Pergamon

Tetrahedron Letters 40 (1999) 6095–6098

TETRAHEDRON
LETTERS

Radical Cyclisations Promoted by Dimanganese Decacarbonyl: A New and Flexible Approach to 5–Membered *N*–Heterocycles

Bruce C. Gilbert[a], Wilhelm Kalz[a], Chris I. Lindsay[b], P. Terry McGrail[b], Andrew F. Parsons[a]* and David T.E. Whittaker[a]

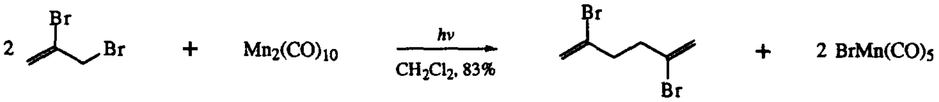
[a]Department of Chemistry, University of York, Heslington, York, YO10 5DD, U.K.
[b]ICI Wilton Research Support Group, Composite Science Group, PO Box 90 Wilton, Middlesbrough, Cleveland, TS90 8JE, U.K.

Received 14 June 1999; accepted 29 June 1999

Abstract: Radical cyclisation of various unsaturated halides using dimanganese decacarbonyl/*hv* has been explored. Substituted pyrrolidinones and a pyrrolidine were isolated in good to excellent yield; the radical produced on cyclisation can undergo iodine or hydrogen atom transfer, or reaction with TEMPO.

Keywords: Manganese and compounds; Radicals and radical reactions; Cyclisation.

Free-radical cyclisation reactions have been extensively studied over the past twenty years[1] and the most common method of cyclisation involves reaction of halide (or related thiophenyl, thiocarbonyl or phenyl selenide) precursors with organotin hydrides. The toxicity and difficulty of removing tin-containing by-products has led to the development of alternative reagents for radical generation.[2] Notable examples include tris(trimethylsilyl)silane, cobaloximes, manganese(III) acetate and samarium(II) iodide but the use of organotin hydrides, which provide a flexible and mild method of radical generation, still dominates. As part of a programme to develop alternative free-radical initiators, we recently reported the use of dimanganese decacarbonyl [$Mn_2(CO)_{10}$] in the coupling/cross-coupling of organobromides.[3] Bromine–atom abstraction by the manganese carbonyl radical (generated on photolytic cleavage of the Mn–Mn bond) produced a carbon-centred radical which undergoes coupling (Scheme 1).[4] This provides a mild and efficient method of coupling and the by-product manganese pentacarbonyl bromide can be easily removed from the product, on workup, by reaction with DBU. We now describe the novel application of this method to cyclisation reactions leading to the formation of substituted 5-membered rings.

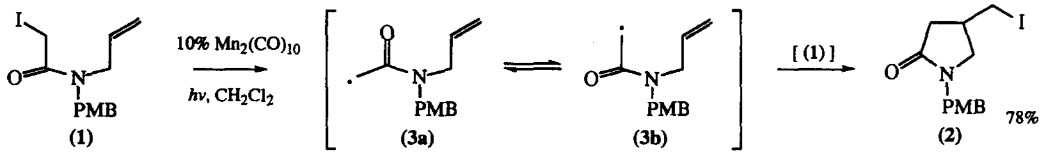


Scheme 1

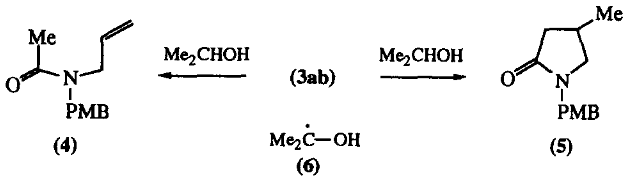
Initially an iodine–atom transfer cyclisation using iodoethanamide (1) was investigated (Scheme 2).[5] This type of reaction to form pyrrolidinones has been reported previously using *e.g.* Bu_6Sn_2 or Et_3B/O_2, typically in boiling benzene.[6] Irradiation of (1) (2.9 mmol) with 10% (0.29 mmol) $Mn_2(CO)_{10}$ in dichloromethane for 1 h afforded the desired primary iodide (2) in 78% yield after column chromatography. Unlike reactions employing Bu_6Sn_2, the presence of excess initiator [*e.g.* using 50% $Mn_2(CO)_{10}$] does not effect

