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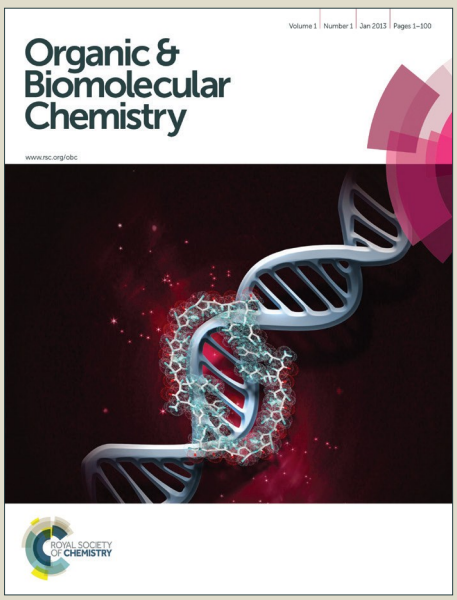

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ARTICLE TYPE

Manganese Catalysed Sulfenylation of *N*-methyl Amides with Arenesulfony Hydrazides

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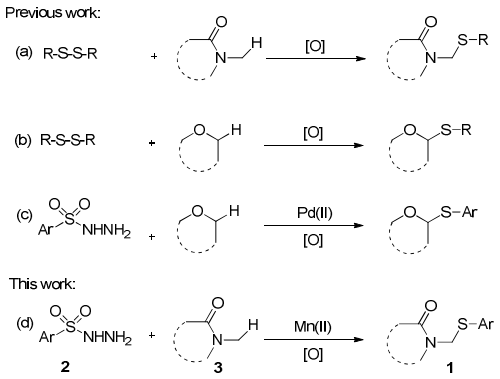
A convenient oxidative sulfenylation method for the formation of various sulfenyl amides has been reported. Arenesulfony hydrazine as sulfur source in the presence of manganese salt can activate sp^3 C-H bond of *N*-methyl amides through free–radical pathway using di-tert-butyl peroxide (DTBP).

Introduction

Direct C-S bond formation has been extensively studied for the synthesis of many organosulfur containing natural products and synthetic drugs.[1] Significant progress has been achieved for direct sp^2-hybridised C-H bond sulfenylation of arenes, indoles and pyrazolones for the construction of the corresponding sulfides.[2] The challenge for the activation of sp^3 C–H bond has also been addressed by free radical initiated C-S bond formation on the heteroatom-adjacent carbons.[3] Li and Xiang have independently reported direct oxidative sulfenylation of amides[3a] and ethers[3b] with disulfides under metal-free conditions (Scheme 1a and 1b).

Sulfonyl hydrazides have commonly been used as reductants and sulfonylation agents but also recently found valuable in the sulfenylation process.[4] This new strategy could not only avoid smelling volatile sulfur sources such as thiols[5], thiolates[6] and disulfides[7], but also expend the limited substrate scope of agents like thiourea[8], thiocyanate[9] and metal sulfides[10]. Various sulfonyl hydrazide reagents have been developed in the sulfenylation of indoles[11], aryl halides[12], activated alkenes[13] and aryl acetylenes[14]. Yuan recently reported a palladium catalysed oxidative sulfenylation of ethers using arenesulfony hydrazide.[15] Presumably, aryl sulfide radicals generated *in situ* from the decomposition of sulfonyl hydrazides that promoted by palladium catalyst, although the exact mechanism was not revealed (Scheme 1c).

N,S-acetals are biologically important molecules present in numerous natural products such as fusaperazine[16] and *β*-lactam antibiotics[17]. Inspired by Li[3a], Xiang[3b] and Yuan's[15] work, we herein report a radical sulfenylation process of *N*-methyl amides with arenesulfony hydrazides catalysed by inexpensive and non-toxic manganese (II) salt, which shows higher efficiency than the classic palladium catalysts. Various *N,S*-acetals tolerating different amides and sulfenylarenes were readily obtained (Scheme 1d).



Scheme 1 Approaches on the sp^3 C-H bond sulfenylation of heteroatom adjacent carbons

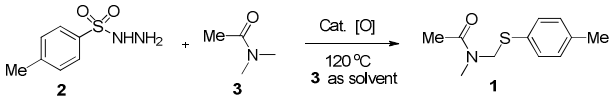
Results and discussion

We started our attempt with *N,N*-dimethylacetamide (DMA) and *p*-toluenesulfonyl hydrazide in the presence of different oxidants and catalysts (Table 1). Using DTBP without any catalyst, no reaction was observed (entry 1). As previously reported,[15] Pd (II) was able to promote the sulfenylation reaction but in a disappointing 45% yield (entry 2) according to literature precedents.[15] Other metal catalysts such as $FeCl_3$, CuI and $Cu(OTf)_2$ failed to provide satisfactory results (entry 3-5). To our delight, $Mn(OAc)_2$ was able to promote the reaction in the presence of DTBP (entry 6, 86% yield). We attributed the efficiency of manganese to the employment of amides as the solvent, compared with palladium that usually in cycloalkanes or ethers.

