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General and efficient one-pot synthesis of novel sugar/heterocyclic(aryl) 1,2-diketones from sugar terminal alkynes by Sonogashira/tetra-*n*- butylammonium permanganate oxidation

Fuyi Zhang [a,*], Xiaopei Wu [a], Liming Wang [a], Hong Liu [a,*], Yufen Zhao [a,b]

[a] The Key Lab of Chemical Biology and Organic Chemistry, The College of Chemistry and Molecular Engineering, Zhengzhou University, Zhengzhou, China
[b] College of Chemistry and Chemical Engineering, Xiamen University, Xiamen, China

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ABSTRACT

A new approach for one-pot synthesis of novel sugar/heterocyclic(aryl) 1,2-diketones has been achieved by the reaction of various sugar terminal alkynes with heterocyclic(aryl) iodides at room temperature. This one-pot protocol includes Sonogashira coupling and mild *n*-Bu_4NMnO_4 oxidation reaction. This method is mild, general and efficient. Fifty-six examples have been given and the sugar/heterocyclic(aryl) 1,2-diketones were obtained in 71–94% yields. The sugar terminal alkynes include 9 structurally different sugars in pyranose, furanose, and acyclic form which have various protecting groups, sensitive groups, and sterically bulky substituents. The heterocyclic(aryl) iodides include sterically bulky heterocyclic compounds and iodobenzenes with electron-donating, electron-neutral, and electron-withdrawing substituents.

1,2-Diketones are valuable building blocks widely used for the synthesis of various biologically active compounds,[1] such as imidazoles, quinoxalines, substituted indoles, and indolone-N-oxide.[2] They have also been used as starting material for the asymmetric synthesis of α-hydroxy ketones[3] and the synthesis of carboxylic acids.[4] Some 1,2-diketones show good antitumor activity[5] and interesting applications as photosensitive agents and photoinitiators.[6] Heteroaryl 1,2-diketones have potential biological activities and they are also precursors for the synthesis of biologically active compounds.[7] Synthetic methods for the preparation of 1,2-diketone have been documented.[8–10] Among them, the oxidation of various precursors such as methylene ketones[1d,9] and α-hydroxyketones or tautomeric 1,2-dihydroxyolefins[7a,b,d,10] is a useful approach. The direct oxidation of internal alkynes, which could be easily accessible via Sonogashira coupling[11] appears to be the most straightforward method to synthesize 1,2-diketone derivatives. Some oxidation systems have been employed for this type of transformation, which include DMSO-based oxidations,[12] transition-metal-catalyzed oxidations,[5,13] and ozonolysis.[14] However, these oxidation methods suffer from various drawbacks such as high temperature,[12] substrate limitations,[13] and complicated oxidative products. Because sugar alkynes have the fragile scaffolds and sensitive protecting groups which are intolerant of harsh reaction conditions, the existing protocols are not suitable for the synthesis of sugar 1,2-diketones. Hitherto no useful method is available for their syntheses. In view of the potential bioactivities and important synthetic applications of sugar 1,2-diketones, an efficient and general method for their syntheses is highly desirable.

We have been working on the synthesis of biologically active carbohydrate analogs[15] and *C*-substituted sugar analogs.[16] Herein we describe an efficient and general one-pot synthesis of novel sugar/heterocyclic(aryl) 1,2-diketones by the reaction of sugar terminal alkynes and heterocyclic(aryl) iodides under mild reaction conditions. In order to get a method tolerant of labile substrates as much as possible, the sterically hindered sugar alkyne **1a** (Scheme 1) prepared from D-galactose[17] with acid sensitive *cis*-isopropylidene next to ethynyl was employed to react with 2-iodo-5-methylthiophene as a model reaction. At the outset, the Sonogashira coupling and oxidation were carried out respectively to search for the optimal reaction conditions. In the study for Sonogashira coupling reaction, **2aa** was obtained in 93% yield using 1.1 equivalent of 2-iodo-5-methylthiophene, 1.0 equivalent of **1a**, 5 mol% of $Pd(PPh_3)_2Cl_2$ and CuI each. The reaction was complete within 1 h at rt in pure degassed Et_3N under argon. It was clean and the side product sugar diyne was not observed from TLC. Increasing temperature resulted in the diminished yield, probably due to the partial deprotection of isopropylidene in the presence of $Pd(PPh_3)_2Cl_2$ and CuI as Lewis acid. The change to the other solvents (such as CH_2Cl_2, THF, CH_3CN, and DMF) gave rise to the prolonged reaction time and slightly diminished yield.

* Corresponding authors. The Key Lab of Chemical Biology and Organic Chemistry, The College of Chemistry and Molecular Engineering, Zhengzhou University, Daxue Road 75, Zhengzhou 450052, China. Tel.: +86 371 67763845; fax: +86 371 67763845.
E-mail addresses: zhangfy@zzu.edu.cn (F. Zhang), liuh6@zzu.edu.cn (H. Liu).

