

Synthesis of New Derivatives for Substituted Malonamic Acids

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ABSTRACT

A number of substituted malonamic acids derivatives were prepared by nucleophilic substitution reactions of substituted malonyl chlorides with phenyl carbamate followed by reaction of the products with water, alcohol and amine. The structures of the synthesized compounds were elucidated by physical and spectroscopic methods.

INTRODUCTION

The nucleophilic substitution reactions of malonyl chloride have been applied in the synthesis of malonic acid derivatives (Morrison and Boyd, 1973). Esterification with hydroxyl group containing compounds gave diesters such as the useful compound, bis (2,2-dinitro-2-flouroethyl) molnate, as explosive or as binder for explosive compounds (Frankel and Rowley, 1975), while the amidation with amino group containing compounds produced diamides such as the thermally stable explosives, bis (2-flouro-2-dinitroethyl) amides (Adolph and Kamlet, 1972). Other amidation gave culture plant protecting carbamoyl compounds (Pallon et al., 1973) and dicyclohexyl amides as potential anti- inflammatory agents (Gioldanowski et al., 1974). The dianilide derivatives of nitroanthranilic acid were found useful as allergy-, ulcer- and hyaluronidase inhibitors (Satoh et al., 1984), also effective antihyaluronidase, antiallergic and antiulcer agents (Satoh et al., 1985). On the other hand, substituted malonyl chlorides were used to prepare substituted malonamic acid 'derivatives and substituted iminohydrazone derivatives (Sheat, 1989).

This paper is concerned with the reaction of substituted malonyl chlorides with phenyl carbamate to give the product which then allowed to react with water, alcohol and amine to give substituted malonamic acid derivatives.

EXPERIMENTAL

Melting points were measured by Gallen Kamp melting point apparatus and are uncorrected. I.R spectra were recorded by Pye Unicam SP 2000 Infrared Spectrophotometer (Nujol). ^1H - and ^{13}C -NMR spectra were determined using a Bruker WH 90 DS FT NMR spectrometer operating at 90 MHz and 22.63 MHz respectively with TMS as Internal reference.

METHODS OF PREPARATION

Preparation of Cyanogen Bromide (1):

A solution of bromine (14 ml) in water (10 ml) was cooled to 10°C , then a solution of potassium cyanide (20 gm) in water (40 ml) was added slowly with shaking until the bromine was disappeared and the liquid becomes coloured (orange). Phosphoric acid (2 ml of 20%) was added followed by dropwise addition of saturated solution of potassium cyanide with continuous shaking until the liquid acquires stable-yellow colour (acidic), if the solution is still alkaline, another (2 ml) of phosphoric acid should be added.

The mixture was distilled very cautiously on a water bath into a water cooled receiver, then the distilled cyanogen bromide was mixed with anhydrous sodium sulphate to remove water and distilled once more giving white crystalline product (1) of 87% yield (Elmer and Laszlo, 1949).

Preparation of Phenyl Cyanate (2):

Cyanogen bromide (1 mole) was added to a solution of freshly distilled phenol (1 mole) in 250 ml of dry acetone at 0°C with stirring, then triethyl amine (1 mole) was added dropwise with vigorous stirring so that the temperature should not exceed more than 10°C . The triethyl amine salt was filtered and washed with (3 x 50 ml) of dry acetone, then the acetone was distilled at (25- 30°C /15) torr followed by distillation of residue under reduced pressure (55°C /0.4 mmHg) giving colourless liquid of 92% phenyl cyanate (Grigat and Puetter, 1964).

Preparation of Phenyl Carbamate (3):

Conc. Hydrochloric acid (3 ml) was added to a mixture of phenyl cyanate (0.05 mole) and water (0.05 mole) in 80ml of petroleum spirit (40 - 60°C). The mixture was left overnight with stirring at room temperature, then the product was filtered and recrystallized from dry benzene giving colourless crystals of phenyl carbamate (80%, m.p. 144 - 146°C , lit. (146 - 147°C) (Martin, 1964). δ ^1H (CDCl_3) 5.1 (b, NH_2) and 7-7.6 (m, Ph) ppm. δ ^{13}C (DMSO-d_6) 154.8, 151.1, 129.1; 124.7 and 121.8 ppm

Preparation of Substituted Malonyl Chlorides:

All the substituted malonyl chlorides were prepared according to the published methods (Stensrud et al., 1971).

