A Facile Aerobic Copper-Catalyzed α-Oxygenation of Aryl Thioacetamides: An Efficient Access to α-Keto Aryl Thioamides

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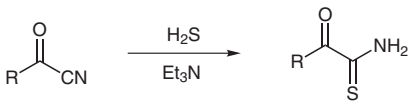
Abstract: Copper(II) efficiently catalyzes the aerobic oxidation of aryl thioacetamides into the corresponding α-keto aryl thioamides in moderate to high yields in the presence of K_2CO_3 under O_2 atmosphere. This protocol is simple, clean, and generates water as the only byproduct. A mechanism is proposed for the reaction course.

Key words: $CuCl_2 \cdot 2H_2O$, oxygenation, α-keto aryl thioamides, thioacetomorpholides

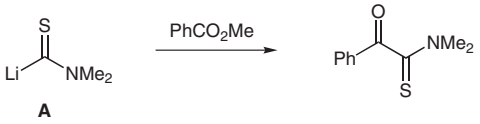
The development of improved oxidation reactions is an area of great current interest owing to their almost ubiquitous nature in both academic and industrial laboratories.[1] Transition-metal-catalyzed oxidation of organic compounds with atom-efficient oxidants such as O_2 or H_2O_2 is rapidly gaining importance as a viable alternative to the environmentally hazardous metal-promoted stoichiometric oxidations.[2] Traditionally, most oxidations are accomplished by at least stoichiometric amounts of often toxic oxidants, especially chromium(VI) reagents.[3] As a consequence, different catalytic methods using small amounts of metallic derivatives and clean oxidants have been developed.

Copper(II) salt catalysis of oxidation and oxygenation reactions is of recognized importance for carrying out selective transformation.[4] The oxidation of hydroxyl and methylene groups to the corresponding carbonyl moieties remains one of the most fundamental reactions in organic synthesis. Benzylic methylene groups of aromatic aldehydes and ketones have been oxidized by copper(II) to the corresponding carbonyl function,[5] but there is no report about oxidation of aryl thioacetamides which leads to the synthesis of α-keto aryl thioamide derivatives. Limited attention has been given to the synthesis of this framework. Addition of H_2S onto acylcyanides according to Scheme 1 gave corresponding N-unsubstituted α-keto aryl thioamides.[6] However, the synthesis of 2-oxothioamides is restricted to the N-unsubstituted derivatives.



Scheme 1

The reaction of (*N*,*N*-dimethylthiocarbomyl) lithium (**A**) with methyl benzoate, afforded α-keto aryl thioamides (Scheme 2).[7] Reagent **A** has been generated by Seebach at –100 °C by deprotonation of dimethylthioformamide with LDA. It is evident that the need for the development of new and flexible protocols is required to access α-keto aryl thioamides without using toxic reagents and avoiding extreme conditions.



Scheme 2

Aryl thioacetamides have been used as useful synthons in the synthesis of heterocycles.[8] The availability of such aryl thioamides in our laboratory[9] provided a unique opportunity for examining further their synthetic utility. In continuation of our research in this area,[10] herein we report a convenient preparation of α-keto aryl thioamides from readily available aryl thioamides in good to excellent yields. To the best of our knowledge, this is the first demonstration of the oxidation of aryl thioacetamides.

To find the optimal conditions, the oxidation of phenyl thioacetomorpholide (**1a**) in the presence of catalyst and base was chosen as a model reaction. A mixture of phenyl thioacetomorpholide (1 mmol), catalyst, base (1 mmol), and solvent (3 mL) was stirred under various reaction conditions (Table 1). Our first experiment showed that the presence of $CuCl_2$ along with K_2CO_3 is required to achieve the oxidation of thioamides and no reaction was observed when the oxidation was performed with $CuCl_2$ alone (Table 1, entries 1, 2). The $Cu(OAc)_2$ was also examined as catalyst for this reaction, however, it was less effective compared to $CuCl_2$ and afforded α-keto aryl thioamides in 80% yield (Table 1, entry 4). We then continued to optimize the model reaction by considering the efficiency of polar and nonpolar solvents. A polar solvent such as DMF was much better than a nonpolar solvent (Table 1, entries 3, 5, 6). The effect of temperature was also studied by carrying out the model reaction in the presence of $CuCl_2$ at room temperature, 50 °C, and 80 °C. It was observed that the yield was increased as the reaction temperature was raised (Table 1, entries 3, 7, 8). Finally, we found that 1 mol% of $CuCl_2$ could effectively catalyze

