X-RAY CRYSTAL STRUCTURE DETERMINATION AS EFFICIENT TOOL FOR ELUCIDATION OF STRUCTURE OF MULTIFUNCTIONAL HETEROAROMATICS

By

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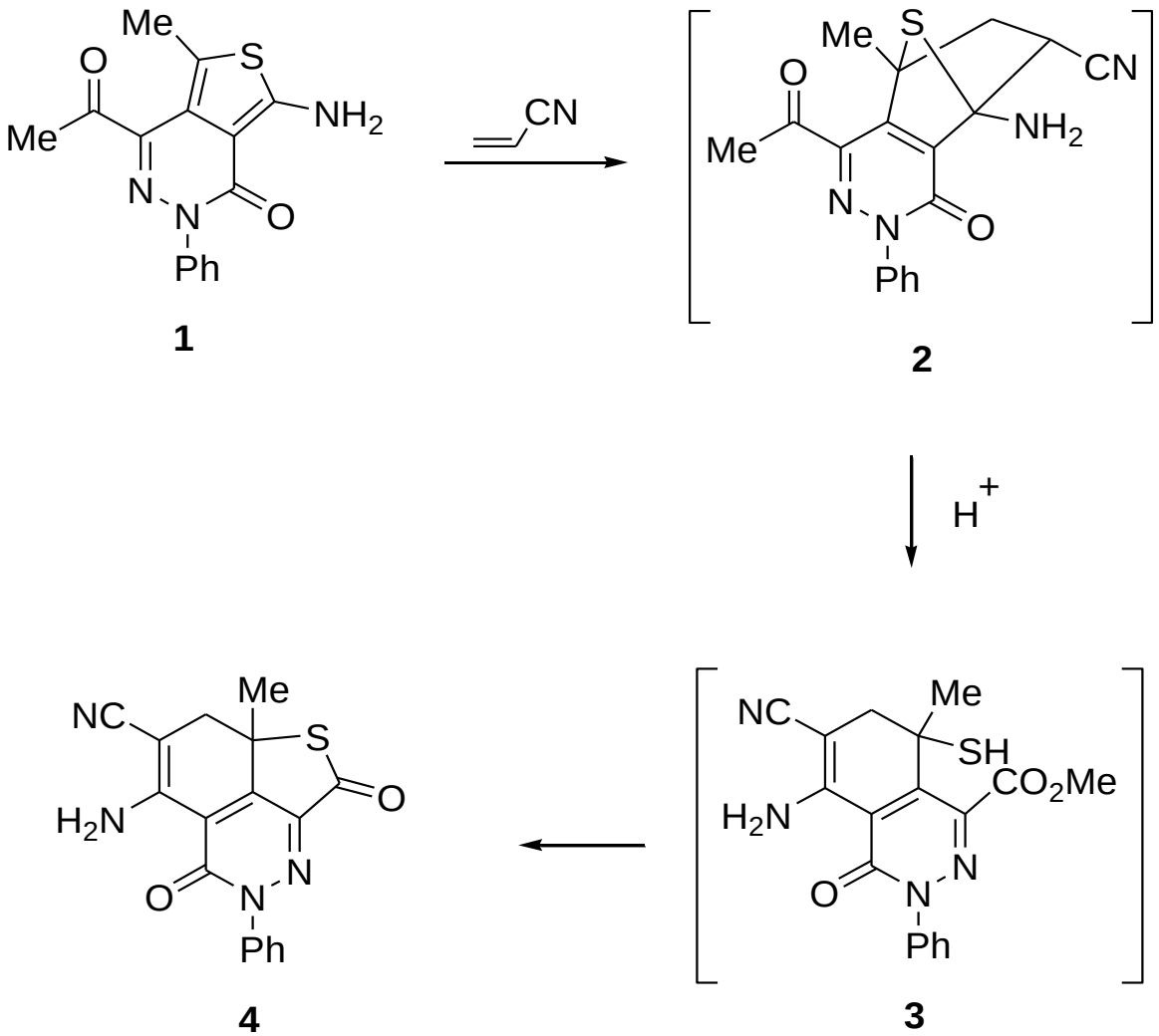
Introduction

- Today I have completed fifty years with organic chemistry. I have devoted almost all my efforts during this period to develop syntheses of multifunctional heterocycles. Already we have till date published 415 papers that are cited 6300 times or 4000 times excluding self-citations. Our *h*-index is now 36 and average citation per paper is now hitting 16 with 140 average citations per year.

- Our results of the 1970's and 1980's has confirmed structures through the work of Chinese authors as we did not have by time facility for X-ray crystal structure determination or even experience with preparing crystals for X-ray.
- Our first ever published X-ray was performed in Madrid as *prof. J. Elguero* could crystallize for us the sample we submitted and obtained X-ray structure that of course led us to revise a conclusion we have reported by that time.


Me
O
S
NH2
Me
N
N
O
Ph
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CN
Me
S
CN
O
NH2
Me
N
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Ph
2
H+
NC
Me
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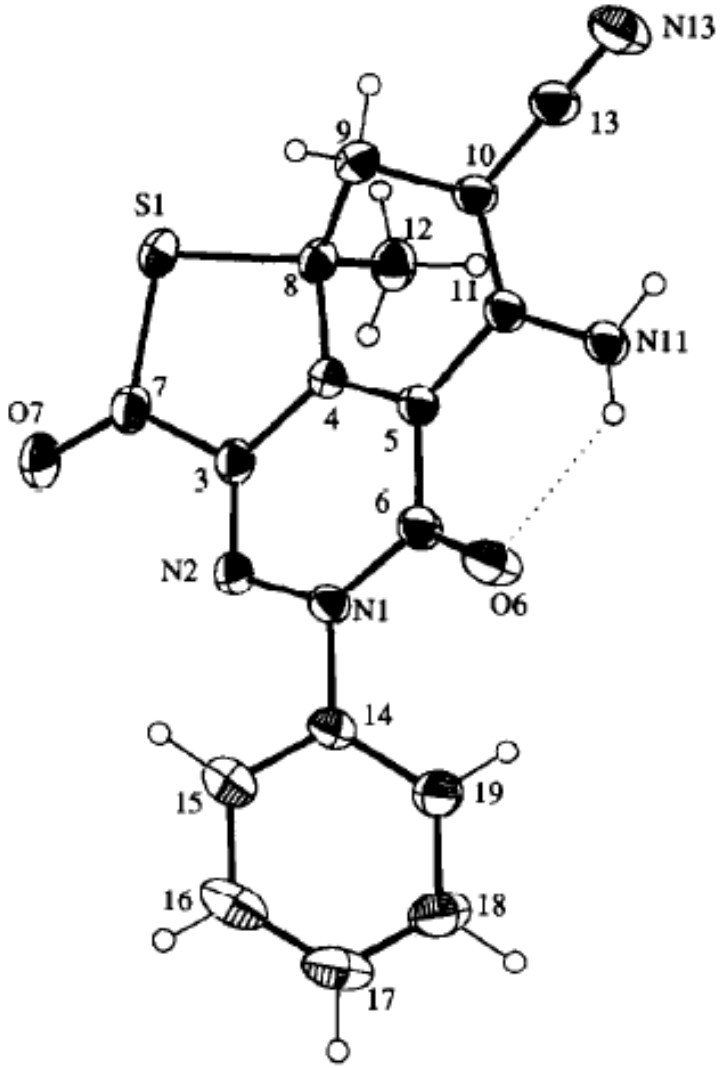
Me
S
O
H2N
N
O
N
Ph
4



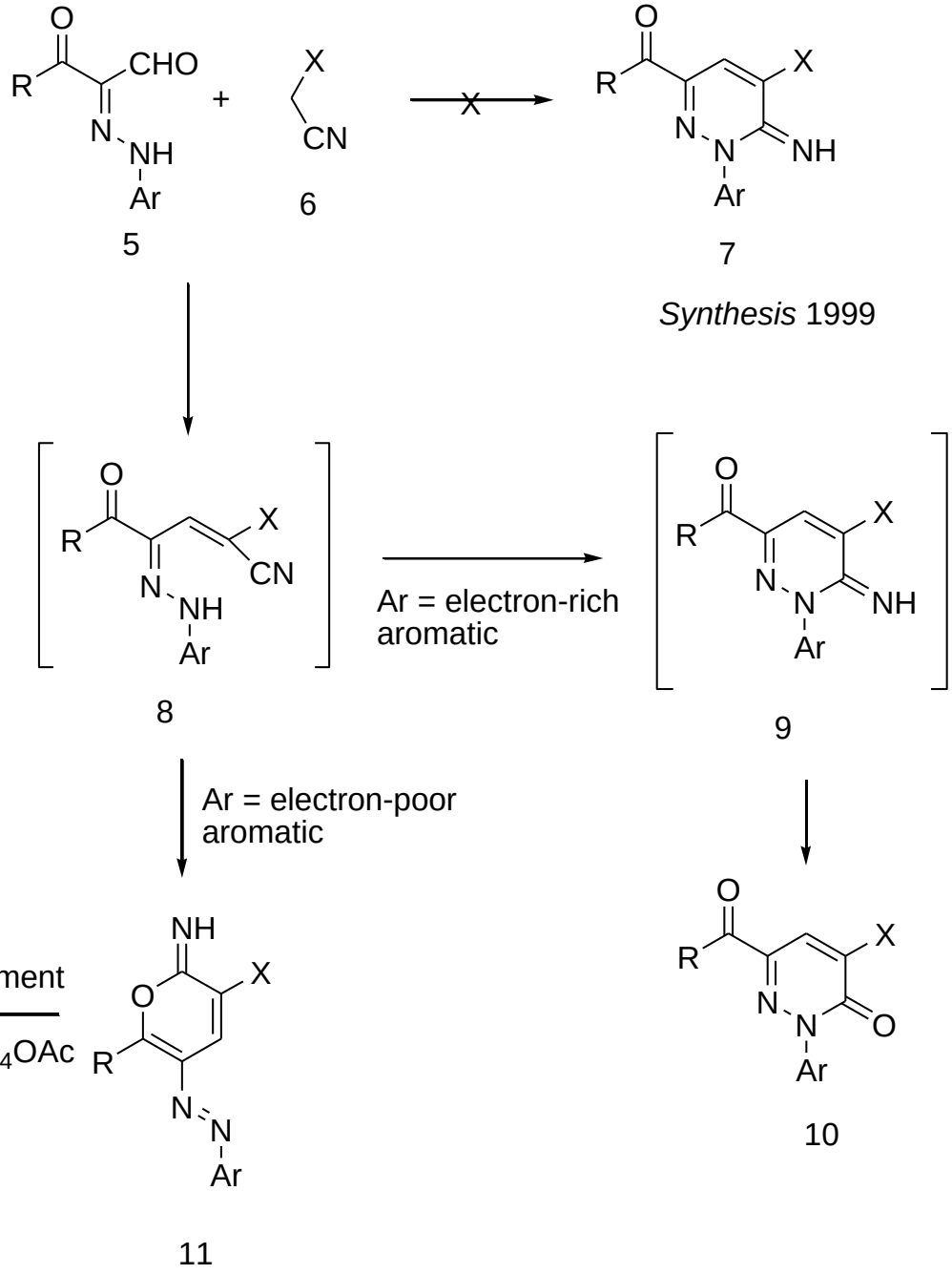
X-Ray crystal structure of compound 4

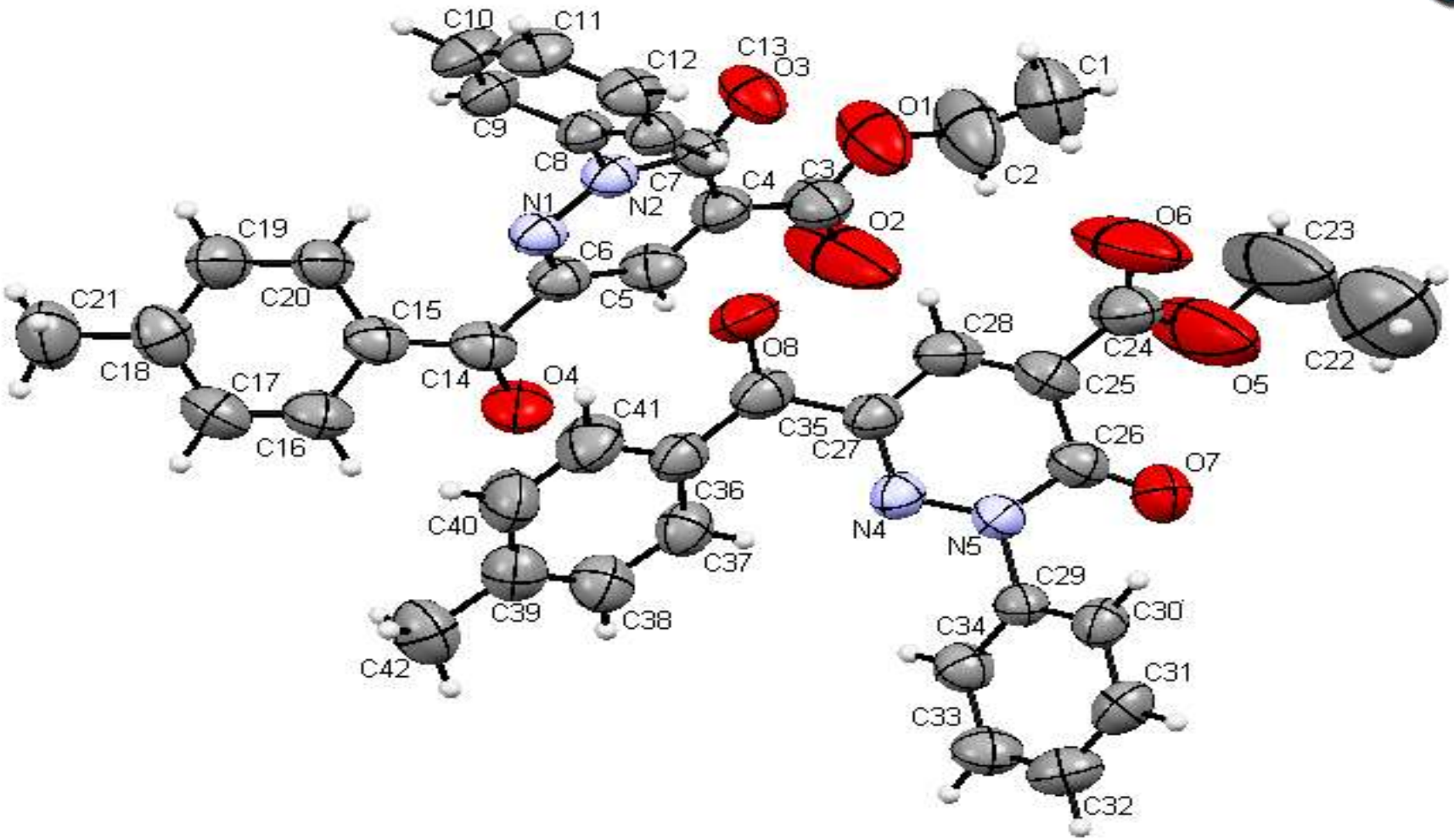
- This finding led us to insist on having X-ray crystal structure determination to confirm structure especially in the light of some '*opportunistic chemists reports'* that from time to time claimed that products we published have in fact alternate isomeric structures.
- In fact these reports led me to resign my job at Cairo University and shift to Kuwait University where I could repeat all the past providing X-ray structure determination for every crystallizable product we could obtain.

- The results of my carrier with chemistry will be published the next month in *Advances in Heterocyclic Chemistry volume 109*. Thanks to Prof. *A. R. Katritzky* who proposed me to do that.
- In this talk, I will only thus tell about X-ray crystal structure determination that enabled confirming a variety of new molecular rearrangements.

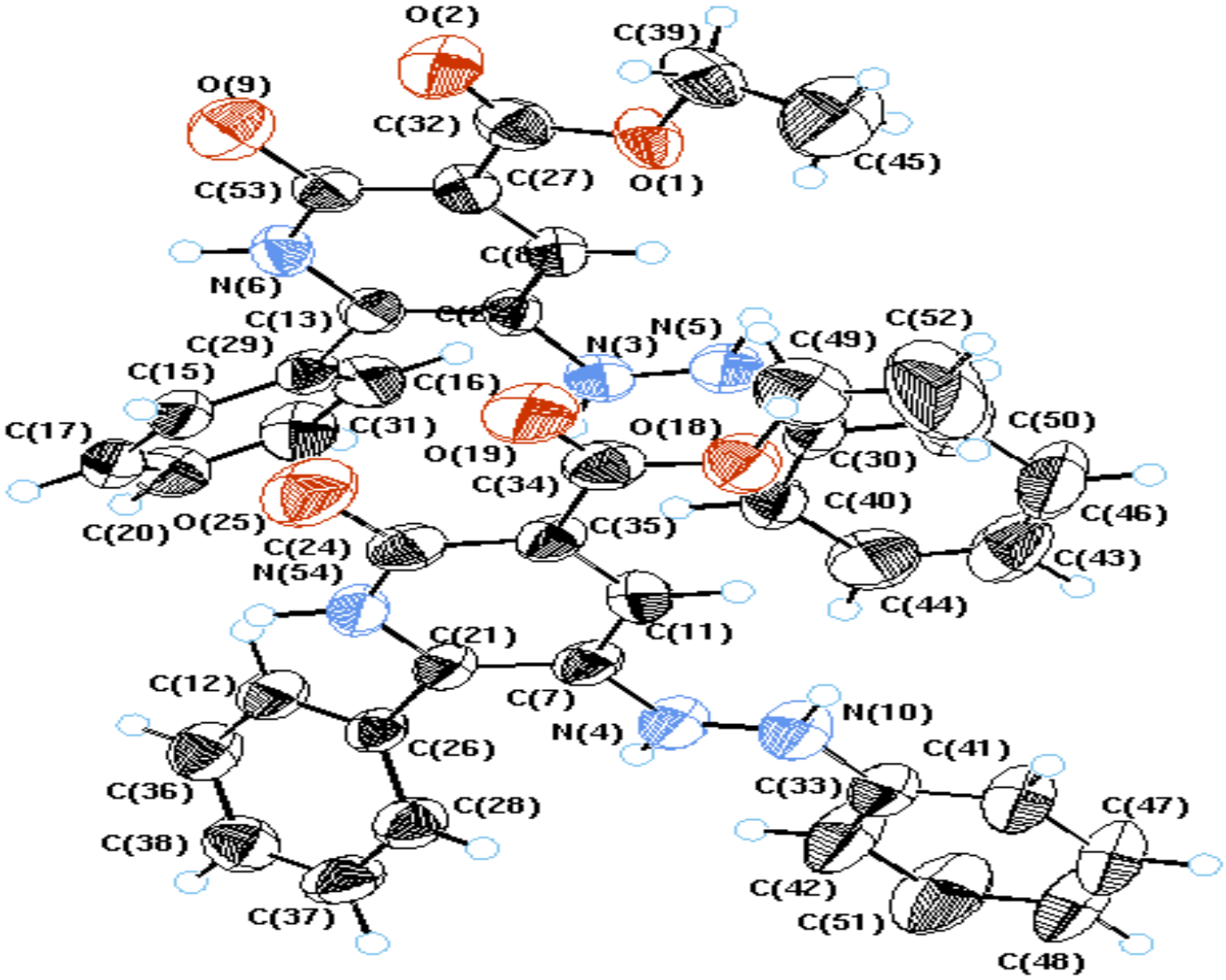
The Reaction of Arylhydrazonals with Active Methylene Nitriles: Pyridazinones or Arylazonicotinates

- In 1999 we have reported that compound **5** condenses with active methylene nitriles to yield **7**. However I suspected the possible stability of imine **7** as I believed that such imines are difficult to isolate and if formed, in contrast to plenty of reports from the third world, they either hydrolyze to the corresponding ones or undergo *Dimroth rearrangement* as I will show later.


