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Some sulphur - containing double combination reagents

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Abstract Research and development of new reagents are very important for organic synthesis. In recent years, some new reagents with universal applicability have been reported, but new reagents of sulphur-containing are rarely reported. Wang's group has developed several new sulphur-containing reagents which are called as Wang reagents: Sodium dithionite - tert-Butyl hydroperoxide ($Na_2S_2O_4$-TBHP). The paper presents the reactions involved in the reagents obtaining and the associated mechanisms. $Na_2S_2O_4$-TBHP is a new reagent for selective oxidation of aromatic alcohols to aldehydes. Wang reagents have universal applicability in organic synthesis.

Keywords: reagents of sulfur-containing, Wang reagents, DMSO-I_2, DMSO-TsCl, $Na_2S_2O_4$-TBHP

1. Introduction

The in-depth researches of new organic reactions and the development of new chemical reagents are of great significance for organic synthetic chemistry. Discovering and developing new reagents is extremely important for expanding new methods of organic synthesis. New chemical reagents have important academic significance and scientific value for synthetic chemistry, which can provide new tools and help to broad range of chemists. New chemical reagents have universal applicability and could provide some solutions in chemical engineering sciences.

Gold-catalyzed domino reaction constitute a useful alternative to C–H functionalization for the synthesis of functionalized (hetero)arenes. *Ariafard* report computational studies on the gold-catalyzed cyclization alkynylation of keto-allenes with ethynylbenziodoxole (EBX) reagents, which identified a gold(I) picolinate complex as the active catalyst, giving the first mechanistic insights into this transformation. Gold-catalyzed domino cyclization–alkynylation reactions with EBX reagents is new method [1].

Grygorenko reported a new reagent for the Suzuki–Miyaura reaction, namely, 2,2-difluorovinyl pinacolborane (CF_2=CHBPin). New reagent (CF_2=CHBPin) is easy-to-handle high-boiling liquid with sufficient stability (no degradation was observed upon storage at +4°C for several months). The Pd(dppf)Cl_2-catalyzed reaction of this reagent with (het)aryl and vinyl bromides proved to be a versatile synthetic method providing a wide range of gem-difluorostyrenes, their heterocyclic analogues, as well as gem-difluorodiene [2].

Knochel developed a new preparation of benzylic zinc reagents via the fragmentation of sterically hindered homobenzylic zinc alcoholates. This method completely avoids the formation of Wurtz-byproducts [3].

Ando reported a new Julia-type methylenation reagent, 1-methyl-2-(methylsulfonyl)-benzimidazole, which can react with a variety of aldehydes and ketones in the presence of either NaHMDS (−55°C to rt) or *t*-BuOK to give the corresponding terminal alkenes in high yields under the mild reaction conditions [4].

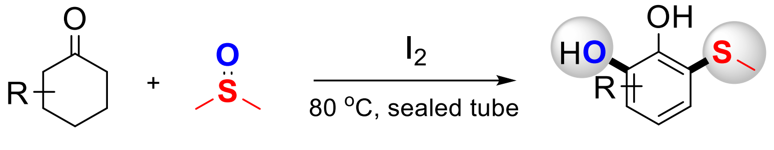
Espinet reported stannylated polynorbornenes as new reagents for a clean Stille reaction. The use of these polynorbornene reagents in the Stille coupling provides an easy reaction workup, better separation of the halostannylated products, and low content of tin in the coupling products [5].

2. Experimental results and discussions

2.1 DMSO-I_2 Reagent

DMSO-I_2 (A) is methyl thiolation and hydroxylation reaction reagent [6].

In the absence of any metal catalyst, the industrial chemicals cyclohexanone, under the action of I_2/DMSO reagent, introduced three functional groups in one step through the mechanism of iodization, oxidation, methylthiolation, aromatization, one stone and three birds, to obtain *o*-dihydroxy at the same time of methylthio, Fig. 1. DMSO serves as a methyl sulfide source, oxidant, and reaction solvent in this reaction. The reaction conditions are mild and the yield is high. The research achievement of professor Nai-Xing Wang's group was published in the core journal of organic chemistry: *Advanced Synthesis & Catalysis* (*Adv. Synth. Catal. 361*, p.3008, 2019).



☑ *Readily available reagents* ☑ *Transition metal-free*
☑ *Facile conditions / Scalabe* ☑ *Atom-economy / One-pot*
up to 84% yield

Fig. 1. Synthesis of Methylthio substituted Catechol.

