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# Ultrasound Effects on the Mn(III) - Promoted Addition of Amidoalkyl Radicals to Olefins

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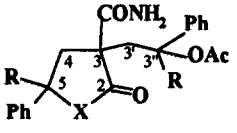
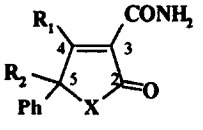
***Abstract***: Amidoalkyl radicals, generated from amides by $Mn(OAc)_3$ in acetic acid react with phenyl substituted alkenes to generate five-membered lactones or lactams. Ultrasound at ambient temperature significantly accelerates these single electron transfer reactions even when compared with conventional conditions under reflux or simple mechanical stirring. In some cases sonication leads to unusual products.

In order to study ultrasonic activation of single electron transfer reactions, we have recently carried out the lactonization reaction of olefins with activated carboxylic acids and $Mn(OAc)_3 \cdot 2H_2O$ under ultrasound irradiation.[1] Ultrasounds showed a marked effect on these reactions, leading to the synthesis of the expected γ-lactones in good yields and in mild reaction conditions.

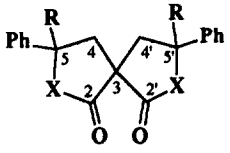
Starting from these results, we decided to study the effects exerted by ultrasound on the analogous reaction of alkenes with enolizable amides and $Mn(OAc)_3$ in glacial acetic acid.



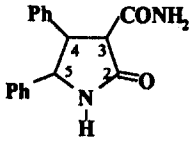
**1** X = O, R = H
**4** X = NH, R = Me



**2** X = O, $R_1$ = H, $R_2$ = Me
**5** X = O, $R_1$ = H, $R_2$ = Ph
**9** X = NH, $R_1$ = Ph, $R_2$ = OAc
**10** X = O, $R_1$ = $R_2$ = Ph
**11** X = NH, $R_1$ = $R_2$ = Ph



**3** X = O, R = Me
**6** X = O, R = Ph
**7** X = NH, R = Ph



**8**

In an early attempt by other Authors, this reaction was carried out at reflux temperature, employing malonamide as the radical source.[2] In these conditions the reaction was quite unselective. Simple alkyl

substituted olefins gave very poor results and only phenyl substituted alkenes reacted effectively. Mixtures of unsaturated γ-lactonic and γ-lactamic products were obtained in low yields, together with a great number of side products, probably due to the severe experimental conditions. The analysis of these results and the knowledge of an ultrasonic activation of manganese(III) acetate[1] drove us to perform the same reaction under ultrasound irradiation.

In the first experiments, malonamide, $Mn(OAc)_3$ and alkenes were kept in glacial acetic acid at room temperature under irradiation with ultrasound at 200 $Wcm^{-2}$ for several hours until the brown colour of $Mn(OAc)_3$ disappeared (method A).

Sonochemical results were compared with those obtained in analogous mechanically stirred reactions ("silent" reactions) carried out at reflux temperature until decoloration of reaction mixture (method B), or at room temperature for 24 hours (method C). In the last procedure disappearance of brown colour was in most cases not observed. None of these three methods led to significant results on alkyl-substituted alkenes; then only polar, phenyl substituted olefins were used. Results obtained are summarized in Table 1.

**Table 1.** Reaction of Alkenes with Malonamide and $Mn(OAc)_3$ in Acetic Acid

| Alkene | Product (Yields %)[a] | Method | Reaction time (hr) |
|---|---|---|---|
| Styrene | **1** (25) | **A** | 3 |
| | **1** (5) | **B** | 0.3 |
| | **1** (10) | **C** | 24 |
| α-Methylstyrene | **3** (55) **4** (30) | **A** | 2.5 |
| | **2** (7) **3** (4) | **B** | 0.5 |
| | **3** (4) **4** (12) | **C** | 24 |
| 1,1-Diphenyl-ethylene | **6** (15) **7** (23) | **A** | 3.5 |
| | **5** (41) | **B** | 0.5 |
| | **6** (4) **7** (21) | **C** | 24 |
| Trans-Stilbene | **8** (15) **9** (25) | **A** | 3 |
| | **9** (13) | **B** | 0.3 |
| | **8** (10) **9** (12) | **C** | 24 |
| 1,1,2- Triphenyl-Ethylene | **11** (60) | **A** | 2 |
| | **10** (56) | **B** | 0.2 |
| | **10** (26) **11** (28) | **C** | 24 |