5
6
7
Synthesis 1999
8
Ar = electron-rich aromatic
9
Ar = electron-poor aromatic
10
11
Dimroth rearrngement
AcOH/NH4OAc
12a,b

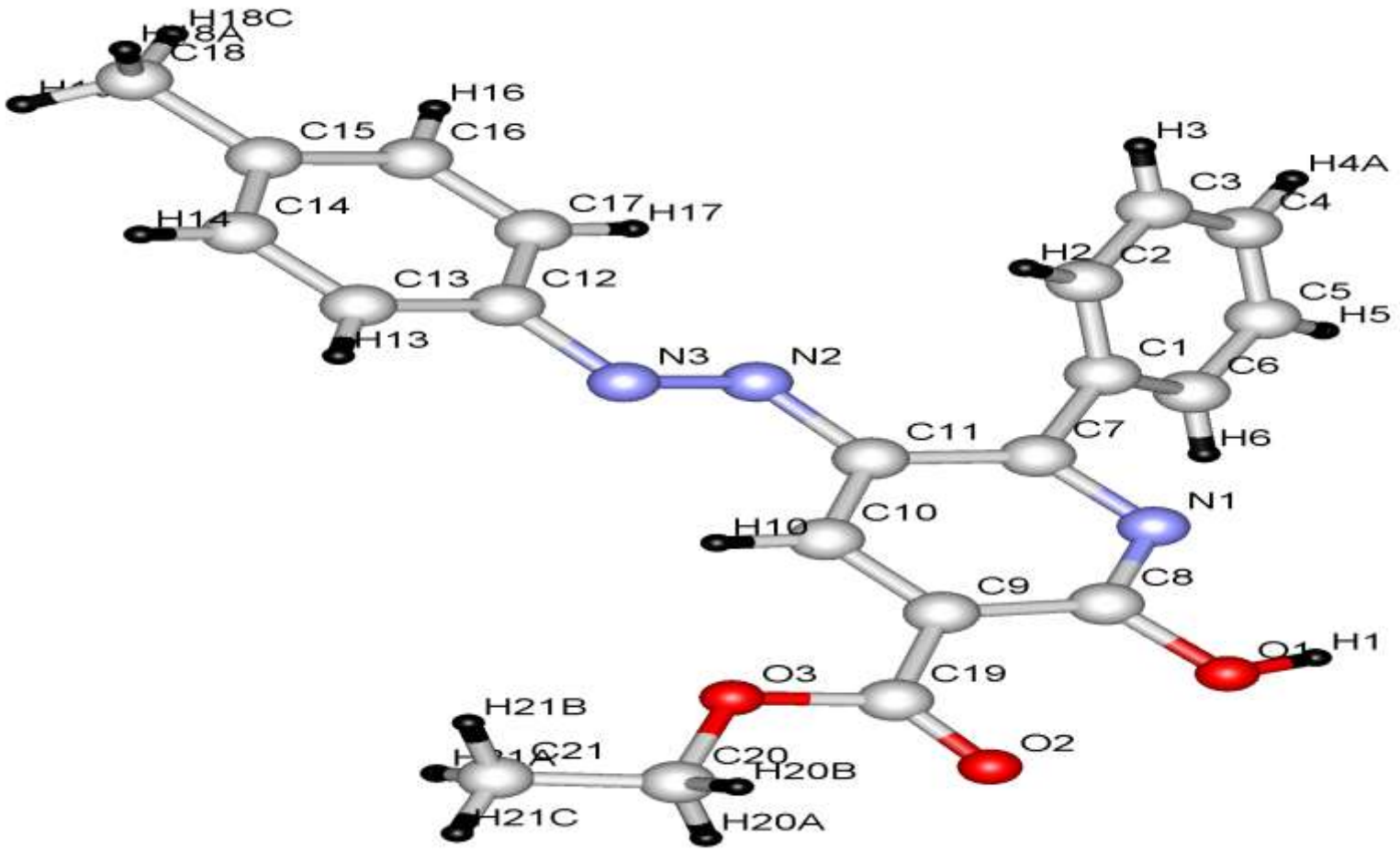


X-Ray crystal structure of compound 10, Ar = Ph, X = CO_2Et, R = $CH_3C_6H_5$-(*p*)



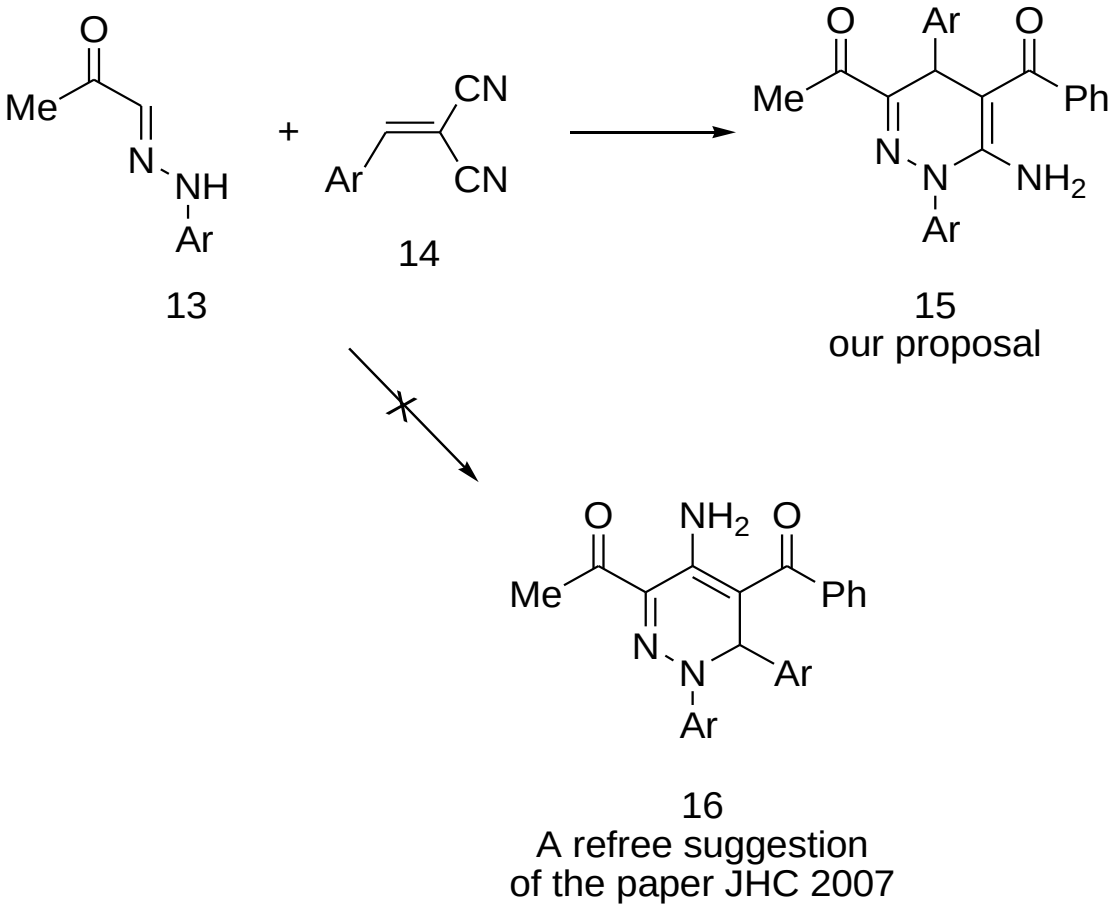
X-Ray crystal structure of compound 12a, R = Ar = Ph & X = CO_2Et

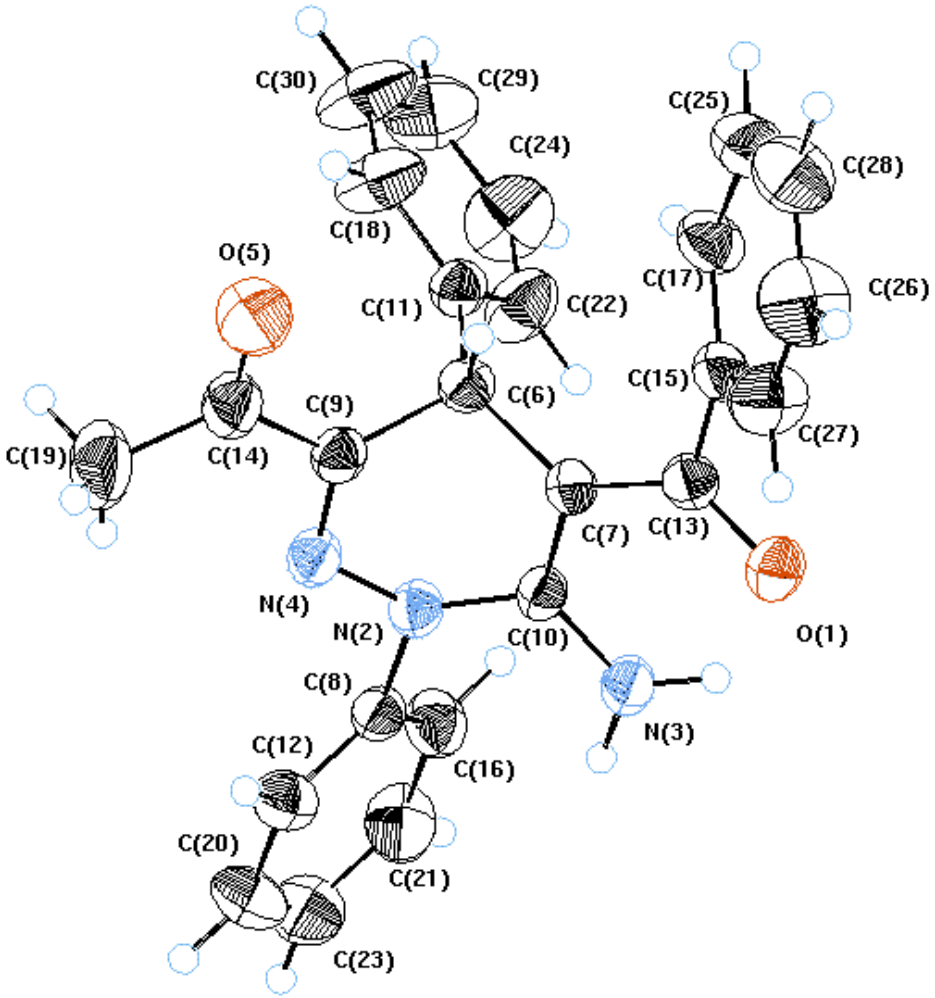
X-Ray crystal structure of compound 12b



Formation of 6-amino-4-substituted-1,6-dihydropyridazine

Addition of 13 to 14 was proposed to yield 15 but a referee suggested alternately 16. We confirmed the structure by X-ray.

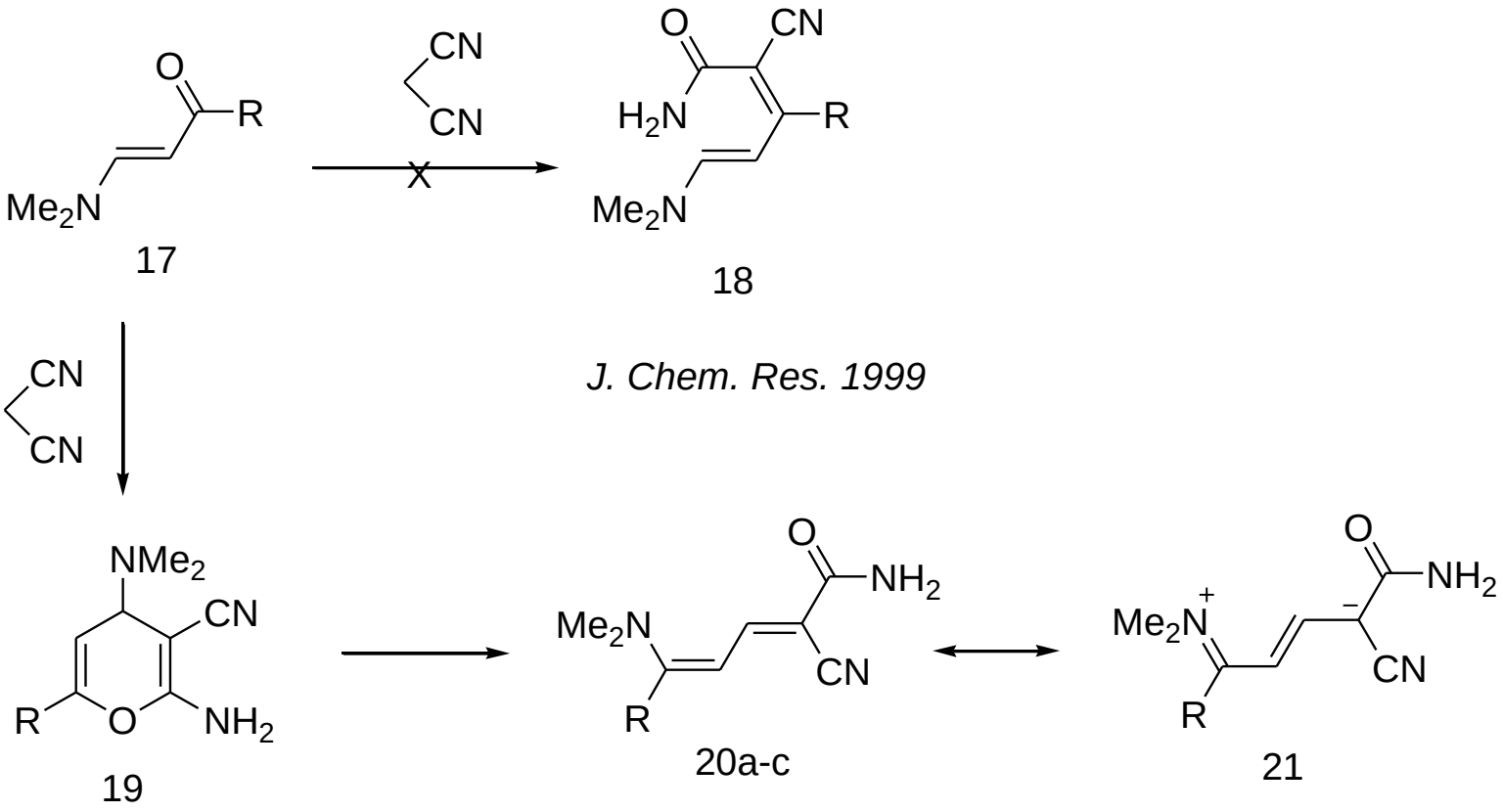




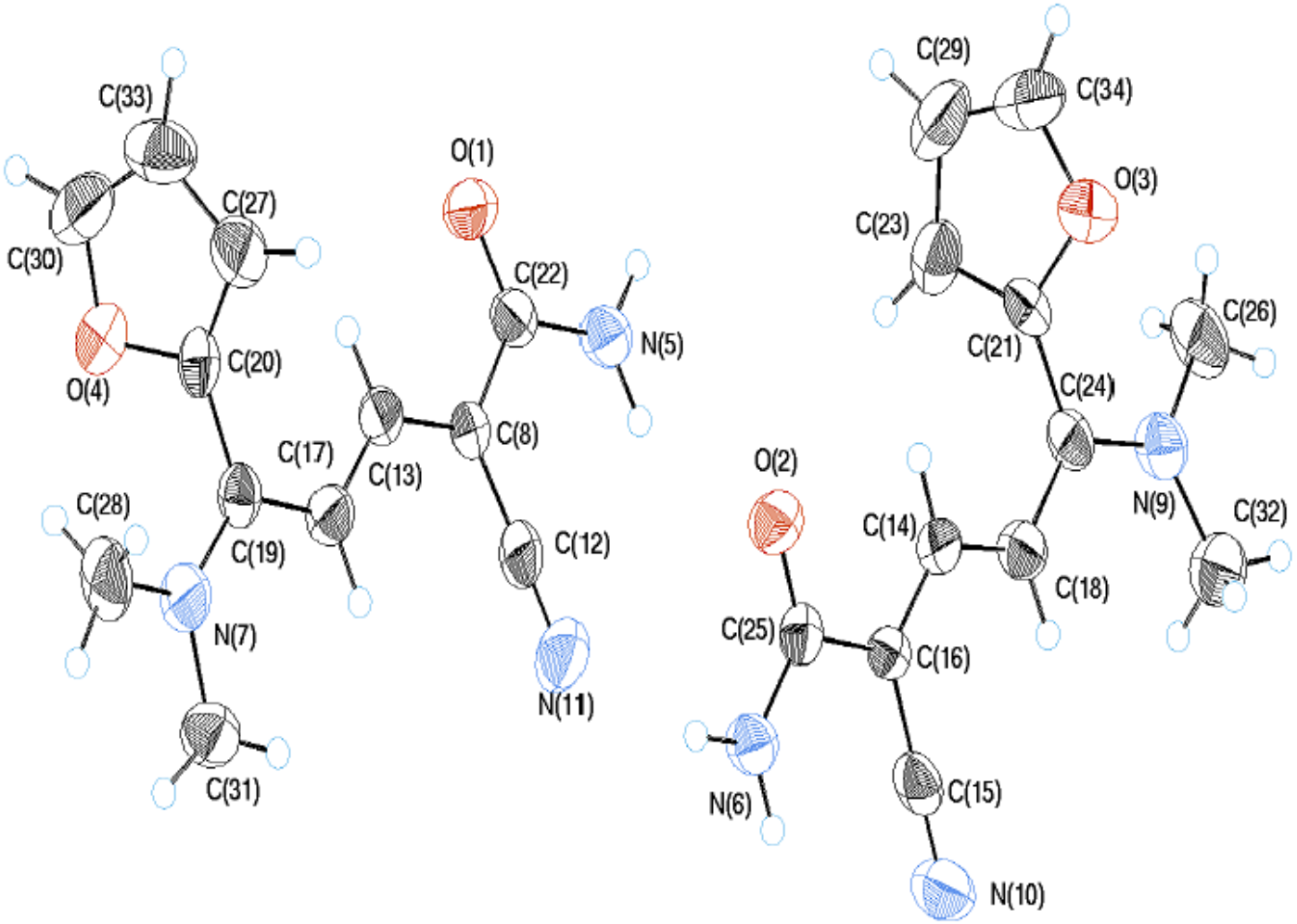
X-Ray crystal structure of compound 15

Formation of enedienes

We initially reported that 17 reacted with malononitrile afforded 18 but reinvestigation through 15N-NMR and X-ray confirmed the formation of 20



