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Synthesis of Cinnamic Derivatives using Pyridine and Piperidine via Simple Knoevenagel Condensation Reaction

Rachid. MAHY, Abdelkader. OULMIDI, Allal. CHALLIOUI

Laboratory of Chemistry Organique Macromoleculaire & Product Naturel- Group Photochemistry, Mohammed first University, Oujda, Morocco

Abstract Cinnamic derivatives were easily prepared in good yield, by using Knoevenagel condensation between aromatic aldehydes and compounds containing an active methylene group. Reactions were performed in pyridine and in presence of piperidine as a basic catalyst. The structures were determined using IR and NMR spectroscopy.

Keywords Cinnamate derivates, Knoevenagel, piperidine, spectroscopy

1. Introduction

Cinnamic acid and their derivatives have been extensively used as photosensitive chromophores for the preparation of photocrosslinkable polymers [1-2]. These kind of polymers have a large interest in different fields, such as photolithography [3], printing materials [4], liquid crystalline and non-linear optical materials [5]. Among the methods commonly used to prepare these structures, Knoevenagel reaction have the advantage to lead to the desired product in one step, in an easier work-up and with a good yield. This reaction is traditionally carried out under homogenous conditions, by condensation of carbonyl compounds with products having active methylene groups, in presence of a weak base as a catalyst. Various catalysts and experimental conditions have been developed. Knoevenagel condesation can be activated by weak bases or acids under homogeneous conditions (piperidine [6], pyridine or $TiCl_4$ [7], pyridinium acetate [8], acetic acid/ammonium acetate [9], etc.) or heterogeneous conditions ($AlPO_4$–Al_2O_3 [10], Xonotlite-tertiobutoxide potassium [11], zeolite [12], Montmorillonite-silylpropylethylenediamine [13], etc.). The reaction rate can be increased by working under infrared or ultrasound irradiation [14]. The catalyst can be immobilized on a support like silica gel [15] to carry out the Knoevenagel reaction under continuous-flow conditions. In this paper we report a convenient method for the preparation of cinnamic derivatives based on the Knoevenagel condensation of aromatic aldehydes with various reagents containing active methylene groups in the presence of piperidine as catalyst.

2. Material and Methods

2.1. Materials

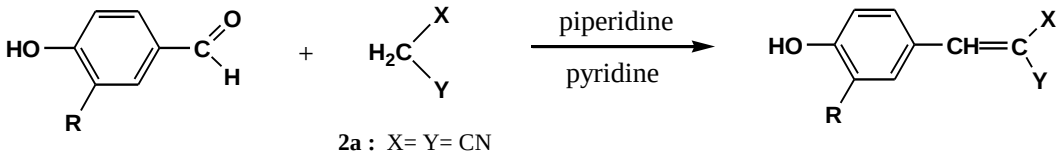
The solvents were distilled before use. p-hydrobenzaldehyde and vanillin were recrystallized. The compounds containing active methylene were used as received (Aldrich).

2.2. Apparatus

Melting points were performed on a Butchi apparatus. Infrared spectra were performed on an ATI MATTSON spectrophotometer. ^{1}H- and ^{13}C-NMR spectra were recorded in DMSO-d_6 as solvent, with tetramethylsilane (TMS) as internal reference, on a BRUKER AC 400 apparatus, operating at 400 MHz for ^{1}H and 125 MHz for ^{13}C .

2.3. General procedure for codensations

A pyridine solution (7.5 ml) of the aromatic aldehyde **1** (25 mmol), the compound having an active methylene group **2** (25 mmol) and piperidine (2 drops) was refluxed for 1 h. Then, the solution was dropped slowly into a flask containing a solution of chloride acid 1.5 N (100 ml) and ice (25 g). The mixture was stirred until a suspension was obtained. The precipited product was filtered, washed with water, and then recristallized in ethanol.



1a : R = H
1b : R = OCH_3

2a : X= Y= CN
2b : X= CN, Y= CO_2Et
2c : X= CN, Y= CO_2H
2d : X= CO_2Et, Y= CO_2Et

3 : R = H
4 : R = OCH_3

Figure 1: Synthesis of various cinnamic derivatives.

The structures were determined using IR and NMR spectroscopy:

- **4-hydroxybenzylidenemalonitrile** (**3a**) :

mp 187°C.

IR (KBr) **:** 3357 (OH) , 2227 (C≡N), 1611 (C=C).

^{1}H -NMR (400MHz, DMSO-d_6) **:** 8.32 (s , 1H, HC= C) , 7.80 (d, J= 11.4 Hz, 2H, Ar- $H_{2,6}$), 7.00 (d, J= 11.4 Hz , 2H, Ar- $H_{3,5}$).

