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Copper-catalyzed domino synthesis of multi-substituted benzo[*b*]thiophene through radical cyclization using xanthate as a sulfur surrogate†

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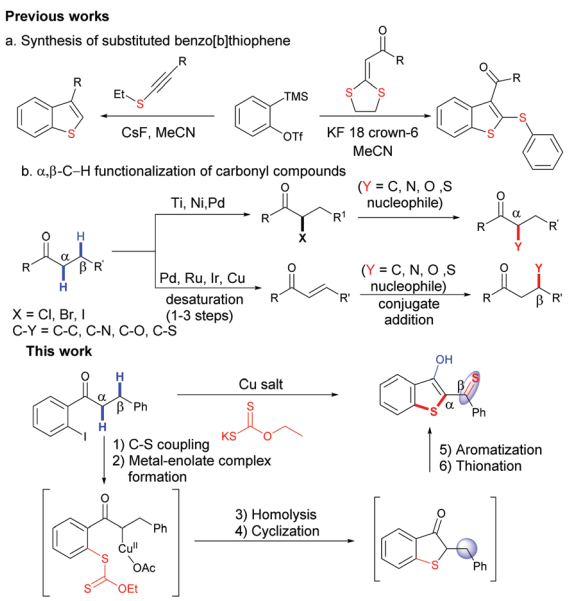
The Cu-catalyzed domino synthesis of multi-substituted benzo[*b*]thiophene through radical cyclization of 2-iodophenyl ketones was developed using xanthate as a sulfur surrogate. This method was extended to obtain tetracyclic Lupinalbin analogues through double C–S/C–O bond formation by changing the substituents. The products were converted to a HTI photoswitch, benzothiophene-fused flavone.

Benzo[*b*]thiophenes are a promising class of organosulfur compounds. In particular, multi-substituted 3-hydroxybenzo[*b*]thiophene is considered essential, as it is used in a broad range of research fields, including medicinal sciences and materials chemistry. 3-Hydroxybenzo[*b*]thiophene is known to exhibit inhibitor activity against human monoamine oxidase (hMAO).[1] It also works as an anti-inflammatory agent,[2] a selective estrogen receptor downregulator (SERD) and a selective estrogen receptor modulator (SERM).[3] Additionally, the 3-hydroxybenzo[*b*]thiophene core is a precursor for the synthesis of hemithioindigo (HTI), which is a chromophore that demonstrates proficient photoswitching properties under visible light irradiation.[4] Benzothiophene synthesis from *o*-silylaryl triflates and acyl-substituted ketene dithioacetals was developed by Singh and co-workers (Scheme 1a).[5a] Very recently, Yoshida and co-workers reported the synthesis of 3-substituted benzothiophenes by reacting aryne with alkynyl sulfides (Scheme 1a).[5b] In spite of their significance, the domino synthesis of multi-substituted benzothiophenes remains difficult in terms of the applicable functional groups and substitution patterns.

On the other hand, copper-catalyzed radical cyclization has been established as a powerful tool for synthesizing complex molecules.[6] In particular, much focus has been placed on the functionalization of carbonyl compounds and their derivatives, due to its importance in organic synthesis. To date, many reports are available on the α-functionalization of saturated carbonyl compounds *via* SN_2 displacement of a halogen atom by nucleophiles (Scheme 1b).[7] In contrast, the incorporation of heteroatom functional groups into the β(sp^3)-C–H bonds of simple ketones is sparsely reported due to their less acidic nature. Conventional methods involve Michael addition[8] to *in situ* synthesized α,β-unsaturated compounds *via* the oxidation of the corresponding saturated carbonyl compounds in one or a few steps (Scheme 1b).[9]

Su and co-workers reported the first Cu-catalyzed direct β-functionalization of saturated ketones involving a tandem ketone dehydrogenation-conjugate addition sequence.[10] Such protocols that involve direct functionalization of unactivated carbonyl compounds appear more attractive; however, there is a dearth of these direct methodologies. Additionally, α,β-sulfenylation reactions are also sparsely reported since sulfur causes catalyst poisoning to the metal catalyst.



Scheme 1 Transition metal-catalyzed Csp^3–H functionalization of carbonyl compounds.

