

4- AND 5-OXOCARBOXYLIC ACIDS AS VERSATILE SYNTHONS FOR THE PREPARATION OF HETEROCYCLES

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Abstract – Conversions of 4- and 5-oxocarboxylic acids for the preparation of heterocycles are discussed. The review illustrates the importance and variability and presents the synthetic applicability of these versatile synthons.

CONTENTS

1. Introduction
2. Reactions with hydrazines
3. Reactions with hydroxylamine
4. Cyclocondensations with bifunctional amino derivatives
5. Cyclizations to lactones
6. Formation of lactams
7. Conversion to thiophene derivatives
8. Syntheses of natural products. Other ring systems

1. INTRODUCTION

In the course of our synthetic work, we have prepared numerous cycloalkane-condensed oxygen- and nitrogen-containing heterocycles and benzologues.^{1,2} New reactions of 4- and some 5-oxocarboxylic acids have been applied and some earlier results have been reinvestigated with special attention to the starting aroylcycloalkanecarboxylic acids. The present survey reports on the versatile applicability of these synthons, which, in spite of their extensive use, have not yet been reviewed.

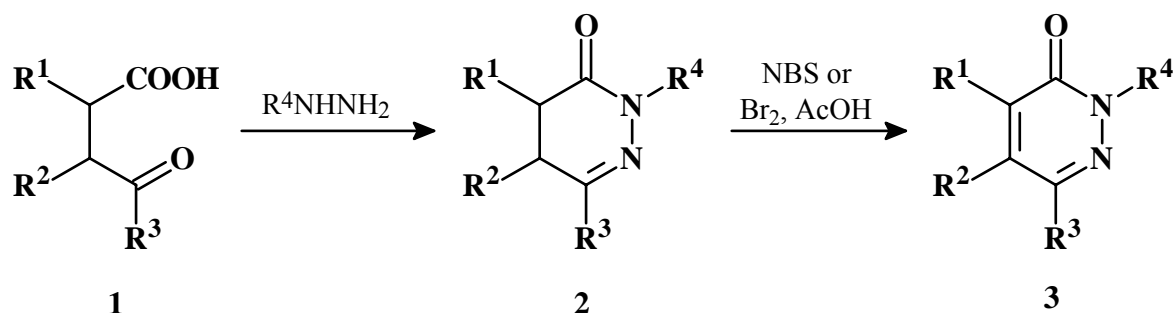
Several methods are known for the synthesis of the starting oxocarboxylic acids. However, because of its simplicity and good to excellent yields, the Friedel-Crafts reaction has been the most widely applied.³⁻⁸ The numerous other methods described involve more steps or usually require special conditions. Besides the Friedel-Crafts preparation, the application of Grignard reactions has proved to be advantageous for variation of the aryl or alkyl substituents on the acyl group, this method resulting in few side-reactions.⁹⁻¹²

The organolithium compounds are also useful in special cases.¹³⁻¹⁶ Other methods are based on the enamine reactions of cyclic ketones with piperidine or pyrrolidine, and then with a haloalkanoic ester,¹⁷ and the Reformatsky reaction of succinic anhydride with a bromoalkanoic ester.¹⁸ Condensation of anhydrides with malonic acid in the presence of triethylamine at 80 °C results in 2-acetylbenzoic acids.^{19,20} When refluxed in toluene in the presence of piperidine, the aromatic aldehydes react with substituted levulinic acids to give arylidene-substituted oxocarboxylic acids.²¹ 2-(2-Pyridylcarbonyl)benzoic acid has been obtained by the thermal condensation of phthalic anhydride with 2-piperidinecarboxylic acid.²² The reaction of acrolein with nitroethane affords 4-nitropentanal; on subsequent treatment with aqueous hydrogen peroxide,²³ 4-oxopentanoic acid is obtained. The reaction of 4-aryloxy-carboxylic acid with phthalic dicarboxaldehyde yields naphthaleneoxocarboxylic acid.²⁴ In protic media, ethyl pyridazinecarboxylate undergoes reaction with aldehydes to furnish heterocyclic oxocarboxylic acids.²⁵ When 2-iodocyclopentanecarboxylate is treated with zinc, and then with acid chlorides in the presence of palladium catalyst,²⁶ arylcyclopentanecarboxylic acids are prepared stereoselectively.

As numerous of the derivatives obtained from oxocarboxylic acids have significant pharmacological activity, these are also reported on in the present survey.

2. REACTIONS WITH HYDRAZINES

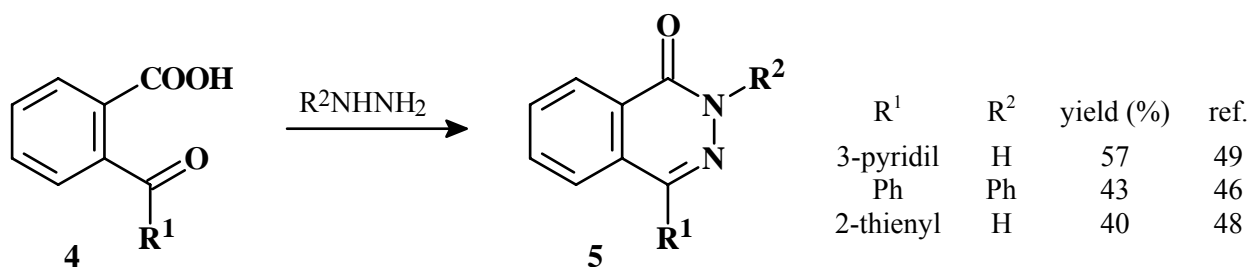
The reactions of 4-oxocarboxylic acids (**1**) with hydrazine or its alkyl or aryl derivatives yield dihydropyridazinones (**2**), which can readily be converted to aromatic heterocycles (**3**).^{6,27-44} (Scheme 1)



Compd	R ¹	R ²	R ³	R ⁴	conditions	yield (%)	ref.
2	H	Me	C ₆ H ₄ NHMe-4	Me	NH ₂ NH ₂ , AcOH, EtOH, reflux 18 h	63	35
2	H	H	C ₆ H ₄ NH ₂ -4	H	NH ₂ NH ₂ , EtOH, reflux	65	34
2	(CH ₂) ₂		C ₆ H ₄ Me-4	H	NH ₂ NH ₂ , EtOH, reflux	72	6
3	(CH ₂) ₄		C ₆ H ₄ F-4	H	SOCl ₂ , benzene, reflux	58	43
3	H	H	Ph	H	CuCl ₂ , MeCN, reflux 30 min	88	44

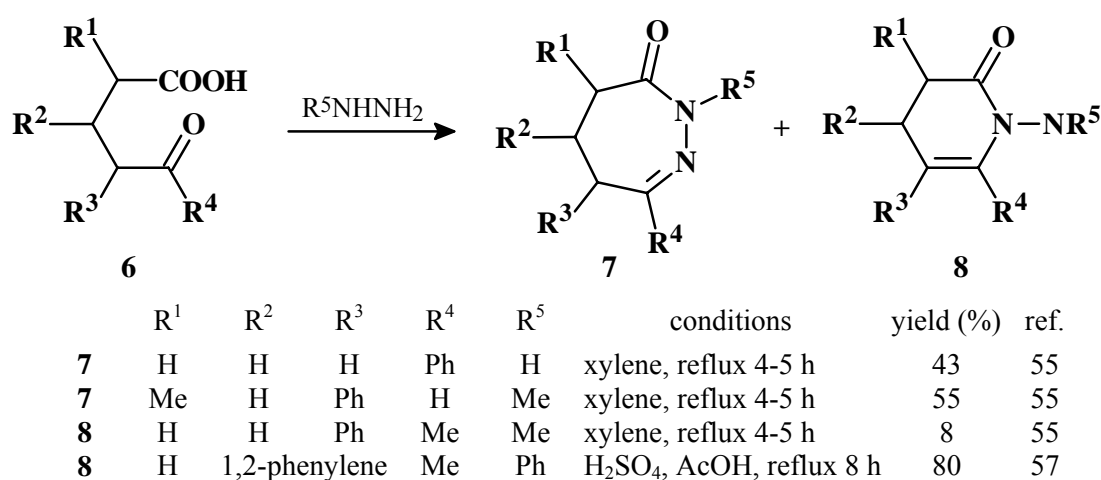
Scheme 1

The reactions of aromatic 4-oxocarboxylic acids (**4**) (e.g. phthalaldehydic acid) with hydrazines result in phthalazinones (**5**).⁴⁵⁻⁵⁵ (Scheme 2)



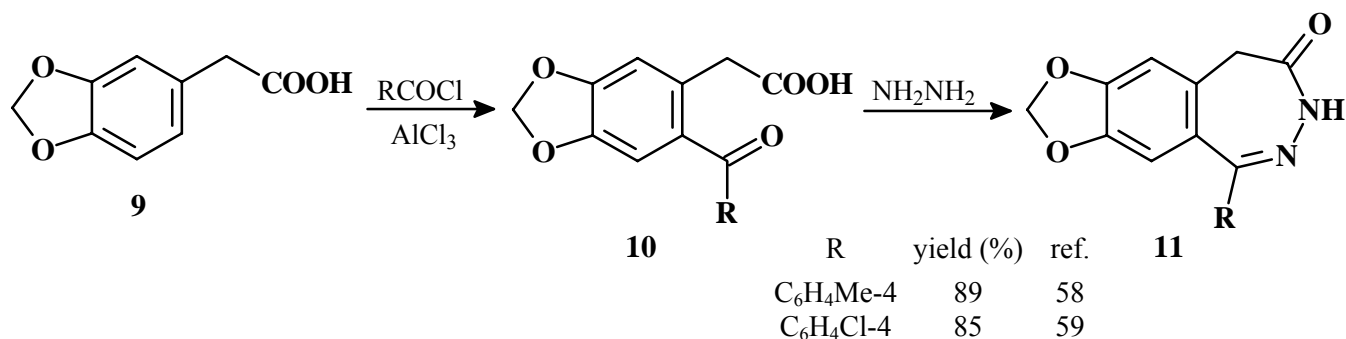
Scheme 2

The 5-oxocarboxylic acids (**6**) undergo cyclization with hydrazine derivatives to afford 1,2-diazepinones (**7**) in low to good yields, with pyridone derivatives (**8**) as by-products.⁵⁵⁻⁵⁷ (Scheme 3)



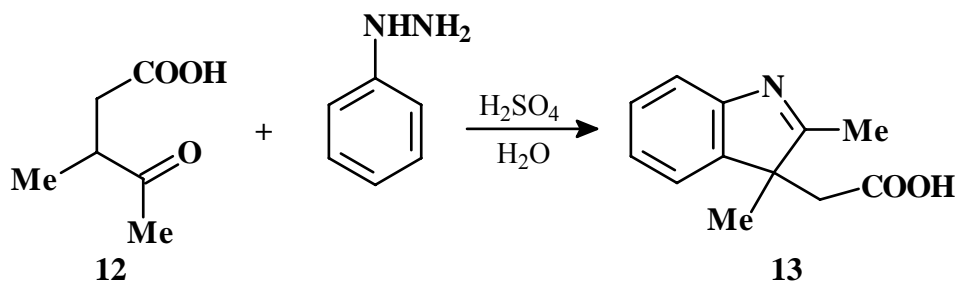
Scheme 3

The pyrolytic reactions of 2-acetylphenylacetic acid (**10**) with hydrazines yield 1-methyl-3*H*-2,3-benzodiazepin-4(5*H*)-ones (**11**) in low yield, with 1-methyl-2-amino-3(2*H*)-isoquinolinones as side-products.⁵⁷ The analogous 1-aryl-2,3-benzodiazepine derivatives (*e.g.* **11**) have noteworthy anxiolytic, anticonvulsant and neuroprotective activity.^{58,59} (Scheme 4)



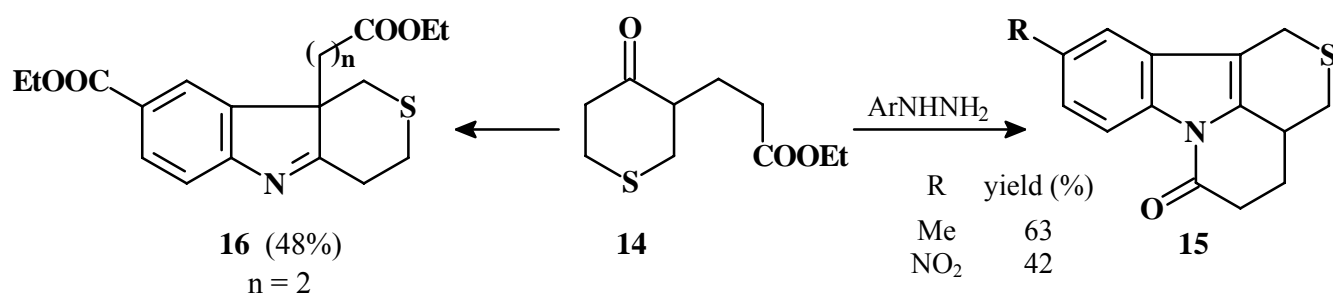
Scheme 4

In aqueous solution, the sulfuric acid-catalysed reaction of 3-methyl-4-oxopentanoic acid (**12**) with phenylhydrazine gives the indole derivative (**13**).⁶⁰ (Scheme 5)



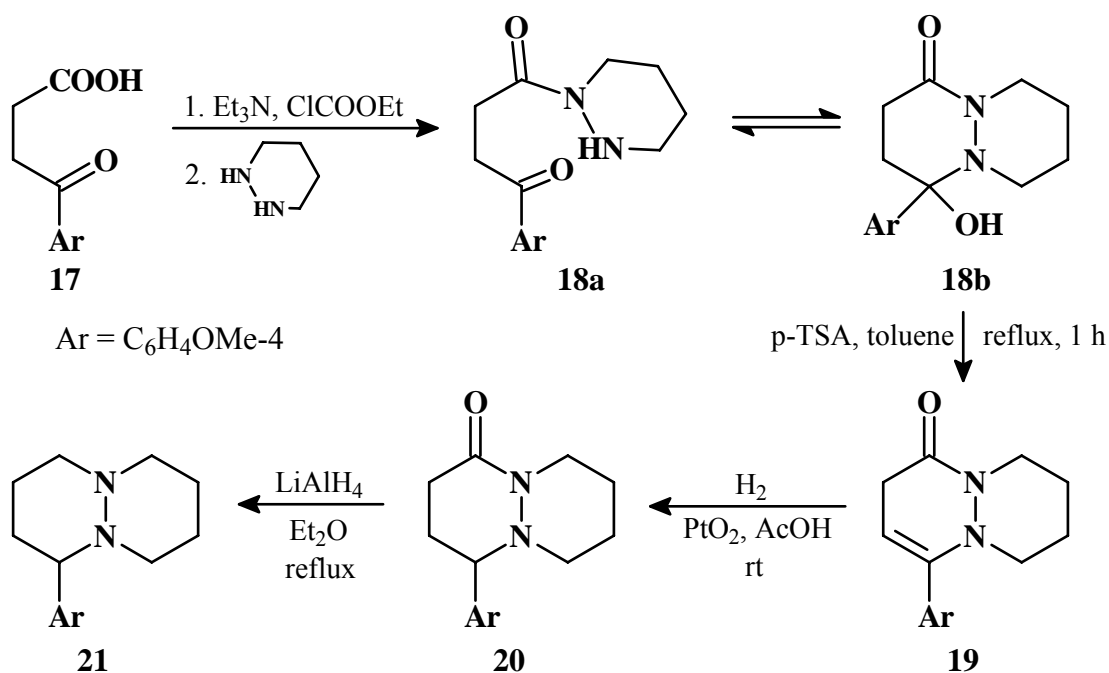
Scheme 5

The phenylhydrazones of **14** have been cyclized to fused tetracyclic compounds containing an indole moiety (**15**).⁶¹ When $\text{R} = \text{COOEt}$, the carbazole (**16**) was formed. (Scheme 6)



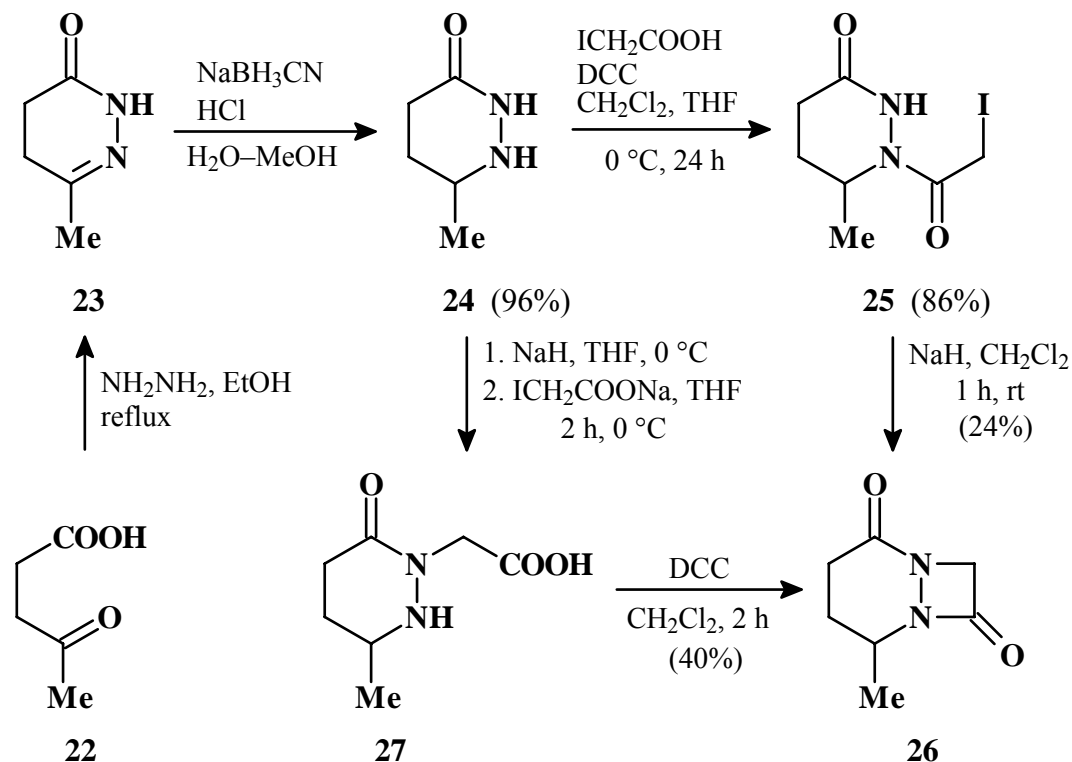
Scheme 6

On reaction with hexahydropyridazine, the mixed anhydride prepared from 3-*p*-methoxybenzoylpropionic acid (**17**) and ethyl chloroformate gives the hydrazides (**18a**) and (**18b**).⁶² Treatment with acid in toluene results in the unsaturated lactam (**19**) and then to **20** by catalytic hydrogenation, which on further reduction with LiAlH_4 yields the 1,6-diazacyclodecane (**21**). (Scheme 7)



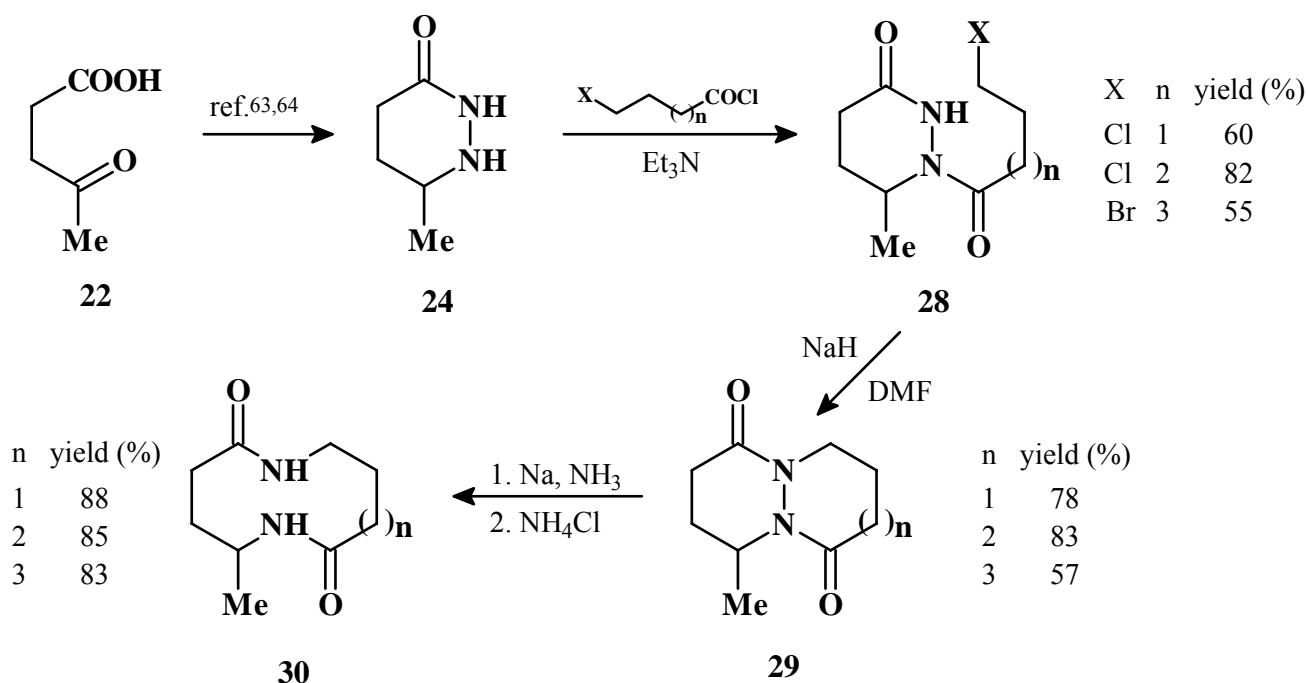
Scheme 7

The 1,2-diazetididin-3-one (**26**) is formed by reduction of the pyridazinone (**23**) with NaBH₃CN in acidic (2 N HCl) medium, followed by acylation–alkylation to **25** and **27**, and cyclization by DCC or NaH.⁶³ (Scheme 8)



