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PAPER

A Practical solution for aqueous reactions of water-insoluble high-melting-point organic substrates†

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A practical solution to the problem of performing aqueous reactions for very sparingly soluble high-melting-point (VSSHMP) organic substrates has been developed, which entails mechanically stirring a mixture of the substrate, the corresponding reagent(s), water, catalytic Aliquat 336 and sand. When the melting points of the substrates which include steroids, ketones, aldehydes, aromatics and alkaloids are around 200 °C, the reactions can be performed at 20 °C. The substrate solubility can be as low as 1×10^{-10} mol L^{-1}.

Introduction

It has been estimated that organic solvents make up approximately 85% of the total mass of chemicals in the manufacture of pharmaceuticals and that only 50–80% can be recovered which results in annual costs of £4 billion.[1] Replacing organic solvents with water as a reaction medium has attracted chemical industrial interests because of water's special properties such as safety, nontoxicity, inflammability, cheapness and environmental friendliness.[2] There have been reports that water-soluble substrates react in aqueous media.[3] However, the vast majority of organic substrates are not water-soluble. For theses substrates, the reactions can be performed "on water" if the reaction temperatures are above their melting points or if the other substrates melt at the reaction temperatures in multi component reactions.[4,5] Although a few exceptions are known where slightly and sparingly soluble high-melting-point substrates (solubility: 2.2×10^{-2} to 5×10^{-6} mol L^{-1}) have been reported to react on water at room temperature,[4,6] there have been no general methods for performing the aqueous reactions of VSSHMP substrates, especially for the VSSHMP substrates with the solubilities at the level of 1×10^{-10} mol L^{-1}.[7] In the literature, more than catalytic amounts of ILs (ionic liquids) plus water or an IL plus an organic co-solvent have been used in the reactions.[2,7,8] We speculated that a combination of catalytic Aliquat 336 (methyltrioctylamonnium chloride) and water could be a solution to the problem. Aliquat 336 is a liquid and can partially dissolve VSSHMP substrates and transfer inorganic reagents from the aqueous phase. If the amount of Aliquat 336 could be catalytic, this solution would be practical and very useful to industries.

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†Electronic supplementary information (ESI) available: Detailed description of the control experiments and ^{1}H NMR, ^{13}C NMR spectra for unknown compounds. See DOI: 10.1039/c2gc16328d

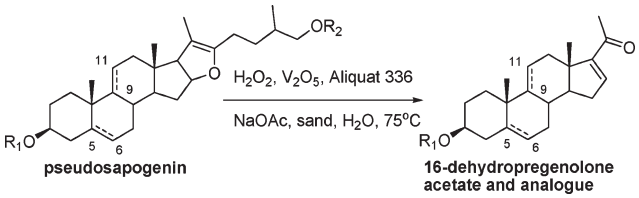
Results and discussion

Oxidations of VSSHMP pseudosapogenins

In the global drug market, steroid drugs rank second only after antibiotics. It is estimated that more than 65% of the steroid drugs are derived from 16-dehydropregenolone acetate (Table 1, **2a**) and its analogues, which are intermediates for producing steroid drugs. Since 1944, the Marker degradation has dominated the productions of these compounds with an overall yield of 78%.[9] The Marker degradation was designated as an International Historic Chemical Landmark by the American Chemical Society in 1999.[10] Even today, the oxidation still consumes thousands of tons of volatile organic solvents and chromium trioxide annually. Chromium trioxide is a toxic and carcinogenic reagent. It would be extremely beneficial to be able to replace CrO_3 and volatile organic solvents required for the Marker degradation with green oxidants such as oxygen or hydrogen peroxide and green reaction media such as water. Fortunately, our continuing research efforts have accomplished this goal.[11]

When **1a** (0.1 g, mp: 98–101 °C, solubility: 4.4×10^{-7} mol L^{-1}, Table 1) was suspended on water (5 mL) and treated with V_2O_5 (0.04 eq.), NaOAc (0.1 eq.), Aliquat 336 (0.15 eq.) and H_2O_2 (2.5 eq.) at 75 °C with mechanical stirring (400 rpm, Teflon blade, D = 4 cm), a selective oxidation of the electron-rich double bond followed by elimination took place, yielding **2a** in 78% yield in 5.5 h. However, when the amount of **1a** was increased to over 0.5 g, the reaction became sluggish and incomplete even after 24 h. This problem was solved by adding 2 g of sea sand or PTFE (polytetrafluoroethylene) sand (70 pieces/g) to 2 g of **1a** under the same conditions. The oxidation of **1a** to **2a** was then completed in 6.5 h. The product of the heterogeneous reaction is a sticky solid that adheres to the sand and the glass reaction vessel. The aqueous solution was decanted and then the solid residue was extracted by Soxhlet extractor with petroleum ether followed by concentration and crystallization to get 71% yield of **2a**.