a) Yields are referred to pure, chromatographically isolated products

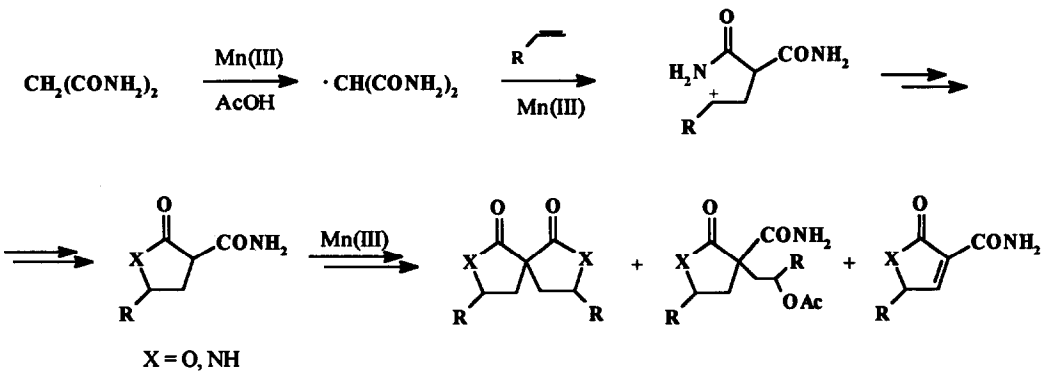
Thermal reactions (method B) afforded in most cases complex product mixtures. This was quite predictable because high temperatures may favour direct oxidation process of olefins by Mn(III).[3] On the contrary, these undesired products were not present in reactions carried out with methods A and C, while

ultrasounds greatly enhanced the reaction rate (the same conversion ratios obtained in 24 hours of "silent" reaction were reached after few hours of ultrasound irradiation).

It seemed evident that an ultrasonic activation could be effective in these reactions as already ascertained in lactonization reactions promoted by manganic acetate. The best yields of final products were obtained using molar ratios 4:4:1 of malonamide, $Mn(OAc)_3$, and alkene respectively. Use of smaller amounts of Mn(III) and malonamide led to a decrease of the yields; on the other hand, higher amounts of Mn(III) did not afford a yield enhancement.

TLC and chromatographical isolation of final products of sonochemical reactions involving malonamide showed a little tendency to formation of side products and a modest selectivity in the formation of lactones or lactams. Furthermore, the overoxidation of the initially formed cyclic intermediate was always observed with formation of saturated, α,β-unsaturated or spiro γ-lactones or γ-lactams (see scheme 1).

**Scheme 1**



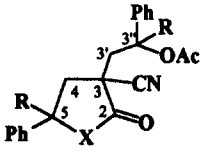

Only in one case (trans-stilbene) we were able to isolate the non-overoxidized product **8** which was thought to be the precursor of **9**. In order to verify this hypothesis and clarify the oxidation mechanism of the intermediates we treated a solution of **8** in acetic acid with $Mn(OAc)_3$, but the compound was recovered unaffected either after refluxing or sonicating the mixture. On the contrary, a slow conversion to **9** was observed when **8** was treated in acetic acid with Mn(III) and malonamide. This seems to suggest the intermediacy of a $\cdot CH(CONH_2)_2$ radical in the overoxidation process, probably trough a hydrogen atom abstraction.

Sonochemical procedure gave good results only with α-methylstyrene and 1,1,2-triphenylethylene, leading to a great yield enhancement in compound **3** and selective formation of **11** respectively. Styrene, trans-stilbene and 1,1-diphenylethylene on the contrary showed lower yields enhancement in the sonochemical procedure probably due to the peculiar reactivity of the tested alkene in the reaction conditions.

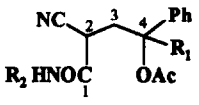
The case of 1,1,2-triphenylethene is significant; in fact, method B afforded lactone **10** as the unique product, while a mixture of **10** and lactam **11** was obtained under mechanical stirring at room temperature. The selective formation of **10** with method B is probably due to a temperature effect that favours the enolization of amidic moiety with consequent attack of oxygen, while at room temperature also the amidic nitrogen could

compete as the nucleophile thus leading to γ-lactam **11**.[2] The selective obtaining of **11** by ultrasound irradiation could be due to a sonochemically induced change in the solvation state of the cationic intermediate, which could be "bare" and prone to nitrogen attack.

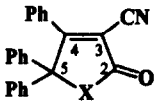
In order to study the effect of other electron-withdrawing groups at amidic α-carbon on the reaction outcome, we subsequently employed cyanoacetamide as radical source.



