 Hz, 2H, Ar-H), 7.32 (d, J= 8.8 Hz, 2H, Ar-H), 7.20-7.27 (m, 6H, Ar-H),

7.12 (d, J= 8.8 Hz, 2H, Ar-H), 6.35 (dd, J= 5.9; 2.0 Hz, 1H, =CH), 6.00 (dd, J= 5.9; 2.0 Hz, 1H =CH), 5.30 (d, J= 7.9 Hz, 1H, CH), 4.58 (dt, J= 7.9; 4.7 Hz, 1H, CH) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz) δ 156.7 (Cq), 141.8 (Cq), 140.7 (2xCq), 139.9 (Cq), 136.1 (2xCq), 134.0 (2xCAr), 131.5 (2xCAr), 130.3 (CAr), 130.2 (2xCAr), 130.0 (CAr), 128.7 (CAr), 128.3 (CAr), 128.2 (CAr), 128.1 (2xCAr), 128.0 (CAr), 127.5 (2xCAr), 86.0 (O-CH), 57.7 (C-CH) ppm. MS (GC-MS): $C_{25}H_{18}BrNO$, m/z 427 (M^+).

3-(4-Bromophenyl)-4-(diphenylmethylene)-4,6a-dihydro-3aH-cyclopenta[d]isoxazole 9: White solid, Yield 18%, m.p. 190-192ºC, FT-IR (ATR) 3051 and 3021 (Aromatic CH), 2940 and 2848 (Aliphatic CH), 1580 (Aromatic C=C), 1480, 1440, 1285 (C-O), 1076 (C-N), 832, 830, 705, 695. ^{1}H NMR ($CDCl_3$, 500 MHz) 7.21-7.29 (m, 6H, Ar-H), 6.90-6.96 (m, 6H, Ar-H), 6.75 (d, J= 8.9 Hz, 2H, Ar-H), 6.42 (d, J= 5.8 Hz, 1H, =CH), 6.10 (dd, J= 5.8; 1.7 Hz, 1H, =CH), 5.80 (dd, J= 8.1; 1.7 Hz, 1H CH), 5.28 (d, J= 8.1 Hz, 1H, CH) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz) δ 157.0 (Cq), 141.2 (2xCq), 140.8 (Cq), 137.9 (Cq), 137.5 (Cq), 136.0 (Cq), 135.4 (2xCAr), 133.8 (2xCAr), 133.5 (2xCAr), 129.1 (CAr), 128.8 (2xCAr), 127.8 (2xCAr), 127.4 (CAr), 127.3 (CAr), 127.1 (CAr), 126.9 (CAr), 126.5 (CAr), 87.1 (O-CH), 52.8 (C-CH) ppm. MS (GC-MS): $C_{25}H_{18}BrNO$, m/z 427 (M^+).

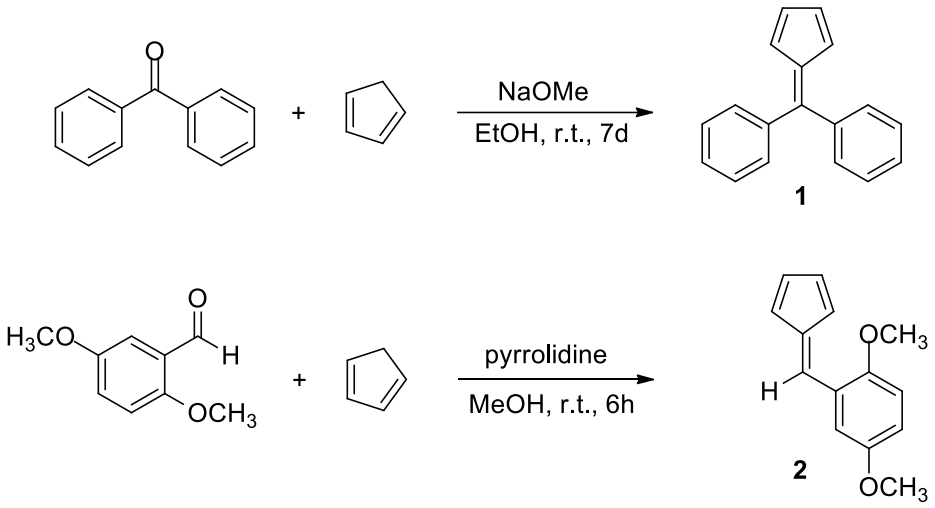
Procedure for the synthesis of compound 10: The 2-(cyclopenta-2,4-dien-1-ylidenemethyl)-1,4-dimethoxybenzene 2 (0.214 g, 1 mmol) and 2,4-dimethoxybenzaldehyde oxime (0.181 g, 1 mmol) was dissolved in CH_2Cl_2 (1 mL). A solution of NaOCl (1.2 mL) was added slowly to the reaction flask at 0 °C. The reaction mixture was stirred at 0 °C overnight. The progress of the reaction was monitored using TLC. After completion of the reaction, the mixture was extracted with CH_2Cl_2 (3x10 mL). The organic phase was dried over Na_2SO_4, filtered, and concentrated. The crude product purified by column chromatography.