Table 1 Oxidation of VSSHMP pseudosapogenins into 16-dehydropregenolone acetate and its analogues using H_2O_2 catalyzed by V_2O_5 and water[a]



Entry	No. of substrate	Mp (°C)	Solubility[b] (mol L^{-1})	OR^1	OR^2	C_{5-6} or C_{5-H}	C_{9-11}	Time (h)	No. of product	Yield[c] (%)
1	**1a**	98–101	4.4×10^{-7}	AcO	AcO	d[d]	s[e]	6.5	**2a**	71
2	**1b**	72–75	4.2×10^{-7}	AcO	AcO	s, α	s	5.5	**2b**	79
3	**1c**	90–94	4.2×10^{-7}	AcO	AcO	s, α	d	5.5	**2c**	79
4	**1d**	89–91	5.7×10^{-10}	BzO	BzO	d	s	6	**2d**	73
5	**1e**	117–120	7.2×10^{-8}	Cl	Cl	d	s	6	**2e**	60
6	**1f**	121–125	1.5×10^{-8}	AcO	BzO	d	s	5.5	**2a**	74
7	**1g**	145–147	3.7×10^{-9}	AcO	4-MeBzO	d	s	5	**2a**	77
8	**1h**	122–125	5.4×10^{-9}	AcO	Hexanoyl	d	s	5.5	**2a**	71
9	**1i**	125–127	4.7×10^{-9}	Cl	BzO	d	s	6.5	**2e**	71
10	**1j**	164–167	2.3×10^{-9}	AcO	4-ClBzO	d	s	6	**2a**	73
11	**1k**	105–108	3.7×10^{-9}	AcO	3-MeBzO	d	s	7	**2a**	71
12	**1l**	197–200	5.4×10^{-8}	AcO	4-NO_2BzO	d	s	10	**2a**	72

[a] All conversions are 100%. [b] **1a–1f**: data from SciFinder; **1g–1l**: data calculated using Software Wskow. [c] Isolated yield. [d] Double bond. [e] Single bond. Reaction conditions: Aliquat 336 (0.15 eq.), NaOAc (0.1 eq.), V_2O_5 (0.04 eq.), H_2O_2 (2.5 eq.), PTFE sand and water at 75 °C.

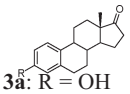
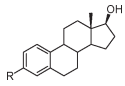
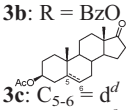
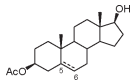
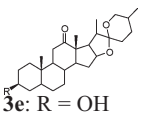
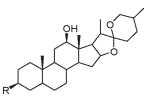
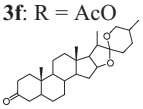
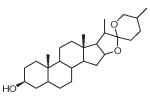
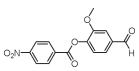
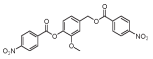
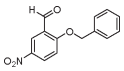
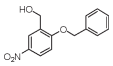
When the amount of water was doubled or tripled, the reaction yield and time remained unchanged. Therefore the function of the water is to reduce the decomposition rate of the H_2O_2. Aliquat 336 was selected because it is inexpensive, commercially available, non-toxic and works in catalytic amounts. It plays dual roles: an IL, which partially dissolves the solid substrates, and a phase transfer catalyst (PTC), which transfers oxodiperoxovanadate[11] to the substrate. This is known because in the control experiments, replacing liquid Aliquat 336 with solid benzyltriethylamonium chloride, or solid tetraethylamonium chloride, or solid tetradecytrimethylammonium chloride, or solid cetyltrimethylammonium bromide, or solid sodium dodecylsulfonate, or liquid *N*-butyl-*N*-methyl imidazolium chloride (1 eq.) did not lead to any oxidations. Oxidation occurred when octadecyltrioctylamonium chloride, a liquid at room temperature, replaced Aliquat 336. When the amount of Aliquat 336 was increased to 0.3 eq., the reaction time decreased to 4.5 h. The sand is a stirring promoter that functions as thousands of abrasives or co-stirrers to smash the sticky semi-molten substrate agglomerations. These agglomerations are the cause of the sluggish oxidation rate in the larger scale reaction. The reaction failed with a microwave reactor because of the lack of mechanical stirring. Therefore we have for the first time established a method of using a catalytic amount of an IL that serves as both solvent and catalyst, the efficiency of which is enhanced by the moving sand.

