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Acid-promoted oxidative methylenation of 1,3-dicarbonyl compounds with DMSO: application to the three-component synthesis of Hantzsch-type pyridines†

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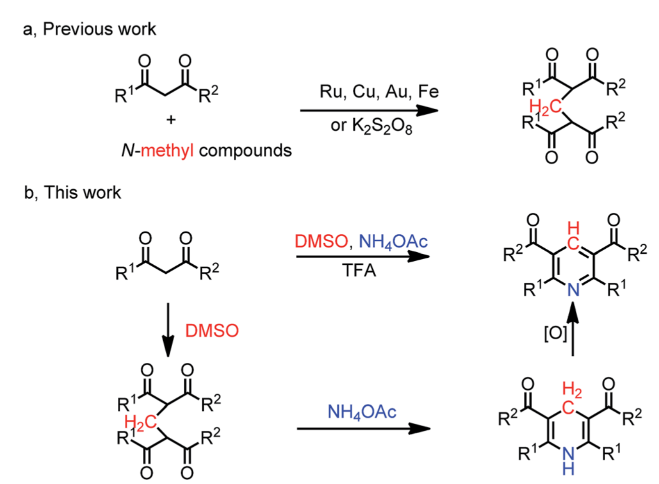
A highly convergent one-pot synthesis of Hantzsch-type pyridines has been developed based on a three-component annulation of 1,3-dicarbonyl compounds, DMSO, and ammonium salt. A transition-metal-free oxidative methylenation reaction/Hantzsch pyridine synthesis cascade reaction was involved in this process. This intermolecular annulation reaction proceeds under mild reaction conditions, wherein DMSO serves as solvent, carbon source, and oxidant. A series of polysubstituted pyridines and methylene-bridged bis-1,3-dicarbonyl compounds were prepared in high yields.

Methylene-bridged bis-1,3-dicarbonyl compounds are useful building blocks or intermediates in organic synthesis.[1] Traditionally, these compounds are synthesized from bis-1,3-dicarbonyl compounds by using CH_2Br_2 (ref. 2) or formaldehyde[3] as one-carbon sources with low efficiency. Meanwhile, these compounds were constructed by using *N*-methyl compounds as one-carbon sources through transition-metal catalysed methylenation reactions, such as Ru,[4] Cu/Au,[5] and Fe,[6] as well as through $K_2S_2O_8$ (ref. 7) oxidative methylenation reactions (Scheme 1a). However external oxidants are always required.

Over the past decades, the solvent-participated reaction is considered as an important strategy for the developing economic chemical methodologies. As a less toxic and inexpensive solvent, dimethyl sulfoxide (DMSO) is commonly employed as an effective oxidant[8] and the source of –SMe,[9] –SOMe,[10] –SO_2Me,[11] –CH_2SMe,[12] –CN,[13] –CHO,[14] =CH_2,[15] –CH_2–,[16] and –Me.[17] We have recently developed a method to 1,3,5-triarylbenzenes[18a] and bis(1*H*-indol-yl)methanes,[18b] in which DMSO served as a precursor of methine and methylene unit, respectively. Despite those advantages, the using of DMSO as methine source is still rare.[19] We hypothesisd that DMSO could be used as methylenation reagent instead of *N*-methyl compounds to form methylene-bridged bis-1,3-dicarbonyl compounds, which could be further trapped with ammonium salt leading to Hantzsch-type pyridines. Recently, multicomponent reactions have emerged as attractive processes for the assembly of complex molecules.[20] During our ongoing investigations in constructing of heterocycle compounds,[21] herein, we wish to report an efficient protocol for the synthesis of Hantzsch-type pyridines *via* a three-component cascade reaction of 1,3-dicarbonyl compounds, DMSO, and ammonium salt, in which two C–C bonds and two C–N bonds were formed in one-pot manner (Scheme 1b).