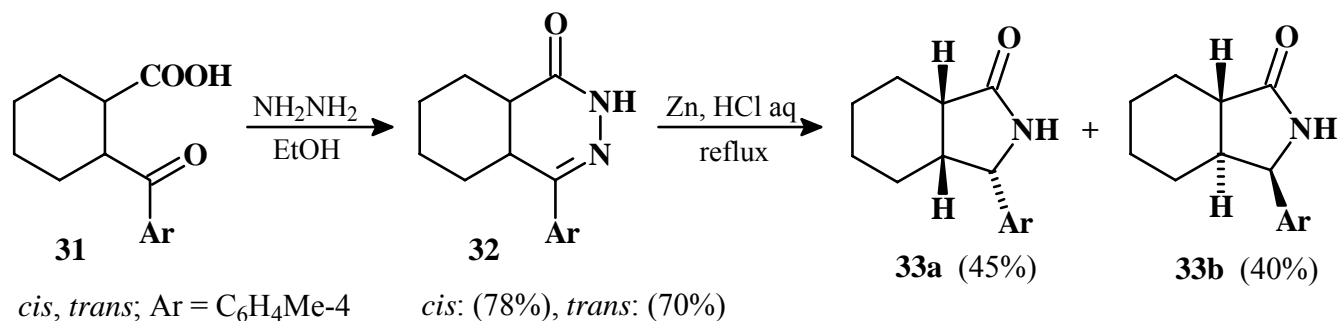
Scheme 8

A similar procedure leads to lactams (**30**) (Scheme 9), which have the skeleton of peptide-type antibiotics, e.g. glidobactin A, isolated recently from a culture broth of *Polyangium brachysporum*.⁶⁴



Scheme 9

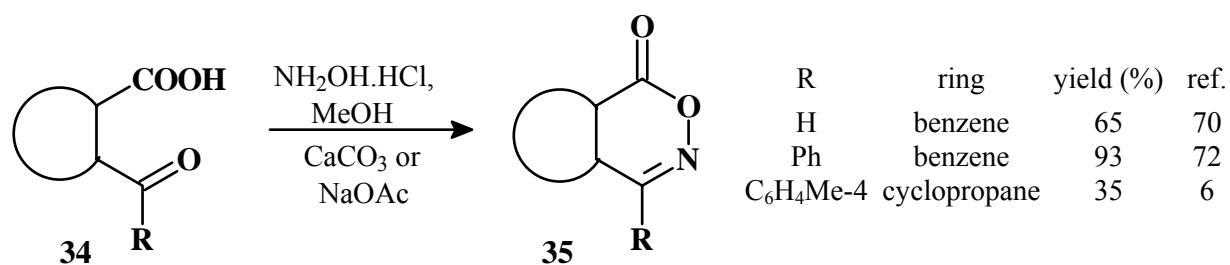
The ring contractions of pyridazinone and phthalazinone derivatives with Zn/HCl to furnish pyrrolidines or isoindolines have been well studied.⁶⁵⁻⁶⁸ For the *cis*- and *trans*-cyclohexane-condensed pyridazinones (**32**), stereoselective ring contraction has been observed.⁶⁹ (Scheme 10)



Scheme 10

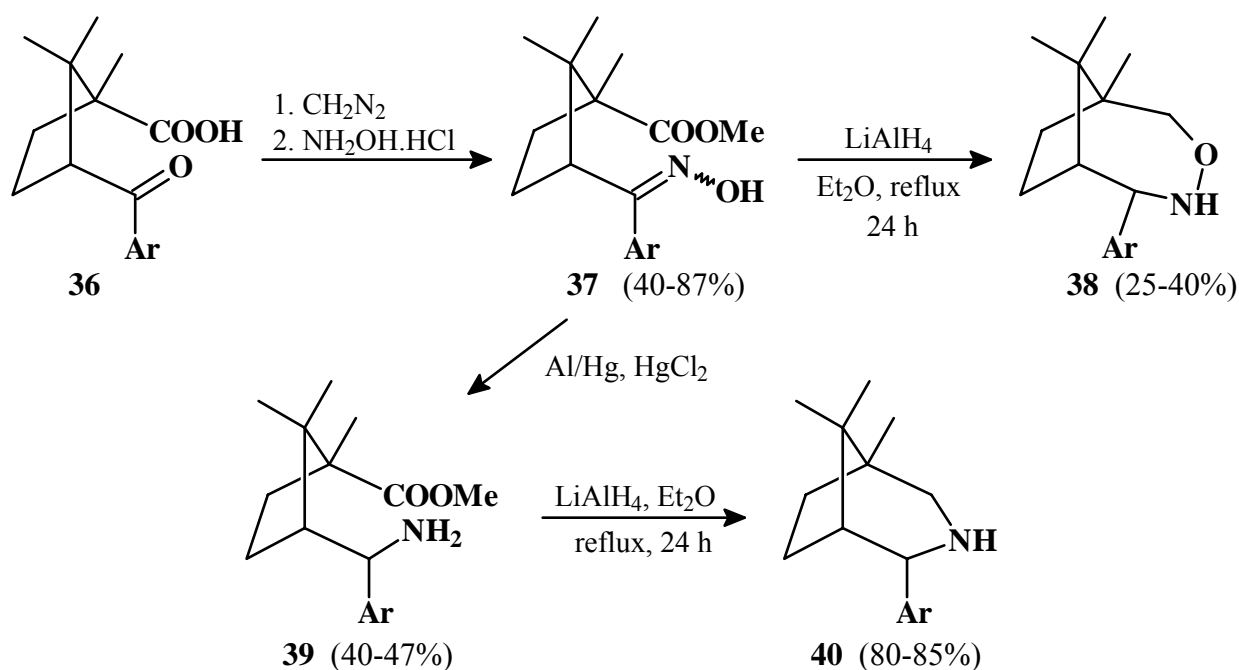
3. REACTIONS WITH HYDROXYLAMINE

Hydroxylamine reacts with oxo acids (**34**) to give 1,2-oxazines (**35**) by ring closure *via* an oxime intermediate.^{6,70-73} (Scheme 11)



Scheme 11

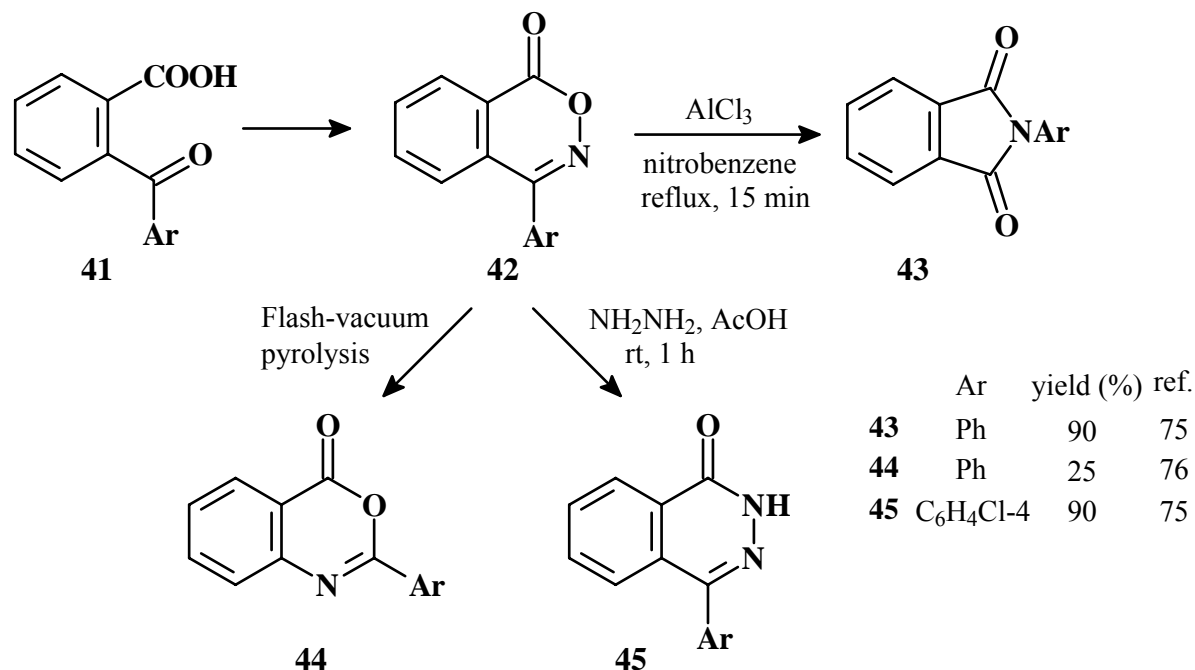
The reactions of 3-arylcyclopentanecarboxylic acid (**36**) esterified with diazomethane then with with hy-



Scheme 12

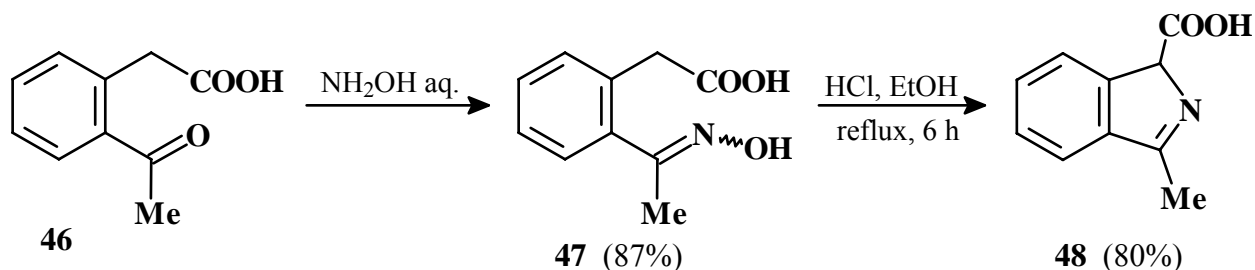
droxylamine result in the oxime (**37**), which may be converted to the saturated 1,2-oxazepine (**38**) and the azabicyclo[3.2.1]octane (**40**).⁷⁴ (Scheme 12)

The formation and further conversion of 2,3-benzoxazin-1-ones (**42**) to phthalimides (**43**), 3,1-benzoxazines (**44**) and phthalazines (**45**) has been described.^{75, 76} (Scheme 13)



Scheme 13

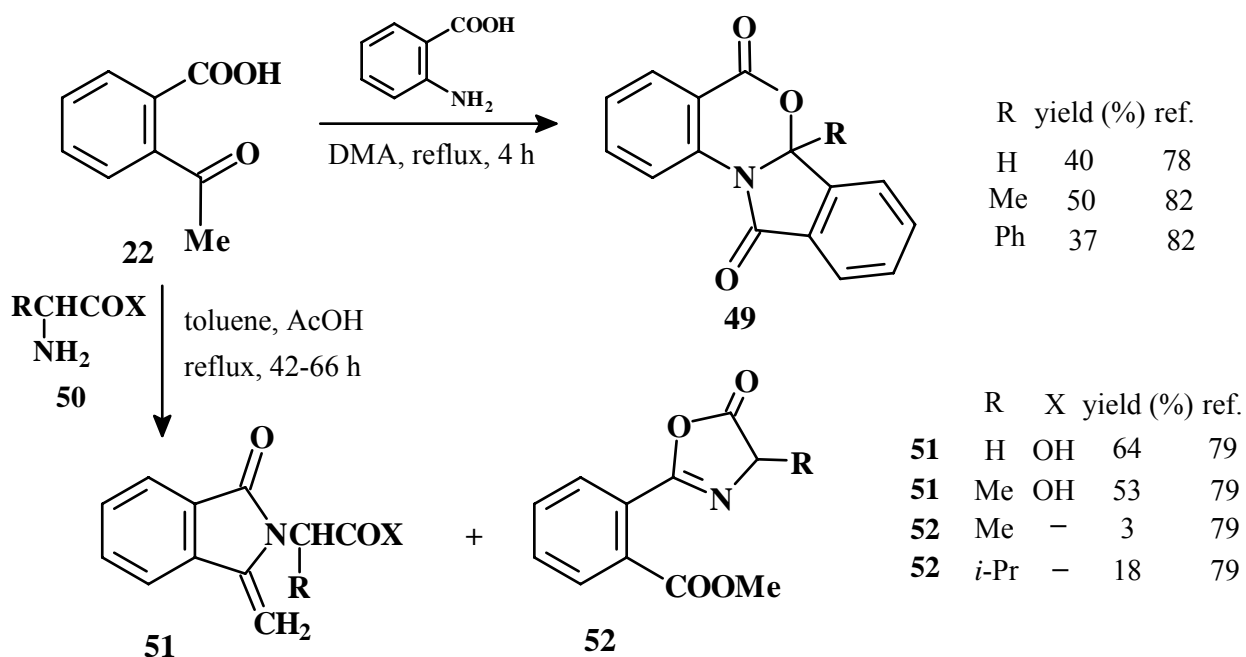
On acid catalysis, the 2-acetylphenylacetic acid (**46**) reacts with hydroxylamine to afford the isoindole-carboxylic acid (**48**) instead of 1,2-oxazepinone.⁷⁷ (Scheme 14)



Scheme 14

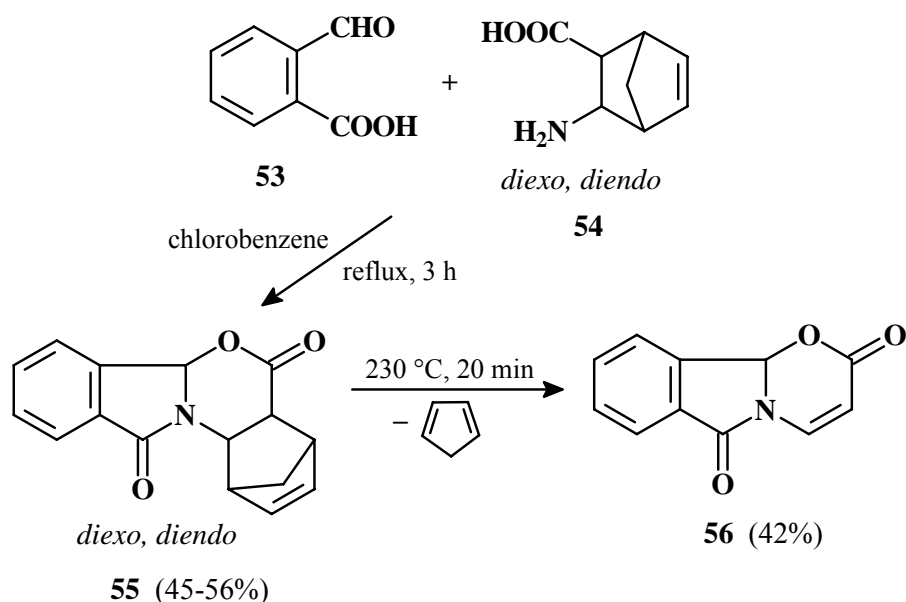
4. CYCLOCONDENSATIONS WITH BIFUNCTIONAL AMINO DERIVATIVES

In spite of the acidity of the carboxyl group and the presence of strong intramolecular hydrogen-bonds, amino acids react with oxocarboxylic acids at higher temperature. The condensation of phthalaldehydic acid or 2-acetylbenzoic acid with anthranilic acid yields 5*H*-isoindolo[2,1-*a*][3,1]benzoxazine-5,11-dione (**49**).⁷⁸ (Scheme 15) α -Amino acids (**50**) readily condense with 2-acetylbenzoic acid to afford the protected amino acid (**51**), with oxazole (**52**) as side-product.⁷⁹ (Scheme 15) These 3-methylenephthalidylamino acids (**51**) are simply cleaved with hydrazine to give the free amino acid and 1-methyl-4-phthalazine.⁷⁹



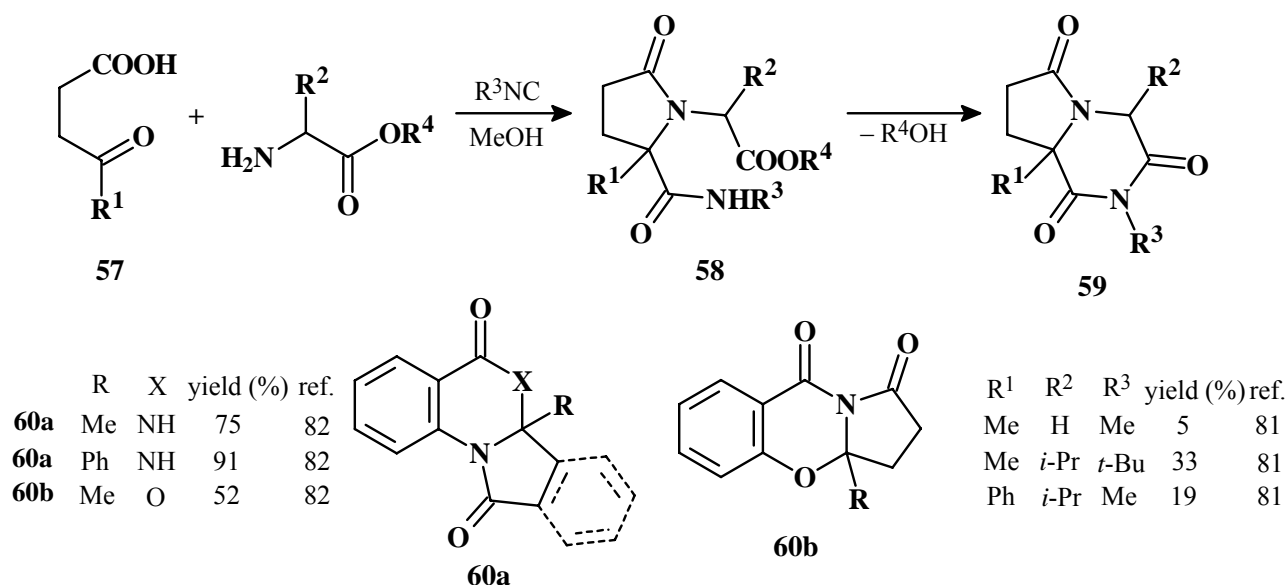
Scheme 15

From phthalaldehydic acid (**53**) and 2-aminobicyclo[2.2.1]hept-5-ene-3-carboxylic acid (**54**), the 1,3-oxazino[2,3-*a*]isoindole-2,6-dione (**56**) (a new ring system) has been obtained in a retro Diels-Alder process.⁸⁰ (Scheme 16) First the parent (**55**) is formed and its decomposition results in (**56**) by the loss of cyclopentadiene.



