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Synthetic Methods

A General Method for N-Methylation of Amines and Nitro Compounds with Dimethylsulfoxide

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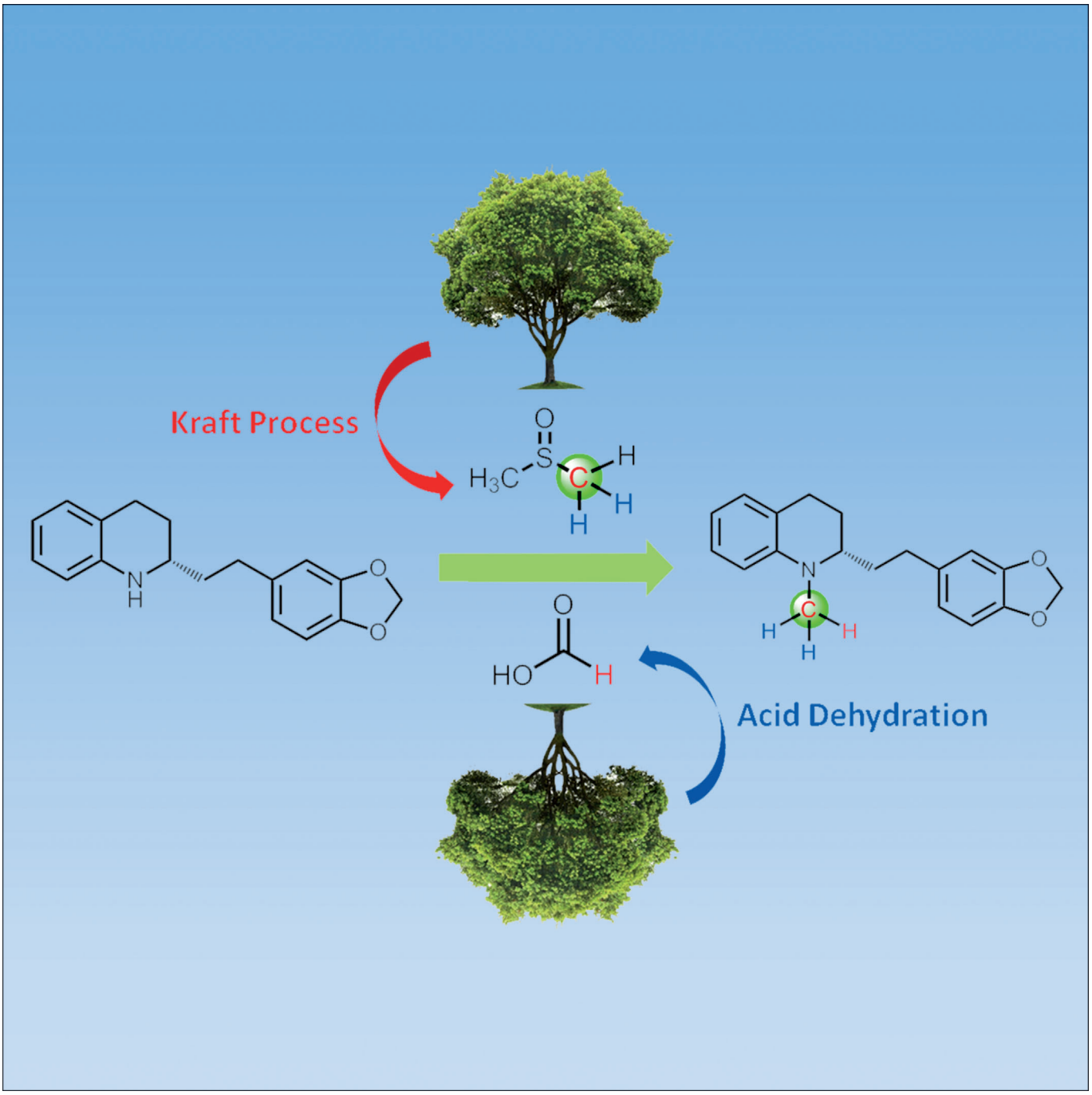
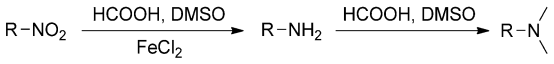


Abstract: DMSO methylates a broad range of amines in the presence of formic acid, providing a novel, green and practical method for amine methylation. The protocol also allows the one-pot transformation of aromatic nitro compounds into dimethylated amines in the presence of a simple iron catalyst.