**12** X = O, R = H
**13** X = O, R = Me
**14** X = NH, R = Ph
**18** X = $N(CH)_2CH_3$, R = H
**20** X = $N(CH)_2CH_3$, R = Ph



**15** $R_1$ = Ph, $R_2$ = H
**19** $R_1$ = Me, $R_2$ = n-Pr



**16** X = O
**17** X = NH
**21** X = $N(CH)_2CH_3$

Results obtained with cyanoacetamide are summarized in Table 2. The general behaviour observed in the sonochemical procedure is a reaction rate enhancement with respect to "silent" reactions at room temperature. As already observed in the case of malonamide, the nature of final products depended on the used alkene.

**Table 2**. Reaction of Alkenes with Cyanoacetamide and $Mn(OAc)_3$ in Acetic Acid

| Alkene | Product (Yields %)[a] | Method | Reaction time (hr) |
|---|---|---|---|
| Styrene | **12** (55) | **A** | 4 |
| | **12** (10) | **B** | 0.3 |
| | **12** (15) | **C** | 24 |
| α-Methylstyrene | **13** (30) | **A** | 2.5 |
| | **13** (7) | **B** | 0.5 |
| | **13** (20) | **C** | 24 |
| 1,1-Diphenyl-ethylene | **14** (47) **15** (30) | **A** | 3.5 |
| | **15** (25) | **B** | 0.5 |
| | **15** (30) | **C** | 24 |
| 1,1,2- Triphenyl-Ethylene | **16** (36) **17** (32) | **A** | 2 |
| | **16** (48) | **B** | 0.2 |
| | **16** (57) **17** (9) | **C** | 24 |

a) Yields are referred to pure, chromatographically isolated products

Styrene and α-methylstyrene reacted to afford always lactonic products. In both cases the effect of ultrasound irradiation consisted in a neat increase of yields. The formation of lactonic products had been previously explained by other authors by the low stabilization of the cationic intermediate favouring the attack of the amidic oxygen.[2]

In the reactions of 1,1-diphenylethylene and 1,1,2-triphenylethylene ultrasound irradiation altered the products distribution leading to the formation of lactamic products that are absent in "silent" reactions. Relevant is the prevalence of the lactam **14** over the acyclic compound **15**, due to the attack of acetic acid to the intermediate from 1,1-diphenylethene. Moreover, the formation of the lactamic product **17** from 1,1,2-triphenylethene is sonochemically enhanced. These results seem to confirm the above mentioned hypothesis of an ultrasonic change in the solvation state of the cationic intermediate.

The study was extended to N-propylcyanoacetamide to verify if the presence of an alkyl group on the amidic nitrogen could increase its nucleophilicity and therefore promote the formation of γ-lactams. Once more ultrasound irradiation was the method of choice to support the reaction and γ-lactams **18** and **20** (from styrene and 1,1-diphenylethylene respectively) were obtained in better yields and in shorter reaction times than with methods B and C. α-Methylstyrene reacted only under ultrasonic activation affording the acyclic product **19**.

Reaction of 1,1,2-triphenylethene with N-propylcyanoacetamide showed a behaviour as similar as that observed in the reaction of the same alkene with malonamide, affording lactonic compound **16** at reflux and γ-lactam **21** under ultrasound irradiation.

**Table 3**. Reaction of Alkenes with N-Propylcyanoacetamide and $Mn(OAc)_3$ in Acetic Acid

| Alkene | Product (Yields %)[a] | Method | Reaction time (hr) |
|---|---|---|---|
| Styrene | **18** (63) | **A** | 4 |
| | **18** (14) | **B** | 0.2 |
| | **18** (38) | **C** | 24 |
| α-Methylstyrene | **19** (30) | **A** | 2.5 |
| | - | **B** | 0.5 |
| | - | **C** | 24 |
| 1,1-Diphenyl-ethylene | **20** (80) | **A** | 3.5 |
| | **20** (28) | **B** | 0.5 |
| | **20** (70) | **C** | 24 |
| 1,1,2- Triphenyl-Ethylene | **21** (56) | **A** | 2 |
| | **16** (48) | **B** | 0.2 |
| | **16** (20) **21** (30) | **C** | 24 |

a) Yields are referred to pure, chromatographically isolated products

In conclusion, ultrasound irradiation proved to be an important tool to ameliorate Mn(III)-promoted reactions. In fact, a relevant feature of all reactions here described is the constant sonochemical acceleration of

reaction rate and the absence of side products formed with method B. This is an important confirmation of the "sensibility" to ultrasound effect of SET reactions promoted by Mn(III). Moreover, in some cases ultrasonic reactions reacted in a quite peculiar way affording final products that are unavailable with other procedures.

