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Homogeneous catalytic aminocarbonylation of 1-iodo-1-dodecene. The facile synthesis of odd-number carboxamides via palladium-catalysed aminocarbonylation

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ABSTRACT

Various amine nucleophiles including glycine methyl ester were used in the palladium-catalysed aminocarbonylation of (*E*)- and (*Z*)-1-iodo-1-dodecene. The substrates were synthesised from 1-dodecanal via the corresponding hydrazone, which was treated with iodine in the presence of tetramethylguanidine. The homogeneous catalytic aminocarbonylation resulted in the corresponding odd-number carboxamides in moderate to good yields. The reaction was accompanied by the formation of some carboxamides with triple bonds in the 2-position. The latter products were formed in relatively high yields with secondary amines such as piperidine and morpholine and were isolated as pure compounds.

1. Introduction

The various palladium-catalysed carbonylation reactions including aminocarbonylation are widely used in synthetic chemistry.[1] Both triflyloxi and iodo derivatives, i.e., aryl/enol-triflates and iodoarenes/iodoalkenes, respectively, have been used as substrates for the synthesis of unsaturated carboxamides and aryl carboxamides. The aminocarbonylation reaction has also been used both for the synthesis of simple building blocks and carboxamides attached to biologically important skeletons.[2,3] The reaction mechanism of the palladium-catalysed carbonylation has thoroughly been investigated by Yamamoto et al.[4,5]

Among the compounds of practical importance steroids,[6] alkaloids like tropene derivatives,[7] and haloindoles[8] with iodoalkene and bromoaryl moiety, respectively, have been functionalised by direct aminocarbonylation. Carbonylative cyclisation reactions have been performed leading to oxazolidinones,[9] free-radical-mediated carbonylation/cyclization reaction sequence leading to 2-piperidinones.[10] The palladium-catalysed carbonylative lactamization has served as a key step in the synthesis of the benzazocine core of a drug with anticancer activity.[11] Recently, a nickel-phosphite catalytic system was published as an efficient catalyst for the aminocarbonylation of aryl halides.[12] This way, the carboxylic acid → carboxylic halide → carboxamide reaction route was avoided, which results often in low yields especially with bulky substituents at the amide nitrogen. The application of various cyclic iodoalkenes as substrates is supported by the excellent yields, the relatively easy work-up of the catalytic mixtures, as well as green chemistry considerations, that is, the avoiding of fluorous containing leaving groups.

As described above, cyclic iodoalkenes have been used as substrates almost exclusively. Only sporadic results on aminocarbonylations carried out with open-chain iodoalkenes have been published.[13] However, our title 1-iodo-1-dodecenes were used in some coupling reactions. (*Z*)-1-Iodo-1-dodecene served as coupling agent in a Suzuki reaction[14] and as a dodecenyl-indium precursor[15] in the alkenylation reaction of α-halo carbonyl compounds. A mixture of (*Z*)- and (*E*)-1-iodo-1-dodecene was obtained via stannylation by bis(triphenylstannyl)zinc–TMEDA complex.[16] Both 1-iodo-1-dodecene isomers have been applied for the synthesis of the corresponding cyclopropylzinc derivative.[17] The iodine–magnesium exchange of (*Z*)- and (*E*)-1-iodo-1-dodecene proceeded with complete retention of configuration of the double bond. The resulting alkenylmagnesates were reacted with several electrophiles.[18]

As for the importance of long chain carboxamides, we have reported that long chain amino acid derivatives and dipeptides inhibit secreted human platelet phospholipase A_2.[19] We have also

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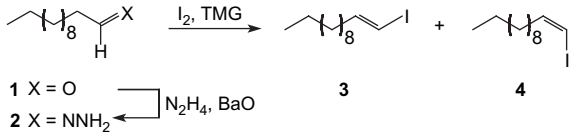
shown that long chain α-keto-carboxamides are potent inhibitors of human cytosolic phospholipase A_2 presenting very interesting antihyperalgesic activity.[20–22] In addition, long chain amides based on non-natural amino acids, like D-tyrosine have been reported as potent inhibitor of secreted phospholipase A_2.[23]

Encouraged by the increasing importance of unsaturated carboxamides, as well as the possibility of the synthesis of odd-number carboxylic acid derivatives (in the fatty acid 'region'), we decided to extend the scope of aminocarbonylation to open-chain iodoalkenes. Accordingly, the high-yielding aminocarbonylation of 1-iodo-1-dodecene, by using various primary and secondary amines including amino acid esters, is published in the present paper.

