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PAPER

Gluconic acid aqueous solution as a sustainable and recyclable promoting medium for organic reactions†

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For the first time, gluconic acid aqueous solution (GAAS), a biobased weakly acidic liquid, was used as an effective promoting medium for organic reactions, such as the Michael addition of indoles to α,β-unsaturated ketones, the electrophilic ring-opening reaction of 3,4-dihydropyran with indoles and Friedel–Crafts alkylation of electron-rich aromatics with benzyl alcohols. The concept of using GAAS as a solvent for organic reactions not only offers a sustainable candidate for progress in solvent innovation, but also opens up a new avenue for the utilization of this biobased polyhydroxylated acid. Among the features that render GAAS as a solvent so interesting is the ability to act as both the reaction medium and catalyst. Moreover, this methodology offers significant improvements with regard to the yield of products, simplicity in operation, cost efficiency and green aspects, in terms of avoiding toxic catalysts and minimizing the generation of waste.

Introduction

Many reactions, extractions, separations and other operations in the chemical process industries involve the use of organic solvents. However, large scale uses of these organic solvents are not only plagued by handling and disposal issues, but can also pose a number of environmental concerns, such as ecotoxicity.[1] In many cases, conventional organic solvents are regulated as volatile organic compounds (VOCs). In addition, certain organic solvents are under restriction due to their ozone layer depletion potential. Therefore, the search for new families of alternative media to replace traditional volatile organic solvents has become a tremendous challenge in academia and industry.[2]

In the last decade, many promising media have appeared as innovative solvents, such as water,[3] ionic liquids,[4] polyethylene glycol,[5] supercritical fluids[6] (particularly supercritical carbon dioxide ($scCO_2$))[7] and perfluorinated solvents.[8] However, the use of these solvents is still limited by many problems, such as corrosion problems and the high cost of equipment for $scCO_2$,[9] or high prices and lack of data about the toxicity and biocompatibility of ionic liquids,[10] or product separation for aqueous-based processes.[11] As a result, researchers working on green solvents realized that a universal green solvent doesn't exist. For this reason, other alternatives that could replace the traditional solvents in a direct way have to be considered, obviously without discarding others. In addition, the replacement of volatile organic solvents by new ones has to be done without stifling the technological development and at moderate economical cost. New solvents should lead to at least the same number of benefits as the traditional ones, if not more.[12]

Nowadays, most solvents are prepared from fossil oil reserves. However, limited supplies of fossil oil and concerns about global warming have created a strong desire to solve the resource issue in the age "beyond petroleum". Out of this consideration, the utilization of biobased chemicals has attracted much attention.[13] This opens up a new avenue for the progress of solvent innovation and many naturally available products, such as glycerol,[14] soy methyl ester,[15] lactate ester[16] and D-limonene[17] amongst others, have been proposed as safer and sustainable solvents for catalysis, organic reactions and separations. Many others have also been used as precursors for the synthesis of potentially safer green solvents,[18] for example, biobased ionic liquids.[19] As compared to the traditional petrochemical-derived solvents, these biobased solvents exhibit advantages not only in minimizing solvent waste, but also in improving laboratory safety. Furthermore, good biocompatibility and known comprehensive data about the toxicity also allow these biobased solvents to be easily acceptable by both the environment and industry. Despite these promising achievements, due to the fact that research on biobased solvents is still at the level of academic study, the importance of biobased solvents needs to be documented, regarding both necessity and versatility. At this

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point, one of the main tasks for researchers in this area is to search for new biobased solvent that possess a specific capacity.

Gluconic acid (GA) is an organic compound with molecular formula $C_6H_{12}O_7$ and condensed structural formula $HOCH_2(CHOH)_4COOH$. This polyhydroxylated acid occurs naturally in fruit, honey, kombucha tea and wine. It is used as a food additive, as an acidity regulator. It is also used in cleaning products, as it dissolves mineral deposits, especially in alkaline solution. GA is prepared in industry by the oxidation of glucose[20] and, recently, cellulose has also been used as a raw material for the preparation of GA.[21] It is normally available as an aqueous solution, which is composed of an equilibrium mixture of GA and the γ- and δ-lactones. The equilibrium between the free acid and the two lactones is affected by the mixture's concentration and temperature. Under normal conditions, GA 50% exhibits a stable equilibrium, in which about 5% of glucono-δ-lactone is present in the solution at room temperature, contributing to its clear to light yellow color with low level corrosiveness and toxicity.

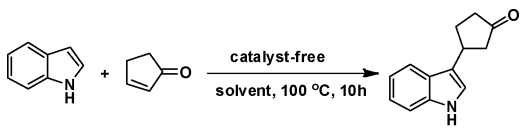
In light of the above description, we viewed that gluconic acid aqueous solution (GAAS) might be a good candidate for acting as a biobased green solvent. The reasons are multifold: (i) an aqueous solution of GA is an inexpensive industrial product and largely available in the market, which allows the use of GAAS as a large quantity solvent to be practically feasible; (ii) GA and the g- and d-lactones are characterized by many hydroxyl groups, which makes these species highly hydrophilic and immiscible with non-polar organic solvents and, consequently, allows an easy product separation by extraction and the following recovery of the solvent; (iii) dissociation of a proton from a GA molecule results in a weakly acidic property of the aqueous solution, which makes this solvent no longer neutral and this can be a great means of promoting some organic reactions that need the assistance of a weak acid; (iv) GA is stable at its boiling point, even in concentrated alkaline solutions. However, it is easily and totally degraded in waste water treatment plants (98% after 2 days). These properties allow not only a successful use of this aqueous solution at relatively high temperatures, but also an easy post-treatment for the waste solvent. Out of these considerations, we believe it would be worthwhile to investigate the use of GAAS as a solvent for organic reactions.

