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Use of tosylated glycerol carbonate to access *N*-glycerylated aza-aromatic species

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ABSTRACT

Tosylated glycerol carbonate was used for *N*-glyceryl functionalization of diverse aza-aromatic systems. Depending on the pK_a of the aza-heterocycle and the reaction conditions applied, original *N*-alkylated or *N*-acylated aza-heterocyclic derivatives were obtained. Those compounds carry an electrophilic appendage—either carbonate or epoxide—which allows further useful transformations.

1. Introduction

The possibility of using glycerol in the creation of value-added chemicals has become increasingly attractive in recent years, partly from the manufacture of biodiesel, where glycerol is formed in large amounts as the main by-product and partly from the renewable aspect of the chemistry developed.[1] Among the readily accessible molecules obtained from glycerol, the cyclic 1,2-carbonate (4-hydroxymethyl-1,3-dioxolan-2-one) **1**—a stable, low vapour pressure, colourless liquid is one major renewable target in glycerol chemistry. Glycerol 1,2-carbonate (GC) is a relatively new and interesting bio-degradable material that can be used as a non-toxic solvent in cosmetics, medicine and industry.[2] In addition to these applications GC, as a bifunctional organic compound, has considerable potential for use as a reagent or a building block in fine chemistry. Five-membered cyclic alkylene carbonates are highly reactive species, which can easily undergo a number of reactions with various nucleophiles, such as amines, alcohols, thiols, and can also take part in ring-opening polymerisation reactions.[3] The primary hydroxyl functionality also broadens the reactivity scope of GC as a nucleophile. Treatment of GC with anhydrides,[4] arylsulfonyl chlorides,[4c] isocyanates[5] readily affords esters, sulfonates and urethanes, respectively. GC nucleophilicity has been used in glycoside synthesis by reaction with saccharides under acid catalysis.[6]

As an inexpensive industrial starting material, GC has been applied in the elaboration of surfactants[4a] and polymeric materials.[5,7] It can easily be converted into glycidol and epichlorohydrin—high value monomers for macromolecular applications.[4b,8] More recently, an advanced building block of GC has been introduced through its conversion into the tosylated form as a new valuable starting material for fine chemistry or polymer applications. Tosylated glycerol 1,2-carbonate (TGC) has also found use as an initiator for cationic ring-opening polymerisations.[9]

The reactivity of *O*-sulfonylated GCs—either mesylate or tosylate—has been explored with various thiols, alcohols and amines as nucleophiles aiming at selectively mono- or bis-functionalised 3-carbon synthons.[10] In this regard, TGC underwent chemoselective reactions (Scheme 1). With aliphatic primary and secondary amines and aliphatic alkoxides, ring-opening of the cyclic carbonate occurred. Aminolysis afforded (2-hydroxy-3-tosylpropyl)carbamates, further transformed into the corresponding glycidyl

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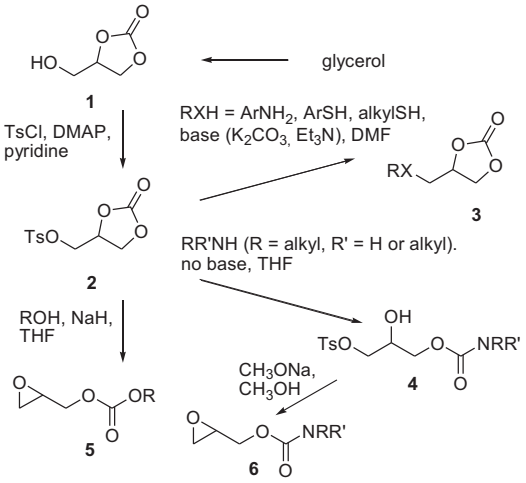
alkylcarbamates, which can be seen as protected intermediates of glycidol derivatives.[10b] Alkoxides reacted to afford glycidyl carbonates, whereas the reactivity observed with softer nucleophiles was centred on the glycerol sulfonylated site.



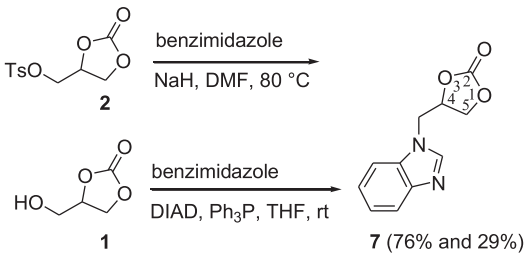
Scheme 1. Reactivity of TGC **2**.

