

Glycerol as An Efficient Promoting Medium for Organic Reactions

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Abstract: Whereas the beneficial effect of water on reaction rate is decreased with an increase of the reactant's hydrophobicity, we report here that the use of glycerol as solvent was able to considerably accelerate the reaction rate of an organic reaction even starting from more hydrophobic substrates than those usually used on water. Moreover, the possibility of directly using crude glycerol generated by the biodiesel industry economically and environmentally improves the interest of using glycerol as solvent.

Keywords: catalysts; glycerol; green solvents; rate acceleration

Since the 1980s, the use of water as solvent has attracted a lot of attention not only because it offers environmentally friendlier pathways but also because water itself is able to considerably increase the reaction rate of an organic reaction. Indeed, thanks to a strong hydrogen bond network, it was clearly demonstrated that the water interface can lower the activation barrier of a process, by solvation of the transition state, and consequently act as a potential catalyst.^[1] Based on this particular property of water, numerous organic transformations such as Diels–Alder^[2a] and hetero-Diels–Alder reactions,^[2b,c] cycloaddition reactions,^[3] Claisen rearrangements,^[4] aldolisation,^[5] oxidation^[6] and many others^[7] were successfully performed on water without addition of any catalyst. Fascinating reviews about this topic may be found in the literature.^[8] However, even if some spectacular rate improvements were observed on water, these on water-based processes are still subject to strict limitations when highly hydrophobic substrates are used.

In seeking further improvements on catalysis on water, we found that glycerol could behave similarly as water. Indeed, like water, glycerol is abundant, biodegradable, cheap (sometimes even cheaper than water!) and non-toxic. Moreover, like water, glycerol is highly hydrophilic, poorly soluble with most of organic substrates and its cohesion is also maintained by a strong hydrogen bond network. Based on the close similarity of its solvent properties with those of water, it occurred to us that the development of organic reactions on glycerol could be a great means to overcome the high hydrophobicity of organic substrates which are now the limiting factor for the development of on-water reactions. Compared to water, it has to be pointed out that glycerol exhibits a very high boiling point (290 °C) making also the development of organic reactions at high temperature technically easier.

From a social and economical point of view, utilisation of glycerol takes a place as one of the most urgent topic of this beginning century.^[9] Indeed, the spectacular and rapid development of the vegetable oil industries generates a tremendous amount of crude glycerol as by-product (1.5 million tons expected in 2008) which is now in urgent need of chemical utilisation. Up to now, most solutions deal with the transformation of glycerol to more valuable chemicals such as monoglycerides,^[10] glycerol ethers,^[11] acrolein,^[12] polymers,^[13] etc. However, the environmental and economical viability of these high tonnage glycerol-based processes are still a subject of strong discussions.

The direct utilisation of glycerol as a green solvent for organic transformations would be conceptually highly interesting since it would offer (i) a sustainable medium able to drive some organic transformations with more hydrophobic substrates than those commonly used on water and (ii) an economically attractive alternative use for the growing production of glycerol.

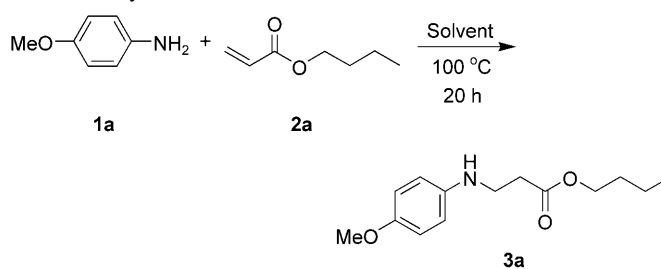
Recently, Wolfson's group in Israel showed that some selected organic reactions such as Pd-catalyzed Heck C–C coupling and Suzuki reactions could be performed in glycerol.^[14] However, compared to other organic solvents, no significant improvement in terms of reaction behaviour and catalytic performance was observed in glycerol. As a result, glycerol has not been recognised yet as a necessary solvent for organic reactions.

In this communication, we report that, like water, the glycerol interface can also act as a potential catalyst and drive many organic transformations such as Michael additions of amines, anilines and indoles, ring opening of styrene oxide with *p*-anisidine, and acid-catalysed dehydrative dimerisation of tertiary alcohol in a friendly manner. Moreover, whereas on-water reactions are limited when more hydrophobic substrates are involved, we show here that on-glycerol reactions tolerate the presence of more hydrophobic reactants.