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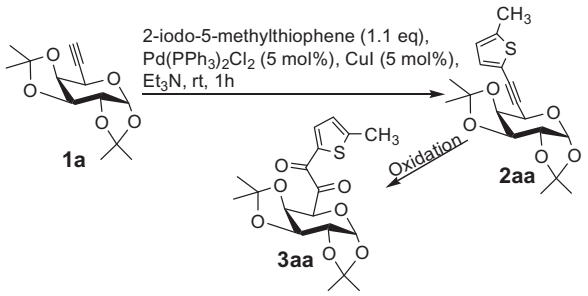

Scheme 1. Synthesis of **2aa** and **3aa** for their optimal reaction condition studies.

In the course of oxidation of **2aa** to sugar/heterocyclic 1,2-diketone **3aa**, several existing methods (such as NBS/DMSO,[12a] I_2/DMSO,[12d,e] $PdCl_2$/DMSO[5,13b]) for oxidizing internal alkyne were examined and no satisfactory result was obtained. This is because sensitive isopropylidenes are intolerant of the harsh oxidation conditions such as high temperature, and some reaction conditions are difficult to be controlled, giving rise to the cleavage of the triple bond. We turned our attention to permanganate. The oxidation of **2aa** by $KMnO_4$ was performed in acetone and H_2O at rt to give **3aa** in 32% yield (Table 1, entry 1). When 1.0 equivalent of $NaHCO_3$ was added to make the reaction in basic solution, it was finished within 13 min and **3aa** was obtained in 52% yield (entry 2). Then the oxidation was carried out using 3.0 equivalent of $KMnO_4$, 0.5 equivalent of $NaHCO_3$ and 2 equivalent of $MgSO_4$ in neutral H_2O/acetone solution. An increase in yield to 58% was obtained (entry 3). However, when the reaction was performed in weak acidic H_2O/acetone solution, only a trace of **3aa** was obtained (entry 4). TLC indicated the reaction was complicated. **3aa** appears to be unstable in basic or acidic water solution. The reaction was then carried out in CH_2Cl_2 using 1.0 equivalent of solid $KMnO_4$ and a catalytic amount of TBAB (*n*-Bu_4NBr) at rt. The oxidation was clean and a large increase in yield to 85% was obtained (entry 5). The reaction was subsequently improved by increasing the amount of TBAB. In the presence of 1.0 equivalent of TBAB, the oxidation was complete within 20 min and **3aa** was obtained in 90% yield (entry 6). When 3.0 equivalent of solid $KMnO_4$ and TBAB each were added to a solution of **2aa** in CH_2Cl_2, they dissolved rapidly and deep purple solution was formed. The oxidation time was reduced to 12 min and **3aa** was obtained in 94% yield (entry 7). Obviously, solid $KMnO_4$ in CH_2Cl_2 directly reacted with TBAB to give soluble *n*-Bu_4NMnO_4 and then oxidation took place, which was different from general phase-transfer catalytic processes. Next, we utilized 3.0 equivalent of newly prepared *n*-Bu_4NMnO_4[18] to repeat this procedure, which gave the similar result to the case of solid $KMnO_4$ and TBAB in situ (entry 8). The change of TBAB to TBAF, TBAC, and BTPB respectively gave rise to **3aa** in slightly diminished yields (entries 9–11). $RuCl_3{\cdot}3H_2O/NaIO_4$ oxidation system[19] was also examined (entries 12–13). The reaction was complete within 20 min using 4.0 equivalent of $NaIO_4$ at rt, but **3aa** was obtained in unsatisfactory yield. Increasing temperature resulted in the diminished yield. Thus, the best oxidation conditions were achieved using 3.0 equivalent of $KMnO_4$ and TBAB each in CH_2Cl_2 at rt, and **3aa** was attained in 94% yield.

Table 1
Oxidation of **2aa** to **3aa** for optimization of reaction conditions[a].

Entry	Oxidation system	Time (min)	Yield (%)[b]
1	$KMnO_4$ (3.0 eq), H_2O, acetone	30	32
2	$KMnO_4$ (3.0 eq), $NaHCO_3$ (1.0 eq), H_2O, acetone	13	52
3	$KMnO_4$ (3.0 eq), $NaHCO_3$ (0.5 eq), $MgSO_4$ (2.0 eq), H_2O, acetone	7	58
4	$KMnO_4$ (3.0 eq), NH_4Cl (2.0 eq), H_2O, acetone	15	Trace
5	$KMnO_4$ (1.0 eq), TBAB (cat. amount), CH_2Cl_2	53	85
6	$KMnO_4$ (1.0 eq), TBAB (1.0 eq), CH_2Cl_2	20	90
7	$KMnO_4$ (3.0 eq), TBAB (3.0 eq), CH_2Cl_2	12	94
8	*n*-Bu_4NMnO_4 (3.0 eq), CH_2Cl_2	13	92
9	$KMnO_4$ (3.0 eq), TBAF (3.0 eq), CH_2Cl_2	15	88
10	$KMnO_4$ (3.0 eq), TBAC (3.0 eq), CH_2Cl_2	13	86
11	$KMnO_4$ (3.0 eq), BTPB (3.0 eq), CH_2Cl_2	16	83
12	$RuCl_3{\cdot}3H_2O$ (0.05 eq), $NaIO_4$ (4.0 eq), H_2O (0.1 mL), CCl_4, MeCN	15	45
13	$RuCl_3{\cdot}3H_2O$ (0.1 eq), $NaIO_4$ (4.0 eq), TBAB (1.0 eq), H_2O, CCl_4	20	42