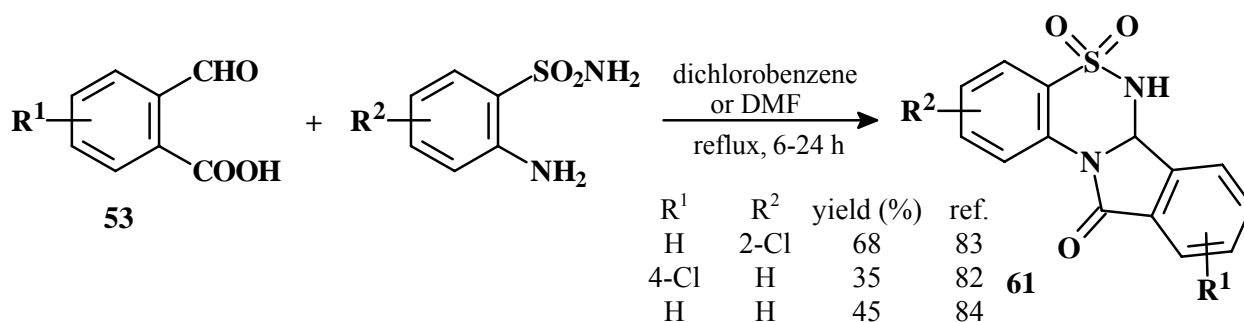
Scheme 16

When the 4-oxo acids (**57**) are condensed with amino esters in the presence of isocyanides, the bicyclic lactams (**59**) may be prepared in a one-pot intramolecular Ugi reaction.⁸¹ (Scheme 17) By reacting 4- and 5-oxoalkanoic acids with anthranilic acid, anthranilamides or salicylamide, Aeberli and Houlihan obtained the heterocycles (**60a,b**).⁸²



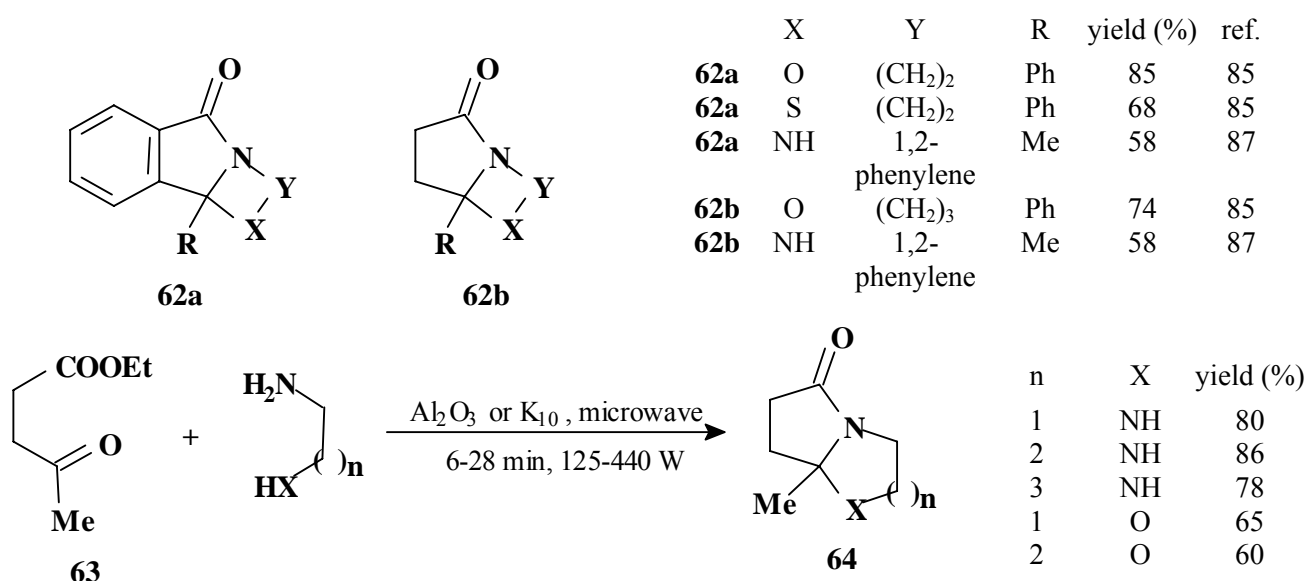
Scheme 17

Phthalaldehydic acids (**53**) react with 2-aminobenzenesulfonamides to afford dihydro-11*H*-isoindolo[1,2-*c*][1,2,4]benzothiadiazin-11-one 5,5-dioxides (**61**).^{83, 84} (Scheme 18)



Scheme 18

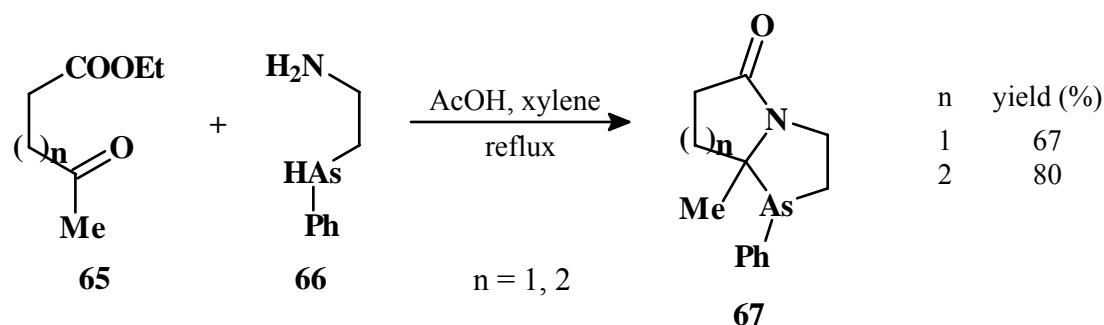
The condensations of oxo acids with 1,2- 1,3- or 1,4-amino alcohols or diamines or aminothiophenol result



Scheme 19

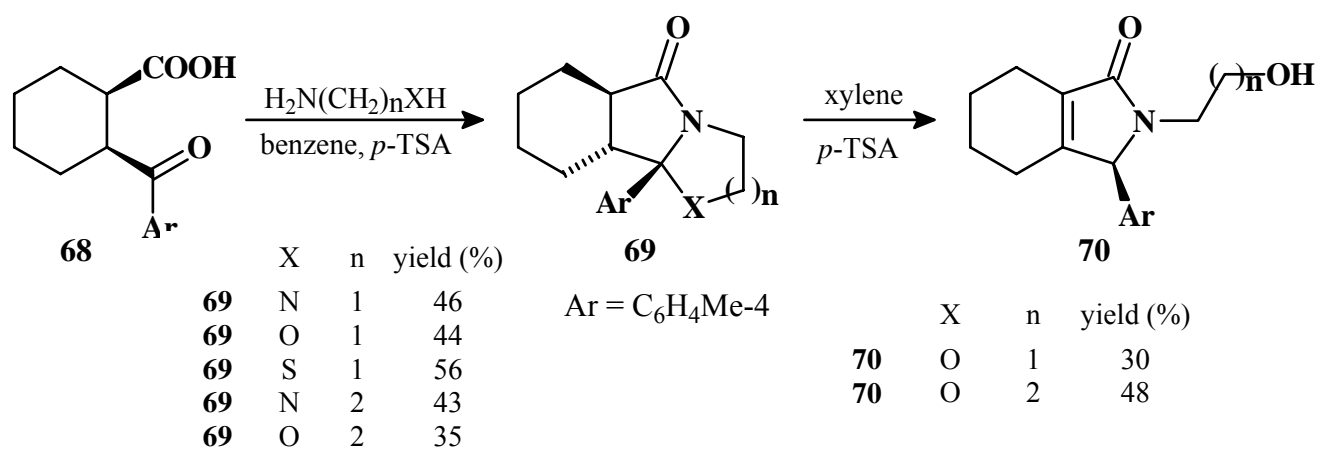
in lactams (**62a,b**) condensed with an *N*-, *O*- or *S*-containing heteroring.⁸²⁻⁸⁸ Starting from ethyl levulinate (**63**), the rapid microwave irradiation in dry media yields the fused pyrrolidinones (**64**).⁸⁹ (Scheme 19)

The reactions of 2-aminoethylphenylarsin (**66**) with 4-oxopentanoic or 5-oxohexanoic acids (**65**), with acetic acid as catalyst, give 1-aza-4-arsabicyclo[3.3.0]octane or 1-aza-7-arsabicyclo[4.3.0]nonane (**67**) in good yields (65-80%).⁹⁰ (Scheme 20)



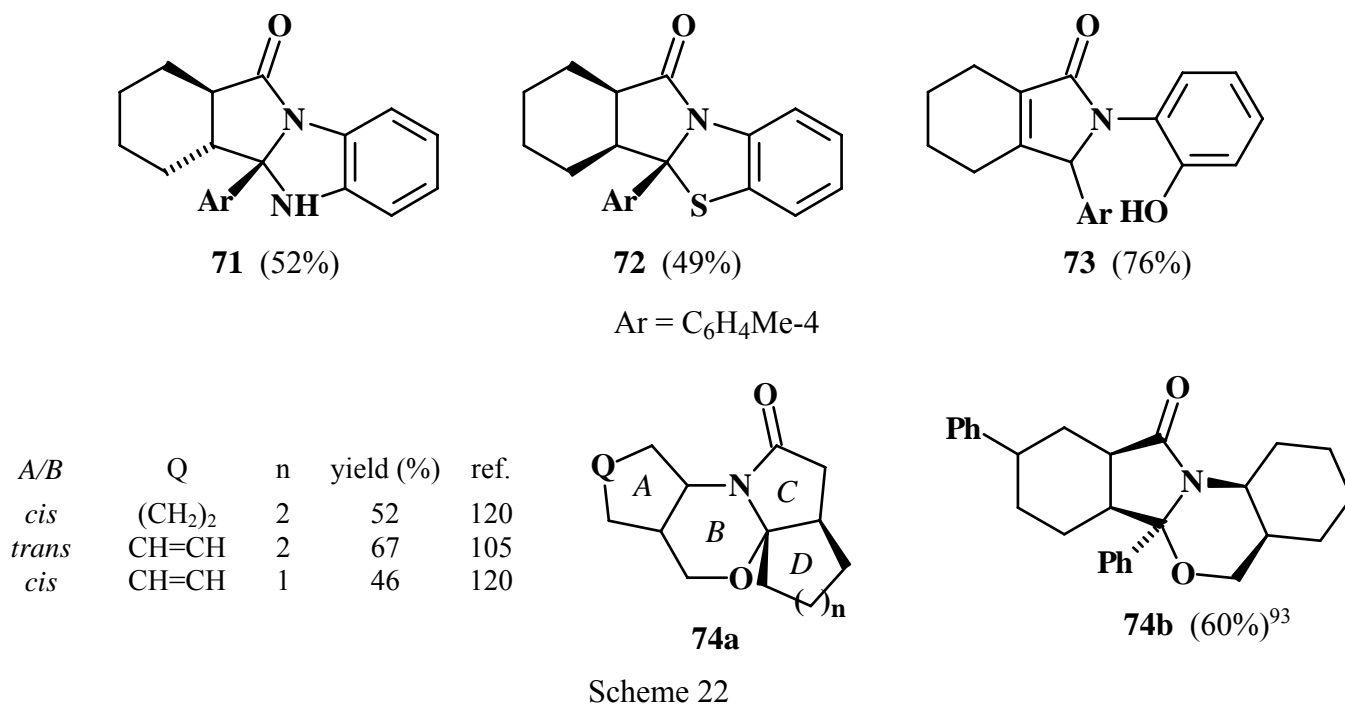
Scheme 20

By the cyclocondensation of *cis*-2-*p*-methylbenzoyl-1-cyclohexanecarboxylic acid (**68**) with diaminoalkanes, aminoalkanols and aminothiols, saturated isoindole-condensed oxazole, 1,3-oxazine, pyrrolidine, piperidine, *etc.* have been prepared.⁹¹ On cyclization, a new chiral centre is formed and isomerization with ring opening occurs. (Scheme 21)



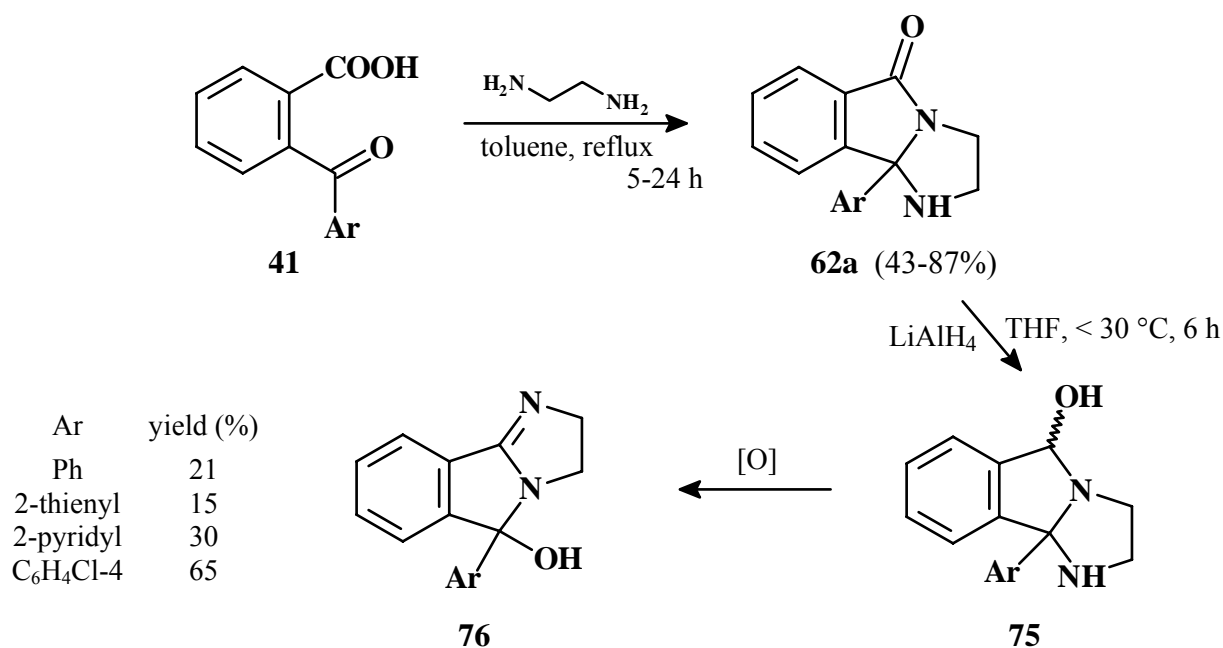
Scheme 21

It is noteworthy that the reaction of **68** with 2-aminoethanol in the presence of a catalytic amount of *p*-TSA results in octahydrooxazolo[2,3-*a*]isoindol-5(9*bH*)-one (**69**) exclusively. However, in toluene or xylene as solvent, the reaction leads to **70**; with different acids, a catalysed rearrangement has been proved experimentally.⁹² With *o*-phenylenediamine, **68** gives the isoindolobenzimidazole (**71**), while the condensation with 2-aminothiophenol results in the thio analogue (**72**). Due to the acidic character of the hydroxy group, however, the reaction with *o*-aminophenol affords the lactam (**73**). (Scheme 22)



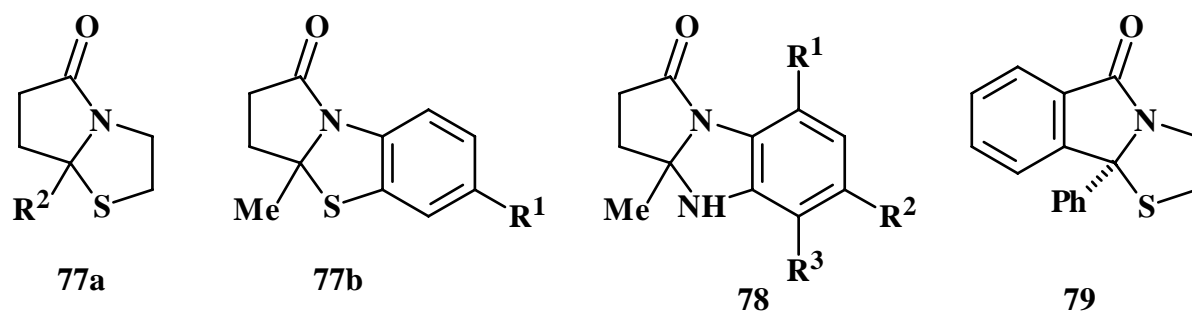
On application of aroylnorbornane- or aroylcyclohexanecarboxylic acid and stereoisomeric cycloalkane 1,3-diamines or aminoalcohols, heterocycles with five or more new chiral centres (**74a, b**) are formed;⁹³⁻¹⁰⁸ the stereoisomers has been isolated by column chromatography.^{109, 110}

The above polycyclic lactams have pharmacological activity: the 5-aryl-2,3-dihydro-5*H*-imidazo[2.1-*a*]isoindoles (**75**) prepared from tetrahydro-5*H*-imidazo[2.1-*a*]isoindol-5-one (**62a**) by reduction with LiAlH₄¹¹¹ (Scheme 23) exhibit an anorexic effect. The activity of **76** (Ar = 4-chlorophenyl) was found to be approximately equal to that of *d*-amphetamine.



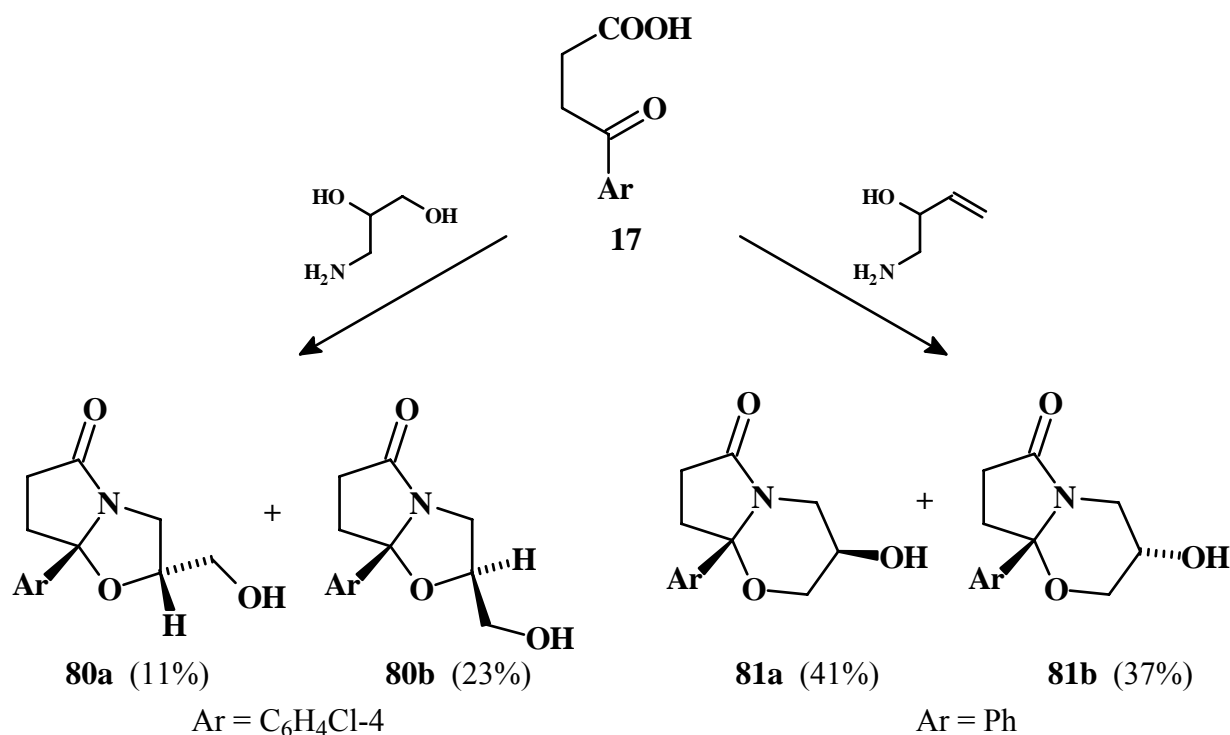
Scheme 23

A series of bicyclic analogues of succinimide and glutarimide have been synthesized by reaction of the oxo carboxylic acid with diamines and evaluated for CNS activity.¹¹² The tetrahydropyrrolothiazolone (**77a**) and -[2,1-*b*]benzothiazolone (**77b**) have anticonvulsant activity.¹¹³ (Scheme 24) Some other tetrahydro-1*H*-pyrrolo[1,2-*a*]benzimidazol-1-one derivatives have been found to be effective in sound- and electroshock-induced seizures.¹¹⁴ Other derivatives, *e.g.* **78** ($R^1, R^2, R^3 = H, Cl, OMe, NO_2$) exert cytotoxic activity on mammalian cell lines and myeloma, ovarian and colon cancer lines.^{115, 116} The substituted 2,3-dihydrothiazolo[2,3-*a*]isoindolone, *e.g.* the R-(+) isomer of **79** inhibits the reverse transcriptase of human immune deficiency virus 1 (HIV-1)¹¹⁷ and replicates the HIV-1 in MT2 cells.



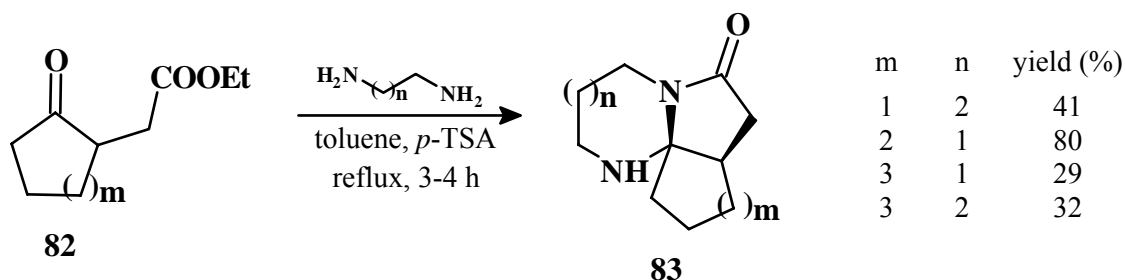
Scheme 24

From aminodiols or hydroxyalkylenamine with oxoacids, tetrahydropyrrolo[2,1-*b*]oxazol-5(6*H*)-ones (**80a,b**) and oxazine homologues (**81a,b**) have been prepared (Scheme 25); one derivative was found to display marked hypoglycaemic activity *in vivo*.¹¹⁸



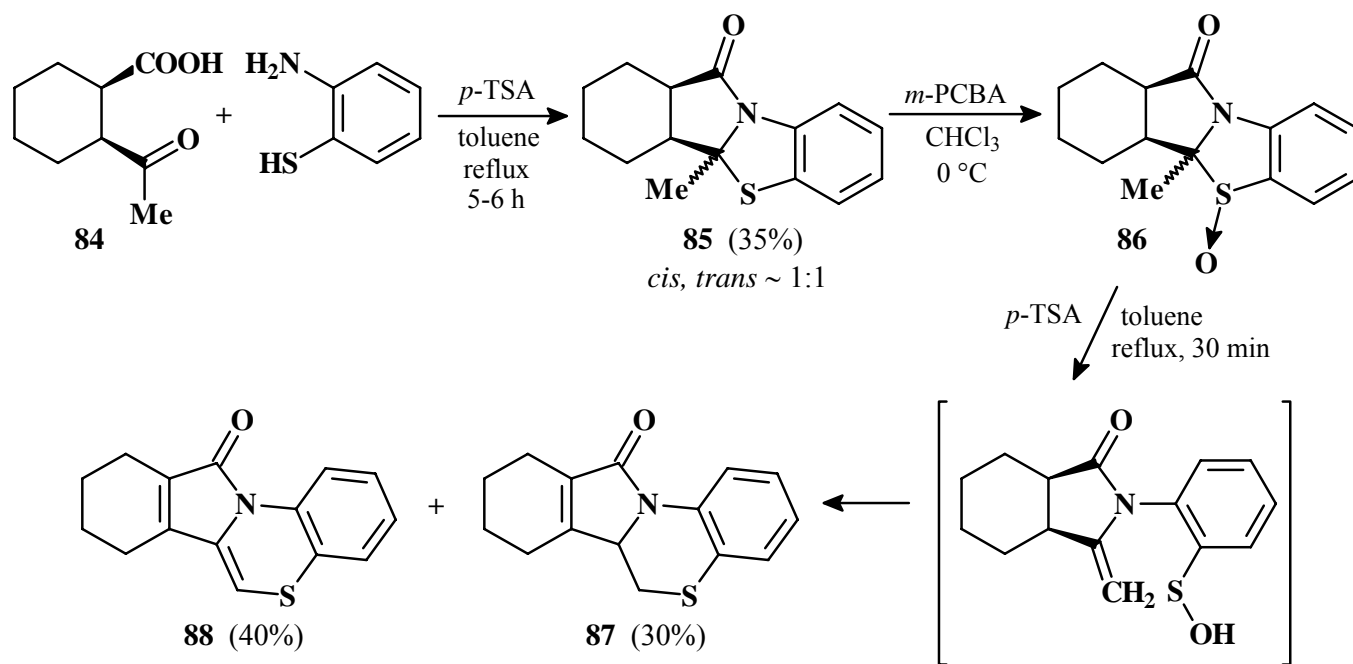
Scheme 25

From the reactions of 2-ethoxycarbonylmethyl-1-cycloalkanones (**82**) with α,ω -diaminoalkanes, the tricyclic lactams (**83**) have been prepared.¹¹⁹ (Scheme 26) The similar reaction with alicyclic 1,3-aminoalcohols result in tetra- and pentacyclic lactams, *e.g.* the pyrrolo[1,2-*a*][3,1]benzoxazines.¹²⁰⁻¹²²



