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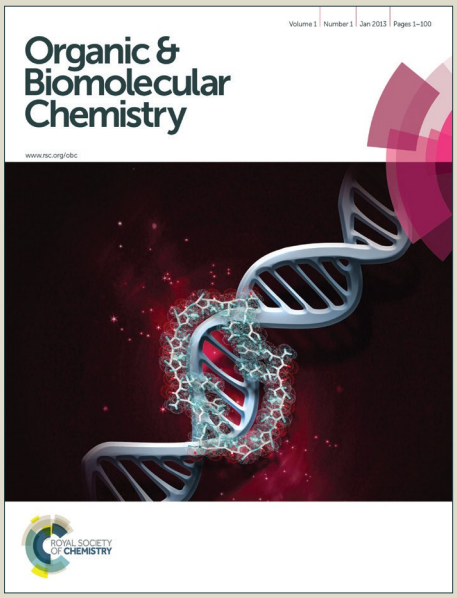

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N,N-dicarboxymethyl hydrazine: an old but neglected reagent for chemoselective derivatization of carbonyl compounds

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The N,N-dicarboxymethyl hydrazine (DCMH) was found to be a chemoselective derivatization reagent of carbonyl compounds and its potential applications in organic synthesis was investigated for the first time. DCMH could be employed as a chemoselective protective reagent of aldehydes and gave parent aldehydes in satisfactory yields. In proof-of-concept systems, DCMH could play the role of scavenger to remove aldehydes in the presence of ketones. It was also used as tagging reagent in the selective isolation of aldehyde from complex mixture.

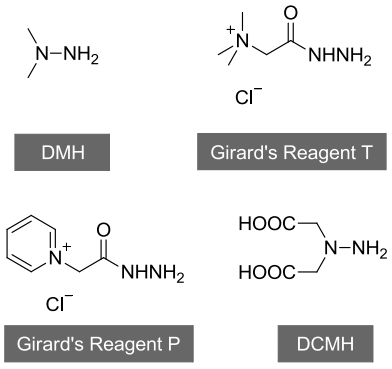
Introduction

As an important category of the organic compounds, aldehydes and ketones have been widely applied in many organic transformations and are key precursors of a variety of valuable fine chemicals including fragrances, vitamins and drugs.[1] Meanwhile, the derivatization of carbonyl compounds is a general task during the identification, protection and isolation procedures.[2] For instance, carbonyl compounds, especially aldehydes, are easily attacked by nucleophilic reagents or oxidizing reagents. The conventional method of overcoming these problems is to form derivatives of carbonyl group, so the sensitive substrate can be protected temporarily.[3]

A number of reagents have been employed in the derivatization of carbonyl compounds. The formation of hydrazones play an important role in the protection of the sensitive carbonyl compounds, as well as used for their purification, characterization and isolation.[4] Hydrazines and hydrazides, such as N,N-dimethylhydrazine (DMH)[5] and Girard's reagents[6] (Scheme 1), are commonly used for these purposes. For example, N,N-dimethylhydrazine could be used as protective reagent of carbonyl compounds and provided parent aldehydes in high yield and purity after be treated with $CeCl_3 \cdot 7H_2O$-SiO_2.[7] Teitelbaum has reported the use of Girard's reagent T to isolate carbonyl compounds from mixtures with higher yields avoiding acidic conditions.[8]

Despite of the successful application in organic synthesis, however, they still have some inherent drawbacks. The acute toxicity and inhalation danger of N,N-dimethylhydrazine used in conventional organic reactions make these process unsafe. Girard's reagents are hygroscopic and deteriorative easily when was exposed in the air. These reagents react smoothly with both aldehydes and ketones; on the other hand, this means relatively poor chemoselectivity between aldehydes and ketones. Therefore, it is necessary to develop novel derivatization reagent of carbonyl compounds with improved safety, stability and chemical selectivity for the protection, purification and isolation of carbonyl compounds.

N,N-dicarboxymethyl hydrazine (DCMH) is a noteless organic compound although it has been prepared one hundred years ago.[9] DCMH was previously employed as a complexant to separate the lanthanons from rare earth mixtures.[10] However, its potential use in organic synthesis has not been explored.



