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COMMUNICATION

Regioselective functionalization of glycerol with a dithiocarbamate moiety: an environmentally friendly route to safer fungicides†

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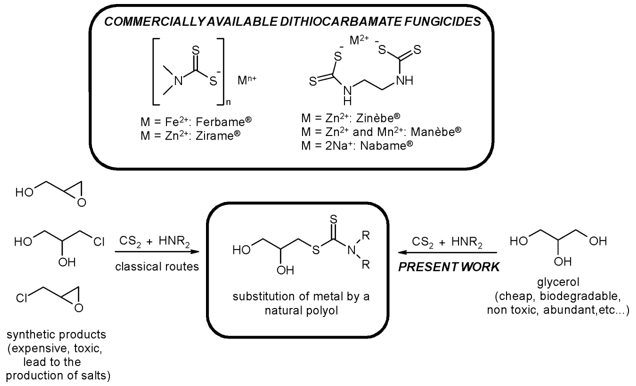
We report here a convenient pathway for the direct functionalization of glycerol with a dithiocarbamate moiety. This work opens up a cost-efficient and environmentally friendly route to safer fungicides. It should be noted that whereas functionalization of glycerol usually suffers from a lack of selectivity, we show here that our process is fully regioselective.

With the rapid emergence of biofuels and bioproducts on the market, the total demand of modern agriculture for phytosanitary chemicals is now dramatically increasing. As an illustration, the quantity of phytosanitaries has increased from 0.49 kg ha^{-1} in 1961 to 2 kg ha^{-1} in 2004. In 2007, the industry of phytosanitary chemicals generated a turnover of 33 billion dollars.[1] Among phytosanitary derivatives, fungicides are an important class. The extensive utilization of fungicides by agriculture raises some serious environmental problems (toxicities, poor biodegradability, human diseases, among others) which significantly increases the global environmental impact of "agro-based" products such as biosurfactants, biolubricants, biofuels, *etc.* Within the framework of sustainable chemistry, the search of safer fungicides has now become a challenging and urgent task, and modern agriculture strongly desires greener solutions. This aspect has been much boosted by the recent launch of the REACH regulation by the European Council, which is now leading to the progressive withdrawal of fungicides that have a harmful impact on the environment.

Among the widely used fungicides, dithiocarbamate derivatives are important.[2] Generally, these molecules are used as salts in order to ensure their solubility in water (Scheme 1).



Scheme 1 Synthesis of analogues of dithiocarbamate salts.

Unfortunately, their utilization on a large scale leads to significant contamination of soils and water-tables with metals.[3] Moreover, some of these chemicals are metabolized to ethylene thiourea, which is highly toxic and responsible for thyroid cancer and Parkinson's disease.[4]

In order to circumvent these issues, the substitution of the metal by natural polyols has been explored by Len and co-workers.[5] In this context, dithiocarbamates of glycerol (DTCG) were reported as promising candidates.[5a–d] Indeed, it has been clearly established in the literature that DTCGs are soluble in water and exhibit antifungal properties that are close to diethyldithiocarbamic acid sodium salt and Maneb®, thus offering promising access to fungicides with a lower impact on the environment.[5a,5c]

From a synthetic point of view, the synthesis of dithiocarbamate esters is rather difficult from alcohols, and in most cases alkyl halides are generally preferred, although this process generates a large amount of salts.[6] It should be noted that the most efficient example involving alcohols has been reported by Chaturvedi and co-workers.[7] Although their methodology afforded satisfactory yields from various alcohols, use of the Mitsunobu reagent unfortunately leads to stoichiometric production of waste, which has to be treated and disposed of.