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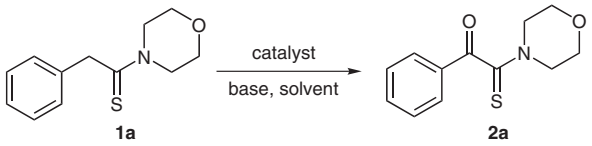
Table 1 Oxidation of Phenyl Thioacetomorpholide Catalyzed by Different Catalytic Systems



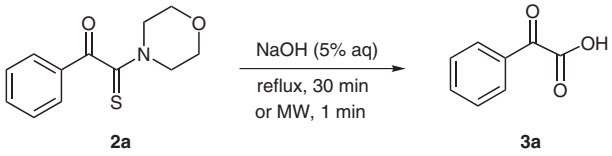
1a **2a**

Entry	Catalyst (mol%)	Solvent	Base	Time (h)	Temp (°C)	Yield (%)[a]
1	none	DMF	K_2CO_3	20	80	trace
2	$CuCl_2$ (10)	DMF	No base	20	80	no reaction
3	$CuCl_2$ (10)	DMF	K_2CO_3	20	80	88
4	$Cu(OAc)_2$ (10)	DMF	K_2CO_3	20	80	80
5	$CuCl_2$ (10)	THF	K_2CO_3	20	65	trace
6	$CuCl_2$ (10)	toluene	K_2CO_3	20	80	no reaction
7	$CuCl_2$ (10)	DMF	K_2CO_3	20	25	trace
8	$CuCl_2$ (10)	DMF	K_2CO_3	20	50	40
9	$CuCl_2$ (10)	DMF	Cs_2CO_3	20	80	90
10	$CuCl_2$ (10)	DMF	K_2CO_3	5	80	trace
11	$CuCl_2$ (10)	DMF	K_2CO_3	10	80	46
12	$CuCl_2$ (1)	DMF	K_2CO_3	20	80	85
13[b]	**$CuCl_2$ (1)**	**DMF**	**K_2CO_3**	**3**	**80**	**94**

[a] Isolated yield.
[b] Reaction carried out under O_2 atmosphere.

the reaction for synthesis of the desired product. Using more than 1 mol% $CuCl_2$ has little effect on the yield of the reaction (Table 1, entries 3, 12). The reaction time is reduced by seven times upon changing the atmosphere from air to oxygen. Considering the reaction time, amount of catalyst and the yield, the optimized conditions are: K_2CO_3 (1 equiv), $CuCl_2$ (1 mol%), aryl thioacetamide (1 equiv) in DMF (3 mL) at 80 °C under oxygen atmosphere for 3 hours. To evaluate the scope of the reaction, the oxidation of some aryl thioacetamide derivatives was studied under these optimized conditions.

The structures of the products were confirmed by GC-MS, ^{1}H NMR, ^{13}C NMR analysis,[12] and finally the compounds were transformed into corresponding known aryl glyoxalic acids by our reported procedure and compared with authentic samples (Scheme 3).[9b]

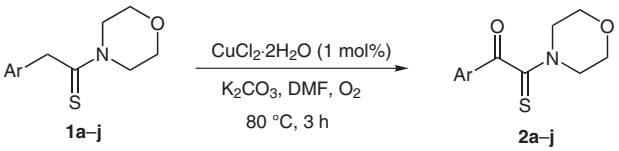


2a **3a**

Scheme 3

As shown in Table 2, all the substrates consistently underwent oxidation selectively to the corresponding α-keto aryl thioamides in high yields. This reaction was not limited to simple benzene-containing aromatics; the pyridine-containing substrate also afforded α-keto aryl thioamide in good yield (Table 2, entry 7). In the case of phenyl dithioacetomorpholide, this conversion was accompanied by C–C bond cleavage, yielding 4-(2-morpholino-2-thioxoacetyl)benzoic acid (Table 2, entry 10).

