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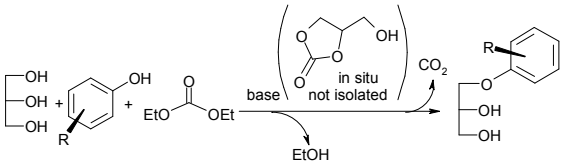
One-pot synthesis of aryloxypropanediols from glycerol: towards valuable chemicals from renewable sources

Ada M. Truscello,* Cristian Gambarotti, Mirvana Lauria, Sergio Auricchio, Gabriella Leonardi, Suresh U. Shisodia and Attilio Citterio

Aryloxypropanediol of known pharmacological activity are directly prepared from glycerol in a one-pot reaction, through *in situ* formed glycerol carbonate, under green and solvent-free conditions. Catalyst and unreacted reagent can be recycled.



One-pot synthesis of aryloxypropanediols from glycerol: towards valuable chemicals from renewable sources

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Glycerol revealed to be an easy and green access for the synthesis of aryloxypropanediol of known pharmacological activity. Performing a one-pot reaction, glycerol is selectively converted to aryloxypropanediols, through *in situ* formed glycerol carbonate, under benign and solvent-free conditions. Catalyst and unreacted reagent can be recycled.

Nowadays, glycerol represents one of the most versatile and valuable chemical substances commercially available in bulk quantities.[1] This is mainly due to the increasing worldwide production of biodiesel as a new generation fuel, which led to an increase in the production of glycerol, because of its inevitable formation as a by-product during biodiesel production.[2] This results in large availability of glycerol, therefore its valorization has aroused great interest in the last decade.

Recently, glycerol has been proposed as a valuable green solvent for catalysis, organic synthesis, separations and materials chemistry.[3]

Certainly, many opportunities have emerged from the conversion of glycerol into value-added chemicals.[4] In this context we focused our attention onto aryloxypropanediols with pharmacological activity (Figure 1), such as guaiphenesin,[5a] used as expectorant drug, mephenesin (Tolseron),[5b] used as muscle relaxant and chlorphenesin,[5c] used both as muscle relaxant, antifungal and biocide in cosmetic[5d]. Phenoxy ethers of glycerol are also intermediates for other drugs such as methocarbamol[5e] or chlorphenesin carbamate[5f].

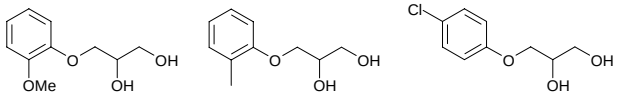


Fig. 1 Investigated aryloxypropanediols

Generally, these products are prepared by nucleophilic attack of the appropriate phenols onto glycidol, 1-chloroglycerol or epichlorohydrin.[6] However, these are well known toxic agents, thus our aim is to propose an innovative, selective and, at the same time, green synthetic way, starting directly from glycerol.

Glycerol carbonate (GC), which is known to be a non toxic reagent widely used in green chemistry,[7] represents a useful access to various substituted derivatives of glycerol and to functionalizations which are not possible directly on glycerol.[8] Recently, Jérôme and co-workers reported the use of not purified, freshly prepared GC in a two step synthesis of dithiocarbamates starting form glycerol and this represents an improvement compared to the use of commercial GC.[8a]

Now we report a one pot functionalization of glycerol via *in situ* formation of GC. As largely reported,[7b] GC can be prepared by several methods, which involve reagents such as ethylene carbonate, dialkyl carbonates, carbon monoxide, phosgene, urea and carbon dioxide. However, generally these protocols require further purifications, therefore we chose the carbonatation by dialkyl carbonates which avoids the presence of undesired by-products in the reaction media.

In the presence of catalytic amount of base and a small excess of diethyl carbonate (DEC), glycerol and appropriate phenols (ArOH) are converted in good yields and with high selectivity by a multicomponent one-pot reaction to the corresponding aryloxypropanediols. In Figure 2 the general approach is reported.

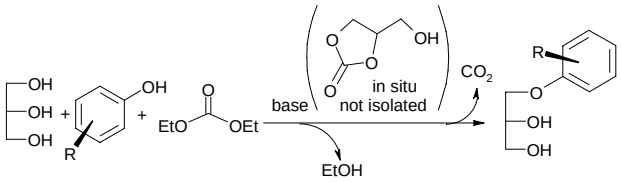


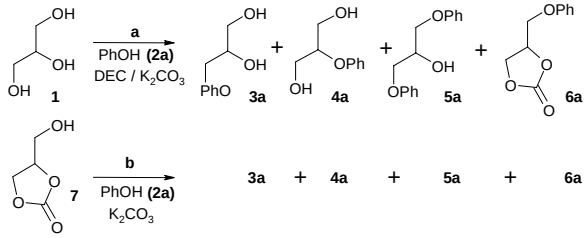
Fig. 2 General approach

Under these reaction conditions, the problem could be the undesired reaction of phenols with alkyl carbonates to give the corresponding alkyl aryl ethers and/or alkyl aryl carbonates as by products.[9]

