Tandem Synthesis and Optical Rotatory Dispersion Studies of a Novel Spiro Lactone

(methyl 3-(benzo[d]thiazol-2-ylamino)-7,9-dimethyl-2,6,8,10-tetraoxo-1-oxa-7,9-
diazaspiro[4.5]dec-3-ene-4-carboxylate)

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Abstract

Spiro compounds are of interest due to their interesting conformational features and their structural implications on biological systems. The asymmetric characteristic of the molecule due to the chiral spiro carbon is one of the important criteria of the biological activities. These structures are a widespread structural motif found as key elements of numerous drugs and designed medicinal agents in medicinal chemistry. Synthesis of these compounds always has been a challenging for organic chemists because it often requires synthetic design based on specific strategies. Due to the great importance of this class of compounds, chemists have a special attention to the synthesis of these compounds and a range of synthesis methods has been reported. In the current research a novel optically active spiro-lactone was synthesized via a tandem protocol (michael addition, aldol reaction and γ-lactonization consecution) between benzo[d]thiazol-2-amine and dimethyl-acetylene dicarboxylate in the presence of 2, 4, 5, 6(1H, 3H)–pyrimidinetetrone (Alloxan). The synthesized compound has been successfully characterized by spectroscopy techniques. Also, evaluation of special optical rotatory on this synthesized spiro-lactone was investigated.

Keywords: Spiro lactone; Tandem reaction; Benzo[d]thiazol-2-amine; Alloxan; Special optical rotatory
1. Introduction

The interesting structure of spiro compounds has led to the biological properties of these systems. The asymmetric structure of the molecule due to the presence of chiral spiro carbon is one of the important reasons for the biological activity of these compounds [1]. Also, the presence of spatial pressure in the structures of spiro in various natural compounds adds to the attractiveness of the study of such compounds. In fact, these compounds have interesting biological activity due to their specific structure [2]. The presence of the spiro structure in various natural products also adds to the interest in the investigations of spiro compounds [3]. Spiro compounds always have an important part of organic synthesis because they make biological activities aware [4-6]. Many natural compounds contain the structure of spiro lactone, and extensive studies have been done [7-10].

In continuation of our interest in the application of spiro compound in multi-component reactions (MCRs) we report here a tandem synthesis of a novel derivative of spiro lactone (methyl3-(benzo[d]thiazol-2-ylamino)-7,9-dimethyl-2,6,8,10-tetraoxo-1-oxa-7,9 diazaspiro[4.5]dec-3-ene-4-carboxylate) 4. The structure of this new synthesized compound was characterized by IR, $^1$H-NMR, $^{13}$C-NMR, elemental analysis, and mass spectroscopy techniques. Also, evaluation of special optical rotatory on this synthesized spiro-lactone was investigated.

2. Result and discussion

As part of our continuing interest in the construction of novel heterocycles via multi-component reactions [11-13], we now report a γ-lactonization reaction of benzo[d]thiazole-2-amine 1, and dimethyl acetylenedicarboxylate 2, in the presence of 2, 4, 5, 6(1H, 3H)–pyrimidinetetrone (alloxan) 3, in toluene reflux condition (Scheme 1). The infrared (IR), $^1$H NMR, $^{13}$C NMR and
mass spectra clearly indicated the formation of methyl 3-(benzo thiazole-2-amino)-7, 9-dimethyl-2-6-8-10-tetraoxo-1-oxa-7, 9-diazo-spiro(4.5)dec-3-one-4-carboxylate 4 in appropriate yield. The $^1$H-NMR spectrum of 4 in CDCl$_3$ exhibited a sharp singlet in the range of $\delta$=3.89 ppm for two symmetric N-methyl protons, a singlet at $\delta$= 4.24 ppm for methoxy protons, a broad singlet at $\delta$=7.60 ppm for the NH group and multiples in the range of $\delta$= 7.20-9.14 ppm have been observed for the aromatic protons. The $^{13}$C-NMR spectrum of 4 showed 15 distinct signals, which confirmed the proposed structure. The IR spectrum of 4 showed strong absorptions at 1739, 1585 and 1525 cm$^{-1}$ due to the carbonyls and the amino group at 3741 cm$^{-1}$ as a weak band. The mass spectrum of 4 displayed the molecular ion peak at 430 m/z, which is in agreement with the proposed structure.
Scheme 1. A three-component reaction of benzothiazole-2-amine (1) with dimethyl acetylenedicarboxylate (2) in the presence of alloxan