In this study, the substrate has a wide range of applications. Both the electron donating substituents and electron withdrawing substituents on cyclohexanone can obtain methylthio substituted catechol compounds in medium to high yields. The yield can be further improved by adding additional dimethyl sulfide to the reaction system. The 22 products were characterized by NMR and HRMS.

Mechanism research has found that the addition of free radical trapping agents cannot quench the reaction, indicating that the reaction is not a free radical reaction but an ion reaction process. By adding tetrahydrothiophene, the intermediates generated during the reaction were successfully captured, and the reaction intermediate was confirmed by high-resolution mass spectrometry, Fig. 2.

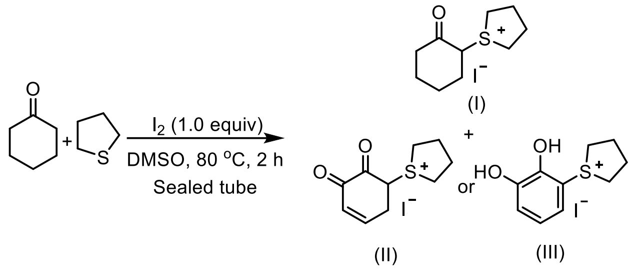


Fig. 2. Intermediate capture.

In terms of further application of the product, Wang used H_2O_2 as oxidant to obtain methyl sulfoxide substituted catechol in 98% high yield with methyl sulfoxide substituted Catechol catalyzed by rare earth catalyst $Sc(OTf)_3$, Fig. 3. This type of sulfoxide compound is an important precursor in organic synthesis.

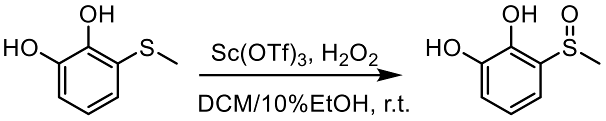


Fig. 3. Further application of the product.

DMSO-I_2 reagent (A) can mediate synthesis of methylthio substituted catechols via oxygenation, methylthiolation, dehydrogenation, and aromatization processes. Various cyclohexanones were smoothly converted to the corresponding products in moderate to good yields. Wang's reagent (A) DMSO-I_2 also provides an efficient way to produce sulfanylphenols.

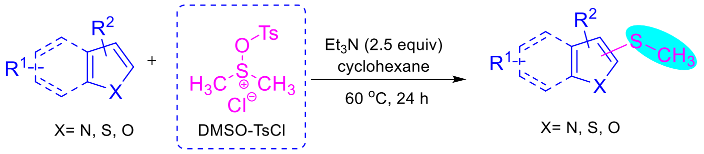
2.2 DMSO-TsCl Reagent

DMSO-TsCl reagent (B) is a heteroarene methylthiolation reagent [7].

Sulfides and their derivatives which are commonly found in many pharmaceuticals and agrochemicals exhibit important biological activities. Especially heteroaromatic sulfides and their derivatives play significant roles in medicinal chemistry and drug development. Additionally, heteroaromatic sulfides can be further transformed into thiols, sulfoxides, sulfones and applied to cross-coupling reaction.

Dimethyl sulfoxide (DMSO) is a readily available and less toxic polar solvent. During the past decades, it was reported as important precursors for many organic motifs such as -CH_3, -CHO, -CN -SMe, -SOMe and -SO_2Me. The previously reported methylthiolation used high amount of catalyst and harsh reaction conditions. The methylthiolation of furan, thiophene and pyrrole using DMSO-TsCl reagent was reported for the first time.

Professor Nai-Xing Wang's group at Technical Institute of Physics and Chemistry, Chinese Academy of Sciences, has developed a heteroarene methylthiolation reagent: DMSO-TsCl, Fig. 4. Not only methylthiolated indoles were abtained in high yield, five-membered heteroarenes such as pyrroles, furans and thiophenes were also give the desired products in moderate to good yields with excellent regioselectivity. And the yield up to 96% among more than 40 methylthiolated products.



♦Readily available reagents ♦ Facile conditions/Scalable
♦up to 96% yield ♦more than 40 examples

Fig. 4. Heteroarene methylthiolation reagent: DMSO-TsCl.

Based on the experimental results, a plausible mechanism was proposed for the reaction. DMSO was originally activated by TsCl to form DMSO-TsCl (A) and acted as the methylthiolation reagent of heteroarene, forming stable intermediate C, Fig. 5. The above key intermediates (A and C) involved in the mechanism were detected by HRMS, confirming the validity of the proposed mechanism.

