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PII: S0040-4020(17)31013-X

DOI: 10.1016/j.tet.2017.10.005

Reference: TET 29008

To appear in: *Tetrahedron*

Received Date: 19 June 2017

Revised Date: 21 September 2017

Accepted Date: 2 October 2017

Please cite this article as: Bovonsombat P, Teecomegaet P, Kulvaranon P, Pandey A, Chobtumskul K, Tungsirisurp S, Sophanpanichkul P, Losuwanakul S, Soimaneewan D, Kanjanwongpaisan P, Siricharoensang P, Choosakoonkriang S, Regioselective monobromination of aromatics via a halogen bond acceptor-donor interaction of catalytic thioamide and *N*-bromosuccinimide, *Tetrahedron* (2017), doi: 10.1016/j.tet.2017.10.005.

Graphical Abstract

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Regioselective monobromination of aromatics via a halogen bond acceptor-donor interaction of catalytic thioamide and *N*-bromosuccinimide

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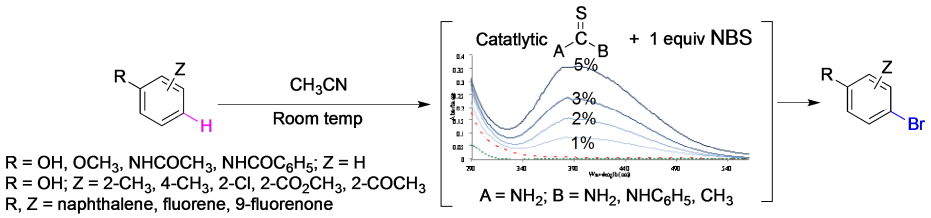

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Regioselective monobromination of aromatics via a halogen bond acceptor-donor interaction of catalytic thioamide and *N*-bromosuccinimide

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ARTICLE INFO

Article history:
Received
Received in revised form
Accepted
Available online

Monobromination
Organocatalyst
Thioamides
N-Bromosuccinimide
Halogen bond

ABSTRACT

Regioselective monobromination of various aromatics was achieved at room temperature using *N*-bromosuccinimide and 5 mol% of thioamides in acetonitrile. With thiourea as catalyst, activated aromatics, such as anisole, acetanilide, benzamide and phenol analogues containing electron donating or withdrawing groups, were brominated with high regioselectivity. Room temperature brominations of weakly activated aromatics and deactivated 9-fluorenone were accomplished by 5 mol% thioacetamide, higher substrates concentrations and longer reaction times. A backbonding of the bromine lone pairs with the π*of C=S group and a halogen bond between the halogen bond donor bromine and the halogen bond acceptor sulfur of the thioamide are thought to be the principal interactions and cause of *N*-bromosuccinimide activation.

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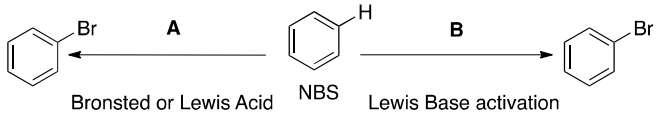
1. Introduction

The bromoaromatic is a motif found in some structures of marine sponge metabolites, such as geodiamolides B and E, jaspamide and barettin,[1] and also in a few approved drugs, that include bromfenac, remoxipride and bromodiphenhydramine.[2] They are useful and often the preferred haloaromatic substrates in palladium catalysed coupling reactions.[3] The typical synthesis route to a bromoaromatic compound is electrophilic aromatic bromination with bromine being the traditional source of the bromonium ion. But, due to its toxicity and handling difficulty, other safer reagents have replaced bromine. Moreover, bromination with molecular bromine poses monobromination and regioselectivity challenges for the highly activated aromatic substrates such as phenol and its derivatives. The alternative sources of bromonium ion suitable for regioselective monobromination of highly activated aromatics, while being safer and easier to handle than the liquid bromine, are reagents or a combination of reagents that include *N*-bromodialkylamine or *N*,*N*-dibromoalkylamine,[4a] *N*-bromosuccinimide,[4b] 1,3-dibromo-5,5-dimethylhydantoin,[4c] tetraalkylammonium tribromide,[4d,4e] halodimethylsulfonium halides,[4f] hexamethylenetetramine tribromide,[4g] 4,4-dibromo-3-methylpyrazol-5-one,[4h] KBr and oxone with H_2O_2,[4i,4j] *N*-methylpyrolidin-2-one hydrotribromide,[4l] KBr and benzyltriphenylphosphonium peroxymonosulfate,[4m] dixoxane dibromide,[4n] $ZrBr_4$ and diazene,[4o] and 1-butyl-3-methylpyridinium tribromide.[4p]

Among the aforementioned reagents, *N*-bromosuccinimide (NBS) has gained prominence as one of the preferred reagents for aromatic bromination. This is due to its low cost, solubility of the by-product (succinimide) in water, the ease of handling and ability to deliver precise stoichiometric amount of bromonium ion in a reaction. In reactions involving less activated substrates such as alkylbenzenes, and deactivated aromatics NBS requires activation, either with a Brønsted or a Lewis acid catalyst. These acid catalysts are SiO_2,[5a] HZSM-5,[5b] $HBF_4.Et_2O$,[5c] tetrabutylammonium bromide,[5d] sulfonic acid-functionalised silica,[5e] ammonium acetate,[5f] and *p*-toluenesulfonic acid (TsOH).[5g] NBS alone in acetonitrile was effective in the bromination of methoxybenzenes and naphthalenes,[6a] but a use of 0.1 to 1 mol % of 70% perchloric acid with NBS was effective in enhancing regioselective monobromination of activated aromatics, particularly of 1,3-dimethoxybenzene and 2,3-dimethylanisole.[6b] A catalytic amount of TsOH added before NBS also gave regioselective monobromination of phenol compounds.[6c] With deactivated aromatics bromination, acid such as concentrated sulfuric acid[7a] or trifluoromethanesulfonic acid with BF_3-H_2O,[7b] was employed as the solvent to activate NBS.



Scheme 1.

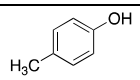
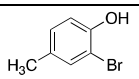
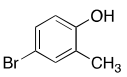
As discussed above, a Brønsted or a Lewis acid, which is fraught with potential acid side reactions, is the prevailing mode of activating NBS (Scheme 1, route A). Therefore, a novel alternative means of activating NBS, that eliminates such use of either a Brønsted or a Lewis acid, is desirable. One possible alternate mode of catalyzing NBS is nucleophilic activation using an organic Lewis base, such as a thioamide (Scheme 1, route B). An activation of the type that utilizes nucleophilic and catalytic thioamides, has previously been demonstrated in our report on aromatic chlorination employing *N*-chlorosuccinimide (NCS) and thioamides.[8] To the best of our knowledge, the activation of NBS in aromatic bromination by a nucleophilic organocatalyst is still largely unexplored.

We herein report the findings of our investigation on electrophilic bromination on a range of aromatics using thioamides as nucleophilic organocatalysts to activate NBS.

2. Results and discussion

Bromination of highly reactive aromatic substrates such as 4-methylphenol (**1**) and 2-methylphenol (**2**) in room temperature acetonitrile with 5 mol% of thiourea and 1.15 equiv of NBS gave excellent yields and high regioselectivity of the products, 2-bromo-4-methylphenol (**1a**) and 4-bromo-2-methylphenol (**2a**) after only 10 minutes of stirring (Table 1, entries 3 and 6). However, catalytic amounts of thioacetamide and *N*-phenylthiourea performed poorer in the bromination of **1** (Table 1, entries 2 and 4). Without catalyst, the bromination reactions of **1** and **2** gave poor yields of **1a** and **2a** and additional increased yields of the dibromo adducts of **1** and **2** (Table 1, entries 1 and 5). The control reactions of **3**-**14**, like those of **1** and **2**, were marked by non-existing or poor yields of the products, admixed with dibrominated side products in some cases, and in the case of phenol, tribromination occurred (Table 2, entries 1, 5, 7, 9, 11, 13 and 15, and Table 3, entries 1, 5, 7, 9 and 11).

