Transacetalization of Acetals with Butane-1,2,4-triol Using Cobalt(II) Chloride and Chlorotrimethylsilane

Umberto Maria Battisti,* Claudia Sorbi, Silvia Franchini, Annalisa Tait, Livio Brasili

Department of Life Sciences, University of Modena and Reggio Emilia, Via G. Campi 183, 41125 Modena, Italy
Fax +39(059)2055131; E-mail: 38512@studenti.unimore.it

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Abstract: Transacetalization of acetals with butane-1,2,4-triol was carried out using cobalt(II) chloride and chlorotrimethylsilane as catalysts. The reaction occurs under mild conditions in acetonitrile and with a short reaction time. The synergic effect of the two Lewis acids catalyzes the conversion of butane-1,2,4-triol into (2-alkyl- or 2-aryl-1,3-dioxan-4-yl)methanol derivatives with high regiospecificity and diasteroselectivity.

Key words: butane-1,2,4-triol, transacetalization, regioselective, stereoselective, cobalt chloride, chlorotrimethylsilane

Current endeavors in our group require the synthesis of 1,3-dioxanes as key intermediates for the preparation of compounds of pharmacological interest such as serotoninergic 5-HT_{1A} and α-adrenergic receptor ligands, nucleoside analogues, and others.[1–6] In particular our efforts are focused on the development of selective and efficient synthesis to obtain (2-alkyl- or 2-aryl-1,3-dioxan-4-yl)methanol derivatives **2**.[7] The reaction of butane-1,2,4-triol with dialkyl acetals can potentially provide three different products: five-membered **1**, six-membered **2**, and seven-membered isomer **3** (Figure 1). Generally the 1,3-dioxepane **3** is not isolated due to its instability and only the more stable 1,3-dioxolane **1** and 1,3-dioxane **2** are recovered.

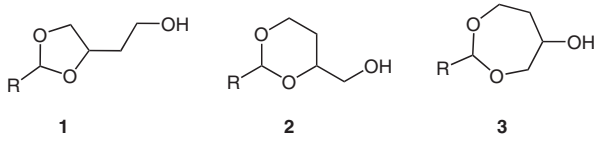
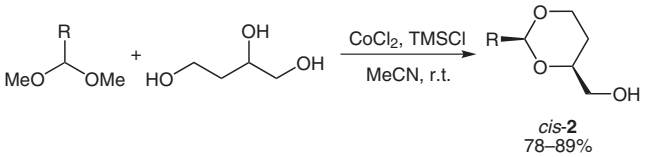


Figure 1 The three possible isomers from the cyclization of butane-1,2,4-triol with dialkyl acetals: 1,3-dioxolan-4-ylethanol **1**, 1,3-dioxan-4-ylmethanol **2**, and 1,3-dioxepan-5-ol **3**

Despite the relevance and the utility of methods that can be selectively used to obtain **1** or **2**, few have been reported.[8–11] We have found that regioselective cyclization of butane-1,2,4-triol occurs under cobalt(II) chloride and chlorotrimethylsilane catalysis (Scheme 1).[12] Diphenylacetaldehyde dimethyl acetal was reacted with butane-1,2,4-triol in the presence cobalt(II) chloride and chlorotrimethylsilane in dry acetonitrile at room temperature to give the desired [2-(diphenylmethyl)-1,3-dioxan-4-yl]methanol (**2a**) in good yield (Table 1, entry 1).



Scheme 1 Cobalt(II) chloride and chlorotrimethylsilane catalyzed transacetalization of butane-1,2,4-triol in acetonitrile at room temperature

Under these reaction conditions, the different reactivity of the hydroxy functions of the triol produced mostly the six-membered ring (1,3-dioxane) product **2a** and only traces of the five-membered isomer 2-[2-(diphenylmethyl)-1,3-dioxolan-4-yl]ethanol.

