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Cite this: DOI: 10.1039/c0xx00000x

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ARTICLE TYPE

Oxidative C–S Bond Cleavage Reaction of DMSO for C–N and C–C Bond Formation: New Mannich-type Reaction for β -amino Ketones

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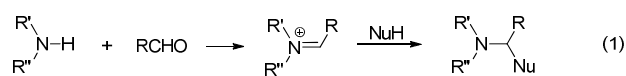
Received (in XXX, XXX) Xth XXXXXXXXX 20XX, Accepted Xth XXXXXXXXX 20XX
DOI: 10.1039/b000000x

A novel oxidative C–S bond cleavage reaction of DMSO for *N*-methylation course and subsequent C–C bond formation is described. A series of aryl ketones as well as acetone derivatives could be selectively converted into the corresponding β -amino ketones. Mechanistic studies suggested that *N*-methylation course between imine and DMSO was involved in the reaction.

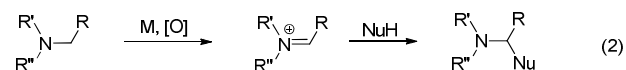
β -amino carbonyl compounds are important biological molecules as well as useful synthetic intermediates for various pharmaceuticals and natural products.¹ The most classic method for the preparation of β -amino carbonyl compounds is the three-component mannich reaction with aldehydes, amines, and a C–H acidic carbonyl compounds, which has been employed numerous times as a key step in natural product synthesis as well as in medicinal chemistry (eqn 1).² In recent years, oxidative mannich reactions, originating from readily available tertiary amines,³ emerges as a powerful method for preparation β -amino carbonyl compounds with the aid of metal catalyst and oxidant (eqn 2).⁴ However, some substrate limitations and side reactions limits its wide application. Alternative methods for preparation β -amino carbonyl compounds suffer from multiple steps such as michael addition reaction between ketene and amine component, or the substitution reaction of β -halo/hydroxyl ketones with nucleophilic nitrogen sources.⁵

In the past decades, the common polar solvents DMF and DMSO was widely used as a multipurpose building block and has played an important role in organic synthesis.⁶ Recently, zhang group reported the first *N*-methylation reaction between N–H bonds of amidines and methyl C(sp³)–H bonds of DMSO and DMF.⁷ Subsequently, Xiao group also reported the *N*-methylation of amines and nitro compounds with DMSO.⁸ It is well known that methylation of amines is a general transformation in organic synthesis⁹ and many methods for preparation of methylated amines have been developed.^{10,11} However, *N*-methylation course using DMF and DMSO as methyl source is rare and to the best of our knowledge, using the common solvents DMF and DMSO in mannich reaction as a methyl source has never been reported. As part of our continuing interest in construction of C–N bonds directly from C–H bonds,¹² we proposed that the indispensable formaldehyde analogues in mannich reactions may be replaced with the cheap and low-toxic solvents DMF/DMSO

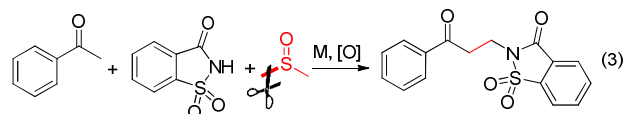
Classic three-component mannich reaction



