

New Method of 2-Amino-4H-Chromene Synthesis

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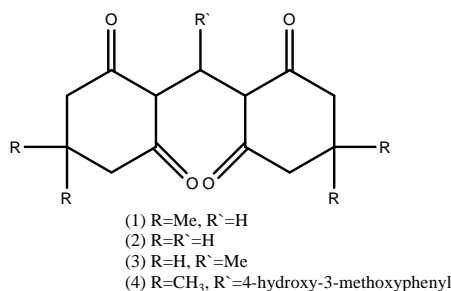
ABSTRACT

Different bis dimedones were synthesized and reacted with malononitrile to obtain different alkylidenes. These reactions were failed to give the desired alkylidenes, instead different 4H-chromenes were obtained in moderate to good yield, Moreover in this work a new method of chromene synthesis has been established.

Key Words: Michael addition; Reaction of bis dimedone; Reaction of malononitrile; Gheath method

INTRODUCTION

Different bis dimedones (1-3) were reacted with 4-nitroaniline in ethanol with a catalytic amount of phosphorus pentoxide afforded 10-(nitrophenyl)-2,3,4,5,6,7,9,10-octahydro-1,8-acridinediones.



The reaction of bis dimedones (1 and 4) with thiosemicarbazide was carried out to afford N-(3,3,6,6-tetramethyl-1,8-dioxo-2,3,4,5,6,7,8,9-octahydro-1H-acridin-10-yl)-thiourea and [9-(4-hydroxy-3-methoxy-phenyl)-3,3,6,6-tetramethyl-1,8-dioxo-2,3,4,5,6,7,8,9-octahydro-1H-acridin-10-yl]-thiourea respectively. Reaction of bis dimedones with ammonium acetate or amines afforded the respective 10-substituted 1,8-acridinediones (Jeyakanthan & Velmurugan, 1999; Gunnlaugsson, Davis & Glynn, 2001).

EXPERIMENTAL

General Remarks:

¹H-NMR Proton magnetic resonance spectra were measured at Micro Analytical Centre University of Cairo in hexadeuterodimethylsulfoxide (DMSO-d₆) or deuteriochloroform (CDCl₃) solution, on Bruker 300 MHz instruments, with chemical shift (δ) expressed in ppm down field from tetramethylsilane as an internal standard (δTMS=0). The multiplicity of the signal is as follow: s (Singlet), d (Doublet), t (Triplet), q (Quartet), m (Multiplet).

^{13}C -NMR spectra were measured at Micro Analytical Centre University of Cairo on Bruker 75 MHz and internal reference TMS $\delta=0$, s, d, t, q; signal multiplicities were measured by DEPT spectroscopy.

Melting points of the synthesized compounds were determined in capillary tubes using Griffin apparatus and are uncorrected.

Chromatography Analytical glass plates were used with Kieselgel Gor Kieselgel GF 254 (Merck). The plates were run in the following systems:

i-chloroform

ii-chloroform-petroleum ether (different ratios)

iii-chloroform- methanol (different ratios)

And examined under ultra-violet light Model UV GL-58/50 Hz Lamp.

Synthesis of Bisdimedones:

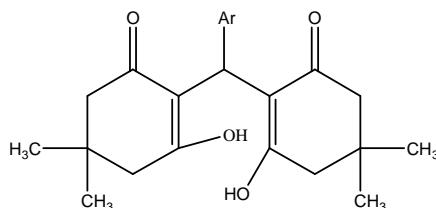
Reactions of Dimedon With Aromatic Aldehydes:

General Procedure (Josephrajan, Ramakrishnan, Kathiravan, & Muthumary, 2005):

In 100 ml conical flask, to a solution of dimedone (0.02 mol) in aq. methanol was added the aromatic aldehyde (0.01 mol) and warmed until the solution became cloudy. when bis dimedone started to separate out, the reaction mixture was diluted with 50 ml water and allowed to stand overnight; the product was collected by filtration, dried and recrystallized from methanol.

