RSC Advances

ROYAL SOCIETY OF CHEMISTRY

www.rsc.org/advances

Journal Name

COMMUNICATION

Oxidative Acylation of Sulfoximines with Methylarenes as Acyl Donor

Cite this: DOI: 10.1039/xoxxoooooox

Zhenguang Zhao,[b] Tao Wang,*[,a,b] Lin Yuan,[b] Xingwang Jia[b] and Junfeng Zhao*[,a,b]

Received ooth January 2012,
Accepted ooth January 2012

DOI: 10.1039/xoxxoooooox

www.rsc.org/

Established herein is an efficient direct oxidative acylation of sulfoximines with methylarenes as acyl donor. Electron-donating as well as -withdrawing groups on the methylarenes are tolerated and even steric demanding *ortho* substituents are compatible. In this case, both coupling partners are used in their native form, thus obviating prior functionalization and activation.

As the monoaza analogues of sulfones, sulfoximines are of great interest for a variety of applications due to their versatile chemistry.[1] For example, enantio-enriched sulfoximines have been studied extensively in asymmetric synthesis as chiral ligands, auxiliaries and organocatalysts.[2] Recent developments in drug discovery illustrate that sulfoximines can be used as an unconventional pharmacophores (Figure 1) for improving solubility, minimizing off-target activity and retention of high level bioactivity.[3] In addition, sulfoximines have been demonstrated to be efficient removable directing groups for

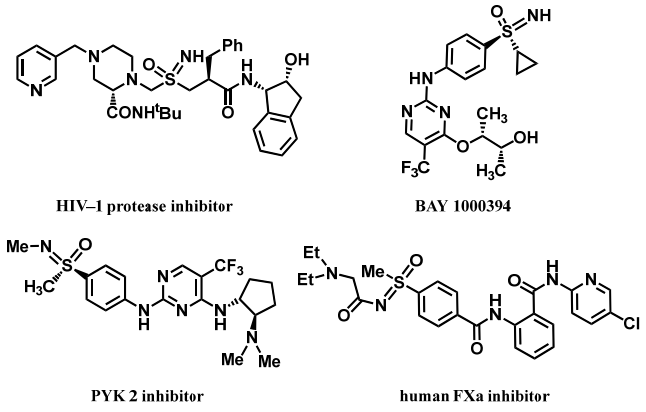
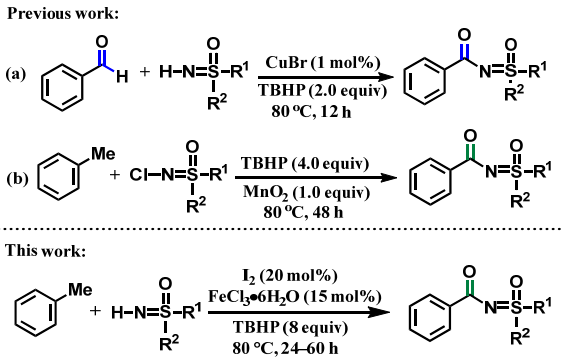


Figure 1. Drug candidates containing sulfoximine moiety

ortho-C-H activation of arenes due to their strong coordination with transition metals.[4] As a consequence, the synthesis and functionalization of sulfoximine unit containing compounds have attracted much attention.[2c,2f,5] Among these strategies, N-acylation has become a powerful method for functionalization of sulfoximines. However, N-acylation of sulfoximines has been generally accomplished by employing conventional amide bond formation strategies involving the use of prior activated acyl donors [6] or coupling