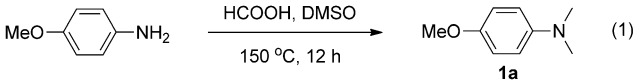
Methylation of amines is a general transformation in organic synthesis as well as in biological processes.[1] Methylated amines are found in dyes, natural products, pharmaceuticals and bulk and fine chemicals.[2] Common methods for preparation of methylated amines include nucleophilic attack of methylating reagents, for example, MeI or dimethyl sulfate, or methylation with formaldehyde in the presence of a reducing reagent, for example, formic acid,[3] metal hydrides[4] or hydrogen gas.[5] However, most of the methylating reagents are toxic or carcinogenic and have issues of over methylation or limited substrate scope. N-Methylation in industry is normally carried out by catalytic hydrogenative alkylation with formaldehyde at relative high pressure.[5c] The use of dimethyl carbonate and methanol as methylating reagents in the presence of catalysts has emerged as green alternatives for amine methylation.[6] Very recently, Cantat,[7] Beller,[8] Klankermayer[9] and their coworkers reported that CO_2 could act as a methylating reagent with Zn or Ru catalysts with hydrosilane or hydrogen gas as reducing reagents.

Dimethyl sulfoxide (DMSO) is a byproduct of the wood industry. It is a cheap, versatile solvent with low toxicity and is widely used in organic synthesis and the pharmaceutical industry. It has even been used as a medicine or presented as a component in some medicines. It is a relatively stable molecule and hence its applications as reactant in organic reactions are few.[10] Methylation of aromatic hydrocarbons with DMSO was reported early in 1966 through a carbanion intermediate.[11] Using the Fenton reagent, methyl radical was found to be generated from DMSO and exploited for the C5 carbon methylation of deoxycytosine nucleotide in biological studies.[12] Apart from these studies, we are not aware of any further examples of methylation reactions with DMSO. Herein we would like to disclose that DMSO is a versatile methylation reagent for amines under catalyst-free conditions (Scheme 1). Moreover, aromatic nitro compounds could be transformed into dimethyl amines directly in the presence of a simple iron catalyst without ligand (Scheme 1).



Scheme 1. Dimethylation of amines and direct transformation of nitro group into dimethyl amine by iron catalysis.

During our study of reductive amination reactions,[13] we found that *p*-anisidine could be methylated to afford *N*′,*N*-dimethyl-*p*-anisidine **1a** in DMSO (3 mL) in the presence of 8 equivalents of formic acid with 31% isolated yield in 12 h at 150 °C [Eq. (1)]. Examination of solvent effect revealed that the reaction only proceeded in DMSO. In all the other solvents tested (e.g., dimethylformamide, acetonitrile, toluene, isopropanol, dioxane) or in pure formic acid, *N*-(4-methoxyphenyl)-formamide was observed as the only product, which resulted from the reaction of *p*-anisidine with formic acid.[14] The yield of **1a** could be improved to 66% by addition of equimolar amount of triethylamine to formic acid. By keeping the ratio of formic acid and triethylamine to 1:1 while increasing the amount of formic acid and triethylamine, the yield increased steadily, reaching 91% with 20 equivalents of formic acid. Decreasing the volume of DMSO to 2 or 1 mL does not affect the yield of the reaction.



