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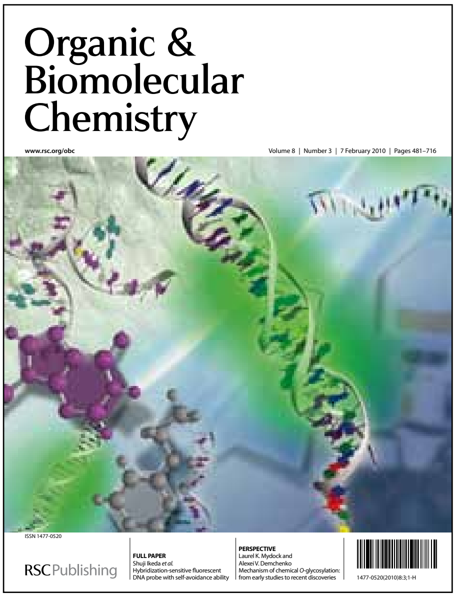

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ARTICLE TYPE

The Ammonium-Promoted Formylation of Indoles by DMSO and H_2O

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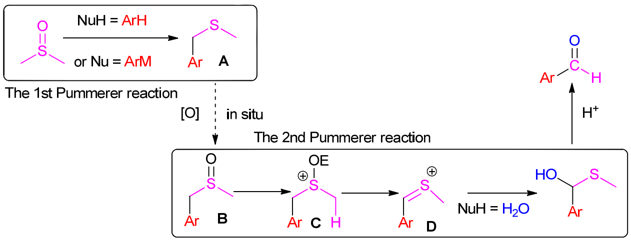
DMSO and H_2O is an efficient combination in the NH_4OAc-promoted formylation of indole, where DMSO serves as a C1 carbon source. The mechanism study reveals that the procedure involves a usual and unusual Pummerer reaction.

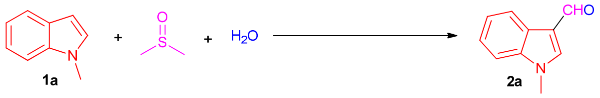
The formylation reaction is an important transformation in organic synthesis.[1] Traditionally, the Vilsmeier-Haack reaction is efficient for such transformation.[2] However, it requires a stoichiometric amount of $POCl_3$, which is not environmentally benign. The Duff reaction,[3] Reimer–Tiemann reaction,[4] and Gattermann-Koch reaction,[5] are also powerful methods leading to formylated products. Nevertheless, some substrates such as indoles have not been tolerated well because of either limited substrate scope of such reactions or strongly acidic conditions. To solve this problem, in 2011, Su reported a mild Ru-catalyzed formylation of indoles using anilines as the carbonyl source.[6] Subsequently, we developed a copper-catalyzed C3-formylation of indole C-H bonds by tertiary amines and molecular oxygen.[7] Our continuous research on the DMSO-mediated organic reaction[8] spurred us to test the feasibility of DMSO serving as a carbonyl reagent, which might open up an expedient synthetic pathway to formylated products.



Scheme 1. A rational strategy for formylation by DMSO and H_2O.

In the Pummerer reaction, the alkyl sulfoxide is attacked by a nucleophile via a thionium ion intermediate.[9] We envisioned the formed sulfide **A** could be oxidized to sulfoxide **B** *in situ* after the first Pummerer reaction with DMSO in proper reaction condition. Then, sulfoxide **B** is attacked by H_2O as the nucleophile in the second Pummerer reaction to afford the formylation product upon hydration (Scheme 1). However, great challenges still remain for this strategy because the traditional Pummerer reaction requires acidic activators, which may induce serious side reactions for indole. To solve this problem, a Pummerer reaction under nearly neutral or weakly basic conditions needs to be developed.