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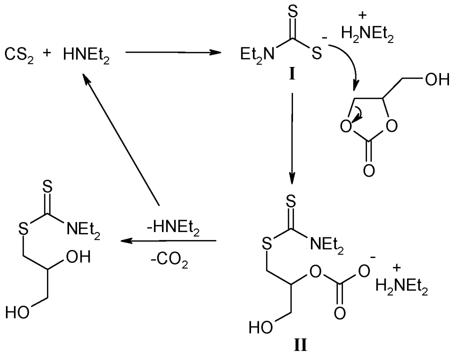
† Electronic supplementary information (ESI) available: Full characterization of the reaction products, experimental procedure for the synthesis of DTCG, and procedure for the recycling experiments. See DOI: 10.1039/c1gc15053g

Synthesis of dithiocarbamate esters from glycerol is even more challenging owing to the presence of three hydroxyl groups, which may lead to the formation of many side-products.[8] For these reasons, natural glycerol has never been used for the synthesis of DTCGs, and more reactive chemicals such as glycidol, 3-chloropropan-1,2-diol or epichlorhydrin are generally preferred (Scheme 1).[5a–d] Even though DTCGs produced by this route exhibit similar biological activities to commercially available fungicides, the toxicity and the price of glycidol, 3-chloropropan-1,2-diol and epichlorhydrin as well as the production of salts (for 3-chloropropan-1,2-diol or epichlorhydrin) hampers their industrial use. From the viewpoint of green chemistry, it seems obvious that the direct use of glycerol as a renewable raw material for the synthesis of DTCGs would be economically and environmentally more attractive.

In this context, we report here a highly selective methodology for substituting a hydroxyl group of glycerol by a dithiocarbamate moiety under very mild conditions. Our strategy is based on the synthesis of glycerol carbonate as a reactive and safe intermediate. Compared to traditional routes involving glycerol as the organic building block, all the reactions presented are fully regioselective. From a green chemistry perspective, these reactions are (i) salt- and metal-free, and (ii) show 100% atom-efficiency for sulfur and nitrogen, which are prerequisites for the use of sulfurized and nitrogenized compounds. Note that this work is not restricted to glycerol, and other polyols can be employed, thus opening a cost-efficient and environmentally friendly route to a diverse array of safer fungicides.

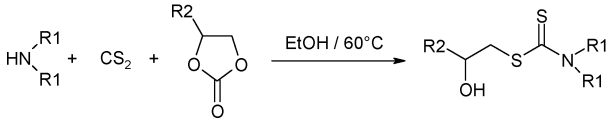
In our first set of experiments, reactions were carried out starting from glycerol carbonate in order to validate our methodology. To this end, equal amounts of carbon disulfide (CS_2, 16.9 mmol) and diethylamine (16.9 mmol) were mixed together and added to 16.9 mmol of glycerol carbonate dissolved in 5 mL of ethanol. To our delight, after 24 h of reaction at 60 °C, the corresponding DTCG was obtained with 91% yield (Table 1, entry 1) showing the efficiency of this reaction. As mentioned above, the reaction was fully regioselective, since only the 1-substituted DTGC was produced.

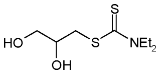
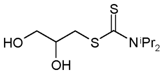
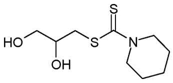
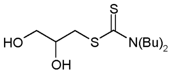
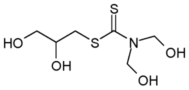
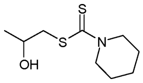
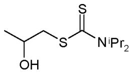
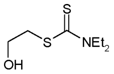
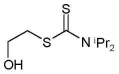
On the basis of the existing literature, we summarize in Scheme 2 a plausible reaction mechanism. First, secondary amine and CS_2 are known to readily react together to generate a dithiocarbamate acid salt (**I**).[9] This then reacts with glycerol carbonate selectively affording **II**, which is rapidly decarboxylated to yield the corresponding DTGC.[10] As observed in the literature, owing to the presence of a $-CH_2OH$ group on the glycerol carbonate, the methylene position is far more reactive than the -CH- group, thus rationalizing the regioselectivity of the reaction.[11]



Scheme 2 Plausible reaction mechanism.

Table 1 Synthesis of DTCG from glycerol carbonate



Entry	R1	R2	Time (h)	Product	Yield (%)[a]
1	-Et	$-CH_2OH$	15		91
2	-*i*Pr	$-CH_2OH$	24		85
3	$-(CH_2)_5-$	$-CH_2OH$	24		84
4	-*n*Bu	$-CH_2OH$	24		78
5	$-CH_2OH$	$-CH_2OH$	24		55
6	$-(CH_2)_5-$	$-CH_3$	24		71
7	-*i*Pr	$-CH_3$	24		55
8	-Et	-H	24		93
9	-*i*Pr	-H	24		55

[a] Isolated yield.