Table 2 Oxidation of Various Aryl Thioamides Catalyzed by $CuCl_2$ (1 mol%) under O_2 Atmosphere



1a–j **2a–j**

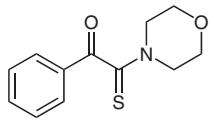
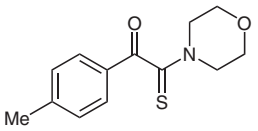
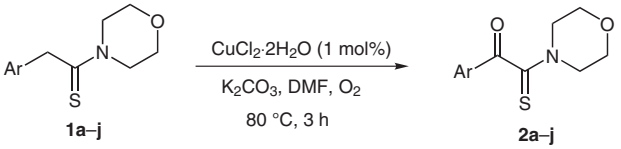
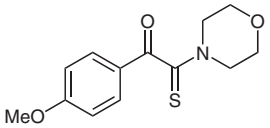
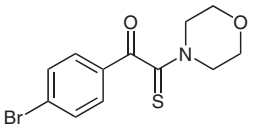
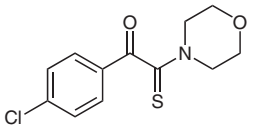
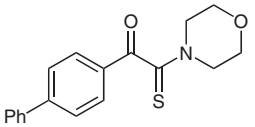
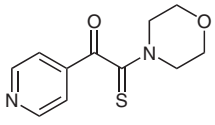
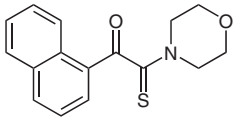
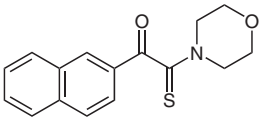
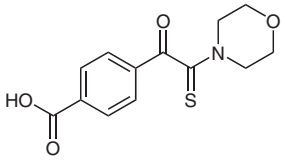
Entry	Thioacetomorpholide **1**	Ar	Product	Mp (°C)	Yield (%)[a]
1	**1a**	Ph	 **2a**	109–111	94
2	**1b**	4-MeC_6H_4	 **2b**	100–102	83

Table 2 Oxidation of Various Aryl Thioamides Catalyzed by $CuCl_2$ (1 mol%) under O_2 Atmosphere (continued)



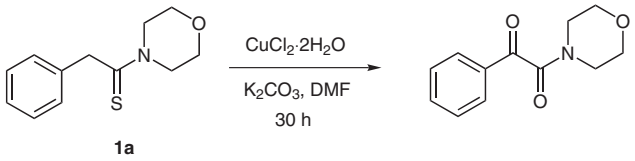
1a–j **2a–j**

Entry	Thioacetomorpholide **1**	Ar	Product	Mp (°C)	Yield (%)[a]
3	**1c**	4-$MeOC_6H_4$	 **2c**	122–124	80
4	**1d**	4-BrC_6H_4	 **2d**	144–145	85
5	**1e**	4-ClC_6H_4	 **2e**	153–155	83
6	**1f**	4-biphenyl	 **2f**	160–162	87
7	**1g**	4-pyridyl	 **2g**	82–83	90
8	**1h**	α-naphthyl	 **2h**	118–120	75
9	**1i**	β-naphthyl	 **2i**	156–158	80
10	**1j**	4-phenylacetothiomorpholide	 **2j**	131–133	69

[a] Isolated yield.

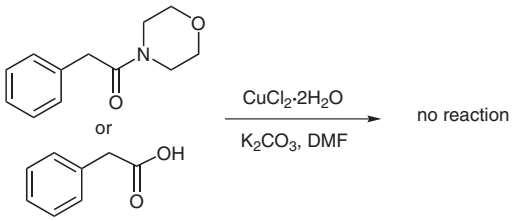
Our observation of the C–C bond cleavage is consistent with a previous finding of Sayre et al.[5] for the ketones promoted by Cu(II), though their reaction conditions were more strongly basic than ours (Et_3N/pyridine vs. K_2CO_3). It should also be mentioned that when the reaction time was extended to 30 hours under air atmosphere, desulfur-

ization of the α-keto aryl thioamide was observed and the corresponding α-keto aryl amides were obtained as the exclusive product (Scheme 4).[12]



