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Efficient Preparations of Acylamides, Acylcarbamates and Acylureas from Alk-1-en-2-yl Esters

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ABSTRACT: Acylamides, acylcarbamates and acylureas have been synthesized by acylation of amides, carbamates and ureas sodium salts with alk-1-en-2-yl esters prepared with $[Ru(\mu\text{-}O_2CH)(CO)_2(PPh_3)]_2$ as catalyst.

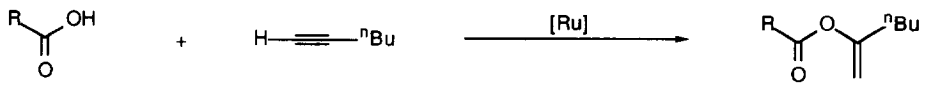
Due to the discovery of their biological activity, *N*-acylcarbamates and *N*-acylureas have undergone a rapid development as pesticides[1] and pharmaceuticals.[2] During the last decade, polymerizable acryloyl carbamates and ureas have found applications as materials containing functional side chains.[3] Optically active acylureas are efficient chiral auxiliaries for the synthesis of optically pure cyclic carboxylic acids[4] and β-hydroxypropionates.[5]

Preparations of acylamides involve acylation of amides with classical reagents such as anhydrides,[6,7] acyl chlorides[8] or ketenes.[9] More recently trichloromethyl carbonyl compounds have also been used.[10] The coupling of amides with isocyanates,[1] carbonates[11] and trichloromethyl carbonyl compounds[10,12] leads to acylated amide derivatives, whereas the condensation of amines or alcohols with acylisocyanates, generated from oxalyl chloride and amines,[13] or acyl chloride and sodium cyanate[14] gives acylureas and acylcarbamates, respectively. The activation of carboxylic acids by addition to carbodiimides is also a convenient route to prepare acylureas.[15]

The straightforward preparation of alk-1-en-2-yl esters, *via* ruthenium-catalyzed regioselective addition of carboxylic acids to the C(2) carbon atom of terminal alkynes has been reported[16] and their usefulness for selective acylation of nucleophiles has been demonstrated,[17] as in formylation of amines and alcohols,[18] protection of amino acids,[19] and preparation of lactones.[20] We now show that the $[Ru(\mu\text{-}O_2CH)(CO)_2(PPh_3)]_2$ catalyst[21] promotes the transformation of deactivated aryl carboxylic acids into alk-1-en-2-yl esters which provides an easy access to acylamides, acylcarbamates and acylureas under mild conditions, and thus competes with the use of traditional reagents derived from phosgene.

PREPARATION OF HEX-1-EN-2-YL ESTERS

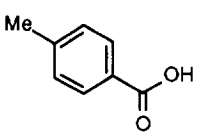
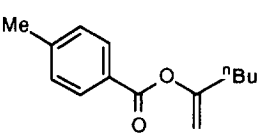
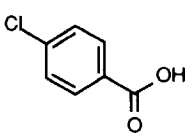
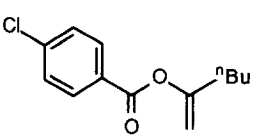
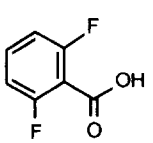
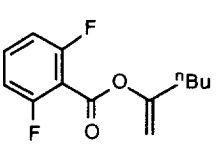
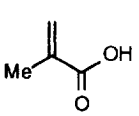
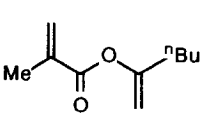
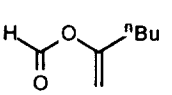
The direct preparation of alk-1-en-2-yl esters from terminal alkynes and carboxylic acids has been made possible by the use of ruthenium catalysts such as (*cyclo*-octadienyl)$_2$Ru,[22] (arene)RuCl$_2$(PR$_3$)[16] or ((arene)RuCl$_2$)$_2$[23] which improve the regioselectivity of the Markovnikov addition. Whereas classical (arene)RuCl$_2$(PR$_3$) catalysts exhibited a poor activity for the addition of halogenated aromatic acids to alkynes, we have found that the binuclear complex [Ru(O$_2$CH)(CO)$_2$(PPh$_3$)]$_2$, which was a very active catalyst for the addition of α-hydroxy acids to alkynes[21] and alkynols,[24] is efficient for the obtention of their alk-1-en-2-yl ester derivatives.



1-5

Scheme 1

Table1. Synthesis of Hex-1-en-2-yl Esters from Hex-1-yne in the Presence of [Ru(O$_2$CH)(CO)$_2$(PPh$_3$)]$_2$

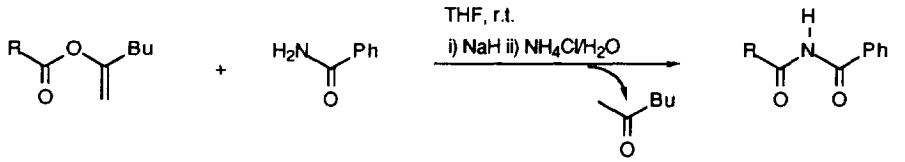
Carboxylic acid	Hex-1-en-2-yl Ester		Yield (%)	Regioselectivity (%)
		**1**	94	94
		**2**	94	93
		**3**	95	85
		**4**	91	>99
		**5**	94	>99

