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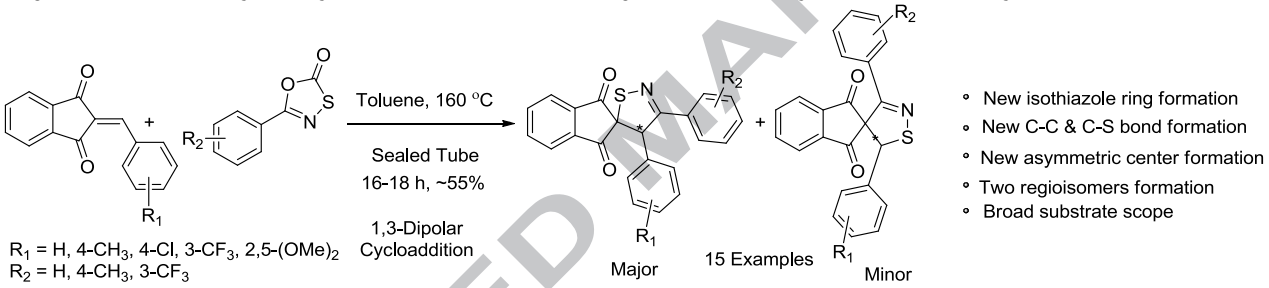

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Synthesis of Spiroindene-1,3-Dione Isothiazolines via a Cascade Michael/1,3-Dipolar Cycloaddition Reaction of 1,3,4-Oxathiazol-2-one and 2-Arylidene-1,3-Indandiones

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Abstract: The reaction of 1,3,4-oxathiazol-2-one derivative with 2-arylidene-1,3-indandione to furnish novel spiroindene-1,3-dione isothiazoline derivatives by Michael/1,3-dipolar [3+2]-cycloaddition reaction was investigated. The key 1,3-dipolar cycloaddition reaction step was examined in toluene solvent at reflux temperature to obtain mixture of two regioisomers (6**a** and 6**b** – 14**a** and 14**b)** and single isomers(**15-20**). The scope of this new reaction was demonstrated with many examples with high reactivity and yields.

The last two decades have witnessed profound changes in indane-1,3-dione chemistry in both quality and quantity. Synthesis of unexplored spiro compounds has been developed and some old problems have been reconsidered. Physiochemical methods and quantum chemical calculations have been extensively used.[1] Indane-1,3-dione constitutes a unique group of compounds due to the simultaneous presence of three characteristic features. a) Enormous synthetic possibilities offered by the presence of β-dicarbonyl derivatives often serve as the starting material for more complex chemical structures. b) Specific physiochemical properties, which offer a wide scope for studies in the problems of theoretical organic chemistry, particularly based on indane-1,3-dione tautomerism, dual reactivity etc. c) A wide range of biological activity, covering analgesic, anti-inflammatory, anticoagulant, anticancer, antipyretic, analgesic and antimicrobial activities.[2] 2-Substituted derivatives of indane-1,3-diones such as 2-(2,4-Dimethylphenyl)indan-1,3-dione was shown to be a potent hypolipidemic,[3] anticoagulant, anticancer, analgesic, anti-inflammatory, fungicidal and bactericidal activity.[4-5]

Isothiazole is a member of a class of compounds known as azoles. In contrast to the isomeric thiazole, the two heteroatoms are in adjacent positions. The first known benzoisothiazole derivative with known biological importance was saccharin and it is five hundred times sweeter than sugar and has gained attention over the past century as an alternative to sugar.[6] The substituted benzoisothiazole compounds have antitumor, anti-allergic, anti-diabetic, anti-inflammatory, anthelmintic and anti-HIV activity.[7] The ring structure of isothiazole is incorporated into larger compounds with biological activity such as the pharmaceutical drugs ziprasidone and perospirone(Figure 1).The ATSAO-T derivatives [2',5'-Bis-O-(tert-butyldimethylsilyl)-β-D-ribo furanosyl]-3'-spiro-5''-(4''-amino-1'',2''-oxathiole-2'',2''-dioxide) thymine bearing a substituted spiro isothiazoline ring system(Figure 1) having anti-HIV-1 activity was reported in literature.[8]

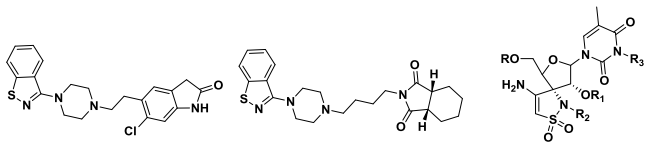

Figure 1: Isothiazoline Compounds

It is expected that the biologically important spiroindan-1,3-dione scaffolds when combined with other biologically active isothiazole ring system could result in more potential benefits for pharmacological activity while retaining high diversity and biological relevance.[9] Accordingly, we envisaged the synthesis of the chiral spiroindene-1,3-dione isothiazoline compounds containing the aforementioned important bioactive fragments.

