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A REVIEW ON SYNTHESIS AND REACTIONS OF CHROMONE AND CHROMENE DERIVATIVES USING THE MULTICOMPONENT REACTION SYSTEM

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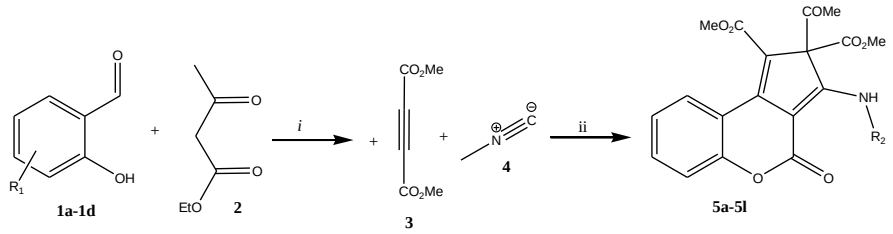
ABSTRACT
For several years, interest has increased in the organic chemistry and pharmaceutical sciences fields to develop new chromene derivatives. The aim of this research was to carry out a review of the synthesis and reactions of some chromene derivatives using multicomponent systems. It is noteworthy that reaction protocols imply conventional and non-conventional methods, in particular the use of different solvents and microwave irradiation conditions. It is noteworthy that protocol reactions could be used for decision-making in the development of new chromene derivatives.

KEYWORDS. Review, chromene, derivatives, synthesis,

INTRODUCTION
For several years, the pharmaceutical industry has shown great interest in the development of chromone and chromene derivatives.[i-v] It is important to mention that different types of substituents bound to the chromone nucleus can play an important role in medicinal chemistry.[vi,vii] Therefore, to design new chromone derivatives, several protocols have been used, including the multicomponent system and others. It is important to mention that multicomponent systems offer different benefits in some types of reactions, such as an increase in speed of reaction and a good yield of reaction product.[viii-xiv]

Synthesis of chromone derivatives via a multicomponent system
A study[xv] showed the synthesis of a series of chromene analogs using a multicomponent system from 2-hydroxybenzaldehyde derivatives (**1a-d**), ethyl acetoacetate (**2**), acetylenedicarboxylate (**3**), and isocyanide (**4**) (Scheme 1, Table 1). The proposed reaction mechanism involves the synthesis of 3-acetyl-chromen-2-one (2) from aldehyde derivatives and ethyl acetoacetate. Then, a zwitterionic intermediate, which was formed via the reaction

of acetylenedicarboxylate with an isocyanide derivative, is bound to a double bond of 2. Finally, an intramolecular cyclization is carried out to form an imino-cyclopentene fragment involved in the chemical structure of chromanone derivative (3).

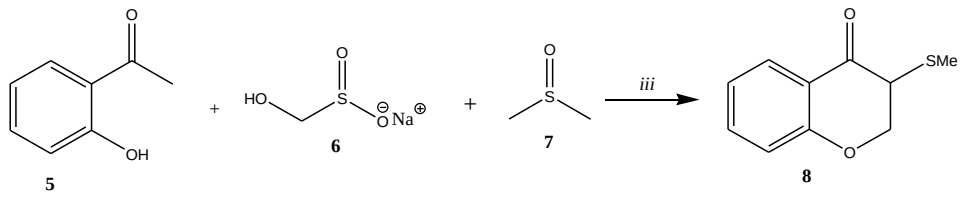


Scheme 1. Synthesis chromene derivatives (**3a-3j**). *Conditions and reagents*: *i* = toluene, piperidine, molecular sieves 4 Å, reflux, 2 h; *ii* = reflux, 5 h.

Table 1. Products obtained (**5a-5l**) using the multicomponent system (aldehyde derivatives (**1a-d**), ethyl acetoacetate, acetylenedicarboxylate, and isoniacide).

Entry	R_1	R_2	product	Yield (%)
1	H	*tert*-butyl	5a	73
2	H	cyclohexyl	5b	75
3	H	tetramethylbutyl	5c	65
4	5-Br	*tert*-butyl	5d	74
5	5-Br	cyclohexyl	5e	75
6	5-Br	tetramethylbutyl	5f	64
7	5-NO_2	*tert*-butyl	5g	58
8	5-NO_2	cyclohexyl	5h	54
9	5-NO_2	tetramethylbutyl	5i	52
10	3-NO_2	*tert*-butyl	5j	59
11	3-NO2	cyclohexyl	5k	63
12	3-NO2	tetramethylbutyl	5l	53

Other studies have shown the synthesis of 3-(methylthio)-4H-chromenone from o-hydroxyaryl acetophenone and rongalite in the presence of dimethyl sulfoxide and iodine.[xvi] The possible mechanism involves the reaction of 1-(2-Hydroxy-phenyl)-ethanone (**4**) with iodine to form the compound 2-OH-α-iodo acetophenone, which is then converted into (2-(2-hydroxyphenyl)-2-oxoethyl)dimethyl-sulfonium iodine in the presence of dimethyl sulfide (generated from the reduction of DMSO). Following, the sulfonium iodide in the presence of HCHO (generated via rongalite-CuO) can produce 1-(2-Hydroxy-phenyl)-2-methyl-sulfanyl-propenone as an intermediary. Subsequently, an intramolecular nucleophilic cyclization is carried out to form (3-methylsulfanyl-chroman-4-one), which undergoes an oxidative aromatization to form a chromone derivative **8** (Scheme 2).