The correct strycture
Arkivoc 2009, Molecules 2008

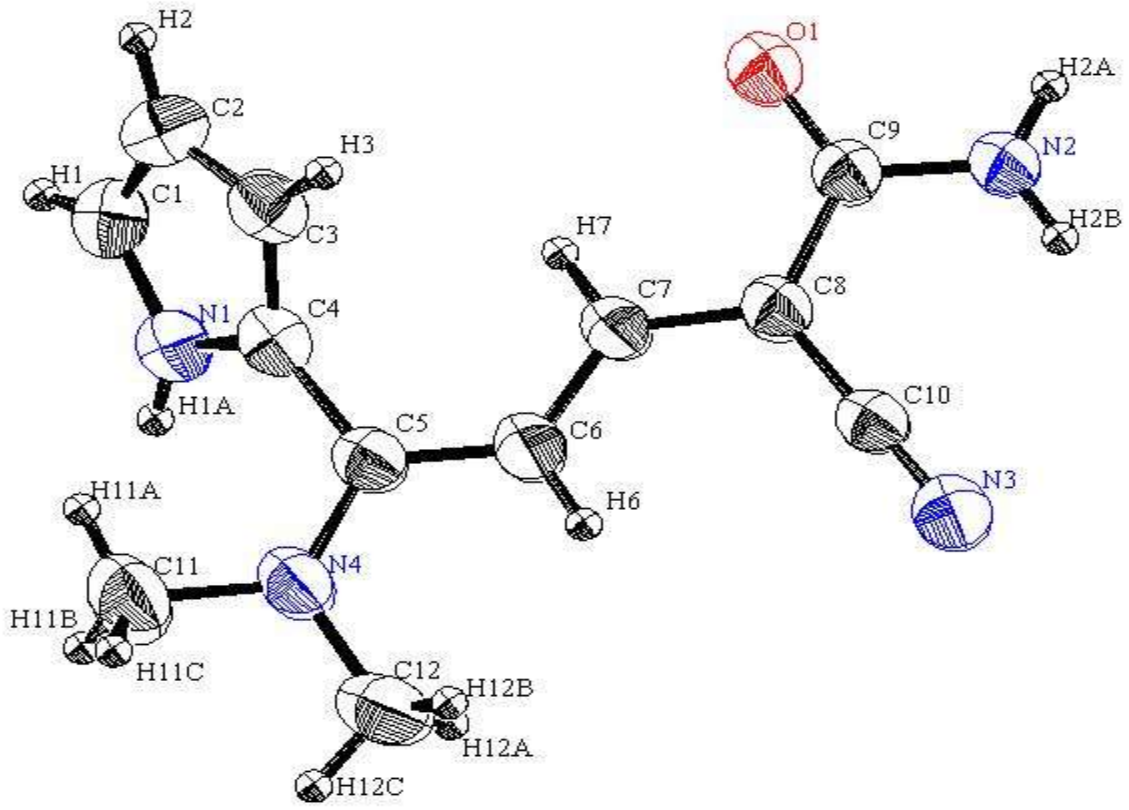


X-Ray crystal structure of compound 20a

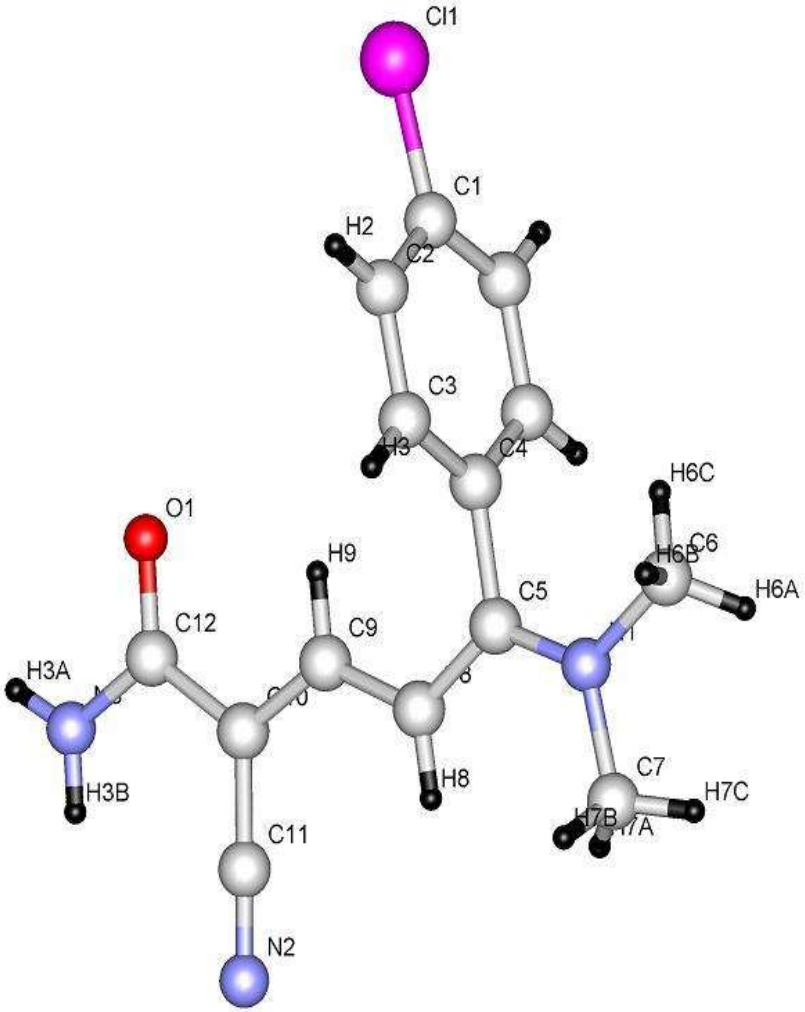
Bond lengths		Bond angles	
Atoms numbers	Geometric parameters (Å,°)	Atoms numbers	Geometric parameters (Å,°)
N7—C19	1.350 (5)	C19—N7—C28	122.6 (3)
N7—C28	1.469 (5)	C19—N7—C31	121.4 (3)
N7—C31	1.451 (5)	C28—N7—C31	115.5 (3)
C8—C13	1.372 (5)	C12—C8—C13	119.8 (3)
C8—C22	1.467 (5)	C12—C8—C22	119.8 (3)
C13—C17	1.406 (5)	C18—C8—C22	120.3 (3)
C17—C19	1.377 (5)	C8—C13—C17	126.3 (3)
		C13—C17—C19	124.2 (3)
		N7—C19—C17	122.2 (3)
		N7—C19—C20	117.0 (3)
		C17—C19—C20	120.8 (3)

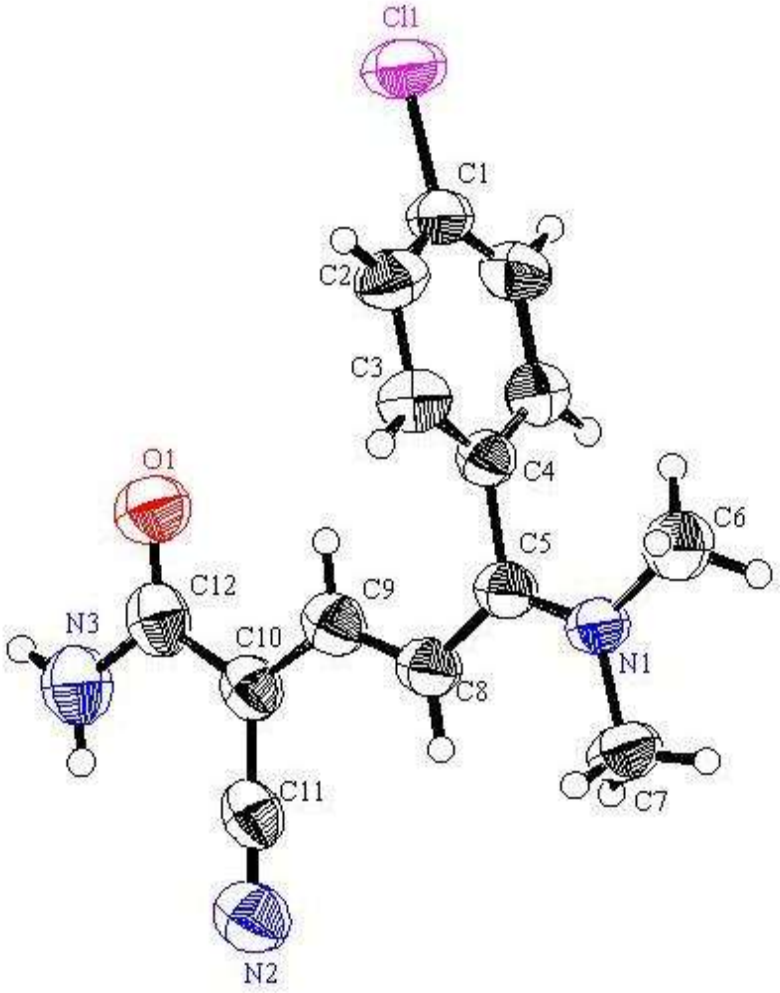
Bond lengths and angles point to existence of lone pair delocalization.

X-Ray crystal structure of compound 20b



X-Ray crystal structure of compound 20c

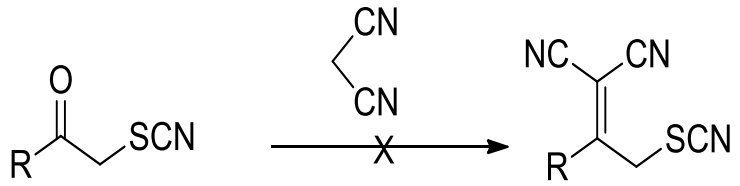




- As usual, some '*opportunistic authors'* have published the same conclusion after two years of publishing *Molecules* paper ignoring our reports.

Had the following reaction ever occurred?

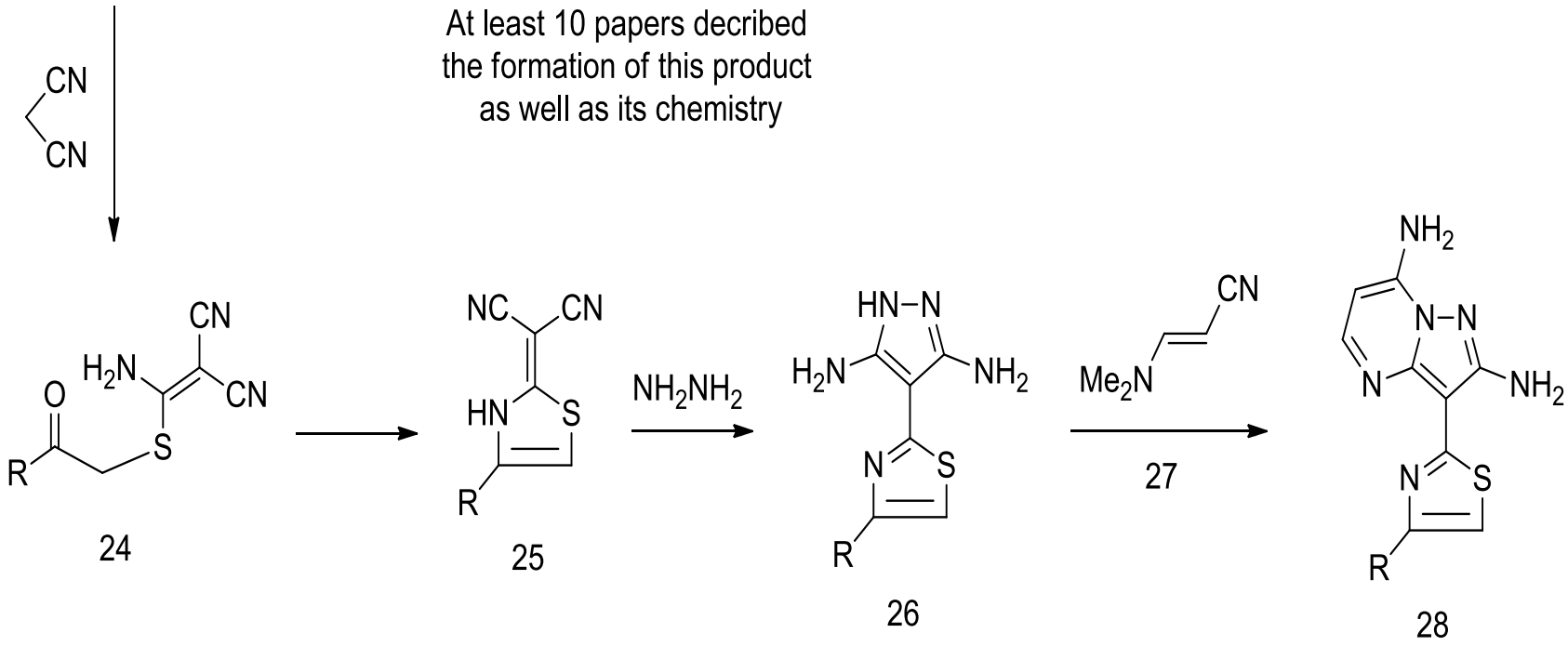
The conversion of 22 into 23 has been reported more than ten times in literature by the same group. It is accepted to come to wrong conclusion once but ten times despite existence of a patent for otherwise is strange?. We confirmed however structure indirectly by X-ray of 28



22

23

At least 10 papers decribed the formation of this product as well as its chemistry