8 equiv. HCOOH 31% yield
8 equiv. HCOOH/Et_3N (1:1) 66% yield
20 equiv. HCOOH/Et_3N (1:1) 91% yield

Although the reaction mechanism was not clear initially, we decided to examine the generality of this new methylation protocol. The substrate scope turned out to be very broad. Table 1 summarises the results obtained from different primary amines. Aromatic amines with different substituents on their phenyl rings were firstly examined. Good to excellent yields were generally obtained (Table 1, **1a**–**q**). Electron-deficient substituents tend to slow down or alter the selectivity of the reaction. Substrate with a *p*-trifluoromethyl group afforded 63% yield of **1h** (Table 1) after a long time of 48 h. A mixture of mono- and dimethylated products was observed for *p*-cyanoaniline in 48 h with almost full conversion. Interestingly, only monomethylated product was obtained for the trichloro-substituted aniline (Table 1, **1n**). Pyridine could be tolerated under the reaction conditions (**1o**). When two amino groups were presented, both of them were methylated (Table 1, **1p** and **q**). This allows the synthesis of Wurster's blue in high yield (Table 1, **1q**), which has found biomedical application.[15]

Various secondary amines, which could be easily obtained from our previously reported reductive amination reaction,[15] were then tested as substrates. The results are presented in Table 2. Secondary amines prepared from aromatic amines and

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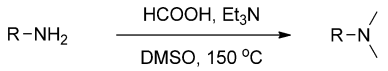
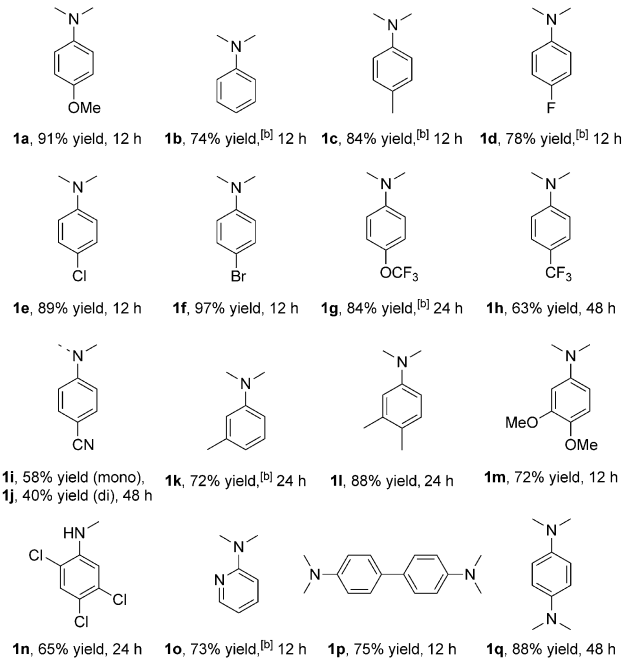
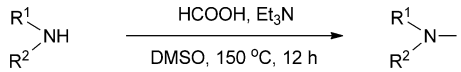
Table 1. Methylation of primary amines in DMSO.[a]

