Improved Direct Acetalisation for (Strained) Cyclic Acetals

M. Anteunis and Chr. Becu

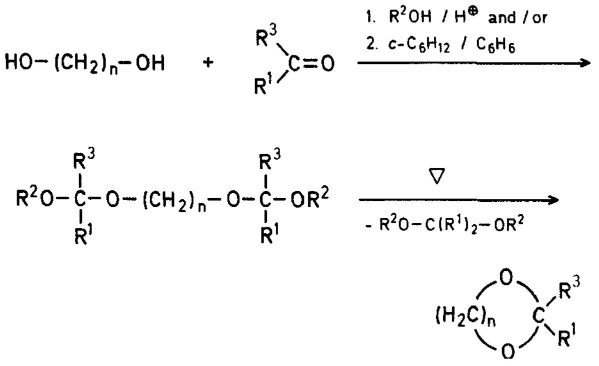
Rijksuniversiteit Gent, Krijgslaan, 271 (S4bis), B-9000 Gent, Belgium.

During the past years we have often been faced with the problem of preparing strained 1,3-dioxacyclanes, for which direct acetalisation methods failed and even more sophisticated procedures were, in preparation, unattractive. Among these, the use of sulfites[1], dialkylsulfates[2], tetraalkoxysilanes[3] may be considered as more or less forcing conditions. A better approach (formation under kinetic control) consists in starting from alcoholates, followed by treatment with CH_2Cl_2 or CH_2BrCl[4,5]. Yields are low to moderate, however, and the method is restricted almost to the formation of formalates[6]. Furthermore, most of the classical methods mentioned above are run under equilibrium conditions and may thus loose their interest when one is faced with the problem of preparing isomeric substituted 1,3-dioxacyclanes, from which the least stable isomer is the desired one. Of course, untimely unterrupted reactions[7] may be an outcome, although this is at the cost of the overall yield. The problem of ultimate separation still remains.

We wish to report on a simple modification of the acid-catalysed cycloacetalisation procedure which affords good to excellent yields, even for moderately strained, and/or thermodynamically least stable 1,3-dioxacyclanes. The reaction may also eventually be used for the 1,3-thioxa-, 1,3-dithia- and other 1,3-diheterocyclanes. It is a kinetically controlled reaction.

The method is simplest for relatively volatile acetals, starting from even more volatile carbonyl compounds, but it can be adapted for other cases too. It is based upon the fact (N.M.R., U.V.) that, on mixing polyalcohols with several carbonyl derivatives (paraformaldehyde, acetaldehyde, acetone, acetophenone, etc.) in an excess of simple alcohols (methanol, ethanol, benzyl alcohol, etc.) under acidic conditions (*p*-toluenesulfonic acid, ion-exchange resins, boron trifluoride, tin(IV) chloride, etc.) *mixed* acetals are readily and almost quantitatively formed, often even at room temperature. Subsequently, benzene or cyclohexane is added, and the excess of alcohol, together with the water formed, are removed by azeotropic entrainment. The optimal condition exists in choosing a pressure suitable to avoid premature thermal decomposition of the mixed acetal, which often in itself turns out not to be serious. In general, the more difficult the formation of the final cyclic acetal, the less the intermediate mixed acetal is affected at this stage.

Once water is completely removed, the residue is heated (occasionally photochemical decomposition was also successful, see Table 1, footnote l) and the mixed acetal desmutates into the cyclic, and the open acetal.



If ion exchange resins have been used formerly, it is necessary to add *p*-toluenesulfonic acid before final pyrolysis. Pertinent examples are gathered in the Table. Some explicit experimental procedures follow.

It is clear that the success of the method is due to the irreversible conditions of formation. It will be noted that

(a) due to the pyrolytic nature of the procedure, the smallest ring compound is formed and no polymer formation is observed (product nos **5**, **6**, **9**, **13** etc.);

(b) highly strained compounds may be isolated even when they are unstable having been left standing (product nos **5**, **6**, **11**, **12**);

(c) pyrolysis may be done on a small scale by gas chromatography (product **6**, footnote j);

(d) the method may afford the least stable isomer as the sole reaction product (product **18**, footnote i).

