SOLVENT-FREE KNŒVENAGEL REACTION OF MALONIC ACID

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ABSTRACT: Knœvenagel reaction is applied to the condensation of malonic acid with aromatics aldehydes in solvent-free conditions under conventional heating. This solvent-free reaction leads in a single step to corresponding unsaturated diacids, when the basic entities such K_2CO_3, Na_2CO_3 $KHCO_3$ and KOH are used. The application of the same reaction with pyridine, piperidine and quinoline, acting as catalysts, leads after decarboxylation, to the insaturated monoacid.

Keywords: malonic acid; Knœvenagel reaction; solvent-free synthesis.

INTRODUCTION

As is known, several studies on the Knœvenagel reaction have been undertaken in homogeneous or heterogeneous basic medium. Thus, many synthetic procedures using condensation between aldehydes and various methylene activated compounds such as diethyl malonate, ethyl cyanoacetate, acetyl aceton, and malonitrile [1-3] have been successfully employed to obtain the corresponding unsaturated diesters, cyanoesters, dicetons or dinitriles. The presence, on the unsatured carbon, of two carboxylic functions confers to this type of molecules specific properties. So these compounds can be used as reagent to obtain cyclic compounds as well as polymers [4]. They present also different biologic activities [5].

The use of malonic acid (MA) as starting material, has received less attention in comparison with the other reagents because of its condensation with arylaldehydes (AA), under conventional heating, did not lead to the expected unsaturated dicarboxylic acids (UDA) when organic bases such as pyridine or piperidine are used as catalysts [6]. The reaction proceeded via unavoidable decarboxylation to give the corresponding unsatured monocarboxylic acids (UMA). Furthermore, polar solvents such as DMF and DMSO or an excess of pyridine or piperidine were required to dissolve MA [7]. Consequently, the synthesis of UDA required several steps such as the preliminary synthesis of diester followed by its hydrolysis [8] or that of diketone followed by its oxidation [9]. Recently, Loupy and Coll. [10] have reported a new synthetic procedure utilizing bentonite-catalyzed condensation of MA and AA under microwave irradiation in the absence of solvent. This procedure appeared to be useful to obtain UDA as main products with good yields and very short time reaction but it was not free of drawbacks: (i) high molar ratio MA/AA (3/1), (ii) high cost, (iii) difficult application to industrial.

Taking these facts into consideration, we were interested in using Knœvenagel reaction for preparing some UDA under conventional heating. We propose in this paper a very simple and novel

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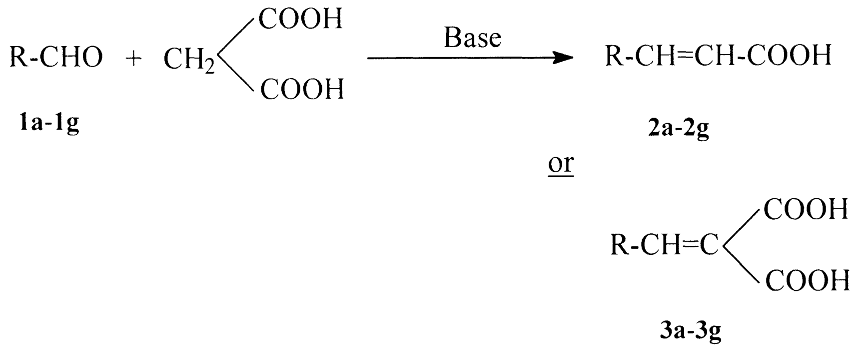
procedure based on solvent-free condensation of MA/AA systems which lead selectively, under certain operating conditions, to the corresponding UDA or UMA.

RESULTS AND DISCUSSION

Condensation of MA and AA **1a-1g** (see Table I) afford, under conventional heating, the corresponding UMA **2a-2g** or UDA **3a-3g** as shown in scheme 1.



Scheme 1

We first concentrated on furfural / MA system and then extended the study to the other aldehydes. The preliminary results put in evidence the importance of the choise of the basic catalyst on the structure of the compound obtained after condensation. We have found that the use of organic basic catalyst such as pyridine, piperidine and quinoleine leaded to furacrylic acid **2a**, whereas inorganic catalyst such as NaOH, KOH, $NaHCO_3$ and K_2CO_3 allowed furylidenemalonic acid **3a** synthesis and the decarboxylation did not take place (see Table I). In addition, some important factors should be considered in order to optimise UDA synthesis. Thus five parameters were varied in this context, namely the quantity of the catalyst, the reaction temperature, the hydration state of reaction media, the reaction time and the molar ratio between the agents. The results were obtained after 3 hours when K_2CO_3 was used as a catalyst at 130°C with a molar ration K_2CO_3 / H_2O: 1/0.54 starting from stœchiometric mixtures furfural/MA. We notice also the importance of the electronic density of aromatic structure on conversion rate in diacids or monoacids. So the presence of attracting group such as NO_2 allows to obtain the unsatured diacids with a high yield, while the presence of a methoxy group inhibits the reaction.

