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Synthesis and Spectral Study of Some New 4-substituted but-2-enolide Derivatives

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Abstract

A variety of some new substituted 4-amino-4-(bromomethyl)butolides (4a-g) have been synthesized by reactions 4-(Bromomethyl)but-2-enolide (2) with some (substituted benzylidene) benzene-1,4-diamine (3a-g) in the presence of absolute ethanol as a solvent to give the Michael addition products, while in the case of its reaction in the presence of pyridine as a solvent and base be added to the β- and γ- positions to be yield substituted 4-amino-4-(aminomethyl)butolides (5a-g). 4-(Bromomethyl)but-2-enolide (2) is prepared by the reaction 3,3-dimethylacrylic acid and N-bromo succinimide with benzoyl peroxide to give 3,3-Bis(bromomethyl)acrylic acid (1) and then the ring-closure reaction is carried out in basic media. All newly synthesized compounds were confirmed by spectral analysis and the corresponding reactions were monitored by TLC.

*Keyword***:** Butenolides, Tetronic acid, Natural compounds, Schiff bases.

Introduction

Tetronic acids (β-substituted butenolides). They are a structural part of a chain of natural compounds, such as, strigol, leptosfaerin, acetogenins and muconolactones [1]. Vitamin C (ascorbic acid) [2] and pennicillic acid [3] are the most well-known members of this family [4]. They signify an interesting template for medicinal chemistry because of their antibiotic. HIV-1 protease inhibitors, antiepileptic, anticoagulant, analgesic, antifungal, insecticidal, , anti-inflammatory activities. Recently, these compounds have also as anticancer agents [5].

In the literature, numerous synthetic methods for preparing nitrogenous naturally occurring butenolids have been described. However, only a few of these approaches are useful for producing substituted amino-butolides, which are used as a precursor in the synthesis of natural compounds [6].

In this presentation we offer a straightforward one-step synthesis of the compounds (4a-g, 5a-g) using the 4-(Bromomethyl)but-2-enolide moiety (2) and several Schiff bases (3a-g). This moiety was synthesized in high yield from commercially available 3,3-dimethyl acrylic acid with N-bromosuccinimide in basic media using our synthesis to the naturally occurring butenolide-piperolide [6].

Experimental:

The melting points were determined by Electrothermal apparatus IA 9300 Digital – Series 1998 (uncorrected). FT-IR spectra was recorded using FT-IR spectrometer (KBr, ν cm^{-1}) Bruker. ^{1}H- NMR spectra (DMSO-d^{6}, δ ppm) was recorded using Bruker advance 400 MHz (Germany). The Thin layer chromatography (TLC) were carried out on Eastman chromatogram sheet (6 * 12) cm, (mesh 120-60) silica gel with Iodine indicator using solvent system ethyl acetate: n-pentane in ratio (3:2) and (4:1).

Synthesis of 3,3-Bis(bromomethyl)acrylic acid (1) & 4-(Bromomethyl)but-2-enolide (2):[7]

These compounds were prepared according to the procedure was described in the literature [7], and gave the following data:- FT-IR (νcm^{-1}): C=O (1745) extra band C=O (1784), C=C (1641), 632 (C - Br)

Synthesis of (substituted benzylidene) benzene-1,4-diamine (3a-g):[8]

In a 100 mL round flask, (0.432 gm, 0.004 moles) p-phenylene diamine was mixed with (0.004 moles) substituted benzaldehyde dissolved in (20 mL) absolute ethanol, then 1-2 drops of glacial acetic acid was added, followed by refluxed for 2-3 h., the precipitate is formed. After the time required for the reaction is completed, then the solution is left

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to cool at room temperature, the formed precipitate was filtered off and washed thoroughly with ethanol, and the product is recrystallized with ethanol. Table1, Scheme2.

Table 1: Physical Properties of (substituted benzylidene) benzene-1,4-diamine (3a-g).

