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Heterocycles

Direct N-Methylation Reaction Using DMSO as One-Carbon Bridge: Convenient Access to Heterocycle-Containing β-Amino Ketones

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Abstract: A novel oxidative C–S bond cleavage reaction of DMSO for dual C–C and C–N bond formation is described. A series of acetyl heteroarenes could be selectively converted into the corresponding β-amino ketones, which are frequently found in biologically active compounds and pharmaceuticals. DMSO acted in this reaction not only as the solvent but also as a one-carbon bridge.

As one of the fundamentally important C–C bond construction method, the Mannich reaction has been widely utilized in the synthesis of natural products and pharmaceuticals.[1] So far, the classic three-component Mannich reaction remains an extremely valuable method and has been fueled by the ubiquitous nature of aimed nitrogen-containing β-amino ketones.[2] Other clever synthesis methods such as the oxidative two-component Mannich approach, have emerged as an important supplementary and provide access to ring-substituted β-amino ketones, which are not available by the classic Mannich approach.[3] Recently, the Seidel group disclosed a smart redox-neutral Mannich reaction using the same combination of starting materials, that is, a tertiary amine, an aldehyde and a ketone.[4] It is noteworthy that in the Seidel system, heterocyclic 2-acetylthiophene as a C–H acidic carbonyl compound was compatible. It is well known that heterocyclic compounds are highly important because of their abundance in numerous natural products and in medicinal chemistry.[5] For example, the five-membered thiophene-containing β-amino derivative Zyprexa was the world's top 200 ranking bestselling drug in 2012. Therefore, the synthesis of heterocycle-containing β-amino ketones is also of great pharmaceutical value.

Dimethyl sulfoxide (DMSO) is a byproduct of the wood industry. However, it has been used widely as a solvent in organic synthesis and in the pharmaceutical industry due to its rather low cost, relative stability, and low toxicity.[6] Particularly, this common polar solvent is increasingly used as a multipurpose building block accompanying with transition-metal-catalyzed C–H bond functionalization.[7] Recently, the groups of Zhang and Xiao realized *N*-methylation reactions between the N–H bonds of amidines and the methyl C(sp^3)–H bond of DMSO.[8] By contrast, the direct *N*-methylation reaction using DMSO as one carbon synthon has remained relatively undeveloped. Therefore, due to the increasing demand for sustainable methods in organic synthesis, we here present a novel oxidative C–S bond cleavage reaction of DMSO for dual formation of C–N and C–C bonds (Figure 1). In this reaction, various heterocycle-containing β-amino ketones were synthesized using DMSO as both solvent and one-carbon bridge. More importantly, the indispensable formaldehyde analogues in Mannich reactions can be replaced with the environmentally benign DMSO as one-carbon bridge in this procedure.

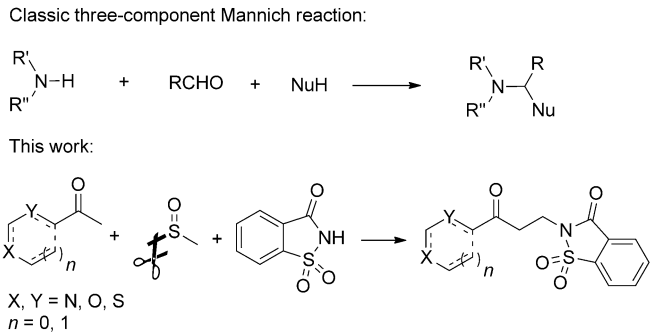

Figure 1. Three-component Mannich reaction.

