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UTILIZATION OF α-BROMOCYCLIC DIKETONES AS MICHAEL DONORS FOR THE SYNTHESIS OF COUMARIN ANALOGUES

Hayat El-Sawah, Mohamed A. El-Bermawy, Eatedal. H. Abdel Aal, Azza. M. Kadry, Mohamed I. Al-Ashmawi
Department of Pharmaceutical Org. Chem., Faculty of Pharmacy, Zagazig University, Zagazig, Egypt

ABSTRACT

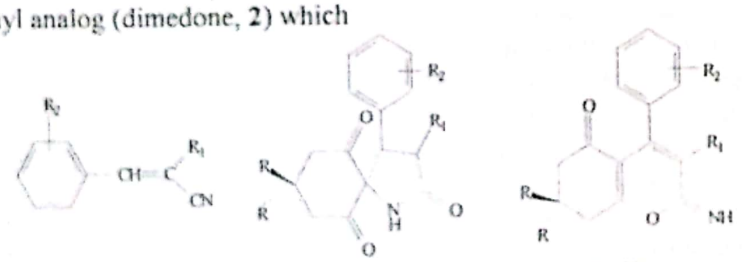
Coumarin nucleus is of biological importance. Anticoagulants which are very common contain coumarin moiety. Herein we describe a facile method to prepare this valuable nucleus. α-Bromocyclic diketones were used as Michael donors and each reacted with various substituted acrylonitriles, which behaved as Michael acceptors. Elimination of hydrobromic acid leads to the formation of the target compounds (**17-30**) in reasonable yields.

INTRODUCTION

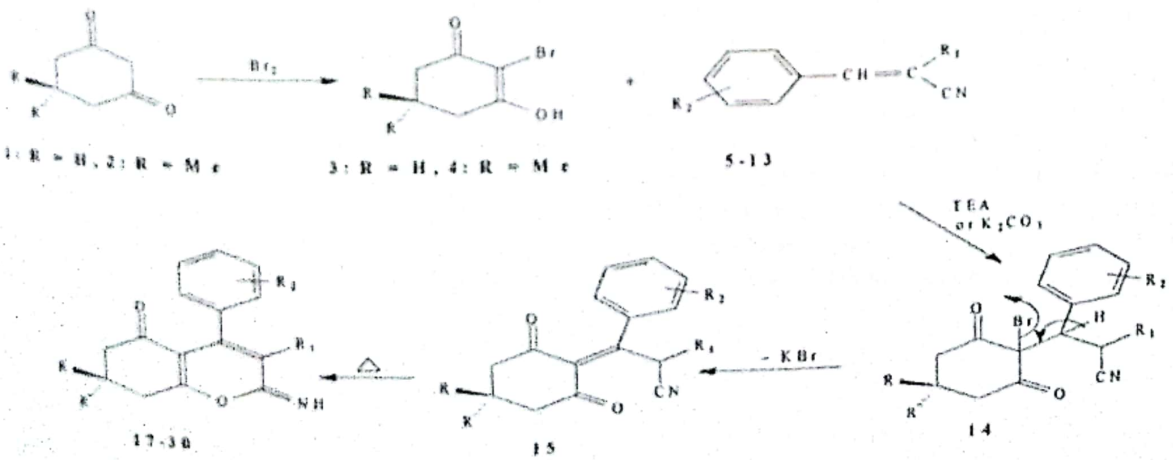
The importance of coumarins was discovered in the 1970s, as oral anticoagulants.[1] The most effective anticoagulants which are used nowadays are coumarin derivatives.[2] Other compounds containing the coumarin moiety showed antitumor [3-5] and antiviral activities (against Human Immunodeficiency Virus (HIV) and Herpes Simplex Virus (HSV)).[3] Several coumarins have been designed to modulate nucleic acid biosynthesis by inhibiting DNA gyrase.[6] Coumarin containing molecules were biologically tested and have proved to possess activity against *Litomosoides carinii*, *Acanthocheilonema viteae* and *Mastomys coucha*.[7] Various research projects indicated that coumarins are effective as antimicrobial agents.[8,9]

