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Highly efficient synthesis of capsaicin analogues by condensation of vanillylamine and acyl chlorides in a biphase $H_2O/CHCl_3$ system

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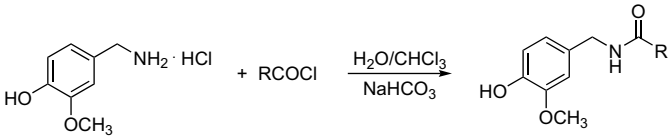
ABSTRACT

Highly efficient synthesis of capsaicin analogues was developed using condensation of vanillylamine with acyl chlorides in a biphase $H_2O/CHCl_3$ system under mild conditions. For C4–C18 aliphatic or aromatic acyl chlorides, the yields were up to 93–96% with high purity after a simple work-up procedure, and only 1–1.16 equiv of acyl chloride was needed in the reaction.

1. Introduction

Fruits of the red pepper (*Capsicum* spp.) have been used for centuries for their medicinal effects, primarily for stomach disorders and as topical counterirritants for relief of pain and inflammation.[1,2] These fruits contain capsaicin analogues (also called capsaicinoids) with a common structure comprising a group of acid amides of vanillylamine and fatty acids. In recent years, a wide variety of physiological and biological activities of capsaicinoids have been reported, including stimulation of the cardiovascular and respiratory systems, application as anti-nociceptive and anti-inflammatory analgesics, and use as neurotoxic drugs or enhancers of adrenal catecholamine secretion.[3–5] Individual capsaicinoids can be isolated from red peppers by TLC or HPLC techniques. However, the relative content of the components depends on the species and sort, and total concentrations can be very low. For example, it has been reported that capsaicin analogues with long alkyl side chains (C14–C20) have no pungency, but still stimulate adrenaline release and increase fat metabolism.[6–8] Unfortunately, these long-chain non-pungent capsaicin analogues are minor components in peppers and are hard to isolate from natural capsaicin. Thus, chemical synthesis of capsaicin analogues has been motivated by the search for spicy substitutes for natural capsaicin and the development of non-irritant drugs, antioxidants, and other useful substances.

The most convenient method for preparation of capsaicinoids is by selective acylation of vanillylamine with acyl chloride. However, vanillylamine is poorly soluble in anhydrous systems, and acyl chloride is easily hydrolysed when water is present, so it is very difficult to obtain a satisfactory yield. The first analogues of capsaicin, vanillylamides of saturated C2–C12 fatty acids and 10-undecylenic acid were synthesised by Nelson by acylation of vanillylamine with acyl chlorides or acid anhydrides in dry ether.[9] Although 2 equiv of vanillylamine was used, the yield was only 44–83%. Janusz et al. liberated the HCl from vanillylamine HCl in an aqueous soda solution and avoided using excess vanillylamine, but obtained yields of only 27–69% for DMF, THF or ether as co-solvent.[10] Kobata et al. reported the enzymatic synthesis of capsaicin analogues by reaction of vanillylamine HCl with fatty acid methyl esters, but only 8–28% yield was obtained.[11] Koreishi et al.[12] and Castillo et al.[13] reported the acylase- or lipase-catalysed synthesis of capsaicins with higher yields. Nevertheless, from an economic point of view, highly efficient base-catalysed condensation of vanillylamine and acyl chlorides is still the most practical method for preparation of capsaicin analogues. Here we report a highly efficient method for synthesis of capsaicin analogues by interfacial reaction of vanillylamine–H_2O with acyl chloride–$CHCl_3$ (Scheme 1).



Scheme 1.

