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RING CLOSURE REACTIONS OF SUITABLY *ORTHO*-SUBSTITUTED MALEANILIC ACIDS: AN AVENUE FOR HETEROCYCLES

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Abstract - This review describes syntheses of structurally interesting and biologically important heterocycles starting from suitably *ortho*-substituted maleanilic acids *via* intramolecular Michael addition, condensation and dehydrative cyclisation reactions.

I. INTRODUCTION

II. INTRAMOLECULAR CYCLISATION REACTIONS

A] Synthesis of indoles, quinolines and pyrroloquinolines with generation of carbon-carbon bond.

B] Synthesis of benzimidazoles, quinoxalines and pyrrolobenzimidazoles with generation of nitrogen-carbon bond.

C] Synthesis of benzoxazinones with generation of oxygen-carbon bond.

D] Synthesis of benzothiazoles, benzothiazines and *bis*-benzothiazines with generation of sulfur-carbon bond.

E] Synthesis of pyrrolobenzoxazinones and benzoxazinylacrylic acids with dehydrative cyclisations and cyclisations are intramolecular reaction.

III. CONCLUSIONS

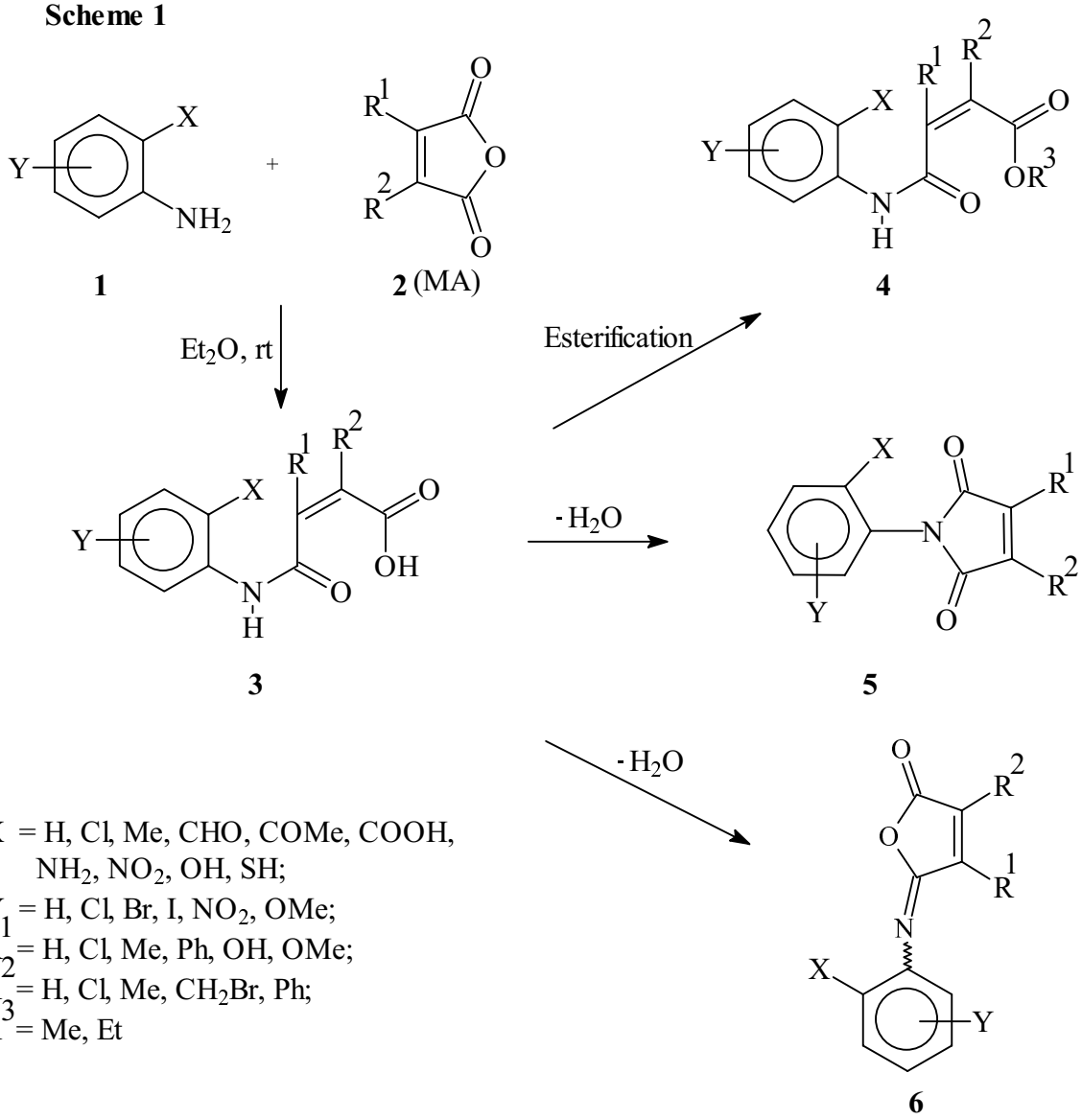
IV. REFERENCES AND NOTES

I. INTRODUCTION

The vast array of nucleophilic reactions undergone by symmetrical and unsymmetrical maleic anhydrides confer on them a high synthetic potential. As such, maleic anhydrides and their derivatives have been extensively used to model a variety of i) heterocyclic skeletons, ii) natural products and their precursors, iii) bioactive molecules, iv) compounds highlighting regiochemical dichotomy, and v) a series of polymers with tailored material characteristics.

The reactions of aniline derivatives (**1**) with maleic anhydrides (MAs, **2**) furnish[1] the corresponding maleanilic acids (**3**) in quantitative yield (Scheme 1). These acids on treatment with a variety of esterifying reagents provide[2] corresponding alkyl maleanilates (**4**), while the maleanilic acids on dehydration yield the corresponding maleimides (**5**)[3] and isomaleimides (**6**)[4a,b] under thermodynamically controlled conditions and kinetically controlled conditions

Scheme 1



respectively. The multifunctional maleanilic acids obtained from suitably *ortho*-substituted aniline derivatives (**1:** X = H, Cl, Me, CHO, COMe, COOH, NH_2, NO_2, OH and SH) and variety of maleic anhydrides have been employed to obtain a diverse menu of structurally interesting and biologically important heterocyclic systems *via* intramolecular Michael addition, condensation and dehydrative ring closure reactions. The Schemes and Tables listing the large number of such reactions have been described in Part-II and these illustrations portray in good measure the scope and diversity of the reactivity in these systems.