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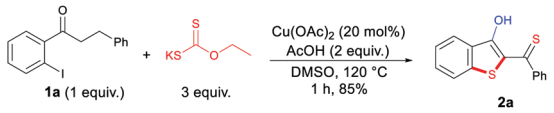


Scheme 2 Optimized reaction conditions for 2-thioaroyl-3-hydroxybenzo[*b*]thiophene.

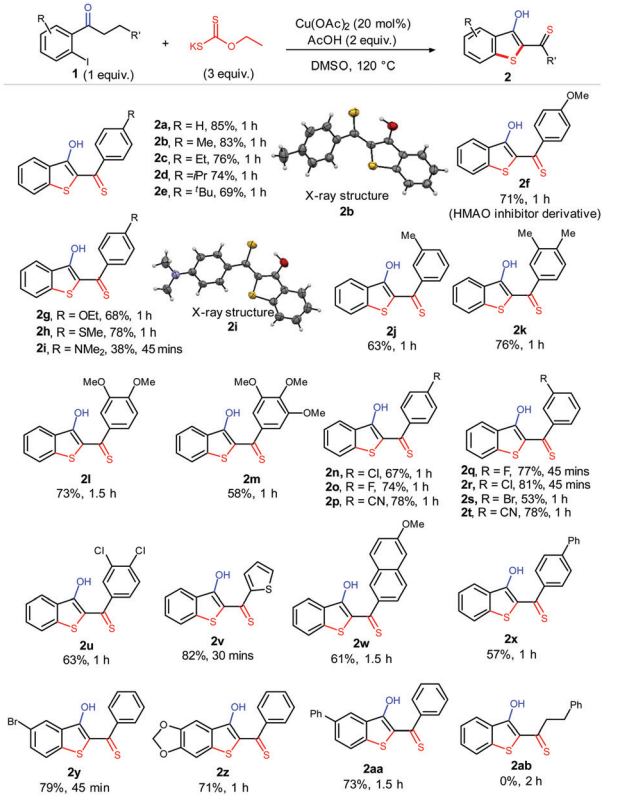
Our group has delved into metal-catalyzed C–S bond formation using xanthate as a sulfur surrogate.[11] Building upon this work, we wanted to develop a methodology to afford 2, 3-disubstituted benzo[*b*]thiophene from unactivated ketones in the presence of copper as a catalyst, through the radical cyclization of the carbonyl compound using xanthate as a sulfur source. It was hypothesized that 2-thioaroyl-3-hydroxybenzo[*b*]thiophenes could be synthesized from 2-halophenyl ketones *via* Cu-catalyzed C–S bond formation through cross-coupling, followed by metal–enolate complex formation and homolytic cleavage of the complex, to eventually provide the cyclized benzo[*b*]thiophene with an active methylene group. It was further expected to undergo oxidation in the presence of DMSO and acetic acid to generate a 2-thioaroylbenzothiophene.

Thus, keeping the above points in mind, a trial reaction was performed with 2-iodophenyl ketone **1a**, and potassium ethyl xanthate (3 equiv.), in the presence of $Cu(OAc)_2$ (10 mol%) and acetic acid (2 equiv.) as additives in DMSO as a solvent at 110 °C. To our delight, the desired product **2a** was isolated in 60% yield within a short time span of 1 h. Encouraged by this, a thorough optimization of the reaction conditions was carried out (see the ESI† for details). The resultant optimized conditions utilize potassium ethyl xanthate (3 equiv.), $Cu(OAc)_2$ (20 mol%) as a catalyst and acetic acid (2 equiv.) as an additive in DMSO (2 mL) solvent at 120 °C to yield 85% of **2a** in 1 h (Scheme 2).

With the optimized reaction conditions in hand, the scope for this domino synthesis of 3-hydroxybenzo[*b*]thiophene was explored with various 2-iodophenyl ketones and the results are summarized in Table 1. The reaction worked well for 2-iodophenyl ketone, with electron-donating substituents on the arene attached to the aliphatic chain, providing the desired products in good to excellent yields (Table 1, **2a–2j**). The structures of **2b** and **2i** were confirmed by single crystal XRD analysis (CCDC 2031230 and 2031231†). Even sterically crowded di- and tri-substituted saturated ketones gave the desired products **2k–2m** in moderate to good yields. The protocol was further employed for 2-iodophenyl ketone substituted with halogen groups and electron withdrawing groups on the arenes. Moderate to good yields of the resultant 3-hydroxybenzo[*b*]thiophene were obtained, irrespective of the position of the halogen substitution (**2n–2u**).