The first reaction we examined is an aza-Michael reaction of amines on α,β -unsaturated compounds, which is one of the most effective ways to prepare β -amino acids and their ester derivatives.^[15] Many catalytic systems, such as Pd and Cu complexes,^[16] Lewis acids,^[17] Brønsted acids,^[18] zeolites^[19] and organic bases including DBU^[20] and [BMIm]OH,^[21] were reported to be effective for aza-Michael reactions of amines. In some cases, assistance of microwave irradiation was found to be helpful for a better catalytic performance.^[22] Some researchers have also examined the reaction in water,^[23] however, acceleration effect of water on the reaction rate was only observed in the reaction of aliphatic amines. Indeed, starting from aniline derivatives, assistance of a catalyst was found to be necessary.

With the aim of showing the great contribution of glycerol as reaction solvent, we investigated the aza-Michael addition of *p*-anisidine (**1a**) to butyl acrylate (**2a**). When this reaction was performed at 100 °C under solvent-free conditions or in the presence of organic solvents such as toluene, DMF, DMSO and 1,2-dichloroethane, no reaction occurred (Table 1, entries 2–6). As reported above, the reaction can proceed on water but a very low reaction rate was observed since only trace amounts of product (<5%) were detected after 20 h of reaction at 100 °C (Table 1, entry 7). Remarkably, when the reaction was now performed on glycerol, a considerable improvement of the reaction rate was observed compared to water and the resulting aza-Michael adduct was isolated with 82% yield after 20 h of reaction (Table 1, entry 1). This example clearly shows that, as expected, the glycerol interface is also able to directly “catalyse” an organic reaction. The difference of behaviour observed here between water and glycerol might come from the better affinity of *p*-anisidine for the glycerol interface inducing thus a faster reaction rate

Table 1. The aza-Michael reaction in different solvents under catalyst-free conditions.^[a]



Entry	Solvent	Yield [%]
1	glycerol	82 (82, ^[b] 80 ^[c])
2	no solvent	< 5 ^d
3	toluene	0
4	DMF	0
5	DMSO	0
6 ^[d]	CICH ₂ CH ₂ Cl	0
7	water	< 5 ^[e]
8	1,2-propanediol	30
9	crude glycerol	81 (80) ^[b]

^[a] *p*-Anisidine: 1.0 mmol, butyl acrylate: 1.0 mmol, solvent: 1 mL.

^[b] Reused in the second time.

^[c] Reused in the third time.

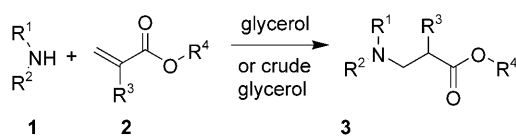
^[d] 90 °C.

^[e] GC yield.

compared to what was observed on water. Theoretical calculations are currently underway in our group and preliminary results will be reported in due course. Interestingly, compared to other high boiling point alcohols such as 1,2-propanediol, a higher reaction yield was obtained in glycerol, further indicating the great contribution of glycerol for driving an aza-Michael reaction (Table 1, entry 8).

Besides the beneficial effects exerted by pure glycerol on the aza-Michael reaction, we also investigated the possibility of conducting the same reaction using industrial grade glycerol (80%) which will be economically and environmentally more attractive. Glycerol generated by the biodiesel industry is not pure and generally contains about 15 wt% of water and 5 wt% of soap. Fortunately, the impurities present in crude glycerol do not significantly change the physical properties of crude glycerol. These aspects led us to directly use crude glycerol in our investigation. Table 1 shows that, using crude glycerol, nearly the same result of using pure glycerol are obtained (81%), increasing thus the interest of using glycerol as reaction media (entry 9).

