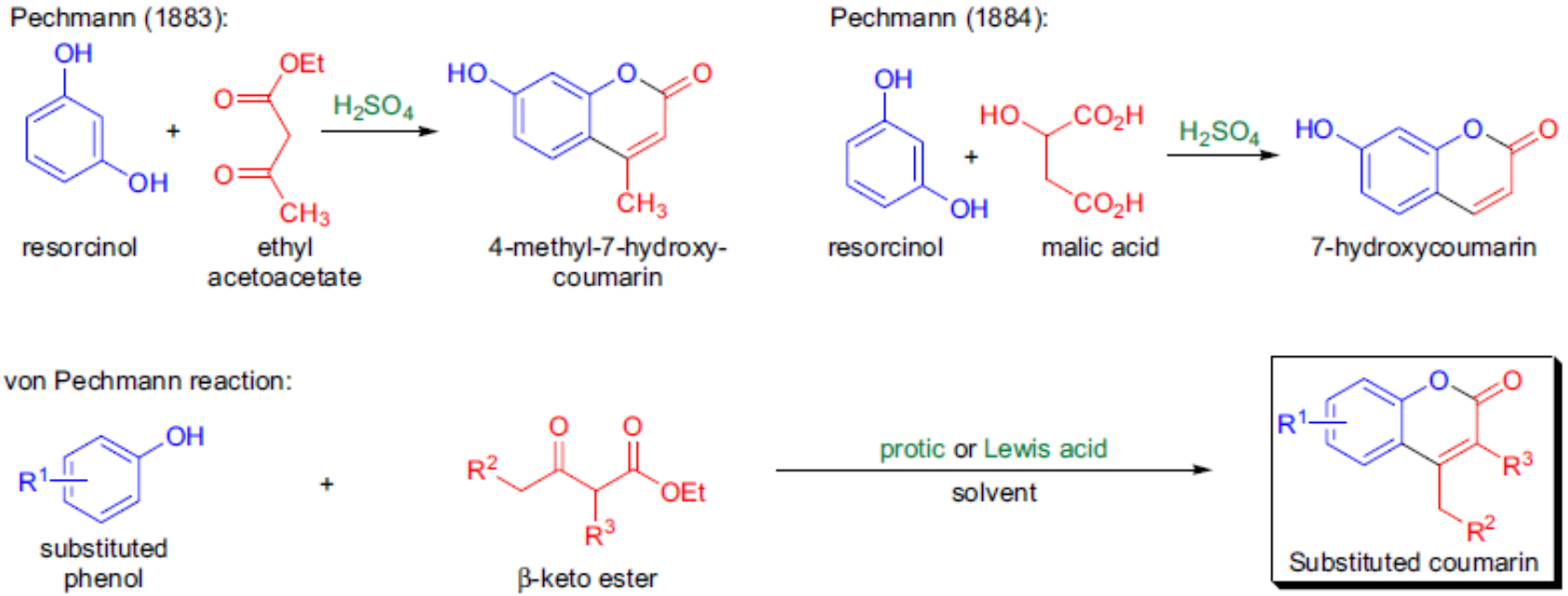
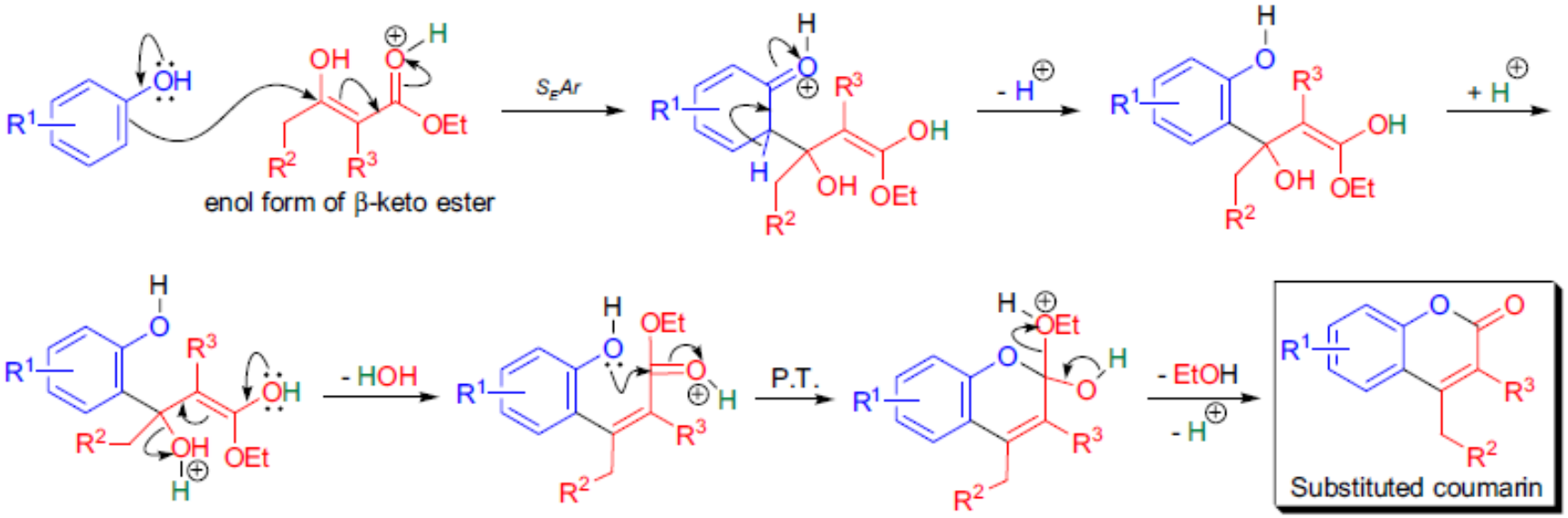
Von Pechmann Reaction



R^1 = H, OH, *O*-alkyl, NH_2, NHR, NR_2; R^2 = H, alkyl, aryl; R^3 = H, alkyl, aryl, Cl; protic acid: H_2SO_4, HCl, H_3PO_4; Lewis acid: $POCl_3$, $ZnCl_2$, $AlCl_3$, $FeCl_3$, $InCl_3$, $Yb(OTf)_3$, $SnCl_2$, $TiCl_4$, $SiCl_4$, PPA

Reaction Mechanism

Mechanism: [28,29]



Reaction Features

1. The best substrates are electron-rich mono-, di-, and trihydric phenols having electron-donating substituents.

2. Phenols with strongly electron-withdrawing substituents (e.g., NO_2 or CO_2H) often fail to react.

3. The position of the substituents on the phenol also has an influence on the reactivity and therefore on the rate of the condensation.

4. Ortho substituents tend to inhibit the reaction completely, para substituents usually do not interfere much, and substituents in the meta position give the best results.

5. Both cyclic and acyclic β-keto esters undergo the reaction.

6. Malic acid, fumaric, and maleic acids also react, but the scope of phenolic substrates is somewhat limited with these reactants.

7. β-keto esters yield coumarins that have substituents at the C4 position while malic acid affords coumarins which are unsubstituted at C4.

8. The nature of the protic or Lewis acid catalyst has a profound effect on the outcome of the reaction: if the reaction does not take place in the presence of one particular catalyst, it may proceed in high yield in the presence of another.

9. During the 1900s the most popular catalyst was concentrated sulfuric acid, but for highly functionalized and sensitive substrates milder condensation conditions have been developed.

10. For highly reactive phenols heating of the reaction mixture is usually not necessary, but for less reactive substrates heating is often required.

Drawbacks and Modifications

1. In the overwhelming majority of the cases the catalyst has to be used in excess so the process is not catalytic.

2. Extended reaction times at high temperatures can lead to side reactions such as to the formation of chromones in addition to coumarins.

