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Sulfoxide-TFAA and nucleophile combination as new reagent for aliphatic C–H functionalization at indole 2α-position†‡

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Aliphatic C–H functionalization at indole 2α-position mediated by acyloxythionium species **1** generated from sulfoxide and acid anhydride has been developed. The combination of sulfoxide and TFAA with *O*-, *N*- and *C*-nucleophiles enabled introduction of various substituents in a one-pot procedure. Especially on utilizing DMSO, the combination provided a practical and efficient method for the synthesis of a wide range of 2α-substituted indoles.

The combination of sulfoxide and acid anhydride is a useful reagent for organic synthesis owing to the powerful electrophilicity of acyloxythionium species **1** generated *in situ*.[1] Typical reactions are Swern–Moffatt type oxidation of alcohols,[2] the oxidation of thiols to disulfides,[3] the conversion of amines to iminosulfuranes,[4] and transformations of alkenes, aromatics and enols to vinyl-,[5,6,7a] aryl-[8] and β-keto-sulfonium salts,[9] and so on.[10] Recently, these reactions have been extended to one-pot multi-component reactions by adding other nucleophiles for the development of efficient synthetic methods. For example, acyloxythionium **1**-mediated substitution of alcohols with enolates,[11] glycosylation of 1-hydroxy-[12] and 1-thiophenyl-glycocyl derivatives,[13] addition of **1** to alkenes followed by amines or imides sequentially to produce aziridines,[7,8a] allyl amines,[7,8b] or enamides,[7,8c] and **1**-activated 2-amido-[14] and 2-hydroxy-glycosylations of glycal enol ethers.[15] Especially, many uses of acyloxythionium species **1** in one-pot multi-component reactions starting from addition to carbon–carbon double bond have been reported, although the application of such a one-pot multi-component reaction to aromatics is limited because of the stability of the initially generated arylsulfonium salts. The only known examples are intramolecular aromatic substitutions.[16] In our recent communication, we reported the acyloxythionium **1**-mediated intermolecular C–H functionalization at indole 2α-position utilizing a DMSO-TFAA-nucleophile combination.[17] In the present paper, we report the full details of the combination of the sulfoxides containing DMSO,

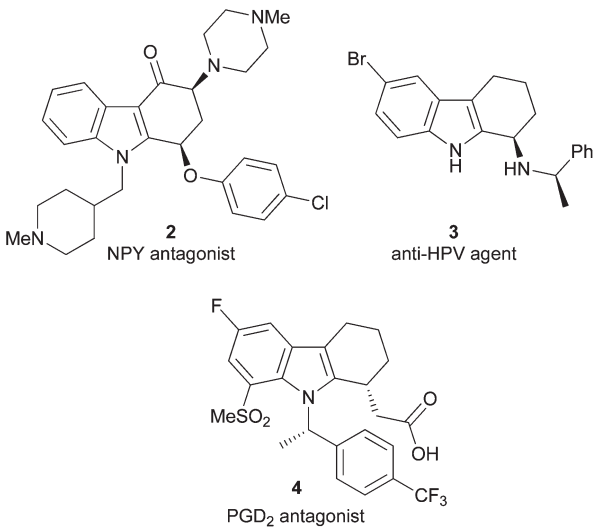

Fig. 1 Biologically active 2α-substituted indoles.

TFAA and nucleophiles as efficient reagents for the synthesis of 2α-substituted indole derivatives, which are attractive intermediates for synthesis of biologically active compounds, NPY antagonist **2**,[18] anti-HPV agent **3**,[19] and PGD_2 antagonist **4**[20] (Fig. 1).