When the above green reaction was applied to other pseudosapogenins (Table 1, mp: 72–200 °C, solubilities: 4.4×10^{-7} to 5.7×10^{-10} mol L^{-1}), such as **1b** derived from tigogenin, and **1c** derived from hecogenin, the corresponding products were produced in good yields. Product **2b** is the intermediate for clinical drugs anordrin, methandrostenolonne and oxymetholone and product **2c** the intermediate for clinical drugs betamethasone and dexamethasone. Similarly, other pseudodiosgenins (Table 1, entries 4–12) were all successfully transformed into the corresponding products in 100% conversions and in good yield.

Reductions of VSSHMP ketones and aldehydes

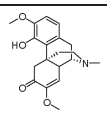
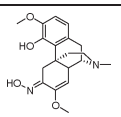
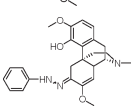
A widely employed procedure for the reduction of aldehydes or ketones is treating a solution of the carbonyl compounds with KBH_4 or $NaBH_4$ in alcohols. A series of VSSHMP ketones and aldehydes (mp: 111–261 °C, solubilities: 4.7×10^{-5} to 2.2×10^{-7} mol L^{-1}, Table 2, entries 1–11) were mixed with Aliquat 336 (0.08 eq.), PTFE sand and water under mechanical stirring (400 rpm, Teflon blade, $D = 4$ cm) and treated with 0.8 eq. of KBH_4 at room temperature or 60 °C. Unlike in the oxidations of pseudosapogenins, the crystals of the substrates changed directly to the crystals of the products during the reductions. After stopping the reaction, the crystalline products were suspended in water while the sand precipitated on the bottom of the flask. The crystalline products were collected by filtration and the sand was left in the flask; the crude products were quantitative and pure enough for most purposes as indicated by the NMR analysis of the crude products (see Supporting Information†). The reduction of aldehyde **3h** was followed by a facile ester exchange reaction, yielding ester **4h** in one pot. The catalyst (Aliquat 336) and sand and water were recycled for 10 times in the case of **3d** with the same reaction yields and rates. In the control experiments, the reduction of VSSHMP ketones and aldehydes did not take place without Aliquat 336 and sand or in the presence of other PTCs such as tetrabutylammonium bromide or benzyltriethylammonium chloride instead of Aliquat 336. This again indicates the dual function of Aliquat 336. For the reductions, water is necessary. In the control experiments of Table 2, entries 3 and 9, the reductions did not occur when water was withdrawn from the systems.

Table 2 Reduction of VSSHMP ketones and aldehydes with KBH_4 and water[a]

Entry	Substrate	No.	Mp (°C)	Solubility[b] (mol L^{-1})	T/°C	Time (h)	Product	No.	Yield[c] (%)
1	 **3a**: R = OH	**3a**	259–261	2.1×10^{-5}	60	1.5		**4a**	92[f]
2	**3b**: R = BzO	**3b**	220–223	2.2×10^{-7}	20	6.5		**4b**	85[f]
3		**3c**	172–175	1.1×10^{-5}	60	1		**4c**	>99
4	**3c**: $C_{5\text{-}6}$ = d[d]	**3c**			20	3		**4c**	>99
5	**3d**: $C_{5\text{-}6}$ = s[e]	**3d**	111–113	4.4×10^{-6}	60	1.5		**4d**	>99
6		**3d**			20	4		**4d**	>99
7	 **3e**: R = OH	**3e**	263–264	1.2×10^{-5}	60	2		**4e**	>99
8	**3f**: R = AcO	**3f**	243–245	1.4×10^{-6}	60	1.5		**4f**	>99
9		**3g**	238–241	1.1×10^{-6}	60	1		**4g**	>99
10		**3h**	187–189	6.8×10^{-6}	20	6		**4h**	>99
11		**3i**	119–120	4.7×10^{-5}	20	1		**4i**	>99

[a] All conversions are 100%. [b] **3a–3i**: data from SciFinder. [c] Isolated yield. [d] Double bond. [e] Single bond. [f] After recrystallization. Reaction conditions: Aliquat 336 (0.08 eq.), KBH_4 (0.8 eq.), PTFE sand and water.