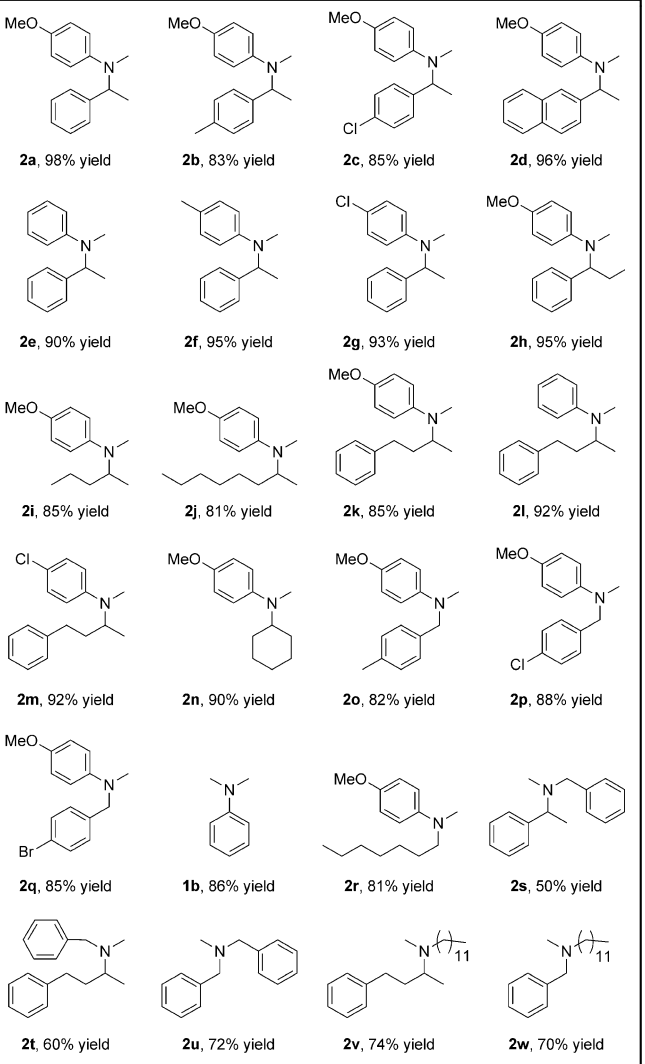




[a] Reaction conditions: 1 mmol amine, 20 mmol HCOOH, 20 mmol Et_3N, 3 mL DMSO, 150 °C, isolated yields. [b] Yields were determined by ^1H NMR with 1,3,5-trimethoxybenzene as internal standard.

Table 2. Methylation of secondary amines in DMSO.[a]



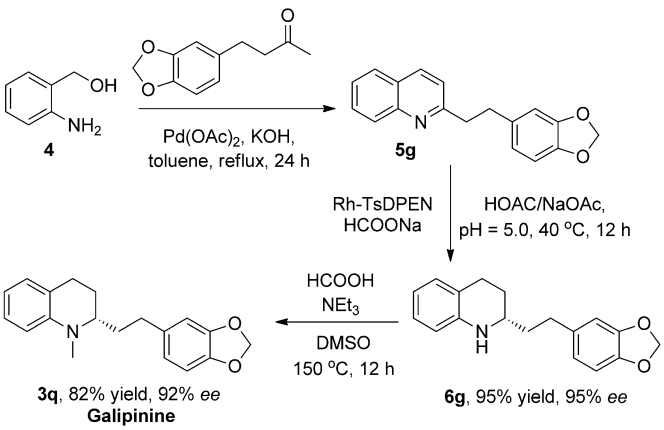


[a] Reaction conditions: 1 mmol amine, 20 mmol HCOOH, 20 mmol Et_3N, 3 mL DMSO, 150 °C,12 h, isolated yields.

aromatic ketones reacted well with yields ranging from 83–98% in 12 h (Table 2, **2a**–**h**). Good yields were obtained for amines synthesised from aliphatic ketones and aromatic amines (Table 2, **2i**–**n**) as well as substrates derived from aldehydes and aromatic amines (Table 2, **1b** and **2o**–**r**). However, only moderate yields were obtained for secondary amines bearing two alkyl groups (Table 2, **2s**–**w**).

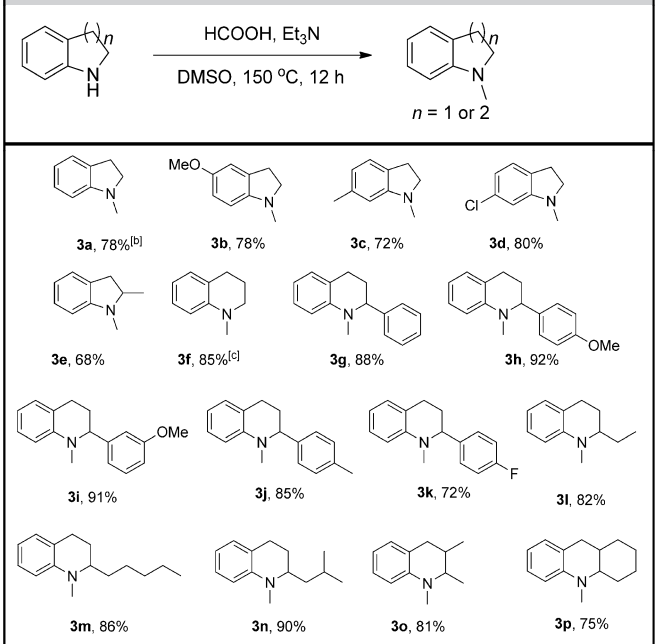
Nitrogen-containing heterocyles are an important class of compounds in organic chemistry. Indolines and tetrahydroquinolines were chosen as substrates to test the viability of this protocol for methylation of nitrogen-containing heterocyles (Table 3). Delightfully, indolines were smoothly converted to N-methylated indolines with acceptable yields (Table 3, **3a**–**e**). Tetrahydroquinolines bearing both aromatic and aliphatic substituents gave good to excellent yields (Table 3, **3f**–**p**). A further example is seen in the synthesis of Galipinine, an alkaloid used against fever, which could be obtained with 82% yield from its corresponding tetrahydroquinoline precursor **6g** (Scheme 2). The latter was conveniently accessed from **5g** using our previously reported aqueous asymmetric transfer hydrogenation system. Only a slight loss of enantiomeric excess was observed on going from **6g** to **3q** (Scheme 2).[16] This route avoids the use of toxic $NaBH(CN)_3$.[17]

