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Synthesis of Five Membered Heterocycles Using Microwaves Technique

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ABSTRACT

A series of N-(5-substituted 1,3,4–thiadiazol-2-yl maleimides (14-18) were prepared by cyclization of corresponding maleamic acids (7-12).These acids were prepared by the reaction of 2-amino-5-aryloxymethyl–1,3,4–thiadiazoles (1-6) with maleic anhydride. The starting amines (1-6) were prepared from different aryloxyacetic acids and thiosemicarbazide .

The structure of the prepared compounds was suggested in the light of IR and UV Spectroscopy.

Key words: Maleimides; 1,3,4-Thiadiazoles; Microwave synthesis

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تشييد مركبات خماسية الحلقة غير متجانسة باستخدام تقنية الميكروويف

الملخص

تم تحضير سلسلة من N – 5 معوض–4،3،1- ثايادايازولات الماليميدات (14-18) بوساطة حوقلة حوامض المالميدات المقابلة (7-12). حضرت هذه الحوامض من تفاعل مركبات 2-امينو-5- اريلوكسى مثيل 4،3،1 – ثايادايازول الاريلوكسى (1-6) مع انهيدريد الماليك. اما الامينات المستخدمة بصفة مواد أولية (1-6) فقد حضرت من تفاعل عدد من مركبات الاريلوكسى حامض الخليك مع الثايوسيمى كاربازيد. تم إقتراح التراكيب الكيميائية للمركبات فى ضوء مطيافية الأشعة تحت الحمراء وفوق البنفسجية.

INTRODUCTION

Several procedures were reported for the synthesis of 2-amino-1,3,4-thiadiazoles, in many of these methods a thiosemicarbazide was the starting material which first acylated to 1-acylthiosemicarbazide (Saied, 1983) which cyclized with a suitable dehydrating agents such as phosphorus pentachloride (Rabjohn *et al*., 1973 and Kulchitskaya *et al*., 1956), phosphorous

oxychloride and thionyl chloride (Rabjohn *et al*., 1973 and Kretov *et al.,* 1956). Acylation and cyclization could be achieved in a one step reaction by heating an acyl halide, or even a carboxylic acid with a thiosemicarbazide in the presence of phosphorous acid or concentrated sulfuric acid (Saied, 1983).

These heterocyclic amines were used as synthon in synthesis of cyclic amides by their reaction with cyclic anhydrides via intermediate maleamic acid (Rabjohn *et al*., 1973). Many dehydrating agents such as phosphorus pentachloride (Rabjohn *et al*., 1973 and Kretov *et al*., 1956), phosphorous oxychloride and thionyl chloride were used to cyclize these intermediates (Kretov *et al.,* 1956).

The pyrolysis accompanied by a number of undesirable products (Saied, 1983) in addition to long reaction times and complications of materials handling were the causes of low yield of these thiadiazoles (Al-Gwady; 2007) .

Because microwave heating had emerged as a powerful technique to promote a variety of chemical reactions, recent applications were used this technology in hetero ring cyclization and in many important reactions (Katritzky and Singh, 2003; Tierney and Westman, 2001 ; Tanaka and Toda, 2000).

As part of continuous program directed toward the synthesis of important heterocyclic compounds, oxygenous and nitrogenous five and six membered rings (Shandala *et al*., 1998); (Shandala *et al*., 2001) (Shandala *et al*., 2002) and (Ayoub *et al*., 2001), it was become of interest to investigate preparative routs to synthesize N-substituted 1,3,4– thiadiazolyl maleimides due to their immunosuppressive properties which were studied by measuring their ability to inhibit nitrogen-induced leukemia-cell by reaction with more cellular thiols (Freed *et al*., 1999)**.**

EXPERIMENTAL

All melting points were determined on a Gallen Kamp and Electro thermal 1A9300 Digital-Series 1998 apparatus and were uncorrected. The IR – spectra (ν cm^{-1}) were recorded on Perkin – Elmer 590B Spectrophotometer. UV-1650, Shimadzu PC Spectrophotometer using methanol as solvent. Thin layer chromatography (T.L.C.) was carried out on silica gel coated plate type linear-KL, Whatman com.

2-Amino-5-aryloxymethyl – 1,3,4 –thiadiazoles (1-6):

Method (a) (conventional procedure): (Saied, 1983)

Phosphorous oxychloride 4.6 g was added drop-wise to an ice cooled mixture of (0.9 gm, 0.01 mole) thiosemicarbazide and 0.01 mole of the proper aryloxyacetic acid with shaking. The reaction mixture was refluxed for an hour, then cooled to room temperature, and added to 250 ml of stirred ice-cold water then neutralized with 10% sodium carbonate solution. The cyclized product that precipitated was filtered, washed with water and crystallized from aqueous ethanol. Purity of compounds was established by a single spot in TLC. Melting points, yields and IR spectral data of compounds (1-6) were listed in Table (1).