Oxidative mannich reaction



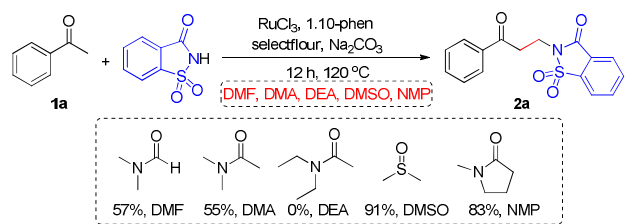
This study



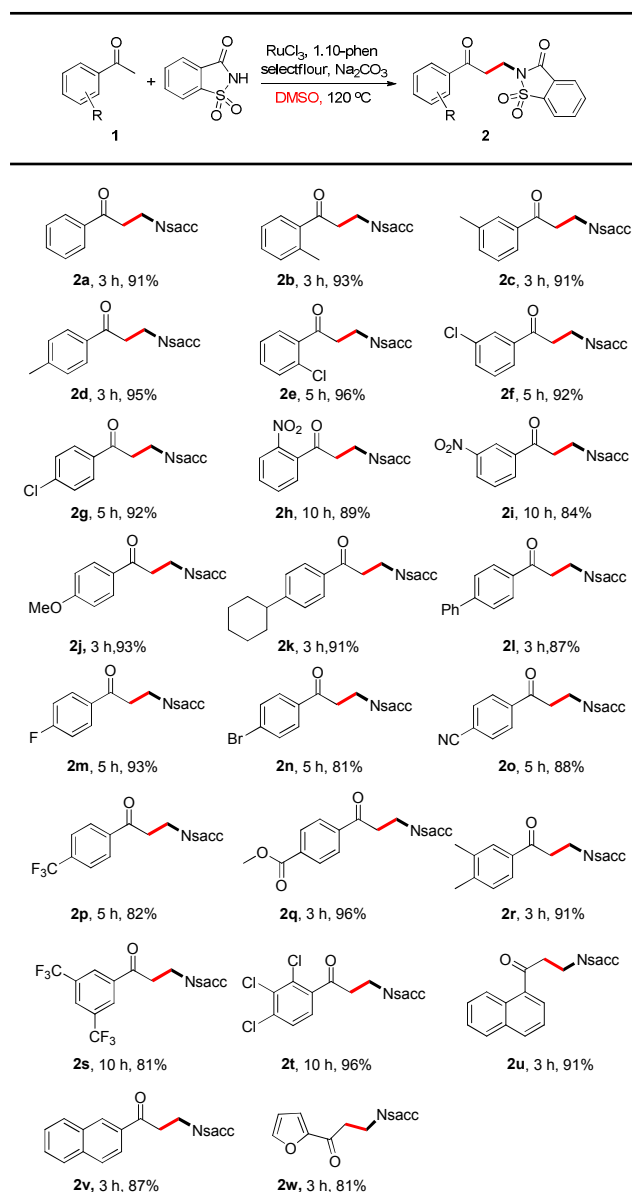
and give the key enamine or methyl amine intermediate through the *N*-methylation course.

Based on this assumption, our initial investigations focused on the effect of various solvents with selectfluor as an oxidant and Cu(OTf)₂ as the catalyst, which was an efficient combination for *N*-methylation reaction in previous report.⁷ To our delight, DMF, *N,N*-dimethylacetamide (DMA), DMSO and *N*-methyl-2-pyrrolidone (NMP) were all effective amine methylation source

Scheme 1 Diverse methyl source in mannich reaction



and gave the desired product **2a** in moderate yields. However, no reaction occurred with *N,N*-diethylacetamide (DEA) as the corresponding methyl source (Scheme 1). After detailed screenings revealed that RuCl₃ was the best catalyst and DMSO was the suitable choice as methyl source and solvent. In the presence of additive Na₂CO₃, the yield of **2a** could be increased to 91% (see ESI). It is highlight that this new-type mannich reaction may be a breakthrough compared to conventional