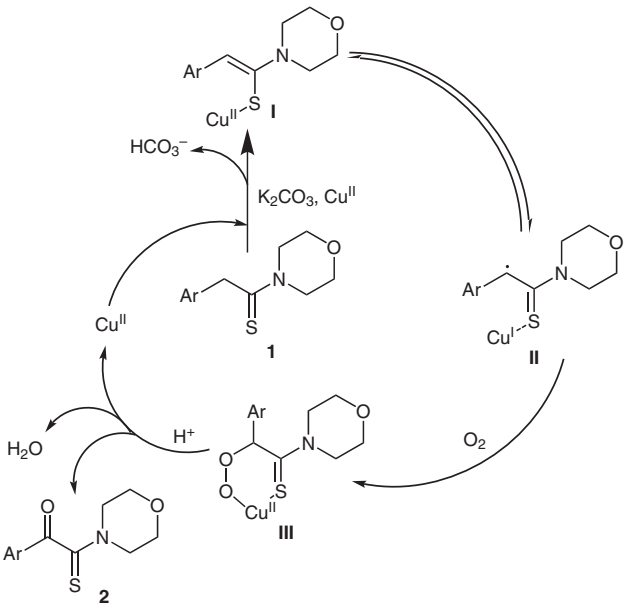
Scheme 4

To examine the chemoselectivity of the reaction we also tested the α-oxygenation of the phenyl acetomorpholide as well as phenyl acetic acid under optimized conditions: no traces of the desired products were observed (Scheme 5).



Scheme 5

The detailed mechanism of reaction is not clear at this stage. A possible reaction mechanism to account for the formation of substituted α-keto aryl thioamides using catalytic amount of $CuCl_2$ and K_2CO_3 is proposed in Scheme 6. The first step is a base-promoted thioenolization then tautomerization of **I** gives **II** and Cu(I).[5] In the presence of molecular O_2, oxygen incorporation occurs and provides a α-hydroperoxide equivalent **III** and regenerates Cu(II). α-Hydroperoxide then undergoes competitive dehydration to the α-keto aryl thioamide. The use of catalytic amount of the Cu(II) indicates that the Cu(I) to Cu(II) regeneration by O_2 occurs during the reaction. It should be noted that when 1,4-hydroquinone (0.1 equiv) was used in the model reaction, the product was obtained in lower yield (62% vs. 94%), which is evidence for a free-radical pathway for the reaction.[11]



Scheme 6

In conclusion, we have reported an efficient procedure for the synthesis of α-keto aryl thioamides using $CuCl_2{\cdot}2H_2O$ as a nontoxic and inexpensive heterogeneous catalyst with easy workup, which make it a useful and attractive strategy for the synthesis of α-keto aryl thioamides. These compounds have the potential to be converted into aryl glyoxalic acids.

General Procedure for the Synthesis of α-Keto Aryl Thioamides

The aryl thioamides were prepared according to previously our reported procedure.[9] To a stirred suspension of $CuCl_2{\cdot}2H_2O$ (1 mol%) in DMF (3 mL) were added aryl thioamide (1 mmol) and K_2CO_3 (1 mmol). The reaction mixture was stirred at 80 °C for 3 h under an O_2 atmosphere. The progress of the reaction was monitored by TLC. After completion of the reaction, the mixture was poured into ice-cold H_2O and stirred for 10 min, which resulted in precipitation of the desired α-keto aryl thioamides. The precipitated solid was filtered, washed with PE, and dried. The structure of the products was confirmed by analytical, GC-MS, ^{1}H NMR, and ^{13}C NMR data.[12]

Acknowledgment

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(12) **Spectral Data of the Products**

Compound **2a**: ^{1}H NMR (500 MHz, $CDC1_3$): δ = 7.93 (d, *J* = 7.18 Hz, 2 H), 7.55 (t, *J* = 7.41 Hz, 1 H), 7.43 (t, *J* = 7.76 Hz, 2 H), 4.27 (t, *J* = 4.94 Hz, 2 H), 3.84 (t, *J* = 4.95 Hz, 2 H), 3.63 (t, *J* = 4.77 Hz, 2 H), 3.53 (t, *J* = 4.76 Hz, 2 H) ppm. ^{13}C NMR (125 MHz, $CDC1_3$): δ = 196.16, 188.31, 134.86, 133.70, 130.27, 129.38, 66.93, 66.81, 52.35, 47.54 ppm. MS (EI): *m/z* (%) = 235 (73) [M$^+$], 177 (30), 130 (100), 105 (53), 86 (71), 77 (46). Anal Calcd for $C_{12}H_{13}NO_2S$: C, 61.25; H, 5.57; N, 5.95. Found: 61.59; H, 5.72; N, 5.94.