Thus, in the presence of 0.1 mmol of $[Ru(O_2CH)(CO)_2(PPh_3)]_2$, the regioselective addition of 30 mmol of carboxylic acid to 33 mmol of hex-1-yne in 30 ml of toluene at 110 °C for 15-18 h afforded hex-1-en-2-yl esters **1-3** according to Scheme 1. These aromatic hex-1-en-2-yl esters were obtained in very good yields and regioselectivities were higher than 85% as determined by ^1H NMR and GLC (Table 1). Under similar conditions, but at 80 °C in hexane, aliphatic hex-1-en-2-yl esters **4-5** were produced in high yields. The halogenated aromatic esters **2** and **3** were selected because of the potential of their derivatives in phytochemistry,[1] the methacrylic ester **4** for the chemical reactivity of the double bond and the possibility of preparing polymerizable derivatives,[3] and the formate **5** for the interest of producing a stable and easy to handle reagent for formylation of amines and alcohols.[18] These compounds were isolated by distillation under reduced pressure and characterized spectroscopically and by satisfactory elemental analyses.

ACYLATION OF AMIDE DERIVATIVES

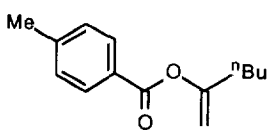
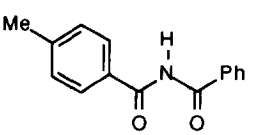
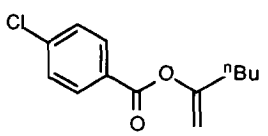
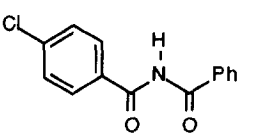
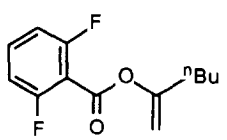
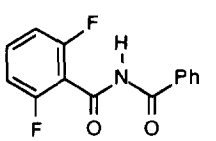
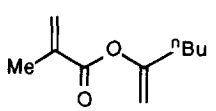
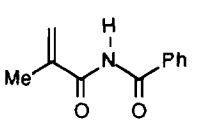
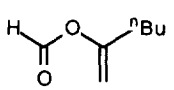
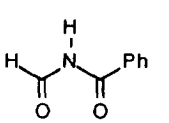
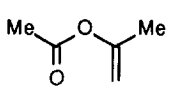
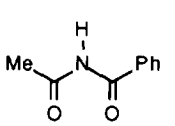
Alkenyl esters are known to acylate ammonia and primary amines under very mild conditions.[17-19] Acylation of secondary amines and hydroxy groups usually requires the presence of an acylation catalyst like imidazole,[18] *N,N*-dimethylaminopyridine or triethylamine,[17b] potassium cyanide,[19] or enzymes.[20] Due to the weak nucleophilicity of the amide group, acylation of amides could not be directly effected with alkenyl esters, e.g. in tetrahydrofuran at 25 °C in the presence of an acylation catalyst such as potassium cyanide and *N,N*-dimethylaminopyridine, or at 60 °C in the presence of 10 mol% of DBN. We have shown that amide salts, generated by simple treatment of primary amides with sodium hydride, were acylated by alkenyl esters to form acylamides according to Scheme 2. Thus, 5 mmol of benzamide, 5.5 mmol of enol ester and 7.5 mmol of NaH reacted at room temperature in 20 ml of tetrahydrofuran to produce acylbenzamides **7-12** (Table 2). Under typical conditions, 1.5 equivalent of NaH was added to the mixture of enol ester and amide in a tetrahydrofuran solution, as the reaction with only one equivalent of the dispersion of NaH in mineral oil led to lower yields in acylated compounds (method A). From hex-1-en-2-yl formate **5** and isopropenyl acetate **6**, which readily reacted with NaH, the sodium salt had to be formed before the addition of the enol ester (method B). The acylbenzamides were isolated in good yields after hydrolysis with a saturated ammonium chloride solution and continuous extraction with diethylether. Hex-1-en-2-yl esters **1-5** exhibited comparable efficiencies and the use of commercial isopropenyl acetate led to acetylbenzamide **12** in 86% yield. Isopropenyl acetate is much more reactive than alkyl esters since no acylation takes place when the benzamide salt is treated at room temperature for 24 h with ethyl acetate. The generation of amide salts by deprotonation of amides with ^{t}BuOK was also

possible,[25] but yields in acylamides were decreased due to the side reaction of the nucleophilic *tert*-butylate with enol esters to produce *tert*-butylate esters. Thus, 2 mmol of hex-1-en-2-yl benzoate reacted with 2.1 mmol of ^{t}BuOK in 5 ml of tetrahydrofuran at room temperature for 2 h to produce *tert*-butylbenzoate in 71% isolated yield.