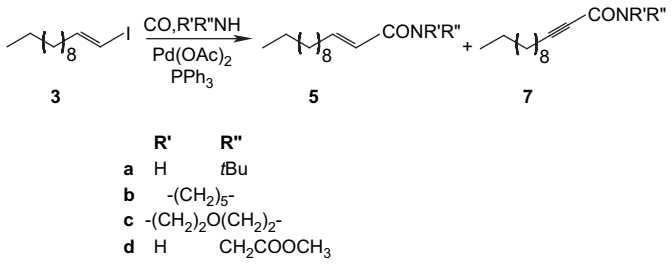
2. Results and discussion

The iodo-alkene substrate, (*E*)-1-iodo-1-dodecene (**3**), was synthesised from 1-dodecanal (**1**) via the corresponding hydrazone (**2**) in the presence of iodine and tetramethylguanidine (TMG) (Scheme 1). It has to be noted that the corresponding (*Z*)-isomer (**4**) was also formed in up to 15% yields depending on the reaction conditions. Furthermore, it was revealed by detailed GC–MS analysis that the reaction is accompanied by the formation of 1-iodo-1-dodecyne in traces (less than 2%). It has to be added that only the (*E*)-isomer (**3**) could be isolated as a pure compound. In spite of our efforts, the isolation of the minor (*Z*)-isomer (**4**) was not successful, i.e., it was isolated as a ca. 1:1 mixture of **3** and **4**.



Scheme 1. The synthesis of iodoalkenes **3** and **4**.

(*E*)-1-Iodo-1-dodecene (**3**) was reacted with *tert*-butylamine (**a**), piperidine (**b**), morpholine (**c**) and glycine methyl ester (**d**) under atmospheric carbon monoxide in the presence of in situ generated palladium(0)-triphenylphosphine catalysts (Scheme 2). Palladium(II) acetate was used as the catalytic precursor. The formation of Pd(0) species from the generally used $Pd(OAc)_2$–PPh_3 system has been proved by cyclic voltammetry and ^{31}P NMR spectroscopy.[24,25] The reduction of Pd(II) to Pd(0) is due to PPh_3, which is itself oxidised to triphenylphosphine oxide.



Scheme 2. Aminocarbonylation of **3**.

The aminocarbonylation of **3** by *tert*-butylamine as amine nucleophile resulted in the formation of the expected conjugated unsaturated carboxamide derivative **5a** with complete retention of the configuration of the double bond, i.e., no (*Z*)-carboxamide was obtained. Surprisingly, careful GC–MS analysis has shown that depending strongly on the reaction conditions, compound **7a** with triple bond could be detected as well even under mild reaction conditions (Table 1, entry 1). Practically complete conversion of the substrate was observed in all cases. The detailed investigations by using **a** as *N*-nucleophile revealed that the chemoselectivity towards **5a** depends on the carbon monoxide pressure. While at atmospheric pressure **5a** was found almost exclusively, the amount of **7a** increased drastically by increasing the carbon monoxide pressure. Compound **7a** was obtained in 33 and 70% under 20 and 95 bar CO pressure, respectively (Table 1, entries 2 and 5). It was also proved that dehydrogenation occurs during the carbonylation process, because if once the conversion is complete, no further change in the composition of the reaction mixture can be observed. It is worth noting that the formation of unsaturated 2-keto-carboxamide was not observed even in traces in the pressure range of 1–95 bar. According to a generally accepted reaction mechanism,[4,5] it means that no double carbon monoxide insertion occurs into the palladium–alkenyl bond formed via oxidative addition of the iodoalkenyl substrate (**3**). The palladium–acyl complex formed by simple carbon monoxide insertion undergoes aminolysis providing the corresponding carboxamide (**5a**) (vide infra).