Table 1. Bromination of selected highly activated aromatic compounds

Entry	Substrate	mmol	Catalyst[a]	NBS (equiv)	Time	Product composition (%)						Product[b]	Isolated (%)[b]
						S	2	3	4	6	2,4 and 2,6		
1		0.5	None	1.15	10 min	56	17	0	-	-	27		-
2		0.5	I	1.15	10 min	27	72	1	-	-	-		-
3	**1**		II	1.15	10 min	4	**93**	0	-	-	3	**1a**	92
4			III	1.15	10 min	19	81	0	-	-	0		-
5		0.5	None	1.15	10 min	22	-	0	45	5	28		-
6		0.5	II	1.15	10 min	2	-	0	**95**	3	0		84
	2											**2a**	

[a]Catalysts: I, thioacetamide; II, thiourea; III, *N*-phenylthiourea.

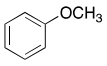
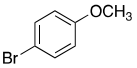
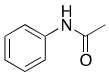
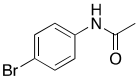
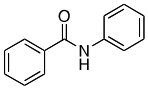
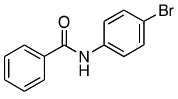
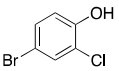
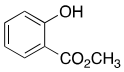
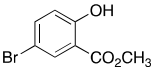
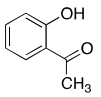
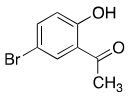
[b]Reaction conditions: The aromatic substrate (0.5 mmol or otherwise stated in the table) was added to the acetonitrile solution (10 mL) containing 1.15 equiv of NBS and 5 mol % of catalyst (0.025 mmol). The reaction mixture was stirred at room temperature for 10 minutes or stated otherwise. For the work-up, the reaction was diluted with diethyl ether (20 mL). The product composition was determined by GC/ MS. The major products were isolated by silica gel column chromatography (5–20% CH_2Cl_2/hexanes) and characterised by GC/MS, IR, ^1H and ^{13}C NMR. The numbers in the product composition denote the positions of bromination relative to the substituent (numbered 1) of the aromatic substrate and S refers to the substrate. Tribromination was not observed for any substrates.

Among the common laboratory solvents studied, acetonitrile was the best in terms of regioselectivity, product yield and monobromination control Table 2, entry 2). Thus acetonitrile was adopted as the solvent of choice in the ensuing reactions in this study.

Thiourea, like in the brominations of **1** and **2**, was also the best performing catalyst in the brominations of phenol (**3**), anisole (**4**), acetanilide (**5**) and *N*-phenylbenzamide (**6**). These compounds underwent bromination with either 1.10 or 1.15 equiv of NBS and 5 mol % of thiourea in room temperature acetonitrile. After 10 minutes of stirring, the yields of 4-bromophenol (**3a**), 4-bromoanisole (**4a**), *N*-(4-bromophenyl)acetamide (**5a**) and *N*-(4-bromophenyl)benzamide (**6a**) ranged from 92 to 100% (89-98% isolated) (Table 2, entries 3, 6, 8 and 10).

For the phenol substrates with electron-withdrawing substituents, such as 2-chlorophenol (**7**), methyl 2-hydroxybenzoate (**8**) and 2-acetylphenol (**9**), thiourea remains the most effective catalyst. Their reaction times though were extended to 2 hours, and their respective monobrominated products, 4-bromo-2-chlorophenol (**7a**), methyl 5-bromo-2-hydroxybenzoate (**8a**) and 2-acetyl-4-bromophenol (**9a**), were obtained in good to excellent yields (81-93% GC yields and 75-87% isolated) (Table 2, entries 12, 14 and 16).

Table 2. Bromination of selected activated aromatic compounds

Entry	Substrate	mmol	Catalyst[a]	NBS (equiv)	Time	Product composition (%)						Product[b]	Isolated (%)[b]
						S	2	3	4	6	2,4 and 2,6		
1	 **3**	0.5	None	1.10	10 min	22	7	0	12	-	59[c]	 **3a**	-
2		0.5	I	1.10	10 min	7	4	0	80	-	9		-
3			II	1.10	10 min	0	3	0	**92**	0	5		89
4			III	1.10	10 min	34	4	0	62	0	0		-
5	 **4**	0.5	None	1.15	10 min	93	0	0	**7**	0	0	 **4a**	-
6		0.5	II	1.15	10 min	0	2	0	**98**	0	0		95
7	 **5**	0.5	None	1.15	10 min	71	0	0	29	0	0	 **5a**	-
8		0.5	II	1.15	10 min	0	1	0	**99**	0	0		97
9	 **6**	0.5	None	1.15	10 min	100	0	0	0	0	0	 **6a**	-
10		0.5	II	1.15	10 min	0	0	0	**100**	0	0		98
11	 **7**	0.5	None	1.15	2 h	15	-	0	13	4	68	 **7a**	-
12		0.5	II	1.15	2 h	7	-	0	**81**	6	6		75
13	 **8**	0.5	None	1.15	2 h	97	-	0	3	0	0	 **8a**	-
14		0.5	II	1.15	2 h	6	-	0	**93**	1	0		84
15	 **9**	0.5	None	1.15	2 h	23	-	0	19	6	52	 **9a**	-
16		0.5	II	1.15	2 h	6	-	0	**91**	0	3		87

[a]Catalysts: I, thioacetamide; II, thiourea; III, *N*-phenylthiourea.

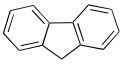
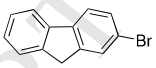
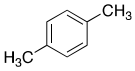
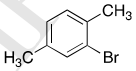
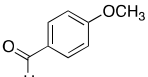
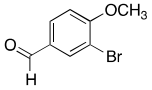
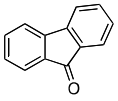
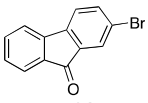
[b]Reaction conditions: The aromatic substrate (0.5 mmol or otherwise stated in the table) was added to the acetonitrile solution (10 mL) containing 1.10-1.15 equiv of NBS and 5 mol % of catalyst (0.025 mmol). The reaction mixture was stirred at room temperature for 10 minutes or stated otherwise. For the work-up, the reaction was diluted with diethyl ether (20 mL) or ethyl acetate (20 mL) in the case of **5a** and **6a**. The product composition was determined by GC/ MS. The major products were isolated by silica gel column chromatography (5–20% CH_2Cl_2/hexanes) and characterised by GC/MS, IR, ^1H and ^{13}C NMR. Compounds **5a** and **6a** were not subjected to chromatography but were instead recrystalized from water. The numbers in the product composition denote the positions of bromination relative to the substituent (numbered 1) of the aromatic substrate and S refers to the substrate. Tribromination was not observed for any substrates except for the control reaction of **3** (Table 2, entry 1).

[C] The mixture comprised of dibromo analogues of **3** (4%) and tribromo analogue of **3** (55%).

For the weakly activated naphthalene (**10**), fluorene (**11**), 1,4-dimethylbenzene (**12**), 4-methoxybenzaldehyde (**13**) and the deactivated 9-fluorenone (**14**), a catalyst changed, higher concentrations of substrate and longer reaction times were necessary for the product optimum yields. Unlike the brominations of **1**-**9**, which were conducted at 0.05 M and a reaction time ranging from 10 minutes to 2 hours, brominations of **10** to **14** needed concentrations of 0.1 to 0.4 M and 19 to 64 hours of stirring at room temperature. Thioacetamide as catalyst was superior to thiourea in the bromination of **10**-**14**. Thus, 0.1 M of **10** was treated with 1.15 equiv of NBS and 5 mol % of thioacetamide and stirred for 19 hours at room temperature to give a good yield of 1-bromonaphthalene (**10a**) (Table 3, entry 2). Similarly, 2-bromofluorene (**11a**) was also obtained in a good yield from 0.1 M of **11** after 19 hours of stirring at room temperature with 1.10 equiv of NBS and 5 mol % thioacetamide (Table 3, entry 6). In addition, the control reaction of **11** gave 19% of the benzylic brominated product, however the same reaction with catalytic amounts of thioacetamide did not produce any unwanted benzylic bromination (Table 3, entries 5 and 6). Brominations of **12** and **13**, both at 0.2 M, required 1.15 equiv of NBS with 16 and 20 hours of stirring at room temperature, respectively. Both **12** and **13** gave 2-bromo-1,4-dimethylbenzene (**12a**) and 3-bromo-4-methoxybenzaldehyde (**13a**) in good yields and high regioselectivity (Table 3, entries 8 and 10). To examine the effectiveness of this methodology, a deactivated aromatic

ketone **14** was brominated in place of the activated aromatics stirring, a moderate yield of 2-bromo-*9H*-fluoren-9-one (**14a**) using a concentration of 0.4 M with 1.15 equiv of NBS and 5 mol % of thioacetamide at room temperature. After 64 hours of was obtained from **14** (Table 3, entry 12).