^{13}C -NMR (MHz, DMSO-d_6) **:** 164.1 (C_4), 160.7 (CH=C), 134.1 (C_2 and C_6), 123.0 (C_1), 116.8 (C_3 and C_5), 115.3 and 114.4 (2 CN), 75.3 (CH=C).

- **Ethyl 2-cyno p-hydroxycinnamate** (**3b**) :

mp 173°C.

IR (KBr) **:** 3299 (OH) , 2228 (C≡N), 1714 (C=O), 1613 (C=C).

^{1}H -NMR (400MHz, DMSO-d_6) **:** 8.17 (s , 1H, HC= C), 7.95 (d, J= 11.4 Hz , 2H, Ar- $H_{2,6}$), 6.90 (d, J= 11.4 Hz , 2H, Ar- $H_{3,5}$), 4.25 (q, J= 7.2 HZ , 2H, CH_3-CH_2-O), 1.27 (t, J= 7.2 Hz , 3H, CH_3-CH_2-O). **^{13}C -NMR** (MHz, DMSO-d_6) **:** 164.1 (CO_2Et),162.6 (C_4), 154.4 (CH=C), 133.8 (C_2 and C_6), 122.0 (C_1), 116.6 (C_3 and C_5), 116.6 (CN), 98.4 (CH=C), 63.0 (CH_3-CH_2-O), 13.9 (CH_3-CH_2-O).

- **2-cyno p-hydroxycinnamate acid** (**3c**) :

mp 248°C.

IR (KBr) **:** 3303 (OH) , 2232 (C≡N), 1672 (C=O), 1617 (C=C).

^{1}H -NMR (400MHz, DMSO-d_6) **:** 8.25 (s , 1H, HC= C) , 7.98 (d, J= 11.4 Hz , 2H, Ar- $H_{2,6}$), 6.98 (d, J= 11.4 Hz , 2H, Ar- $H_{3,5}$).

^{13}C -NMR (MHz, DMSO-d_6) **:** 168.1 (CO_2H),162.8 (C_4), 154.8 (CH=C), 134.1 (C_2 and C_6), 122.7 (C_1), 116.6 (C_3 and C_5), 116.6 (CN), 97.3 (CH=C).

- **Diethyl p-hydroxybenzylidenemalonate** (**3d**) :

mp 75°C.

IR (KBr) : 3300 (OH) ; 1715 and 1680 (C=O); 1610 (C= C).

^{1}H -NMR (400MHz, DMSO-d_6) : 7.67 (s, 1H, HC=C) , 7.30 (d, J= 11.4 Hz, 2H, Ar- $H_{2,6}$), 6.80(d, J= 11.4 Hz, 2H, Ar- $H_{3,5}$), 4.38 and 4.30 (2q, J= 7.2 HZ , 4H, CH_3-CH_2-O), 1.32 (2t, J= 7.2 Hz , 6H, CH_3-CH_2-O).

^{13}C -NMR (MHz, DMSO-d_6) : 167.9 and 164.9 (2 CO_2Et),158.7 (C_4), 142.6 (CH=C), 131.7 (C_2 and C_6), 125.0 (C_1), 123.0 (CH=C), 116.0 (C_3 and C_5), 62.0 and 61.7(2 CH_3-CH_2-O), 14.2 and 13.9 (CH_3-CH_2-O).

- **3-methoxy p-hydroxybenzylidenemalonitrile** (**4a**) :

mp 134°C.

IR (KBr) **:** 3378 (OH), 2219 (C≡N) , 1600 (C=C).

^{1}H -NMR (400MHz, DMSO-d_6) **:** 7.73 (d, J= 2 Hz, 1H, Ar- H_2), 7.67 (s , 1H, HC= C), 7.35 (dd, J= 2.0 and 8.3 Hz , 1H, Ar- H_6), 7.02 (d, J= 8.3 Hz , 1H, Ar-H_5), 3.99 (s , 3H, CH_3- O).

^{13}C -NMR (MHz, DMSO-d_6) **:** 159.4 (CH=C), 152.2 (C_4), 147.1 (C_3), 128.9(C_6), 124.0 (C_1), 115.3 (C_5), 114.4 and 113.7 (2 CN), 110.6(C_2), 70.0 (CH=C), 56.2 (OCH_3).

- **Ethyl 2-cyano (4-hydroxy-3-methoxyphenyl)propanoate** (**4b**) :

mp 110°C.

IR (KBr) **: 3376** (OH) , 2220 (C≡N) , 1703 (C=O), 1604 (C=C).

^{1}H -NMR (400MHz, DMSO-d_6) **:** 8.17 (s, 1H, HC= C), 7.87 (d, J= 2 Hz, 1H, Ar- H_2), 7.42 (dd, J= 2.0 and 8.3 Hz, 1H, Ar- H_6), 7.02 (d, J= 8.3 Hz , 1H, Ar- H_5), 4.38 (q, J= 7.1 HZ , 2H, CH_3-CH_2-O), 3.99 (s , 3H, CH_3- O), 1.40 (t, J= 7.1 Hz , 3H, CH_3-CH_2-O).