Our current interest in developing TGC seeked for extension of its abilities as a bis-electrophile with involvement of a new family of aza-nucleophiles based on heteroaromatic structures containing an acidic *N*–H bond. In this regard, our aim was to explore the site selectivity and the potentiality to develop new building blocks for fine organic chemistry. Reacting aza-heteroaromatics with TGC would lead to molecular hybrids in which the aryl system is *N*-connected to a glyceryl-derived appendage, thus delivering building blocks of general interest in the preparation of pharmaceuticals and advanced materials particularly.[11]

2. Results and discussion

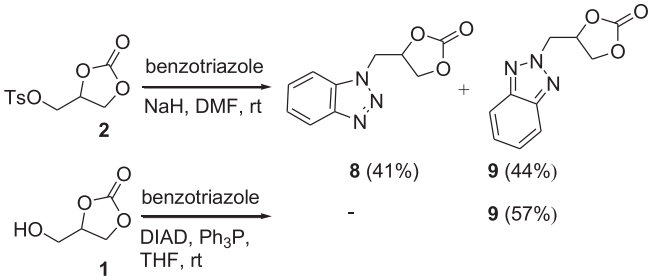
Stable crystalline TGC **2** was prepared in quantitative yield from GC **1** following our previously described procedure (TsCl in the presence of pyridine and DMAP in dichloromethane).[10a] Reagent **2** was confronted to different *N*H-containing aza-heteroaromatics, namely 9*H*-carbazole, 1*H*-indole, 1*H*-benzimidazole and 1*H*-benzotriazole. All of the above mentioned heterocycles are *N*–H acids, with pK_a values (measured in DMSO) ranging between 20.95 (for 1*H*-indole) and 11.9 (for 1*H*-benzotriazole).[12] The direct nucleophilicity of these aromatic *N*H-heterocycles is very weak and requires deprotonating activation to the corresponding anion.[13] The *N*-alkylation of heterocyclic compounds bearing a *N*–H acidic hydrogen atom is accomplished either by treatment of the substrate with a base such as sodium hydride, potassium hydroxide or *n*-BuLi, followed by reaction of the resulting anion with an alkylating agent,[14] or by direct N-alkylation under phase-transfer catalysis conditions.[14a,c,15] Another alternative alkylation method involves Mitsunobu reaction of *N*–H heteroaromatics with alcohols.[16]

The study was initiated with 1*H*-benzimidazole. Alkylation of ambident benzimidazole anion with alkyl halides or alkyl sulfonates can be readily accomplished in both protic and aprotic solvents.[17] The reaction of TGC **2** with the benzimidazole anion generated with NaH in DMF afforded the crystalline carbonate **7** in 76% yield using a 1:1 stoichiometric ratio of reactants. The formation of the *N*-acylated derivative was not observed. A comparative direct *N*-alkylation of 1*H*-benzimidazole with GC **1** using Mitsunobu reaction conditions (DIAD, Ph_3P, THF) afforded compound **7** in only 29% yield (Scheme 2). Analysis of the unpurified reaction mixture by LC/MS and ^{1}H NMR spectroscopy revealed also the formation of high molecular weight side products. Variations of the reaction parameters such as reaction temperature and time, and the use of DEAD as a Mitsunobu reagent, did not result in a significant improvement of the yield of the target product.



Scheme 2. Reactions of benzimidazole with TGC **2** and GC **1**.

Comparatively, the more acidic 1*H*-benzotriazole was then investigated. It is known that the ambident anion of benzotriazole reacts with electrophiles to afford mixtures of 1- and 2-substituted regioisomers.[18] Reacting TGC **2** at room temperature with the benzotriazolyl anion generated with NaH in DMF afforded an equimolar mixture of *N*-alkylated regioisomers **8** and **9** in 85% global yield. As expected, applying the Mitsunobu reaction to 1*H*-benzotriazole with 1,2-glycerol carbonate **1** regioselectively afforded the 2-substituted product **9** in 57% yield (Scheme 3).



Scheme 3. Reactions of benzotriazole with TGC **2** and GC **1**.

X-ray crystallographic study of **8** (Fig. 1)[19] was performed to ascertain the regioisomeric issue in both reactions.[20]

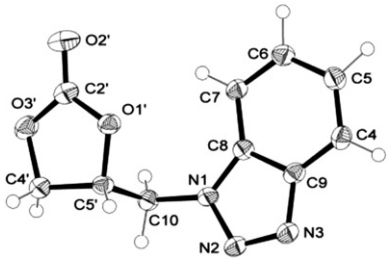


Fig. 1. ORTEP drawing of compound **8**.

Switching to less acidic aza-heterocyclic systems, we now considered the reaction of 1*H*-indole derivatives.[21] Indole **10** has shown in some cases to undergo exclusive *N*-alkylation, whereas different conditions oriented substitution at C-3. The rate and regioselectivity of the reaction mainly depend on the solvent, the counter-cation and on the structure of the electrophilic partner.

The reaction of TGC **2** with deprotonated 1*H*-indole in DMF exclusively gave *N*-alkylated compound **10a** in 34% yield (Table 1, entry 1). When performed in THF instead of DMF, the reaction afforded compound **10b** in 39% yield (Table 1, entry 2). Low yield of the both reactions can be explained by the tendency of 3-unsubstituted indoles to polymerize (Scheme 4).[22]