Table 1: Scope of the mannich reaction. ^{a, b}

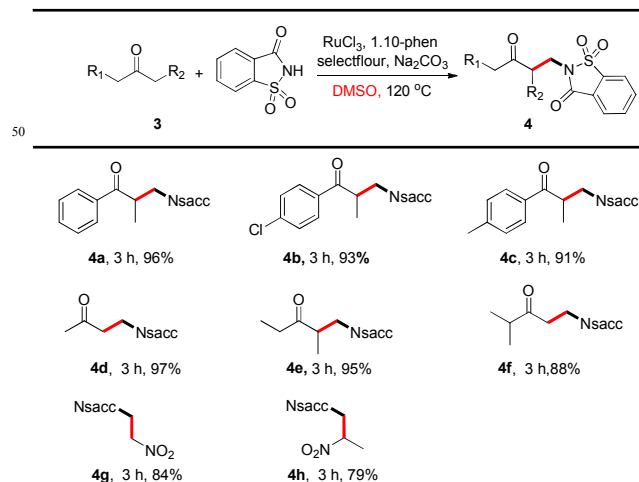
^aReaction conditions: **1** (0.5 mmol), saccharin (1.0 mmol), RuCl₃ (5 mol%), 1,10-phen (0.025 mmol), selectfluor (1.0 mmol), Na₂CO₃ (1.0 mmol) and DMSO (2 mL) at 120 °C for 3-10 h.
^bYield of the isolated products.

mannich reaction with toxic formaldehyde analogues as an indispensable methyl source.

With the optimal conditions in hand, we continued to evaluate the substrate scope of this method for the synthesis of various β-amino ketones. Different aryl ketones are subjected to react with saccharin and the results are summarized in Table 1. Functional group compatibility was quite broad as those demonstrated with both electron-rich Me, MeO, cyclohexy, Ph and -deficient F, Cl, Br, CN, CF₃, NO₂ and ester groups which were obtained in good to excellent yields (**2a–2q**). The results of this work are significant considering that the ester unit may be used as a readily manageable protecting group in organic

synthesis, as well as F, Cl, Br, CN can be converted into various functional groups under ambient conditions. Similarly smooth coupling was observed for aromatic ketones bearing substitution groups at different positions such as 2-Cl, 3-Cl, 4-Cl and 2-Me, 3-Me, 4-Me, and no previous yield disparity was observed. (Table 1, **2b–2g**). The multisubstituted substrate **1r**, **1s** and **1t** can also provide the desired products **2r**, **2s** and **2t** in high yields (91%, 81% and 96%). Furthermore, the fused bicyclic acetylnaphthalene **1u**, **1v** and heterocyclic ketones **1w** were all effective substrates under these conditions, the yields of the corresponding **2u**, **2v** and **2w** were up to 91%, 87% and 81%, respectively.

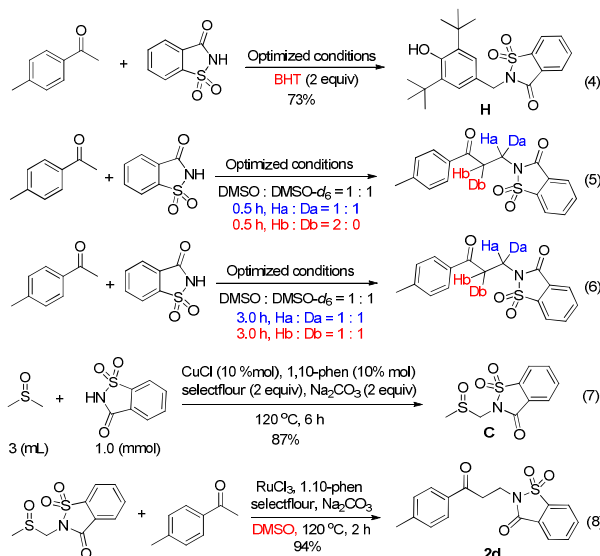
The substrate scope of this reaction can be extended to propiophenone derivatives such as propiophenone (**4a**), 1-(4-chlorophenyl)propan-1-one (**4b**) and 1-(p-tolyl)propan-1-one (**4c**), the desired products could be obtained in 96%, 93% and 91% yields. It is highlight that the potential of this reaction for catalytic asymmetric mannich-type reaction might promote more research interests in this area.¹³ In addition, the present catalytic system was amenable to the reaction of alkyl ketone compounds **3d**, **3e** and **3f**, gave the corresponding products **4d**, **4e** and **4f** in high yields (97%, 95, and 88%), respectively. To our delight, this reaction was also applicable to other acidic C–H compounds such as nitromethane and nitroethane, the desired products were obtained in 84% and 79% yields. It is noteworthy that this new reaction not only expanded the methyl source in mannich reaction but also enriched the content of the mannich synthetic methodology.

