Available online www.jocpr.com

Journal of Chemical and Pharmaceutical Research, 2012, 4(8):3929-3933

Research Article

ISSN : 0975-7384
CODEN(USA) : JCPRC5

Synthesis of some new derivatives of 2-methyl-4*H*-4-chromenone

Azimvand J

Organic Chemistry Research Laboratory, Chemistry Department, Faculty of Science, Payame Noor University, Tehran, Iran

---

ABSTRACT

A novel and simple method for the synthesis of functionalized 2-methyl-4H-4-chromenone is Reported . The 2-methyl-4H-4-chromenone were prepared from 2-acetyl phenol. 2-acetyl phenol could condense with ethyl acetate under sodium catalyzation, so 2-acetylacetyl phenol could be prepared though their sodium salt. Then substituted 2-methyl chromones were formed by 2-acetylacetyl phenol under catalytic amounts of concentrated hydrochloric acid and HOAc . chromones provides with a variety of substituents on the aromatic ring , and the described characterized 4H-4-chromenone drivatines by short reaction times, high yields (68 to 92%). The structure of the isolated compounds has been determined by means of IR , ^{1}HNMR and Mass Spectroscopy.

Keywords: 4-chromenone , 2-acetyl phenol

INTRODUCTION

Chromones constitute one of the major classes of naturally occurring compounds, and interest in their chemistry continues unabated because of their usefulness as biologically active agents [1]. Some of the biological activities attributed to chromone derivatives include cytotoxic (anticancer) [2-4], neuroprotective [5] , HIV-inhibitory [6] , antimicrobial [7, 8] , antifungal [9] and antioxidant activity [10] . Due to their abundance in plants and their low mammalian toxicity, chromone derivatives are present in large amounts in the diet of humans [11] .

The synthesis of chromone derivatives is a research field of great interest and long history [12] . In general, chromones are synthesized by the cyclodehydration of 1-(*o*-hydroxyaryl)- 1,3- diketones or equivalent intermediates catalyzed by strong acids or strong bases (Vilsmeier- Haack reaction) [13] .They have been prepared on a large scale by the Allan-Robinson synthesis involving acylation-rearrangement, and subsequent cyclization [14] . This methodology has been followed in the synthesis of chromone derivatives with quaternary ammonium functionalities which show not only activity of cosmetic interest but also for hair sustainability, as well as in the asymmetric synthesis of optically active 4-chromone derivatives [15] . In the Baker-Venkataraman synthesis [16] , internal Claisen condensation of 2-aryloxy-1-acetylarenes is employed as a key step. More recently the synthesis of chromone derivatives was accomplished by intramolecular ester carbonyl olefination [17] or Pd-catalyzed regiospecific carbonylative annulation of *o*-iodophenol acetates and acetylenes [1, 18] . 3-Cyanochromones have been synthesized in a mild and facile method from oximes derived from 3-formyl chromones using dimethyl formamide/ thionyl chloride complex [19] . As for aminochromones, useful for the prevention of allergic and asthmatic reactions in mammals, as indicated by tests in rats, they have been synthesized either by rearrangement of isoxazoles [20] or from chlorinated salicylic acids and malononitrile in aqueous NaOH or NaH [21] .

EXPERIMENTAL SECTION

General Procedures

Melting points were taken on a Yanaco MP-S3 micro melting point apparatus. The IR spectra were recorded in KBr pellets on a Bruker FT-IR Equinox apparatus. The ^{1}HNMR spectra were recorded on an INOVA-400 (using TMS as internal standard, d6-DMSO as solvent). Mass specteroscopy were recorded on a HP 5890. Elemental analyses were performed on a Yanaco CHN Corder MT-3 analyzer. The TLC was performed by GF-254 and 0.5% CMC. Detection made use of UV light; the mobile phase was petroleum ether and ethyl acetate (1:1) .

Synthesis of 1-(2-hydroxyphenyl)-1,3-butanedione (2) :

Under nitrogen atmosphere, the mixture of 0.2 mol 2-acetyl phenol and 165 mL ethyl acetate (free ethanol) was added dropwise into 8 g powdered sodium; when the vigorous reaction had ceased, the mixture was heated in an oil bath for an hour. The product was shaken with 150 g crushed ice. And the yellow sodium salt was filtered, washed with icecold water, then ether, and decomposed by treatment with 32% acetic acid. The crude product was filtered off as precipitate.