In connection with our continued interest in C–N bond formation reactions,[9] we selected 1,2-benzisothiazole-3-one 1,1-dioxide (saccharin) as the imide source. Initially, we evaluated numerous reaction conditions for the direct coupling of acetophenone (**1a**) and saccharin (**2a**) using DMSO as the solvent and one carbon synthon. To our delight, we found that product **3a** can be obtained under transition-metal-free conditions in the presence of selectfluor at 80 °C, although the yield of **3a** was only 37% (Table 1, entry 1). Selectfluor was essential for the formation of the desired product; in its absence, product **3a** was not detected (Table 1, entry 2). Increasing the reaction

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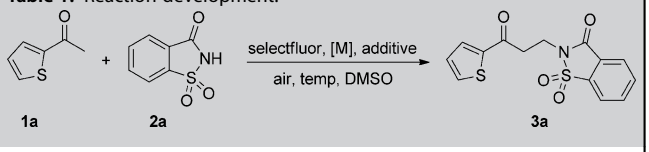
Table 1. Reaction development.[a]



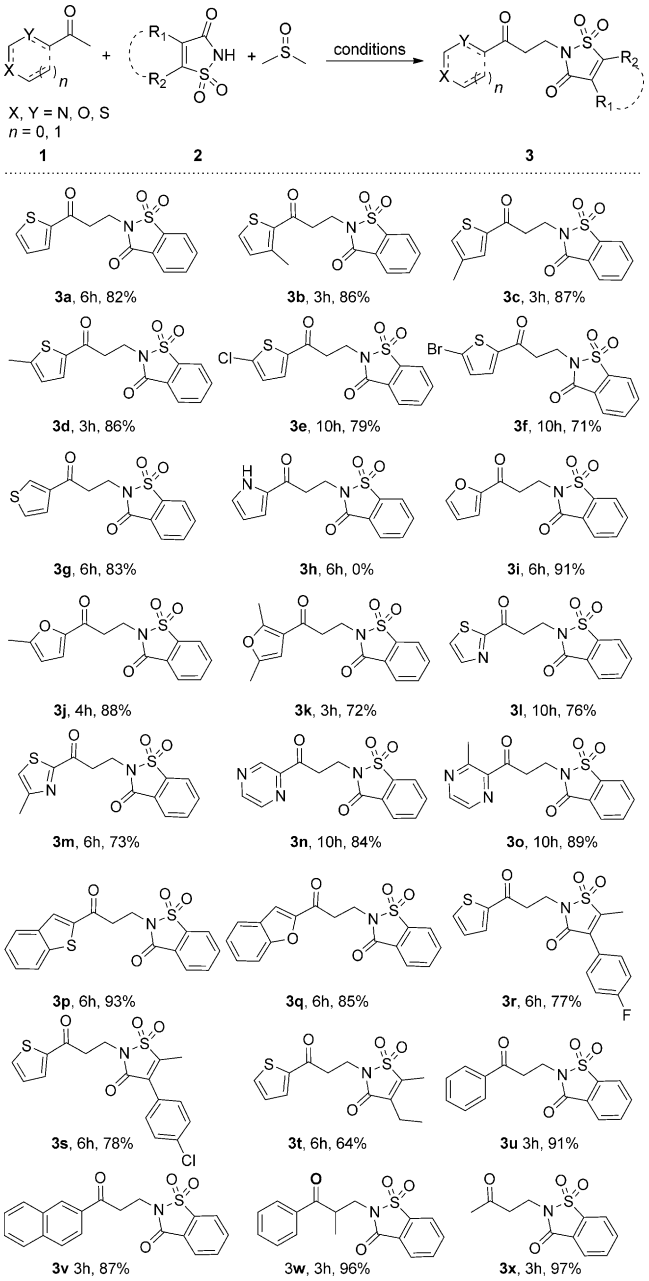
Entry	Metal salt	*T* °C	Additive	Yield[b] [%]
1	no	80	no	37
2	no	80	no	0
3	no	120	no	55
4	CuCl	120	no	41
5	$CuCl_2$	120	no	42
6	$Pd(OAc)_2$	120	no	63
7	$AgNO_3$	120	no	41
8	$FeCl_2$	120	no	22
9	$RuCl_3$	120	no	67
10	$RuCl_3$	120	K_2HPO_4	61
11	$RuCl_3$	120	Na_2CO_3	82
12	$RuCl_3$	120	KOAc	78
13	$RuCl_3$	120	CH_3COOH	42
14	$RuCl_3$	120	Na_2CO_3	63[c]