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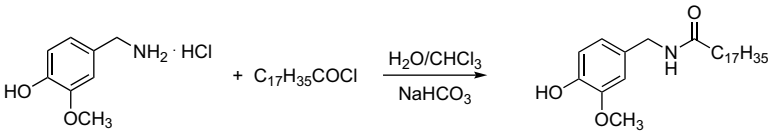
Table 1
Effect of temperature on the condensation reaction[a]



Run	*T* (°C)	Isolated yield (%)
1	12	88
2	18	96
3	25	96

[a] Reaction conditions: vanillylamine hydrochloride (28.04 mmol), stearoyl chloride (28.04 mmol), $NaHCO_3$ as base (91.7 mmol), reaction time 30 min.

2. Results and discussion

During condensation of acyl chloride and vanillylamine, which can be freed from its HCl in aqueous $NaHCO_3$, esterification of the phenolic hydroxyl and hydrolysis of the acyl chloride can occur, as well as the expected acylation of the amino group to produce the target compound. Hence, there are three competing reactions in this system. To inhibit side reactions, a biphase $H_2O/CHCl_3$ system was used. The reaction rate was adjusted by controlling the temperature and altering the reactant molar ratio.

2.1. Effect of temperature on condensation

Condensation with stearoyl chloride was used as the model reaction. The free vanillylamine base was dissolved in aqueous $NaHCO_3$ and added dropwise to a solution of stearoyl chloride in chloroform at different temperatures. The results are listed in Table 1.

The results in Table 1 reveal that when the reaction was carried out at 12 °C, only 88% yield of *N*-(4-hydroxy-3-methoxybenzyl)-octadecanamide was obtained (run 1, Table 1). TLC analysis revealed that stearic acid was formed. This suggests that the reaction rate was slower at lower temperature, leading to the hydrolysis of stearoyl chloride. For reaction at 18 °C, satisfactory results were obtained (run 2, Table 1). A further increase in temperature to 25 °C did not increase the yield. Therefore, the temperature of subsequent reactions was controlled at approximately 20 °C.

2.2. Influence of reactant molar ratio

It was found that the acyl chloride/vanillylamine molar ratio influenced the reaction selectivity (Table 2). For long-chain acyl chlorides such as stearoyl chloride, which have good hydrophobic property and it could present stably in the aqueous system, equimolar amounts of the acyl chloride and vanillylamine HCl gave an excellent result (run 1, Table 2). When a 10% molar excess of the acyl chloride was used, only 87% yield was obtained (run 2, Table 2) and a diacyl by-product compound was produced. For short-chain acyl chlorides such as butyryl chloride, equimolar amounts of the acyl chloride and vanillylamine gave an 89% yield (run 3, Table 2) owing to its hydrophility and it may hydrolyse partially in the aqueous system, so a slight excess of acyl chloride was needed. A change in molar ratio to 1.16:1 increased the yield of the product *N*-(4-hydroxy-3-methoxybenzyl)butanamide to 93% (run 4, Table 2).

Table 2
Influence of molar ratio on the condensation reaction[a]

Run	RCOCl	RCOCl/vanillylamine HCl molar ratio	Isolated yield (%)
1	$CH_3(CH_2)_{16}COCl$	1:1	96
2	$CH_3(CH_2)_{16}COCl$	1.10:1	87
3	$CH_3(CH_2)_2COCl$	1:1	89
4	$CH_3(CH_2)_2COCl$	1.16:1	93

[a] Reaction conditions: vanillylamine hydrochloride (28.04 mmol), $NaHCO_3$ as base (91.7 mmol); temperature 20 °C; reaction time 30 min.

2.3. Condensation of vanillylamine with various acyl chlorides in $H_2O/CHCl_3$

Under optimum reaction conditions, condensation of vanillylamine with various acyl chlorides was assayed. The results are summarised in Table 3.

