Oxidative deprotection of oximes, phenylhydrazones and semicarbazones using pyridinium chlorochromate in catalytic amount with t-butyl hydroperoxide and in the solid state on montmorillonite K-10 clay support under microwave irradiation

Nemai C. Ganguly*, Mrityunjoy Datta and Prithwiraj De

Department of Chemistry, University of Kalyani, Kalyani-741 235, India

E-mail: nemai@klyuniv.ernet.in Fax: 91-33-25828282

Manuscript received 8 July 2003, revised 20 October 2003, accepted 21 October 2003

Pyridinium chlorochromate (PCC) and other oxochromium(VI) reagents have been extensively employed in excess of the stoichiometric amount (2 equivalents or more) for efficient cleavage of oximes to carbonyl compounds. The aim of this study is to replace excess use of toxic chromium(VI) reagents and develop cleaner environment-friendly general methods of cleavage of imine derivatives such as oximes, phenylhydrazones and semicarbazones using PCC in catalytic or stoichiometric amount. Two approaches of greening the deprotection process with PCC are conceived of which the first one is based on the catalytic use of the reagent (0.1 equiv.) in combination with an excess of 70% t-butyl hydroperoxide as the cooxidant. Mild selective regeneration of carbonyl compounds from oximes, phenylhydrazones and semicarbazones has been accomplished in good-to-excellent yields (70-98%) by this method. With focus on rate enhancement coupled with efficiency of cleavage, an alternative microwave-assisted solid-state solventless protocol of deprotection employing a stoichiometric amount of PCC dispersed on montmorillonite K-10 clay is also evaluated. It offers an expeditious efficient (74-98% yields) general route of cleavage of these procarbonyl compounds. Absence of overoxidation, particularly for oxidation-prone aryl aldehydes, is the key advantage of both these methods.

Developing mild efficient methods of oxidative deprotection of procarbonyl compounds is an area of considerable contemporary interest to organic chemists because of the central importance of carbonyl compounds in organic syntheses. Although the cleavage of oximes has clearly engaged most attention and a multitude of reagents have been employed for this purpose, other similar imine derivatives such as semicarbazones, phenylhydrazones and 2,4-dinitrophenylhydrazones are often preferred over oximes for isolation and purification of widely occurring natural carbonyl compounds thereby necessitating search for general protocols of cleavage of such derivatives. Among the reagents developed for oxidative deoximation, oxochromium(VI) reagents such as PCC, PCC and 30% H$_2$O$_2$, CrO$_3$, trimethylsilyl chlorochromate-chromium trioxide, pyridinium fluorochromate-30% H$_2$O$_2$ are particularly appealing because of their cost effectiveness, commercial availability and efficiency. However, despite their usefulness, an excess of the reagent is invariably required for successful cleavage often resulting in overoxidation of regenerated aldehydes and demanding isolation procedures caused by trapping of oxidation products in a large mass of reduced chromium species. Excess use of chromium(VI) reagents also poses serious environmental hazards due to their pronounced capacity of DNA cleavage and destruction of cellular reductants. To circumvent these problems and enhance environmental compatibility of Cr(VI) reagents, we set out to find cleaner general conditions of cleavage of procarbonyl compounds that avoid their excess use. We chose PCC as the representative Cr(VI) reagent for our study because of its easy availability and versatility as an oxidant. Our attention was drawn to the application of chromium-catalysed oxidations in organic synthesis and we decided to explore the catalytic use of PCC along with 70% t-butyl hydroperoxide. A solid-state solventless method of deprotection with PCC impregnated on lamellar montmorillonite K-10 clay with microwave heating was also investigated aiming at reduction of cleavage time. Herein we describe the results of oxidative cleavages with...
Ganguly et al.: Oxidative deprotection of oximes, phenylhydrazones and semicarbazones etc.

Results and discussion

(1) Cleavage of carbonyl derivatives with catalytic amount of PCC and 70% t-butyl hydroperoxide:

