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4-Substituted Dioxolanes by Chemoselective Reactions on Glycerol Formal

Jean-Louis Gras[a*], Hervé Dulphy[a], Christophe Marot[b], Patrick Rollin[b]

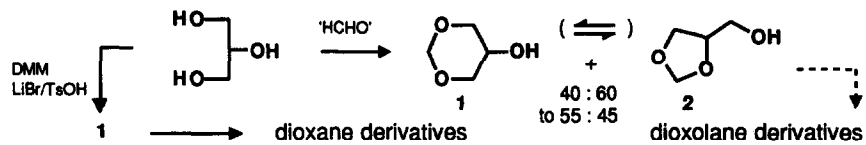
a) Laboratoire de Synthèse Organique associé au CNRS, Faculté des Sciences de Saint-Jérôme D12 - F-13397 - Marseille Cedex 20

b) Laboratoire de Chimie Bioorganique et Analytique associé au CNRS, Université d'Orléans, B.P. 6759, F-45067 Orléans Cedex 2

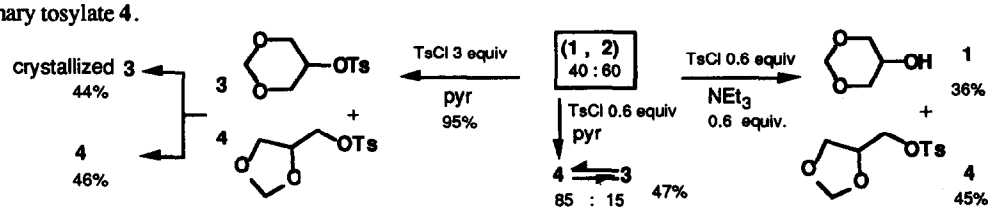
Key Words : Glycerol formal; dioxolanes; chemoselectivity

Abstract: *4-Hydroxymethyl-1,3-dioxolane contained in glycerol formal undergoes chemoselective transformations, which constitute a direct entry to 4-substituted-1,3-dioxolanes.*

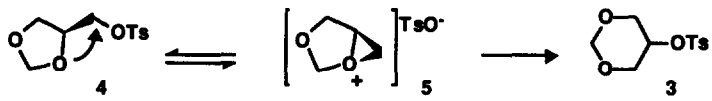
Methylene acetals have recently attracted more attention as synthetic intermediates or as templates for asymmetric synthesis. Unlike other acetals the formal moiety is stable toward moderate acidic conditions, and easily removed by acetolysis.[1] It is able to direct stereoselective additions[2] and can also behave as a chelating unit for metal-promoted reactions.[3] We have been interested in diverse aspects of the chemistry of "glycerol formal", a *ca* 1:1 mixture of 1,3-dioxan-5-ol **1** and 4-hydroxymethyl-1,3-dioxolane **2** which is easily obtained on the industry level by condensing formaldehyde on glycerol.[4] Such compounds are non-toxic to humans and have therefore found a wide range of applications.[5] The formation of both isomers is a reversible reaction and we have developed a procedure for the selective synthesis of symmetrical dioxane **1** through transacetalization of dimethoxymethane.[6] In contrast, no selective method is known to afford pure compound **2** albeit many 4-substituted 1,3-dioxolanes exhibit biological activity like in acetal phospholipids or quaternary amines.[7]



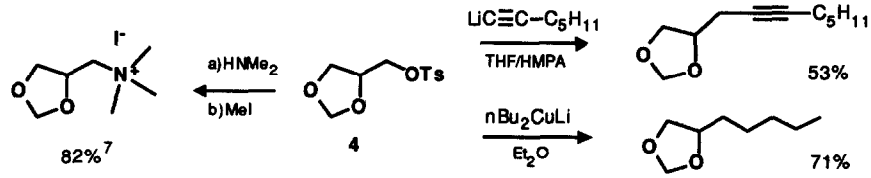
The higher reactivity of the primary as compared to the secondary hydroxyl group led us to explore chemoselective derivatizations of **2** from the glycerol formal mixture. The conversion of (**1**, **2**) to the corresponding ethers is not selective.[4] Neither could we isolate alcohol **2** as its acetate. Tosylate **4** indirectly prepared in four steps from glycerol is an intermediate to biologically active muscarine analogs.[7] We converted glycerol formal into the corresponding mixture of tosylates from which symmetrical **3** crystallizes, leaving pure primary tosylate **4**.



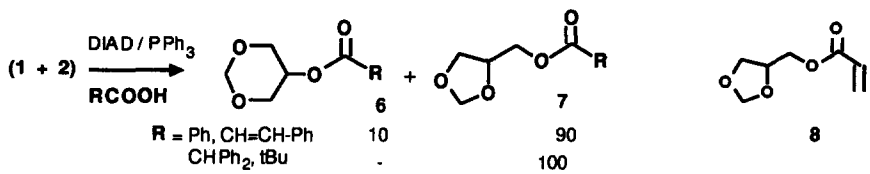
When kept in solution, tosylate **4** partially isomerizes into **3** with a constant 85:15 ratio. This equilibrium arises from a 1,2 shift of one of the C-O bonds via the oxonium cation **5**, a transposition process analogous to that observed during the hydrolysis of oxiranylcarbinyl tosylates.[8]



Chemoselective tosylation of glycerol formal with tosyl chloride (0.6 equiv.) in pyridine leads to the equilibrated mixture regardless of the reaction time. Recovery of the mixed tosylates then crystallization of **3** affords pure tosylate **4**. When triethylamine is the base, TEA^+Cl^- that precipitates on Et_2O addition is filtered, and chemoselective tosylation of (**1**, **2**) affords tosylate **4** and unconverted **1**, both directly isolated from the reaction mixture. When using mesyl chloride the same procedure affords the corresponding mesylate (95% pure) along with unconverted **1** (92% pure). Compound **4** exhibits the usual reactivity of primary tosylates: the tosyl group can for example be displaced by nucleophiles such as amines, acetylides or alkylcuprates.



Carboxylic esterification was next explored in order to test the chemoselectivity level of the formal mixture **1+2**. The Mitsunobu conditions - which are known to induce preferential substitution on primary hydroxyl sites[9] - were applied to glycerol formal. Using benzoic acid and (E)-cinnamic acid - or the corresponding zinc salts[10] - as nucleophilic partners, chemoselective esterification to **6** and **7** was attained in a *ca* 1:9 ratio. However, use of acrylic acid or of the more bulky diphenylacetic and pivalic acid exclusively yielded the expected dioxolane esters.



In addition, acrylate **8** obtained by the above procedure was examined as dioxolane chelating unit liable to induce asymmetry in Lewis acid-promoted Diels-Alder additions to cyclopentadiene. The diastereomeric excess observed though was modest (~30%) due to the geometrical change when compared with the successful dioxane homolog.[11]

This work shows that glycerol formal is a source of synthetically useful pure 4-substituted dioxolanes, obtained by chemoselective reactions on its hydroxymethyl segment.[12]

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12. Analytical and spectroscopic data for the synthesized compounds were satisfactory.

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