Scheme 1

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Electronic Supplementary Information (ESI) available: characterization of all the prepared compounds, copies of ^{1}H NMR and ^{13}C NMR spectra. See DOI: 10.1039/x0xx00000x

During our medicinal research on new enzyme inhibitors, we need to introduce a hydrophilic tag to water-insoluble substrates containing carbonyl groups. We found the candidate tagging agent N,N-dicarboxymethyl hydrazine has some interesting behavior in treating with different aldehydes and ketones. In this paper, we wish to report our work on the chemoselective interaction between DCMH and carbonyl compounds and its potential application in organic synthesis.

Results and Discussions

Initially, we attempt to prepare hydrazones of DCMH with different aldehydes and ketones. To our surprise, however, aliphatic cyclic ketones (e.g. cyclohexanone) and aromatic ketones (e.g. acetophenone) are difficult to react with DCMH. Only trace of expected hydrazones was detected while most of ketones kept unchanged. In contrast, DCMH reacted with aldehydes smoothly in satisfactory yields under the same conditions.

The reaction was further investigated in detail with 4-chlorobenzaldehyde and 4-chloroacetophenone as model substrates. A mixture of 4-chlorobenzaldehyde (1 mmol) and 4-chloroacetophenone (1 mmol) were treated with DCMH (2 mmol) in different solvents at different temperatures. The reactions were monitored by HPLC. As shown in Figure 1A, when the reaction was performed at 25 °C in methanol, 4-chlorobenzaldehyde was completely consumed after 3 hours, while the conversion of 4-chloroacetophenone was less than 1.3%.

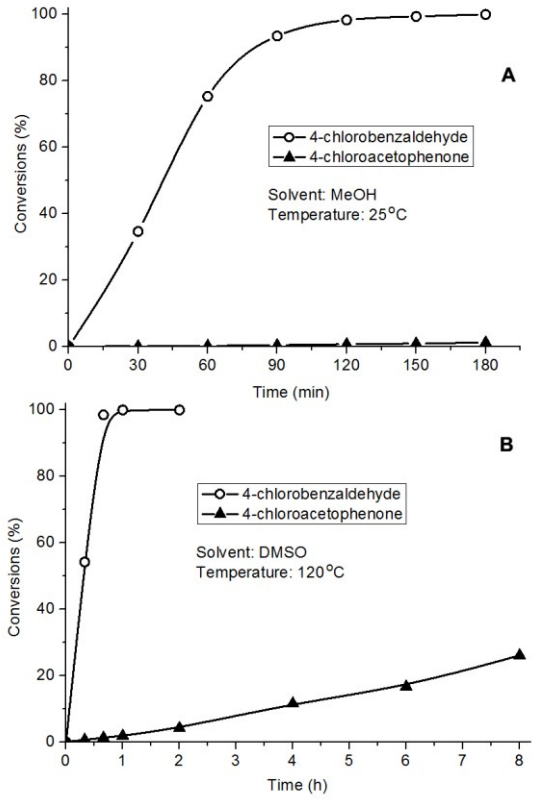

Figure 1. Kinetic study on the chemoselectivity of DCMH between aldehydes and ketones

As expected, the reaction rates of both 4-chlorobenzaldehyde and 4-chloroacetophenone with DCMH were enhanced at higher temperature (120 °C) using DMSO as a solvent. After 8 hours, the conversion of 4-chloroacetophenone reached to 23.1%. In comparison, the reaction of 4-chlorobenzaldehyde was also promoted and the ramp of conversion curve (nearly 100% about 0.5 h) can be seen in Figure 1B. In other words, the reaction between DCMH and ketones could still be carried out successfully at higher temperature in prolonged reaction time (>24 h). For example, the reaction between 4-chloroacetophenone and DCMH (Table 1, Entry 12) afford desired hydrazone in acceptable isolated yield (58%) after 24 h. These results demonstrated that DCMH has prominent chemoselectivity between aldehydes and ketones. Moreover, the chemoselectivity could be regulated by control of the reaction conditions.