Table 1. Screening the optimized reaction conditions.[a]



Entry	Metal(equiv)	Additive	Yield(%)
1	$CuF_2(3)$	$NH_3{\bullet}H_2O$	20
2	$Cu(OAc)_2(3)$	$NH_3{\bullet}H_2O$	23
3	$Cu(OAc)_2(3)$	$(NH_4)_2CO_3$	38
4	$Cu(OAc)_2(3)$	$HCOONH_4$	44
5	$Cu(OAc)_2(3)$	NH_4OAc	69
6	$Pd(OAc)_2(0.1)$	NH_4OAc	74
7	--	NH_4OAc	62
8	--	NH_4OAc	57[b]
9	--	NH_4OAc	79[c]
10	--	$HCOONH_4$	47[c]
11	--	NH_4F	50[c]

[a] All reactions were run with *N*-methyl indole **1a** (0.2 mmol), ammonium (0.8 mmol) and DMSO/H_2O (1.5 mL/80 μL), 150 °C, under air, 30 h. [b] Under O_2. [c] Under N_2.

With this in mind, initially, we tested the reaction of *N*-methyl indole in DMSO as the model reaction. After tedious screening, we found heating the combination of CuF_2 (3 equiv), *N*-methyl indole and aqueous ammonia (4 equiv) at 150 °C for 30 h afforded 3-formylated product in 20% yield. $Cu(OAc)_2$ was slightly more effective than CuF_2. To our delight, the yield dramatically increased to 69% by using NH_4OAc (4 equiv) with 3 equivalents of $Cu(OAc)_2$. Replacing $Cu(OAc)_2$ with 10 mol % of $Pd(OAc)_2$ afforded the formylated product in 74% yield. Interestingly, the formylation reaction proceeded smoothly under air in 62% yield with 4 equivalents of NH_4OAc in the absence of any transition-metal catalyst (Table 1, entry 7). The yield increased to 79% under N_2 and decreased to 57% under O_2. Other tested ammonium salts, such as NH_4F and $HCOONH_4$, were inferior to NH_4OAc. No product was detected in the absence of ammonium salt. Under standard procedure, a comparable 73% yield was obtained in the presence of 0.2 mL of Hg(0), ruling out the possibility of trace of transition-metal as the true catalyst.

With the optimized reaction conditions in hand, the substrate scope and the limitation for this formylation reaction studied, as shown in Figure 1. As expected, both electron-donating and electron-withdrawing groups such as methoxy, fluoro, chloro, bromo, nitro and cyano groups on the aromatic moiety were tolerated well under this procedure. Generally,