In order to verify whether or not a liquid material can be used as a new solvent for performing organic reactions, two points have to be considered: (i) the feasibility of using this liquid as solvent, which could answer the question whether it will work as well as a traditional one and (ii) the necessity of using this liquid as a solvent; in other words, compared to the traditional one, what is the real advantage of this new solvent that makes this liquid distinguishable? Because an aqueous solution of GA has never been used as a solvent for performing organic reactions before, in order to promote GAAS as a feasible solvent, we do not evade these questions. In continuation of our research to explore new biobased solvents,[22] herein, we report the use of GAAS as a promoting medium for organic reactions for the first time. Some selected reactions that conventionally need the assistance of an acid catalyst, such as the Michael reaction of indoles with α,β-unsaturated ketones, the electrophilic ring-opening reaction of 3,4-dihydropyran with indoles and Friedel–Crafts alkylation of electron-rich aromatics with benzyl alcohols, proceeded well in aqueous solution of GA.

Results and discussion

Initially, the Michael addition of indole (**1a**) to cyclopent-2-enone (**2a**) was selected as a model reaction for evaluating the efficiency of GAAS. This reaction is usually generally catalyzed by acid catalysts. Some homogeneous catalysts, including $InBr_3$,[23] $Bi(OTf)_3$,[24] $Hf(OTf)_4$,[25] $Cu(OTf)_2$,[26] scandium tris(dodecylsulfate)[27] and aluminum tris(dodecylsulfate),[28] have been reported to be effective in this type of reaction. In order to facilitate the recycling of the catalyst, some solid acids were also used, such as nanocrystalline titanium(IV) oxide,[29] sulfonated amorphous carbon,[30] a $CeCl_3 \cdot 7H_2O$–NaI combination supported on a silica gel[31] and silica-supported scandium or sodium with ionic liquids.[32] A literature survey also stated that protic solvents, such as water[33] and glycerol,[34] have a unique ability to promote this type of reaction. Considering the fact that GAAS is a protic solvent, it would not be unreasonable to expect that GAAS has, to some extent, an ability to promote this Michael-type reaction. In order to shed light on the efficiency of the promoting effect of the solvent on the model reaction, we performed the reaction in the absence of any catalyst. As shown in Table 1, at 100 °C, no product was detected in solvent-free conditions and also in non-polar organic solvents, such as toluene and *n*-butyl acetate (entries 1–3). Similarly, no or only a trace amount of product was observed in polar aprotic solvents, such as 1,2-dichloroethane, nitromethane, DMF and DMSO (entries 4–7). The reaction also proceeded sluggishly in water and glycerol, which are well known polar protic solvents (entries 8 and 9). These results verified that the promoting effect of water and glycerol is far less efficient at pushing the model reaction toward completion. To our great delight, under identical conditions, an 83% yield was obtained using GAAS

Table 1 The Michael addition of an indole to cyclopent-2-enone in different conditions[a]



1a *2a* *3a*

Entry	Solvent	Remark	Yield (%)
1	—	No solvent	0
2	toluene	non-polar solvent	0
3	*n*-butyl acetate	non-polar solvent	0
4	1,2-dichloroethane	polar aprotic solvent	0
5	CH_3NO_2	polar aprotic solvent	0
6	DMF	polar aprotic solvent	< 5
7	DMSO	polar aprotic solvent	< 5
8	water	polar protic solvent	< 5
9	glycerol	polar protic solvent	< 5
10	GAAS (50%)	polar protic solvent	**83**
11	AcOH	polar protic solvent	46
12	AcOH *aqu.* (50%)	polar protic solvent	55
13	GAAS (50%)	The fourth run of GAAS	82
14	GAAS (50%)	20 mmol scale	82

[a] Solvent: 1 ml, **1a**: 0.5 mmol, **2a**: 0.6 mmol, temperature: 100 °C, reaction time: 10 h.

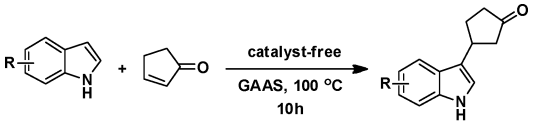
(50%) as the solvent (entry 10). Interestingly, acetic acid and acetic acid aqueous solution (50%) can also promote the model reaction, but the yield obtained is inferior to that when GAAS is used (entries 11 and 12). Furthermore, using acetic acid as the solvent generates a lot of waste because, in order to isolate the product, the acid solvent has to be neutralized with an inorganic base after the reaction. In this regard, GAAS exhibited a great advantage for facilitating the product isolation. Because no catalyst was used, the quenching step that is necessary for stopping a normal acid-catalyzed reaction was omitted. The unreacted starting materials and the formed product could easily be extracted by a non-polar organic solution composed of ethyl acetate and petroleum ether (v/v = 1/1). Because of the fact that GA and its lactones are characterized by many hydroxyl groups, a non-polar organic solvent cannot dissolve these hydrophilic species. As a result, this procedure rules out the possibility of leaching of the GA and its derivatives from the aqueous phase. To test the reusability of GAAS, the used GAAS was recycled 3 times, as shown in Table 1; the yield obtained in the fourth run is still very good (entry 13). Importantly, no significant change in the pH value and conductivity was observed by testing GAAS before and after use (see ESI†), indicating good stability of GAAS under the reaction conditions. The simple operation also allowed easy scale-up of the reaction and, as shown in Table 1, a 20 mmol reaction also proceeded well in GAAS, indicating a good effectiveness of our system for practical synthesis (entry 14).