Other oxidants including CAN, $PhI(OAc)_2$ and benzoquinone did not afford the desired product (entry 7-9), while $K_2S_2O_8$, TBHP

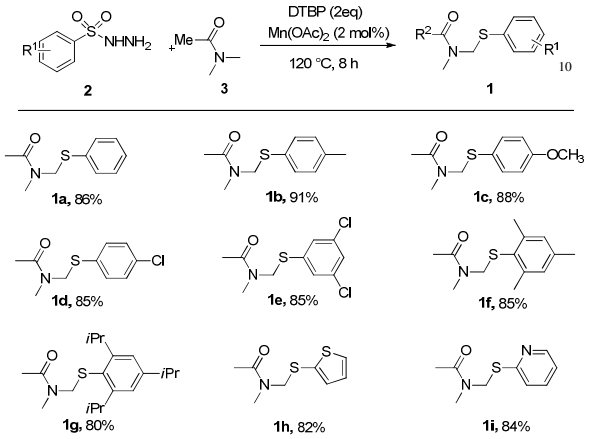
or dicumyl peroxide (DCP) showed very low conversion (entry 10-12). After evaluating the loading of the catalyst and oxidant (entry 13-17), the conditions were set as 2 equivalents of DTBP with 2 mol% of $Mn(OAc)_2$ (entry 6).

Table 1. Optimisation of Reaction Conditions [a].



Entry	Oxidant (eq)	Catalyst (mol%)	Isolated yield (%) [b]
1	DTBP(2.0)	N.A.	N.D.
2	DTBP(2.0)	$PdCl_2$(2.0)	45
3	DTBP(2.0)	$FeCl_3.6H_2O$ (2.0)	23
4	DTBP(2.0)	CuI (2.0)	N.D.
5	DTBP(2.0)	$Cu(OTf)_2$ (2.0)	N.D.
6	DTBP(2.0)	$Mn(OAc)_2$ (2.0)	86
7	CAN(2.0)	$Mn(OAc)_2$ (2.0)	N.D.
8	$PhI(OAc)_2$(2.0)	$Mn(OAc)_2$ (2.0)	N.D.
9	BQ(2.0)	$Mn(OAc)_2$ (2.0)	N.D.
10	$K_2S_2O_8$(2.0)	$Mn(OAc)_2$ (2.0)	15.
11	TBHP (2.0) [c]	$Mn(OAc)_2$ (2.0)	18.
12	DCP(2.0)	$Mn(OAc)_2$ (2.0)	58
13	DTBP(0.5)	$Mn(OAc)_2$ (2.0)	56
14	DTBP(1.0)	$Mn(OAc)_2$ (2.0)	72
15	DTBP(3.0)	$Mn(OAc)_2$ (2.0)	83
16 [d]	DTBP(2.0))	$Mn(OAc)_2$ (1.0)	70
17	DTBP(2.0)	$Mn(OAc)_2$ (0.5)	56

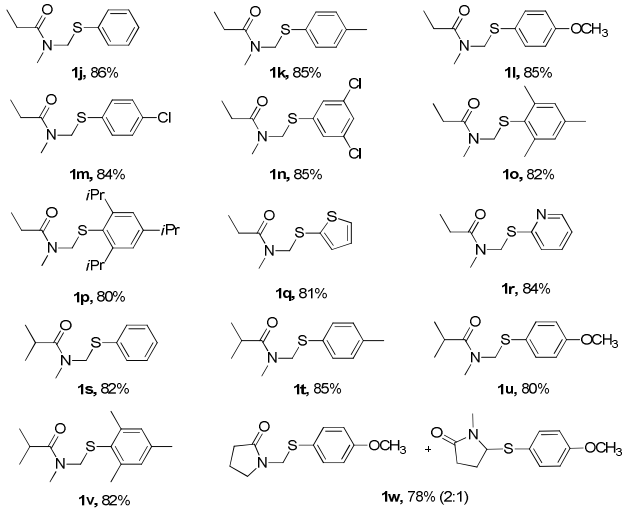
[a] Catalytic conditions: arenesulfony hydrazide **2** (0.5 mmol), DMA **3** (2 mL, 20 mmol, also served as solvent), oxidant, catalyst, 8 h. [b] isolated yield based on **2.** [c] 70% in water solution. [d] Reaction time 24 h.