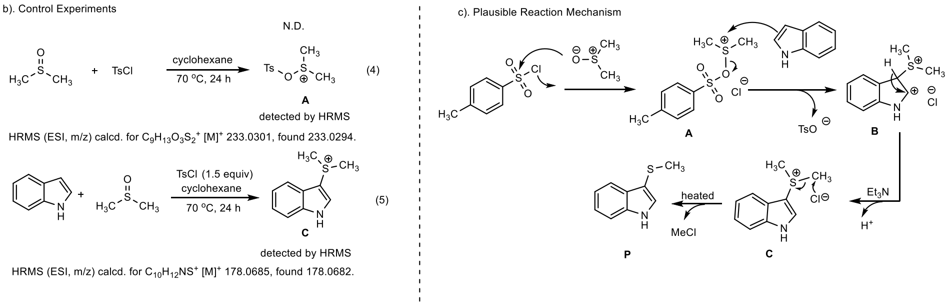


Fig. 5. Plausible mechanism for the reaction.

Wang's group also carried out gram-scale reaction (88% yield) and further derivatization of the methylthiolated product. The DMSO-TsCl reagent provides a practical and powerful methodology for the synthesis of useful heteroaromatic sulfides and other thioethers compounds. Wang's reagent (B) DMSO-TsCl is a good new tool for constructing C-S bonds in heteroarene compounds. This research achievement of professor Nai-Xing Wang's group was published in *Eur. J. Org. Chem.,* p.1446, 2021.

2.3 Wang's reagent: $Na_2S_2O_4$-TBHP

Wang's reagent (C) $Na_2S_2O_4$-TBHP is a new reagent for selective oxidation of aromatic alcohols to aldehydes [8].

Professor Nai-Xing Wang's research team of the Chinese Academy of Sciences has found and developed valuable new reagents $Na_2S_2O_4$-TBHP. Wang's group accidentally discovered this new reagent during the synthesis process of a novel coenzyme NADH model molecules. After expansion, it was found that multi substituted primary aryl alcohols and some heterocyclic primary alcohols can undergo this reaction producing to aldehydes with moderate or higher yields by $Na_2S_2O_4$-TBHP reagent. In 2016, after Wang's group published this new reagent $Na_2S_2O_4$-TBHP, China Science Daily reported this work on April 14, 2016. Afterwards, $Na_2S_2O_4$-TBHP also is called as Wang's reagent.

Nai-Xing Wang's group at Technical Institute of Physics and Chemistry, Chinese Academy of Sciences has discovered a new reagent: $Na_2S_2O_4$-TBHP, which can selectively oxidize primary alcohols to aldehydes. Wang's reagent $Na_2S_2O_4$-TBHP has the advantages of mild reaction conditions, high product yields, and convenient operation, Fig. 6.

The selective oxidation of alcohols into corresponding aldehyde compounds is a classic and challenging topic in organic chemistry. The traditional reactions for oxidizing primary alcohols to corresponding aldehyde compounds include the Swern reaction and the Dess Martin reaction. However, these classic methods not only generate a large amount of toxic and harmful waste, but also are not conducive to the post-treatment of reactants. Therefore, it is necessary to develop green controllable oxidants.

Wang's reagent $Na_2S_2O_4$-TBHP can efficiently convert primary aromatic alcohols into corresponding aromatic aldehydes at room temperature, which is green and environmentally friendly, and easy to operate with high yield. The selective oxidation of alcohols into corresponding aldehyde compounds is a classic and challenging topic in organic chemistry. The traditional reactions for oxidizing primary alcohols to corresponding aldehyde compounds include the Swern reaction and the Dess Martin reaction. However, these classic methods not only generate a large amount of toxic and harmful waste, but also are not conducive to the post-treatment of reactants. Therefore, it is necessary to develop green controllable oxidants.

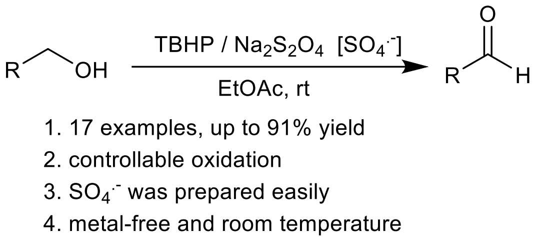


Fig. 6. Reagent $Na_2S_2O_4$-TBHP for selective oxidation of aromatic alcohols to aldehydes.

Wang’s reagent $Na_2S_2O_4$-TBHP can efficiently convert primary aromatic alcohols into corresponding aromatic aldehydes at room temperature, which is green and environmentally friendly, and easy to operate with high yield.

