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An Efficient Synthesis of Novel Fused Cycloheptatrienes through Mn(II)-Mediated Formal Intermolecular [2 + 2 + 2 + 1] Cycloaddition

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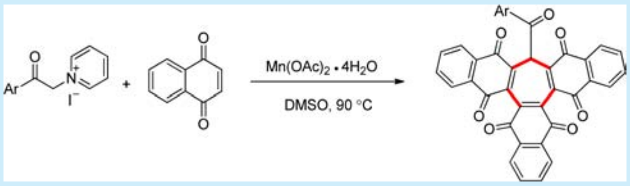
Supporting Information

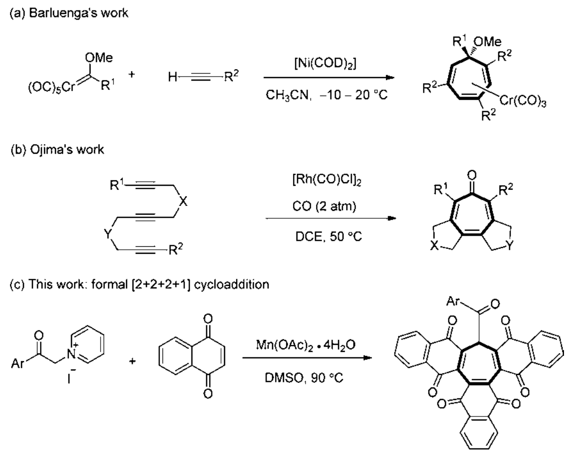
ABSTRACT: A new method for manganous acetate tetrahydrate mediated formal intermolecular [2 + 2 + 2 + 1] cycloaddition was developed for the synthesis of fused cycloheptatriene derivatives from *N*-(acylmethyl)pyridinium iodides and naphthoquinone. This method provides an innovative route for the efficient and convenient construction of fused seven-membered carbocycles from simple starting materials.



The development of new strategies for the synthesis of biologically active compounds, natural products, and non-natural products with interesting molecular structures is of great importance in organic chemistry.[1] Much effort has therefore been devoted to this activity, and considerable advances have been made in the development of cycloaddition reactions.[2,10c] Cycloaddition is widely regarded as one of the most efficient means for the construction of cyclic compounds on account of its ability to form at least two bonds in one operation.[3] The transition-metal-catalyzed cycloaddition reactions are the most useful processes for the rapid construction of a complex ring system.[4,10] Various transition metals have been commonly used to promote these processes, such as nickel, ruthenium, cobalt, rhodium, palladium, and so on.[5,10c]

Trimeric naphthoquinone derivatives have widely existed in various natural products and pharmaceutical molecules, which exhibited good biological activity. For example, conocurvone shows good HIV-inhibitory activity;[6] cyclotrisjugnone has been used to treat cardiovascular disease;[7] and trimeric compound **5**, as an organic pigment and vat dye, has wide applications in organic materials (Figure 1).[8] Therefore, it is very intresting and useful for the efficient construction of trimeric analogue **3** by cycloadditions. Among the various types of cycloadditions, the [2 + 2 + 2 + 1] cycloaddition is rarely reported for the synthesis of cycloheptatriene derivatives, since it is a higher self-sequential process than others.[10b−e] In 2003, Barluenga's group reported a novel nickel-mediated [2 + 2 + 2 + 1] cyclization for the construction of the cycloheptatriene chromium complexes by the reaction of Fischer carbene complexes and alkynes (Scheme 1a).[9] Ojima and co-workers subsequently reported a novel Rh-catalyzed intramolecular [2 + 2 + 2 + 1] cycloaddition reaction for the synthesis of fused tropones from triyne substrates and CO (Scheme 1b).[10] Herein, a Mn(II)-mediated formal intermolecular [2 + 2 + 2 + 1] cycloaddition reaction is described for the efficient construction of novel fused cycloheptatriene derivatives from easily available *N*-(acylmethyl)pyridinium iodides and naphthoquinone (Scheme 1c). This new formal [2 + 2 + 2 + 1] cycloaddition provides a

Scheme 1. Protocols for [2 + 2 + 2 + 1] Cycloaddition Reactions



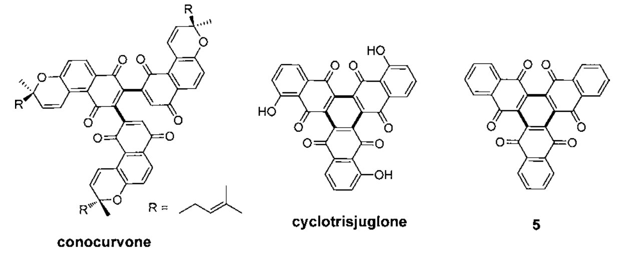


Figure 1. Examples of trimeric naphthoquinone derivatives.

