J. Chem. Sci., Vol. 121, No. 6, November 2009, pp. 1011–1015.

Conversion of α, α'-dichlorodiazene dioxides using levulinic acid under solvent-free conditions to α-chloroketones through a three-step domino process

B C VIMALA and GOPALPUR NAGENDRAPPA*

Department of Chemistry, Bangalore University (Central College Campus), Bangalore 560 001
e-mail: bcvimala@yahoo.com; gnagendrappa@gmail.com

MS received 12 May 2008; revised 6 July 2009; accepted 10 July 2009

Abstract. α-Chloroketones find numerous synthetic uses. We have developed a simple method of preparation of these compounds starting from alkenes adopting the *Green Chemistry* principle of solvent-free reaction. The procedure involves addition of NOCl generated *in situ* by the reaction of AcOH–HCl (3 : 1) with amyl nitrite to alkenes and treating the α-chloronitroso compounds obtained as dimers with levulinic acid in presence of a few drops of 6N HCl, the latter being a three-step domino reaction, in which the first is dissociation of dimer to monomer, the second is tautomerisation of the nitroso function to oxime followed by deoximation in the third step. The yields are excellent. Since the starting compounds are readily available alkenes and the reaction is carried out under mild conditions leading to excellent yields of highly useful α-chloroketones, the procedure has the potential of wide application.

Keywords. α-Chloroketones; NOCl addition to alkenes; nitroso-oxime tautomerisation; deoximation; levulinic acid; transoximation.

1. Introduction

α-Chloroketones have numerous synthetic applications. Favorskii reaction,[1] semibenzilic acid rearrangement,[2] Perkow reaction,[3] arylation,[4] catalytic cross-coupling with alkylzinc halides[5] and organotin enolates,[6] reaction with ethanolamine and mercaptoethanol,[7] Reformatsky-type reaction[8], carbonylation using palladium carbene catalysts,[9] intramolecular cyclopropanation reaction,[10] preparation of heterocyclic compounds,[11] synthesis of olefins,[12] combinatorial carbohydrate synthesis[13], are some of the examples.

α-Chloroketones are usually prepared by chlorination of ketones using various chlorinating agents such as chlorine,[14] sulfuryl chloride,[15,16] N-chlorosuccinimide,[17] trichlorocyanuric acid,[18] titanium trichloride,[19] cupric chloride,[20] Me_3SiCl–Me_2SO,[21] Me_3SiCl–MnO_2,[22] hexachloroethane,[23] and hexachloro-2,4-cyclohexadiene-1-one.[24] The ketone is directly chlorinated or through its enamine or silylenol ether derivative. α-Chloroketones are also prepared from alkyl esters,[25] 5-methylene oxazolines,[26] aromatic aldehydes by coupling with trichloromethyl derivatives,[27] and protected amino acids.[28]

Because of their wide ranging uses, we thought of their synthesis from α-chloronitroso compounds, based on our experience of nitrosochlorination of vinylsilanes,[29] and ketones.[30] We planned to develop a solvent-free route to α-chloroketones from α-chloronitroso compounds, which are readily obtained from NOCl addition to olefins, by tautomerisation of the nitroso function to oxime, followed by deoximation.

2. Experimental

Cyclopentene, cyclohexene and cycloheptene were prepared by known methods.[35] Cyclooctene, cyclododecene and norbornene were purchased from Aldrich Company. Amyl nitrite was prepared by literature procedure.[29]

The melting points were recorded by capillary method and are uncorrected. Infrared spectra were taken on a Nicolet Impact 400D instrument, for solids as KBr pellets and for liquids as thin films between NaCl plates. The NMR spectra were recorded

*For correspondence

on Bruker AC-250 instrument. Gas chromatographic analyses were carried out on a Varian Vista 6000 instrument.