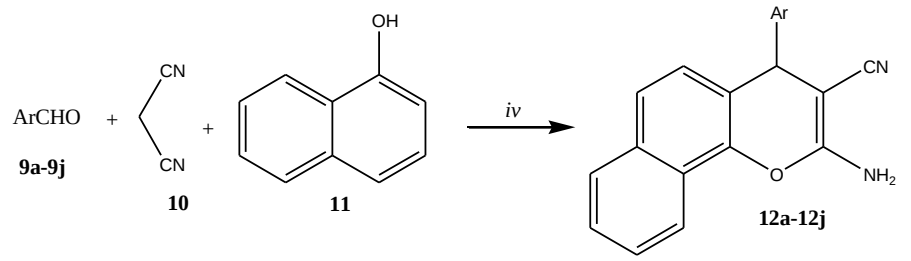


Scheme 2. Synthesis a 3-(methylthio)-4H-chromenone (**8**). *Conditions and reagents*: *iii* = I_2, DMSO (**7**), 1,8-Diazabicyclo 5.4.0 undec-7-ene (DBU), CuO, 100 ^{O}C, 3h.

Another report[xvii] showed the preparation of a series of chromene derivatives via a multicomponent system (aromatic aldehydes, α-cyanomethylene, and α-naphthol) using the single-step continuous flow protocol on a ThalesNano H-Cube Pro™. The authors suggest that the reaction mechanism involves the reaction of an aldehyde derivative with malononitrile in the presence of DBU to form an arylidene-malonitrile via the Knoevenagel condensation.[xviii-xxii] Then, arylidene-malononitrile reacted with α-naphthol to form the chromone derivative (Table 2 and Scheme 3).

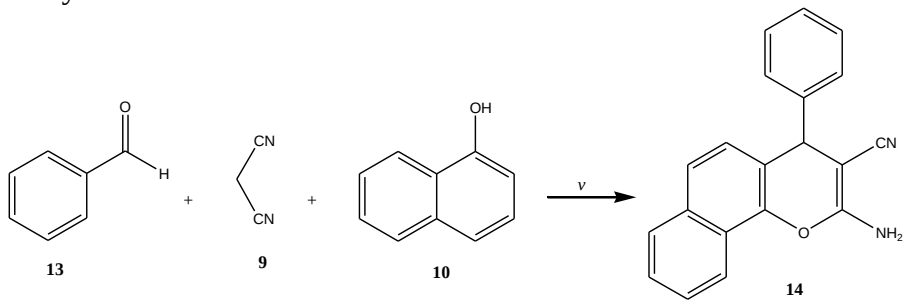
Table 2. Chromone derivatives obtained (**12a-12j**) using multicomponent system (aromatic aldehydes, α-cyanomethylene, and α-naphthol).

Entry	Ar	Product	Yield (%)	m.p. (°C)
1	C_6H_5	12a	95	215-217
2	4-$CH_3OC_6H_4$	12b	93	182-183
3	4-ClC_6H_4	12c	92	232-234
4	2-Furanyl	12d	87	171-172
5	2-Thienyl	12e	91	192-194
6	4-BrC_6H_4	12f	94	241-243
7	3-ClC_6H_4	12g	88	228-230
6	3-$NO_2C_6H_4$	12h	94	215-216
9	4-$NO_2C_6H_4$	12i	96	237-238



Scheme 3. Synthesis of chromone derivatives (**12a-j**). *Conditions and reagents*: *iv* = aldehyde derivatives (**9a-j**), malononitrile (**10**), α-naphthol (**11**), and DBU, 2-methyl-tetrahydrofuran.

Furthermore, a study[xxiii] showed the synthesis of a 2-amino-3-cyano-4-phenyl-4H-benzo[h]chromene via a multicomponent system (benzaldehyde, malononitrile, and 1-napthol) under different conditions (Scheme 4, Table 3). The reaction product was higher using the *t*-ZrO_2 catalyst in the presence of water. The authors suggest a reaction mechanism that involves a Knoevenagel condensation to produce 2-phenylidenemalononitrile and, subsequently, a Michael addition[xxiv-xxvii] to 1-napthol, followed by tautomerization and intramolecular cyclization to form the chromone derivative.



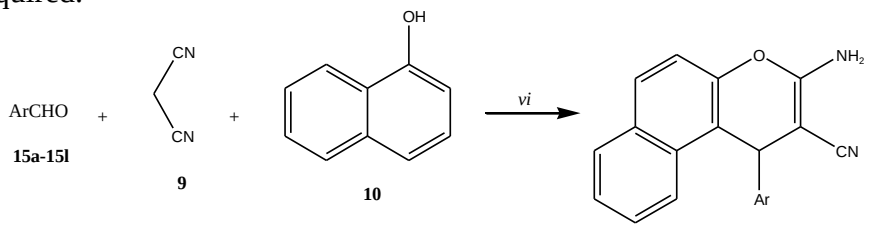
Scheme 4. Synthesis of 2-amino-chromene derivative (**14**). *Conditions and reagents*: *v* = benzaldehyde (**12**), malononitrile (**9**), 1-napthol (**10**), t-ZrO2/H_2O, rt.

Table 3. Different conditions of reaction to produce 2-amino-3-cyano-4-phenyl-4H-benzo[h]chromene (**14**).