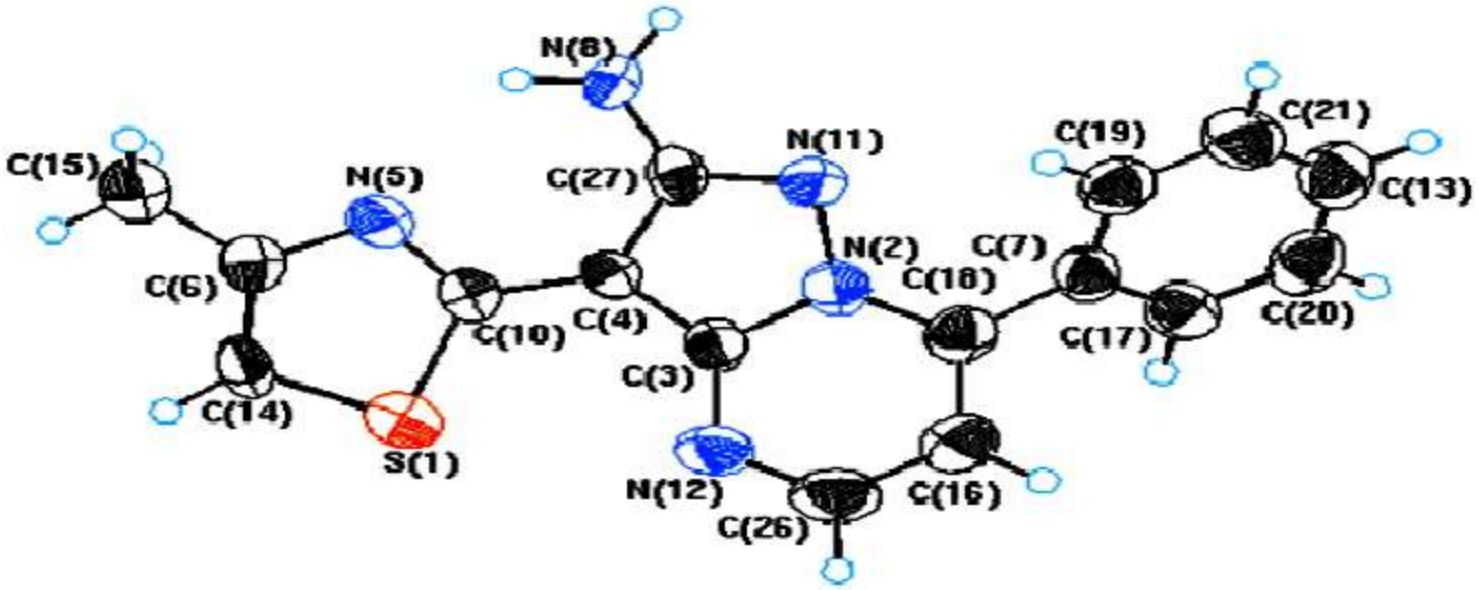
24

25

26

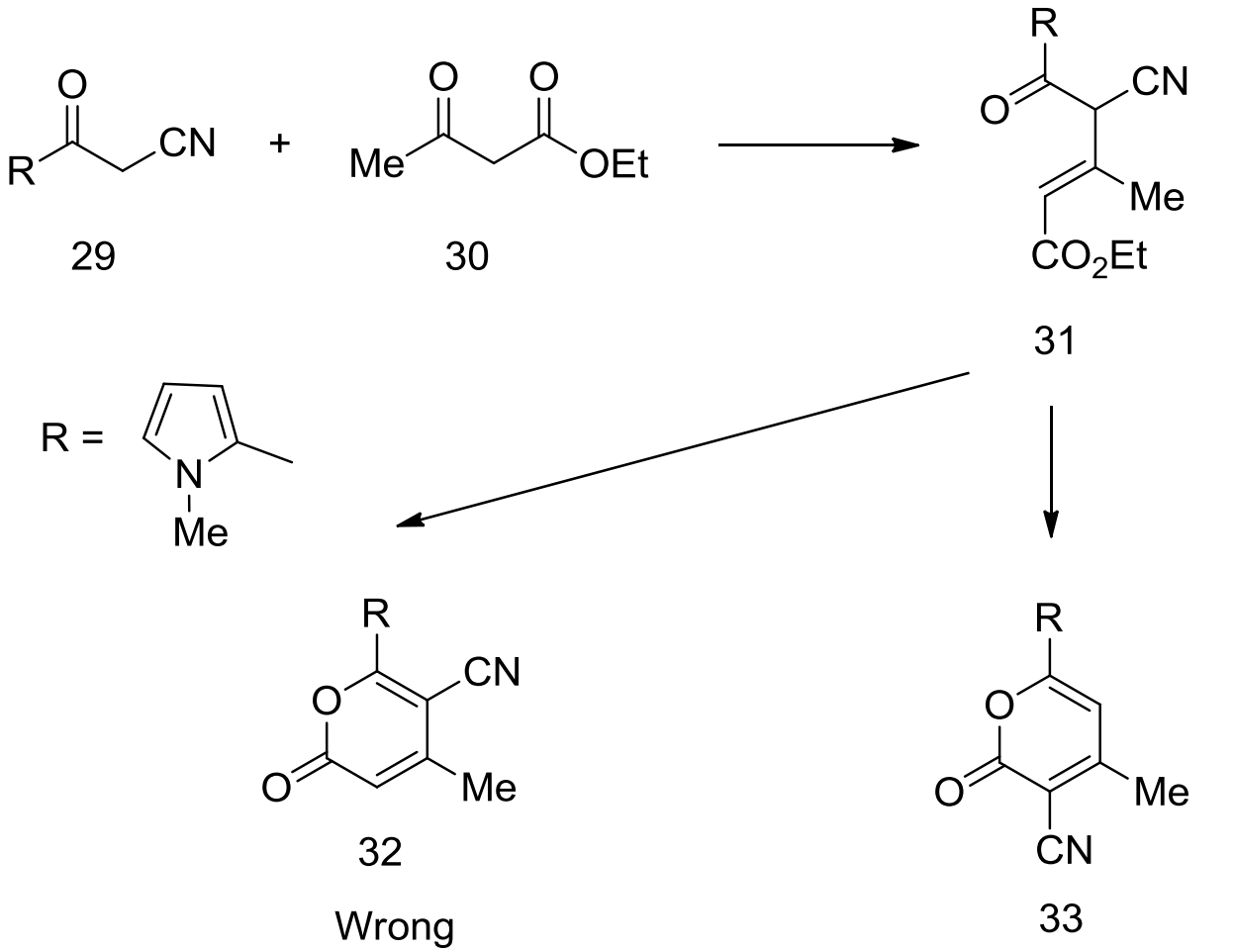
27

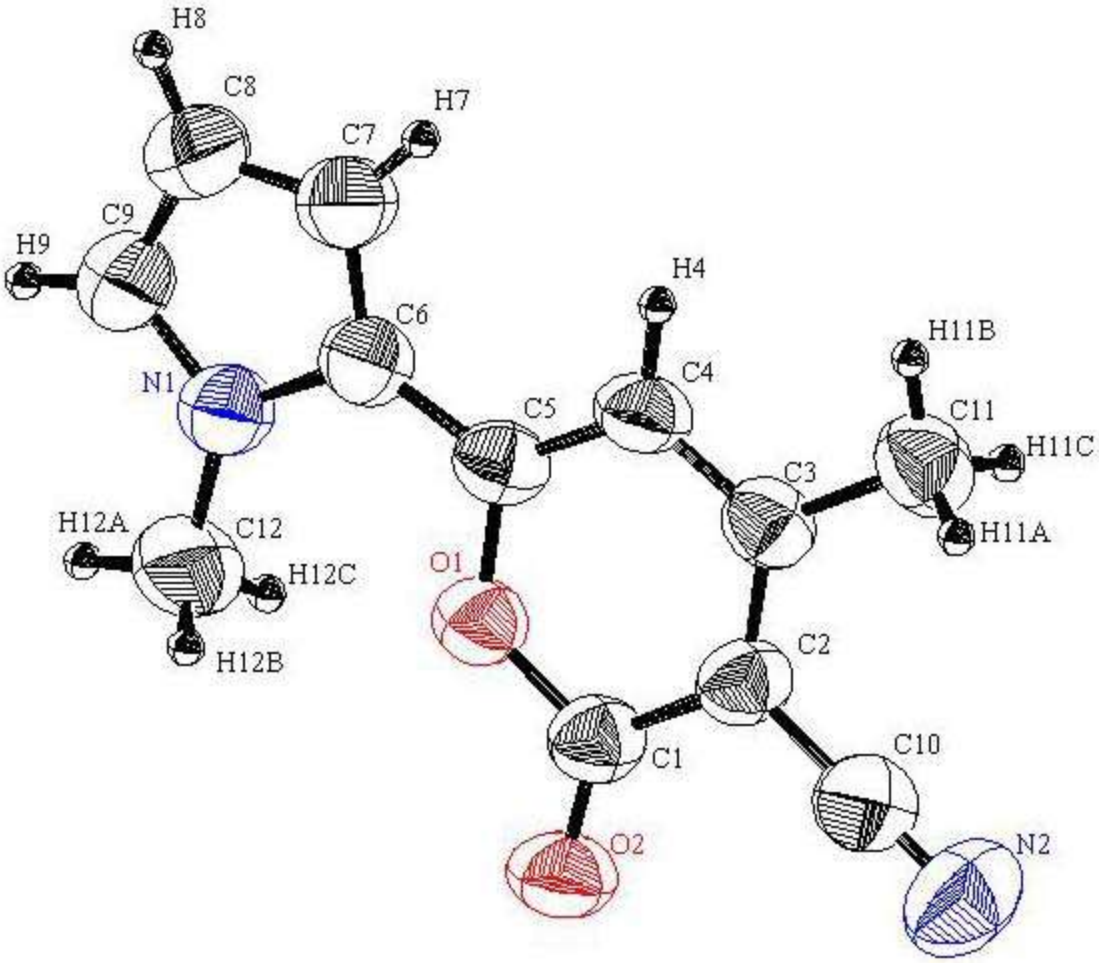
28



X-Ray crystal structure of compound 28

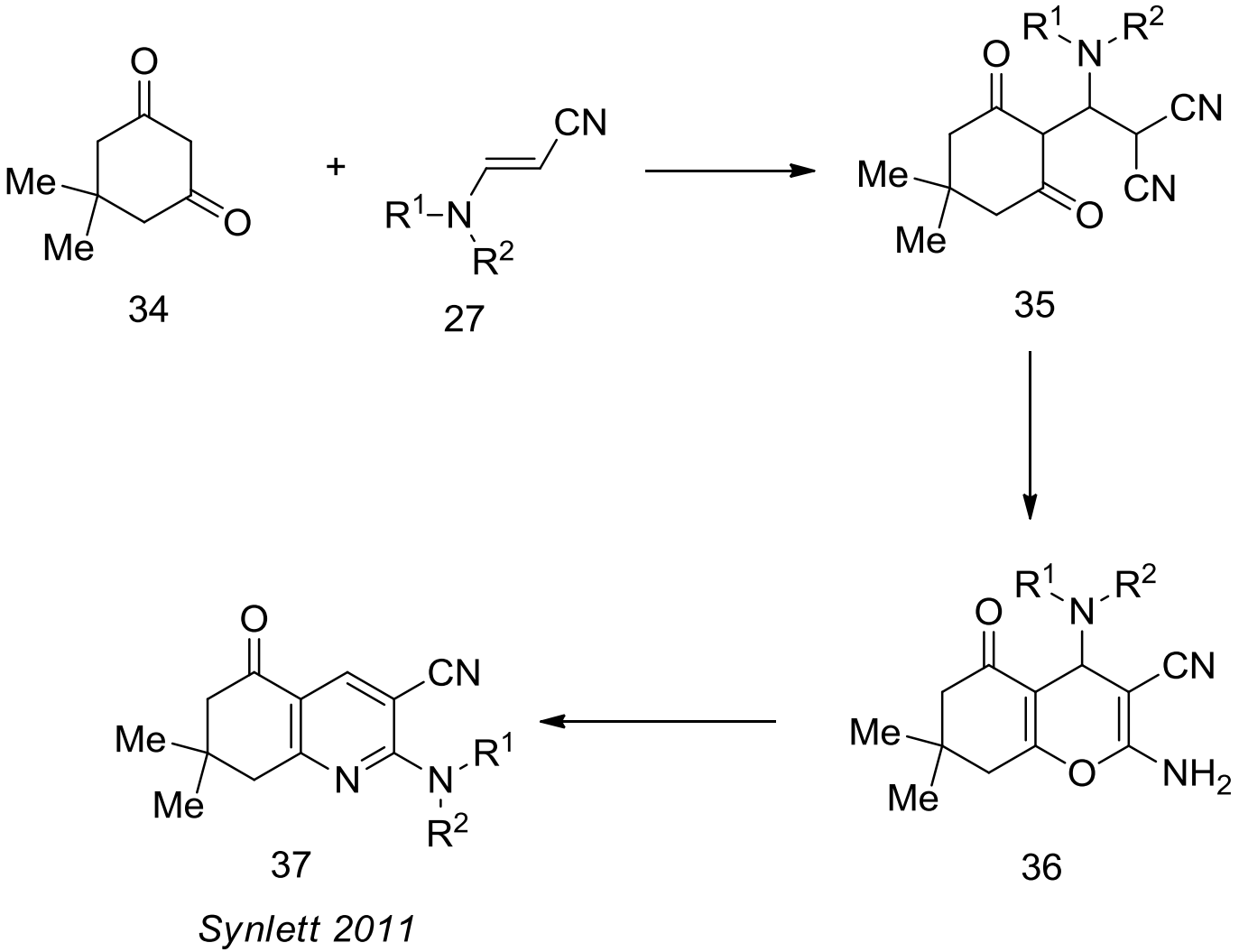
The reaction of 3-oxoalkane nitriles with β-ketoesters.



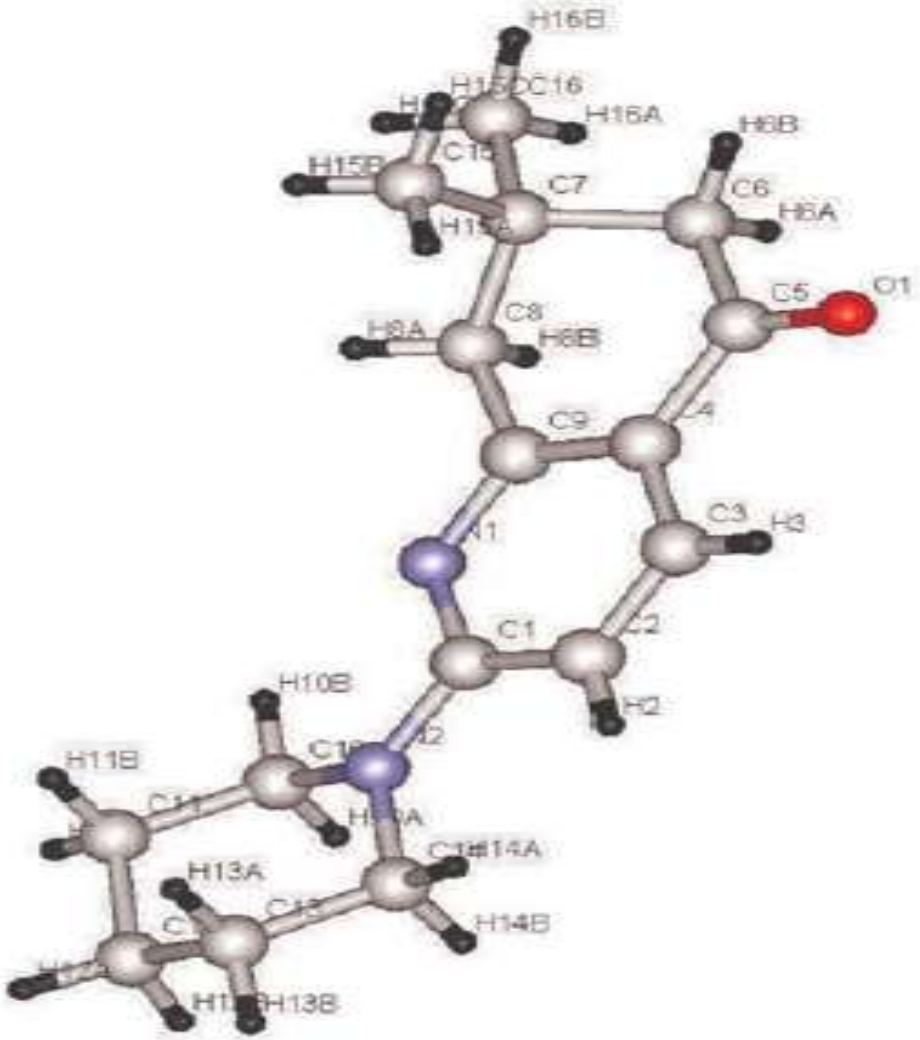


- **X-Ray crystal structure of compound 33**

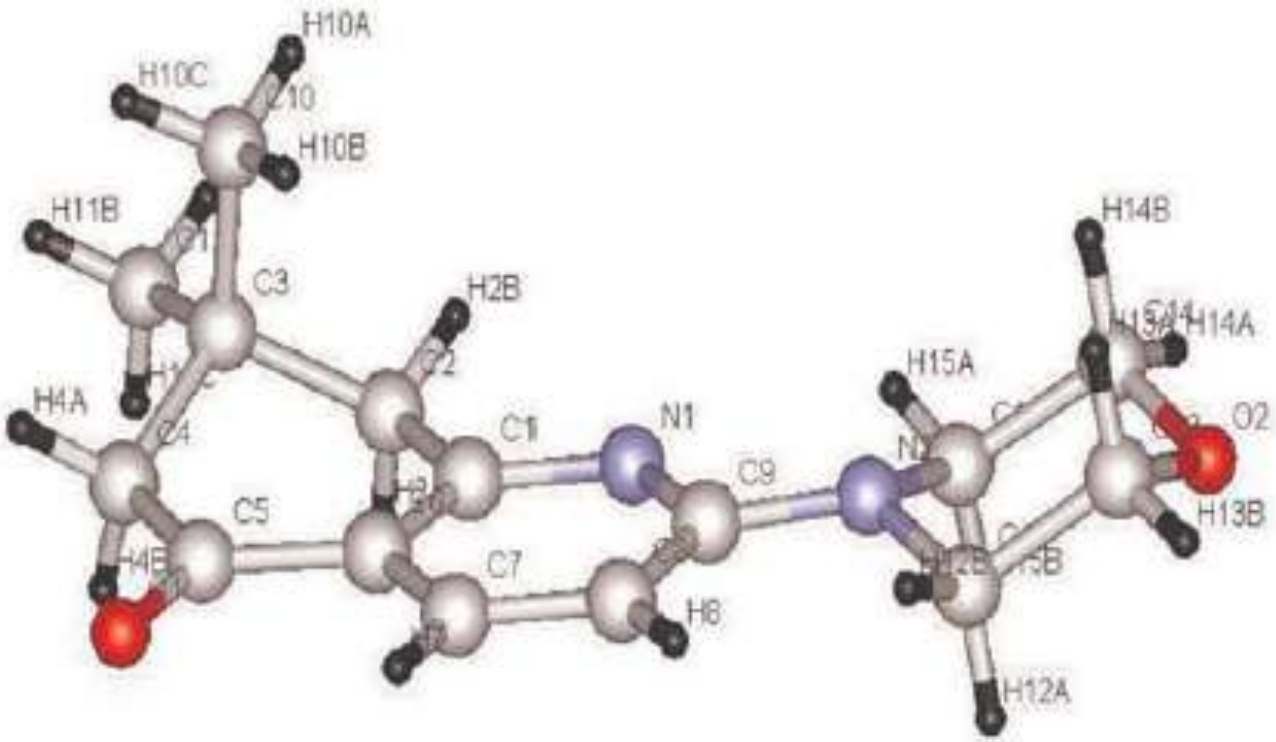
Unexpected formation of 2-dialkylaminopyridines



Synlett 2011

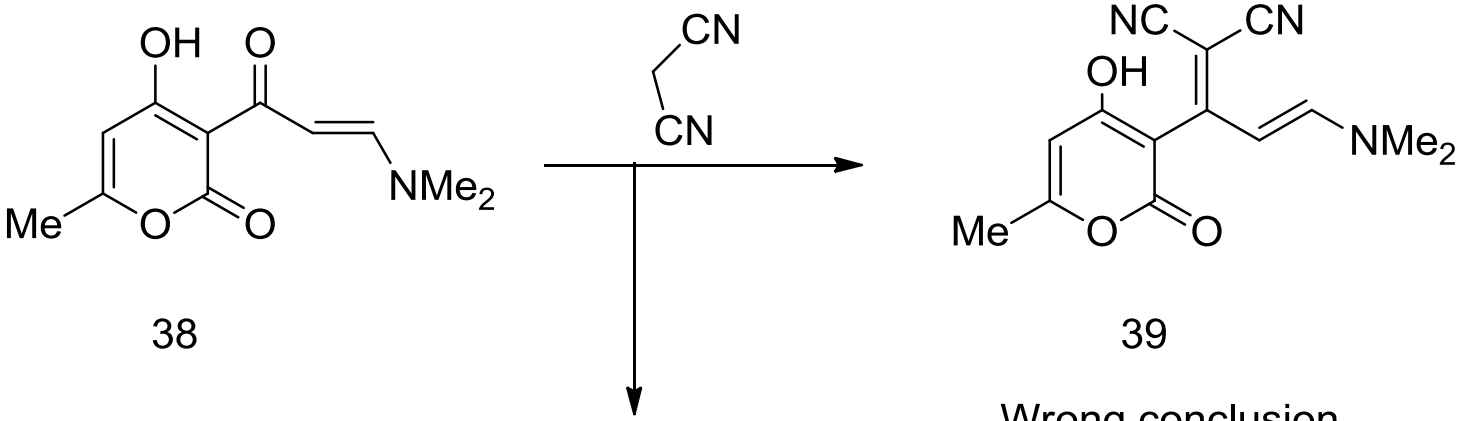


X-Ray crystal structure of compound 37, R^1-R^2 = $(CH_2)_5$



- **X-ray crystal structure of compound 37,** R^1-R^2 = $(CH_2)_2O(CH_2)_2$

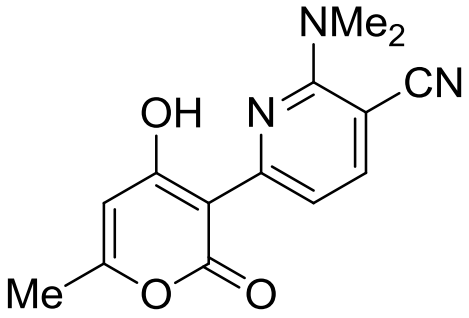
How about literature?



