

Nucleophilic Substitution Reactions of Methyl Malonyl Chloride with Some Nucleophilic Reagents

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Abstract:

New method for synthesis of new methyl malonamic acid derivatives have been employed successfully via the nucleophilic substitution reactions of methyl malonyl chloride with urethane followed by the reaction with some of nucleophilic reagents (amine, alcohol and water) in the same medium and reaction vessel. The structural formulas of the synthesized compounds were elucidated by physical and spectroscopic methods.

Introduction:

Malonyl chloride and substituted malonyl chlorides were found to be a very good precursor for organic synthesis specially in malonic acid derivatives and heterocyclic synthesis [1]. Some of the malonic acid derivatives were found of a high interest compounds such as bis(2,2-dinitro-2-flouroethyl) malonate used as explosive or as a binder for explosive compounds [2] and the thermally stable explosive compound, bis (2-flouro-2-dinitroethyl) amides [3]. Other diamides derivatives used as culture plant protecting [4] and dicyclohexyl amides as potential antiinflammatory agents [5]. Moreover, the dianilide derivatives of nitroanthranilic acid yielded useful compounds as allergy-, ulcer- and hyaluronidas inhibitors [6], also effective antihyaluronidase, antiallergic and antiulcer agents [7]. On the other hand, The nucleophilic substitution reactions of substituted malonyl chlorides were employed to synthesis substituted malonamic acids dervatives and substituted iminohydrazine derivatives [8], also a number of substituted malonamates and mlonamanildes have been synthesized in this field [9]. In the heterocyclic synthesis field, malonyl chloride and substituted malonyl chloride were employed to synthesize heterobicyclic compounds of interest biological activity such as anti-microbial activity [10] and anti-cancer cells activity [11,12].

This paper is concerned with the applying of new method for synthesis of 2-methyl malonamic acid derivatives from the reaction of 2-methyl malonyl chloride with urethane followed by reaction with some nucleophiles (amine, alcohol and water) in the same medium and reaction vessel.

Experimental:

Melting points were measured by Electrothermal 1A9000 Digital-Series Melting point (1998) Apparatus and are uncorrected. I.R. spectra were recorded by Thermo-Nicolet. Fourier-Transform Infrared (FT-IR) spectrophotometer as KBr disc. U.V. spectra were obtained from Shimadzu UV-Vis spectrophotometer in CHCl_3 .

Methods of Preparation:

The new methylmalonamic acid derivatives (2, 3_{a-e}) were synthesized according to the application of new method .

Preparation of Methylmalonyl Chloride:

Finely powdered methyl malonic acid (0.022 mole, 2.6 gm) and thionyl chloride (5 ml) was heated under

unhydrous conditions on a sand bath at 70°C with stirring for 8 hrs. The excess of thionyl chloride was evaporated at 100°C to yield an oily pale yellow of methylmalonyl chloride.

Reaction of Methylmalonyl Chloride with Urethane:

All the amount of the above prepared oily methylmalonyl chloride in the same reaction vessel was dissolved in dry benzene (25 ml) followed by adding of urethane (0.018 mole, 1.6 gm), then the mixture was refluxed for (2-3 hrs) with stirring.

After cooling and decantation of the solvent, the product was triturated with dry n-hexane (20 ml) to give a white powder which was recrystallized from dry ether-pet. spirit (40-60°C) giving a white powder of 2-methyl-N-(ethoxycarbonyl) malonamoyl chloride (1), as shown in Table (1).