Entry	Catalyst	Solvent/Conditions	Time (min)	Yield (%)
1	*t*-ZrO_2 NPS	H_2O/80 ^OC	30	92
2	*t*-ZrO_2 NPS	H_2O/rt	240	-
3	No catalyst	H_2O/80 ^OC	240	-
4	*t*-ZrO_2 NPS	CH_3CN/80 ^OC	60	77
5	*t*-ZrO_2 NPS	Toluene/80 ^OC	60	62
6	*t*-ZrO_2 NPS	DMF/80 ^OC	60	60
7	Bulk ZrO_2 NPS	H_2O/80 ^OC	60	41
8	m-ZrO_2 NPS	H_2O/80 ^OC	60	52
9	Fe_3O_4 NPS	H_2O/80 ^OC	60	57
10	SiO_2 NPS	H_2O/80 ^OC	60	51
11	CuO NPS	H_2O/80 ^OC	60	79
12	ZnO NPS	H_2O/80 ^OC	60	66

rt = room temperature; NPS = nanoparticles

Besides, a study showed that aldehyde derivatives (**15a-15l**), malonitrile and α-naphtol reacted in the presence of N,N-dimethylamino-ethylbenzyldimethyl-ammonium chloride under solvent-free condition to form the compound 2-Amino-chromene-3-carbonitrile analogs (**16a-16l**).[xxviii] The authors indicate that aromatic aldehydes that contain electron-donating groups (hydroxyl, alkoxy or methyl), require higher reaction time compared to electron-accepting groups (nitro, haluro) bound to aromatic ring (Scheme 5 and Table 4). Furthermore, the data indicates that to carry out the reaction the presence of an ionic liquid catalyst is required.



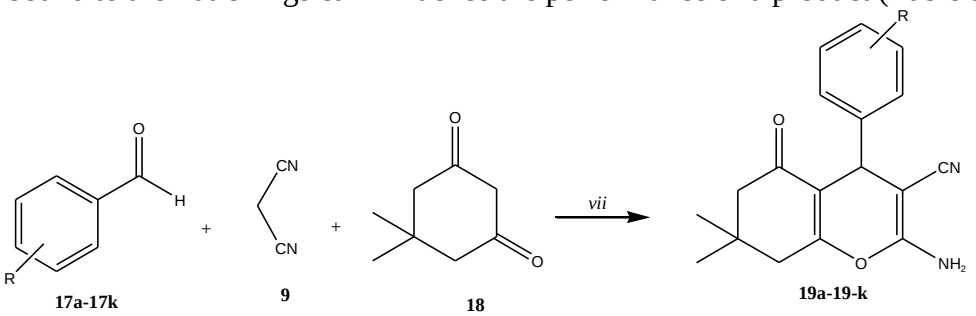
Scheme 5. Synthesis of 2-Amino-chromene-3-carbonitrile (**16a-16l**). *Conditions and reagents*: *vi* = N,N-dimethylaminoethylbenzyldimethylammonium chloride, 80 ^oC, 35 min.

Table 4. Different aryl groups involved in the synthesis of 2-chromene derivatives (**16a-16l**).

Entry	Aryl	Product	Time (min)	Yield (%)
1	C_6H_5	16a	35	91
2	4-Cl-C_6H_4	16b	30	93
3	2-Cl-C_6H_4	16c	100	70
4	2,4-Cl-C_6H_4	16d	50	82
5	4-NO_2-C_6H_4	16e	40	95

6	3-NO_2-C_6H_4	16f	80	94
7	4-Me_2-N-C_6H_4	16g	60	53
8	4-Me-C_6H_4	16h	100	82
9	4-OH-C_6H_4	16i	40	46
10	4-MeO-C_6H_4	16j	120	65
11	3-MeO-4OH-C_6H_3	16k	130	62
12	2-Furanyl	16l	120	56

On the other hand, some chromone derivatives have been prepared using non-conventional methods such as microwave irradiation.[xxix-xxxiii] For example, Lambat in 2018 showed the synthesis of a series of chromone derivatives (**19a-19k**) using the multicomponent system (aldehyde derivatives (**17a-17k**), dimedone, and malonitrile) through microwave irradiation assisted (Scheme 6).[xxxiv] This study shows that variations in functional groups at different positions bound to aromatic rings can influence the performance of a product (Table 5).



17a-17k **9** **18** **19a-19-k**

R = -H, -F, -Cl, -CH_3, -OCH_3, -NO_2, -OH

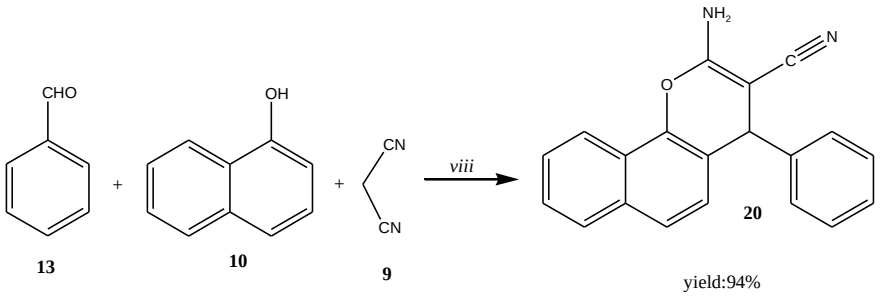
Scheme 6. Synthesis of chromone-carbonitrile derivative (**19a-19k**). *Conditions and reagents*: *vii* = scolecite, EtOH/H_2O, microwave irradiation.

Table 5. Cromonone derivatives (**19a-19k**) obtained from aldehyde derivatives, dimedone, and malonitrile.