As far as we know from literature, reactions with *in situ* formation of GC have not been published.[10] In a similar protocol, the reaction of ethylene glycol and anilines in the presence of dimethyl carbonate (DMC) and various catalysts gave at least a 2.6% yield of by-products arised from the direct attack of aniline to the linear carbonate.[11]

Phenol was used as model in our screening. Regarding the catalyst, it is well known that K_2CO_3 can promote the carbonatation of glycerol by dialkyl carbonates[12a] as well as the nucleophilic attack of phenols on cyclic carbonates[12b-d].

Reaction of glycerol (**1**) with stoichiometric amount of phenol (**2a**) and DEC, in the presence of catalytic quantity of K_2CO_3, gave 3-phenoxypropane-1,2-diol **3a**, 2-phenoxypropane-1,3-diol **4a**, 1,3-diphenoxypropan-2-ol **5a** (Scheme 1, **a**) and traces of 4-(phenoxymethyl)-1,3-dioxolan-2-one **6a**. Yields are reported in Table 1, entry 1. Only trace amount of ethoxybenzene was found (< 0,1% by HPLC analysis of the crude). Under these conditions, the reaction was almost total chemoselective: DEC reacted basically only with glycerol to form GC.



Scheme 1 General synthetic pathway

The reaction was also performed with DMC as carbonating agent. Also in this case, only trace amount (< 0,1%) of alkylated product (anisole) was detected. This showed that DMC could be used in the reaction. However, we found a lower conversion due also to the lower reaction temperature reached in this case.

Although GC was not present at the end of the reaction, it was found as main product at low conversion of reagents. Moreover similar yields and selectivity were found when GC (**7**) and phenol (**2a**) reacted under the same conditions (Scheme 1, b; Table 1, entry 2). Therefore it was reasonable to think that the reaction proceeded through nucleophilic attack of phenol (**2a**) on the *in situ* formed intermediate GC. The base played a double role, it catalysed both the formation of GC through carbonatation of glycerol by DEC and the subsequent nucleophilic attack of **2a**.

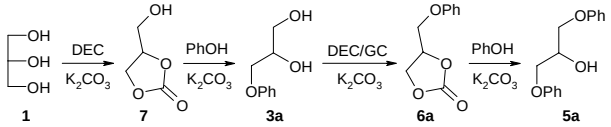
Table 1 Reactions of **2a** with various amounts of DEC and glycerol.*

Entry	Glycerol or GC (eq.)	DEC (eq.)	Time (h)	**2a** (%)	**3a** (%)	**4a** (%)	**5a** (%)	**6a** (%)	GC (%)
1	Glycerol (1)	1	8	19	51	2	19	1	-
2	GC (1)	-	8	20	44	2	21	2	1**
3	Glycerol (3)	1	12	26	60	2	3	-	-
4	Glycerol (3)	1.4	12	9	71	3	8	3	9
5	Glycerol (3)	1.4	18	1	82	4	8	-	-

*Yields of **3a**, **4a**, **5a** and **6a** were referred to phenol **2a**; yields of GC were referred to DEC and evaluated by NMR analysis after work up.
**Unconverted GC (glycerol found in variable amounts in the crude).

The yield of the desired product **3a** was affected by the incomplete conversion of reagents (part of DEC distilled) and by the formation of **5a**. To increase yield of **3a**, we focused our attention onto these two key points: to maximize the selectivity and at the same time the conversion.

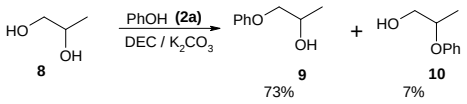
Formation of by product **5a** was due to four consecutive reactions: *in-situ* formation of the intermediate GC, nucleophilic attack by phenol with corresponding decarbonatation affording **3a**, further carbonatation either from DEC or GC and final attack of another molecule of phenol **2a** on the formed phenoxycarbonate **6a** (Scheme 2).