Table 3. Bromination of selected weakly activated aromatic compounds

Entry	Substrate	mmol	Catalyst[a]	NBS (equiv)	Time	Product composition (%) S	2	3	4	6	2,4 and 2,6	Product[b]	Isolated (%)[b]
1	 **10**	1.0	None	1.15	19 h	100	0	0	0	-	0	 **10a**	-
2		1.0	I	1.15	19h	17	**82**	0	0	-	1		78
3		1.0	II	1.15	19h	21	78	0	0	-	1		
4		1.0	III	1.15	19h	24	75	0	0	-	1		
5	 **11**	1.0	None	1.10	19 h	36	41	0	0	19[c]	4	 **11a**	-
6		1.0	I	1.10	19 h	19	**73**	0	0	0[d]	8		71
7	 **12**	2.0	None	1.15	16 h	100	0	0	-	0	0	 **12a**	
8		2.0	I	1.15	16 h	17	**77**	0	-	2[d]	4		72
9	 **13**	2.0	None	1.15	20 h	84	16	0	-	0	0	 **13a**	-
10		2.0	I	1.15	20 h	12	**85**	0	-	0	3		77
11	 **14**	4.0	None	1.15	64h	100	0	0	0	0	0	 **14a**	-
12		4.0	I	1.15	64h	56	0	44	0	-	0		38
13			II	1.15	64h	96	0	4	0	-	0		
14			III	1.15	64h	92	0	8	0	-	0		

[a]Catalysts: I, thioacetamide; II, thiourea; III, *N*-phenylthiourea.

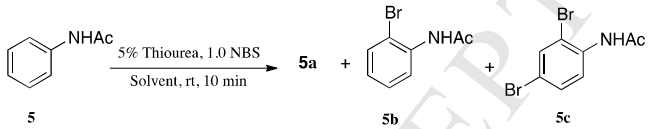
[b]Reaction conditions: The aromatic substrate (0.5 mmol or otherwise stated in the table) was added to the acetonitrile solution (10 mL) containing 1.10-1.15 equiv of NBS and 5 mol % of catalyst (0.025 mmol). The reaction mixture was stirred at room temperature for 10 minutes or stated otherwise. For the work-up, the reaction was diluted with diethyl ether (20 mL). The product composition was determined by GC/ MS. The major products were isolated by silica gel column chromatography (5–20% CH_2Cl_2/hexanes) and characterised by GC/MS, IR, ^1H and ^{13}C NMR. The numbers in the product composition denote the positions of bromination relative to the substituent (numbered 1) of the aromatic substrate and S refers to the substrate.

[c] Bromination at C-9 of **11**.

[d] Benzylic bromination.

3. Solvent and Catalyst effects on bromination

3.1. Solvent study



5 **5b** **5c**

Table 4. Solvent effect on the bromination of **5**

Entry	Solvent	**5** (%)	Yield (%) **5a**	**5b**	**5c**
1	Acetonitrile	4	96	0	0
2	Acetonitrile[b]	82	18	0	0
3	Formamide	40	60	0	0
4	DMF	41	57	2	0
5	Acetone	13	87	0	0
6	2-Butanone	12	88	0	0
7	3-Heptanone	12	88	0	0
8	2-Heptanone	52	48	0	0
9	CH_2Cl_2 or $CHCl_3$	100	0	0	0
10	Ethanol	82	18	0	0
11	Methanol	17	83	0	0
12	Water	58	38	0	4
13	THF	84	16	0	0
14	MTBE or 1,4-dioxane	100	0	0	0
15	Cyclohexane or n-heptane	100	0	0	0

[a]Reaction conditions: Compound **5** (0.5 mmol) was added to a solution of NBS (1.0 equiv) and 5 mol % of thiourea (0.025 mmol) in the solvent specified above (10 mL) at room temperature and the resulting mixture was stirred for 10 minutes. The reaction was quenched by 10% aqueous solution of $Na_2S_2O_3$ (10 mL) and extracted with ethyl acetate (2 x 20 mL). The product composition of the organic layer was determined by GC/MS.

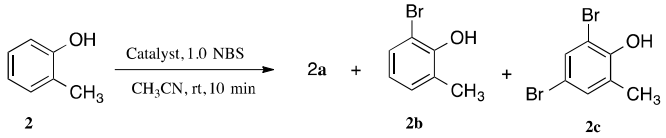
[b]Without thiourea

The choice of solvent is important in the bromination reaction of NBS and thiourea. Acetanilide, due to its medium activity in electrophilic aromatic substitution, was chosen as a test substrate in this study, and also in the subsequent halogenations studies. Excellent bromination was achieved with acetonitrile (Table 4 entries 1-2). Acetone performed well but other polar aprotic solvents such as formamide and DMF were mediocre, even though they can completely dissolve NBS and thiourea similar to acetonitrile (Table 4, entries 3-5). Longer chain ketone, 2-heptanone, was disappointing as the bromination solvent but 3-heptanone and 2-butanone did as

well as acetone (Table 4, entries 6-8). Interestingly, among the polar protic solvents, methanol fared the best while ethanol was poor and water gave unwanted dibromination of **5** (Table 4, entries 10-12). The solubilities of NBS and thiourea were poor in ethanol and water. Among the ether solvents, only THF gave products, albeit few, while others failed in the bromination (Table 4, entries 13 and 14). Poor solubilities of NBS and thiourea hindered these solvents. Chlorinated solvents, such as dichloromethane and chloroform (Table 4, entry 9), and nonpolar solvents like cyclohexane and n-heptane (Table 4, entry 15), failed to brominate acetanilide. The insolubilities of NBS and thiourea in these solvents are believed to be the cause of the bromination inactivity.

3.2. Catalyst study

A variety of thioamides and amides were screened for their catalytic activity. As shown in Table 5, the bromination of **2** (chosen for its medium activity and a comparison to **5**) catalysed by thioamides, such as thiourea, thioacetamide, *N*-phenylthiourea, thioacetanilide *N*-phenylthiobenzamide and *N*,*N*,*N*,*N*-tetramethylthiourea, were superior than their oxygen counterparts in terms of the product yields, regioselectivity and dibromination suppression (Table 5, entries 2-13). Among the thioamides, thiourea is the most effective catalyst, followed by thioacetamide, thioacetanilide, *N*-Phenylthiobenzamide, *N*-phenylthiourea and *N*,*N*,*N*,*N*-tetramethylthiourea (Table 5 entries 2, 4, 6, 8, 10 and 12).



2 **2b** **2c**

Table 5. Catalytic effects of thioamides and amides on the bromination of **2**.

Entry	Catalyst	Yield (%)[a]			
		2 (%)	**2a**	**2b**	**2c**
1	None	38	53	7	2
2	Thiourea	4	92	4	0
3	Urea	44	45	10	1
4	Thioacetamide	7	90	3	0
5	Acetamide	30	64	5	1
6	*N*-Phenylthiourea	15	83	2	0
7	*N*-Phenylurea	38	44	11	7
8	Thioacetanilide	8	89	3	0
9	Acetanilide	36	53	8	3
10	*N*-Phenylthiobenzamide	13	85	2	0
11	*N*-Phenylbenzamide	65	22	9	4
12	*N*,*N*,*N*,*N*-Tetramethylthiourea	17	71	11	1
13	*N*,*N*,*N*,*N*-Tetramethylurea	43	52	5	0
14	DMSO	58	29	11	2
15	Triphenylphosphine	8	88	4	0

[a] Reaction conditions: Compound **2** (0.5 mmol) was added to an acetonitrile (10 mL) solution containing NBS (1.0 equiv) and 5 mol % of catalyst (0.025 mmol) and the resulting room temperature mixture was stirred for 10 minutes. The reaction was quenched by 10 mL of 10% aqueous solution of $Na_2S_2O_3$ and extracted with 20 mL of diethyl ether. The product composition of the organic layer was determined by GC/ MS.