The recyclability of glycerol was also investigated. At the end of the reaction, the aza-Michael adduct is not soluble in the glycerol phase and can be directly extracted after decantation. However, as in the case of water, this technique is not so easy to handle and

Table 2. Substrate scope for aza-Michael reactions in glycerol.^[a]**2a:** R³ = H, R⁴ = *n*-Bu**2b:** R³ = H, R⁴ = cyclohexyl (C₆H₁₁);**2c:** R³ = CH₃, R⁴ = C₆H₅CH₂;**2d:** methacrylonitrile;**2e:** crotononitrile.**1a:** R¹ = 4-CH₃OC₆H₄, R² = H**1b:** R¹ = 4-CH₃C₆H₄, R² = H;**1c:** R¹ = C₆H₅, R² = H;**1d:** R¹ = C₆H₅CH₂, R² = CH₃;**1e:** R¹ = 4-Cl-C₆H₄CH₂, R² = H;**1f:** R¹ = R² = C₆H₅CH₂;**1g:** R¹ = C₆H₅CH₂CH₂, R² = H;**1h:** R¹ = [3,4-(MeO)₂]C₆H₃CH₂CH₂, R² = H;**1i:** 1,2,3,4-tetrahydroisoquinolin;**1j:** tryptamine.

Entry	Amines	Olefin	Product	Temp. [°C]	Time [h]	Yield [%]		
						Glycerol	Crude glycerol	Neat conditions
1	1a	2b	3b	100	38	77	76	< 5 ^[b]
2	1b	2a	3c	100	20	78	74	< 5 ^[b]
3	1b	2b	3d	100	20	72	70	< 5 ^[b]
4	1c	2a	3e	100	20	66	64	< 5 ^[b]
5	1c	2b	3f	100	38	60	60	< 5 ^[b]
6 ^[c]	1d	2c	3g	100	5	85	77	29
7 ^[d]	1d	2d	3h	80	14	92	88	< 5 ^[b]
8 ^[d]	1d	2e	3i	80	14	93	90	< 5 ^[b]
9 ^[d]	1e	2d	3j	80	14	77	80	< 5 ^[b]
10 ^[c]	1f	2a	3k	100	14	83	80	< 5 ^[b]
11 ^[d]	1g	2d	3l	80	4.5	72	62	< 5 ^[b]
12 ^[d]	1h	2d	3m	80	4.5	74	67	< 5 ^[b]
13 ^[d]	1h	2e	3n	80	14	65	66	41
14 ^[c]	1i	2c	3o	100	5	65	55	< 5 ^[b]
15 ^[d]	1i	2d	3p	80	4.5	91	90	< 5 ^[b]
16 ^[d]	1j	2e	3q	80	14	90	87	< 5 ^[b]
17 ^[d]	1j	2d	3r	80	14	80	72	< 5 ^[b]

^[a] Ratio of amine/olefin = 1/1.2.^[b] GC yield.^[c] Ratio of amine/olefin = 1/1.^[d] Ratio of amine/olefin = 1/2.

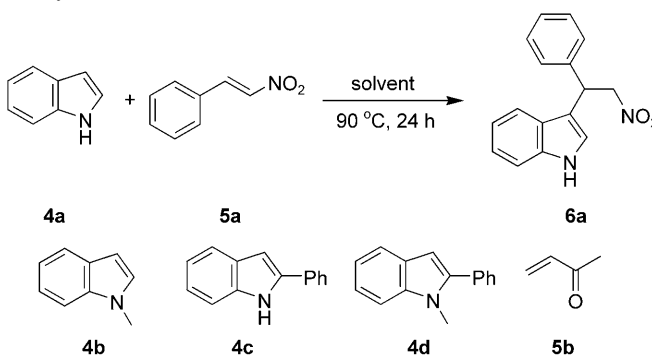
an important loss of product is observed during the extraction stage. With the aim of showing the possible recyclability of the glycerol phase, complete and easier extraction of the reaction product was performed with ethyl acetate. Before the next run, the recovered glycerol was maintained under vacuum (14 mmHg) at 60°C for 30 min in order to remove all residual traces of ethyl acetate. The yields obtained after three cycles were comparable to that of fresh glycerol or crude glycerol, indicating a good stability of glycerol (Table 1, entry 1).