Table 1.

| No. | Ar | R.time | Yield(%) | m.p(°C) | m.p(°C) lit. |
|-----|------------------|----------|----------|---------|--------------|
| 5 | phenyl | 28 mins. | 56.81 | 194-196 | 194-195 |
| 6 | 2-Methoxy phenyl | 9 mins. | 95.5 | 174-177 | 187-188 |
| 7 | 3-Methoxy phenyl | 13 mins. | 79.7 | 186-187 | 185-186 |
| 8 | 4-Methoxy phenyl | 28 mins. | 89 | 145-147 | - |
| 9 | 2-Hydroxy phenyl | 9 mins. | 97 | 208-210 | 205-206 |
| 10 | 4-Hydroxy phenyl | 2 hrs. | 91 | 191-194 | 188-189 |
| 11 | 4-Chloro phenyl | 10 mins. | 87.5 | 137-138 | - |
| 12 | 2-Nitro phenyl | 10 mins. | 52 | 192-193 | - |
| 13 | 4-Nitro phenyl | 15 mins. | 48.23 | 191-193 | 188-190 |

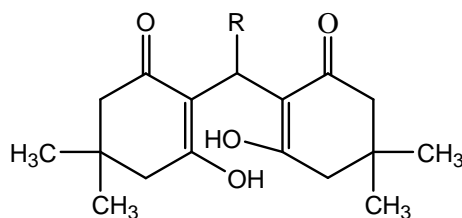


Comp. (5-13)**Reaction of Bimedones With Aliphatic Aldehyde:****General Procedure** (Horning, 1946):

In 100 ml round-bottom flask, 30 ml 50% ethanol-water was mixed with (0.02 mol) of dimedone and (0.01 mol) of aliphatic aldehyde. Drops of morpholine were added and the mixture was heated under reflux on a water-bath for half an hour. The formed precipitate was filtered and washed with 50% ethanol-water, then re-crystallized from aqueous methanol.

Table 2.

| No. | R | R.time | Yield(%) | m.p.(°C) | m.p.(°C) lit. |
|-----|--------|----------|----------|----------|---------------|
| 14 | Methyl | 30 mins. | 86.9 | 143-144 | 141-142 |
| 15 | Ethyl | 30 mins. | 90.9 | 157-158 | 157-158 |

**Comp. (14,15)****Reactions of Bisdimedones With Malononitriles:****General Procedure** (Gheath, 1997):

In 50 ml round-bottom flask equipped with condenser bisdimedone (0.01 mol) was refluxed and stirred for three hours with (0.02mol) malononitrile in 30 ml ethanol and few drops of morpholine. The reaction mixture was left overnight in refrigerator, the formed precipitate was filtered, washed with cold ethanol and re-crystallized from ethanol.

Table 3.

| No. | Ar (R) | Yield(%) | m.p.(°C) | m.p.(°C) lit. |
|-----|-----------------|----------|-----------|----------------|
| 16 | 4-chlorophenyl | 47.69 | 216-217 | 208-211 |
| 17 | 2-Methoxyphenyl | 50 | 203-205 | 197-200 |
| 18 | 3-Methoxyphenyl | 75 | 206-209 | 201-203 |
| 19 | 4-Methoxyphenyl | 58.3 | 201-202 | 198-200 |
| 20 | phenyl | 62.5 | 234-237 | 223-226 |
| 21 | 4-Hydroxyphenyl | 37.5 | 203-205 | 215-218 |
| 22 | 4-Nitrophenyl | 75 | 182-183 | - |
| 23 | 2-Nitrophenyl | 54.5 | 244-245 | - |
| 24 | Methyl | 66.6 | 195-197 | - |
| 25 | Ethyl | 66.6 | 187-188 | - |

2-Amino-4-(4-chloro-phenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydr-4H-chromene-3-carbonitrile (16):

¹H-NMR (DMSO-d₆): δ=0.94 (s, 3H, CH₃), 1.02 (s, 3H, CH₃), 2.13 (d, 1H, H_{8a}), 2.27 (d, 1H, H_{8b}), 2.5 (s, 2H, H₆), 4.21 (s, 1H, H₄), 7.00 (s, 2H, NH₂), 7.2 (d, 2H, Ar-H), 7.4 (d, 2H, Ar-H).