Having this first result in hand, we next investigated the scope of this reaction. To this end, glycerol carbonate was reacted with CS_2 and various secondary amines. All reactions were performed in ethanol at 60 °C. As summarized in Table 1, diethyl-, dibutyl- and diisopropylamine and piperidine successfully reacted with CS_2 and glycerol carbonate, affording the corresponding DTCGs with 78–91% yield (Table 1, entries 1–4). In the particular case of diethanolamine, the yield was lower (55%) due to the formation of side-products (Table 1, entry 5). Note that this reaction is not restricted to the use of glycerol carbonate. Indeed, other five-membered ring carbonates such as propylene carbonate and ethylene carbonate smoothly reacted with CS_2 and either piperidine or diisopropyl- or diethylamine, affording the desired dithiocarbamate esters with 55–93% yield (Table 1, entries 6–9). As in the case of glycerol carbonate, reactions performed from propylene carbonate were found to be fully regioselective. It should be noted that reaction yields presented in Table 1 are not governed by the nucleophilicity of the starting secondary amines but more by the difference of solubility of the corresponding dithiocarbamic ammonium salt in the reaction medium. Indeed, concentrated solutions of reactants in ethanol (3.4 M) were used. Therefore, the solubility of dithiocarbamic ammonium salt closely relies on the nature of the starting cyclic carbonates and amines. All reactions (except for entry 1) were stopped after 24 h of reaction, although yields of the desired DTCGs improved with a prolonged reaction time.

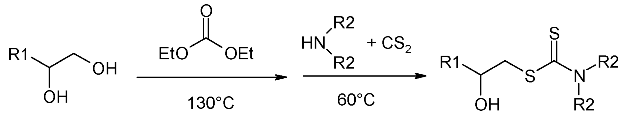
Next, considering that glycerol carbonate can be readily produced by reaction of glycerol either with urea[12] or diethylcarbonate[13] or CO_2,[14] we explored the possibility of directly producing DTCGs from glycerol in a one-pot two-step process. To the best of our knowledge, the reaction between diethylcarbonate and glycerol gives the highest yield of glycerol carbonate, and for this reason this reaction pathway was preferred in our investigations. Production of glycerol carbonate from diethylcarbonate and glycerol is catalyzed by a strong base such as NaOH.[13d] In our investigations, we decided to use glycerol both as a solvent and a reactant in order to ensure not only the dissolution of reactants but also to favor the *in situ* formation of glycerol carbonate. In our first set of experiments, diethylcarbonate (16.9 mmol) was mixed with 5-fold excess of glycerol and heated at 130 °C in the presence of 2 mol% NaOH for 1 h. Then, diethylamine (16.9 mmol) and carbon disulfide (16.9 mmol) were directly added to the crude, and the mixture was stirred for 24 h at 60 °C. Remarkably, under these conditions, the corresponding DTCG was isolated in 75% yield, thus opening a direct route to the synthesis of DTCGs from glycerol.

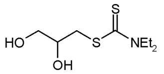
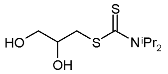
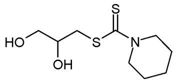
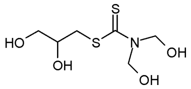
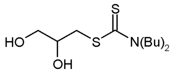
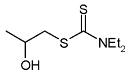
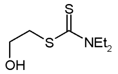
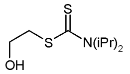
According to this pathway, various DTCGs were successfully synthesized directly from glycerol. Starting from diisopropylamine, piperidine and diethanolamine, the corresponding DTGCs were isolated with 45–70% yield (Table 2, entries 2–5). As mentioned above, this four-component reaction is not restricted to glycerol, and other polyols such as propanediol and ethylene glycol were successfully coupled with diethylcarbonate, secondary amines and CS_2, affording the desired dithiocarbamate esters with 69–75% yield (Table 2, entries 6–8). Note that in all cases, the first step corresponding to the *in situ* carbonation of polyols with diethylcarbonate is quantitative. Therefore, the global yield is determined by the second step of the process and, as mentioned above, this second step is only limited by the solubility of the dithiocarbamic ammonium salt in the glycerol phase (and not by the nucleophilicity of amines), and reaction yields can be improved with a prolonged reaction time.