C–H functionalization by combination of diaryl sulfoxide-TFAA

In order to realize the acyloxythionium species-mediated intermolecular C–H functionalization at the 2α-position of indoles, we initially studied the reaction of tetrahydrocarbazole and the acyloxythionium species generated from diphenyl sulfoxide

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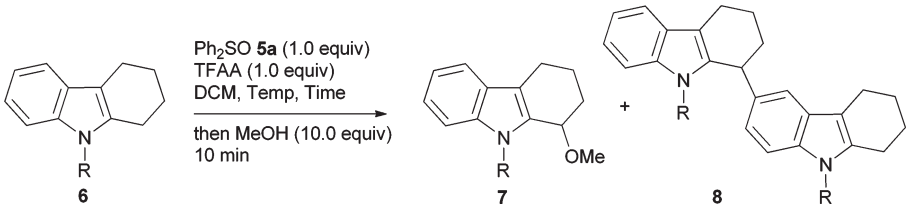
†This work is dedicated to Dr Masanori Sakamoto, Professor Emeritus of Meiji Pharmaceutical University, on the occasion of his 77th birthday (KIJU).

‡Electronic supplementary information (ESI) available: General synthetic procedures and NMR data of compounds. See DOI: 10.1039/c2ob26944a

Table 1 Reactivity of *N*-substituted indoles



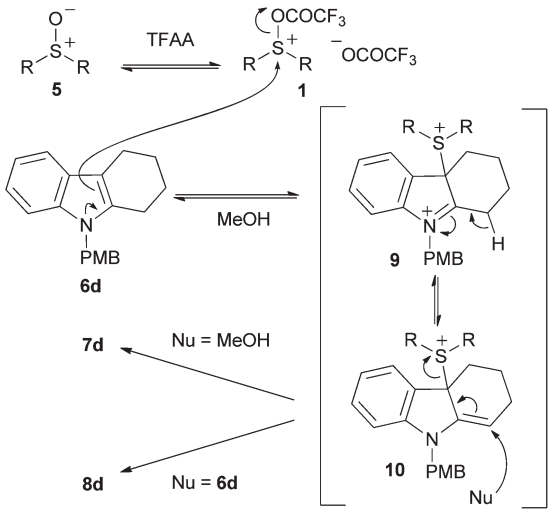
					Yield[a] (%)				
Entry	**6**	R	Temp (°C)	Time (min)	**7**		**8**		Recovery of **6** (%)
1	**6a**	Ac	−40 to r.t.	10	**7a**	9	**8a**	ND[b]	87
2	**6b**	CO_2Me	−40 to r.t.	30	**7b**	20	**8b**	ND	71
3	**6c**	H	−40	30	**7c**	ND	**8c**	ND	ND
4	**6d**	PMB	−40	10	**7d**	32	**8d**	33	ND

[a] Isolated yield. [b] ND = Not detected.

and TFAA (Table 1). To a solution of *N*-acetyl tetrahydrocarbazole **6a** and diphenyl sulfoxide (**5a**) in dichloromethane was added TFAA. After the consumption of **6a**, MeOH was added to afford 2α-methoxy compound **7a** in 9% yield with recovery of **6a** (87%) (entry 1). In the case of *N*-methoxycarbonyl compound **6b**, the desired product **7b** was obtained in 20% yield with recovery of **6b** (71%) (entry 2). Since this is attributed to reduced reactivity of **6a** and **6b** with an electron-withdrawing group, we performed the reactions involving *N*-unsubstituted **6c** and electron-donating *N*-*p*-methoxybenzyl (PMB) compound **6d**. In the case of **6c**, the result was disappointing, but the reaction of **6d** afforded desired compound **7d** (32%) together with dimer **8d** (33%) (entry 4).[21]

A plausible reaction mechanism is shown in Scheme 1. The reaction of sulfoxide **5** and TFAA generates the acyloxythionium species **1**, which is subjected to nucleophilic attack of **6d** to produce thionium intermediate **9**. After deprotonation to form enamine **10**, subsequent S_N2'-type reaction of **10** with MeOH occurs at the 2α-position of indole to give **7d**. Excess MeOH also attacks the sulfur atom[14] of intermediate **9** to regenerate **6d**, which is introduced at the 2α-position of **10** to afford dimer **8d**.[22]