Another potential application of DCMH is to introduce a hydrophilic tag onto aldehydes selectively in the presence of ketones. A colorimetric test was designed using Michler's ketone and 2-hydroxy-5-phenylazo salicylaldehyde as chromogenic substrates. Initially, Michler's ketone (purple) and 2-hydroxy-5-phenylazo salicylaldehyde (orange) were dissolved in the organic phase (lower layer) and DCMH distributed in the aqueous layer (Figure 2, **A**). After the mixture was stirred for 4 h at room temperature, 2-hydroxy-5-phenylazo salicylaldehyde was transferred into the aqueous layer by forming a water-soluble derivative, while unchanged Michler's ketone was still in the organic layer (Figure 2, **B**). This process was identifiable intuitively through color changes of two phases.

The origin of chemoselectivity was speculated during this research work. It might be attributed to the (1) zwitterion between amino group and carboxyl group, and/or (2) electron-withdrawing induced effect of two carboxyl groups. By using bis-sodium salt of DCMH, however, the chemoselectivity still remained. Hence the zwitterion is not the critical factor.

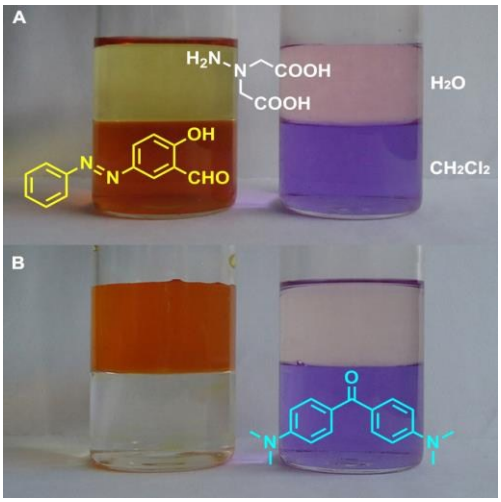

Figure 2. Colorimetric demonstration of chemoselective tagging

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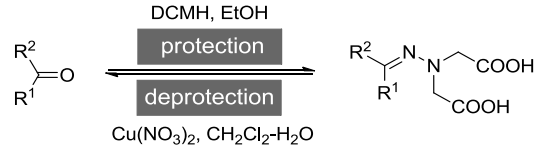
Table 1. Protection and deprotection of carbonyl compounds



Entry	Substrates		Protection[a]		Deprotection[c]	
	R^1	R^2	Yield (%)[d]	Time (h)	Yield (%)[d]	Time (h)
1	H	Ph	85	3	88	4
2	H	4-ClC_6H_4	88	2	89	3
3	H	2-$O_2NC_6H_4$	78	4	78	6
4	H	3-HOC_6H_4	81	4	83	5
5	H	2,4-$(Cl)_2C_6H_3$	84	3	86	3.5
6	H	4-MeC_6H_4	82	3	81	5
7	H	4-$MeOC_6H_4$	80	3	84	5
8	H	2-Thienyl	89	2.5	82	4
9	H	2-Pyridyl	91	2	88	3
10	H	PhCH=CH	85	2	80	6
11	H	$CH_3(CH_2)_2$	76	4	75	5
12[b]	CH_3	4-ClC_6H_4	58	24	70	9

[a] Reagents and conditions: aldehydes (2 mmol), DCMH (2.4 mmol), EtOH, room temperature.
[b] Reagents and conditions: 4-chloroacetophenone (2 mmol), DCMH (2.4 mmol), DMSO, 120 °C.
[c] Reagents and conditions: substrates (1 mmol), $Cu(NO_3)_2 \cdot 6H_2O$ (1.2 mmol), CH_2Cl_2–H_2O (1:1), room temperature.
[d] Isolated yields.

Application of DCMH as a novel and chemoselective protective reagent of aldehydes

The introduction and removal of protecting groups is one of the most important and widely carried out synthetic transformations in preparative organic chemistry.[11] As acetals (thioacetals),[12] oximes [13] and 1,1-diacetates,[14] hydrazones [15] are often employed for the protection of carbonyl groups. In the family of hydrazine derivatives, N,N-dimethylhydrazine (DMH) are widely used as protective reagent of carbonyl compounds in multi-step synthesis, and provided parent aldehydes through deprotection. Despite the broader scope of application, DMH has its own drawbacks and limitations. During our investigation, the potential of DCMH (an analogue of DMH) as protective reagent was evaluated at the first time.