Having these results in hand, we then investigated the substrate scope of the present aza-Michael reaction in glycerol or crude glycerol, and the results are listed in Table 2. In order to confirm the promoting effect of glycerol solvent on the reaction rate, results under neat conditions were also collected. As summarized in Table 2, whatever the reactant considered, use of glycerol as solvent significantly boosted the reaction rate of the aza-Michael reactions offering thus a great alternative to the use of expensive metal-con-

taining catalysts. Substituted anilines with electron-donating groups gave better reaction yields than that of aniline itself (entries 1 to 5).^[24] Primary and secondary amines, such as 4-chlorobenzylamine, phenylethylamine, 2-(3,4-dimethoxyphenyl)-ethylamine, *N*-benzylmethylamine and 1,2,3,4-tetrahydroisoquinoline reacted smoothly with methacrylonitrile at 80°C in glycerol or crude glycerol affording the corresponding mono-adducts in good to excellent yields (entries 7, 9, 11, 12 and 15). Some less reactive α,β -unsaturated carbonyl compounds, such as benzyl methacrylate and crotononitrile, could also react in the presence of glycerol (entries 6, 8, 13 and 16). Finally, a selective Michael addition of tryptamine was examined using methacrylonitrile as substrate, and it was observed that the reaction occurs selectively on the NH₂ position in glycerol leading to the corresponding monoadduct with 80% yield (entry 17). From these results, it is evident that our methodology is reasonably general and can be applied to many anilines, amines and α,β -unsaturated carbonyl compounds.

Encouraged by the above-mentioned results, we then investigated the Michael reaction of indole in glycerol. This type of reaction was generally carried out in the presence of either Brønsted^[25] or Lewis acid catalysts.^[26] Water has shown a beneficial effect on this reaction as solvent but always with the assistance of acidic or neutral catalysts.^[27] As shown in Table 3, the Michael reaction of indole with β -nitro-

Table 3. Michael reaction of indoles in different solvents at catalyst-free conditions.^[a]



Entry	Indole	Olefin	Product	Solvent	Yield [%]
1	4a	5a	6a	glycerol	80
2	4a	5a	6a	no solvent	< 5 ^[b]
3	4a	5a	6a	toluene	< 5 ^[b]
4	4a	5a	6a	DMF	< 5 ^[b]
5	4a	5a	6a	H ₂ O	55
6	4a	5a	6a	crude glycerol	78
7	4b	5a	6b	glycerol	75
8	4c	5a	6c	glycerol	70
9	4d	5a	6d	glycerol	62
10 ^[c]	4b	5b	6e	glycerol	84

^[a] Indole/olefin: 1/1.

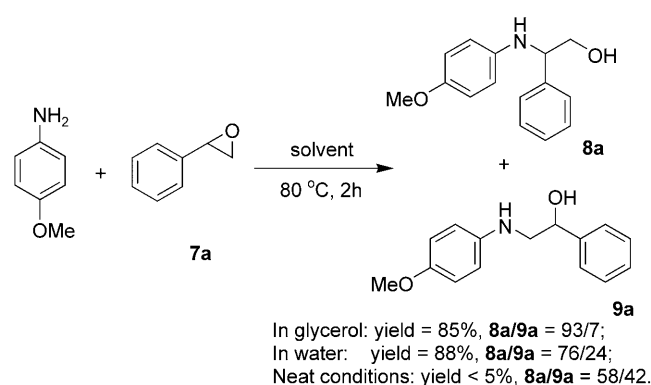
^[b] GC yield.

^[c] Indole/olefin: 1/2, 80 °C.

styrene proceeded very well in pure glycerol at 80 °C, and 80% yield was obtained after 24 h (entry 1). Under similar conditions, we found that water can also drive this reaction without assistance of any catalyst but the reaction rate was still lower than that observed in glycerol since the reaction product was obtained with only 55% yield after 24 h of reaction (entry 5). As mentioned above, we assume that this better improvement of the reaction rate observed with glycerol could be ascribed to a better affinity of indole derivatives for glycerol than for water. Here again, only a trace amount of product was detected using organic solvents such as toluene, DMF or solvent-free conditions (entries 2 to 4) confirming, as in the case of water, the key role played by the glycerol hydrogen bond network on the reaction progress. As observed above, crude glycerol also showed a similar

performance as pure glycerol for the model reaction (entry 6). Other substrates such as 1-methylindole, 2-phenylindole, 1-methyl-2-phenylindole and methyl vinyl ketone were also successfully used in this system (entries 7 to 10). To the best of our knowledge, it is the first example of catalyst-free Michael reactions of indoles.

