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INTRAMOLECULAR TRAPPING OF ESTERS AND AMIDES BY 1-LITHIO-1-BROMOCYCLOPROPANES

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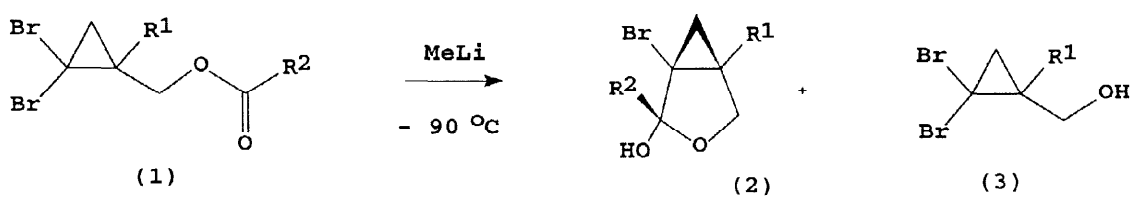
Reaction of 2-acyloxymethyl or 2-acylaminomethyl-1,1-dibromocyclopropanes with methyllithium at -90 °C leads to selective bromine-lithium exchange and intramolecular cyclisation to give a 1-bromo-3-oxa- or 1-bromo-3-aza-bicyclo[3.1.0]hexan-2-ol.

The reaction of 1,1-dibromocyclopropanes with methyllithium is known to lead to a very rapid lithium -halogen exchange, followed in most cases by formal elimination of lithium bromide to produce a cyclopropylidene (or a related carbenoid). If the reaction is carried out at low temperature or, in some cases, if there is a co-ordinating group present in the molecule, the organolithium may be trapped in intermolecular processes by reaction with electrophiles.[1] Although there are many examples of intramolecular trapping of the cyclopropylidene, there are fewer cases of intramolecular reactions of the lithiobromides; one possible example is the 1,3-elimination of BrCl from 1,1-dibromo-2-chloromethylcyclopropanes on reaction with methyllithium.[2] It is to be noted that with the related 2-(2-haloethyl)- or 2-(3-halopropyl)- systems no cyclisation is observed and only allenes derived from the cyclopropylidene are isolated.[2] We now report that reaction of the esters (**1**) or amides (**11**), (**13**) with methyllithium leads to the intramolecular trapping of a lithiobromocyclopropane with the formation of a five-membered ring.

The esters (**1**) were simply prepared by acylation of the corresponding alcohol.[3] Reaction of (**1**) with a slight excess of methyllithium at -90 °C for 30 min. followed by quenching with ammonium chloride either at low temperature or after warming to 0 °C led to the hemiacetals (**2**) in each case as a single diastereoisomer, in one case together with the alcohol (**3**) (see Table 1):



(1) (2) (3)

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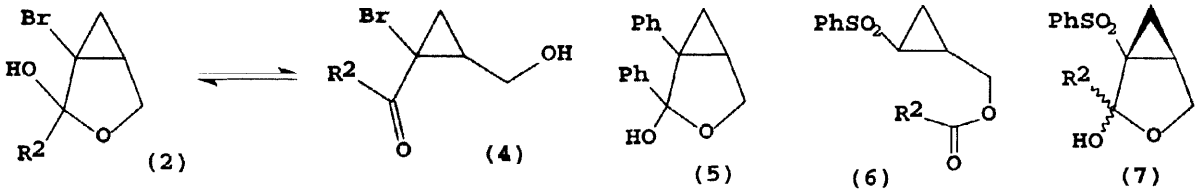
Table 1: Reactions of esters with methyllithium in diethyl ether at -90 °C

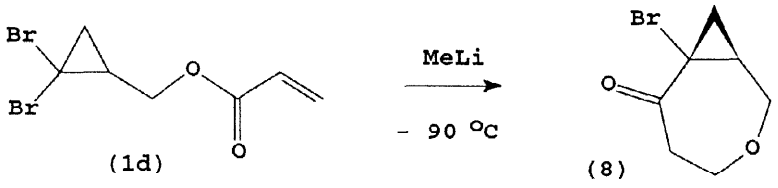
$R^1 = H$			$R^1 = Me$	
R^2	ester	product	ester	product
Me	**1a**	**2a** (55 %) + **3** (10 %)	**1f**	**2f** (60 %)[4]
n-Pr	**1b**	**2b** (46 %)	**1g**	**2g** (74 %)
Ph	**1c**	**2c** (64 %)	**1h**	**2h** (82 %)
Vinyl	**1d**	**8** (39 %)	**1i**	**2i** (68 %)
CF_3	**1e**	**3** (90 %)		

In the cases of the hemiacetals (**2f**) - (**2i**), the n.m.r. spectra in deuterochloroform showed only the presence of the cyclic form. However, for the hemiacetals (**2a**) - (**2c**), the ^1H n.m.r. spectra in $CDCl_3$ or C_6D_6 were more complicated and could be interpreted in terms of an equilibrium between hemiacetal (**2**) and keto-alcohol (**4**). A similar equilibrium has been reported in closely related acetals (**5**).[5] The stereochemistry at C-2 of the hemiacetals (**2**) is provisionally assigned as that with the R^2-substituent syn- to the cyclopropane on the basis of n.O.e. effects and by comparison of chemical shifts with those for related systems.[6-8]