Entry	**Aldehyde derivative**	**Product**	**Time (min)**	**Yield (%)**
1	benzaldehyde	19a	35	91
2	4-Fluoro-benzaldehyde	19b	30	93
3	4-Methyl-benzaldehyde	19c	100	70
4	4-Methoxy-benzaldehyde	19d	50	82
5	2,5-Dimethoxy-benzaldehyde	19e	40	95
6	4-Chloro-benzaldehyde	19f	80	94
7	2-Chloro-benzaldehyde	19g	60	53

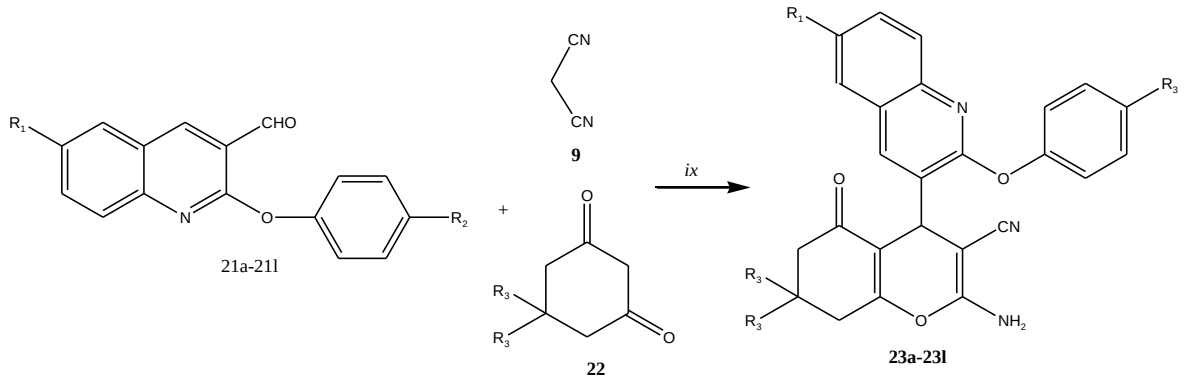
8	3-Chloro-benzaldehyde	19h	100	82
9	3-Nitro-benzaldehyde	19i	40	46
10	4-Nitro-benzaldehyde	19j	120	65
11	4-Hydroxy-benzaldehyde	19k	130	62

Another study indicates the synthesis of a chromone derivative from an analogous benzalaldehyde (**12**), α-naphthol (**13**), and malononitrile (**9**) in an aqueous medium using microwave radiation (Schem 7).[xxxv] The proposed mechanism involves the addition of aldehyde to malononitrile through Knoevenagel condensation to form propanenitrile, which reacts with α-naphthol via Michael addition. Finally, there is an intramolecular cyclization to produce a chromone derivative (**14**).



Scheme 7. Synthesis of chromone-carbonitrile derivative (14). *Conditions and reagents*: *viii* = NaTPS, aq. Medium, microwave irradiation, 5 min.

Besides other report (Schem 8 and Table 6) indicates the synthesis of 4H-chromene derivatives (**23a-23l**) using a multicomponent system (Aryloxyquinoline-3-carbaldehyde (**21a-21l**) malononitrile (**9**) and cyclohexane-1,3-dione (**22**).[xxxvi] The reaction mechanism suggested may involve the Knoevenagel condensation of aldehyde and malononitrile to give heterylidenenitrile derivative followed by Michael addition of **22** to heterylidenenitrile to produce the 4-chromone derivative.



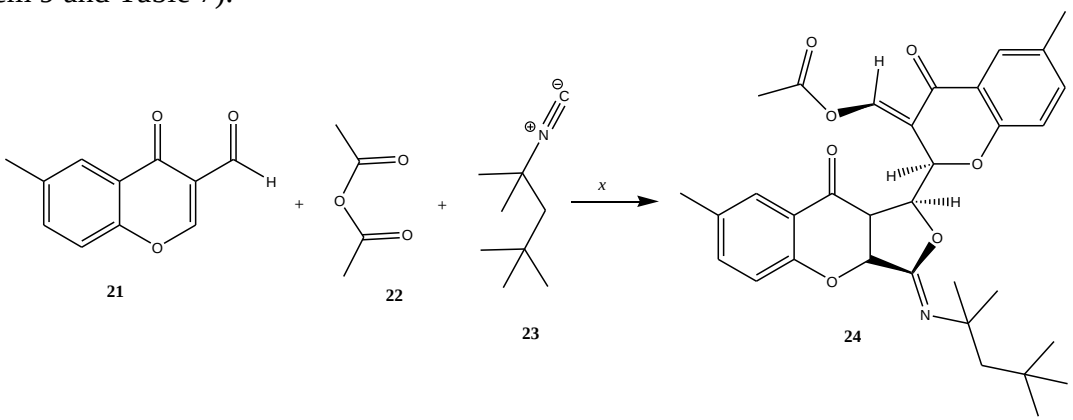
Scheme 8. Synthesis of two 4-chromone derivative (**23a**-23x). *Conditions and reagents*: *ix* = Ethanolic NaOH, microwave irradiation, 350 W, 170–190 s.

Table 6. Different functional groups involved in chemical structure of 4-chromene derivatives (**23a-23l**).

Entry	R_1	R_2	R_3	Yield (%)
23a	H	H	H	73
23b	H	CH_3	H	78
23c	H	OCH_3	H	80
23d	H	F	H	66
23e	CH_3	H	H	76
23f	CH_3	CH_3	H	80
23g	CH_3	OCH_3	H	84
23h	CH_3	F	H	64
23i	OCH_3	H	H	67
23j	OCH_3	CH_3	H	80
23k	OCH_3	OCH_3	H	88
23l	OCH_3	F	H	70

Reaction of chromone derivatives via multicomponent reactions system.