^{13}C -NMR (MHz, DMSO-d_6) **:** 162.8 (CO_2Et), 154.5 (CH=C), 150.5 (C_4), 146.5 (C_3), 128.4 (C_6), 123.8 (C_1), 116.0 (CN), 114.5 (C_5), 110.4 (C_2), 98.5 (CH=C), 62.1(CH_3-CH_2-O), 55.7 (OCH_3), 13.8 (CH_3-CH_2-O).

- **2-cyno (4-hydroxy-3-methoxyphenyl)propanoate acid** (**4c**) :

mp 210°C.

IR (KBr) **:** 3475 (OH) , 2223 (C≡N) , 1687 (C=O), 1608 (C=C).

^{1}H -NMR (400MHz, DMSO-d_6) **:** 8.22 (s, 1H, HC= C), 7.80 (d, J= 2 Hz, 1H, Ar- H_2), 7.62 (dd, J= 2.0 and 8.3 Hz , 1H, Ar- H_6), 7.05 (d, J= 8.3 Hz , 1H, Ar- H_5), 3.90 (s , 3H, CH_3- O)

^{13}C -NMR (MHz, DMSO-d_6) **:** 164.1 (CO_2H), 154.5 (CH=C), 150.8 (C_4), 148.0 (C_3), 127.0 (C_6), 123.1 (C_1), 115.7 (CN), 114.1 (C_5), 110.9 (C_2), 98.6 (CH=C), 55.9 (OCH_3).

- **Diethyl 4-hydroxybenzylidenemalonate** (**4d**) :

mp 108°C.

IR (KBr) **:** 3480 (OH), 1775 and 1682 (C=O), 1608 (C=C).

^{1}H -NMR (400MHz, DMSO-d_6) **:** 7.67 (s , 1H, HC= C), 7.20 (d, J= 2.0 Hz, 1H, Ar- H_6), 7.05 (dd, J= 2.0 and 8.3 Hz , 1H, Ar- H_2), 6.92 (d, J= 8.3 Hz, 1H, Ar-H_5), 4.36 and 4.30 (2q, J= 7.2 HZ , 4H, CH_3-CH_2-O), 3.89 (s , 3H, CH_3- O), 1.38 (2t, J=7.2 Hz , 6H, CH_3-CH_2-O).

^{13}C -NMR (MHz, DMSO-d_6) **:** 167.3 and 164.5 (2 CO_2Et), 148.3 (C_4), 146.6 (C_3), 142.2 (CH=C), 125.2 (C_1), 124.8 (C_6), 123.5 (CH=C), 114.8 (C_5), 111.4 (C_2), 61.7 and 61.5(2 CH_3-CH_2-O), 14.2 and 14 (CH_3-CH_2-O), 55.9 (OCH_3).

3. Results and Discussion

Aromatic aldehydes **1** were mixed with compounds having active methylene group **2** in pyridine and in presence of piperidine as a catalyst (Fig. 1). The condensations were carried out in reflux of pyridine for 1 h and pure cinnamic products were easily obtained after precipitation by dropping the mixture into a flask containing a solution of chloride acid 1.5 N. The various cinnamic compounds synthesized are summarized in Table 1.

Table 1: Products of type **3** and **4** synthesized according to the Knoevenagel condensation

Entry	R	X	Y	Yield
3a	H	CN	CN	95
3b	H	CN	COOEt	80
3c	H	CN	COOH	75
3d	H	COOEt	COOEt	58
4a	OCH_3	CN	CN	90
4b	OCH_3	CN	COOEt	85
4c	OCH_3	CN	COOH	71
4d	OCH3	COOEt	COOEt	60

The above results show that the yield decreases in the following order: malonitrile > ethylcyanoacetate > cyanoacetic acid > diethylmalonate. The reactivity of these reagents is in accordance with their respective pK_as (malonitrile 11.2; diethylmalonate 13, and ethylcyanoacetate 11.2 < pK_a < 13). It decreases when pK_a increases.

On the other hand, the comparison of the yields obtained with p-hydroxybenzaldehyde **3** and vanillin **4** respectively (table 1), shows that the presence of a methoxy substituent in meta position (case of vanillin) does not affect the

condensation reactivity. Thus when the methoxy group is in ortho or para position, Knoevenagel reaction is deactivated.

In the case of the condensation products (**3b-c** and **4b-c**), the configuration of unsaturated bond was not determined. A previous study on structures **5** (Fig. 2) reported that **E** isomer was formed in highly stereoselectivity . The author was based on long distance heteronuclear coupling constants $^{3}J_{H-13CO}$ = 6.6 Hz and $^{3}J_{H-13CN}$ = 14.1 Hz ($J_{tans} > J_{cis}$ would be expected for these systems).