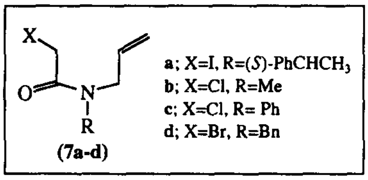
0040-4039/99/$ - see front matter © 1999 Published by Elsevier Science Ltd. All rights reserved.
PII: S0040-4039(99)01271-X

the yield of the desired compound (**2**). Once formed, the primary iodide (**2**) does not undergo fast atom abstraction by the manganese pentacarbonyl radical. This is consistent with our finding that irradiation of a mixture of n-hexyl iodide and $Mn_2(CO)_{10}$ over 4 h,[7] produced no radical coupling and the starting iodide was recovered in 77% yield after column chromatography. The high yield of cyclisation of (**1**) at room temperature is noteworthy; reactions of this type are generally[6] carried out at 80°C to increase the rate of rotation of the amide bond to convert *syn*– radicals (**3a**) to *anti*– radicals (**3b**) (which can then cyclise). In this case, the use of a bulky *N*–protecting group (known[6,8] to increase the proportion of the *anti*– amide conformer) was effective in promoting efficient cyclisation even at room temperature.



Scheme 2





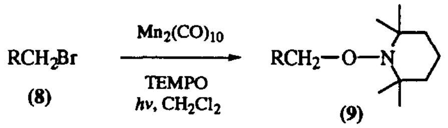
Concentration of (1)/mol dm^{-3}	Equivalents of 2-propanol	Addition time/h[¶]	Products/%		
			(2)	(4)	(5)
0.11	179	–	76	4	4
0.02	838	–	53	20	–
0.07	5[§]	2.0	27	16	20
0.07	2[§]	4.0	30	2	41
0.02	2[§]	6.0	–	8	54

[¶] Syringe pump addition of iodide (1) in dichloromethane (5-10 cm^{-3}).
[§] Reactions carried out using a mixed dichloromethane:2-propanol solvent.

Table

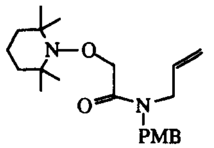
The reaction of (**1**) with $Mn_2(CO)_{10}$ in the presence of a hydrogen atom donor was then investigated. It was envisaged that radical cyclisation could be followed by trapping the intermediate primary radical with a hydrogen atom from 2-propanol to give (**5**) and the tertiary radical (**6**) (Table). Two processes were expected to compete with this: (i) iodine atom transfer to give (**2**) and (ii) reaction of the first-formed amide radical with the H-atom donor to give (**4**), the product of simple reduction. Initial experiments using 2-propanol as the solvent and varying the concentration of (**1**) were disappointing; a good yield of (**2**) was observed at 0.11 mol dm^{-3} while at lower concentration (0.02 mol dm^{-3}) only iodine atom transfer and simple reduction were observed. When the reaction was carried out in dichloromethane, using 5 equivalents of 2-propanol, and iodide (**1**) added dropwise to the reaction mixture over 2 h, the desired product (**5**) was isolated in 20% yield. Increasing the addition time, lowering the concentration and reducing the number of equivalents of 2-propanol produced a further increase in the yield of (**5**), to a maximum of 54%. TLC analysis indicated that these reactions produced pinacol as a by-product, this being derived from coupling of the tertiary radical **(6)**. It should be noted that no products derived from cross-coupling of **(6)** with, for example, the carbamoylmethyl radical **(3ab)**, were observed. The use of 1,4-cyclohexadiene (1.1 equiv.), rather than 2-propanol (as the H-donor) was found to be give lower yields of cyclisation; simple reduction to give **(4)** was observed in 14% yield while pyrrolidinone **(5)** was isolated in 30% yield (at 0.07 mol dm^{-3}). This method compares favourably with similar tributyltin hydride reactions; cyclisation of related substrates **(7a-c)** produced pyrrolidinones in 54, 24 and 12% yield respectively.[9] Electroreductive cyclisation [using a Ni(II) perchlorate complex/Ph_2PH] of the corresponding bromide **(7d)** was also less efficient and cyclisation was observed in only 11% yield.[10]