Interestingly, whereas the direct functionalization of polyols generally leads to a mixture of regioisomers and polysubstituted adducts,[8] this route was still fully regioselective owing to the formation of the five-membered ring carbonate as the intermediate. During the reaction, only ethanol and CO_2 are released as waste. It should be noted that ethanol was continuously distilled out of the reaction medium, affording a very convenient purification and work-up.[15]

In order to minimize as much as possible the cost and environmental impact of this process, we then investigated the recycling of NaOH and the excess of glycerol used as solvent. In this context, we found that the addition of ethyl acetate to the crude mixture allows the selective extraction of DTGCs from the glycerol/NaOH phase. Titration of the glycerol phase with an aqueous solution of HCl revealed that NaOH was completely retained in the glycerol phase. On the basis of these results, we investigated the recycling of NaOH and the excess of glycerol. After the first extraction with ethyl acetate, a stoichiometric amount of glycerol, diethylcarbonate, diethylamine and carbon disulfide was reloaded according to the same procedure (described in Table 2). As shown in Fig. 1, during the second cycle, 75% yield of DTCG was still obtained. This procedure can be repeated at least 6 times without

Table 2 One-pot two-step synthesis of DTCG from glycerol



Entry	R1	R2	Time (h)	Product	Yield (%)[a]
1	$-CH_2OH$	-Et	15		75
2	$-CH_2OH$-	-*i*Pr	24		70
3	$-CH_2OH$	$-(CH_2)_5-$	24		65
4	$-CH_2OH$	$-CH_2OH$	24		45
5	$-CH_2OH$	-*n*Bu	24		63
6	$-CH_3$	-Et	24		75
7	-H	-Et	24		81
8	-H	-*i*Pr	24		69

[a] Isolated yield.

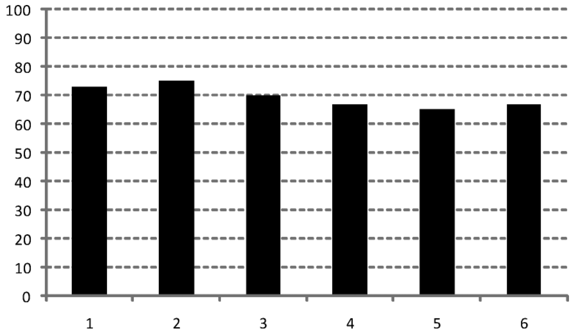


Fig. 1 Recycling experiments.

significant decrease of yield, thus showing the environmental and economical advantage of this route.

Because of the important industrial applications of DTCGs, we then scaled up the process. Using our strategy, we successfully produced 1 kg of DTCG from glycerol, diethyl carbonate, CS_2 and diethylamine, thus showing the viability of this process. Note that at the kilogram scale, the ethyl acetate used for the selective extraction of the DTCG from the glycerol/NaOH phase was recycled for use in further extractions, in order to minimize as much as possible the environmental and economical impact of the process. A schematic representation of the process is given in Scheme S1†.

Conclusions

We report here that glycerol carbonate can be considered as a highly valuable intermediate for the direct and regioselective functionalization of glycerol by a dithiocarbamate moiety. From the viewpoint of green chemistry, this procedure has many advantages, such as: (i) utilization of glycerol as a renewable raw material; (ii) 100% sulfur and nitrogen efficiency, (iii) CO_2 and ethanol as only waste; (iv) the possibility of recycling NaOH and the excess of glycerol used as solvent; and (v) the possible scale-up of the process. The biological activities of these DTCGs are currently being tested in an open field over sunflower, wheat and soy crops – the results of these tests will be published in a more specialized journal. This procedure opens an avenue for the synthesis of safer fungicides, but also provides new synthetic tools for the selective conversion of glycerol to higher-value chemicals. Generalization of this method to other nucleophiles and other natural polyols is now a topic of current investigation.

Acknowledgements

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