The trend of the reaction, which preferentially gives 1,3-dioxanes, could be related to the mild conditions involved in this type of transacetalization. Indeed all acid-catalyzed acetalizations of carbonyl compounds take place by the same mechanism, but through reversible steps. Therefore this type of reaction is thermodynamically controlled. In principle, this means that when different acetals can potentially be produced from these reagents, the most stable acetal should be produced as the main product. The mild conditions reported here probably lead to the more thermodynamically favored isomer. The use of protic or stronger Lewis acids generally results in lower regioselectivity since they require harsher reaction conditions. We observed also that only one of the two possible diastereomers (*cis*/*trans*) of the desired product **2a** was recovered and it was assigned the *cis* configuration. It was possible to assign the configuration through NMR 2D experiments, in which a positive NOE effect was detected between H2 and H4 of the 1,3-dioxane ring. In general, under these reaction conditions, the predominant stereochemistry is the *cis* configuration since a strain-free six-membered ring is obtained in the chair conformation and this accommodates both ring substituents in the energetically more favorable equatorial orientation resulting in a *cis* configuration (Scheme 2). The synergic effect of cobalt(II) chloride and chlorotrimethylsilane was also investigated. The use of cobalt(II) chloride or chlorotrimethylsilane alone led to partial conversion of the acetals into 1,3-dioxanes/1,3-dioxolanes.

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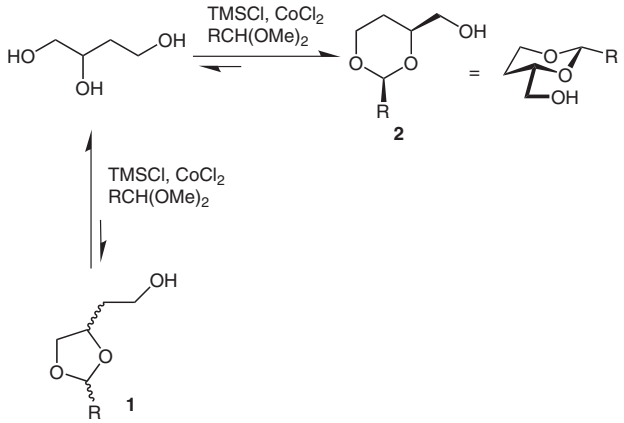


Scheme 2 Regioselective acetalization of butane-1,2,4-triol

Accordingly the higher efficacy of the transacetalization reaction, which exploits both the catalysts, could be related to the increased electrophilicity of the silicon nucleus as a consequence of cobalt(II) chloride complexation with chlorotrimethylsilane.[12] Moreover the same protocol was applied to benzaldehyde and diphenylacetaldehyde and no significant results were obtained (Table 1, entries 2 and 4). These data suggest that the entropic contribution provided by the acetals in this type of transacetalization reaction plays a crucial role, since the corresponding aldehydes do not react under the same reaction conditions. Some aromatic and aliphatic dialkyl acetals underwent this cyclization reaction and the corresponding 1,3-dioxanes were isolated as main products (Table 1, entries 3, 5–10).

In the case of the aliphatic dialkyl acetals shown in Table 1, reaction times were considerably shorter due to the higher electrophilic character of the acetalic carbon atom. In conclusion, the experimental protocol is simple, convenient, and quite fast. It could be applied as a method for the protection of hydroxyl groups in a large number of polyols. Moreover we have developed an efficient transacetalization reaction in order to obtain 1,3-dioxane-based derivatives by reacting butane-1,2,4-triol in the presence of the catalytic complex originated from cobalt(II) chloride and chlorotrimethylsilane. The process occurs with good diastereoselectivity employing dialkyl acetals as reaction substrates. The results obtained make this procedure very attractive for the preparation of these useful synthetic intermediates.[13,14]

Reagents, solvents, and other chemicals were used as purchased without further purification unless otherwise specified. Air- or moisture-sensitive reactants and solvents were employed in reactions carried out under an N_2 atmosphere unless otherwise noted. Flash column chromatography purifications (MPLC) used Merck silica gel 60 (230–400 mesh, ASTM). The structures of all isolated compounds were ensured by NMR and elemental analysis (C,H,N). NMR data (^{1}H and ^{13}C, 1D and 2D experiments) were obtained using a DPX 400 Avance spectrometer (Bruker). ^{1}H NMR chemical shifts are relative to TMS (internal standard). ^{13}C NMR chemical shifts are relative to internal TMS at δ = 0.0 or to the ^{13}C signal of solvent: $CDCl_3$ δ = 77.04, CD_3OD δ = 49.8, DMSO-d_6 δ = 39.5. Elemental analysis was performed on a Carlo Erba 1106 Analyzer in the Microanalysis Laboratory of the Life Sciences Department of Università degli Studi di Modena e Reggio Emilia and the results here reported are within ±0.4% of the theoretical values.