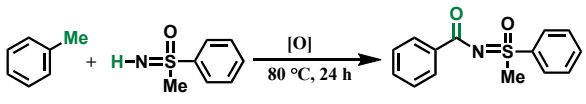
Scheme 1. Oxidative Acylation of Sulfoximine

reagents.[6a,7] Recently, Bolm and co-workers developed a method for direct oxidative acylation of sulfoximines by using an aldehyde as the acyl donor (Scheme 1a). Employing this strategy precluded the need for activation of carboxylic acids or the use of coupling reagents.[8] Later report from the same group described a remarkable improvement of this concept by employing methylarene as the acyl donor (Scheme 1b).[9] Compared with aldehydes, the readily available methylarenes are cheap, stable and easy to handle. However, it is noticed that N-chlorosulfoximines were needed as the activated sulfoximine surrogate. Although N-chlorosulfoximines can be easily prepared from N-chlorosuccinimide and sulfoximines, an addition

reaction step is required and stoichiometric chlorinated waste is produced during the oxidative acylation. Regarding sustainability as well as atom and step-economic issues, sulfoximines appear to be the ideal nitrogen source for the desired transformation. However, the direct oxidative acylation between methylarenes and sulfoximines remains unprecedented. Herein, we report an efficient direct oxidative acylation of sulfoximines by employing methylarenes as the acyl donor under mild reaction conditions.

In the past decade, significant advances have been made in the field of oxidative cross coupling of C-H and X-H bonds to construct C-X bond because it is an atom and step-economic, environmentally friendly and sustainable synthetic strategy in which pre-functionalization is unnecessary.[10] Recent studies demonstrate that methylarenes are well applied as acyl donors with direct oxidation of three SP^3 C-H bonds.[11] Such efforts are very attractive from the standpoint of green chemistry and sustainable development. On the other hand, the combination of *ter*-butyl hydroperoxide (TBHP) and an iodide catalyst such as tetrabutylammonium iodide (TBAI) or KI proven to be an efficient oxidation system for the oxidation of methylarenes.[12] These oxidation systems have also been used successfully for the oxidative amidation.[11a,11c,13] However, while not free amines, more reactive amine surrogates were employed as nitrogen source.[13d,13e] Very recently, our group developed a powerful TBHP/TBAI/$FeCl_3$ oxidation system for general use.[14] A significant synergistic effect was observed between $FeCl_3$ and the TBHP/TBAI oxidant system and this effect proved to be crucial for oxidative amidations. This novel oxidation system facilitates smooth oxidative acylation of free amines under mild reaction conditions.

Table 1. Optimization of reaction conditions[a]

