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Unusual access to 5-methoxy or 5,5-dimethoxy-4-methyl-3-pyrrolin-2-ones from chlorinated 4-methyl-pyrrolidin-2-ones

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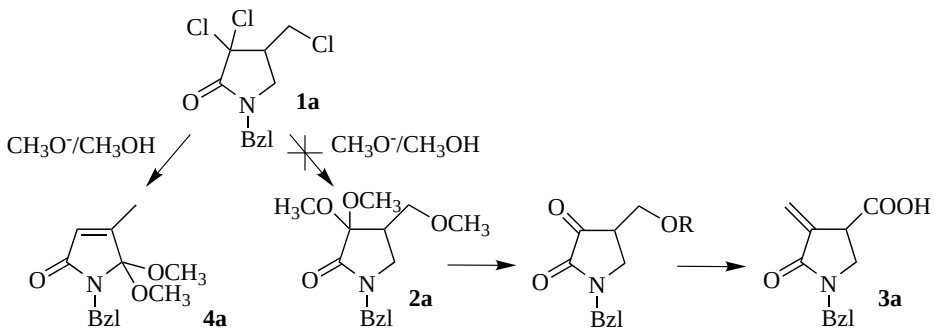
Abstract—The reaction of *N*-substituted 4-methyl-2-pyrrolidinones, carrying not less than two chlorine atoms on the C(3) and C(6) carbons afforded with alkaline methoxide in methanol, under mild conditions, the corresponding 5-methoxy or 5,5-dimethoxy-4-methyl-3-pyrrolin-2-ones in satisfactory yields.

The synthesis of isosteric aza-analogues of biologically active lactones is gaining interest among organic chemists.[1,2] The replacement of the endocyclic oxygen with a nitrogen atom leads to lactams of comparable activity, but which are less toxic and/or less metabolically labile than their natural counterparts. Therefore, these are more suitable for chemotherapeutic applications.[2–4] Recently, we were involved in a project aiming at the chemo-enzymatic synthesis of aza-analogues[5] of α-methylene paraconic acids.[6–8] The synthetic strategy to the paraconic acids target **3a** started from the *N*-benzyl-4-chloromethyl-3,3-dichloropyrrolidin-2-one **1a** (Scheme 1), a material readily available through halogen atom transfer radical cyclisation, promoted by $CuCl(TMEDA)_2$, of the *N*-allyl-*N*-benzyl-2,2,2-trichloroacetamide.[9] The halogenated pyrrolidin-2-one **1a** was selected, after retro-analysis, in view of the straightforward introduction of the 3-alkylidene group at C(3) from the 3,3-dihalo function via an intermediate 3-oxo function (Scheme 1).

Our first endeavour was routed to the alkoxy-dehalogenation of compound **1a,** using lithium methoxide in methanol. A range of conditions were evaluated. The reaction gave generally a single, easy recoverable, product. Astonishingly, after spectroscopic analysis



Scheme 1.

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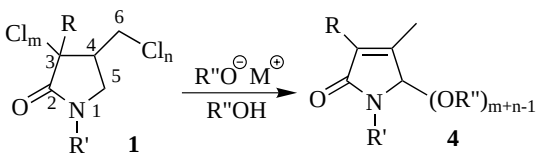
(GC–MS, ^{1}H NMR, ^{13}C NMR, HMQC, HMBC) the isolated material emerged as the *N*-benzyl-5,5-dimethoxy-4-methyl-3-pyrrolin-2-one **4a** rather than the expected acetal **2a**. The compound **4a** was generated by an unusual functional rearrangement of the polyhalogenated pyrrolidin-2-one **1a** (Scheme 2), leading to the normally difficult functionalisation at C(5).[10] To our knowledge, no reports on the functional rearrangement in polychlorinated 2-pyrrolidinones have appeared in the literature. A sporadic example of dehydrochlorination of trichloro-γ-lactones by non nucleophilic bases was, however, reported.[11]

By a variation of the temperature, the reagent concentration and the operational procedures, the best reaction conditions for the model compound **1a** were established. Yields of **4a** can be considered satisfactory given the dense functionalisation of the ring. However, the yields are not very high (62%) because of parasitic polymerisation phenomena, probably due to the opening of the lactam ring through alkaline alcoholate attack on the 2-oxo group. We were not able to get rid of this drawback by working at temperatures below 0°C, by using a stoichiometric amount of base or by changing to less basic systems, such as Li_2CO_3/CH_3OH. The desired conversions, in fact, were in all these cases



Scheme 2.

drastically reduced or absent. Interestingly, under the mildest conditions tested, small amounts of *N*-benzyl-3-chloro-4-methyl-5-methoxy-3-pyrrolin-2-one were sometimes observed. Since this side-product was smoothly converted into **4a**, it can be considered as a precursor of the *N*-benzyl-5,5-dimethoxy-4-methyl-3-pyrrolin-2-one.