Key words: 1,3-Dipolar Cycloaddition, 1,3,4-Oxathizole-2-one, Indanedione, Isothiazoline, Regioisomers

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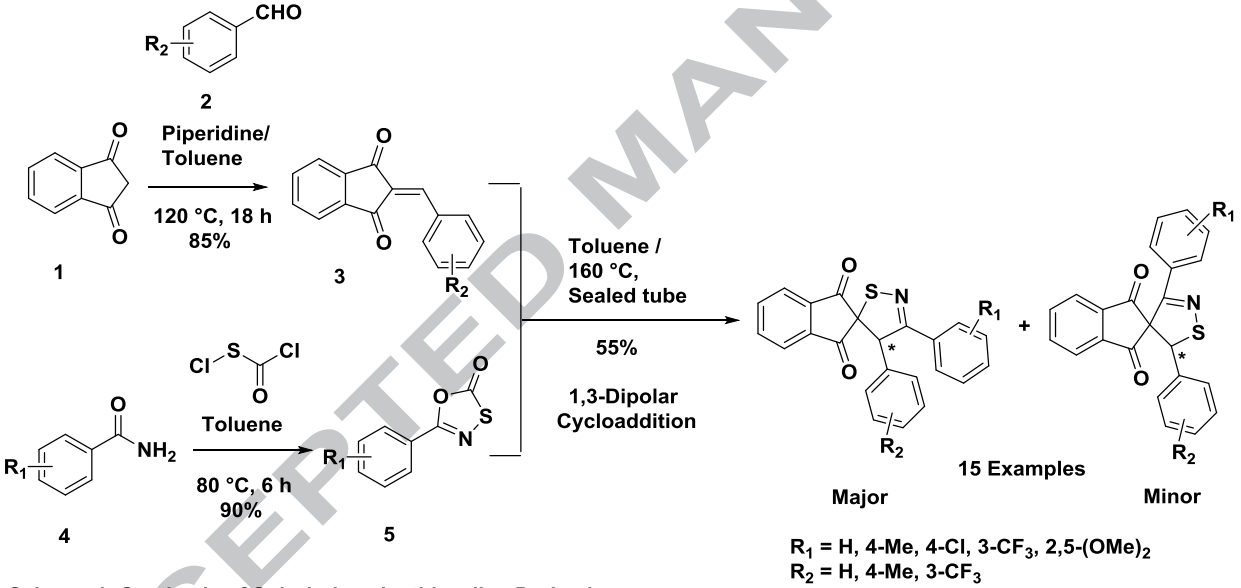
Several of benzoisothiazole compounds have been reported in literature.[5-9] But there are no reports of chiral spiroindene-1,3-dione isothiazoline compounds, as per the literature search. The promising biological results of spiroindene-1,3-dione and isothiazoline derivatives motivated us to synthesize new chiral heterocyclic compounds. We herein, report the synthesis of novel substituted spiroindene-1,3-dione isothiazoline compounds with one chiral center as new molecules to identify more potent biologically active compounds. The 2-arylidene-1,3-indandiones are mostly attractive Michael acceptors[10] for the resulted substituted 1,3-indandiones had been widely found in many natural products with useful biological activities.[11]

In our laboratory we previously prepared 1,2,4-thiadiazole ring system by treating of substituted 5-phenyl-1,3,4-oxathiazol-2-one with p-toluenesulfonylcyanide via 1,3-dipolar cycloaddition reaction successfully.[12] In the present work, we utilized the same substituted 5-phenyl-1,3,4-oxathiazol-2-one and which was treated with 2-arylidene-1,3-indandione to furnish novel chiral spiroindene-1,3-dione isothiazoline derivatives by Michael/1,3-dipolar [3+2]-cycloaddition reaction protocol. To the best of our knowledge, this is the first example of a cascade Michael/1,3-Dipolar[3+2] cycloaddition reaction to get spiroindene-1,3-dione isothiazoline derivatives as two regioisomers.