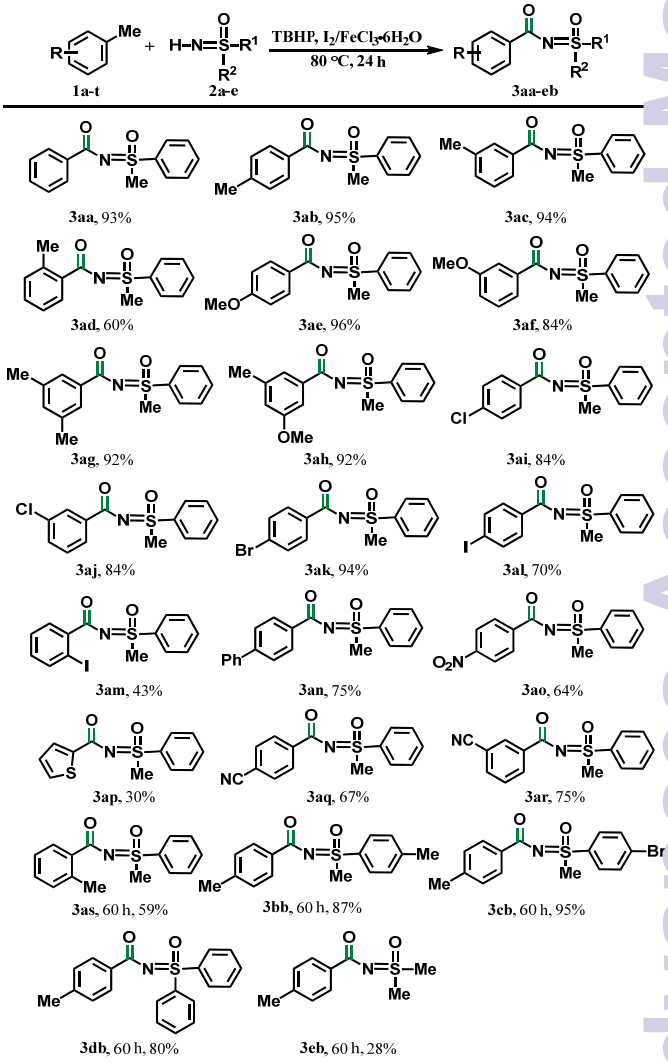


1a 2a 3aa

entry	oxidant (10 equiv)	catalyst (20 mol%)	additive (15 mol%)	yield (%)[b]
1	TBHP	TBAI	$FeCl_3·6H_2O$	25
2	DTBP	TBAI	$FeCl_3·6H_2O$	-
3	H_2O_2	TBAI	$FeCl_3·6H_2O$	-
4	O_2	TBAI	$FeCl_3·6H_2O$	-
5	TBHP	TBAI	$FeBr_2$	37
6	TBHP	TBAI	$CuCl_2$	19
7	TBHP	TBAI	CuI	8
8	TBHP	TBAI	AgI	7
9	TBHP	TBAB	$FeCl_3·6H_2O$	69
10	TBHP	KI	$FeCl_3·6H_2O$	77
11	TBHP	I_2	$FeCl_3·6H_2O$	95
12[c]	**TBHP**	**I_2**	**$FeCl_3·6H_2O$**	**95**
13[d]	TBHP	I_2	$FeCl_3·6H_2O$	84
14	TBHP	-	$FeCl_3·6H_2O$	16
15	TBHP	I_2	-	48

[a]Reaction conditions: methylarene **1** (5 mmol), sulfoximine **2** (0.25 mmol), 80 ℃, 24 h. [b]Isolated yield. [c]2.0 mmol TBHP (8 equiv. 70% in water) was used. [d]1.5 mmol TBHP (6 equiv. 70% in water) was used.

The low reactivity of sulfoximines is the main challenge for direct oxidative acylation of sulfoximines. Encouraged by previous successes in oxidative amidation, we attempted to apply our powerful TBHP/TBAI/ $FeCl_3$ oxidation system to the challenging oxidativ acylation of sulfoximines. We initiated our studies by examining the TBHP/TBAI/ $FeCl_3$ system employed in our previous work.[14] To our disappointment, the target N-acylsulfoximines was obtained in only 25% yield (Table 1, entry 1). Extensive optimization of reaction conditions was performed, for which the selected examples are listed in Table 1. No target product was observed when other oxidants such as di-*t*-butyl peroxide (DTBP), H_2O_2 and O_2 were employed in this reaction (Table 1, entries 2-4). Other additives proved to be less effective than $FeCl_3·6H_2O$ (Table 1, entries 5-8). The effect of other co-catalysts was then evaluated, and significantly improved reaction efficiency was observed when tetrabutylammonium bromide (TBAB) was used as the co-catalyst (Table 1, entry 9). This result indicated that the nature of chosen

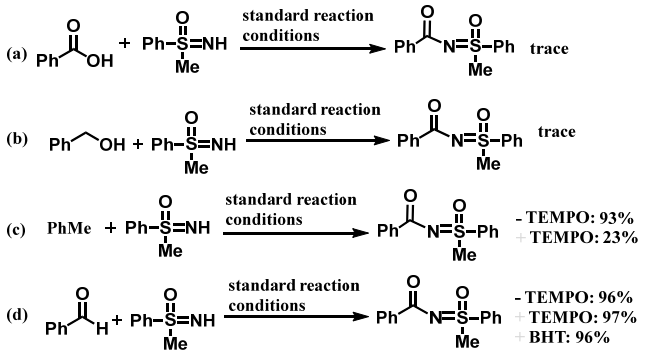


Scheme 2. Oxidative Acylation of Sulfoximines[a]. [a]Reactions were carried out on a 0.25 mmol scale of sulfoximines with 8 equiv. of methylarene, unless noted otherwise.

catalyst has a remarkable influence on this reaction. Further screening of other iodide reagents illustrated that I_2 was the best choice of

