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Article

Metal-free aerobic oxidative coupling of amines in dimethyl sulfoxide *via* a radical pathway†

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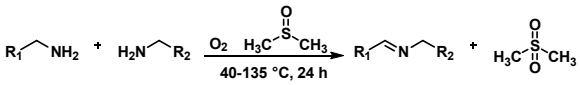
Mu Lin‡, Zikuan Wang‡, Huayi Fang, Lianghui Liu, Haolin Yin, Chun-Hua Yan*, and Xuefeng Fu*

Metal-free oxidative coupling of amines is achieved simply by heating their dimethyl sulfoxide (DMSO) solution under oxygen as oxidant without any other catalysts or additives, accompanied by the formation of an equimolar amount of dimethyl sulfone ($DMSO_2$). EPR experiments indicate that the reaction proceeds via a radical pathway. DMSO may play a triple role as solvent, radical initiator and co-reductant.

Introduction

Amines are among the most widely used synthetic precursors in a variety of organic transformations and industry for important and ubiquitous building blocks. Among them, imines and azo compounds are popular synthetic intermediates for pharmaceuticals, valuable chemicals, molecular motors and biomolecules.[1] As an alternative strategy for the synthesis of both imines and azo compounds, oxidative coupling of amines has attracted increasing attention in recent years.[2] However, most reported catalytic systems on imines were based on metal catalysts, including Fe,[3] Au,[4] Cu,[5] Ru,[6] V,[7] Pt/Ir,[8] and TiO_2.[9] The introduction of metals incurs cost problems and metal residual contamination issues, which is particularly important for the pharmaceutical industry. Thus, great endeavors are highly required from the synthetic community to develop metal-free oxidative coupling reactions of amines.

DMSO is not only an important polar aprotic solvent but also a good reactant for many novel transformations, like Kornblum[10] and Swern oxidation,[11] in which DMSO functions as an oxidant for the oxidation of alcohols. Recently, metal-free oxidative radical cyclization[12] and skeletal rearrangment[13] reactions were reported to proceed smoothly in DMSO under aerobic conditions. Herein by taking advantage of the redox-active feature of DMSO, the aerobic oxidative coupling of amines under metal-free conditions was achieved (Scheme 1). In this case, DMSO acted not only as a solvent, but also a radical initiator and a reducing agent.



Scheme 1. Aerobic oxidative coupling of amines in DMSO.

Beijing National Laboratory for Molecular Sciences, State Key Laboratory of Rare Earth Materials Chemistry and Applications, College of Chemistry and Molecular Engineering, Peking University, Beijing 100871, China. Fax: +86-10-62756787; Tel: +86-10-62756787; Email: fuxf@pku.edu.cn, yan@pku.edu.cn

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‡These authors contributed equally.

Results and discussion

Formation of imine was observed when heating a 0.6 M DMSO solution of benzylamine under an atmosphere of oxygen. A sufficient concentration of oxygen was found to be necessary for the reaction (Table 1, entry 1-2), with the reaction rate retarded under air and no reaction was observed under N_2 (Table 1, entry 3-4). Hydrogen peroxide also functioned as an effective oxidant, but the conversion and the yield were lower and most of the hydrogen peroxide was consumed in oxidizing the solvent DMSO to dimethyl sulfone ($DMSO_2$, Table 1, entry 5). A very interesting phenomenon was that almost an equal amount of $DMSO_2$ was also formed in all aerobic conditions as that of the imine product (Table 1, entry 1-2), in contrast to that no $DMSO_2$ formed in the absence of amine (Table 1, entry 6). Consequently, hydrogen peroxide is probably generated during the oxidation of amine to imine, which subsequently oxidized DMSO to $DMSO_2$. The use of other sulfoxide solvents like DMSO-d_6 and tetrahydrothiophene 1-oxide (THTO) gave similar yields (Table 1, entry 8-9) and the byproducts $DMSO_2$-d_6 and sulfolane from oxidation of the solvents were also observed by GC and GC-MS. Sliwka and co-workers also observed weaker radical signals by adding bases to DMF.[14a] Herein we observed 24% of imine product using DMF as the solvent as well (Table 1, entry 9). When other solvents were employed, little imine product was observed under the same reaction condition (Table 1S, supporting information).