Initially, 1,3-dipheylpropane-1,3-dione **1a** was selected as a model substrate with NH_4Cl as nitrogen source in DMSO to explore the reaction efficiency (Table 1). To our delight, the desired pyridine product **4a** was afforded in 16% yield in the



Scheme 1 Methods for the synthesis of methylene-bridged bis-1,3-diketones.

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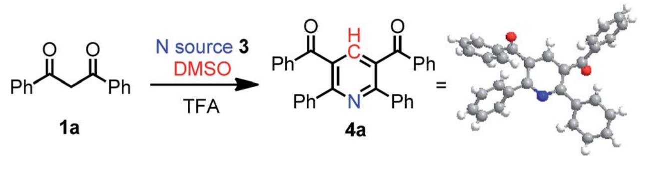
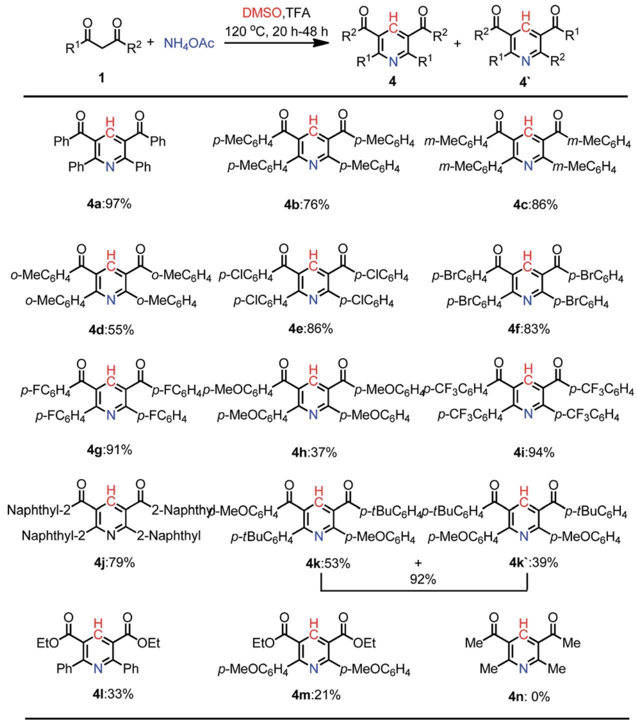
Table 1 Optimization of reaction conditions[a]



Entry	N source	TFA (eq.)	Temp. (°C)	*T* (h)	Yield[b] (%)
1	NH_4Cl	12	100	24	16
2	NH_4Cl	12	120	24	37
3	NH_4Cl	12	140	24	30
4	NH_4Cl	6	120	24	71
5	NH_4Cl	3	120	24	31
6	NH_4Cl	6	120	24	73[c]
7	NH_4Cl	6	120	24	56[d]
8	NH_4OH	6	120	24	78
9	NH_4HCO_3	6	120	24	62
10	NH_4OAc	6	120	24	83
11	NH_4OAc	6	120	48	97
12	NH_4OAc	0	120	24	np
13	NH_4OAc	6	120	48	56[e]
14	NH_4OAc	6	120	48	81[f]

[a] General conditions: **1a** (0.5 mmol) and **3a** (1.0 mmol) with TFA in 2 mL DMSO under air. [b] Isolated yield. [c] 3.0 equiv. of **3a**. [d] 1.0 equiv. of **3a**. [e] The reaction was carried out under N_2. [f] AcOH was used instead of TFA.

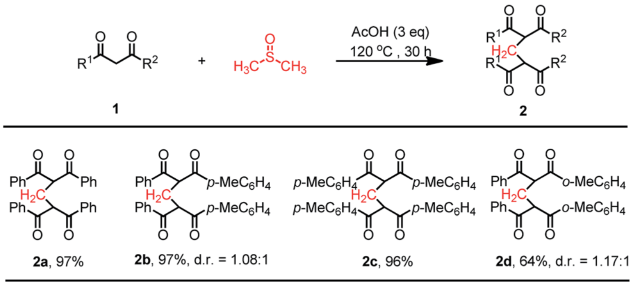


Scheme 2 Representative results.