2-Amino-4-(2-methoxy-phenyl)-7,7-dimethyl-5-oxo-5,6,7,8- tetrahydro-4H-chromene-3-carbonitrile (17):

¹H-NMR (DMSO-d₆): δ=0.97 (s, 3H, CH₃), 1.04 (s, 3H, CH₃), 2.22 (d, 1H, H_{8a}), 2.27 (d, 1H, H_{8b}), 2.47 (d, 1H, H_{6b}), 2.51 (d, 1H, H_{6a}), 3.75 (s, 3H, OCH₃), 4.49 (s, 1H, CH₄), 6.78 (s, 2H, NH₂), 6.85-7.16 (m, 4H, Ar-H).

2-Amino-4-(3-methoxy-phenyl)-7,7-dimethyl-5-oxo-5,6,7,8- tetrahydro-4H-chromene-3-carbonitrile (18):

¹H-NMR (DMSO-d₆): δ=0.97 (S, 3H, CH₃), 1.03 (s, 3H, CH₃), 2.09 (d, 1H, H_{8a}), 2.14 (d, 1H, H_{8b}), 2.29 (s, 2H, H₆), 3.71 (s, 3H, OCH₃), 4.15 (s, 1H, H₄), 6.96 (s, 2H, NH₂), 6.66-7.23 (m, 5H, Ar-H)

2-Amino-4-(4-methoxy-phenyl)-7,7-dimethyl-5-oxo-5,6,7,8- tetrahydro-4H-chromene-3-carbonitrile (19):

¹H-NMR (DMSO-d₆): δ=0.94 (s, 3H, CH₃), 1.03 (s, 3H, CH₃), 2.11 (d, 1H, H_{8a}), 2.21(d, 1H, H_{8b}), 2.5 (s, 2H, H₆), 3.7 (s, 3H, OCH₃), 4.1 (s, 1H, H₄), 6.8 (d, 2H, Ar-H), 6.9 (s, 2H, NH₂), 7.00 (d, 2H, Ar-H).

2-Amino-7,7-dimethyl-5-oxo-4-phenyl-5,6,7,8-tetrahydro-4H- chromen-3- carbonitrile (20):

¹H-NMR (DMSO-d₆):δ=0.96 (s, 3H, CH₃), 1.04 (s, 3H, CH₃), 2.13 (d, 1H, H_{8a}), 2.23 (d, 1H, H_{8b}), 2.52 (s, 2H, H₆), 4.19 (s, 1H, H₄), 6.96 (s, 2H, NH₂), 7.17(m, 3H, Ar-H), 7.29 (m, 2H, Ar-H).

2-Amino-4-(4-hydroxy-phenyl)-7,7-dimethyl-5-oxo-5,6,7,8- tetrahydro-4H-chromene-3-carbonitrile (21):

¹H-NMR (DMSO-d₆): δ=0.94 (s, 3H, CH₃), 1.02 (s, 3H, CH₃), 2.1 (d, 1H, H_{8a}), 2.26 (d, 1H, H_{8b}), 2.49 (s, 2H, H₆), 4.1 (s, 1H, H₄), 6.89 (s, 2H, NH₂), 6.65 (d, 2H, Ar-H), 6.92 (d, 2H, ArH), 9.25 (s,1H,OH).

2-Amino-4-(4-nitro-phenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro- 4H-chromene-3-carbonitrile (22):

¹H-NMR(DMSO-d₆): δ=1.04 (s, 3H, CH₃), 1.06 (s, 3H, CH₃), 2.14 (d, 1H, H_{8a}), 2.23 (d, 1H, H_{8b}), 2.54 (s, 2H, H₆), 4.38 (s, 1H, H₄), 7.06 (s, 2H, NH₂), 7045 (d, 2H, ArH), 8.15 (d, 2H, ArH).