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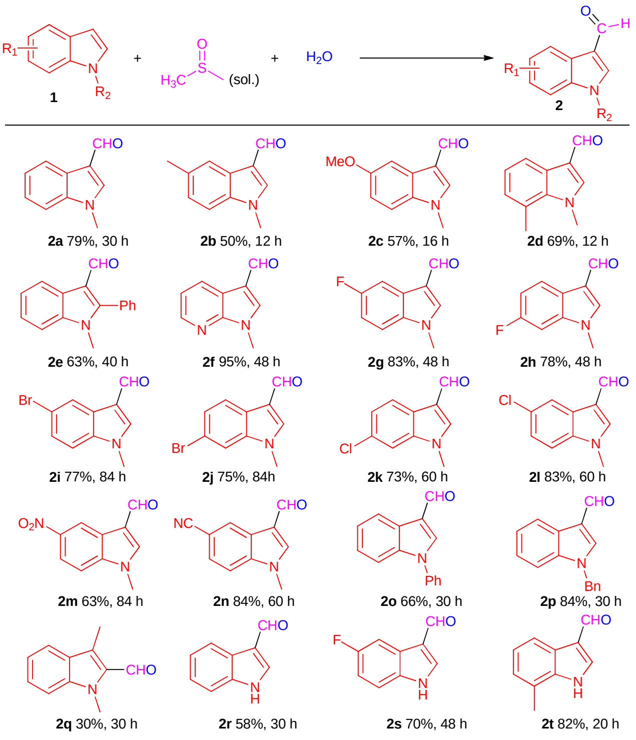
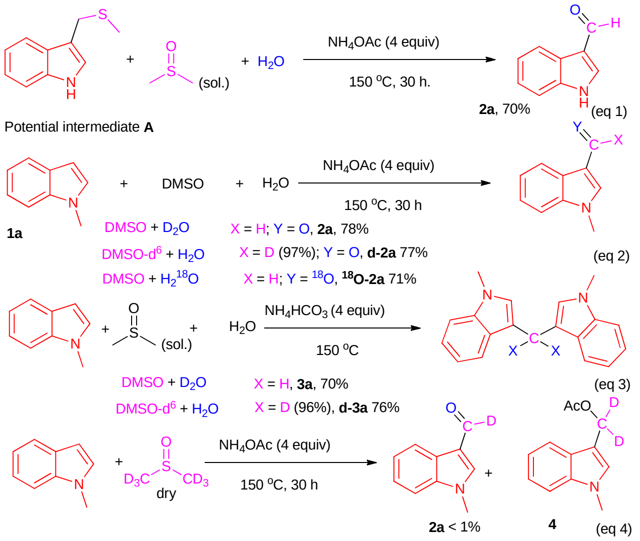
the reaction became sluggish for those substrates possessing an electron-withdrawing group. Thus, a longer reaction time is required. However, moderate yields were obtained for indoles containing electron-donating groups since serious side reactions took place, leading to 3,3'-diindolylmethanes. It is noteworthy that the transformation proceeded smoothly regardless of the *N*-substituent groups of the indoles (**2o** and **2p**). Notably, the chloro and bromo functional groups survived well under the standard procedures, offering handles for further functionalization (**2i–2l**). Particularly, the heteroaryl indoles, such as *N*-methyl-1*H*-pyrrolo[2,3-b]pyridine, provided the desired product **2f** in 95% yield. For the *N*-methyl indoles blocked with a phenyl group on the C-2 positions, the formylation reaction furnished the corresponding product **2e** in 63% yield. However, only 30% of the 2-formylation product **2q** was formed if the 3- position of *N*-methyl indole was blocked with a methyl. To evaluate the practical utility further, the reaction was conducted on a 2 mmol scale, and the desired product **2a** was furnished in a comparable 70% yield. Importantly, the free (NH)-indole delivered the formylated products in acceptable yields (**2r** and **2s**).

Figure 1. The formylation of indoles by DMSO and H_2O.[a]



[a] Reaction conditions: indole derivative **1** (0.2 mmol), NH_4OAc (0.8 mmol) and DMSO/H_2O (1.5 mL/80 μL), 150 °C, under N_2.

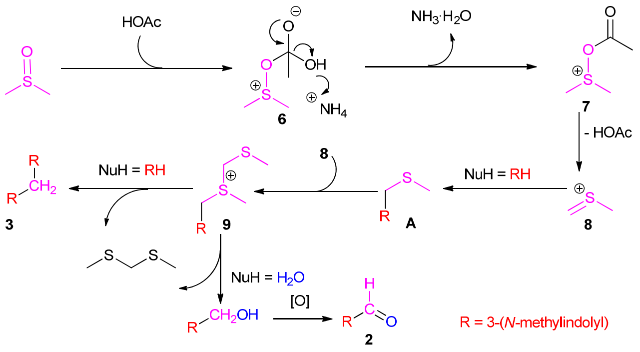
Interestingly, this procedure was applicable for the synthesis of 3,3'-diindolylmethane (DIM) **3a** in 70% yield in 48 h by replacing NH_4OAc with NH_4HCO_3. The presumed intermediate 3-(methylthiomethyl)-1*H*-indole **A** in Scheme 1 was detected during the reaction by GC-MS. When it was subjected to the standard reaction condition, the formylated product was isolated in a comparable 70% yield (Scheme 2, eq 1). Replacing H_2O with D_2O, no deuterium atom was incorporated into the formylation product (Scheme 2, eq 2). However, heating the combination of *N*-methyl indole, DMSO-d^6 and H_2O under 150 °C resulted in the thorough deuteration of aldehydic hydrogen (Scheme 2, eq 2). The 3-formyl *N*-methyl indole with ^{18}O in the carbonyl group was the major product using the combination of DMSO and $H_2{}^{18}O$ (Scheme 2, eq 2). Under the reaction leading to 3,3'-diindolylmethane (DIM), no deuterium atom was detected in the product from the combination of DMSO and D_2O (Scheme 2, eq 3). However, two deuterium atoms were incorporated in the methylenyl of 3,3'-diindolylmethane by heating the combination of d^6-DMSO and H_2O (Scheme 2, eq 3). Moreover, heating the combination of *N*-methyl indole and NH_4OAc (4 equiv) in dry DMSO-d^6 for 30 h, compound **4** with two deuterium atoms in the methylenyl, instead of the formylation product with aldehydic deuterium atom, was detected by GC-MS (Scheme 2, eq. 4). According to the experimental facts in eqs 3 and 4, an S_N2 type reaction of intermediate **C** in Scheme 1 attacked by nucleophile may be involved in the second transformation.