Amides such as urea, *N*-phenylurea, acetanilide, *N*-phenylbenzamide and *N*,*N*,*N*,*N*-tetramethylurea failed to activate NBS in the bromination of **2** (Table 5, entries 1, 3, 7, 9, 11 and 13). Interestingly urea and *N*-phenylbenzamide appear to have inhibitory effect on NBS. However, acetamide showed a slight activity but compared to the thioamides it would be considered as an ineffective catalyst activator of NBS (Table 5, entry 5).

DMSO and triphenylphosphine were also screened for their catalytic activities. DMSO, when compared to the bromination control reaction, was ineffective in the bromination reaction of **2** and like some amides, it inhibited NBS (Table 5, entries 1 and 14). Triphenylphosphine, on the other hand, was almost as active as thioacetanilide in the bromination of **2**. It gave high *para*-selectivity and no dibromination. Moreover, there appeared to be a slight increase in the yield of **2b**, making it an alternate potential catalyst for NBS activation. (Table 5, entry 15).

3.3. Effects of thioamides and amides on halogenations

Selected thioamides, amides, DMSO and triphenylphosphine, shown in Table 6, were investigated for their catalytic halogenation activities using acetanilide (**5**) as the test substrate with an equivalent of NBS, NCS, and *N*-iodosuccinimide (NIS). Each catalyst candidate was screened using 5 mol % with respect to **5**. As shown in Table 6, the thioamides, except for *N*,*N*,*N*,*N*-tetramethylthiourea, are superior to the amides in the bromination of **5**, both in terms of the yields and the *para*-selectivity to the product, *N*-(4-bromophenyl)acetamide (**5a**). Thiourea was the best among the thioamides, which, listed in the decreasing order of activity, included thioacetanilide, thioacetamide, *N*-phenylthiourea and *N*-phenylthiobenzamide (Table 6, entries 2, 4, 6, 8 and 10). Surprisingly *N*,*N*,*N*,*N*-tetramethylthiourea, which gave a moderate catalytic activity in the bromination of **2** with NBS, failed in the bromination of **5** (Table 6, entry 12). In contrast, all amides, except for *N*-phenylurea and *N*,*N*,*N*,*N*-tetramethylurea, failed to activate the bromination of **5** (Table 6, entries 3, 5, 9 and 11). Acetamide was inactive in the bromination of **5** (Table 6, entry 5), but showed a low activity with **2** (Table 5, entries 1 and 5). The catalytic activity differences of acetamide in the bromination of **2** and **5** could be due to **2** being more activated than **5**. For the exceptions in amides, *N*-phenylurea and *N*,*N*,*N*,*N*-tetramethylurea showed moderate catalytic activities, albeit a modest 43% yield of **5a** for the former and 33% of **5a** for the latter (Table 6, entries 7 and 13). While the exception in thioamides, *N*,*N*,*N*,*N*-tetramethylthiourea, gave a good catalytic activity in the bromination of **2** (Table 5, entry 12), the same reaction with **5** showed complete inactivity (Table 6, entry 12). The reactivity differences between **2** and **5** could also be the underlying reason in the contrasting results of *N*,*N*,*N*,*N*-tetramethylthiourea, *N*-phenylurea and *N*,*N*,*N*,*N*-tetramethylurea.

The catalytic activation of thioamides in the chlorination of **5** was superior to the amides, except for *N*-phenylthiobenzamide, which showed identical activities with its amide counterpart in terms of the product yields (*N*-(4-chlorophenyl)acetamide, **15a**) and regioselectivity (Table 6, entries 10 and 11). Among the thioamides, thiourea gave the best chlorination of **5** while *N*,*N*,*N*,*N*-tetramethylthiourea gave a moderate conversion to **15a** but its potential was hampered by a low *para*/*ortho* ratio (Table 6, entries 2 and 12).

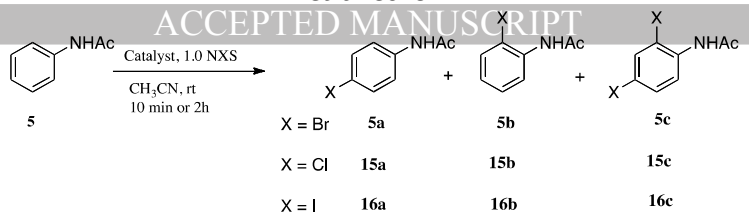


Table 6. Effects of various catalysts on halogenations of **5** via *N*-halosuccinimides

Entry	Catalyst	Halogenation yields via NXS (%)[a]											
		X = Cl				X = Br				X = I			
		5	**15a**	**15b**	**15c**	**5**	**5a**	**5b**	**5c**	**5**	**16a**	**16b**	**16c**
1	None	85	8	7	0	100	0	0	0	100	0	0	0
2	Thiourea	6	71	23	0	3	95	2	0	11	89	0	0
3	Urea	92	8	0	0	100	0	0	0	100	0	0	0
4	Thioacetamide	9	69	22	0	9	90	1	0	15	85	0	0
5	Acetamide	53	33	14	0	100	0	0	0	100	0	0	0
6	*N*-Phenylthiourea	12	67	21	0	13	87	0	0	14	86	0	0
7	*N*-Phenylurea	92	8	0	0	56	43	1	0	100	0	0	0
8	Thioacetanilide	9	67	23	1	7	93	0	0	33	67	0	0
9	Acetanilide	100	0	0	0	100	0	0	0	100	0	0	0
10	*N*-Phenylthiobenzamide	7	71	22	0	13	87	0	0	51	48	0	1
11	*N*-Phenylbenzamide	4	71	25	0	100	0	0	0	100	0	0	0
12	*N*,*N*,*N*,*N*-Tetramethylthiourea	21	52	27	0	100	0	0	0	100	0	0	0
13	*N*,*N*,*N*,*N*-Tetramethylurea	100	0	0	0	67	33	0	0	100	0	0	0
14	DMSO	44	40	16	0	100	0	0	0	100	0	0	0
15	Triphenylphosphine	6	65	20	9	2	97	1	0	91	0	0	9

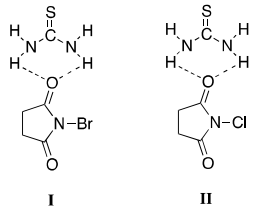
[a] Reaction conditions: Compound **5** (0.5 mmol) was added to the acetonitrile solution (10 mL) containing 1.0 equiv of NXS and 5 mol% of catalyst (0.025 mmol). The reaction mixtures were stirred at room temperature for 10 minutes for NBS and 2 hours for NCS and NIS. The reaction was quenched by 10 mL of 10% aqueous solution of $Na_2S_2O_3$ and extracted with 20 mL of ethyl acetate. The product composition of the organic layer was determined by GC/ MS.

Iodination of **5** with NIS was effective only with the thioamides, except for the inactivity of *N*,*N*,*N*,*N*-tetramethylthiourea. The amides failed to activate NIS (Table 6, entries 3, 5, 7, 9 and 11). Among the thioamides studied, thiourea gave the best iodination of **5**, and this was followed by *N*-phenylthiourea, thioacetamide and thioacetanilide (Table 6, entries 2, 4, 6 and 8). *N*-Phenylthiobenzamide was the least active, converting only 48% of **5** to the product, *N*-(4-iodophenyl)acetamide (**16a**), (Table 6, entry 10).

Triphenylphosphine and DMSO were investigated as potential catalysts in the halogenations of **5**. DMSO showed a moderate activity in chlorination, but ineffective with both NBS and NIS (Table 6, entry 14). Triphenylphosphine was potent in the bromination. Its catalytic activity was even slightly better than that of thiourea. In chlorination triphenylphosphine's activity was as active as thiourea but its usefulness was hampered by its lower regioselectivity and dibromination of **5** (Table 6, entries 15). For iodination, triphenylphosphine was a poor catalyst, furnishing only the diiodination by-product and none of the desired **16a** (Table 6, entries 15). Despite triphenylphosphine's notable performances in chlorination and bromination, thiourea stood out as an excellent universal catalyst with high regioselectivity and the best monohalogenation control in all three halogenations (Table 6, entry 2).

