Nazarov Reaction

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1,4-Diketones from Cross-Conjugated Dienones: Potassium Permanganate-Interrupted Nazarov Reaction**

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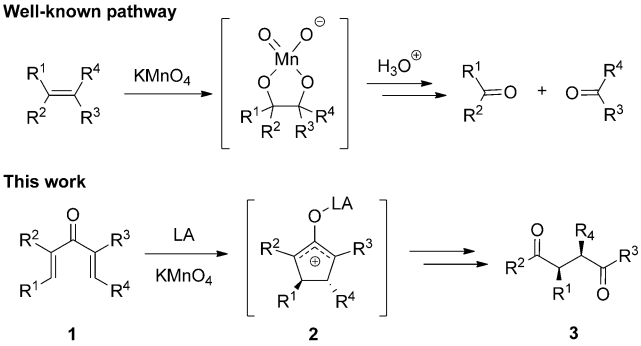
Abstract: *A domino potassium permanganate-interrupted Nazarov reaction to yield syn-2,3-disubstituted 1,4-diketones via a decarbonylative cleavage of the Nazarov oxyallyl intermediate, believed to be without precedent, is presented. This process allows syn substituents to be established stereospecifically on the 2-carbon bridge connecting the ketone carbonyl carbons, and the formation of one carbon–carbon and two carbon–oxygen bonds. Two carbon–carbon bonds are cleaved in this process.*

There has been considerable development in the Nazarov reaction[1,2] over the past two decades, particularly in the exploration of alternative substrates,[3] catalytic asymmetric variants,[4] skeletal rearrangement,[5] and domino/cascade processes[6] involving the Nazarov intermediate. The latter approach (interrupted Nazarov reaction) entails trapping the oxyallyl cation intermediate with a variety of π nucleophiles such as electron-rich arenes and enol derivatives or σ nucleophiles from organoaluminum reagents.[7] Additionally, [4+3], [3+3], and [2+3] cycloadditions on the Nazarov intermediates to afford bridged bicyclic ring systems have been studied.[6a,b,g,h,j] To date, the synthetic utilities of the Nazarov reaction and the interrupted Nazarov reaction have been limited to the formation of cyclopentanones and their derivatives.

Carbon–carbon bond cleavage is an important process in synthetic organic chemistry.[8] Along with ozonolysis, a well-known classical C−C bond cleaving reaction is potassium permanganate oxidation of alkenes and oxidative cleavage of the resulting diols under acidic conditions.[9] Considering the high oxidizing potential of permanganate, we were curious to see if permanganate could intercept the intrinsically electrophilic oxyallyl cation intermediate via a [3+3] cycloaddition. We envisioned the formation of α,α′-dihydroxycyclopentanones, or further oxidation to the decarbonylated 1,4-diketone products (Scheme 1). We were particularly interested in the potential transformation to 1,4 diketones because they are widely used as synthetic building blocks to construct heterocyclic 5-membered rings.[10]



Scheme 1. Use of potassium permanganate in the Nazarov cyclization.

With a goal of probing the proposed reactivity of permanganate in the Nazarov reaction, we embarked on screening reaction conditions (Table 1). As a control experiment, dienone **1a** was treated with $KMnO_4$, and stirred for 18 h in dichloromethane. Direct oxidation of **1a** was not observed in this case and starting material was fully recovered (entry 1). This result demonstrated that premature oxidation of the starting dienone could be avoided. In anticipation of the need for various additives to aid in solubilizing the $KMnO_4$, moisture sensitive Lewis acids were excluded from the screening conditions. Initial attempts at using $FeCl_3{\cdot}6\,H_2O$ resulted in the formation of *syn*-2,3-disubstituted 1,4-diketone **3a** with an 11% isolated yield (entry 2). To the best of our knowledge, this degradative transformation has no precedent. The relative configuration of **3a** was determined by single-crystal X-ray diffraction analysis.[11] The *syn* relative configurations of the other diketone products were assigned by analogy to **3a**.

Efforts to enhance the dissolution of permanganate in the reaction mixture and promote higher yields produced two conditions that were investigated further due to similar yields of **3a** (entries 7 and 9). When methanol was used as the solvent (entry 7), side products incorporating a methoxide group were observed by ^{1}H NMR analysis. Therefore, we decided to further investigate conditions involving dichloromethane, $FeCl_3{\cdot}6\,H_2O$, and a phase transfer catalyst, $BnNEt_3Cl$. However, the addition of substoichiometric amounts of $BnNEt_3Cl$ resulted in a reduced yield of **3a** despite full consumption of the starting material **1a** (entry 10). A solvent screening process was then used to determine if a two-solvent system would be more effective. It was found that treating **1a** with 1.5 equiv $FeCl_3{\cdot}6H_2O$ and 2.5 equiv $KMnO_4$ in a 2:1 mixture of CH_2Cl_2/CH_3CN at low temperature (entry 14) furnished 71% yield of **3a**. Additionally, when 18-crown-6 was used as the additive, the solubility