Oximes and phenylhydrazones of aryl aldehydes and ketones (entries 1–7) are cleaved with ease with a catalytic amount of PCC (0.1 mol equiv.) and an excess of t-butyl hydroperoxide (2 ml per mmol of substrate) in 78–98% yields. Use of 0.05 equivalent of PCC in combination with an identical amount of t-BuOOH led to disappointingly sluggish cleavage. Our attempt to use 30% hydrogen peroxide as an alternative cooxidant was a failure which may be attributed primarily to its poor solubility in methylene chloride. Rapid irreversible consumption of PCC by hydrogen peroxide to form diperoxooxochromium(VI) species¹¹, as suggested by violet colour formation upon addition of 30% H₂O₂ to a methylene chloride solution of PCC, inhibiting its catalytic role might also be responsible for the failure. No concomitant oxidation of aryl aldehydes (entries 1–3) to carboxylic acids was observed during the cleavage process. It is noteworthy that deoxidations based on PCC-30% H₂O₂ and PFC-30% H₂O₂ led to considerable overoxidation with consequent decrease in yields of carbonyl compounds. Selective nature of this protocol is demonstrated by sequential deprotection of benzil dioxime to Z-benzil monoxime (entry 7a) and finally to benzil (entry 7b) by controlling the reaction time. This method also works well for oximes of α,β-unsaturated ketone (entry 10) and sterically hindered ketones (entry 13, 14). However, we failed to isolate the α-hydroxyketone, such as benzoin by cleaving its oxime and benzil was the sole oxidation product in this case. The method is compatible with phenolic, methoxy, conjugated and unconjugated olefinic groups. No allylic oxidation was observed in the case of deoximation of cholester-3-one oxime. Deprotection of semicarbazones is found to be comparatively slower, presumably due to their poor solubility in dichloromethane (Table 1). 2,4-Dinitrophenylhydrazones of representative aryl aldehydes, ketones and cyclic ketones such as benzaldehyde, benzenophene and cyclohexanone are found to be completely resistant to the catalytic system and, significantly, to an excess of PCC (2 equiv.) and 30% H₂O₂ (2 ml per mmol of substrate) as well. Electron-withdrawal by nitro groups in 2- and 4-positions deactivates these derivatives sufficiently hindering oxidative cleavage with PCC. Although the precise nature of the catalytic process of cleavage of oximes has not been investigated, a radical route involving Cr IV, Cr V and t-BuOOH in a catalytic cycle seems likely.

Table 1. Cleavage of oximes, phenylhydrazones and semicarbazones with catalytic amount of PCC and 70% t-BuOOH

| Entry | Substrate                  | Reaction time | Yield of the carbonyl compound |
|-------|----------------------------|---------------|--------------------------------|
| 1.    | (a) Benzaldehyde oxime     | 1h            | 94                             |
|       | (b) Benzaldehyde phenylhydrazone | 45 min       | 92                             |
|       | (c) Benzaldehyde semicarbazone | 30 h         | 78                             |
| 2.    | (a) 3,4-Methylenedioxybenzaldehyde oxime | 1h       | 94                             |
|       | (b) 3,4-Methylenedioxybenzaldehyde phenylhydrazone | 1.5 h | 90                             |
| 3.    | (a) p-Nitrobenzaldehyde oxime | 10h           | 96                             |
|       | (b) p-Nitrobenzaldehyde phenylhydrazone | 2h       | 98                             |
|       | (c) p-Nitrobenzaldehyde semicarbazone | 15 h      | 90                             |
| 4.    | (a) Acetophenone oxime     | 2h            | 86                             |
|       | (b) Acetophenone phenylhydrazone | 1.5 h      | 84                             |
| 5.    | (a) Benzophenone oxime     | 2h            | 98                             |
|       | (b) Benzophenone phenylhydrazone | 1h         | 96                             |
| 6.    | (a) Z-Benzilmonoxime       | 2h            | 92                             |
|       | (b) E-Benzil monoxime      | 40 min        | 90                             |
| 7.    | (a) Benril dioxime         | 1.5 h         | 98b                            |
|       | (b) Benril dioxime         | 3.5 h         | 96c                            |
| 8.    | (a) Cyclohexanone oxime    | 2.5 h         | 90                             |
|       | (b) Cyclohexanone semicarbazone | 6h       | 78                             |
| 9.    | Salicylaldehyde oxime      | 2h            | 84                             |
| 10.   | Mesityl oxide oxime        | 4h            | 70                             |
| 11.   | Benzin oxime               | 1h            | 48d                            |
| 12.   | Cholester-3-one            | 3h            | 88                             |
| 13.   | Anthrone oxime             | 8h            | 72                             |
| 14.   | Camphor oxime              | 10h           | 74                             |

*Refers to yields isolated after chromatographic purification; the identity of the carbonyl compounds were verified by comparison with authentic samples (mixed m.p., co-TLC and superimposable IR). The isolated carbonyl compound is Z-benzil monoxime. Yield refers to benzil. Yield refers to benzil formed by overoxidation of benzoin.
(2) **Solid-state microwave-assisted deprotection of carbonyl derivatives with PCC on montmorillonite K-10 clay:**