Firstly, the reaction of indane-1,3-dione (**1**), with aromatic aldehydes (**2**) in the presence of piperidine as base in toluene solvent for the synthesis of 2-arylidene-1,3-indandiones (**3**) was the successful condensation. Although similar condensations have reported with different bases in the past, we found the reaction to take place readily and in very good yields in the presence of piperidine as base. The key intermediate 1,3,4-oxathiazol-2-one moiety (**5**) was prepared from compound (**4**) as per our earlier reported method[12].



Scheme 1: Synthesis of Spiroindene Isothiazoline Derivatives

The cascade Michael/1,3-dipolar cycloaddition reaction of 2-arylidene-1,3-indandione (**3**) and substituted 5-phenyl-1,3,4-oxathiazol-2-one(**5**) was examined in toluene solvent at 160-180 °C in sealed tube and obtained a majority of them are mixture of two regioisomeric isothiazoline cyclo adducts **Table 1; Entry 1-9**) and few of them as single isomers **Table 1: Entry 10-15**) **(Scheme 1)**. Initial screening of the reaction conditions demonstrated with and without bases, and found that the organic and inorganic bases had not much significant role to play in both reactivity and ratio of regioisomers formation. However, without base the cascade Michael/Alkylation majority products was obtained as mixture of two regioisomers and few of them as single isomers in moderate to high yields ~ 50-55% (**Table 1, Entry 1-15**).

To get a better reaction conditions, we next screened the effects of solvents, among the solvents tested, toluene, xylene, 1,2-dichlorobenzenene, chloroform and dichloromethane. In chloroform and dichloromethane, starting material was as such even after 24 h reflux and there will be no reaction occurred. However, in toluene and xylene at 160-180 ^{o}C in sealed tube both starting materials consumed and gave similar results and were found to be best solvents to give the good yield as mixture of two regioisomers (**Table 1; Entry 1-9**) and single isomers **Table 1; Entry 10-15**). A slightly lower yields but also similar ratio of results were observed with the 1,2-dichlorobenzene as solvent. Unexpectedly, the major product **Table 1; 1-9**) of this reaction was isolated as major, representing formation of a highly substituted isothiazoline derivative. These two regioisomers were having very close retardation values and therefore whose

separation by flash column chromatography was unsuccessful. However, majority of regioisomers (**Table 1; Entry 1-6**) from their corresponding mixtures were successfully separated by Grace flash column chromatography. Three of regioisomers (**Table 1; Entry 7-9**) separation by even Grace flash column chromatography was unsuccessful due to very close retardation factor values. The 1,3-dipolar cycloaddition reaction of some of the 2-arylidene-1,3-indandione (**3**) reaction with 5-phenyl-1,3,4-oxathiazol-2-one(**5**) derivatives possessing dimethoxy substitution compounds afforded exclusively single isomers (**Table 1; Entry 11-13**) due to steric effect. Surprisingly the compounds with 3-trifluomethyl and 4-methyl substituents afforded minor isomers as major compound (**Table 1; Entry 14-15**). The regioisomer **18a** was purified by chiral SFC method and obtained two enantiomers with 99% ee and the details was furnished in **Figure 4 (Supporting Information page 135)**. The major and minor regioisomers and single isomers were characterized by IR, 1H NMR, 13C NMR, HRMS and NOE experiments (**Supporting Information page 28-133**).

Table 1. Regioisomers Ratio and Yields of Spiroindane Isothiazoline Derivatives

Entry	Compound (Major / Minor)	R_1, R_2	Regio isomers Ratio (Major/ Minor)	Yield (%)*
1	**6a / 6b**	H; 3-CF_3	3:1	46
2	**7a / 7b**	4-CH_3; 4-Cl	1:2	54
3	**8a / 8b**	4-CH_3; 3-CF_3	1:1	55
4	**9a / 9b**	3-CF_3; 4-CH_3	2:1	56
5	**10a / 10b**	3-CF_3; 4-Cl	1:1	57
6	**11a / 11b**	3-CF_3; 3-CF_3	1:1	58
7	**12a / 12b**	H; H	1:3	40
8	**13a / 13b**	H; 4-CH_3	1:2	49
9	**14a / 14b**	4-CH_3; H	1:1	51
10	**15a****	H; 4-Cl	----	50
11	**16a****	H; 2,5(OMe)$_2$	----	48
12	**17a****	3-CF_3; 2,5(OMe)$_2$	----	58
13	**18a****	4-CH_3; 2,5(OMe)$_2$	----	58
14	**19b*****	3-CF_3; H	----	57
15	**20b*****	4-CH_3; 4-CH_3	----	51