Intriguingly, the reaction proceeded smoothly with 2-iodophenyl ketone containing heterocyclic thiophene to give the cyclized product **2v** in 82% yield within 30 min. Sterically demanding naphthalene and biphenyl-derived ketones underwent the domino reaction successfully to afford **2w** and **2x** in moderate yields. Next, the methodology was applied to 2-iodophenyl ketones bearing substitution on the iodo-attached aryl ring. Bromo- and dioxolanyl

Table 1 Cu-catalyzed synthesis of 2-thioaroyl-3-hydroxybenzo[*b*]-thiophene[a]



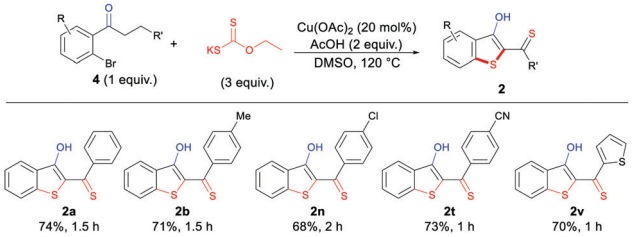
[a] Reaction conditions: **1** (0.5 mmol), xanthate (1.5 mmol), $Cu(OAc)_2$ (20 mol%), AcOH (1 mmol) in DMSO (2 mL) at 120 °C. All yields are isolated yields.

ketones were subjected to the optimized reaction conditions to produce **2y** and **2z** in 79% and 71% yield, respectively. The reaction was even suitable for the biphenyl-substituted ketone, giving the desired product **2aa** in good yield. However, the reaction was not successful when it was performed with an aliphatic substrate, such as 2-iodophenyl pentyl ketone **2ab**. This result suggests that the benzylic position is necessary for thioketone formation.

The protocol was examined for less reactive bromo substrates, such as 2′-bromophenylketone **4** (Table 2). On subjecting 2′-bromophenylketone **4a** to the optimized reaction conditions, the desired cyclized product **2a** was obtained in 74% yield in 1.5 h. Further, 2′-bromophenylketones with various substituents (4-Me, 4-Cl, 4-CN) underwent the cyclization successfully irrespective of the electronic nature of the substituent, to provide the desired products **2b**, **2n**, and **2t** in moderate to good yields. Even 2′-bromophenylketone bearing thiophene also furnished the corresponding product **2v** in 70% yield.

When the optimized reaction conditions were applied to iodophenyl ketone **1z** with a methoxy group at the *ortho*-position on the arene ring attached to the aliphatic chain, a tetracyclic ring **3a** was obtained in 12 h in 92% yield (Table 3). The tetracyclic ring possesses benzothiophene-fused thioflavones, which are analogues of Lupinalbin that are known to be

Table 2 Domino synthesis of 3-hydroxybenzo[*b*]thiophene from 2′-bromophenylketone[a]



[a] Reaction conditions: **4** (0.5 mmol), xanthate (1.5 mmol), $Cu(OAc)_2$ (20 mol%), AcOH (1 mmol) in DMSO (2 mL) at 120 °C. All yields are isolated yields.

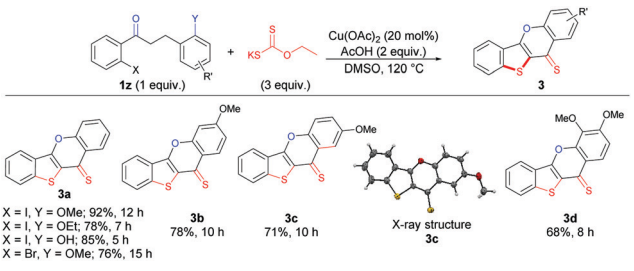
a potent estrogen receptor.[12] Considering the importance of this privileged scaffold, the scope of the tetracyclic moiety was examined.

