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A mild oxidative method for the preparation of γ-hydroxy-α-nitroolefins from α,β-epoxyketoximes using IBX

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ABSTRACT

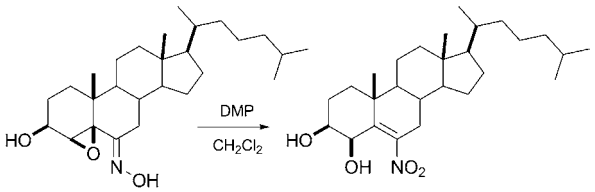
An efficient method for the preparation of γ-hydroxy-α-nitroolefins from α,β-epoxyketoximes has been developed using IBX. The reaction occurs at room temperature without the formation of over-oxidation products and also has an easy work-up procedure.

The nitro group is particularly versatile in synthesis as it can be transformed into a plethora of functionalities. The Nef reaction, nucleophilic displacement, reduction to an amino group and conversion into a nitrile oxide are only some examples of the possible transformations.[1] More specifically, conjugated nitroolefins have found numerous applications in organic synthesis.[2] The character of these systems as electron-deficient alkenes allows easy 1,4-addition reactions and this opens the way to synthetically useful C–C and C–X (X = N, O) bond-forming reactions.[3] These compounds are also powerful dienophiles or dipolarophiles in cycloaddition reactions to generate new carbon–carbon single or double bonds. A number of methods have already been developed for the preparation of nitroolefins, such as the nitroaldol (Henry) reaction,[4] but there is considerable interest in developing new and simple methods for the preparation of this type of compound.

On the other hand, organic derivatives of hypervalent iodine reagents have found extensive applications in synthetic organic chemistry because of their selectivity, efficiency and simplicity of use.[5] Among these compounds, 2-iodoxybenzoic acid (IBX) is becoming the reagent of choice due to its ease of handling, stability/longer shelf life, tolerance to moisture and zero toxic waste generation. IBX was initially used for the oxidation of alcohols to carbonyl compounds,[6] but its synthetic value has been extended to a variety of other useful transformations.[7]

The oxidative conversion of oximes into nitro functions using trifluoroperoxyacetic acid was reported a long time ago.[8] Some years later Takamoto et al. reported the transformation of α,β-epoxyketoximes to γ-hydroxy-α-nitroolefins using the same reagent.[9] The products were employed for the synthesis of 3-nitrocycloalkenones for use as dienophiles.[10] Furthermore, the oxidative elimination of α-haloketoximes using trifluoroperoxyacetic acid to give α-nitroolefins has been reported.[11] However, the wider reactivity of the trifluoroperoxyacetic acid (Baeyer–Villiger oxidation, epoxidation of alkenes, etc.) narrowed the applications of this reagent in that chemical transformation.

We report here a new oxidative method for the conversion of α,β-epoxyketoxime compounds to γ-hydroxy-α-nitroolefins in good to moderate yields. The method employs IBX as a very mild oxidant that overcomes some of the disadvantages associated with the use of trifluoroperoxyacetic acid. Our method can be characterised by two striking features: (a) easy work-up procedure, (b) the reaction occurs at room temperature without the formation of



Scheme 1.

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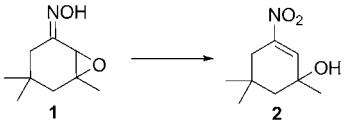
Table 1
Effect of oxidant, additives and reaction conditions on yield



1 2

Oxidant (equiv)	Additive	Solvent/*T* (°C)	Product	Time (h)	Yield (%)
DMP (1.1)	Thiourea (0.2 equiv)/CH_3COONa (1.0 equiv)	CH_3CN/0	**2**	8.5	71
IBX (2.5)	—	CH_3CN/60	Complex mixture	0.5	—
IBX (3.0)	TEAB (3.0 equiv)	CH_3CN/60	**2** and α-hydroxyisophorone (4:5)	0.5	20
IBX (1.5)	NMO (1.5 equiv)	DMSO/rt	**2**	24	81

over-oxidation products as a result of the high chemoselectivity and the mild nature of IBX. To the best of our knowledge, the applicability of IBX in the preparation of γ-hydroxy-α-nitroolefins from α,β-epoxyketoximes has not been reported previously.