38

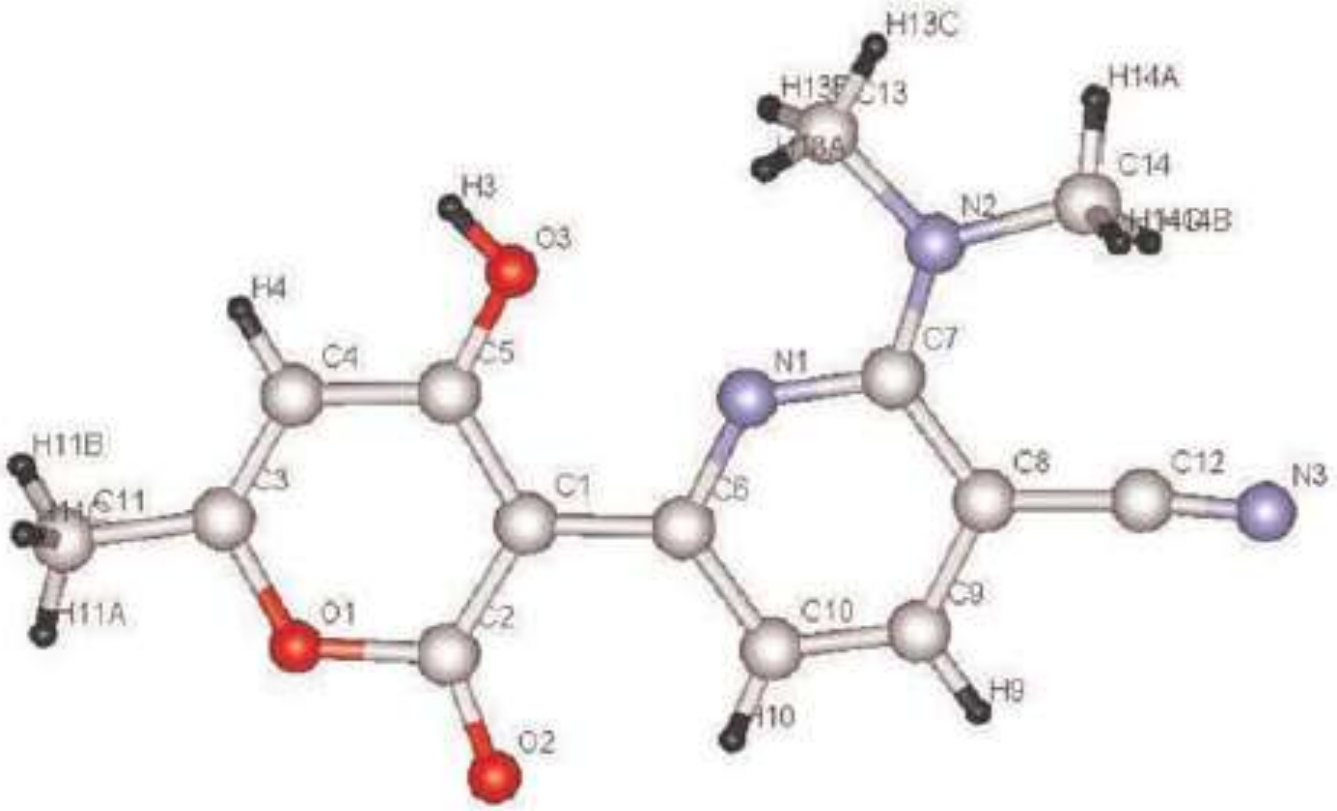
39

Wrong conclusion



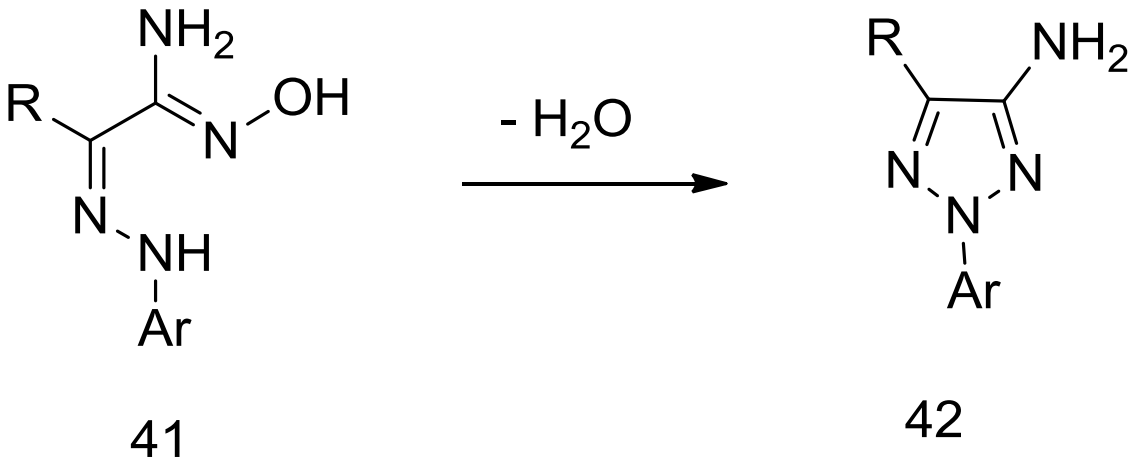
40

Synlett 2011



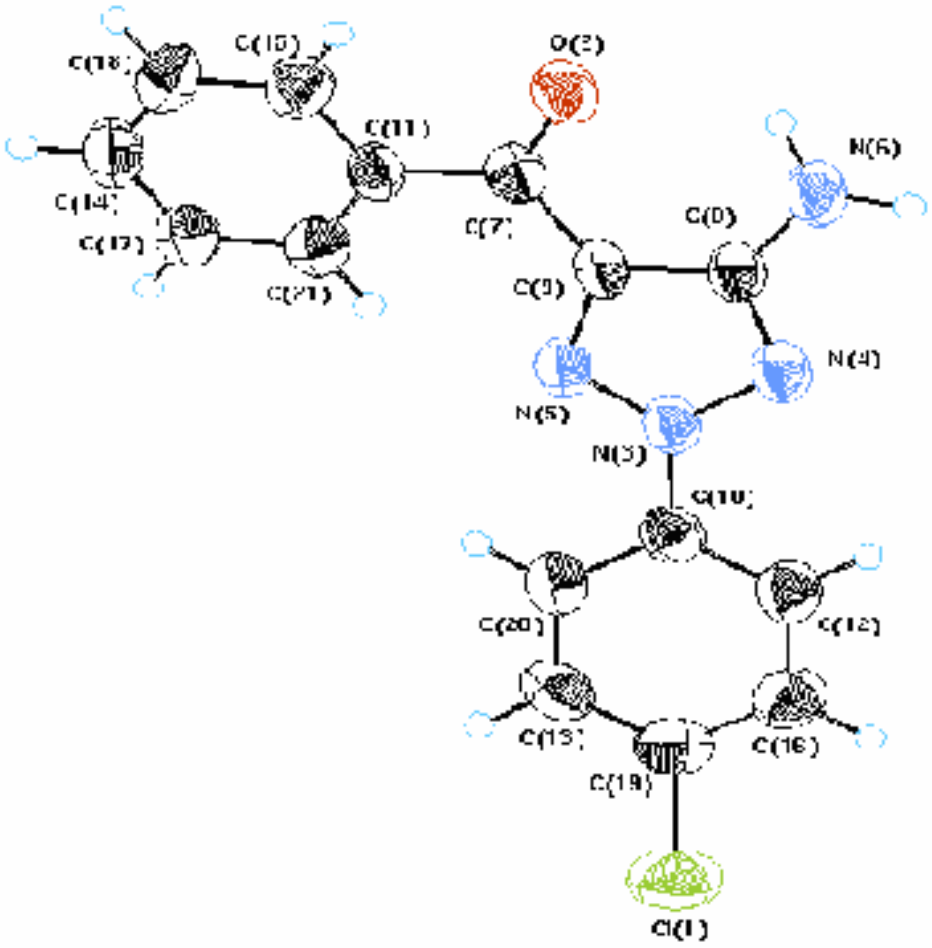
X-Ray crystal structure of compound 40

A rare Tiemann rearrangement

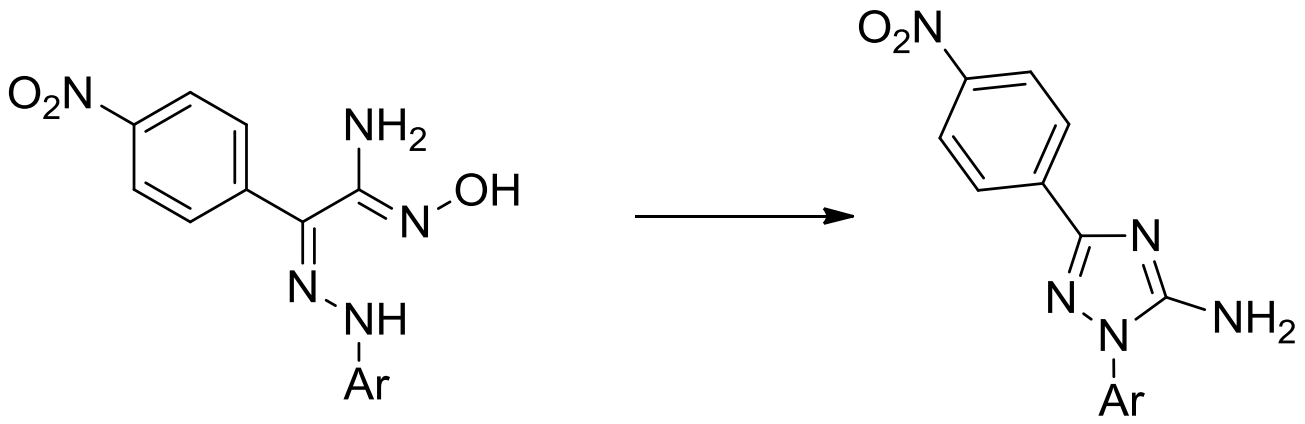


41 42

Confirmed by the X-ray of 42

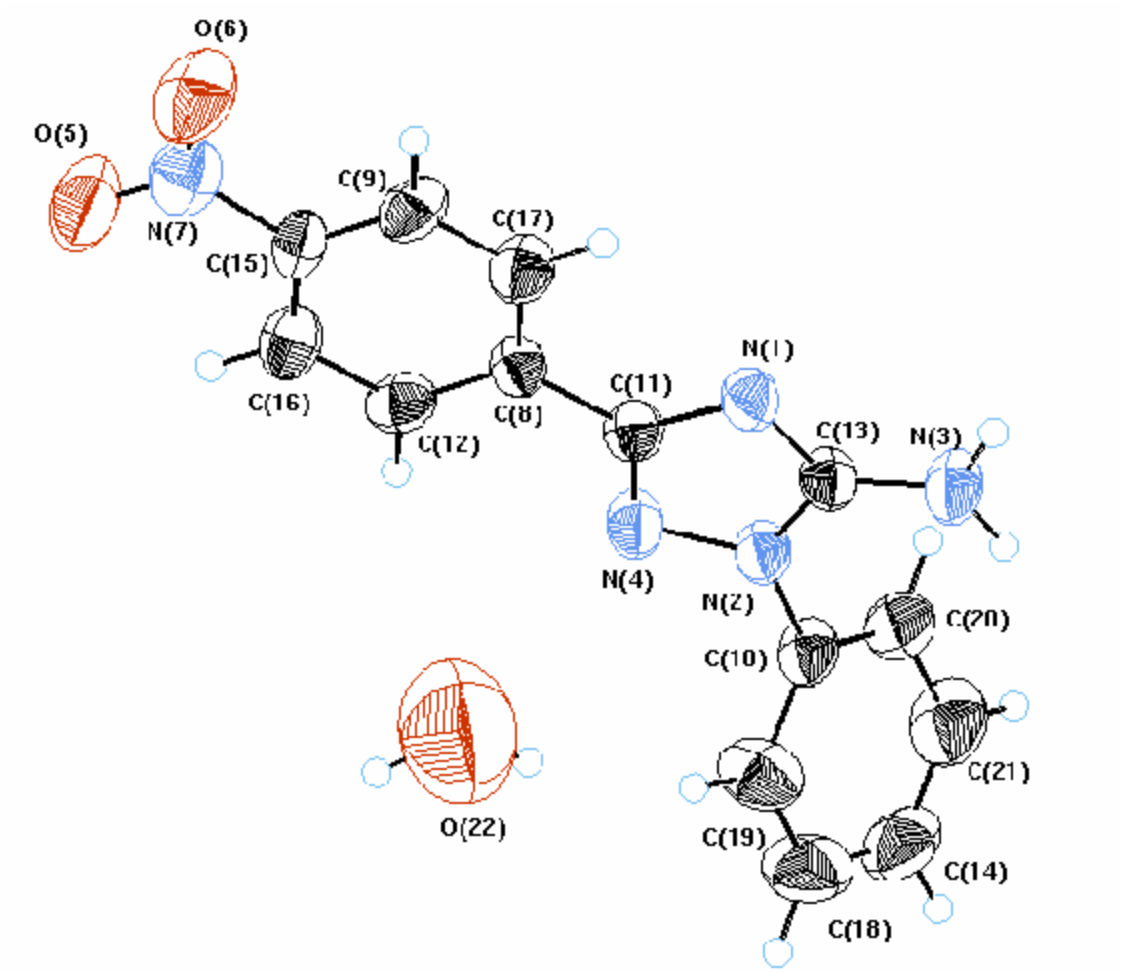


X-Ray crystal structure of compound 42

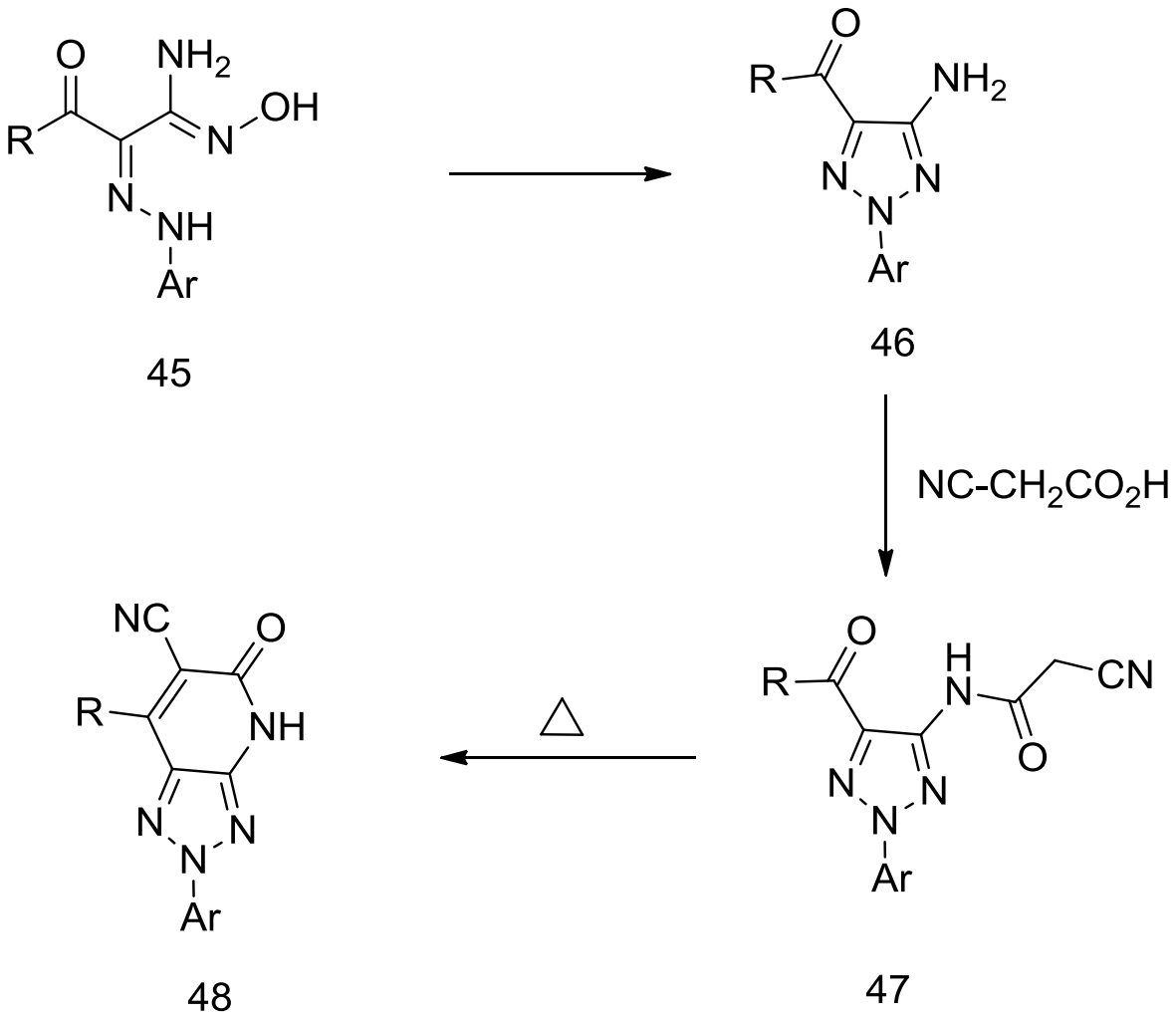


43 44

Confirmed by the X-ray of 44



X-Ray crystal structure of compound 44


O
NH2
R
OH
N
N
NH
Ar
45
O
R
NH2
N
N
N
Ar
46
NC-CH2CO2H
NC
O
R
NH
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Ar
48
△
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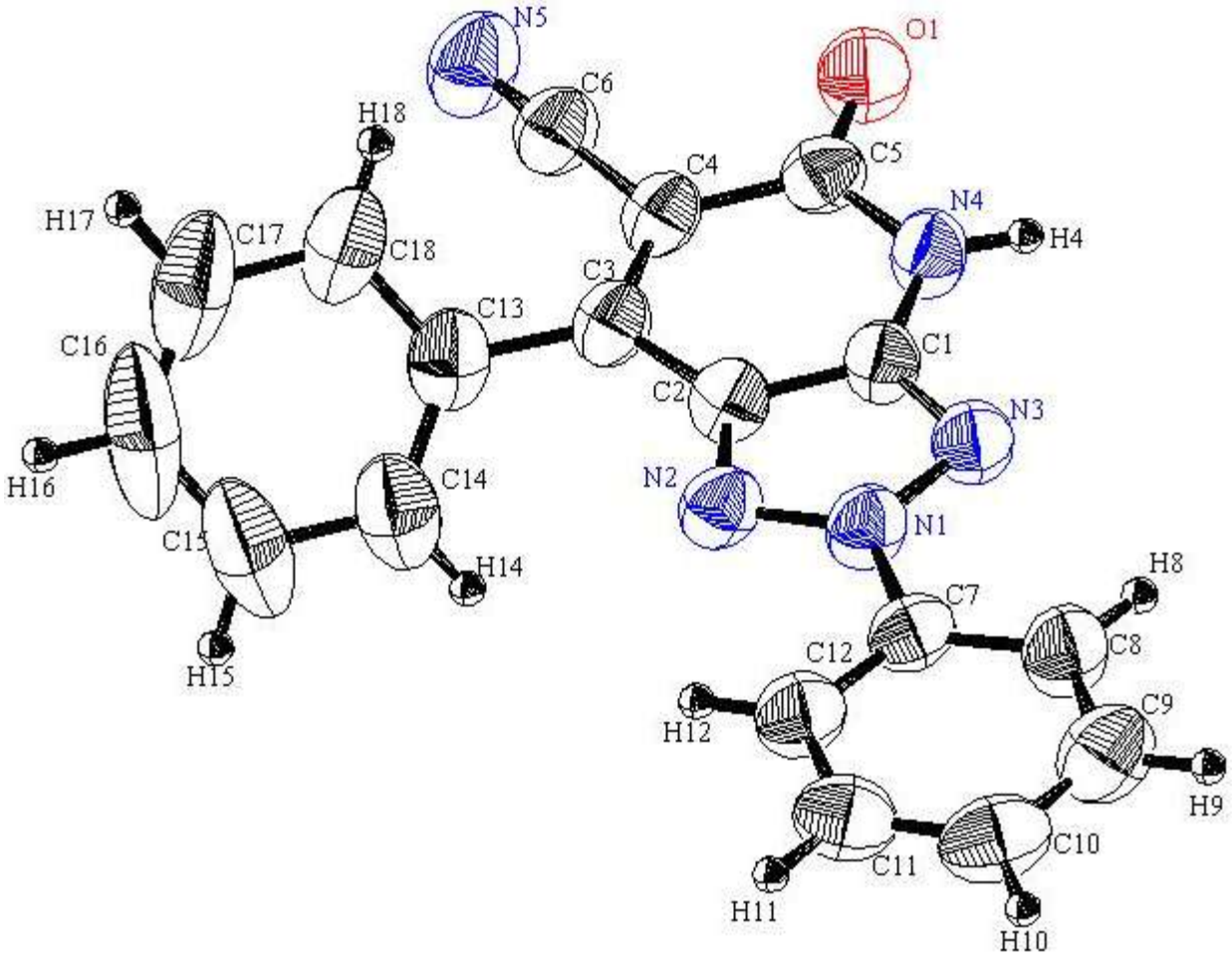
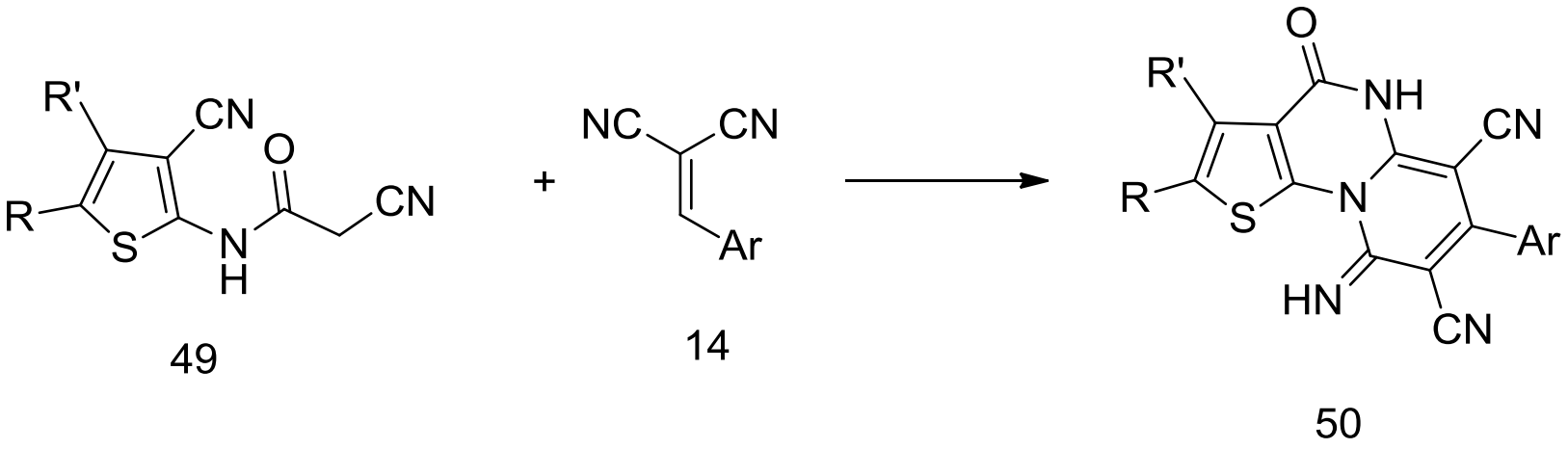