(E)-6-(2,5-Dimethoxybenzylidene)-3-(2,5-dimethoxyphenyl)-6,6a-dihydro-3aH-cyclopenta[d]isoxazole 10: White solid, Yield 25%, m.p. 174-176ºC, FT-IR (ATR) 3071 and 3021 (Aromatic CH), 2927 (Aliphatic CH), 1493, 1316, 1287 (C-O), 1087 (C-N), 873 cm^{-1}. ^{1}H NMR ($CDCl_3$, 500 MHz) 7.32 (d, J= 8.9 Hz, 1H, Ar-H), 6.80-6.95 (m, 5H, Ar-H), 6.60 (s, 1H, =CH), 6.10 (dd, J= 5.8; 1.7 Hz, 1H, =CH), 5.65 (dd, J= 5.8; 1.7 Hz, 1H, =CH), 5.20 (d, J= 8.1 Hz, 1H, CH), 4.62 (m, 1H, CH) 3.40 (s, 6H, OCH_3), 3.38 (s, 6H, OCH_3) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz) δ 153.0 (Cq), 152.6 (Cq), 152.4 (Cq), 151.8 (Cq), 151.5 (Cq), 151.3, 140.1, 131.2, 124.6, 118.2 (CAr), 117.6 (CAr), 115.9 (Cq), 115.4 (CAr), 115.2 (CAr), 114.5 (CAr), 114.3 (CAr), 111.5 (CAr), 68.3 (O-CH), 56.2 (OCH_3), 55.8 (2xOCH_3), 55.7 (OCH_3), 42.9 (C-CH) ppm. MS (GC-MS): $C_{23}H_{23}NO_5$, m/z 393 (M^+)

RESULT AND DISCUSSION

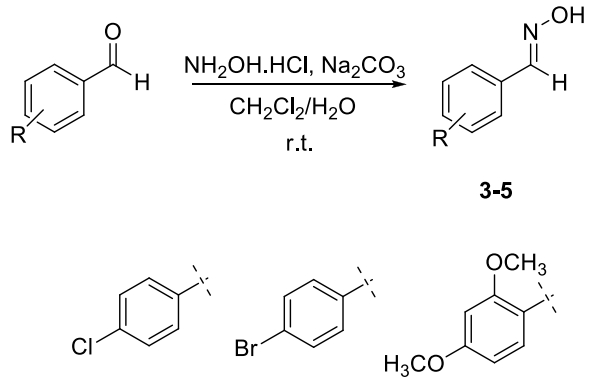
The present paper shows my work employing the reaction of various oxime derivatives that are reacted with fulvene derivatives in the presence of NaOCl.

My first key intermediate was the (cyclopenta-2,4-dienylidenemethylene)dibenzene 1 which was easily prepared from benzophenone and cyclopentadiene (36). It was recrystallized from hot ethanol and characterized by recording its spectral data. My other key intermediate was the 2-(cyclopenta-2,4-dien-1-ylidenemethyl)-1,4-dimethoxybenzene 2 which was easily obtained with a known procedure (32) (Scheme 1). It was purified with column chromatography.