¹³C-NMR (DMSO-d₆): δ= 27.07 (q, 1C), 28.27 (q, 1C), 31.8 (s, 1C), 35.84 (d, 1C), 50.05 (t, 1C), 57.42 (t, !C), 111.03 (s, 1C), 119.18 (s, 1C), 123.60 (d, 2C), 128.63 (d, 2C), 146.42 (s, 1C), 152.22 (s, 2C), 158.74 (s, 1C), 163.10 (s, 1C), 195.56 (s, 1

2-Amino-4-(2-nitro-phenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-chromen-3-carbonitrile (23):

$^1\text{H-NMR}$ (DMSO- d_6): δ = 0.90 (s, 3H, CH_3), 1.02 (s, 3H, CH_3), 2.05 (d, 1H, H_{8a}), 2.18 (d, 1H, H_{8b}), 2.495 (d, 1H, H_{6b}), 2.51 (d, 1H, H_{6a}), 4.99 (s, 1H, H_4), 7.03 (s, 2H, NH_2), 7.35-7.81 (m, 4H, ArH).

$^{13}\text{C-NMR}$ (DMSO- d_6): δ = 26.61 (q, 1C), 28.10 (q, 1C), 29.96 (s, 1C), 31.55 (d, 1C), 49.51 (t, 1C), 56.65 (t, 1C), 112.16 (s, 1C), 118.66 (s, 1C), 123.46 (d, 1C), 127.57 (d, 1C), 130.1 (d, 1C), 133 (d, 1C), 138.72 (s, 2C), 148.79 (s, 1C), 158.98 (s, 1C), 162.48 (s, 1C), 195.39 (s, 1C).

2-Amino-4-methyl-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H- chromene-3-carbonitrile (24):

$^1\text{H-NMR}$ (CDCl_3): δ = 1.07 (s, 3H, CH_3), 1.08 (s, 3H, CH_3), 1.19 (d, 3H, CH_3), 2.25 (d, 1H, H_8), 2.32 (d, 1H, H_6), 3.30 (q, 1H, H_4), 4.66 (s, 2H, NH_2).

$^{13}\text{C-NMR}$ (CDCl_3): δ = 22.38 (q, 1C), 24.77 (q, 1C), 27.45 (q, 1C), 28.69 (d, 1C), 31.95 (s, 1C), 40.66 (t, 1C), 50.89 (t, 1C), 115.35 (s, 1C), 118.88 (s, 2C), 157.92 (s, 1C), 161.46 (s, 1C), 196.41(s,1c).

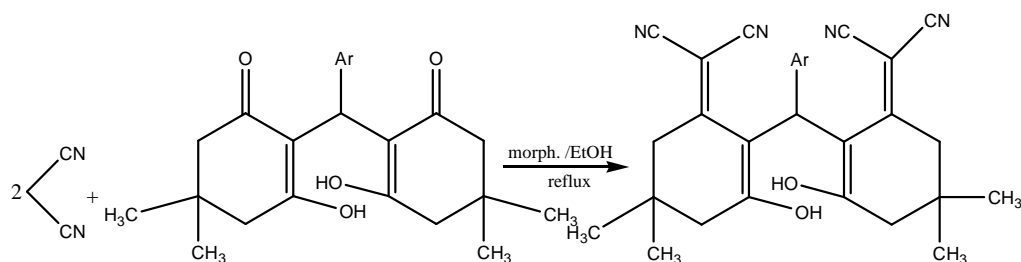
2-Amino-4-ethyl-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H- chromene-3-carbonitrile (25):

$^1\text{H-NMR}$ (CDCl_3): δ =0.81 (t, 3H, CH_3), 1.11 (s, 3H, CH_3), 1.12 (s, 3H, CH_3), 1.59-1.70 (m, 2H, CH_2), 2.29 (d,1H, H_8), 2.36 (d, 1H, H_6), 3.44 (t, 1H, CH), 4.52 (s, 2H, NH_2).

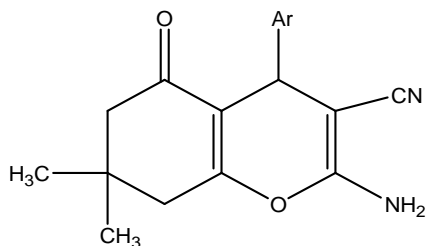
$^{13}\text{C-NMR}$ (CDCl_3): δ = 8.86 (q, 1C), 26.93 (q, 1C), 27.48 (q, 1C), 29.1 (t, 1C), 30.24 (d, 1C), 32.02 (s, 1C), 40.69 (t, 1C), 50.87 (t, 1C), 113.35 (s, 1C), 158.91 (s, 2C), 162.78 (s, 2C), 196.52 (s, 1C).

