Efficient and rapid conversion of 3-amino-imidazo [1,2-a]pyridin-2-yl-4H-chromene-4-ones to its corresponding thio analogues using Lawesson’s reagent †

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Abstract: An expeditious, efficient and high yield conversion of ketone group in GBB adducts was obtained by the reaction with 3-formyl chromone, 2-amino pyridine and isocyanide to corresponding thio analogues is described utilizing Lawesson’s reagent. The reaction was involved microwave irradiation for both GBBR and the functional group transformation from ketone to thio ketone using Lawesson’s reagent through sequential fashion. The thio heterocyclic analogs of GBB products were characterized by using NMR.

Keywords: GBB reaction; Lawesson’s reagent; 3-formyl chromone.

1. Introduction

Chromones and its thio analogues are privileged molecules and these have considerable attention now a days due to their potential biological applications [1] such as antiproliferative Figure 1[2], antiangiogenic activity [3] The functional group transformation from oxygen to its thio analogues of ketones, flavones have considerable attention now a days due to their biological importance of these molecules [4]. Organosulfur compounds have unique place in synthetic organic chemistry due to their rich and versatile chemistry [5]. Thionation, the functional group transformation carbonyl group to thiocarbonyl is broadly applied procedure in synthesis of organosulfur compounds. This transformation has been accomplished by several reagents especially phosphorous pentasulfide [6], bis(trimethylsilyl) sulfide with CoCl₂·6H₂O [7], and thiation of gendichlorides with sodium hydrogen sulfide [8].

Figure 1: Bioactive thiooxoflavonoids
The above process involves lengthy procedures and require excess of reagents, aromatic hydrocarbon-based solvents benzene, toluene under dry conditions affording only moderate yields. The Lawesson’s reagent, 2,4-bis(pmethoxyphenyl)-1,3-dithiaphosphetane2,4-disulfide has been commonly used for efficient transformation of oxygen group to their thio analogues [9].

Here in we present an efficient rapid conversion of 3-amino-imidazo[1,2-a]pyridine-2-yl-4H-chromene-4-ones [10] to its corresponding thio analogues. In continuation of our research we report the combination of Groebke– Blackburn–Bienaymé [11] IMCR with Lawesson’s reagent conversion of carbonyl to thiocarbonyl group as post transformation process (Scheme1). The present work gives scope and diversity in obtaining variation in Bis-heterocycles via IMCR. As in our research group of investigation had significant progress in GBBR obtaining Bis-heterocycles. So, this contribution of using Lawesson’s reagent in IMCR strategy are hitherto unreported. The GBB adducts were obtained by the reaction with 3-formyl chromone, 2-amino pyridines, and Isocyanide. In this reaction we combine two privileged molecules were bound to form a Bis-heterocycle where the chromone based GBB adduct (4a, 4b) carbonyl group were transformed to its thio analogues (5a,5b). under microwave irradiation.

![Scheme1 Synthesis of thio analogues of 3-amino-imidazo[1,2-a]pyridine-2-yl-4H-chromene-4-ones.](image1)

The two privileged structures were bound were separately represents as pharmacophores whereas the chromone present a vast biological activity such as antioxidants [12], anti-HIV [13], antitumoral [14], anticancer [15], antiviral [16] antiasthmatics [17], anti-Parkinson [18], antiallergics [19] and as antimicrobials [20]. On the other hand imidazo[1,2-a]pyridine also have a broad spectrum of biological activities such as anticancer [21], antiviral [22], antimicrobials [23], anti-Parkinson [24], antimutagenics [25] and as anti-inflammatory [26]. For example, the zolpidem is the most prescribed drug for insomnia [27]. Due the importance of these pharmacological properties and our interest in developing novel molecules and their functionalization by modifying groups that gives promising feature for biological activity. This is reason we use the post transformation as thiocarbonyl conversion using Lawesson’s reagent.

2. Results and Discussion.

The reaction is conducted in two step process initially we obtained GBB adducts according to one our recent literature reports mentioned by K.G Kishore et al. [28].

![Scheme 2: Synthesis of 3-amino-imidazo[1,2-a]pyridine-2-yl-4H-chromene-4-ones.](image2)
There we blindly used the same conditions and reproduced 4a, 4b derivatives, the advantage of this method was acid free and catalyst free reaction under microwave irradiation. Here we have 100% conversion the isolated yield was above 90% for the mentioned derivatives. (Scheme 2). The second step involves the transformation of carbonyl to its thio carbonyl group. (Scheme 3).