We then explored the possibility of cyclisation followed by trapping with an oxygen-centred radical, namely tetramethylpiperidine oxide (TEMPO). Initial model studies had shown that primary radicals, formed from reaction of bromides **(8a-d)** with $Mn_2(CO)_{10}$, could be efficiently trapped in the presence of TEMPO; the product hydroxylamines **(9a-d)** being isolated in excellent yield (85-99%) after column chromatography (Scheme 3).[11-13] Irradiation of a mixture of iodoethanamide **(1)**, TEMPO (1.1 equivalents) and $Mn_2(CO)_{10}$ in dichloromethane led to the predominant formation of **(10)** (in 61% yield), derived from reaction of the initial carbamoylmethyl radical with TEMPO. However, when TEMPO was added slowly (over 5 h) to a mixture of iodide **(1)** and $Mn_2(CO)_{10}$, cyclisation was observed to give the desired pyrrolidinone **(11)** in excellent (78%) yield. Reaction of the related trichloroethanamide **(12)** under the same conditions, gave the cyclised TEMPO adduct **(13)** in similar yield (72%). These cyclisation–trapping sequences, to introduce an oxygen substituent at the product radical centre, are very useful. Similar hydroxylamines have been shown to undergo a variety of transformations including reduction (using Zn/AcOH)[11,12] to alcohols and oxidation (using MCPA)[14] to aldehydes.

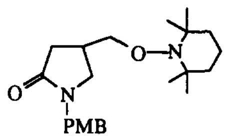


(8) **(9)**

a; R= $C(CO_2{}^tBu)=CH_2$ (85%) c; R= (*E*)-PhCH=CH (99%)
b; R= Ph (88%) d; R= (*E*)-$EtO_2CCH=CH$ (89%)

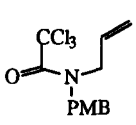


(10)

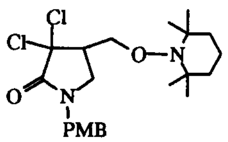


(11)

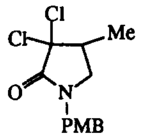
Scheme 3



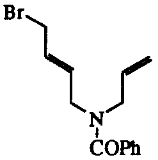
(12)



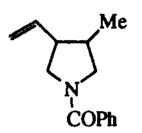
(13)



(14)



(15)



(16)

The cyclisation of **(12)** also produced a small amount of the 4-methyl derivative **(14)** (in 10% yield), derived from trapping of the intermediate primary radical with a hydrogen atom (most likely from dichloromethane). When the same reaction was carried out in the presence of 2 equivalents of 2-propanol (rather than TEMPO) the yield of **(14)** could be increased to 53%; as with the TEMPO reaction, no trapping of the first-formed dichlorocarbamoylmethyl radical was observed.

This method of cyclisation could also be applied to the synthesis of substituted pyrrolidines. Photolysis of allylic bromide **(15)** with $Mn_2(CO)_{10}$ in the presence of 2–propanol resulted in radical cyclisation followed by hydrogen atom trapping to give the unsaturated pyrrolidine **(16)** in 43% yield (as a 1:1 mixture of diastereoisomers).

This work has demonstrated that α-haloamides can be efficiently cyclised using $Mn_2(CO)_{10}$. Radical cyclisation followed by iodine or hydrogen atom transfer, or trapping with TEMPO can produce a variety of 5-membered rings. Although the cost of dimanganese decacarbonyl may prohibit large scale synthesis, for small scale preparations this method has a number of advantages over existing methods. These include mild reaction conditions, clean and efficient cyclisation–trapping and simple removal of the manganese by-products (on DBU work-up).

Typical Procedure

Preparation of **(11)** : To a stirred solution of iodide **(1)** (0.5 g, 1.45 mmol) and $Mn_2(CO)_{10}$ (0.28g, 0.73 mmol) in degassed CH_2Cl_2 (75 cm^3) was added a solution of TEMPO (0.25 g, 1.59 mmol) in CH_2Cl_2 (5 cm^3) over 5 h while the solution was irradiated (ICL 302 UV xenon lamp, 300 W) under an atmosphere of nitrogen. After the addition was complete, the solution was irradiated for a further 1 h and then DBU (0.44 g, 2.92 mmol) added dropwise. After stirring for a further 1 h, the dark coloured solution was adsorbed on to silica and column chromatography afforded **(11)** (0.42 g, 78%) and **(10)** (0.04 g, 7%) as colourless oils.

Acknowledgements

We thank ICI and The University of York for a University studentship (to D.T.E.W.) and the EU (under the SOCRATES scheme) for funding (W.K.).