A possible mechanism for the present reaction is shown in Scheme 2, which shows a tandem sequence. At first, nucleophilic Michael-addition of the 2-aminobenzothiazole 1 to the b-carbon of the electron-deficient alkyne 2 generates the dimethyl 2-(benzo[d]thiazol-2-ylamino)fumarate 5 as an electron-rich enaminone. Subsequent nucleophilic aldol-like attack of aminobutendioate 5 to the central carbonyl group of the alloxan 3 would yield iminium intermediate 6 that can be tautomerized to enamine 7. γ-Lactonization of Z-7 (compound 7 with the Z-configuration around the C-C double bond), would produce the methyl 3-(benzo[d]thiazol-2-ylamino)-7,9-dimethyl-2,6,8,10-tetraoxo-1-oxa-7,9-diazaspiro[4.5]dec-3-ene-4-carboxylate 4.
2.1. Optical activity:

When a molecule in four different groups is attached to a carbon atom, that carbon is called the chiral (space center or chiral center). The carbon contained in these molecules is called asymmetric carbon or the center of the chiral. Relationship between the enantiomers is the same as the relation between the left and right hands, and if four different groups are connected to the four-faced carbon. Molecules with at least a chiral center are not compatible with their mirror
image and are in the form of a pair of enantiomers. Physical properties such as melting point, boiling point, solubility and density of a pair of enantiomers are similar, and these two methods cannot separate the two enantiomeric compounds. Symmetry in molecules helps detect chiral molecules from non-chiral (Achiral). The screen of symmetry is a hypothetical page that passes through the center of the object or molecule (like a mirror from the middle of half), and half of the object or molecule in the mirror image of the other half. In fact, the screen of symmetry is one of the symmetric elements that, if a molecule has a symmetry plane, is non-chiral, as in the case of a methane molecule, a large number of molecules can be categorized by detecting the symmetry plane into the chiral and non-chiral molecules. For example, one hand has no symmetry. Half a hand, the mirror image is not half the other. The amount of rotation in a device called polarimetry that can be measured at the following screen. By placing a solution of organic molecules with optical activity in the sample tube, the polarizing light is passed through the tube and the rotation and polarity will be measured. The light output then enters another polarizer called the analyzer. By rotating the analyzer until the light passes through it, you can find the new polarized screen and obtain the amount of light rotation. The amount of rotation is expressed by the Greek alpha and degree.

Scheme 3. The projection of a polarimetric device by a polarized light travels through the dissolution of the active molecules that rotate the polarization plane.
In addition to determining the amount of rotation, it can be specified. From a viewer who looks directly at the analyzer, some of the active optical molecules rotate the polarized light to the left (in the opposite of the clockwise direction), and the left-hand rotates, while the other molecules are polarized light they rotate right (clockwise) and called right – hand rotates. By convention, the left turn is marked with a negative sign (-) and a right turn with a positive sign (+) [14]. The amount of rotation observed in a polarimetric experiment depends on the number of active light molecules. The more molecules the light hits them, the larger the observed rotation will be. Therefore, the amount of rotation depends on the sample concentration and the length of the routing path of the sample. If the density of the sample is doubled, the observed rotation will also double, and the amount of rotation will depend on the wavelength of the applied light. In order to express the optical rotation data meaningfully, comparisons can be made, standard conditions must be selected. Specific rotation ([α] D) is a combination of the observed rotation for a sample whose length of the passageway (L), in one decimeter (1dm = 10cm), the sample concentration (C) is 1gr / ml, and the wavelength of light is 589 nm (nm). (Light line D sodium, yellow sodium light is also used in street bubbles (1 nm = 10⁻⁹)).

\[ [\alpha]_D = \alpha / C \times L \]

When the optical rotation data is expressed as a standard, the special rotation ([α] D), becomes a definite physical constant for the active optical composition [15]. It can be used to measure the specific rotation of the spiro compounds that are self-acting light. So there are significant studies on specific rotation of spiro compounds have been done [16-18].
2.2. Specific rotation of the Compound 4:

By the evaluation of the optical activity and special rotation on methyl 3-(benzo[d]thiazol-2-ylamino)-7,9-dimethyl-2,6,8,10-tetraoxo-1-oxa-7,9-diazaspiro[4.5]dec-3-ene-4-carboxylate 4, the following results were obtained.