To improve the yield of **7d**, the suppression of the above dimerization was required. Therefore we examined the substituent effect on the aryl sulfoxide **5** (Table 2). Initially, the use of sulfoxides **5b** and **5c** with an electron-donating group increased the yield of desired product **7d** (42% and 54%) along with suppressing the formation of **8d**, respectively (entries 2 and 3). This result implies that the electron-donating substituent of sulfoxide **5** decreased the positive charge on the sulfur atom of **9** to prevent the attack of MeOH. In the cases of **5d** and **5e** with electron-withdrawing groups, the reactions gave the undesired dimer **8d** (22% and 13%) with recovery of starting material **6d** (entries 4 and 5). Electron-deficient sulfoxides were inefficient to react with TFAA. Therefore, dimerization occurred before consumption of **6d**. On using sulfoxides **5f** and **5g** with *ortho* substituent, desired product **7d** was obtained in poor yields with recovery of **6d**. This result could



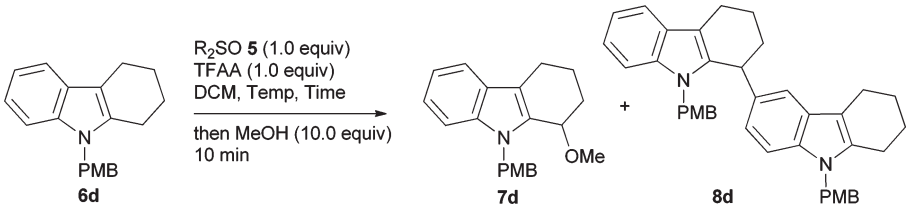
Scheme 1 Plausible reaction mechanism for acyloxythionium mediated reaction.

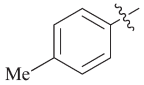
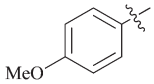
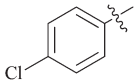
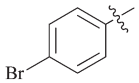
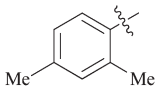
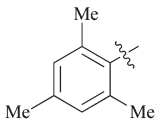
be explained by assuming that the crowded sulfur atom of the acyloxythionium species **1** could not come close to **6d** to form **9** (entries 6 and 7).

Next, we investigated the equivalent ratio of sulfoxide **5b** and TFAA (Table 3). The yield of **7d** was improved by increasing the ratio of **5b** and TFAA to **6d**. As a result, the use of 3 equiv. to **6d** dramatically improved the yield of **7d** to 93% without dimerization. This can be explained in terms of an equilibrium shift toward thionium intermediate **9** by use of excess acyloxythionium species **1**.

Under the optimized conditions, we examined the scope and limitation of this reaction (Table 4). In addition to 6-membered ring-fused indole **6d** (Table 3, entry 3), this reaction could be applied to 5- and 7-membered ring-fused indoles **6e** and **6f** to give **7e** and **7f** in moderate yields, respectively (entries 1 and 2). On using 2,3-dimethylindole **6g**, **7g** was obtained in 29% yield with recovery of **6g** in 12% (entry 3).

Table 2 Substituent effect on aromatic rings of diaryl sulfoxides



Entry	5	R	Temp (°C)	Time (min)	Yield[a] (%) 7d	8d	Recovery of 6d (%)
1	5a		−40	10	32	33	ND[b]
2	5b		−40	10	42	27	ND
3	5c		−40	10	54	10	ND
4	5d		−40 to r.t.	90	ND	22	42
5	5e		−40 to r.t.	90	ND	13	60
6	5f		−40 to r.t.	90	4	8	38
7	5g		−40 to r.t.	90	ND	29	28

[a] Isolated yield. [b] ND = Not detected.

Next, we investigated the reaction of **6d** with various nucleophiles (Table 5). Secondary alcohol afforded 51% yield of the corresponding product **7h** (entry 1), but tertiary alcohol and *n*-octanethiol did not form **7i** and **7j** (entries 2 and 3). Azide and primary amine were introduced as nitrogen substituents in good yields (entries 4 and 5). Subsequently, to apply this reaction to C–C bond formation, we tried utilizing several carbon nucleophiles. Although trimethylsilyl cyanide did not undergo the desired reaction (entry 6), *N*-methylindole gave product **7n** quantitatively (entry 7).