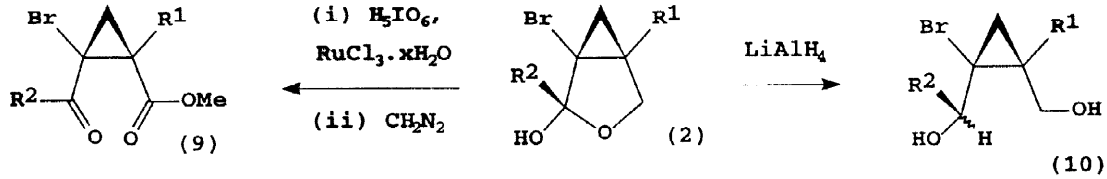
The formation of products (**2**) apparently involves a lithium-bromine exchange in (**1**) and cyclisation of the derived lithiocyclopropane by intramolecular attack at the ester group. It is not clear whether the exchange leads stereoselectively to the syn-lithio-ester, or whether a more complex process occurs in which the two isomeric lithiobromides are formed and equilibrate but only one isomer cyclises. Nonetheless, no products of intermolecular trapping of the anti-lithio ester have been observed. Although this appears to be the first example of such a cyclisation by reaction of 1,1-dibromides with an alkyllithium, it is known that the sulphones (**6**) react with *n*-butyllithium by proton removal from C-1 followed by cyclisation to give a hemiacetal (**7**).[7]

The reaction of the dibromide (**1d**) with methyllithium followed a rather different course, leading to the bicyclic ketone (**8**):[9]



This may be explained in terms of initial formation of the hemiacetal (**2**, R^2 = vinyl) as above followed by ring-opening to the keto-aclohol (**4**) and recyclisation by attack of the alcoholate at the β-position of the derived α,β-unsaturated ketone.

The hemiacetals (**2**) could be oxidatively ring-opened to the corresponding 2-bromo-2-acylcyclopropanecarboxylic acid which were isolated as their methyl esters.[10]

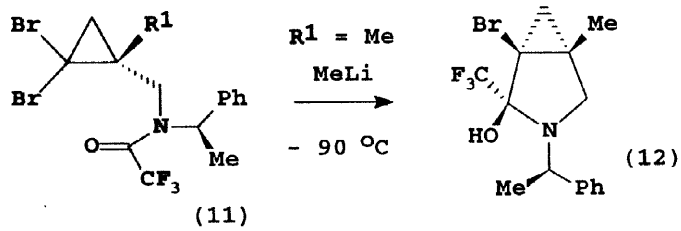


R^1 = H, R^2 = *n*-Pr: 66 %
R^2 = Me, R^2 = *n*-Pr: 72 %

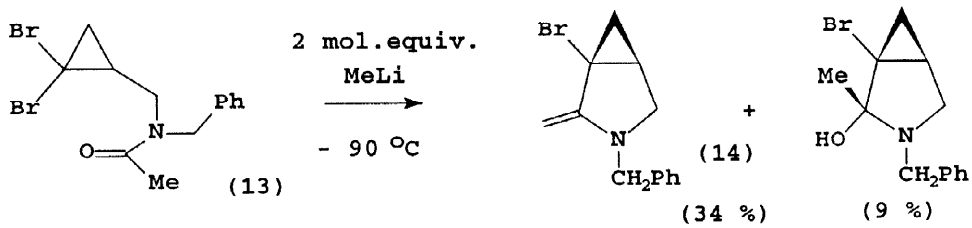
R^1 = H, R^2 = *n*-Pr: 74 %

Reduction of the hemiacetal (**2b**) with lithium aluminium hydride in ether was, however, not stereoselective, leading to a 1:1 mixture of isomeric diols (**10**).

In the same way, reaction of the amide (**11**, R^1 = Me) with methyllithium led to the hemiaminal (**12**) in high yield, although the reaction with the non-methylated system (**11**, R^1 = H) was much less efficient:[11]



In the case of the acetamide (**13**), reaction with 2 mol.equiv. of methyllithium led to the enamine (**14**), albeit only in 34 % yield. The methylene group of the enamine showed two singlets in the ^{1}H n.m.r. spectrum at 3.82 and 4.02 and two ^{13}C signals at 75.5 (CH_2) and 154.1 (C);[12] these values are very close to those reported for N-alkyl-2-methylenetetrahydropyrrole.[13]



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References and Notes

1. For collected references see J.Bakkes, U.H.Brinker, Cyclopropylidene in *Methoden der Organischen Chemie*, Houbel-Weyl, Verlag Stuttgart, E19b, 1989, 391.
2. N.O.Nilsen, L.Skattebol, M.S.Baird, S.R.Buxton and P.D.Slowey, *Tetrahedron Lett.*, 1984, 2887.