A variety of arylmethylamines were oxidized to imines in good to excellent yields (Table 2). Benzylamines having either electron rich or electron withdrawing substituents on the phenyl ring gave good yields, except for 4-chlorobenzylamine giving a moderate yield (Table 2, entry 3). Sterically hindered imine **P7** was obtained in a good yield (Table 2, entry 7). It's worth noting that excess dehydrating agent and an acid catalyst are usually needed for the condensation between benzophenone and diphenylmethanamine.[15] Naphthalene- and heterocycle-substituted amines were also tolerated (Table 2, entry 8-11). The oxidation of furfurylamine was rarely reported, and the yields were relatively low;[7a, 9] however in our system, 52% yield of **P10** could be achieved (Table 2, entry 10).

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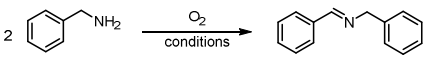
Because of its stronger alkalinity and higher reactivity,[16] oxidation of pyridine-2-ylmethylamine was accomplished at a very low temperature 40 °C with a moderate yield (Table 2, entry 11).

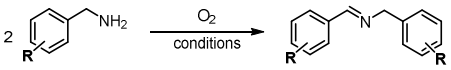
Table 1. Optimization of the reaction conditions.[a]

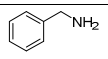
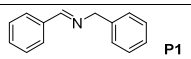
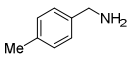
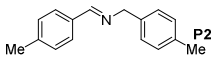
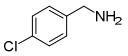
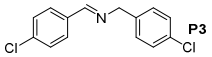
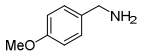
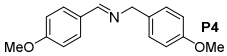
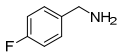
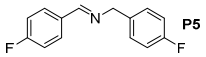
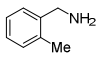
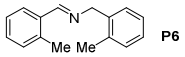
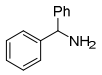
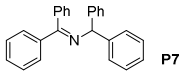
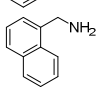
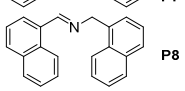
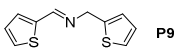
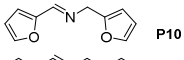
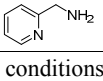
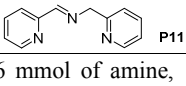


Entry	Solvent	T (°C)	Gas	C (%)[b]	Y (%)[b]	R[c]
1	DMSO	105	O_2	100	84	0.9
2	DMSO	110	O_2	100	78	1.0
3	DMSO	105	Air	76	63	0.5
4	DMSO	105	N_2	1	1	N[d]
5[e]	DMSO	105	N_2	80	62	5.8
6[f]	DMSO	105	O_2	-	-	N[d]
7	DMSO-D6	100	O_2	88	82	-
8	THTO	100	O_2	94	78	-
9	DMF	100	O_2	66	24[g]	-

[a] Reaction conditions: 0.6 mmol of benzylamine in the solvent of 1 mL. Gas pressure: 1 atm. Reaction time: 24 h. [b] C = conversion of substrate , Y = yield of GC results. [c] R (ratio) = n (sulfone) / n (imine). [d] No $DMSO_2$ was observed. [e] 1.8 mmol of H_2O_2 was added. [f] No benzylamine was added. [g] 42% of $PhCH_2NHCHO$ was detected.