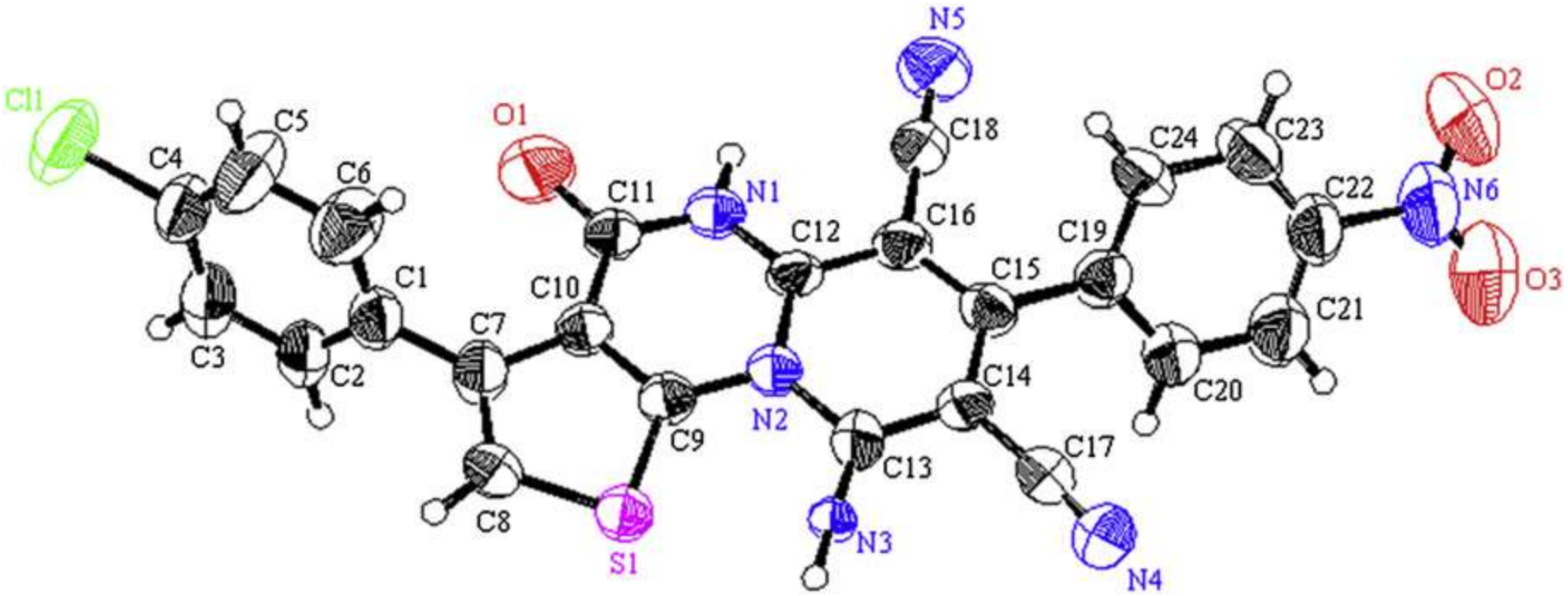
R
H
N
CN
O
N
N
N
Ar
47



X-Ray crystal structure of compound 48

Rare case for isolating heterocyclic imine



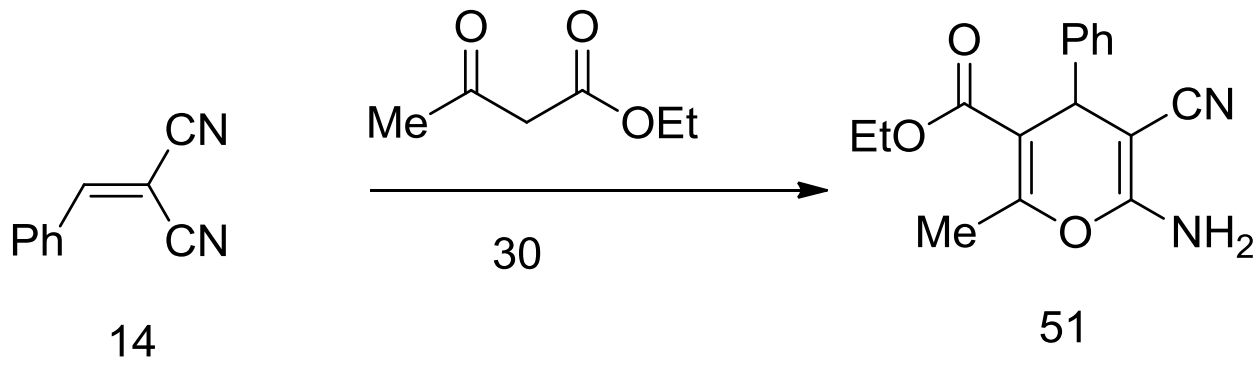


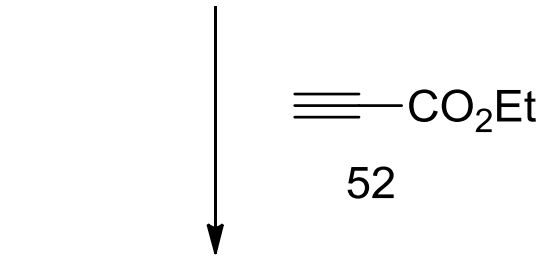
X-Ray crystal structure of compound 50, Ar = $NO_2C_6H_4$-(*p*), R = H, R' = ClC_6H_4-(*p*)

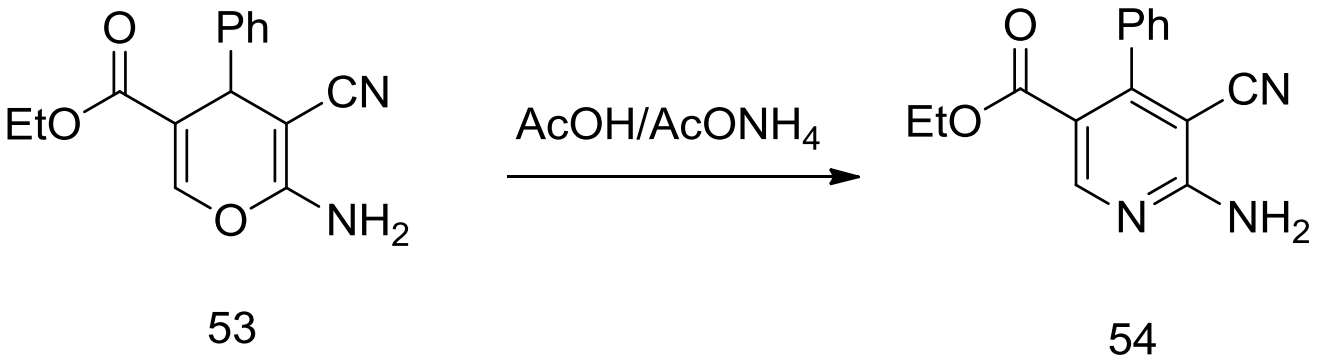
X-Ray crystal structure determination

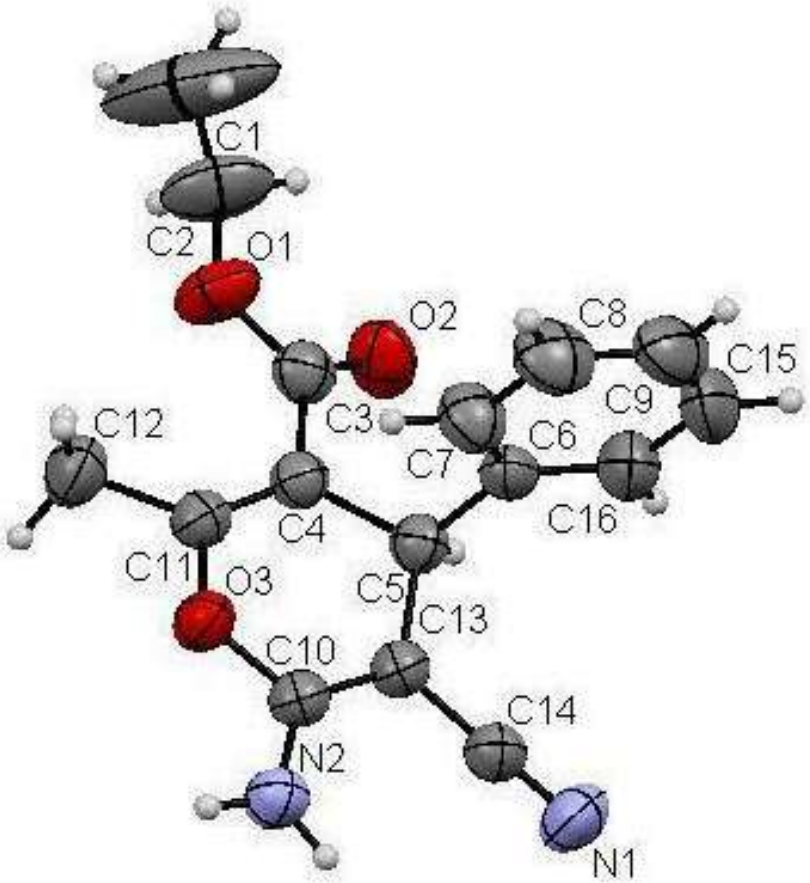
Major conclusions of the past fifty years

- I do like to confirm that these structures were quite confirmed and most of the products were used by others as starts and also reported in patent literature for utility but to *cut route for devils*, we managed obtaining X-ray for most of the past products. Here I will list some.