Table 1. Step-Wise Acetal Preparation by the „Mixed Acetal" Procedure

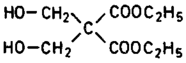
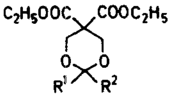
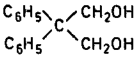
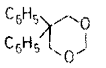
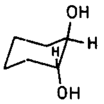
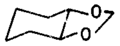
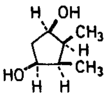
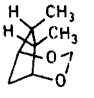
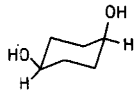
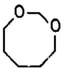
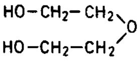
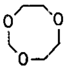
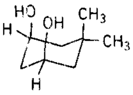
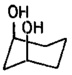
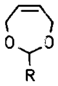
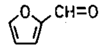
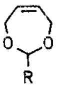
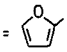
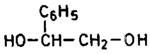
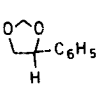
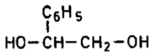
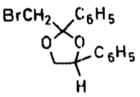
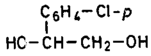
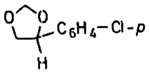
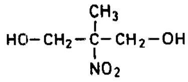
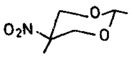
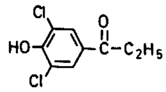
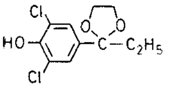
Diol	Carbonyl compound	Product		Number	Yield (%)	b.p.
	$H_2C{=}O$[a]		$R^1 = R^2 = H$	**1**	91	140°/12 torr
	$H_3C{-}CH{=}O$[b]		$R^1 = CH_3$, $R^2 = H$	**2**	85[c,g]	145°/12 torr
	$(H_3C)_2C{=}O$[b]		$R^1 = R^2 = CH_3$	**3**	92	150°/12 torr
	$H_2C{=}O$[a]			**4**	98[d]	151/0.01 torr
	$H_2C{=}O$[a]			**5**	88[c]	–
	$H_2C{=}O$[a]			**6**	–[j]	185°
	$H_2C{=}O$[a]			**7**	90[k]	m.p. 170°
$HC{-}(CH_2)_5{-}OH$	$H_2C{=}O$[a]			**8**	85	43°/12 torr
$HO{-}(CH_2)_6{-}OH$	$H_2C{=}O$[a]			**9**	65	50°/12 torr
	$H_2C{=}O$[a]			**10**	86[l]	60°/14 torr
	$H_2C{=}O$[a]			**11**	85[c]	125°/12 torr
	$H_2C{=}O$[a]			**12**	90[h,m]	70°/12 torr
$HO{-}CH_2{-}CH{=}CH{-}CH_2{-}OH$	$H_2CCl{-}CH(OC_2H_5)_2$[b]		R = CH_2Cl	**13**	72[f]	63°/12 torr
$HO{-}CH_2{-}CH{=}CH{-}CH_2{-}OH$			R = 	**14**	70	120°/12 torr
 $HO{-}\overset{\overset{C_6H_5}{\vert}}{C}H{-}CH_2{-}OH$	$H_2C{=}O$[a]			**15**	80	120°/12 torr
 $HO{-}\overset{\overset{C_6H_5}{\vert}}{C}H{-}CH_2{-}OH$	$C_6H_5{-}CO{-}CH_2Br$			**16**	90[g]	136°/0.01 torr
 $HC{-}\overset{\overset{C_6H_4{-}Cl{-}p}{\vert}}{C}H{-}CH_2{-}OH$	$H_2C{=}O$[a]			**17**	88	120°/0.5 torr
 $HO{-}CH_2{-}\overset{\overset{CH_3}{\vert}}{\underset{\underset{NO_2}{\vert}}{C}}{-}CH_2{-}OH$	$H_3C{-}CH{=}O$	 *cis*		**18**	30[i]	~ 50°/0.1 torr

Table 1, continued

Diol	Carbonyl compound	Product	Number	Yield (%)	b.p.
HO—CH$_2$—CH$_2$—OH			**19**	93	m.p. 88°

[a] Mixed acetal detected by N.M.R.

[b] Mixed acetal not found after evaporation of the original mixture.

[c] All other methods failed.

[d] All other methods failed except with conc. sulfuric acid, but this procedure is unreliable.

[e] Usually *trans*-2,4,6-trioxabicyclo[0.4.5]undecane is formed, which may be transformed into the dioxolane on treatment with conc. orthophosphoric acid[8].