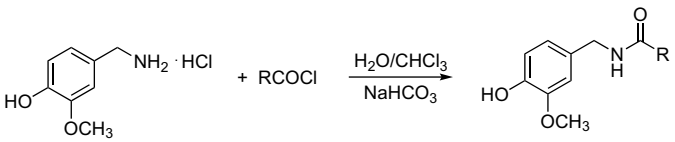
The results show that all the acyl chlorides selectively reacted with vanillylamine at the NH_2 position in the biphase system to produce the corresponding capsaicin derivatives. Regardless of the acyl chlorides used (saturated, unsaturated or aromatic) the yield isolated was 93–96%. We consider that the critical point for the excellent yield is the use of a biphase system, which slows down the rate of acyl chloride hydrolysis. Although Janusz et al. liberated the HCl from vanillylamine HCl in the same aqueous solution, they used DMF/THF as the organic solvent, which mixed with the water to form a homogeneous reaction system, and thus the reaction gave a lower yield.[10]

Owing to the special stability of benzoyl chloride, a yield of 96% of acylation product was obtained, and 2-Cl-substituted benzoyl chloride gave likewise excellent result, 94% yield.

It is worth noting that the free vanillylamine base is soluble in water and insoluble in $CHCl_3$, so it reacts with acyl chloride, which is soluble in $CHCl_3$, at the interface. A schematic drawing of this two-phase system is shown in Figure 1.

Since all these capsaicin derivatives are soluble in chloroform, the product can easily be separated after the reaction by decantation.

Table 3
Condensation of vanillylamine with acyl chlorides in $H_2O/CHCl_3$[a]



Run	Acyl chloride	RCOCl/vanillylamine HCl molar ratio	Isolated yield (%)
1	$CH_3(CH_2)_{16}COCl$	1:1	96
2	$CH_3(CH_2)_{14}COCl$	1:1	95
3	$CH_3(CH_2)_{12}COCl$	1:1	95
4	$CH_3(CH_2)_{10}COCl$	1:1	95
5	$CH_3(CH_2)_8COCl$	1:1	95
6	$(CH_3)_2CH(CH_2)_6COCl$	1:1	95
7	$CH_3(CH_2)_6COCl$	1:1	94
8	$CH_3(CH_2)_4COCl$	1.01:1	94
9	$CH_3(CH_2)_2COCl$	1.16:1	93
10	$CH_3(CH_2)_7CH{=}CH(CH_2)_7COCl$	1:1	96
11	C_6H_5COCl	1:1	96
12	$2\text{-}ClC_6H_4COCl$	1:1	94

[a] Reaction conditions: vanillylamine hydrochloride (28.04 mmol), $NaHCO_3$ as base (91.7 mmol), temperature 20 °C, reaction time 30 min.

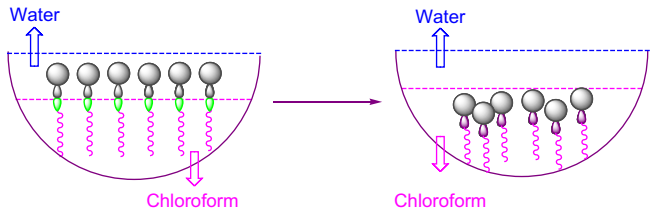


Figure 1. Schematic drawing of the condensation reaction.

3. Conclusions

We developed a highly efficient biphase reaction system for the preparation of vanillylamides with near equimolar acyl chlorides under mild conditions. This method avoids the hydrolysis of acyl chloride and diacylation of vanillylamine and improves the yield to 93–96%. High-purity capsaicinoid products were obtained after a simple work-up procedure.

4. Experimental

4.1. General remarks

Commercially available reagents and solvents were used without further purification. Melting points were measured using a Yanaco Mp 500 instrument and the thermometer was uncorrected. ^{1}H NMR spectra were recorded on a Bruker AM-500 MHz spectrometer with tetramethylsilane as the internal standard. Mass spectra were recorded by the EI method. All reactions were monitored by TLC. Flash column chromatography was carried out with silica gel at increased pressure.

