

Manganese(III) acetate mediated synthesis of oxygen heterocycles. Influence of copper(II) salts on product distribution †

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Unsaturated malonates bearing pendant alcohols yield carbocycles tethered to oxygen heterocycles on exposure to manganese(III) acetate and an appropriate copper(II) salt.

Manganese(III) acetate has been widely used in organic synthesis to generate electrophilic C-centred radicals from malonates and similar compounds.¹ For example, Snider has shown² that the C-centred radical **1** ($R' = H$) readily cyclises to provide the corresponding radical **2** (Fig. 1). The fate of this adduct radical depends on the reaction conditions. In the presence of copper(II) acetate, a copper(III) intermediate is formed which furnishes the alkene **3** by β -hydride elimination. The adduct radical may also abstract a hydrogen atom from solvent to yield the corresponding alkane **5**, or undergo reaction with the β -dicarbonyl moiety to give **4**. The aim of this research is to develop a general oxidative substitution reaction which allows adduct radicals to react with pendant nucleophiles to provide heterocyclic products. ‡ Herein we report our preliminary results towards this goal. We demonstrate that δ - and ϵ -hydroxy adduct radicals **2** [$R' = (CH_2)_3OH, (CH_2)_4OH$] readily yield products of oxidative substitution (**6**) in the presence of an appropriate transition metal salt.§ These cyclisations allow the one-step transformation of acyclic starting materials into oxygen heterocycles linked to carbocycles; a structural motif present in a wide variety of natural products.⁷ We have also discovered that the product distribution in these reactions is strongly influenced by the nature of the copper(II) additive.

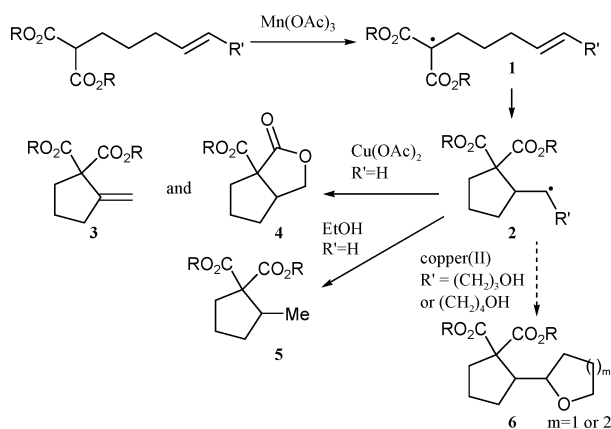


Fig. 1 Termination pathways for adduct radical **2**.

We were pleased to discover that exposure of the malonate **7a** (Scheme 1, Table 1) to manganese(III) acetate in acetonitrile at reflux provided the desired tetrahydrofuran (THF) **8** (46%) along with recovered starting material (49%) (entry 1). In an attempt to improve the yield of **8** we conducted the reaction in the presence of copper(II) additives. Kochi has demonstrated

that the oxidation of alkyl radicals by copper(II) salts containing poorly coordinating anions results in an increase in products arising from oxidative substitution compared with β -hydride elimination.⁸ We therefore compared the results of using copper(II) triflate as additive with the use of copper(II) acetate as additive¶—a copper(II) salt known to yield predominantly products of β -hydride elimination.^{8,10} With both copper(II) additives the only isolable product was the THF **8** albeit in lower yield (entries 2 and 3).

Treatment of the homologous malonate **7b** with manganese(III) acetate in ethanol at reflux provided the desired THF **9** (56%) along with recovered starting material (30%) (entry 4). Again copper(II) acetate and a range of copper(II) salts containing poorly coordinating anions were screened as additives. With copper(II) acetate the major product was the THF **9** (45%) which was isolated along with the alkene **12** (19%) and recovered starting material (entry 5). Complete consumption of **7b** was achieved using copper(II) tetrafluoroborate|| as the additive in acetonitrile yielding the THF **9** (51%) as well as the cyclopentanes **11** (15%) and **12** (9%) (entry 6). A further product was also isolated which proved difficult to purify and was tentatively assigned as the alkenes **10** by analogy with the formation of the alkenes **17** (*vide infra*).**