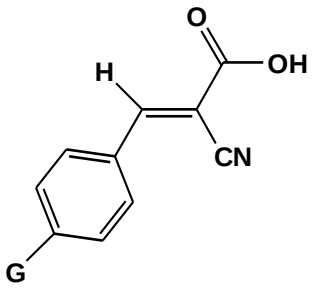


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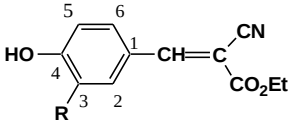
Figure 2 : G = H, p-NO_2, o-NO_2, p-$N(Me)_2$, p-MeO, o-MeO, p-Cl, o-Cl, p-Br

Structures of cinnamic derivatives were determined using IR and more especially NMR spectroscopy.

^{1}H-NMR shows the absence of the characteristic peak of the aldehyde proton (9.80-9.82 ppm) and the appearance of the signal of the benzylidene proton (7.50 to 8.40 ppm).

In the case of cinnamic derivatives obtained from vanilline, the respective structures were characteriwed without ambiguity. So the small coupling constant J^4 (≈ 2 Hz) possibily only between H_2 and H_6 protons allowed us to distinguish H_5 from H_6 (see for example spectrum **4b**; Fig. 3).

For compounds **3b**, aromatic protons H_5 and H_6 were assigned by comparison with the chemical shifts of H_5 and H_6 in **4b** (compare for example spectra **3b** and **4b** ; Fig.3).



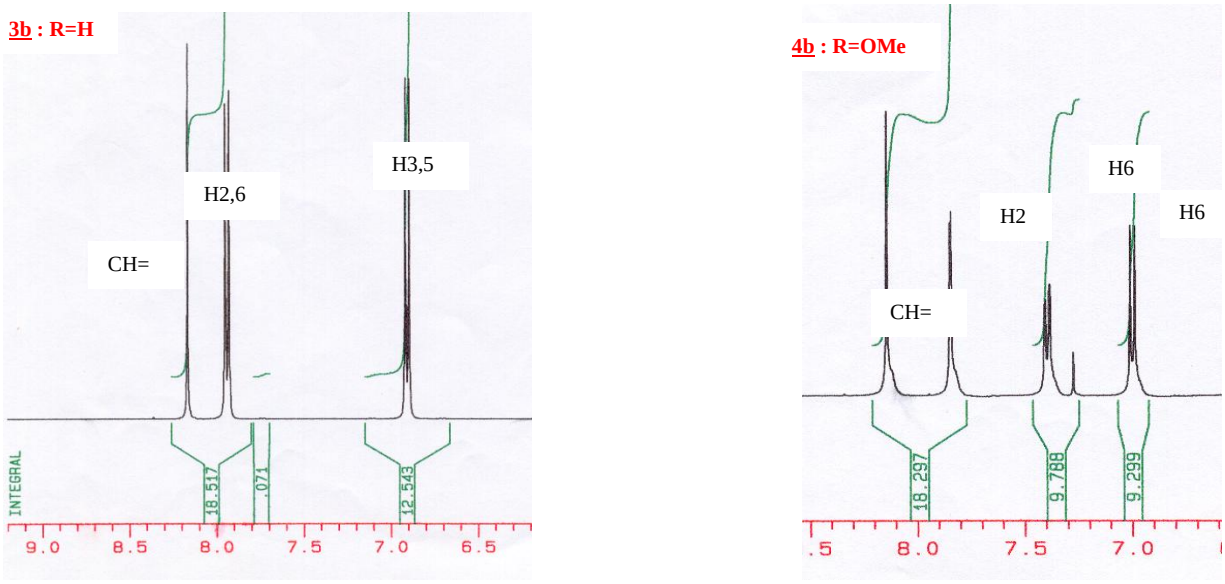


*Figure 3: Spectra **3b** and **4b***

For the ^{13}C-NMR data, the signals of benzylidene carbons (CH=C and CH=C) rise respectively in range of 70 to 123.5 ppm and 142.2 to 160.7 ppm according to the nature of X and Y substituents. In addition, spectra indicate the disappearance of aldehyde carbon signal and the rising of carbon characteristic peaks of X and Y groups.

Conclusion

Knoevenagel condensation between aromatic aldehydes and compounds containing active methylene groups was successfully carried out in presence of piperidine as a catalyst. By using this reaction, various cinnamic derivatives were synthesized. This method presents numerous advantages: it is very easily to perform and leads to good yields in cinnamic derivatives.

The structures obtained were determined without ambiguity using spectral data, in particular ^{1}H-NMR spectroscopy.

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