Method (b) (microwave irradiation): (Saied,2007)

Phosphorous oxychloride 1g was added drop-wise to an ice–cooled mixture of (0.9 g, 0.1 mole) thiosemicarbazide and 0.01 mole of the proper aryloxyacetic acid with shaking. The reaction mixture was irradiated for 3 minutes in 210W domestic microwave oven, and it was then worked up as in method (a).

Table 1: Melting points, yields and IR spectral data of compounds (1-6).

Compd No.	X	Y	M.P. ^{O}C	Yield % method		IR ν cm $^{-1}$ KBr disc					UV λmax (nm) MeOH
				a	b	Aromatic C-H bending	N-H Stretching and Bending	C-O-C	Ring C=N & C=C stretching	Others	
1	H	H	198-200	40	80	750	3100 1650	1220	1595;1520	-	240
2	Cl	H	204-5	44	88	830	3300 1590	1200	1595;1520	-	240
3	Cl	Cl	167-8	50	90	850	3150 1590	1160	1600;1520	-	255
4	Br	Br	157-8	40	85	850	3150 1590	1166	1595;1520	-	260
5	F	H	209-10	30	85	760	3100 1590	1190	1595;1520	-	260
6	NO_2	H	210-11	40	84	750	3300 1560	1200	1600;1520	1510 1345 NO_2	270

N-(2-Amino-5-aryloxymethyl-1,3,4–thiadiazol-2-yl) maleamic acids (7-12): (El-Emam and Lehmann, 1994) and (Rabjohn, 1973).

In a three-necked flask provided with a paddle type stirrer, a reflux condenser and a dropping funnel, (9.8 gm, 0.1 mole) of maleic anhydride and 100 ml of ethanol was placed. When the entire compound was dissolved by stirring, a solution of (0.1mole) of appropriate amine (1-6) in 20 ml of dimethyl formamide was run dropwise through the dropping funnel. The resulting thick suspension was stirred at room temperature for one hour and was then cooled to 15-20 ^{o}C in an ice bath. The product was obtained by suction filtration, and treated with 5 % solution of sodium carbonate, filtered and acidified with dilute hydrochloric acid.

The precipitate was filtered, washed with cold water, and dried in oven at (100 ^{o}C), then recrysytallized from ethanol. Melting points, yields and IR spectral data of compounds (7-12) were listed in Table (2).

N-(2-Amino-5-aryloxymethyl–1,3,4–thiadiazol-2-yl) maleimides (13-18): Method (c) (conventional procedure): (El-Emam and Lehmann, 1994)**.**

Appropriate maleamic acid (0.05 mole) was dissolved in 2 ml dimethyl formamide. To this solution (0.1mole) phosphorous pentoxide was added. The mixture was heated at 70-80 ^{o}C for two hours.

After cooling to room temperature and evaporating of the solvent, the solid material was crushed well and washed with 5% sodium carbonate solution to dissolve the un-reacted maleamic acid. The precipitate was filtered off, washed well with water and dried in oven at (100 ^{o}C) to give the crude maleimide, which was purified by recrystallization from DMF . Purity of compounds was established by a single spot in TLC. Melting points, yields and IR spectral data of compounds (13-18) were listed in Table (3).

Method (d) (microwave irradiation): (El-Emam and Lehmann, 1994) and (Rabjohn, 1973).

Appropriate maleamic acid (0.05 mole) was irradiated for 12 minutes in 210W microwave oven. The resulting liquid, which solidified when cooled, was worked up as in method (c).

Table 2: Melting points, yields and IR spectral data of compounds (7-12).