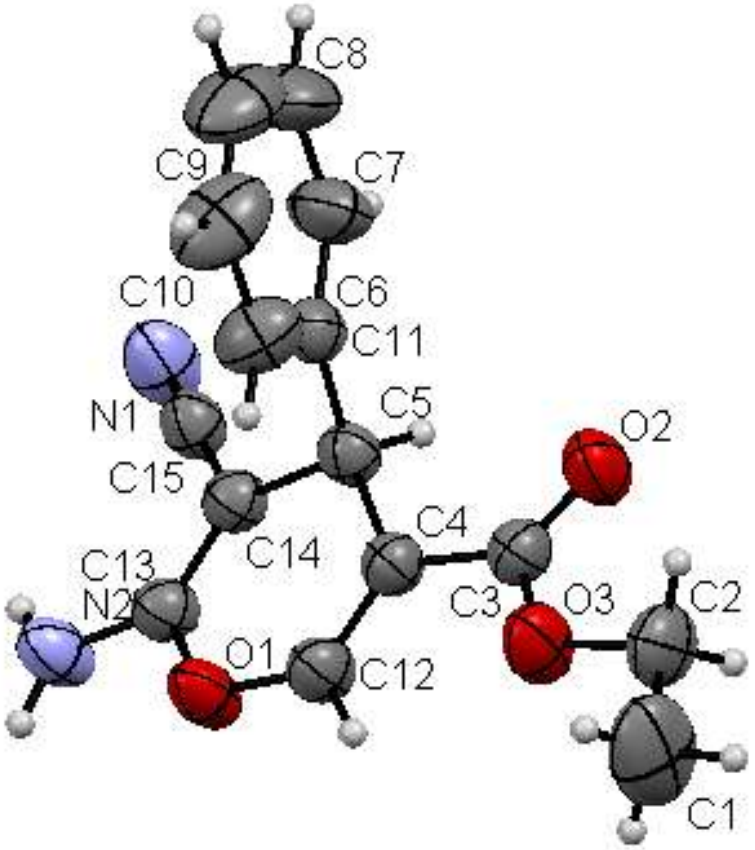

CN
Ph
CN
14
O
O
Me
OEt
30
O
Ph
EtO
CN
Me
O
NH2
51


CO2Et
52

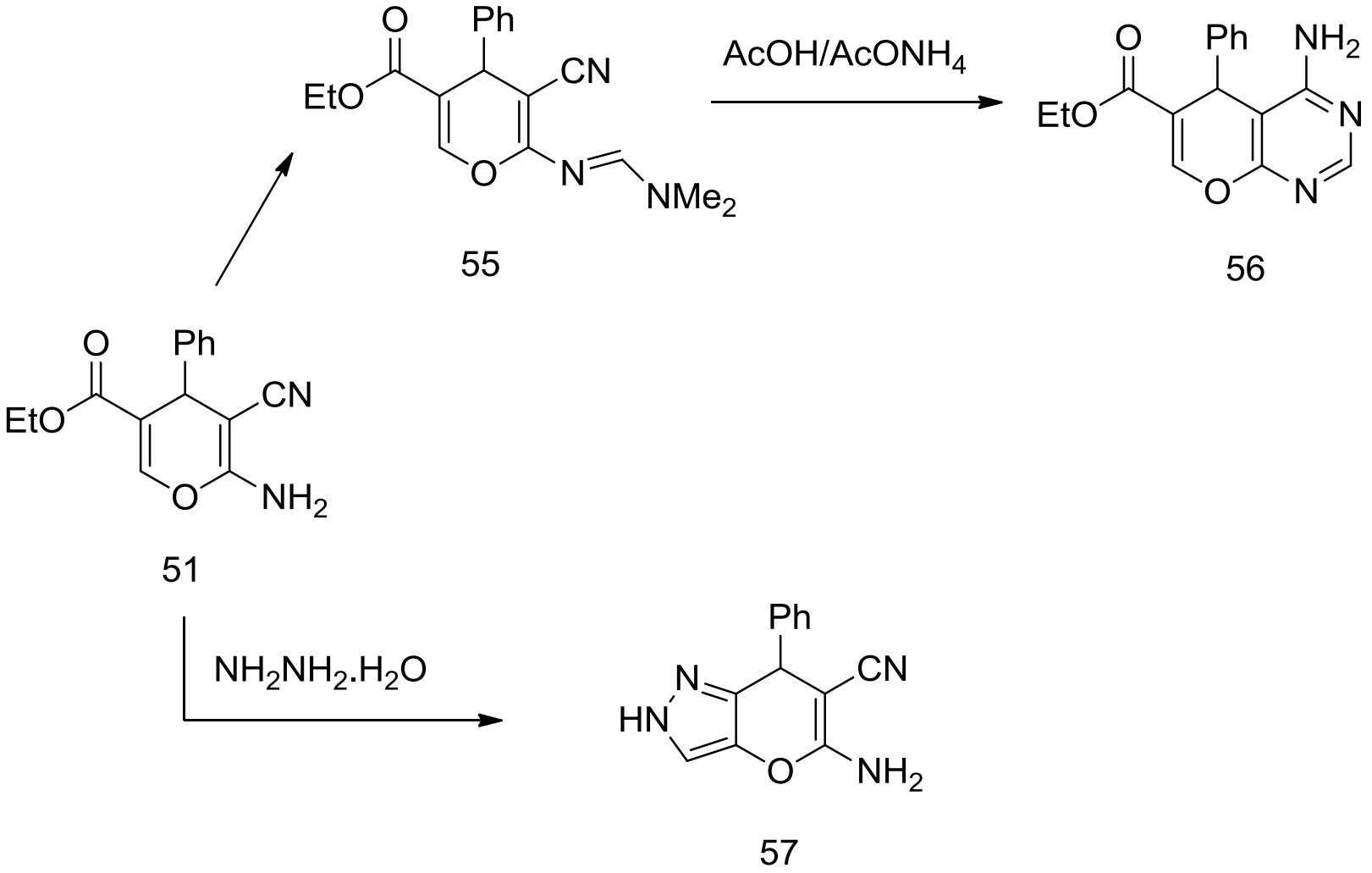

O
Ph
EtO
CN
O
NH2
53
AcOH/AcONH4
O
Ph
EtO
CN
N
NH2
54

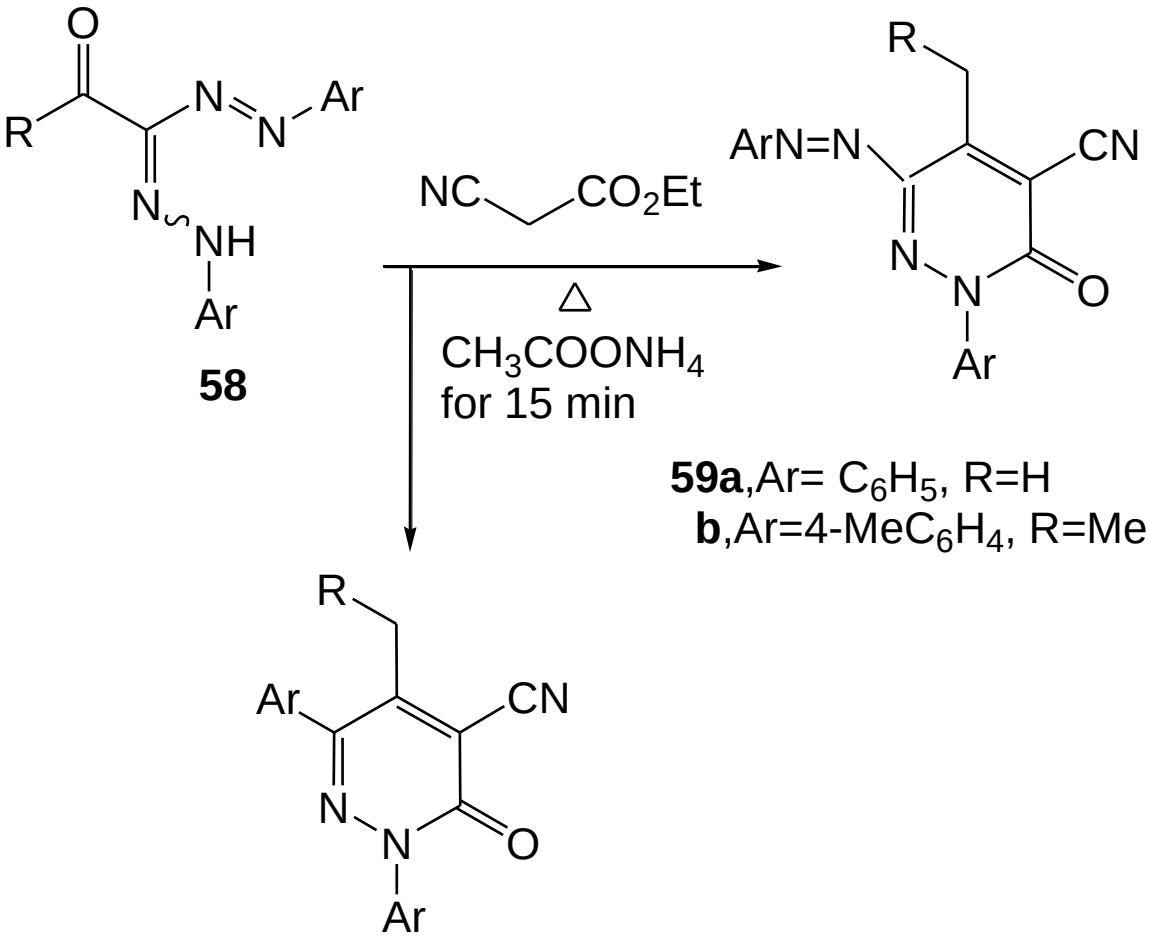


X-Ray crystal structure of compound 51

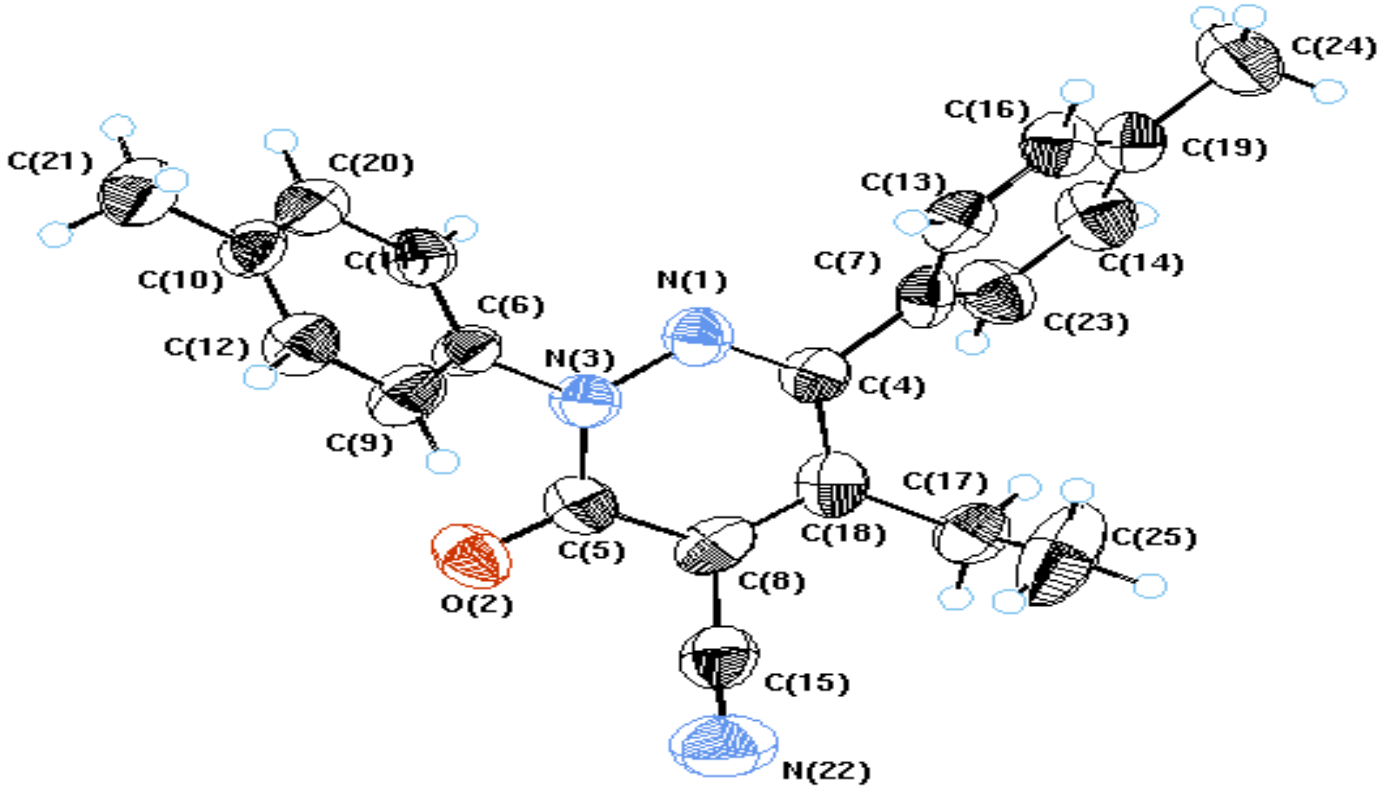


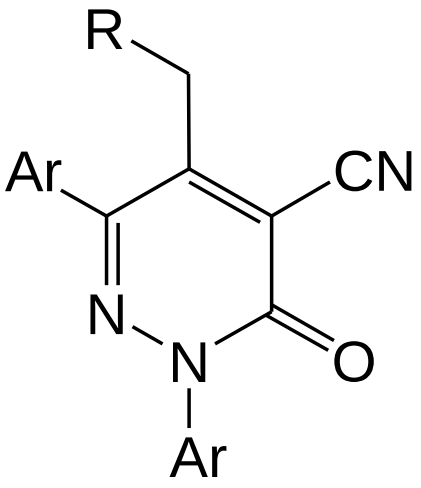
X-Ray crystal structure of compound 53


O
Ph
CN
EtO
O
N
NMe2
55
AcOH/AcONH4
O
Ph
NH2
EtO
N
O
N
56
O
Ph
CN
EtO
O
NH2
51
NH2NH2.H2O
Ph
N
CN
HN
O
NH2
57


O
R
N
N
Ar
N
NH
Ar
58
NC
CO2Et
△
CH3COONH4
for 15 min
R
ArN=N
CN
N
N
O
Ar
59a,Ar= C6H5, R=H
b,Ar=4-MeC6H4, R=Me
R
Ar
CN
N
N
O
Ar
60 Ar=4-MeC6H4, R=Me

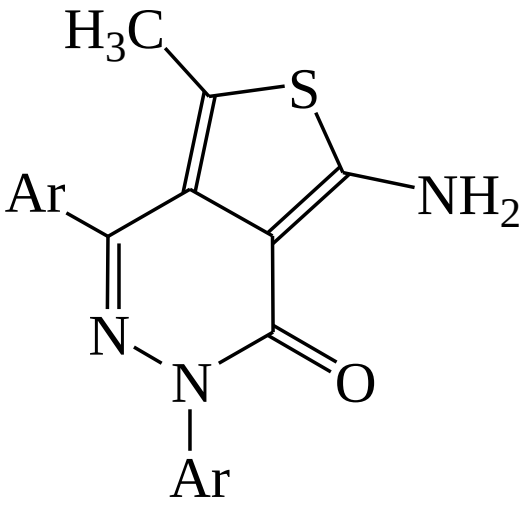
X-Ray crystal structure of compound **60**





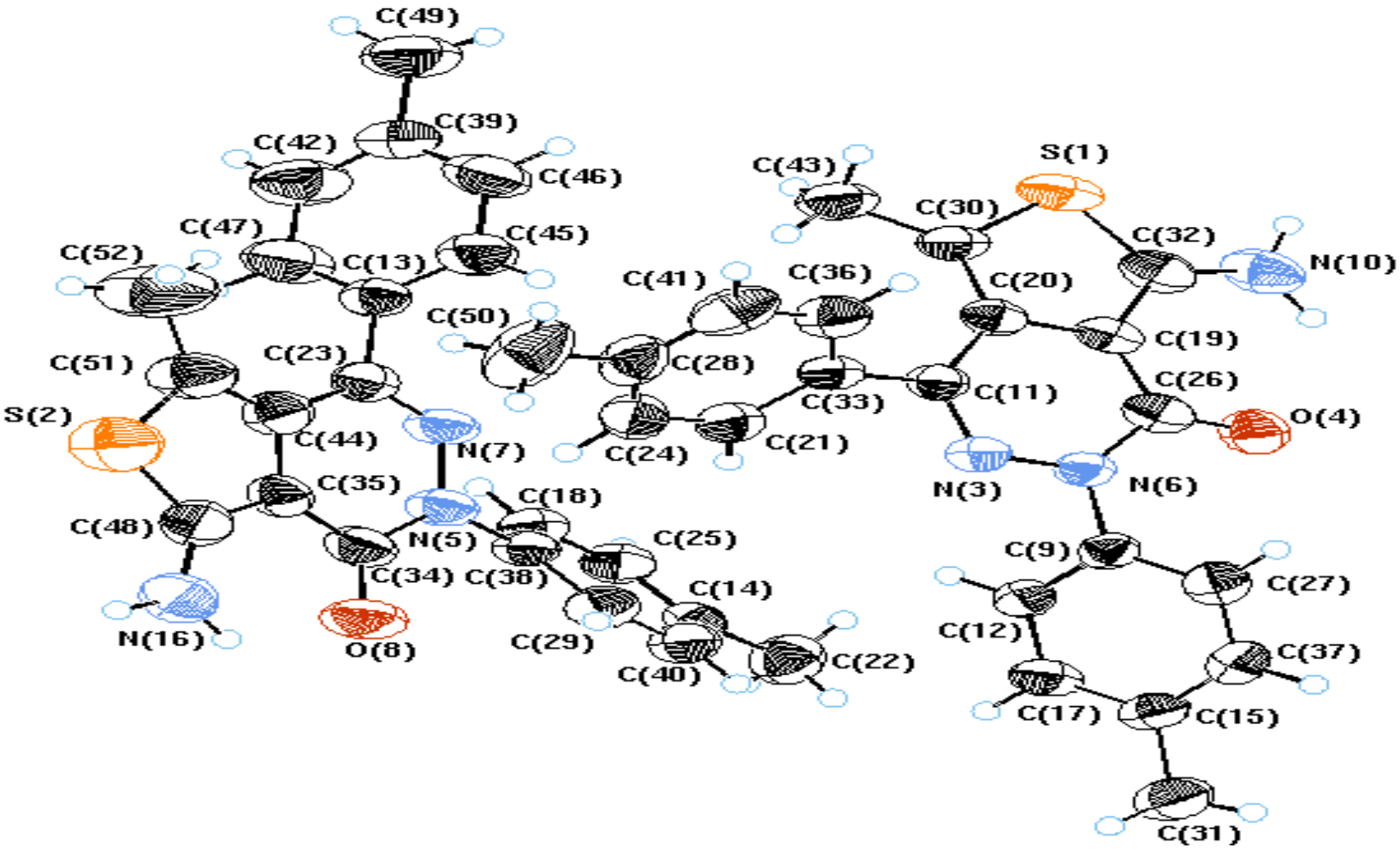
60 Ar=4-MeC_6H_4, R=Me

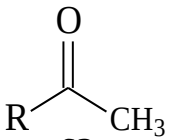
S / piperidine
in dioxane for
10 min using
microwave



