Electron transfer-induced sequential transformations of malonates by the ferrocenium ion

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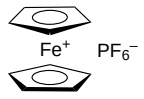
Malonate enolates undergo single electron oxidation with the ferrocenium ion followed by radical cyclisation and radical or cationic termination of the reaction sequence.

In the course of investigations towards the incorporation of oxidative electron transfer in tandem reactions, we became interested in the development of general strategies for the use of enolates as precursors for the generation of radicals, with the choice of subsequent oxidation of the latter to carbocations in 'heterointermediate reaction sequences' [eqn. (1)].

$$\text{Educt} \rightarrow (R^1)^- \rightarrow (R^2)^- \xrightarrow{-e^-} (R^3)^{\cdot} \rightarrow (R^4)^{\cdot} \xrightarrow{-e^-} (R^5)^+ \rightarrow (R^6)^+ \rightarrow \text{Product} \quad (1)$$

Enolates have been used in oxidative dimerisations involving various metal salts.[1] Cyclisations of highly acidic β-dicarbonyl compounds onto phenolates with alkaline $K_3[Fe(CN)_6]$ were reported by Kende.[2] The electrochemical oxidation of enolates is known, but these reactions are often limited by low yields and competing reaction pathways.[3] For the generation of α-carbonyl radicals from neutral carbonyl compounds, $Mn(OAc)_3$[4] or cerium ammonium nitrate (CAN)[5] were employed, but these reagents are not applicable to enolates.

Here we introduce ferrocenium hexafluorophosphate **1** as an efficient and selective single electron oxidant for enolates and certain radical types in reaction sequences.† In addition to its mildness, **1** is easily recovered and recycled and is thus more economical than other heavy metal oxidants.



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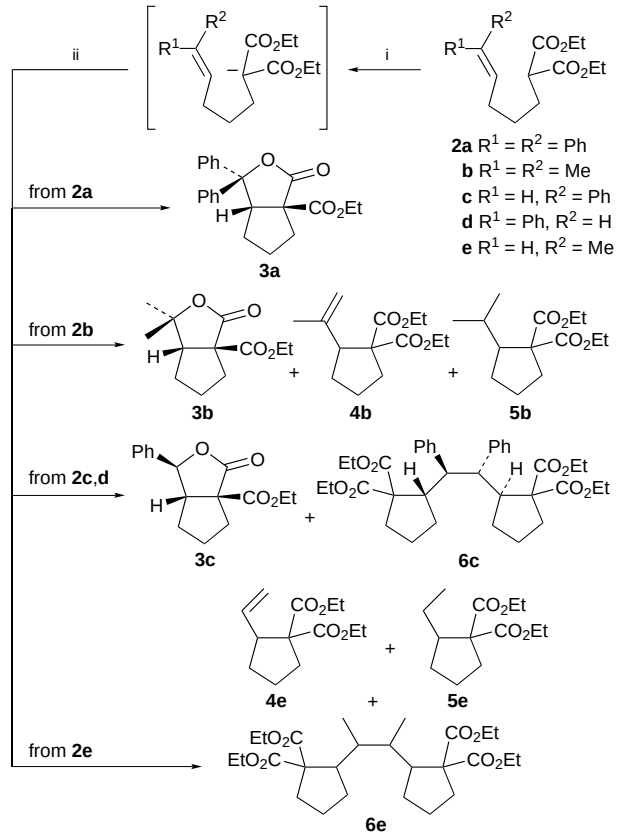
The starting point of our studies was the 5-*exo* cyclisations of the substituted malonates **2a**–**e** (Scheme 1). After deprotonation with $(Me_3Si)_2NLi$ or LDA at −78 °C in DME (50 mM), the enolate solutions were treated with portions of **1** at 0 °C.‡ The course of the reactions was easily monitored by the colour change of the mixtures. The reactions were finished when the colour of the solution remained green.

Depending on the structure of the acceptor double bonds in **2**, different products were obtained (Scheme 1, Table 1). Malonate **2a** gave a single bicyclic lactone **3a**§ in 64% yield (entries 1 and 2). The dimethyl derivative **2b** yielded the lactone **3b** and the elimination product **4b** together with a small amount of the disproportionation product **5b**. $(Me_3Si)_2NLi$ was the more efficient base for the bicyclisation to lactone **3b** (entries 3 and 4). Oxidative cyclisation of the phenyl compounds **2c** or **2d** afforded a partly separable mixture of the diastereoisomerically pure lactone **3c** and the dimer **6c** (entries 5 and 6). The



Scheme 1 *Reagents and conditions:* i, LDA or $(Me_3Si)_2NLi$, −78 °C, DME; ii, **1**, 0 °C