Catalysts development as follows

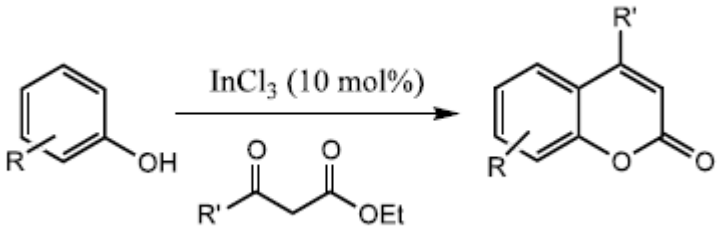
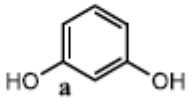
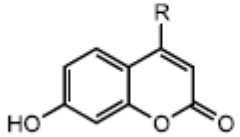
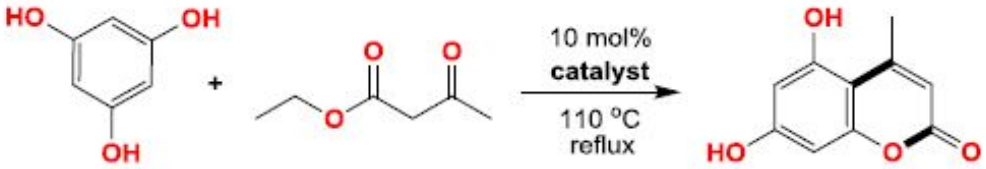


Table 1. Synthesis of coumarins via von Pechmann condensation of phenols with β-ketoesters induced by $In(III)Cl_3$

Entry	Subsrate **1**	Time (min.)	Temperature (^{0}C)	Product **2**[a]	Yield (%)[b]
1.		30	65	 **a**: R = CH_3	98
		30	65	**b**: R = CF_3	96
		30	65	**c**: R = CH_2Cl	93

Tetrahedron Letters. 2002, 43, 9195–9197.

Table 1. Catalytic Screening for the Coumarin Synthesis by Pechmann Condensation[a]



1a 2a 3a

entry	catalyst	time (h)	yield (%)*	TON/TOF (h)
1	no catalyst	24		0/0
2	ZnO	5	Trace	0/0
3	$Zn_{0.975}Ti_{0.025}O$	3	37	270/90
4	$Zn_{0.950}Ti_{0.050}O$	4	60	201/50.44
5	$Zn_{0.925}Ti_{0.075}O$	3	88	203/67.69
6	$Zn_{0.900}Ti_{0.100}O$	3	88	149/49.91

[a]Reaction conditions: EAA (2 mmol), phloroglucinol (2 mmol), catalyst (10 mol %), temp. (110 °C), isolated yields*, TON = moles of product/moles of active sites in the catalyst.

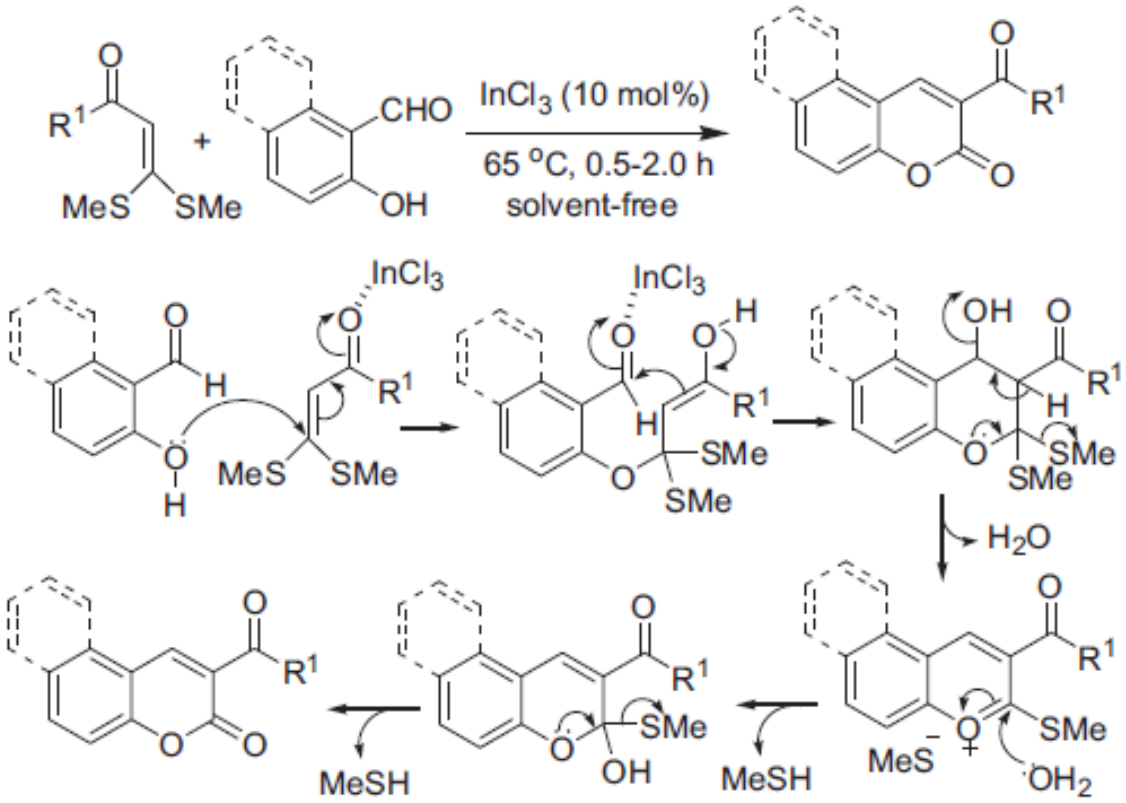
Various catalysts such as mineral acids like H_2SO_4, HCl, H_3PO_4, CF_3COOH, $HClO_4$, $ClSO_3H$, PTSA, and oxalic acid as well as Lewis acids such as $ZnCl_2$, $FeCl_3$, $SnCl_4$, $SnCl_2 \cdot H_2O$, $TiCl_4$, $AlCl_3$, $ZrCl_4$, $InCl_3$, $BiCl_3$, $Sm(NO_3)_3$, $BF_3 \cdot H_2O$, CAN, $Cu(ClO_4)_2$, $BaCl_2$, and $NbCl_5$.

Similarly, different heterogeneous catalysts were also employed for Pechmann condensation such as Al-MCM-41, Al-SBA-1 molecular sieves, Keggin structures heteropolyacids, graphite-montmorillonite K10, $H_{14}[NaP_5W_{30}O_{110}]$, silica triflate, mesoporous zirconium phosphate, $ZrOCl_2 \cdot 8H_2O/SiO_2$, pentafluorophenyl ammonium triflate, periodic mesoporous silica chloride, melamine–formaldehyde resin-supported H+, PEG-SO_3H, poly(4-vinylpyridinium) hydrogen sulfate, PVP-supported phosphotungstic acid, poly(4-vinylpyridine)- supported copper iodide, 1-butyl-3-methylimidazolium chloroaluminate, and 1-butyl-3-methylimidazolium hexafluorophosphate ionic liquid.

ACS Omega. 2019, 4, 8522–8527.