The reaction worked well with the iodophenyl ketone bearing ethoxy and hydroxy groups at the *ortho*-position on the arene group attached to the aliphatic chain, to furnish **3a** in 78% and 85% yield, respectively. The reaction also gave good yields of **3a** with 2-bromophenylketone. When the reaction was carried out with iodophenyl ketone containing a 2,4-dimethoxy substituent on the arene ring attached to the aliphatic chain, the desired product **3b** was isolated in 14 h in 76% yield by the selective cleavage of the *ortho*-methoxy groups.

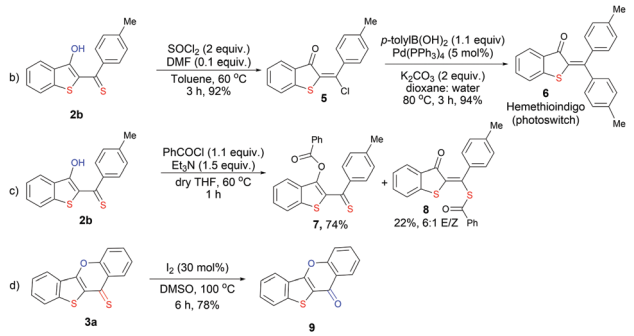
Iodophenyl ketone with 2,5-dimethoxy and 2,3,4-trimethoxy substituents on the arene ring attached to the aliphatic chain were also found to be compatible under the reaction conditions and gave **3c** and **3d** in moderate yields. The structure of the tetracyclic benzothiophene-fused thioflavone was confirmed by single crystal XRD analysis of **3c** (CCDC 2043956†).

Furthermore, the synthetic utility of 2-thioaroyl-3-hydroxybenzothiophene **2b** was demonstrated when it was derivatized to produce hemithioindigo **6** with a 4-fold-substituted double bond, which is known to function as an efficient photoswitch (Scheme 3b). In addition, the hydroxy group in **2b** was benzoylated to give the ester-bearing benzothiophene **7** along with the thioacylated by-product **8** (Scheme 3c). Also, the thioketone moiety in the tetracyclic Lupinalbin analogue **3a** was converted to ketone **9** in 78% yield using iodine and DMSO (Scheme 3d).

Table 3 Synthesis of tetracyclic thiophene-fused thioflavone[a]



[a] Reaction conditions: **1z** (0.5 mmol), xanthate (1.5 mmol), $Cu(OAc)_2$ (20 mol%), AcOH (1 mmol) in DMSO (2 mL) at 120 °C. All yields are isolated yields.

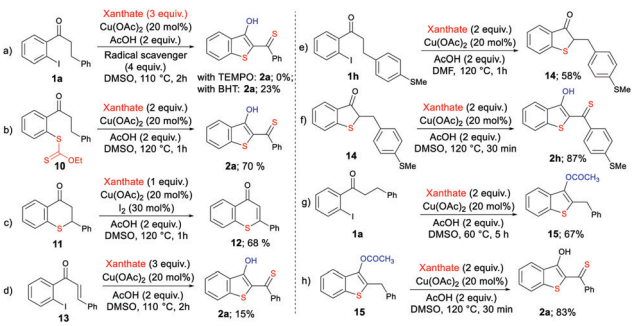


Scheme 3 Gram scale and synthetic applications of current protocol through post synthetic modifications.

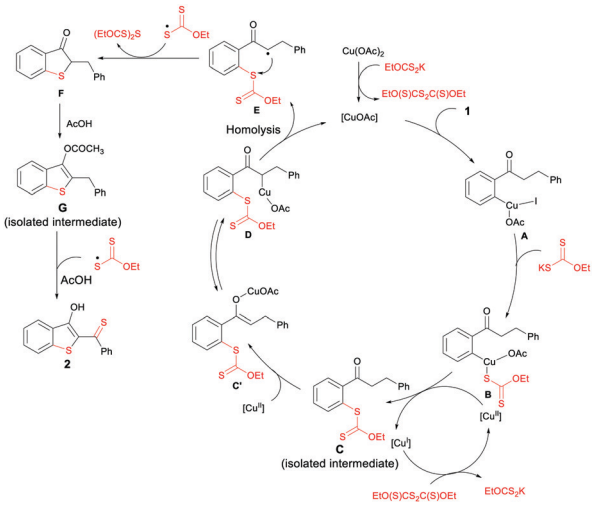
To gain mechanistic insight, a series of controlled experiments were performed. In the presence of the radical scavenger BHT, a drastic decline in the yield to 23% was observed, while in the presence of TEMPO, not even a trace amount of the desired product was formed (Scheme 4a). When the expected intermediate xanthate ester **10** was used under the optimized conditions, the reaction proceeded to give 70% of **2a**, indicating that **10** forms in the due course of reaction (Scheme 4b).