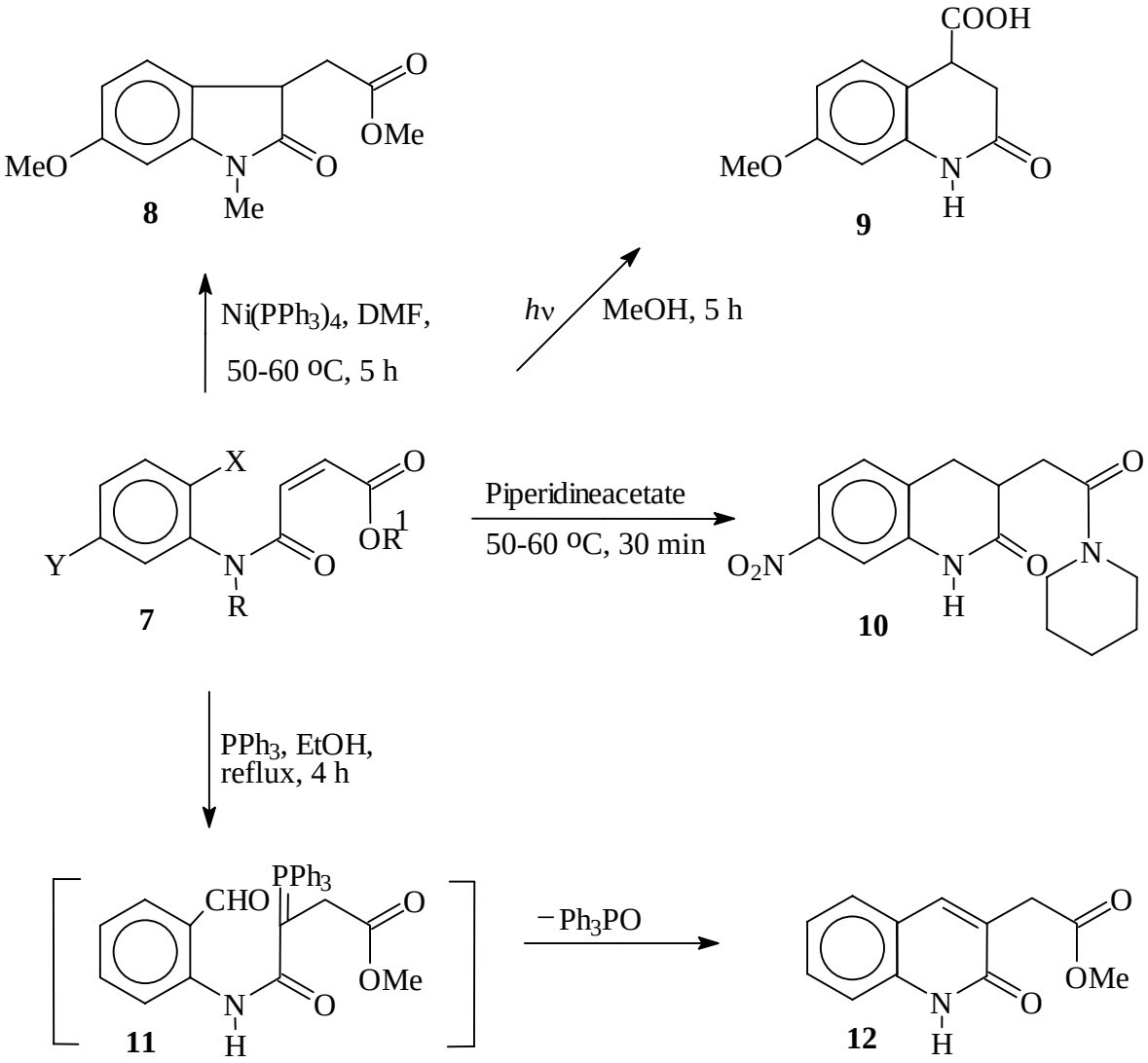
II. INTRAMOLECULAR CYCLISATION REACTIONS

A] Synthesis of indoles, quinolines and pyrroloquinolines with generation of carbon-carbon bond

A plethora of synthetic approaches to indole and quinoline nucleus are known in the literature and their utilities have been well-proved in practice.[4c] They are the building blocks to several naturally occurring alkaloids. One synthesis of indole and three syntheses of quinoline derivatives have been accomplished starting from suitably *ortho*-substituted maleanilic acids (Scheme 2).

Mori's synthesis[5] of indoles (**8**) by using zerovalent nickel substituted maleanilates *via* intramolecular Michael addition is an elegant approach and can be further exploited. The course of photochemically induced intramolecular Michael addition in maleanilic acid using aromatic ring carbon as an internal nucleophile appears to be inverted leading to quinoline derivative (**9**)[6] (activation is normally -COOH>CONHAr). An apparently attractive general route to quinoline-3-acetic acids starting from 2-methylmaleanilates employing a series of bases has met with failure;[7] subsequently, this conversion was successfully achieved[7] starting from the activated substrate alkyl 2-methyl-5-nitromaleanilates using piperidine as a base. The intramolecular Michael addition and aminolysis of the thus-formed saturated ester takes place in one-pot with isolation of **10** as a sole product. In yet another and interesting synthesis of quinoline derivative (**12**), the maleanilic acid obtained from *o*-aminobenzaldehyde and MA has been esterified in methanol using catalytic amount of sulfuric acid at 0 °C. The methyl *o*-formylmaleanilate with triphenylphosphine in refluxing ethanol generates the inisolable phosphorane (**11**) *via* Michael addition at β-carbon and a subsequent prototopic shift, which on