Pechmann Type Reactions

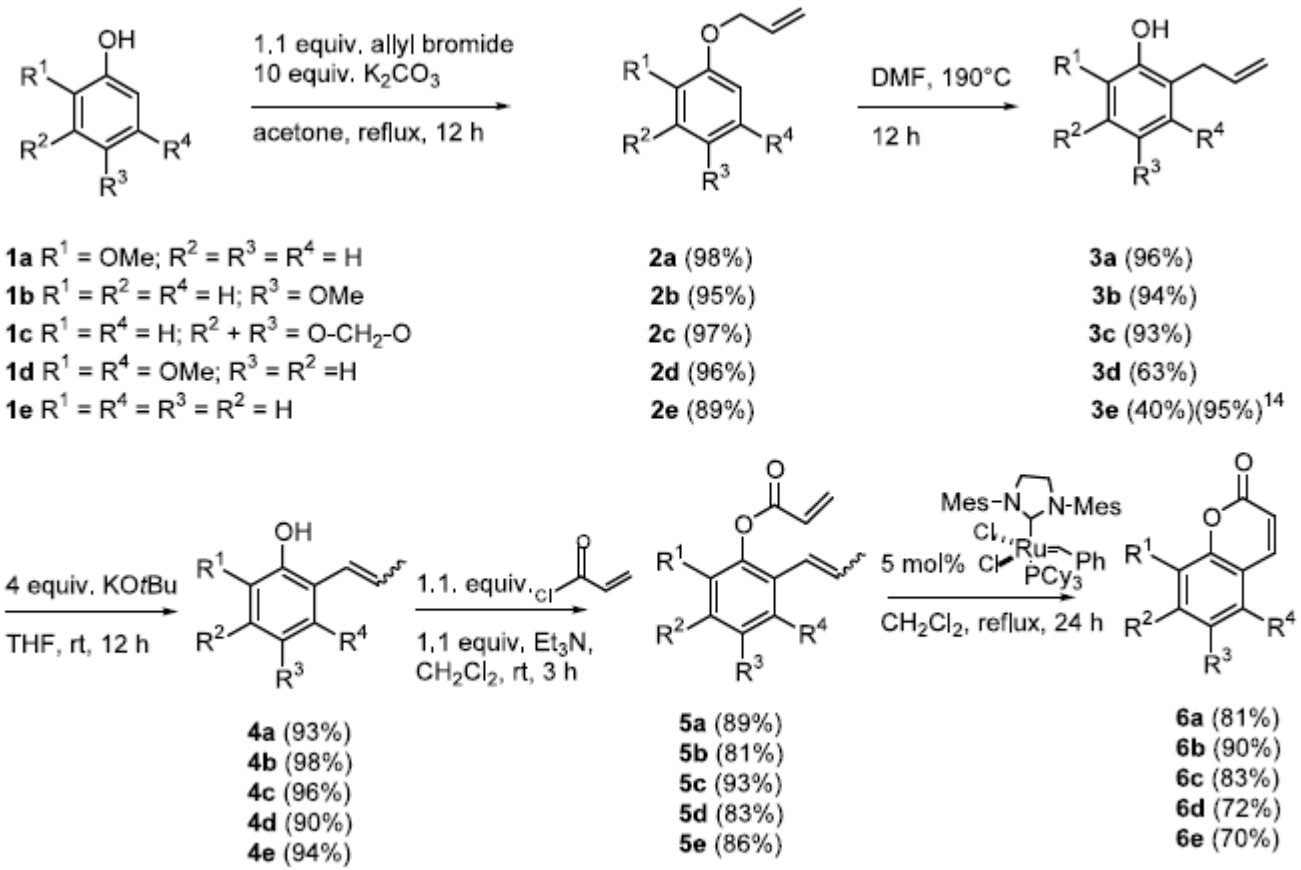
1. Two-component condensation of 2-hydroxyarylaldehydes and a-oxoketene dithioacetals



Scheme 47. Synthesis of coumarin derivatives.

Tetrahedron Letters. 2012, 68, 8683–8697.

2. Synthesis of coumarins by ring-closing metathesis using Grubbs' catalyst.



1a R^1 = OMe; R^2 = R^3 = R^4 = H
1b R^1 = R^2 = R^4 = H; R^3 = OMe
1c R^1 = R^4 = H; R^2 + R^3 = O-CH_2-O
1d R^1 = R^4 = OMe; R^3 = R^2 =H
1e R^1 = R^4 = R^3 = R^2 = H

2a (98%)
2b (95%)
2c (97%)
2d (96%)
2e (89%)

3a (96%)
3b (94%)
3c (93%)
3d (63%)
3e (40%)(95%)[14]

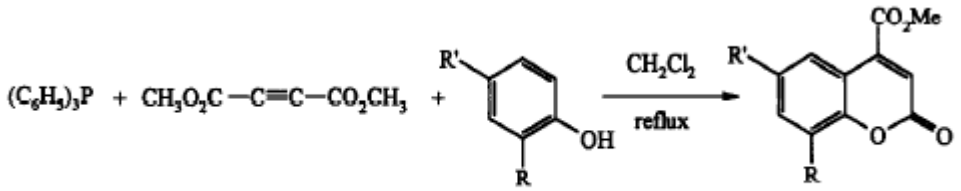
4a (93%)
4b (98%)
4c (96%)
4d (90%)
4e (94%)

5a (89%)
5b (81%)
5c (93%)
5d (83%)
5e (86%)

6a (81%)
6b (90%)
6c (83%)
6d (72%)
6e (70%)

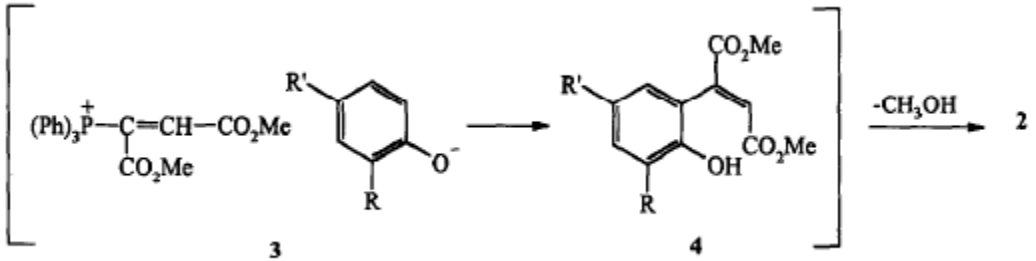
Tetrahedron Letters. 2003, 44, 4199–4201.

3. Vinyltriphenylphosphonium Salt.



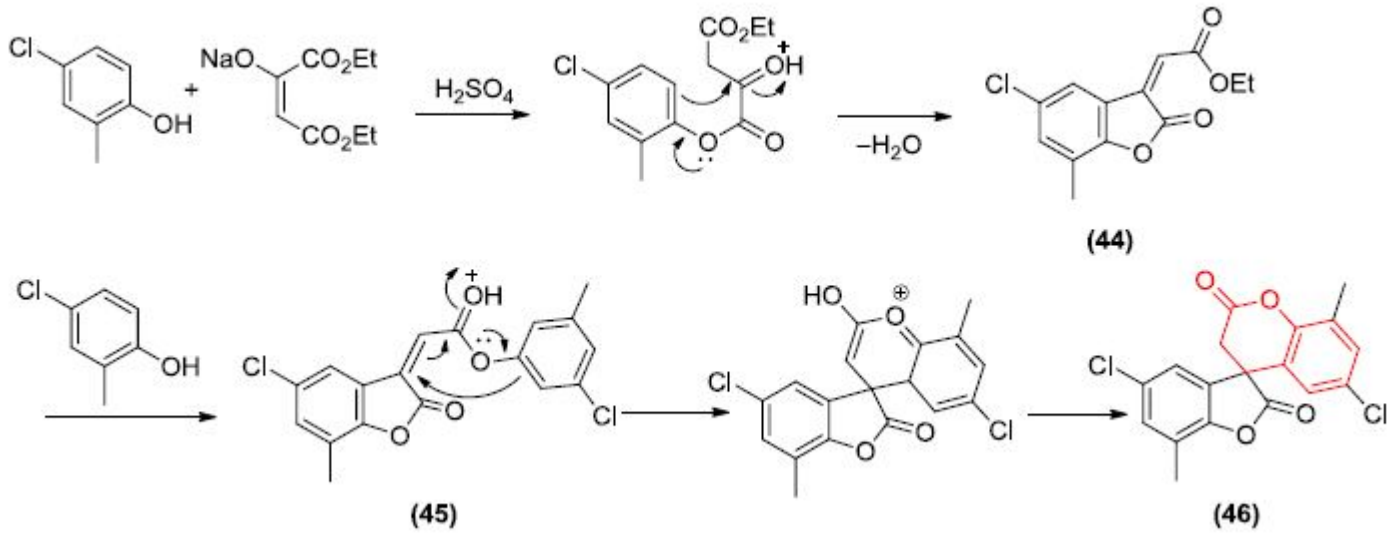
1 2

1,2	R	R'	%Yield of 2	1,2	R	R'	%Yield of 2
a	H	Me	65	h	H	F	83
b	H	*t*-Bu	72	i	H	CO_2Me	55
c	H	OMe	85	j	Cl	Cl	90
d	H	COMe	90	k	NO_2	NO_2	40
e	H	NO_2	70	l	Me	Cl	79
f	H	NHCOMe	75	m	OMe	CHO	60
g	H	CO_2H	70	n	OMe	CH_2-CH=CH_2	65