3.4. UV-vis spectra of NBS, NCS-thiourea complexes

One of the possible models, shown in figure 1, that could account for the activating interaction of NBS and thiourea, is complex **I**. This complex is a derivative of **II**, a model proposed in 2008 by Bentley *et al* to account for the activation of NCS by thiourea in the chlorohydration of alkenes.[9] The important interaction of **I** (also for **II**) is the hydrogen bonding of the NH_2 group of thiourea with an oxygen of the succinimide. But critically, the thiourea's C=S group in **I** is non-participating and as a result its n→π* transition, λ_{max} 291 nm and ε_{max} 71,[10] is unperturbed or, in the case of any slight hydrogen bond perturbation, a small deviation from the original λ_{max} value might be possible.



I **II**

Figure 1. Possible activation of NBS by hydrogen bonding

However, the results of our UV-vis absorption studies of 1 to 5 mol% of thiourea in 0.05 M NBS acetonitrile solution do not support the unperturbed C=S model of **I** (Figure 2). On the contrary, our results, which show a λ_{max} of 393 nm (ε_{max} 597), suggest a direct and significant interaction of the C=S group in the activation of NBS. Furthermore, due to the low molar absorptivity value of 597 for the new λ_{max}, the observed electronic transition of thiourea-NBS, is likely one of n→π* transition and not a π→π*, and therefore this absorption represents an electronic transition of the C=S group and a $\Delta\lambda_{max}$ shift of 102 nm (from 291 to 393 nm).

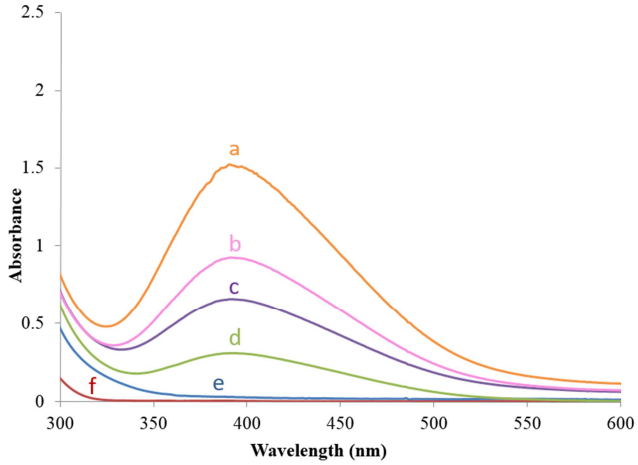


Figure 2. Absorption spectra of 0.05 M NBS with 1-5 mol% thiourea
a: 0.05 M NBS with 5% thiourea (2.5 mM), b: 0.05 M NBS with 3% thiourea (1.5 mM), c: 0.05 M NBS with 2% thiourea (1.0 mM), d: 0.05 M NBS with 1% thiourea (0.5 mM), e: 0.05 M NBS, f: 2.5 mM thiourea.

An alternative model for the NBS-thiourea interaction, accounting for the bathochromic shift of thiourea C=S absorption, are complex **III** and its variant **IV** and **V** (Figure 3). This model, originating from an earlier proposal for the NCS-thiourea interaction in the aromatic chlorination with NCS and thiourea,[8] consists of two principal interactions; one between the sulfur lone pair, acting as a halogen bond acceptor, and the halogen bond donor sigma hole of the bromine, and the second one comprising of a hydrogen bond between the NH_2 group of thiourea with the oxygen of the succinimide. The latter interaction orients the sulfur close to the bromine, allowing the sulfur to be in effective range with the bromine for a halogen bond interaction and a back bonding of the bromine p orbital with the π* orbital of C=S group (Figure 4).

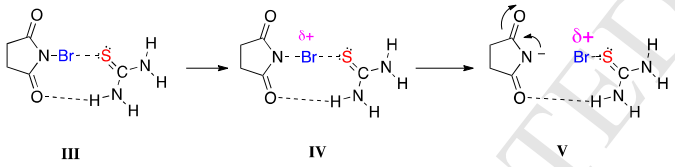


Figure 3. A proposed interaction of NBS and thiourea C=S

The λ_{max} of 393 nm for the NBS-thiourea complex represents a decrease in energy (ΔE) of the n→π* transition of C=S. The decreases in the non-bonding level and the π* level, involving either one or both, could have led to this observed ΔE decline. However, for such a large bathochromic shift and a $\Delta\lambda_{max}$ of 102 nm, the decrease in the energy level must involve both the non-bonding and the π* levels decrease. The decrease of the non-bonding level is thought to be slight due to the weak Br-sulfur lone pair halogen-bond interaction. However, the decrease in the energy of the π* level is thought to be more significant, which together with the change in non-bonding level results in a net decrease of the ΔE of the n→π* transition of C=S. A backbonding of the bromine's filled p-orbital with the π* of the sulfur is postulated to be responsible for the significant decrease of the π* level (Figure 4).

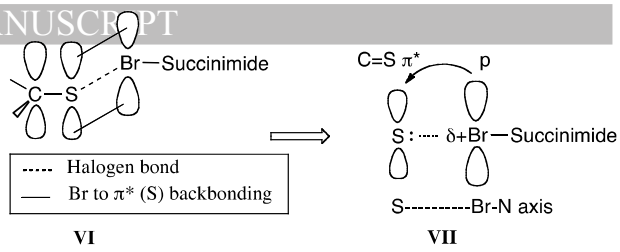


Figure 4. Bromine-sulfur halogen bond and p-orbital-π* interaction

The link between the NBS-thiourea interaction and the observed brominating activities was established by the UV-vis recordings of 0.5 and 0.25 equivalents of acetanilide, separately combined, in acetonitrile solutions containing 0.05 M NBS and 5 mol % thiourea.

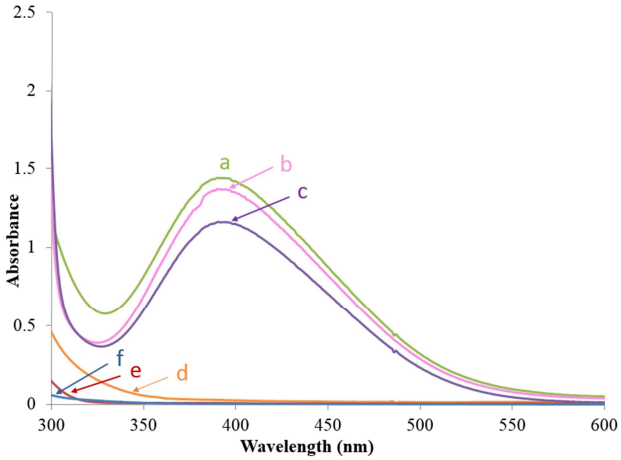


Figure 5. Absorption spectra of 0.05 M NBS with 5 mol% thiourea and 0.25 and 0.5 equivs of acetanilide (**5**)
a: 0.05 M NBS with 2.5 mM thiourea (5%), b: 0.05 M NBS with 2.5 mM thiourea and 0.0125 M **5**, c: 0.05 M NBS with 2.5 mM thiourea and 0.025 M **5**, d: 0.05 M NBS, e: 2.5 mM thiourea, f: 0.025 M **5**.

In contrast to the NBS-5% thiourea absorption spectrum (marked "a" in figure 5), the absorbance of 0.25 and 0.5 equivalents of acetanilide are proportionately less. The lower absorbance of 0.25 equivalent of acetanilide and an even lower one for 0.5 equivalents of the bromonium-trapping aromatic indicate proportionately the diminished concentrations of NBS-thiourea complex. These findings thus support that the NBS-thiourea interaction observed in the absorption spectra is one of the same involved in the aromatic bromination. Whether the actual species involved is **III**, **IV** or **V** or a varying combination of them, one could only be ascertained by future studies.