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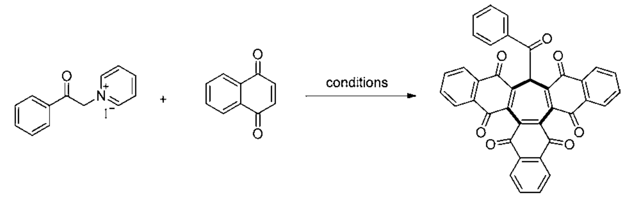
powerful method for the convenient synthesis of complex fused seven-membered ring systems. To the best of our knowledge, this is the first report on the use of transition-metal manganese(II) as a promoter for a formal cycloaddition reaction.

Initially, the reaction of *N*-phenacylpyridinium iodide (**1a**) and naphthoquinone (**2a**) was explored under the conditions shown in Table 1. Interestingly, the desired product **3aa** was obtained in 45% yield when the reaction was performed in DMSO at 90 °C for 18 h without any additives (Table 1, entry 1). The influence of acid and base in the reaction was subsequently examined. HOAc and TFA were shown to have little significant effect on the reaction (entries 2 and 3). Moreover, the desired product was not detected in the presence of K_2CO_3 or Cs_2CO_3 (entries 4 and 5). The effect of additives was then examined in the reaction. To our delight, $Mn(OAc)_2\cdot 4H_2O$, $Co(OAc)_2\cdot 4H_2O$, and $Pd(OAc)_2$ were all found to promote the reaction in varying degrees. $Mn(OAc)_2\cdot 4H_2O$ was the most effective one, and the product was obtained in 85% yield (entry 14). Other additives, such as $CrCl_3\cdot 4H_2O$, $FeCl_3$, $Ni(NO_3)_2\cdot 6H_2O$, $Cu(OAc)_2\cdot H_2O$, $ZnCl_2$, and $AgNO_3$, were found to be ineffective for the reaction (entries 6–7, 9–11, and 13). Next, the influences of temperature and additive quantitiies were investigated. The yield was not improved with increases or decreases in the amount of $Mn(OAc)_2\cdot 4H_2O$ (entries 15 and 16). Moreover, yields were decreased when the reaction was performed at a lower or higher temperature (entries 17 and 18). The screening of various solvents revealed that the choice of solvent had great influence on the reaction (entries 19–22). Surprisingly, DMSO was identified as the only solvent so far suitable for the formation of **3aa** (entry 14). The desired product was not obtained with other solvents (C_2H_5OH, THF, DMF, and toluene) (entries 19–22).

Table 1. Optimization of the Reaction Conditions[a]



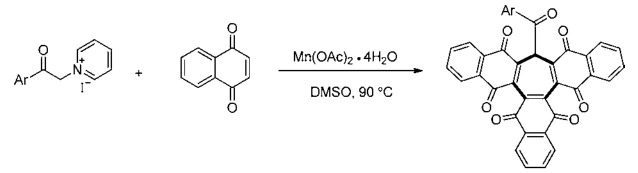
1a **2a** **3aa**

entry	solvent	addictive	temp (°C)	yield (%)[b]
1	DMSO	–	90	45
2	DMSO	HOAc	90	41
3	DMSO	TFA	90	38
4	DMSO	K_2CO_3	90	0
5	DMSO	Cs_2CO_3	90	0
6	DMSO	$CrCl_3\cdot 6H_2O$	90	40
7	DMSO	$FeCl_3$	90	42
8	DMSO	$Co(OAc)_2\cdot 4H_2O$	90	78
9	DMSO	$Ni(NO_3)_2\cdot 6H_2O$	90	47
10	DMSO	$Cu(OAc)_2\cdot H_2O$	90	20
11	DMSO	$ZnCl_2$	90	48
12	DMSO	$Pd(OAc)_2$	90	82
13	DMSO	$AgNO_3$	90	35
14	**DMSO**	$\mathbf{Mn(OAc)_2\cdot 4H_2O}$	**90**	**85**
15	DMSO	$Mn(OAc)_2\cdot 4H_2O$	90	66[c]
16	DMSO	$Mn(OAc)_2\cdot 4H_2O$	90	84[d]
17	DMSO	$Mn(OAc)_2\cdot 4H_2O$	80	78
18	DMSO	$Mn(OAc)_2\cdot 4H_2O$	100	83
19	C_2H_5OH	$Mn(OAc)_2\cdot 4H_2O$	78	0
20	THF	$Mn(OAc)_2\cdot 4H_2O$	66	0
21	DMF	$Mn(OAc)_2\cdot 4H_2O$	90	0
22	Toluene	$Mn(OAc)_2\cdot 4H_2O$	90	0