Scheme 2 Reactions of *N,N*-dimethylacetamide with various arenesulfonyhydrazides

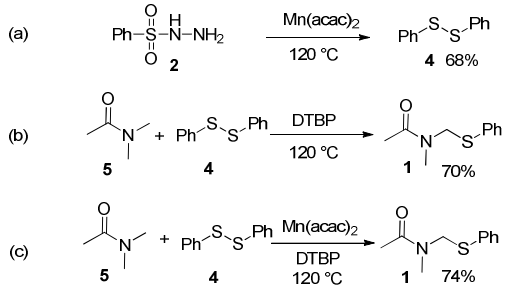
Under the optimised conditions, the scope of this arenesulfenylation reaction was explored. As shown in Scheme 2, arenesulfony hydrazides bearing both electron-withdrawing and electron-donating substitutions could react with *N,N*-dimethylacetamide to form sulfenyl amides in 80-91% yields (**1b**-**1g**). To our delight, heteroarene sulfonyl hydrazides such as thiophene and pyridine derivatives displayed high reactivity towards the target sulfenyl amide products in over 80% yield (**1h**, **1i**).[18]

It was found that propionamides and isobutyramides could also be employed for such transformation to obtain highly substituted sulfenyl amide products with good yields (scheme 3). Interestingly, when the two substituents on the nitrogen atom were different, the reaction tended to happen on the less substituted side. Using *N*-methyl pyrrolidone, the corresponding sulfenyl amides were obtained with 78% overall yield with two regioisomers in 2:1 ratio in favour of the primary carbon (Scheme 2, **1w**)



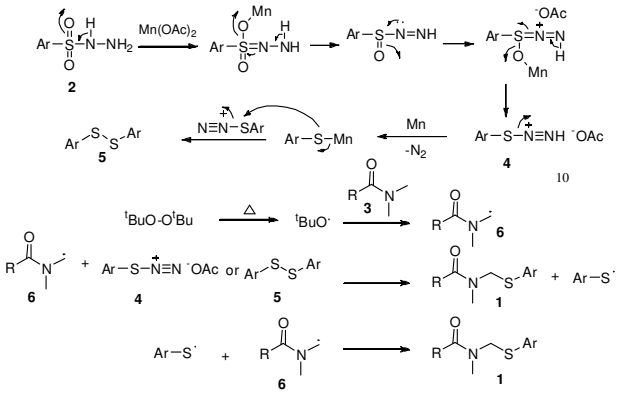
Scheme 3 Reactions of other amides with arenesulfony hydrazides

To understand the mechanism for such arenesulfenylation, a control reaction with phenylsulfonyl hydrazide and $Mn(acac)_2$ was carried out. Expectedly, disulfide was obtained in 68% yield (Scheme 4a), suggesting that the decomposition of sulfonyl hydrazide could be catalysed by Mn (II), in a similar way as the palladium catalysts. It was also proven by that phenyl disulfide could react with *N,N*-dimethylacetamide to form the same sulfenyl amides product **1** in similar yields with or without Mn (II) catalyst (Scheme 4c and 4b, 74% and 70% respectively), which indicated that disulfides could be the key intermediates for the sulfenylation pathway, while manganese might not participate in the subsequent radical process.



Scheme 4. Control experiments

Based on the control reactions above and the evidence shown in the previous reports by Tian[11], Singh[14] and Yuan[15], we proposed a plausible mechanism for this sulfenylation reaction. Promoted by $Mn(OAc)_2$, arenesulfony hydrazide **2** is first reduced to thiodiazonium **4** and eliminated to aryl disulfide **5**. Then tert-butoxyl radical generated by DTBP abstracts hydrogen from *N*-methyl group to form alkyl radical **6**, which reacts with disulfide **4** to give the product **1** and ArS radical (Scheme 5).



Scheme 5. Possible mechanism for Mn(II) catalysed sulfenylation of *N*-methyl amides with arenesulfony hydrazides.

Conclusions

In summary, we have developed a convenient direct sulfenylation reaction of sp^3-hybridised C-H bonds of *N*-methyl amides with sulfonyl hydrazide and peroxide in the presence of Mn (II) catalyst. This study has investigated the role of metal catalyst in the sulphonyl hydrazide decomposition process and has broadened the scope of sulphonyl hydrazides as electrophilic sulfenylation reagents in the free-radical-initiated C-H bond activation pathway. Further investigation of this reaction is undergoing.

Acknowledgements

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18. The rotamer ratios were determined based on the integrations of methylene peaks on each NMR spectrum. See Supporting Information.