Scheme 2

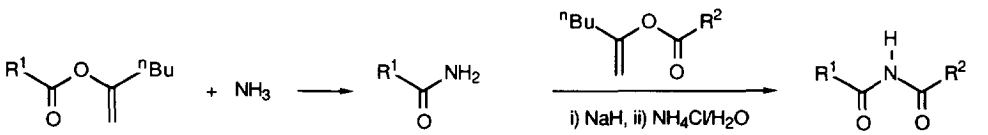
Table 2. Preparation of Acylbenzamides from Benzamide and Hex-1-en-2-yl Esters

Hex-1-en-2-yl Ester	Acylbenzamide		Reaction time (h)	Yield (%)
		**7**	4	83[a]
		**8**	6	78[a]
		**9**	3	93[a]
		**10**	1	60[a]
		**11**	2.5	78[b]
		**12**	1	86[b]

Reagents and conditions : benzamide (5 mmol), enol ester (5.5 mmol), NaH (7.5 mmol), tetrahydrofuran (20 ml), room temperature, [a] method A, [b] method B (methods A and B are described in the experimental section)

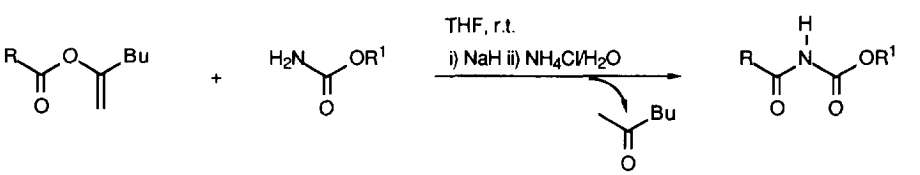
Similar syntheses of acylamides involve the acylation of amides with anhydrides in the presence of a strong acid at high temperatures and yields are moderate.[6] The use of acyl chlorides mainly leads to diacylation compounds.[8] Our reaction provides an efficient and selective monoacylation method which takes place under mild conditions.

It is known that alk-1-en-2-yl esters can be transformed into primary amides on reaction with ammonia.[19] A variety of symmetrical and unsymmetrical acylamides can be prepared according to the two-step sequence shown in Scheme 3.



Scheme 3

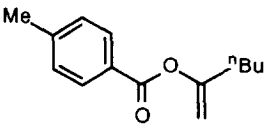
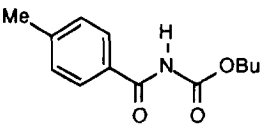
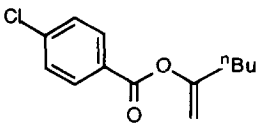
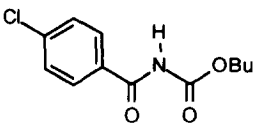
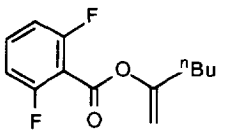
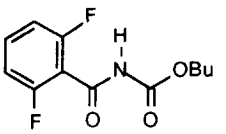
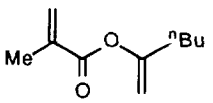
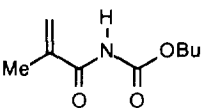
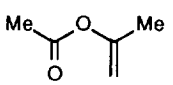
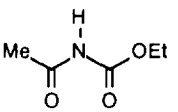
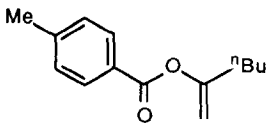
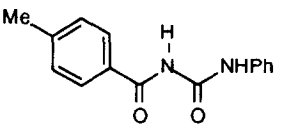
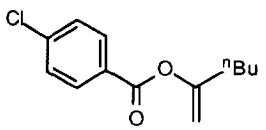
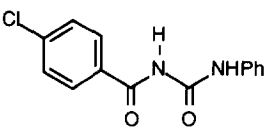
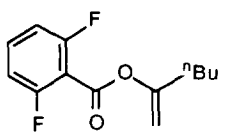
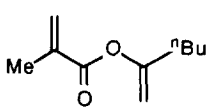
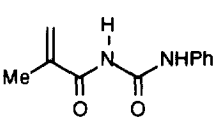
Under similar conditions, acylation of primary carbamates led to the formation of acylcarbamates at room temperature (Scheme 4, Table 3). Aromatic hex-1-en-2-yl esters **1-3** reacted with *n*-butylcarbamate to afford *n*-butyl 4-methyl (**13**), 4-chloro (**14**) and 2,6-difluoro (**15**) benzoylcarbamates in 66, 79 and 62% yield, respectively. Butyl methacryloylcarbamate **16** was also obtained in 81% yield from hex-1-en-2-yl methacrylate **4**. This methacryloyl carbamate **16** has been shown to be a useful synthetic intermediate for Diels-Alder[4] and Michael reactions.[26] This new route presents a potential for the production of functional methacrylate monomers.[3] The acylation of carbamates was extended to other primary carbamates as shown by the formation of ethyl acetylcarbamate **17** in 72% yield from isopropenyl acetate and ethylcarbamate. This general synthetic method based on selective monoacylation of primary carbamates by alk-1-en-2-yl esters avoids the preparation and use of noxious acylisocyanates.[3]