Additionally, we attempted to introduce carbon substituents with various organometallic reagents (Table 6). Methylmagnesium iodide gave methylated product **7o** in 44% yield (entry 1). When methylmagnesium chloride and bromide were used, ketone **11** and 5-brominated ketone **12** were obtained without formation of the desired **7o**, respectively (entries 2 and 3). In the cases of trimethylaluminum, dimethylzinc and diethylzinc, the corresponding alkylated products **7o** and **7p** were obtained in good yields (entries 4–6). By using divinylzinc or lithium dimethylcuprate, however, **11** was obtained instead of desired products **7q** and **7o**, respectively (entries 7 and 8).

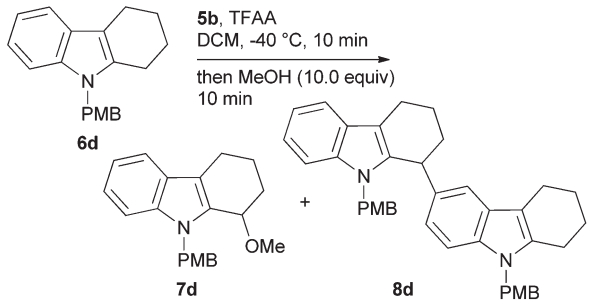
Although the combination of diaryl sulfoxide and TFAA has the limitation in some of the applied carbon nucleophiles, we revealed that the combination of diaryl sulfoxide-TFAA and carbon nucleophile realized its potential for carbon–carbon bond formation.

A plausible mechanism of the formation of **11** is shown in Scheme 2. On the way of the reaction with some organometallic reagents, regenerated sulfoxide **5** attacks to 2α-position of **10**, and Kornblum-type oxidation[23] of **13** proceeds to afford **11**.

C–H functionalization by the combination of alkyl sulfoxide-TFAA and nucleophile

As described above, the reaction utilized the acyloxythionium species, generated from diaryl sulfoxide, required excess reagent and restricted the kind of nucleophile to be introduced. Therefore, we further optimized the combined reagent using various sulfoxides for the expansion of the reaction scope.

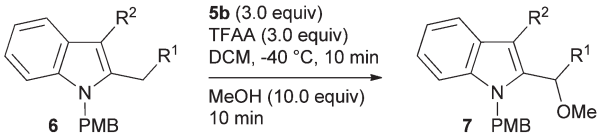
Table 3 Effect of the amount of acyloxythionium species



Entry	5b (equiv.)	TFAA (equiv.)	Yield[a] (%) 7d	8d
1	1.0	1.0	42	27
2	2.0	2.0	79	4
3	3.0	3.0	93	ND[b]

[a] Isolated yield. [b] ND = Not detected.

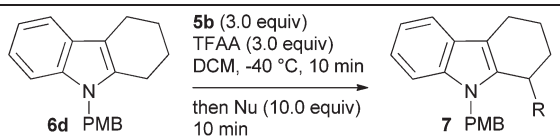
Table 4 Application of *p*-Tol_2SO-TFAA system to other indole derivatives

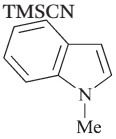
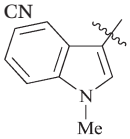


Entry	6	R^1	R^2	7	Yield[a] (%)	Recovery (%)	
1	6e	$-(CH_2)_2-$		7e	72	6e	ND[b]
2	6f	$-(CH_2)_4-$		7f	57	6f	ND
3	6g	H	Me	7g	29	6g	12

[a] Isolated yield. [b] ND = Not detected.