Scheme 2. Mechanism study.

However, there are still two questions that remain to be addressed. Firstly, what serves as the oxidant during the transformation of thioether intermediate **A** to sulfoxide **B** depicted in Scheme 1. We reasoned DMSO may act as an oxidant for this transformation. However, to our surprise, no sulfoxide was detected by heating of the potential intermediate 3-(methylthiomethyl)-1*H*-indole **A** in DMSO at 150 °C for 30 h, even in the presence of 4 equivalents of HOAc, which may act as a promoter in this oxidative transformation.[10] During the formylation reaction, a large amount of bis(methylthio)methane was detected as byproduct (Scheme 2, eq 4).[11] However, heating the potential intermediate 3-(methylthiomethyl)-1*H*-indole **A** in DMSO-d^6 at 150 °C for 30 h, a species with slightly longer retention time than $CH_3SCH_2SCH_3$ and the molecular ion peak as 113, was detected by GC-MS, which was assignable to

$CH_3SCD_2SCD_3$ (see Supporting Information). In combination with the aforementioned results, we deduced the nucleophilic attack of the thionium ion derived from DMSO by the sulfur atom of 3-(methylthiomethyl)-1*H*-indole **A** formed the sulfonium cation **9** (in Scheme 3, R = 3-(*N*-methylindolyl)),[12] which underwent an S_N2 reaction by H_2O to deliver the hydroxymethylation product as the precusor of the formylation product.[13]



Scheme 3. Proposed mechanism.

The second is how NH_4OAc promotes the Pummerer reaction. Huang reported the NH_4OAc and $CuBr(PPh_3)_3$-induced Pummerer reaction between free (NH)-indole and DMSO leading to 3-methylthiomethyl indoles.[14] Based upon this and the property of DMSO, a postulated mechanism is illustrated in Scheme 3. Firstly, NH_4OAc is decomposed to HOAc and NH_3. Then, DMSO is activated by HOAc to form intermediate **6**. Secondly, the cleavage of the C-OH bond assisted by NH_4^+ forms intermediate **7**. No reaction takes place without ammonium, suggesting that the ammonium is crucial for this transformation. The role of NH_4^+ is likely to facilitate the cleavage of the C-OH bond by changing the strongly basic OH^- group to $NH_3{\cdot}H_2O$ as a weakly basic leaving group. Thirdly, the thionium ion **8** is formed in the presence of $NH_3{\cdot}H_2O$ as a base. Then, it is attacked by *N*-methyl indole as a nucleophile to form intermediate **A**. Fourthly, the attack of sulfur atom in **A** to the thionium ion **8** affords sulfonium **9**. Finally, the S_N2 nucleophilic reaction of intermediate **9** attacked by H_2O takes place to form the hydroxymethylation product, which is oxidized to the formylation product **2** by **7** in similar with Swern oxidation.[15] Meanwhile, the nucleophilic attack of **9** by another molecular *N*-methyl indole produces 3,3'-diindolylmethane (DIM).

In conclusion, we have developed an NH_4OAc promoted procedure involving a sequential traditional and unusual Pummerer reaction under nearly neutral conditions, leading to 3-formyl indole. This procedure uses DMSO and H_2O as the carbonyl source with good functional group tolerance. Thus, it represents an important development in DMSO-mediated transformation and the Pummerer reaction.

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Notes and references

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