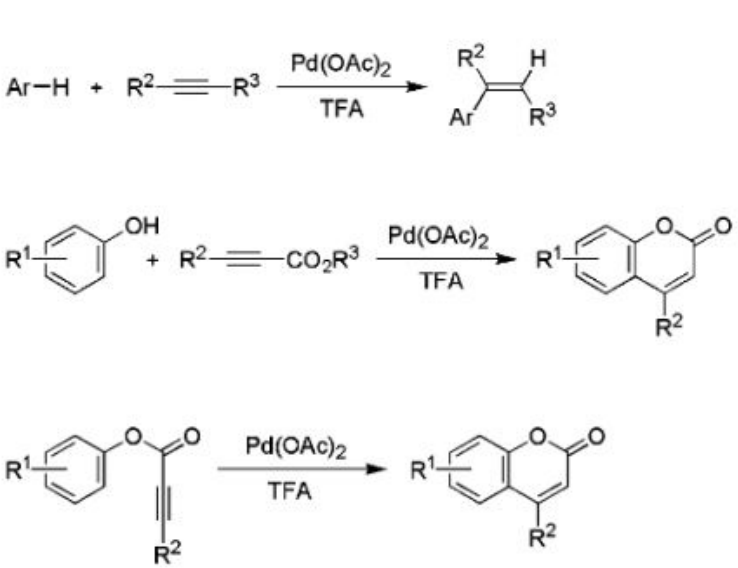
Tetrahedron Letters. 1998, 39, 2391–2392.

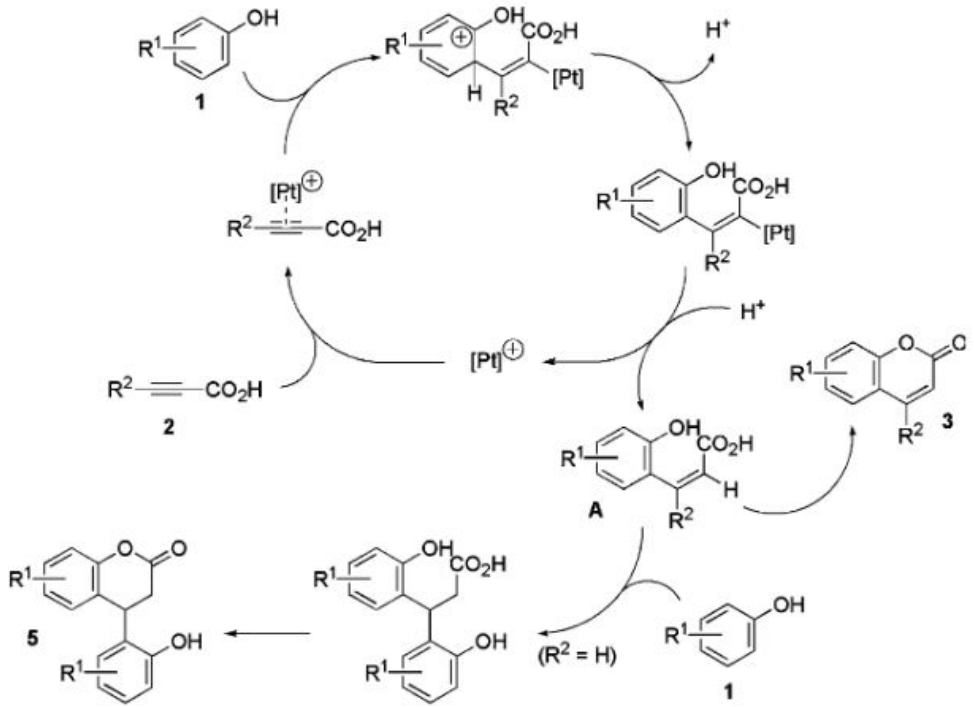
4. The condensation of 4-chloro-2-methylphenol with sodium salt of hydroxyl diethyl ester.



Journal of Heterocyclic Chemistry. 1989, 16, 803-804.

5. Metal catalyzed hydroarylation of alkyne with phenols Salt.

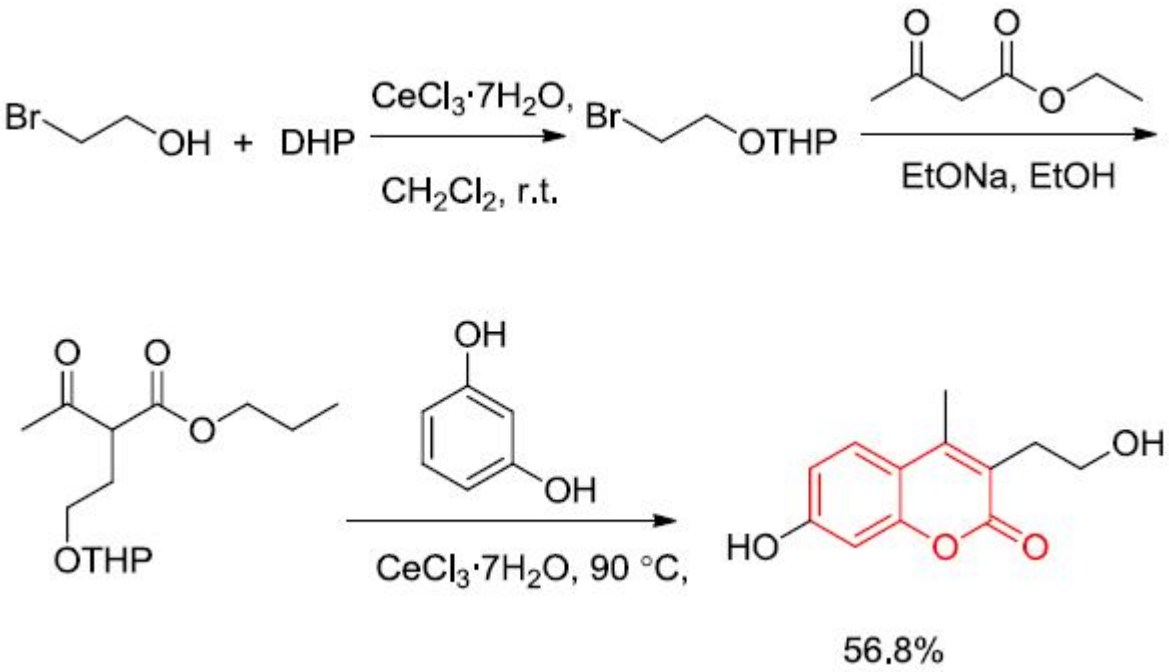




Tetrahedron Letters. 1998, 39, 2391–2392.

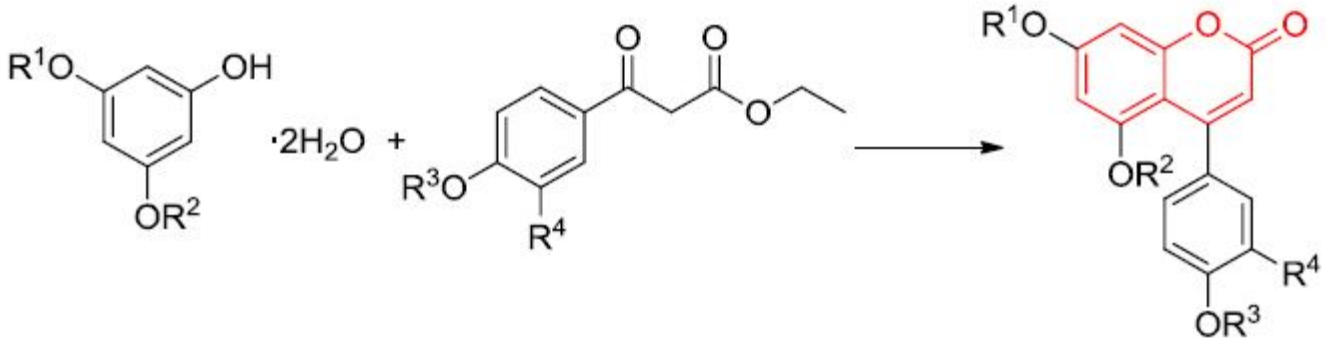
Applications in nature products

1. Ocimarin-Its leaves have long been used to treat a variety of ailments, including ozena, skin diseases, and gastric and hepatic disorders and are used as a diaphoretic, and an expectorant.