EXPERIMENTAL

AA, MA and different bases are commercial products. Melting points were taken using a Electrothermal 9100 apparatus. IR Spectra were obtained on a Jasco FT-IR 420 spectrophotometer apparatus (in KBr pellets). ^1H and ^{13}C NMR spectra were recorded with a Bruker WP 200 spectrometer at 300 MHz in DMSO-d_6 with TMS as internal standard (chemical shift in ppm).

Synthesis of monoacids 2a-2g:

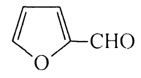
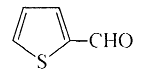
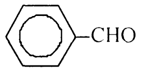
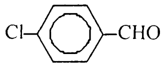
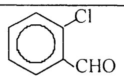
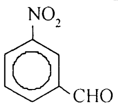
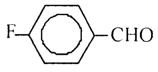
A mixture of MA (50 mmol), quinoleine (25 mmol) is introduced into 100 ml flask and stirred for 15 min at 130°C. After that AA (50 mmol) is added and the mixture is stirred 3 hours at the same temperature.

After the completion of the reaction we first add a 20% solution of sodium carbonate until $pH \geq 8$. The reaction medium is extracted with 20 ml of ether. The aquous phase is acidified with diluted solution of HCl until $pH \leq 5$. The resulting precipitate is filtred, washed with ice cold water and vacuum dried at 80°C.

Synthesis of diacids 3a-3g:

A mixture of MA (50 mmol), potassium carbonate (25 mmol) and water (5 ml) is introduced into 100 ml flask and stirred for 10 min at 130°C. After that AA (50 mmol) is added and the mixture is stirred 3 hours at the same temperature. Diacids were isolated by the method described previously.

Table I: Solvent-free condensation of MA and AA:

Compound	AA	Catalysts	Yield (%)		Mp (°C)
			2	3	
2a/3a		K_2CO_3	-	81	199
		quinoleine	70	-	139
2b/3b		K_2CO_3	-	62	204
		quinoleine	45	-	140
2c/3c		K_2CO_3	-	63	193
		quinoleine	75	-	129
2d/3d		K_2CO_3	-	47	200
		quinoleine	63	-	245
2e/3e		K_2CO_3	-	51	189
		quinoleine	44	-	202
2f/3f		K_2CO_3	-	83	200
		quinoleine	50	-	190
2g/3g		K_2CO_3	-	50	207
		quinoleine	51	-	189

2a: Mp: 139°C. RMN ^1H (300 MHz, DMSO) δ ppm: 6.17 (d, H7), 6.61 (dd, H_4), 6.91 (d, H3), 7.31 (d, H_6), 7.82 (d, H_5). RMN ^{13}C (75 MHz, DMSO) δ ppm: 113.0 (C_4), 115.8 (C_3), 116.3 (C_7), 131.1 (C_6), 146.0 (C_5), 150.6 (C_2), 167.7 (C_8).

3a: Mp: 199°C. RMN ^1H (300 MHz, DMSO) δ ppm: 6.64 (dd, H_4), 6.97 (d, H3), 7.30 (s, H_6), 7.87 (d, H_5). RMN ^{13}C (75 MHz, DMSO) δ ppm: 113.3 (C_4), 118.3 (C_3), 124.3 (C_7), 125.6 (C_6), 147.3 (C_5), 149.1 (C_2), 165.7/167.7 (C_8/C_9).

2b: Mp: 138°C. RMN ^{1}H (300 MHz, DMSO) δ ppm: 6.18 (d, H_7), 7.13 (dd, H_4), 7.50 (d,H_3), 7.72 (s, H_6), 7.71 (d, H_5). RMN ^{13}C (75 MHz, DMSO) δ ppm: 117.9 (C_4), 128.8 (C_3), 129.8 (C_7), 132.0 (C_6), 137.0 (C_5), 139.2 (C_2), 167.6 (C_8).

3b: Mp: 204°C. RMN ^{1}H (300 MHz, DMSO) δ ppm: 7.15 (m, H_4), 7.48 (d, H_3), 7.72 (s, H_6), 7.82 (d, H_5). RMN ^{13}C (75 MHz, DMSO) δ ppm: 124.5 (C_4), 128.2 (C_3), 132.6 (C_7), 132.8 (C_6), 135.2 (C_5), 136.1 (C_2), 165.8/168.0 (C_8/C_9).

2c: Mp: 129°C. RMN ^{1}H (300 MHz, DMSO) δ ppm: 6.54 (d, H_8), 7.40 (d, H_3/H_5), 7.43 (s, H_4), 7.62 (d, H_7), 7.68 (m, H_2/H_6). RMN ^{13}C (75 MHz, DMSO) δ ppm: 119.5 (C_8), 128.5 (C_6/C_2), 129.2 (C_3/C_5), 130.5 (C_4), 134.5 (C_1), 144.2 (C_7), 167.9 (C_9).