Having successfully synthesised carbocycles tethered to THFs in one step from acyclic precursors we turned our attention to the formation of the corresponding carbocycles linked to tetrahydropyrans (THPs). Exposure of **7c** to manganese(III) acetate in ethanol did not provide the desired THP **13**, but solely the aldehyde **15** and the acetal **14** (entry 7). In this instance, the use of copper(II) acetate as an additive provided the alkenes **17** which arise *via* β -hydride elimination from the initial adduct radical (entry 8). Pleasingly, the use of copper(II) triflate as the additive, to promote oxidative substitution reactions,⁸ resulted in the formation of the desired THP **13** (30%) as well as the γ -lactone **16** (21%) and the alkenes **17** (20%) (entry 9).**

With the malonate **7d**, successful THP formation was achieved on treatment with manganese(III) acetate in the presence of copper(II) hexafluoroantimonate in acetonitrile (entry 10). The THP **18** was isolated along with the alkenes **21** and the cyclopentane **19**. A further compound was also isolated which was tentatively assigned as the THP **20** by analogy with the formation of the THF **12** (*vide supra*).**

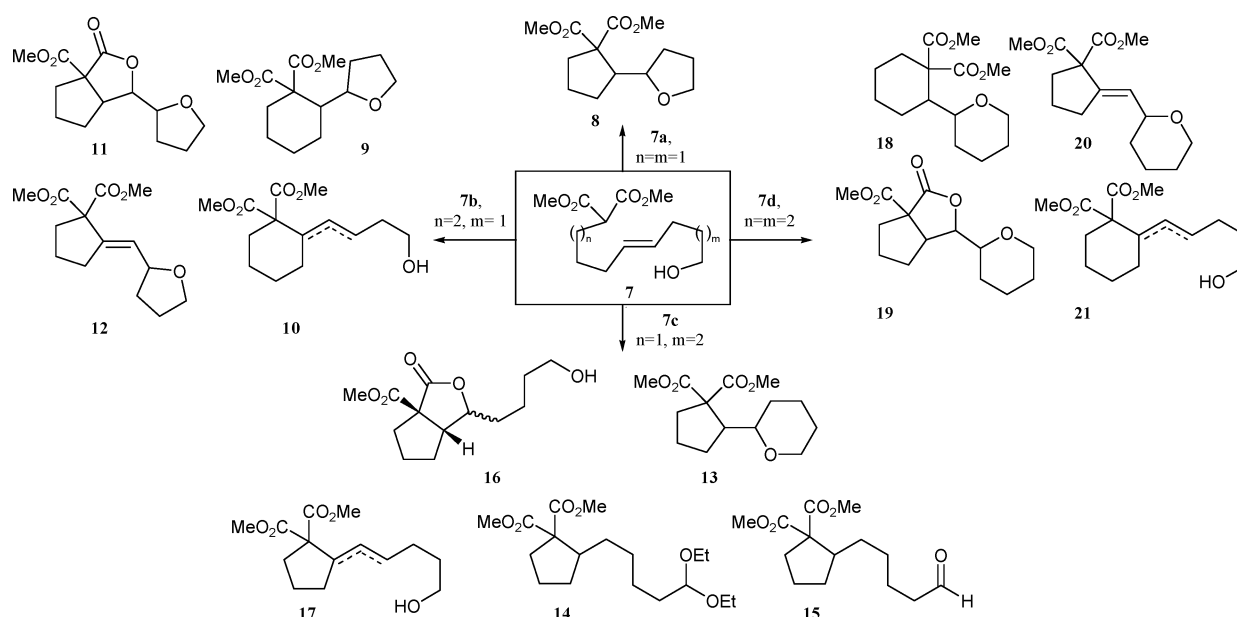
The above results demonstrate that it is possible to form carbocycles linked to oxygen heterocycles in one step from acyclic precursors. The formation of THFs does not require the addition of copper(II) salts, in fact copper(II) salts are deleterious to product yield; however, in the presence of copper(II) salts carrying poorly coordinating anions, complete conversion is achieved and in the case of **7b** a range of other products is formed. The formation of THPs can only be accomplished in the presence of copper(II) salts bearing poorly coordinating anions. In their absence the formation of alkenes or aldehydes/acetals predominates. Our mechanistic understanding of these reactions is presented below.