Several reactions have been used to prepare some compounds from chromone derivatives[xxxvii-xLii]; for example, a study displayed the preparation of (R,E)-6-methyl-2-((S,Z)-7-methyl-9-oxo-3-((2,4,4-trimethylpentan-2-yl)imino)-3,9-dihydro-1H-furo-[3,4-b]- chromen-1-yl]-4-oxochroman-3-ylidene)methyl acetate (**24**) using the multicomponent system (6-Methyl-4-oxo-4H-chromene-3-carbaldehyde (**21**), acetyl acetate (**22**), 2-isocyano-2,4,4-trimethyl-pentane (**23**)) under different conditions.[xLiii] In Table 6, there are several solvents used for this reaction; it should be noted that methylene chloride at 25 ^{o}C and 72 h showed good yielding (Schem 9 and Table 7).



Scheme 9. Synthesis a chromane derivative (**24**). *Conditions and reagents*: *x* = see Table 7.

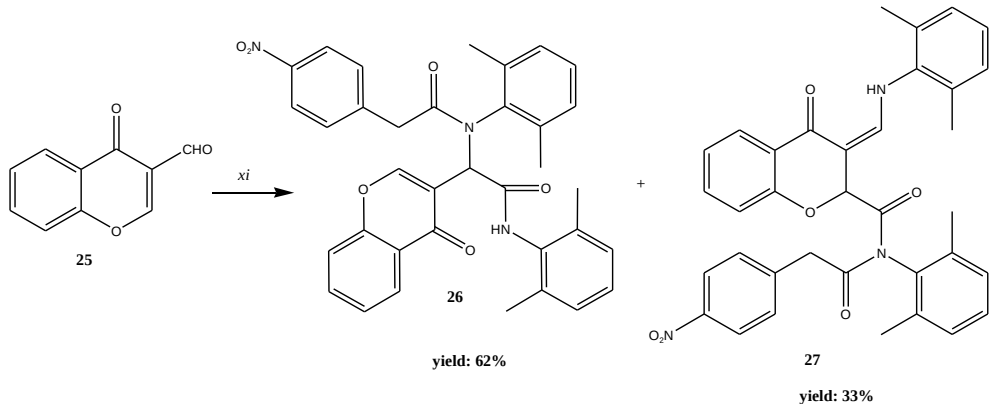
Table 7. Different solvents to produce chromone derivative (**24**).

Entry	Solvent	Temp (^{o}C)	Time (h)	Yield (%)
1	CH_2Cl_2	25	24	43
2	$CHCl_3$	25	24	38
3	CH_3CN	25	24	32
4	THF	25	24	35
5	DMSO	25	24	22
6	DMF	25	24	29

7	Toluene	25	24	11
8	CH_3OH	25	24	ND
9	CH_3CH_2OH	25	24	ND
10	CH_2Cl_2	25	48	58
11	CH_2Cl_2	25	72	67
12	CH_2Cl_2	25	96	67
13	CH_2Cl_2	reflux	72	18
14	THF	reflux	72	10

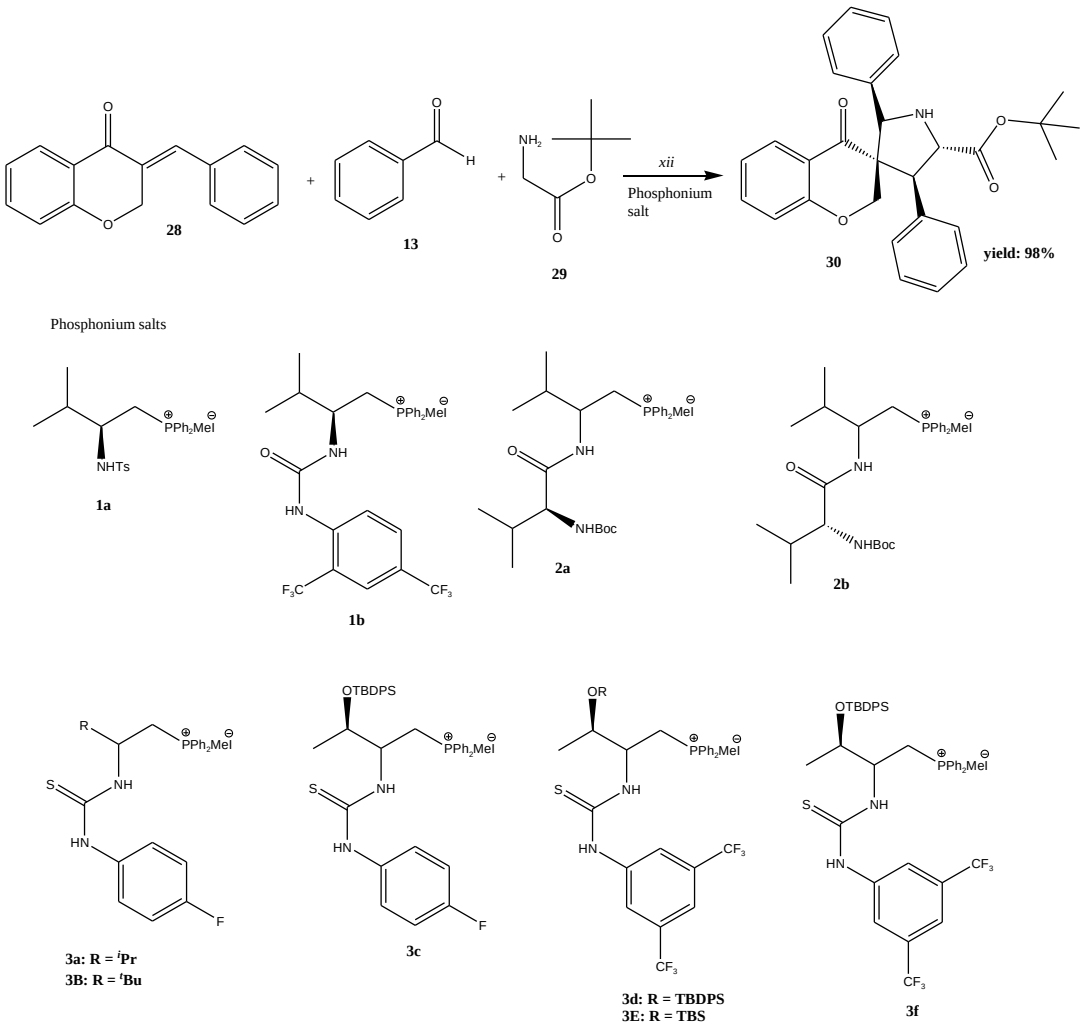
ND = not detected.