[f] Tin(IV) chloride as catalyst.

[g] See experimental section.

[h] Yield < 10% via sodium salt, see ref. 5.

[i] Classical procedure gives 85% yield, but as well as 20–30% of the *cis*-derivative, the main product is 70–80% of the more stable[9] *trans*-derivative. Thus, although the new procedure afforded a lower yield, the reaction product was the pure, less-stable isomer.

[j] This reaction was run on a small scale. Pyrolysis was affected by direct injection on a G.C.-column (6 m SE.30 on Chromosorb W, T. inj. 200°); yield: good to excellent.

[k] M.W. (camphor Rast-method) 128.8. Mass spectrum: m/e = 128 (M$^{\oplus}$).

[l] The intermediate mixed acetal (N.M.R.) was decomposed by irradiation in a quartz tube under reduced pressure at 100°. A high-pressure, broad spectrum U.V. lamp (Philips MLU 300 W) was used and the acetal formed was continuously distilled off. By interruption of the irradiation, the formation of acetal ceased.

[m] For a conformational study on this compound see ref. 10.

trans-4,5-Tetramethylene-1,3-dioxolane (5):

trans-1,2-Cyclohexanediol (11.8 g, 0.1 mol) is mixed with paraformaldehyde (9.6 g, 0.3 mol) in ethanol (50 ml) and benzene (250 ml). After addition of *p*-toluenesulfonic acid (0.2 g) or, alternatively Dowex 50 (0.5–1.0 g), the mixture is heated for one hour and the solvent is slowly distilled off until the head temperature has reached 80°. Evaporation (rotary evaporator) affords a residue which is almost quantitatively the mixed acetal. This residue is heated (some *p*-toluenesulfonic acid can be added) up to 200°/13 torr. The methylal (formed by decomposition of the mixed acetal) may be detected in quantitative yields by trapping. Redistillation affords the dioxolane; yield: 11.5 g (88%); b.p. 65°/12 torr. See Table 2 for elemental analysis.

I.R. (neat): ν_{max} = 2980, 2890, 2770, 1115, 1100 cm^{-1}.

^{1}H-N.M.R. (CCl$_4$): δ = 4.88 (s, 2H, —O—CH$_2$—O—), 2.91 (m, 2H, O—CH$<$), 1.68 ppm (m, 8H, —(CH$_2$)$_4$—).

Table 2. Elemental Analyses for some Acetals

Product No.	Analysis			
1	C$_{10}$H$_{16}$O$_6$	calc.	C 51.72	H 6.94
		found	51.86	6.82
2	C$_{11}$H$_{18}$O$_6$	calc.	C 53.65	H 7.36
		found	54.00	7.13
3	C$_{12}$H$_{20}$O$_6$	calc.	C 55.37	H 7.74
		found	55.08	7.68
4	C$_{16}$H$_{16}$O$_2$	calc.	C 79.97	H 6.71
		found	80.08	6.51
5	C$_7$H$_{12}$O$_2$	calc.	C 65.60	H 9.44
		found	65.75	9.59
6	C$_8$H$_{14}$O$_2$	calc.	C 67.57	H 9.92
		found	67.44	9.70
11	C$_9$H$_{16}$O$_2$	calc.	C 69.19	H 10.32
		found	69.02	10.45
14	C$_9$H$_{10}$O$_3$	calc.	C 65.05	H 6.07
		found	64.79	5.88
16	C$_{16}$H$_{15}$O$_2$Br	calc.	C 60.02	H 4.73
		found	59.83	4.51
17	C$_9$H$_9$O$_2$Cl	calc.	C 58.55	H 4.91
		found	57.70	4.78
19	C$_{10}$H$_9$O$_3$Cl$_2$	calc.	C 48.41	H 3.65
		found	48.95	3.79

2-Bromomethyl-2,4-diphenyl-1,3-dioxolane (_cis_ and _trans_ 16):

Phenacyl bromide (4.4 g, 0.022 mol), phenyl ethyleneglycol (2.8 g, 0.020 mol), and *p*-toluenesulfonic acid (0.2 g) in methanol (50 ml) are heated under reflux for ~1 hr. Subsequently, cyclohexane (200 ml) is added and the water is removed azeotropically (Dean-Stark, separator; ca. 2 hrs). Complete evaporation (rotavap) and subsequent pyrolysis of the residual mixed acetal (N.M.R.) affords the dioxolane; yield: 5.4 g (88%); b.p. 136°/0.01 torr. This consists of two isomers in the ratio 61:39; assignments of *cis-trans* structures are not yet possible (see Table 2 for elemental analysis).

