------ Raf. J. Sci., Vol. 24, No.2 pp. 31-38, 2013------

Synthesis of some Acetylenic Morpholine Derivatives via Grignard Reactions

Asmaa H. Sultan
Department of Chemistry
College of Science
University of Mosul

(Received 30/ 5 / 2012 ; Accepted 10 / 9 / 2012)

ABSTRACT

New derivatives for acetylenic morpholine were prepared. Acetylenic amine (N-propargyl morpholine 1) was synthesized by the reaction of propargyl bromide with morpholine in aqueous medium. This compound was used as a synthone for hydroxy acetylenic compounds. Compound (1) was converted to the Grignard reagent (2) by the reaction with methyl magnesium iodide. The reaction of the intermediate (2) with different carbonyl compounds afforded hydroxy acetylenic compound (3). Finally, prepared N-propargyl ether morpholino (4a-i) was prepared by the reaction of the hydroxy acetylenic compound with chloro acetanilide, benzyl chloride via willamson reaction. The structure of the synthesized compounds has been elucidated by the available physical and spectral methods.

Keywords: Grignard reagent, acetylenic amines, hydroxy acetylenic compounds, propargyl morpholine ether.

تحضير بعض مشتقات الاستيلين مورفولين باستخدام كاشف كرينيارد

الملخص

تم تحضير بعض المشتقات جديدة للاستيلين مورفولين. حضر (N-بروبرجيل مورفـولين I) مـن تفاعل بروميد البروبرجيل مع المورفولين في وسط مائي، ثم استخدم هذا المركب مـادة أوليـة لتحـضير مركبات الـهيدروكسي الاستيلينية. حول المركب (1) إلى كاشف كرينيارد (2) بتفاعله مع مثيـل ايوديـد المغنيسيوم. ان تفاعل المركب الوسطي (2) مع مركبات الكاربونيل المختلفة أعطى مركبـات هيدروكـسي الاستيلينية (3a-i). أخيرا حضرت مركبات -بروبرجيل مورفولين ايثـر مـن خـلال تفاعـل مركبـات هيدروكسي الاستيلينية (3a-i) مع كلورواستناليد اوكلوريد البنزيل من خلال تفاعل وليامـسون للايثـرات (4a-i). شخصت المركبات المحضرة باستخدام الطرائق الفيزيائية والطيفية.

الكلمات الدالـة: كاشـف كرينيـارد، الامينـات الاسـتيلينية، مركبـات هيدروكـسي الاسـتيلين، N-مورفولينوبروبرجيل ايثر.

INTRODUCTION

Acetylenic amines have been reported to be pharmaceutically active compounds for possessing several biological activities such as antispasmodics anticancer agents, hypertensive agent (AL-Obaidi, 2011), anticancer (Sheat and Dawood, 2005), antineoplastic agent (Sheat and Saeed, 2006), inflammatory agent (Hussin, 2009), cholinergic or anticholinergic agents (Sharb and Jawad, 2002). On the other hand, the ether derivatives also showed a biological activity such as acetylenic amine which acts as an antipyretic agent (Sheat and Ali, 2005), anti-inflammatory (Logen, 1997), herbcidic (Hart *et al*., 1995).

Antimicrobial activity (Chakrabothy, 2008), antimaterial activity (Eyong *et al*., 2006), as solvent in chemical reactions (George, 1996). The Grignard reaction is one of the important reactions in organic chemistry is one where a C-C bond is formed (Clevenger and Kathleen, 2007), the Grignard reagent acts as a catalyst (Gerard *et al*., 2007), (Terao and kamba, 2008), Grignard reagents are key building blocks for many pharmaceutical and synthesis drug (Das *et al*., 1993), also Grignard reagent is used to prepare tricyclic drug (Oko *et al*., 2001) and synthesis heterocyclic and 5-membered ring compounds (Baumann *et al*., 2011).

EXPERIMENTAL

Melting points were determined on an electrothermal 9300 melting point apparatus and were uncorrected. The IR spectra were determined as potassium bromide disk on Pye Unicam SP.2000 FTIR spectrophotometer. The UV spectra were recorded on Shimadzu (UV-160) UV-visible spectrophotometer using $CHCl_3$ as a solvent. CHN micro analyses were achieved by costech instruments elemental combustion system model 4010 international S.P.A.