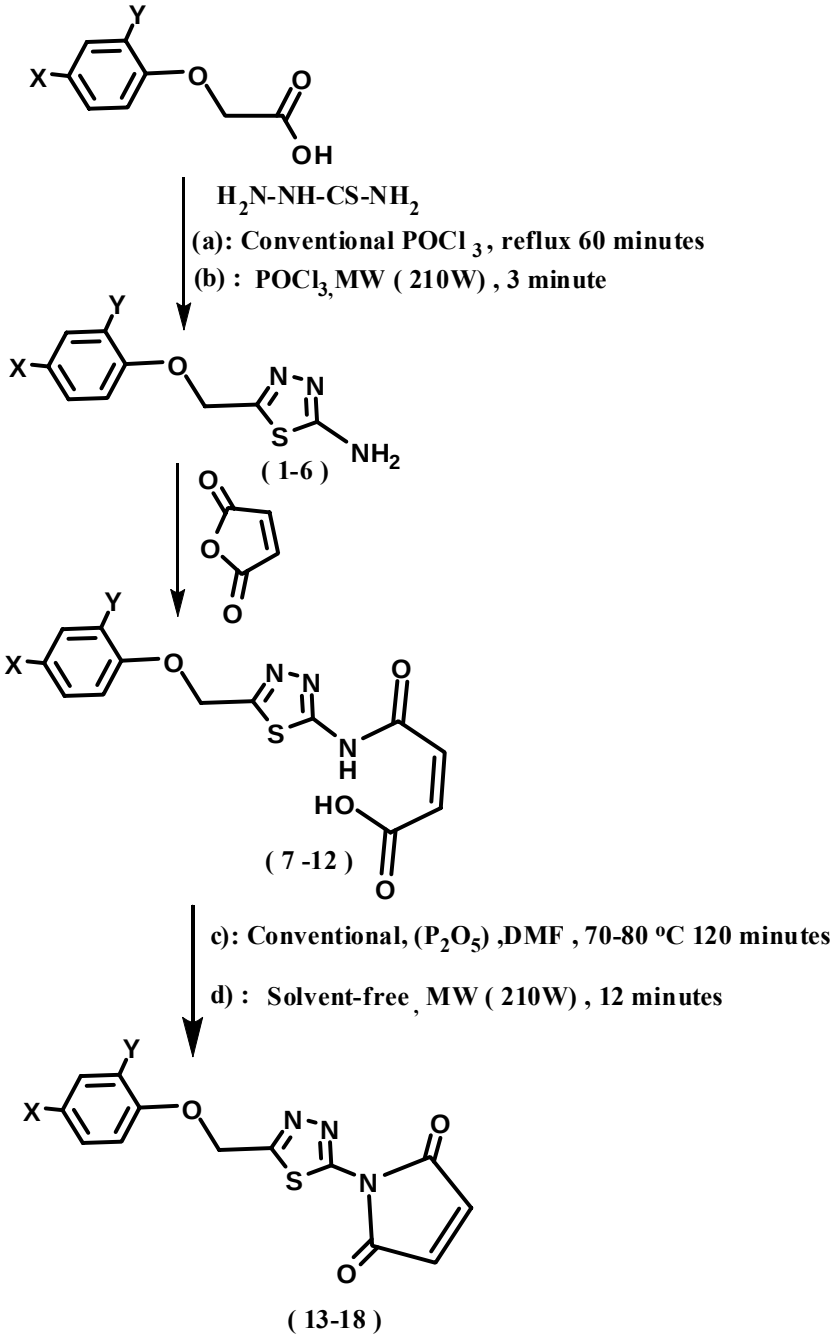
Compd. No.	X	Y	M.P. ^{O}C	Yield %	I.R ν cm $^{-1}$ KBr disc					UV λmax (nm) MeOH
					C=O acid	C=O amide	C-O-C	C=N	others	
7	H	H	190-2	40	1250	1608	1170	1220	-	290
8	Cl	H	185-7	44	1250	1608	1170	1220	-	300
9	Cl	Cl	156-7	50	1300	1620	1160	1220	-	310
10	Br	Br	138-140	40	13000	1610	1166	1200	-	310
11	F	H	196-8	30	1270	1620	1190	1200	-	310
12	NO_2	H	200-202	40	1300	1620	1166	1220	1510 1345 (NO_2)	290

Table 3: Melting points, yields and IR spectral data of compounds (13-18)

Compd. No.	X	Y	M.P. ^{O}C	Yield,% Method		I.R ν cm^{-1} KBr disc				UV λmax (nm) MeOH
				c	d	C=O Imide	C=N	C-O-C	Others	
13	H	H	144-5	56	85	1690	1595	1170	- -	334
14	Cl	H	150-3	56	89	1690	1590	1170	- -	334
15	Cl	Cl	130-3	50	84	1700	1595	1160	-	340
16	Br	Br	155-2	45	85	1720	1590	1166	-	340
17	F	H	145-6	45	80	1720	1590	1190	-	340
18	NO_2	H	152-3	44	84	1700	1590	1166	1510 1345 (NO_2)	340