Scheme 2

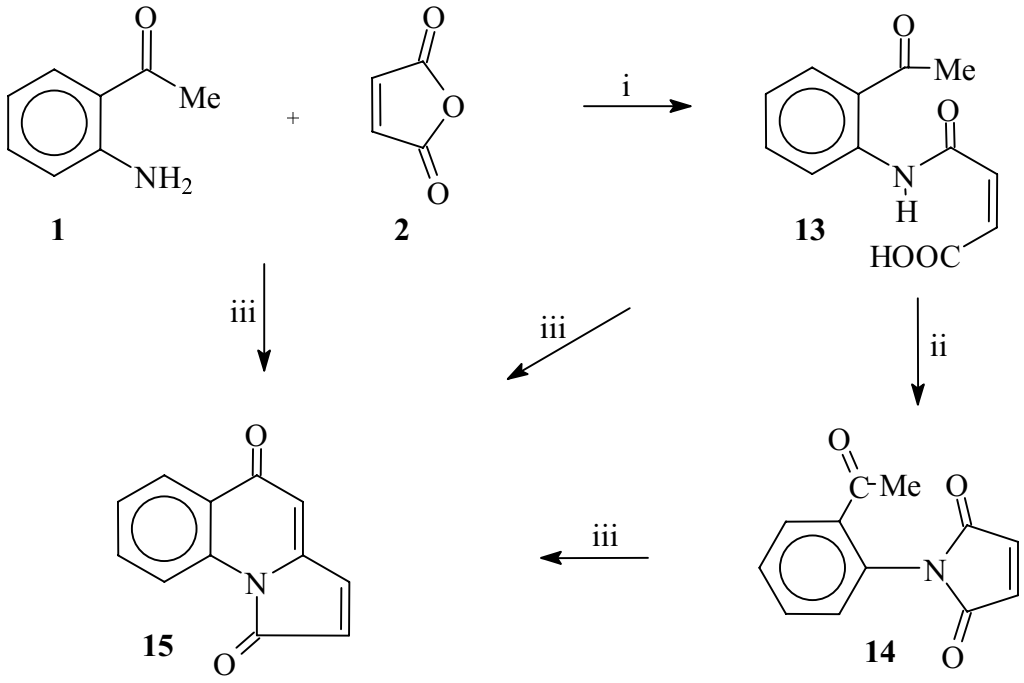


Entry	In Compound 7				Product	Yield %	Ref.
	X	Y	R	R^1			
1	Cl	OMe	Me	Me	**8**	61	5
2	H	OMe	H	H	**9**	38	6
3	Me	NO_2	H	Me	**10**	60	7
4	CHO	H	H	Me	**12**	60	8

intramolecular Wittig reaction yields the quinoline (**12**) in about 60% yields.[8]

The reactions of *o*-aminoacetophenone (*o*-AAP) with several anhydrides have been exhaustively investigated[9] by Alkhathlan (Scheme 3). He has demonstrated that the reaction of *o*-AAP with MA in refluxing xylene/TEA directly furnishes the pyrroloquinoline derivative (**15**) in 90%