Scheme: 3 Synthesis of thio analogues of 3-amino-imidazo[1,2-a]pyridine-2-yl-4H-chromene-4-ones.

For the basic transformation of carbonyl to its thio carbonyl formation we used Lawesson’s reagent (2,4-bis(pmethoxyphenyl)-1,3-dithiapophetane2,4-disulfide). Initially as reaction model we use 5a for reaction optimization under conventional reflux and according to recent literature procedures mentioned by Varma et al. [3] for obtaining the thiocarbonyl derivative mention in the Table 1. However conventional methods usually require excess of Lawesson’s reagent and (0.5-1 molar equiv) in lengthy reactions (more than 25h) under elevated temperatures and results in low conversion and low isolation yield. To get rid of the above disadvantages we applied microwaves as irradiation source. The advantages of microwave -expedited functional group transformation are cleaner reactions, shorter reaction times and ease of manipulation. Here in we developed the efficient conversion of carbonyl group GBB adduct 4a, 4b to their thio analogue under microwave irradiation. In this reaction process we have used only 0.5 equivalents of Lawesson’s reagent and the 4a we have used 1 equiv.

<table>
<thead>
<tr>
<th>LR (Equiv)</th>
<th>TIME</th>
<th>%YIELD</th>
</tr>
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<tbody>
<tr>
<td>0.5</td>
<td>rt, 48hrs</td>
<td>NR</td>
</tr>
<tr>
<td>0.5</td>
<td>reflux, 24hrs</td>
<td>30%</td>
</tr>
<tr>
<td>0.8</td>
<td>reflux, 48hrs</td>
<td>30%</td>
</tr>
<tr>
<td>0.5</td>
<td>),, 3hrs</td>
<td>50%</td>
</tr>
<tr>
<td>0.5</td>
<td>MW, 20 min</td>
<td>95%</td>
</tr>
</tbody>
</table>

The reaction progress was monitored by TLC using 6:4 hexane/Ethyl Acetate as eluent. After optimizing reaction, we have characterized the compound with $^1$HNMR & $^{13}$C NMR. Mainly the product conversion was observed clearly in $^{13}$C NMR where we can observer the change of chemical
shift from C=O is $\delta$ 176.7 ppm to C=S is $\delta$ 198.34 ppm with respect to CDCl$_3$ as internal reference confirms the transformation of carbonyl to its thio analogue.

In summary we have developed new methodology with efficient and rapid conversion of 3-amino-imidazo[1,2-а] pyridine-2-yl-4H-chromene-4-ones to its thio analogues under microwave irradiation using Lawesson’s reagent in good to excellent yields.

Supplementary Materials: The following are available online at http://www.xxxxx, Figure S1: title, Table S1: title, Video S1: title.

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Conflicts of Interest: The authors declare no conflict of interest.

3. Appendix A

3.1 Materials and Methods:

General Information. $^1$H and $^{13}$C NMR spectra were acquired on 400 or 500 MHz Bruker Avance III HD spectrometers. The solvent for NMR samples was CDCl$_3$. Chemical shifts are reported in parts per million ($\delta$/ppm). Internal reference for NMR spectra is TMS at 0.00 ppm. Coupling constants are reported in Hertz (J/Hz). Multiplicities of the signals are reported using the standard abbreviations: singlet (s), doublet (d), triplet (t), quartet (q) and multiplet (m). IR spectra were recorded by ATR method using neat compounds. The wavelengths are reported in reciprocal centimeters (v$_{max}$/cm$^{-1}$). HRMS spectra were acquired via electrospray ionization ESI (+) and recorded via the TOF method. Reactions in heating were performed in round-bottomed flasks using a sand bath. Ultrasound irradiated reactions were performed in vials placed into a water bath of a Branson 1510 sonicator cleaner working at 42 kHz $\pm$ 6% frequencies. The reaction progress was monitored by TLC and the spots were visualized under UV light (254 or 365 nm). Flash column chromatography was performed using silica gel (230–400 mesh) and mixtures in different proportions of hexanes with ethyl acetate as mobile phase. Melting points were determined on a Fisher-Johns apparatus and were uncorrected.

4. Experimental Section:

4.1 General Procedure for synthesis of 4a-b: In a MW sealed-tube equipped with a magnetic stirring bar, to a 0.5 M solution of aldehyde (1.0 equiv.) in anhydrous toluene [0.5 M], amine (1.0 equiv.) and isocyanide (1.0 equiv.) were added sequentially and the reaction mixture was MW-heated (100 oC, 150 W) for 10 minutes. Then, the solvent was removed until dryness and the crude were immediately purified by silica-gel column chromatography using a mixture of hexanes with ethyl acetate (7/3; v/v) to afford the corresponding products.

