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Synthesis via carbon suboxide and pharmacological activity of coumarin derivatives☆

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Abstract

This report sums up the research work since 1993 on the synthesis of coumarin derivatives using carbon suboxide as reagent.

Keywords: Carbon suboxide; Coumarins; Pharmacological activity

1. Introduction

Coumarin derivatives are known to be a very interesting class of natural or synthetic compounds [1,2] whose biological activity varies according to the substituents on the benzopyran ring [3,4].

In recent years many works have been published on coumarin derivatives with different pharmacological activities: anti-bacterial [5–7], anti-fungal [8], anti-tumoral [9,10], anti-HIV [11,12], etc., but their synthesis often requires many reaction steps.

For several years our research group has been interested in the synthesis of heterocyclic derivatives using carbon suboxide (C_3O_2) as reagent. Considering their pharmacological importance, particular attention has been dedicated to the synthesis of coumarins and coumarin derivatives, which can be carried out in one reaction step with C_3O_2, unlike the traditional syntheses that require a number of reaction steps.

2. Carbon suboxide O=C=C=C=O

Though discovered by Diels in 1906 while studying the reaction between P_2O_5 and diethylmalonate, the use of carbon suboxide is still topical today, even after more than 90 years.

Carbon suboxide can be considered a bisketene derived from the double dehydration of malonic acid, and is extremely reactive both at room temperature and at low temperatures. It is a particularly versatile reagent for a few syntheses that are normally carried out with poor yields and formation of secondary products; it can be considered a formally pure reagent, since all its reaction products are adducts of carbon suboxide at the substrate. Up to the 1960s it was only used to prepare simple derivatives of malonic acid. Subsequently, it was used in various reactions: heterocyclic reactions, cycloadditions, polymerisations, photochemical reactions, etc.

2.1. Synthesis of the coumarin nucleus: reaction mechanism

Carbon suboxide reacts with aromatic azomethines, oximes and hydrazones, bearing *o*-hydroxy, -amino, and -mercapto substituents, to give benzopyran, quinoline and benzothiopyran derivatives [13–18]. The mechanism of this reaction was elucidated with a kinetic study of the reaction of 4- or 5-substituted 2-hydroxybenzaldehyde oximes and carbon suboxide [19]. The first fast step of the reaction involves the attack of carbon suboxide (II) on the phenol hydroxy group of

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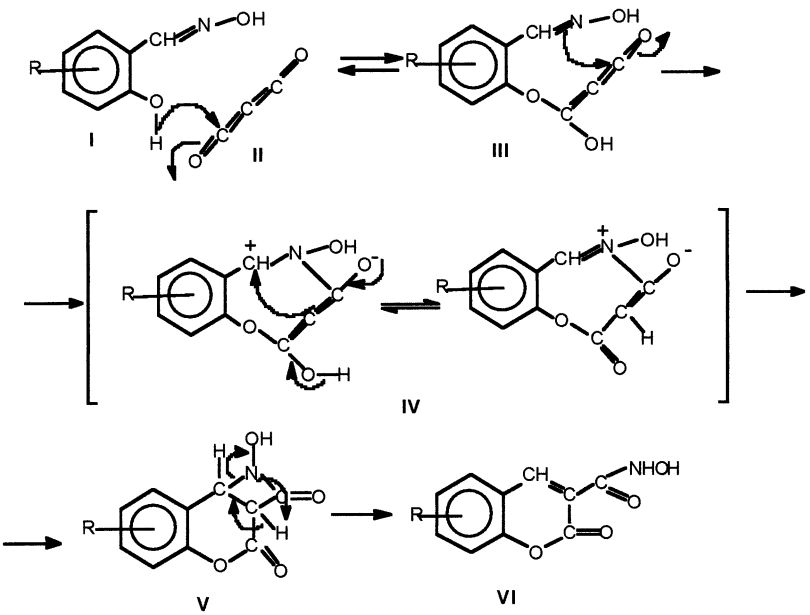
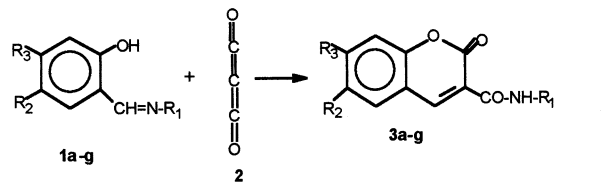


Scheme 1.

benzaldehyde oxime (I) to give an enol intermediate (III). Subsequently, attack of the carbonyl carbon on oxime nitrogen provides an ionic eight-membered ring intermediate (IV) which gives the coumarin derivative (VI) through the intermediate (V) (Scheme 1).