2.1 *General procedure for the addition of NOCl to cycloalkenes*

Cycloalkene (10 mmol), taken in a 250 ml two-necked flask, was cooled to −10°C in an ice-salt bath. Keeping the contents of the flask stirred magnetically, 12 mmol of amyl nitrite and 1 ml of glacial acetic acid were introduced through a dropping funnel. A mixture of acetic acid and concentrated hydrochloric acid (3 : 1) was added drop-wise till the reaction was complete, as indicated by the disappearance of cycloalkene in GC, the temperature being maintained around −10°C during the reaction. Initially, the solution turned green, and became blue as the addition was continued. Eventually a white solid (the dimer) separated, which was rapidly filtered, washed with 5 ml of cold ethanol. In the case of norbornene **(6)** the dimer **(12a)** separated instantaneously, but for other adducts the dimer formation took different lengths of time, which depended not only on the cycloalkene, but on temperature, rate of addition of AcOH–HCl mixture, and even rate of stirring. The reaction time, yields, m.p.s of the dimers, and the IR spectral data of all the nitroso compounds are given in table 1.

2.2 *General procedure for conversion of α-chloronitroso compounds to α-chloroketones using levulinic acid*

An intimate mixture of 5 mmol of chloronitroso compound, 10 mmol of levulinic acid and 4 drops of 6 N HCl taken in a small flask with a short condenser was heated to about 75°C on a water bath for 4–6·5 h, the reaction being followed by TLC. Then, 50 ml of water was added, and the mixture was extracted with ether (2 × 25 ml). The combined ether extracts were washed with water (2 × 25 ml), saturated $NaHCO_3$ solution (2 × 25 ml), again water (25 ml), and finally saturated NaCl solution, and dried over Na_2SO_4. The solvent was removed and the residue was chromatographed on silica gel using petroleum ether (40–60°C) containing 1% ethyl acetate to get pure α-chloroketone. The reaction time, yields, IR and ^{1}H NMR spectral data of α-chloroketones are given in table 2.

3. Results and discussion

Nitroso compounds undergo two reactions, if structural constraints do not prevent them. One is dimerisation to diazene dioxides, and the other is tautomerisation to oximes (scheme 1). Though the stabilities of diazene dioxides vary widely, in solid state they can be stored over long periods. They dissociate in solution into monomers, and monomer-dimer equilibrium is established. Since monomers are green or blue in colour, the dissociation can be observed with naked eye. The monomer can tautomerise to the corresponding oxime, if hydrogen is present on the geminal position, under acid or base catalysis. Tautomerisation is very facile and is normally irreversible.[29,31]

The preparation of α-chloronitroso compounds is one of the classic electrophilic addition reactions of alkenes, achieved by adding nitrosyl chloride generated *in situ* or passed from an external source.[32] Conversion of α-chloronitroso to α-chloro-oxime is a simple transformation and the oxime can then be converted to ketone,[33] to get finally the desired α-chloroketone.

We planned to develop an efficient solvent-free procedure for the preparation of α-chloroketones, which find a variety of application as mentioned. After trying a few hydrolytic and oxidative procedures to bring about deoximation to ketone, we

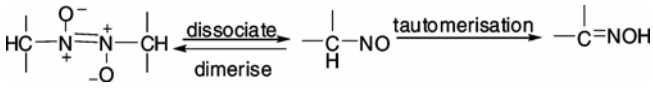
Table 1. Preparation of α-chloronitrosocycloalkanes.

α-Chloronitroso compound	Reaction time (h)	Yield (%)	m.p. (°C)	IR (cm^{-1})
7a	2	80	86–87	2965, 2940, 1647, 1570, 1472, 1261, 808, 776
8a	2·5	75	154–155	2960, 2883, 1662, 1595, 1481, 1274, 762
9 (monomer)	2·5	70	Liquid	2934, 2872, 1641, 1569, 1460, 1264, 809
10a	3	75	98–99	2934, 2857, 1672, 1528, 1331, 1284, 752
11a	4	80	134–135	2924, 2867, 1641, 1595, 1466, 1233, 778
12a	0·5	85	156–157	2960, 2878, 1636, 1559, 1455, 1238, 778

Table 2. α-Chloroketones from α-chloronitroso compounds.