Table 1 Cyclisation products of the malonates **2** with **1** and product ratio of cationic or radical termination of the sequence

			Products (%)				
Entry	Educt	Base (equiv.)	**3**	**4**	**5**	**6**[a]	Cationic : radical
1	**2a**	LDA (2.5)	64	—	—	—	100 : 0
2	**2a**	$(Me_3Si)_2NLi$ (1.75)	54	—	—	—	100 : 0
3	**2b**	$(Me_3Si)_2NLi$ (1.75)	52	26	6	—	6 : 1
4	**2b**	LDA (3)	27	28	2	—	13 : 1
5	**2c**	$(Me_3Si)_2NLi$ (2.5)	7	—	—	24	1 : 3.4
6	**2d**	LDA (1.75)	28	—	—	48	1 : 1.7
7	**2e**	$(Me_3Si)_2NLi$ (2)	—	25	25	34[b]	0 : 100

[a] Yield based on **2**. [b] Diastereoisomeric mixture, stereochemistry not assigned.

Table 2 Termination of the oxidative cyclisations of the malonates **2** with TEMPO **10**

Entry	Educt	Base (equiv.)	Equiv. TEMPO	Product (%) **3**	**11**	**12** (dr)[a]	Cyclic : acyclic
1	**2a**	$(Me_3Si)_2NLi$ (1.75)	2	26	33	—	1 : 1.3
2	**2a**	LDA (1.75)	2	25	47	—	1 : 1.9
3	**2b**	$(Me_3Si)_2NLi$ (1.75)	2	—	—	87	100 : 0
4	**2c**,**d**	$(Me_3Si)_2NLi$ (1.75)	2	—	—	72 (100 : 0)	100 : 0
5	**2e**	$(Me_3Si)_2NLi$ (1)[b]	1	—	—	69 (1.8 : 1[c])	100 : 0
6	**2e**	$(Me_3Si)_2NLi$ (2)	2	—	41	42 (2 : 1[c])	1 : 1

[a] Diastereoisomeric ratio. [b] 6% Educt recovered. [c] Stereochemistry could not be assigned.

stereochemical assignment is based on spectral data and is in agreement with the stereochemistry of the TEMPO-trapping product (*vide infra*). The (*E*)-Hex-4-enylmalonate **2e** provided the disproportionation products **4e** and **5e** and a diastereomeric mixture of the dimer **6e** in a ratio of 1.5 : 1.5 : 1 (entry 7).

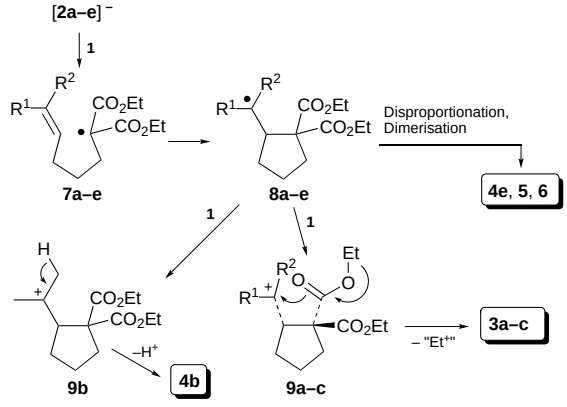
Clear trends emerge from these results. Enolates **2** are efficiently oxidised to radicals **7** by **1** (Scheme 2). The 5-*exo* cyclisation provides the rearranged radicals **8**. The structure of **8** determines their stabilisation. Radicals **8a,b** are oxidised to carbocations **9a,b**, which undergo intramolecular nucleophilic trapping to lactones **3a,b** or elimination to **4b**, respectively. The endergonic oxidation of the benzylic radical **8c** occurs,[6] but is slower than radical dimerisation and yields a mixture of **3c** and **6c**. Secondary alkyl radicals are not oxidised and undergo typical radical processes to products **4e**, **5e** and **6e**.

Trapping experiments with TEMPO **10** confirm these hypotheses and give rise to an efficient oxidative radical cyclisation/termination process with remote oxy-functionalisation (Scheme 3, Table 2). Addition of **1** to the reaction mixtures in the presence of 1–2 equiv. of **10**, as described above, gave the following results. Malonate **2a** yielded a mixture of the acyclic TEMPO adduct **11a** and lactone **3a** (entry 1). Substrates **2b**–**e** provided the cyclised TEMPO adducts **12** with moderate to excellent stereoselectivity (entries 2–5). The acyclic compounds **11** were detected in traces if at all, but by using a larger excess of **10** their amount increased (entry 6). The structure and stereochemistry of **12c** was proved by X-ray analysis.§ Thus on one hand, radical 5-*exo* cyclisation of **7** is (except in the case of **7a**) faster than their trapping by **10**. On the other hand, trapping of the cyclised radicals **8b**,**c** is strongly favoured over their oxidation and allows selective remote oxygenation.

