AN EFFECIENT ONE-POT SYNTHESIS OF 6-ARYL-5-CYANO-2-THIOPYRIMIDINONE DERIVATIVES AND THEIR TETRA-BUTYL AMMONIUM IONIC FORMS

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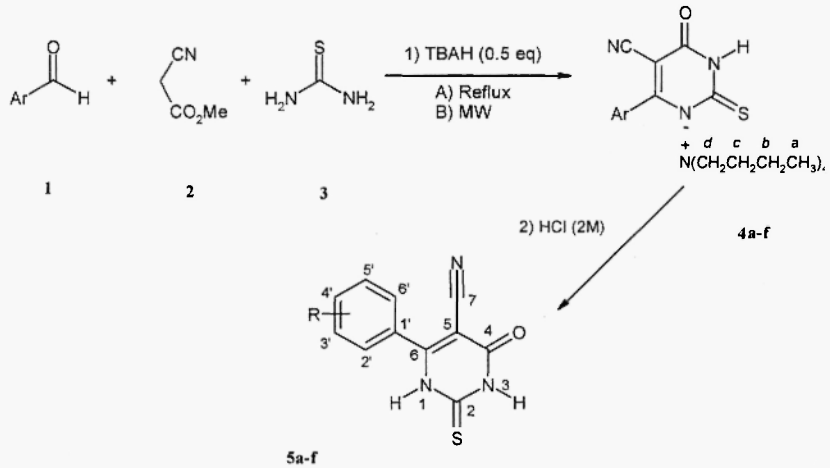
Abstract : Three-component condensation of benzaldehyde derivatives, methylcyanoacetate and thiourea in the presence of tetra-butyl ammonium hydroxide in reflux condition to afford the corresponding tetra-butyl ammonium 6-aryl-5-cyano-2-thiopyrimidonate ionic forms.These reactions were also carried out under microwave irradiation. The yields of products under the microwave condition were better as compared to the reflux media. The acidification of these ionic forms resulted 6-aryl-5-cyano-2-thiopyrimidone derivatives.

Introduction

Various analogues of thiopyrimidones have effective antibacterial, antifungal, antiviral, fungicidal, insecticidal, miticidal[1-3] and antileishmanial activities.[4] They are also starting materials for the production of some uracil derivatives and nucleosides.[5-7]Ammonolysis of 4-thiouracil is cornerstone in the preparation of cytosines. The versatile biological activities of thiopyrimidones prompted us to undertake the synthesis of these novel derivatives.

There are several methods for the synthesis of these compounds.[8] 6-Aryl-5-cyano-2-thiopyrimidone derivatives could be obtained from the condensation of aldehydes, alkyl cyanoacetate and thiourea in the presence of potassium carbonate[9]; the reaction of benzylidene cyanoacetate with thiourea in the presence of sodium alkoxides[10] and also the reaction of 3-aryl-3-chloro-2-cyano propenoates with symmetrically substituted thioureas.[11] The major drawbacks of the reported methods lie in a considerably low yield, long reaction time and the presence of strong bases such as sodium alkoxides. Therefore, the search for milder, more convenient and efficient methods for the preparation of thiopyrimidones continued to attract our attention. Recently we reported one-pot three component reaction of benzaldehyde derivatives, thiourea and alkyl cyanoacetate in the presence of piperidine as a base.[12] We wish to report here a facile and improved one-pot three-component condensation of benzaldehyde derivatives, methyl cyanoacetate and thiourea in the presence of 0.5 equivalent tetra-butyl ammonium hydroxide (12.5% mole) [TBAH] as a base in MeOH under reflux and microwave irradiation conditions (**Scheme-1**). The reaction is completed after 3-4 h of reflux and 2-4 min under microwave irradiation.



Scheme-1

Results and Discussions

TBAH has been used as a basic catalyst for a variety of organic transformations such as: Knoevenagel condensation,[13] arylation,[14] Robinson annulation,[15] intramolecular Horner-Emmons closure,[16] dehydration[17] and also formation of carbenes.[18] This reagent is a 12.5 mole% solution in H_2O which is an advantage for this reaction, because the reaction could be carried out in aqueous phase, and it could also be used as a charge transfer catalyst.