a: $R_1 = C_6H_5$; $R_2 = R_3 = H$
b: $R_1 = p\text{-}CH_3\text{-}C_6H_4$; $R_2 = R_3 = H$
c: $R_1 = p\text{-}OCH_3\text{-}C_6H_4$; $R_2 = R_3 = H$
d: $R_1 = C_6H_5$; $R_2 = H$, $R_3 = CH_3$
e: $R_1 = C_6H_5$; $R_2 = CH_3$, $R_3 = H$
f: $R_1 = p\text{-}CF_3\text{-}C_6H_4$; $R_2 = R_3 = H$
g: $R_1 = \text{-}CH_2\text{-}C_6H_5$; $R_2 = R_3 = H$

Scheme 2.

Table 1
Diuretic activity

Comp.	Dose (mg/kg)	Urine excretion (ml/24 h)
Control	–	4 ± 0.7
3a	50	8 ± 0.4
3b	50	8 ± 0.63
3c	50	14 ± 1.13
3d	50	11 ± 1.20
3e	50	3 ± 0.28
3f	50	15 ± 0.84
3g	50	6 ± 0.88
HCTZ[a]	10	9 ± 0.7

[a] Hydrochlorothiazide.

2.2. Applications

2.2.1. Synthesis of coumarin derivatives with diuretic and analgesic activity

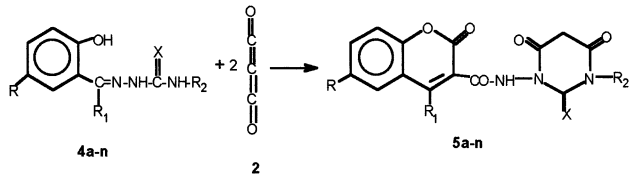
Using the reaction between C_3O_2 (**2**) and the azomethine **1a–g** in equimolecular amounts the 2-oxo-(2H)1-benzopyran-3-carboxamide derivatives **3a–g** are obtained (Scheme 2) [20].

Compounds **3c**, **3d**, and **3f** show interesting diuretic activity (Table 1). All the compounds, except for **3f,** also have greater analgesic activity than indomethacine,

Table 2
Analgesic activity

Comp.	Dose (mg/kg)	No. contractions (20 min observation)	Inhibition (%)
Control	–	45 ± 4	
3a	5	22 ± 2	50.3*
	50	23 ± 5	49*
3b	5	22 ± 3	50*
	50	19 ± 5	57*
3c	5	9 ± 5	80*
	50	17 ± 6	61*
3d	5	20 ± 2	55*
	50	40 ± 3	11*
3e	5	18 ± 4	60*
	50	23 ± 5	49*
3f	5	25 ± 3	45*
	50	19 ± 5	58*
3g	5	13 ± 3	72*
	50	10 ± 4	77*
INDO[a]	5	22 ± 4	50.3*

[a] Indomethacin.
* Significant at $P < 0.05$.



a: $R=R_1=R_2=H$; X=O
b: $R=R_1=R_2=H$; X=S
c: $R=R_1=H$; $R_2=C_6H_5$; X=O
d: R=Br; $R_1=R_2=H$; X=O
e: R=Br; $R_1=R_2=H$; X=S
f: $R=NO_2$; $R_1=H$; $R_2=C_6H_5$; X=S
g: R=Br; $R_1=H$; $R_2=C_6H_5$; X=S
h: $R=R_1=H$; $R_2=C_6H_5$; X=S
i: R=Br; $R_1=H$; $R_2=C_2H_5$; X=S
l: R=Br; $R_1=H$; $R_2=CH_3$; X=S
m: R=H; $R_1=C_2H_5$; $R_2=C_2H_5$; X=S
n: R=H; $R_1=C_2H_5$; $R_2=CH_3$; X=S

Scheme 3.

besides the advantage of not producing gastric lesions (Table 2).

Using the semicarbazones **4a–n** as substrate, the reaction with C_3O_2 (**2**) leads to the compounds **5a–n** that may be considered barbituric or thiobarbituric substituted coumarin rings [21] (Scheme 3).

Many compounds have notable analgesic (Table 3) and diuretic (Table 4) activity.

2.2.2. Synthesis of 2H,4H-benzopyrano[3,5-b]pyridine-1,3,5-trione

Benzopyran-trionic derivatives may be structurally correlated to analogous compounds of known pharmacological activity [22].