Scheme 4

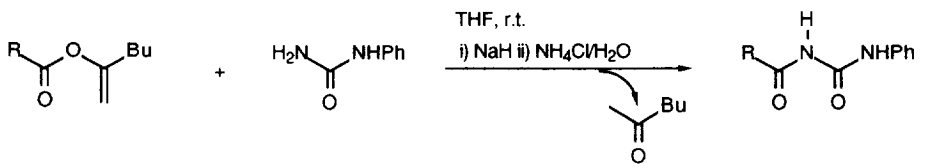
Since *N*-acylureas are of interest to phytochemistry and medicinal chemistry, we applied this new and clean acylation method to primary ureas. On reaction with *N*-phenylurea sodium salt, generated by treatment of *N*-phenylurea with NaH in tetrahydrofuran, aromatic enol esters led to acylated *N*-phenylureas according to

Table 3. Preparation of Acylcarbamates and Acylureas from Hex-1-en-2-yl Esters

Hex-1-en-2-yl Ester	Acylated compound		Reaction time (h)	Yield (%)
		**13**	7	66[a]
		**14**	5	79[a]
		**15**	4	62[a]
		**16**	7	81[a]
		**17**	1	72[b]
		**18**	3	84[a]
		**19**	4	64[a]
		**20**	2	74[a]
		**21**	2	73[a]

Reagents and conditions : carbamate or phenylurea (5 mmol), enol ester (5.5 mmol), NaH (7.5 mmol), tetrahydrofuran (20 ml), room temperature, [a] method A, [b] method B (methods A and B are described in the experimental section)

Scheme 5. Alkylated and halogenated benzoylureas **18-20** were prepared in good yields (Table 3). The polymerizable methacryloyl *N*-phenylurea **21**[3] was also easily prepared in 73% yield from hex-1-en-2-yl methacrylate. Indeed, we have shown that a copolymer (Mn= 24120, Mw= 35900) could be obtained from 2.45 mmol of **21** and 12.25 mmol of methyl methacrylate in the presence of 0.015 mmol of 2,2'-azobis(2-methylpropionitrile) in 15 ml of tetrahydrofuran at 60 °C for 18 h. This general synthesis of acylureas appears to be a good alternative to that using acylisocyanates.



Scheme 5

CONCLUSION

The efficient Markovnikov addition of functional carboxylic acids to terminal alkynes, catalyzed by $[Ru(O_2CH)(CO)_2(PPh_3)]_2$, provides a selective access to a variety of alk-1-en-2-yl esters. These esters are useful monoacylation reagents for the obtention of acylamides, acylcarbamates and acylureas on reaction with deprotonated primary amides, carbamates and ureas under mild conditions. Alk-1-en-2-yl esters offer a new route to these classes of compounds, which presents the advantages of avoiding isocyanates and acylisocyanates, and releasing a neutral ketone as the sole by-product.

EXPERIMENTAL

Preparation of $[Ru(O_2CH)(CO)_2(PPh_3)]_2$.[21] 320 mg of $Ru_3(CO)_{12}$ (0.5 mmol) were heated at 110 °C for 10 h in 5 ml of formic acid under an inert atmosphere of nitrogen. After removal of formic acid under vacuum, 395 mg of triphenylphosphine (1.5 mmol) in 10 ml of diethylether were added under inert atmosphere to the air-sensitive polymeric $[Ru(O_2CH)(CO)_2]_n$. This reaction mixture was then refluxed at 40 °C for 4 h. The canary yellow precipitate was filtered, washed with diethylether and dried. Isolated yield 99% (688 mg). IR (KBr) ν/cm^{-1} 1595 (OCO), 1950, 1980 and 2025 (CO) ; ^1H NMR δ (300 MHz, $CDCl_3$) 7.30 (m, 18 H, Ph), 7.50 (m, 12 H, Ph), 8.17 (s, 2 H, O_2CH) ; ^{31}P NMR δ (121.5 MHz, $CDCl_3$) 13.2 (s, PPh_3) ; ^{13}C NMR. δ (75.5 MHz, $CDCl_3$) 126.90-134.60 (PPh_3), 176.32 (dt, $^3J_{PC}$ = 8.0 Hz, $^1J_{CH}$ = 208.3 Hz, O_2CH), 204.71 (t,

$^2J_{PC} = {}^3J_{PC} = 3.9$ Hz, CO). Found : C, 53.50 ; H, 3.38 ; P, 6.66. Calcd for $Ru_2C_{42}H_{32}O_8P_2$: C, 54.31 ; H, 3.47 ; P, 6.67.

Typical procedure for the preparation of hex-1-en-2-yl esters ***1-3***.

30 mmol of acid, 33 mmol of hex-1-yne and 0.1 mmol of $[Ru(O_2CH)(CO)_2(PPh_3)]_2$ were stirred at 110 °C for 15-18 h in 30 ml of toluene under a nitrogen atmosphere. After treatment with $NaHCO_3$ and evaporation of the solvent, enol esters were isolated by distillation under reduced pressure.