Three component reaction of benzaldehyde derivatives, thiourea and methyl cyanoacetate in the presence of TBAH as a base proceeds in refluxing MeOH and by the end of the reaction, *tetra*butyl ammonium 2-thiopyrimidonate ionic forms were formed. Moreover, by following acidification of the ionic form, 2-thiopyrimidinone is obtained in a greater yield as compared to the yield of the previously described procedure.[9] These salts are stable and could be stored for a long time. Since these compounds are starting materials for the synthesis of some biologically active ingredients, they may be used directly for other reactions without the need for further purification or addition of any base.

Moreover, microwave-assisted rapid organic reactions constitute an emerging technology that makes experimentally and industrially important organic syntheses more effective and more eco-friendly than conventional reactions .[19] Hence, microwaves have been applied to accelerate reaction rates in a variety of chemical transformations and to improve the yields of products in most cases. When a mixture of thiourea, benzaldehyde derivatives, methyl cyanoacetate and TBAH in MeOH was heated under either reflux or microwave irradiation (100% power, 850 W) conditions, 2-thiopyrimidone derivatives **5a-f** were formed as precipitate after evaporation of the solvent and acidification of the mixture with HCl (2M).The yields are of the pure isolated products. TBAH acts both as a reactant and catalyst for this cyclocondensation. One-pot three-component condensation reactions were carried out in the presence of 0.1, 0.3, 0.5 and 1 molar equivalent of TBAH as a base; in the presence of 0.1 and 0.3 molar equivalent of the base, the reaction was not complete and unreacted alkenes were recovered; when concentration of the base was increased to 1 molar equivalent the purity of the isolated product was lower. High concentration of TBAH couldn't be used for this reaction, because the Cannizzaro products will be formed as by-product. The best results were obtained with 0.5 molar equivalent of TBAH.

The structures of the products **4a-f** were identified according to their ^1H and ^{15}C-NMR data. The ionic forms **4a-f** were dissolved in hot water and then neutralized by the addition of 2M HCl. The products were 2-thiopyrimidones **5a-f.** Only when 4-trifluromethyl benzaldeyde was used as starting material at the same conditions, the expected tetra-butyl ammonium thiopyrimidonate was formed with 45% yield **(4g).** After acidification of compound **4g**, the desired 2-thiopyrimidone was not obtained and a complex mixture was recovered. We carried out these reactions on the surface of basic and neutral alumina in the presence of TBAH as the base, but the results were not satisfactory. We supposed that this reaction is a Tandem reaction and a character of the reaction is very effective and plays a key role in the progress of the reaction. Considering the shown results in **Table-1** indicates that the withdrawing character of substituted groups accelerates the rate of reaction. Reactions of benzaldehyde derivatives with electron-donating groups reduce the activity of aldehyde and the desired alkenes and the yields of the reactions are low.

Table-1 : Synthesis of 2-thiopyrimidinone derivative in the presence of TBAH **5a-f** in reflux and microwave irradiation conditions

No.	Ar	Yield (%) (reflux) *	Yield (%) (Microware) *
a	C_6H_5	43	49
b	*p*-Br-C_6H_4	46	51
c	*m*-Cl-C_6H_4	40	43
d	*p*-CN-C_6H_4	50	52
e	*p*-Me-C_6H_4	36	40
f	4-Pyridyl	62	70

* In all reactions, the reflux and MW irradiation times are 3-4 hours and 2-4 minutes respectively. In all cases, the yields are measured in pure forms.