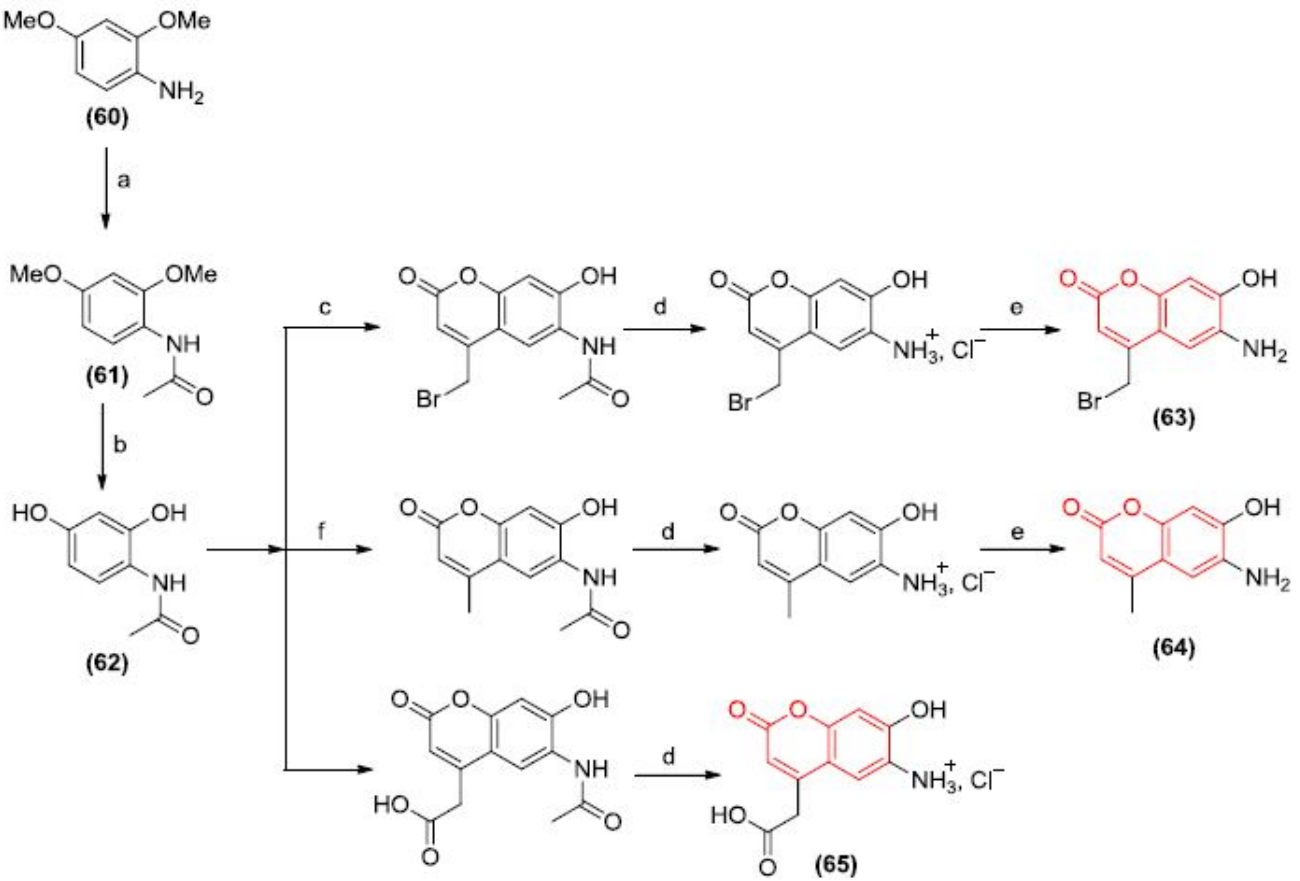
Chinese Chemical Letters. 2010, 21, 1165–1166.

2. A plant growing in northeastern Brazil and used in traditional medicine as an antimalarial or antidiabetic agent.



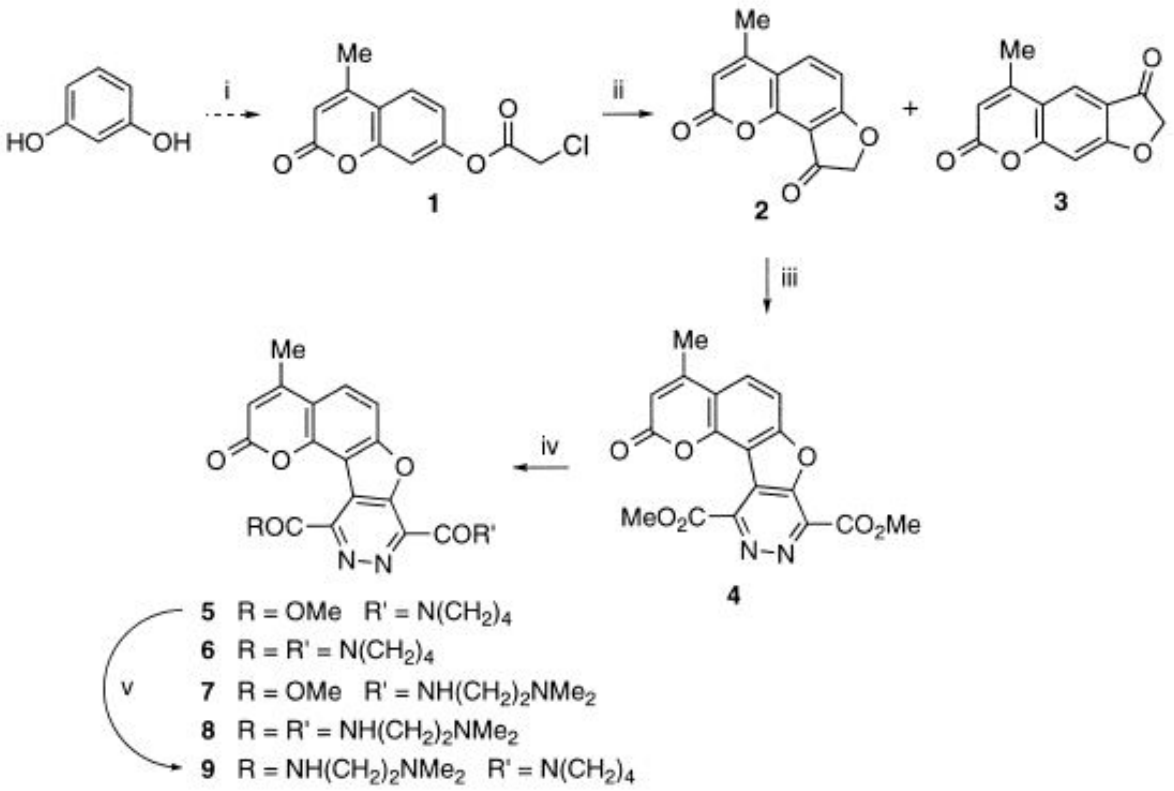
Phytochemistry. 1985, 24, 1355-1357.

3. Great commercial importance since they are usually used as antibiotics such as novoviokin and coumermycin antibacterials, antitumor, antiviral agents, anticoagulants, against psoriasis, aldose reductase inhibitors



Synthesis Communication. 2004, 34, 4233-4242.