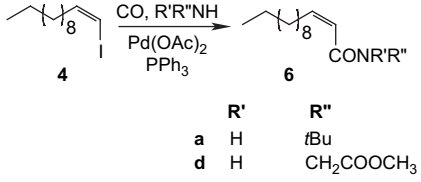
Table 1
Palladium-catalysed aminocarbonylation of (*E*)-1-iodo-1-dodecene (**3**)[a]

Entry	Amine	*p*(CO) (bar)	Reaction time (h)	Ratio of the carboxamide derivatives[b] (isolated yields)[c]	
				'trans-Amide', **5**	'Alkyne-amide', **7**
1	**a**	1	24	97 (**5a**); (71)	3 (**7a**); (n.d.)
2	**a**	20	24	67 (**5a**); (55)	33 (**7a**); (n.d.)
3	**a**	40	72	69 (**5a**); (55)	31 (**7a**); (n.d.)
4	**a**	40	24	68 (**5a**); (n.d.)	32 (**7a**); (n.d.)
5	**a**	95	116	30 (**5a**); (n.d.)	70 (**7a**); (58)
6[d]	**a**	95	60	22 (**5a**); (n.d.)	78 (**7a**); (62)
7[e]	**a**	90	310	17 (**5a**); (n.d.)	83 (**7a**); (69)
8	**b**	1	24	60 (**5b**); (51)	40 (**7b**); (27)
9	**b**	85	66	27 (**5b**); (n.d.)	73 (**7b**); (61)
10	**c**	85	66	25 (**5c**); (15)	75 (**7c**); (67)
11	**d**	1	24	>98 (**5d**); (73)	<2 (**7d**); (n.d.)

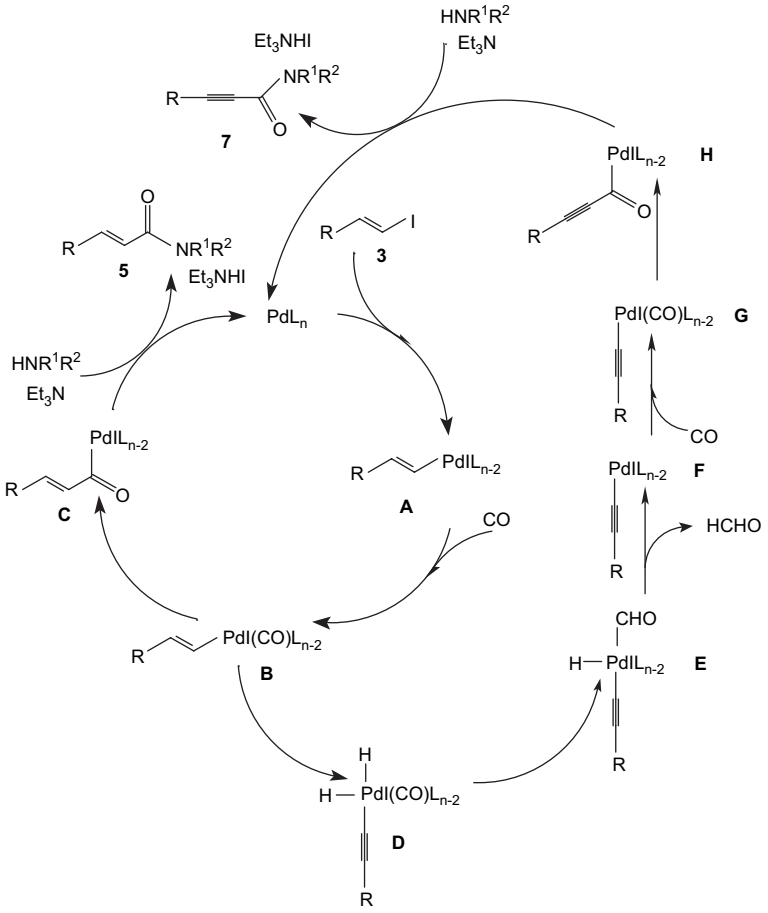
[a] Reaction conditions (unless otherwise stated): 1 mmol of **1**, 0.025 mmol of $Pd(OAc)_2$, 0.05 mmol PPh_3, 50 °C, solvent DMF. Conversion of the substrate was found higher than 98% in all cases.
[b] Determined by GC–MS.
[c] Isolated yields are based on the amount of the starting material (**1**).
[d] dppf (1,1′-bis(diphenylphosphino)ferrocene) was used instead of PPh_3.
[e] Temp: 70 °C.

A profound effect of the amine on the chemoselectivity was found. With secondary amines like piperidine and morpholine, in addition to the expected products **5b** and **5c**, the high-yielding formation of alkyne-type amides **7b** and **7c** was observed, respectively (entries 9 and 10). However, the use of glycine methyl ester (**d**), like that of the *tert*-butylamine, yielded the corresponding (*E*)-alkene-type carboxamide (**5d**) in high chemoselectivity. In case of **d**, the high tolerance of the aminocarbonylation reaction towards ester functionality was observed (entry 11).