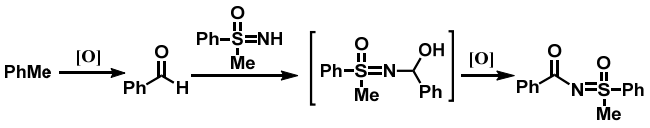
catalyst. Yield up to 95% was achieved in the presence of 10 equiv. of TBHP (Table 1, entry 11). It is found that the amount of TBHP could be decreased to 8 equiv. without affecting the reaction efficiency (Table 1, entry 12). Considering that three C-H and one N-H bonds were oxidized simultaneously, on average, 2 equiv. of TBHP was consumed by each X-H oxidation. The results from control experiments illustrated that both I_2 and $FeCl_3 \cdot 6H_2O$ are crucial for this transformation (Table 1, entries 14 & 15). Notably, the reaction was carried out in neat methylarene, thus no additional organic solvent was requested.

Next, the substrate scope of this transformation was evaluated under the optimized reaction conditions. As shown in Scheme 2, a broad range of substituted methylarenes proved to be good substrates for this direct oxidative acylation of sulfoximines. Unlike MnO_2 mediated N-acylation of sulfoximines,[9] which is limited to electron-deficient substrates, the electronic property of the substituents on the phenyl ring of methylarenes appear to have little effect in our case. Interestingly, the methyl arenes containing electron-donating groups appeared to be better substrates than their congeners containing electron-withdrawing groups. For example, good to excellent yields were obtained using methyl or methoxy substituted toluene as substrates (**3ad-3ah**). Good yields were obtained with electron-withdrawing groups such as Cl, Br, I, NO_2- or CN- presents on the substrates (**3ai-3as**). Even the steric demanding substrates with a substituent such as methyl, cyano and iodo groups at *ortho* position were compatible, albeit with slightly decreased yields (**3ad, 3am** and **3as**). Furthermore, some other sulfoximines had also been prepared and examined in this transformation. No significant electronic effect of the substituents on the phenyl ring of sulfoximine moiety was observed. Both methyl and bromide substituted sulfoximines proceeded smoothly to produce the acylated products in excellent yields (**3bb** and **3cb**). However, aryl substituent on the sulfur atom appeared to be crucial, as indicated by the remarkable decrease in yield when dimethyl substituted sulfoximine was employed as nitrogen donor (**3eb**).



Scheme 3. Control Experiments

To gain some insight on the reaction mechanism, a series of control experiments were conducted (Scheme 3). No target product was obtained when benzoic acid was used as acid donor (Scheme 3a). Unlike our previous work,[14] in which benzyl alcohol could be used as acyl donor, only trace amounts of the target product were detected when benzyl alcohol was treated under the standard reaction conditions (Scheme 3b). Due to the large excess of benzyl alcohol and low reactivity of sulfoximine, the major products of the reaction were benzaldehyde and benzyl benzoate. It was noted that benzaldehyde provided the target acylated product in quantitative yield (Scheme 3d) suggesting that benzaldehyde might be the intermediate for this transformation. Although the reaction of toluene was significantly suppressed by 2 equiv. of TEMPO (Scheme 3c), the reaction efficiency of benzaldehyde remained intact in the presence of either 2 equiv. of TEMPO or BHT (Scheme 3d, for details of control experiments, see supporting information). This result indicates that the oxidation of toluene to benzaldehyde might involve a $FeCl_3$ catalyzed single electron transfer process. A possible mechanism is



Scheme 4. Proposed Mechanism

proposed in scheme 4. Toluene can be oxidized to benzyladehyde under the optimized reaction conditions. The N, O-semiaminal, formed *in situ* from benzaldehyde and sulfoximine, was further oxidized to release the corresponding acylated product. However, the radical process proposed for the oxidative acylation of sulfoximine with aldehyde as the acyl donor cannot be excluded at this stage.