By reaction of 3-amino-2H-1-benzopyran-2-one **8a–f** [23–25], obtained starting from the coumarin acids **6a–f** [16,26] via the *N*-(*tert*-butoxycarbonyl)-3-amino-2H-1-benzopyran-2-one derivatives **7a–f** [27], with C_3O_2 (**2**) in equimolecular amounts and in presence of catalytic quantities of $AlCl_3$, good yields of pyridine coumarin **9a–f** ($\sim$ 40%) are obtained [28] (Scheme 4).

Starting from substituted 2-hydroxybenzamides (**10a–h**), by varying the molar ratio of the reagents, satisfying yields (55–70%) of the coumarin derivatives **11a–h** and **12a–h** or of the derivatives 2H,3H-[1]-benzopyran-2-hydroxy-3-carboxamide-4,5-dione **13a–h** may be obtained in one stage [29] (Scheme 5).

Table 3
Diuretic activity

Compound	Dose (mg/kg)	Urine excretion (ml/24 h)
Control	–	4 ± 0.5
4b	50	8 ± 0.4
4c	50	8 ± 0.63
4g	50	8 ± 0.73
4h	50	10 ± 1.4
HCTZ[a]	10	10 ± 0.5

[a] Hydrochlorothiazide. Only active compounds are reported.

Table 4
Analgesic activity

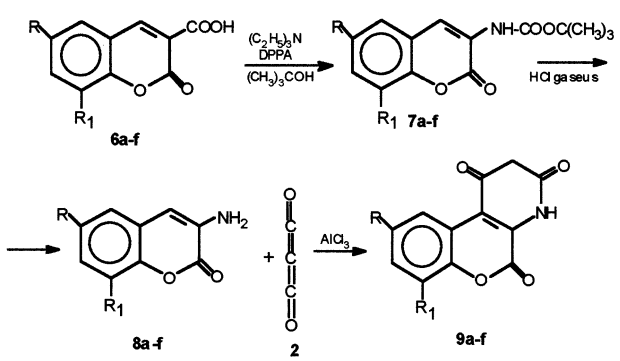
Compound	Dose (mg/kg)	No. contractions (20 min observation)	Inhibition (%)
Control	–	46.9 ± 2	
4a	5	30 ± 6	35 ± 1*
	50	12 ± 4	73 ± 8*
4d	5	20 ± 5	58 ± 1*
	50	12 ± 2	76 ± 8*
4e	5	32 ± 54	35 ± 2*
	50	32 ± 2	36 ± 3*
4f	5	30 ± 6	40 ± 2*
	50	27 ± 3	46 ± 2*
4g	5	32 ± 5	36 ± 1*
	50	20 ± 5	60 ± 2*
INDO[a]	5	24 ± 2	49 ± 2*

[a] Indomethacin.
* Significant at $P<0.01$. Only active compounds are reported.

2.2.3. Synthesis of coumarin penicillins and cephalosporins with antimicrobial activity

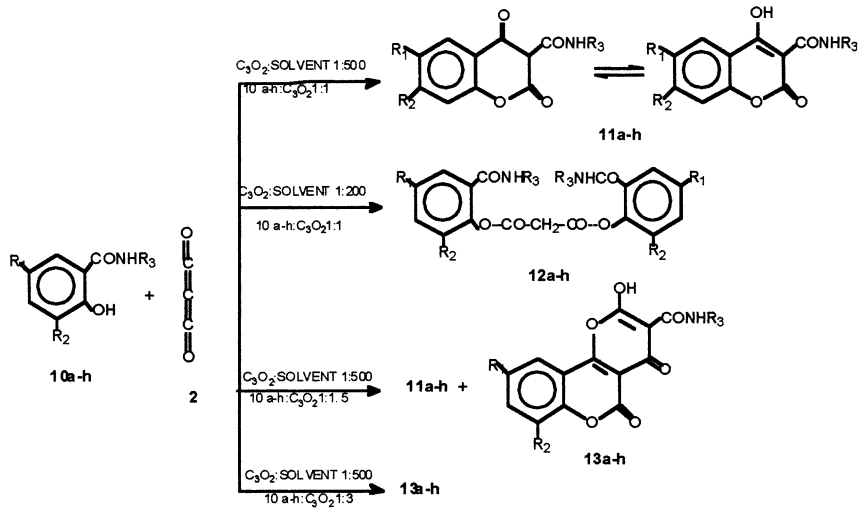
The reaction of the azomethines with C_3O_2 was conveniently applied to the synthesis of a few penicillins [30] and cephalosporins [31]. Initially Schiff bases of 6-amino penicillanic acid (**16a–f**) and 7-amino cephalosporanic acid (**20a–f**) were prepared by reaction of 6-APA and 7-ACA with 2-hydroxyaldehydes **14a–f** and **18a–f**, respectively. The subsequent reaction with C_3O_2 (**2**) leads directly to the formation of the 6-coumarin substituted penicillins **17a–f** and the 7-coumarin substituted cephalosporines **21a–f** (Scheme 6).