Although not as pure starting material (ca. 1:1 mixture of **3** and **4**), **4** was also subjected to aminocarbonylation under the same conditions and the corresponding (*Z*)-carboxamides were obtained with **a** and **d** (Scheme 3). While the *tert*-butyl carboxamide with (*Z*) geometry (**6a**) was isolated in 28% yield, the corresponding *N*-methoxycarbonylmethyl compound (**6d**) could have been characterised by GC–MS only.



Scheme 3. Aminocarbonylation of **4**.



Scheme 4. A proposed mechanism for the formation of **5** and **7**.

Furthermore, it has to be noted that the aminocarbonylation of iodoalkene derivatives (in general) is accompanied by the carbonylation of the amines used in excess. This reaction is especially favoured with *tert*-butylamine where both *N*,*N*′-di-*tert*-butyl-urea and *N*,*N*′-di-*tert*-butyl-oxalylamide were formed (the latter in relatively small amount) in mono- and double carbonylation reaction, respectively.

The formation of the two types of unsaturated amides (**5** and **7**) can be rationalised as follows on the basis of a simplified reaction mechanism (Scheme 4). The oxidative addition of the iodoalkene (**3**) to palladium(0) complexes (PdL_n, where L stands for triphenylphosphine and solvent donor ligands), formed in situ from palladium(II)-acetate and triphenylphosphine, resulted in the corresponding iodo-alkenyl-palladium catalytic intermediate (**A**). It is followed by carbon monoxide activation yielding a complex with a terminal carbonyl ligand (**B**). The carbon monoxide insertion into the palladium–alkenyl bond results in the corresponding highly reactive palladium–acyl complex (**C**). From one side, the reaction of this catalytic intermediate with a primary or secondary amine provides the organic product (**5**), from the other side, the reductive elimination of the hydrogen iodide from the hydrido-iodo-palladium intermediate provided the palladium(0) 'starting' complex.

The formation of the unexpected '2-yn carboxamide' (**7**) can be explained as follows. By the intermediacy of palladium(IV)-alkynyl species (**D** and **E**), i.e., the formation of a formyl complex and the reductive elimination of formaldehyde, an iodo-alkynyl palladium(II) intermediate (**F**) can be obtained. The relatively high stability of the Pd-alkynyl catalytic intermediates was already observed in Stille coupling when ethynyl-stannane was used.[26] On the other hand, the palladium(IV) complexes, like the widely known trimethyl compounds $PdX(L–L)Me_3$, are much less stable than the corresponding platinum(IV) complexes, being susceptible to reductive elimination.[27,28] This way, although the intermediacy of palladium(IV) species of this type is highly speculative, their fast reduction to palladium(II) upon reductive elimination of formaldehyde could be justified (**D**→**E**→**F** reaction sequence). (It is worth noting that in case of the most widely used cyclic enoltriflates/iodoalkenes there is no possibility to form carbon–carbon triple bonds from clear structural reasons. Consequently, no side-reactions leading to acetylenic carboxamides could be observed.)

The carbon monoxide activation (**G**) and its insertion, resulting in the corresponding acyl complex (**H**), is followed by aminolysis and reductive elimination of hydrogen iodide (see above). This way, the reactive, coordinatively unsaturated palladium(0) complex is re-formed.

The influence of the increased carbon monoxide pressure on the formation of **7** still needs further mechanistic investigations.

3. Conclusion

Palladium-catalysed aminocarbonylation proved to be an efficient method for the functionalisation of open-chain iodoalkenes using simple primary and secondary amines including amino acid esters as *N*-nucleophiles. The aminocarbonylation of even-number iodoalkenes, easily available from the corresponding even-number aldehydes of practical importance, can be carbonylated to odd-number linear carboxamides of 'low' availability in nature under very mild reaction conditions. This way, a protocol for a facile chain

lengthening by one carbon was described: based on an aldehyde, a higher carboxamide could be obtained by using a simple reaction sequence.

4. Experimental

4.1. General procedures

^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ on a Varian Inova 400 spectrometer at 400.13 MHz and 100.62 MHz, respectively. Chemical shifts δ are reported in parts per million relative to $CHCl_3$ (7.26 and 77.00 ppm for ^{1}H and ^{13}C, respectively). Elemental analyses were measured on a 1108 Carlo Erba apparatus. Samples of the catalytic reactions were analysed with a Hewlett–Packard 5830A gas chromatograph fitted with a capillary column coated with OV-1.