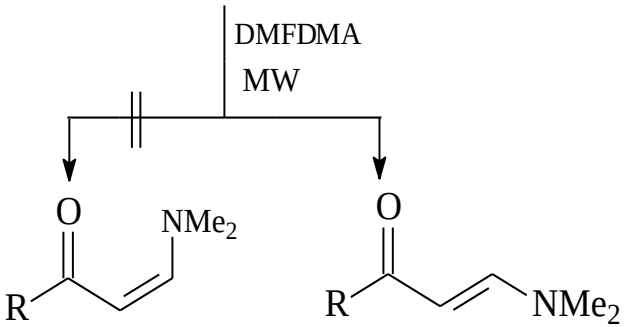
61 Ar=4-MeC_6H_4

X-Ray crystal structure of compound 6**1**

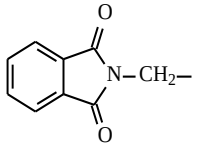




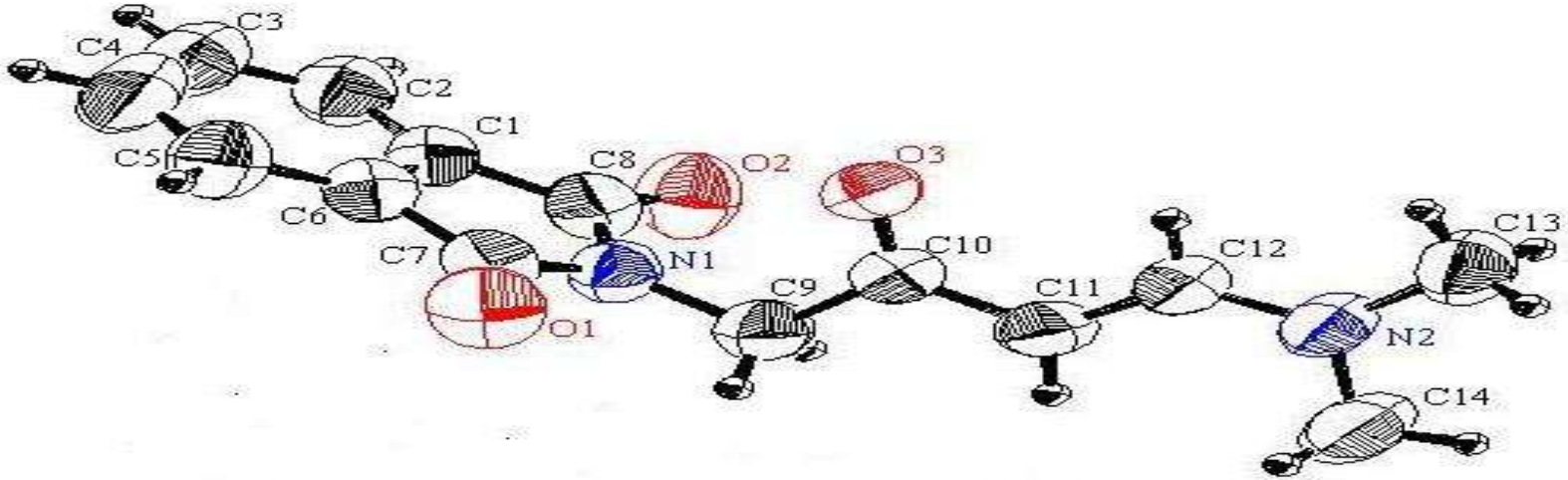
62

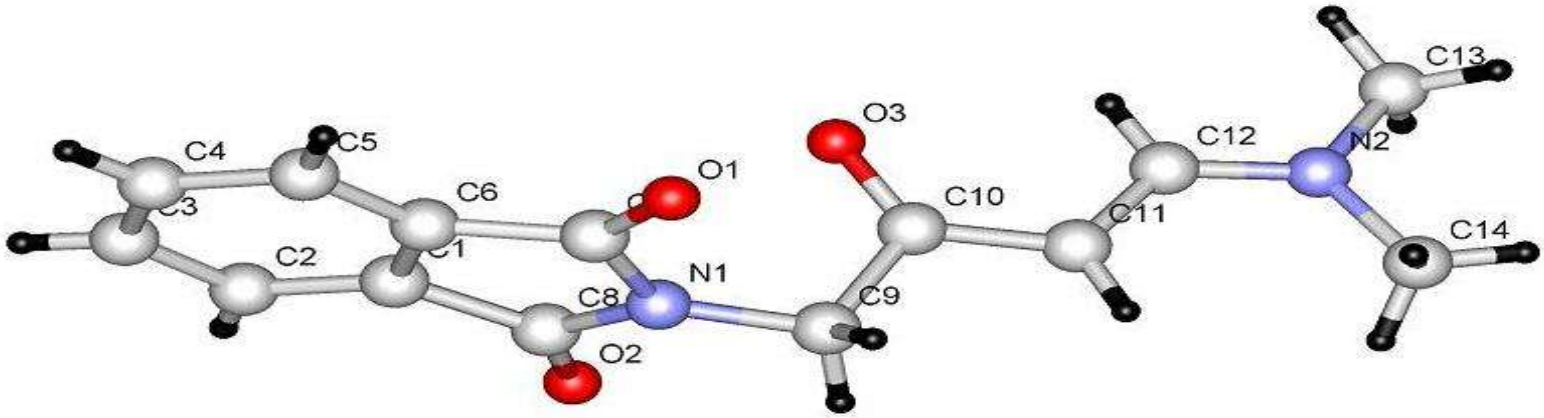


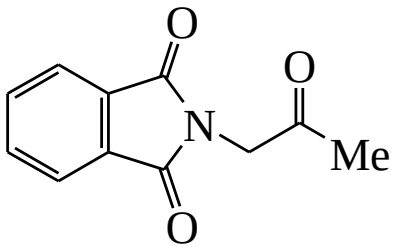
63 **64**

62,64a, R = 2-Pyrrolyl
b, R = 2-Furyl
c, R = 2-Thienyl
d, R = C_6H_5
e, R = 4-ClC_6H_4
f, R = 

X-Ray crystal structure of compound **64f**



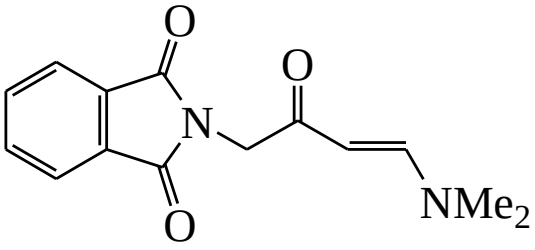




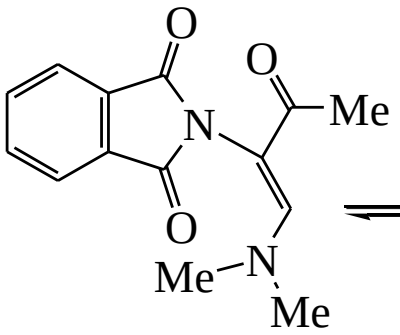
62f

DMFDMA

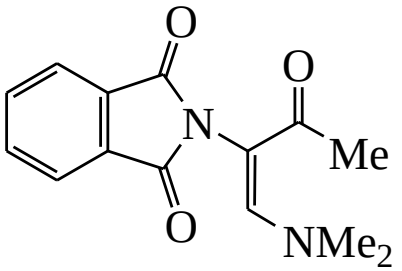
MW



64f

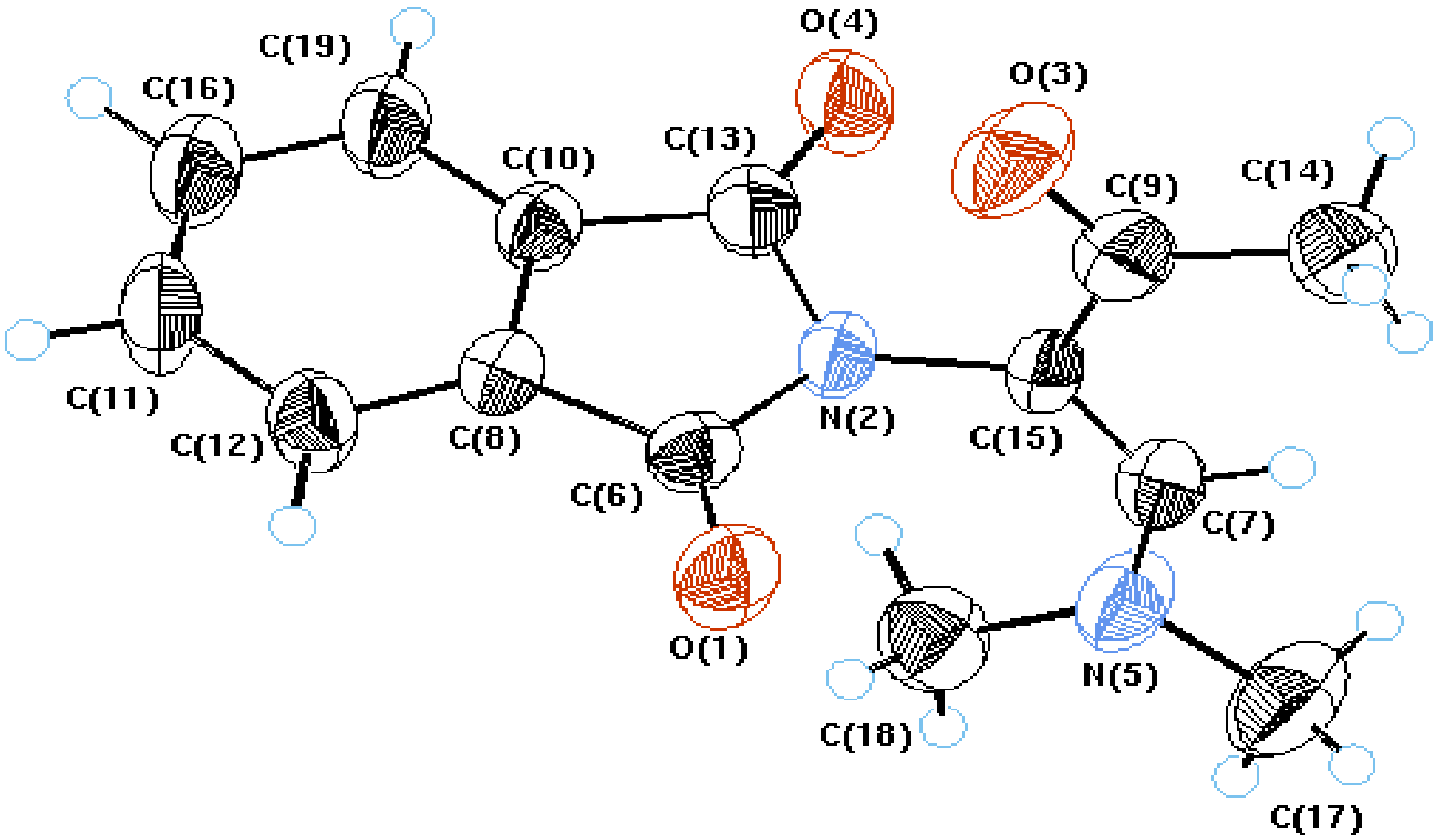


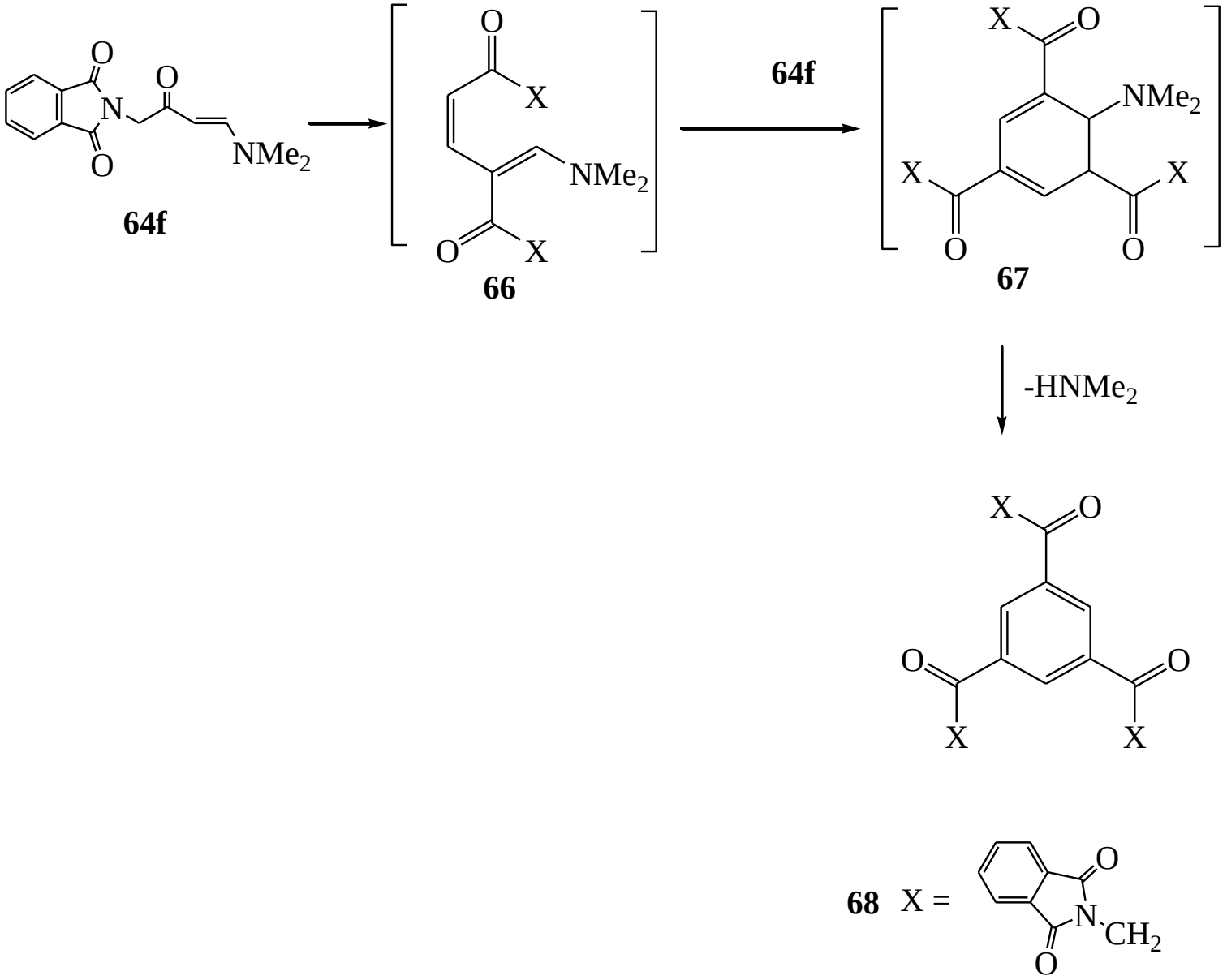
65



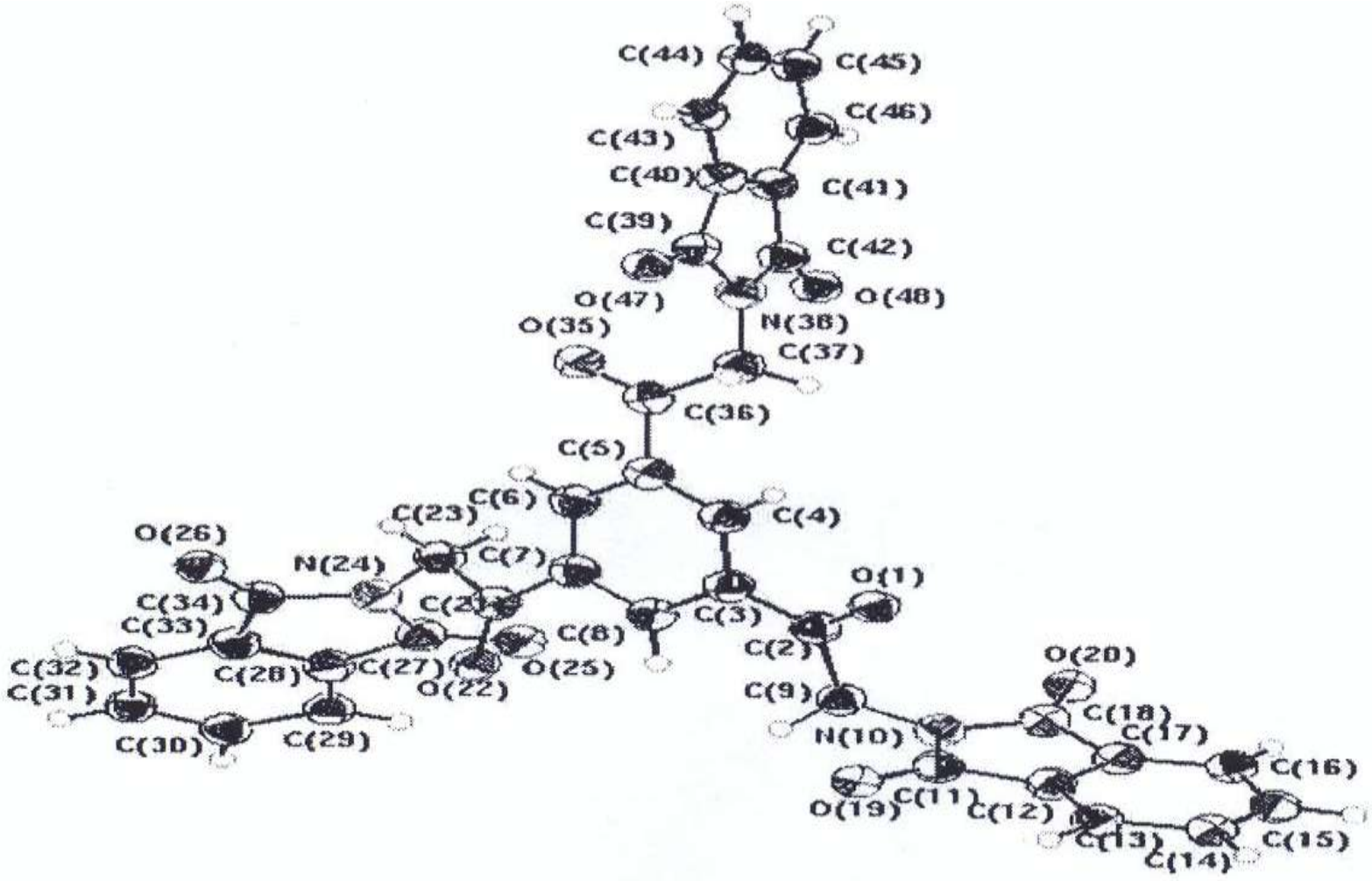
65A

X-Ray crystal structure of compound **65**




64f
66
64f
67
-HNMe2
68 X =

X-Ray crystal structure of compound **68**



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