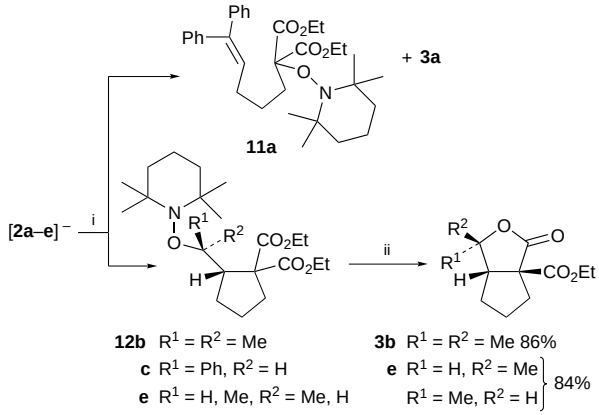
Reductive N–O bond cleavage of **12b**,**e** with spontaneous lactonisation was achieved with Zn–AcOH and allows the preparation of **3b** and the otherwise not accessible lactone **3e** (*vide supra*) in a two-step procedure in 86 and 84% yield .

In conclusion, we have shown that enolates serve as a convenient source of radicals. Electron transfer-induced reaction sequences provide a simple access to bicyclic lactones with **1** as oxidant.

We thank the Fonds der Chemischen Industrie (Liebig-Stipendium for U. J.) for financial support and Professor Dr H. Hopf for ongoing support of this project.



Scheme 2



Scheme 3 *Reagents and conditions*: i, TEMPO, **1**, 0 °C, DME; ii, Zn, AcOH, THF, 70 °C

Footnotes and References

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† Salt **1** has found widespread use in transition metal oxidation (ref. 7), although applications in organic chemistry are scarce (ref. 8). Ferrocenes have been employed as redox catalysts for enzymatic oxidations (ref. 9).

‡ The excess of base was applied to ensure complete deprotonation under dilution conditions. A control experiment showed that the free base was also oxidised with **1**. The outcome of the cyclisations was, however, only slightly influenced by the amount of base.

§ All new compounds exhibit satisfactory analytical data. X-Ray analyses of **3a** and **12c** proved their structures and will be published separately.

1 Reviews: P. I. Dalko, *Tetrahedron*, 1995, **51**, 7579; J. Iqbal, B. Bhatia and N. K. Nayyar, *Chem. Rev.*, 1994, **94**, 519.
2 A. S. Kende, K. Koch and C. A. Smith, *J. Am. Chem. Soc.*, 1988, **110**, 2210 and references cited therein.
3 Reviews: M. Schmittel, *Top. Curr. Chem.*, 1994, **169**, 183; H. J. Schäfer, *Angew. Chem., Int. Ed. Engl.*, 1981, **20**, 911.
4 Reviews: G. G. Melikyan, *Organic Reactions*, Wiley, New York, 1997, vol. 49, p. 427; B. B. Snider, *Chem. Rev.*, 1996, **96**, 339.
5 Review: V. Nair, J. Mathew and J. Prabhakaran, *Chem. Soc. Rev.*, 1997, **26**, 127.
6 D. D. M. Wayner and V. D. Parker, *Acc. Chem. Res.*, 1993, **26**, 287.
7 Review: N. G. Connelly and W. E. Geiger, *Chem. Rev.*, 1996, **96**, 877.
8 T. Langer, M. Illich and G. Helmchen, *Synlett*, 1996, 1137; H.-J. Knölker, F. Budei, J.-B. Pannek and G. Schlechtingen, *Synlett* 1996, 587; K. Narasaka and Y. Kohno, *Bull. Chem. Soc. Jpn.*, 1993, **66**, 3456; K. Narasaka, N. Arai and T. Okauchi, *Bull. Chem. Soc. Jpn.*, 1993, **66**, 2995; T. R. Kelly, S. K. Maity, P. Meghani and N. S. Chandrakumar, *Tetrahedron Lett.*, 1989, **30**, 1357; C. P. Casey, E. A. Austin and A. L. Rheingold, *Organometallics*, 1987, **6**, 2157; J. Lubach and W. Drenth, *Recl. Trav. Chim. Pays-Bas*, 1970, **89**, 144.
9 Review: W. A. Herrmann and B. Cornils, *Angew. Chem., Int. Ed. Engl.*, 1997, **36**, 1047.

Received in Cambridge, UK, 23rd September 1997; 7/06879D