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A Preparation Of Haloalkylidene Cyclopentanones

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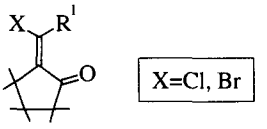
Abstract: A radical-based 5-*exo-dig* cyclisation, initiated by addition of a trichloromethyl radical to an acyclic acetylenic ketone with an appropriately positioned double bond, has been employed to produce a variety of cyclic haloalkylidene cyclopentanones in moderate to excellent yields and with a high degree of stereoselectivity for the (*E*)-isomer. © 1997 Elsevier Science Ltd.

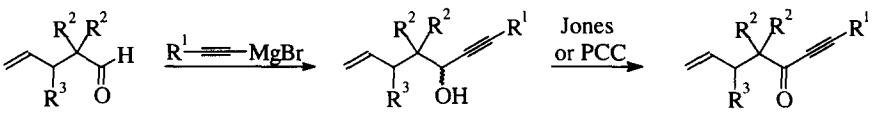
Previously we have developed a radical-based method for the stereoselective preparation of iodoalkylidenelactones[1], and are now endeavouring to extend this work towards the synthesis of similar unsaturated ketones. Like their more common lactone counterparts, cyclic *exo*-methylene ketones often display biological activity. Specific examples include sarkomycin[2], an anti-tumour agent, and hypnophilin[3], which exhibits antibiotic activity.

We felt that it would be advantageous to develop a synthetic method which extended beyond the target of α-methylene ketones. A route which provided cyclic haloalkylidene ketones (**1**) would enable access to a range of β-substituted derivatives suitable for structure/activity studies.



(**1**)

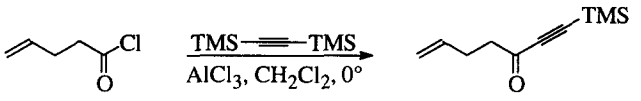
Our strategy was to synthesise appropriately substituted acyclic ynones (**2**) with a suitably placed double bond, then induce a 5-*exo-dig* cyclisation by addition of an electrophilic radical to the double bond. With one exception, substrates were prepared via addition of acetylenic Grignard reagents to aldehydes as shown in Scheme 1.



(**2**)

Scheme 1. Synthesis of cyclisation substrates

The TMS substituted compound (**2j**) was conveniently prepared directly from the acid chloride and bis(trimethylsilyl)acetylene (Scheme 2)[4].

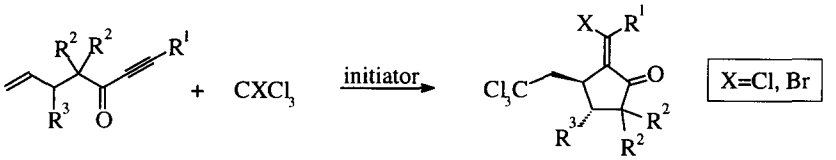


(**2j**)

Scheme 2. Preparation of TMS derivative (2j)

Cyclisation to the haloalkylidene ketones (**3**) could be induced by addition of an electrophilic free radical to the double bond (Table 1). This was achieved most conveniently by reaction with neat bromotrichloromethane using AIBN as the initiator. Reactions using this procedure proceeded rapidly to completion, with purification usually involving a simple filtration of the crude product through a short silica-gel column.

Table 1. (*E*)-Haloalkylidene cyclopentanone preparations.

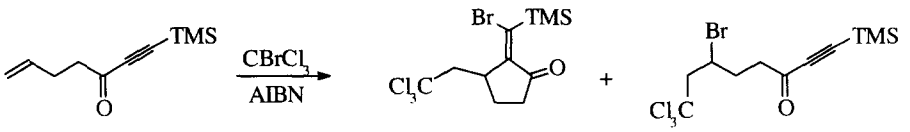


(**2**) (**3**)

Substrate	R^1	R^2	R^3	X	Method[5]	Yield (%)[6]
(**2a**)	C_6H_{13}	CH_3	H	Br	A	78
(**2b**)	C_6H_{13}	CH_3	H	Cl	C	60
(**2c**)	C_6H_5	CH_3	H	Br	A	91
(**2d**)	C_6H_5	CH_3	H	Cl	C	89
(**2e**)[7]	TMS	CH_3	H	Br	A	90
(**2f**)	C_6H_{13}	CH_3	CH_3	Cl	C	80
(**2g**)	C_6H_5	CH_3	CH_3	Br	A	80
(**2h**)	TMS	CH_3	CH_3	Br	A	88
(**2i**)	TMS	CH_3	CH_3	Cl	C	73
(**2j**)[7]	TMS	H	H	H	B	78
(**2k**)	C_6H_{13}	$-(CH_2)_5-$	H	H	A	52
(**2l**)	C_6H_5	$-(CH_2)_5-$	H	H	A	79
(**2m**)	TMS	$-(CH_2)_5-$	H	H	A	71

Substrates with a geminal dialkyl grouping in the chain were cyclised satisfactorily using this method, but a reactant with an unsubstituted chain (**2j**) gave a 1:1 ratio of the cyclised ketone (**3j**) and the simple addition product (**4**) (Scheme 3). In this case, reducing the concentration of bromotrichloromethane by using toluene as

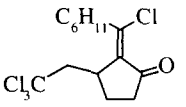
solvent and proceeding with slow addition of the tetrahalomethane suppressed the formation of (**4**) and resulted in a good yield of (**3j**).