Table 3 Condensation reactions of sinomenine and water[a]

Entry	Substrate **1**	No.	Mp (°C)	Solubility[b] (mol L^{-1})	Substrate **2**	Time (h)	Product	No.	Yield[c] (%)
1		**5a**	164–166	1.9×10^{-2}	$NH_2OH{\cdot}HCl$	1		**6a**	>99
2					$PhNHNH_2{\cdot}HCl$	3		**6b**	96

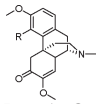
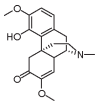
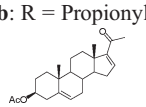
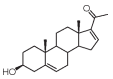
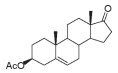
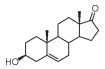
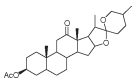
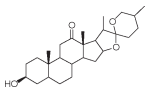
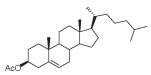
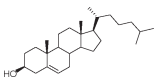
[a] All conversions are 100%. [b] **5a**: data from SciFinder. [c] Isolated yield. Reaction conditions: Aliquat 336 (0.08 eq.), PTFE sand and water at 60 °C.

Among these products, estradiol (**4a**) and estradiol benzoate (**4b**) are two well-known clinical drugs. Estradiol was among the top 200 generic drugs by retail dollars in 2006–2008.[12] Industrially, estradiol is mainly manufactured by $NaBH_4$ or KBH_4 reduction of estrone in alcohols in 82–90% yields.[13,14] In our green synthesis, the yield was 92% after recrystallization. $NaBH_4$ reduction of estrone benzoate in alcohols has been reported in a patent, which suffers from a severe hydrolysis, yielding a mixture of *ca.* 50% estradiol benzoate and 50% estradiol.[13] In our control experiment, KBH_4 reduction of estrone benzoate in ethanol led to a mixture of estradiol and estradiol benzoate as analyzed by HPLC (see Supporting Information†). Fortunately, in our green reduction of estrone benzoate, the hydrolysis was so depressed that the yield of estradiol benzoate was 85% after recrystallization. The reasons are that both Aliquat 336 and estrone benzoate are hydrophobic, and the latter is only dissolved and surrounded by the former, so that the dissolved latter and estradiol benzoate have no contact with water. While in the classic reductions, reaction media alcohols bring estrone benzoate or estradiol benzoate into contact with water, which leads to the significant hydrolysis of the esters. These procedures are better than the current ones and good enough for industry adoption.

Condensations of alkaloid sinomenine

Alkaloid sinomenine (mp: 164–166 °C, solubility: 1.9×10^{-2} mol L^{-1}, Table 3) is an anti-rheumatic drug clinically used in China.[15] Two derivatives were prepared using our green method by condensation with hydroxylamine hydrogen chloride and phenyl hydrazine hydrogen chloride with nearly quantitative

Table 4 Hydrolysis of VSSHMP esters using KOH and water[a]

Entry	Substrate	No.	Mp (°C)	Solubility[b] (mol L^{-1})	Time (h)	Product	No.	Yield[c] (%)
1	 **7a**: R = AcO	**7a**	105–107	5.4×10^{-3}	1		**5a**	>99
2	**7b**: R = Propionyl	**7b**	95–98	2.5×10^{-3}	2		**5a**	>99
3		**2a**	169–172	2.7×10^{-6}	5.5		**8b**	>99
4		**3c**	172–175	1.1×10^{-5}	1.5		**8c**	>99
5		**3f**	245–246	1.4×10^{-6}	7		**8d**	>99
6		**7f**	117–119	1.2×10^{-9}	1.5		**8e**	>99

[a] All conversions are 100%. [b] Data from SciFinder. [c] Isolated yield. Reaction conditions: Aliquat 336 (0.08 eq.), KOH (1.5 eq.), PTFE sand and water at 60 °C.

yields. In the control experiments without Aliquat 336 and PTFE sand, the reaction yielded a mixture and could not be completed.