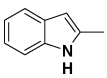
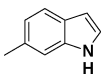
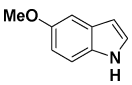
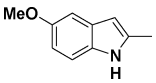
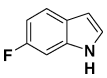
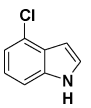
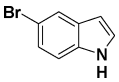
With these results in hand, we then investigated the substrate scope of the GAAS-mediated Michael addition of indoles to α,β-unsaturated ketones. As shown in Table 2, various substituted indoles, such as *N*-methylindole, 2-methylindole, 6-methylindole, 5-methoxyindole, 5-methoxy-2-methylindole, 6-fluoroindole, 4-chloroindole and 5-bromoindole, readily react in GAAS with **2a** to form the corresponding adducts in good to excellent yields (entries 1–8). The scope of the reaction, with respect to the α,β-unsaturated ketone, was next investigated and also found to be excellent. As Table 3 illustrates, many α,β-unsaturated ketones could be employed without significantly affecting the yield of the Michael adduct (entries 1–4). Particularly, α,β-unsaturated ketones containing S- or O-heterocycle functionalities were also applied in the reaction uneventfully. In addition, 3,4-dimethoxy-β-nitrostyrene (2 g) was also proved to be applicable in the GAAS system to react with **1c** and the corresponding product was obtained in 99% yield (entry 5).

All the results of the Michael reactions of indoles in GAAS demonstrated, for the first time, that GAAS can indeed be used as an effective promoting medium for organic reactions. The salient features of using GAAS as a solvent for organic reactions were observed not only in the way it significantly promotes the reaction rate in the absence of a catalyst, but also in the simplification of the work-up procedure and the recycling of the reaction solvent. These promising results encouraged us to further explore organic reactions by using GAAS as a dual solvent–catalyst.

The second reaction we investigated in GAAS was electrophilic ring-opening reactions of 3,4-dihydropyran with indoles. This type of reaction has been performed in the presence of Lewis acids, such as $InCl_3$ and $MnCl_2$, in organic solvents.[35] Particularly when simple 3,4-dihydropyran was used, the generated

Table 2 The Michael reaction of different indoles with **2a**[a]

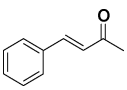
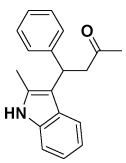
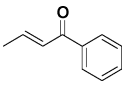
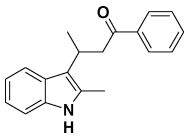
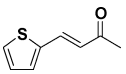
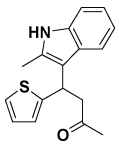
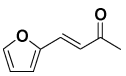
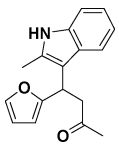
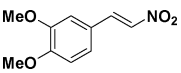
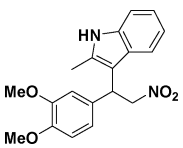


Entry	Indole		Product	Yield (%)
1		**1b**	**3b**	93
2		**1c**	**3c**	99
3		**1d**	**3d**	65
4		**1e**	**3e**	84
5		**1f**	**3f**	90
6		**1g**	**3g**	74
7[b]		**1h**	**3h**	61
8		**1i**	**3i**	73

[a] Solvent: 1.0 ml, indole derivative: 0.5 mmol, **2a**: 0.6 mmol, temperature: 100 °C; [b] 130 °C.

bis(indolyl)hydroxyalkyl derivatives not only have unique abilities for enhancing the cytodifferentiating properties of retinoids in myeloid leukemia cells,[36] but also can be used as important intermediates for the synthesis of cycloalkanoindoles[37] that have been studied for their anti-inflammatory,[38] antidepressant[39] and analgesic properties.[40] In view of the fact that the generated products are generally used in pharmaceutical synthesis, particular attention has to be paid to the removal of any residue metal catalyst in the product. For this purpose, a metal-free system for the electrophilic ring-opening reaction of 3,4-dihydropyran with indoles is appealing. Encouraged by the outstanding performance of GAAS in the above-mentioned Michael reactions of indoles, we thus treated 3,4-dihydropyran with indoles in GAAS at 110 °C and, after 11 h of reaction, the expected ring-opening product was obtained in 82% of yield (Table 4, entry 1). Interestingly, only a trace or small amount of product was obtained under solvent-free conditions, in toluene, 1,2-dichloroethane, DMF, DMSO, water and glycerol, indicating that GAAS has a specific promoting effect on this reaction (entries 2–8). Acetic acid and an aqueous solution of

Table 3 The Michael reaction of **1c** with α, β-unsaturated ketones[a]

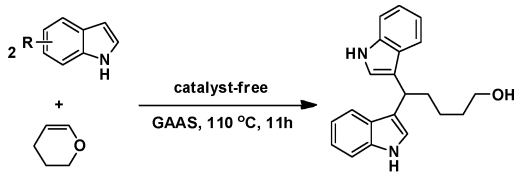
Entry	α,β-Unsaturated ketone	Product	Yield (%)
1		**2b** 	**3j** 92
2		**2c** 	**3k** 55
3		**2d** 	**3l** 58
4		**2e** 	**3m** 67
5		**2g** 	**3n** 99

[a] Solvent: 1.0 ml, **1c**: 0.5 mmol, α,β-unsaturated ketone: 0.6 mmol, temperature: 100 °C, reaction time: 10 h.

acetic acid (50%) were then examined and only moderate yields were obtained in the ring-opening reaction (entries 9 and 10). The advantages of GAAS were also exhibited in the product isolation. Although the generated product possesses a polar hydroxyl group, extraction of the product from GAAS is, in fact, not as difficult as we thought, and a mixture of ethyl acetate and petroleum ether (v/v = 1/1) is sufficiently enough for removing the product from GAAS. Many other indoles can also be used in this reaction and good to excellent yields were obtained in this system (entries 11–15). With this method, an efficient and metal-free synthesis of bis(indolyl)hydroxyalkyl derivatives was accomplished for the first time, indicating again the usefulness of GAAS as a solvent for organic reactions.