Compound **2b**: ^{1}H NMR (500 MHz, $CDC1_3$): δ = 7.82 (d, *J* = 8.21 Hz, 2 H), 7.22 (t, *J* = 8.11 Hz, 2 H), 4.26 (t, *J* = 4.95 Hz, 2 H), 3.83 (t, *J* = 4.95 Hz, 2 H), 3.62 (t, *J* = 4.77 Hz, 2 H), 3.53 (t, *J* = 4.71 Hz, 2 H), 2.36 (s, 3 H) ppm. ^{13}C NMR (125 MHz, $CDC1_3$): δ = 196.47, 188.30, 146.13, 131.19, 130.40, 130.10, 66.93, 66.81, 52.32, 47.51, 22.29 ppm.

Compound **2c**: ^{1}H NMR (500 MHz, $CDC1_3$): δ = 7.88 (d, *J* = 8.80 Hz, 2 H), 6.87 (d, *J* = 8.82 Hz, 2 H), 4.24 (t, *J* = 4.23 Hz, 2 H), 3.81 (t, *J* = 4.63 Hz, 2 H), 3.80 (s, 3 H), 3.60 (t, *J* = 4.02 Hz, 2 H), 3.51 (s, 2 H) ppm. ^{13}C NMR (125 MHz, $CDC1_3$): δ = 196.54, 188.31, 165.07, 132.73, 126.46, 114.73, 66.95, 66.79, 56.10, 52.33, 47.57 ppm.

Compound **2d**: ^{1}H NMR (500 MHz, $CDC1_3$): δ = 7.79 (d, *J* = 8.40 Hz, 2 H), 7.56 (d, *J* = 8.40 Hz, 2 H), 4.24 (t, *J* = 4.87 Hz, 2 H), 3.80 (t, *J* = 4.90 Hz, 2 H), 3.63 (t, *J* = 4.75 Hz, 2 H), 3.52 (t, *J* = 4.65 Hz, 2 H) ppm. ^{13}C NMR (125 MHz, $CDC1_3$): δ = 195.49, 185.86, 141.22, 132.30, 131.49, 129.55, 66.90, 66.72, 52.33, 47.58 ppm.

Compound **2e**: ^{1}H NMR (500 MHz, $CDC1_3$): δ = 7.94 (d, *J* = 8.56 Hz, 2 H), 7.46 (d, *J* = 8.52 Hz, 2 H), 4.31 (t, *J* = 4.95 Hz, 2 H), 3.89 (t, *J* = 4.95 Hz, 2 H), 3.69 (t, *J* = 4.82 Hz, 2 H), 3.58 (t, *J* = 4.82 Hz, 2 H) ppm. ^{13}C NMR (125 MHz, $CDC1_3$): δ = 195.54, 186.76, 141.38, 132.34, 131.57, 129.69, 66.92, 66.75, 52.35, 47.61 ppm. Anal. Calcd for $C_{12}H_{12}ClNO_2S$: C, 53.43; H, 4.48; N, 5.19. Found: C, 53.44; H, 4.44; N, 5.08.

Compound **2f**: ^{1}H NMR (500 MHz, $CDC1_3$): δ = 8.00 (d, *J* = 6.81 Hz, 2 H), 7.65 (d, *J* = 8.38 Hz, 2 H), 7.56 (d, *J* = 7.20 Hz, 2 H), 7.42 (t, *J* = 6.53 Hz, 2 H), 7.37 (t, *J* = 5.28 Hz, 1 H), 4.29 (t, *J* = 4.93 Hz, 2 H), 3.86 (t, *J* = 4.93 Hz, 2 H), 3.66 (t, *J* = 4.71 Hz, 2 H), 3.58 (t, *J* = 4.63 Hz, 2 H) ppm. ^{13}C NMR (125 MHz, $CDC1_3$): δ = 196.20, 187.97, 147.64, 139.98, 132.42, 130.87, 129.48, 129.02, 128.04, 127.76, 66.99, 66.63, 52.40, 47.59 ppm.