Scheme 3



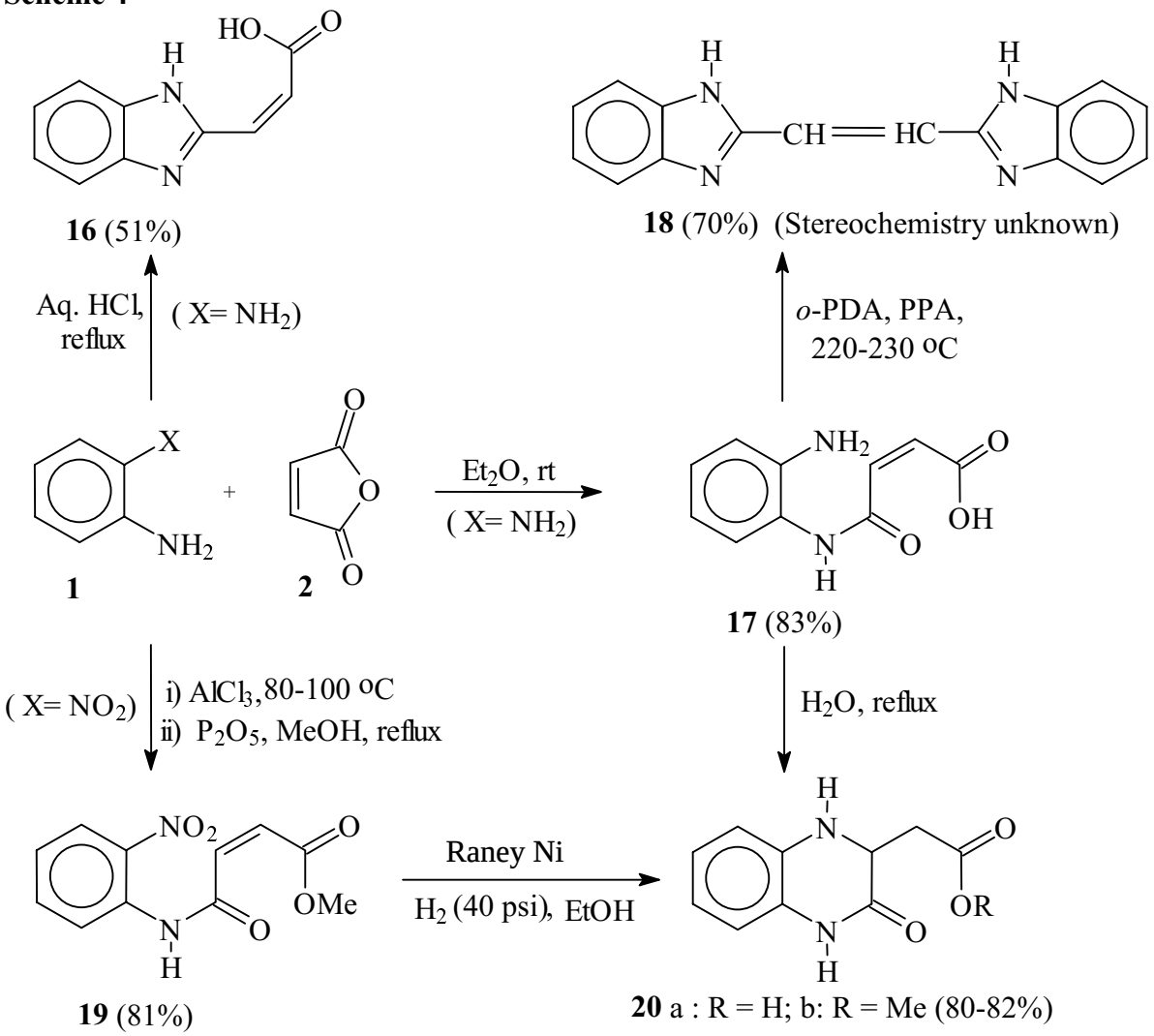
i) Toluene, catalytic amount of TEA, 120 °C (quant); ii) Toluene, TEA, 110 °C, (90%); iii) Xylene, excess TEA, 120 -140 °C (90%)

yield *via* intermediate maleanilic acid (**13**) and imide (**14**). By varying the amount of TEA used, he has also isolated the intermediates (**13**) and (**14**) in very good yields.