* Overall Yield of Major and Minor isomers
** Only Major isomer formed
*** Only Minor isomer formed

1,3-Dipolar Cycloadditions are one type of cycloaddition reactions in which multiple unsaturated molecules combine to form cyclic addition products. Three types of selectivity must be considered in 1,3-dipolar cycloaddition reactions, regioselectivity, diastereoselectivity and enantioselectivity. The regioselectivity is controlled by both steric and electronic effects.[13-14] They combine 1,3-dipoles and dipolarophiles to generate five-membered rings.[15] The first dipole and 1,3-Diploar Cycloaddition were discovered by Curtius[16] and Buchner[17] in the 1880's. Evidence for the existence of nitrile sulphides was first obtained by Franz and Black.[18] Kinetic studies of the thermolysis of oxathiazolone (**5**) in the presence and absence of dipolarophiles have also been performed.[19-20]

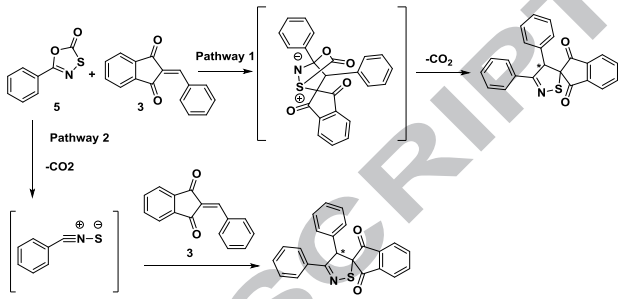


Figure 2: Proposed Mechanism for Formation of Spiroindene-1,3-dione Isothiazoline Ring System

Based on literature evidence[18], we propose that the rate of disappearance of oxathiazolone (**5**) and the rate of formation of isothiazole derivatives found to be, first order, and independent of the concentration of dipolarophile. These findings are consistent with the existence of benzonitrile sulphide as a discrete intermediate in the reaction pathway **2 (Figure 2)**.

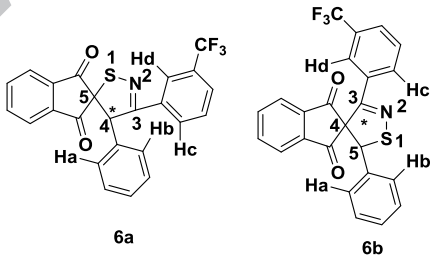


Figure 3: NOE Connectivity of Regioisomers 6a and 6b

The NOE spectroscopic data (**Supporting Information page.134**) was used to confirm the major (**6a**) and minor (**6b**) regioisomers (**Figure 3**). In major isomer (**6a**), when we irradiate C4 attached hydrogen at δ 5.586 ppm, the corresponding Ha, Hb, Hc and Hd at 7.0 ppm, 7.0 ppm, 7.63 ppm, and 7.91 ppm respective signal intensities were enhanced. Hence, this spatial correlation supporting that two phenyl groups are attached adjacent to each other on 3 & 4 carbons of isothiazoline ring in **6a**. Whereas in minor isomer (**6b**), when we irradiate C5 attached hydrogen at 5.944 ppm, only Ha and Hb at 7.2 ppm signal intensity was enhanced. Hence, this spatial correlation supporting that phenyl group is attached on C5 carbon in (**6b**).

CONCLUSION

In summary, we have developed an efficient approach towards synthesis of chiral spiroindene isothiazoline derivatives as a mixture of two regioisomers in three steps with good yield in toluene as solvent. Though the approach for the formation of chiral spiroindene

isothiazoline derivatives were limited with the use of 1,3,4-oxathiazol-2-one moiety, we report the synthesis of chiral spiroindene isothiazoline heterocycles for the first time. We have successfully separated majority of two regioisomers from mixture by Grace column purification. One of the regioisomeric compound **18a** was purified by chiral SFC method and confirmed two enantiomers. Further applications of this methodology and bioactivity study of these new heterocycles are in progress.

Supplementary Material

The spectroscopic data (experimental procedure, ^{1}H NMR, ^{13}C NMR, IR and HRMS) associated with this article can be found in the online version.

ACKNOWLEDGMENT

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Research Highlights

- Novel spiroindene-1,3-dione isothiazoline derivatives were synthesized
- Michael/1,3-dipolar [3+2]-cycloaddition reaction was investigated using 1,3,4-oxathiazol-2-one moiety
- Two regioisomers of spiroindene-1,3-dione isothiazoline was separated
- The regioisomer **18a** was successfully separated into its two enantiomers