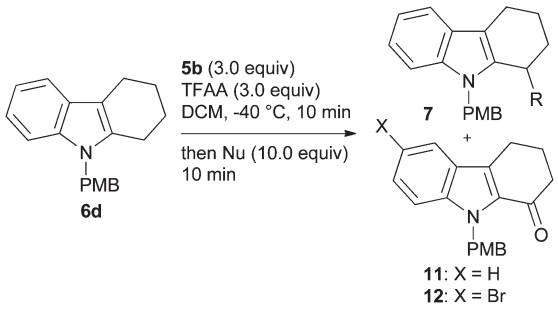
Table 5 Scope of nucleophiles with *p*-Tol_2SO-TFAA system

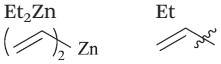


Entry	Nu	7	R	Yield[a] (%)
1	$^{i}PrOH$	7h	^{i}PrO	51
2	$^{t}BuOH$	7i	^{t}BuO	ND[b]
3	$^{n}OctSH$	7j	$^{n}OctS$	ND
4	$TMSN_3$	7k	N_3	93
5	$BnNH_2$	7l	BnNH	75
6	TMSCN	7m	CN	ND
7		7n		99

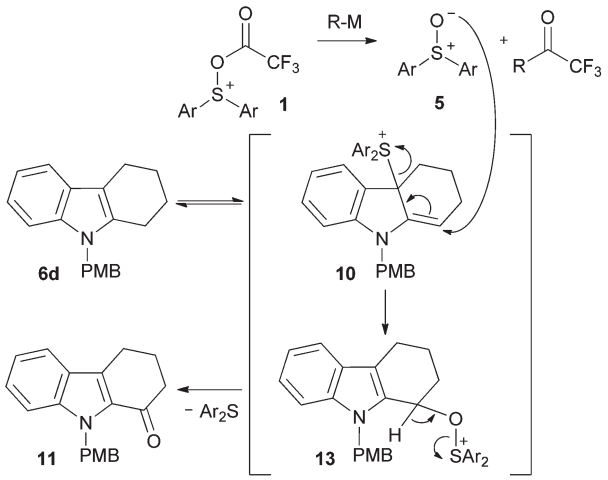
[a] Isolated yield. [b] ND = Not detected.

Table 6 C–C bond formation with organometallic reagents



Entry	Nu	R	7	Yield[a] (%) 11	12
1	MeMgI	Me	7o	44	ND	ND[b]
2	MeMgCl	Me	7o	ND	37	ND
3	MeMgBr	Me	7o	ND	ND	47
4	Me_3Al	Me	7o	58	ND	ND
5	Me_2Zn	Me	7o	76	ND	ND
6	Et_2Zn	Et	7p	76	ND	ND
7			7q	ND	70	ND
8	Me_2CuLi	Me	7o	ND	38	ND

[a] Isolated yield. [b] ND = Not detected.

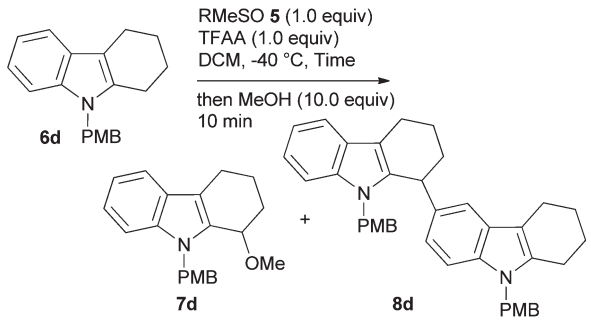


Scheme 2 Plausible reaction mechanism of oxidation at 2α-position.

Initially, we examined the use of aryl methyl and dimethyl sulfoxides instead of diaryl sulfoxide (Table 7). In comparison with diphenyl sulfoxide (**5a**) (Table 2, entry 1), the use of methyl phenyl sulfoxide (**5h**) improved the yield of desired product **7d** (57%) through decreased formation of dimer **8d** (15%) (Table 7, entry 1). On using *p*-tolyl and *p*-anisyl methyl sulfoxides (**5i** and **5j**), the yield of **7d** were dramatically increased (entries 2 and 3). To our surprise, we found that DMSO **5k** gave **7d** in 93% yield without the formation of dimer **8d** (entry 4).