References and Notes

1. (a) Giese, B.; Kopping, B.; Göbel, T.; Dickhaut, J.; Thoma, G.; Kulicke, K.J.; Trach, F. *Organic Reactions* **1996**, *48*, 301-856. (b) Aldabbagh, F.; Bowman, W.R. *Contemp. Org. Synth.* **1997**, 261-280.
2. Baguley, P.A.; Walton, J.C. *Angew. Chem. Int. Ed.* **1998**, *37*, 3072-3082.
3. Gilbert, B.C.; Lindsay, C.I.; McGrail, P.T.; Parsons, A.F.; Whittaker, D.T.E. *Synth. Commun.* in press.
4. This is a simplistic representation of the reaction mechanism. Manganese pentacarbonyl bromide has been isolated from these reactions, but previous workers have shown that photolysis of dimanganese decacarbonyl or manganese pentacarbonyl bromide can lead to decarbonylation. See for example, (a) Meyer, T.J.; Caspar, J.V. *Chem. Rev.* **1985**, *85*, 187-218. (b) Pan, X.; Philbin, C.E.; Castellani, M.P.; Tyler, D.R. *Inorg. Chem.* **1988**, *27*, 671-676.
5. All new compounds exhibited satisfactory spectral and analytical (high resolution mass) data.
6. (a) Belvisi, L.; Gennari, C.; Poli, G.; Scolastico, C.; Salom, B.; Vassallo, M. *Tetrahedron* **1992**, *48*, 3945-3960. (b) Curran, D.P.; Tamine, J. *J. Org. Chem.* **1991**, *56*, 2746-2750. (c) Jolly, R.S.; Livinghouse, T. *J. Am. Chem. Soc.* **1988**, *110*, 7536-7538. (d) Ikeda, M.; Teranishi, H.; Iwamura, N.; Ishibashi, H. *Heterocycles* **1997**, *45*, 863-866.
7. EPR spin–trapping studies showed that radicals were most readily formed on photolysis of dimanganese decacarbonyl with α-iodo amides, allylic and benzylic bromides/iodides and polyhalogenated substrates (e.g. CCl_4). Unpublished results.
8. (a) De Riggi, I.; Gastaldi, S.; Surzur, J.-M.; Bertrand, M.P.; Virgili, A. *J. Org. Chem.* **1992**, *57*, 6118-6125. (b) Stork, G.; Mah, R. *Heterocycles* **1989**, *28*, 723-727.
9. (a) Cardillo, B.; Galeazzi, R.; Mobbili, G.; Orena, M.; Rossetti, M. *Heterocycles* **1994**, *38*, 2663-2676. (b) Sato, T.; Wada, Y.; Nishimoto, M.; Ishibashi, H.; Ikeda, M. *J. Chem. Soc., Perkin Trans. 1* **1989**, 879-886.
10. Ozaki, S.; Matsushita, H.; Ohmori, H. *J. Chem. Soc., Perkin Trans. 1* **1993**, 2339-2344.
11. For related cobalt-mediated reactions see (a) Howell, A.R.; Pattenden. G. *J. Chem. Soc., Perkin Trans. 1* **1990**, 2715-2720. (b) Gill, G.B.; Pattenden, G.; Reynolds, S.J. *J. Chem. Soc., Perkin Trans. 1* **1994**, 369-378. (c) Gage, J.L.; Branchaud, B.P. *Tetrahedron Lett.* **1997**, *38*, 7007-7010. (d) Goswami, S.; Mahapatra, A.K. *Tetrahedron Lett.* **1998**, *39*, 1981-1984.
12. For related tin-mediated reactions see (a) Boger, D.L.; McKie, J.A. *J. Org. Chem.* **1995**, *60*, 1271-1275. (b) Boger, D.L.; Garbaccio, R.M.; Jin, Q. *J. Org. Chem.* **1997**, *62*, 8875-8891.
13. For an alternative photochemical approach to (similar) TEMPO derivatives see Connolly, T.J.; Baldoví, M.V.; Mohtat, N.; Scaiano, J.C. *Tetrahedron Lett.* **1996**, *37*, 4919-4922.
14. Semmelhack, M.F.; Schmid, C.R.; Cortés, D.A. *Tetrahedron Lett.* **1986**, *27*, 1119-1122.