α-Chloro-ketone	Reaction time (h)	Yield (%)	IR (cm^{-1})	^1H NMR ($CDCl_3$, δ)
13	5	75	2966, 2924, 1755, 1455, 1403, 1279, 1155, 845	4·15 (*t*, 1H), 1·9–2·4 (*m*, 6H)
14	4	89	2950, 2872, 1724, 1455, 1393, 1264, 1129, 798	4·5–4·0 (*m*, 1H), 2·9–2·7 (*m*, 1H), 2·5–2·3 (*m*, 2H), 2·0–1·75 (*m*, 5H)
15	4·5	85	2955, 2883, 1719, 1466, 1362, 1212, 1160, 767	4·2–4·0 (*t*, 1H), 3·0–1·5 (*m*, 10H)
16	4	86	2955, 2872, 1729, 1471, 1357, 1166, 1036, 747	4·2–4·0 (*t*, 1H), 2·75–1·25 (*m*, 12H)
17	6·5	80	2929, 2867, 1714, 1471, 1367, 1295, 1171, 736	4·5–4·0 (*t*, 1H), 2·9–2·7 (*m*, 2H), 2·6–2·0 (*m*, 2H), 2·0–1·0 (*m*, 18H)
18[a]	5	82	2966, 2883, 1771, 1466, 1305, 1181, 1083, 757	3·7–3·5 (*s*, 1H), 3·0–2·9 (*d*, 2H), 2·75–1·5 (*m*, 6 H)

[a]NOCl addition to norbornene and its derivatives is known to be *cis-exo.*[29] Hence, we presume that chlorine in 3-chloro-2-norbornanone (**18**) is *exo*



Scheme 1.

found that oxime exchange or transoximation reaction with levulinic acid[33,34] is a highly satisfactory procedure for conversion of the oxime to ketone under solvent-free condition, without affecting the chlorine at the α-position.

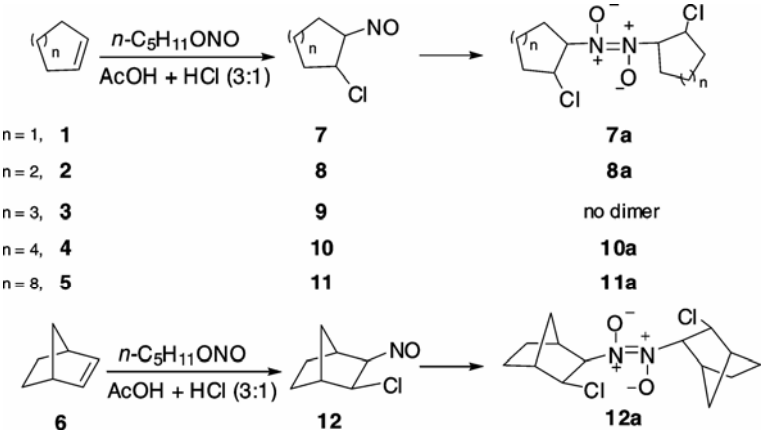
Six chloronitroso compounds were prepared by adding NOCl to cycloalkenes **1–6**. Nitrosyl chloride was generated *in situ* by the reaction of amyl nitrite with acetic acid-conc HCl (3 : 1) mixture. The products were isolated in good yields.

The NOCl adducts of cyclopentene, cyclohexene, cyclooctene, cyclododecene, and norbornene were obtained only as white dimeric solids, while the NOCl-cycloheptane adduct, α-chloronitrosocycloheptane (**9**) remained as blue monomeric liquid at ambient conditions (scheme 2) table 1. The stereochemistry of addition, in the case of **1–5**, is likely to be *trans* addition, while in the case of **6**, it is known to be *exo-cis* addition.[29,32]

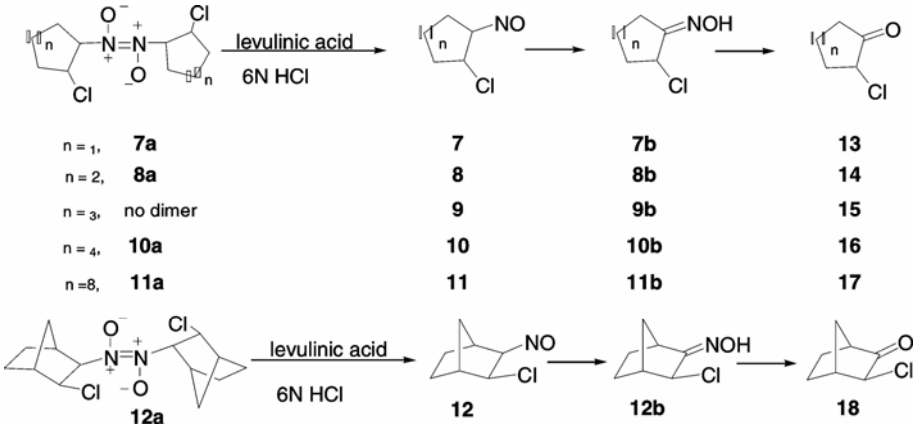
Dissociation of dimer to monomer, tautomerisation of the nitroso function to oxime and deoximation of the latter to keto function were a one pot three-step domino reaction brought about by heating to about 70°C in an oil bath for 4–6 h of a well-mixed paste of chloronitroso compound (5 mmol) with 2 equivalents of levulinic acid and 3–4 drops of 6 N HCl (scheme 3). The isolated yields of α-chloroketones are presented in table 2.