DISCUSSION

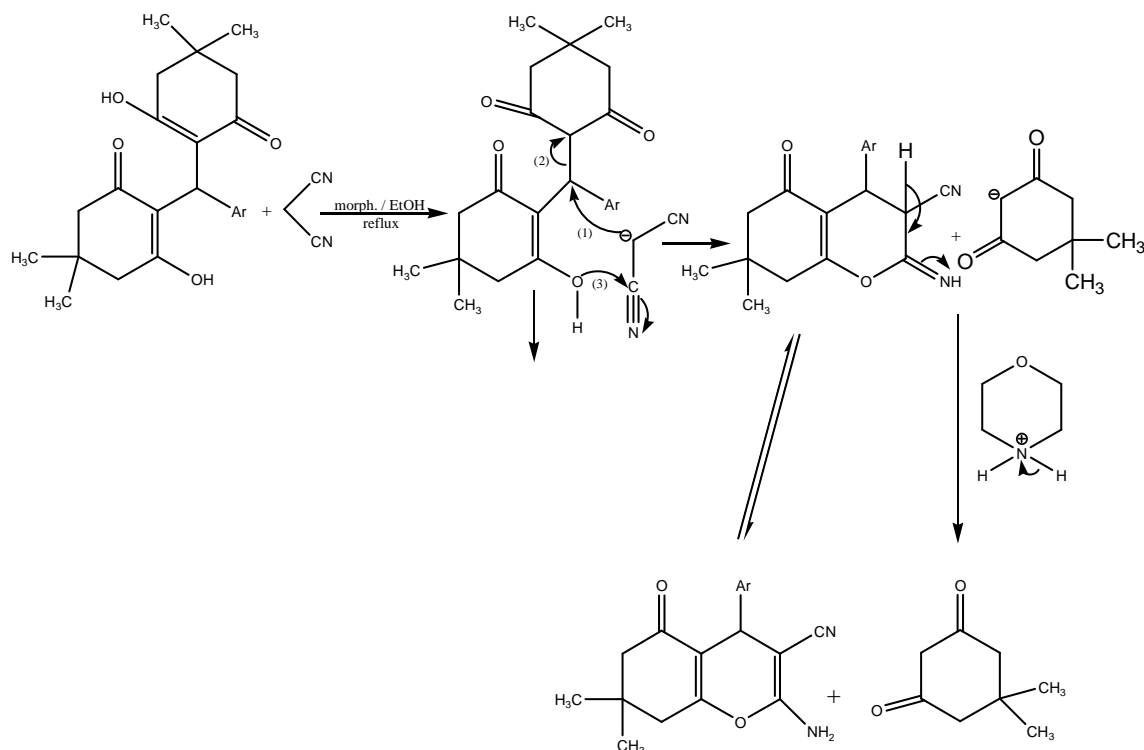
Bis dimedones were designed to react with malononitrile in order to obtain dialkylidenes (Cope & Hoyle, 1941) of the corresponding ketones.



In all reactions of malononitrile with bis dimedones, the desired alkylidenes were failed to form, although several modifications were applied, instead a well known system (4H-chromene) was obtained.