Comp. No.	R	m.p °C	Yield %	R_f
3a	H	135-138	47	0.237
3b	4-Br	236-238	49	0.253
3c	4-$N(CH_3)_2$	286-288	66	0.271
3d	4-NO_2	243-245	69	0.193
3e	3,4-$(OCH_3)_2$	195-197	40	0.112
3f	4-OCH_3	203-205	71	0.150
3g	3-OCH_3	108-110	68	0.194

Synthesis of substituted 4-amino-4-(bromomethyl)butolides(4a-g):[9]

In a 100 mL round flask, mixed (0.265 gm, 0.0015 moles) of the but-2-enolide (2) with (0.0015 moles) of 4-aminoSchiff bases (3a-g) in 20 mL of absolute ethanol. The reaction mixture is refluxed for 4-5 h. the reaction process is tracked through TLC, and upon completion of the reaction, the reaction mixture is slightly concentrated and left at room temperature, and the formed precipitate was filter off and recrystallized from aqueous ethanol. Table2, Scheme4.

Table 2: Physical Properties of substituted 4-amino-4-(bromomethyl) butolides (4a-g).

Comp. No.	R	m.p °C	Yield %	R_f
4a	H	Decomposed	23	0.275
4b	4-Br	228-230	20	0.253
4c	4-$N(CH_3)_2$	Decomposed	37	0.341
4d	4-NO_2	233-235	68	0.231
4e	3,4-$(OCH_3)_2$	204-206	24	0.250
4f	4-OCH_3	210-212	36	0.431
4g	3-OCH_3	105-108	27	0.129

Synthesis of substituted 4-amino-4-(aminomethyl)butolides (5a-g):[10]

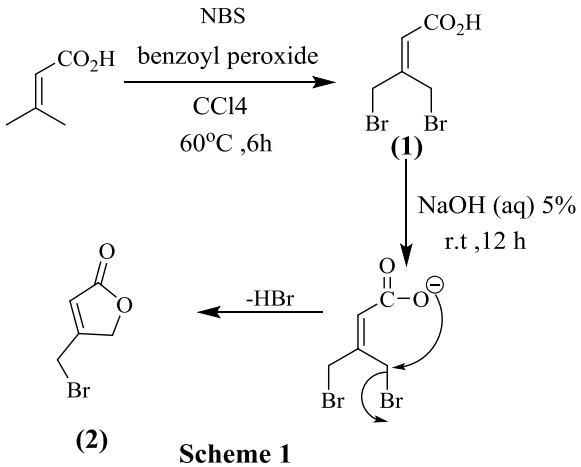
In a 100 mL round flask, (0.177gm, 0.001 mole) of the but-2-enolide (2) is mixed with (0.001 mole) of Schiff bases (3a-g) in 5 mL of pyridine and stirred for 15 min. at r. t., then sterring in a water bath at 50°C with continuous stirring for 3-4 h., the reaction process is tracked through TLC, and upon completion of the reaction, the reaction mixture is concentrated and left to stand at room temperature, the precipitate was filtered off and crystallized from ethanol. Table3. Scheme 5.

Table 3: Physical Properties of substituted 4-amino-4-(aminomethyl) butolides (5a-g)

Comp. No.	R	m.p °C	Yield %	R_f
5a	H	Decomposed	37	0.312
5b	4-Br	202-205	41	0.307
5c	4-$N(CH_3)_2$	231-233	48	0.378
5d	4-NO_2	Decomposed	47	0.462
5e	3,4-$(OCH_3)_2$	Decomposed	25	0.426
5f	4-OCH_3	208-211	40	0.201
5g	3-OCH_3	198-200	38	0.250

Result and Discussion

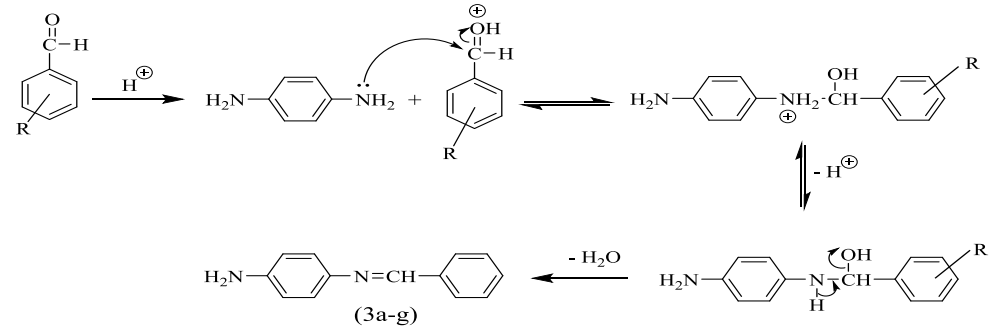
4-(Bromomethyl)but-2-enolide (2) is prepared by the reaction of 3,3-dimethylacrylic acid (1eq) and N-bromo succinimide (NBS) (2.2 eq) in aq. NaOH Scheme1.[7]