† Electronic supplementary information (ESI) available: spectroscopic data. See <http://www.rsc.org/suppdata/ob/b4/b402411g/>

Table 1 Products and reaction conditions for cyclisation of the malonates **7**

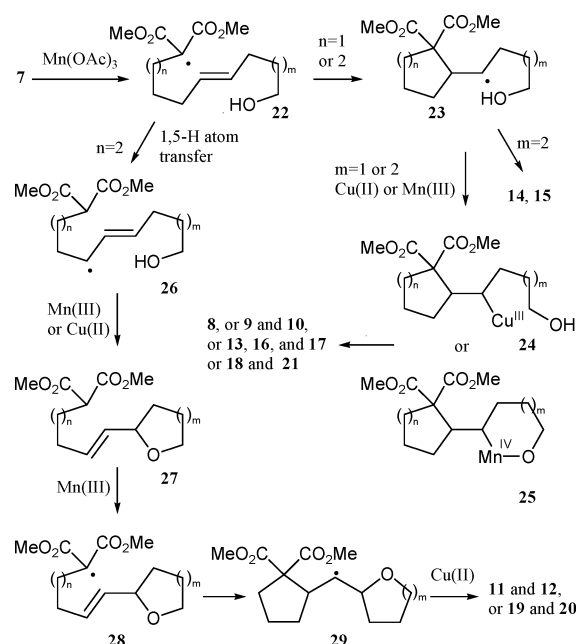
Entry ^a	Substrate	Solvent	Additive ^b	Products (yield %)			
1	7a ^c	MeCN	none	8 ^e (46)			
2	7a ^c	MeCN	Cu(OAc) ₂	8 ^e (16)			
3	7a ^c	MeCN	Cu(OTf) ₂	8 ^e (38)			
4	7b	EtOH	none	9 ^e (56)			
5	7b	EtOH	Cu(OAc) ₂	12 (19)			
6	7b	MeCN	Cu(BF ₄) ₂ ^d	9 ^e (51)	10 ^f (< 10)	11 (15)	12 (9)
7	7c	EtOH	none	14 (17)	15 (62)		
8	7c	EtOH	Cu(OAc) ₂	17 ^f (79)			
9	7c	MeCN	Cu(OTf) ₂ ^d	13 ^e (30)	16 ^e (21)	17 ^f (20)	
10	7d	MeCN	Cu(SbF ₆) ₂ ^d	18 ^e (32)	19 (18)	20 (< 4)	21 ^f (39)

^a All reactions conducted with two equivalents of Mn(OAc)₃ at reflux. ^b One equivalent of additive was used. ^c The (Z)-alkene was used. ^d A range of highly dissociated copper(II) salts bearing poorly coordinating anions was tested. ^e Formed as a mixture of diastereomers. ^f Formed as a mixture of regioisomers.

**Scheme 1** Reagents and conditions: see Table.

The THFs **8** and **9** are formed by simply heating the substrate (**7a** or **7b**) in the appropriate solvent in the presence of two equivalents of manganese(III) acetate. This novel transformation proceeds through the C-centred radical **22** ($n = 1$ or 2 , $m = 1$) (Fig. 2) which undergoes an *exo*-trig cyclisation to deliver **23** ($n = 1$ or 2 , $m = 1$).¹ Manganese(III) acetate does not readily oxidise secondary radicals,¹ however, oxidative substitution may occur in this case from the manganese alkoxide **25** ($n = 1$ or 2 , $m = 1$) to deliver **8** or **9**.^{††} When copper(II) acetate was used as an additive the THFs **8** and **9** were isolated in lower yield. It is likely, therefore, that the Cu(III) intermediate **24** ($n = 1$ or 2 , $m = 1$) is formed from the adduct radical **23**. Ordinarily intermediates such as **24** ($n = 1$ or 2 , $m = 1$) would suffer β -hydride elimination. In these systems oxidative substitution to form a 5-membered ring (THF) must be more favourable.^{‡‡}

Exposure of **7c** to manganese(III) acetate in ethanol yields none of the desired THP **13**. In this instance the initially formed radical **22** ($n = 1$, $m = 2$) provides adduct radical **23** ($n = 1$, $m = 2$) on 5-*exo*-trig cyclisation. The radical **23** undergoes a 1,5-H-atom transfer to yield the corresponding α -hydroxy radical which is rapidly oxidised by manganese(III) acetate¹ to deliver **15**. The aldehyde **15** is converted into the acetal **14** under the reaction conditions. That THP formation does not occur is probably because 1,5-atom transfer is very favourable. Furthermore, metalloheptane formation (**25**, $n = 1$, $m = 2$) is likely to be less favourable than metallopyran formation (**25**, $m = 1$), which leads to the THFs **8** and **9**. The use of copper(II) acetate as an additive delivered the alkenes **17** as the sole products