Reduction of reaction time is an important goal of high-throughput chemistry. The fairly long deprotection times required in the catalytic method particularly for the semicarbazones prompted us to find a faster method of cleavage making PCC more useful for high-throughput chemistry. To this aim, we investigated the regeneration of carbonyl compounds from their derivatives using stoichiometric amount of PCC on montmorillonite K-10 clay support under microwave irradiation. The process was optimized using one mol equivalent of the oxidant. The results, as recorded in Table 2, show that there is dramatic acceleration in cleavage rates under this condition. The nonexcess stoichiometry employed also results in high yields of carbonyl compounds unattended with overoxidation. The good atom economy, manipulative simplicity of isolation and purification of products and eco-friendly nature due to minimisation of use of organic solvents are the advantageous features over the solution-phase oxidation with an excess of PCC and 30% H₂O₂. Oximes of aromatic aldehydes, ketones, 1,2-diketones, cyclic ketones and α,β-unsaturated carbonyl compounds are smoothly converted to carbonyl compounds within minutes in high yields. Cleavage of oximes of aromatic ketones was found to be comparatively faster than that of aromatic aldehydes. In a model experiment, it was possible to discriminate acetophenone oxime from piperalonal oxime by taking advantage of this cleavage rate differential. Thus a mixture of the oximes in 1:1 molar ratio upon being exposed to one equivalent of clay-supported PCC and microwave heating for 2 minutes afforded acetophenone and unreacted piperalonal oxime in near quantitative yields. This method is compatible with easily

| Entry | Substrate | Reaction time (in min) | Yield of the carbonyl compound |
|-------|-----------|-----------------------|-------------------------------|
| 1.    | (a) Benzaldehyde oxime | 3                     | 94                            |
|       | (b) Benzaldehyde phenylhydrazone | 3                     | 92                            |
|       | (c) Benzaldehyde semicarbazone | 3                     | 88                            |
| 2.    | (a) 3,4-Methylenedioxy-benzaldehyde oxime | 5                     | 90                            |
|       | (b) 3,4-Methylenedioxy-benzaldehyde phenylhydrazone | 4                     | 93                            |
| 3.    | (a) 4-Hydroxy-3-methoxy-benzaldehyde oxime | 4                     | 98                            |
|       | (b) Vanillin semicarbazone | 6                     | 96                            |
|       | (c) Vanillin phenylhydrazone | 3                     | 96                            |
| 4.    | (a) Salicylaldehyde oxime | 3                     | 90                            |
|       | (b) Salicylaldehyde phenylhydrazone | 2                     | 92                            |
| 5.    | (a) p-Nitrobenzaldehyde oxime | 6                     | 90                            |
|       | (b) p-Nitrobenzaldehyde semicarbazone | 4                     | 74                            |
|       | (c) p-Nitrobenzaldehyde phenylhydrazone | 4                     | 80                            |
| 6.    | (a) Acetophenone oxime | 2                     | 98                            |
|       | (b) Acetophenone semicarbazone | 2                     | 94                            |
|       | (c) Acetophenone phenylhydrazone | 2                     | 96                            |
| 7.    | (a) Benzil dioxime | 3                     | 98                            |
|       | (b) Benzil disemicarbazone | 3                     | 92                            |
| 8.    | (a) Cyclohexanone oxime | 1                     | 98                            |
|       | (b) Cyclohexanone semicarbazone | 2                     | 90                            |
|       | (c) Cyclohexanone phenylhydrazone | 2                     | 96                            |
| 9.    | 3-Methylcyclohexanone oxime | 2                     | 92                            |
| 10.   | (a) Mesityl oxide semicarbazone | 6                     | 80                            |
|       | (b) Mesityl oxide phenylhydrazone | 6                     | 88                            |
| 11.   | Anthrone oxime | 6                     | 85                            |
| 12.   | Camphor oxime | 7                     | 88                            |
| 13.   | Cholester-3-one oxime | 2                     | 96                            |
| 14.   | Lupeone oxime | 2                     | 90                            |
| 15.   | Taraxerone oxime | 3                     | 98                            |

*Yields refer to chromatographically isolated products characterised by comparison with authentic samples.*
oxidisable terminal carbon–carbon double bond (entry 14) and allylic oxidation sites (entry 15). The present study clearly demonstrates the generality of the protocol as applied to oximes, phenylhydrazones and semicarbazones. Notably, semicarbazones which are slowly cleaved by the catalytic method due to poor solubility in dichloromethane undergo clean and facile cleavage in the solid state. The method, however, failed for 2,4-dinitrophenylhydrazones.

To summarise, two eco-friendly protocols of conversion of procarbonyl compounds to carbonyl compounds using (1) catalytic amount of PCC alongwith 70% t-butyl hydroperoxide and (2) PCC impregnated on montmorillonite K-10 clay with microwave assistance have been developed. Both the methods substantially reduce consumption of toxic but efficient PCC making its use cleaner and environmentally acceptable. The balance of efficiency, selectivity, cost effectiveness and environmental compatibility represented by these cleavage methods will hopefully make them useful to organic chemists.