Scheme 1

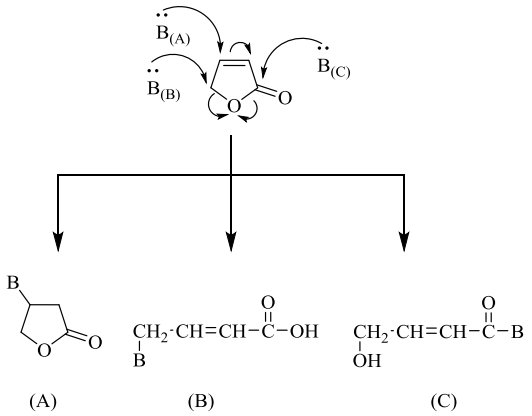
On the other hand, 4-aminoSchiff bases (3a-g) are prepared by reacting substituted benzaldehyde in eq. molar with p-phenylenediamine in absolute ethanol in the presence of glacial acetic acid Scheme2, Table 4.

Butenolide (γ-lactone) has three sites for reactions with the amine group (Scheme 3). It is possible: Michael addition of the amine to the double bond in the lactone ring, the amine group attacks the carbonyl group to give the amide derivatives, and the γ –position on the lactone to give the carboxylic acid derivatives [6].

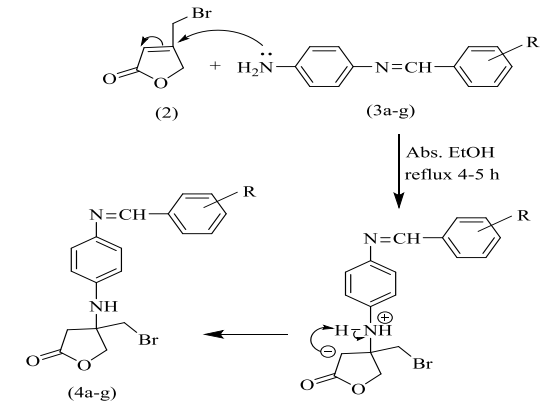


R = H, 4-Br, 4-N(CH$_3$)$_2$, 4-NO$_2$, 3,4-Di(OCH$_3$)$_2$, 4-OCH$_3$, 3-OCH$_3$

Scheme 2



Scheme 3

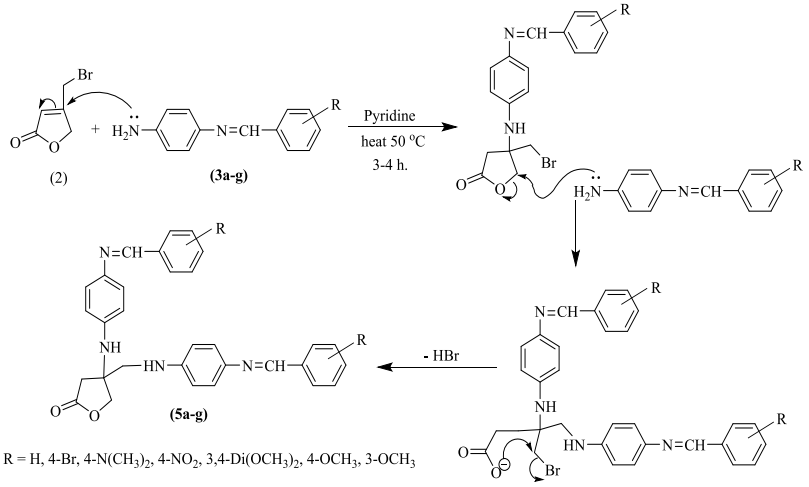


R = H, 4-Br, 4-N(CH$_3$)$_2$, 4-NO$_2$, 3,4-Di(OCH$_3$)$_2$, 4-OCH$_3$, 3-OCH$_3$

Scheme 4

In our present work, some new tetronic acid derivatives containing amines (Schiff bases) (4a-g , 5a-g) were prepared in different solvents such as ethanol and pyridine. Through the reaction of 4-(Bromomethyl)but-2-enolide (2) with some 4-aminoSchiff bases (3a-g) using ethanol as a solvent, it was found that the addition occurs on the β-position, Michael addition is favoured and this is in agreement with mechanism (Scheme 4) and the values of FT-IR and ^{1}H-NMR, Table 5,6.