[a] Reaction conditions: **1a** (0.1 mmol, 1.0 equiv), **2a** (0.3 mmol, 3.0 equiv), addictive (0.05 mmol, 0.5 equiv), and solvent (2 mL) for 18 h. [b] Isolated yields. [c] 0.3 equiv of $Mn(OAc)_2\cdot 4H_2O$ was used. [d] The amount of $Mn(OAc)_2\cdot 4H_2O$ was 1.0 equiv.

With the optimized conditions in hand, the scope of the reaction was further investigated, as shown in Table 2. To our delight, various *N*-(acylmethyl)pyridinium iodides **1** proceeded smoothly to afford the corresponding products in good to excellent yields (64–86%), regardless of their electronic or steric properties. Moreover, electron-neutral (H, 4-Me), electron-donating (3-OMe, 4-OMe, 3,4-2OMe, 3,4-2OCH_2), and electron-withdrawing (4-NO_2) substrates attached to the benzene ring were smoothly transformed into their corresponding products in good to excellent yields (64–86%; entries 1–7). Much to our satisfaction, good yields were also obtained for halo-substituted substrates (68–76%; entries 8–12). Heteroaryl groups were also investigated. Unfortunately, the desired product was not detected with 2-furyl as the substituted group (entry13). However, the 2-thienyl substituted substrate proceeded to obtain the target product in 81% yield (entry 14). In addition, even when the substrate contained a sterically hindered 2-naphthyl group, the corresponding product was obtained in 75% yield (entry15). The structure of **3ia** was further determined by X-ray crystallographic analysis (see Supporting Information (SI)).

Table 2. Synthesis of Fused Cycloheptatriene Derivatives[a]



1 **2a** **3**

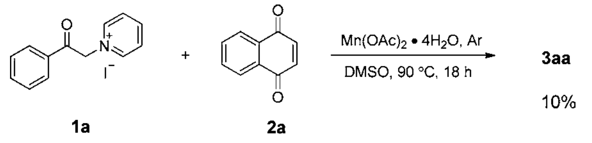
entry	Ar	product	yield (%)[b]
1	Ph	**3aa**	85
2	4-MeC_6H_4	**3ba**	86
3	3-$MeOC_6H_4$	**3ca**	72
4	4-$MeOC_6H_4$	**3da**	75
5	3,4-$(MeO)_2C_6H_3$	**3ea**	65
6	3,4-$(CH_2O)_2C_6H_3$	**3fa**	71
7	4-$NO_2C_6H_4$	**3ga**	64
8	2-ClC_6H_4	**3ha**	73
9	4-ClC_6H_4	**3ia**	76
10	2,4-$Cl_2C_6H_3$	**3ja**	71
11	3-BrC_6H_4	**3ka**	68
12	4-BrC_6H_4	**3la**	74
13	2-furyl	**3ma**	0
14	2-thienyl	**3na**	81
15	2-naphthyl	**3oa**	75

[a] Reaction conditions: *N*-(acylmethyl)pyridinium iodides **1** (1.0 mmol, 1.0 equiv) with naphthoquinone **2a** (3.0 mmol, 3.0 equiv) and $Mn(OAc)_2\cdot 4H_2O$ (0.5 mmol, 0.5 equiv) was stirred in DMSO (20 mL) at 90 °C for 18 h. [b] Isolated yields.

We next investigated the scope of quinones in the standard conditions. To our disappointment, when 1,4-benzoquinone, juglone, and 1,4-anthracenedione were employed, their corresponding products were not afforded. The reason may be the difficulty in forming the corresponding trimeric intermediate, due to the intramolecular hydrogen bond, solubility, and other factors of quinones.

