Notes

Preparation of 4,4-Dimethoxybutyl Iodide from 1,4-Butanediol via the Corresponding Tosylate

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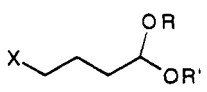
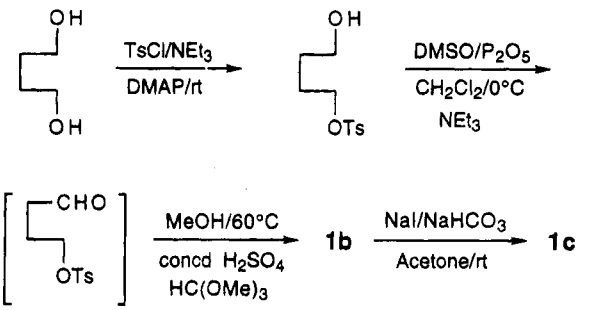
As building blocks that can lead to 1,5- or 1,6-dicarbonyl functionalities (the most common entries to five- and/or six-membered rings) as well as many other synthetically useful partial structures, 4-halobutanal acetals[1] (**1a**) are obviously underused in organic synthesis so far (especially compared with their analogs 2-(3-halopropyl)-1,3-dioxolane[2] or the acetals of 3-halo-propanal[3]). Judging from the available synthetic routes,[1] lack of easy access[4] is highly likely to be the main cause. Therefore, developing new facile syntheses is undoubtedly important.



1a X = Cl, Br, I
1b X = TsO, R = R' = Me
1c X = I, R = R' = Me

Herein we wish to report a convenient and inexpensive synthesis of the title compound (Scheme 1). The key step in this route is a selective mono-tosylation of 1,4-butanediol, which was realized in the absence[5] of solvent. The mono-tosylate (highly polar, almost insoluble in diethyl ether) was then isolated from the excess diol and triethylamine hydrochloride by partitioning[6] the reaction mixture between CH_2Cl_2 and aqueous HCl. The subsequent oxidation was effected under Taber's conditions (PDT oxidation[7]). The reaction could be accomplished

Scheme 1



without particular precautions (e.g., oven-dried glassware and nitrogen atmosphere or drying tubes) against moisture (at expenses of excess P_2O_5). The triethylamine, however, should be added slowly to ensure that deprotonation mainly occurred at the carbon to be oxidized. Otherwise, the transient excess of free amine might abstract a proton from the α-carbon of the newly-released aldehyde, leading to undesired aldol condensation or elimination of the tosylate (similar to the formation[8] of cyclopropyl methyl ketone from 5-chloropentan-2-one); both would result in lower yields of the acetal. The crude aldehyde was then converted *in situ* to the dimethyl acetal **1b** by MeOH/$CH(OMe)_3$ at reflux after acidifying the reaction mixture with concd H_2SO_4. If desired, the tosylate–acetal (**1b**) could be isolated as an almost colorless oil in 51% overall yield (based on TsCl).

Corresponding ethylene acetal–tosylate could also be prepared from the crude aldehyde and either isolated by chromatography or directly converted to iodide as below. The yields were, however, significantly lower. Since the ethylene acetal does not seem to have much advantage[9] over the dimethyl acetal, no further efforts were made along that line.

Clean conversion of the pure tosylate to iodide can be easily achieved in less than 3.5 h at rt with 7 equiv of NaI in acetone. The reaction must be buffered with finely powdered $NaHCO_3$. Insufficient stirring and/or larger particle size of the $NaHCO_3$ may lead to significant deacetalization. If the solvent (acetone) is free from aldols (e.g., from a freshly opened bottle), the resulting crude iodide contains only negligible amounts of impurities (as shown by ^1H NMR) and can be directly used for most preparative purposes. The iodide (**1c**) can also be obtained from the crude tosylate under similar conditions. In this case, only one chromatography is needed for the whole synthesis.

Compared with the previous routes, the present one is remarkably practical. Although the overall yield is lower than Yamada's,[10] it is fully compensated by the much cheaper/easily accessible reagents involved and the

(1) Stowell, J. C.; Polito, M. A. *J. Org. Chem.* **1992,** *57,* 2195 and references cited therein.

(2) Wu, Y.; Ahlberg, P. *Synthesis* **1994**, 463 and references cited therein.

(3) For two recent preparations, see: (a) Larson, G.; Klesse, R. *J. Org. Chem.* **1985,** *50,* 3627. (b) Stowell, J. C.; King, B. T.; Hauck, H. F., Jr. *J. Org. Chem.* **1983,** *48,* 5381.

(4) The hidden problems with preparing these simple compounds stem from the 1,4-difunctionality. The OH easily bonds to the unmasked carbonyl group to form an intramolecular hemiacetal, which cannot (see refs 1 and 15) be cleaved by acidic treatment of monools or simple diols. This makes the desired transformation of OH into halides very difficult. Therefore, in earlier syntheses the halide atom was introduced from the beginning. For stability and commercial availability reasons, only chloride and bromide could be used. The syntheses consequently suffered from the difficulty caused by the relatively low boiling points of the intermediates/products and the absence of UV chromophore (which made chromatographic purification much less convenient). The reagents introduced by Stowell and Polito (ref 1) are indeed easier to prepare. However, the deprotection of these acetals, which is often required at later stages of the syntheses, is no easy task, since they are remarkably stable to acids (formed in strongly acidic aqueous solutions).