Secondly, the effect of nucleophile usage under DMSO-TFAA conditions was optimized. Several experiments showed

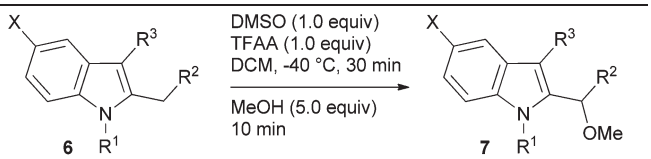
Table 7 Further optimization with alkyl sulfoxides



Entry	5	R	Time (min)	MeOH (equiv.)	Yield[a] (%) 7d	8d
1	**5h**	Ph	10	10.0	57	15
2	**5i**	*p*-Tol	10	10.0	74	10
3	**5j**	*p*-An	10	10.0	80	9
4	**5k**	Me	30	10.0	93	ND[b]
5	**5k**	Me	30	5.0	95	ND
6	**5k**	Me	30	5.0	76	ND

[a] Isolated yield. [b] ND = Not detected.

Table 8 Application of the DMSO-TFAA system to various indole derivatives



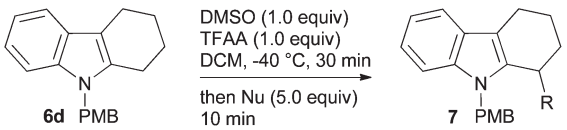
Entry	6	R^1	R^2	R^3	X	7	Yield[a] (%)
1	**6e**	PMB	$-(CH_2)_2-$		H	**7e**	72
2	**6f**	PMB	$-(CH_2)_4-$		H	**7f**	90
3	**6r**	PMB	$-(CH_2)_3-$		MeO	**7r**	76
4	**6s**	PMB	$-(CH_2)_3-$		Br	**7s**	70
5	**6t**	PMB	Me	Me	H	**7t**	82
6	**6u**	$-(CH_2)_3-$		Me	H	**7u**	61

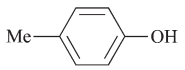
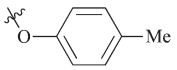
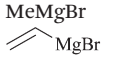
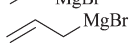
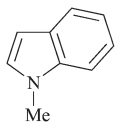
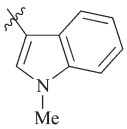
[a] Isolated yield.

that the amount of MeOH could be reduced to 5 equiv. (entry 5).

With these improvements (Table 7), we found a practical method for C–H functionalizing at the indole 2α-position by utilizing the DMSO-TFAA system. We applied the optimized reaction conditions to various indoles (Table 8). As a result, indoles **6e**, **6f** and **6r–6u** gave the corresponding products in high yields. Subsequently, we investigated a variety of nucleophiles (Table 9). In addition to MeOH as oxygen nucleophile, *p*-cresol afforded aryl ether **7v** in 70% yield (entry 1). Azide and amine as nitrogen nucleophiles also gave the corresponding products **7k** and **7l** in high yields (entries 2 and 3). With Grignard reagents, methyl, vinyl and allyl groups were introduced quantitatively (entries 4–6). When *N*-methylindole as aromatic nucleophile was used, the desired product **7n** was

Table 9 Introduction of various nucleophiles using DMSO-TFAA system



Entry	Nu	7	R	Yield[a] (%)
1		**7v**		70
2	$TMSN_3$	**7k**	N_3	Quant
3	$BnNH_2$	**7l**	NHBn	82
4	MeMgBr	**7o**	Me	99
5		**7q**		Quant
6		**7w**		Quant
7		**7n**		97

[a] Isolated yield.

obtained in excellent yield (entry 7). The DMSO-TFAA system achieved remarkable improvement in the yield of **7** with Grignard reagents in comparison with that of the *p*-Tol_2SO-TFAA system (Table 6).

Conclusions

We have developed a new procedure for C–H functionalization at the indole 2α-position mediated by the combination of sulfoxide-TFAA and nucleophile. Especially, the DMSO-TFAA system gave the best results in the desired C–H functionalization including C–C bond formation, which is a useful method for the synthesis of natural products and biologically active compounds.[24]

Our extended studies of this reaction to an asymmetric version and synthesis of biologically active compounds such as **2** and **3** are under investigation in our laboratory.

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