(**2j**) (**3j**) (**4**)

Scheme 3. Competition between cyclisation and addition.

Carbon tetrachloride additions proceeded more slowly and required dibenzoyl peroxide as the initiator. In this case, work up using aqueous ammonia was employed to facilitate complete separation of the product from residual peroxide. For each cyclisation, ^{1}H NMR spectral data indicated that only one isomer had been formed. This proved to have the (*E*)-geometry at the double bond as photochemical isomerisation of (**3b**) gave an (*E*)/(*Z*) mixture from which the (*Z*)-isomer (**5**) was isolated. The side chain allylic methylene proton signal of (**5**) appeared at δ2.59 (t, *J* = 7.5 Hz) compared to the corresponding signal for (**3a**) at δ3.03. This (*E*)-selectivity matches that which has already been observed in the formation of iodoalkylidene lactones by a similar free radical process, and which has been explained in terms of the charge developing in the heteroatom transfer step of the reaction[1].



(**5**)

Alkyne substitution was required as reaction with a substrate with R^1=H produced a complex mixture. However, the TMS derivatives provide potential access to halomethlene derivatives[8].

Substrates (**2f**)-(**2i**) contained an existing chiral centre and had the potential to yield either *cis* or *trans* substituted ring systems. In all cases only a single diastereoisomer of the cyclic product (**3f-3i**) was obtained and, in the case of (**3f**) this was shown to be the *trans*-isomer by ^{1}H NMR nuclear Overhauser enhancement studies. Key enhancements are summarised in Figure 1.

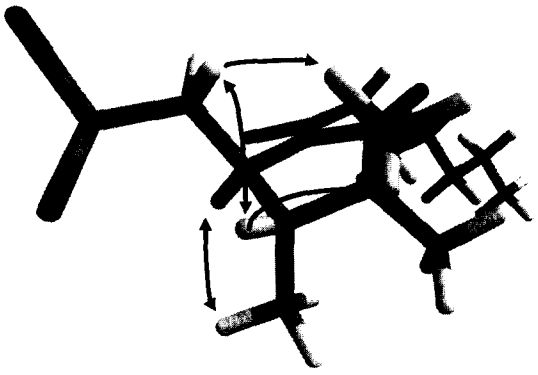


Figure 1. NOE enhancements for (3f).

Molecular modelling[9] of this structure predicted that the conformation with pseudoaxial groupings illustrated in Figure 1 would be lower in energy by 2.5 kJ mol^{-1} than that with pseudoequatorial groupings. Predicted coupling constants for the two conformations were 1.2 and 11.9 Hz respectively. The observed coupling constant (1.5 Hz) matches that predicted for the conformation shown.

In conclusion, we have established a route to α-haloalkylidene cyclopentanones by way of a radical-based 5-*exo-dig* cyclisation which proceeds stereoselectively in moderate to excellent yields. The resulting vinyl halide lends itself to further modification as we have already demonstrated for the similar lactone systems[10,11].

ACKNOWLEDGEMENTS

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5. *Method A:* The substrate (0.4 mmol) and AIBN (0.02 mmol) in CCl_3Br (4.5 ml), were heated under reflux. Reaction was monitored by TLC and further AIBN added if required. The reaction mixture was filtered through a short silica column (5 g) eluting with ether/hexanes (1:9 or 1:4 as appropriate). *Method B:* To the substrate (1.1 mmol) in toluene (4.0 ml), were added CCl_3Br (1.3 mmol) and AIBN (0.05 mmol) and the solution heated under reflux. The reaction was monitored by TLC and four further portions of AIBN and CCl_3Br were added at 15 min. intervals. **CAUTION**- benzyl bromide is formed (**LACHRYMATOR**). Work up as for A. *Method C:* The substrate (0.4 mmol) and DBP (0.02 mmol) in CCl_4 (4.5 ml), were heated under reflux. Reaction was monitored by TLC and further DBP was added after 7 h if required. After removal of the solvent, rectified spirits (2 ml) and aqueous NH_3 (1 ml, 25% w/v) were added to the crude product. The reaction mixture was stirred at room temperature until TLC showed no DBP. Concentration under reduced pressure was followed by work up as for A.
6. Isolated yields. All new substrates (**2**) and all products (**3**) were characterised fully.
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