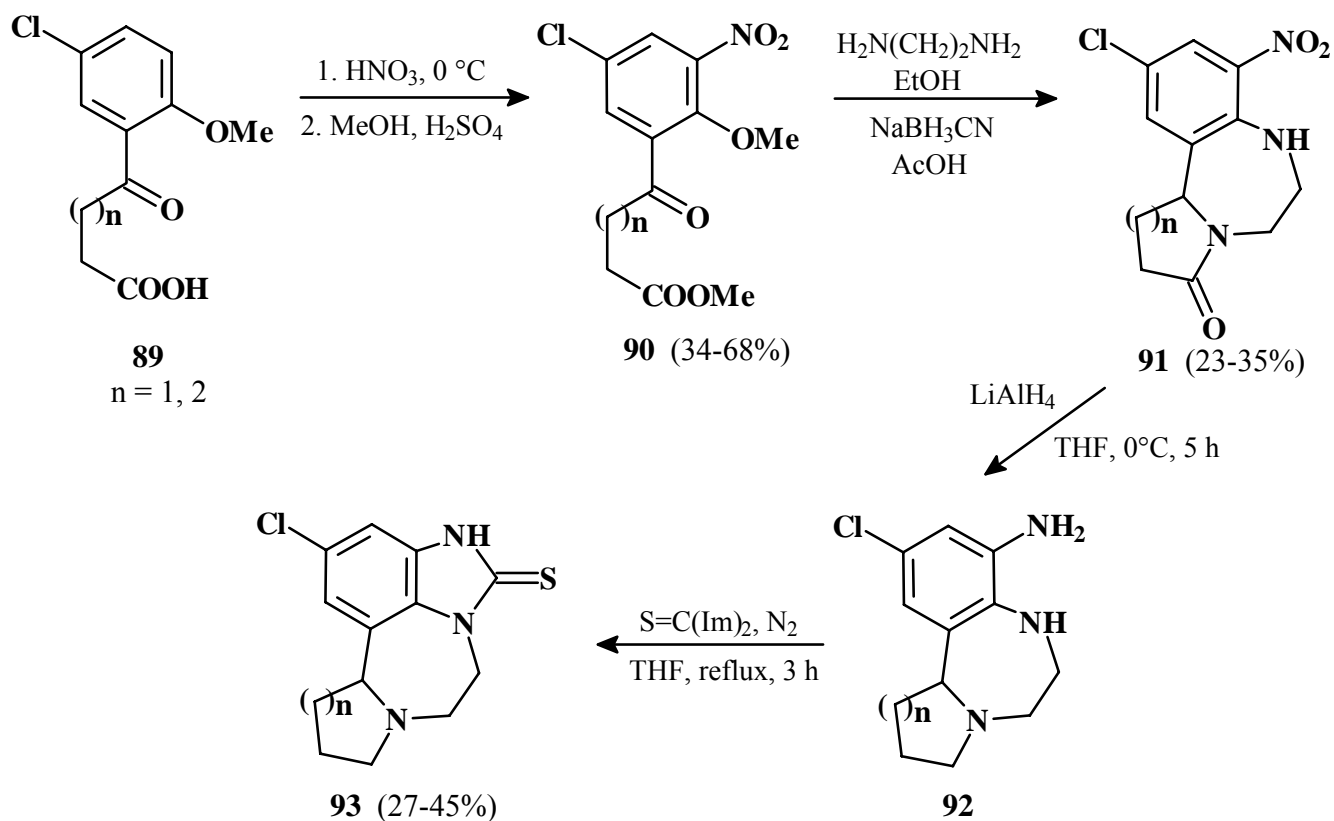
Scheme 26

Treatment of the isoindolo[1,2-*b*]benzothiazol-10(5*aH*)-one *S*-oxide (**86**) with *p*-TSA in toluene results in the thiazine (**87**) by oxidative ring expansion. As a mechanism, the formation of a sulfenic acid intermediate was supposed. The new isoindolo[1,2-*c*][1,4]benzothiazin-11-one (**88**) was also formed.²⁰ (Scheme 27)



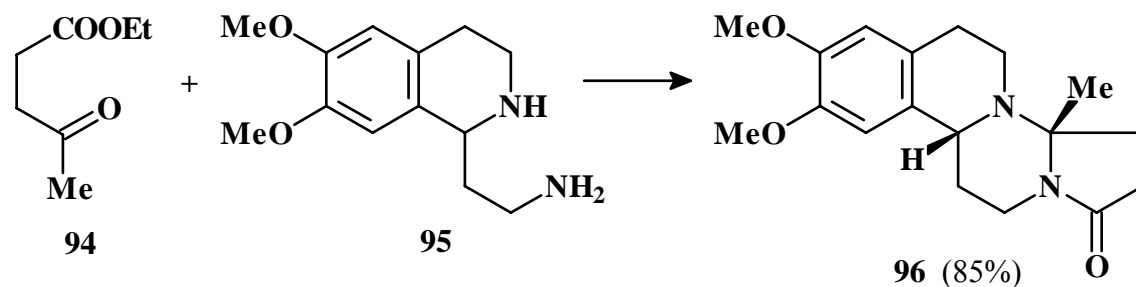
Scheme 27

The tetracyclic thiolactams (**93**) have been prepared in several steps.¹²³ The oxo acids (**89**) were nitrated, and then esterified and treated with ethylenediamine to furnish the intermediate (**91**) in a multistep one-pot reaction. Reduction and subsequent thiourea ring formation proceed through **92** to result in the hexahydroimidazo[4,5,1-*j,k*]pyrrolo[1,2-*d*][1,4]benzodiazepine-10(11*H*)-thiones (**93**). (Scheme 28) These compounds significantly inhibit HIV-1 replication *in vitro*.



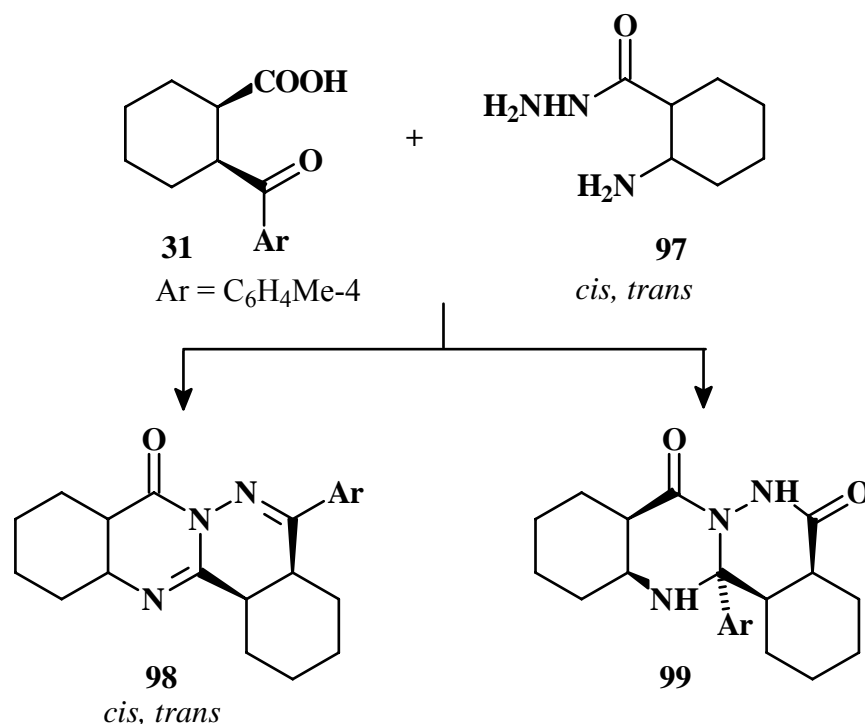
Scheme 28

Synthesis of the diazasteroid-like **96** was achieved by the condensation of levulinic ester (**94**) with aminoethylisoquinoline (**95**).¹²⁴ (Scheme 29)



Scheme 29

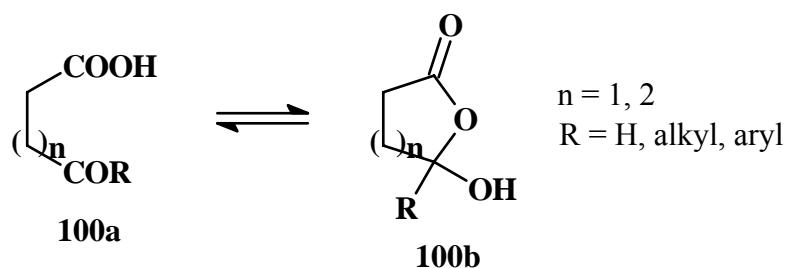
For the preparation of 1*H*-phthalazino[1,2-*b*]quinazolin-8-ones, other multifunctional amines, *e.g.* anthranilic hydrazide, have been applied.¹²⁵⁻¹²⁸ The reaction has been extended to aminocyclohexanecarbohydrazides, furnishing regio- and stereoisomers (**98**) and (**99**).¹²⁹ (Scheme 30)



Scheme 30

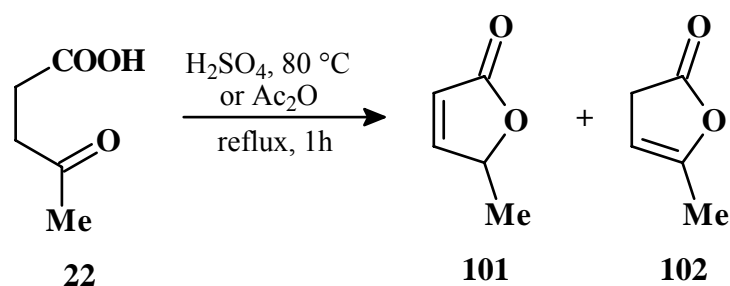
5. CYCLIZATIONS TO LACTONES

For 4- and 5-oxocarboxylic acids, the ring-chain tautomeric interconversion proceeding *via* intramolecular reversible addition to the C=O group has been well studied.¹³⁰⁻¹³² (Scheme 31)



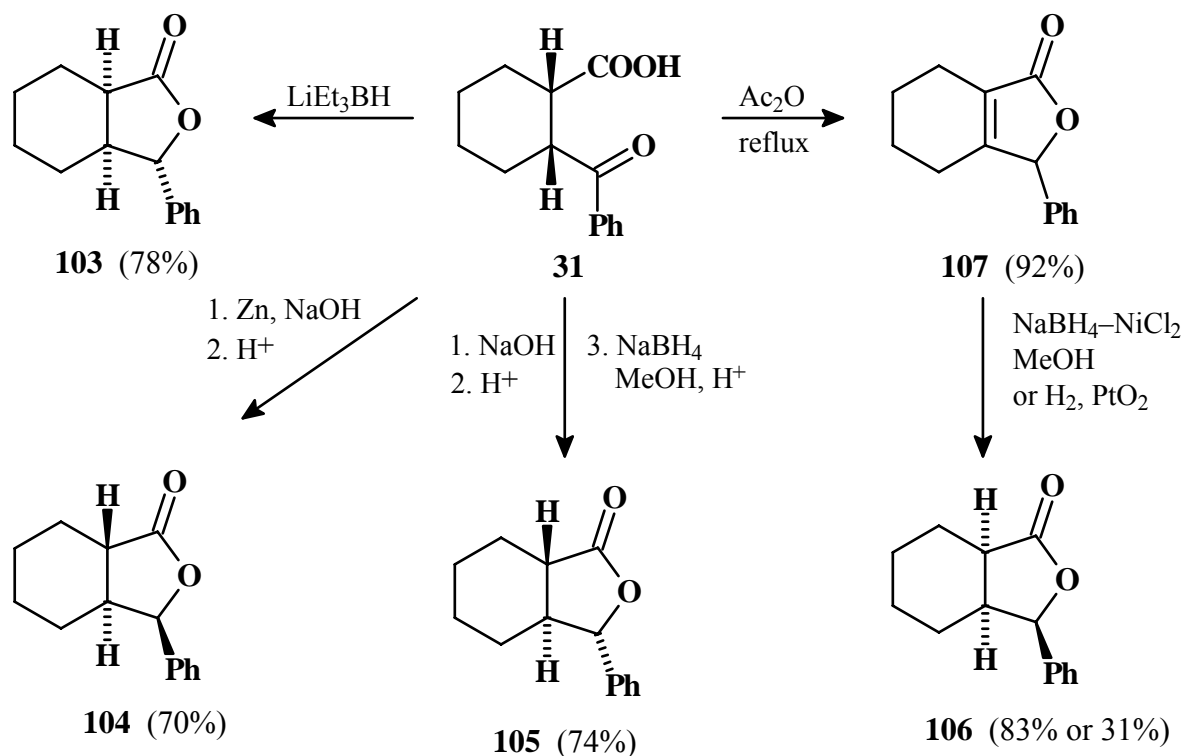
Scheme 31

The dehydration of levulinic acid (**22**) by means of strong acids or acetic anhydride results in 2(5*H*)-furanone (**101**) and 2(3*H*)-furanone (**102**), with different positions of the C=C bond.¹³³⁻¹³⁷ (Scheme 32)



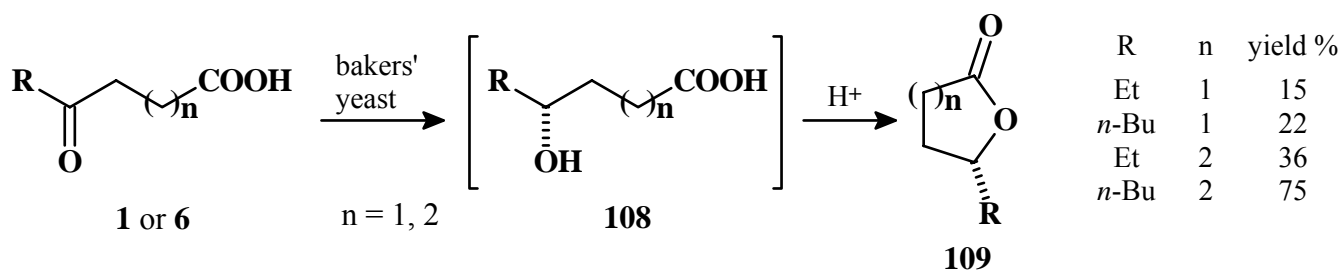
Scheme 32

Miyano *et al.* isolated four diastereoisomeric 3-phenylhexahydro-1(3*H*)-isobenzofuranones (**103-106**).¹³⁸



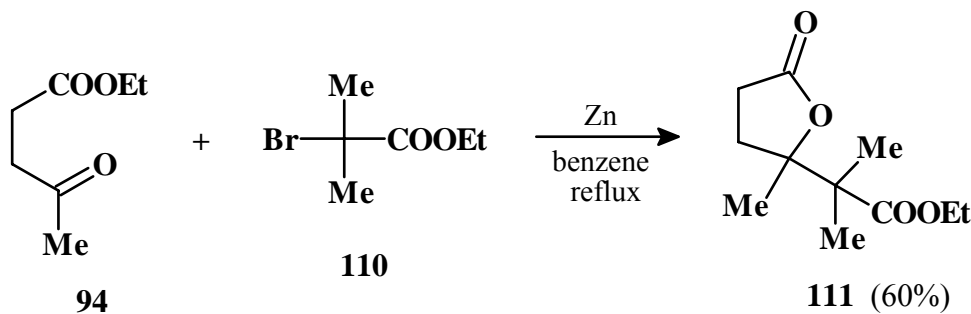
Scheme 33

Stereoisomeric 3-methylhexahydrophthalides¹³⁹ and similar lactones have been prepared by reduction with metal hydrides or H_2/PtO_2 catalyst.¹⁴⁰ Clemmensen reduction of 2-arylbenzoic acids gave 3-phenylphthalides in good yield.¹⁴¹ Another route to lactones is the asymmetric reduction with bakers' yeast (*Saccharomyces cerevisiae*), with >98% ee.¹⁴²⁻¹⁴⁷ (Scheme 34) The optically active lactones (**109**) are key intermediates in the synthesis of natural products.



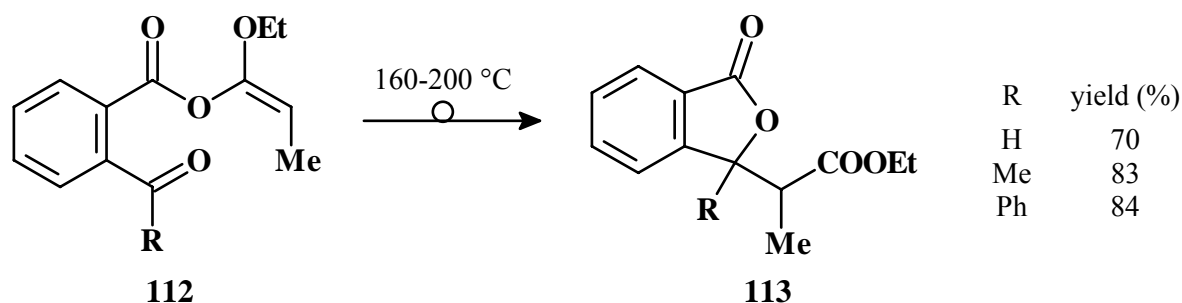
Scheme 34

The Reformatsky reaction and spontaneous cyclization of **94** result in lactone **111**.¹⁴⁸ (Scheme 35)



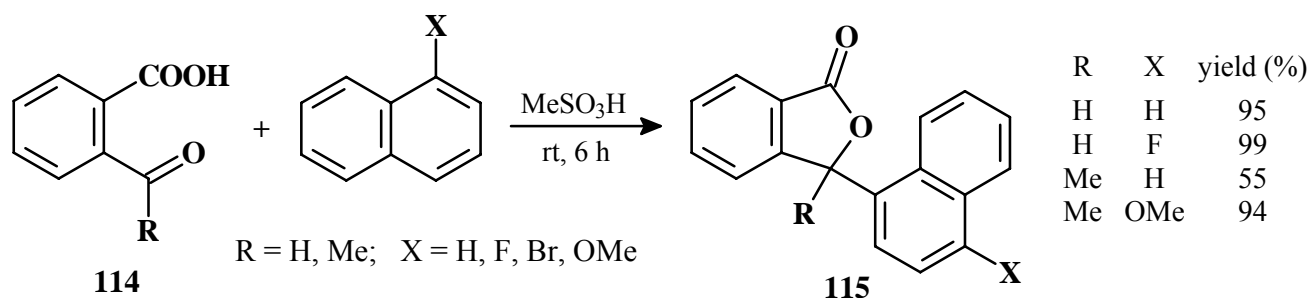
Scheme 35

The pyrolysis of 1-ethoxypropenyl esters of 2-formyl and 2-acylbenzoic acids (**112**) affords ethyl α -(1-substituted-1-phthalidyl)propionates (**113**) in high yields.¹⁴⁹ **113** can also be prepared by the Reformatsky reaction of ethyl α -bromopropionate with ethyl 2-acylbenzoates, but with low yields. (Scheme 36)



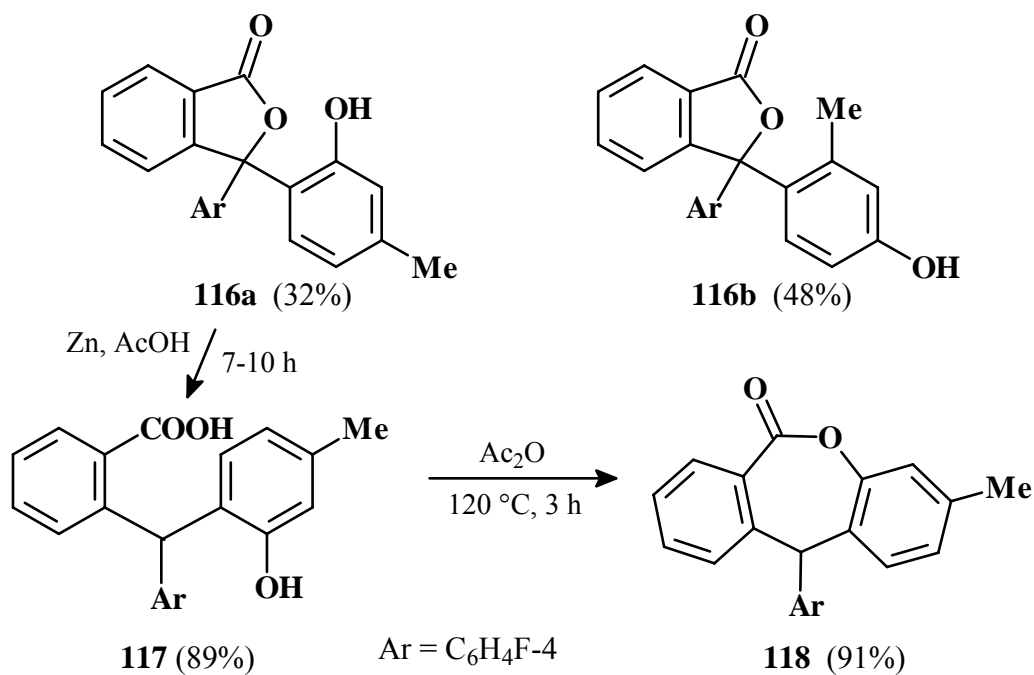
Scheme 36

Further methods are known for the formation of lactones, *e.g.* the acid-catalysed condensations of phthalaldehydic acid or 2-acetylbenzoic acid with benzene and naphthalene derivatives yield 3-phenyl- and 3-(1-naphthyl)phthalides.^{19, 150, 151} (Scheme 37)