Experimental

PCC and 70% t-butyl hydroperoxide were procured from Fluka AG, Basel and used as such. Montmorillonite K-10 clay was purchased from Lancaster Chemicals, U.K. Oximes, semicarbazones and phenylhydrazones were prepared by standard literature methods12. Solvents used for experiments and chromatographic purifications were used without additional purification. A domestic microwave oven (B.P.L., India) operating at 2450 MHz was used for microwave irradiation. Silica gel (60–120 mesh, B.D.H., India) was used for chromatographic experiments.

Representative procedure for the catalytic cleavage of oximes and related imines with PCC and 70% t-butyl hydroperoxide :

To a well-stirred solution of benzaldehyde oxime (710 mg, 5.87 mmol) in dichloromethane (6 ml) was added PCC (125 mg, 0.58 mmol) and then 70% t-butyl hydroperoxide (12 ml) slowly. The reaction mixture was stirred for 1 h (with TLC-monitoring) when the initial dark brown colour of the solution became pale yellow. It was then poured into cold water (50 ml) and the organic layer was separated. The aqueous layer was extracted with ether (2 x 10 ml) and the extract was combined with the dichloromethane layer. The combined organic layer was washed successively with 10% aqueous sodium hydrogen sulphite solution (2 x 5 ml), 2 N HCl (10 ml) and brine (10 ml) and then dried over anhydrous sodium sulphate. The crude residue obtained after removal of organic solvents was chromatographed over silica gel employing chloroform-light petrol (25 : 75) as the eluent to give pure benzaldehyde (616 mg, 94%).

Typical procedure used for cleavage of oximes, phenylhydrazones and semicarbazones using solid PCC on montmorillonite K-10 support under microwave irradiation :

Acetophenone oxime (900 mg, 6.67 mmol) in dichloromethane solution (1 ml) was mixed with montmorillonite K-10 clay (0.6 g) and vacuum-dried. PCC (140 mg, 0.65 mmol) in dichloromethane (1 ml) was separately impregnated with K-10 clay (0.7 g) and similarly dried. The oxime and PCC, both on clay support, were then intimately mixed and irradiated with microwaves for 2 min at 300 Watt. After the reaction was over, the cooled reaction mixture was extracted with dichloromethane (30 ml), evaporated to a thick liquid and then subjected to chromatographic purification over silica gel using light petrol (60–80°) as the eluent to give acetophenone (780 mg, 98%).

Acknowledgement

We sincerely thank Dr. J. Muzart, Universite de Reims, France for encouragement and helpful suggestions. One of the authors (M.D.) thanks University of Kalyani for financial assistance by way of a research fellowship.

References

1. T. W. Greene and P. G. M. Wuts, "Protective Groups in Organic Synthesis", 3rd ed., John Wiley & Sons, New York, 1991, pp. 352-359; A Corsaro, U. Chiacchia and V. Pistara, Synthesis, 2001, 1003.
2. N. C. Ganguly, A. K. Sukai, S. De and P. De, Synth. Commun., 2001, 31, 1607 and the references cited therein.
3. J. R. Maloney, R. E. Lyle, J. E. Saavedra and G. G. Lyle, Synthesis, 1978, 212.
4. J. Drabowicz, Synthesis, 1980, 125.
5. H. C. Araujo, G. A. L. Ferreira and J. R. Mahajan, J. Chem. Soc., Perkin Trans. 1, 1974, 2257.
6. J. M. Aizpurua, M. Juaristi, B. Lecea and C. Palomo, Tetrahedron, 1985, 41, 2903.
7. (a) T. K. Ganesan, S. Rajagopal and J. B. Bharathy, Tetrahedron, 2002, 56, 5885; (b) P. A. Lay and A. Levin, J. Am. Chem. Soc., 1998, 120, 6704.
8. M. Cieslak-Golonska, Polyhedron, 1996, 15, 3667.
9. J. Muzart, Chem. Rev., 1992, 92, 113.
10. (a) R. S. Varma, Green Chemistry, 1999, 1, 43; (b) For an extensive review on the use of clays as catalysts in organic synthesis, see: M. Balogh and P. Laszlo, "Organic
Chemistry Using Clays", Springer-Verlag, New York, 1993; (c) R. S. Varma, "Expeditious Solvent-free Organic Synthesis Using Microwave Irradiation", pp. 292-312. in "Green Chemical Syntheses and Processes", eds. P. T. Anastas, L. G. Heine and T. C. Williamson, ACS Symposium Series 767, American Chemical Society, Washington DC, 2000.

11. F. A. Cotton, G. Wilkinson, C. A. Murillo and M. Bochmann, "Advanced Inorganic Chemistry", 6th. ed., John Wiley & Sons, New York, 1999, p. 755.

12. Oximes, phenylhydrazones and semicarbazones were prepared by standard methods: A. I. Vogel, "A Textbook of Practical Organic Chemistry", 3rd. ed., ELBS and Longman Group Ltd., London, 1973.