1-(2-hydroxyphenyl)-1,3-butanedione (o- acetoacetylphenole) was recrystallized from ethanol.
mp 318-327 °C; IR (KBr, cm^{-1}) 1125 (Ar-H) , 1223 (C-O) , 1620 (C=O) , 2916 (CH_2) , 2952 (CH_3) , 3605 (O-H) ; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.3 (S , 3H) , 2.31 (S , 3H) , 4.02 (S , 2H) , 7.28 (d , J=7.68 , 1H) , 7.36 (d , 1H) , 7.46 (d , J=7.37 , 1H) , 7.72 (d , J=7.88 , 1H) ; MS (m/z): 178 .

Synthesis of 2-methyl-4H-4-chromenone (3) :

1-(2-hydroxyphenyl)-1,3-butanedione (0.01 mol) was boiled for 2 min with acetic acid (10 mL), then a few drops of concentrated hydrochloric acid were added and refluxed for 15 min. After cooling, the mixture was poured into ice-water. The crude product was filtered off as precipitate and 2-methyl-4H-4-chromenone was recrystallized from ethanol.

mp 336-341 °C; IR (KBr, cm^{-1}) 1105 (Ar-H) , 1112 (C-O) , 1695 (C=O), 1609 (C=C) , 2921 (CH_3) ; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.12 (S , 3H) , 5.7 (S , 1H) , 7.39 (d , 1H) , 7.50 (d , J=8.34 , 1H) , 7.62 (d , j=7.3 , 1H) , 8.17 (d , J=8.06 , 1H) ; MS (m/z): 160 .

SPECTROSCOPIC DATA OF 2-METHYL-4-4H-4-CHROMENONE (3) DRIVATIVES

3a. 2,7-dimethyl-4H-4-chromenone :
mp 298-303 °C; IR (KBr, cm^{-1}) 1105 (Ar-H) , 1112 (C-O) , 1695 (C=O), 1609 (C=C) , 2921 (CH_3) , 2942 (Ar-CH_3) ; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.12 (S , 3H) , 2.46 (S , 3H) , 5.7 (S , 1H) , 6.98 (S , 1H) , 7.13 (S , 1H) , 7.62 (d , j=7.55 , 1H) ; MS (m/z): 174 .

3b. 2-chloro-2-methyl-4H-4-chromenone :
mp 287-292 °C; IR (KBr, cm^{-1}) 752 (C-Cl) , 1105 (Ar-H) , 1112 (C-O) , 1695 (C=O), 1609 (C=C) , 2921 (CH_3) , 2942 (Ar-CH_3) ; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.12 (S , 3H) , 5.7 (S , 1H) , 7.44 (S ,j=2.4 , 1H) , 7.46 (d , 1H) , 7.52 (d , j=8.3 , 1H) ; MS (m/z): 194 .

3c. 2-methyle-7-(4-methylphenile)-4H-4-chromenone :
mp 299-301 °C; IR (KBr, cm^{-1}) 1113 (Ar-H) , 1118 (C-O) , 1698 (C=O), 1611 (C=C) , 2932 (CH_3) , 2952 (Ar-CH_3) ; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.12 (S , 3H) , 2.3 (S , 3H) , 5.7 (S , 1H) , 7.03 (d , j=8.05 , 2H) , 7.35 (S , 1H) ,7.5 (d , 1H) , 7.7 (d , 2H) , 7.73 (d , j=7.55 , 1H); MS (m/z): 250 .

3d. 2-methyle-7-(2-methylphenile)-4H-4-chromenone :
mp 335 °C< ; IR (KBr, cm^{-1}) 1113 (Ar-H) , 1118 (C-O) , 1698 (C=O), 1611 (C=C) , 2932 (CH_3) , 2952 (Ar-CH_3) ; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.12 (S , 3H) , 2.64 (S , 3H) , 7.14 (t , j=7.71 , 1H) , 7.22 (d , j=7.68 , 1H) , 7.34 (t , j=7.37 , 1H) ,7.44 (d , 1H) , 7.6 (d , 1H) , 7.67 (d , j=7.55 , 1H); MS (m/z): 250 .

3e. 7-(4-methoxyphenil)-2-methyle-4H-4-chromenone :
mp 305-307 °C; IR (KBr, cm^{-1}) 1113 (Ar-H) , 1118,1124 (C-O) , 1698 (C=O), 1611 (C=C) , 2932 (CH_3) , 2952 (Ar-CH_3) ; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.12 (S , 3H) , 3.86 (S , 3H) , 5.7 (S , 1H) , 7.03 (d , j=8.05 , 2H) , 7.35 (S , 1H) ,7.5 (d , 1H) , 7.7 (d , 2H) , 7.73 (d , j=7.55 , 1H); MS (m/z): 266 .