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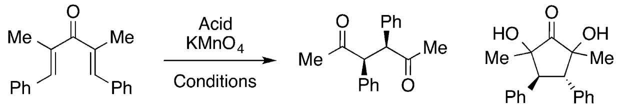
Table 1: Screening conditions for the $KMnO_4$-interrupted Nazarov reaction.[a]



1a **3a** (not found)

No.	Acid [equiv]	$KMnO_4$ [equiv]	Solvent	Temp. [°C]	Yield of **3a** [%][b]
1	none	2	CH_2Cl_2	rt[c]	no rxn
2	1.2 $FeCl_3{\cdot}6H_2O$	2	CH_2Cl_2	rt[d]	11
3	1.2 $FeCl_3{\cdot}6H_2O$	2	MeOH	rt	no rxn
4	0.2 $Sc(OTf)_3$	2	MeOH	rt	no rxn
5	excess HCl	2	CH_2Cl_2	rt	NA[e]
6	excess HCl	2	CH_3CN	rt[j]	NA[e]
7	excess HCl	2	MeOH	rt	28
8	H_2SO_4	2	CH_2Cl_2	rt	NA[e]
9	1.2 $FeCl_3{\cdot}6H_2O$	3	CH_2Cl_2/additive[f]	rt	31
10	1.2 $FeCl_3{\cdot}6H_2O$	3	CH_2Cl_2/additive[g]	rt	22
11	1.2 $FeCl_3$	3	CH_2Cl_2/additive[f]	rt	NA[e]
12	1.2 $FeCl_3{\cdot}6H_2O$	3	CH_3CN	rt[c]	trace[h]
13	1.2 $FeCl_3{\cdot}6H_2O$	3	CH_2Cl_2/CH_3CN[i]	rt	49
14	**1.5 $FeCl_3{\cdot}6H_2O$**	**2.5**	**CH_2Cl_2/CH_3CN[i]**	**−15 to rt**	**71**
15	1.5 $FeCl_3{\cdot}6H_2O$	2.5	CH_2Cl_2/additive[k]	−15 to rt	trace[h]

[a] Standard reaction time was 4 h unless otherwise noted. [b] Isolated yield. [c] Reaction mixture was stirred 18 h. [d] Reaction mixture was stirred 14 h. [e] **1a** was fully consumed, but **3a** was not found in a complex mixture. [f] $BnNEt_3Cl$ (0.2 equiv) was added to dissolve $KMnO_4$. [g] $BnNEt_3Cl$ (0.4 equiv) was added. [h] Starting material was present with a trace amount of **3a**. [i] 2:1 v/v ratio [j] Reaction time was 30 min. [k] 18-crown-6 (0.2 equiv) was added.

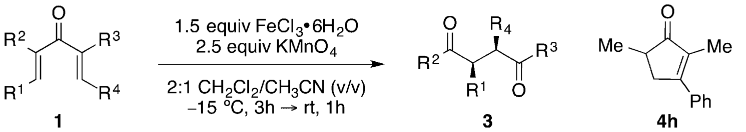
of $KMnO_4$ increased in dichloromethane, but only trace amounts of **3a** were observed (entry 15).

To investigate the substrate scope of this reaction, a series of substituted dienone Nazarov substrates was prepared (in one step from 3-pentanone or two steps from the corresponding enones via aldol condensations). First, symmetrical divinyl ketones were tested using the optimal conditions discovered during the initial screening process (Table 2). Dienone **1b** afforded 1,4-diketone **3b** in good yield (60%). Under these oxidizing conditions, we observed that **1c**, bearing an electron-rich arene, was converted to **3c** with a reduced yield (26%). Maintaining the reaction temperature at −15 °C was necessary to obtain a higher yield (45%) in this case. Compound **1d** containing heteroaromatic substituents was converted to **3d** in low yield (17%). Substrates such as **3c**,**d** bearing electron-rich β substituents have previously undergone efficient interrupted Nazarov reaction,[7] so the low yields in this case are likely due to competing C=C oxidative cleavage by permanganate, a process that has previously been observed with enones.[12] These reaction conditions were not applicable to substrate **1e**, containing aliphatic substituents, and no desired product was formed. Other acid activators (TMSOTf, $TiCl_4$, or HCl) and exposure to room temperature failed to effect conversion of **1e** to **3e**.