All of known compounds were characterized by comparison of their physical properties and spectroscopic data with those of previously reported. The ionic forms IR spectra showed peaks at 3300-3550 Cm^{-1} assignable to the NH groups and strong absorption at about 1670-1700 Cm^{-1}assignable to the carbonyl group. In all of the ionic forms; we have proton abstraction from the 2-thiopyrimidone skeletons.^{1}H-NMR spectra of these ionic forms **4a-f** show the peaks of *n-butyl* hydrogenes. ^{13}C-NMR spectra of *tetra*-butyl ammonium 2-thiopyrimidinate ionic forms **4a-f** exhibited the carbonyl groups at δ 183-184 ppm and the carbon atom of carbonyl groups in thiopyrimidones **5a-f** resonate at δ 176-178 ppm. The same change in chemical shift forC-2(C=S) was seen in ionic forms **4a-f** and also **5a-f.** In all of ionic forms **4a-f**, the chemical shifts are greater than **5a-f.** Deshilding of carbonyl and thiocarbonyl groups in ionic forms can confirm the intermolecular electrostatic interaction between tetra-butyl ammonium ion and oxygen or sulfur in thiopyrimidinate ionic forms **4a-f.** In our last reported work, [12] it was shown that the former N (1)-H is more acidic. This can be ascribed to the mesomeric effect of the cyano group and thus the better delocalization possibilities for the negative charge, X-ray data for piperidinium thiopyrimidinate confirmed our assumption.[12a,12b] It seems that in ionic forms, the thiopyrimidinate structure could be stabilized with *tetra*- butyl ammonium ion with electrostatic forces such as N^+ ...O, N^+...S or N^+...N. In conclusion, we were able to synthesize 6-aryl -5-cyano-2–thiopyrimidones and their tetra-butyl ammonium thiopyrimidonate using an efficient one-pot three-component condensation under reflux and microwave irradiation conditions. Good yields of products compared to the previously reported yield, [9] short reaction times in the case of microwave irradiation and also mild reactioin conditions make this protocol complementary to the existing methods. The tetra-butyl ammonium 2-thiopyrimidinate ionic forms are stable and could be used for further transformation.

Experimental

Melting points are uncorrected and were recorded on an *Electrothermal 9100* and *BÜCHI Melting point B-545* apparatuses. IR spectra were run on a *Shimadzu IR-460* spectrometer or FTIR Mattson 1000 Unicam in cm^{-1} (KBr). ^{1}H and ^{13}CNMR spectra were recorded on Bruker DRX 300 (300 MHz) AVANCE spectrometer at 300, 75MHz respectively with in DMSO-d_6 solution using TMS as the internal standard.EI^+ (70ev) Mass spectra were recorded on a VC Zab-2F- Mass spectrometer and HP 59970 CD GC/MS-MSD- (HP-5, 30m, He). High-resolution Mass spectra were obtained on the instrument using peak-matching techniques at EPSRC.

General procedure for the synthesis of tetra-butyl ammonium 6-aryl-5-cyano-2-thiopyrimidonate ionic forms and 2-thiopyrimidones in reflux condition (5a-g):
Tetra-butyl ammonium hydroxide 12.5% mole (2.60 ml, 1 mmole, and 0.5 equivalents) was added to a solution of the aromatic aldehyde (2mmol), thiourea (3mmol, 225mg) and methyl cyanoacetate (0.2 ml, 2.2 mmol) in 40 ml MeOH, the mixture was stirred for 3-4 h in the reflux condition. After completion of the reaction (monitored by TLC eluent: EtOAc: MeOH 10:1), the solvent was removed under reduced pressure and the remained was washed with a little water and also mixture of CH_2Cl_2: Petroleum ether (70:30). Pure Ionic forms of **4a-g** were obtained. The ionic forms (1 mmol) were dissolved in water (10 ml) and the solutions were neutralized by the slow addition of 2M HCl which resulted in the crystalline of the pure compounds. The crystals were washed with mixture of (Petroleum ether: CH_2Cl_2 (60:40).

General procedure for the synthesis of tetra-butyl ammonium 6-aryl-5-cyano-2-thiopyrimidonate ionic forms and 2-thiopyrimidones under microwave irradiation (5a-f):
A solution of benzaldehyde derivative (2 mmol), thiourea (3 mmol, 225 mg), methyl cyanoacetate (0.2 ml, 2.2 mmol) and *tetra*-butyl ammonium hydroxide 12.5% mole ((2.60 ml, 0.5 equivalent) in 5 ml MeOH in Teflon vessel was subjected to microwave irradiation (domestic microwave oven operated at 2450 MHz, power, 850W) for 2-4 min. After completion of the reaction, solvent was removed under reduced pressure and the mixture was neutralized by the slow addition of 2M HCl which resulted in the precipitate form. After filtration, the precipitate was washed with a little water were washed with mixture of (Petroleum ether: CH_2Cl_2 (60:40). Products are 2-thiopyrimidones **5a-f.**

Selected data for tetra-butyl ammonium 2-thiopyrimidonate (4a-g)