The iodoalkene substrate (**3**) was synthesised according to a described method.[29,30] However, due to some modifications, a detailed description of the synthetic procedure is given below. (It has to be noted that an independent iodogermylation process was described for the synthesis of (*Z*)-1-iodo-1-dodecene.[31]) The amine reactants and 1-dodecanal were purchased from Aldrich and used without further purification for aminocarbonylation and for the synthesis of **3**, respectively.

4.2. Synthesis of 3

Dodecanal (**1**) (10 g, 54.3 mmol), freshly distilled hydrazine hydrate (98%, 13.84 g, 276.8 mmol) and triethylamine (54.90 g, 542.6 mmol, 75.52 mL) in ethanol (100 mL) were refluxed for a day. After completion of the reaction the mixture was concentrated under reduced pressure. The residue was dissolved in chloroform (150 mL), and washed with water and brine. It was dried over sodium sulfate and evaporated to give dodecanal-hydrazone derivative (**2**). The product was used in the next step without further purification.

To a stirred solution of iodine (13.25 g, 52.2 mmol) in diethyl ether (80 mL), 1,1,3,3-tetramethylguanidine (TMG, 26.13 g, 226.9 mmol) was added slowly and cooled by iced water bath during the addition. The solid hydrazone derivative (**2**) (5 g 25.2 mmol) was added at room temperature over 3 h. After the addition was complete, the mixture was stirred vigorously for an hour. Then the solvent was evaporated and the residue was heated at 90 °C under argon atmosphere for 2 h. The mixture was poured onto water and extracted with diethyl ether. The combined organic layer was washed with 1 N aqueous HCl, water, 5% aqueous $NaHCO_3$, water, saturated aqueous $Na_2S_2O_3$ and water again, dried on sodium sulfate and evaporated. Purification by column chromatography (silica gel, hexane) gave pure (**3**) as a pale yellow oil. Yield: 1.14 g; 15.4%.

4.3. Characterisation of the iodoalkene products

*4.3.1. (E)-1-Iodo-1-dodecene (**3**)*

^{1}H NMR ($CDCl_3$) δ: 6.49 (dt, J=7.2, 14.3 Hz, 1H, =CH), 5.96 (dt, J=14.3, 1.5 Hz, 1H, =CH), 2.04 (dq, J=7.2, 1.5 Hz, 2H, CH_2), 1.2–1.4 (m, 16H, chain methylenes), 0.87 (t, J=6.8 Hz, 3H, CH_3). ^{13}C NMR ($CDCl_3$) δ: 147.0, 74.4, 36.3, 32.1, 29.6, 29.5, 29.3, 29.0, 28.8, 28.3, 22.9, 14.3. IR (KBr, (cm^{-1})): 2931 (ν_{as}-CH_3), 2922 (ν_{as}-CH_2), 2854 (ν_s-CH_2), 1670 (ν-C=C), 1465 (β-CH_2). MS m/z (rel int. %): 294 (34) (M^+), 167 (39), 154 (15), 111 (17), 97 (57), 83 (87), 69 (100), 55 (98). Anal. Calcd for $C_{12}H_{23}I$ (294.22): C, 48.99; H, 7.88. Found: C, 48.78; H, 7.61. R_f (hexane) 0.80. Pale yellow viscous material.

*4.3.2. (Z)-1-Iodo-1-dodecene (**4**)*

^{1}H NMR ($CDCl_3$) δ: 6.81 (dt, J=7.2, 10.3 Hz, 1H, =CH), 6.13 (dt, J=10.3, 1.1 Hz, 1H, =CH), 2.10–2.14 (m, 2H, CH_2), 1.2–1.4 (m, 16H, chain methylenes), 0.87 (t, J=6.8 Hz, 3H, CH_3). ^{13}C NMR ($CDCl_3$) δ: 141.7, 82.3, 35.0, 32.0, 29.6, 29.5, 29.3, 29.0, 28.8, 28.3, 22.8, 14.3. IR (KBr, (cm^{-1})): 2930 (ν_{as}-CH_3), 2922 (ν_{as}-CH_2), 2855 (ν_s-CH_2), 1666 (ν-C=C), 1466 (β-CH_2). MS m/z (rel int. %): 294 (23) (M^+), 167 (30), 154 (13), 111 (22), 97 (62), 83 (90), 69 (100), 55 (99). R_f (hexane) 0.82. (The spectral data above were obtained as a ca. 1:1 mixture with **3** and are in good agreement with those published earlier.[31])