Nai-Xing Wang's group conducted in-depth research on the reaction process of selective oxidation of alcohols to aldehydes under this reagents $Na_2S_2O_4$-TBHP. Electron Paramagnetic Resonance (EPR) was used to confirm this reaction process through free radical intermediates. By using the common electron trapping agent DMPO (5,5-dimethyl-1-pyrroline-*N*-oxide) to capture the sulfate radical produced in the reaction, the EPR test for the reaction was carried out at room temperature.

Firstly, ethyl acetate was used as the reaction solvent, the capture agent DMPO was added to the reaction system, and the reaction solution was subjected to EPR testing at 5 minutes, 20 minutes, and 40 minutes respectively. Four sets of almost equal content quadruple signal peaks appeared in the EPR spectrum. According to relevant literature that has been reported, [9, 10], it can be effectively confirmed that SO_4^- was generated in the reaction system. Moreover, it can be clearly observed from the experimental results that the content of free radicals gradually increases with the extension of reaction time.

In addition, from the experimental results obtained by optimizing the reaction conditions, it was found that different reaction solvents would have a certain impact on this selective oxidation reaction. In addition, through other confirmatory experiments, such as adding free radical blockers BHT (2,6-di-tert-butyl-4-methylphenol) and TEMPO (2,2,6,6-tetramethylpiperidine oxide) to the reaction system, we found the reaction yield dropped. Replacing $Na_2S_2O_4$ in the $Na_2S_2O_4$-TBHP reagent with Na_2SO_4 to carry out this reaction, and also replacing the $Na_2S_2O_4$-TBHP reagent with $K_2S_2O_8$-TBHP, or using $K_2S_2O_8$ alone for confirmatory experiments. However, we found that the desired product could not be obtained. By testing the HRMS of reaction solution, all of the experiments further confirmed the existence of sulfate radicals in this reaction, Fig. 7.

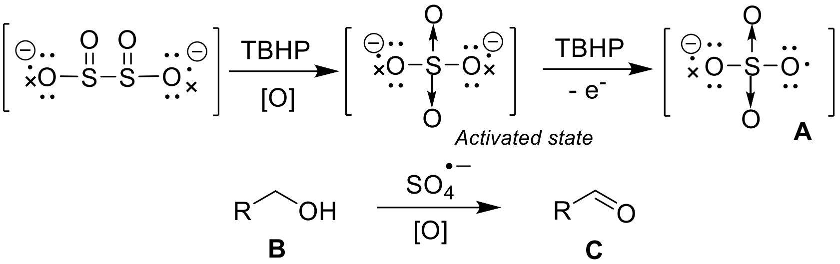


Fig. 7. Plausible reaction mechanism of the oxidation of aromatic alcohols to aldehydes.

A plausible reaction mechanism of the oxidation of aromatic alcohols to aldehydes is proposed. The reaction was performed in the presence of TBHP-$Na_2S_2O_4$ under N_2 atmosphere and the results showed that TBHP as the terminal oxidant in this reaction. Furthermore, the reaction yield dropped when radical inhibitor BHT (butylated hydroxytoluene) and TEMPO (2,2,6,6-tetramethylpiperidin-1-yloxyl) was added, respectively. It indicated that the reaction should undergo a radical oxidation process. A radical anion (A) (sulfate radical anion) could be generated by action of TBHP and $Na_2S_2O_4$ in this reaction. (A) was found to be an excellent controllable oxidant for oxidation of aromatic alcohols (B) to aldehydes (C) under this reaction conditions.

Nai-Xing Wang's group has developed a new sulfur-containing reagent $Na_2S_2O_4$-TBHP, which was called Wang's reagent (C), Wang's reagent (C) $Na_2S_2O_4$-TBHP was applied to oxidize various primary aromatic alcohols to corresponding aldehydes in good yields at room temperature. This Wang's reagent provides a new tool for alcohol controllable oxidation under mild conditions, and also could be used widely in general organic synthesis.

Mechanism research confirms that the generation of free radical anion SO_4^- is the key to the achievement of this $Na_2S_2O_4$-TBHP reagent.

3. Conclusion

Some sulfur-containing double combination reagents DMSO-I_2 and DMSO-TsCl were introduced herein, Wang's group has made great progress in applying DMSO-I_2 and DMSO-TsCl reagents. $Na_2S_2O_4$-TBHP is called as Wang reagent. Wang reagent, $Na_2S_2O_4$-TBHP, is a new reagent for selective oxidation of aromatic alcohols to aldehydes, which has universal applicability in organic synthesis.

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