## EXPERIMENTAL

Sonochemical reactions were carried out in a Vibracell 600 Watt probe transducer, operating at 200-300w/cm$^2$ equipped with a titanium microtip ($\phi$ 6.5 mm), directly connected to the horn. The irradiation with ultrasound was pulsed (50% of total time) to obtain a good control of reaction temperature. Reactions were carried out into a glass tube ($\phi$ 2.0 cm, h 20 cm) and only 10% of the entire lenght of the microtip was immersed into reaction mixture. All the alkenes, malonamide and cyanoacetamide were purchased from Fluka and Aldrich and used without further purification.

The numbering of product skeletons were arbitrary and given to allow an easy comparison of NMR spectral data. $^1$H-NMR were recorded on a Varian XL-200 Gemini spectrometer, using TMS as internal standard in $CDCl_3$. Chemical shifts are reported in parts per million and are given in $\delta$ units; coupling constants are given in Hertz. We used the following symbols to report the multiplicity and shape of signals: bs (broad signal), d (doublet), dd (double doublet), dt (double triplet), m (multiplet), q (quartet), qp (quintuplet), s (singlet), se (sextet), t (triplet). $^{13}$C-NMR were recorded on the same spectrometer, operating at 50 MHz. $^{13}$C-NMR assignments marked with * may be interchangeable. The progress of reactions and chromatographic separations were monitored by TLC on silica gel plates (Merck Kieselgel 60 $F_{254}$ $\phi$ 0.25 mm). Column chromatography was performed on silica gel (Merck Kieselgel, 70-230 mesh).

**Reaction of alkenes with activated amides and $Mn(OAc)_3 \cdot 2H_2O$ under ultrasound irradiation (Method A)** - To a solution of 2.0 mmol of olefin in 30 ml of glacial acetic acid, 8.0 mmol of amide and 1.6 g of $Mn(OAc)_3 \cdot 2H_2O$ (8.0 mmol) were added. The resulting suspension was irradiated with ultrasound (200 W/cm$^2$) at room temperature and under an argon athmosphere until the brown colour of the solution disappeared. The temperature was kept under control by cooling. At the end of the reaction the reaction mixture was then poured into water (100 ml). The mixture was then extracted with $CH_2Cl_2$ (5x50 ml), the organic phase was washed with saturated $NaHCO_3$ solution to remove acetic acid, then with brine, and was finally dried over anhydrous $Na_2SO_4$. Removal of the solvent under reduced pressure at room temperature afforded an oily residue in most cases. This residue was chromatographed on a silica gel column eluted with $CH_2Cl_2$ or $CH_2Cl_2/Et_2O$ mixtures to afford pure products.

**Reaction of alkenes with activated amides and $Mn(OAc)_3 \cdot 2H_2O$ at reflux temperature under mechanical stirring (Method B)** - To a solution of 2.0 mmol of olefin in 30 ml of glacial acetic acid, 8.0 mmol of amide and 1.6 g of $Mn(OAc)_3 \cdot 2H_2O$ (8.0 mmol) were added. The resulting suspension was heated at 110°C under an argon athmosphere for a few minutes until the brown colour of the solution disappeared. Then the reaction mixture was cooled and poured into water (100 ml). The mixture was then extracted with $CH_2Cl_2$ (5x50 ml), the organic phase was washed with saturated $NaHCO_3$ solution to remove acetic acid, then with brine, and was finally dried over anhydrous $Na_2SO_4$. Removal of the solvent under reduced pressure at room temperature afforded an oily residue in most cases. This residue was chromatographed on a silica gel column eluted with $CH_2Cl_2$ or $CH_2Cl_2/Et_2O$ mixtures to afford pure products.

**Reaction of alkenes with activated amides and $Mn(OAc)_3{\cdot}2H_2O$ at room temperature under mechanical stirring (Method C)** - To a solution of 2.0 mmol of olefin in 30 ml of glacial acetic acid, 8.0 mmol of amide and 1.6 g of $Mn(OAc)_3{\cdot}2H_2O$ (8.0 mmol) were added. The resulting suspension was kept under stirring at room temperature under an argon athmosphere for 24 hours. Then the reaction mixture was poured into water (100 ml). The mixture was then extracted with $CH_2Cl_2$ (5x50 ml), the organic phase was washed with saturated $NaHCO_3$ solution to remove acetic acid, then with brine, and was finally dried over anhydrous $Na_2SO_4$. Removal of the solvent under reduced pressure at room temperature afforded an oily residue in most cases. This residue was chromatographed on a silica gel column eluted with $CH_2Cl_2$ or $CH_2Cl_2/Et_2O$ mixtures to afford pure products.