Scheme 1: Synthesis of fulvene derivatives 1-2

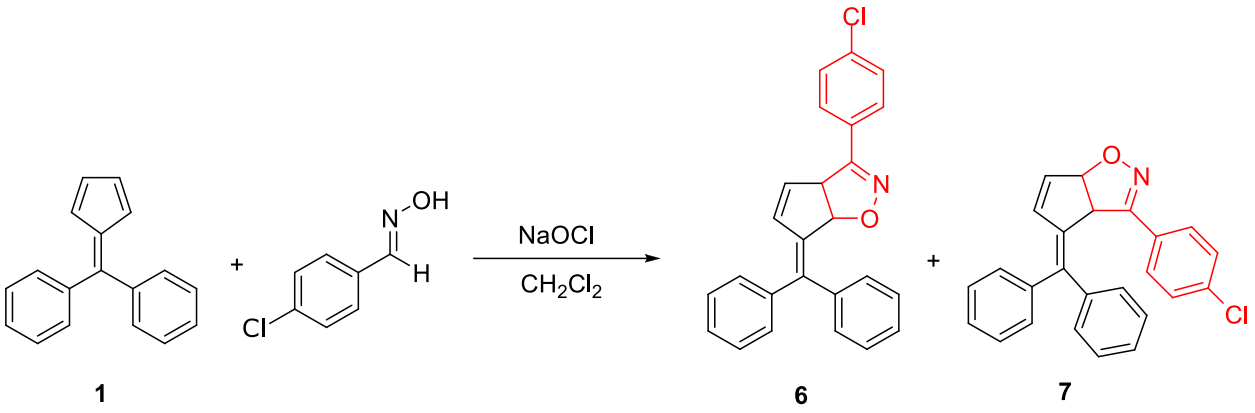
My goal is to prepare new fulvene derivatives with isoxazoline group. Because of this synthetic strategy, I firstly synthesized oxime derivatives 3-5 with known procedure (33, 34) (Scheme 2). Usually, oxime derivatives can be prepared by the reaction of aromatic aldehyde with hydroxyl amine hydrochloride in the presence of a base like sodium carbonate. They were obtained in almost quantitative yields with Na_2CO_3.



Scheme 2: Synthesis of oxime derivatives 3-5.

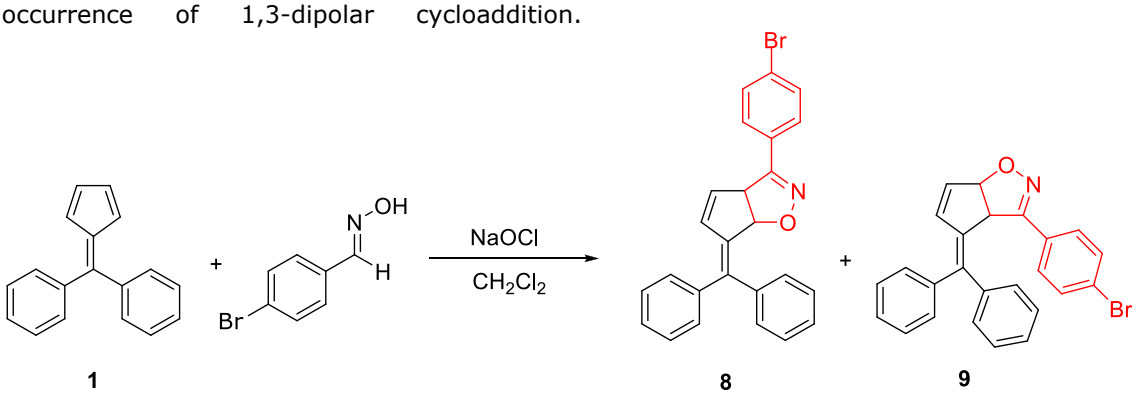
Compound 1 and p-chlorobenzaldehyde oxime 3 were stirred at 0 °C in dichloromethane. Adding NaOCl to the reaction mixture afforded compound 6 and compound 7 (Scheme 3) which were identified on the basis of their spectral analyses. In fact, increasing the reaction temperature from 20 °C in dichloromethane up to 40 °C results in a significant lowering of the yields. Both NMR spectra of compound 6 and 7 consistent with assigned structures.