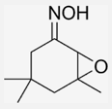
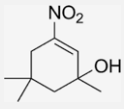
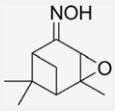
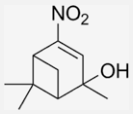
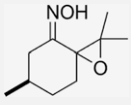
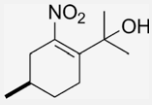
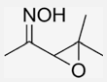
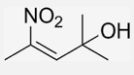
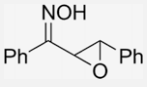
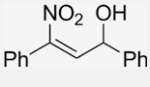
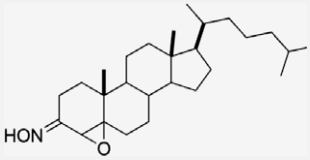
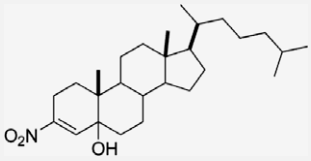
During our studies directed at the synthesis of several hydroximinosteroids as antitumour agents,[12] we observed that 3β,4β-dihydroxy-6-nitrocholest-5-ene was formed when 4β,5β-epoxy-3β-hydroxy-6*E*-hydroximinocholestane was treated with Dess–Martin Periodinane (DMP) in CH_2Cl_2 (Scheme 1). The chemical structure of the product was deduced from its NMR spectra and MS data.[13]

We then investigated the action of DMP and IBX on a variety of structurally simplified α,β-epoxyketoximes in order to study this reaction.

Initial studies were carried out using epoxyisophorone oxime as a model substrate with variations in the solvent, temperature and additives. Although DMP and IBX are suitable for this chemical transformation, IBX has become the reagent of choice because it is cheaper and more widely available.[14] The use of a standard solvent (such as acetonitrile) in conjunction with IBX was not fruitful (Table 1). On the basis of the studies performed, the optimum conditions involved carrying the reaction out in DMSO in the presence of 1.5 equiv of IBX and *N*-methylmorpholine-N-oxide (NMO) as an additive at room temperature for 24 h.[15]

The scope and limitations of our new method for the synthesis of these nitroolefins were studied by preparing a variety of other compounds using the optimised conditions. The α,β-epoxyketoxime starting materials were prepared from their corresponding α,β-unsaturated ketones by treatment with H_2O_2 in basic media followed by oximination with NH_2OH. The results are summarised in Table 2. Good yields were obtained with epoxyketoximes generating tertiary hydroxy derivatives except in the

Table 2
Oxidative conversion of α,β-epoxyketoximes to γ-hydroxy-α-nitroolefins with IBX/NMO in DMSO

Entry	Substrate	Product[a,b]	Yield[c] (%)
1			81
2			74[d]
3			41
4			52
5			0
6			91

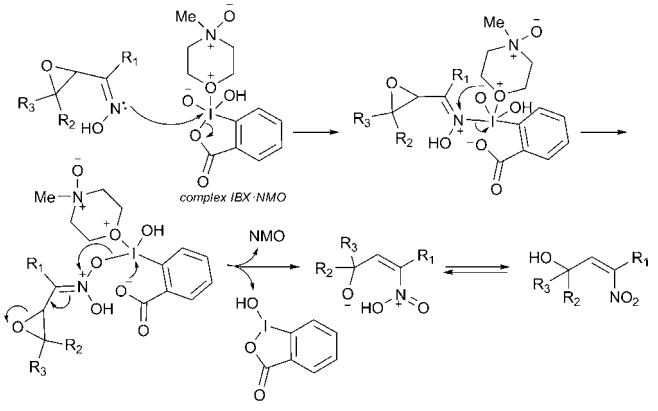
[a] Structures were confirmed from their NMR and MS data.
[b] Spectral data for compounds which have not been reported previously are given in Ref. 19.
[c] Yields of products isolated after column chromatography.
[d] Diastereoisomeric mixture in a ratio (5:1).

case of exocyclic (entry 3) and acyclic (entry 4) epoxides. A complex mixture including some trace of starting material is observed in the ^{1}H and ^{13}C NMR spectra of the reaction product corresponding to entry 5, probably because the epoxyketoxime is acylic and the hydroxylated derivative would be secondary.