As shown in Table 1, a serial of aromatic aldehydes, aliphatic aldehydes and unsaturated aldehyde can be protected by DCMH under mild conditions. The reaction performed smoothly without catalyst (approx. 2-4 h) to give corresponding hydrazones in good yields. In general, substituted aldehydes bearing both electron-withdrawing and electron-donating groups on the aromatic ring gave good yields of hydrazones. Aliphatic aldehydes, heterocyclic

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Table 2 Screening of deprotection reagents

Reagent[a]	Time (h)	Yield (%)[b]
$FeCl_3$	5	81
$Cu(NO_3)_2{\cdot}6H_2O$	4	88
oxalic acid	8	70
TMSCl-NaI	7	65

[a] Reagents and conditions: benzylidenehydrazinodiacetic acid (2 mmol), deprotection reagent (2.4 mmol), CH_2Cl_2–H_2O, room temperature.
[b] Isolated yields.

aldehydes and unsaturated aldehyde all reacted well with good yields. It has been discussed in the kinetic study on the chemoselectivity of DCMH that 4-chloroacetophenone can also give desired hydrazone in acceptable isolated yield (58%) after 24 h (Table 1, Entry 12).

The cleavage of N,N-dimethylhydrazones to afford carbonyl compounds has been studied extensively.[16] The classical method is hydrolysis of N,N-dimethylhydrazones under strong acidic condition, but this is not appropriate for acid sensitive aldehydes.[17] Hence, various alternative reagents were developed for this purpose. In the present work, several representative reagents, including cheap and nontoxic Lewis acids (Fe [18] and Cu [19] salts), a mild Brønsted acid (oxalic acid [20]) and a mixed reagents system (TMSCl-NaI [21]), were chosen for the screening of deprotection reagent by using benzylidenehydrazinodiacetic acid (hydrazone of DCMH with benzaldehyde) as a substrate. The comparative study shown that cupric salts was the optimal deprotection reagents in terms of reaction time, yield, mild condition and simple operation. Copper(II) chloride and copper(II) nitrate shown similar activities so the copper(II) nitrate was used in subsequent experiments (Table 2). The deprotection reactions were carried out in dichloromethane-water biphase system. Reaction occurred in aqueous solution of copper (II) nitrate, and the parent aldehydes thus formed was extracted in to organic phase. With optimal cleavage reagent in hand, the deprotection of various hydrazones was tested subsequently. As shown in Table 1, high yields of carbonyl compounds were obtained after deprotection. No byproducts and possible impurities were detected in dichloromethane phase.

In comparison with N,N-dimethyl hydrazine, DCMH has several prominent superiorities when that is being used in organic synthesis. (1) Excellent chemoselectivity. The present work has demonstrated the chemoselectivity of DCMH in the presence of aldehydes and ketones. This provides an opportunity to derive aldehydes selectively in the presence of ketones. So DCMH could be employed as a chemoselective protective reagent. In a mixture containing both aldehydes and ketones, the aldehydes would be protected specifically. In the case of a compound with multiple carbonyl groups, the aldehyde carbonyl would be protected while ketone carbonyl remained unchanged. (2) Easier isolation. Most of aldehydes (especially aromatic ones) as well as their hydrazone derivatives with DMH are less polar hydrophobic compounds; however, their hydrazone derivatives with DCMH are often much polar and hydrophilic. Hence, after derivation, hydrazone derivatives of DCMH could be separated readily from less polar organic compounds by extraction (or other) processes. (3) Safer handling. DMH is a volatile and highly toxic chemical which should be handled with care. Inhalation and skin contact with DMH must be strictly avoided. On the contrary, DCMH is a non-volatile and relatively low toxic compound.