Table 2. The scope of the substrates.[a]



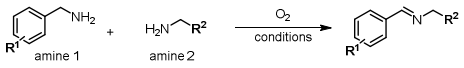
Entry	Substrate	Product	T (°C)	C (%)[b]	Y (%)[b]
1		 P1	105	100	84 (51)
2		 P2	105	93	85 (60)
3		 P3	80	100	66 (58)
4		 P4	110	93	80 (76)
5		 P5	110	95	91 (85)
6		 P6	105	98	88 (71)
7		 P7	105	92	81 (71)
8		 P8	100	100	84 (69)
9		 P9	85	92	81 (73)
10		 P10	80	100	52 (43)
11		 P11	40	91	53 (47)

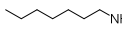
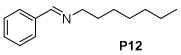
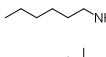
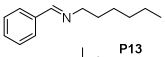
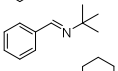
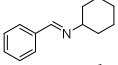
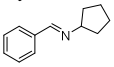
[a] Reaction conditions: 0.6 mmol of amine, 1 mL of DMSO, 1 atm oxygen, 24 h. [b] C = conversion of substrate , Y = yield of GC results. Isolated yields after column chromatography are given in parentheses.

Although the homo-coupling of aliphatic amines failed due to their low reactivity, the oxidative cross-coupling between benzylamine and aliphatic amines was successful (Table 3). Heating a DMSO solution containing benzylamine and linear aliphatic amines at 120 °C for 24 hours, 54%-61% yields of cross-coupling products were formed (Table 3, entry 1-2). At a higher temperature (135 °C), 72% yield of *N*-benzylidene-*tert*-butylamine was accomplished (Table 3, entry 3). The reaction between benzylamine and cyclic aliphatic amines was also feasible with satisfying yields (Table 3, entry 4-5).

To gain insight into the mechanism, we added one equivalent of 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO) to the reaction mixture, which resulted in complete inhibition of the oxidation reaction. A weak radical signal was observed *in situ* by EPR after heating a mixture of benzyl amine and DMSO under 1 atmosphere of oxygen at 110 °C (Figure 1S, supporting information).

Table 3. Oxidative cross-coupling reactions of benzylamines and aliphatic amines.[a]



Entry	Amine 1	Amine 2	Product	T (°C)	Y (%)[b]
1			 P12	120	61 (53)
2			 P13	120	54 (36)
3			 P14	135	72 (54)
4			 P15	100	70 (51)
5			 P16	95	68 (62)

[a] Reaction condition: 0.6 mmol of **Amine 1**, 1.8 mmol of **Amine 2**, 1 mL of DMSO, 1 atm oxygen, 24 h. [b] C = conversion of substrate , Y = yield of GC results. Isolated yields after column chromatography are given in parentheses. The conversions of benzylamine were over 95% and the yields of N-benzylidene-1-benzylamine were less than 5%.

When the spin trapping reagent *N*-*tert*-butyl-α-phenylnitrone (PBN) was present in the oxidation of 4-methoxybenzylamine, an EPR signal with a *g*-value of 2.0060 (A_N =15.1G and A_H = 3.1G) was observed, typical of a PBN radical adduct (Figure 1). Thus an oxygen- or carbon-centered radical (e.g. $HO^{\bullet}$, O_2^{-}, (4-methoxy-Ph)(H)(NH_2)C$^{\bullet}$, etc.) is most likely formed during the reaction. Further identification of the PBN-trapped radical is still on the way.