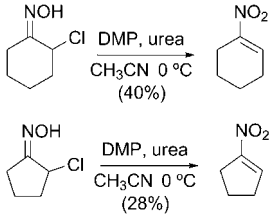
Although detailed mechanistic studies have not been carried out, a plausible mechanism for the IBX reaction is presented in Scheme 2. We suggest that the reaction proceeds through the formation of an intermediate by the direct attack of the nitrogen atom to iodine, which would then evolve to form the O=N double bond to originate the nitro functionality, opening of the epoxy group to generate a hydroxyl group at the γ-position and the subsequent expulsion of iodosobenzoic acid (IBA). In fact, during the work-up, the formation of a white precipitate, which was mainly composed of IBA, was indicative of a successful result.[16] Additionally, this mechanism is supported by the proposal that the formation of an NMO·IBX complex in DMSO improves the reactivity.[17] Interestingly, it has been reported that IBX and DMP oxidatively deoximate ketoximes smoothly at room temperature in very high yields.[18] Thus, we anticipated that the treatment of oximes bearing a good leaving group at the α-position with a hypervalent iodine reagent such as DMP or IBX favours the formation of the nitroolefin rather than the regeneration of the ketone.

This hypothesis would also explain the transformation of an α-acetoxyoxime to a nitroolefin using DMP reported by Ganem and co-workers to obtain 2-nitroglycals.[20] In an effort to find evidence for this process, we carried out the reaction of two 2-chlorooximes with DMP. Treatment of 2-chlorocyclohexanone oxime or 2-chlorocyclopentanone with DMP at 0 °C gave the corresponding nitroolefins (Scheme 3) without the regeneration of the carbonyl group, a finding that is consistent with the aforementioned hypothesis.

In summary, we have found that IBX is an efficient oxidant for the conversion of α,β-epoxyketoximes to their corresponding γ-hydroxy-α-nitroolefins. This transformation is also possible using DMP. Thus, α,β-unsaturated carbonyl compounds can be converted to γ-hydroxy-α-nitroolefins using this transformation. The deoximation of ketoximes with DMP is hampered by the presence of a good leaving group at the α-position as this leads to the corresponding conjugated nitrolefins instead of regeneration of the ketone. Further research on this reaction is underway.



Scheme 2. Plausible mechanism for the formation of γ-hydroxy-α-nitroolefins from α,β-epoxyketoximes.



Scheme 3.