Application of DCMH as a scavenger to remove excess aldehyde in the presence of ketone

In most of organic synthetic reactions, an excess of certain reagent is intentionally employed to accelerate the reaction or to obtain higher yield of desired products. Over the past decades, solution-phase high throughput synthesis has emerged as a powerful tool for the rapid generation of chemical libraries, especially in drug-like lead discovery and optimization tool in drug screening.[22] Solution-phase synthesis allows for diverse and homogeneous reaction conditions, and products are readily analyzed and identified, but the rapid purification or isolation of products from a reaction mixture is difficult. To overcome this drawback, several purification protocols have also been developed to simplify the time-consuming purification procedures often associated with solution-phase reactions. The most widely employed method among them is the use of polymer-supported scavenger reagents.[23] Most of commercially available scavengers are reticulated polymers and the major drawbacks of these supported scavengers are the high cost and the large amount generally required to clean up the reaction product. To address these issues, many innovative purification approaches have been disclosed. Some fluorous-phase[24] scavengers and PEG supported scavenger reagents[25] have been designed to avoid these limitations.

As a quaternary ammonium type hydrazide, Girard's reagent T has been used in scavenging excess acid chlorides to obtain water-soluble byproducts, which could be removed from the desired products by extraction with water.[26] However, this reagent could not be employed to remove aldehydes in the presence of ketones due to its poor chemoselectivity between aldehydes and ketones. In comparison, DCMH is a stable, nonhygroscopic (non-deliquescent) white powder which has excellent chemoselectivity. In this paper, therefore, the application of DCMH for replacement of Girard's reagent as a water-soluble and selective scavenger was then investigated in two proof-of-concept reactions.

Firstly, Mannich reaction among benzaldehyde, acetophenone and aniline was selected as a model reaction to test the ability of DCMH as a scavenger in selective removal of benzaldehyde **2** in the presence of the *β*-amino ketone product **1** (Figure 3A). Acetophenone (2 mmol) and aniline (2mmol) in ethanol were treated with an excess of benzaldehyde (2.4 mmol, 1.2 equiv.) in the presence of a catalytic amount of sulfamic acid (0.1 equiv.). On completion (6 h, room temperature, monitored by HPLC), DCMH (0.4 equiv.) was added and stirred for an additional 3 h to react with excess aldehyde. Aqueous sodium

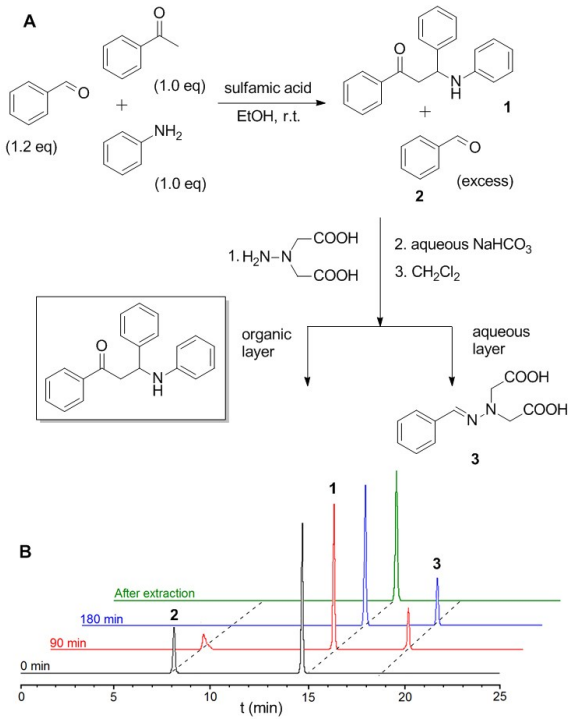

Figure 3 (A) Isolation of *β*-amino ketone by selected removal of excess benzaldehyde (B) HPLC tracing