Scheme 37

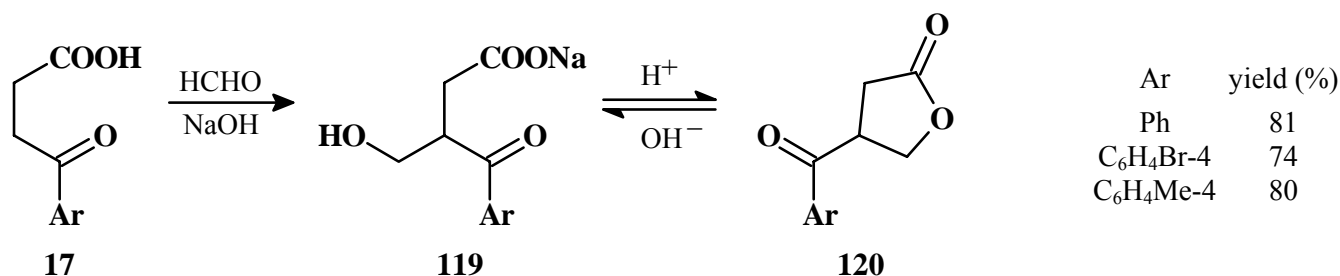
The condensation of 2-(4-fluorobenzoyl)benzoic acid with *m*-cresol in the presence of anhydrous ZnCl_2 at



Scheme 38

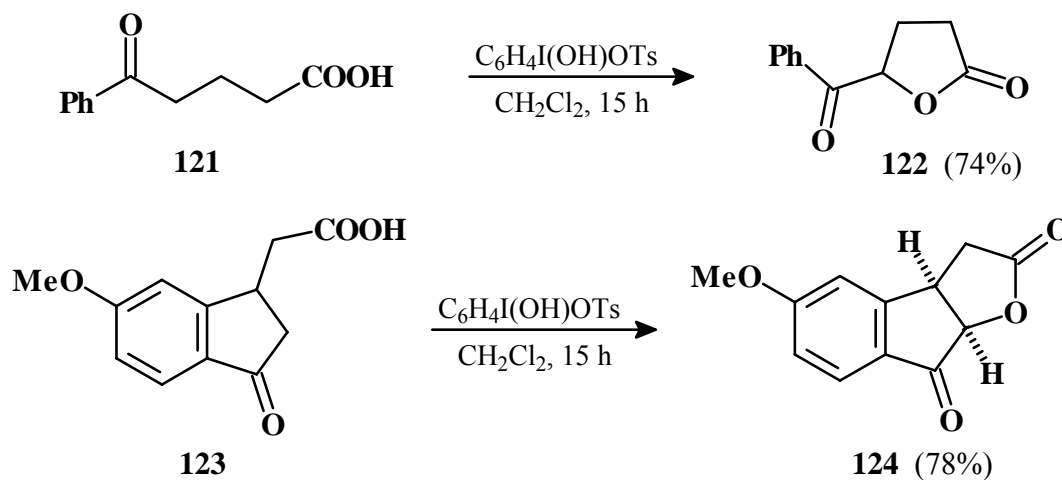
115-120 °C for 8 h furnishes two isomeric products (**116a**) and (**116b**) in different ratios.^{152,153} (Scheme 38) **116a** can be converted to dibenzo[*b,e*]oxepinone (**118**) via **117**, which is obtained by the reduction of **116a** with zinc–acetic acid.¹⁵⁴

The hydroxymethylation of 3-arylpropionic acids leads to 4-aryl-2(3*H*)-dihydrofuranones (**120**), which are in a pH-dependent equilibrium with the open form (**119**).¹⁵⁵ (Scheme 39)



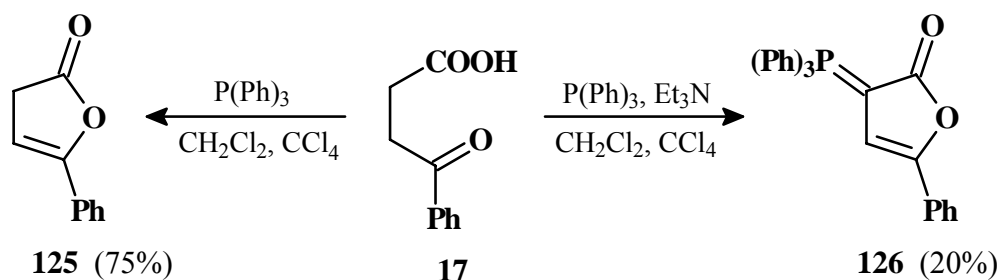
Scheme 39

Hypervalent iodine oxidation with hydroxy(tosyloxy)iodobenzene yields aryl- γ -lactones.¹⁵⁶ In the case of 4-benzoylbutyric acid (**121**), 5-benzoyldihydro-2(3*H*)-furanone (**122**) was obtained. From the oxo acid (**123**), by oxidative cyclization, the tricyclic ring system (**124**) was formed stereoselectively in good yield (78%). (Scheme 40)



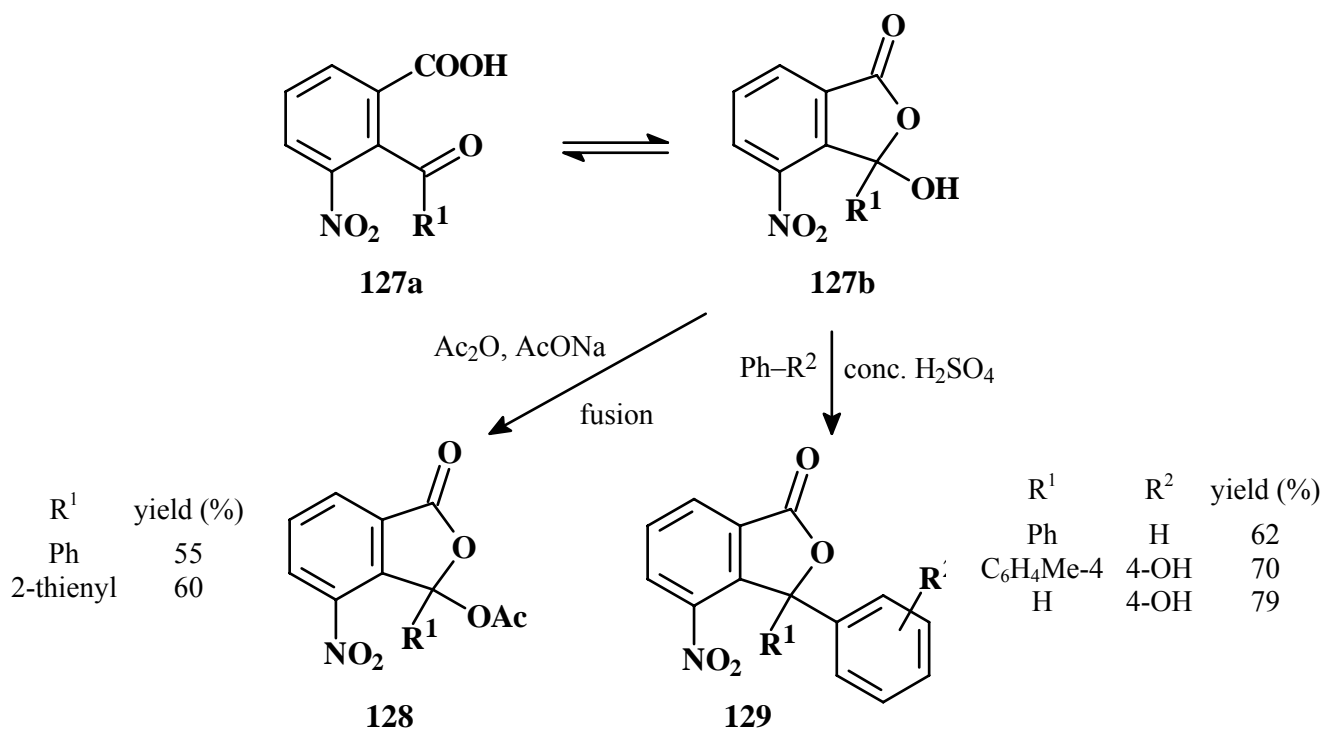
Scheme 40

The readily enolizable 3-benzoylpropionic acid (**17**) has been cyclized with triphenylphosphine to enol lactones (**125**) and (**126**), in 75% yield. (Scheme 41)¹⁵⁷



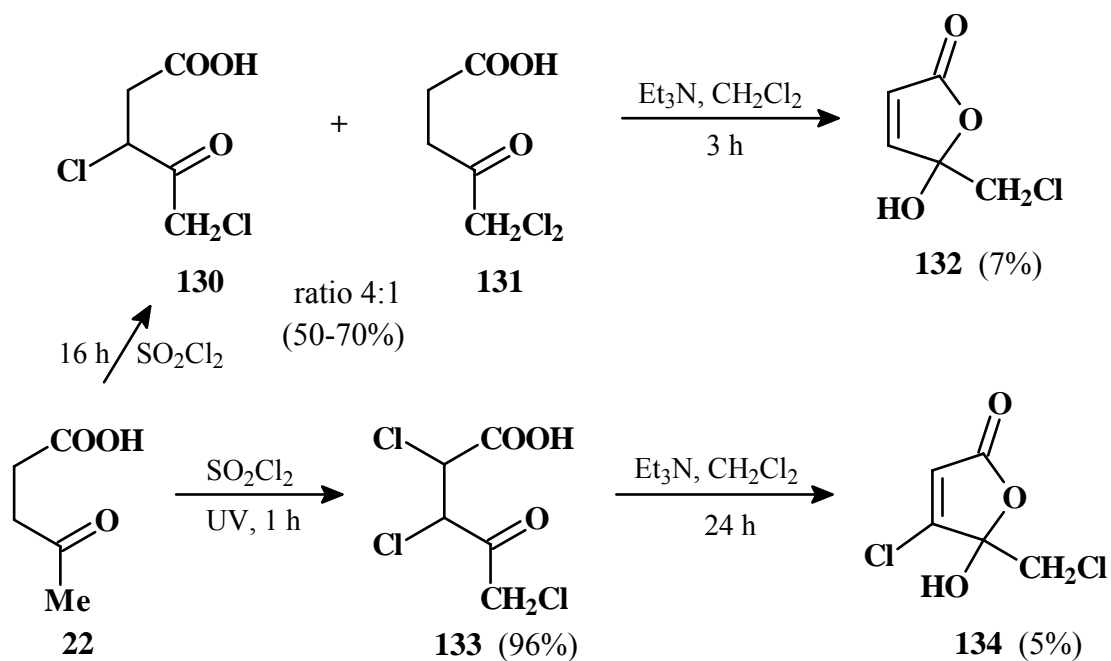
Scheme 41

Treatment of 2-acyl-3-nitrobenzoic acid (**127a,b**) with Ac₂O in the presence of sodium acetate results in nitrophthalide (**128**) on fusion, or **129** on reaction with substituted benzene and conc. sulfuric acid.¹⁵⁸ (Scheme 42)



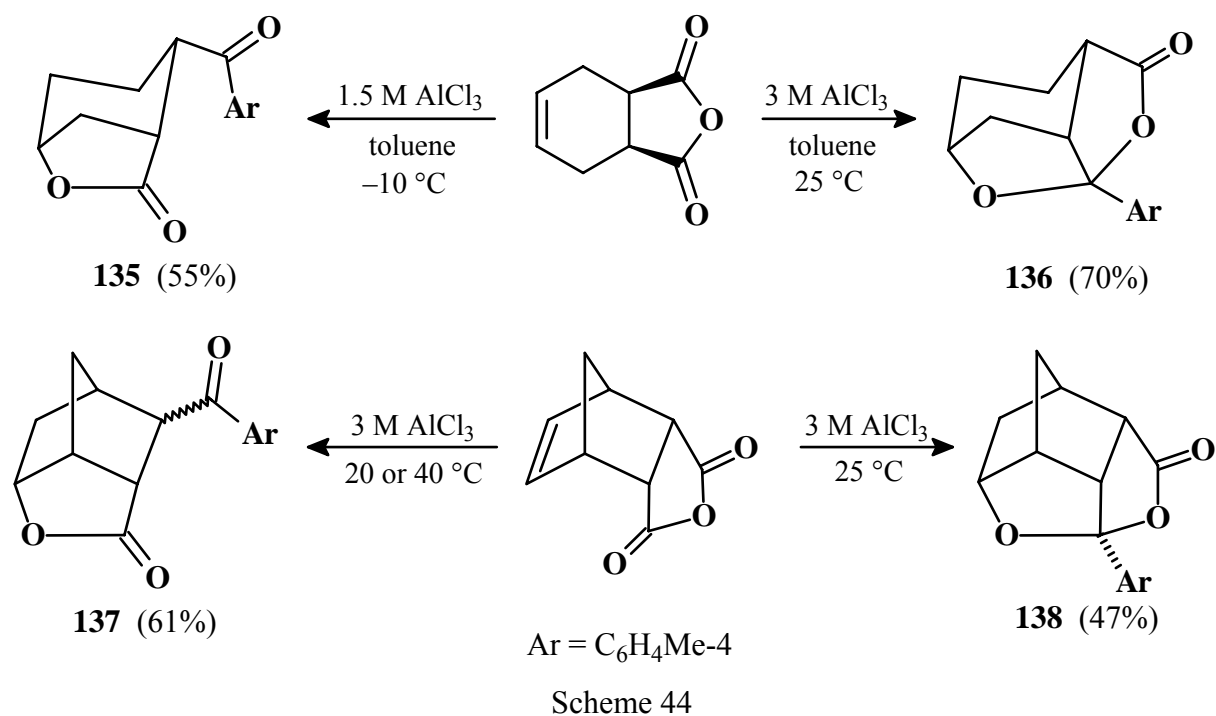
Scheme 42

Chlorination of levulinic acid (**22**), followed by triethylamine treatment, promotes the elimination of HCl to lead to the formation of 5-(chloromethyl)hydroxyfuranones (**132**) and (**134**).¹⁵⁹ (Scheme 43)

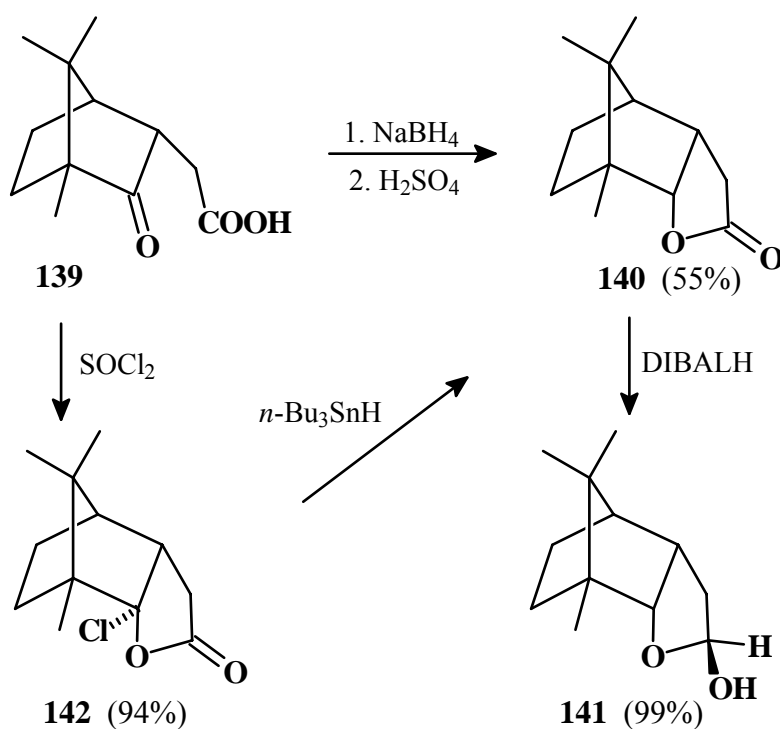


Scheme 43

The Friedel-Crafts reaction of *cis*-tetrahydrophthalic anhydride with toluene at $-10\text{ }^{\circ}\text{C}$ proceeds *via* the oxocarboxylic acid to afford the 2-(4-methylphenyl)-6-oxabicyclo[3.2.1]octan-7-one (**135**).^{160, 161} In the presence of more (1:2) AlCl_3 , the reaction yields the 7-(4-methylphenyl)-6,10-dioxatricyclo[5.2.1.0^{4,8}]decan-5-one (**136**).¹⁶¹ With *diendo*-5-norbornene-2,3-dicarboxylic anhydride as starting material, the methylene-bridged analogues (**137**) and (**138**) are obtained.¹⁶¹ (Scheme 44)



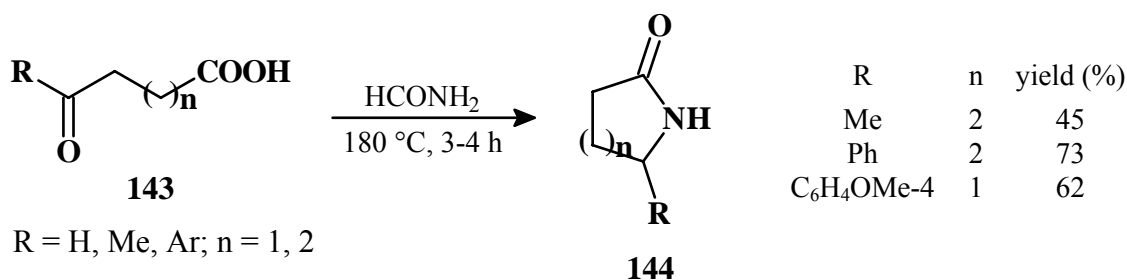
When camphoracetic acid (**139**) is reacted with NaBH_4 , and then with sulfuric acid, the *endo*-fused lactone



(**140**) is obtained. (Scheme 45) Treatment with thionyl chloride yields the chloro compound (**142**). Subsequent reduction with tributyltin hydride and DIBALH, through **140**, results in the lactol (**141**), which is a useful reagent in racemate resolution and asymmetric syntheses.¹⁶²

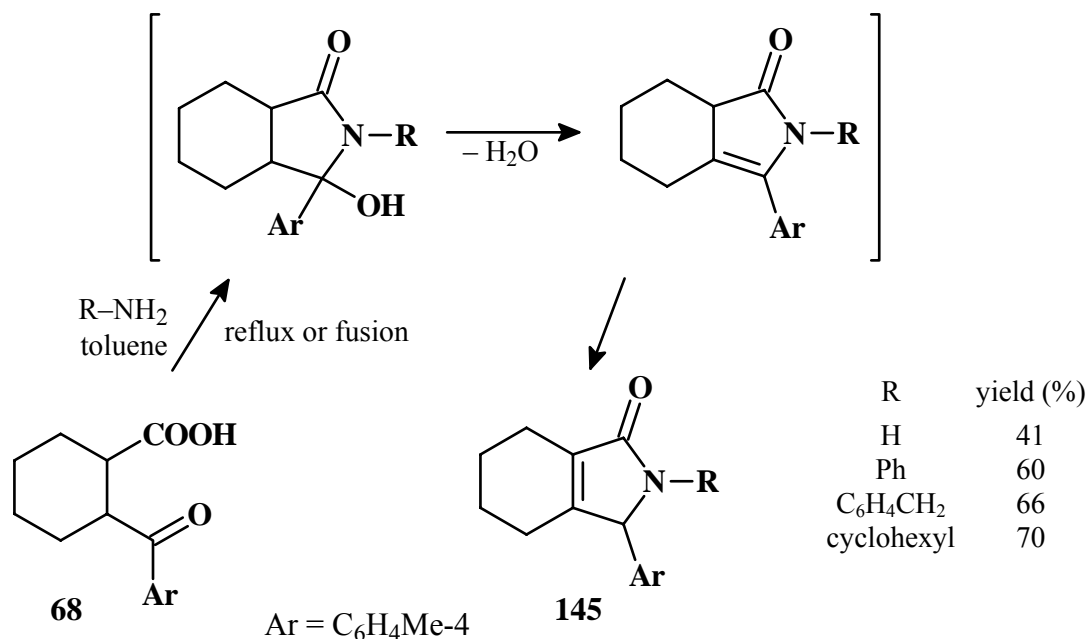
6. FORMATION OF LACTAMS

The 4- and 5-oxocarboxylic acids (**143**) or their esters react facilyly with amines to give γ - or δ -lactams. In the Leuckart reaction with formamide at 180 °C, the oxo acids give 2-pyrrolidones or 2-piperidinones (**144**).¹⁶³ (Scheme 46)