1,3-Dioxane-4-methanols 2; General Procedure

To a solution of $CoCl_2$ (0.6 mmol) in anhyd MeCN (4 mL), the selected dialkyl acetal (1 mmol), TMSCl (1.1 mmol), and butane-1,2,4-triol (3 mmol) were added, with stirring, at r.t. At the end of the reaction, the mixture was extracted with EtOAc and the combined extracts were washed with 5% $NaHCO_3$. The organic layer was dried (anhyd Na_2SO_4) and filtered, and the solvent was evaporated under vacuum. The oils obtained were purified by flash chromatography to give the desired compounds.

***cis*-[2-(Diphenylmethyl)-1,3-dioxan-4-yl]methanol (*cis*-2a)**

Yellow oil; yield: 0.222 g (78%).

IR: 3397 (br), 2955, 2875, 1100, 1024, 750, 702 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.38–1.43 (m, 1 H, H5a$_{diox}$), 1.55–1.67 (m, 1 H, H5b$_{diox}$), 3.21–3.41 (m, 2 H, C*H*$_2$OH), 3.76–3.91 (m, 2 H, H4$_{diox}$, H6a$_{diox}$), 4.02 (dd, *J* = 5.2, 11.4 Hz, 1 H, H6b$_{diox}$), 4.22 (d, *J* = 6.0 Hz, 1 H, C*H*Ph$_2$), 4.56 (t, *J* = 5.5 Hz, 1 H, OH), 5.24 (d, *J* = 6.0 Hz, 1 H, H2$_{diox}$), 7.19–7.31 (m, 4 H, H3$_{Ph}$, H5$_{Ph}$, H3′$_{Ph}$, H5′$_{Ph}$), 7.30–7.41 (m, 2 H, H4$_{Ph}$, H4′$_{Ph}$), 7.47–7.53 (m, 4 H, H2$_{Ph}$, H6$_{Ph}$, H2′$_{Ph}$, H6′$_{Ph}$).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 26.9 (C5$_{diox}$), 46.8 (*C*HPh$_2$), 65.7 (C6$_{diox}$), 66.9 (C4$_{diox}$), 77.8 (CH$_2$OH), 103.5 (C2$_{diox}$), 126.2 (C3$_{Ph}$, C5$_{Ph}$, C3′$_{Ph}$, C5′$_{Ph}$), 128.9 (C2$_{Ph}$, C6$_{Ph}$, C2′$_{Ph}$, C6′$_{Ph}$), 129.7 (C4$_{Ph}$, C4′$_{Ph}$), 141.6 (C1$_{Ph}$, C1′$_{Ph}$).

Anal. Calcd for: $C_{18}H_{20}O_3$: C, 76.03; H, 7.09. Found: C, 76.20; H, 7.15.

***cis*-(2-Phenyl-1,3-dioxan-4-yl)methanol (*cis*-2b)**

Colorless oil; yield: 0.163 g (84%).

IR: 3425 (br), 3085, 3045, 2943, 2859, 1654, 1462, 1365, 1108 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.42–1.51 (m, 1 H, H5a$_{diox}$), 1.87–2.02 (m, 1 H, H5b$_{diox}$), 2.41 (br s, 1 H, OH), 3.61–3.74 (m, 2 H, C*H*$_2$OH), 3.93–4.08 (m, 2 H, H4$_{diox}$, H6a$_{diox}$), 4.40 (dd, *J* = 6.2, 12.5 Hz, 1 H, H6b$_{diox}$), 5.57 (s, 1 H, H2$_{diox}$), 7.32–7.47 (m, 3 H, H2$_{Ph}$, H4$_{Ph}$, H6$_{Ph}$), 7.47–7.57 (m, 2 H, H3$_{Ph}$, H5$_{Ph}$).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 26.7 (C5$_{diox}$), 65.4 (C6$_{diox}$), 66.6 (C4$_{diox}$), 77.4 (CH$_2$OH), 101.4 (C2$_{diox}$), 126.3 (C3$_{Ph}$, C5$_{Ph}$), 128.1 (C2$_{Ph}$, C6$_{Ph}$), 129.0 (C4$_{Ph}$), 138.4 (C1$_{Ph}$).

Anal. Calcd for $C_{11}H_{14}O_3$: C, 68.02; H, 7.27. Found: C, 68.15; H, 7.41.