3c: Mp: 193°C. RMN ^{1}H (300 MHz, DMSO) δ ppm: 7.63 (d, H_2/H_6), 7.69 (s, H_4), 7.88 (d, H_7), 7.89 (m, H_3/H_5). RMN ^{13}C (75 MHz, DMSO) δ ppm: 129.2 (C_6/C_2), 131.2 (C_3/C_5), 131.9 (C_4), 139.4 (C_1), 148.2 (C_7), 170.0 (C_9).

2d: Mp: 245°C. RMN ^{1}H (300 MHz, DMSO) δ ppm: 6.52 (dd, H_8), 7.38 (d, H_2/H_6), 7.56 (d, H_7), 7.63 (d, H_3/H_5). RMN ^{13}C (75 MHz, DMSO) δ ppm: 120.3 (C_8), 129.1 (C_3/C_5), 130.0 (C_2/C_6), 133.4 (C_1), 135.0 (C_4), 142.7 (C_7), 167.8 (C_9).

3d: Mp: 200°C. RMN ^{1}H (300 MHz, DMSO) δ ppm: 7.48 (d, H_2/H_6), 7.52 (s, H_7), 7.57 (d, H_3/H_5). RMN ^{13}C (75 MHz, DMSO) δ ppm: 129.6 (C_3/C_5), 131.5 (C_2/C_6/C_8), 132.1 (C_1), 135.3 (C_4), 137.6 (C_7), 165.4/168.1 (C_9/C_{10}).

2e: Mp: 202°C. RMN ^{1}H (300 MHz, DMSO) δ ppm: 6.60 (d, H_8), 7.40 (m, H_5/H_4), 7.54 (d, H_3), 7.87 (d, H_7), 7.92 (dd, H_6). RMN ^{13}C (75 MHz, DMSO) δ ppm: 122.6 (C_8), 128.0 (C_5), 128.5 (C_3), 130.2 (C_6), 132.0 (C_4), 132.1 (C_2), 133.9 (C_4) 138.9 (C_7), 167.5 (C_9).

3e: Mp: 189°C. RMN ^{1}H (300 MHz, DMSO) δ ppm: 7.42 (m,H_5/H_4,), 7.51 (d, H_3/H6), 7.73 (s, H_7). RMN ^{13}C (75 MHz, DMSO) δ ppm: 127.9 (C_8), 129.3 (C_5), 130.1 (C_3), 131.5 (C_6), 131.8 (C_4), 131.9 (C_2), 133.7 (C_1) 135.4 (C_7), 165.1/167,5 (C_9,C_{10}).

2f: Mp: 190°C. RMN ^{1}H (300 MHz, DMSO) δ ppm: 6.70 (d, H_8), 7.65 (d, H_5), 7.66 (d,H_7), 8.12 (d, H_6), 8.17 (dd, H_4), 8.43 (s, H_2). RMN ^{13}C (75 MHz, DMSO) δ ppm: 122.5/123.0 (C_2/C_8), 124.6 (C_4), 130.6 (C_5), 134.3 (C_6), 134.8 (C_1), 141.7 (C_7), 148.5 (C_3), 167.4 (C_9).

3f: Mp: 200°C. RMN ^{1}H (300 MHz, DMSO) δ ppm: 7.63 (s, H_7), 7.67 (t, H_5), 7.93 (d, H_6), 8.16 (d, H_4), 8.40 (s, H_2). RMN ^{13}C (75 MHz, DMSO) δ ppm: 123.4/124.7 (C_2/C_8), 130.8 (C_4), 131.1 (C_5), 134.9 (C_6), 135.9 (C_1), 136.7 (C_7), 148.3 (C_3), 165.2/167.8 (C_9/C_{10}).

2g: Mp: 189°C. RMN ^{1}H (300 MHz, DMSO) δ ppm: 6.50 (d, H_8), 7.24 (m, H_2/H_6), 7.58 (d, H_7), 7.76 (m, H3/H_5). RMN ^{13}C (75 MHz, DMSO) δ ppm: 119.4 (C_8), 116.0/116.3 (C_3/C_5), 130.7/130.9 (C_2/C_6), 131.21/131.25 (C_4/C_1), 143.0 (C_7), 167.9 (C_9).

3g: Mp: 207°C. RMN ^{1}H (300 MHz, DMSO) δ ppm: 7.28 (m, H_2/H_6), 7.56 (s, H7), 7.65 (m, H3/H_5). RMN ^{13}C (75 MHz, DMSO) δ ppm: 116.2/116.5 (C_3/C_5), 131.1/131.2 (C_2/C_6), 137.8 (C_7), 165.5/168.3 (C_9/C_{10}).

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