3f. 7-(3,4-dimethoxyphenil)-2-methyle-4H-4-chromenone :
mp 278-281 °C; IR (KBr, cm^{-1}) 1113 (Ar-H) , 1118,1124 (C-O) , 1698 (C=O), 1611 (C=C) , 2932 (CH_3) , 2952 (Ar-CH_3) ; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.12 (S , 3H) , 3.8 (S , 6H) , 5.7 (S , 1H) , 6.79 (d , j=8.46 , 1H) , 6.89 (S , 1H) ,7.17 (d , 1H) , 7.4 (S , 1H) , 7.56 (d , 1H) , 7.6 (d , j=7.55 , 1H) ; MS (m/z): 296 .

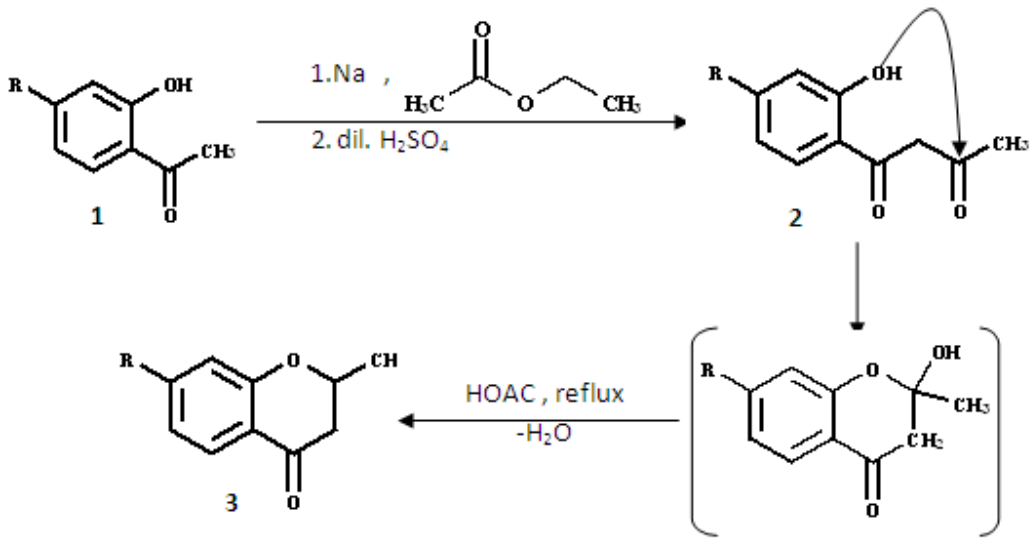
3g. 7-(4-dimethylaminophenile)-2-methyl-4H-4-chromenone :
mp 330 °C; IR (KBr, cm^{-1}) 1113 (Ar-H) , 1118 (C-O) , 1149 (C-N) , 1698 (C=O), 1611 (C=C) , 2932 (CH_3) , 2952 (Ar-CH_3) , 3329 (N-H) ; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.12 (S , 3H) , 2.9 (S , 1H) , 5.7 (S , 1H) , 6.13 (d , j=8.6 , 2H) , 7.37 (S , 1H) ,7.5 (d , 2H) , 7.53 (d , 1H) , 7.71 (d , j=7.55 , 1H); MS (m/z): 279 .

3h. 7-(5-chloro-2-hydroxyphenile) -2-methyl-4H-4-chromenone :
mp 334 °C; IR (KBr, cm^{-1}) 784 (C-Cl) , 1113 (Ar-H) , 1118 (C-O) , 1149 (C-N) , 1698 (C=O), 1611 (C=C) , 2932 (CH_3) , 2952 (Ar-CH_3) , 3329 (N-H) , 3623 (O-H) ; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.12 (S , 3H) , 4.7 (S , 1H) , 5.7 (S , 1H) , 6.64 (d , 1H) , 7.12 (d , j=8.6 , 1H) ,7.42 (d , 1H) , 7.55 (S , 1H) , 7.7 (d , j=7.5 , 1H) ; MS (m/z): 286 .

RESULTS AND DISCUSSION

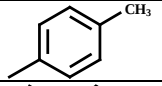
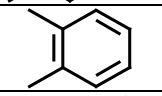
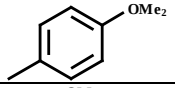
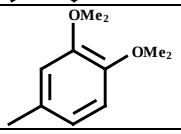
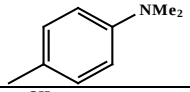
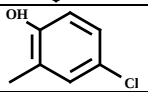
The 2-methyl-4H-4-chromenone were prepared from 2-acetyl phenol. 2-acetyl phenol could condense with ethyl acetate under sodium catalyzation, so 2-acetylacetyl phenol could be prepared though their sodium salt. Then substituted 2-methyl chromones were formed by 2-acetylacetyl phenol under catalytic amounts of concentrated hydrochloric acid and HOAc (scheme 1).