Methylmalonyl chloride (4a) showed δ ^1H (CDCl_3) 1.66 (d, $J=7\text{Hz}$, CH_3), 4.33 (q, $J=7\text{Hz}$, CH) ppm.

Benzylmalonyl chloride (4b) showed δ ^1H (CDCl_3) 3.37 (d, $J=7\text{Hz}$, CH_2), 4.48 (t, $J=7\text{Hz}$, CH), 7.1-7.44 (m, Ph) ppm.

Phenylmalonyl chloride (4c) showed δ ^1H (CDCl_3) 5.42 (s, CH), 7.33-7.55 (m, Ph) ppm.

Reaction of Substituted Malonyl Chlorides with Phenyl Carbamate:

A mixture of phenyl carbamate (0.0084 mole) and substituted malonyl chloride (0.0084 mole) in dry n-hexane (30 ml) was heated under anhydrous conditions in an oil bath at 70°C with stirring for 2.30 hrs. After cooling, the product was filtered and washed with dry n-hexane (30 ml) then recrystallized from chloroform-petroleum spirit ($40-60^\circ\text{C}$) giving a white powder of 2-substituted-N-(phenoxy carbonyl) malonamyl chlorides (5a-c) (Sheat, 1989).

5a (65%, m.p. $120-122^\circ\text{C}$), 5b (45%, m.p. $102-104^\circ\text{C}$) and 5c (89%, m.p. $73-75^\circ\text{C}$). The spectroscopic data of compounds (5a-c) were illustrated in Tables (1 and 2).

Reaction of 2-Substituted-N-(Phenoxy carbonyl) Malonamyl Chlorides (5a-c) with Water:

A mixture of compounds (5a-c) (0.02 mole) and water (2 ml) in dry benzene (30 ml) was refluxed with stirring for 30 mins, then the mixture was stirred at room temperature until solid product was obtained. The product was filtered and recrystallized from dry benzene giving a fine white crystals of 2-substituted-N-(phenoxy carbonyl) malonamic acids (6a-c). 6a (57%, m.p. $120-122^\circ\text{C}$), 6b (50%, m.p. $105-107^\circ\text{C}$) and 6c (72%, m.p. $138-140^\circ\text{C}$). The spectroscopic data of compounds (6a-c) was illustrated in Tables (1 and 2).

Reaction of 2-Substituted-N-(Phenoxy carbonyl) Malonamyl Chlorides (5a-c) with Alcohol:

A mixture of compounds (5a-c) (0.02 mole) and absolute ethanol (0.02 mole) in dry benzene (30 ml) was refluxed with stirring for 1 hr. After cooling, the product was filtered and recrystallized from acetone petroleum spirit ($40-60^\circ\text{C}$) giving a white crystals of ethyl-2-substituted N-(phenoxy carbonyl) malonamates (7a-c).

7a(63%, m.p. $71-73^\circ\text{C}$), 7b (42%, m.p. $58-60^\circ\text{C}$), and 7c (51%, m.p. $86-88^\circ\text{C}$). The spectroscopic data of compounds (7a-c) was illustrated in Tables (1 and 2).