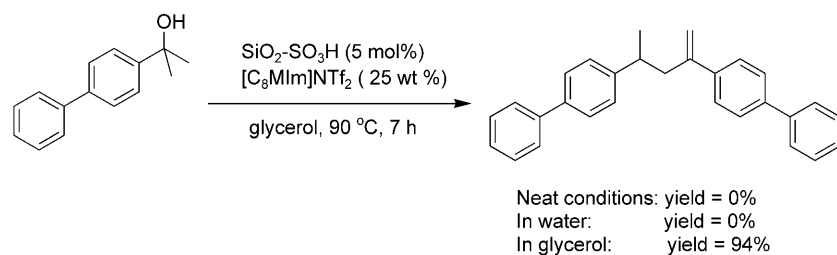
Taking advantage of this remarkable property of glycerol, we then moved on to the ring opening of styrene oxide with *p*-anisidine in order to show the great versatility of these glycerol-based processes.^[28] In this reaction, water and glycerol both exhibited a great advantage compared to solvent-free conditions since, in these cases, the resulting amino alcohol was still obtained with more than 85% yield without addition of any catalyst (Scheme 1).



Scheme 1. Ring-opening of styrene oxide with *p*-anisidine.

Having now demonstrated that glycerol was able to act as a promoting medium for some organic reactions, we finally tested whether it would be possible to develop much more complex reactions in/on glycerol. Following this goal, we decided to check if it was possible to observe a kind of synergistic effect between the glycerol phase and a solid catalyst. Recently, we have reported that, compared to conventional homogeneous or heterogeneous catalysts, silica-supported sulfonic acid coated with ionic liquid (IL-SiO₂-SO₃H) was able to catalyse various highly complex reactions in water.^[28]

Based on this observation, we investigated the acid-catalysed tandem dehydration/dimerisation of 2-(4-biphenyl)-2-propanol in glycerol. Interestingly, whereas in neat conditions or in the presence of water, extensive polymerisation of 2-(4-biphenyl)-2-propanol was observed over IL-SiO₂-SO₃H^[29], we found that in glycerol, the IL-SiO₂-SO₃H solid catalyst was able to selectively drive a tandem dehydration/dimerisation reaction affording 2,4-bis(4-biphenyl)-1-pentene with 94% yield (Scheme 2). This last example clearly shows that the use of glycerol as solvent offers a sus-



Scheme 2. Acid-catalysed dehydrative dimerization of alcohol.

tainable and efficient alternative to the use water when more hydrophobic substrates are used.

In conclusion, we have found that the use of glycerol and crude glycerol as solvent can behave similarly to water in organic synthesis and could be familiarly considered as “organic water”. Indeed, like water, we showed that glycerol was able to promote an organic reaction without addition of any catalyst. In addition, like water, glycerol is cheap, safe, biodegradable and reusable. Moreover, whereas with more hydrophobic substrates the beneficial effect of water on reaction rate becomes limited, we showed here that glycerol is still able to efficiently drive the selected organic transformation. In particular, glycerol and crude glycerol were found to be highly efficient for conducting many organic transformations such as aza-Michael reactions of amines or anilines, Michael reaction of indoles and ring opening of styrene oxide with *p*-anisidine without addition of any catalyst as is generally the case. In a last example, we showed that association of a solid catalyst with glycerol as solvent allowed us to selectively control the mechanism pathway of more complex reaction such as a tandem dehydrative/dimerisation of a tertiary alcohol.

We do believe that using glycerol as solvent for organic reactions not only opens a new strategy to use glycerol but also offers an attractive way to conduct green organic synthesis.

Experimental Section

All reactions were conducted in a 10-mL V-type flask equipped with a triangular magnetic stirring bar. In a typical reaction, *p*-anisidine (123 mg, 1.0 mmol) and butyl acrylate (128 mg, 1.0 mmol) were mixed with glycerol (1.0 g) under air. The mixture was stirred for 24 h at 100 °C. After the reaction, the products were extracted at 60 °C with ethyl acetate (6 mL × 2). After concentration of the organic phase, the crude products were purified by flash chromatography over silica (Carlo Erba, KG-60).

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