Table (1): Physical and spectroscopic data of the synthesized compounds

Compd. No.	Yield %	m.p. °C	$\nu^1_{\text{C=O}}$	Imidic group		$\nu_{\text{N-H}}$	U.V. λ_{max} (nm) CHCl_3
				$\nu^2_{\text{C=O}}$	$\nu^3_{\text{C=O}}$		
1	69	80-82	1800	1695	1733	3385	238
2 _a	45	136-138	1700	1700	1752	3293	239
2 _b	46	64-66	1705	1705	1749	3233	250
2 _c	30	125-127	1692	1692	1740	3269	250
2 _d	36	112-115	1695	1695	1745	3220	249
2 _e	40	128-130	1701	1701	1733	3250	241
3 _a	40	138-140	1745	1702	1745	3278	239
3 _b	60	143-145	1750	1698	1750	3280	240
3 _c	30	150-152	1742	1695	1742	3287	239
3 _d	43	132-135	1736	1700	1736	3271	239
3 _e	60	158-160	1758	1699	1758	3278	242
4	66	188-190	1746	1700	1730	3397	239

Reactions of Methylmalonyl Chloride with Urethane and Amines:

General Procedure:

All the amount of the above prepared oily methylmalonyl chloride in the same reaction vessel was dissolved in dry benzene (25 ml) followed by adding of urethane (0.018 mole, 1.6 gm), then the mixture was refluxed for (2-3 hrs) with stirring. After cooling, amine (0.018 mole) was added and the mixture was refluxed again for 3hrs with stirring.

The solvent was evaporated to dryness, then cold water (50 ml) was added followed by neutralization with sodium bicarbonate solution (10%). The oily product was

extracted with benzene (3×10 ml) and the extracts was evaporated giving an gummy product, washed several times with petroleum ether (60-80°C) to obtain an powder product, recrystallized from ethanol giving a white crystals of 2-methyl-N-(ethoxy carbonyl) malonamides (2_{a-e}) as shown in Table (1).

Reactions of Methylmalonyl Chloride with Urethane and Alcohols:

On following the above general procedure using alcohols or phenolic compound (0.018 mole) instead of amines, a white crystals of 2-methyl-N-(ethoxy carbonyl) malonamates (3_{a-e}) were obtained as shown in Table (1).

Reactions of Methylmalonyl Chloride with Urethane and water:

The above general procedure was followed and instead of using amine, water (1ml) was added and the mixture was refluxed with stirring for 30 mint, then the mixture was stirred at room temperature untill solid product was obtained. The product was filtered and recrystallized from ethanol giving a white crystals of 2-methyl-N-(ethoxycarbonyl) malonamic acid (4) as shown in Table (1).

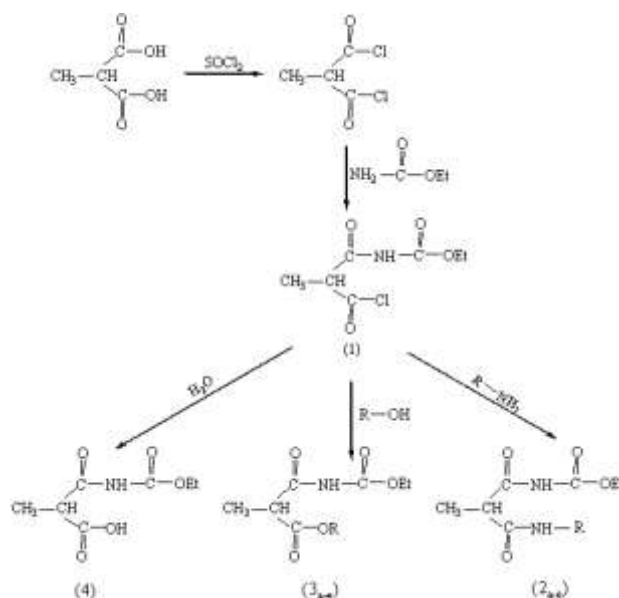
Results and Discussion:

As the carboxylic acids undergo nucleophilic substitution reactions [13], also the substituted malonic acids undergo the same type of reactions. In these reactions, methyl malonamic acid derivatives were obtained from two steps. The first step involved reaction of methyl malonic acid with thionyl chloride to obtain methyl malonyl chloride. The second step which is the important is involved reaction of methyl malonyl chloride with urethane followed by the reaction with nucleophiles (amine, alcohol and water) in the same medium and reaction vessel to obtain these new derivatives (2, 3_{a-e}) as shown in Scheme (1).