**Fig. 2** Cyclisation mechanisms.

which arise by β -hydride elimination from **24** ($n = 1$, $m = 2$) (Fig. 2). In this case the usual pathway of β -hydride elimination is favoured as oxidative substitution to form a 6-membered ring

(THP) is likely to be slower than that to form a 5-membered ring (THF). Oxidation of **7c** with manganese(III) acetate and copper(II) triflate as the additive delivered the oxidative substitution products **13** and **16**, as well as the alkenes **17**. Reaction of the alkyl radical **23** ($n = 1, m = 2$) with a copper(II) salt provides the copper(III) intermediate **24** ($n = 1, m = 2$) from which **13**, **16** and **17** are formed *via* oxidative substitution or β -hydride elimination. In line with the research of Kochi,⁸ products of β -hydride elimination predominate with copper(II) acetate whereas when copper(II) salts bearing poorly coordinating anions are present, the major products arise *via* oxidative substitution. §§

The use of copper(II) hexafluoroantimonate in conjunction with manganese(III) acetate and the malonate **7d** yielded the desired THP **18** along with the γ -lactone **19** and the alkenes **20** and **21**. The products all arise from the educt radical **22** ($n = m = 2$) (Fig. 2) which is partitioned between a 6-*exo*-trig cyclisation giving the radical **23** ($n = m = 2$) and a 1,5-H-atom transfer which generates the allylic radical **26** ($n = m = 2$). The copper(III) intermediate **24** ($n = m = 2$), formed from the adduct radical **23** ($n = m = 2$), gives rise to **18** and **21** *via* oxidative substitution and β -hydride elimination respectively. The allylic radical **26** ($n = m = 2$) is readily oxidised under the reaction conditions¹ to provide the corresponding allylic cation from which the THP **27** ($n = m = 2$) is formed. Oxidation of **27** ($n = m = 2$) with manganese(III) generates the electrophilic radical **28** ($n = m = 2$) which undergoes a 5-*exo*-trig cyclisation to deliver the adduct radical **29** ($m = 2$). The secondary radical **29** ($m = 2$) furnishes the γ -lactone **19** and the alkene **20** on oxidation with copper(II). The formation of **11** and **12** from **7b** in the presence of copper(II) tetrafluoroborate occurs analogously. Again, utilising copper(II) salts carrying poorly coordinating anions as additives provides products of oxidative substitution (*e.g.* **18** and **19**) in preference to products of β -hydride elimination (*e.g.* **20** and **21**).

In summary, we have demonstrated that acyclic, unsaturated malonates bearing pendant alcohols readily form carbocycles tethered to oxygen heterocycles on exposure to manganese(III) acetate and a copper(II) salt. The formation of THFs may be achieved without copper(II) additives whereas the formation of THPs necessitates the presence of copper(II) salts bearing poorly coordinating anions. With both THFs and THPs the use of copper(II) additives bearing poorly coordinating anions produces products of oxidative substitution in preference to products arising from β -hydride elimination. Work is ongoing to utilise less conformationally flexible substrates in these cyclisation reactions and to access topologically distinct bicyclic heterocycles.

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Notes and references

‡ The reaction of adduct radicals with alcohols in the presence of manganese(III) acetate has been used to form epoxides (ref. 3), and in a low yielding (11%) synthesis of a polycyclic THF (ref. 4).

§ Tetrahydrofurans are frequently formed as by-products in Barton remote functionalisation reactions *via* cyclisation of δ -hydroxy radicals (refs. 5,6).

¶ Copper(II) acetate is a common additive in manganese(III) acetate mediated reactions. The use of copper(II) chloride has been reported (refs. 1,9).

|| Copper(II) tetrafluoroborate has been used as a co-oxidant in oxidative radical reactions of malonates mediated by cerium(IV) (ref. 11).

** Cu(OTf)₂, Cu(BF₄)₂ and Cu(SbF₆)₂ all gave similar results.

†† Snider has proposed a metallooxetane as a potential intermediate in the synthesis of epoxides (ref. 3.)

‡‡ Treatment of the corresponding protected substrates with manganese(III) acetate in the presence of copper(II) acetate provides good yields of products arising from cyclisation followed by β -hydride elimination.

§§ Kochi has proposed that oxidative substitution products arise *via* an S_N1-like reaction which is initiated by dissociation of one (or both) of the ligands from the copper(III) intermediate. Hence, the use of copper(II) salts bearing poorly coordinating anions may promote the formation of oxidative substitution products, whereas the use of copper(II) acetate leads predominantly to products arising *via* β -hydride elimination (ref. 8).

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