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A mild preparation of α-halo-α,β-enones from cyclic enones.

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Abstract
A simple one pot procedure for the selective transformation of cyclic enones into α-halo-α,β-enones is reported using dimethyldioxirane and metal halides / Amberlyst 15. The method appears particulary appealing for the preparation of labelled molecules for use with the CMIA techinique. © 1999 Published by Elsevier Science Ltd. All rights reserved.

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In the last few years a new immunoassay technique, coined carbonylimmunoessay (CMIA) has been developed.[1] In conjunction with a project in this field we planned to introduce metallocarbonyl fragments in biomolecules by the Stille[2] reaction between α-halo-α,β-enones and trimethyltin derivatives. Introduction of bromine in position 4 of testosterone, for example, seemed to be a reasonable way of labelling that molecule while minimising structural changes to the molecular framework.

This project prompted us to develop a mild and efficient direct transformation of enones into α-haloenones, substrates also employed for several types of synthetic transformations, e.g. as α-acyl vinyl anion equivalents.[3] Some methods are reported in the literature for performing such transformations,[4] but they failed when applied to complex substrates such as steroids.

In recent years we have performed a series of epoxidations, with dimethyldioxirane (DMD), of electron poor and highly hindered double bonds, such as those found on the framework of steroid systems, that are usually much less reactive alkenes.[5] On the other hand we have also extensively studied the opening of oxirane rings by metal halides.[6]

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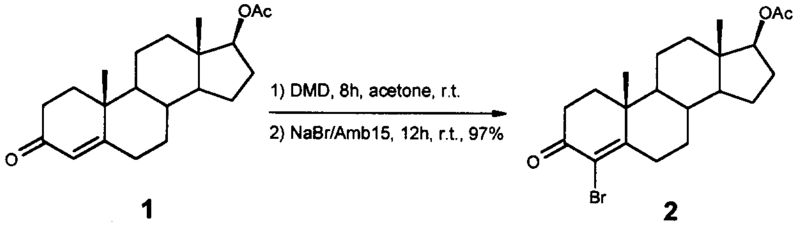
Among the methodologies explored, the use of a NaBr/Amberlyst 15 system was shown to allow the highly regioselective conversion of epoxides to halohydrins.[7]

Since the reaction conditions for this process (acetone, r.t.) were compatible with those used in the DMD oxidation step, we considered the possibility of using the two methodologies in sequence to perform a direct "one pot" transformation (presuming that the acidity of Amberlyst 15 would allow dehydration of intermediate bromohydrins).

The first experiment was carried out on testosterone acetate **1** (scheme 1) and was in perfect agreement with our hypothesis; the expected 4-bromotestosterone acetate **2** being obtained in excellent yield (97%) using mild reaction conditions and in a 'one pot' procedure.

Scheme 1.



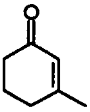
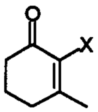
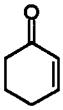
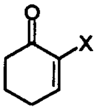
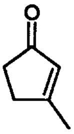
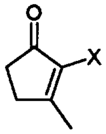
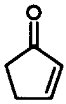
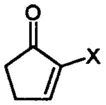
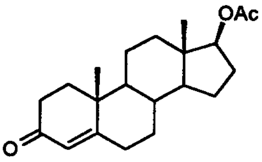
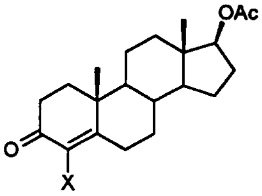
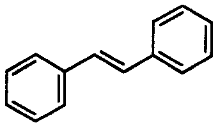
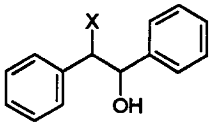
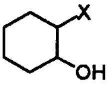
In view of this good result we extended the reaction to other substrates so as to explore the generality of the method.

As shown in table 1, typically with cyclic enones submitted to the "one pot" reaction the corresponding α-halo-α,β-enones were formed in good to excellent yields. Substitution on the β-position does not appear to be detrimental to the success of the process; meanwhile entries 11-13 show that conjugation of the double bond with a carbonyl group is necessary. This suggests that the driving force for the elimination step must be the restoration of the enone system; in fact the same transformation on stilbene (entry 11) or on a simple olefin (entry 13) leads exclusively to the corresponding halohydrin.

Mechanistically, the first step of the process is undoubtedly epoxide formation; subsequent treatment with NaX/Amberlyst 15 gives the halohydrin intermediates which are then spontaneously dehydrated to afford the enone products. To confirm this hypothesis for some less reactive substrates (entries 3 and 7) it was possible to isolate the 2-bromo-3-hydroxy ketones which, when subsequently treated with Amberlyst 15 in acetone, yielded the enone products.

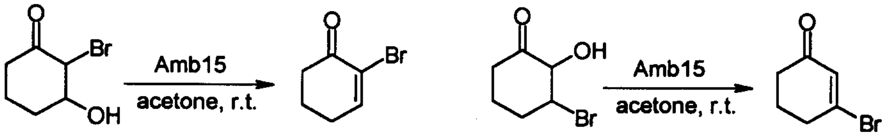
The regioselectivity of halide introduction at the C-2 position occurs in the opening of the oxirane ring and not in the dehydration step.

Table 1.

Entry	Substrate	Method[a]		Product	Yield%
1		A	X = Br		96
2		B	X = Cl		92
3		A	X = Br		95
4		B	X = Cl		90
5		A	X = Br		96
6		B	X = Cl		93
7		A	X = Br		95
8		B	X = Cl		88
9		A	X = Br		97
10		B	X = Cl		89
11		A	X = Br		82
12		A	X = Br		85
13		B	X = Cl		76

[a] method A: DMD, then NaBr/Amb15 or LiBr/Amb15[8]; method B: DMD, then NaCl/Amb15 or LiCl/Amb15[8]

Scheme 2.



3 4 5 6

To support this hypothesis we dehydrated, under the same reaction conditions, separately the two regioisomeric bromohydrins **3** and **5** (**3** was isolated from the mixture before reaction completition; **5** was prepared from 2,3-epoxycyclohexanol, by a procedure of oxirane ring opening and selective diol oxidation as described in previous work[9]). Both compounds gave products in which the halogen atom retained its original position (Scheme 2).

As a general procedure for the one-pot preparation of cyclic 2-bromoenones, 1 mmol of α,β-unsaturated ketone was treated with 1 eq. of a 0.09M solution of DMD in acetone in the dark at room temperature for 8 hrs. When the reaction was complete, by TLC analysis, 4 eq. of NaBr or LiBr and 860 mg of Amberlyst 15 were added and the mixture stirred at r.t. for an additional 12 hrs. The mixture was filtered and the solvent evaporated. If necessary, products were purified by flash chromatography, but usually they were fully characterised without any need for further purification. Studies on the application of these methods in the synthesis of biologically active compounds are in progress.

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