As formic acid is a reducing reagent, nitro compounds might be directly transformed into dimethylated amines through amine intermediates. Indeed, dimethylated **1a** was



Scheme 2. Synthesis of Galipinine.

Table 3. Methylation of heterocyles in DMSO.[a]

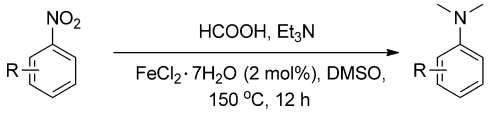


[a] Reaction conditions: 1 mmol amine, 20 mmol HCOOH, 20 mmol Et_3N, 3 mL DMSO, 150 °C,12 h, isolated yields. [b] Yields were determined by ^1H NMR with 1,3,5-trimethoxybenzene as internal standard. [c] The reaction time was 24 h.

formed in 38% yield in 12 h, when 1-methoxy-4-nitrobenzene (1 mmol) was subjected to the standard reaction conditions. The yield could be improved to 47% by using a larger amount of formic acid (26 mmol) and NEt_3 (21 mmol). Under these conditions, the starting material was fully consumed in 12 h, but uncharacterised side products were formed. Beller and coworkers have shown that aromatic nitro compounds can be reduced under iron catalysis with formic acid as hydrogen source.[18] Inspired by this finding, catalytic amount (2 mol%) of various iron salts, for example, $Fe_3(CO)_{12}$, $Fe(BF_4)_2{\cdot}6H_2O$, $Fe(OAc)_2$, together with the tetraphos ligand tris[(2-diphenylphosphino)-ethyl]phosphine (PP_3) were added to the above reaction. The yields were indeed improved, to over 80% for all the iron catalysts tested. Surprisingly, in the absence of the PP_3 ligand, similar yields were observed. For example, with 2 mol% of $FeCl_2{\cdot}7H_2O$, 1-methoxyl-4-nitrobenzene was converted to **1a** with 83% yield. With this result in hand, a range of aromatic nitro compounds were examined using the cheap and easily available $FeCl_2{\cdot}7H_2O$ as catalyst. As can be seen from Table 4, satisfactory yields were obtained for substrates with various substituents, including even a methylthio group. It is worth noting that the reduction of nitro groups with formic acid under catalyst-free or iron catalysis without ligands is unprecedented in the literature, to the best of our knowledge.