Conclusions

In summary, we have developed an efficient direct oxidative amidation between methylarenes and sulfoximines. The reaction was carried out in neat methylarene with a broad substrate scope. Both electron-donating and -withdrawing groups on methylarenes are tolerated and even steric demanding *ortho* substituents are compatible. This protocol offers a straightforward approach to the N-aroylated sulfoximines from easily available raw chemicals. Both methylarenes and sulfoximines are used in their native form thus avoiding activation or prior functionalization. Undoubtedly, such an efficient strategy will shed light on the further application of TBHP/I_2 oxidant system.

Notes and references

[a] National Research Center for Carbohydrate Synthesis and Key Laboratory of Chemical Biology, Jiangxi Province, Nanchang 330022, Jiangxi, P. R. China
[b] College of Chemistry and Chemical Engineering, Jiangxi Normal University, Nanchang, 330022, Jiangxi, P. R. China
E-mail: wangtao@jxnu.edu.cn; zhaojf@jxnu.edu.cn

This work is supported by the National Natural Science Foundation of China (21462023, 21262018) and the Natural Science Foundation of Jiangxi Province (20143ACB20007, 20133ACB20008).

† Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/c000000x/

1 (a) C. R. Johnson, *Aldrichim. Acta* 1985, **18**, 3; (b) M. Reggelin and C. Zur, *Synthesis*, 2000, 1.
2 (a) H. Okamura and C. Bolm, *Chem. Lett.* 2004, **33**, 482; (b) H.-J. Gais, *Heteroat. Chem.* 2007, **18**, 472; (c) V. Bizet, R. Kowalczyk and C. Bolm, *Chem. Soc. Rev.* 2014, **43**, 2426; (d) M. Frings, I. Thome, I. Schiffers, F Pan and C. Bolm, *Chem. Eur. J.* 2014, **20**, 1691; (e) M. Langner, C. Bolm, *Angew. Chem. Int. Ed.* 2004, **43**, 5984; (f) C. R. Johnson, *Acc. Chem. Res.* 1973, **6**, 341; (g) M. Frings, I. Thome and C. Bolm, *Beilstein J. Org. Chem.* 2012, **8**, 1443; (h) Benetskiy, E. B. and Bolm, C. *Tetrahedron-Asymmetry* 2011, **22**, 373.
3 U. Lücking, *Angew. Chem. Int. Ed.* 2013, **52**, 9399.
4 (a) M. R. Yadav, R. K. Rit and A. K. Sahoo, *Chem. Eur. J.* 2012, **18**, 5541; (b) R. K. Rit, M. R. Yadav and A. K. Sahoo, *Org. Lett.* 2012, **14**, 3724; (c) K. Parthasarathy and C. Bolm, *Chem. Eur. J.* 2014, **20**, 4896; (d) W. Dong, L. Wang, K. Parthasarathy, F. Pan, and C. Bolm, *Angew. Chem. Int. Ed.* 2013, **52**, 11573.
5 (a) L. Wang, H. Huang, D. L. Priebbenow, F.-F. Pan and C. Bolm, *Angew. Chem. Int. Ed.* 2013, **52**, 3478; (b) V. Bizet, L. Buglioni and C. Bolm, *Angew. Chem. Int. Ed.* 2014, **53**, 5639; (c) J. Sauer and K. K. Mayer, *Tetrahedron Lett.* 1968, **9**, 319; (d) F. Teng, J.-T. Yu, Y. Jiang, H. Yang and J. Cheng,

Chem. Commun. 2014, **50**, 8412; (e) L. Wang, D. L. Priebbenow, W. Dong and C. Bolm, *Org. Lett.* 2014, **16**, 2661; (f) J. Kim, J. Ok, S. Kim, W. Choi and P. H. Lee, *Org. Lett.* 2014, **16**, 4602; (g) Y. Cheng, W. Dong, L. Wang, K. Parthasarathy and C. Bolm, *Org. Lett.* 2014, **16**, 2000; (h) X. Y. Chen, L. Wang, M. Frings and C. Bolm, *Org. Lett.* 2014, **16**, 3796; (i) D. L. Priebbenow, P. Becker and C. Bolm, *Org. Lett.* 2013, **15**, 6155; (j) R. Pirwerdjan, D. L. Priebbenow, P. Becker, P. Lamers and C. Bolm, *Org. Lett.* 2013, **15**, 5397.