(5) With CH_2Cl_2 as solvent bis-tosylate became the predominant product, no matter how large of an excess of the diol was used, presumably due to the better solubility of the mono-tosylate in CH_2Cl_2 than the diol (the reaction mixture was not quite homogeneous).

(6) Two additional advantages of using CH_2Cl_2 as extracting solvent are that the drying (since water quenches PDT oxidation) was much easier (compared with using, e.g., EtOAc) and the filtrate could be directly used in the next step.

(7) Taber, D. F.; Amedio, J. C., Jr.; Jung, K.-Y. *J. Org. Chem.* **1987,** *52,* 5621.

(8) Cannon, G. W.; Ellis, R. C.; Leal, J. R. *Organic Syntheses*; Wiley: New York, 1963, Collect. Vol. 4, p 597.

(9) On the contrary, the dimethyl acetal gives a simpler ^1H NMR spectrum and the deprotection is also easier. A better yield with **1c** than the ethylene acetal–iodide as alkylating agent has been reported, see ref 10.

(10) Niwa, H.; Hasegawa, T.; Ban, N.; Yamada, K. *Tetrahedron* **1987,** *43,* 825.

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simpler procedure. The advantage over other routes[11] is even more evident.

Experimental Section

All chemicals were used as received without any further purification. The sources are as follows: from Fluka, 1,4-butanediol (purum), NEt_3 (puriss), TsCl (*p*-toluenesulfonyl chloride, puriss), $NaHCO_3$ (Purum); from Aldrich, DMAP (4-(dimethylamino)pyridine, 99%), $HC(OMe)_3$ (98%); from Merck, P_2O_5 (pro analysi); from M&B, acetone (Analytical Reagent); from Riedel-deHën, MeOH (pro analyse). The $NaHCO_3$ was ground with a pestle and mortar before being used in the tosylate to iodide conversion. The ^1H and ^{13}C NMR spectra were recorded at 399.952 and 100.577 MHz, respectively, with $CDCl_3$ as solvent and Me_4Si (for ^1H, set to 0 ppm) or the middle line of the $CDCl_3$ triplet (for ^{13}C, set to 77 ppm) as reference.

4,4-Dimethoxybutyl Tosylate (1b) and 4,4-Dimethoxybutyl Iodide (1c). To a 50-mL round-bottomed flask were added 1,4-butanediol (4.85 g, 53 mmol), NEt_3 (1.0 mL, 7.17 mmol),[12] DMAP (32 mg, 0.26 mmol), and TsCl (1.314 g, 6.823 mmol). The mixture was stirred at rt for 1.5 h, before being partitioned between CH_2Cl_2 (40 mL) and aqueous HCl (made from 2 mL of 37% HCl and 28 mL of H_2O, containing ca. 24 mmol of HCl). The lower phase was washed once more with H_2O (20 mL). The first and the second aqueous phases were sequentially back-extracted with another 10 mL of CH_2Cl_2. The combined CH_2Cl_2 phases were then stirred with anhydrous Na_2SO_4 (ca. 8 g). When the liquid phase became a clear solution (ca. 30 min), anhydrous $MgSO_4$ (ca. 2 g) was introduced to further reduce the water content. The mixture (containing ca. 1.3 g of crude oil if the solution was evaporated to dryness at this stage) was then filtered into a 100-mL round-bottomed flask (the solids were washed with CH_2Cl_2). The volume of the colorless filtrate/washings was reduced to ca. 40 mL by rotary evaporation before DMSO (1.5 mL, 21 mmol) was introduced. With cooling (ice–water bath) and rapid stirring, P_2O_5 (ca. 2.59 g, 18.3 mmol; normally a small portion of it was stuck on the weighing paper/spatula) was added as quickly as possible (to avoid absorbing moisture in the air). The flask was then stoppered, and the mixture (soon became rather thick and therefore an efficient stirring bar was preferred) was vigorously stirred at 0 °C for ca. 1 h. The stopper was removed, and NEt_3 (3.6 mL, 26 mmol) was introduced *dropwise* over 15 min (most conveniently via a syringe). The stirring was then continued for another 3–5 min (at 0 °C), when the white mixture began to turn yellowish. MeOH (30 mL) and $HC(OMe)_3$ (1.5 mL, 14 mmol) were introduced, (immediately) followed by concentrated H_2SO_4 to acidify the reaction mixture to ca pH 1 (ca. 0.35–0.40 mL, 6.5–7.5 mmol). The cooling bath was then removed, and the mixture was refluxed (60 °C hot plate) with stirring for 70 min. (Some Me_2S might escape at this stage, and the cloudy mixture thus became clearer). After being cooled to rt, the mixture was diluted with CH_2Cl_2 (20 mL) and washed *quickly* (a few seconds) with H_2O (20 mL; neutralizing first would lead to difficulty in removing NEt_3), saturated aqueous $NaHCO_3$ (30 mL), and brine (20 mL). The three aqueous phases were sequentially back-extracted twice with CH_2Cl_2 (2 × 10 mL). The combined CH_2Cl_2 phases were then dried over anhydrous Na_2SO_4. Filtration and rotary evaporation left a yellowish oil[13] (≈1.9 g, still containing some $HC(OMe)_3$).