1 : 94% yield ; colorless liquid, bp 150 °C (2 mm Hg) ; IR (film) ν/cm^{-1} 1740 (C=0) and 1665 (C=C) ; ^1H NMR δ (300 MHz, $CDCl_3$) 0.91 (t, 3 H, ^3J = 7.3 Hz, CH_3), 1.38 (sext, 2 H, ^3J = 7.3 Hz, CH_2), 1.51 (quint, 2 H, ^3J = 7.3 Hz, CH_2), 2.33 (t, 2 H, ^3J = 7.3 Hz, CH_2), 2.43 (s, 3 H, CH_3), 4.82 (m, 1 H, =C<u>H</u>H), 4.84 (m, 1 H, =CH<u>H</u>), 7.26 (m, 2 H, Ph), 7.97 (m, 2 H, Ph). Found : C, 77.23 ; H, 8.43. Calcd for $C_{14}H_{18}O_2$: C, 77.03 ; H, 8.31.

2 : 94% yield ; colorless liquid, bp 150 °C (2 mm Hg) ; IR (film) ν/cm^{-1} 1735 (C=0) and 1665 (C=C) ; ^1H NMR δ (300 MHz, $CDCl_3$) 0.85 (t, 3 H, ^3J = 7.3 Hz, CH_3), 1.31 (sext, 2 H, ^3J = 7.3 Hz, CH_2), 1.44 (quint, 2 H, ^3J = 7.3 Hz, CH_2), 2.23 (t, 2 H, ^3J = 7.3 Hz, CH_2), 4.77 (m, 1 H, =C<u>H</u>H), 4.78 (m, 1 H, =CH<u>H</u>), 7.35 - 7.98 (m, 4 H, Ph). Found : C, 65.50 ; H, 6.73 ; Cl, 14.55. Calcd for $C_{13}H_{15}O_2Cl$: C, 65.41 ; H, 6.33 ; Cl, 14.85.

3 : 95% yield ; colorless liquid, bp 150 °C (2 mm Hg) ; IR (film) ν/cm^{-1} 1750 (C=0) and 1670 (C=C) ; ^1H NMR δ (300 MHz, $CDCl_3$) 0.93 (t, 3 H, ^3J = 7.4 Hz, CH_3), 1.38 (sext, 2 H, ^3J = 7.4 Hz, CH_2), 1.54 (quint, 2 H, ^3J = 7.4 Hz, CH_2), 2.35 (t, 2 H, ^3J = 7.4 Hz, CH_2), 4.85 (d, 1 H, ^2J = 1.5 Hz, =C<u>H</u>H), 4.93 (d, 1 H, ^2J = 1.5 Hz, =CH<u>H</u>), 6.94 - 7.49 (m, 3 H, Ph). Found : C, 64.75 ; H, 5.93. Calcd for $C_{13}H_{14}O_2F_2$: C, 64.99 ; H, 5.87.

4 : prepared at 90 °C for 35 h in hexane. 91% yield ; colorless liquid, IR (film) ν/cm^{-1} 1735 (C=O), 1665 and 1640 (C=C) ; ^1H NMR δ (300 MHz, $CDCl_3$) 0.87 (t, 3 H, ^3J = 7.2 Hz, CH_3), 1.28 - 1.48 (broad signal, 4 H, 2 CH_2), 1.94 (t, 3 H, ^4J = 1.2 Hz, CH_3), 2.21 (t, 2 H, ^3J = 7.5 Hz, CH_2), 4.71 (s, 2 H, CH_2), 5.60 (m, 1 H, =C<u>H</u>H), 6.14 (m, 1 H, =CH<u>H</u>).

5 : prepared at 80 °C for 15 h in hexane. 94% yield ; colorless liquid, IR (film) ν/cm^{-1} 1735 (C=O), 1660 (C=C) ; ^1H NMR δ (300 MHz, $CDCl_3$) 0.90 (t, 3 H, ^3J = 6.5 Hz, CH_3), 1.40 (m, 4 H, 2 CH_2), 2.20 (t, 2 H, ^3J = 7.0 Hz, CH_2), 4.69 (s, 2 H, =CH_2), 8.08 (s, 1 H, CHO).

Typical procedure for the preparation of N-acyl compounds.

Method A : 7.5 mmol of NaH were slowly added into a solution containing 5 mmol of amide derivative, 5.5 mmol of enol ester in 20 ml of anhydrous tetrahydrofuran, and the mixture was stirred for 1 to 16 h at room temperature. 10 ml of a saturated NH_4Cl solution were added to the reaction mixture which was then isolated by overnight continuous liquid-liquid extraction with ether. The organic phase was dried over $MgSO_4$ and evaporated, and the remaining white solid was washed with hexane and dried under vacuum.

*Method B for compounds **11, 12, 17*** : 7.5 mmol of NaH were slowly added into a solution containing 5 mmol of benzamide (**11**, **12**) or ethyl carbamate (**17**). After 2 h at room temperature, 5 mmol of enol ester were added to the reaction mixture. After 2 additional hours at room temperature, 10 ml of a saturated NH_4Cl solution were added. The reaction mixture was then isolated by continuous liquid-liquid extraction with ether. The organic phase was dried over $MgSO_4$ and evaporated, and the remaining white solid was washed with hexane and dried under vacuum.

7 : 83% yield ; white solid, m. p. 116-118 °C ; IR (KBr) ν/cm^{-1} 3275 (N-H), 1720 and 1665 (C=O) ; ^1H NMR δ (300 MHz, $CDCl_3$) 2.36 (s, 3 H, CH_3), 7.19 - 7.81 (m, 9 H, Ph), 8.92 (s, 1 H, NH). Found : M^+, 239.093. Calcd for $C_{15}H_{13}NO_2$: M, 239.095.