The mechanism of the methylation reaction was then studied. First, both formic acid and DMSO were shown to be essential for the methylation reaction; in the absence of either component, no methylation took place. As formamides can be easily formed from amines and formic acid, we initially thought that the methylation might proceed via the reduction of a

Table 4. One-pot methylation of aromatic nitro compounds.[a]

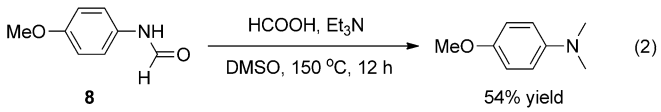


	R	Product	Yield [%][b]
1	4-OMe	**1a**	83
2	4-H	**1b**	70
3	4-CH_3	**1c**	73
4	4-Cl	**1d**	81
5	4-Br	**1e**	80
6	4-I	**7a**	62
7	4-SCH_3	**7b**	75
8	4-*tert*-Butyl	**7c**	89
9	3-Cl	**7d**	80
10	3-I	**7e**	71

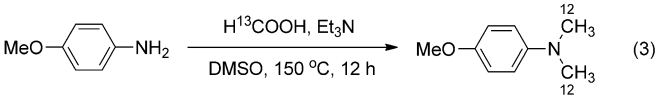
[a] Reaction conditions: 1 mmol amine, $FeCl_2{\cdot}7H_2O$ (0.02 mmol), 26 mmol HCOOH, 21 mmol Et_3N, 3 mL DMSO, 150 °C, 12 h. [b] Isolated yields.

formamide intermediate by formic acid. Indeed, in the reaction of *p*-anisidine, *N*-(4-methoxyphenyl)-formamide **8** was observed. Compound **8** was then separately synthesised and subjected to the reaction conditions of methylation [Eq. (2)]. Dimethylated product **1a** was formed, however, at a slower rate compared with starting from *p*-anisidine, suggesting that the formamide is not involved in the process of methylation.

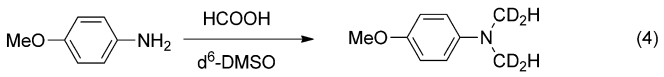
Isotope labelling was then pursued, leading to more insight into the mechanism. Thus, when ^{13}C labelled formic acid was used to methylate *p*-anisidine under the standard reaction conditions, no ^{13}C labelled methylation product was observed, showing that the methyl groups in the product are not from formic acid [Eq. (3)]. Furthermore, when [D_6]DMSO was used instead of DMSO, four of the six protons from the $-NMe_2$ group of **1a** were replaced by deuterium atoms [Eq. (4)]. When DCOOH was used instead of HCOOH, two of the six protons were replaced by deuterium atoms [Eq. (5)]. Full deuteration happened only when [D_6]DMSO and DCOOH was used [Eq. (6)]. The same deuterium labelling results were observed when starting from **8**, supporting the non-involvement of formamide in the methylation. Still further, when starting from monomethylated *p*-anisidine using [D_6]DMSO or DCOOH, the deuteration pattern shown in Equations (7) and (8) was ob-



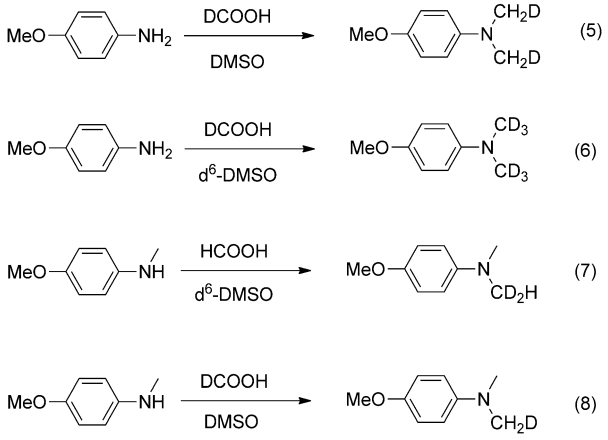
8 54% yield (2)



(3)

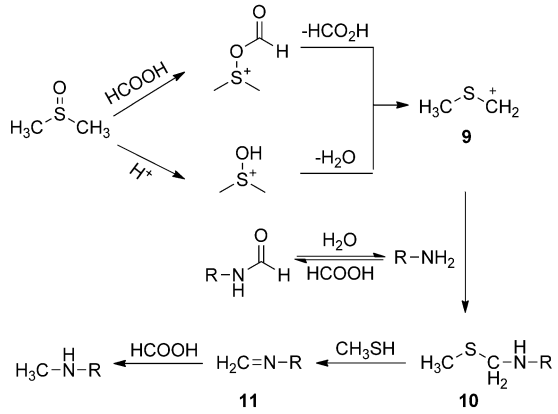


(4)