RESULTS AND DISCUSSION

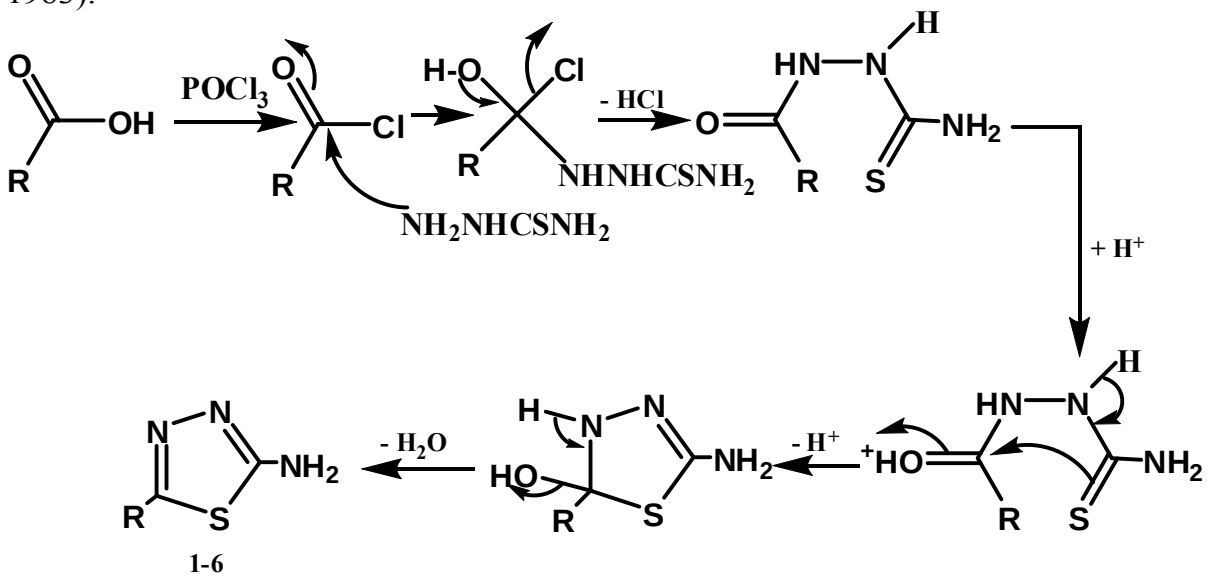
Scheme (1) summarized the synthetic route for the preparation of the designed compounds.



Scheme (1)
X and Y are given in Tables (1-3)

2-Amino-5-aryloxymethyl–1,3,4–thiadiazoles (1-6) were prepared via a one step acylation and cyclization of carboxylic acid with a thiosemicarbazide in the presence of phosphorous oxychloride as shown in Scheme (2) (Al-Gawady , 2009) and (Zheng Li *et al*., 2005).

Two different procedures were used, in method (a), a conventional procedure in which large amounts of phosphorous oxychloride are used to give (30 -50%) yield in one hour (Saied, 1983).



Scheme (2)
R = C_6H_5 ; 4-Cl-C_6H4- ; 2,4-$(Cl)_2$-C_6H_3-;
2,4-$(Br)_2$-C_6H_3- ;4-F-C_6H_4- or 4-NO_2-C_6H_4- respectively

While in method (b), the microwave irradiation for 3 minutes in present of small amounts of dehydrating agent (only one gram of Ca SO_4) was used to give the highest yield (80-90%) (El-Emam and Lehmann, 1994) and (Rabjohn, 1973). Here the microwave radiation accelerated solvent-free cyclization (Zheng Li *et al*., 2005).

The disappearance of C=O stretching in IR spectra was good indication of conversion of acid to heteroring, in addition to the following frequencies: 3100-3300 cm^{-1} and 1560-1590 cm^{-1} due to NH stretching and bending respectively, 1595-1600 cm^{-1} for C=N stretching, and 1520 cm^{-1} for C=C ring stretching, Table (1). The UV spectra showed absorption peaks at λmax 240-270 nm for (n→π*) electronic transitions.

N- (2-Amino-5-aryloxymethyl-1,3,4–thiadiazol-2-yl) maleamic acids (7-12) were prepared by treatment of primary amines with maleic anhydride (El-Emam and Lehmann, 1994). These acids were identified by IR spectra which showed two carbonyl absorption bands, one for the acid carbonyl at (1250-1300 cm^{-1}) and the other for amide carbonyl at (1608-1620 cm^{-1}). The increase in the values λmax in the spectra of these compounds about (20-40nm) relatives λmax of compounds (1-6) was due to the first $\pi \rightarrow \pi^*$ transition bands shift of acid conjugation effect.

N-(2-Amino-5-aryloxymethyl – 1,3,4 –thiadiazol-2-yl) maleimides (13-18) were prepared using a conventional procedure (c) to yield (44 -56%) during two hours heating in DMF solvent, while the solvent free microwave-assisted procedure (d) gave yield (80-89%) through only twelve minutes irradiation time. The driving force for these rings formation was the water elimination in the last step (Al-Gwady, 2009). These compounds were assigned from their IR and UV spectra which came in agreement with the published data (Matsuo, 1964).

Imides (13-18) showed characteristic absorption bands in the 1690-1710 cm $^{-1}$ region of their IR spectra, Table (3), these two bands come from a mechanical coupling of the two carbonyl groups in acid anhydrides (Matsuo, 1964). The increase in the values λmax in the spectra of these compounds about (64-66 nm) due to the $\pi \rightarrow \pi^*$ transition due to ring system.

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