Table 1. Observed rotation and specific rotation at various concentrations in the chloroform solvent

<table>
<thead>
<tr>
<th>ENTRY</th>
<th>CHCL₃</th>
</tr>
</thead>
<tbody>
<tr>
<td>C(gr/ml)</td>
<td>0.05</td>
</tr>
<tr>
<td>α⁽⁽⁰⁾</td>
<td>+0.066</td>
</tr>
<tr>
<td>[α]₀⁰</td>
<td>+6.6</td>
</tr>
</tbody>
</table>

Scheme 4. Read rotation based on the concentration for the compound 4

Specific rotation evolutions of the compound 4 confirmed that this compound changed the polarized light to the right. Investigation showed that this compound is an optical activator and
the amount of rotation is varies in different concentrations indeed by increasing the concentrations the specific rotation rate naturally increased (Table 1 and Scheme 4).

4. Experimental:

4.1. Materials and methods

The Solvents and chemicals used were from Merck's representative office and were used without further purification. $^1$H and $^{13}$C-NMR characters with Bruker DRX -300AVNCE FT-NMR were recorded at 300 and 75 MHz, respectively in CDCl$_3$ solvent and the IR spectra were taken with the Perkin Elmer-spectrum 100 and the MASS spectrum was taken with a 5973 Network Mass Selective Detector and in the special rotation section of the Perkin Elmer 241 (polarimeter) Used.

4.2. General procedure

To a magnetically stirred solution of aminobenzo thiazole (0.154 g, 1.0 mmol) and dimethyl acetylenedicarboxylate (0.122 ml, 1.0 mmol) in toluene (10ml) was added alloxan (0.163 g, 1.0 mmol) at reflux condition. After completion of the reaction [12-24 h; TLC (AcOEt/hexane 1:3)], the solvent was removed under reduced pressure and the product was purified by column chromatography [silica gel (230–240 mesh; Merck), hexane/AcOEt 3:1)].

\textit{methyl 3-(benzo[d]thiazol-2-ylamino)-7,9-dimethyl-2,6,8,10-tetraoxo-1-oxa-7,9-diazaspiro[4.5]dec-3-ene-4-carboxylate}

Yellow oil, yield: 0.32gr (75%).IR (KBR) ($\nu_{\text{max}}$/cm$^{-1}$): 3741(N-H), 1739, 1585, 1525 (C=O); $^1$HNMR (300.1MHZ,CDCL$_3$): 3.89 (6H, s, 2CH$_3$), 4.24 (3H ,s, OCH$_3$), 7.60 (1H, br s, NH), 7.20 - 9.14 (4H, m, 4CH). $^{13}$C-NMR (75MHZ, CDCl$_3$): 29.6 (2N-CH$_3$), 53.4 (OCH$_3$), 109.1 (C$_{\text{spiro}}$), 120.24, 121.92, 124.81, 127.27, 127.81, 149.6, 153.2, 160.97, 162.42, 164.15, 167.2,
170.4 (C=C,C=N,C=N). MS: (m/z, %) 430 (M+, 59), 296 (56), 241 (11), 134 (100), 98 (85), 15 (48); Anal. Calcd for C\textsubscript{18}H\textsubscript{14}N\textsubscript{4}O\textsubscript{7}S (430.39): C, 50.23%; H, 3.28%; N, 13.02%; found: C, 48.39%; H, 300%; N, 11.61%.

In studying the specific rotation of the compound 4 with respect to the positive rotation, we found that the above composition changed the polarized light to the right. The composition is considered to be a chiral atom and is an optical activator, and in different concentrations, the amount of rotation is different. With increasing concentrations of the amount of rotation, the specific rotation of the obtained result naturally increased.

3. Conclusion:

The interesting structure of spiro-carbon is one of the important reasons for the interesting activities of spiro-compounds. The present research describes a tandem protocol for the synthesis of a novel spiro-lacton (methyl 3-(benzo[d]thiazol-2-ylamino)-7,9-dimethyl-2,6,8,10-tetraoxo-1-oxa-7,9-diazaspiro[4.5]dec-3-ene-4-carboxylate) 4 in appropriate yield via a Michael addition, stereo-controlled aldol-type reaction, and γ-lactonization sequence of 2-amino-benzothiazole and dimethyl acetylene dicarboxylate in the presence of alloxan. These tandem route include superior atom economy, simplified workup procedures, more efficiency, and better yield. Also the synthesized compound showed optically active properties and converts the polarized light to the right.

Acknowledgments:

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5. References and Notes