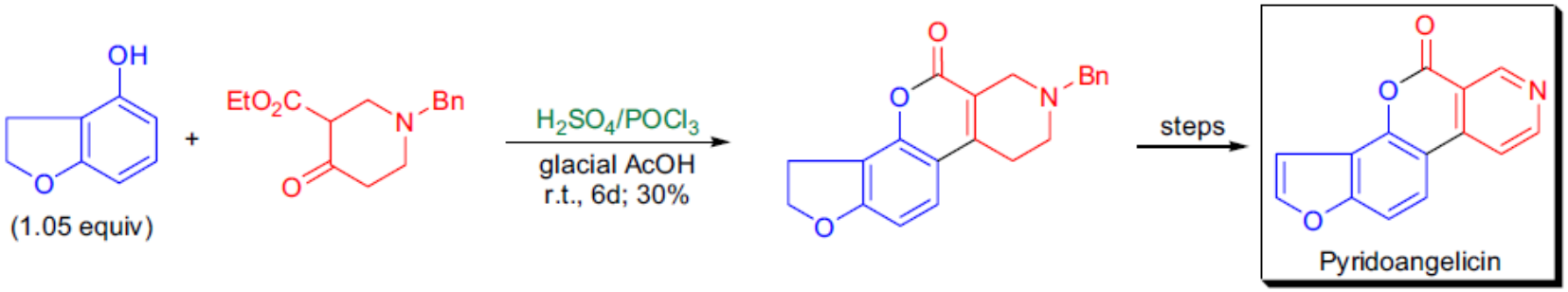
4. Pyridazinofurocoumarins-potent DNA inhibitors



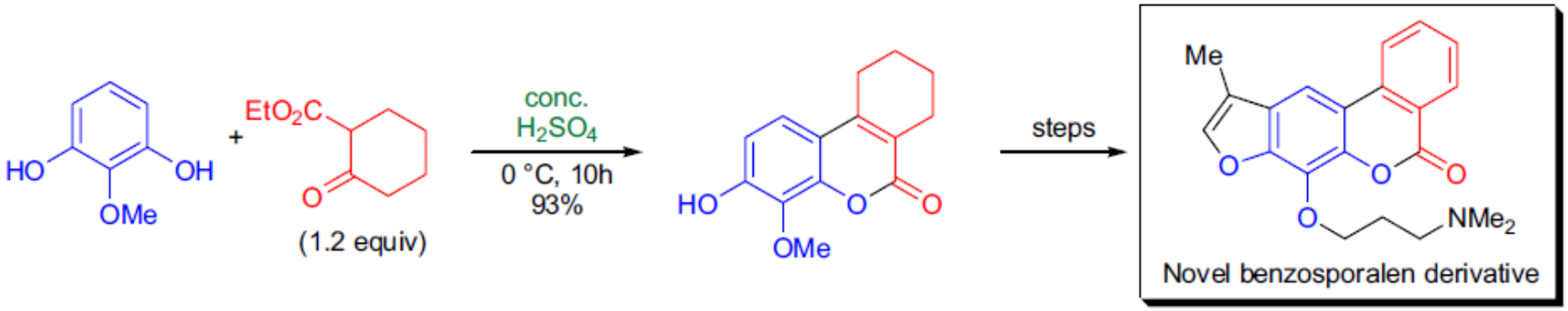
Scheme 1. *Reagents and conditions*: (i) (a) $CH_3COCH_2CO_2Et$, H_2SO_4, rt, (b) $ClCOCH_2Cl$, DMAP, dioxane, reflux; (ii) $AlCl_3$, 120°C; (iii) 3,6-bis-(methoxycarbonyl)-1,2,4,5-tetrazine, *p*-TsOH, CH_2Cl_2, 100°C; (iv) amine, $MgCl_2$, CH_2Cl_2, rt; (v) *N*,*N*-dimethyletilenediamine, $MgCl_2$, CH_2Cl_2, rt.

Tetrahedron Letters. 2004, 34, 4233-4242.

5. Pyridoangelicins-exhibit high affinity toward DNA

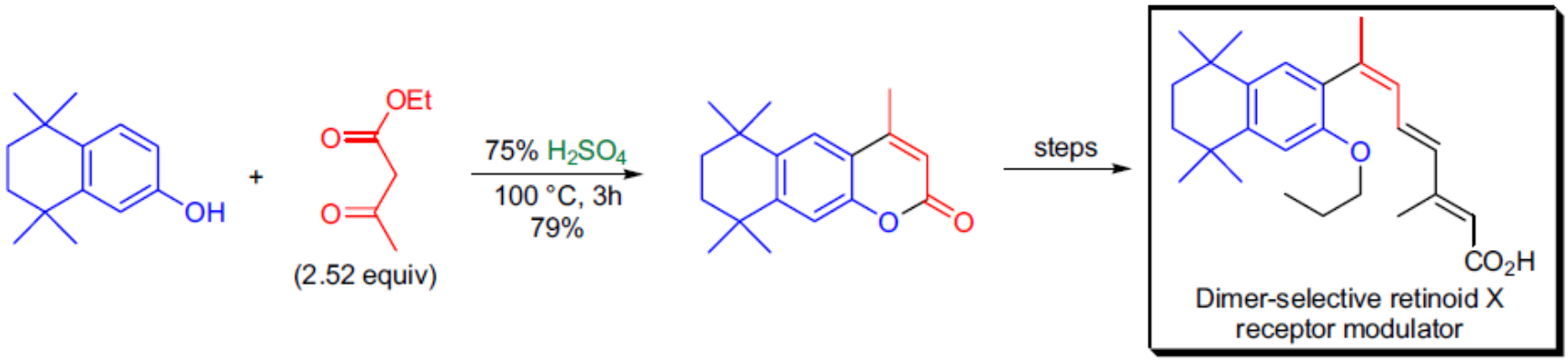


6. Photochemotherapy is an efficient way to treat hyperproliferative diseases.



Journal of Medicine Chemistry. 2003, 46, 3800-3810.

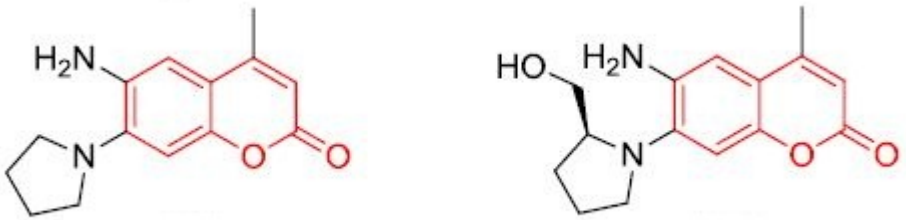
7. Dimer-selective retinoid X receptor modulator.



Journal of Organic Chemistry. 2000, 65, 3233-3235.

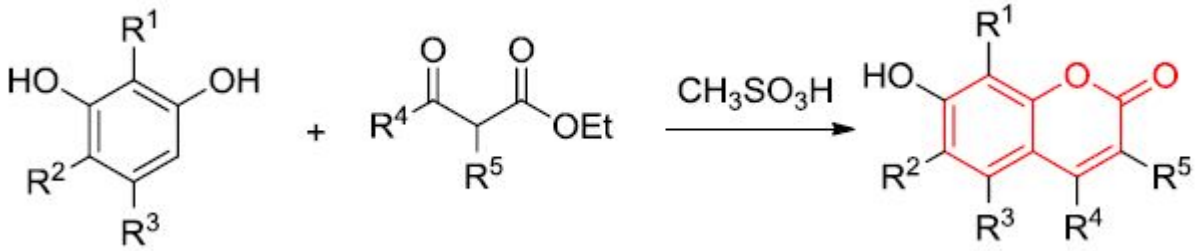
Applications in Dyes

1. Suitable candidates for being used as dyes, fluorescent substrates in enzymatic tests, or reagents for synthesis of various derivatives in analytical tests.



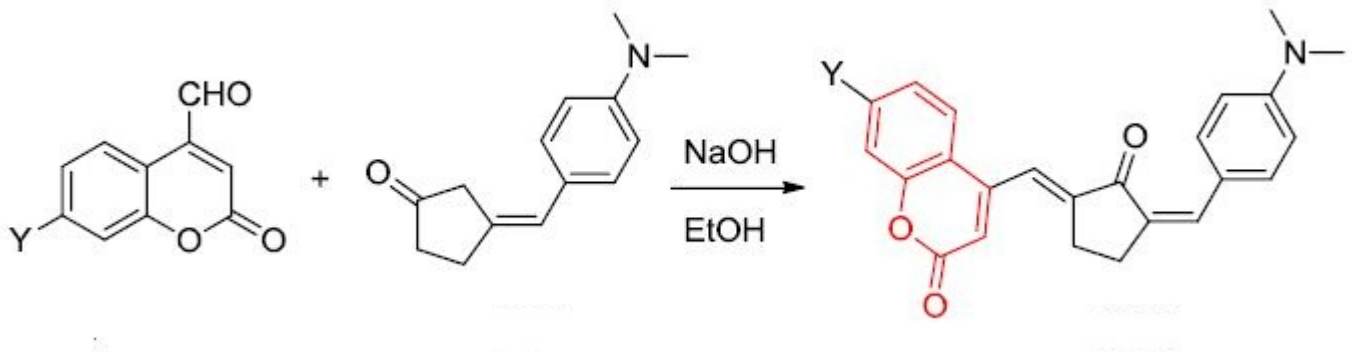
Tetrahedron Letters. 2003, 44, 845-848.