Unsymmetrically substituted dienones (**1f**–**1j**) did undergo the permanganate-interrupted Nazarov reaction. Adding a larger substituent at the C-5 position of dienone **1f** furnished **3f** in 52% yield. Notably, this product was isolated as a mixture of atropisomers, presumably as a result of the higher rotational energy barrier. Substrate **1g**, differing from **1a** in the substitution of the methyl group with a propyl group at C-4, provided **3g** in good yield (66%). Substrate **1h**, lacking a substituent at the C-1 position, was transformed into an α-substituted 1,4-diketone **3h** in moderate yield (44%). In this case, cyclopentenone **4h** was isolated as a side product in 16% yield. The incompatibility of electron-rich arenes with these conditions (e.g., entries 3 and 4) is supported by the lower yield in the conversion of **1j** to **3j** (entry 10) as compared with structurally similar **1i**→**3i**, differing only in the absence of a 4-methoxy group on the arene.

As this process involves scission of two carbon–carbon bonds, any mechanistic scheme must involve multiple oxidation events, a postulate supported by the requirement of at least 2 equiv of $KMnO_4$. In the absence of any relevant mechanistic precedent for this type of transformation, we have considered two possible mechanisms, either of which requires 2 equiv of $KMnO_4$ (Scheme 2). Nucleophilic trapping of the oxyallyl cation intermediate by permanganate anion after the 4π electrocyclization would afford an electron-rich enolate intermediate (Mechanism A). The resulting enolate could then be oxidized by second equivalent of permanganate to cleave a carbon–carbon bond, resulting in

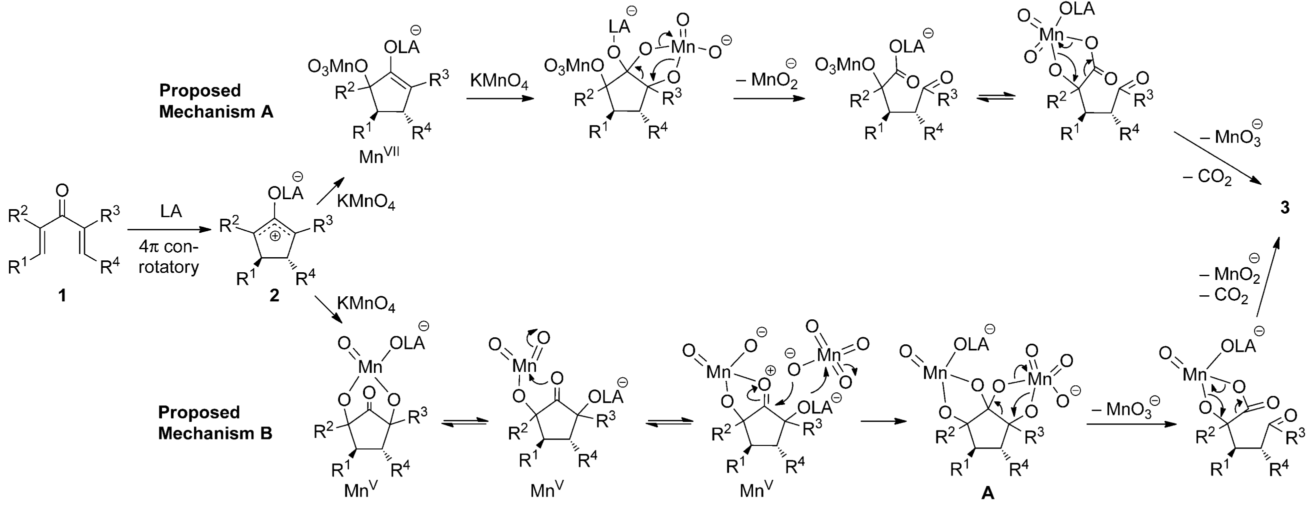
Table 2: Synthesis of 1,4-diketones by $KMnO_4$ interruptions of the Nazarov intermediates.[a]



1 **3** **4h**

No.	Substrate	R^1	R^2	R^3	R^4	Product (yield)[b]
1	**1a**	Ph	Me	Me	Ph	**3a** (71%)
2	**1b**	4-Cl-C_6H_4	Me	Me	4-Cl-C_6H_4	**3b** (60%)
3[c]	**1c**	4-MeO-C_6H_4	Me	Me	4-MeO-C_6H_4	**3c** (45%)
4[d]	**1d**	2-furyl	Me	Me	2-furyl	**3d** (17%)
5	**1e**	*i*Pr	Me	Me	*i*Pr	NA[e]
6	**1f**	Ph	Me	Me	1-Naph	**3f** (52%)[f]
7	**1g**	Ph	Me	*n*-Pr	Ph	**3g** (66%)
8	**1h**	H	Me	Me	Ph	**3h** (45%) + **4h** (16%)
9	**1i**	*i*Pr	Me	Me	Ph	**3i** (55%)
10	**1j**	*i*Pr	Me	Me	4-MeO-C_6H_4	**3j** (36%)