The application of this method in preparation of methyl malonamic acid derivatives (2, 3_{a-e}) was found more easier and faster than that previous method [9] because there is no need to separate methyl malonamyl chloride (1) formed during the reaction and as soon as be formed it will be ready to react with the nucleophiles either amine, alcohol or water in the same medium and reaction vessel, while the previous method need more than two steps in which methyl malonamyl chloride (1) should be separated and used as starting material before its reaction with amine, alcohol and water to obtain methyl malonamic acid derivatives.

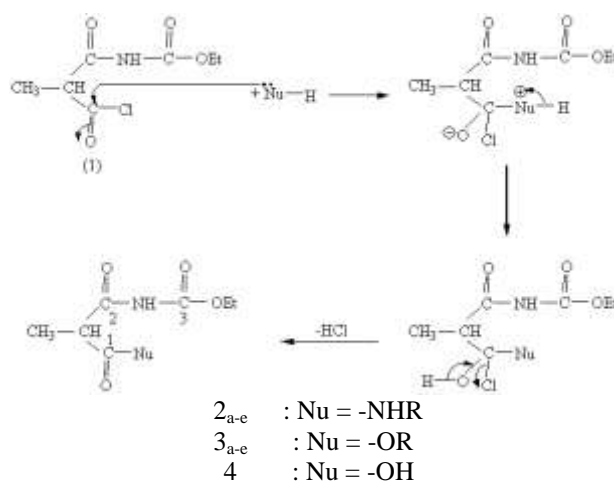
The nucleophilic substitution reactions of methyl malonamoyl chloride (1) with different nucleophiles could be proceeded through the following suggested mechanism, Scheme (2).

The structural investigation of the synthesized methylmalonamic acid derivatives (2, 3_{a-e}) was achieved according to their physical properties and spectroscopic data (I.R. and U.V.) as shown in Table (1). Other supporting evidences were obtained from the positive amide formation test for the malonamoyl chloride (1) and the positive iodate-iodide test for the malonamic acid (4) [14].



Scheme (1)

Compd. No.	-NHR	Compd. No.	-OR
2 _i		3 _i	
2 _o		3 _o	
2 _l		3 _l	
2 _d		3 _d	
2 _e		3 _e	



Scheme (2)

The I.R. spectra of the synthesized methyl malonamic acid derivatives (2, 3_{a-e}) showed three strong absorption bands due to the asymmetric and symmetric stretching vibrations of the two imidic carbonyl groups ($\nu^3_{C=O}$ and $\nu^2_{C=O}$) [15] and the other for the carbonyl group ($\nu^1_{C=O}$), sometimes two of the absorption bands were overlapped into one broad band. The stretching vibration (ν_{N-H}) was appeared at the region (3233-3397) cm^{-1} as a broad band

and the stretching vibration (ν_{O-H}) in compound (4) was appeared as a broad band at 2700 cm^{-1} [16].

In U.V. spectra, the synthesized methyl malonamic acid derivatives (2, 3_{a-e}) showed the maximum values for the absorption bands at wavelengths (λ_{max} 238-250 nm) which are in a quite agreement with the expected structures of the compounds (2, 3_{a-e}) as compared with methylmalonamyl chloride (λ_{max} 238 nm) and methylmalonamic acid (λ_{max} 239 nm). This is due to the same electronic transition ($n \rightarrow \pi^*$) [13] which occurred in these compounds (2, 3_{a-e}) as shown in Table (1).

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تفاعلات التعويض النيوكليوفيلية لمثيل كلوريد المالونيل مع بعض الكواشف النيوكليوفيلية

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الملخص:

نفس محيط وإناء التفاعل، وتم اثبات الصيغ التركيبية للمركبات المحضرة باستخدام الطرائق الفيزيائية والطيفية.

أُستخدِمت طريقة جديدة لتحضير مشتقات جديدة لمثيل حامض المالوناميك عبر تفاعلات التعويض النيوكليوفيلية لمثيل كلوريد المالونيل مع اليوريثان يتبعها مفاعلة بعض الكواشف النيوكليوفيلية (الامين، الكحول والماء) في