The dimers dissociate into monomers in solution, and equilibrium between monomer and dimer is established. The dissociation of dimer depends on several factors, such as the ring size, the polarity of solvent, temperature, the presence of even traces of acidic or basic impurity, etc. and it is not easy to quantify each. In the present case the most stable dimer was the norbornene-NOCl adduct (**12a**), and the least stable seems to be the dimer of α-chloronitrosocycloheptane. We had noted in an earlier study of cycloalkenyltrimethylsilane-NOCl adducts that dimerisation occurs between only enantiomer pairs.[29] In the present study also we presume that only enantiomer pairs self-assemble into dimeric forms. If it were not so, the dimers of same enantiomer could be easily separated by simple separation techniques, thus resolving the racemic mixture.

We found that the levulinic acid-6N HCl combination is the best catalyst for bringing about the three-step domino reaction, namely, dissociation of the dimer, tautomerisation of the nitroso to oxime, and finally deoximation to α-chloro-ketone. The role of levulinic acid seems to be to catalyse the deoximation of the substrate by transoximation process. That is, the oxime functionality from the substrate is transferred to the carbonyl group of



Scheme 2.



Scheme 3.

levulinic acid. This has been noted by earlier studies.[33,34] However, the mechanism is not clear. It is also noted that in the absence of levulinic acid the reaction needs more vigorous conditions such as refluxing in presence of conc. HCl and produces Beckmann rearrangement and other decomposition products, which makes it difficult to isolate the α-chloroketones and their yields would be poor. The reaction we have described here is solvent-free and only the final product needs to be extracted with ether. We did not attempt to isolate the oximes, since at the intermediate stage, the reaction mixture contained substrates, intermediates, and final products and it was difficult to isolate the oxime. The reaction is essentially, a *Green Reaction* as it does not need any solvent. The solvent ether is used only to extract the final chloroketone product, and is almost fully recovered after workup.

Acknowledgements

B C Vimala thanks the University Grants Commission (UGC), New Delhi for Teacher Fellowship under Faculty Improvement Programme, and the management of Rashtreeya Shikshana Samithi Trust, Bangalore, for granting leave and their encouragement.

References

1. (a) Kende A S 1960 *Org. React.* **11** 261; (b) Akhrem A A, Ustynyuk T K and Titov Y A 1970 *Russ. Chem. Rev.* (*Engl. Transl.*) **39** 732
2. (a) Verniest G, Bombeke F, Kubinkovich O G and De Kempe N 2002 *Tetrahedron Lett.* **43** 599; (b) Tchoubar B and Sackur O 2008 *C.R. Acad. Sci*. **1939** 1020
3. (a) Perkow W 1954 *Chem. Ber.* **87** 755; (b) Fohlisch B and Reiner S 2004 *Molecules* **9** 1
4. Durandetti M, Sibille S, Nedelec J-Y and Perichon J 1994 *Synth. Commun.* **24** 145