Acknowledgements

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13. *Spectral data*: ^{1}H NMR (200 MHz, $CDCl_3$) δ_H: 4.40 (d, J = 3.5 Hz, 1H), 3.47 (br d, J = 10.6 Hz, 1H), 2.36 (d, J = 1.9 Hz, 1H), 2.32 (d, J = 4.1 Hz, 1H), 2.04 (td, J = 12.4 and 3.1 Hz, 1H), 1.28 (s, 3H), 0.91 (d, J = 6.4 Hz, 3H), 0.86 (d, J = 6.6 Hz, 6H), 0.68 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ_C: 149.90 (s), 140.36 (s), 71.00 (d), 68.03 (d), 56.21 (d), 55.94 (d), 48.90 (d), 42.33 (s), 39.44 (t), 39.26 (t), 37.14 (s), 36.08 (t), 35.68 (t), 35.68 (s), 33.32 (t), 31.59 (d), 28.06 (t), 27.96 (d), 24.45 (t), 24.01 (t), 23.79 (t), 22.77 (q), 22.52 (q), 21.39 (q), 20.37 (t), 18.64 (q), 11.78 (q). (+)-LRESIMS m/z (%): 470 ([M+Na]$^+$, 36).
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15. *General experimental procedure*: A mixture of IBX (1.5 equiv) and NMO (1.5 equiv) was dissolved in dry DMSO by stirring at room temperature until complete dissolution (~15 min), that is until the suspension becomes transparent. To this solution was added the α,β-epoxyketoxime (1 equiv) and the mixture was stirred vigorously at the same temperature until completion of the reaction, which was monitored by thin-layer chromatography. The reaction mixture was diluted with an equal volume of aqueous $NaHCO_3$ (5%), filtered through a pad of Celite and extracted with diethyl ether for three times. The combined organic phase was washed with saturated $NaHCO_3$ solution, water, brine and dried ($MgSO_4$). Evaporation of the solvent left the crude product, which was in some cases further purified by column chromatography on silica gel to provide the pure γ-hydroxy-α-nitroolefin. All products were characterised by ^{1}H NMR, ^{13}C NMR and MS, and identified in some cases by comparison with reported values.
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19. *Nitroolefins from verbenone* (entry 2): Major isomer: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.78 (t, J = 1.8 Hz, 1H), 3.18 (td, J = 5.7, 1.7 Hz, 1H), 2.61 (dt, J = 10.7, 5.7 Hz, 1H), 2.10 (td, J = 5.7, 1.7 Hz, 1H), 1.63 (d, J = 10.7 Hz, 1H), 1.48 (s, 6H), 0.94 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.08 (s), 130.99 (d), 71.91 (s), 53.12 (d), 47.73 (s), 42.98 (d), 32.28 (t), 26.74 (q), 25.87 (q), 23.44 (q); minor isomer: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.78 (t, J = 1.8 Hz, 1H), 3.06 (br t, J = 5.6 Hz, 1H), 2.41–2.29 (m, 1H), 1.84 (s, 1H), 1.69 (s, 1H), 1-44 (s,3H), 1-42 (s,3H), 1.01 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.08 (s), 130.99 (d), 61.98 (s), 52.57 (d), 47.73 (s), 41.36 (d), 29.67 (t), 26.74 (q), 25.87 (q), 23.44 (q); (−)-HRESIMS m/z: 196.0971 [M−H]$^-$, (calcd for $C_{10}H_{14}NO_3$, 196.0979). *Nitroolefin from pulegone* (entry 3): ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.66–2.55 (m, 1H), 2.19–2.11 (m, 2H), 2.06 (m, 1H), 1.91 (brs, 1H), 1.78 (m, 2H), 1.42 (s, 3H), 1.36 (s, 3H), 1.01 (d, J = 6.5 Hz, 3H). ^{13}C

NMR (75 MHz, $CDCl_3$) δ 144.20 (s), 136.87 (s), 73.28 (s), 36.71 (t), 29.99 (t), 28.58 (q), 28.58 (q), 28.28 (d), 26.12 (t), 20.81 (q); (+)-HRESIMS *m/z*: 222.1101 $[M+Na]^+$, (calcd for $C_{10}H_{17}NNaO_3$, 222.1100). *Nitroolefin from cholesterol derivative* (entry 6): ^1H NMR (300 MHz, CDCl3) δ 6.99 (d, J = 1.8 Hz, 1H), 1.03 (s, 3H), 0.91 (d, J = 6.6 Hz, 3H), 0.88 (d, J = 6.6 Hz, 6H), 0.68 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.38 (s), 136.43 (d), 72.60 (s), 56.06 (d), 55.92 (d), 43.54 (d), 42.41 (s), 39.62 (t), 39.47 (t), 38.80 (s), 36.09 (t), 35.71 (d), 35.47 (t), 34.79 (d), 28.76 (t), 28.12 (t), 27.98 (d), 27.45 (t), 24.09 (t), 23.79 (t), 22.77 (q), 22.57 (q), 22.25 (t), 21.06 (t), 18.64 (q), 15.54 (q), 11.86 (q); (+)-LRFABMS *m/z*: 432 $([M+H]^+$, 5), 416 $([M-O+H]^+$, 15), 385 (100); (+)-HRESIMS *m/z*: 416.3506 $[M-O+H]^+$, (calcd for $C_{27}H_{46}NO_2$, 416.3523).

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