Other study showed (Scheme 10) the preparation of two amide derivatives (**26** and **27**) via multicomponent system (chromone-3-carboxaldehyde (**25**), 2,6-dimethylaniline, 4-nitrophenyl)acetic acid, and 2,6-dimethylphenyl isocyanide). The authors suggest that 2-(2,6-dimethyl-*N*-[2-(4-nitrophenyl)acetyl]anilino)-*N*-(2,6-di-methylphenyl)-2-(4-oxo-chromen-3-yl)acetamide was produced via an Ugi-4CR reaction.[xLiv-xLvii] For the second product ((3*Z*)-3-[(2,6-dimethylanilino)-methylene]-*N*-(2,6-dimethyl-phe-nyl)-*N*-[2-(4-nitrophenyl)acetyl]-4-oxo-chromane-2-carboxami- de), the reac-tion mechanism involve an imino group formation. Then, an addition of 6-dimethylphenyl isocyanide to double bond and subsequently a nucleophilic addition of the carboxylic acid anion to cyanide group and finally an intramolecular rearrangement to form amide derivatives.[xLviii]



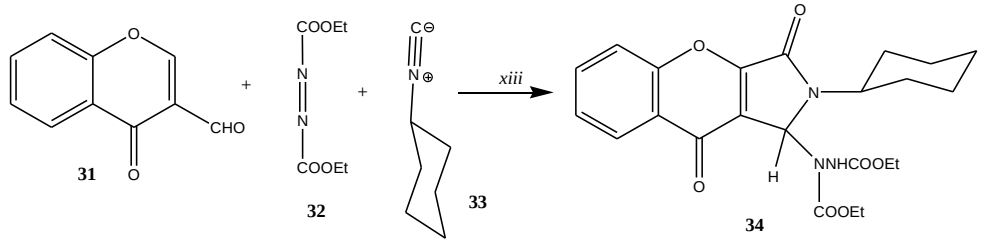
Scheme 10. Synthesis of two amide analogs (**26** and **27**). *Conditions and reagents*: *xi* = chromone-3-carboxaldehyde (**25**), 2,6-dimethylaniline, 4-nitro-phenyl) acetic acid, 2,6-dimethylphenyl isocyanide,

Another study carried out by Zhu and coworkers (2019), showed the synthesis of tert-butyl(2'S,3S,3'S)-4-oxo-3',5'-diphenyl-spiro-[chromane-3,4'-pyrrolidine]-2'-carboxylate (**30**) using a three-component system (3-Benzylidene-chroman-4-one (**28**), benzaldehyde (**13**), and amino-acetic acid tert-butyl ester (**29**) in the presence of some phosphonium salts (Scheme 11). It is important to mention that yield was higher using the 3d phosphonium salt.[xLix]



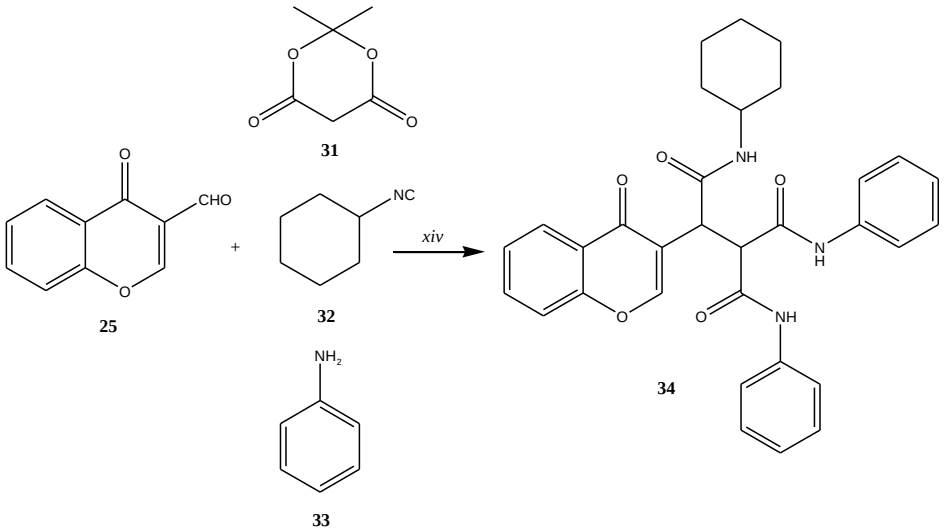
Scheme 11. Synthesis of a spiro-pyrrolidine derivative (**30**). Conditions and reagents. *xii* = $CsCO_3$, c-pentene, 3 Å molecular sieves, rt, 48 h.