Tetra-butyl ammonium 5-cyano-6-phenyl-4-oxo-2-thiopyrimidinate (4a):
M.p: 128 °C; IR (KBr, cm^{-1}): 3451, 2963, 2205, 1653, 1489, 1467, and 1236^{1}H-NMR (δ, DMSO-d_6): 0.92 (t, 3H, J= 7.24 Hz, CH_3), 1.29 (m, 2H, CH_2), 1.54 (m, 2H, CH_2), 3.15 (t, 2H, J=8.06 Hz, CH_2), 7.42-7.74 (m, 5H, Ar), 11.53 (brs, 1H, NH);^{13}C-NMR (δ, DMSO-d_6):13.96(a), 19.66(b), 23.50(c), 57.94(d), 85.54(C-5), 119.40(C-7,CN), 128.41(C-2′,6′), 128.64(C-3′, 5′), 130.48(C-4′), 138.14(C-1′), 162.92(C-6), 167.74(C=S, C-2), 183.45(C=O, C-4) ppm.

Tetra-butyl ammonium 5-cyano-6-(4-bromophenyl)-4-oxo-2-thiopyrimidinate (4b):
M.p: 165°C; IR (KBr, cm^{-1}): 3451, 2963, 2209, 1639, 1594, 1467, 1253; ^{1}H-NMR (δ, DMSO-d_6): 0.66 (t, 3H, J=6.96 Hz, CH_3), 1.03 (m, 2H, CH_2), 1.29 (m, 2H, CH_2), 2.89 (m, 2H, CH_2), 7.43 (s, 4H, Ar), 11.44 (brs, 1H, NH); ^{13}C-NMR (δ, DMSO-d_6):13.46(a), 19.16(b), 22.99(c), 57.44(d), 84.97(C-5), 118.73(C-7,CN), 123.55(C-4′), 130.23(C-2′, 6′), 130.99(C-3′, 5′), 136.77(C-1′), 162.29(C-6), 165.97(C=S, C-2), 183.10(C=O, C-4) ppm.

Tetra-butyl ammonium-5-cyano-6-(3-chlorophenyl)-4-oxo-2-thiopyrimidinate (4c):
M.p: 143 °C; IR (KBr, cm^{-1}): 3450, 2959, 2210, 1638, 1496, 1460, 1246; ^{1}H-NMR (δ, DMSO-d_6): 0.91 (t, 3H, J=7.22 Hz, CH_3), 1.28 (m, 2H, CH_2), 1.52 (m, 2H, CH_2), 3.15 (t, 2H, J=8.16 Hz, CH_2), 7.45-7.73 (m, 4H, Ar), 11.44 (brs, 1H, NH); ^{13}C-NMR (δ, DMSO-d_6):13.45(a), 19.16(b), 22.99(c), 57.44(d), 84.17(C-5), 118.59(C-7, CN), 126.78(C-6′), 127.84(C-2′), 129.80(C-5′), 129.94(C-4′), 132.70(C-3′), 139.58(C-1′), 162.23(C-6), 165.45(C=S, C-2), 183.17(C=O, C-4) ppm.

Tetra-butyl ammonium 5-cyano-6- (4-cyanophenyl)-4-oxo-2-thiopyrimidinate (4d):
M.p: 208 °C; IR (KBr, cm^{-1}):3418, 2960, 2230, 2206, 1638, 1496, 1250; ^{1}H-NMR (δ, DMSO-d_6): 0.91 (t, 3H, J=7.28 Hz, CH_3), 1.29 (m, 2H, CH_2), 1.54 (m, 2H, CH_2), 3.15 (t, 2H, J=8.18 Hz, CH_2), 7.89 (d, 2H, J=8.25 Hz, Ar), 7.95 (d, 2H, J=8.25 Hz, Ar), 11.79 (brs, 1H, NH); ^{13}C-NMR (δ, DMSO-d_6):13.95(a), 19.65(b), 23.49(c), 57.94(d), 86.00(C-5), 112.83(C-4′), 118.88(C-7,CN), 118.96(CN), 129.49(2′, 6′), 132.54(C-3′, 5′), 142.52(C-1′), 162.59(C-6), 166.10(C=S, C-2), 183.88(C=O, C-4) ppm.