The ^{1}H NMR spectrum of compound 6 revealed signals at 7.64, 7.42, 7.34, 7.23 and 7.15 ppm due to the presence of fourteen aromatic protons. The analysis of the ^{13}C NMR spectrum revealed that the signal of the alifatic carbons appeared at δ 58.9 ppm.



Scheme 3: Syntheses of compounds 6-7.

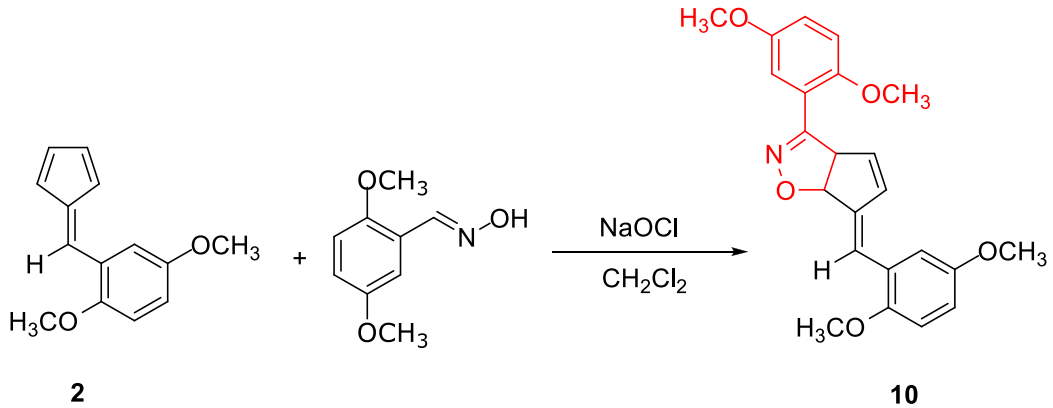
The ^{1}H and ^{13}C NMR spectrum of compound 7 showed the similar results and confirmed the structure of compound 7. The ^{1}H and ^{13}C NMR spectrum of compound 6 and 7 proved the the occurrence of 1,3-dipolar cycloaddition. Compound 7's yield was lower than that of compound 6 yield because of the steric hindrance.



Scheme 4: Synthesis of compound 8-9.

The ^{1} H and ^{13}C NMR spectral data were also similar to those of compound 8, apart from an additional CH at 5.30 and 4.58, an extra aromatic doublet signals at 7.62 and 7.45, and a lack of a cyclopentadiene two =CH protons. The ^{13}C NMR spectrum was also similar to that of compound 8, except two upfield signals of a CH carbons at 57.7.

Indeed, there was no inconsistency between the proposed structure 9 and the spectral data. Compound 9's yield was lower than compound 8's yield because of the steric hindrance.



Scheme 5: Synthesis of compound 10.

Finally, we could obtain the desired compound 10 by the reaction of compound 2 with oxime derivative 5 in dichloromethane in the presence of a small amount of NaOCl. The spectral features of the fulvene analog 10 agree with the structure of the product as summarized in the Experimental Section. As was expected, no significant change was observed at the oxime aromatic ring signals. The ^{1}H NMR spectrum of compound 10 revealed 2 single signals at 3.40 and 3.38 ppm due to the presence of four methoxy groups. And also the ^{13}C NMR spectrum of compound 10 revealed signals at 56.2, 55.8 and 55.7 due to the methoxy group. Single crystals of the products could not be obtained from any organic solvents, thus no definite structures can be described.

CONCLUSION

In conclusion, I designed and synthesized new fulvene derivatives containing isoxazoline ring as possible anti-cancer agents. I characterized all of the new molecules with ^{1}H NMR, ^{13}C NMR, FTIR and GC-MS spectral data. Compound 9 yield was lower than compound 8 yield because of the steric hindrance. Compound 6 and 7 obtained together with the 52% and 24%, respectively.

Further work toward exploring anticancer activity of all newly synthesized compounds with MTT essay will be forthcoming.

ACKNOWLEDGEMENTS

The author expresses his grateful thanks to late Prof. Dr. Nuket OCAL.