4.2 Synthesis and characterization of selected 3-(3-(tert-butylamino)imidazo[1,2-а]pyrdin-2-yl)-4H-chromen-4-one (4a):

According to GP 3-Formylchormone (1 mmol, 1 equiv), 2-aminopyridine (1mmol, 1equiv) and isocyanide were sequentially added and reacted together to afford 4a of 98% as pale-yellow solid; mp = 206 oC; Rf = 0.17 (hexane-EtOAc 7:3 v/v). Spectral data for compd 4a: FT-IR (ATR)m$_{max}$/cm$^{-1}$ 3281,
2966, 2926, 1629, 1138; 1H NMR (400 MHz; CDCl3; 25°C; TMS): δ 8.80 (s, 1 H), 8.36 (d, J = 7.0 Hz, 2 H), 7.73–7.67 (m, 1 H), 7.55 (d, J = 8.4 Hz, 1 H), 7.51–7.42 (m, 2 H), 7.16–7.10 (m, 1 H), 6.78–6.73 (m, 1 H), 4.70 (bs, 1 H), 1.05 (s, 9 H); 13C NMR (100 MHz, CDCl3; 25°C; TMS): δ 176.7, 156.6, 156.4, 142.7, 133.9, 130.4, 128.2, 126.5, 125.5, 124.4, 124.3, 124.1, 121.6, 118.1, 116.9, 111.0, 56.0, 29.3; HRMS (ESI+): m/z calcd for C20H16N3O+: 334.1556, found 334.1553.

4.3 General procedure for synthesis of 5a-b

In a MW sealed-tube equipped with a magnetic stirring bar, to 1 equiv of 4a in a solution of toluene 0.5 equiv of LR was added and the reaction mixture was heated (100°C, 200W) for 20 minutes. Then the solvent was removed under reduced pressure and the crude was purified by silicon-gel column chromatography using the mixture of 6:4 hexane/EtOAc v/v to afford corresponding thio analogues.

4.3.1 Synthesis and characterization of selected 3-[3-(tert-butylamino)imidazo[1,2-a]pyridin-2-yl]-4H-chromene-4-thione 5a:

According to GP 4a and LR were reacted to afford 5a in 95% as reddish brown sticky substance 1H NMR (500 MHz, Chloroform-d) δ 8.77 (d, J = 8.3 Hz, 1H), 8.52 (s, 1H), 8.37 (d, J = 6.9 Hz, 1H), 7.75 (t, J = 7.7 Hz, 1H), 7.57 (d, J = 8.4 Hz, 1H), 7.53 – 7.46 (m, 2H), 7.18 – 7.14 (m, 1H), 6.79 (t, J = 6.8 Hz, 1H), 3.63 (s, 1H), 1.01 (s, 8H). 13C NMR (126 MHz, CDCl3) δ 198.31, 150.85, 150.53, 142.25, 133.79, 131.94, 130.91, 129.51, 127.19, 126.57, 124.18, 123.55, 118.5, 116.99, 111.23, 55.79, 29.74.

4.3.2 Synthesis and characterization of selected 3-[3-(tert-butylamino)-7-methylimidazo[1,2-a]pyridin-2-yl]-4H-chromene-4-thione 5b:

According to GP 4b and LR were reacted to afford 5b in 92% as reddish-brown sticky substance. 1H NMR (500 MHz, Chloroform-d) δ 8.77 (d, J = 8.2 Hz, 1H), 8.51 (s, 1H), 8.23 (d, J = 7.0 Hz, 1H), 7.77 – 7.72 (m, 0H), 7.57 (d, J = 7.3 Hz, 0H), 7.49 (t, J = 7.6 Hz, 1H), 7.25 (d, J = 9.3 Hz, 2H), 6.62 (d, J = 7.0 Hz, 1H), 3.60 (s, 1H), 2.40 (s, 3H), 1.00 (s, 9H). 13C NMR (126 MHz, CDCl3) δ 198.48, 151.16, 150.78, 142.82, 134.00, 129.78, 126.80, 123.07, 118.80, 115.42, 113.32, 55.98, 29.98, 21.47.

References


29. Title of Site. Available online: URL (accessed on Day Month Year).