Preparation of N-propargyl morpholine (1)(Mohammed, 1979):

Propargyl bromide (0.1 mole, 2g) was added solution of (0.2 mole, 1 g) morpholine in 30 ml of water with ice-cooled with stirred, the mixture was stirred for one hour at 50 ºC, the upper organic layer was separated and the aqueous layer was extracted with ether (3 ×30 ml) and the ether was evaporated under reduced pressure to give a colourless liquid, with boiling point 175 ºC in 70% yield, the IR spectrum (υ) showed the following characteristic bands: 3340 cm^{-1} due to ≡C-H, 2110 cm^{-1} for C≡C; 1455 cm^{-1} for C-N and 1230 cm^{-1} due to C-O.

Preparation of chloroacetanilide (2)(Vogel, 1972)

A mixture of chloroacetic acid (0.03 mole, 1.4 g) and thionyl chloride (0.04 mole, 2ml) used calcium chloride tube, the reaction mixture is stirred and heated at 70-75 ºC for 30 min. Evaporation of thionyl chloride afforded chloroacetyl chloride.

The mixture was cooled to 0ºC in ice bath and dry benzene (25 ml) and aniline (2 ml, 0.033 mole) were added dropwise with shaking. The mixture was refluxed for 30 min, washed with cold water, and made alkaline with 10%, sodium hydroxide. The precipitate was filtered, washed with water and recrystalized from methanol-water to obtain the desired product as white colour crystals of 72%. Yield, mp 132-134 ºC. the IR υC=O 1685 cm^{-1}, υN-H 3290, λmax ($CHCl_3$) 262 nm.

Preparation of N-(1,1-disubstituted-2-butyl-ol-4-yl) morpholine (3a-i) (Zakariea and radeef, 1984).

A solution of methyl iodide (0.063 mole, 5 ml) in ether (10 ml) was added to magnesium powder (0.02 mole 0.5 g) and an iodine crystal. After magnesium was completely disappeared, the solution N-propargyl morpholine (0.02, 5 ml) in dry peroxide tetrahydrofuran (10 ml) was then added dropwise, the mixture was refluxed for 30 min., cooled and the solution of carbonyl compound (0.01 mole) in 5 ml of dry ether was added. The mixture was refluxed for 15 min., cooled and added to 10 g of crushed ice. The mixture was acidified with 10% hydrochloric acid (3 ml) and the organic layer was separated and washed, then dried over anhydrous magnesium sulfate. The evaporation of the solvent afford hydroxy acetylenic morpholine compound, as solid the precipitate was recrystallized from benzene, the physical and the spectral data of compounds (3a-i) are listed in Table (1 and 2).

Preparation of N-(1,1-disubstituted-2-propargyl ether) morpholine(4a-f) (sheat and Ali, 2006).

Sodium (0.4 g) was dissolved in absolute ethanol (25 ml). the solution was cooled and (0.33mole) hydroxy acetylenic compound and (0.048 mole) chloro acetanilide or benzyl chloride were added slowly. The reaction mixture was refluxed with stirring for 3 hours and the cooled in an ice bath .The formed precipitate was filtered, washed and recrystallized from methanol, the physical and spectral data of compounds (4a-f) are listed in Table (3 and 4).

Table 1: Physical data of solid compounds (3a-i).

Compd (No.)	m.p. ^{o}C	Yield%	CHN Found / cal.		
			% C	% H	%N
3a	166-169	85	78.13/ 78.39	6.49/ 6.53	4.78/ 4.98
3b	179-181	80	81.39/ 81.91	7.81/ 7.84	4.78/ 4.98
3c	217 dec.	60	76.89/ 77.55	7.36/ 7.48	4.78/ 4.98
3d	195-197	70	80.44/ 81.08	7.01/ 7.02	4.78/ 4.98
3e	180 dec.	73	83.89/ 84.40	6.31/ 6.42	4.78/ 4.98
3f	155-158	77	85.79/ 86.42	5.10/ 5.26	4.78/ 4.98
3g	185-187	81	78.13/ 78.39	6.46/ 6.53	4.78/ 4.98
3h	103 dec.	80	79.45/ 80.04	7.02/ 7.03	4.78/ 4.98
3i	160-163	66	80.40/ 82.30	6.50/ 6.70	4.78/ 4.98

Table 2: Spectroscopic data of compounds (3a-i).