Gluconic acid lactone was also present in the GAAS, although this lactone is normally only formed in small amount. Therefore, the reactivity of gluconic acid lactone in the presence of **1a**, **2a**, **3a**, **4a** and **5a** was then investigated. In order to facilitate detection of the reaction, the reactions were conducted under two conditions: with (i) acetic acid and (ii) $InCl_3$ (10 mol %)/DCE. In both cases, no significant reaction was observed, indicating that gluconic acid lactone is quite stable toward these compounds (see ESI†). Therefore, the potential effects of gluconic acid lactone on these reactions were precluded. However, in view of the fact that gluconic acid lactone is a compound that contains not only many hydroxyl groups, but

Table 4 Electrophilic ring-opening reactions of 3, 4-dihydropyran with indoles[a]



4a *5a-5f*

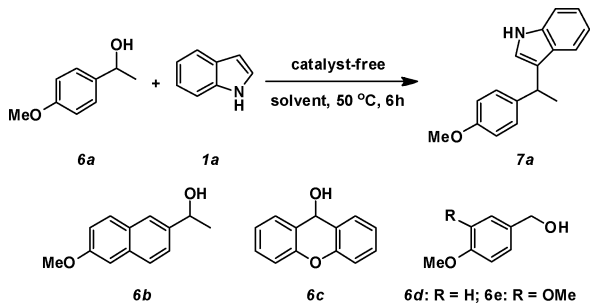
Entry	Indole	Solvent	Product	Yield (%)
1	**1a**	GAAS	**5a**	82
2	**1a**	solvent-free	**5a**	< 5
3	**1a**	toluene	**5a**	< 5
4	**1a**	1,2-dichloroethane	**5a**	< 5
5	**1a**	DMF	**5a**	< 5
6	**1a**	DMSO	**5a**	< 5
7	**1a**	water	**5a**	25
8	**1a**	glycerol	**5a**	< 5
9	**1a**	AcOH	**5a**	55
10	**1a**	AcOH aq. (50%)	**5a**	50
11	**1b**	GAAS	**5b**	91
12	**1e**	GAAS	**5c**	81
13	**1g**	GAAS	**5d**	80
14[b]	**1h**	GAAS	**5e**	74
15[b]	**1i**	GAAS	**5f**	70

[a] Indole derivative: 1.0 mmol, **4a**: 0.75 mmol, solvent: 1.0 ml; temperature: 110 °C, reaction time: 11 h; [b] 130 °C, 14 h.

also an ester group, which are both chemically reactive under the appropriate conditions, and in order to avoid some possible side reactions, we had to carefully choose the model reaction when using GAAS as a solvent.

The next reaction we investigated was the Friedel–Crafts alkylation of indoles with benzyl alcohols. This type of reaction has been realized by Cozzi and his co-workers in water under catalyst-free conditions.[41] However, we found that at a low temperature of 50 °C, water as the solvent is ineffective for promoting the model nucleophilic substitution reaction, perhaps due to the low reactivity of 4-methoxy-α-methylbenzenemethanol, **6a** (Table 5, entry 1). In order to improve the reaction rate, acid catalysts, such as $NbCl_5$ and triflic acid, have to be used.[42] However, the reported acid systems often suffer from a tedious aqueous work-up procedure because the acid catalyst has to be removed after the reaction. In order to avoid the quenching step, we are particularly interested in the possibility of realizing this reaction by means of utilizing an appropriate solvent. As shown in Table 5, no or only a trace amount of product was detected in toluene,> 1,2-dichloroethane, DMF and DMSO (entries 2–5). Glycerol also exhibited a poor performance, like water as the solvent, in this reaction (entry 6). Surprisingly, in the GAAS system, a lot of solid was formed (Fig. 1). By adding water into the system, the solid product could be directly precipitated out. After washing with water and drying under atmospheric pressure, this could be obtained in high purity. NMR analysis revealed that this solid product is the expected product, **7a**, and the yield reached 97%. The reasons for why **7a** could be solidified in the GAAS system include (i) **7a** has a melting point of 156–157 °C and is insoluble in GAAS solvent and (ii) using GAAS as the solvent allows the reaction to be performed at a relatively low temperature, 50 °C. Therefore, at the reaction temperature,

Table 5 Friedel–Crafts alkylation of indoles with benzyl alcohols[a]



Entry	Indole	Alcohol	Solvent	Product	Yield (%)
1	**1a**	**6a**	water	**7a**	50
2	**1a**	**6a**	toluene	**7a**	< 5
3	**1a**	**6a**	1,2-dichloroethane	**7a**	< 5
4	**1a**	**6a**	DMF	**7a**	0
5	**1a**	**6a**	DMSO	**7a**	0
6	**1a**	**6a**	glycerol	**7a**	20
7	**1a**	**6a**	GAAS	**7a**	97
8	**1b**	**6a**	GAAS	**7b**	80
9	**1c**	**6a**	GAAS	**7c**	99
10	**1e**	**6a**	GAAS	**7d**	81
11	**1g**	**6a**	GAAS	**7e**	90
12	**1h**	**6a**	GAAS	**7f**	81
13	**1i**	**6a**	GAAS	**7g**	98
14	**1a**	**6b**	GAAS	**7h**	50
15[b]	**1a**	**6c**	GAAS	**7i**	95
16[b,c]	**1a**	**6d**	GAAS	**7j**	90
17[b,c]	**1a**	**4c**	GAAS	**7k**	70

[a] Benzyl alcohol: 0.5 mmol, indole: 0.55 mmol, solvent: 1.0 ml; temperature: 50 °C, reaction time: 6 h; [b] 80 °C; [c] 8 h.