Scheme 2 Formation of by-product **5a**

To avoid the carbonatation of **3a** we decided to increase the amount of glycerol. In this case the carbonatation of the excess of glycerol was competitive with carbonatation of **3a** and this increased the yield of desired product **3a** (Table 1, entry 3). We found also that, in these conditions, a 1.4 molar excess of DEC was sufficient to ensure a good conversion of phenol (Table 1, entries 4-5). In all cases phenoxycarbonate **6a** was not present or present in very low yield. The best selectivity was obtained at incomplete conversion (entry 3). Moreover, the isomer **4a,** arising from the attack on the 2 position, was found in 2-4% yield (Table 1) confirming the high regioselectivity onto GC.[8a]

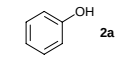
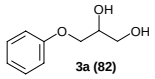
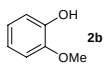
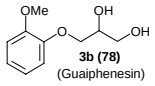
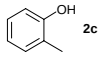
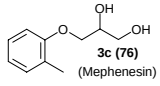
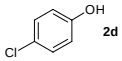
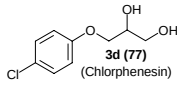
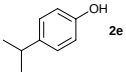
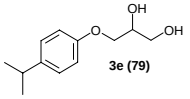
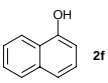
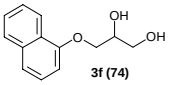
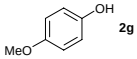
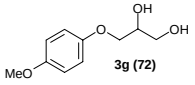
Extending the procedure to propandiol (**8**),[13] reaction gave good yields (Scheme 3) but lower selectivity (Table 1, entry 5).



Scheme 3 Reaction of **8** with **2a.**

Afterwards, we carried out the reaction of glycerol with other phenols of interest (**2b-g**) to obtain pharmaceutically important products such as guaiphenesin (**3b**), mephenesin (**3c**) and chlorphenesin (**3d**). All the reactions gave good conversions and yields (Table 2). Products **3a-g** were extracted with ethyl acetate and further purified by recrystallization.

Table 2 Reactions of glycerol with various phenols

Entry	ArOH	Time (h)	Conv. %	Products (yields %)*
1		18	99	 **3a (82)**
2		8	99	 **3b (78)** (Guaiphenesin)
3		28	97	 **3c (76)** (Mephenesin)
4		20	95	 **3d (77)** (Chlorphenesin)
5		12	99	 **3e (79)**
6		18	99	 **3f (74)**
7		14	98	 **3g (72)**

Conditions: 1 eq. of phenols **2a-g**, 3 eq. of glycerol, 1.4 eq. of DEC, 0.1 eq. of K_2CO_3, 105-110 °C. Conversions and yields were referred to phenols. * Yields were evaluated by NMR analysis after work up.

We tested the recyclability of both excess glycerol and catalyst for the synthesis of one of our target product i.e. mephenesin (**3c**). The products after each run were extracted from the crude mixture with toluene and analyzed by NMR. After the first run (conditions as reported in Table 2) and likewise after the second run, 1 equivalent of cresol (**2c**), 1.4 equivalents of glycerol and 1.4 equivalents of DEC were added to the residue recovered after the extraction and the resulting mixture was reacted for 28 h at 105-110 °C. As shown in Fig. 3, the reaction gave very good yields (76-80%), which means that the catalyst kept its efficiency. More details are given in the supplementary information.

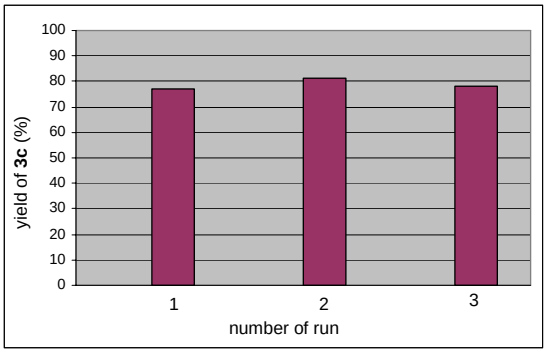


Fig. 3 Yield of mephenesin (**3c**) after the recycle of glycerol and K_2CO_3 (runs 2 and 3).

Conclusions

We believe that although linear and cyclic carbonate reactions were deeply investigated, little study was done on competitive reactions. Our protocol allows the use of more available hydroxy derivatives and DEC instead of cyclic carbonates as reagents. This method represents a green and easy access to aryloxyproapanediols **3** which, beside their own importance, are also in fact used as intermediates in biological products and in polymer chemistry. The great advatage of this synthetic protocol comes from the use of largely available and benign glycerol instead of epoxides or chlorinated derivatives and the synthesis does not involve toxic intermediates. The base potassium carbonate, is readily available and cheap and can be recycled as well as the excess of glycerol. No solvent is required for reaction.

Notes and references

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† Electronic Supplementary Information (ESI) available: Experimental procedures and copies of ^{1}H NMR and ^{13}C NMR spectra. See DOI: 10.1039/b000000x/

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