Table 1 : Spectroscopic data of the substituted malonamic acids derivatives

Compd. No.	I. R. (Nujol) cm^{-1}			$^1\text{H-NMR}$ (CDCl_3) ppm
	$\nu^1 \text{C=O}$	$\nu^3 \text{C=O}$	$\nu^4 \text{C=O}$	
5a	1800	1710	1775	1.6(d, J=7.2 Hz, CH_3), 4.75 (q, J=7.2 Hz, CH), 7-7.6 (m, Ph), 8.3 (b, NH)
5b	1800	1715	1760	3.3 (d, J=7 Hz, CH_2), 4.6 (t, J=7Hz, CH), 6.8-7 (m, 2Ph), 8.4 (b, NH)
5c	1805	1710	1785	6.0 (s, CH), 6.8-7.5 (m, 2Ph), 8.0 (b, NH)
6a	1730	1710	1800	1.4 (d, J=7.4 Hz, CH_3), 4.15 (q, J=7.4 Hz, CH), 6.1 (b, NH), 7-7.6 (m, Ph), 10.1 (b, OH)
6b	1710	1710	1795	2.9 (d, J=7 Hz, CH_3), 3.7 (t, J=7.2 Hz, CH), 6.5(b, NH), ; 6.95-7.4 (m, 2Ph), 9.6 (b, OH)
6c	1700	1700	1775	4.7 (s, CH), 6.2 (b, NH), 6.8-7.4 (m, 2Ph), 9.7 (b, OH)
7a	1745	1710	1780	1-1.3 (m, 2 CH_3), 3.42 (q, J=7.2 Hz, CH), 4.3 (q, J=7 Hz, CH_2), 6.42 (b, NH), 7-7.7 (m, Ph)
7b	1740	1710	1775	1.24 (t, J=7 Hz, CH_3), 3.2 (d, J=7.2 Hz, CH_2), 3.62 (t, J=7.2 Hz, CH), 4.11(q, J=7 Hz, CH_2), 6.6 (b, NH), 7- 7.5 (m, 2Ph)
7c	1745	1705	1780	1.22 (t, J=7 Hz, CH_3), 4.22 (q, J=7 Hz, CH_2), 4.6 (s, CH), 6.64 (b, NH), 7-7.78(m, 2Ph)
8a	1700	1700	1775	1.3 (d, J=7.2 Hz, CH_3), 4.4 (q, J=7.2 Hz, CH), 6.8 (b, NH), 7-7.6 (m, 2Ph), 8.4(b, NH)
8b	1700	1700	1780	3.3 (d, J=7.2 Hz, CH_2), 3.6 (t, J=7.2 Hz, CH), 6.7(b, NH), 7-7.7 (m, 3Ph), 8.3(b, NH)
8c	1700	1700	1770	4.61 (s, CH), 6.72(b, NH), 7-7.8(m, 3Ph), 8.4 (b, NH)

Reaction of 2-Substituted-N-(Phenoxycarbonyl) Malonamyl Chlorides (5a-c) with Amine:

A mixture of compounds (5a-c) (0.02 mole) and freshly distilled aniline (0.04 mole) in dry benzene (30 ml) was refluxed with stirring for 30 mints. The solvent was evaporated under reduced pressure, then the product was washed with NaOH solution (40 ml of 10%), with water and recrystallized from acetone-petroleum spirit (60-80°C) giving a white powder of 2-substituted-N-(phenoxycarbonyl) malonamanilides (8a-c).

8a (64%, m.p. 150-152 °C), 8b (71%, m.p. 158-160°C) and 8c (54% m.p. 178-180°C). The spectroscopic data of compounds (8a-c) was illustrated in Tables (1 and 2).

Table 2: ^{13}C -NMR chemical shift assignments of compounds (5a, 6a, 7a and 8a) in (CDCl_3) ppm