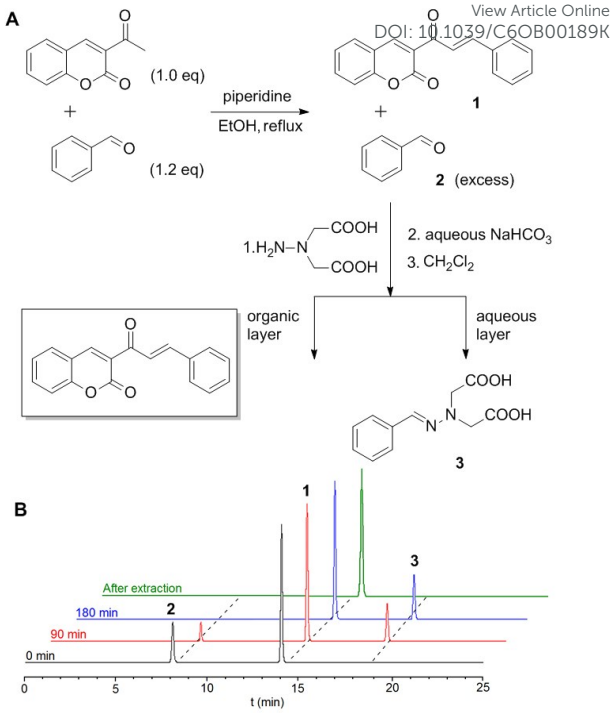

Figure 4 (A) Isolation of *α, β*-unsaturated ketone by selected derivatization of aldehyde (B) HPLC tracing

bicarbonate was then added to the mixture under stirring. The product was extracted with dichloromethane while the water soluble hydrazine **3** stayed in the aqueous phase. The organic layers were dried over anhydrous magnesium sulfate and evaporated to yield the desired product in 91% yield. The resulting *β*-amino ketone was free from the starting aldehyde and possible impurities as determined by ^{1}H NMR.

Figure 3B illustrates a typical HPLC tracing observed in this study. The peak at 8.1 min retention time is due to unreacted aldehyde **2**, while the peak at 14.8 min is due to the desired Mannich base **1**. In this case, treating with DCMH led to derivatization of unreacted aldehyde as indicated by the formation of hydrazone **3** (peak at 20.1 min). After be extracted with dichloromethane and aqueous sodium bicarbonate, hydrazone could be removed completely and essentially pure Mannich base was obtained in high yield.

Another model reaction of choice was the aldol condensation between 3-acetyl coumarin and benzaldehyde to afford *α, β*-unsaturated ketone **1** (Figure 4A). The reaction and scavenging processes were monitored by HPLC as shown in Figure 4. DCMH could also be used as an efficient and selective scavenger just as in Mannich reaction. After the derivatization and extraction work-up, desired product 3-(3-phenyl-acryloyl)-chromen-2-one **1** could be obtained in 95% yield with high purity (98%) as confirmed by ^{1}H NMR. The process was monitored by HPLC as illustrated in Figure 4B.

In principle, DCMH might be considered to be a suitable scavenger for other type of reactions which need to purify ketone type product in the presence of excess aldehyde by derivatization. It is also worth mentioning that the DCMH reagent does not suffer from the extensive mechanical degradation experienced by polymer-supported scavengers under vigorous stirring.

Application of DCMH in the isolation of aldehydes from natural plant products

The isolation of specific kinds of natural products is important to the scientific community because many of natural products have medicinal activities and often be evaluated for finding new biologically active scaffolds and drug candidates. Unfortunately, these isolation procedures are difficult endeavours. In general, these isolation procedures relies upon extraction and/or chromatographic separation techniques which are dependent upon the physicochemical properties of the compounds rather than the difference in chemical reactivity. Recently, Carlson group has reported a functional group targeted method for chemoselective enrichment and isolation of natural products with certain functional groups from complex mixtures based on controllably reversible covalent enrichment tags.[27] In this paper, we wish to describe our research work on the practicability of using DCMH as a tagging reagent for the isolation of natural aldehyde from a complex mixture.

Carbonyl compounds are common constituents of natural plant products in which they usually mixed with esters, hydrocarbons and steroids.[28] Star anise (*Illicium verum Hook. f.*) is not only used as a flavoring ingredient in foods but also used in aromatherapy and pharmaceutical industries. Dozens of chemical constituents have been identified from star anise (*Illicium verum Hook. f.*), but the major components are *trans*-anethole **1**, anisole **2**, *α*-pinene **3**, fenchone, and anisaldehyde **4**; although there is great difference in the ratio of constituents