REFERENCES

1. Gothelf KV, Jorgensen KA. Asymmetric 1,3-Dipolar Cycloaddition Reactions. Chem Rev. 1998;98(2):863-910.

2. Pandey G, Banerjee P, Gadre SR. Construction of enantiopure pyrrolidine ring system via asymmetric [3+2]-cycloaddition of azomethine ylides. Chem Rev. 2006;106(11):4484-517.

3. Stanley LM, Sibi MP. Enantioselective copper-catalyzed 1,3-dipolar cycloadditions. Chem Rev. 2008;108(8):2887-902.

4. Adrio J, Carretero JC. Novel dipolarophiles and dipoles in the metal-catalyzed enantioselective 1,3-dipolar cycloaddition of azomethine ylides. Chem Commun (Camb). 2011;47(24):6784-94.

5. Huisgen R, Mloston G, Polborn K. 1,3-Dipolar Activity in Cycloadditions of an Aliphatic Sulfine(,)(1). J Org Chem. 1996;61(19):6570-4.

6. Woodward RB. Recent advances in the chemistry of natural products. Science. 1966;153(3735):487-93.

7. Hoffmann R, Woodward RB. Orbital symmetry control of chemical reactions. Science. 1970;167(3919):825-31.

8. Furukawa M, Sugita M, Kojima Y. Reaction of epoxides. V. 1,3-Dipolar cycloaddition reactions of epoxides with carbon-nitrogen double bond compounds. Chem Pharm Bull (Tokyo). 1974;22(7):1468-76.

9. Kano T, Hashimoto T, Maruoka K. Asymmetric 1,3-dipolar cycloaddition reaction of nitrones and acrolein with a bis-titanium catalyst as chiral Lewis acid. J Am Chem Soc. 2005;127(34):11926-7.

10. Siadati SA, Mahboobifar A, Nasiri R. A theoretical study on the reaction pathways and the mechanism of 1,3- dipolar cycloaddition of vinyl acetylene and methyl azide. Comb Chem High Throughput Screen. 2014;17(8):703-8.

11. Beckhaus R, Lutzen A, Haase D, Saak W, Stroot J, Becke S, et al. A Novel Route to Fulvene Complexes of Titanium-Diastereoselective Complexation of Pentafulvenes to Cyclopentadienyltitanium Fragments. Angew Chem Int Ed Engl. 2001;40(11):2056-8.

12. Bryan CS, Lautens M. A tandem catalytic approach to methyleneindenes: mechanistic insights into gem-dibromoolefin reactivity. Org Lett. 2010;12(12):2754-7.

13. Ye S, Yang X, Wu J. Rapid access to 1-methyleneindenes via palladium-catalyzed tandem reactions of 1-(2,2-dibromovinyl)-2-alkynylbenzenes with arylboronic acids. Chem Commun (Camb). 2010;46(17):2950-2.

14. Ye S, Gao K, Zhou H, Yang X, Wu J. Synthesis of 1-methyleneindenes via palladium-catalyzed tandem reactions. Chem Commun (Camb). 2009(36):5406-8.

15. Abdur Rahman SM, Sonoda M, Ono M, Miki K, Tobe Y. Novel synthesis of bridged phenylthienylethenes and dithienylethenes via

Pd-catalyzed double-cyclization reactions of diarylhexadienynes. Org Lett. 2006;8(6):1197-200.

16. Schmittel M, Vavilala C. Kinetic isotope effects in the thermal C2-C6 cyclization of enyne-allenes: experimental evidence supports a stepwise mechanism. J Org Chem. 2005;70(12):4865-8.

17. Kovalenko SV, Peabody S, Manoharan M, Clark RJ, Alabugin IV. 5-Exo-dig radical cyclization of enediynes: the first synthesis of tin-substituted benzofulvenes. Org Lett. 2004;6(14):2457-60.

18. Bekele T, Christian CF, Lipton MA, Singleton DA. "Concerted" transition state, stepwise mechanism. Dynamics effects in C2-C6 enyne allene cyclizations. J Am Chem Soc. 2005;127(25):9216-23.