A small excess of the ketone is necessary, otherwise substantial formation of 2-benzyl-4-phenyl-1,3-dioxolane occurs. This side product is formed through dehydration of the phenyl glycol, forming phenylacetaldehyde, and subsequent condensation on the original glycol.

I.R. (neat): ν_{max} = 3030, 1500, 1220, 1040, 700 cm^{-1}.

^{1}H-N.M.R. (CCl$_4$; 300 MHz):

Isomer 1 (61%): δ = 7.25 (m, 10H$_{arom}$), 4.81 (2d, 1H, C$_6$H$_5$—C$\underline{H}$—O—, J_{AX} = 6.6 Hz, J_{BX} = 8.7 Hz), 4.18 (2d, 1H, C$_6$H$_5$—CH—C$\underline{H}_A$, J_{AB} = −7.3 Hz), 3.86 (2d, 1H, C$_6$H$_5$—CH—C$\underline{H}_B$); 3.66 ppm (2d, 2H, C$\underline{H}_2$Br, ^2J = −11.5 Hz).

Isomer 2 (39%): δ = 7.25 (m, 10H$_{arom}$), 5.33 (2d, 1H, C$_6$H$_5$—C$\underline{H}$—O—, J_{AX} = 5.7 Hz, J_{BX} = 9.3 Hz), 4.40 (2d, 1H, C$_6$H$_5$—CH—C$\underline{H}_A$ J_{AB} = −8.1 Hz), 3.60 (2d, 2H, C$\underline{H}_2$Br, ^2J = −11.0 Hz), 3.50 ppm (2d, 1H, C$_6$H$_5$—CH—C$\underline{H}_B$).

Received: June 29, 1973; (Revised form: August 24, 1973)

---

[1] Cf. G. Hesse, M. Farderreuther, *Chem. Ber.* **93**, 1249 (1960); preparation of sulfites: *Org. Synth. Coll. Vol. II*, 112 (1943).

[2] T. Langvad, *Acta Chem. Scand.* **8**, 336 (1954).

[3] J. B. Helferich, J. Hausen, *Chem. Ber.* **57**, 795 (1924).

[4] W. S. Allen, M. Weiss, *J. Org. Chem.* **26**, 4153 (1961).

W. Bonthrone, J. W. Cornforth, *J. Chem. Soc.* [C] **1969**, 1202.

J. Brimacombe, A. Foster, G. Jones, J. Willard, *J. Chem. Soc.* **1967**, 2404; *Chem. Commun.* **1965**, 174.

M. Anteunis, G. Swaelens, F. Anteunis-De Ketelaere, P. Dirinck, *Bull. Soc. Chim. Belges* **80**, 421 (1971).

M. Anteunis, G. Swaelens, *Org. Magn. Res.* **2**, 395 (1970).

[5] G. Swaelens, M. Anteunis, *Bull. Soc. Chim. Belges* **78**, 471 (1969).

[6] For reactions on dichloroacetic acid: *Org. Synth. Coll. Vol. IV*, 427 (1963); for the closely related cyclic acetalisation using β-bromoethyl esters of cyanoacetic acid: C. O. Parker, *J. Amer. Chem. Soc.* **78**, 4944 (1956) (ketene-acetal formation).

[7] E. L. Eliel, C. M. Knoeber, *J. Amer. Chem. Soc.* **90**, 3444 (1968).

[8] P. V. Bonsignore, M. D. Harwitz, *J. Org. Chem.* **28**, 3535 (1963); cf. F. S. Head, *J. Chem. Soc.* **1960**, 1778.

[9] E. L. Eliel, R. M. Enonza, *J. Amer. Chem. Soc.* **94**, 8075 (1972). M. Anteunis, F. Borremans, unpublished results.

[10] G. Swaelens, M. Anteunis, *Bull. Soc. Chim. Belges* **78**, 471 (1969).