**Compound 1** - (diastereomeric mixture) $^1$H-NMR ($CDCl_3$, δ) : 2.0 and 2.03 (3H, s, $CH_3$ of OAc), 2.33 (1H, m, H-4), 2.70 (2H, cm, H-4 overlapped to H-3'), 2.92 (1H, d, J = 7.6 Hz, H-3'), 5.45 (1H, t, J = 7.6 Hz, H-3"), 5.97 (1H, m, H-5), 6.10 (1H, bs, NH), 7.3 (11H, cm, aromatic protons overlapped to NH); $^{13}$C-NMR ($CDCl_3$, ppm) : 37.71*, 39.29*, 42.39*, 43.58* (C-4, C-3'), 53.42, 53.75 (C-3), 71.85, 72.42 (C-3"), 78.38, 78.80 (C-5), 125.45-139.88 (aromatic carbons), 170.24*, 170.61*, 171.01* (C-2, CO of $CONH_2$, CO of OAc). Anal. calcd for $C_{21}H_{21}O_5N$ : C 68.64, H 5.76, N 3.81. Found : C 68.42, H 5.72, N 3.79.

**Compound 2** - $^1$H-NMR ($CDCl_3$, δ) : 1.83 (3H, s, $CH_3$ at C-5); 6.05 (1H, bs, NH), 7.35 (5H, m, aromatic protons), 7.70 (1H, bs, NH), 8.42 (1H, s, H-4); $^{13}$C-NMR ($CDCl_3$, ppm) : 25.95 ($CH_3$ at C-5), 87.57 (C-5), 124.66-129.42 (aromatic carbons), 137.85 (C-3), 160.54 (C-4), 165.61 (CO of $CONH_2$), 170.64 (C-2). Anal. calcd for $C_{12}H_{11}O_3N$ : C 66.34, H 5.11, N 6.45. Found : C 66.41, H 5.05, N 6.40.

**Compound 3** - (diastereomeric mixture of "symmetrical anti" and "asymmetrical" in a 6:5 ratio) For spectral data see ref. 4.

**Compound 4** - (diastereomeric mixture); $^1$H-NMR ($CDCl_3$, δ) : 1.50, 1.58, 1.67, 1.88, 1.95, 2.00 (9H, s, $CH_3$ at C-5, $CH_3$ at C-3", $CH_3$ of OAc), 2.20-3.20 (4H, cm, 2H-4, 2H-3'), 5.68 and 5.78 (1H, NH), 6.70 and 6.82 (1H, NH), 7.20 (11H, cm, aromatic protons overlapped to NH); $^{13}$C-NMR ($CDCl_3$, ppm) : 21.76 ($CH_3$ of OAc), 25.29*, 30.01*, 41.37, 50.30, 55.24 (C-3, C-4, C-3'), 82.79*, 80.08* (C-5, C-3"), 169.24 (C-2), 170.19 (CO of OAc), 177.98 (C-3'). Anal. calcd for $C_{23}H_{26}O_4N_2$ : C 70.02, H 6.65, N 7.10. Found : C 69.98, H 6.70, N 7.02.

**Compound 5** - $^1$H-NMR ($CDCl_3$, δ) : 6.25 (1H, s, NH), 7.30 (10H, m, aromatic protons), 7.72 (1H, bs, NH), 8.75 (1H, s, H-4); $^{13}$C-NMR ($CDCl_3$, ppm) : 90.75 (C-5), 124.89-129.25 (aromatic carbons), 138.00 (C-3), 160.44 (C-2), 164.03 (C-4), 170.54 (CO of $CONH_2$). Anal. calcd for $C_{17}H_{13}O_3N$ : C 73.09, H 4.69, N 5.02. Found : C 72.99, H 4.64, N 5.00.

**Compound 6** - $^1$H-NMR ($CDCl_3$, δ) : 2.60 (2H, d, $J_{AB}$= 14.0 Hz, $H_A$-4, $H_A$-4'), 3.00 (2H, d, $J_{AB}$= 14.0 Hz, $H_B$-4, $H_B$-4'), 7.30 (20H, m, aromatic protons); $^{13}$C-NMR ($CDCl_3$, ppm) : 45.57 (C-3), 53.85 (C-4, C-4'), 88.62 (C-5, C-5'), 125.64-142.41 (aromatic carbons), 173.78 (C-2, C-2'). Anal calcd for $C_{31}H_{24}O_4$ : C 80.84, H 5.26. Found : C 80.81, N 5.20.