2. Excellent UV-Light excitable fluorescent dyes.



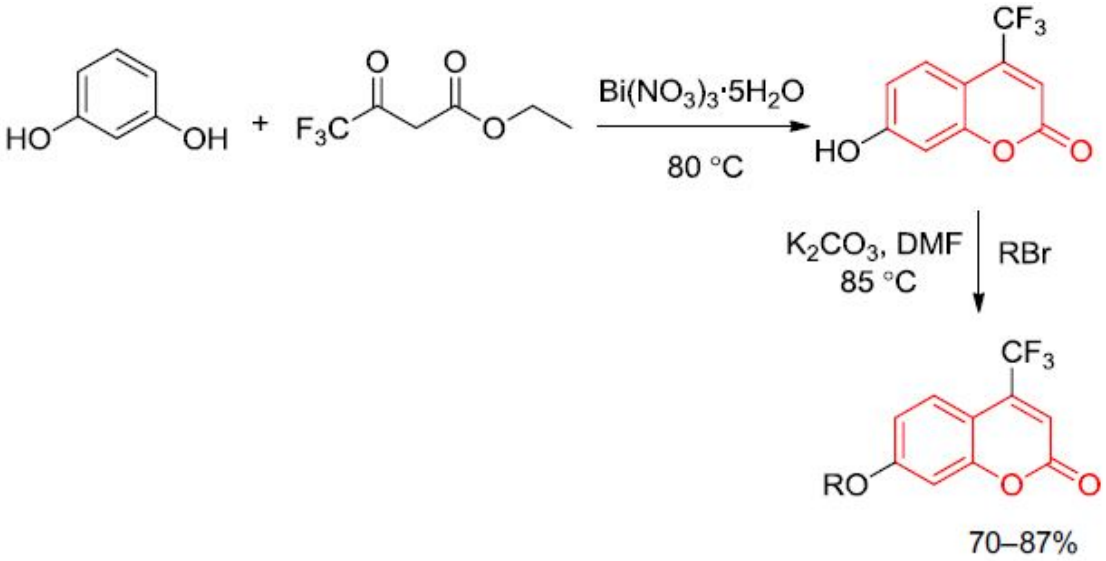
Bioorganic & Medicinal Chemistry Letters. 1998, 8, 3107-3110.

3. Excellent photon-absorbing properties.



Dyes and Pigments. 2007, 75, 104-110.

4. Strong fluorescence under UV light.



Coloration Technology. 2011, 127, 335-339.

5. Photophysical properties of fluorochromes.

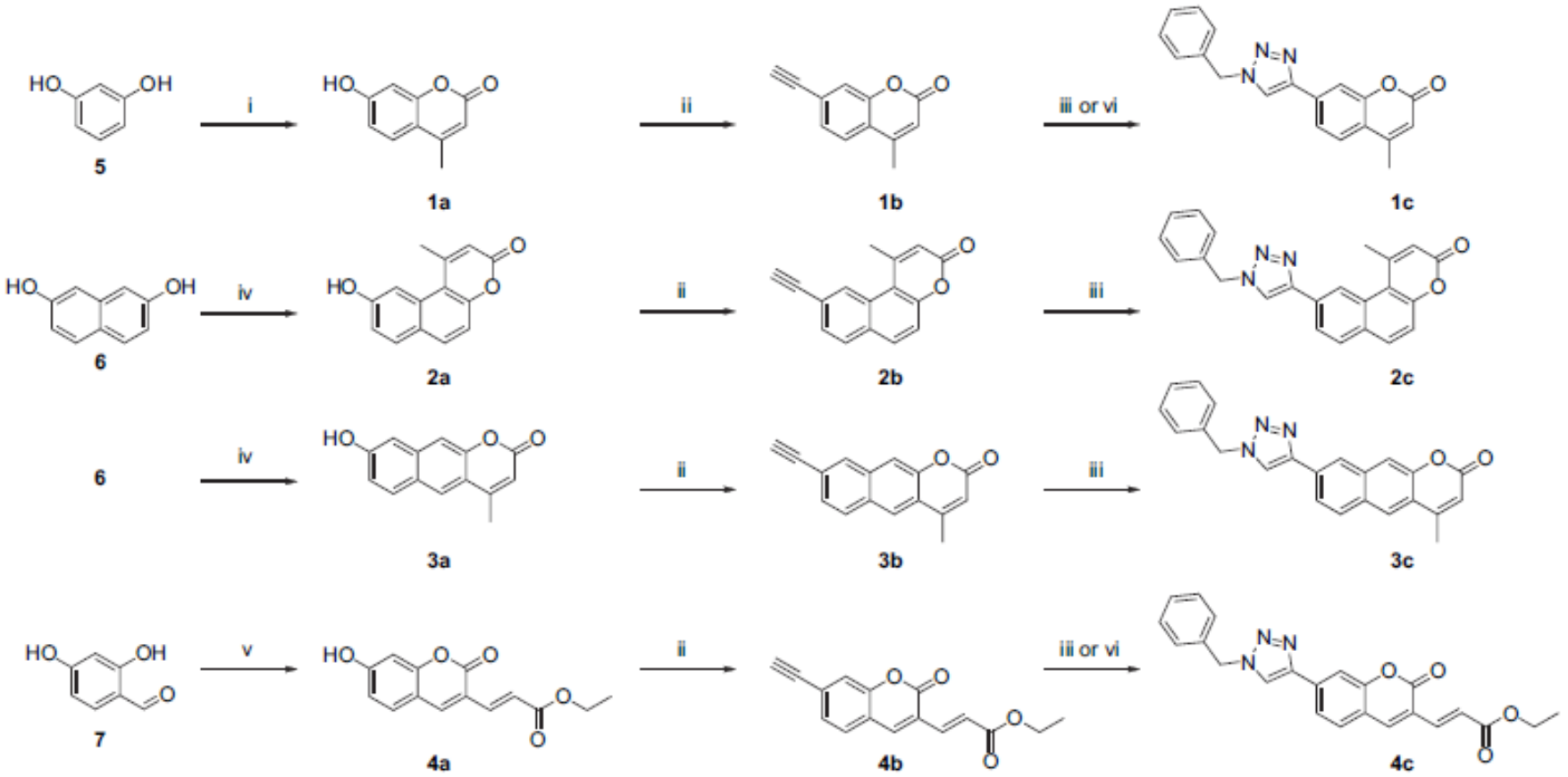


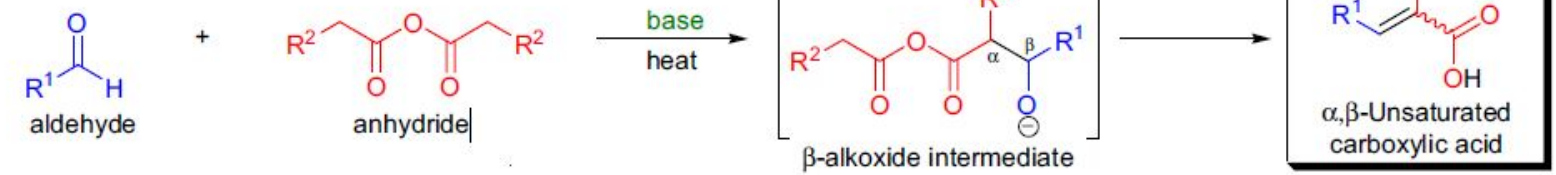
Fig. 1. Synthetic scheme for the generation of click substrates and fluorophores. Reagents and conditions: (i) ethyl acetoacetate, $TiCl_4$, rt, 5 min; (ii) (a) $PhN(SO_2CF_3)_2$, DIPEA, CH_3CN, rt, 30 min; (b) TMS acetylene, CuI, $Pd(PPh_3)_4$, DIPEA, CH_3CN, rt, 48 h; (c) TBAF, MeOH, 60 °C, 30 min; (iii) benzylazide, CuI, TEA, MeOH/H_2O, rt, 2–24 h; (iv) ethyl acetoacetate, 80% H_2SO_4, rt, 24 h; (v) diethyl glutaconate, EtOH, piperidine, reflux 89 °C, 24 h; (vi) $CuSO_4$, ascorbic acid, EtOH/H_2O, rt, 2–7 d.