4. Conclusion

An aromatic bromination methodology, free of a Brønsted acid or a Lewis acid catalyst activation, has been outlined. This new method employs a different and a novel means of catalytically activating *N*-bromosuccinimide to generate the bromonium ion, namely using the nucleophilic C=S group of thioamide as a halogen bond acceptor. Thus, a regioselective monobromination of various aromatics was achieved using a combination of NBS and 5 mol % of thioamides in room temperature acetonitrile. Thiourea, employed in catalytic amount, activated NBS and gave highly regioselective monobromination among the highly activated aromatics, that include anisole, acetanilide, benzamide and phenol analogues containing either electron donating groups (such as *o*-cresol and *p*-cresol) and withdrawing groups like a chlorine, a methyl ketone and a methyl ester. For the weakly activated aromatics and a deactivated

aromatic, 9-fluorenone, thioacetamide, in place of thiourea, gave the most effective regioselective monobrominations and their reactions, without heating and at room temperature, were possible by employing higher substrates concentrations and longer reaction times. Although bromination of 9-fluoreonone gave a low yield of 2-bromofluorenone, it was significant to note that room temperature bromination of the deactivated 9-fluorenone was possible. The thioamide-NBS interaction, that leads to the activation of *N*-bromosuccinimide, is postulated to occur via a halogen bond between the halogen bond donor bromine and the halogen bond acceptor sulfur (lone pair) of the thioamide, and enhanced by a backbonding of the bromine lone pairs with the π* of C=S group.

5. Experimental

5.1 Materials

Acetanilide, fluorene and naphthalene were purchased from Fluka while all other aromatic substrates were from Aldrich. All solvents, obtained from Labscan Co. Ltd. (Thailand), are of AR grade and were used without further purification. *N*-Chlorosuccinimide and *N*-iodosuccinimide were obtained from Acros and *N*-bromosuccinimide was from Aldrich and was recrystallized from water according to the procedure of Dauben and McCoy to eliminate any acid and Br_2 contaminations.[11] Thiourea and *N*-phenylthiocarbamide were from Aldrich, while thioacetamide was purchased from Fluka. They were used without further purification. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance 300 MHz spectrometer in $CDCl_3$, CD_3OD or CD_3COCD_3 using TMS as an internal standard. The product composition and relative yields were carried out on a gas chromatograph-mass spectrometer (Agilent 6890 GC system and Agilent 5973 Mass Select Detector) using HP-1 capillary column (0.32 mm x 24.8 m x 0.17 mm). IR spectra were recorded on a Perkin-Elmer Spectrum 100 FT-IR Spectrometer equipped with ATF mode. UV-visible spectra were recorded on a Hewlett-Packard spectrophotometer 3854 using a 1cm quartz cuvette. All solutions were recorded from 200 to 700 nm at 480 nm per minute and a data interval of 1 nm. The separations of the products were carried out on a centrifugal thin-layer chromatography (Harrison Research, USA) using a plate coated with 2 mm silica gel $60GF_{254}$.

5.2 General procedure for bromination

Reaction conditions: Thiourea (5.1 mol%, 2 mg, 0.026 mmol) was added to an acetonitrile solution (10 mL) containing NBS (1.15 equiv, 104.4 mg, 0.587 mmol). Anisole (56.3 mg, 0.51 mmol) was added immediately to the resulting stirred solution and allowed to stir at room temperature for 10 minutes. The reaction was quenched by the addition of 10% aqueous solution of $Na_2S_2O_3$ (10 mL) and extracted with ethyl acetate (70 mL). The organic solution was then washed with additional 10% $Na_2S_2O_3$ (2 x 10 mL), followed by deionized water (3 x 15 mL) and brine (2 x 10 mL). The organic solution was then dried over anhydrous Na_2SO_4 and the solvent was evaporated *in vacuo*. The major product of each reaction was isolated by centrifugal thin-layer chromatography using a 2 mm thick silica gel $60GF_{254}$ coated plate (5% CH_2Cl_2/hexanes). The products reported herein are known compounds and were characterized by GC-MS, IR, ^{1}H and ^{13}C NMR. Their spectroscopic data are in agreement with those reported in the literature.

*5.2.1. 2-Bromo-4-methylphenol (**1a**).*[6c] Light yellow liquid; yield: 92% (0.0860 g). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.27 (1H, d, *J* 2 Hz, H at C-3), 7.01 (1H, dd, *J* 8, 2 Hz, H at C-5), 6.90 (1H, d, *J* 8 Hz, H at C-6), 2.27 (3H, s, C<u>H</u>$_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 150.0, 132.1, 131.4, 129.8, 115.7, 109.8, 20.2; GC-MS (EI), m/z (rel int.): 188 (51, $(M+2)^+$), 186 (53, M^+), 159 (0.48, $((M+2)\text{-CHO})^+$), 157 (0.43, $(M\text{-CHO})^+$), 107 (100, $(M\text{-Br})^+$), 79 (11), 78 (19), 77 (44), 63 (7), 51 (21); IR (neat): 3397 cm^{-1}.

*5.2.2. 4-Bromo-2-methylphenol (**2a**).*[12] Colourless liquid; yield: 84% (0.0785 g). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.23 (1H, d, *J* 2 Hz, H at C-3), 7.15 (1H, dd, *J* 8, 2 Hz, H at C5), 6.63 (1H, d, *J* 8 Hz, H at C-6), 5.09 (1H, br, O<u>H</u>), 2.20 (3H, s, C<u>H</u>$_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 152.9, 133.5, 129.7, 126.3, 116.6, 112.6, 15.6; GC-MS (EI), *m/z* (rel int.): 189 (7, $(M+3)^+$), 188 (100, $(M+2)^+$), 187 (15, $(M+1)^+$), 186 (98, M^+), 185 (8, $(M\text{-H})^+$), 107 (62, $(M\text{-Br})^+$), 93 (2), 89 (8), 79 (17), 78 (18), 77 (46), 53 (7), 52 (6), 51 (15), 50 (8); IR (neat): 3369, 2925, 1116, 1079, 1040 cm^{-1}.

*5.2.3. 4-Bromophenol (**3a**).*[6c] Colourless liquid; yield: 89% (0.0774 g). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.28 (2H, d, *J* 9 Hz, Hs at C-3 and C-5), 6.70 (2H, d, *J* 9 Hz, Hs at C-2 and C-6); ^{13}C NMR (75 MHz, $CDCl_3$): δ 154.8, 132.5, 117.2, 112.8; GC-MS (EI), *m/z* (rel int.): 175 (6, $(M+3)^+$), 174 (97, $(M+2)^+$), 173 (7, $(M+1)^+$), 172 (100, M^+), 145 (3, $((M+2)\text{-CHO})^+$), 143 (4, $(M\text{-CHO})^+$), 119 (3), 117 (3), 93 (30), 74 (5), 66 (6), 65 (68), 64 (10), 63 (22), 62 (11), 39 (24); IR (neat): 3307, 1069 cm^{-1}.

*5.2.4. 1-Bromo-4-methoxybenzene (**4a**).*[13] Colourless liquid; yield: 95% (0.0893 g). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.37 (2H, dd, *J* 9, 2 Hz, Hs at C-3 and C-5), 6.78 (2H, dd, *J* 9, 2 Hz, Hs at C-2 and C-6), 3.78 (3H, s, OC<u>H</u>$_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 158.7, 132.2, 115.7, 112.8, 55.4; GC-MS (EI), *m/z* (rel int.): 189 (7, $(M+3)^+$), 188 (97, $(M+2)^+$), 187 (8, $(M+1)^+$), 186 (100, M^+), 174 (3, $((M+3)\text{-CH}_3)^+$), 173 (42, $((M+2)\text{-CH}_3)^+$), 172 (4, $((M+1)\text{-CH}_3)^+$), 171 (42 $(M\text{-CH}_3)^+$), 146 (2), 145 (36), 144 (3), 143 (37), 119 (5), 117 (4), 92 (9), 79 (3), 78 (1), 77 (11), 76 (5), 75 (7), 74 (7); IR (neat): 1485, 1289, 1071, 1031cm^{-1}.