**Compound 7** - $^1$H-NMR (DMSO-d$^6$, δ) : 2.93 (2H, d, $J_{AB}$= 16.2 Hz, $H_A$-4, $H_A$-4'), 3.04 (2H, d, $J_{AB}$= 16.2 Hz, $H_B$-4, $H_B$-4'), 7.10 (20H, m, aromatic protons); $^{13}$C-NMR ($CDCl_3$, ppm) : 46.65 (C-3), 59.03 (C-4, C-4'), 85.03 (C-5, C-5'), 121.79-148.68 (aromatic carbons), 173.83 (C-2, C-2'). Anal. calcd for $C_{31}H_{26}O_2N_2$ : C 81.49, H 5.72, N 6.11. Found : C 81.38, H 5.70, N 6.10.

**Compound 8** - $^1$H-NMR (DMSO-d$^6$, δ) : 3.85-4.15 (1H, cm, H-3), 3.98 (1H, d, J = 10.7 Hz, H-4), 5.64 (1H, d, J = 10.7 Hz, H-5), 7.30 (12H, cm, aromatic protons overlapped to 2NH), 7.79 (1H, bs, NH); $^{13}$C-NMR ($CDCl_3$, ppm) : 53.49*, 55.38* (C-3, C-4), 84.26 (C-5), 126.90-137.14 (aromatic carbons), 168.03 (C-2), 172.52 (CO of $CONH_2$). Anal. calcd for $C_{17}H_{16}O_2N_2$ : C 72.83, H 5.76, N 10.00. Found : C 72.80, H 5.72, N 9.97.

**Compound 9** - $^1$H-NMR ($CDCl_3$, δ) : 2.10 (3H, s, $CH_3$ of OAc), 6.22 (1H, bs, NH), 6.98 (2H, m, aromatic protons), 7.30 (9H, cm, aromatic protons overlapped to NH), 7.61 (1H, bs, NH); $^{13}$C-NMR ($CDCl_3$, ppm) : 21.27 ($CH_3$ of OAc), 105.09 (C-5), 121.09-133.20 (aromatic carbons and C-3), 160.83 (C-4), 168.04 (C-2), 169.92 (CO of $CONH_2$), 170.01 (CO of OAc). Anal. calcd for $C_{19}H_{16}O_4N_2$ : C 67.83, H 4.80, N 8.33. Found : C 67.80, H 4.79, N 8.31.

**Compound 10** - $^1$H-NMR (DMSO-d$^6$, δ) : 7.30 (15H, m, aromatic protons), 7.79 (1H, bs, NH), 8.18 (1H, bs, NH); $^{13}$C-NMR (DMSO-d$^6$, ppm) : 91.98 (C-5), 126.33-130.87 (aromatic carbons), 137.34 (C-3), 163.26 (C-4), 168.90 (C-2). Anal. calcd for $C_{23}H_{17}O_3N$ : C 77.72, H 4.82, N 3.94. Found : C 77.68, H 4.80, N 3.91.

**Compound 11** - $^1$H-NMR ($CDCl_3$, δ) : 5.76 (1H, bs, NH), 7,15 (15 H, m, aromatic protons), 7.51 (1H, bs, NH), 9.19 (1H, bs, NH); $^{13}$C-NMR ($CDCl_3$, ppm) : 95.04 (C-5), 122.21 (C-3), 128.83-143.58 (aromatic carbons), 162.14 (C-4), 167.61*, 169.49* (C-2, CO of $CONH_2$). Anal. calcd for $C_{23}H_{18}O_2N_2$ : C 77.94, H 5.12, N 7.91. Found : C 77.99, H 5.08, N 7.88.

**Compound 12** - (diastereomeric mixture) $^1$H-NMR ($CDCl_3$, δ) : 2.10 (3H, s, $CH_3$ of OAc), 2.30-3.20 (4H, cm, 2H-4, 2H-3'), 5.52 (1H, t, J = 8.0 Hz, H-3"), 6.1 (1H, m, H-5), 7.35 (10H, m, aromatic protons); $^{13}$C-NMR ($CDCl_3$, ppm) : 20.80 ($CH_3$ of OAc), 40.11, 40.59, 41.37, 42.14 (C-4, C-3'), 71.36, 72.25 (C-3"), 78.90, 79.09 (C-5), 117.34 (CN), 125.59-138.92 (aromatic carbons), 169.83*, 170.29* (C-2, CO of OAc). Anal. calcd for $C_{21}H_{19}O_4N$ : C 72.18, H 5.48, N 4.01. Found : C 72.15, H 5.46, N 3.97.