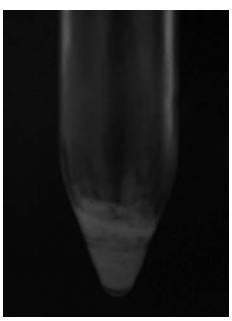


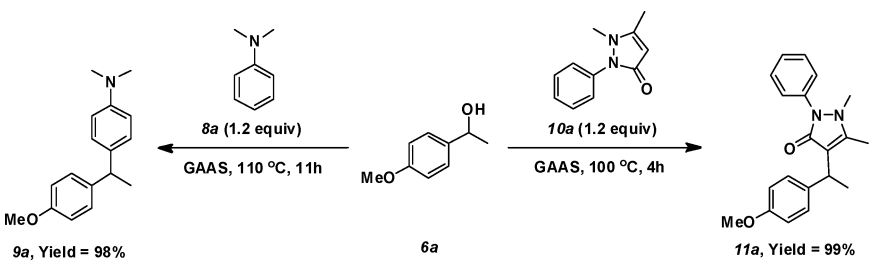
Fig. 1 The solid product formed at the end of the model reaction.

7a could be formed as a solid. This isolation method is quite simple, but during washing of the solid a lot of waste water containing GAAS was also generated. Fortunately, the waste aqueous solution containing GAAS could easily be degraded in waste water treatment plants. Therefore, the negative effect of the waste GAAS solution on the environment could be minimized. It should also be noted that, for the Friedel–Crafts alkylations of indoles with benzyl alcohols, this is the first example of isolation of the reaction product without the use of silica column chromatography. Unfortunately, this method only works for **7a**, while for the other alkylation reactions the formed products have to be isolated with conventional methods because no fine solid could be observed at the end of the reaction. In spite of this fact, the yields obtained in the alkylations of indoles with benzyl alcohols in the GAAS system are still very good (entries 8–17). Many indoles and benzyl alcohols could be uneventfully used.

Inspired by these promising results, we then investigated the alkylation reactions of some basic nucleophiles with **6a**, which are normally difficult to be used in conventional acid catalyst systems. As shown in Scheme 1, in the GAAS system, both *N*,*N*-dimethylaniline and antipyrine react readily with **6a** to form the corresponding alkylation products in high yields. In particular, no strong interaction between the basic product and GAAS could be observed. Thus, the formed products could be easily extracted by an organic solvent. These results again indicated the usefulness of GAAS for organic synthesis.

Conclusion

In conclusion, GAAS was demonstrated to be a promising green solvent for performing organic reactions for the first time. The concept of using GAAS as a solvent for organic reactions not only offers a sustainable candidate for progress in solvent innovation, but also opens a new avenue for utilization of this biobased polyhydroxylated acid. Among the features that render GAAS as a solvent so interesting is the ability to act as both the reaction medium and catalyst. Many reactions, including Michael addition of indoles to α,β-unsaturated ketones, electrophilic ring-opening reaction of 3,4-dihydropyran with indoles and Friedel–Crafts alkylations of carbon-based nucleophiles with benzyl alcohols, proceeded very well in GAAS without the use of any additional catalyst. Moreover, this methodology offers significant improvements, with regard to the yield of products, simplicity of operation, cost efficiency and green aspects, in terms of avoiding toxic catalysts and of minimizing the generation of waste. The strong hydrogen bond network and weak acidic environment should be partially responsible for the excellent performance of GAAS. Furthermore, in view of the fact that GAAS is a hydrophilic solvent that may not be able to dissolve lipophilic compounds well under the reaction conditions, a rate acceleration resulting from the "on water"



Scheme 1 The GAAS-mediated electrophilic alkylation of **6a** with basic nucleophiles.

effect might also be involved in the reaction system.[43] However, despite the observed beneficial effects exerted by GAAS on all of these reactions, the exact nature of this influence cannot be ascribed to a single effect, such as the acidic environment or "on-water" effect, but rather to a combination of several factors. We will extend our research along these lines in order to shed light on these factors.

Experimental section

All of the reactions were conducted in a 10 ml V-type flask equipped with a triangular magnetic stirrer bar. In a typical reaction, gluconic acid aqueous solution (1.0 ml) was mixed with an indole (**1a**, 58.5 mg, 0.50 mmol) and cyclopent-2-enone (**2a**, 49.3 mg, 0.60 mmol) under air. The mixture was stirred for 10 h at 100 °C. After reaction, the mixture was cooled to room temperature and the reaction mixture was extracted with a mixed solution composed of ethyl acetate and heptane (v/v = 2/1, 6 ml × 3). After concentration of the combined organic phase under reduced pressure, the desired product, **3a**, was obtained by preparative TLC using a mixed solution of ethyl acetate and petroleum ether (40–60 °C) as the eluting solvent (the ratio of ethyl acetate/petroleum ether was 1/7). 82.7 mg, yield = 83%. The recovered GAAS phase could be reused after 20 min of treatment at 70 °C under reduced pressure. The 20 mmol scale reaction of **1a** and **2a** was performed in a 100 ml flask using an increased amount of GAAS (60 ml) as the medium. Other reactions and examination of substrate scope were all performed according to similar procedures.

Spectroscopic data of new compounds

3-(6-Methyl-1*H*-indol-3-yl)cyclopentanone (3d). Red oil, ^{1}H NMR ($CDCl_3$): 2.00–2.14 (m, 1H), 2.16–2.43 (m, 4H), 2.45 (d, J = 8.0 Hz, 3H), 2.56–2.76 (m, 1H), 3.64 (sext, J = 7.2 Hz, 1H), 6.81 (d, J = 6.0 Hz, 1H), 6.96 (t, J = 7.6 Hz, 1H), 7.10 (d, J = 7.6 Hz, 1H), 7.48 (t, J = 8.0 Hz, 1H), 8.11 (bs, 1H); ^{13}C NMR ($CDCl_3$): 21.8, 30.0, 33.9, 38.3, 45.4, 111.5, 118.3, 118.8, 119.5, 121.2, 124.5, 132.2, 137.3, 220.0; IR (cm^{-1}) 3405, 3082, 2936, 2917, 1733, 1626, 1551, 1457, 1401, 1339, 1311, 1284, 1231, 1152, 1098, 1037, 978, 907, 855, 800, 733, 648, 580; HRMS m/z (ESI) calcd for $C_{14}H_{15}NNaO$ $[M + Na]^+$ 236.1051, found 236.1045.