B] Synthesis of benzimidazoles, quinoxalines and pyrrolobenzimidazoles with generation of nitrogen-carbon bond

The reactions of *o*-phenylenediamine (*o*-PDA) with MA's have been summarised in Schemes 4 and 5. The course of these reactions was found to be dependent on the following three factors (i) mode of addition; (ii) solvent used for the reaction and, (iii) substituents on MA's. The reaction of MA with *o*-PDA in refluxing aqueous hydrochloric acid is known[10] to yield benzimidazolylacrylic acid (**16**). The addition of an ether solution of MA to *o*-PDA furnishes[11] amino acid (**17**), whereas the inverse addition of *o*-PDA to MA leads[12] to the corresponding diacid. The mono acid (**17**) with an additional mole of *o*-PDA in presence of PPA at higher temperature gives[13] *bis*-benzimidazolylethylene (**18**), while in boiling water it yields[11] quinoxaline (**20a**); the latter (**20b**) has been also obtained from reductive cyclization of methyl *o*-nitromaleanilate (**19**)[14,15] (Scheme 4).

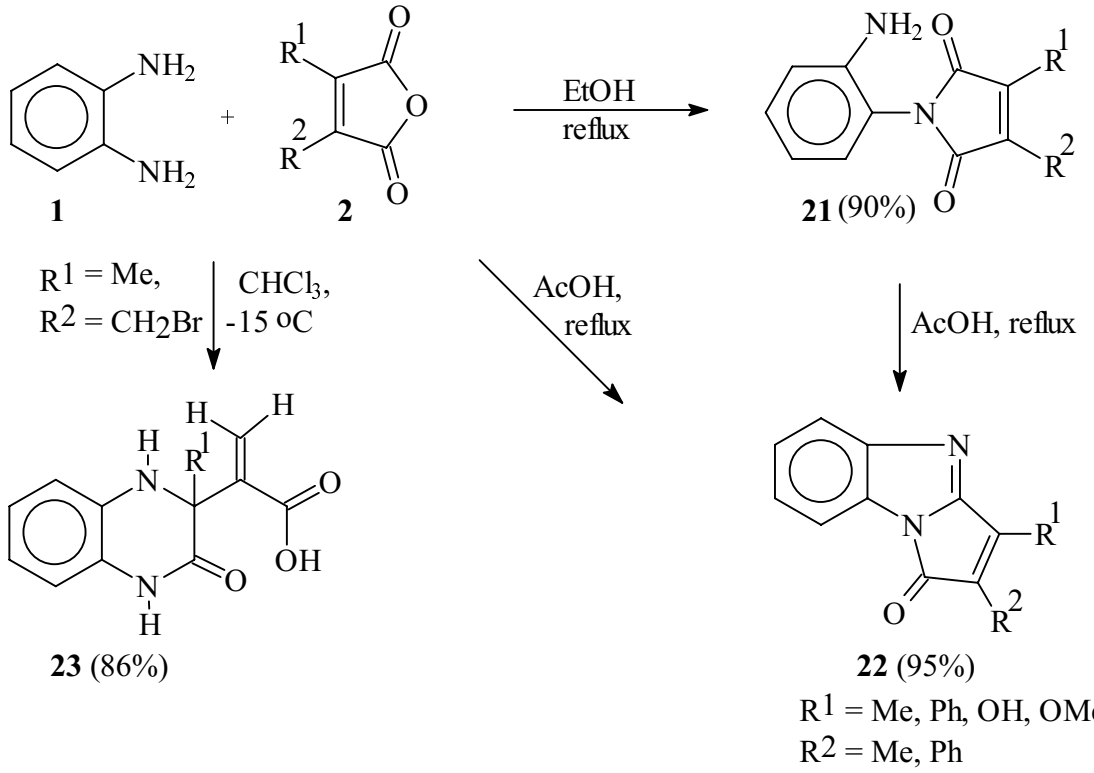
Scheme 4



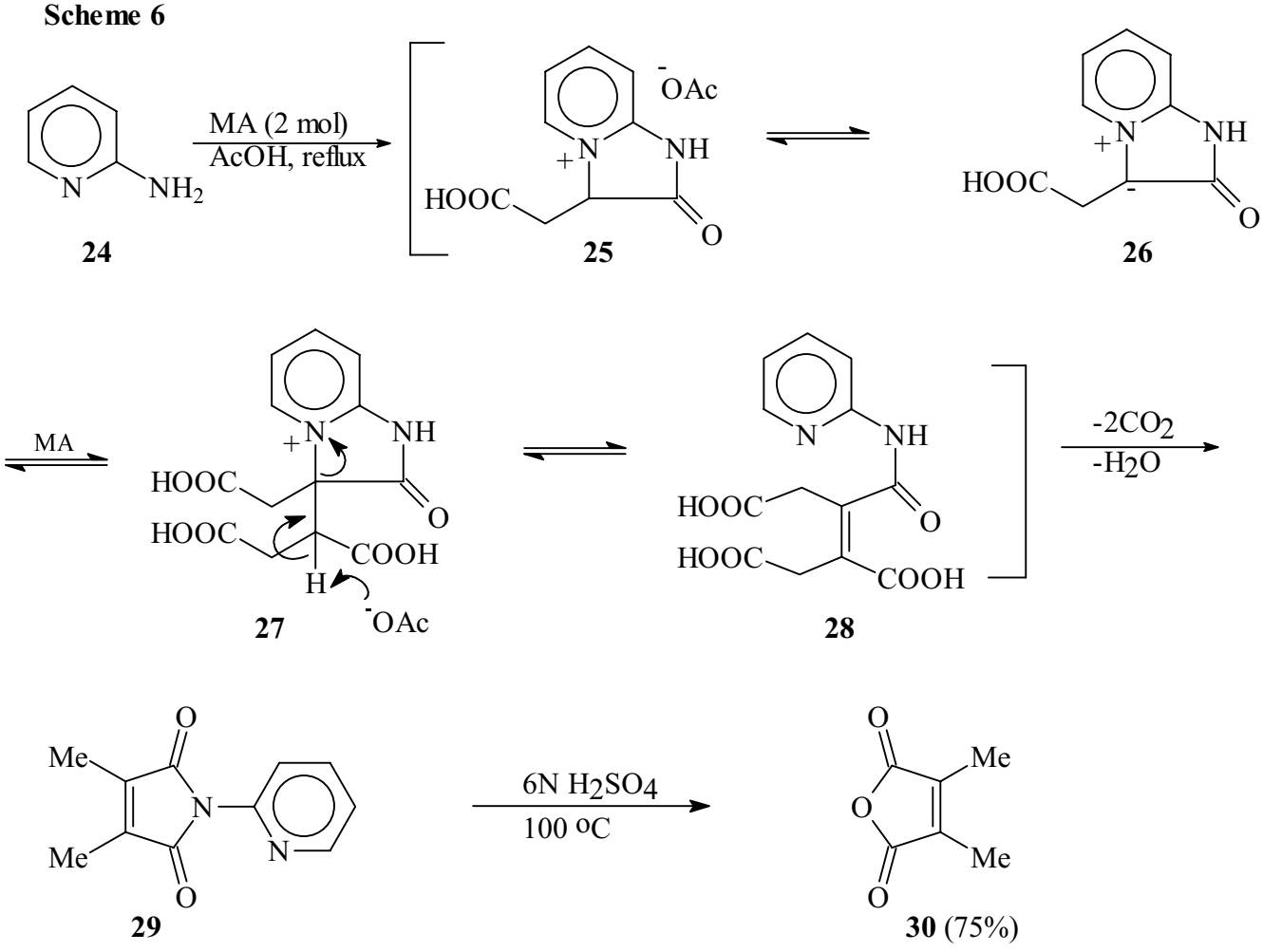
Disubstituted MA's react with *o*-PDA in boiling acetic acid to furnish pyrrolobenzimidazoles (**22**) in one-pot.[16-18] This conversion can be accomplished stepwise through the intermediate *o*-aminomaleimide (**21**) in boiling ethanol, which in turn gets transformed to **22** in boiling acetic acid.[17] In the conversion of **21** to **22**, the observed regioselectivity in hydroxyphenylmaleic anhydride and methoxyphenylmaleic anhydride has been dictated by mesomeric effects of -OH and -OMe. In yet another interesting conversion, the (bromomethyl)methylmaleic anhydride on reaction with *o*-PDA underwent a chemo- and regioselective ring opening followed by intramolecular Michael type addition and 1,4-elimination reactions to furnish[19] kinetically controlled products α-quinoxalinylacrylic acid (**23**) (Scheme 5).