4.4. Aminocarbonylation experiments at normal pressure

In a typical experiment a solution of $Pd(OAc)_2$ (5.6 mg, 0.025 mmol), PPh_3 (13.1 mg, 0.05 mmol), 0.5 mmol iodo substrate (**3**), 1.5 mmol *tert*-butylamine (or 0.65 mmol other amines including amino acid methyl esters) were dissolved in DMF (10 mL) under argon. Triethylamine (0.5 mL) was added to the homogeneous yellow solution and the atmosphere was changed to carbon monoxide. The colour changed to dark red. The reaction was conducted under the given reaction conditions (see Table 1). Some metallic palladium was formed at the end of the reaction, which was filtered. (A sample of this solution was immediately analysed by GC–MS.) The mixture was then concentrated and evaporated to dryness. The residue was dissolved in chloroform (20 mL) and washed with water (20 mL). The organic phase was thoroughly washed twice with 5% HCl (20 mL), saturated $NaHCO_3$ (20 mL), brine (20 mL), dried over Na_2SO_4 and concentrated to a yellow waxy material or a thick oil. Chromatography (silica, chloroform then chloroform/ethanol=1:1) yielded the desired compounds as yellow solids.

4.5. Aminocarbonylation experiments at high pressure

The DMF solution of the catalyst precursor and reactants (amounts given in Section 4.3) was transferred under argon into a 100 mL stainless steel autoclave. The reaction vessel was pressurised up to 40 bar total pressure with carbon monoxide and the magnetically stirred mixture was heated in an oil bath at 50 °C for 6 h. The work-up procedure is identical with that given above.

4.6. Characterisation of the amide products

*4.6.1. (E)-Tridec-2-enoic acid tert-butylamide (**5a**)*

^{1}H NMR ($CDCl_3$) δ: 6.70 (dt, J=7.2, 15.3 Hz, 1H, =CH), 5.65 (d, J=15.3 Hz, 1H, =CH), 5.40 (br s, 1H, NH), 2.10 (q, J=7.2 Hz, 2H, CH_2), 1.32 (s, 3H, ^{t}Bu), 1.2–1.4 (m, 16H, chain methylenes), 0.82 (t, J=6.8 Hz, 3H, CH_3). ^{13}C NMR ($CDCl_3$) δ: 165.4, 143.8, 124.7, 51.1, 31.8, 29.6, 29.5, 29.4, 29.3, 29.1, 28.8, 28.3, 22.6, 14.0. IR (KBr, (cm^{-1})): 3293 (NH), 1668 (CON), 1632 (C=C). MS m/z (rel int. %): 267 (17) (M^+), 252 (60), 212 (93), 195 (99), 154 (7), 128 (67), 98 (20), 58 (100). Anal. Calcd for $C_{17}H_{33}NO$ (267.46): C, 76.34; H, 12.44; N, 5.24. Found: C, 76.20; H, 12.60; N, 5.05. R_f (5% EtOAc/$CHCl_3$) 0.71. Yellow viscous material.

*4.6.2. (Z)-Tridec-2-enoic acid tert-butylamide (**6a**)*

^{1}H NMR ($CDCl_3$) δ: 5.80–5.85 (m, 1H, =CH), 5.59 (d, J=10.2 Hz, 1H, =CH), 5.35 (br s, 1H, NH), 2.55 (m, 2H, CH_2), 1.33 (s, 3H, ^{t}Bu), 1.2–1.4 (m, 16H, chain methylenes), 0.82 (t, J=6.8 Hz, 3H, CH_3). ^{13}C NMR ($CDCl_3$) δ: 165.7, 144.2, 123.6, 51.3, 31.8, 29.6, 29.5, 29.4, 29.3, 29.1, 28.8, 28.3, 22.6, 14.1. MS m/z (rel int. %): 267 (20) (M^+), 252 (7), 212 (15), 195 (19), 154 (34), 98 (100). Anal. Calcd for $C_{17}H_{33}NO$ (267.46): C, 76.34; H, 12.44; N, 5.24. Found: C, 76.22; H, 12.55; N, 5.09. R_f (5% EtOAc/$CHCl_3$) 0.73. Yellow viscous material.