3-(2-Methyl-5-methoxy-1*H*-indol-3-yl)cyclopentanone (3f). Red oil, ^{1}H NMR ($CDCl_3$): 2.14–2.34 (m, 2H), 2.34–2.40 (m, 4H), 2.40–2.58 (m, 2H), 2.73 (dd, J_a = 12.0 Hz, J_b = 18.4 Hz, 1H), 3.50–3.62 (m, 0.6H), 3.68–3.78 (m, 0.4H), 3.82 (s, 3H), 6.77 (dd, J_a = 2.4 Hz, J_b = 8.8 Hz, 1H), 6.98 (d, J = 2.4 Hz, 1H), 7.14 (d, J = 8.8 Hz, 1H), 8.09 (bs, 1H); 29.6, 34.5, 39.5, 44.1, 56.2, 101.8, 110.1, 111.4, 111.4, 127.3, 130.8, 132.2, 153.6, 220.1, 220.1; IR (cm^{-1}) 3397, 3063, 2955, 2908, 2831, 2248, 1735, 1625, 1586, 1484, 1400, 1364, 1284, 1253, 1216, 1152, 1097, 1032, 909, 827, 732, 621, 568; HRMS m/z (ESI†) calcd for $C_{15}H_{17}NNaO_2$ $[M + Na]^+$ 266.1157, found 266.1148.

3-(4-Chloro-1*H*-indol-3-yl)cyclopentanone (3h). Red solid, mp: 110–111 °C, ^{1}H NMR ($CDCl_3$): 2.07 (qd, J_a = 4.0 Hz, J_b = 17.2 Hz, 1H), 2.28–2.46 (m, 3H), 2.49–2.60 (m, 1H), 2.82 (dd, J_a = 8.0 Hz, J_b = 18.4 Hz, 1H), 4.21 (quint, J = 8.4 Hz, 1H), 7.00 (d, J = 2.0 Hz, 1H), 7.08 (d, J = 2.0 Hz, 1H), 7.09 (s, 1H), 7.23–7.29 (m, 1H), 8.46 (bs, 1H); ^{13}C NMR ($CDCl_3$): 31.0, 33.9, 38.1, 47.0, 110.2, 119.2, 120.7, 121.0, 122.8, 123.8, 126.1, 138.2, 220.1; IR (cm^{-1}) 3340, 3128, 3059, 2962, 2890, 1731, 1615, 1486, 1427, 1397, 1339, 1255, 1231, 1188, 1164, 1136, 1044, 940, 827, 773, 738, 679, 613, 572; HRMS m/z (ESI†) calcd for $C_{13}H_{12}ClNNaO$ $[M + Na]^+$ 256.0505, found 256.0493.

4-(2-Methyl-1*H*-indol-3-yl)-4-(2-thienyl)-2-butanone (3l). Red oil, ^{1}H NMR ($CDCl_3$): 1.98 (s, 3H), 2.03 (d, J = 2.8 Hz, 2H), 2.34 (s, 3H), 3.33 (dd, J_a = 7.6 Hz, J_b = 16.8 Hz, 1H); 3.42 (q, J = 8.0 Hz, 1H); 5.01 (t, J = 7.6 Hz, 1H), 6.74–6.79 (m, 1H), 6.83 (dd, J_a = 3.6 Hz, J_b = 4.8 Hz, 1H), 6.99 (dt, J_a = 1.2 Hz, J_b = 8.0 Hz, 1H), 7.03–7.09 (m, 2H), 7.17 (t, J = 7.6 Hz, 1H), 7.42 (d, J = 8.0 Hz, 1H), 7.88 (bs, 1H); ^{13}C NMR ($CDCl_3$): 12.0, 30.8, 32.9, 49.5, 110.7, 112.9, 119.1, 119.2, 120.9, 123.5, 123.7, 126.6, 126.9, 132.1, 135.5, 149.0, 207.4; IR (cm^{-1}) 3401, 3057, 2962, 2918, 1709, 1617, 1583, 1488, 1460, 1432, 1359, 1300, 1245, 1162, 1133, 1040, 966, 848, 827, 743, 699, 601, 584, 530; HRMS m/z (ESI†) calcd for $C_{17}H_{17}NNaOS$ $[M + Na]^+$ 306.0929, found 306.0925.

4-(2-Methyl-1*H*-indol-3-yl)-4-(2-furyl)-2-butanone (3m). Red oil, ^{1}H NMR ($CDCl_3$): 2.01 (s, 3H), 2.35 (s, 3H), 3.22 (q, J = 8.0 Hz, 1H), 3.34 (dd, J_a = 6.0 Hz, J_b = 15.6 Hz, 1H), 4.83 (t, J = 7.2 Hz, 1H), 5.94 (d, J = 3.2 Hz, 1H), 6.22 (q, J = 1.6 Hz, 1H), 6.99 (dt, J_a = 0.8 Hz, J_b = 8.0 Hz, 1H), 7.06 (dt, J_a = 0.8 Hz, J_b = 8.0 Hz, 1H), 7.18 (d, J = 8.0 Hz, 1H), 7.27 (s, 1H), 7.43 (d, J = 7.6 Hz, 1H), 7.92 (bs, 1H); ^{13}C NMR ($CDCl_3$): 11.9, 30.7, 31.4, 46.8, 105.6, 110.2, 110.6, 110.8, 119.0, 119.2, 120.9, 127.1, 132.2, 135.5, 141.1, 156.9, 207.4; IR (cm^{-1}) 3401, 3115, 3056, 2919, 1710, 1616, 1586, 1501, 1460, 1429, 1359, 1301, 1246, 1161, 1076, 1010, 968, 912, 884, 806, 739, 597, 534, 505; HRMS m/z (ESI†) calcd for $C_{17}H_{17}NNaO_2$ $[M + Na]^+$ 290.1157, found 290.1146.