presence of TFA as an additive (entry 1). The configuration of **4a** was determined by single crystal X-ray diffraction analysis. With this preliminary result in hand, we continued to optimize the reaction conditions. Gratifyingly, increasing the reaction temperature resulted in a positive effect on the reaction (entry 2). However, higher temperature (140 °C) gave slight poorer result (entry 3). When the loading of TFA was decreased to 6 equivalents, the corresponding yield sharply enhanced from 30% to 71%. Further decreasing the amount of TFA gave a reduced yield of 31% (entries 4, 5). The formation of product was also affected by the loading of **3a** (entries 6, 7). After a brief screening of different ammonium salts, such as NH_4OH, NH_4HCO_3, and NH_4OAc, we found that NH_4OAc was the most effective nitrogen source (entries 8–10). The yield increased with the extension of the reaction time from 24 h to 48 h (entry 11). The reaction did not proceed in the absence of acid (entry 12). When the reaction was performed under N_2 atmosphere, the yield was lower than that under air atmosphere (entry 13). This result clearly revealed that O_2 as an oxidant sharply increased the yield and DMSO may serve as an oxidant in the absence of O_2. A control experiment showed that the yield was decreased to 81% when AcOH was used instead of TFA (entry 14). These studies indicate that the optimal one-pot system for this annulation reaction was **1a** (0.5 mmol), **3b** (1.0 mmol), TFA (3.0 mmol) in DMSO (2 mL) at 120 °C under air for 48 h.

Having identified the reaction conditions for the synthesis of pyridine derivatives, a wide variety of substituted 1,3-dicarbonyl compounds were submitted to investigate the substrate scope and generality. As displayed in Scheme 2, the reaction exhibited satisfactory tolerance of the substrates containing substitutions of distinct properties, such as Me, MeO, F, Cl, Br, CF_3, and CO_2Me. The steric hindrance influenced this reaction obviously. The substrates with *ortho*-substituent gave lower yield than those with *para-* or *meta*-substituent (**4d** *vs.* **4c**, **4b**). On the other hand, 1,3-diketones with *p*-halogen-substituents reacted smoothly to provide the desired products in good yields (**4e**, **4f** and **4g**). In addition, substitution with strong electron-withdrawing groups such as 4-CF_3 was also tolerated under the reaction conditions, giving pyridine **4i** in 94% yield. However, strong electron-donating substituent such as methoxyl gave the desired product only in 37% yield (**4h**). A naphthalene derivative (**1j**) reacted in the same condition, producing the corresponding **4j** in 79% yield. From comparison with symmetrical 1,3-dione substrates, unsymmetric substrate tended to give two major products (**4k** and **4k′**). Moreover, β-ketone esters reacted smoothly with NH_4OAc and give the desired products in 33% and 21%, respectively (**4l** and **4m**). An aliphatic 1,3-dione failed to give the corresponding product (**4n**).

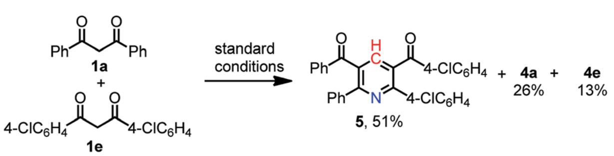
As mentioned above, methylene-bridged bis-1,3-dicarbonyl compounds are synthetically important chemicals. Thus, we began to synthesize these compounds by using our strategy. However, in the absence of NH_4OAc, the desired methylene-bridged bis-1,3-dicarbonyl compound **2a** was obtained in only 43% yield. NH_4OAc is a more suitable ammonium salt than NH_4Cl or NH_4HCO_3, in the abovementioned three-component annulation reaction (Table 1). We thus presume that acetate anion may play a significant role in this transformation. Then, AcOH was used instead of TFA. To our delight, the use of 3 equivalent of AcOH in DMSO at 120 °C could produce **2a** in 97%