[a] Standard procedure: $KMnO_4$ was dissolved in a 2:1 mixture of CH_2Cl_2 and CH_3CN for 30 min at room temperature. To the solution of $KMnO_4$, $FeCl_3{\cdot}6H_2O$ was added and the mixture was stirred for 10 min. The temperature was then lowered to −15 °C. The dienone was added at −15 °C and stirred for 3 h, followed by additional stirring at room temperature for 1 h. [b] Yields are based on isolated product after chromatography. [c] The reaction mixture was stirred at −15 °C for 4 h and filtered through silica. [d] 2.0 equiv $FeCl_3{\cdot}6H_2O$ was used. The reaction mixture was stirred for 1 h at −15 °C and additional 4 h at 0 °C. [e] Starting material was recovered from an intractable mixture of minor products. [f] Mixture of atropisomers.



Scheme 2. Two proposed mechanisms for the permanganate interruption of the Nazarov reaction.

the loss of Mn^{III}[9] to generate a carboxylate and a ketone. Carboxylate addition into the permanganate(VII) species in equilibrium followed by loss of Mn^{V} and carbon dioxide would afford a decarbonylated 1,4-diketone. The by-product Mn^{III} could then disproportionate to Mn^{II} and Mn^{IV}, or the Mn^{III} and Mn^{V} could undergo redox conversion to two Mn^{IV} species.[9]

On the other hand, the oxyallyl cation could undergo a concerted or stepwise [3+3] cycloaddition with permanganate to produce a hypomanganate ester (Mechanism B), in a homologous process to the [3+2] step that initiates alkene cleavage. Through equilibrium of the Mn^{V} complexes, the α-oxyanion could react with an additional Mn^{VII}, affording tricyclic manganese complex **A**. Considering the initial [3+3] cycloaddition provides *syn*-α,α′ substituents, the tricyclic complex **A** would be a *cis,trans*-angular structure bearing significant strain, which may disfavor this pathway. Notably, in either mechanism the discharge of carbon dioxide rather than carbon monoxide is proposed. Qualitative analysis via conversion of $Ba(OH)_2$ to $BaCO_3$ provides support for the formation of CO_2.[13] However, further mechanistic studies entailing characterization of minor side-products and attempts to intercept proposed intermediates remain to be done.

In summary, we have demonstrated the first oxidative decarbonylative cleavage of oxyallyl cation species in an interrupted Nazarov reaction, employing the inexpensive inorganic oxidant $KMnO_4$. Potassium permanganate-interrupted Nazarov reactions afforded *syn*-2,3-disubstituted 1,4-diketones in moderate yield. This new method allows formation of two C–O bonds as well as one C–C bond, and the disconnection of two C–C bonds. Efforts to extend the generality of the oxidative cleavage reaction to a base-induced oxyallyl cation species and mechanistic studies of the reaction are underway, and will be disclosed in near future.

Experimental Section

Representative procedure for the potassium permanganate-interrupted Nazarov reaction (**3a**): Solvents (dichloromethane and acetonitrile) were taken directly from fresh bottles without further purification/drying processes. The reaction was carried out in an open flask. 2.5 equiv $KMnO_4$ (0.076 g, 0.48 mmol) was dissolved in a mixture of CH_2Cl_2:CH_3CN (2:1 ratio, 3 mL) and stirred for 30 min at room temperature. 1.5 equiv $FeCl_3 \cdot 6H_2O$ (0.077 g, 0.29 mmol) was then added and the mixture was stirred for a further 10 min. The reaction temperature was lowered to −15 °C and **1a** (solid, 0.050 g, 0.19 mmol) was added in one portion. Stirring at −15 °C was continued for 3 h, then the reaction was allowed to warm to room temperature. After 1 h, the solution was filtered through a silica gel plug (2 cm thickness), which was then rinsed with 50 mL ethyl acetate. The organic filtrate was concentrated by a rotary evaporation and the residue was purified by flash column chromatography (silica gel, 19:1→9:1 hexane:EtOAc) to provide the desired product **3a** (0.036 g, 71 %) as a white crystalline solid: R_f 0.24 (hexanes/EtOAc 9:1); mp = 105–107 °C; IR (cast film) 3029, 2930, 1708, 1495, 1454 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) $\delta = 7.16$–7.09 (m, 6H), 6.97–6.92 (m, 4H), 4.40 (s, 2H), 2.15 ppm (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) $\delta = 208.0$, 135.5, 128.7, 128.6, 127.3, 62.0, 29.3 ppm; HRMS (EI, M^+) for $C_{18}H_{18}O_2$ calcd. 266.1307, found: *m/z* 266.1307.

Keywords: 1,4-diketones · electrocyclization · Nazarov reaction · oxidative cleavage · potassium permanganate

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[13] See Supporting Information for experimental details of these experiments.

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