*5.2.5. N-(4-Bromophenyl)acetamide (**5a**).*[14] White solid; yield: 97% (0.1036 g). Mp (water) 164-166 °C, lit.[15] 165-167 °C; ^{1}H NMR (300 MHz, CD_3COCD_3): δ 9.31 (1H, br, N<u>H</u>), 7.62 (2H, d, *J* 9 Hz, Hs at C-2 and C-6), 7.45 (2H, d, *J* 9 Hz, Hs at C-3 and C-5), 2.09 (3H, s, COC<u>H</u>$_3$); ^{13}C NMR (75 MHz, CD_3COCD_3): δ 168.2, 138.9, 131.5, 120.9, 114.9, 23.4; GC-MS (EI), *m/z* (rel int.): 215 (24, (M+2)+), 213 (25, M+), 174 (7), 173 (98, $((M+2)\text{-COCH}_3\text{+H})^+$), 172 (10), 171 (100, $(M\text{-COCH}_3\text{+H})^+$), 170 (2), 145 (3), 143 (3), 119 (2), 117 (2), 92 (18), 91 (9), 65 (12), 43 (22); IR (neat): 3291, 3258, 1667, 1070 cm^{-1}.

*5.2.6. N-(4-Bromophenyl)benzamide (**6a**).*[15] White solid; yield: 98% (0.1355 g). Mp (water) 203-204 °C, lit.[16] 203-204 °C; ^{1}H NMR (300 MHz, CD_3OD): δ 7.92 (2H, d, *J* 8 Hz, Hs at C-3 and C-5), 7.64 (2H, d, *J* 9 Hz, Hs at C2 and C6), 7.59-7.45 (5H, m, C_6H_5); ^{13}C NMR (75 MHz, CD_3OD): δ 178.0, 139.1, 136.0, 133.1, 132.9, 129.8, 128.7, 123.9, 118.2; GC-MS (EI), *m/z* (rel int.): 277 (20, $(M+2)^+$), 275 (20, M^+), 145 (2) 143 (2), 119 (1, $(M\text{-C}_6\text{H}_4\text{Br-H})^+$), 106 (8), 105 (100, $(C_6H_5CO)^+$), 91 (5), 78 (3), 77 (39), 76 (2), 51 (8), ; IR (neat): 3330, 1645, 1073 cm^{-1}.

*5.2.7. 4-Bromo-2-chlorophenol (**7a**).*[6c] Colourless liquid; yield: 75% (0.0778 g). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.46 (1H, d, *J* 2 Hz, H at C-3), 7.29 (1H, dd, *J* 9, 2 Hz, H at C5), 6.91 (1H, d, *J* 9 Hz, H at C-6), 5.55 (1H, s, O<u>H</u>); ^{13}C NMR (75 MHz, $CDCl_3$): δ 151.9, 131.3, 129.8, 121.0, 117.3, 109.9; GC-MS (EI), m/z (rel int.): 210 (26, $(M+4)^+$), 209 (7, $(M+3)^+$), 208 (100, $(M+2)^+$), 207 (6, $(M+1)^+$), 206 (79, M^+), 181 (0.85, $((M+4)\text{-CHO})^+$), 179 (3, $((M+2)\text{-CHO})^+$), 177 (3, $(M\text{-CHO})^+$), 172 (6), 170 (6), 144 (9), 142 (9), 129 (3), 128 (2), 127 (7), 126 (3), 99 (16), 64 (5), 63 (47), 62 (14), 61 (8); IR (neat): 3501, 1080 cm^{-1}.

*5.2.8. Methyl 5-Bromo-2-hydroxybenzoate (**8a**).*[6c] Colourless liquid; yield: 84% (0.0964 g). ^{1}H NMR (300 MHz, $CDCl_3$): δ

10.67 (1H, s, OH), 7.94 (1H, d, *J* 2 Hz, H at C-6), 7.52 (1H, dd, *J* 9, 2 Hz, H at C4), 6.87 (1H, d, *J* 9 Hz, H at C-3), 3.95 (3H, s, OCH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.0, 161.0, 138.6, 132.4, 119.9, 114.1, 110.9, 52.7; GC-MS (EI), m/z (rel int.): 233 (3, $(M+3)^+$), 232 (36, $(M+2)^+$), 231 (4, $(M+1)^+$), 230 (37, M^+), 200 (98, $((M+2)\text{-}HOCH_3)^+$), 199 (20), 198 (100, $(M\text{-}HOCH_3)^+$), 173 (8), 172 (37), 171 (8), 170 (37), 143 (9), 136 (2), 119 (5), 91 (8), 64 (11), 63 (50), 62 (16), 53 (13), 38 (5); IR (neat): 3183, 1737, 1079 cm^{-1}.

*5.2.9. 2-Acetyl-4-Bromophenol (**9a**).*[6c] White solid; yield: 87% (0.0937 g). ^1H NMR (300 MHz, $CDCl_3$): δ 12.16 (1H, s, OH), 7.84 (1H, d, J *2* Hz, H at C-3), 7.55 (1H, dd, *J* 9, 2 Hz, H at C5), 6.90 (1H, d, *J* 9 Hz, H at C-6), 2.64 (3H, s, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 203.5, 161.3, 139.1, 132.9, 125.0, 120.5, 110.4, 26.7; GC-MS (EI), m/z (rel int.): 217 (5, $(M+3)^+$), 216 (51, $(M+2)^+$), 215 (5, $(M+1)^+$), 214 (52, M^+), 202 (8), 201 (97, $((M+2)\text{-}CH_3)^+$), 199 (100, $(M\text{-}CH_3)^+$), 173 (17), 172 (3), 171 (17), 145 (12), 143 (13), 119 (3) 117 (4), 92 (7), 64 (9), 63 (28), 62 (11), 53 (11), 43 (24, CH_3CO^+); IR (neat): 2923, 1643, 1084 cm^{-1}.

*5.2.10. 1-Bromonaphthalene (**10a**).*[16] Colourless liquid; yield: 78% (0.1623 g). ^1H NMR (300 MHz, $CDCl_3$): δ 8.24 (1H, d, *J* 8 Hz, H at C-2), 7.84-7.78 (3H, m, Hs at C-4, C-5 and C-8), 7.60-7.53 (2H, m, Hs at C-6 and C-7), 7.32 (1H, t, *J* 8 Hz, H at C-3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 134.7, 129.9, 128.3, 127.9, 127.3, 127.1, 126.7, 126.2, 122.9, 118.8; GC-MS (EI), *m/z* (rel int.): 209 (10, $(M+3)^+$), 208 (97, $(M+2)^+$), 207 (12, $(M+1)^+$), 206 (100, M^+), 128 (8, $((M+1)\text{-}Br)^+$), 127 (75, $(M\text{-}Br)^+$), 104 (7), 103 (8), 87 (3), 86 (2), 77 (8), 76 (4), 75 (8), 74 (8), 63 (13); IR (neat): 3053, 1591, 1561, 1056 cm^{-1}.

*5.2.11. 2-Bromofluorene (**11a**).*[17] White solid; yield: 71% (0.1744 g). Mp 103-104 °C, lit.[18] 102-103 °C; ^1H NMR (300 MHz, $CDCl_3$): δ 7.75 (1H, d, *J* 8 Hz, H at C-3), 7.68 (1H, d, *J* 1 Hz, H at C-1), 7.64 (1H, d, *J* 8 Hz, H at C-4), 7.50 (1H, d, *J* 8 Hz, H at C-5), 7.54 (1H, d, *J* 8 Hz, H at C-8), 7.41-7.30 (2H, m, Hs at C-6 and C-7), 3.89 (2H, s, Hs at C-9); ^{13}C NMR (75 MHz, $CDCl_3$): δ 145.2, 142.9, 140.7, 130.2, 129.9, 128.3, 127.2, 127.0, 125.1, 121.1 120.4, 120.0; GC-MS (EI), *m/z* (rel int.): 247 (3, $(M+3)^+$), 246 (26, $(M+2)^+$), 245 (5, $(M+1)^+$), 244 (25, M^+), 166 (14, $((M+1)\text{-}Br)^+$), 165 (100, $(M\text{-}Br)^+$), 164 (13), 163 (23), 162 (4), 139 (3), 115 (2), 83 (13), 82 (7), 63 (2); IR (neat): 3031, 1601, 1567, 1061 cm^{-1}.