Chromatography of the crude oil from a duplicate run (silica gel, 2:1 diethyl ether/hexane) gave the pure tosylate[14] (**1b**) in 51% overall yield (from TsCl) as an almost colorless oil: ^1H NMR δ 1.63 (m, 2 H), 1.72 (m, 2 H), 2.46 (s, 3 H), 3.28 (s, 6 H), 4.05 (t, J = 5.6 Hz, 2 H), 4.30 (t, J = 6.1 Hz, 1 H), 7.35 (d, J = 8.4 Hz, 2 H), 7.79 (d, J = 8.4 Hz, 2 H); ^{13}C NMR δ 21.63, 24.07, 28.48, 52.97 (2C), 70.24, 103.82, 127.88, 129.81, 133.06, 144.70.

The crude tosylate obtained above (≈1.9 g) was dissolved in acetone (20 mL, swirled with some powdered $NaHCO_3$ before use) and stirred vigorously with *finely powdered* $NaHCO_3$ (2.7 g, 32.13 mmol) and NaI (3.5 g, 23.3 mmol) for 3.5 h at rt in the dark. The mixture (white to yellowish) was then partitioned between diethyl ether (50 mL) and H_2O (ca. 30 mL). The ethereal phase was washed with H_2O and brine (ca. 15 mL each). The aqueous phases were back-extracted sequentially with diethyl ether (20 mL), and the combined ethereal phases were dried over anhydrous Na_2SO_4 (together with some $NaHCO_3$). After filtration and evaporation, the crude oil (1.12 g) was chromatographed on silica gel (with a 1-mm-thick layer of powdered $NaHCO_3$ on the top of the column, 10:3 hexane/diethyl ether) to afford the pure iodide[10,11a] (**1c**) as an almost colorless oil (818 mg, 49% overall yield from TsCl): ^1H NMR δ 1.73 (m, 2 H), 1.90 (m, 2 H), 3.21 (t, J = 6.8 Hz, 2 H), 3.33 (s, 6 H), 4.32 (t, J = 5.6 Hz, 1 H); ^{13}C NMR δ 6.58, 28.62, 33.31, 52.86 (2C), 103.51.

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(11) (a) Chow, H.-F.; Fleming, I. *J. Chem. Soc., Perkin Trans. 1* **1984**, 1815. (b) Fleming, I.; Pearce, A. *J. Chem. Soc., Perkin Trans. 1* **1981**, 251. See also: (c) Vedejs, E.; Arnost, M. J.; Hagen, J. P. *J. Org. Chem.* **1979**, *44*, 3230. (d) Roush, W. R.; Hall, S. E. *J. Am. Chem. Soc.* **1981**, *103*, 5200. (e) Segi, M.; Takahashi, M.; Nakajima, T.; Suga, S. *Synth. Commun.* **1989**, *19*, 2431. (f) We have also examined another route consisting of ring opening of 2,3-dihydrofuran with 1,2-ethanedithiol, tosylation with TsCl/NEt_3/DMAP, and conversion of the thioacetal to dimethyl acetal with $PhI(O_2CCF_3)_2$. The whole synthesis could be fulfiled in one flask in 42–53% yield. However, since the workup was troublesome and the $PhI(O_2CCF_3)_2$ could not be replaced by other cheaper reagents, this route was abandoned.

(12) Using excess NEt_3 here led to significantly reduced yields. Presumably, the excess NEt_3 deprotonates the OH and the resulting alkoxide attacks the tosylate intramolecularly to form a tetrahydrofuran ring. It is interesting to note that if the carbon chain contains one more CH_2 (1,5-pentanediol) the yields of the corresponding monotosylate are not affected by the presence of excess NEt_3. On larger scales, cooling (ice–water bath) is recommended for the first 5–10 min after mixing the reactants.

(13) The crude oil easily turns from yellowish to light brown if being stored at rt overnight. The pure tosylate is much more stable (only became a bit more yellow after a few days at rt). The main reason of the color darkening is presumably the methoxy group-assisted decomposition (see ref 14), followed by aldol condensation. This process is greatly suppressed at lower temperature; both the crude and the pure oil (**1b**) can be safely stored at 5 °C (refrigerator) at least for a few weeks. The iodide (**1c**), however, is not very stable even at −20 °C (turned yellow after several days in a freezer).

(14) Hazen, J. R. *J. Org. Chem.* **1970**, *35*, 973.

(15) Lawson, A. P.; Klang, J. A. *Synth. Commun.* **1993**, *23*, 3205.