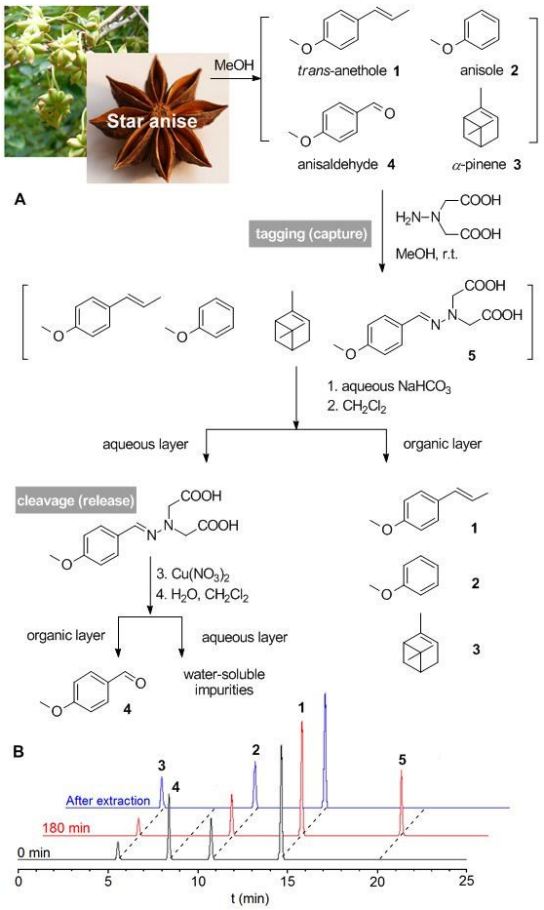

Figure 5 (A) Isolation of anisaldehyde through a capture-and-release strategy (B) HPLC tracing

which largely depend on internal and external factors such as genetic structures, geographic locations, even storage time.[29] To demonstrate the potential of DCMH for chemoselective enrichment of natural aldehyde, 15 g of crushed Star anise was extracted by methanol (20 mL) for 12 h. The major components in obtained extract were identified as *trans*-anethole, anisole, *α*-pinene and anisaldehyde by GC-MS. The mixture was concentrated to approximately 5 mL and then treated with excess of DCMH (222 mg, 1.5 mmol). As shown in the HPLC tracing in Figure 5B, anisaldehyde was tagged completely within 3 h. Following capture, the hydrazone derivative **5** was separated from lipophilic compounds by extraction. Anisaldehyde (114 mg) could be recovered by cleavage of the hydrophilic tag with stoichiometric copper (II) nitrate after liquid-liquid extraction. The product was checked by HPLC followed by ^{1}H NMR and was essentially pure (99%).

Conclusions

In conclusion, N,N-dicarboxymethyl hydrazine is a water-soluble, non-volatile, non-hygroscopic and stable reagent with excellent chemoselectivity between aldehydes and ketones. DCMH can be used as chemoselective derivatization reagent of carbonyl compounds such as protective reagent, scavenger and tagging reagent as have been demonstrated in this paper. In some cases, DCMH might be employed as an efficient alternative reagent of N,N-dimethylhydrazine and Girard's reagents in organic synthesis and isolation processes.

Experimental

General remarks

All reagents and solvents were purchased from commercial suppliers and used without further purification. ^{1}H NMR (400 Hz) and ^{13}C NMR (100 Hz) spectra were recorded on Bruker AM-400 spectrometer using TMS as an internal standard. Melting points were measured on BUCHI Melting Point B-450. Mass spectra were recorded on a Shimadzu QP 1100 EX mass spectrometer with 70eV ionization potential. IR spectra were recorded with a Thermo Nicolet 6700 IR spectrophotometer using KBr pellets. Elemental analyses were carried out with a Thermo Flash 2000 CHNS/O analyzer. HPLC analysis was performed on a Hewlett-Packard 1100 instrument.

Synthesis of DCMH

Chloroacetic acid (950 mg, 10 mmol) in water (10 mL) was neutralized with sodium carbonate (530 mg, 5 mmol) followed by the addition of hydrazine hydrate (310 mg, 5 mmol). Next, a second portion of sodium carbonate (530 mg, 5 mmol) was gradually added at room temperature. On completion, the temperature was elevated to 70 °C and the solution was stirred until the gas generation stopped. After cooling, the solution was acidified to pH 3–4 by hydrochloric acid and the crude DCMH was then precipitated. Recrystallization from water gave 614 mg (83% yield) of pure DCMH as white powder. M.p. 168–169 °C, lit.[9] 166–167 °C.