**Compound 13** - (diastereomeric mixture) $^1$H-NMR ($CDCl_3$, δ) : 1.50-3.20 (12H, s, $CH_3$ at C-5, $CH_3$ at C-3", $CH_3$ of OAc, 2H-4, 2H-3'), 7.30 (10H, m, aromatic protons);$^{13}$C-NMR ($CDCl_3$, ppm) : 29.10 ($CH_3$ of OAc), 29.70*, 29.90* ($CH_3$ at C-5, $CH_3$ at C-3"), 41.49, 45.61, 47.52, 48.67 (C-4, C-3', C-3), 81.75, 81.99 (C-5), 85.85, 85.98 (C-3"), 118.44, 118.66 (CN), 123.69-143.97 (aromatic carbons). Anal. calcd for $C_{23}H_{23}O_4N$ : C 73.18, H 6.15, N 3.71. Found : C 73.11, H 6.09, N 3.65.

**Compound 14** - (diastereomeric mixture) $^1$H-NMR ($CDCl_3$, δ) : 1.96 (1H, d, $J_{AB}$= 13.9 Hz, $H_A$-3'), 2.15 (3H, s, $CH_3$ of OAc), 2.47 (1H, d, $J_{AB}$= 13.9 Hz, $H_B$-3'), 2.55 (2H, d, $J_{AB}$= 14.7 Hz, $H_A$-4), 4.21 (2H, d, $J_{AB}$= 14.7 Hz, $H_B$-4), 7.25 (20H, m, aromatic carbons), 8.62 (1H, bs, NH); $^{13}$C-NMR ($CDCl_3$, ppm) : 22.15 ($CH_3$

of OAc), 41.11*, 41.33*, 46.15* (C-3, C-4, C-3'), 65.48*, 83.87 (C-5, C-3"), 118.14 (CN), 125.68, 144.40 (aromatic carbons), 169.52*, 171.41* (C-2, CO of OAc). Anal. calcd for $C_{33}H_{28}O_3N_2$ : C 79.17, H 5.64, N 5.60. Found : C 79.12, H 5.63, N 5.68.

**Compound 15** - $^1$H-NMR ($CDCl_3$, δ) : 2.18 (3H, s, $CH_3$ of OAc), 3.13 (2H, m, 2H-3), 3.71 (1H, m, H-2), 6.03 (1H, bs, NH), 6.21 (1H, bs, NH), 7.30 (10H, m , aromatic protons). Anal. calcd for $C_{19}H_{18}O_3N_2$ : C 70.78, H 5.63, N 8.69. Found : C 70.76, H 5.63, N 8.66.

**Compound 16** - $^1$H-NMR ($CDCl_3$, δ) : 7.30 (m, aromatic protons); $^{13}$C-NMR ($CDCl_3$, ppm) : 94.10 (C-5), 103.55 (C-3), 111.88 (CN), 129.31-136.30 (aromatic carbons), 165.93 (C-4), 177.77 (C-2). Anal. calcd for $C_{23}H_{15}O_2N$ : C 81.87, H 4.48, N 4.15. Found : C 81.82, H 4.43, N 4.11.

**Compound 17** - $^1$H-NMR ($CDCl_3$, δ) : 7.30 (15H, m, aromatic protons), 7.50 (1H, bs, NH); $^{13}$C-NMR ($CDCl_3$, ppm) : 76.35 (C-4), 112.51 (CN), 128.12-137.79 (aromatic carbons, C-3). Anal calcd for $C_{23}H_{16}ON_2$ : C 82.11, H 4.80, N 8.33. Found : C 82.05, H 4.78, N 8.30.