***cis*-[4-(Hydroxymethyl)-1,3-dioxan-2-yl]methyl Benzoate (*cis*-2c)**

Dark brown oil; yield: 0.200 g (80%).

IR: 3492 (br), 3053, 2982, 2885, 2304, 1720, 1421, 1275, 1114, 1069, 763, 717, 695 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.43–1.46 (m, 1 H, H5a$_{diox}$), 1.63 (br s, 1 H, OH), 1.82–1.97 (m, 1 H, H5b$_{diox}$), 3.63–3.67 (m, 2 H, C*H*$_2$OH), 3.83–3.96 (m, 2 H, H4$_{diox}$, H6a$_{diox}$), 4.18–4.30 (m, 1 H, H6b$_{diox}$), 4.34–4.50 (m, 2 H, C*H*$_2$OCO), 4.82 (t, *J* = 4.6 Hz, 1 H, H2$_{diox}$), 7.48 (dd, *J* = 7.6, 7.8 Hz, 2 H, H3$_{Ph}$, H5$_{Ph}$), 7.61 (t, *J* = 7.6 Hz, 1 H, H4$_{Ph}$), 8.09 (d, *J* = 7.8 Hz, 2 H, H2$_{Ph}$, H6$_{Ph}$).

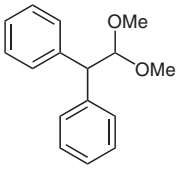
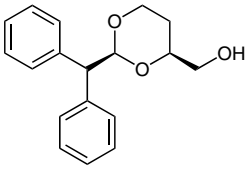
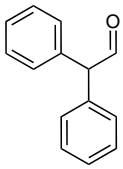
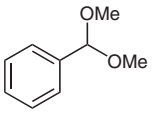
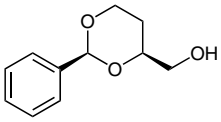
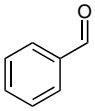
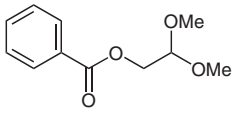
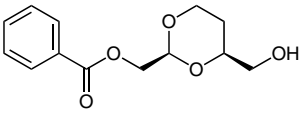
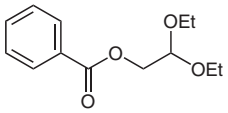
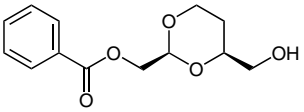
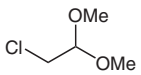
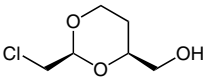
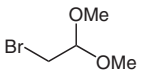
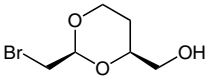
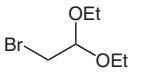
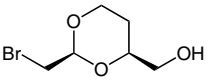
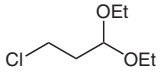
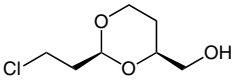
^{13}C NMR (100 MHz, $CDCl_3$): δ = 26.1 (C5$_{diox}$), 65.0 (C*H*$_2$OCO), 65.2 (C6$_{diox}$), 65.8 (C4$_{diox}$), 76.7 (CH$_2$OH), 98.2 (C2$_{diox}$), 128.1 (C3$_{Ph}$, C5$_{Ph}$), 129.5 (C2$_{Ph}$, C6$_{Ph}$), 132.9 (C1$_{Ph}$, C4$_{Ph}$), 165.9 (CO).

Anal. Calcd for $C_{13}H_{16}O_5$: C, 61.90; H, 6.39. Found: C, 62.00; H, 6.45.

***cis*-[2-(Chloromethyl)-1,3-dioxan-4-yl]methanol (*cis*-2d)**

Yellow oil; yield: 0.132 g (79%).