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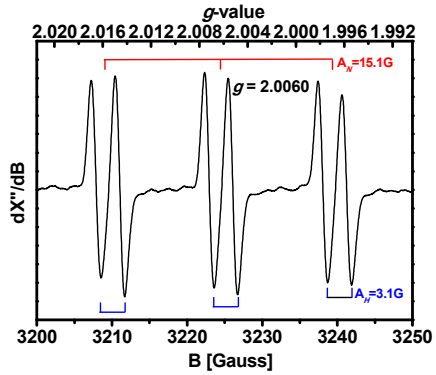
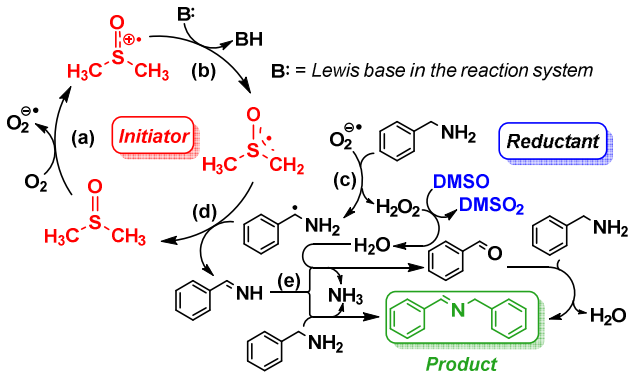


Figure 1. X-band EPR spectrum of radicals formed after heating a 0.6 M 4-methoxybenzylamine DMSO solution containing 1 mg of PBN at 110 °C under 1 atm O_2 for 1 h.

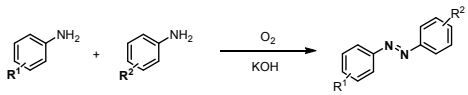
The aforementioned preliminary mechanistic studies indicate a radical chain pathway (Scheme 2) proposed to occur through (a) the reaction of DMSO with O_2 which leads to the formation of DMSO cation and the very active superoxide radical; (b) deprotonation of the newly formed DMSO cation, in which the acidity of the C−H bond is stronger than that in DMSO, by the Lewis base, which is benzylamine in this system, producing the DMSO radical; (c) generation of aminomethyl radical by the reaction of the superoxide radical $O_2^{\bullet-}$ with the amine substrates accompanied with the formation of H_2O_2 which can then oxidize the DMSO solvent; (d) the key imine intermediate forms via the reaction of the aminomethyl radical with DMSO radical; (e) conversion of the imine intermediate to the final coupling product. DMSO functions as solvent, radical initiator and reductant simultaneously throughout the whole reaction process.

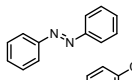
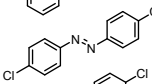
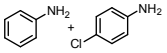
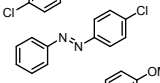
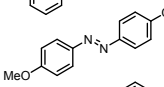
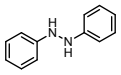
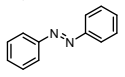
Scheme 2. Proposed radical chain mechanism.



Inspired by the mechanistic insights of amine oxidation by DMSO and oxygen, we also introduced aromatic amines into this DMSO based system. However, no reaction occurred under the standard conditions, possibly because the basicity of aromatic amines acting as Lewis base is lower than that of benzylamines and the process b of deprotonation in Scheme 2 could not happen. Thus, KOH was added to take the deprotonation and azo compounds could be achieved under similar conditions as shown in Table 4. Proposed mechanism for azo compounds is shown in Scheme S1 (see ESI), in which the function of DMSO is similar as shown in Scheme 2.

Table 4. Oxidative coupling reactions of aromatic amines.[a]



Entry	Substrates	Product	T (°C)	Y (%)[b]
1		 P17	90	81
2		 P18	90	61
3		 P19	90	73
4		 P20	90	52
5		 P17	90	96

[a] Reaction condition: 0.5 mmol of Substrate, 1.5 mmol of KOH, 1mL of DMSO, 1 atm oxygen. [b] C = conversion of substrate , Y = yield of isolated results after column chromatography.

Conclusion

In this work, a simple but efficient protocol for aerobic oxidative coupling of amines to form imines and azo compounds, just by heating the mixture of amines and DMSO under aerobic conditions, was reported. This green and low-cost system using O_2 as the sole oxidant may find a wide range of application in green oxidation chemistry. Detailed investigation on the mechanism and further extension of this system to more practical reactions are currently under investigation.

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