General procedure for the protection of aldehydes with DCMH

To a stirred solution of aldehyde (2 mmol) in ethanol (4 mL) was added DCMH (360 mg, 2.4 mmol). The mixture was stirred at room temperature and monitored by TLC. Upon completion, the solution was concentrated while the crude product was obtained by filtration (washed with ice water). The pure product was obtained by recrystallization from ethanol.

General procedure for the deprotection with $Cu(NO_3)_2{\cdot}6H_2O$

To a stirred solution of $Cu(NO_3)_2{\cdot}6H_2O$ (338 mg, 1.2 mmol) in water (2 mL) was added the hydrazone derivatives (1 mmol) and dichloromethane (2 mL). The mixture is stirred for several hours (monitored by TLC) at room temperature. Upon completion, the solution was diluted with 10 mL of aqueous sodium bicarbonate (100 mg, 1.2 mmol). The organic layer was separated and the aqueous solution was further extracted with dichloromethane (2×5 mL). The combined dichloromethane solution was dried over anhydrous magnesium sulfate and concentrated under reduced pressure to give the pure aldehydes.

Purification of 1,3-diphenyl-3-(phenylamino)propan-1-one with DCMH

To a stirred solution of benzaldehyde (250 mg, 2.4 mmol) in ethanol (4 mL) was added acetophenone (240 mg, 2 mmol), aniline (190 mg, 2 mmol) and sulfamic acid (20 mg, 0.2 mmol)

at room temperature. The reaction completed after 6 h as monitored by TLC. 120 mg of DCMH (0.8 mmol) was then added and the mixture was stirred for an additional 3 h. The mixture was diluted with 10 mL of aqueous sodium bicarbonate (100 mg, 1.2 mmol) and the organic layer was separated. Aqueous layer was extracted with dichloromethane (3×5 mL) subsquently. The combined organic solution was dried over anhydrous magnesium sulfate and concentrated under reduced pressure to give 547 mg of pure 1,3-diphenyl-3-(phenylamino)propan-1-one (91% yield). M.p. 168–169 °C, lit.[30] 168–170 °C.

Purification of 3-(3-phenyl-acryloyl)-chromen-2-one with DCMH

A stirred solution of benzaldehyde (250 mg, 2.4 mmol), 3-acetyl coumarin (380 mg, 2 mmol) and piperidine (17 mg, 0.2 mmol) in ethanol (4 mL) was refluxed for 5 h. On completion of the reaction (monitored by TLC), DCMH (120 mg, 0.8 mmol) was added followed by stirring for further 3 h. The mixture was then diluted with 10 mL of aqueous sodium bicarbonate (100 mg, 1.2 mmol) while the organic layer was separated. Aqueous layer was extracted with dichloromethane (3×5 mL). The combined organic solution was dried over anhydrous magnesium sulfate and concentrated under reduced pressure to give the essentially pure 3-(3-phenyl-acryloyl)-chromen-2-one (525 mg, 95% yield). M.p. 141–142 °C, lit.[31] 142–143 °C.

Isolation of anisaldehyde from the extract of Star anise with DCMH

Crushed Star anise (15 g) was extracted with refluxed methanol (20 mL) for 12 h. After filtration, the solution containing *trans*-anethole, anisaldehyde, anisole and α-pinene (identified by GC-MS) was concentrated to 5 mL, and then treated with excess of DCMH (222 mg, 1.5 mmol). The mixture was stirred for 3 h at room temperature, diluted with 10 mL of aqueous sodium bicarbonate (168 mg, 2 mmol) and extracted with dichloromethane (3×5 mL) to remove hydrophobic components. The aqueous layer was added $Cu(NO_3)_2{\cdot}6H_2O$ (422 mg, 1.5 mmol) and stirred for an additional 5 h. The reaction mixture thus formed was extracted with dichloromethane (3×5 mL). The combined organic solution was dried over anhydrous magnesium sulfate and concentrated under reduced pressure to give the pure anisaldehyde (114 mg).

Acknowledgements

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