To check whether this unusual transformation had a general character, we prepared the educts **1b–h**, which were then treated with alkaline methylate/methanol under the optimum conditions (Table 1). All the compounds tested displayed the same behaviour as **1a**, i.e. a dehydrohalogenation associated with the introduction in position C(5) of as many methoxy groups as the number of remaining halogens. It should be noted that the final product (Table 1, items 1, 2, 11, 12 and 7, 8, 14, 15) is related to the total number of halide atoms and not to their distribution. A more active system was obtained by replacing the lithium ion with the sodium ion, a less acidic counterion (Table 1, items 7, 11 and 8, 12). Interestingly, substrate **1e** gave the highest yields; this is probably due to the steric protection exerted by the methyl substituent at C(3), which should prevent the opening of the 'lactam' ring. Other alcoholate/alcohol combinations can replace the alkaline methylate/methanol, however, it appears that on increasing the size of the alcoholate, the yields decrease to some extent (Table 1, item 6).

All the transformations from **1** to **4** must begin with a dehydrohalogenation, since, otherwise, the methoxy group could not be located at the C(5) position. The lack of reactivity under the usual conditions of *N*-benzyl-4-chloromethyl-3,3-dichloro-4-methyl-pyrrolidin-2-

Table 1. Reaction of the polychloro 2-pyrrolidinones **1** with $R''O^-/R''OH$[a]

No.		Educts				Products	R″OM	*t* (h)	*T* (°C)	Conversion (%)[b]	Yield (%)[c]
		R	R′	m	n						
1	**1a**	–	Bzl	2	1	**4a**	CH_3OLi	2.5	0	97	62
2[d]	**1a**	–	Bzl	2	1	**4a**	CH_3OLi	2.5	25	100	56
3[e]	**1a**	–	Bzl	2	1	**4a′**	EtOLi	1.5	0	100	56
4	**1b**	–	$N(CH_3)_2$	2	1	**4b**	CH_3OLi	3	25	100	45
5	**1c**	–	$CH_2PO(OEt)_2$	2	1	**4c**	CH_3ONa	15	25	100	66
6	**1c**	–	$CH_2PO(OEt)_2$	2	1	**4c′**	*i*-PrONa	15	25	100	40
7	**1d**	H	Bzl	1	1	**4d**	CH_3OLi	16	25	93	61
8[d]	**1d**	H	Bzl	1	1	**4d**	CH_3ONa	2.33	25	100	60
9	**1e**	CH_3	Bzl	1	1	**4e**	CH_3OLi	24	25	100	57
10[d]	**1e**	CH_3	Bzl	1	1	**4e**	CH_3OLi	24	25	91	78
11	**1f**	H	Bzl	1	2	**4b**	CH_3OLi	1.5	80	100	47
12	**1f**	H	Bzl	1	2	**4b**	CH_3ONa	2	25	100	64
13	**1g**	–	Bzl	2	0	**4d**	CH_3OLi	6	25	100	6
14	**1h**	H	Bzl	0	2	**4d**	CH_3OLi	24	80	100	56
15	**1h**	H	Bzl	0	2	**4d**	CH_3ONa	6	80	100	60

[a] 4 mmol of substrate, 16 ml of R″OH and 4 equiv. of base were used.
[b] GC value.
[c] Determined on isolated material.
[d] Reaction performed in 16 ml of CH_3OH/ether (1/1).
[e] Reaction performed in 8 ml of ethanol.

one, apart from some polymerisation, strongly supports this hypothesis. For the moment, however, nothing can be said about the regioselectivity of the starting elimination, if it is an *endo*-dehydrochlorination between C(3) and C(4) positions or, alternatively, an *exo*-dehydrochlorination between the C(4) and C(6) carbons. In any case, it is clear from the data of items 13 and 14 (Table 1) that satisfactory results can be achieved, only if, at least, one chlorine atom is attached to C(6).

In summary, we have described a satisfactory and unusual preparation of *N*-substituted 5-methoxy or 5,5-dimethoxy-4-methyl-3-pyrrolin-2-ones by reaction of the corresponding 4-methyl-pyrrolidin-2-ones, polychlorinated at C(3) and C(6), with alkaline methoxide in methanol under mild conditions. The functional rearrangement is fairly appealing since the 3-pyrrolin-2-ones obtained can be envisaged as precursors for cyclic *N*-acyliminium ions,[12] which are in turn very useful intermediates in organic synthesis.[13] The availability of polychloro 2-pyrrolidinones makes this route to cyclic *N*-acyliminium ions alternative or competitive in comparison with the usual approach, which starts from succinimide derivatives.[14] Further studies directed towards the rationalisation of the reaction mechanism, and the application of the methodology in biologically active compounds synthesis are currently under investigation.

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