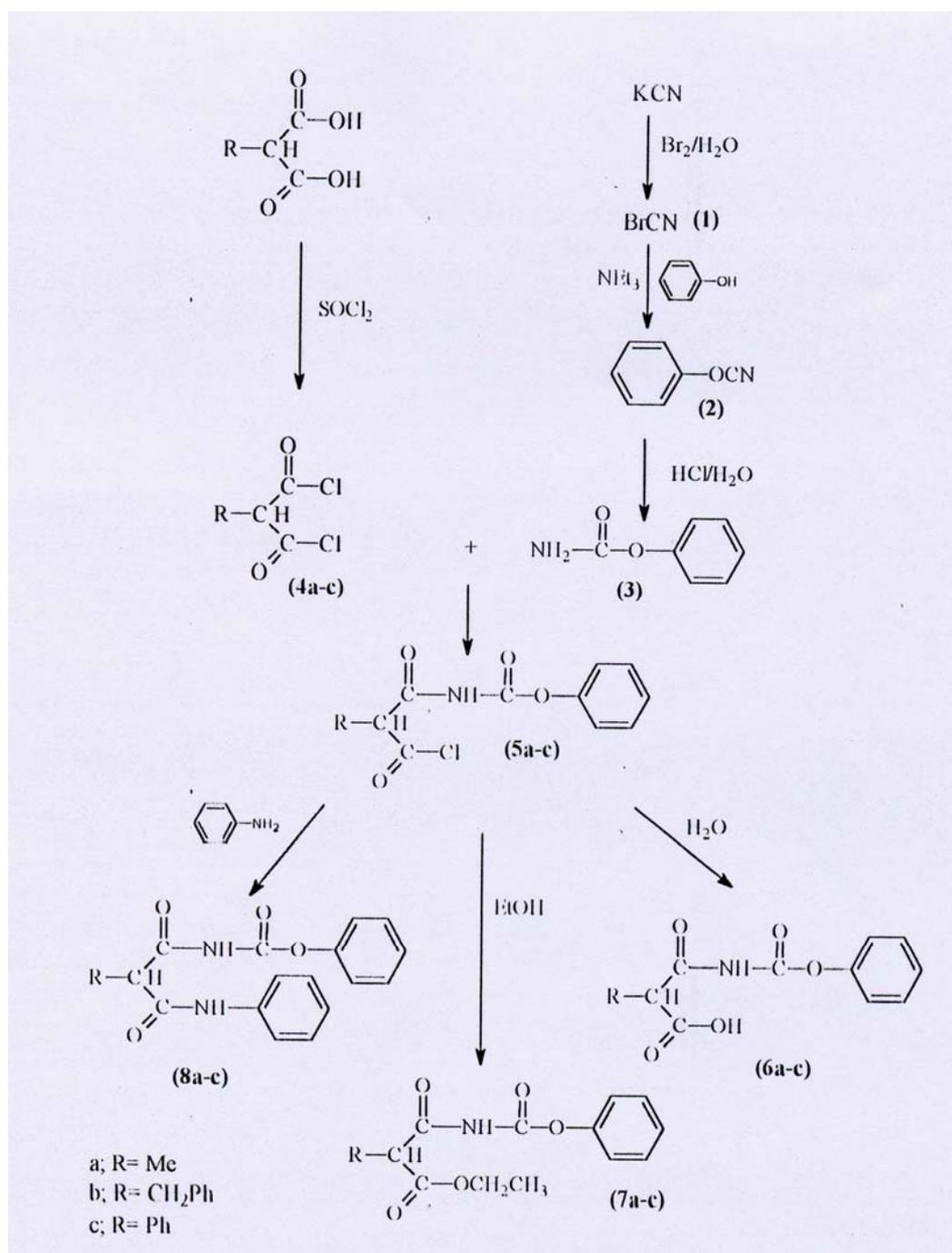
Carbon No.	5a	6a	7a	8a
C-1*	170.9	168.7	170.9	170.2
C-2	47.4	57.3	46.6	46.8
C-3*	171.8	171.1	171.2	171.4
C-4	151.4	150.6	150.2	151.8
C-5, 5'	153.0	149.9	151.9	152.1, 151.6
C-6, 6'	122.4	121.4	115.5	121.8, 123.2
C-7, 7'	130.3	129.8	129.5	129.6, 130.1
C-8, 8'	126.8	126.8	126.2	126.6, 128.3
C-9	13.7	13.7	13.6	13.6
C-10			61.5	
C-11			14.7	

*assignments could be exchanged.

RESULTS AND DISCUSSION

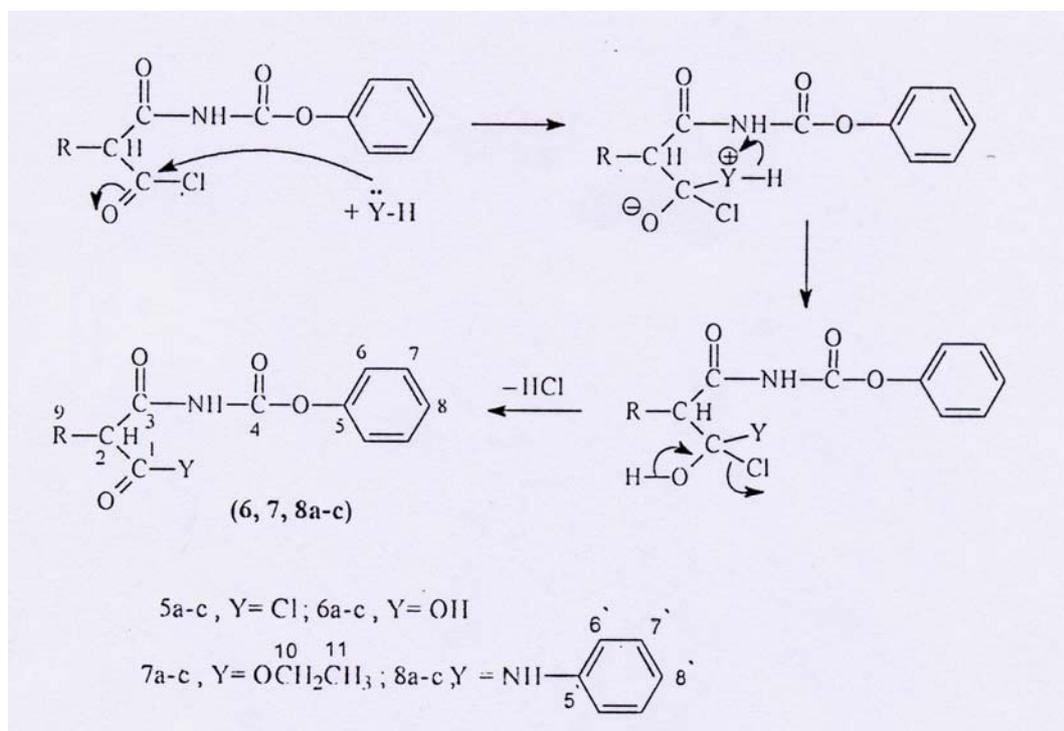
Substituted malonyl chlorides undergo nucleophilic substitution reactions similar to that of acid halides (Morrison and Boyd, 1973) to produce other substituted malonamic acids derivatives. These derivatives were prepared from the reactions of substituted malonyl chlorides (4a-c) with phenyl carbamate (3) to produce compounds (5a-c) which reacted with water, EtOH and aniline by nucleophilic substitution reactions as shown in Scheme (1).