Other data (Scheme 12) displayed the reaction of cyclohexylisocyanide (**33**) and diethyl azodicarboxylate (**32**) with 4-Oxo-4H-chromene-3-carbaldehyde (**31**) to form the compound ethyl *N*-[(2-cyclohexyl-3,9-dioxo-1*H*-chromeno[2,3-c]pyrrol-1-yl)-amino]-*N*-ethoxycarbo-nyl-carbamate (**34**). The proposed reaction mechanism indicates that isoniacide is added to the double bound of the chromone nucleus, followed by an intramolecular cyclization to form an amino group as an intermediate, which serves to produce an aminofurochromene. Then there is an electrophilic attack from the double link of furan to the nitrogen of ethyl ethyl (NE)-N-ethoxycarbonylimino carbamate to form an azodicarboxylate. Finally, this intermediate gives rise to the formation of the Chromeno-pyrrol derivative.[L]



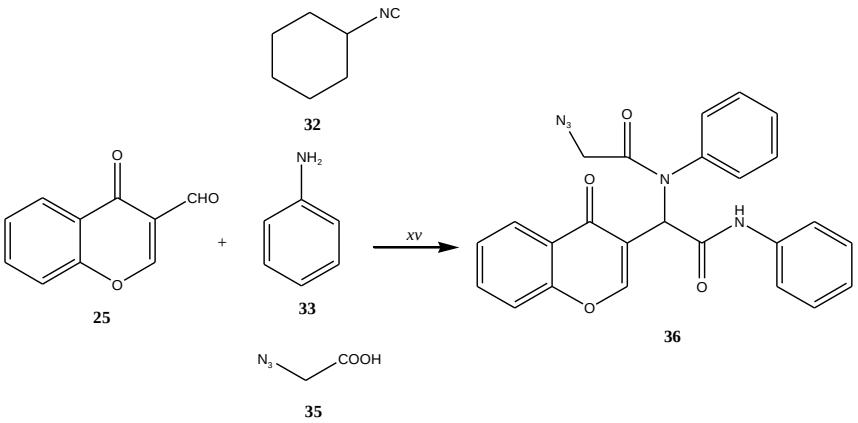
Scheme 12. Synthesis of a chromeno-pyrrol derivative (**34**). *Conditions and Reagents*: *xiii* = 4-Oxo-4H-chromene-3-carbaldehyde (31), diethyl azodicarboxylate (**32**), cyclohexylisocyanide (**33**), toluene, 80 ^{o}C, 12 h.

Besides, a study (Scheme 13) showed the synthesis of the compound N^2-cyclohexyl-2-(4-oxo-chromen-3-yl)-N^1,N^1-diphenyl-ethane-1,1,2-tricarboxamide (**34**) via a multicomponent system (4-oxo-chroman-3-carbaldehyde (**25**), Meldrum's acid (**31**), isocyano-cyclohexane (**32**), and aniline (**33**)). The reaction mechanism involves the addition of Meldrum acid to formylchromone via Knoevenogel condensation to form the compound 2,2-dimethyl-5-[(4-oxochromen-3-yl)methyl-ene]-1,3-dioxane-4,6-dione, followed by a [1 + 4] cycloaddition reaction with isocyano-cyclohexane to produce an iminolactone. Then, this compound reacted with aniline to produce an amide group. Finally, there is a nucleophilic attack of a second molecule of arylamine on the activated carbonyl of dihydrofuran-2-one, followed by opening the ring to form a chromone derivative.[Li]



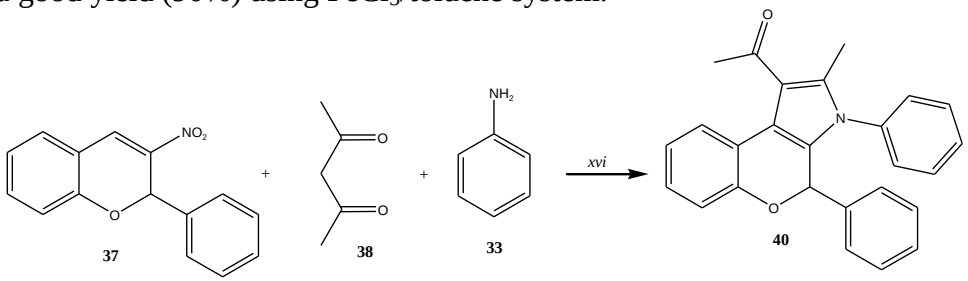
Scheme 13. Preparation of *N*2-cyclohexyl-2-(4-oxochroman-3-yl)-*N*1,*N*1-diphenyl-ethane-1,1,2-tricarboxamide (**34**). *Conditions and reagents*: *xiv* = 4-Oxo-chroman-3-carbaldehyde (**25**), Meldrum's acid (**31**), isocyano-cyclohexane (**32**), and aniline (**33**), anhydrous dichloromethane, rt, 3 h.