Scheme 46

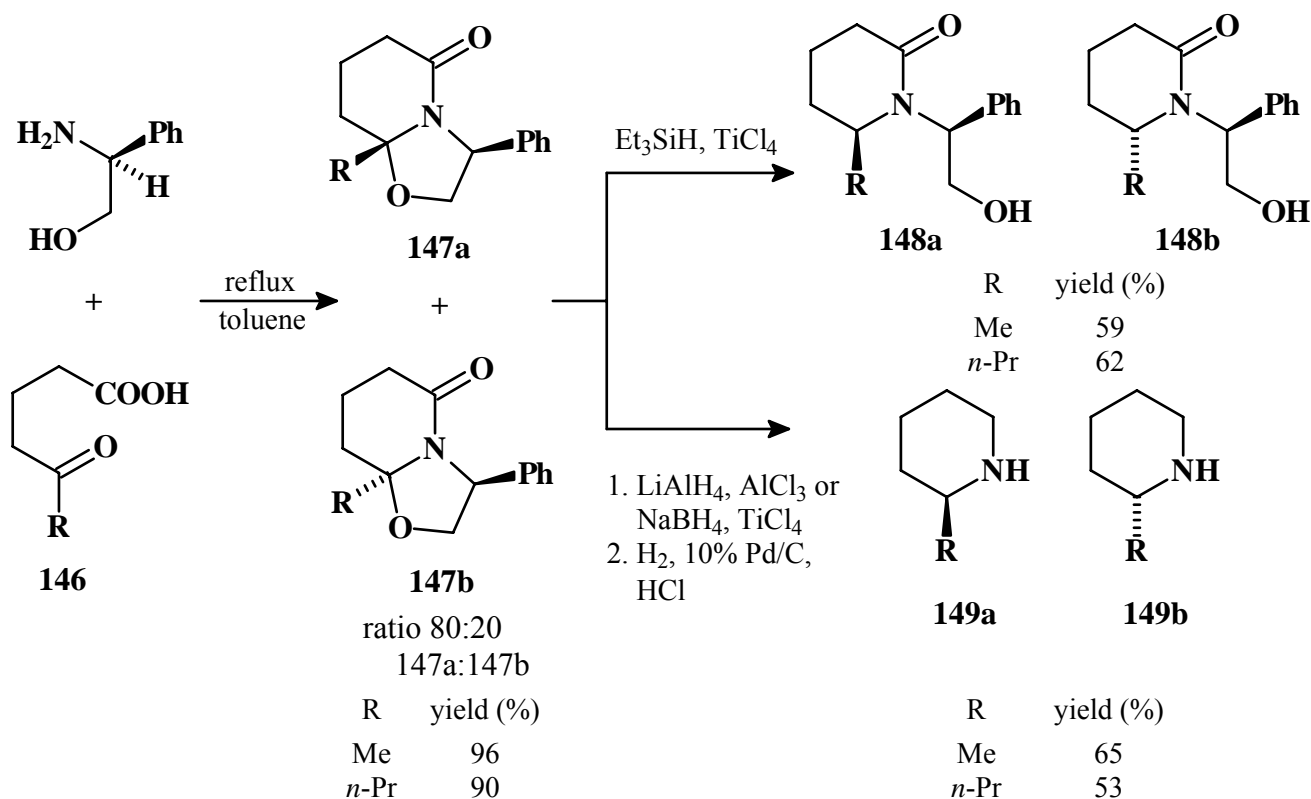
The *cis*- and *trans*-2-arylcyclohexanecarboxylic acids (**68**) condense with primary amines under mild conditions, while the aryl- or hetaryl amines react only under forceful conditions (*e.g.* fusion), to result in hexahydroisindolones (**145**).⁶⁹ (Scheme 47)



Scheme 47

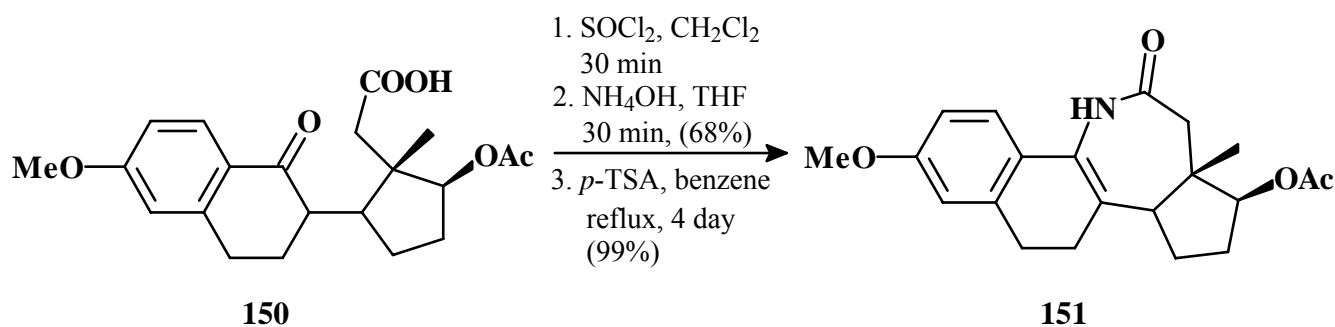
A one-step conversion of 2-acylbenzoic acids to 3-oxodihydroisindoles has been developed, involving reductive amination with sodium cyanoborohydride or sodium borohydride in acetonitrile.¹⁶⁴ Another modified method of reductive amination with sodium triacetoxyborohydride and primary amines has also

been described.¹⁶⁵ Highly enantioselective preparations of 6-alkylpiperidin-2-one derivatives (**148a,b**) and (**149a,b**) have been achieved by using 2-amino alcohols as chiral auxiliaries.¹⁶⁶⁻¹⁷¹ In the first step, bicyclic lactams (**147a,b**) are formed, which are then opened with reducing agents (Scheme 48).



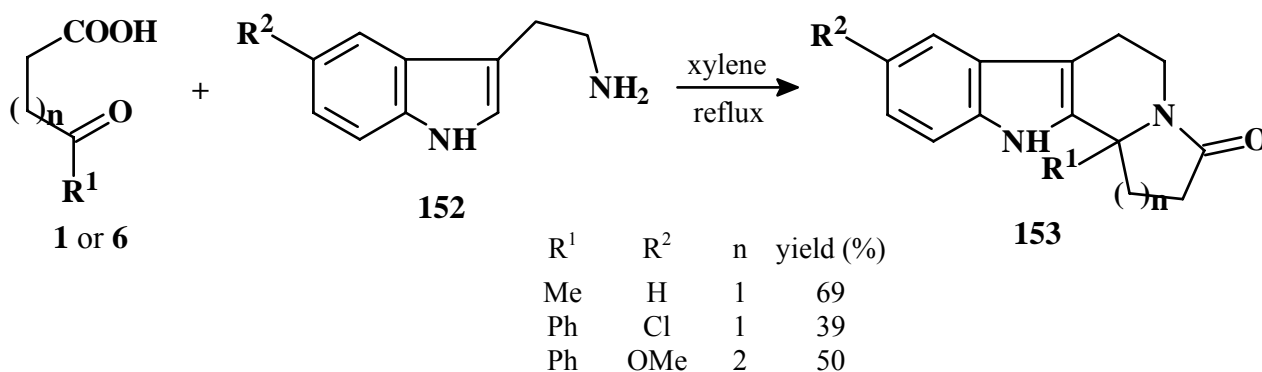
Scheme 48

The synthesis of an azasteroid from estrone has been achieved.¹⁷² The 11-aza-*C*-homoestrane (**151**) was prepared from the oxo acid (**150**) by treatment with thionyl chloride and ammonia, and subsequent acid-catalysed cyclization. (Scheme 49)



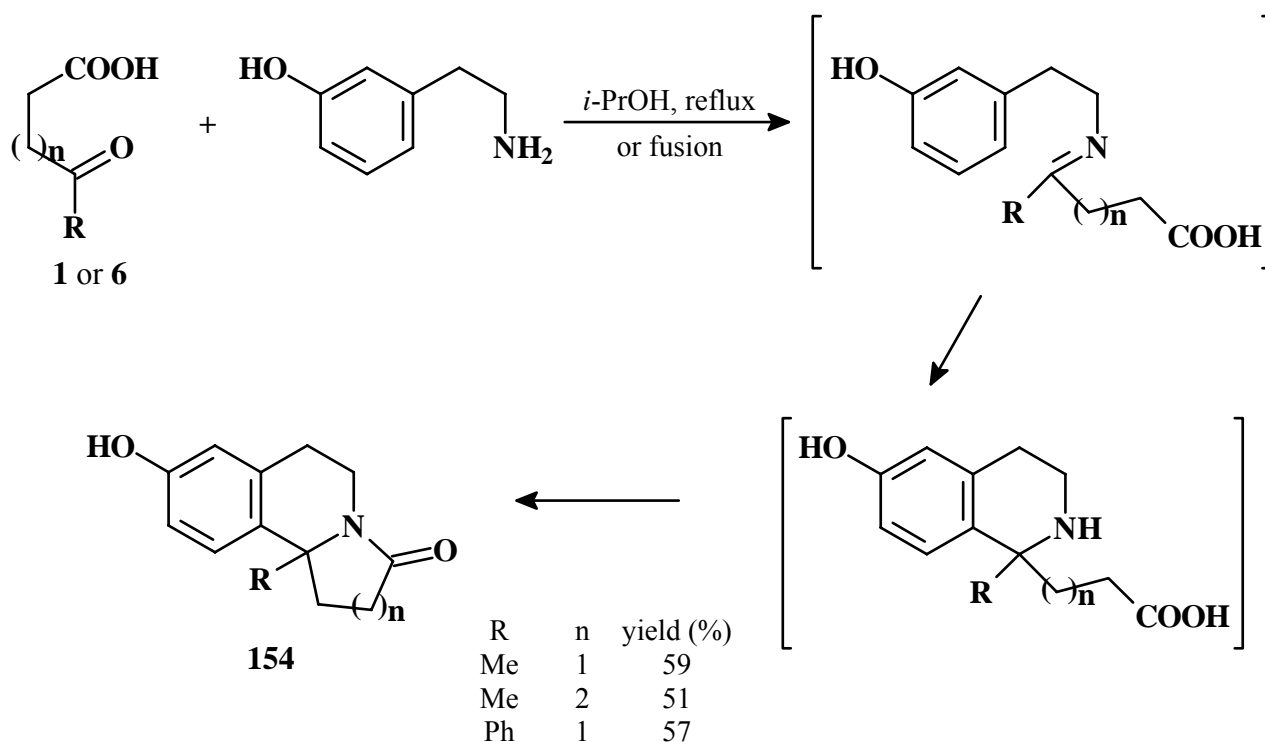
Scheme 49

The condensations of oxocarboxylic acids (**1**) or (**6**) with 2-phenylethylamines, tryptophane or tryptamine to furnish isoquinoline or β -carboline derivatives **153** have been reported.¹⁷³⁻¹⁷⁶ (Scheme 50)



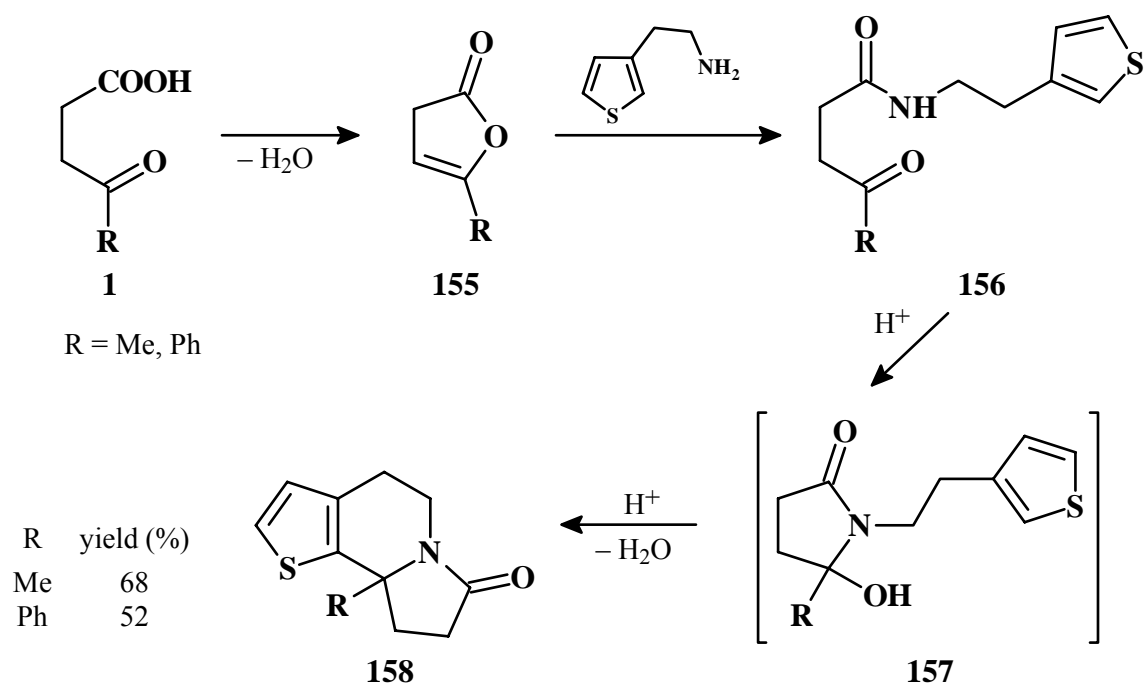
Scheme 50

On application of the Pictet-Spengler reaction in aprotic media, tetracyclic lactams were obtained in good yields (80%) from oxoglutaric acid.¹⁷⁶ The treatment of 3-hydroxyphenylethylamine with oxoacids in the presence of solvent and an acidic catalyst, or by fusion at 150-200 °C, results in the hexahydropyrrolo[2,1-*a*]isoquinolin-3-ones (**154**) and benzo[*a*]quinolizinsones.^{177, 178} (Scheme 51)



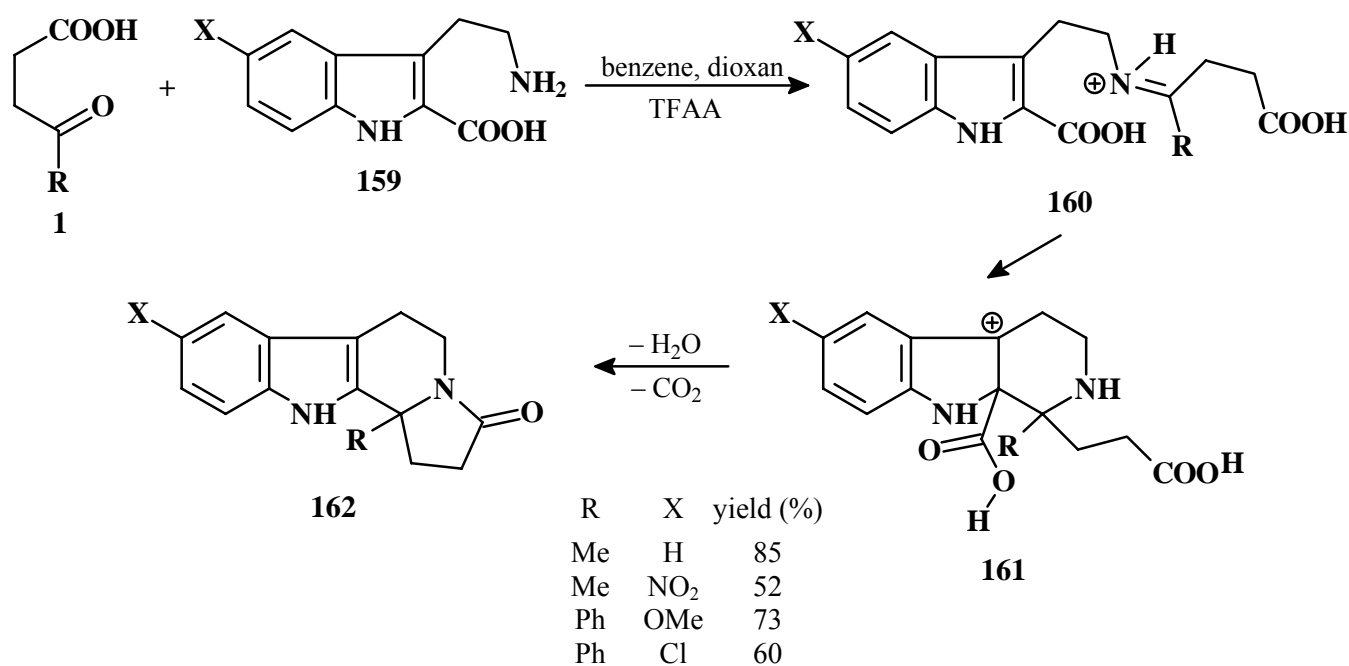
Scheme 51

In the reaction with thienylethylamine, an intramolecular amidoalkylation by acidic catalysis *via* the α -hydroxylactam (**157**) was initially presumed.¹⁷⁹ (Scheme 52) The intermediate (**157**) forms an acyliminium ion by water elimination and this, on cationic cyclization, yields the tricyclic lactam (**158**).¹⁷⁹⁻¹⁸²



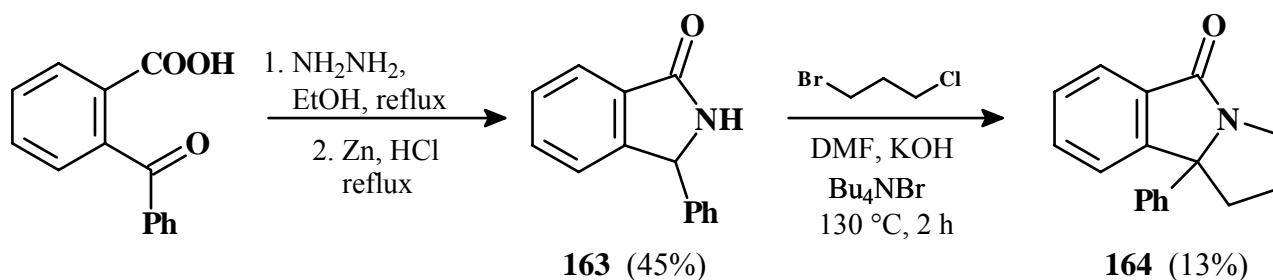
Scheme 52

The synthesis of hexahydro-3-oxo-1*H*-indolizino[8,7-*b*]indoles (**162**) from tryptamine-2-carboxylic acids (**159**), based on the carboxyl-mediated Pictet-Spengler reaction, has been described.¹⁸³ (Scheme 53)



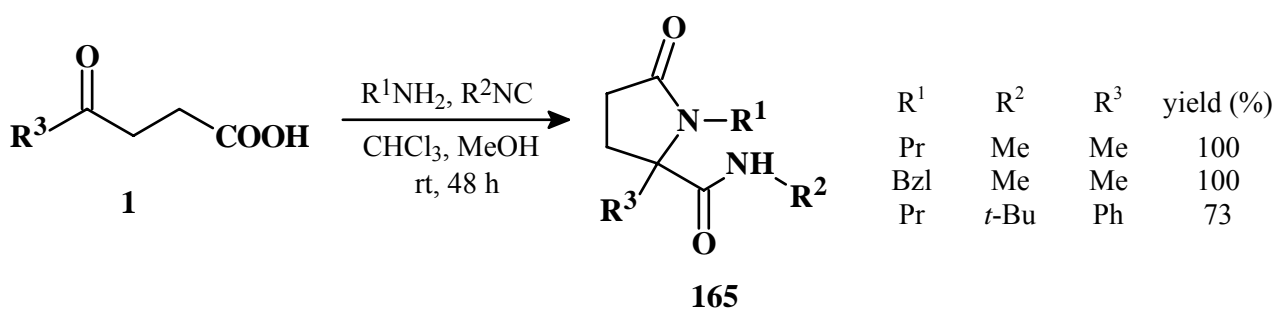
Scheme 53

Another route could be the condensation of an oxo acid to the phenylphthalimidine (**163**), followed by transformation by phase-transfer alkylation with 1-bromo-3-chloropropane to the tricyclic lactam.¹⁸⁴ (Scheme 54) **164** and its pyrido analogues display virucidal activity.