6-Fluoro-ε-(6-fluoro-1*H*-indol-3-yl)-1*H*-indole-3-pentanol (5d). Red oil, ^{1}H NMR ($CDCl_3$): 1.24–1.37 (m, 2H), 1.40–1.53 (m, 2H), 2.06 (q, J = 7.6 Hz, 2H), 2.36 (bs, 1H), 3.45 (t, J = 6.8 Hz, 2H), 4.26 (t, J = 7.2 Hz, 1H), 6.70 (dt, J_a = 2.0 Hz, J_b = 9.6 Hz, 2H), 6.75 (d, J = 2.0 Hz, 2H), 6.83 (dd, J_a = 2.0 Hz, J_b = 9.6 Hz, 2H), 7.34 (dd, J_a = 5.6 Hz, J_b = 8.8 Hz, 2H), 8.24 (bs, 2H); ^{13}C NMR ($CDCl_3$): 24.4, 32.7, 34.0, 35.4, 62.8, 97.4, 97.6, 107.5, 107.7, 119.8, 120.1, 120.2, 121.9, 121.9, 123.6, 136.5, 136.6, 158.6, 160.9; IR (cm^{-1}) 3420, 3067, 2937, 2861, 1713, 1625, 1553, 1496, 1455, 1404, 1342, 1303, 1252, 1217, 1139, 1090, 1042, 993, 950, 907, 836, 804, 732, 606; HRMS m/z (ESI†) calcd for $C_{21}H_{20}F_2N_2NaO$ $[M + Na]^+$ 377.1441, found 377.1430.

4-Chloro-ε-(4-chloro-1*H*-indol-3-yl)-1*H*-indole-3-pentanol (5e). Red solid, mp: 148–150 °C, ^{1}H NMR ($CDCl_3$): 1.43–1.60 (m, 4H), 1.96 (q, J = 7.2 Hz, 2H), 2.16 (bs, 1H), 3.50 (t, J = 6.0 Hz, 2H), 5.62 (t, J = 7.2 Hz, 1H), 6.50 (d, J = 1.6 Hz, 2H), 6.88–6.97 (m, 4H), 7.03 (dd, Ja = 1.2 Hz, Jb = 7.6 Hz, 2H), 8.19 (d, J = 1.6 Hz, 2H); ^{13}C NMR ($CDCl_3$): 24.5, 32.8, 33.5, 38.3, 62.9, 110.1, 120.3, 121.3, 122.1, 123.2, 123.6, 126.4, 138.2; IR (cm^{-1}) 3424, 3123, 2937, 2855, 1709, 1612, 1562, 1426, 1338, 1281, 1250, 1186, 1144, 1102, 1033, 996, 93, 819, 773, 739, 625, 586, 516; HRMS m/z (ESI†) calcd for $C_{21}H_{20}Cl_2N_2NaO$ $[M + Na]^+$ 409.0850, found 409.0837.

3-[1-(4-Methoxyphenyl)ethyl]-5-methoxy-1*H*-indole (7d). Red oil, ^{1}H NMR (acetone-d_6): 1.63 (d, J = 7.2 Hz, 3H), 3.66 (s, 3H), 3.72 (s, 3H), 4.28 (q, J = 7.2 Hz, 1H), 6.71 (dd, J_a = 2.4 Hz, J_b = 8.8 Hz, 1H), 6.78–6.83 (m, 3H), 7.14 (d, J = 1.6 Hz, 1H), 7.20–7.27 (m, 3H), 9.83 (bs, 1H); ^{13}C NMR (acetone-d_6): 22.1, 36.1, 54.5, 54.9, 101.4, 111.1, 111.7, 113.4, 120.4, 122.1, 127.4, 128.2, 132.4, 139.4, 153.5, 157.9; IR (cm^{-1}) 3417, 3030, 2960, 2932, 2833, 1717, 1611, 1582, 1510., 1484, 1455, 1300, 1244, 1211, 1175, 1089, 1034, 921, 833, 798, 734, 634, 560; HRMS m/z (ESI†) calcd for $C_{18}H_{19}NNaO_2$ [M + Na]$^+$ 304.1313, found 304.1301.

3-[1-(4-Methoxyphenyl)ethyl]-6-fluoro-1*H*-indole (7e). Red solid, mp: 138–139 °C, ^{1}H NMR (acetone-d_6): 1.63 (d, J = 7.2 Hz, 3H), 3.72 (s, 3H), 4.29 (q, J = 7.2 Hz, 1H), 6.69 (ddd, J_a = 2.4 Hz, J_b= 8.8 Hz, J_c = 10.8 Hz, 1H), 6.80 (td, J_a = 2.8 Hz, J_b = 9.6 Hz, 2H), 7.09 (dd, J_a = 2.4 Hz, J_b = 10.4 Hz, 1H), 7.17–7.23 (m, 3H), 7.24 (dd, J_a = 5.2 Hz, J_b = 8.4 Hz, 1H), 10.10 (bs, 1H); ^{13}C NMR (acetone-d_6): 22.1, 36.0, 54.5, 97.0, 97.3, 106.6, 106.8, 113.5, 120.1, 120.2, 120.9, 121.9, 122.0, 123.8, 128.2, 139.2, 158.0, 160.8; IR (cm^{-1}) 3398, 3001, 2969, 2931, 2862, 1894, 1725, 1609, 1550, 1510, 1456, 1401, 1338, 1301, 1234, 1173, 1023, 967, 947, 836, 805, 727, 600, 558; HRMS m/z (ESI†) calcd for $C_{17}H_{16}FNNaO$ [M + Na]$^+$ 292.1114, found 292.1106.