But in the case of using pyridine as a solvent and base here, the reaction mechanism as well as the products differ. Where the solvent had an active role in directing the nucleophile addition to the 4-(Bromomethyl)but-2-enolide (2), where the preferred nucleophilic addition occurs on the β and γ positions of the lactone ring, then followed by the ring-closing reaction by attacking the carboxylate-oxygen anion of the methylene group attached to the bromide and this agrees with the spectroscopic measurements ^{1}H-NMR , FT-IR, Table 7,8 and mechanism (Scheme 5).



R = H, 4-Br, 4-N(CH$_3$)$_2$, 4-NO$_2$, 3,4-Di(OCH$_3$)$_2$, 4-OCH$_3$, 3-OCH$_3$

Scheme 5

Table 4: FT-IR data of 4-aminoSchiff Bases (3a-g).

Comp. No.	FT-IR, ν (cm^{-1})			
	R	NH_2	C = N	Others
3a	H	3475, 3342	1611	------
3b	4-Br	3080, 3020	1616	(C-Br) 557
3c	4-$N(CH_3)_2$	3438, 3126	1586	------
3d	4-NO_2	3386, 3134	1614	(NO_2) Asym. 1580, Sym. 1322
3e	3,4-$(OCH_3)_2$	3230, 3132	1614	(OCH_3) Asym. 1238, Sym.1139
3f	4-OCH_3	3144, 3118	1592	(OCH_3) Asym. 1244, Sym.1153
3g	3-OCH_3	3082, 3020	1620	(OCH_3) Asym. 1209, Sym.1147

Table 5: FT-IR data of substituted 4-amino-4-(bromomethyl) butolides (4a-g).

Comp. No.	FT-IR, ν (cm^{-1})					
	R	NH	C = O	C = N	C - Br	Others
4a	H	3414	1745, 1776*	1639	619	------
4b	4-Br	3414	1743, 1776*	1639	557	(C-Br) 557
4c	4-$N(CH_3)_2$	3408	1743, 1776*	1645	619	-------
4d	4-NO_2	3429	1743, 1776*	1624	688	(NO_2) Asym. 1514, Sym. 1342
4e	3,4-$(OCH_3)_2$	3452	1743, 1776*	1645	667	(OCH_3) Asym. 1286, Sym. 1147
4f	4-OCH_3	3406	1743, 1776*	1651	559	(OCH_3) Asym. 1276, Sym. 1176
4g	3-OCH_3	3367	1743, 1776*	1653	688	(OCH_3) Asym. 1261, Sym.1145

* Extra band for C=O. Reference [11].

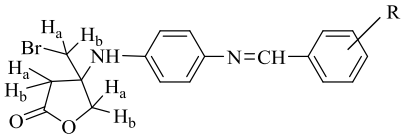


Table 6: The ^{1}H-NMR spectral data of substituted 4-amino-4-(bromomethyl) butolides (4a-g).