[a] Conditions: **1a** (0.5 mmol), H_2O (2 mL), acetone (4 mL), CH_2Cl_2 (5 mL), MeCN (2 mL), CCl_4 (1 mL), at rt.
TBAB = tetra-*n*-butylammonium bromide, TBAF = tetra-*n*-butylammonium fluoride, TBAC = tetra-*n*-butylammonium chloride, BTPB = *n*-butyltriphenylphosphonium bromide.
[b] Isolated yield.

After the optimal conditions were obtained, Sonogashira coupling and oxidation were successfully performed in one pot. A mixture of **1a**, 2-iodo-5-methylthiophene, $Pd(PPh_3)_2Cl_2$, CuI and degassed Et_3N was stirred at rt until TLC indicated the complete conversion of **1a**. The mixture was evaporated to remove Et_3N and treated with $KMnO_4$ and TBAB in CH_2Cl_2 at rt to give **3aa** in 86% yield (Table 2, entry 1). Then we extended the scope of iodides, and sterically bulky 2-iodobenzo[*b*]thiophene, 2-iodobenzo[*b*]furan and aryl iodides with various substituents were employed to react with **1a**. All the reactions proceeded smoothly and the corresponding products **3ab**–**3ah** were obtained in good to excellent yields (entry 1). Aryl iodides are superior to heterocyclic iodides and the desired products were given in higher yields. Aryl iodide with an electron-donating substituent gave a slightly higher yield than that with an electron-neutral or electron-withdrawing one.

To examine the scope and generality of this method and to synthesize more sugar/heterocyclic(aryl) 1,2-diketones further, various sugar terminal alkynes **1b**–**1e**,[17,20a] **1f**,[20b] **1g**,[17,20a] **1h**,[20c,d,e] **1i**,[20d,e,f] (Table 2, entries 2–9) in pyranose, furanose, and acyclic form prepared from natural sugars with various protecting groups and different steric hindrance were used to react with various heterocyclic(aryl) iodides. The results were also summarized in Table 2. The benzyl protected pyranoside alkyne **1b** from D-glucose gave the desired products **3ba**–**3be** in 71–89% yields (entry 2). The D-fructose derived pyranoside alkyne **1c** reacting with substituted aryl iodides gave the corresponding sugar/aryl 1,2-diketones **3ca**–**3ce** in 88–93% yields (entry 3). After investigation of the cases of pyranoside alkynes, we utilized various terminal furanoside alkynes with different steric hindrance to test this synthetic method (entries 4–7). These alkynes include **1d** having *trans*-isopropylidene and *cis*-methoxy to ethynyl, **1e** and **1f** having *cis*-isopropylidene and *trans*-methoxy and none-methoxy to ethynyl respectively, and **1g** with *cis*-benzyloxy and *trans*-isopropylidene to ethynyl. Their reactions with various heterocyclic(aryl) iodides were clean and very efficient. The twenty-nine desired products were obtained in 78–94% yields. The reaction with aryl iodide having an electron-donating substituent gave a slightly higher yield than that with an electron-neutral or electron-withdrawing one. This is the same as the case of pyranoside alkyne. Next, we changed substrates to acyclic sugar alkynes. The reaction of **1h** with substituted aryl iodides gave the desired sugar/aryl 1,2-diketones **3ha**–**3hc** in 86–87% yields (entry 8). When **1i** was employed to react with 2-iodobenzo[*b*]furan, the desired product **3ia** was obtained in 80% yield (entry 9). The reaction with substituted aryl iodides gave the sugar/aryl 1,2-diketones **3ib**–**3if** in 86–92% yields. All the new compounds were characterized by ^1H NMR, ^{13}C NMR, DEPT-135, 2D NMR, HRMS and IR.

Novel synthesis of sugar/heterocyclic(aryl) 1,2-diketones has been developed from sugar terminal alkynes and heterocyclic(aryl) iodides at rt. The method has several advantages such as one-pot operation, broad substrate scope, mild reaction conditions, and good functionality compatibility. Fifty-six examples have been given and