Due to the significance of the coumarin moiety we planned to effectively synthesize various coumarin containing compounds in good yields and with efficient methods. The starting molecules were 1,3-cyclohexanedione (**1**) and its 5,5-dimethyl analog (dimedone, **2**) which were allowed to react with bromine (Br_2) in chloroform to provide the 2-bromo derivatives (**3** and **4**).[10-12] Michael acceptors 3-aryl-2-substituted acrylonitriles (**5-13**) which were prepared by reacting aromatic aldehydes with equimolar amounts of malondinitrile.[13-16] Reaction of 2-bromo-3-hydroxy-2-cyclohexenone (**3**) and its 5,5-dimethyl derivative (2-bromodimedone, **4**) with the Michael acceptors 3-aryl-2-substituted acrylonitriles (**5-13**) provided the Michael adduct (**14**) which went under subsequent elimination of HBr to provide the corresponding alkenes (**15**). The alkenes were heated under reflux for about two days to provide the final compounds, α-iminochromones (**17-30**).

Using a base such as triethylamine or K_2CO_3 shortened the reaction time and improved the yield. Intramolecular cyclization of the alkenes (**15**) produced the target α-iminochromones (**17-30**) as shown in **scheme 1**.



Scheme 1



R_1= CN, COOET

One might assume that spiro compounds (**16**) could be obtained via nucleophilic attack of the nitrogen atom of the CN group at the α carbon of the cyclohexanedione or dimedone moieties. Our proton NMR and IR data did not show any sign of the spiro compounds formation. All final products (α-iminochromones (**17-30**) showed equimolar ratios of aromatic and aliphatic protons. They appear as singlet at δ 1.2 -1.3 (6 H, s, 2 CH_3), 2.3 (2 H, s, CH_2), 2.5 (2 H, s, CH_2) and finally at 7.8-8.2 (aromatic protons) ppm. The dimethyl residues of the dimedone moiety appear as singlet signal, which means that both methyl groups are magnetically equivalent. We believe that this is additional evidence to rule out the formation of the Spiro compounds (**16**), which will have magnetically unequivalent methyl groups of the dimedone part of the final α-iminochromones (**17-30**). The α-iminochromones (**17-30**) are planar and rigid molecules, which forbid the twisting or conformational flexibility of the molecules, therefore the methyl groups will not appear at different chemical shifts in the proton NMR. The Infrared spectra for α-iminochromones showed a strong absorption band at 1620 cm^{-1} which correspond to the C=NH of the α-iminochromones. The stretching band appeared at 3400 cm^{-1} in the IR spectra of the α-iminochromones due to the NH of the imino group.

In summary, we herein report simple and efficient synthetic procedures to synthesize coumarin derivatives. The commercially available starting materials, 1,3-cyclohexanedione and its 5,5-dimethyl analog (dimedone) were brominated to produce the 2-bromo compounds **3** and **4**, respectively in quantitative yields. The bromo compounds were subjected to Michael addition followed by cyclization to afford the final products (**17-30**) in fairly good yields. We are currently pursuing a wider application of these procedures in order to synthesize coumarins in a more versatile manner.

EXPERIMENTAL

Melting points were determined using an electrothermal digital melting point apparatus, they were uncorrected. Proton magnetic resonance spectra were obtained with a Bruker 300 spectrophotometer using tetramethylsilan as an internal standard and D_2O, $CDCl_3$ as solvents (PA, USA) and Varian EM-390, 90 MHz (Cairo, Egypt). The chemical shift values were recorded in δ (ppm, parts per million) relative to tetramethylsilane (TMS). Infrared spectra were recorded on a Philips FT-IR spectrophotometer.

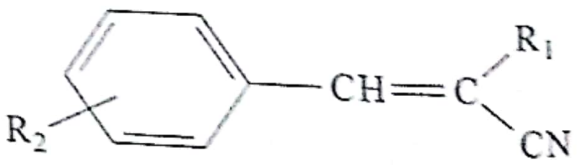
2-Bromo-3-hydroxy-2-cyclohexenone (3) and its 5,5-dimethyl derivative (2-bromo-dimedone, 4).