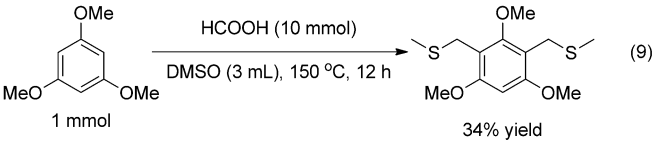
served. Together, these experiments clearly show that the *N*-methyl groups arise from DMSO instead of HCOOH; but for each methyl group, two protons come from DMSO and one from the C–H hydrogen of HCOOH. It is worth noting that these labelling studies provide a convenient method to access methylated amines with various level of deuterium labelling.[3d]

Based on the above mechanistic studies and the literature,[10] we propose a mechanism for this new methylation reaction. It is known that DMSO can react with anhydrides to form an acylated intermediate, which could undergo Pummerer rearrangement to afford intermediate **9**.[19] Alternatively, **9** could be formed by protonation and dehydration under acidic conditions.[10] We believe that the intermediate **9** is also involved in this reaction. DMSO might be acylated by formic acid or by the formic acid anhydride that is formed in-situ, or protonated by formic acid, which will all lead to the formation of **9** (Scheme 3). The presence of **9** is supported by the Friedel–



Scheme 3. Proposed mechanism for methylation of amines.

Crafts reaction shown in Equation (9), in which **9** is intercepted by 1,3,5-trimethoxybenzene.[20] Under our conditions, **9** could be intercepted by an amine to form intermediate **10**.[20f] The elimination of methane thiol from **10** results in the imine intermediate **11**, which could be reduced by formic acid, affording the methylated amine product. The smell in the reaction tube after the reaction supports the presence of methane thiol, although it was not characterised by spectroscopic means. In this mechanism, the methyl group is transferred as a methylene from DMSO to the product; of the three protons on the methyl group of product, two come from DMSO and one from formic acid, which fits well with the deuterium labelling experiments. The formamide intermediate observed is probably in equilibrium with the amine substrate under the reaction condition. This explains why slower reaction was observed when starting from **8**. Triethylamine may play a role in tuning the acidity of the system, thus insure that free amine substrate is available to participate in the nucleophilic attack of **9**.



Concerning the mechanism of methylation of nitro compounds, we believe that the nitro compound is first reduced to an amine and this is then followed by the pathway shown in Scheme 3. Support for this proposition is found in the experiment that replacing DMSO with DMF in the iron-catalysed methylation of 1-methoxyl-4-nitrobenzene afforded only 75% of **8** and 8% of *p*-anisidine as products; **1a** was not observed.

In conclusion, a new amine methylation protocol has been developed with very broad substrate scope. The cheap and low-toxic DMSO has been identified as the methylating reagent under catalyst-free conditions. Aromatic nitro compounds could be directly transformed into dimethylated amines in the presence of a cheap iron catalyst for the first time. The method provides a simple and convenient way to synthesise deuterium or ^{13}C labelled methyl amines. Mechanistic studies suggest that the methylation involves the transfer of a methylene group from DMSO to an amine and the reduction of the resulting imine by formic acid.

Experimental Section

General procedure for methylation of amine: Amine (1 mmol), HCOOH (99%, 20 mmol), triethylamine (20 mmol) and a magnetic stir bar were placed in a pressure tube. The mixture was bubbled with argon for 15 min, and then stirred at 150 °C for 12–48 h.

Caution! Pressure build-up during the reaction. Suitable pressure vessel must be chosen when scaling-up the reaction.

After being cooled to room temperature, the reaction was basified with NaOH solution, and the resulting solution was extracted with CH_2Cl_2 (3×10 mL). The organic layers were washed with brine and dried over Na_2SO_4. CH_2Cl_2 was then removed under reduced pressure and the product was purified by flash chromatography using petroleum ether and ethyl acetate as eluent.

Acknowledgements

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Keywords: amines · deuterium labelling · DMSO · formic acid · methylation

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