To gain an insight into the reaction mechanism, a control experiment was performed (Scheme 2). When the reaction was carried out under an argon atmosphere, **3aa** was afforded only in 10% yield. The result clearly shows that air is playing a vital role in this reaction.

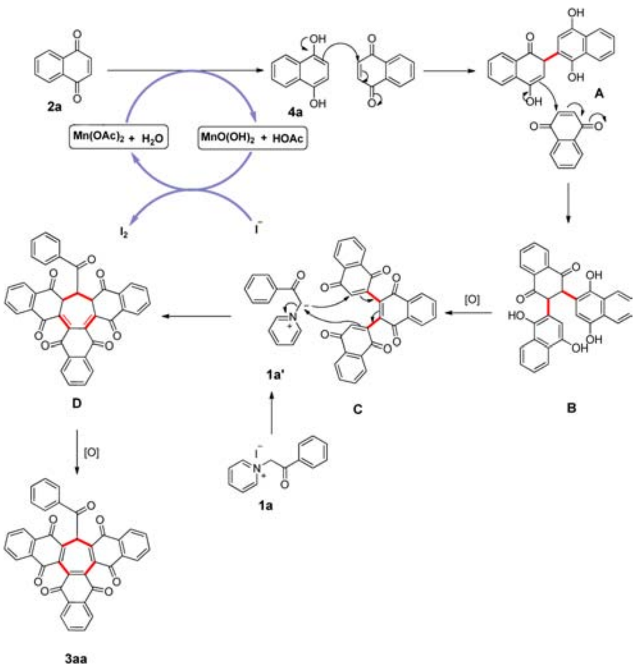
Scheme 2. Control Experiment[a]



[a]Isolated yields.

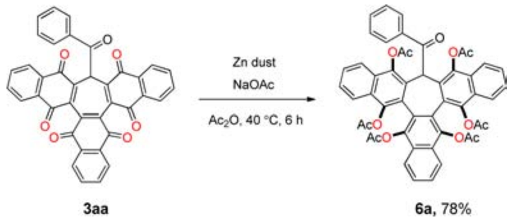
On the basis of the results described above, a plausible mechanism is proposed as outlined in Scheme 3 (**3aa** as example). Initially, naphthoquinone **2a** is reduced by manganous acetate to form 1,4-naphthalenediol **4a**. At the same time, the dihydroxy(oxo)manganese and acetate acid are generated in the process, which trigger the oxidation of iodide ions to iodine.[11] The 1,4-naphthalenediol **4a** easily reacts with **2a** to form the dimeric intermediate A via a Michael addition,[12d,e] which subsequently reacts with another molecule of **2a** via another Michael addition to afford the trimeric intermediate **B**.[12e] Then, the intermediate **B** is oxidized to another trimeric intermediate **C**.[12] (Intermedate **C** was detected by MS: see the SI). Next, **1a** is converted to the *N*-phenacylpyridinium ylide (**1a′**),[13] which reacts with **C** via a cyclocondensation reaction leading to the intermediate **D**. Finally, the intermediate **D** is oxidized by air leading to the desired product **3aa** (see SI).

Scheme 3. A Plausible Mechanism



We further explored the facile acetylation of products (**3aa** as example), shown in Scheme 4. We expect that these acetylated derivatives could have potential applications in medicine or materials chemistry. The product **3aa** readily underwent reductive acetylation[6] to give a peracetylated derivative **6a** in 78% yield with NaOAc and Zn dust in acetic anhydride at 40 °C for 6 h.

Scheme 4. Acetylation of Trimeric Derivatives[a]



[a]Reaction conditions: **3aa** (1.0 mmol, 587 mg) with Zn dust (25.0 mmol, 1.625 g) and NaOAc (25.0 mmol, 2.05 g) was stirred in Ac_2O (15 mL) at 40 °C for 6 h. Isolated yields.

In conclusion, a novel Mn(II)-mediated formal intermolecular [2 + 2 + 2 + 1] cycloaddition reaction has been developed for the construction of fused cycloheptatriene derivatives. This transformation provides a direct and efficient method for the construction of seven-membered carbocyclic rings from easily available *N*-(acylmethyl)pyridinium iodides and naphthoquinone under mild conditions. Further investigations into the mechanism and applications of this reaction are currently underway in our laboratory.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental procedures, product characterization, crystallographic data, and copies of the ^1H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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