A solution of 1,3-cyclohexanedione or its 5,5-dimethyl analog, dimedone (7.14 mmol) in chloroform (20 mL) mixed with equimolar amount of bromine previously dissolved in chloroform. The reaction mixture was allowed to stir at room temperature for one hour. The resulted solid was filtered and recrystallized from aqueous ethanol to afford compounds (**3**) mp, 160-162 °C, ^{1}HNMR ($CDCl_3$) δ 2.2 (2 H, *s*, CH_2), 2.3 (2 H, *s*, CH_2-C=C), 2.41 (2 H, *s*, CH_2-CO), 6.8 (1 H, *s*, enolic proton), CH analysis Found: 37.8, 3.9 respectively, Calcd: 37.70, 3.69. IR (KBr) Cm^{-1}, 2950-2900 (CH aliphatic). 1680-1690 (conjugated carbonyl). For 2-bromodimedone, **4** (mp. 175-177 °C as reported [4]. Both compounds **3** and **4** were formed in quantitative yields.

3-Aryl-2-substituted acrylonitriles (5-13)

To a mixture of equimolar amounts of malondinitrile or ethyl cyanoacetate (10 mmol) and the appropriate aromatic aldehyde in absolute ethanol (15 mL), triethylamine (0.5 mL) was added. The reaction mixture was allowed to stir for one hour at room temperature. We slightly modified the previously reported techniques.[13-15] The formed solid was collected by filtration and recrystallized from ethanol (Table 1).

Table 1. Melting points and Percentage yield of 3-Aryl-2-substituted acrylonitriles (**5-13**)



No	R_1	R_2	MP, °C	% Yield
5	CN	H	130-32	90
6	CN	2-Cl	155-57	90
7	CN	4-Cl	163-65	90
8	CN	4-OH	120-22	75
9	CN	4-OMe	110-12	85
10	CN	4-NO_2	175-77	95
11	CO_2Et	H	60-62	85
12	CO_2Et	4-Cl	80-82	80
13	CO_2Et	4-OMe	70-72	85

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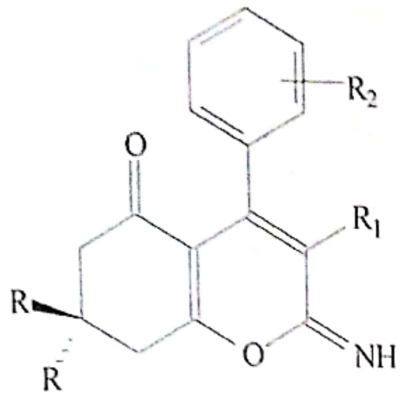
Table 2. Physicochemical Properties of α- Iminochromones **(17-30)**