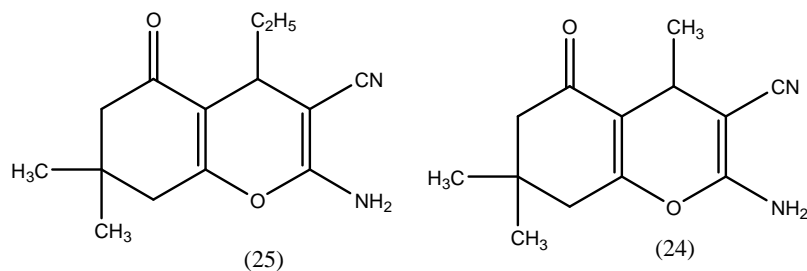


Using ammonium acetate /acetic acid (Stanetty, Frohlich, & Sauter, 1984) in absolute benzene was failed to give the proposed dialkylidenes. According to the obtained results the reaction products guided us to a new method of chromene synthesis with yields ranging from (38-75 %) in time less than three hours with high purity. The spectroscopic analysis [$^1\text{H-NMR}$ and $^{13}\text{C-NMR}$] showed two methyl groups and two methylene groups indicating only one molecule of dimedone as a part of the obtained product, beside the distinct signals of 2-amino- 4H-chromene (El-Shawish, 2005) indicating that the bis dimedone was fragmented into two parts by the attacking of the nucleophilic carbon of malononitrile to a methin carbon followed by attacking of enolic hydroxyl group to cyano group giving two resonance structures, only 4H-chromene compound was isolated. The proposed mechanism of the new method can be explained as in the following scheme



Varying the nature of the aldehyde was proposed to give another mode of reaction, using aliphatic aldehydes with methyl and ethyl substituent did not show any change of the reaction path, also 2-amino-4H-chromenes were obtained.

New Method of 2-Amino-4H-Chromene Synthesis



Compound (24) showed $^1\text{H-NMR}$ signals at 1.07 and 1.08 ppm represents the methyl groups at C_7 followed by a doublet signal at 1.19 ppm indicates methyl group at C_4 , also H_8 and H_6 appears at 2.25 and 2.32 ppm respectively and did not show any geminal coupling. All the obtained compounds showed mostly the same spectroscopic feature, The difference have been noticed only in the coupling and splitting pattern (Silverstein & Webster, 1998) of H_6 and H_8 . Two factors have possibly the main effect for the noticed difference, firstly is the type of substituent at C_4 was showed noticeable effect with aromatic substituent rather than aliphatic one. Secondly is the position and the type of the substituent on the aromatic ring. Substituents at 4-position has a larger effect on H_8 than H_6 giving two doublet at ≈ 2.10 and 2.20 for H_{8a} and H_{8b} , and a singlet signal at ≈ 2.5 for H_6 .

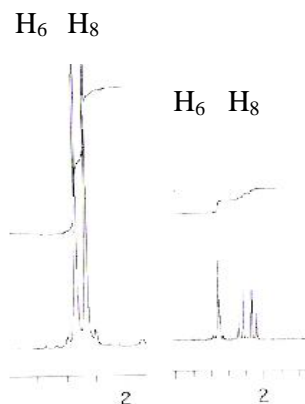


Fig. 1 H8 and H6 of compounds (24 and 20)

When the substituent at C_4 is unsubstituted aromatic H_8 shows two doublets at 2.13 and 2.23 while H_6 show a singlet signal, also when 3-Methoxyphenyl, 4-Methoxyphenyl, 4-Chlorophenyl, 4-Hydroxyphenyl and 4-Nitrophenyl groups at C_4 gave the same features except a small difference in coupling constant of the geminal coupling. When 2-Nitrophenyl and 2-Methoxyphenyl groups at C_4 gave a quite different effect on H_6 and H_8 in which both show a geminal coupling on H_8 much stronger than on H_6 .

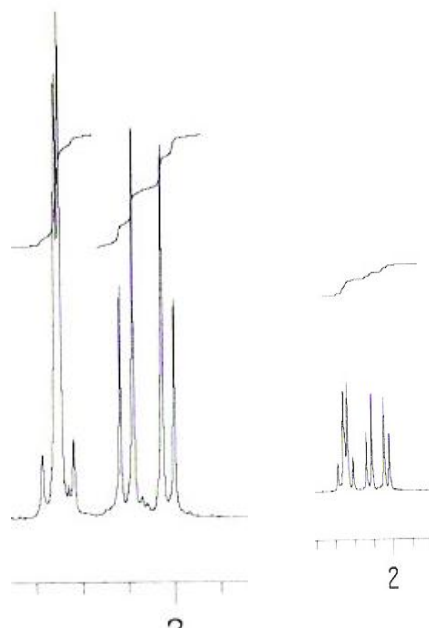


Fig. 2 H6 and H8 of Compounds (17 and 23)

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