8 : 78% yield ; white solid, m. p. 129-131 °C ; IR (KBr) ν/cm^{-1} 3290 (NH) 1740 and 1680 (C=O) ; ^1H NMR δ (300 MHz, DMSO), 7.50 - 7.96 (m, 9 H, Ph), 11.40 (s, 1 H, NH). Found : M^+, 259.039. Calcd for $C_{14}H_{10}NO_2Cl$: M, 259.040.

9 : 93% yield ; white solid, m. p. 162-164 °C ; IR (KBr) ν/cm^{-1} 3260 (NH) and 1745, 1730 (C=O) ; ^1H NMR δ (300 MHz, DMSO), 7.19 - 7.95 (m, 8 H, Ph), 12.00 (s, 1 H, NH). Found : C, 64.23 ; H, 3.69 ; N, 5.25 ; M^+, 261.061. Calcd for $C_{14}H_9NO_2F_2$: C, 64.37 ; H, 3.47 ; N, 5.36 ; M, 261.060.

10 : 60% yield ; white solid, m. p. 66-68 °C ; IR (KBr) ν/cm^{-1} 3270 (NH), 1710 (C=O) and 1672 (C=C) ; ^1H NMR δ (300 MHz, $CDCl_3$), 2.03 (m, 3 H, CH_3), 5.60 (m, 1 H, =C<u>H</u>H), 5.81 (d, 1 H, ^2J = 0.9 Hz, =CH<u>H</u>), 7.81 - 7.44 (m, 5 H, Ph), 8.75 (s, 1 H, NH). Found : C, 69.88 ; H, 5.99 ; N, 7.61 ; M^+, 189.079. Calcd for $C_{11}H_{11}NO_2$: C, 69.83 ; H, 5.86 ; N, 7.40 ; M, 189.079.

11 : 78% yield ; white needles, m. p. 111-113 °C ; IR (KBr) ν/cm^{-1} 3270 (N-H), 1725 and 1690 (C=O) ; ^1H NMR δ (300 MHz, $CDCl_3$), 7.52 - 7.97 (m, 5 H, Ph), 9.39 (d, 1 H, ^3J = 9.7 Hz, CHO), 9.59 (broad signal, 1 H, NH). Found : C, 64.63 ; H, 4.80 ; N, 9.55 ; M^+, 149.048. Calcd for $C_8H_7NO_2$: C, 64.42 ; H, 4.73 ; N, 9.39 ; M, 149.048.

12 : 86% yield ; white solid ; IR (KBr) ν/cm^{-1} 3275 (NH), 1740 and 1680 (C=O) ; ^1H NMR δ (300 MHz, $CDCl_3$) 2.55 (s, 3 H, CH_3), 7.81 - 7.41 (m, 5 H, Ph), 8.82 (broad signal, 1 H, NH).

13 : 66% yield ; white solid, m. p. 69 °C ; IR (KBr) ν/cm^{-1} 3280 (NH), 1780 and 1760 (C=0) ; ^{1}H NMR δ (300 MHz, $CDCl_3$) 0.94 (t, 3 H, ^{3}J = 7.3 Hz, CH_3), 1.41 (sext, 2 H, ^{3}J = 7.4 Hz, CH_2), 1.67 (quint, 2 H, ^{3}J = 7.3 Hz, CH_2), 2.40 (s, 3 H, CH_3), 4.23 (t, 2 H, ^{3}J = 7.3 Hz, CH_2), 7.25 - 7.72 (m, 4 H, Ph), 8.06 (s, 1 H, NH). Found : C, 66.28 ; H, 7.28 ; N, 5.90 ; M$^+$, 235.123. Calcd for $C_{13}H_{17}NO_3$: C, 66.36 ; H, 7.28 ; N, 5.95 ; M, 235.121.

14 : 79% yield ; white needles ; m. p. 107-108 °C ; IR (KBr) ν/cm^{-1} 3285 (NH), 1770 and 1750 (C=0) ; ^{1}H NMR δ (300 MHz, $CDCl_3$) 0.94 (t, 3 H, ^{3}J = 7.3 Hz, CH_3), 1.41 (sext, 2 H, ^{3}J = 7.4 Hz, CH_2), 1.67 (quint, 2 H, ^{3}J = 7.3 Hz, CH_2), 4.24 (t, 2 H, ^{3}J = 7.3 Hz, CH_2), 7.43 - 7.78 (m, 4 H, Ph), 8.04 (s, 1 H, NH). Found : M$^+$, 255.066. Calcd for $C_{12}H_{14}NO_3Cl$: M, 255.066.