Comp.	^{1}H-NMR, (ppm), DMSO-d6
4a	2.41, 2.61(d-d, 2$H_{a,b}$, -**CH_aH$_b$**-CO), 4.33, 4.81 (s-d, 2$H_{a,b}$, -**CH_aH$_b$**-Br), 4.89, 5.93 (s-s, 2$H_{a,b}$, -**CH_aH$_b$**-O-CO), 6.67-7.94 (m, 9H, Ar-**H**), 8.48 (s, 1H, -**CH**=N-), 9.88 (s, 1H, -N**H**-)
4b	2.41, 2.60(d-d, 2$H_{a,b}$, -**CH_aH$_b$**-CO), 4.28, 4.33 (s-s, 2$H_{a,b}$, -**CH_aH$_b$**-Br), 4.89, 5.34 (s-s, 2$H_{a,b}$, -**CH_aH$_b$**-O-CO), 6.59-7.16 (d-d, 4H, Ar_1-**H**), 7.74-7.92 (d-d, 4H, Ar_2-**H**), 8.60 (s, 1H, -**CH**=N-), 10.00 (s, 1H, -N**H**-)
4c	2.42, 2.61(d-d, 2$H_{a,b}$, -**CH_aH$_b$**-CO), 3.05 (s, 6H, -N(C**H_3**)$_2$), 3.18 (s, 2H, -**CH_2**-Br), 4.93 (s, 2H, -**CH_2**-O-CO), 6.79-7.42 (d-d, 4H, Ar_1-**H**), 6.96-7.71 (d-d, 4H, Ar_2-**H**), 8.03 (s, 1H, -**CH**=N-), 9.68 (s, 1H, -N**H**-)
4d	2.41, 2.60(d-d, 2$H_{a,b}$, -**CH_aH$_b$**-CO), 3.24,3.42 (d-s, 2$H_{a,b}$, -**CH_aH$_b$**-Br), 4.95 (s, 2H, -**CH_2**-O-CO), 6.62-7.27 (d-d, 4H, Ar_1-**H**), 8.11-8.44 (d-d, 4H, Ar_2-**H**), 8.91 (s, 1H, -**CH**=N-), 10.18 (s, 1H, -N**H**-)
4e	2.41, 2.60(d-d, 2$H_{a,b}$, -**CH_aH$_b$**-CO), 3.84 (s, 3H, 4-OC**H_3**), 3.88 (s, 3H, 3-OC**H_3**), 4.33, 4.89 (s-s, 2$H_{a,b}$, -**CH_aH$_b$**-Br), 4.91, 5.93 (d-s, 2$H_{a,b}$, -**CH_aH$_b$**-O-CO), 7.17-7.58 (d-d, 4H, Ar_1-**H**), 6.66-7.96 (m, 3H, Ar_2-**H**), 8.14 (s, 1H, -**CH**=N-), 9.85 (s, 1H, -N**H**-)
4f	2.41, 2.60(d-d, 2$H_{a,b}$, -**CH_aH$_b$**-CO), 3.87 (s, 3H, OC**H_3**), 4.33, 4.89 (d-s, 2$H_{a,b}$, -**CH_aH$_b$**-Br), 4.92, 5.93 (d-d, 2$H_{a,b}$, -**CH_aH$_b$**-O-CO), 7.08-7.89 (d-d, 4H, Ar_1-**H**), 7.13 -7.99 (d-d, 4H, Ar_2-**H**), 8.01 (s, 1H, -**CH**=N-), 9.88 (s, 1H, -N**H**-)
4g	2.41, 2.60(d-d, 2$H_{a,b}$, -**CH_aH$_b$**-CO), 3.84 (s, 3H, OC**H_3**), 4.33, 4.89 (s-s, 2$H_{a,b}$, -**CH_aH$_b$**-Br), 4.93, 5.20 (d-s, 2$H_{a,b}$, -**CH_aH$_b$**-O-CO), 6.67-7.31 (m, 4H, Ar_1-**H**), 7.43 -7.54 (d-d, 4H, Ar_2-**H**), 7.55 (s, 1H, -**CH**=N-), 9.99 (s, 1H, -N**H**-)

Table 7: FT-IR data of substituted 4-amino-4-(aminomethyl) butolides (5a-g)

Comp. No.	FT-IR, ν (cm^{-1})				
	R	NH	C = O	C = N	Others
5a	H	3362	1753	1662	------
5b	4-Br	3398	1759	1620	(C-Br) 557
5c	4-$N(CH_3)_2$	3431	1749	1595	-------
5d	4-NO_2	3392	1766	1622	(NO_2) Asym. 1516, Sym. 1344
5e	3,4-$(OCH_3)_2$	3365	1757	1602	(OCH_3) Asym. 1267, Sym. 1141
5f	4-OCH_3	3414	1757	1602	(OCH_3) Asym. 1251, Sym. 1168
5g	3-OCH_3	3373	1759	1602	(OCH_3) Asym. 1263, Sym. 1163