4.2. General procedure

To a solution of vanillylamine hydrochloride (5.3 g, 28.04 mmol) in water (58 mL), $NaHCO_3$ (7.7 g, 91.7 mmol) was added. The mixture was stirred for 30 min at 20 °C and then chloroform (80 mL) was added. After stirring for 15 min, a solution of acyl chloride in chloroform (20 mL) was added dropwise. The mixture was stirred for 30 min (monitored by TLC) and then heated to 35–40 °C. The organic layer was separated and the water layer was extracted with chloroform (3×20 mL). The organic layer was washed with 2% HCl and brine and then dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure and the residue was subjected to flash column chromatography (if needed) to yield the product as a solid.

4.2.1. *N-(4-Hydroxy-3-methoxybenzyl)octadecanamide*

White solid; mp 93–95 °C [lit[14] 90–91 °C]; yield 11.28 g (96.0%); ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.86 (1H, d, J=8.0 Hz, ArH-5), 6.81 (1H, d, J=1.5 Hz, ArH-2), 6.76 (1H, dd, J=8.0, 1.5 Hz, ArH-6), 5.63 (1H, br s, OH), 5.60 (1H, s, NH), 4.35 (2H, d, J=5.5 Hz, H-7), 3.88 (3H, s, OCH_3), 2.20 (2H, t, J=7.5 Hz, H-2′), 1.65 (2H, m, H-3′), 1.30–1.26 (28H, m, H-4′–17′), 0.88 (3H, t, J=7.0 Hz, H-18′); MS (EI): m/z 419 $[M]^+$.

4.2.2. *N-(4-Hydroxy-3-methoxybenzyl)oleamide*

White solid; mp 31–33 °C [lit[14] 36 °C]; yield: 11.2 g (95.8%); ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.86 (1H, d, J=8.1 Hz, H-5), 6.80 (1H, d, J=1.6 Hz, H-2), 6.76 (1H, dd, J=8.0, 1.6 Hz, H-6), 5.64 (1H, br s, O*H*), 5.60 (1H, s, NH), 5.37–5.30 (2H, m, CH=CH), 4.35 (2H, d, J=5.6 Hz, NCH_2), 3.88 (3H, s, OCH_3), 2.19 (2H, t, J=7.5 Hz, H-2′), 2.04–1.98 (2H, m, H-3′), 1.66–1.62 (2H, m, H-4′), 1.29–1.26 (22H, m, H-5′–8′, H-11′–17′), 0.88 (3H, t, J=7.1 Hz, H-18′); MS (EI): m/z 417 $[M]^+$ (16), 137 $[M-RCONH]^+$ (100).

4.2.3. *N-(4-Hydroxy-3-methoxybenzyl)hexadecanamide*

White solid; mp 83–85 °C [lit[15] 79 °C]; yield 10.43 g (95.1%); ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.86 (1H, d, J=8.0 Hz, ArH-5), 6.81 (1H, d, J=1.5 Hz, ArH-2), 6.76 (1H, dd, J=8.0, 1.5 Hz, ArH-6), 5.62 (1H, br s, OH), 5.59 (1H, s, NH), 4.35 (2H, d, J=6.0 Hz, H-7), 3.88 (3H, s, OCH_3), 2.19 (2H, t, J=7.5 Hz, H-2′), 1.65 (2H, m, H-3′), 1.29–1.25 (24H, m, H-4′–15′), 0.88 (3H, t, J=7.0 Hz, H-16′); MS (EI): m/z 391 $[M]^+$, 195, 152, 137.

4.2.4. *N-(4-Hydroxy-3-methoxybenzyl)tetradecanamide*

White solid; mp 76–78 °C [lit[14] 76–77 °C]; yield 9.63 g (94.6%); ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.86 (1H, d, J=8.0 Hz, ArH-5), 6.81 (1H, d, J=1.5 Hz, ArH-2), 6.76 (1H, dd, J=8.0, 1.5 Hz, ArH-6), 5.64 (1H, s, OH), 5.60 (1H, s, NH), 4.35 (2H, d, J=5.5 Hz, H-7), 3.88 (3H, s, OCH_3), 2.19 (2H, t, J=7.0 Hz, H-2′), 1.64 (2H, m, H-3′), 1.29–1.25 (20H, m, H-4′–13′), 0.88 (3H, t, J=7.0 Hz, H-14′); MS (EI): m/z 363 $[M]^+$, 195, 152, 137.