Next, thioflavone **11** was subjected to the optimized conditions with iodine, since it is known that thioflavone rearranges to a benzothiophene moiety in the presence of molecular iodine. However, only the dehydrogenated thioflavone **12** was isolated in 68% yield, which shows that benzothiophene is not generated *via* the rearrangement of thioflavone **11** (Scheme 4c). When chalcone **13** was used under the standard reaction conditions, only 15% of the desired product **2a** was isolated, which might be due to the corresponding *in situ* generated saturated ketone (Scheme 4d). The chalcone can become reduced by xanthate and acetic acid through PCET,[13] thus, giving rise to the saturated ketone. This result suggests that chalcone **13** may not play any role in the reaction mechanism.

Further, a reaction was performed using iodophenyl ketone **1h** with DMF as the solvent, keeping the other reaction parameters constant (Scheme 4e). Although the reaction took a longer time (6 h) to complete during the optimization in DMF, here the reaction was quenched after 1 h, and 2-benzyl benzothiophenone **14** was isolated in 58% yield. When the intermediate **14** was subjected to the optimized reaction conditions, 87% of the desired 2-thioaroyl-3-hydroxybenzo[*b*]thiophenone



Scheme 4 Controlled reactions.



Scheme 5 Plausible mechanism.

2h was isolated in 30 min (Scheme 4f). Thus, Schemes 4e and f indicate that **14** acts as reaction intermediate which undergoes oxidation and thionation to eventually provide the desired product **2h**. Further, on reacting iodophenyl ketone **1a** under the optimized reaction conditions at lower temperature, intermediate **15** was isolated in 67% yield (Scheme 4g). On subjecting intermediate **15** to the optimized reaction conditions, 83% of the desired product **2a** was obtained (Scheme 4h).

A plausible reaction mechanism for the synthesis of 3-hydroxybenzo[*b*]thiophenethiones has been proposed by taking inferences from control experiments and literature reports (Scheme 5). Initially, 1-(2-iodophenyl)-3-phenylpropan-1-one might undergo oxidative addition in the presence of copper(I) to give intermediate **A**, which subsequently would provide intermediate **B** by ligand exchange with potassium ethyl xanthate. Reductive elimination of intermediate **B** would provide Cu(I) and xanthate ester.

This Cu(I) may be oxidized to Cu(II) by the xanthate dimer,[15] which will reacting with the keto group of the xanthate ester to form metal–enol complex **C′**. The intermediate might undergo keto–enol tautomerism to give **D**. Eventually, intermediate **D** might undergo a homolytic cleavage[9] to give the radical intermediate **E**. Consequently, the thiyl radical is generated through cleavage of the xanthate ester by *in situ*-generated xanthate radicals[14] which would cyclize to produce **F**. The intermediate **F** should give the stable aromatic intermediate **G** *via* keto–enol tautomerism. The methylene group in intermediate **G** might be converted to a thiocarbonyl group under the reaction conditions to yield the product 3-hydroxybenzo[*b*]thiophenethione **2**. However, a detailed mechanistic study is currently underway in our laboratory.

In conclusion, an efficient copper-catalyzed domino protocol has been developed for the synthesis of 2-thioaroyl-3-hydroxybenzothiophene from saturated ketones *via* radical cyclization using xanthate as an odorless sulfur source. This methodology was extended to less reactive 2-bromophenylketones without changing any parameters. The reaction also resulted in the formation of a tetracyclic Lupinalbin analogues by introducing the *ortho*-methoxy substituent in the iodophenyl ketones. Also, 2-thioaroyl-3-hydroxybenzo[*b*]thiophene was derivatized to produce hemithioindigo, which is known to function as an efficient photoswitch, and a dethionated Lupinalbin analogue using the I_2/DMSO system.

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Conflicts of interest

There are no conflicts to declare.