Scheme 1



The Chromone derivatives were synthesized successfully in moderate to good yields. The newly synthesized compounds were identified on the basis of melting point range; IR, ^{1}HNMR, Mass spectral analysis and elemental analysis. All the newly synthesized derivatives were screened for antibacterial activity using agar diffusion method. Table 1 shows the efficiencies obtained from the derivatives of 3 compound .

Table 1 . Yield value of 2-methyl-4H-4-chromenone (3) derivatives

Compound	R	Molecular formula	Yield value(%)
2	H	$C_{10}H_{10}O_3$	96
3	H	$C_{10}H_8O_2$	89
3a	CH_3	$C_{11}H_{10}O_2$	91
3b	Cl	$C_{10}H_7ClO_2$	92
3c		$C_{17}H_{14}O_2$	86
3d		$C_{17}H_{14}O_2$	88
3e		$C_{17}H_{14}O_3$	84
3f		$C_{18}H_{16}O_4$	79
3g		$C_{18}H_{17}NO_2$	72
3h		$C_{16}H_{11}ClO_3$	68

CONCLUSION

In the current research some substituted 2-methyl-4H-4-chromenone have been synthesized . From the above results, it can be conclude that chromenone compounds are moderately active against all used bacterial strain .

Although the compounds synthesized are not much significant against microbes under investigation but the further purification and modification of synthesized derivatives give scope for further development in the same heterocyclic nucleus.

REFERENCES

[1] (a) Miao H; Yang Z. , Org Lett., **2000**, 2(4), 1765-1776 and refs. therein. (b) Silva, A. M. S.; Pinto, D. C. G. A.; Cavaleiro, J. A. S.; Levai, A.; Patonay, T. Arkivoc , J. Nat. Prod. , **2004**,6 (9), 106-121. (c) Levai, A. Arkivoc, J. Nat. Prod., **2004**, 15(14),, 235-249.
[2] Valenti, P; Bisi A; Rampa A; Belluti F; Gobbi, S.; Zampiron A; Carrara, M. Biorg, Med. Chem., **2000**, 239(17),128-137.
[3] Lim L.-C; Kuo Y.-C; Chou C.-J. J, Nat. Prod., **2000**, 63(8), 627-638.
[4] Shi Y. Q; Fukai T; Sakagami H; Chang W.-J; Yang P.-Q; Wang F.-P; Nomura, T. J. Nat. Prod., **2001**, 64(3), 181-189.
[5] Larget R; Lockhart B; Renard P; Largeron M. Biorg, Med. Chem. Lett., **2000**, 10(27), 835-867.
[6] Groweiss A; Cardellins J. H; Boyd M. R, J. Nat. Prod., **2000**, 63(12), 1537-1543.
[7] Deng Y; Lee J. P; Ramamonjy M. T; Synder J. K; Des Etages S. A; Kanada, D; Synder M. P; Turner, C. J. J. Nat. Prod., **2000**, 63(15), 10821124.
[8] Khan I. A; Avery M. A; Burandt C. L; Goins D. K; Mikell J. R; Nash T. E; Azadega A; Walker, L. A. J. Nat. Prod., **2000**, 63(24), 1414-1427.
[9] Mori K; Audran G; Monti, H. Synlett ., **1998**,15(27), 259273.
[10] Pietta P. J, J. Nat. Prod., **2000**, 63(7), 1035-1059.
[11] (a) Beecher G. R, J. Nutr., **2003**, 133(3), 3248-3278. (b) Hoult J. R. S, Moroney; M. A Paya, M.Methods Enzymol., **1994**, 234(14), 443-452.
[12] Horton D. A; Bourne G. T; Smythe, M. L. Chem. Rev., **2003**, 103(16), 893-928.

[13] Livingstone R; Coffey, S. Eds, Elsevier., **1977**, 21(21), 198-204 .
[14] Allan J; Robinson , R. J. Chem. Soc., **1924**, 125(16), 2192-2236.
[15] Walenzyk T; Carola C; Buchholz H; Konig , B. Tetrahedron., **2005**, 61(17), 366-378.
[16] Baker W, J. Chem. Soc., **1933**,34(22), 1381-1392.
[17] Kumar P; Bodas, M. S. Org. Lett., **2000**, 2(6), 3821-3833.
[18] Davies S. G; Mobbs B. E; Goodwin C. J, J. Chem. Soc., Perkin Trans 1, **1987**, 12(15), 2597-2634.
[19] Reddy G. J; Latha D; Rao, K. S. Heterocyclic Commun., **2004**, 10(21), 279-286.
[20] Ghosh T; Saha S; Bandyopadhya, C. Synthesis., **2005**, 11(3), 1845-1865.
[21] Brown R. E; Lustgarten D. M. US Patent 3932466, **1976**.