5. Yasuda M, Tsuji S, Shigeyoshi Y and Baba A 2002 *J. Am. Chem. Soc.* **124** 7440
6. Malosh C F and Ready J M 2004 *J. Am. Chem. Soc.* **126** 1024
7. Guseinov F I and Yudina N A 1997 *Chem. Hetero. Compounds* **33** 1001
8. (a) Yamasisawa A, Takahashid H and Arai T 2004 *Chem. Commun.* 580; (b) Estevez R E, Paradas M, Millan A, Jimenez T, Robles R, Cuerva J M and Ohra J E 2008 *J. Org. Chem.* **73** 1616
9. Zoeller J R 2006 U.S. Patent No. 2006149095
10. Bremeyer N, Smith S C, Ley S V and Gaunt M J 2004 *Angew. Chem. Int. Ed.* **43** 2681
11. (a) Kulka M 1981 *Can. J. Chem.* **59** 1557; (b) Adamo M F A, Adlington R M, Baldwin J E and Day A L 2004 *Tetrahedron* **60** 841; (c) Hirano K, Urban S, Wang C and Glorius F 2009 *Org. Lett.* **11** 1019
12. Barluenga J, Yus M and Bernad P 1978 *Chem. Commun.* 8470
13. Nacak Baystas S and Linhardt R J 2004 *Mini-Rev. Org. Chem.* **1** 27
14. Saufert W and Effenberger F 1979 *Chem. Ber.* **112** 1670
15. Warnhoff E W, Martin D G and Johnson W S 1963 *Org. Synth.* **IV** 162
16. Tabushi I and Kitaguchi H 1981 In *Synth. React.* (ed.) J S Pizey (New York: Wiley) vol 4, pp. 336–396
17. (a) Vaz A D N and Schoellmann G 1984 *J. Org. Chem.* **49** 1286; (b) Halland N, Braunton A, Bachmann S, Marigo M and Jorgensen K A 2004 *J. Am. Chem. Soc.* **126** 4790
18. Hiegel G A and Peyton K B 1985 *Synth. Commun.* **15** 385
19. Glaser J and Toth I 1986 *Chem. Commun.* 1336
20. Nigh W G and Trahanovsky W S 1973 *Oxidation in organic chemistry* (New York: Academic Press), Part B, pp. 67–81
21. (a) Bellesia F, Ghelfi F, Grandi R and Pagnoni U M 1986 *J. Chem. Res.* (*S*) **426**; (b) Fraser R R and Kong F 1988 *Synth. Commun.* **18** 1071
22. Bellesia F, Ghelfi F, Pagnoni U M and Pinetti A 1990 *J. Chem. Res.* (*S*) 188
23. Glinski M B, Freed J C and Durst T 1987 *J. Org. Chem.* **52** 2749
24. Brochu M P, Brown S P and MacMillan D W C 2004 *J. Am. Chem. Soc.* **126** 4108
25. (a) Wang D, Schwinden M D, Radesca L, Patel B, Kronenthal D, Huang M H and Nugent W A 2004 *J. Org. Chem.* **69** 1629; (b) Nugent W A and Wang D 2005 U.S. Patent No. 6924397
26. Rayle H L, Roemmele R C and Stephens R W 1999 U.S. Patent No. 5925763
27. Montana M, Terme T and Vanelle P 2006 *Tetrahedron Lett.* **47** 6573
28. Ping C, Cheng P T W, Spergel S H, Zahler R, Xuebao W, Thottathil J, Barrish J C and Polniaszek R P 1997 *Tetrahedron Lett.* **38** 3175
29. (a) Mallya M N, Nagendrappa G, Prasad J S, Sridhar M A, Lokanath N K and Begum N S 2001 *Tetrahedron Lett.* **42** 2565; (b) Mallya M N and Nagendrappa G 2006 *Arkivoc.* **14** 155
30. (a) Mohammed A H A and Nagendrappa G 2003 *Tetrahedron Lett.* **44** 2753; (b) Girija C R, Begum N S, Karim H A M A and Nagendrappa G 2004 *Acta Cryst.* **E60** 1276
31. (a) Glaser R, Murmann R K and Barnes C L 1996 *J. Org. Chem.* **61** 1047 and references cited therein; (b) Boyer H J 1969 *The chemistry of the nitro and nitroso groups* (eds) H Feues and S Patai (New York: John Whiley) Part 1
32. Gowenlock B G and Richter-Addo G B 2004 *Chem. Rev.* **104** 3315
33. For review see Corsano A, Chiacchio U and Pistara V 2001 *Synthesis* 1903
34. (a) Depuy C H and Ponder B W 1959 *J. Am. Chem. Soc.* **81** 4629; (b) Meinwald J, Meinwald Y C and Baker T N 1964 *J. Am. Chem. Soc.* **86** 4074; (c) Ponder B W and Walker D P 1967 *J. Org. Chem.* **32** 4136; (d) Timokhin V, Baranasky V A and Eliseeva G D 1999 *Russ. Chem. Rev.* **68** 73
35. Bandodakar B S and Nagendrappa G 1990 *Synthesis* **843**