3-[1-(4-Methoxyphenyl)ethyl]-4-chloro-1*H*-indole (7f). Yellow solid, mp: 170–172 °C, ^{1}H NMR (acetone-d_6): 1.62 (d, J = 7.2 Hz, 3H), 2.85 (s, 3H), 3.72 (s, 3H), 4.90 (q, J = 6.8 Hz, 1H), 6.78 (td, J_a = 3.2 Hz, J_b = 10.0 Hz, 2H), 6.92 (dd, J_a = 0.8 Hz, J_b = 7.6 Hz, 1H), 7.01 (t, J = 7.6 Hz, 1H), 7.15 (d, J = 8.4 Hz, 2H), 7.24 (d, J = 1.6 Hz, 1H), 7.34 (d, J = 8.0 Hz, 1H), 10.37 (bs, 1H); ^{13}C NMR (acetone-d_6): 23.6, 35.7, 54.5, 110.4, 113.4, 119.7, 121.0, 121.9, 123.6, 125.6, 128.4, 138.6, 140.0, 157.8; IR (cm^{-1}): 3351, 3058, 2964, 1723, 1645, 1610, 1509, 1421, 1338, 1232, 1179, 1142, 1024, 939, 829, 782, 751, 634, 613, 572; HRMS m/z (ESI†) calcd for $C_{17}H_{16}ClNNaO$ [M + Na]$^+$ 308.0818, found 308.0802.

3-[1-(4-Methoxyphenyl)ethyl]-5-bromo-1*H*-indole (7g). Red oil, ^{1}H NMR (acetone-d_6): 1.63 (d, J = 7.2 Hz, 3H), 3.72 (s, 3H), 4.30 (q, J = 7.2 Hz, 1H), 6.81 (td, J_a = 2.8 Hz, J_b = 9.6 Hz, 2H), 7.15 (dd, J_a = 2.0 Hz, J_b = 8.4 Hz, 1H), 7.20 (td, J_a = 3.2 Hz, J_b = 10.0 Hz, 2H), 7.27 (d, J = 1.6 Hz, 1H), 7.33 (d, J = 4.8 Hz, 1H), 7.44 (d, J = 2.0 Hz, 1H), 10.2 (bs, 1H); ^{13}C NMR (acetone-d_6): 22.2, 35.8, 54.5, 111.3, 113.1, 113.6, 120.5, 121.6, 123.1, 123.8, 128.1, 128.8, 135.8, 139.0, 158.1; IR (cm^{-1}) 3424, 3063, 2962, 2930, 2870, 2835, 1699, 1610, 1582, 1509, 1457, 1371, 1299, 1243, 1177, 1099, 962, 882, 832, 795, 756, 662, 588, 554; HRMS m/z (ESI†) calcd for $C_{17}H_{16}BrNNaO$ [M + Na]$^+$ 352.0313, found 352.0311.

1-(6′-Methoxy-2-naphthyl)ethyl-1*H*-indole (7h). White solid, mp: 176–178 °C, ^{1}H NMR (acetone-d_6): 1.75 (d, J = 7.2 Hz, 3H), 2.86 (s, 3H), 3.87 (s, 3H), 4.51 (q, J = 7.2 Hz, 1H), 6.84 (dt, J_a = 0.8 Hz, J_b = 8.0 Hz, 1H), 7.02 (dt, J_a = 1.2 Hz, J_b = 8.0 Hz, 1H), 7.09 (dd, J_a = 2.8 Hz, J_b = 9.2 Hz, 1H), 7.21 (d, J = 2.4 Hz, 1H), 7.27 (d, J = 1.6 Hz, 1H), 7.32 (d, J = 8.0 Hz, 1H), 7.36 (d, J = 8.4 Hz, 1H), 7.40 (dd, J_a = 2.0 Hz, J_b = 8.8 Hz, 1H), 7.67 (d, J = 8.4 Hz, 1H), 7.71 (d, J = 8.8 Hz, 1H), 7.76 (s, 1H), 10.06 (bs, 1H); ^{13}C NMR (acetone-d_6): 21.9, 36.9, 54.7, 100.0, 105.7, 111.2, 118.3, 118.4, 119.2, 120.3, 121.2, 121.6, 125.0, 126.7, 126.9, 127.1, 129.0, 129.2, 133.4, 137.2, 142.6, 157.4; IR (cm^{-1}) 3370, 3011, 2963, 1723, 1631, 1605, 1460, 1483, 1460, 1336, 1261, 1225, 1172, 1100, 1020, 921, 861, 810, 769, 745, 668, 549; HRMS m/z (ESI†) calcd for $C_{21}H_{19}NNaO$ [M + Na]$^+$ 324.1364, found 324.1358.

4-[1-(4-Methoxyphenyl)ethyl]antipyrine (11a). White solid, mp: 111–112 °C, ^{1}H NMR ($CDCl_3$): 1.66 (d, J = 7.6 Hz, 3H), 2.04 (s, 3H), 2.92 (s, 3H), 3.74 (s, 3H), 3.97 (q, J = 7.2 Hz, 1H), 6.81 (td, J_a = 2.4 Hz, J_b = 11.6 Hz, 2H), 7.20 (sept, J = 4.0 Hz, 1H), 7.35 (d, J = 8.8 Hz, 2H), 7.40 (d, J = 4.4 Hz, 4H); ^{13}C NMR ($CDCl_3$): 11.3, 19.3, 33.8, 36.2, 55.2, 113.7, 114.8, 123.4, 125.9, 128.3, 129.0, 135.5, 137.5, 152.7, 157.9, 165.6; IR (cm^{-1}) 3042, 2993, 2965, 1658, 1593, 1511, 1454, 1398, 1343, 1272, 1246, 1178, 1135, 1057, 1030, 831, 751, 694, 654, 588; HRMS m/z (ESI†) calcd for $C_{20}H_{22}N_2NaO_2$ [M + Na]$^+$ 345.1579, found 345.1555.

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