Hydrolyses of VSSHMP esters

Classically, volatile organic solvents have to be used in hydrolysis reactions. Our method was applied to the hydrolysis of VSSHMP esters: two alkaloid esters and four steroid esters (mp: 95–246 °C, solubilities: 5.4×10^{-3} to 1.2×10^{-9} mol L^{-1}, Table 4). Treating a mixture of ester, water, PTFE sand and a catalytic amount of Aliquat 336 (0.08 eq.) with KOH at 60 °C for 1–7 h yielded the corresponding alcohol. After stopping the reaction, the crystalline products were suspended in water while the sand precipitated on the bottom of the flask. After filtration, the crude products were obtained in quantitative yields and the sand was left in the flask and recovered. When the reaction scale of **7f** was enlarged to 10 g from 2 g, the reaction rate and yield remained unchanged. In the control experiments, treating a mixture of ester and water with KOH at room temperature or 60 °C for 24 h led to only trace amounts of the alcohol; treating a mixture of **3c**, KOH (1.5 eq.), tetrabutylammonium bromide (0.08 eq.) and water (10 ml) at 60 °C for 1.5 h (*vs* Table 4, entry 4) gave almost no hydrolysis products (see Supporting Information†). In contract, methyl benzoate (2 g), a liquid ester, was found to undergo smooth hydrolysis in the presence of KOH (1.5 eq.) and water (10 ml) at room temperature in 3 h. This indicates the dramatic difference between the liquid ester and the VSSHMP esters in aqueous reactions.

Conclusions

In conclusion, the substitution of volatile organic solvents with a mixture of water, sand and a catalytic amount of Aliquat 336 has been successful for aqueous reaction of VSSHMP substrates. This green method has provided green and improved syntheses of three pharmaceutical intermediates and two clinical drugs. Large amounts of volatile organic solvents could be saved if this method is applied to industries. This method will at a minimum provide a partial solution to dealing with the VSSHMP substrates without using large amounts of organic solvents or co-solvents or expensive ILs.

Experimental

All of the chemicals were obtained from commercial sources or prepared according to standard methods. The ^{1}H-NMR (400 MHz) and ^{13}C-NMR (100 MHz) were recorded on a Bruker AM-400 spectrometer. Chemical shifts (δ) are reported relative to TMS (^{1}H) or $CDCl_3$ (^{13}C). IR spectra were recorded on BIO-RAD FTS 3000 spectrometer. Melting points were obtained on an X-4 Micro-melting Point Apparatus. Mass spectra (ESI) were obtained on a Finnigan LCQ Advantage MAX spectrometer. High resolution mass spectra (ESI) were obtained on Bruker micrOTOF-QII. The size of PTFE sand is 70 pieces/g.

General procedure for the oxidation of pseudosapogenins (Table 1, 1a–1l)

To a mixture of pseudosapogenin (2 g), V_2O_5 (0.04 eq.), Aliquat 336 (0.15 eq.), NaOAc (0.1 eq.), PTFE sand (2 g) and water (10 mL) was added H_2O_2 (30%, 2.5 eq.). The reaction mixture was heated to 75 °C and mechanically stirred (400 rpm, Teflon blade, D = 4 cm) for 5–10 h. TLC showed the completion of the reaction. After the decantation of the aqueous phase, the solid residue was mixed with silica gel (2 g) and extracted by Soxhlet extractor with petroleum ether containing 2% ethyl acetate or filtered through silica gel (petroleum ether:ethyl acetate 5:1), which was concentrated and crystallized from methanol to give

16-dehydropregenolone acetate and its analogues **2a–2e**. The yields and reaction durations are listed in Table 1 in the text.

General procedure for the reduction of ketones and aldehydes (Table 2, 3a–3i)

To a mixture of ketone/aldehyde (2 g), Aliquat 336 (0.08 eq.), PTFE sand (2 g) and water (10 mL) was added KBH_4 (0.8 eq.) in portions. The mixture was mechanically stirred (400 rpm, Teflon blade, D = 4 cm) at 20 °C or 60 °C for 1–6.5 h. TLC showed the completion of the reaction. After stopping the reaction, the crystalline product was suspended in water while the sand precipitated on the bottom. The suspension was filtrated to give **4a–4i** in quantitative yields leaving the sand to be recovered. The yields and reaction durations are listed in Table 2 in the text.

General procedure for the condensation of sinomenine (Table 3, 5a)

A mixture of sinomenine **5a** (2 g), $NH_2OH{\cdot}HCl$/$PhNHNH_2{\cdot}HCl$ (1.0 eq.), Aliquat 336 (0.08 eq.), PTFE sand (2 g) and water (10 mL) was mechanically stirred (400 rpm, Teflon blade, D = 4 cm) at 60 °C for 1 h or 3 h. TLC showed the completion of the reaction. The reaction mixture was decanted from the sand and neutralized with ammonium hydroxide, and filtrated to give **6a**/**6b** in quantitative yields. The yields and reaction durations are listed in Table 3 in the text.