15 : 62% yield ; white needles ; m. p. 118-120 °C ; IR (KBr) ν/cm^{-1} 3260 (NH) and 1760 (C=0) ; ^{1}H NMR δ (300 MHz, $CDCl_3$) 0.85 (t, 3 H, ^{3}J = 7.3 Hz, CH_3), 1.29 (sext, 2 H, ^{3}J = 7.4 Hz, CH_2), 1.50 - 1.59 (m, 2 H, CH_2), 4.09 (t, 2 H, ^{3}J = 6.7 Hz, CH_2), 6.86 - 7.41 (m, 3 H, Ph), 7.77 (s, 1 H, NH). Found : C, 55.90 ; H, 5.14 ; N, 5.45 ; F, 14.22 ; M$^+$, 257.087. Calcd for $C_{12}H_{13}NO_3F_2$: C, 56.03 ; H, 5.09 ; N, 5.44 ; F, 14.77 ; M, 257.086.

16 : 81% yield ; white solid, m. p. 90 °C ; IR (KBr) ν/cm^{-1} 3275 (NH), 1775, 1755 (C=0) and 1680 (C=C) ; ^{1}H NMR δ (300 MHz, $CDCl_3$) 0.95 (t, 3 H, ^{3}J = 7.3 Hz, CH_3), 1.41 (sext, 2 H, ^{3}J = 7.4 Hz, CH_2), 1.67 (quint, 2 H, ^{3}J = 7.3 Hz, CH_2), 2.00 (s, 3 H, CH_3), 4.21 (t, 2 H, ^{3}J = 7.3 Hz, CH_2), 5.56 (s, 1 H, =C<u>H</u>H) 5.76 (s, 1 H, =CH<u>H</u>), 7.83 (s, 1 H, NH). Found : C, 57.73 ; H, 8.27 ; N, 7.44 ; M$^+$, 185.106. Calcd for $C_9H_{15}NO_3$: C, 58.36 ; H, 8.16 ; N, 7.56 ; M, 185.105.

17 : 72% yield ; white solid, ; IR (KBr) ν/cm^{-1} 3260 (NH), 1765 and 1705 (C=O) ; ^{1}H NMR δ (300 MHz, $CDCl_3$), 1.29 (t, 3 H, ^{3}J = 7.1 Hz, CH_3), 2.41 (s, 3H, CH_3), 4.20 (q, 2 H, ^{3}J = 7.1 Hz, OCH_2), 7.88 (broad signal, 1 H, NH). Found : C, 45.91 ; H, 6.95 ; N, 10.46. Calcd for $C_5H_9NO_3$: C, 45.80 ; H, 6.92 ; N, 10.68.

18 : 84% yield ; white solid ; IR (KBr) ν/cm^{-1} 3430, 3255 (NH), 1700 and 1660 (C=O) ; ^{1}H NMR δ (300 MHz, $CDCl_3$), 2.38 (s, 3 H, CH_3), 7.06 - 7.91 (m, 9 H, Ph), 9.80 (s, 1 H, NH), 10.95 (s, 1 H, NH). Found : C, 70.36 ; H, 5.53 ; N, 11.09 ; M$^+$, 254.106. Calcd for $C_{15}H_{14}N_2O_2$: C, 70.85 ; H, 5.59 ; N, 11.02 ; M, 254.106.

19 : 64% yield ; white solid, m. p. 239-241 °C ; IR (KBr) ν/cm^{-1} 3250, 3255 (NH), 1700 and 1675 (C=O) ; ^{1}H NMR δ (300 MHz, DMSO), 7.09 - 8.05 (m, 9 H, Ph), 10.50 (s, 1 H, NH), 10.74 (s, 1 H, NH). Found : C, 61.24 ; H, 4.03 ; N, 10.16 ; Cl, 13.24. Calcd for $C_{14}H_{11}N_2O_2Cl$: C, 61.21 ; H, 4.04 ; N, 10.20 ; Cl, 12.91.

20 : 74% yield ; white solid, m. p. 180-181 °C ; IR (KBr) ν/cm^{-1} 3285 (NH), 1690 and 1650 (C=O) ; ^{1}H NMR δ (300 MHz, $CDCl_3$), 7.00 - 7.55 (m, 8 H, Ph), 9.37 (s, 1 H, NH), 10.42 (s, 1 H, NH). Found : C, 61.10 ; H, 3.65 ; N, 10.14 ; F, 13.75 ; M$^+$, 276.071. Calcd for $C_{14}H_{10}N_2O_2F_2$: C, 60.87 ; H, 3.62 ; N, 10.14 ; F, 13.76 ; M, 276.071.

21 : 73% yield ; white solid, m. p. 195-197 °C ; IR (KBr) ν/cm^{-1} 3250, 3150 (NH), 1695, 1650 (C=O) and 1620 (C=C) ; ^{1}H NMR δ (300 MHz, $CDCl_3$), 1.98 (s, 3 H, CH_3), 5.60 (d, 1 H, ^{2}J = 0.5 Hz, CH), 5.98 (d, 1 H, ^{2}J = 0.5 Hz, CH), 7.03 - 7.47 (m, 5 H, Ph), 8.96 (s, 1 H, NH), 10.68 (s, 1 H, NH).