4.2.5. *N-(4-Hydroxy-3-methoxybenzyl)dodecanamide*

White solid; mp 71–73 °C [lit[9] 60–61 °C]; yield 8.93 g (95.1%); ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.86 (1H, d, J=8.0 Hz, ArH-5), 6.81 (1H, d, J=1.5 Hz, ArH-2), 6.76 (1H, dd, J=8.0, 1.5 Hz, ArH-6), 5.61 (1H, s, OH), 5.59 (1H, s, NH), 4.35 (2H, d, J=5.5 Hz, H-7), 3.88 (3H, s, OCH_3), 2.19 (2H, t, J=7.0 Hz, H-2′), 1.65 (2H, m, H-3′), 1.27 (16H, m, H-4′, 5′, 6′, 7′, 8′, 9′, 10′, 11′), 0.88 (3H, t, J=7.0 Hz, H-12′); MS (EI): m/z 335 $[M]^+$, 195, 151, 137.

4.2.6. *N-(4-Hydroxy-3-methoxybenzyl)decanamide*

White solid; mp 48–50 °C [lit[10] 61–63 °C]; yield 8.15 g (94.7%); ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.86 (1H, d, J=8.0 Hz, ArH-5), 6.81 (1H, d, J=1.5 Hz, ArH-2), 6.76 (1H, dd, J=8.0, 1.5 Hz, ArH-6), 5.65 (1H, s, OH), 5.62 (1H, s, NH), 4.35 (2H, d, J=5.5 Hz, H-7), 3.88 (3H, s, OCH_3), 2.19 (2H, t, J=7.5 Hz, H-2′), 1.64 (2H, m, H-3′), 1.29–1.25 (12H, m, H-4′–9′), 0.87 (3H, t, J=7.0 Hz, H-10′); MS (EI): m/z 307 $[M]^+$, 195, 152, 137.

4.2.7. *N-(4-Hydroxy-3-methoxybenzyl)isodecanamide*

White solid; mp 62–64 °C [lit[14] 64–65 °C]; yield 8.13 g (94.5%); ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.86 (1H, d, J=8.0 Hz, ArH-5), 6.81 (1H, d, J=1.5 Hz, ArH-2), 6.76 (1H, dd, J=8.0, 1.5 Hz, ArH-6), 5.64 (1H, s, OH), 5.60 (1H, s, NH), 4.35 (2H, d, J=6.0 Hz, H-7), 3.88 (3H, s, OCH_3), 2.19 (2H, t, J=7.5 Hz, H-2′), 1.65 (2H, m, H-3′), 1.50 (1H, m, H-8′), 1.32–1.26 (6H, m, H-4′–6′), 1.15 (2H, m, H-7′), 0.85 (6H, d, J=6.5 Hz, H-9′, 10′); MS (EI): m/z 307 $[M]^+$.

4.2.8. *N-(4-Hydroxy-3-methoxybenzyl)octanamide*

White solid; mp 42–44 °C [lit[10] 44–45 °C]; yield 7.36 g (94.1%); ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.86 (1H, d, J=8.0 Hz, ArH-5), 6.81 (1H, d, J=1.5 Hz, ArH-2), 6.76 (1H, dd, J=8.0, 1.5 Hz, ArH-6), 5.64 (1H, s, OH), 5.62 (1H, s, NH), 4.35 (2H, d, J=6.0 Hz, H-7), 3.88 (3H, s, OCH_3), 2.19 (2H, t, J=7.5 Hz, H-2′), 1.65 (2H, m, H-3′), 1.31–1.26 (8H, m, H-4′, 5′, 6′, 7′), 0.87 (3H, t, J=7.0 Hz, H-8′); MS (EI): m/z 279 $[M]^+$.