Compd. No.	IR (KBr) υ cm^{-1}				UV ($CHCl_3$) λ_{max}, nm
	C≡C	OH	C----C	Others	
3a	2157	3297	1599	----	264
3b	2119	3450	1635	C-O-C 1247 assy 1229 sy	274
3c	2129	3443	1633	----	270
3d	2076	3415	1616	----	250
3e	2102	3492	1971	C-Cl 1971assy 1928 sy	244
3f	2119	3451	1652	----	284
3g	2137	3389	1653	C-O-C 1287 assy 1240 sy	310
3h	2119	3493	1280	N=O 1491 assy 1380 sy	320
3i	2119	3167	----	----	242

Table 3 : Physical properties of compound (4a-f).

Compd (No.)	m.p. ^oC	Yield%	CHN Found / cal.		
			% C	% H	%N
4a	68-70	82	85.49/ 85.71	7.36/ 7.48	4.78/ 4.98
4b	159-161	50	81.39/ 81.91	7.01/ 7.02	4.78/ 4.98
4c	146-148	65	80.44/ 81.08	6.49/ 6.53	8.66/ 8.75
4d	214-216	55	83.89/ 84.40	5.10/ 5.26	8.66/ 8.75
4e	136-138	35	78.79/ 79.38	6.18/ 6.20	8.66/ 8.75
4f	140-142	25	78.13/ 78.39	6.55/ 6.64	8.66/ 8.75

Table 4 : Physical properties of compound (4a-f).

Compd (No.)	I.R. cm^{-1} υ (KBr)				U.V($CHCl_3$) λmax, nm
	C-O-C	C≡C	C----C	N-H	
4a	1136	2852	1610	----	331
4b	1176	2871	1570	----	234
4c	1192	2854	1580	3197	232
4d	1186	2852	1508	3275	220
4e	1194	2856	1575	3132	316
4f	1212	2865	1572	3275	266

RESULT AND DISCUSSION

Many compounds comprising both amino and ethyl functions have been reported to possess potential pharmacological values (Sharb and Jawad, 2002). Also the ether function has a pharmacological and medical value (Sheat and Ali, 2005). Therefore the acetylenic N-morpholine ether compound (4a-i) were synthesized by three stages, the first is the formation of N-propargyl morpholine (1) which accomplished simple nucleophilic substitution reaction. The second stage is the formation of the hydroxyl acetylenic morpholine compounds (3a-i) scheme (1) and the third stage is the formation of the acetylenic N-morpholine ether compounds (4a-f) scheme (1).