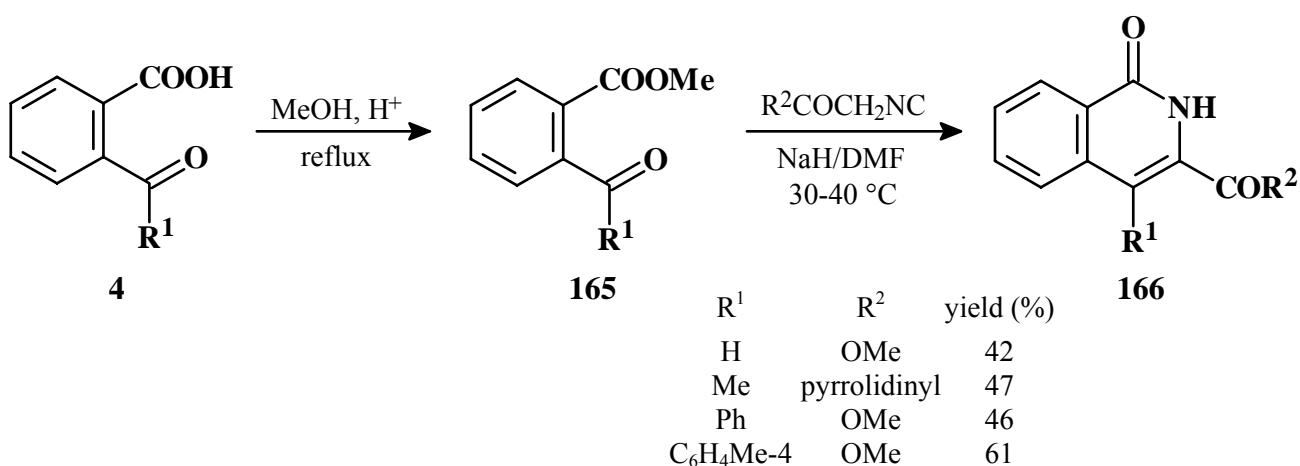
Scheme 54

A simple synthesis of *N*-substituted lactams (**165**) is the condensation of oxo acid with alkylamines in the presence of isocyanides at room temperature.¹⁸⁵ (Scheme 55)



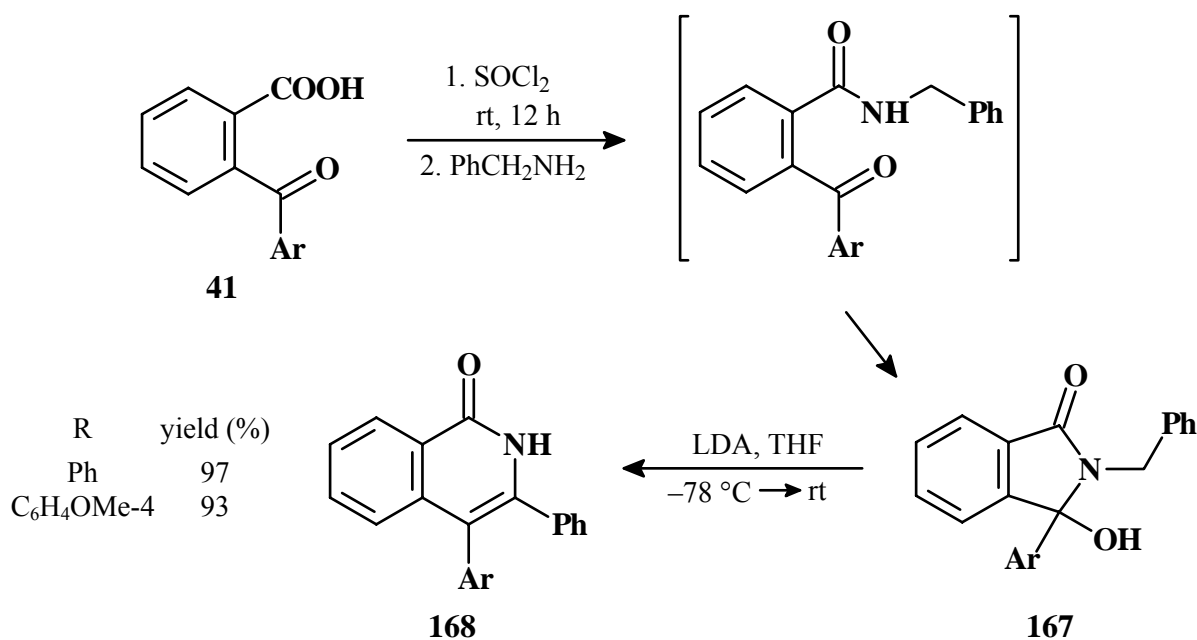
Scheme 55

Isocyanides have also been used for preparations from 2-formyl- or 2-acylbenzoates with the application of isocyanatoacetates and sodium hydride in DMF; by means of this route, the one-step synthesis of 1-oxo-1,2-dihydroisoquinoline derivatives (**166**) has been achieved.¹⁸⁶ (Scheme 56)



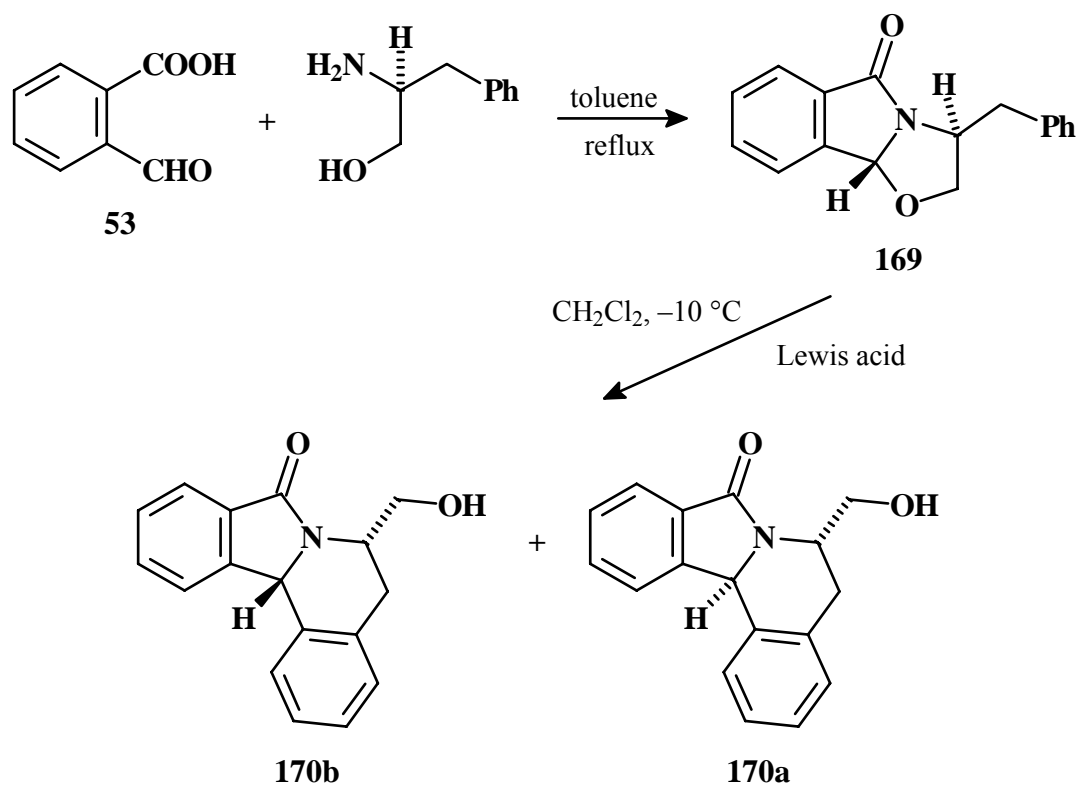
Scheme 56

3,4-Diarylisquinolones (**168**) have been prepared by treatment of 2-aryloxybenzoic acid with thionyl chloride, and then with benzylamine; the lactams (**167**) obtained are converted through ring opening with LDA to isoquinolones.¹⁸⁷ (Scheme 57)



Scheme 57

A facile and highly stereoselective formation of the polycyclic isoindolinones (**170a,b**) has been attained with strong Lewis acids (*e.g.* SnCl₄, TiCl₄, BF₃·OEt₂ and TMSOTf) by *N*-acyliminium ion cyclization.¹⁸⁸ (Scheme 58)

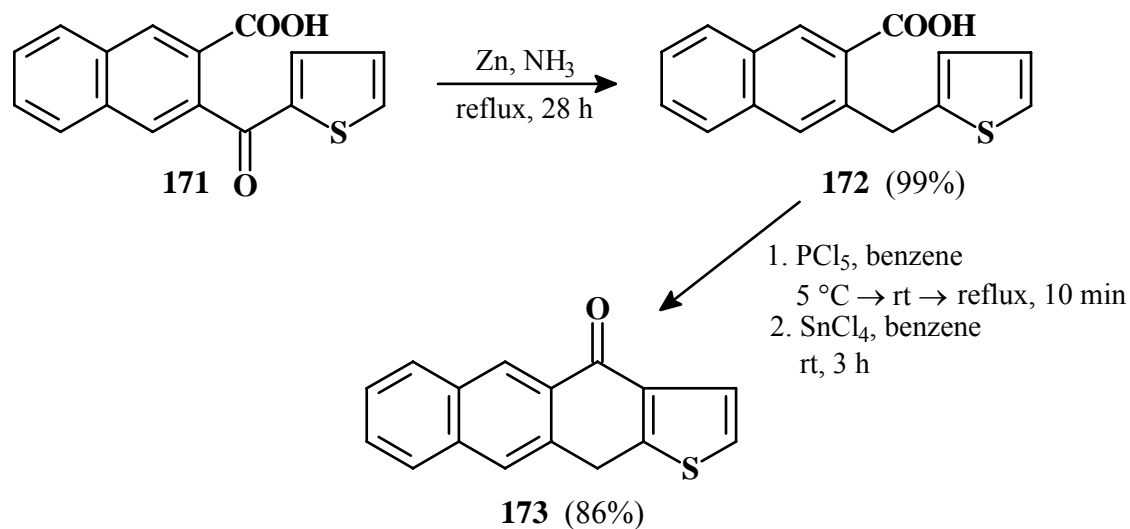


yield 93-99%; ratio 2:1-49:1

Scheme 58

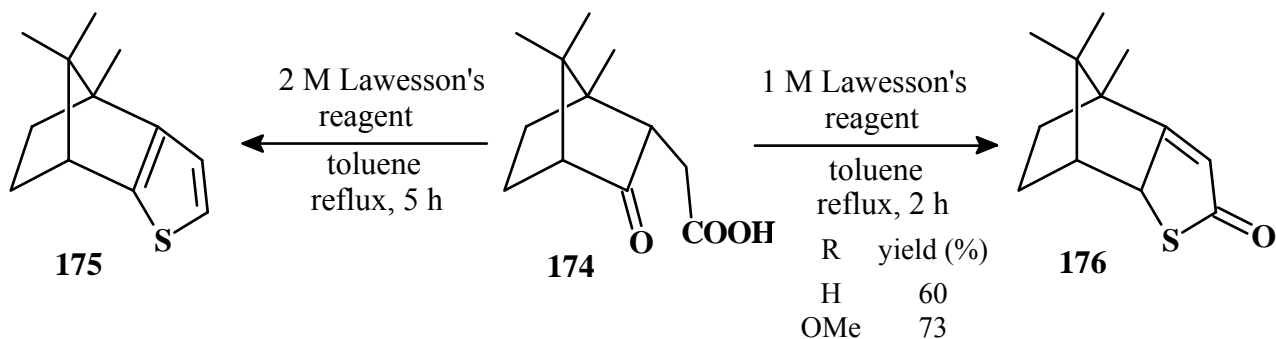
7. CONVERSION TO THIOPHENE DERIVATIVES

The AlCl_3 -catalysed Friedel-Crafts acylation of thiophene with naphthalene dicarboxylic anhydride in 1,2-dichloroethane affords the oxo acid (**171**) in good yield; this can then be reduced and cyclized to a thiophene analogue of tetralone, anthrone or naphthacenone (**173**).¹⁸⁹⁻¹⁹² (Scheme 59)



Scheme 59

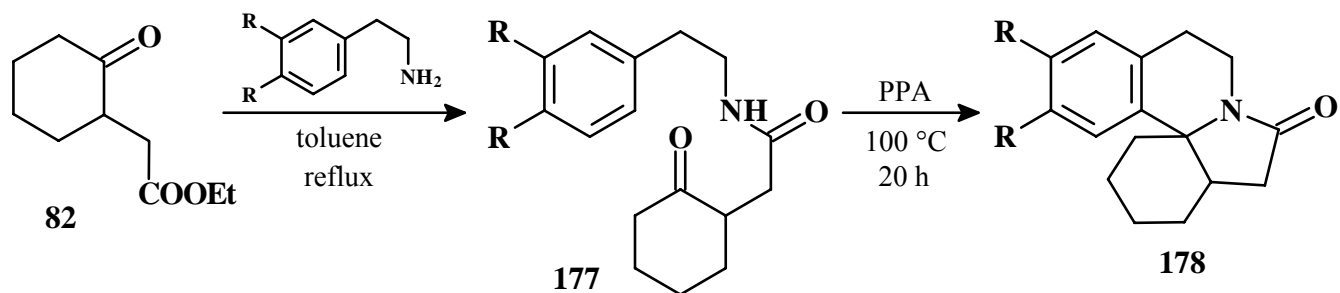
Oxocarboxylic acids can be converted to thiophene derivatives with the Lawesson's reagent in toluene;^{193, 194} depending on the molar ratio, **175** or **176** is formed. (Scheme 60)



Scheme 60

8. SYNTHESSES OF NATURAL PRODUCTS. OTHER RING SYSTEMS

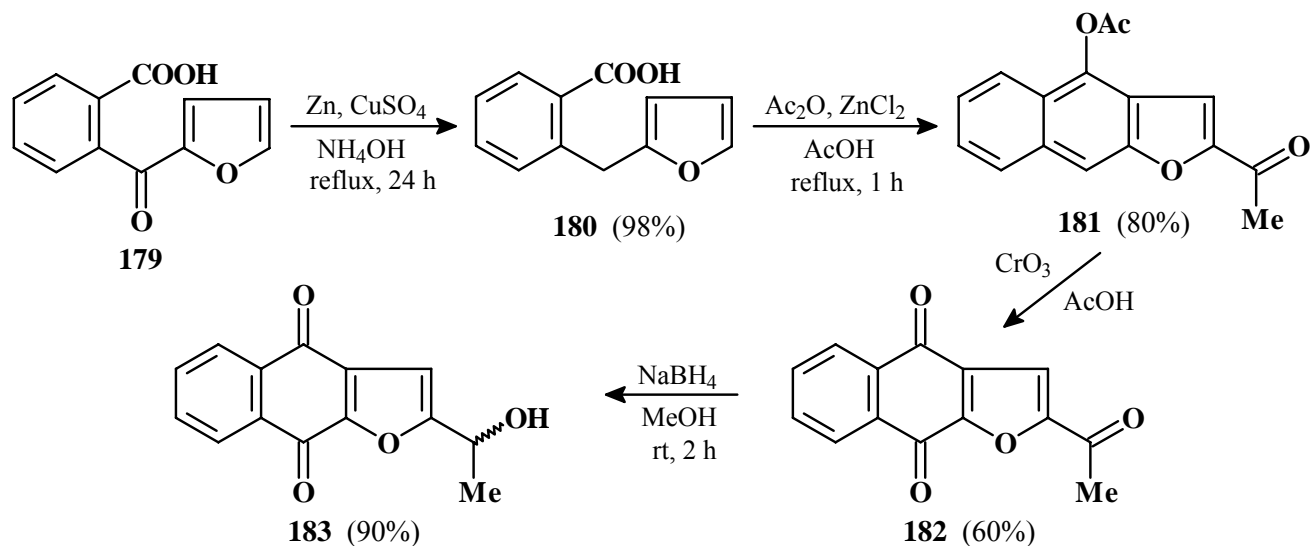
Certain parts of the total synthesis of alkaloids have been performed from cyclic 4-oxocarboxylic acids,



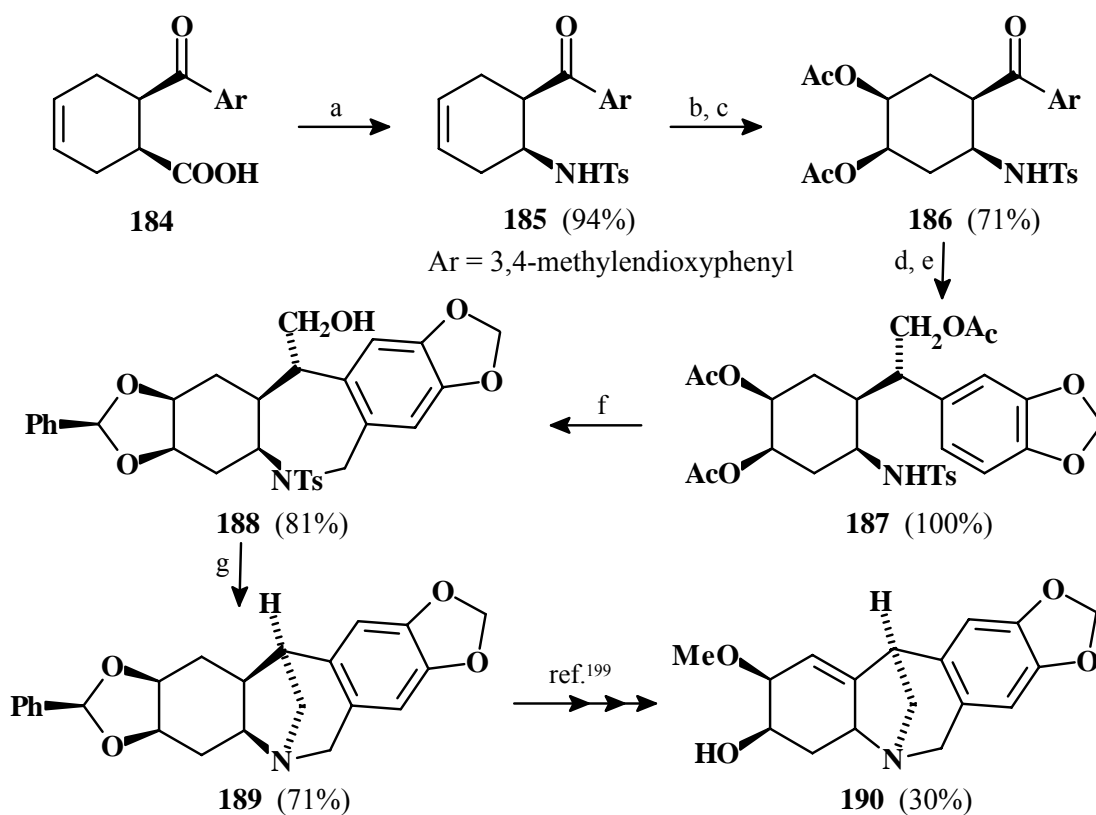
Scheme 61

e.g. in the preparation of *Erythrina* alkaloids by the cyclization of 2-phenylethylamines with ethoxycarbonylmethylcyclohexanone (**82**).^{195,196} (Scheme 61)

The cytotoxic quinonone (**183**) has been synthesized from furan and phthalic anhydride,¹⁹⁷ and also isolated from the stem bark of *Tabebina cassindes*. (Scheme 62)

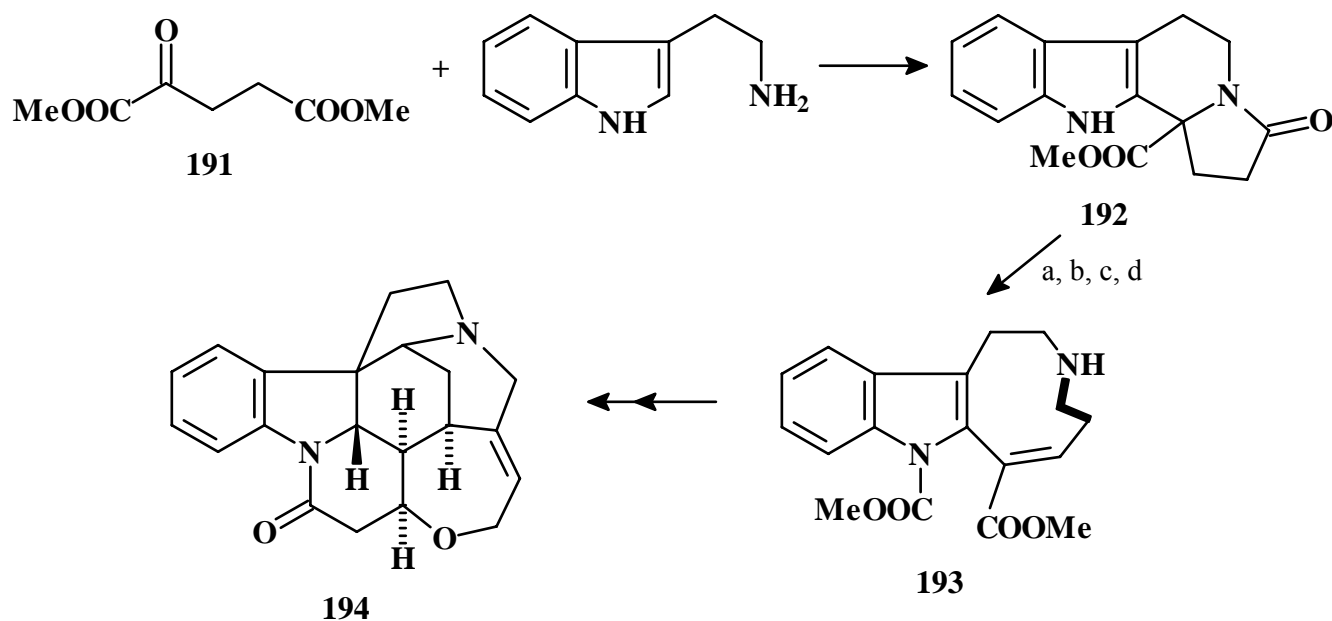


Montaine-type *Amaryllidaceae* alkaloids, which possess a 5,11-methanomorphanthridine ring system *e.g.* **190**, have been prepared stereoselectively from aroylcyclohexenecarboxylic acids (**184**).^{198, 199} (Scheme 63)



- a) 1. ClCO₂Et, Et₃N, 2. NaN₃, 3. *t*-BuOH, reflux; b) 1. TFA, CHCl₃, 2. TsCl, Et₃N; c) OsO₄, NMO, 4. Ac₂O, pyridine; d) PPh₃, MeBr, *t*-BuOK, THF; e) 1. BH₃, THF, 2. NaOH, H₂O₂, 3. Ac₂O, pyridine; f) 1. (CH₂O)_n, Ac₂O, MeSO₃H, 2. NaOMe, 3. PhCH(OMe)₂, *p*-TSA; g) SMEAH, *o*-xylene, reflux