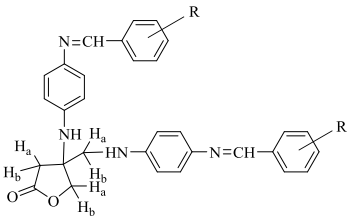


Table 8: The ^{1}H-NMR spectral data of substituted 4-amino-4-(aminomethyl) butolides (5a-g)

Comp.	^{1}H-NMR, (ppm), DMSO-d6
5b	2.41(s, 2H, -**CH**$_2$-CO), 2.60 (s, 2H, -**CH**$_2$-N), 3.24 (s, 2H, -**CH**$_2$-O-CO), 6.58-7.82 (m, 16H, Ar-**H**), 7.85 (s,1H, -N**H**-), 7.90 (s, 1H, -**CH**=N-), 7.92 (s, 1H, -**CH**=N-), 8.71 (s, 1H, -N**H**-)
5c	2.41(s, 2H, -**CH**$_2$-CO), 2.60 (s, 2H, -**CH**$_2$-N), 2.99 (s, 2H, -**CH**$_2$-O-CO), 3.02 (s, 6H, -N(C**H**$_3$)$_2$), 3.05 (s, 6H, -N(C**H**$_3$)$_2$),6.56-7.79 (m, 16H, Ar-**H**), 8.39 (s,1H, -N**H**-), 8.47 (s, 1H, -**CH**=N-), 8.59 (s, 1H, -**CH**=N-), 9.68 (s, 1H, -N**H**-)
5d	2.41(s, 2H, -**CH**$_2$-CO), 2.60 (s, 2H, -**CH**$_2$-N), 3.24 (s, 2H, -**CH**$_2$-O-CO), 6.61-8.41 (m, 16H, Ar-**H**), 8.59 (s,1H, -N**H**-), 8.79 (s, 1H, -**CH**=N-), 8.91 (s, 1H, -**CH**=N-), 10.22 (s, 1H, -N**H**-)
5e	2.41(s, 2H, -**CH**$_2$-CO), 2.60 (s, 2H, -**CH**$_2$-N), 3.24 (s, 2H, -**CH**$_2$-O-CO), 3.82 (s, 6H, (-OC**H**$_3$)$_2$), 3.88 (s, 6H, (-OC**H**$_3$)$_2$), 6.58-7.56 (m, 14H, Ar-**H**), 7.58 (s,1H, -N**H**-), 7.79 (s, 1H, -**CH**=N-), 8.48 (s, 1H, -**CH**=N-), 8.59 (s, 1H, -N**H**-)
5f	2.41(s, 2H, -**CH**$_2$-CO), 2.61 (s, 2H, -**CH**$_2$-N), 3.25 (s, 2H, -**CH**$_2$-O-CO), 3.82 (s, 3H, -OC**H**$_3$), 3.87 (s, 3H, -OC**H**$_3$), 6.57-7.92 (m, 16H, Ar-**H**), 8.51 (s,1H, -N**H**-), 8.58 (s, 1H, -**CH**=N-), 8.61 (s, 1H, -**CH**=N-), 9.88 (s, 1H, -N**H**-)
5g	2.41(s, 2H, -**CH**$_2$-CO), 2.60 (s, 2H, -**CH**$_2$-N), 3.25 (s, 2H, -**CH**$_2$-O-CO), 3.82 (s, 3H, -OC**H**$_3$), 3.84 (s, 3H, -OC**H**$_3$), 6.59-7.44 (m, 16H, Ar-**H**), 7.53 (s,1H, -N**H**-), 7.54 (s, 1H, -**CH**=N-), 8.57 (s, 1H, -**CH**=N-), 8.59 (s, 1H, -N**H**-)

Conclusion

Fourteen new compounds, including substituted 4-amino-4-(bromomethyl) butolides and substituted 4-amino-4-(aminomethyl) butolides have been synthesized. The compounds are expected to have a variety of pharmacological actions, which make their synthesis is interesting and has a valuable view.

Conflicts of interest

There are no conflicts to declare.

Acknowledgments

University of Mosul.

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