On the other hand, Akbarzadeh and coworkers (2014) showed the reaction of from chromone-3-carbaldehyde (**25**), aniline (**33**), cyclohexyl isoniacide (**32**), and 2-azidoacetic acid (**35**) via Ugi reaction to produce the compound 5-(Cyclohexylamino)-6-(4-oxo-4H-chromen-3-yl)-1-(p-tolyl)-3,6-dihydropyrazin-2(1H)-one (**36**) (Scheme 14).[Lii]



Scheme 14. Synthesis of a 6-(4-oxo-chromen-3-yl)-dihydropyrazinone (**36**). *Conditions and reagents*: *xv* = tetrahydrofurane, rt, 24 h

In addition, a study displayed the synthesis of 1-(2-methyl-3,4-diphenyl-4*H*-chromeno[3,4-b]pyrrol-1-yl)ethenone from 3-Nitro-2-phenyl-2H-chromene, Pentane-2,4-dione, and aniline under microwave irradiation (Scheme 15 and Table 8). It is noteworthy that this reaction presents a good yield (90%) using $FeCl_3$/toluene system.[Liii]

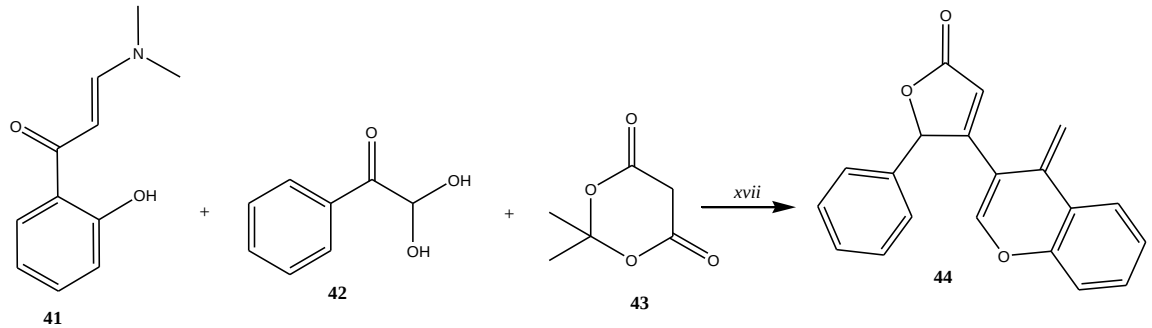


Scheme 15. Synthesis of a 6-(4-oxo-chromen-3-yl)- pyrazinone (**40**). *Conditions and reagents*: *xvi* = $FeCl_3$, toluene, microwave irradiation (60W), 90 ^oC, 15 min.

Table 8. Different solvents to produce chromone derivative (**40**)

Entry	Catalyst	Solvent	MW	Temp.	Time (min)	Yield (%)
1	SiO_2	THF	30W	60	10	55
2	SiO_2	THF	30W	60	20	50
3	AlO_3	THF	30W	70	20	32
4	AlO_3	Toluene	30W	90	20	40
5	PTSA	Toluene	30W	90	20	42
6	PTSA	THF	30W	80	20	35
7	$FeCl_3$	Toluene	30W	90	10	88
8	$ZnCl_2$	Toluene	30W	80	20	70
9	$TsOH/H_2O$	DMSO	30W	80	20	38
10	AcOH	DMSO	30W	80	20	45
11	AcOH	Toluene	30W	80	20	47
12	I_2	DMSO	30W	80	20	42
13	$FeCl_3$	Toluene	30W	60	5	35
14	$FeCl_3$	Toluene	40W	70	10	45
15	$FeCl_3$	Toluene	50W	80	15	62
16	$FeCl_3$	Toluene	60W	90	15	90
17	$FeCl_3$	Toluene	70W	90	15	80
18	$FeCl_3$	Toluene	80W	100	15	75

Finally, a study displayed the preparation of 4-(4-Methylene-4H-chromen-3-yl)-5-phenyl-5H-furan-2-one (**45**) from 3,3-Dimethylamino-1-(2-hydroxy-phenyl)-propenone (**41**), 2,2-Dihydroxy-1-phenyl-etha-none (**42**), and 2,2-Dimethyl-[1,3]dioxane-4,6-dione (**44**) using several solvents (Scheme 16 and Table 9). It is important to note that among the employed solvents, the best results were achieved using MeCN to room temperature for 48 h. The reaction mechanism involves the addition of Meldrum acid to arylglyoxal. Subsequently, the enaminone reacts with arylglyoxal to form the imine adduct, followed by an intramolecular cycle by reaction of the imine and the hydroxyl group to produce a salt that contains a fragment of 4H-chromen-4-one. Subsequently, this compound in acidic medium gives rise to a cyclization which includes enolization of carbonyl moiety and interaction of hydroxy group with Meldrum's acid fragment to form a chromone derivative.[Liv]



Scheme 16. Synthesis of a 4-(4-Methylene-4H-chromen-3-yl)-5-phenyl-5H-furan-2-one. *Conditions and reagents*: *xvii* = see Table 9.

Table 9. Solvent used to preparation of chromone derivative (**44**).

Entry	Solvent	Time (h)	Temp (^{o}C)	Yield (%)
1	MeCN	2	reflux	15
2	MeCN	8	reflux	22
3	MeCN	24	reflux	17
4	MeCN	8	-	25
5	MeCN	24	-	41
6	MeCN	48	-	52
7	MeCN	60	-	50
8	EtOH	48	-	23
9	Dioxane	48	-	42
10	THF	48	-	33
11	Toluene	48	-	25
12	CH_2Cl_2	48	-	44
13	MeCN	48	Et_3N	36
14	MeCN	48	DBU	15
15	MeCN	48	DABCO	22

CONCLUSIONS

The multicomponent reactions system is a chemical tool to develop several compounds; these reactions can provide high yields and high reaction speeds and can be used for the synthesis and reactions of different chromone derivatives. It is important to mention in this review that several reaction protocols were analyzed, which involve conventional and non-conventional

methods, in particular the use of different solvents and microwave irradiation conditions. It is noteworthy that these data can be used to make decisions in the development of new chromone derivatives.

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Keywords: Chromone • derivative • molonitrile • aldehyde • ethyl acetoacetate

CONFLICT OF INTEREST
The authors declare no conflict of interest

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