*4.6.3. Tridec-2-ynoic acid tert-butylamide (**7a**)*

^{1}H NMR ($CDCl_3$) δ: 5.52 (br s, 1H, NH), 2.21 (t, J=7.1 Hz, 2H, CH_2), 1.50 (br qi, J=7.1 Hz, 2H, CH_2), 1.36 (s, 3H, ^{t}Bu), 1.2–1.4 (m, 14H, chain methylenes), 0.84 (t, J=6.8 Hz, 3H, CH_3). ^{13}C NMR ($CDCl_3$) δ: 159.6, 152.7, 85.1, 76.6, 52.0, 31.8, 29.5, 29.4, 29.3, 29.0, 28.9, 28.6, 28.2, 27.8, 22.6, 18.5, 14.0. IR (KBr, (cm^{-1})): 3329 (NH), 2241 (C≡C), 1634 (CON). MS m/z (rel int. %): 265 (10) (M^+), 250 (94), 210 (100), 193 (12), 152 (5), 58 (42). Anal. Calcd for $C_{17}H_{31}NO$ (265.44): C, 76.92; H, 11.77; N, 5.28. Found: C, 77.08; H, 11.95; N, 4.98. R_f (3% EtOAc/$CHCl_3$) 0.58. Yellow viscous material.

*4.6.4. (E)-1-(Piperidin-1-yl)-tridec-2-en-1-one (**5b**)*

^{1}H NMR ($CDCl_3$) δ: 6.78 (dt, J=7.1, 15.1 Hz, 1H, =CH), 6.20 (d, J=15.1 Hz, 1H, =CH), 3.40–3.60 (m, 4H, $N(CH_2)_2$), 2.15 (q, J=7.2 Hz, 2H, CH_2), 1.58–1.63 (m, 2H, CH_2), 1.48–1.55 (m, 4H, 2×CH_2), 1.40 (qi, J=7.2 Hz, 2H, CH_2), 1.25 (br s, 14H, chain methylenes), 0.84 (t, J=6.8 Hz, 3H, CH_3). ^{13}C NMR ($CDCl_3$) δ: 165.6, 145.8, 120.3, 46.8 (br), 43.0 (br), 32.5, 31.9, 29.6, 29.5, 29.4, 29.3, 29.2, 28.4, 26.6, 25.6, 24.6, 22.6, 14.0. IR (KBr, (cm^{-1})): 1659 (CON), 1620 (C=C). MS m/z (rel int. %): 279 (16) (M^+), 250 (4), 222 (3), 180 (12), 166 (100), 138 (63), 127 (30), 84 (30). Anal. Calcd for $C_{18}H_{33}NO$ (279.47): C, 77.36; H, 11.90; N, 5.01. Found: C, 77.28; H, 12.11; N, 4.88. R_f (10% EtOAc/$CHCl_3$) 0.50. Yellow viscous material.

*4.6.5. 1-(Piperidin-1-yl)-tridec-2-yn-1-one (**7b**)*

^{1}H NMR ($CDCl_3$) δ: 3.65 (br t, J=5.6 Hz, 2H, NCH_2), 3.53 (br t, J=5.6 Hz, 2H, NCH_2), 2.32 (t, J=7.2 Hz, 2H, CH_2), 1.48–1.66 (m, 6H, 3×CH_2), 1.37 (br qi, J=7.2 Hz, 2H, CH_2), 1.25 (br s, 14H, chain methylenes), 0.85 (t, J=6.8 Hz, 3H, CH_3). ^{13}C NMR ($CDCl_3$) δ: 153.1, 93.1, 73.9, 48.1, 42.2, 31.9, 29.5, 29.4, 29.3, 29.0, 28.9, 27.8, 26.4, 25.3, 24.5, 22.6, 18.9, 14.0. IR (KBr, (cm^{-1})): 1632 (CON), 2240 (C≡C). MS m/z (rel int. %): 277 (3) (M^+), 248 (5), 220 (7), 207 (21), 178 (5), 164 (55), 150 (100), 136 (12), 84 (40). Anal. Calcd for $C_{18}H_{31}NO$ (277.45): C, 77.92; H, 11.26; N, 5.05. Found: C, 77.81; H, 11.32; N, 4.92. R_f (10% EtOAc/$CHCl_3$) 0.74. Yellow viscous material.