The suggested mechanism for the formation of the substituted malonamic acids derivatives proceed through nucleophilic substitution reactions in which the nucleophile (water, EtOH and aniline molecules) attack the carbonyl group to give the product with the elimination of hydrogen chloride as illustrated in Scheme (2).



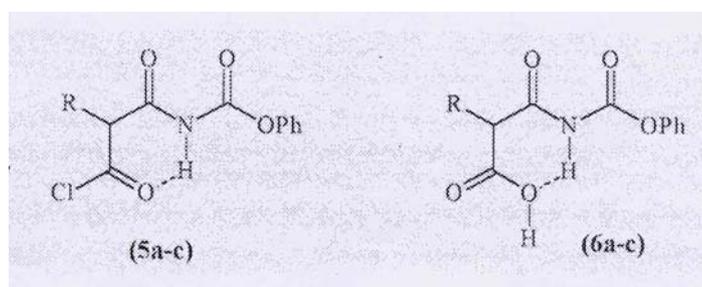
Scheme (1)

The substituted malonamic acids derivatives have been investigated according to their spectroscopic data ($^1\text{H-NMR}$ and I.R.) in addition to $^{13}\text{C-NMR}$ spectra of some compounds as shown in Tables (1 and 2).



Scheme (2)

The $^1\text{H-NMR}$ spectra of compounds (6, 7, and 8a-c) shows the chemical shift of the NH proton appeared at downfield region (δ 6.0-6.8 ppm) compared with that in the substituted malonamic acid chlorides (5a-c) which appeared at upfield region (δ 8-8.4 ppm). The differences in these shifts may be due to the type of the expected intramolecular hydrogen bonding in their structures as shown below:



The I.R. spectra of the substituted malonamic acids derivatives showed three strong absorption bands due to the ester carbonyl group ($\nu^4 \text{C=O}$), amidic carbonyl group ($\nu^3 \text{C=O}$) and the carbonyl group ($\nu^1 \text{C=O}$), sometimes two of the absorptions were overlapped into one band. The stretching vibration of the N-H bond in the amidic group gave two broad bands at region ($3300\text{-}3200 \text{ cm}^{-1}$) due to its symmetric and asymmetric stretching, also another broad band was appeared at the same region due to $\nu_{\text{N-H}}$ of the anilidic group in compounds (8a-c). The $\nu_{\text{O-H}}$ of the malonamic acids derivatives (6a-c) appeared as a strong broad band at 2900 cm^{-1} (Parikh; 1985).

The assignments of carbon-13 signals of the compounds (5a, 6a, 7a and 8a) were achieved according to ^{13}C -chemical shifts of phenyl carbamate and the related compounds such as diethylmalonate, phenol and acetanilide (Breitmaier et al, 1978). In this assignments, it was noticed that the most deshielded signals were appeared at around $\delta 170$, $\delta 171$ and $\delta 150$ ppm due to the carbonyl carbon (C-1, C-3 and C-4) respectively, while the other remaining carbons were easily assigned to the corresponding structure as shown in Table (2).

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