Notes and references

1 P. Guglielmi, D. Secci, A. Petzer, D. Bagetta, P. Chimenti, G. Rotondi, C. Ferrante, L. Recinella, S. Leone, S. Alcaro, G. Zengin, J. P. Petzer, F. Ortuso and S. Carradori, *J. Enzyme Inhib. Med. Chem.*, 2019, **34**, 1511–1525.
2 M. R. Bleavins, F. A. de la Iglesia, J. A. McCay, K. L. White, Jr. and A. E. Munson, *Toxicology*, 1995, **98**, 111–123.
3 R. Xiong, J. Zhao, L. M. Gutgesell, Y. Wang, S. Lee, B. Karumudi, H. Zhao, Y. Lu, D. A. Tonetti and G. R. J. Thatcher, *J. Med. Chem.*, 2017, **60**, 1325–1342.
4 A. Gerwien, T. Reinhardt, P. Mayer and H. Dube, *Org. Lett.*, 2018, **20**, 232–235.
5 (*a*) P. Garg and A. Singh, *Org. Lett.*, 2018, **20**, 1320–1323; (*b*) T. Matsuzawa, T. Hosoya and S. Yoshida, *Chem. Sci.*, 2020, **11**, 9691–9696.
6 (*a*) J.-S. Lin, X.-Y. Dong, T.-T. Li, N.-C. Jiang, B. Tan and X.-Y. Liu, *J. Am. Chem. Soc.*, 2016, **138**, 9357–9360; (*b*) Q.-S. Gu, Z.-L. Li and X.-Y. Liu, *Acc. Chem. Res.*, 2020, **53**, 170–181; (*c*) Z.-L. Li, G.-C. Fang, Q.-S. Gu and X.-Y. Liu, *Chem. Soc. Rev.*, 2020, **49**, 32–48; (*d*) C.-J. Yang, C. Zhang, Q.-S. Gu, J.-H. Fang, X.-L. Su, L. Ye, Y. Sun, Y. Tian, Z.-L. Li and X.-Y. Liu, *Nat. Catal.*, 2020, **3**, 539–546.
7 (*a*) A. M. R. Smith and K. K. Hii, *Chem. Rev.*, 2011, **111**, 1637–1656; (*b*) C. C. C. Johansson and T. J. Colacot, *Angew. Chem., Int. Ed.*, 2010, **49**, 676–707; (*c*) Z. Yuan, C. Zhu, Z. Ma and C. Xia, *Chem. Commun.*, 2018, **54**, 11033–11036.
8 K. Zheng, X. Liu and X. Feng, *Chem. Rev.*, 2018, **118**, 7586–7656.
9 (*a*) M. T. Pirnot, D. A. Rankic, D. B. C. Martin and D. W. C. MacMillan, *Science*, 2013, **339**, 1593–1596; (*b*) M. Chen and G. Dong, *J. Am. Chem. Soc.*, 2019, **141**, 14889–14897; (*c*) W. Xie, D. Kim and S. Chang, *J. Am. Chem. Soc.*, 2020, **142**, 20588–20593.
10 X. Jie, Y. Shang, X. Zhang and W. Su, *J. Am. Chem. Soc.*, 2016, **138**, 5623–5633.
11 (*a*) N. Sundaravelu and G. Sekar, *Chem. Commun.*, 2020, **56**, 8826–8829; (*b*) N. Sundaravelu and G. Sekar, *Org. Lett.*, 2019, **21**, 6648–6652.
12 C. P. Miller, M. D. Collini and H. A. Harris, *Bioorg. Med. Chem. Lett.*, 2003, **13**, 2399–2403.
13 R. Prasanna, S. Guha and G. Sekar, *Org. Lett.*, 2019, **21**, 2650–2653.
14 A. Tazhe Veetil, T. Solomek, B. P. Ngoy, N. Pavlikova, D. Heger and P. Klan, *J. Org. Chem.*, 2011, **76**, 8232–8242.
15 (*a*) S. Sangeetha and G. Sekar, *Chem. Commun.*, 2020, **56**, 10906–10909; (*b*) Z. Zhu, X. Tang, J. Cen, J. Li, W. Wu and H. Jiang, *Chem. Commun.*, 2018, **54**, 3767–3770.