19. Clegg NJ, Paruthiyil S, Leitman DC, Scanlan TS. Differential response of estrogen receptor subtypes to 1,3-diarylindene and 2,3-diarylindene ligands. J Med Chem. 2005;48(19):5989-6003.

20. Krief A, Laval AM. Coupling of Organic Halides with Carbonyl Compounds Promoted by SmI(2), the Kagan Reagent. Chem Rev. 1999;99(3):745-78.

21. Hong BC, Shr YJ, Wu JL, Gupta AK, Lin KJ. Novel [6 + 2] cycloaddition of fulvenes with alkenes: a facile synthesis of the anislactone and hirsutane framework. Org Lett. 2002;4(13):2249-52.

22. Barluenga J, Martinez S, Suarez-Sobrino AL, Tomas M. New reaction pathways for Fischer carbene complexes: [6 + 3] cycloaddition of chromium alkenyl carbene complexes with fulvenes. J Am Chem Soc. 2001;123(44):11113-4.

23. Coskun N, Ma J, Azimi S, Gartner C, Erden I. 1,2-Dihydropentalenes from fulvenes by [6 + 2] cycloadditions with 1-isopropenylpyrrolidine. Org Lett. 2011;13(22):5952-5.

24. Cassady JM, Baird WM, Chang CJ. Natural-Products as a Source of Potential Cancer Chemotherapeutic and Chemopreventive Agents. J Nat Prod. 1990;53(1):23-41.

25. Vijesh AM, Isloor AM, Shetty P, Sundershan S, Fun HK. New pyrazole derivatives containing 1,2,4-triazoles and benzoxazoles as potent antimicrobial and analgesic agents. Eur J Med Chem. 2013;62:410-5.

26. Soares MIL, Brito AF, Laranjo M, Paixao JA, Botelho MF, Melo TMVDPE. Chiral 6,7-bis(hydroxymethyl)-1H,3H-pyrrolo[1,2-c]thiazoles with anti-breast cancer properties. Eur J Med Chem. 2013;60:254-62.

27. Kamal A, Bharathi EV, Reddy JS, Ramaiah MJ, Dastagiri D, Reddy MK, et al. Synthesis and biological evaluation of 3,5-diaryl isoxazoline/isoxazole linked 2,3-dihydroquinazolinone hybrids as anticancer agents. Eur J Med Chem. 2011;46(2):691-703.

28. Shi L, Hu R, Wei Y, Liang Y, Yang Z, Ke S. Anthranilic acid-based diamides derivatives incorporating aryl-isoxazoline pharmacophore as potential anticancer agents: design, synthesis and biological evaluation. Eur J Med Chem. 2012;54:549-56.

29. Shaala LA, Youssef DT, Sulaiman M, Behery FA, Foudah AI, Sayed KA. Subereamolline A as a potent breast cancer migration, invasion and proliferation inhibitor and bioactive dibrominated alkaloids from the Red Sea sponge Pseudoceratina arabica. Mar Drugs. 2012;10(11):2492-508.

30. Sadashiva MP, Basappa, NanjundaSwamy S, Li F, Manu KA, Sengottuvelan M, et al. Anti-cancer activity of novel dibenzo[b,f]azepine tethered isoxazoline derivatives. BMC Chem Biol. 2012;12:5.

31. Miller SA, Bercaw JE. Mechanism of isotactic polypropylene formation with C-1-symmetric metallocene catalysts. Organometallics. 2006;25(15):3576-92.

32. Ocal N, Bagdatli E, Arslan M. Diels-Alder reactions of new methoxysubstituted-6-arylfulvenes. Turk J Chem. 2005;29(1):7-16.

33. Puerto Galvis CE, Kouznetsov VV. An unexpected formation of the novel 7-oxa-2-azabicyclo[2.2.1]hept-5-ene skeleton during the reaction of furfurylamine with maleimides and their bioprospection using a zebrafish embryo model. Org Biomol Chem. 2013;11(3):407-11.

34. Alam MI, Alam MA, Alam O, Nargotra A, Taneja SC, Koul S. Molecular modeling and snake venom phospholipase A(2) inhibition by phenolic compounds: Structure-activity relationship. Eur J Med Chem. 2016;114:209-19.