No	R	R_1	R_2	%[a]	MP, °C	MF[b]	C,H,N analysis
17	Me	CN	H	75	210-12	$C_{18}H_{16}N_2O_2$	73.95,5.52,9.58[c] 74.30,5.80,9.80[d]
18	Me	CN	4-Cl	72	235-37	$C_{18}H_{15}ClN_2O_2$	66.16,4.62,8.57 66.40,4.70,8.80
19	Me	CN	4-OMe	70	207-08	$C_{19}H_{18}N_2O_3$	71.01,5.65,8.72 71.20,5.80,8.90
20	Me	CN	4-NO_2	71	260-62	$C_{18}H_{15}N_3O_4$	64.1,4.48,12.46 64.2,4.60,12.70
21	Me	CN	2-Cl	68	215-17	$C_{18}H_{15}ClN_2O_2$	66.16,4.62,8.57 66.20,4.50,8.50
22	Me	CN	4-OH	65	270-72	$C_{18}H_{16}N_2O_3$	70.12,5.23,9.09 70.30,5.50,9.30
23	H	CN	H	70	220-22	$C_{16}H_{12}N_2O_2$	72.71,4.58,10.6 72.80,4.80,10.8
24	H	CN	4-Cl	73	240-42	$C_{16}H_{11}ClN_2O_2$	64.33,3.71,9.38 64.60,4.10,9.70
25	H	CN	4-NO_2	68	200-02	$C_{16}H_{11}N_3O_4$	62.14,3.6,13.59 62.60,3.6,13.80
26	H	CN	4-OMe	78	230-32	$C_{17}H_{14}N_2O_3$	69.38,4.79,9.52 69.60,4.90,9.80
27	Me	CO_2Et	H	60	100-02	$C_{20}H_{21}NO_4$	70.78,6.24,4.50 71.00,6.50,4.20
28	Me	CO_2Et	4-Cl	62	110-12	$C_{20}H_{20}ClNO_4$	64.26,5.39,3.75 64.70,5.80,3.90
29	Me	CO_2Et	4-OMe	55	130-32	$C_{21}H_{23}NO_5$	68.28,6.27,3.79 68.50,6.30,3.90
30	Me	CO_2Et	4-OH	52	120-22	$C_{20}H_{21}NO_5$	67.59,5.96,3.94 67.80,6.20,4.10

[a] %Yield, [b] Molecular Formula, [c] Calculated, [d] Found

4-Aryl-2-imino-3-substituted 5-oxo-5,6,7,8- tetrahydro (8)-2H-pyran-2-one and their 7,7-dimethyl analogs (17-30).

A mixture of equimolar amounts of 2-bromo-1,3-cyclohexanedione (3) or its 5,5-dimethyl derivative (2-bromodimedone (4), and the appropriate 3-aryl-2-substituted acrylonitrile (5-13) in absolute ethanol was heated under reflux for 4 hours. A base of either 4 drops of triethyl amine or anhydrous K_2CO_3 was added to the reaction mixture. The mixture was heated under reflux for additional 2-3 hours. The solids formed after cooling to room temperature were filtered and recrystallized from aqueous ethanol to provide the final compounds, α-iminochromones, in good yields as shown in Table 2. Examples of the spectrophotometrical analysis: IR (KBr, major frequencies, cm^{-1}) 3400 (NH), 3010-3000 (CH aromatic), 2250 (CN), 1730 (ester carbonyl), 1650-1640(conjugated carbonyl). ^{1}HNMR ($CDCl_3$, compound 20), δ 1.1-1.3 (6H, s, 2 CH_3), 2.3 (2H, s, CH_2), 2.46 (2H, s, CH_2), 7.8 (2H, d, aromatic protons), 8.2 (2H, d, aromatic protons). ^{1}HNMR ($CDCl_3$, compound 21), δ 1.2-1.4 (6H, s, 2 CH_3), 2.4 (2H, s, CH_2), 2.51 (2H, s, CH_2), 7.9-8.1 (4H, m, aromatic protons).

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توظيف الفا برومو داي كيتون الحلقي كمعطي في تفاعل ميخائيل الإضافية في تحضير مشابهات الكومارين.

مجدي عبد الحي السواح، محمد عبد الشافي البرماوي ، اعتدال حسن عبد القادر، عزة محمد قدري، محمد إبراهيم العشماوي

الكيمياء العضوية الصيدلية – كلية الصيدلة – جامعة الزقازيق – الزقازيق – مصر

إن لنواة الكومارين أهمية بيولوجية خاصة و كذلك الأدوية المحتوية علي جزئ الكومارين خصوصاً في علاج و الوقاية من التجلط . و في هذا البحث قمنا بتحضير مشتقات الكومارين من خلال تفاعل ميخائيل الإضافية باستخدام البرمودايميدون و البرموسيكلوهكسان داي يون الحلقي كمعطيات ، و استخدام مشتقات الأكريلونيتول كمستقبلات لتفاعل ميخائيل و بإزالة حامض الهيدروبروميد أثناء التفاعل و تم تحضير المركبات المستهدفة (١٧ - ٣٠) .