The data relating to the antimicrobial screening for cephalosporin **21a–f** are reported in Table 5 while for all penicillins the MIC was >100 μg/ml.



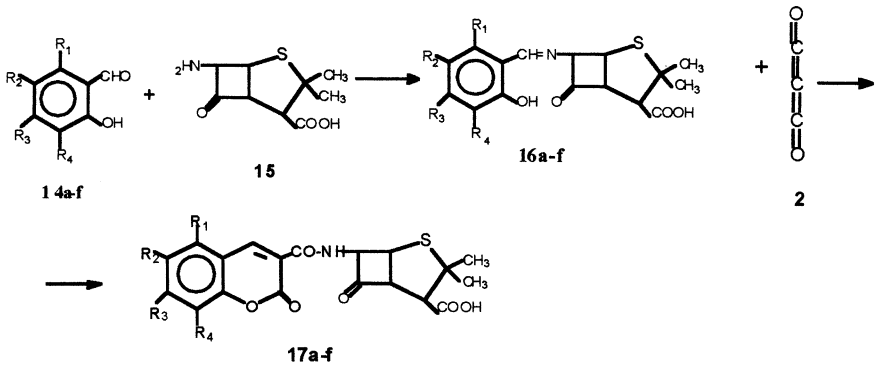
a: $R=R_1=H$
b: $R=NO_2$; $R_1=H$
c: R=Br; $R_1=H$
d: R=Cl; $R_1=H$
e: R=Br; $R_1=Br$
f: R=Cl; $R_1=Cl$

Scheme 4.

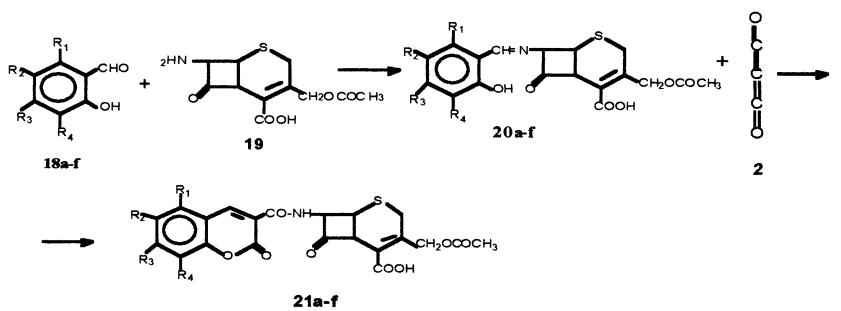


a: $R_1=R_2=R_3=H$
b: $R_1=R_2=H$; $R_3=C_6H_5$
c: $R_1=Cl$; $R_2=H$; $R_3=CH_2COOH$
d: $R_1=Cl$; $R_2=R_3=H$
e: $R_1=Cl$; $R_2=H$; $R_3=C_6H_5$
f: $R_1=R_2=Cl$; $R_3=H$
g: $R_1=Br$; $R_2=R_3=H$
h: $R_1=R_2=Br$; $R_3=H$

Scheme 5.



a: $R_1=R_2=R_4=H$; $R_3=OCF_3$
b: $R_1=R_3=H$; $R_2=R_4=OH$
c: $R_1=R_2=R_4=H$; $R_3=Br$
d: $R_1=R_3=Br$; $R_2=R_4=H$
e: $R_1=R_3=R_4=H$; $R_2=OCH_3$
f: $R_1=R_2=R_4=H$; $R_3=Cl$



a: $R_1=R_3=R_4=H$; $R_2=$ Br
b: $R_1=R_3=H$; $R_2=R_4=Br$
c: $R_1=R_3=R_4=H$; $R_2=Cl$
d: $R_1=R_3=H$; $R_2=R_4=Cl$
e: $R_1=R_2=R_4=H$; $R_3=OCH_3$
f: $R_1=R_3=OCH_3$; $R_2=R_4=H$

Scheme 6.

Table 5
MICs and MBCs of compounds **21a–f**

Comp.	MIC (μg/ml)			MBC (μg/ml)		
	S. aureus	*E. coli*	*P. aeruginosa*	*S. aureus*	*E. coli*	*P. aeruginosa*
21a	16	>100	>100	32	>100	>100
21b	64	>100	>100	>100	>100	>100
21c	>100	>100	>100	>100	>100	>100
21d	4	>100	>100	8	>100	>100
21e	64	>100	>100	64	>100	>100
21f	64	>100	>100	64	>100	>100

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