Dyes and Pigments. 2009, 82, 196–203.

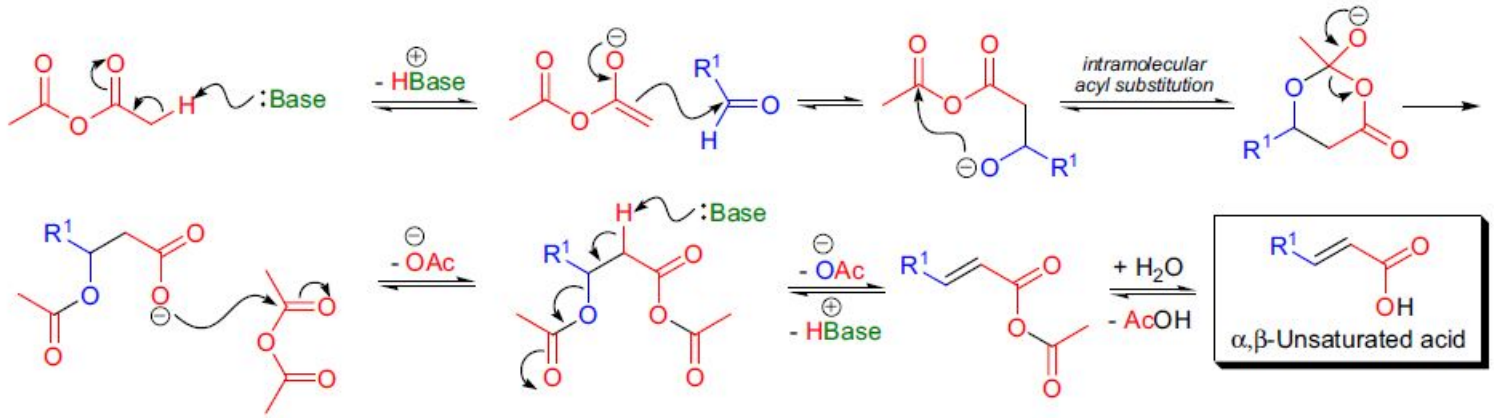
Relevant Name Reactions

1. Perkin Reaction

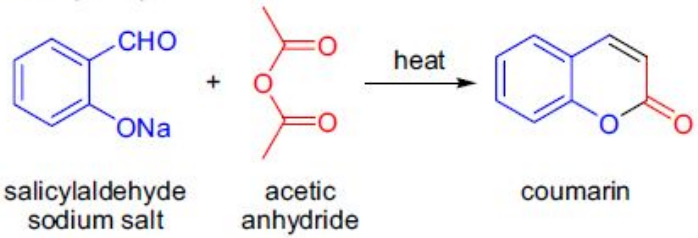
Perkin reaction:



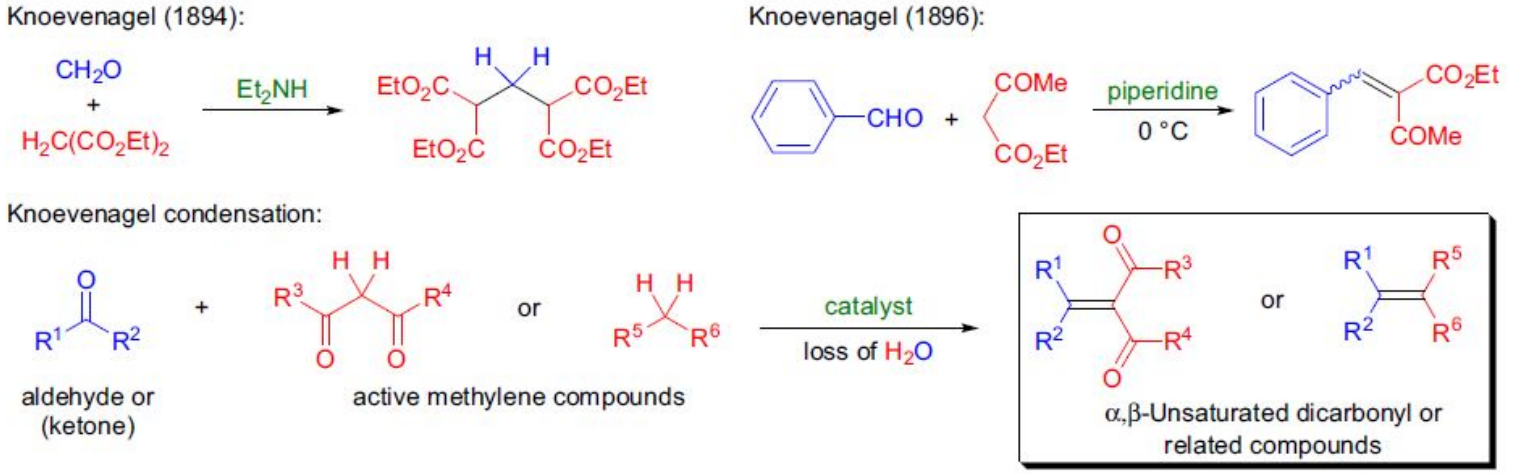
Mechanism: [23,3,24-31,4,32-35]

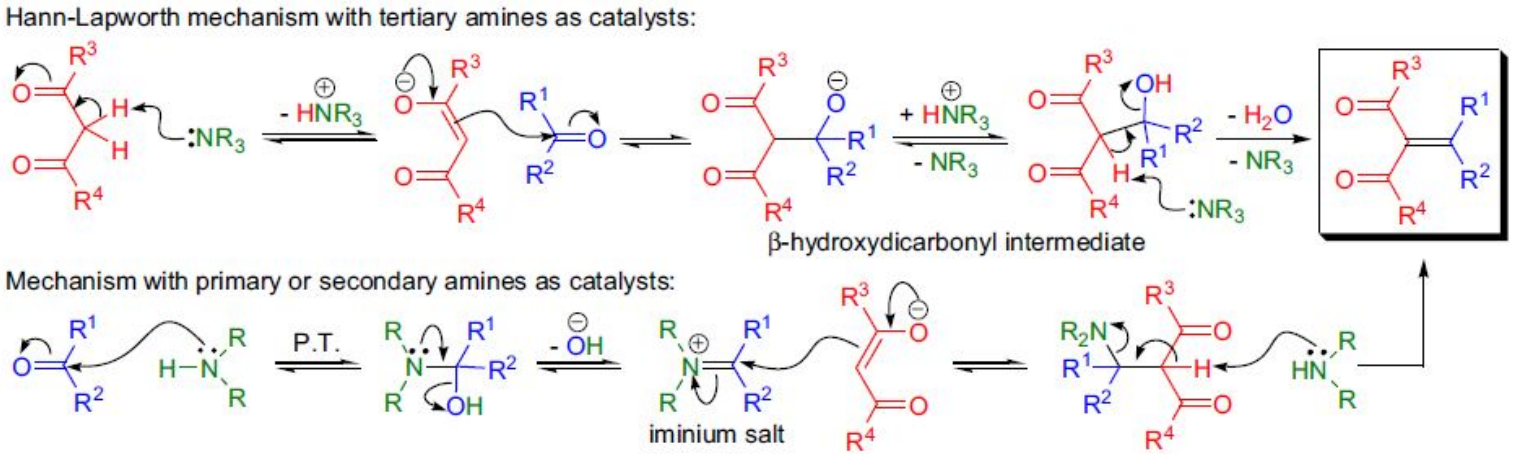


Perkin (1868):



2. Knoevenagel condensation





Thanks For Your Attention