Table 2: Scope of the mannich reaction. ^{a, b}

^aReaction conditions: **3** (0.5 mmol), saccharin (1.0 mmol), RuCl₃ (5 mol%), 1,10-phen (0.025 mmol), selectfluor (1.0 mmol), Na₂CO₃ (1.0 mmol) and DMSO (2mL) at 120 °C for 3 h. ^bYield of the isolated products.

The mechanism of this reaction was then studied. First, radical inhibitor BHT (2,6-di-tert-butyl-4-methylphenol) was introduced into the reaction mixture, the reaction progress were completely suppressed and an unexpected methyl imidated product **H** derived from BHT was isolated in 73% yield [eqn. (4)]. When TEMPO (2,2,6,6-tetra-methyl-piperid-ine-*N*-oxyl) was added, the reaction was suppressed severely and the yield of **2d** decreased

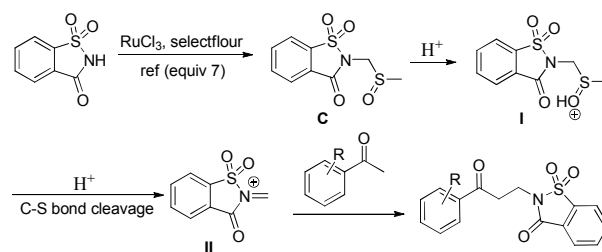
from 92% to 18%. These results suggesting that radical intermediate may be involved during the transforming. Intermolecular kinetic isotope effect (KIE, K_H/K_D) was then carried out, leading to more insight into the mechanism. Thus, equimolar amounts of DMSO and DMSO- d_6 was added as the solvent, after 0.5 h, one proton of methylene adjacent to nitrogen atom was replaced by deuterium atom [eqn. (5)]. Longer reaction time to 3 h, approximate 1:1 protons of the both methylene were replaced by deuterium atoms [eqn. (6)]. These results clearly show that the new methylene adjacent to nitrogen arise from DMSO and keto-enol tautomerism of ketone is involved during this reaction. To get further evidence about the mechanism, the C(sp³)-H imidate product 2-((methylsulfinyl)-methyl)benzo[d]isothiazol-3(2H)-one 1,1-dioxide **C** was isolated by the reaction of DMSO with saccharin [eqn. (7)]. Its structure was confirmed by ¹H and ¹³C NMR spectra (see ESI). A stoichiometric reaction between 1-(*p*-tolyl)ethanone **1d** and the possible intermediate **C** was also performed. To our delight, after 2 h, we obtained the desired product **2d** in 94% yield [eqn. (8)]. This result signified the C-N bond formation reaction between sulfonamide and methyl C(sp³)-H bonds of DMSO was involved and compound **C** is a temporary intermediate in this reaction.



Based on the above experimental results, a possible mechanism is proposed for the present catalytic recycle (Scheme 2): The first step is likely to be an oxidative amination process by RuCl₃ and F⁺ (selectfluor) combination, thus affording the intermediate **C**.¹⁴ Subsequently C-S bond cleavage in the presence of H⁺ delivers the enamine intermediate **II**.¹⁵ Finally, carbon-carbon bond formation between **II** and tautomer of ketone delivers the aimed products.

In summary, we have succeeded in developing a new-type mannich reaction between ketone methyl C(sp³)-H bonds and N-H bond of saccharin with the addition of DMSO as one carbon bridging group for the first time. Detail mechanism study revealed that N-methylation between saccharin and DMSO was involved during this procedure, which is an important transformation in organic synthesis as well as in biological

Scheme 2 Plausible mechanism of this reaction.



processes. Considering its excellent reaction efficiency and wide substrate scope, the strategy would be highly desirable for convenient synthesis of β -amino ketone derivatives, which were widely exist in natural products. Further application of the reaction is currently underway in our lab.

Notes and references

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