Table 1 Cobalt(II) Chloride and Chlorotrimethylsilane Catalyzed Cyclization of Butane-1,2,4-triol at Room Temperature

Entry	Reagent	Main product[a]	Time (h)	Yield[a] (%)	Ratio[b] **1**/**2**	Ratio[c] *cis*/*trans*
1		 *cis*-**2a**	0.2	78	88:12	*cis* only
2		–[d]	20	–[d]	–[d]	–[d]
3		 *cis*-**2b**	12	84	88:12	*cis* only
4		–[d]	20	–[d]	–[d]	–[d]
5		 *cis*-**2c**	0.1	80	89:11	95:5
6		 *cis*-**2c**	0.1	82	87:13	93:7
7		 *cis*-**2d**	0.1	79	83:17	92:8
8		 *cis*-**2e**	0.1	78	81:19	92:8
9		 *cis*-**2e**	0.1	85	90:10	95:5
10		 *cis*-**2f**	0.1	89	95:5	*cis* only

[a] Yields refer to the isolated pure main product.
[b] The isomeric ratio were determined by ^{1}H NMR analysis of the crude reaction mixture.
[c] The diastereomeric ratio were determined by ^{1}H NMR analysis of the crude reaction mixture.
[d] Only starting material was isolated.

IR: 3512 (br), 3054, 2984, 2305, 1422, 1270, 1140, 1022, 895, 763, 714, 694 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.38–1.50 (m, 1 H, $H5a_{diox}$), 1.70 (br s, 1 H, OH), 1.81–2.00 (m, 1 H, $H5b_{diox}$), 3.49–3.56 (m, 2 H, CH_2Cl), 3.59–3.77 (m, 2 H, CH_2OH), 3.79–3.95 (m, 2 H, $H4_{diox}$, $H6a_{diox}$), 4.19–4.30 (m, 1 H, $H6b_{diox}$), 4.76–4.85 (m, 1 H, $H2_{diox}$).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 26.5 ($C5_{diox}$), 48.5 (CH_2Cl), 65.0 (CH_2OH), 66.2 ($C6_{diox}$), 76.3 ($C4_{diox}$), 99.1 ($C2_{diox}$).

Anal. Calcd for $C_6H_{11}O_3Cl$: C, 43.26; H, 6.65. Found: C, 43.40; H, 6.70.

***cis*-[2-(Bromomethyl)-1,3-dioxan-4-yl]methanol (*cis*-2e)**
Brown oil; yield: 0.165 g (78%).

IR: 3492 (br), 3051, 2982, 2865, 1422, 1271, 1142, 1021, 895, 763, 697 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.35–1.49 (m, 1 H, $H5a_{diox}$), 1.67 (br s, 1 H, OH), 1.78–2.00 (m, 1 H, $H5b_{diox}$), 3.45–3.53 (m, 2 H, CH_2Br), 3.56–3.77 (m, 2 H, CH_2OH), 3.79–3.93 (m, 2 H, $H4_{diox}$, $H6a_{diox}$), 4.24 (dd, *J* = 5.1, 10.3 Hz, 1 H, $H6b_{diox}$), 4.74–4.86 (m, 1 H, $H2_{diox}$).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 26.2 ($C5_{diox}$), 31.6 (CH_2Br), 64.9 (CH_2OH), 66.0 ($C6_{diox}$), 76.6 ($C4_{diox}$), 99.0 ($C2_{diox}$).

Anal. Calcd for $C_6H_{11}O_3Br$: C, 34.14; H, 5.25. Found: C, 34.50; H, 5.47.

***cis*-[2-(2-Chloroethyl)-1,3-dioxan-4-yl]methanol (*cis*-2f)**
Yellow oil; yield: 0.160 g (89%).

IR: 3471 (br), 3054, 2982, 2303, 1422, 1272, 1143, 1026, 895, 766, 692 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.37–1.46 (m, 1 H, $H5a_{diox}$), 1.68 (br s, 1 H, OH), 1.74–1.90 (m, 1 H, $H5b_{diox}$), 2.10–2.18 (m, 2 H, CH_2CH_2Cl), 3.56–3.74 (m, 4 H, CH_2Cl, CH_2OH), 3.76–3.90 (m, 2 H, $H4_{diox}$, $H6a_{diox}$), 4.16 (dd, *J* = 5.2, 10.1 Hz, 1 H, $H6b_{diox}$), 4.74–4.86 (t, *J* = 5.1 Hz, 1 H, $H2_{diox}$).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 26.6 ($C5_{diox}$), 37.5 (CH_2Cl), 39.5 (CH_2CH_2Cl), 65.3 (CH_2OH), 65.9 ($C6_{diox}$), 76.7 ($C4_{diox}$), 90.7 ($C2_{diox}$).

Anal. Calcd for $C_7H_{13}O_3Cl$: C, 46.55; H, 7.25. Found: C, 46.80; H, 7.36.

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