**Compound 18** - $^1$H-NMR ($CDCl_3$, δ) : 0.90 (3H, t, J = 7.2 Hz, N-C-C-**$CH_3$**), 1.52 (2H, se, J = 7.2 Hz, N-C-**$CH_2$**-$CH_3$), 2.10 (3H, s, $CH_3$ of OAc), 2.50-3.45 (6H, cm, 2H-4, 2H-3', N-**$CH_2$**), 5.90 (1H, m, H-3"), 6.40 (1H, m, H-5), 7.30 (10H, m, aromatic protons); $^{13}$C-NMR ($CDCl_3$, ppm) : 10.94 (N-C-C-**$CH_3$**), 20.85 ($CH_3$ of OAc), 22.26 (N-C-**$CH_2$**-$CH_3$), 34.80, 35.23, 36.10 (C-4, C-3, C-3'), 42.00 (N-**$CH_2$**), 72.76*, 73.65 (C-5, C-3"), 117.88, 117.99 (CN), 126.31-138.83 (aromatic carbons), 163.81 (C-2), 170.27 (CO of OAc). Anal calcd for $C_{24}H_{26}O_3N_2$ : C 73.81, H 6.72, N 7.18. Found : C 73.78, H 6.67, N 7.13.

**Compound 19** - (diastereomeric mixture) $^1$H-NMR ($CDCl_3$, δ) : 0.90 (3H, m, N-C-C-**$CH_3$**), 1.45 (2H, m, N-C-**$CH_2$**-C), 1.90 (1.76H, s, $CH_3$ at C-4), 1.94 (1.24H, s, $CH_3$ at C-4), 2.12 (1.25H, s, $CH_3$ of OAc), 2.15 (1.75H, s, $CH_3$ of OAc), 2.50-3.40 (5H, cm, H-2, 2H-3, N-**$CH_2$**), 6.30 (1H, bs, NH), 7.30 (5H, m, aromatic protons); $^{13}$C-NMR ($CDCl_3$, ppm) : 11.35 (N-C-C-**$CH_3$**), 22.24 ($CH_3$ of OAc), 22.62 (N-C-**$CH_2$**-), 24.78, 26.92 ($CH_3$ at C-4), 34.19 (C-2), 40.77 (C-3), 42.41 (N-**$CH_2$**), 82.25, 83.27 (C-4), 118.87, 119.15 (CN), 124.95-143.49 (aromatic carbons), 164.58 (C-1), 170.06, 170.60 (CO of OAc). Anal. calcd for $C_{17}H_{22}O_3N_2$ : C 67.51, H 7.34, N 9.27. Found : C 67.42, H 7.29, N 9.22.

**Compound 20** - $^1$H-NMR ($CDCl_3$, δ) : 0.52 (3H, t, J = 7.2 Hz, N-C-C-**$CH_3$**), 0.80 (2H, m, N-C-**$CH_2$**-$CH_3$), 2.00 (1H, d, $J_{AB}$= 14.3 Hz, $H_A$-3'), 2.13 (3H, s, $CH_3$ of OAc), 2.38 (1H, d, $J_{AB}$= 14.3 Hz, $H_B$-3'), 2.60 (1H, d, $J_{AB}$= 14.7 Hz, $H_A$-4), 3.10 (2H, m, N-**$CH_2$**-), 4.23 (1H, d, $J_{AB}$= 14.7 Hz, $H_A$-4), 7.20 (20H, m, aromatic protons); $^{13}$C-NMR ($CDCl_3$, ppm) : 11.12 (N-C-C-**$CH_3$**), 20.82 (N-C-**$CH_2$**-$CH_3$), 22.18 ($CH_3$ of OAc), 40.57 (C-4), 41.97 (N-**$CH_2$**-), 45.73 and 46.52 (C-3), 71.05*, 83.49* (C-5, C-3"), 118.91 (CN), 126.15-144.44 (aromatic carbons), 169.13*, 169.46* (C-2, CO of OAc). Anal. calcd for $C_{36}H_{34}O_3N_2$ : C 79.67, H 6.32, N 5.16. Found : C 79.65, H 6.30, N 5.12.

**Compound 21** - $^1$H-NMR ($CDCl_3$, δ) : 0.95 (3H, t, J = 7.2 Hz, N-C-C-**$CH_3$**), 1.67 (2H, se, J = 7.2 Hz, N-C-**$CH_2$**-$CH_3$), 3.48 (2H, t, J = 7.2 Hz, N-**$CH_2$**-), 7.30 (15H, m, aromatic protons); $^{13}$C-NMR ($CDCl_3$, ppm): 11.79 (N-C-C-**$CH_3$**), 23.70 (N-C-**$CH_2$**-$CH_3$), 49.70 (N-**$CH_2$**-), 96.18 (C-5), 112.76 (CN), 127.99-

131.55 (aromatic carbons), 138.45 (C-3). Anal. calcd for $C_{26}H_{22}ON_2$ : C 82.50, H 5.86, N 7.41. Found : C 82.66, H 5.85, N 7.36.

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