General procedure for the hydrolysis of esters (Table 4, entry 1–6)

A mixture of ester (2 g), Aliquat 336 (0.08 eq.), KOH (1.5 eq.), PTFE sand (2 g) and water (10 mL) was mechanically stirred (400 rpm, Teflon blade, D = 4 cm) at 60 °C for 1–7 h. TLC showed the completion of the reaction. After stopping the reaction, the crystalline product was suspended in water while the sand precipitated on the bottom. The suspension was filtrated to give the corresponding products in quantitative yields leaving the sand to be recovered. The yields and reaction durations are listed in Table 4 in the text.

NMR, IR, MS, mp and HRMS data of new compounds

4-(4-Nitrobenzoxy)benzyl 4-nitrobenzoate (4h). ^{1}H NMR: ($CDCl_3$, 400 MHz) δ 8.40 (q, J = 8.8 Hz, 4H), 8.30 (dd, J = 8.8 Hz, J = 22 Hz, 4H), 7.22–7.24 (m, 1H), 7.14–7.15 (m, 2H), 5.44 (s, 2H), 3.88 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 164.7, 163.0, 151.4, 151.1, 150.9, 139.9, 135.6, 134.9, 131.7, 131.1, 123.9, 123.8, 123.1, 121.3, 113.1, 67.5, 56.3; IR (KBr): 1738, 1730, 1607, 1520, 1263, 1099, 852, 717 cm^{-1}; mp: 198–201 °C; MS (ESI): m/z (%) $[M + Na]^+$ = 475.4 (5); HRMS (ESI): m/z $[M + Na]^+$ calcd for $C_{22}H_{16}N_2O_9$ + Na: 475.0753; found 475.0761.

(*Z*,*E*)-Sinomenine oxime (6a). ^{1}H NMR: ($CDCl_3$, 400 MHz) δ 8.95 (s, 1H), 6.62 (d, J = 8.4 Hz, 1H), 6.53 (d, J = 8 Hz, 1H), 5.99 (s, 1H), 5.14 (d, J = 16 Hz, 1H), 4.90 (s, 1H), 3.80 (s, 3H), 3.52, (s, 3H), 2.43 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 150.9, 150.8, 144.9, 144.8, 131.0, 123.7, 118.0, 108.5, 104.6, 57.1, 55.9, 54.7, 47.8, 44.3, 42.7, 37.3, 35.9, 33.3, 24.1; IR (KBr): 3402, 2911, 2836, 1638, 1611, 1583, 1485, 1438, 1277, 1205, 1152, 1067, 809, 746 cm^{-1}; MS (ESI): m/z (%) $[M + H]^+$ = 345.6 (100), 346.8 (40), 348.3 (8), $[2M + H]^+$ = 689.6 (35), 690.5 (17), 691.4 (9), $[3M + H]^+$ = 1033.1 (3), $[M + Na]^+$ = 367.5 (4), $[2M + Na]^+$ = 711.5 (30), 712.6 (15), 713.7 (5), $[3M + Na]^+$ = 1055.2 (25), 1056.3 (15), 1057.3 (5); HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{19}H_{24}N_2O_4$ + H: 345.1814; found 345.1816.

(*Z*,*E*)-*N*-Phenyl sinomenine hydrazone (6b). ^{1}H NMR: ($CDCl_3$, 400 MHz) δ 7.84 (s, 1H), 6.53–7.27 (m, 7H), 6.03 (s,1H), 4.61–4.83 (m, 2H), 3.75–3.82 (m, 3H), 3.51–3.57 (m, 3H), 2.41–2.45 (m, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 153.2, 152.6, 145.5, 144.8, 144.5, 139.3, 131.1, 129.0, 128.9, 123.4, 119.7, 118.8, 118.5, 117.9, 114.3, 113.1, 112.2, 108.9, 102.3, 57.3, 56.0, 54.9, 54.3, 48.0, 47.7, 47.1, 44.8, 43.2, 42.7, 38.0, 37.8, 35.5, 34.0, 31.6, 29.0, 24.2, 22.5, 14.0; IR (KBr): 3492, 3346, 2933, 2839, 1601, 1503, 1485, 1438, 1278, 1204, 1160, 1055, 796, 750 cm^{-1}; MS (ESI): m/z (%) $[M + H]^+$ = 420.6 (100), 421.7 (70), 422.7 (33); HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{25}H_{29}N_3O_3$ + H: 420.2287; found 420.2288.

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