6 (a) C. P. R. Hackenberger, G. Raabe and C. Bolm, *Chem. Eur. J.* 2004, **10**, 2942; (b) T. Siu and A. K. Yudin, *Org. Lett.* 2002, **4**, 1839.

7 A. Garimallaprabhakaran and M. Harmata, *Synlett* 2011, 361.

8 (a) L. Wang, D. L. Priebbenow, L.-H. Zou and C. Bolm, *Adv. Synth. Catal.* 2013, **355**, 1490; (b) W.-J. Qin, Y. Li, X. Yu and W.-P. Deng, *Tetrahedron* 2015, **71**, 1182.

9 D. L. Priebbenow and C. Bolm, *Org. Lett.* 2014, **16**, 1650.

10 (a) D. Liu and A. Lei, *Chem. Asian J.* 2015, **10**, 806; (b) J. Wencel-Delord, T. Droge, F. Liu and F. Glorius, *Chem. Soc. Rev.* 2011, **40**, 4740; (c) Z. M. Zhang, O. Y. Lu, W. Q. Wu, J. X. Li, Z. C. Zhang and H. F. Jiang, *J. Org. Chem.* 2014, **79**, 10734.

11 (a) G. Majji, S. Guin, A. Gogoi, S. K. Rout and B. K. Patel, *Chem. Commun.* 2013, **49**, 3031; (b) S. Guin, S. K. Rout, A. Banerjee, S. Nandi and B. K. Patel, *Org. Lett.* 2012, **14**, 5294; (c) R. Vanjari, T. Guntreddi and K. N. Singh, *Org. Lett.* 2013, **15**, 4908; (d) S. K. Rout, S. Guin, W. Ali, A. Gogoi and B. K. Patel, *Org. Lett.* 2014, **16**, 3086.

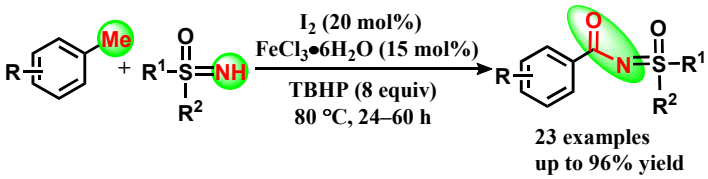
12 X.-F. Wu, J.-L. Gong and X. Qi, *Org. Biomol. Chem.* 2014, **12**, 5807.

13 (a) Y. Wang, K. Yamaguchi and N. Mizuno, *Angew. Chem. Int. Ed.* 2012, **51**, 7250; (b) L. Liu, L. Yun, Z. Wang, X. Fu and C.-H. Yan, *Tetrahedron Lett.* 2013, **54**, 5383; (c) D. L. Priebbenow, and C. Bolm, *Org. Lett.* 2014, **16**, 1650; (d) J.-B. Feng, D. Wei, J.-L. Gong, X. Qi and X.-F. Wu, *Tetrahedron Lett.* 2014, **55**, 5082; (e) K. Azizi, M. Karimi and A. Heydari, *RSC Advances* 2014, **4**, 31817.

14 (a) T. Wang, L. Yuan, Z. Zhao, A. Shao, M. Gao, Y. Huang, F. Xiong, H. Zhang and J. Zhao, *Green Chem.* 2015, **17**, 2741; (b) Z. Zhao, T. Wang, L. Yuan, X. Hu, F. Xiong and J. Zhao, *Adv. Synth. Catal.* 2015, DOI: 10.1002/adsc.201500310.

Oxidative Acylation of Sulfoximines with Methylarenes as Acyl Donor

Zhenguang Zhao,[b] Tao Wang,*[a,b] Lin Yuan,[b] Xingwang Jia[b] and Junfeng Zhao*[a,b]



An efficient direct oxidative acylation of sulfoximines with methylarenes as acyl donor was finally achieved.