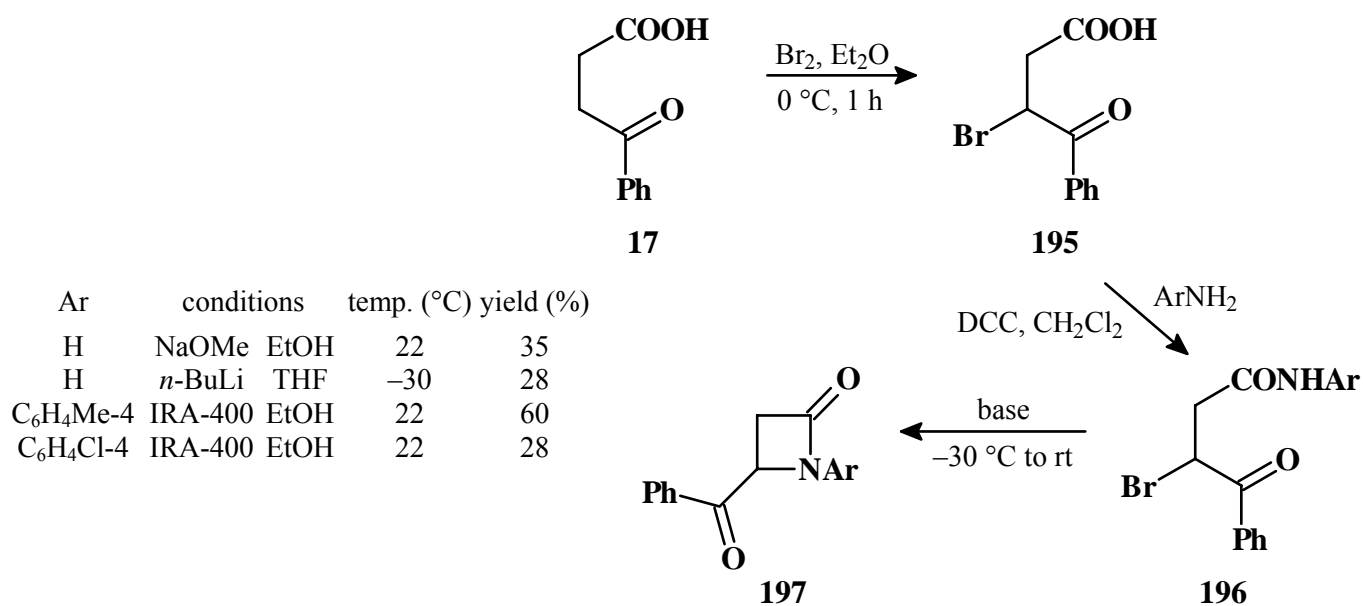
The formal synthesis of strychnine started from the 2-oxoglutaric acid ester (**191**) and tryptamine.²⁰⁰ After reduction and ring expansion of **192**, the tricyclic **193** containing a nine-membered ring was obtained, which is a key intermediate for the preparation of strychnine. (Scheme 64)



a) $\text{Cl}_3\text{CCH}_2\text{OCOC}_2\text{H}_5$, CH_2Cl_2 ; b) NaOMe, MeOH; c) 50% aq. NaOH, CH_2Cl_2 , $\text{MeOCOC}_2\text{H}_5$, benzyl-triaethylammonium chloride; d) Zn, MeCOOH, THF

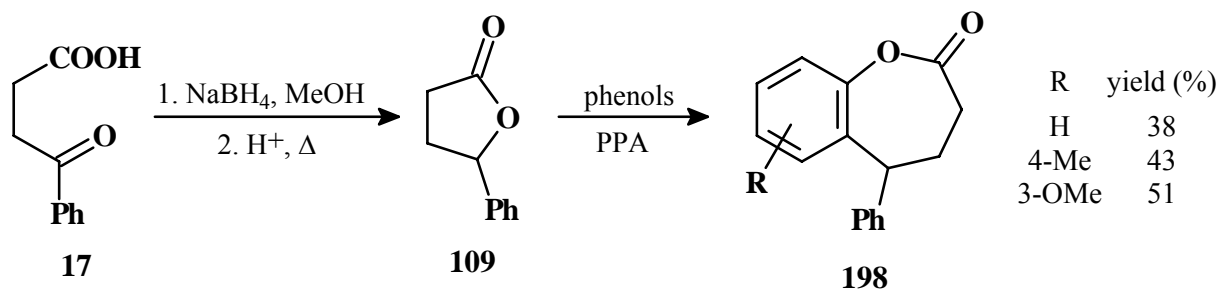
Scheme 64

From oxocarboxylic acids, special ring systems involving both small and large heterocyclic rings can be prepared. Thus, the synthesis of 4-benzoyl-2-azetidinones (**197**) starts from 3-benzoylpropionic acid (**17**);²⁰¹ by bromination and condensation with anilines, **196** is obtained. Cyclization with a base (Et_3N , NaOMe, *n*-BuLi or Amberlite IRA-400), furnishes the azetidinones (**197**) in poor to good yield. (Scheme 65)



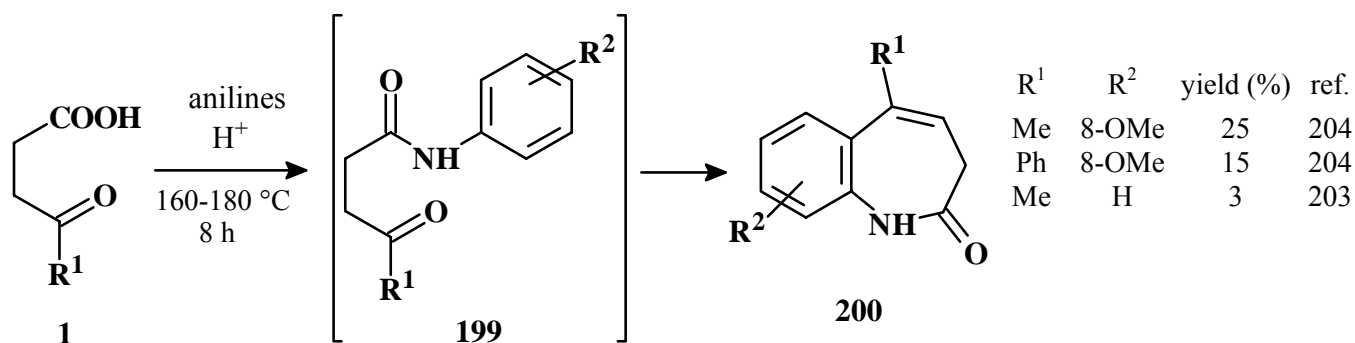
Scheme 65

From **17**, the phenylphthalide (**109**) is obtained by reduction (see Section 5); its condensation with substituted phenols results in benzoxepinones (**198**).²⁰² (Scheme 66)



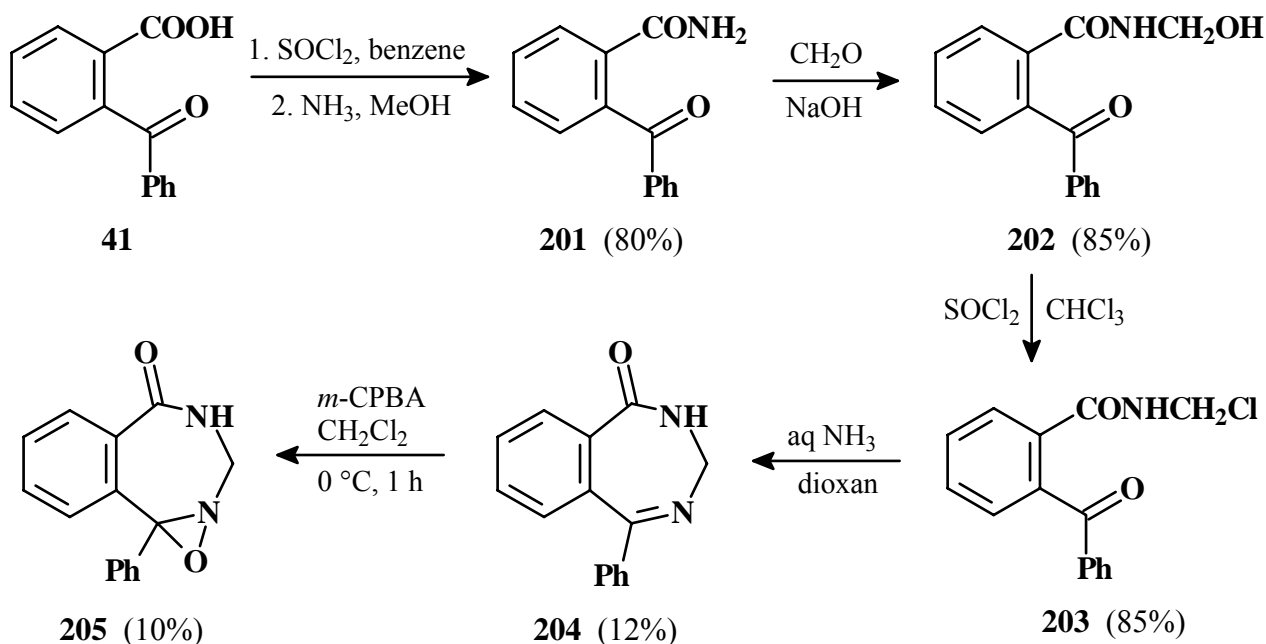
Scheme 66

On reaction with anilines, 2,3-dihydro-1*H*-benzazepin-2-ones (**200**) are obtained;²⁰³ their structures have been proved.²⁰⁴ (Scheme 67)



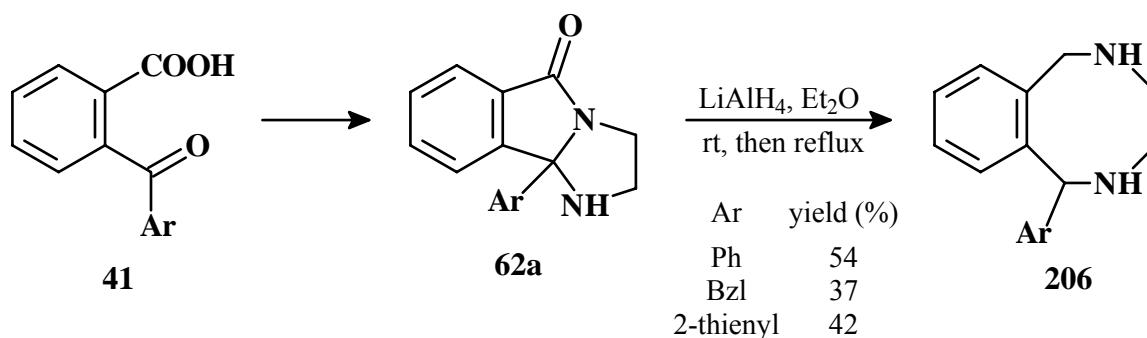
Scheme 67

From 2-benzoylbenzoic acid, 2,4-benzodiazepin-1-ones (**204**) are synthesized and then oxidized to **205**.²⁰⁵ (Scheme 68)



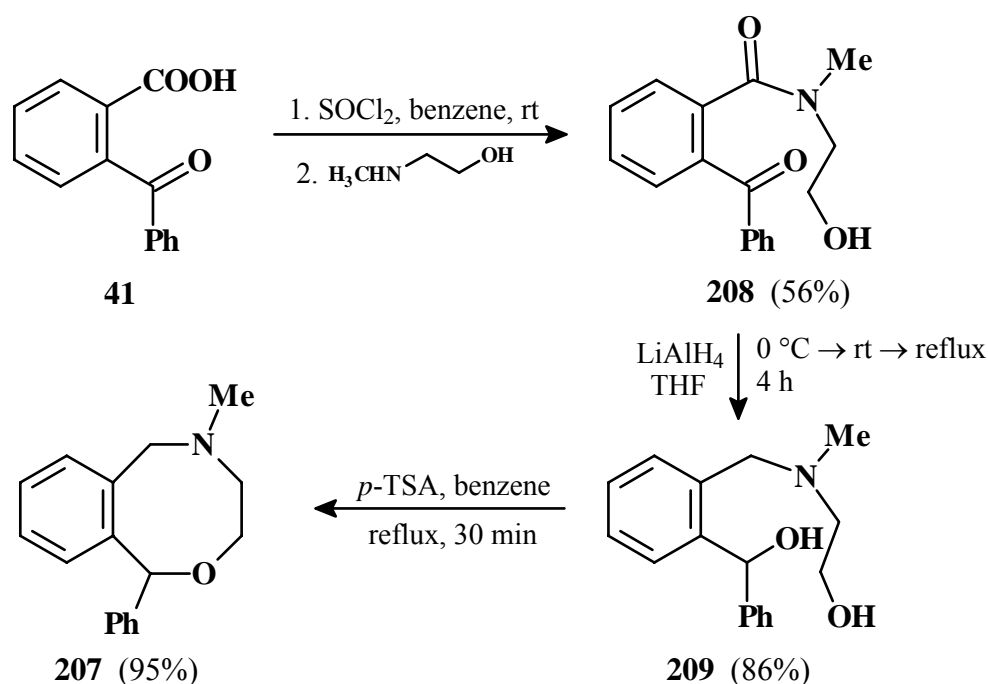
Scheme 68

The formation of condensed systems containing an eight-membered ring is another field of application of 4-oxocarboxylic acids. Imidazo[2,1-*a*]isoindol-5-ones (**62a**) (see Section 4) have been prepared by the reactions of 2-arylbenzoic acids with ethylenediamine; on reduction with LiAlH_4 in dry ether, this affords the hexahydro-2,5-benzodiazocines (**206**); the isomers may be resolved with *d*-camphorsulfonic acid.²⁰⁶ (Scheme 69)



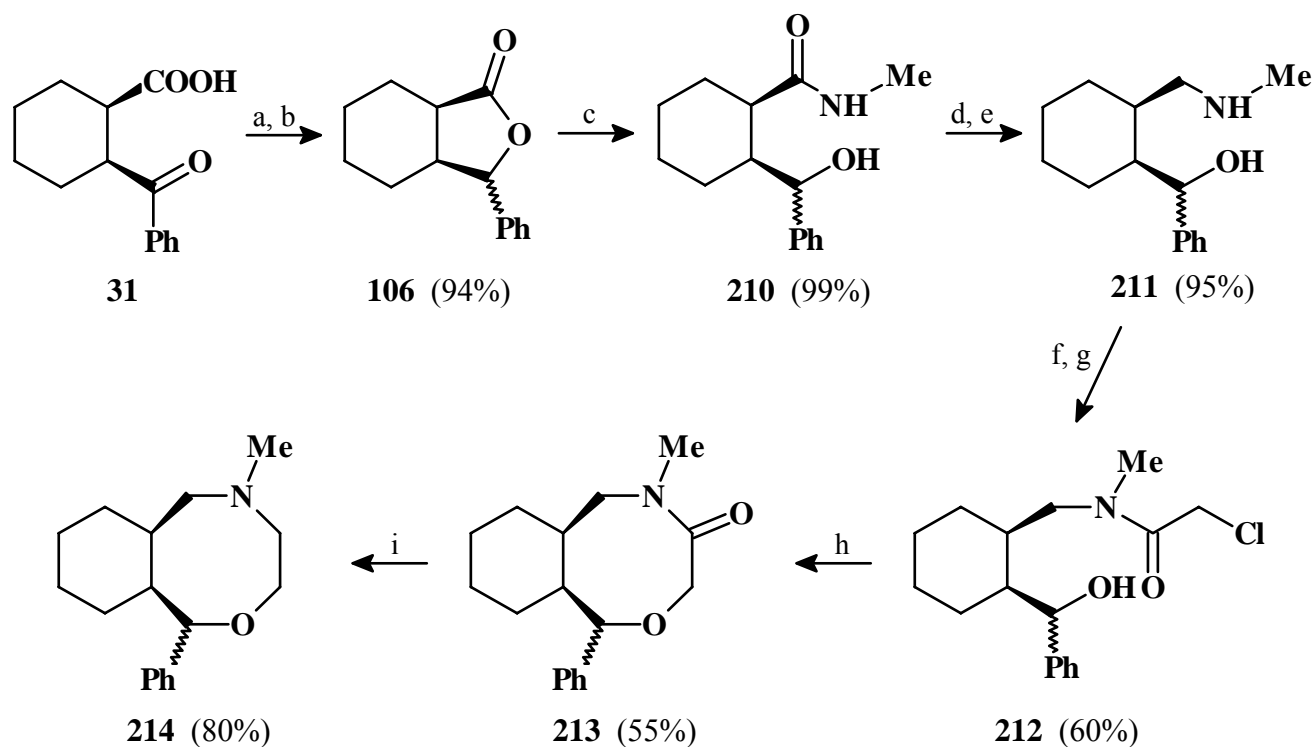
Scheme 69

3,4,5,6-Tetrahydro-5-methyl-1-phenyl-1*H*-2,5-benzoxazocine (**207**) (Nefopam[®]) has excellent analgetic and muscle relaxant activity. Several alternative methods have been developed for its preparation;^{207,208} one of them starts from **41**. (Scheme 70)



Scheme 70

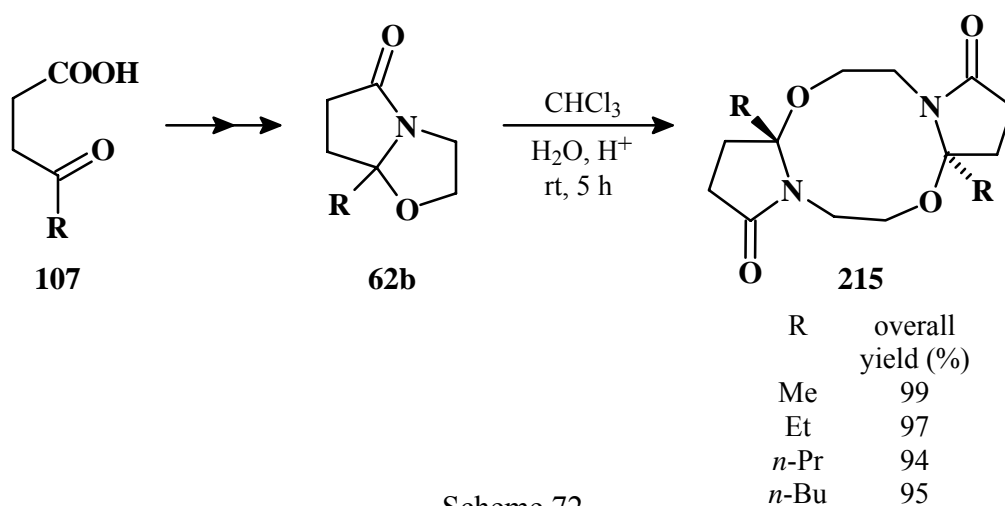
On reaction of dihydroisoindolylalkanol precursors with cyanogen bromide *via* ring enlargement, a modified preparation of Nefopam and a homologue has been devised.²¹⁰ The fully saturated derivatives have been prepared from **31** in a number of steps.²¹¹ (Scheme 71)



a) NaBH_4 , EtOH; b) HCl, Et₂O; c) 40% MeNH₂, THF; d) LiAlH_4 , THF; e) HCl, Et₂O; f) ClCH_2COCl , pyridine, THF; g) NaOH, MeOH, 0 °C; h) NaOH, THF; i) LiAlH_4 , THF

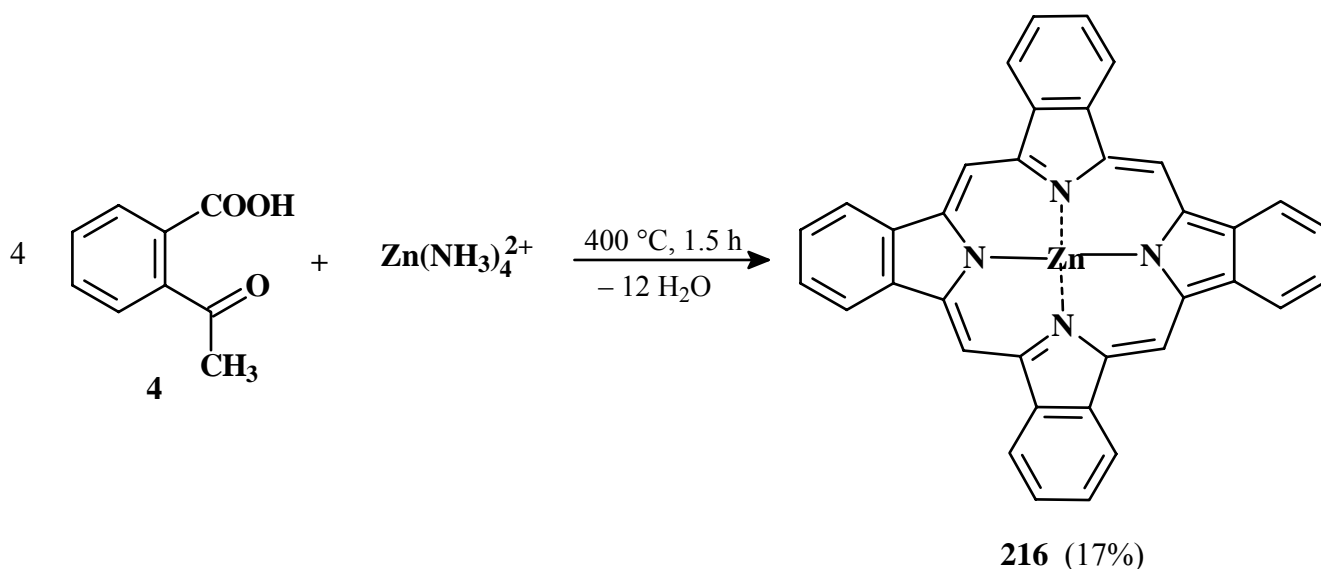
Scheme 71

The synthesis of two macrocyclic rings illustrates the versatility of the 4-oxocarboxylic acid synthons; the tricycle **215** containing a ten-membered ring has been prepared by dimerization of the lactam (**62b**) in protic media. (Scheme 72) The structure was confirmed by X-Ray analysis.²¹²



Scheme 72

From 2-acetylbenzoic acid (**4**), a simple and template synthesis of zinc tetrabenzo[*b,g,l,q*]porphine (**216**) has been achieved in one step.²¹³ (Scheme 73)



ACKNOWLEDGEMENTS

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