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REFERENCES

1. (a) Wellinga, K.; Mulder, R.; van Daalen, J. J. *J. Agr. Food Chem.* **1973**, *21*, 348-354; *Chem. Abstr.* **1973**, *79*, 88264d. (b) Nakagawa, Y.; Kitahara, K.; Nishioka, T.; Iwamura, H.; Fujita, T. *Pestic. Biochem. Physiol.* **1984**, *21*, 309-325; *Chem. Abstr.* **1984**, *101*, 19044t.
2. Goodman Gilman, A.; Goodman, L. S.; Gilman, A. *The Pharmacological Basis of Therapeutics 6th ed.*; MacMillan : New York, 1980.
3. Mitsuo, Y.; Hiroshi, A.; Satoru, U. *Jpn. Kokai Tokkyo Koho* JP 04 29,964 (1992); *Chem. Abstr.* **1992**, *117*, 27390y. (b) Satoshi, U.; Noriyuki, T.; Tetsuji, K.; Katsuya, W. *Eur. Pat. Appl.* EP 478,268 (1992); *Chem. Abstr.* **1992**, *117*, 36192n.
4. Kishikawa, K.; Yamamoto, M.; Kohmoto, S.; Yamada, K. *J. Org. Chem.* **1989**, *54*, 2428-2432.
5. Kishikawa, K.; Yamamoto, M.; Kohmoto, S.; Yamada, K. *Chem. Lett.* **1989**, 787-790.
6. Baburao, K.; Costello, A. M.; Petterson, R. C.; Sander, G. E. *J. Chem. Soc. (C)* **1968**, 2779-2781.
7. Davidson, D.; Skovronek, H. *J. Am. Chem. Soc.* **1958**, *80*, 376-379.
8. Lalonde, R. T.; Davis, C. B. *J. Org. Chem.* **1970**, *35*, 771-774.
9. Dunbar, R. E.; Swenson, W. M. *J. Org. Chem.* **1958**, *23*, 1793-1794.

10. Atanassova, I. A.; Petrov, J. S.; Ognjanova, V. H.; Mollov, N. M. *Synth. Commun.* **1990**, *20*, 2083-2090.

11. Könnecke, A.; Grehn, L.; Ragnarsson, U. *Tetrahedron Lett.* **1990**, *31*, 2697-2700.

12. Atanassova, I. A.; Petrov, J. S.; Mollov, N. M. *Synthesis* **1987**, 734-736.

13. (a) Nuridzhanyan, K. A. *Russ. Chem. Rev.* **1970**, *39*, 130-139. (b) Speziale, A. J.; Smith, L. R. *J. Org. Chem.* **1962**, *27*, 3742-3743.

14. Deng, M. -Z.; Caubère, P.; Senet, J. P.; Lécolier, S. *Tetrahedron* **1988**, *44*, 6079-6086.

15. Kishikawa, K.; Horie, K.; Yamamoto, M.; Kohmoto, S.; Yamada, K. *Chem. Lett.* **1990**, 1009-1010.

16. (a) Ruppin, C.; Dixneuf, P. H. *Tetrahedron Lett.* **1986**, *27*, 6323-6324. (b) Bruneau, C.; Neveux, M.; Kabouche, Z.; Ruppin, C.; Dixneuf, P. H. *Synlett* **1991**, 755-763.

17. (a) Neveux, M.; Bruneau, C.; Lécolier, S.; Dixneuf, P. H. *Tetrahedron* **1993**, *49*, 2629-2640. (b) Chen, S.-T.; Chen, S.-Y.; Chen, S.-J.; Wang, K.-T. *Tetrahedron Lett.* **1994**, *35*, 3583-3584. (c) Kita, Y.; Maeda, H.; Omori, K.; Okuno, T.; Tamura, Y. *J. Chem. Soc. Perkin Trans. I* **1993**, 2999-3005.

18. (a) Neveux, M.; Bruneau, C.; Dixneuf, P. H. *J. Chem. Soc. Perkin Trans. I* **1991**, 1197-1199. (b) van Melick, J. E. W.; Wolters, E. T. M. *Synth. Commun.* **1972**, *2*, 83-86.

19. Kabouche, Z.; Bruneau, C.; Dixneuf, P. H. *Tetrahedron Lett.* **1991**, *32*, 5359-5362.

20. Lobell, M. ; Schneider, M. P. *Tetrahedron : Asymmetry* **1993**, *4*, 1027-1030.

21. Neveux, M.; Seiller, B.; Hagedorn, F.; Bruneau, C.; Dixneuf, P. H. *J. Organomet. Chem.* **1993**, *451*, 133-138.

22. Mitsudo, T.; Hori, Y.; Yamakawa, Y.; Watanabe, Y. *J. Org. Chem.* **1987**, *52*, 2230-2239.

23. Kita, Y.; Maeda, H.; Omori, K. ; Okuno, T.; Tamura, Y. *Synlett* **1993**, 273-274.

24. (a) Darcel, C.; Bruneau, C.; Dixneuf, P. H.; Neef, G. *J. Chem. Soc., Chem. Commun.* **1994**, 333-334. (b) Bruneau, C.; Kabouche, Z.; Neveux, M.; Seiller, B.; Dixneuf, P. H. *Inorg. Chim. Acta* **1994**, *222*, 154-163.

25. Gassman, P. G.; Hodgson, P. K. G.; Balchunis, R. J. *J. Am. Chem. Soc.* **1976**, *98*, 1275-1276.

26. Seiller, B.; Bruneau, C.; Dixneuf, P. H. submitted for publication.

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