Compound **2g**: ^{1}H NMR (500 MHz, $CDC1_3$): δ = 8.81 (d, *J* = 4.68 Hz, 2 H), 7.79 (d, *J* = 4.79 Hz, 2 H), 4.27 (t, *J* = 4.33 Hz, 2 H), 3.88 (t, *J* = 4.40 Hz, 2 H), 3.69 (t, *J* = 4.23 Hz, 2 H), 3.57 (t, *J* = 4.41 Hz, 2 H) ppm. ^{13}C NMR (125 MHz, $CDC1_3$): δ = 193.71, 185.27, 150.79, 140.28, 123.01, 66.90, 66.73, 52.41, 47.69 ppm.

Compound **2h**: ^{1}H NMR (500 MHz, $CDC1_3$): δ = 9.21 (d, *J* = 8.70 Hz, 1 H), 8.07 (d, *J* = 8.15 Hz, 1 H), 8.02 (d, *J* = 7.10 Hz, 1 H), 7.90 (d, *J* = 8.15 Hz, 1 H), 7.69 (t, *J* = 7.40 Hz, 1 H), 7.58 (t, *J* = 7.50 Hz, 1 H), 7.50 (t, *J* = 7.72 Hz, 1 H), 4.37 (t, *J* = 4.86 Hz, 2 H), 3.42 (t, *J* = 4.87 Hz, 2 H), 3.71–3.69 (m, 4 H) ppm. ^{13}C NMR (125 MHz, $CDC1_3$): δ = 197.38, 189.76, 135.85, 134.62, 133.27, 131.93, 129.84, 129.55, 129.14, 127.37, 126.48, 124.66, 66.91, 66.79, 52.47, 47.88 ppm.

Compound **2i**: ^{1}H NMR (500 MHz, $CDC1_3$): δ = 8.54 (s, 1 H), 7.97 (d, *J* = 8.52 Hz, 1 H), 7.90 (d, *J* = 8.15 Hz, 1 H), 7.86 (d, *J* = 8.62 Hz, 1 H), 7.82 (d, *J* = 8.09 Hz, 1 H), 7.57 (t, *J* = 7.47 Hz, 1 H), 7.50 (t, *J* = 7.53 Hz, 1 H), 4.32 (t, *J* = 4.89 Hz, 2 H), 3.87 (t, *J* = 4.90 Hz, 2 H), 3.63 (t, *J* = 4.54 Hz, 2 H), 3.57 (t, *J* = 4.28 Hz, 2 H) ppm. ^{13}C NMR (125 MHz, $CDC1_3$): δ = 196.25, 188.46, 136.61, 132.94, 132.85, 131.04, 130.27, 129.78, 129.39, 128.36, 127.60, 124.76, 66.98, 66.85, 52.44, 47.67 ppm.

Compound **2j**: ^{1}H NMR (500 MHz, $CDC1_3$): δ = 10.11 (s, 1 H), 8.15 (d, *J* = 8.28 Hz, 2 H), 7.99 (d, *J* = 8.25 Hz, 2 H), 4.34 (t, *J* = 4.93 Hz, 2 H), 3.92 (t, *J* = 4.95 Hz, 2 H), 3.71 (t, *J* = 5.23 Hz, 2 H), 3.62 (t, *J* = 5.15 Hz, 2 H) ppm. ^{13}C NMR (125 MHz, $CDC1_3$): δ = 194.98, 191.65, 186.43, 140.14, 138.34, 130.74, 130.30, 66.94, 66.79, 52.44, 47.69 ppm.

Compound **2k**: ^{1}H NMR (500 MHz, $CDC1_3$): δ = 7.88 (d, *J* = 7.19 Hz, 2 H), 7.60 (t, *J* = 6.90 Hz, 1 H), 7.45 (t, *J* = 7.78 Hz, 2 H), 3.75–3.71 (m, 4 H), 3.59 (t, *J* = 2.82 Hz, 2 H), 3.31 (t, *J* = 4.82 Hz, 2 H) ppm. ^{13}C NMR (125 MHz, $CDC1_3$): δ = 191.56, 165.89, 135.37, 133.48, 130.10, 129.53, 67.16, 67.09, 46.70, 42.06 ppm.