[a] Reaction conditions: **1a** (0.5 mmol), **2a** (1.0 mmol), metal salt (10 mol%), selectfluor (1.0 mmol), additive (1.0 mmol), and DMSO (2 mL) at 120 °C for 10 h. [b] Isolated products. [c] DMSO (2.5 mmol) and H_2O (2 mL) as the solvent.

temperature to 120 °C increased the yield of **3a** to 55% (Table 1, entry 3). In additional experiments, various metal salts were tested. The best result, 67% of **3a**, was obtained using $RuCl_3$ as the promoter (Table 1, entries 9). Other metal salts did not obviously affect the yield or gave **3a** in lower yields (Table 1, entries 4–8). Afterwards, various additives were tested, and Na_2CO_3 proved to be the best, giving the desired product **3a** in 82% yield (Table 1, entry 11). Further increases in the amount of Na_2CO_3 and variations in the amounts of selectfluor did not lead to a significant difference in the yield of **3a**. From the viewpoint of green chemistry, H_2O is a good choice as the solvent, although the yield of **3a** was only 63% (Table 1, entry 14).

With the optimized reaction conditions in hand, we determined the generality of the reaction with regard to acetyl heteroarenes (Scheme 1). The scope turned out to be broad. Various 2-acetylthiophene derivatives with substituents at the 3-, 4- and 5-position reacted smoothly, giving the corresponding β-amino ketones **3b–f** in good yields ranging from 71% to 87%. The electron-donating substituent –Me and electron-withdrawing halogen substituents (–Cl, –Br) did not affect the yields significantly. The reaction of 3-acetylthiophene also worked well and afforded the desired product **3g** in good yield. However, pyrrole, a very important heteroarene, was inactive under these conditions (Scheme 1, **3h**). Furthermore, numerous other heteroaromatics, including furan, thiazole, pyrazine, thianaphthene, benzofuran and their derivatives were tested, and all of them afforded the desired products in moderate to high yields (Scheme 1, **3i–q**).

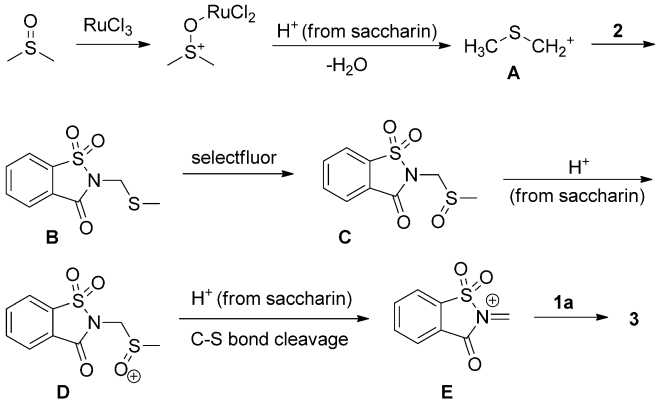
In fact, saccharin has been widely incorporated into a variety of biologically active compounds. The saccharin moiety has been identified as an important molecular component in various classes of 5HT1a antagonists,[10] human leukocyte elastase (HLE) inhibitors,[11] analgesics,[12] human mast cell tryptase inhibitors,[13] a1-a adrenergic receptor antagonists[14] and aldehyde dehydrogenase inhibitors.[15] Therefore, we used saccharin derivatives as an imide source for this Mannich reaction. Various saccharin derivatives with alkyl and aryl substituents on the isothiazol-3(2H)-one 1,1-dioxide were tested, and the desired products were obtained as shown in Scheme 1 (**3r**, **3s** and **3t**). It is worth mentioning that although heterocycle-containing β-amino ketones are of great pharmaceutical value, other aromatic ketones such as acetophenone **1u**, 1-(naphthalen-2-yl)ethanone **1v**, propiophenone **1w**, and aliphatic ace-



Scheme 1. Scope of acetyl heteroarenes. [a] Reaction conditions: **1** (0.5 mmol), **2** (1.0 mmol), $RuCl_3$ (0.05 mmol), selectfluor (1.0 mmol), Na_2CO_3 (1.0 mmol), and DMSO (2 mL) at 120 °C for 3–10 h. [b] Isolated yield.

tone **1x** were all effective substrates and gave the desired products in high yields (87–97%, **3u**–**x**).