Tetra-butyl ammonium 5-cyano-6-(4-methylphenyl)-4-oxo-2-thipyrimidinate (4e):
M.p:145°C; IR (KBr, cm^{-1}) 3451, 3155, 2200, 1619, 1559, 1475, 1230; ^{1}H-NMR (δ, DMSO-d_6): 0.91 (t, 3H, J=7.28 Hz, CH_3), 1.26 (m, 2H, CH_2), 1.54 (m, 2H, CH_2), 2.35 (s, 3H, CH_3), 3.14 (t, 2H, J=7.85 Hz, CH_2), 7.25 (d, 2H, J=7.65 Hz, Ar), 7.64 (d, 2H, J=7.17 Hz, Ar), 11.59 (brs, 1H, NH); ^{13}C-NMR (δ, DMSO-d_6):12.8(a), 18.5(b), 20.27(Me), 22.34(c), 56.78(d), 84.07(C-5), 118.38(C-7,CN), 127.08(C-3′,5′), 127.5(C-2′,6′), 134.12(C-4′), 139.17(C-1′), 161.86(C-6), 166.37(C=S,C-2), 183.06(C=O, C-4) ppm.

Tetra-butyl ammonium 5-cyano-6- (4-pyridyl)-4-oxo-2-thio-pyrimidinate (4f):
M.p:163 °C; IR (KBr, cm^{-1}):3555, 3145, 2200, 1641, 1592, 1483, 1238; ^{1}H-NMR (δ, DMSO-d_6): 0.91 (t, 3H, J=7.26 Hz, CH_3), 1.29 (m, 2H, CH_2), 1.54 (m, 2H, CH_2), 3.15 (m, 2H, CH_2), 7.65 (d, 2H, J=6.01, 1.5 Hz, Ar), 8.7 (d, 2H, J=5.99, 1.5 Hz, Ar), 11.83 (brs, 1H, NH); ^{13}C-NMR (δ, DMSO-d_6):13.46(a), 19.16(b), 23.01(c), 57.46(d), 85.54(C-5), 118.22(C-7,CN), 122.29(C-2′,6′), 144.85(C-1′), 149.68(C-3′,5′), 162.04(C-6), 165.09(C=S,C-2), 183.57(C=O, C-4) ppm.

Tetra-butyl ammonium 5-cyano-6- (4-trifluorophenyl)-4-oxo-2-thioydro-pyrimidinate (4g):
M.p: 109 °C; IR (KBr, cm^{-1}):3345, 3165, 2865, 2200, 1626, 1567, 1244; ^{1}H-NMR (δ, DMSO-d_6): 0.91 (t, 3H, J=7.2 Hz, CH_3), 1.28 (m, 2H, CH_2), 1.55 (m, 2H, CH_2), 3.15 (t, 2H, J=8.1 Hz, CH_2), 7.84 (d, 2H, J=8.28 Hz, Ar), 7.91 (d, 2H, J=8.07 Hz, Ar), 11.77 (brs, 1H, NH); ^{13}C-NMR (δ, DMSO-d_6):13.45(a), 19.16(b), 23.00(c), 57.43(d), 85.48(C-5), 118.52(C-7,CN), 122.22(C-1′), 124.94(C-3′, 5′), 124.99(C-2′, 6′), 129.72(CF_3), 141.57(C-4′), 162.16(C-6), 165.91(C=S, C-2), 183.36(C=O, C-4) ppm.

Selected data for 6-aryl-5-cyano- 2-thiopyrimidones (5a-f):

5-Cyano-6-phenyl-2-thiopyrimidone (5a):
M.p:299°C; IR (KBr, cm^{-1}) 3400, 3184, 2230, 1692, 1546, 1230; ^{1}H-NMR (δ, DMSO-d_6), 7.60-7.90 (brs, 5H, Ar),13.20(brs,1H, NH); ^{13}C-NMR (δ, DMSO-d_6), 91.13(C-5), 115.10(C-7,CN), 129.02(C-2′,6′), 129.23(C-3′,5′), 129.68(C-4′), 132.68(C-1′) , 158.00(C-6), 161.52(C=S,C-2), 178.00(C=O, C-4) ppm. HRMS (EI)$^+$: Calcd. ($C_{11}H_7N_3OS$) 229.0310 Found 229.0296.