4.2.9. *N-(4-Hydroxy-3-methoxybenzyl)hexanamide*

White solid; mp 58–60 °C [lit[10] 54–55 °C]; yield 6.58 g (93.6%); ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.86 (1H, d, J=8.0 Hz, ArH-5), 6.81 (1H, d, J=1.5 Hz, ArH-2), 6.76 (1H, dd, J=8.0, 1.5 Hz, ArH-6), 5.64 (1H, s, OH), 5.62 (1H, s, NH), 4.35 (2H, d, J=5.5 Hz, H-7), 3.88 (3H, s, OCH_3), 2.19 (2H, t, J=7.5 Hz, H-2′), 1.65 (2H, m, H-3′), 1.32 (4H, m, H-4′, 5′), 0.88 (3H, t, J=7.0 Hz, H-6′); MS (EI): m/z 251 $[M]^+$.

4.2.10. *N-(4-Hydroxy-3-methoxybenzyl)butanamide*

White solid; mp 74–76 °C [lit[9] 68–70 °C]; yield 5.80 g (92.9%); ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.86 (1H, d, J=8.5 Hz, ArH-5), 6.81 (1H, d, J=1.5 Hz, ArH-2), 6.76 (1H, dd, J=8.5, 1.5 Hz, ArH-6), 5.63 (1H, s, OH), 5.61 (1H, s, NH), 4.36 (2H, d, J=6.0 Hz, H-7), 3.88 (3H, s, OCH_3), 2.18 (2H, t, J=7.5 Hz, H-2′), 1.68 (2H, q, J=7.5 Hz, H-3′), 0.96 (3H, t, J=7.5 Hz, H-4′); MS (EI): m/z 223 $[M]^+$, 194, 152, 137.

4.2.11. *N-(4-Hydroxy-3-methoxybenzyl)benzoylamide*

White solid; mp 142–144 °C [lit[9] 140–142 °C]; yield 6.75 g (93.7%); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.78 (d, J=7.7 Hz, 2H), 7.50

(t, J=7.2 Hz, 1H), 7.42–7.45 (m, 2H), 6.90–6.84 (m, 3H), 6.33 (br s, 1H, OH), 5.61 (s, 1H, NH), 4.56 (d, J=5.6 Hz, 2H, H-7), 3.89 (s, 3H, OCH_3); MS (EI): m/z 257 $[M]^+$, 152, 105, 77.

4.2.12. 2-Chloro-[N-(4′-hydroxy-3′-methoxybenzyl)]benzoylamide

White solid; mp 157–159 °C; yield 7.81 g (95.7%); ^1H NMR (500 MHz, $CDCl_3$): δ 7.68 (d, J=7.6 Hz, 1H), 7.40–7.31 (m, 3H), 6.93 (s, 1H), 6.89–6.84 (m, 2H), 6.41 (br s, 1H, OH), 5.62 (s, 1H, NH), 4.58 (d, J=5.6 Hz, 2H, NCH_2), 3.89 (s, 3H, OCH_3); ^{13}C NMR (125 MHz, $CDCl_3$): δ 166.3 (C═O), 147.5, 145.4, 137.1, 130.7, 129.9, 129.8, 129.6, 128.8, 127.1, 119.7, 115.2, 111.5, 55.5, 42.2; MS (EI): m/z 291 $[M]^+$ (61), 256 $[M-Cl]^+$ (10), 139 $[2\text{-}ClC_6H_4CO]^+$ (100), 111 $[2\text{-}ClC_6H_4]^+$ (30); HRMS (EI) m/z calcd for $C_{15}H_{14}ClNO_3$ 291.0655, found 291.0662.

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Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2009.04.046.

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