*5.2.12. 1-Bromo-2,5-dimethylbenzene (**12a**).*[18] Colourless liquid; yield: 72% (0.2670 g). ^1H NMR (300 MHz, $CDCl_3$): δ 7.37 (1H, s, H at C-3), 7.11 (1H, d, *J* 8 Hz, H at C-6), 7.01 (1H, d, *J* 8 Hz, H at C-5), 2.36 (3H, s, CH_3), 2.30 (3H, s, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 137.2, 134.6, 132.8, 130.5, 128.0, 124.7, 22.4, 20.6; GC-MS (EI), *m/z* (rel int.): 187 (6, $(M+3)^+$), 186 (64, $(M+2)^+$), 185 (11, $(M+1)^+$), 184 (64, M^+), 171 (7, $((M+2)\text{-}CH_3)^+$), 169 (7, $((M\text{-}CH_3)^+$), 106 (9, $((M+1)\text{-}Br)^+$), 105 (100, $(M\text{-}Br)^+$), 104 (11), 103 (25), 89 (4), 79 (19), 78 (15), 77 (25), 63 (9), 51 (17); IR (neat): 3019, 2922 cm^{-1}.

*5.2.13. 3-Bromo-4-methoxybenzaldehyde (**13a**).*[19] White solid; yield: 77% (0.3318 g). Mp 45-46 °C, lit.[20] 43-44 °C; ^1H NMR (300 MHz, $CDCl_3$): δ 9.84 (1H, s, CHO), 8.07 (1H, d *J* 2 Hz, H at C-2), 7.82 (1H, dd, *J* 8, 2 Hz, H at C-6), 7.01 (1H, d, *J* 8 Hz, H at C-5), 3.99 (3H, s, OCH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 189.5, 160.6, 134.5, 131.2, 130.8, 112.7, 111.6, 56.6; GC-MS (EI), *m/z* (rel int.): 216 (75, $(M+2)^+$), 215 (100, $((M+2)\text{-}H)^+$), 214 (76, M^+), 213 (96, $(M\text{-}H)^+$), 188 (1), 187 (5), 186 (1), 185 (5), 157 (7), 155 (6), 145 (11), 143 (12), 119 (8), 92 (3), 78 97), 77 (9), 76 (8), 75 (9), 74 (8), 63 (22); IR (neat): 1683, 1048 cm^{-1}.

*5.2.14. 2-Bromo-9H-fluoren-9-one (**14a**).*[20] Yellow solid; yield: 38% (0.3912 g). Mp 129-131 °C, lit.[21] 128-130 °C; ^1H NMR (300 MHz, $CDCl_3$): δ 7.76 (1H, d, *J* 2 Hz, H at C-1), 7.61 (1H, dd, *J* 8, 2 Hz, H at C-3), 7.51 (2H, d, *J* 4 Hz, Hs at C-5 and C-8), 7.40 (1H, d, *J* 8 Hz, H at C-6), 7.39 (1H, d, *J* 8 Hz, H at C-4), 7.37-7.30 (1H, m, H at C-7); ^{13}C NMR (75 MHz, $CDCl_3$): δ 192.3, 143.6, 143.0, 137.1, 135.8, 135.0, 133.7, 129.4, 127.5, 124.6, 122.7, 121.7, 120.4; GC-MS (EI), m/z (rel int.): 260 (98, $(M+2)^+$), 258 (100, M^+), 232 (3, $((M+2)\text{-}CO)^+$), 230 (4, $(M\text{-}CO)^+$), 179 (2, $(M\text{-}Br)^+$), 152 (7, $((M+1)\text{-}Br\text{-}CO)^+$), 151 (49, $(M\text{-}Br\text{-}CO)^+$), 116 (4), 115 (4), 98 (4), 75 (13); IR (neat): 1716, 1076 cm^{-1}

5.3 Iodination of acetanilide

Thiourea (5.2 mol%, 2 mg, 0.026 mmol) was added to an acetonitrile solution (10 mL) containing *N*-iodosuccinimide (1.0 equiv, 113 mg, 0.5 mmol). Acetanilide (67.4 mg, 0.5 mmol) was added immediately to the resulting stirred solution and allowed to stir at room temperature for 2 hours. The reaction was quenched by the addition of 10% aqueous solution of $Na_2S_2O_3$ (10 mL) and extracted with ethyl acetate (70 mL). The organic solution was then washed with additional 10% $Na_2S_2O_3$ (2 x 10 mL), followed by deionized water (3 x 15 mL) and brine (2x 10 mL). The organic solution was then dried over anhydrous Na_2SO_4 and the solvent was evaporated *in vacuo* to give an off-white crude solid, which was purified by centrifugal thin-layer chromatography using a 2 mm thick silica gel $60GF_{254}$ coated plate (5% $EtOAc/CH_2Cl_2$) to give *N*-(4-iodophenyl)acetamide (0.0972 g, 74%) as an off-white solid; Mp (H_2O) 179-181 °C, lit.[18] 180-182 °C; ^1H NMR (300 MHz, CD_3OD): δ 7.58 (2H, d, *J* 9 Hz, Hs at C-3 and C-5), 7.33 (2H, d, *J* 9 Hz, Hs at C2 and C6), 2.08 (3H, s, $COCH_3$); ^{13}C NMR (75 MHz, CD_3OD): δ 171.8, 140.0, 139.0, 123.1, 87.8, 24.0; GC-MS (EI), *m/z* (rel int.): 262 (6, $(M+2)^+$), 261 (58, M^+), 220 (8, $((M+2)\text{-}COCH_3+H)^+$) 219 (100, $(M\text{-}COCH_3+H)^+$), 191 (3), 127 (2, I), 92 (21, $(M\text{-}COCH_3+H\text{-}I)^+$), 91 (5), 65 (11), 64 (6), 63 (8), 43 (13, $(COCH_3)^+$); IR (neat): 3287, 3252, 1664, 1061 cm^{-1}.

5.4 UV-vis experiments

5.4.1 Preparation of UV-vis spectra of NBS with 1-5% thiourea

The solutions of thiourea, NBS, and NBS with 1-5% thiourea were prepared in the same manner as those of NCS-thiourea studies. The amounts of thiourea used for the 50 mL acetonitrile stock solution was 0.0190 g (mmol). The aliquots of freshly-made thiourea stock solution for 1%, 2%, 3% and 5% solutions of thiourea with 0.5 mmol of NBS (0.0890 g) were 1, 2, 3 and mL, respectively. These solutions were stirred for 10 minutes before their UV-vis spectra were recorded. The order of spectra recording was the same as in the NCS study with the 1% solution first and 5% solution last. A UV-vis spectrum of 5% thiourea, made in the same manner as stated above for NCS, was recorded after the NBS and 5% thiourea solution recording. A UV-vis spectrum of NBS (0.0890 g, 0.5 mmol) in 10 mL of acetonitrile was recorded 10 minutes after it was made but before the recording of the NBS and 1% thiourea solution.

5.4.2 Preparation of UV-vis spectra of NBS with 5% thiourea and acetanilide

A 10 mL solution of 5% thiourea (2.5 mM) was prepared in a 10 mL volumetric flask by dissolving thiourea (0.0190 g, mol) in acetonitrile. Three 10 mL solutions of 0.5 mmol of NBS (0.0890 g) were made in separate 10 mL volumetric flasks with the first one also containing 5% thiourea (1 mL of the 5% stock solution, the second containing 5% thiourea (1 mL aliquot) and 0.0125 M acetanilide (0.0169 g, mmol) and the third containing 5%

thiourea (1 mL aliquot) and 0.025 M acetanilide (0.0338 g, mmol). All three solutions were stirred for 10 minutes before their UV-vis spectra were recorded, with the first solution recorded first and the solution containing thiourea and 0.025 M acetanilide last. Prior to the spectra recording of these three solutions, UV-vis spectra of NBS in acetonitrile (0.089 g, 0.5mmol of NBS in 10 mL of acetonitrile) and 5% thiourea (from the 5% thiourea stock solution) were recorded 10 minutes after both solutions were made.

Acknowledgments

We express our gratitude to Dr. Supachai Supaluknari of the Chemistry Department of Silpakorn University for the NMR experiments. We are grateful for the support from Mahidol University International College.

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