3. The alcohols are readily available as single enantiomers by reduction of the methyl esters or acid chlorides of the corresponding 2,2-dibromocyclopropanecarboxylic acids (which may be conveniently resolved using dehydroabietylamine),[14] or by resolution of (2,2-dibromocyclopropyl)methanol through diastereomeric α-glucosides.[15] These dibromocyclopropanes represent valuable chirons in a range of reactions, e.g. in the synthesis of methanoproline.[16]
4. Compound (**2f**) showed δ_H 0.89 (1H, d, J 5.9 Hz), 1.10 (1H, d, J 5.9 Hz), 1.35 (3H, s), 1.50 (3H, s), 3.14 (1H, s broad), 3.72 (1H, d, J 8.4 Hz), 3.88 (1H, d, J 8.4 Hz); δ_C 15.2, 21.9, 23.8, 28.1, 47.4, 70.8, 104.5.
5. C.Berrier, B.Bonnaud, J.F.Patoiseau, D.Bigg, *Tetrahedron*, 1991, **46**, 9629.
6. A single isomer was isolated in each case after chromatography; minor signals in the crude mixture could not be assigned with certainty to a second isomer. The stereochemistry of (**2f**) was established by an n.O.e. study which showed a 2.5 % enhancement for the endo-H-6 when the signal for the 2-methyl group was irradiated (thanks are due to Dr.I.H.Sadler and the Edinburgh EPSRC High Field n.m.r. service for this determination). Other stereochemistries are assigned by analogy with this.
7. Y.Gaoni, *Tetrahedron Lett.*, 1983, 2833.
8. B.M.Trost, P.L.Ornstein, *J.Org.Chem.*, 1982, **47**, 748.
9. Compound (**8**) showed δ_H (benzene-d_6) 1.21 (1H, dd, J 5.8, 9.1 Hz), 1.40 (1H, dddd, J 2.5, 4.3, 7.7, 9.1 Hz), 1.49 (1H, dd, J 5.8, 7.7 Hz), 2.04 (1H, ddd, J 4.3, 10.6, 13.5 Hz), 2.28 (1H, ddd, J 2.3, 5.0, 13.5 Hz), 2.69 (1H, ddd, J 2.3, 10.6, 12.4 Hz), 3.20 (1H, ddd, J 4.3, 5.0, 12.4 Hz), 3.21 (1H, dd, J 2.5, 13.6 Hz), 3.28 (1H, dd, J 4.3, 13.6 Hz); δ_C 23.2, 29.8, 42.3, 43.2, 67.2, 69.7, 199.3.
10. M.T.Nunez, V.S.Martin, *J.Org.Chem.*, 1990, **55**, 1928.
11. (1R,2R,5S)-1-Bromo-2-hydroxy-2-trifluoroacetyl-5-methyl-N-(R)-α-methylbenzyl-3-azabicyclo-[3.1.0]hexane (**12**) showed δ_H 0.95 (1H, d, J 5.9 Hz), 1.20 (3H, s), 1.36 (3H, d, J 7.1 Hz), 1.63 (1H, d, J 5.9 Hz), 2.60 (1H, d, J 8.6 Hz), 2.83 (1H, s), 2.99 (1H, d, J 8.6 Hz), 4.60 (1H, q, J 7.1 Hz), 7.22 - 7.38 (5H, m); δ_C 17.52, 19.3, 24.7, 25.5, 46.1, 50.8, 52.7 (q, J_{CF} 2.6 Hz), 91.5 (q, J_{CF} 29.6 Hz), 124.15 (q, J_{CF} 289.6 Hz), 127.32, 128.26, 128.64, 141,12; $[\alpha]_D^{25}$ = + 34.0° (c 1.0, $CHCl_3$).
12. The enamine (**14**) showed δ_H 1.19 (1H, t, J 5.0 Hz), 1.53 (1H, dd, J 5.0, 8.9 Hz), 2.03 (1H, m, J 5.0, 8.9 Hz), 3.04 (1H, d, J 9.2 Hz), 3.40 (1H, dd, J 5.0, 9.2 Hz), 3.82 (1H, s), 4.06 (1H, d, J 15.3 Hz), 4.07 (1H, s), 4.25 (1H, d, J 15.3 Hz), 7.20-7.40 (5H, m); δ_C 23.4, 24.6, 34.2, 50.8, 52.1, 75.5, 127.0, 127.5, 128.5, 137.8, 154.1.
13. Y.Li and T.J.Marks, *J.Am.Chem. Soc.*, 1996, **118**, 9295.
14. M.S.Baird, P.Licence, V.V.Tverezovsky, I.G.Bolesov, W.Clegg, submitted for publication.
15. V.V.Tverezovsky, Y.K.Grishin, I.G.Bolesov, M.S.Baird, *J.Org.Chem.USSR*, 1997, **33**, 924.
16. V.V.Tverezovsky, M.S.Baird and I.G.Bolesov, *Tetrahedron*, 1997, **53**, 14773.