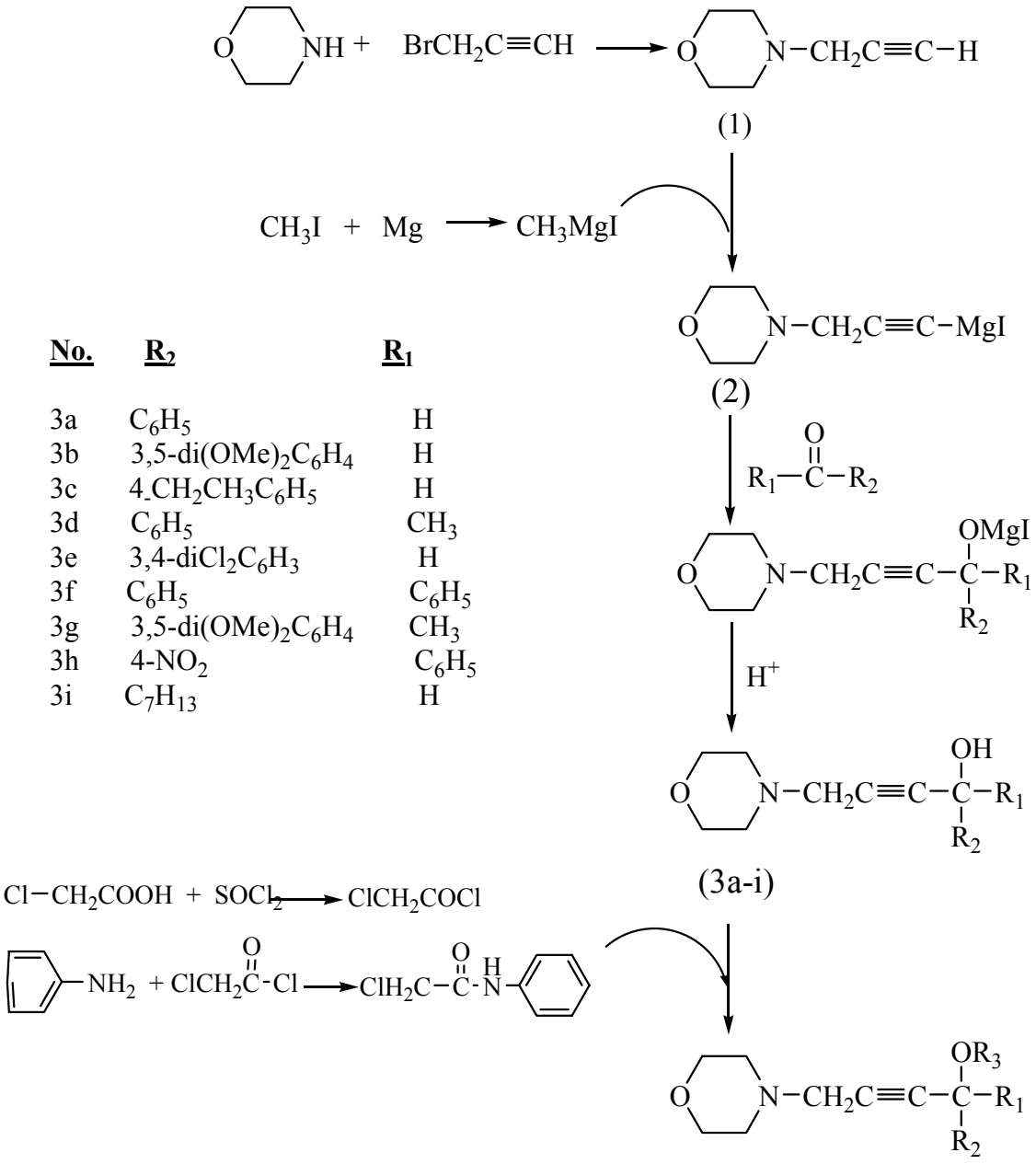
The synthesis of hydroxy acetylenic compounds (3a-i) were accomplished in two steps. The first is reaction of methyl magnesium iodide with N-propargyl morpholine to form N- propargyl morpholino magnesium iodide (2), which is used immediately to prepare compound (3a-i) by reaction with various carbonyl compounds. The synthesized acetylenic morpholine derivatives have been investigated according to their physical an a spectroscopic data (IR,UV) and CHN microanalysis. The other supporting evidence for the formation of compounds (3a-i) is the classifical test about the terminal acetylenic hydrogen which was obtained in the negative Tollen's test.

The IR spectra of hydroxy acetylenic compound (3a-i) indicated the presence of the characteristic absorption at (2157-2076cm^{-1}) attributed to the (C≡C) bond stretching, at 3493-3297cm^{-1} related to the O-H bond stretching. The stretching vibration of the terminal acetylenic hydrogen in compound (1) at 3340 cm^{-1} was disappeared in the IR spectra of compound (3a-i).

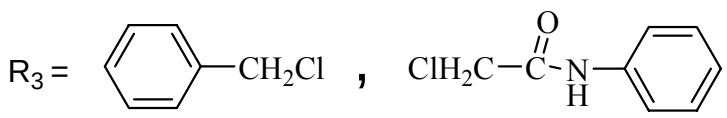
In UV spectra of the synthesized compounds (3a-i) showed bathochromic shift (λmax 320-242 nm) due to the conjugation effect on the electronic transition ($n \longrightarrow \pi^*$) as shown in Table (2).

The IR. Spectra of compound (4a-f) showed a strong absorption band at the regions (1212-1136) cm^{-1} due to the C-O-C group, weak band for C≡C at (2871-2852) cm^{-1} and showed a strong absorption band for amidic C=O at (1650-1670) cm^{-1} (Parkh, 1985).

UV. Spectra of acetylenic N-morpholine ether compounds (4a-f) showed a bathochromic shift in λmax (331-220) nm due to the conjugation effect on the electronic transition ($n \longrightarrow \pi^*$) as showed in Table (4).



No.	R_2	R_1
3a	C_6H_5	H
3b	3,5-di$(OMe)_2C_6H_4$	H
3c	4-$CH_2CH_3C_6H_5$	H
3d	C_6H_5	CH_3
3e	3,4-di$Cl_2C_6H_3$	H
3f	C_6H_5	C_6H_5
3g	3,5-di$(OMe)_2C_6H_4$	CH_3
3h	4-NO_2	C_6H_5
3i	C_7H_{13}	H



Scheme (1)

REFERENCES

AL-Iraqi, M. (1979). Chemical investigation of acetylenic amine oxides. M.Sc., Thesis, College of Science, University of Mosul.