Having established the scope of the method, we performed a preliminary study on the reaction mechanism. We supposed that the reaction between imine and DMSO, similar to the reaction between imine and formaldehyde, was the first step during this Mannich reaction. Therefore, the C(sp^3)–H imidated product 2-((methylsulfinyl)-methyl)benzo[*d*]isothiazol-3(2*H*)-one 1,1-dioxide **C** was prepared by the reaction between DMSO and saccharin [Eq. (1)]. To our delight, the stoichiometric reaction between 2-acetylthiophene **1a** and **C** worked well, and after 2 h, the desired product **3a** was obtained in 76% yield [Eq. (2)]. To gain more insight into the reaction mechanism, equimolar amounts of DMSO and [D_6]DMSO were added as the solvent. The observed isotope effect ($k_H/k_D = 4.0$) implies that the C–S bond cleavage of DMSO is involved in the rate-limiting step [Eq. (3)].[16] In addition, this result also shows that a keto–enol tautomerism of the ketone is involved during this reaction (see the Supporting Information). Based on these experimental results and to obey the classic Mannich reaction mechanism, a possible mechanism is proposed in Scheme 2 for the present catalytic recycle, although further mechanistic studies are needed. First, intermediate **A** would be formed by activation and dehydration under acidic conditions.[17] Subsequently, **A** would be intercepted by a nucleophilic imide to form intermediate **B**.[18] Under our conditions, intermediate **C** would be oxidized by selectfluor, and subsequently C–S bond cleavage in the presence of H^+ delivers the enamine intermediate **E**. Finally, carbon–carbon bond formation between **E** and the tautomer of the ketone delivers the desired product **3**.[19]



Scheme 2. Plausible catalytic cycle.

In summary, we have succeeded in developing an efficient method for the synthesis of heterocycle-containing β-amino ketones using DMSO as one-carbon bridge. More importantly, compared to the common Mannich reaction, DMSO may be an alternative to the indispensable formaldehyde analogues. Considering its excellent reaction efficiency and wide substrate scope, this strategy could be highly desirable for the convenient synthesis of hetercycle-containing β-amino ketone derivatives, which widely exist in natural products. A preliminary study on the reaction mechanism revealed that C–S bond cleavage of DMSO might be the rate-limiting step and that the role of DMSO is similar to that of formaldehyde in this Mannich reaction. Further mechanistic studies and synthetic applications of this transformation are ongoing in our laboratory.

Experimental Section

General Procedure: 1-(Thiophen-2-yl)ethanone **1a** (63.0 mg, 0.5 mmol), saccharin **2a** (183.0 mg, 1.0 mmol), $RuCl_3$ (10.3 mg, 0.05 mmol), selectfluor (354.2 mg, 1.0 mmol), and Na_2CO_3 (106.0 mg, 1.0 mmol) were added to DMSO (2 mL). The mixture was stirred at 120 °C for 3–10 h (monitored by TLC), quenched with water (10 mL), and extracted with dichloromethane (5×3 mL), and the organic layer was dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure, and the residue was purified by silica gel column chromatography (EtOAc/petroleum ether = 1:6) to give compound **3a** as a white solid (252.0 mg, 82%).

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Keywords: heterocycles · Mannich reaction · N-methylation · one-carbon synthon · β-amino ketones

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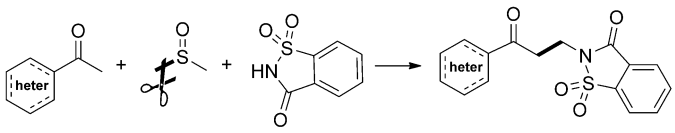

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Direct N-Methylation Reaction Using DMSO as One-Carbon Bridge: Convenient Access to Heterocycle-Containing β-Amino Ketones