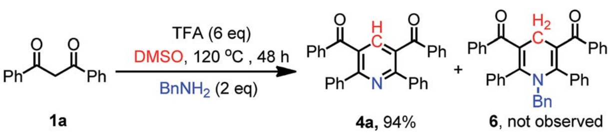
Scheme 3 Oxidative methylenation for the synthesis of methylene-bridged bis-1,3-diketones.

yield. These conditions were subsequently employed when we examined the substrate scope of this reaction. Gratifyingly, a variety of 1,3-diketones **1a–d** successfully reacted under the aforesaid conditions to afford the desired methylene-bridged bis-1,3-dicarbonyl compounds **2a–d** in good to excellent yields (Scheme 3). Two diastereomers were obtained in ratios between 1.2 and 1, when unsymmetric substrates were used.

Moreover, the novel pyridine compound **5** containing four different substituents could be generated from the cross-over reaction in 51% yield from **1a** and **1e** (eqn (1)). When benzyl amine was used as nitrogen source, the aromatic product **4a** was obtained in 94% and the desired *N*-benzyl dihydropyridine **6** was not observed. This result suggests that the methylenation reaction/Hantzsch pyridine synthesis cascade reaction is substantially slower than the final oxidation reaction under the optimized conditions (eqn (2)).

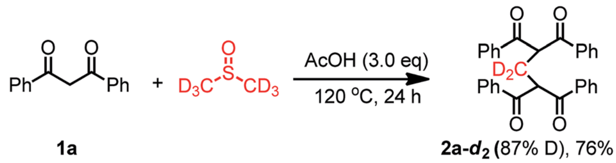


(1)

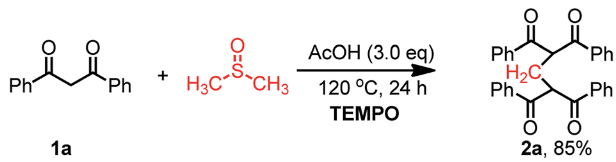


(2)

To gain more insight into the reaction mechanism, control reactions were conducted. DMSO-d_6 was used as solvent instead of DMSO under the standard reaction conditions. D-labeled product **5** was obtained in 76% yield with 87% incorporation of deuterium, confirming that DMSO is the methylene source (eqn (3)). The radical scavengers, such as TEMPO (2,2,6,6-tetramethylpiperidinooxy) did not influence this reaction obviously (eqn (4)), which indicated that a radical pathway may not be involved in this reaction.

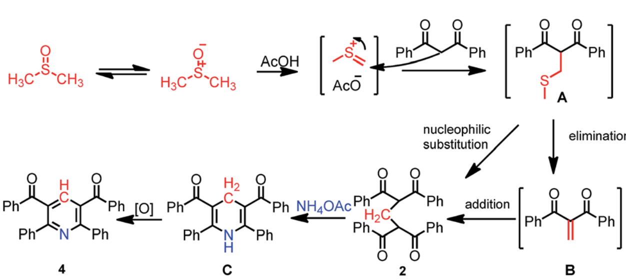


(3)



(4)

Subsequently, the proposed reaction mechanism was shown as Scheme 4. The acetate acid-promoted reaction of **1** and DMSO affords the oxidative coupling product **A** (Pummerer-type reaction). **2** is formed by either nucleophilic substitution reaction or the tandem reaction of elimination and Michael addition *via* an intermediate **B**.[22] In addition, the substituted 1,4-dihydropyridine (1,4-DHP) **C** was obtained by the reaction of **B** with ammonium acetate, then *via* oxidation reaction to obtain the final pyridine products (Scheme 4).



Scheme 4 Possible pathways for the reactions.

Conclusions

In conclusion, we have developed a general and efficient method for the synthesis of substituted pyridines from readily available 1,3-dicarbonyl compounds. In this system, DMSO could serve as a simple, cheap solvent, and easy-to-handle one carbon source, and directly reacted with 1,3-dicarbonyl compounds to give the corresponding methylene-bridged bis-1,3-dicarbonyl compounds, which could be further transformed to the Hantzsch-type pyridines in the presence of NH_4OAc.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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