Al-obaidy, O. H. Sh. (2011). Preparation and theoretical study of some transition metal complexes with acetylenic amine and study of biological activity. *Int. J. Appl. Sci. Tech*., **1**, 41-43.

Baumann, M.; Baxendeale, I. R.; Steven, V. ; Nikbin, N.(2011). Anover view of the key results to the best selling 5-membred ring heterocyclic pharmaceutical. *Beilstin J. Org. Chem.*, **7**, 442-495.

Cabil, G.; Habiak, V.; Duplais, C.; Moyeux, A. (2007). Iron-catalyzed Alylation of aromatic grignard reagents. *J. Ang. Chim. Int. Edn*., **46**, 4364 -4366.

Chakraborthy, G.S. (2008). Antimicrobial activity of the left extracts of calenula officinalis. *J. Herbal Medicine and Toxicology*, **2**(2), 65-66.

Clevernger, R.; Viklway, K. (2007). Macroscale and microscale organic experiments. University of Missouri-kansas city. pp. 856-866

Das, B. C.; Genisson, Y.; Morazono, C. (1993). A stereo controlled alkylation of chiral pyridinium salt with grignard reagents: synthesis of (+) normetazocine and (+) – Nordextrophan". *J. Org. Chem*., **58**, 2052-2057.

Eyong, K.O.; Hussain, H.; Ngosong, G.; Kuete, F. (2006). " New bouldion quinon A:A naphthoquinon anthraquinone ether coupled pigment, asapotential antimclobial and antimalarial agent from new bouldia laevis. *Phytochemistry*, **67**, 605-609.

George, H.S (1996). "Organic Chemistry", University of Toronto, pp. 550-566.

Hart, O.; Claine, L.E.; Hort, H. (1995). "Organic Chemistry a Short Course". 9th ed., Houghton Mifflin Company, Toronto , 204, 344.

Hussin, Y. H. (2009). Synthesis of some acetylenic amines derivatives by mannich reaction . *J. Raf. Sci*., **20**(4), 52-57.

Kambe, N.; Tareo, J. (2008). Cross-coupling reaction of alkyl halides with grignard reagents catalyzed by Ni, Pd, or Cu complexes with π-CARBON LIGAND (s). *J. Am. Chem. Soc*., **41**(11), 1545-1554.

Logen, R.H. (1997). "Synthesis of Ethers". Instructor Dalls County Community College District, North Lake College.

Mitsuru, O.; Yoshiro, I.; Noriyuki, I.; Naoki, H. ; Takuji, K. G. (2001). Synthesis and anti-influenza virus activity of tricyclic compounds with a unique amine moiety. *J. Chem. Pharm. Bull.*, **49**(4), 379-383.

Oko, M.; Ishiwata, Y.; Iwata, N.; Hond, N. (2001). Synthesis and anti-influenza virus activity of tricyclic compound with a unique amine moiety. *J. Chem. Pharm*., **49**, 379-383.

Parch, V. M. (1985). " Absorption spectroscopy of organic molecules", London, pp. 189-588.

Parkh, (1985). "Absorption Spectroscopy of Organic Molecules". Addition-wesley Publishing company, London, 70, 243 p.

Sheat, M. A. ; Saed, Z. F. (2006). Synthesis and study of acetylenic amines derevitives containing sulfonamide, β-naphthoxy and hippurate groups. *National J. Chemistry*, **21**, 53-62.

Sheat, M. ; Dawood, A. A. (2005). Preparation of some acetylene amnine derivative of saccharine as expected biologically active agents. *J. Edu. Sci*., **15**(2), 44-51.

Sheat, M.A. ; Ali, S.R. (2005). Synthesis and study of acetylenic amines derevitives frome p-amino phenol. *Nat. J. Chem*., **22**, 269-280.

Sharb, A.H. ; Jawad, H. (2002). Acetylenic compounds derevitives from piperazine (part 2) synthesis of pharmacologically important acetylenic amines. *Nat. J. Chem*., **7**, 466-47.

Vogel, A.I. (1972). "Text Book of Practical Organic Chemistry". Longman, London, 4th ed., 401 p.

Zakareia, M.; Radeef, F. (1984). "Practical Organic Chemistry". Mosul University. 156p.