*4.6.6. (E)-1-(Morpholin-4-yl)-tridec-2-en-1-one (**5c**)*

^{1}H NMR ($CDCl_3$) δ: 6.86 (dt, J=7.1, 15.0 Hz, 1H, =CH), 6.15 (d, J=15.0 Hz, 1H, =CH), 3.50–3.65 (m, 8H, 2×$(CH_2)_2$), 2.15 (q, J=7.3 Hz, 2H, CH_2), 1.40 (qi, J=7.3 Hz, 2H, CH_2), 1.25 (br s, 14H, chain methylenes), 0.84 (t, J=6.7 Hz, 3H, CH_3). ^{13}C NMR ($CDCl_3$) δ: 165.8, 147.3, 119.3, 66.8, 46.0 (br), 42.2 (br), 32.6, 31.8, 29.6, 29.5, 29.4, 29.3, 29.2, 28.3, 22.6, 14.1. IR (KBr, (cm^{-1})): 1660 (CON), 1624 (C=C). MS m/z (rel int. %): 281 (17) (M^+), 252 (5), 210 (6), 195 (23), 168 (32), 140 (100), 129 (23), 114 (12), 86 (32). Anal. Calcd for $C_{17}H_{31}NO_2$ (281.44): C, 72.55; H, 11.10; N, 4.98. Found: C, 72.39; H, 11.22; N, 4.80. R_f (30% EtOAc/$CHCl_3$) 0.45. Yellow viscous material.

*4.6.7. 1-(Morpholin-4-yl)-tridec-2-yn-1-one (**7c**)*

^{1}H NMR ($CDCl_3$) δ: 3.60–3.72 (m, 8H, 2×$(CH_2)_2$), 2.32 (t, J=7.2 Hz, 2H, CH_2), 1.54 (qi, J=7.2 Hz, 2H, CH_2), 1.32–1.40 (m, 2H, CH_2), 1.25 (br s, 12H, chain methylenes), 0.84 (t, J=6.8 Hz, 3H, CH_3). ^{13}C NMR ($CDCl_3$) δ: 153.4, 94.2, 73.3, 66.9, 66.5, 47.2, 41.8, 31.8, 29.5, 29.4, 29.3, 29.0, 28.9, 27.8, 22.6, 18.9, 14.1. IR (KBr, (cm^{-1})): 2240 (C≡C), 1650 (CON). MS m/z (rel int. %): 279 (6) (M^+), 250 (12), 209 (58), 166 (59), 153 (45), 123 (30), 86 (100). Anal. Calcd for $C_{17}H_{29}NO_2$ (279.42): C, 73.07; H, 10.46; N, 5.01. Found: C, 72.88; H, 10.54; N, 4.89. R_f (20% EtOAc/$CHCl_3$) 0.56. Yellow crystalline material, mp 40–41 °C.

*4.6.8. ((E)-Tridec-2-enoylamino)-acetic acid methyl ester (**5d**)*

^{1}H NMR ($CDCl_3$) δ: 6.82 (dt, J=7.1, 15.5 Hz, 1H, =CH), 6.00 (br s, 1H, NH), 5.80 (d, J=15.5 Hz, 1H, =CH), 4.07 (d, J=5.2 Hz, 2H, CH_2COO), 3.75 (s, 3H, OCH_3), 2.15 (q, J=7.3 Hz, 2H, CH_2), 1.38–1.42 (m, 2H, CH_2), 1.25 (br s, 14H, chain methylenes), 0.85 (t, J=6.8 Hz, 3H, CH_3). ^{13}C NMR ($CDCl_3$) δ: 170.6, 166.0, 146.0, 122.7, 52.3, 41.2, 32.0, 31.9, 29.6, 29.5, 29.4, 29.3, 29.1, 28.2, 22.6, 14.1. IR (KBr, (cm^{-1})): 3305 (NH), 1745 (COO), 1671 (CON), 1633 (C=C). MS m/z (rel int. %): 283 (4) (M^+), 252 (5), 195 (100), 152 (10), 131 (15), 81 (25), 55 (47). Anal. Calcd for $C_{16}H_{29}NO_3$ (283.41): C, 67.81; H, 10.31; N, 4.94. Found: C, 67.70; H, 10.45; N, 4.79. R_f (30% EtOAc/$CHCl_3$) 0.59. Pale-yellow crystalline material, mp 64–65 °C.

*4.6.9. ((Z)-Tridec-2-enoylamino)-acetic acid methyl ester (**6d**)*

MS m/z (rel int. %): 283 (8) (M^+), 252 (10), 195 (27), 194 (32), 152 (31), 131 (20), 81 (100), 55 (67) (obtained in catalytic mixture only).

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