5-Cyano-6- (4-bromophenyl)-2-thiopyrimidone (5b):
M.p. 284°C; IR (KBr, cm^{-1}) 3500, 3215, 2230, 1707, 1569, 1230; ^{1}H-NMR (δ, DMSO-d_6), 7.62 (d, 2H, J= 9 Hz, Ar), 7.80 (d, 2H, J= 9 Hz, Ar), 13.20 (brs, 2H, NH_2); ^{13}C-NMR (δ, DMSO-d_6): 91.33(C-5), 114.89(C-7,CN), 126.30(C-4′), 128.85(C-2′,6′), 131.35(C-3′,5′), 132.10(C-1′), 158.87(C-6′), 160.51(C=S, C-2), 176.68(C=O, C-4) ppm. HRMS (EI)$^+$: Calcd. ($C_{11}H_6{}^{81}Br\ N_3OS$) 308.9394, Found 308.9420; Calcd. ($C_{11}H_6{}^{79}Br\ N_3OS$) 306.9427 Found 306.9434.

5-Cyano-6- (3-chlorophenyl)-2-thiopyrimidone (5c):
M.p: 229°C; IR (KBr, cm^{-1}): 3369, 3184, 2230, 1707, 1553, 1223; ^{1}H-NMR (δ, DMSO-d_6): 7.62-7.85 (m, 4H, Ar), 13.30 (brs, 2H, NH_2); ^{13}C-NMR (δ, DMSO-d_6): 91.53(C-5′), 114.78(CN, C-7), 127.90(C-6′), 129.09(C-2′), 130.89(C-5′), 131.62(C-4′), 132.28(C-3′), 133.44(C-1′), 158.80(C-6), 160.02(C=S, C-2), 176.77(C=O, C-4) ppm. HRMS (EI)$^+$: Calcd:($C_{11}H_6{}^{37}ClN_3OS$) 264.9891, Found 264.9875; Calcd. ($C_{11}H_6{}^{35}Cl\ N_3OS$) 262.9920 Found 262.9913.

5-Cyano-6- (4-cyanophenyl)-2-thiopyrimidone (5d):
M.p: 310°C (decomposed); IR (KBr, cm^{-1}): 3430, 3100, 2227, 2214, 1677, 1569, 1407, 1231; ^{1}H-NMR (δ, DMSO-d_6), 7.9 (d, 2H, J=9Hz, Ar), 8.05 (d, 2H, J=9Hz, Ar), 13.30(brs, 2H, NH); ^{13}C-NMR (δ, DMSO-d_6): 85.54(C-5), 112.37(C-4′), 118.34(CN), 118.48(C-7, CN), 129.01(C-2′,6′), 132.06(C-3′,5′), 141.99(C-1′), 162.21(C-6), 165.71(C=S, C-2), 183.33(C=O, C-4) ppm. HRMS (EI)$^+$: Calcd. ($C_{12}H_6N_4OS$) 254.0262 Found 254.0297.

5-Cyano-6-(4-methylphenyl) -2-thiopyrimidone (5e):
M.p: 288 °C; IR (KBr, cm^{-1}): 3430, 3215, 3110, 2190, 1668, 1551, 1217; ^{1}H-NMR (δ, DMSO-d_6): 2.4 (s, 3H, CH_3) 7.37 (d, 2H, J=7.89 Hz, Ar), 7.56 (d, 2H, J=7.86 Hz, Ar), 13.17 (s, 1H, NH); 13.27 (brs, 1H, NH); ^{13}C-NMR (δ, DMSO-d_6): 22.73(CH_3), 92.02(C-5), 116.45(C-7, CN), 127.94(C-4′), 130.38(C-2′,6′), 130.61(C-3′,5′), 144.13(C-1′), 160.15(C-6), 162.49(C=S, C-2), 177.78(C=O, C-4) ppm.

5-Cyano-6-(4-pyridyl) -2-thiopyrimidone (5f):
M.p: 340 °C; IR (KBr, cm^{-1}): 3190, 3000, 2200, 1683, 1557, 1467, 1227; ^{1}H-NMR (δ, DMSO-d_6): 7.67 (d, 2H, J=5.79 Hz, Ar), 8.81 (d, 2H, J=5.7 Hz, Ar), 13.29 (s, 1H, NH); ^{13}C-NMR (δ, DMSO-d_6): 91.47(C-5), 114.07(C-7, CN), 122.73(C-2′,6′), 137.08(C-1′), 149.86(C-3′,5′), 158.10(C-6), 158.69(C=S, C-2), 176.15(C=O, C-4) ppm.

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