The reaction of 2-aminopyridine (**24**) with MA has been studied by Baumann *et al*. in detail[20-22] to obtain dimethylmaleic anhydride (**30**) (Scheme 6), wherein the lone pair on ring nitrogen plays a key role of *ortho*-substituent to yield nitrogen ylide (**26**). The detailed mechanistic studies and applications of this reaction have been reported.[21-23]

Scheme 5



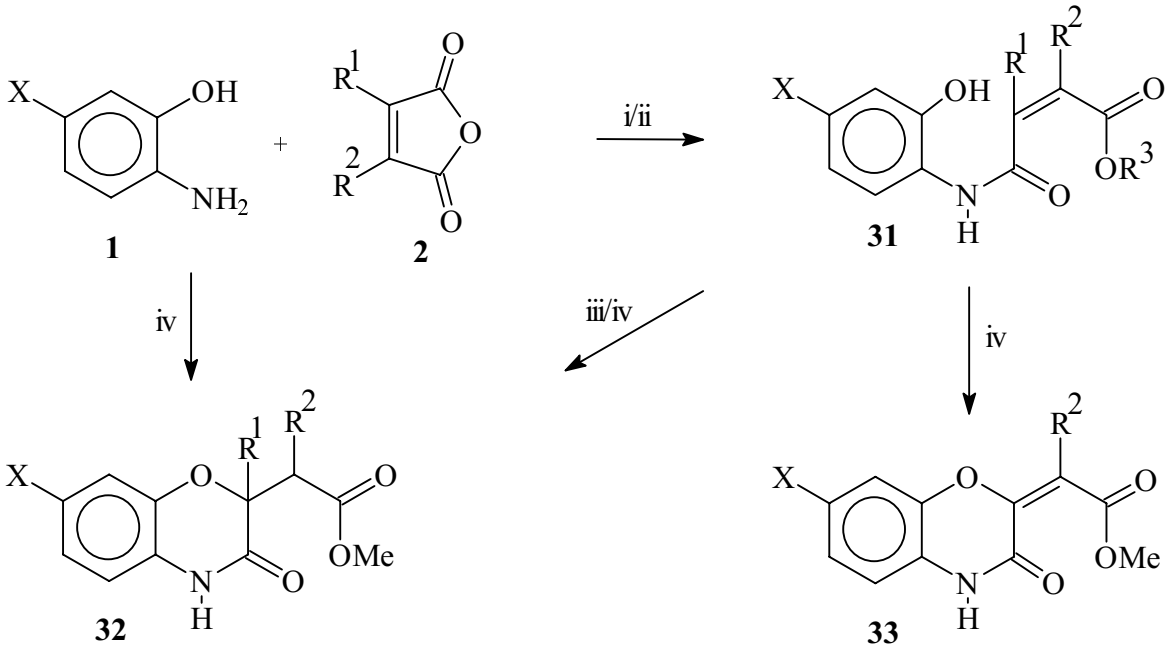
Scheme 6



C] Synthesis of benzoxazinones with generation of oxygen-carbon bond

The reactions of *o*-aminophenols (*o*-AP) with MA's have been studied by different groups of investigators and are summarised in Scheme 7. The benzoxazinylacetate (**32**) (Entry 1) was first obtained[24] in our group, starting from methyl *o*-hydroxymaleanilate using piperidineacetate as a base. The same has also been obtained[25] in an improved one-pot reaction of *o*-AP and MA

Scheme 7



i) (a) Et_2O, rt, (b) $MeOH/H^+$; ii) Acetone, rt; iii) Piperidineacetate, 90 °C; iv) TEA, MeOH, reflux

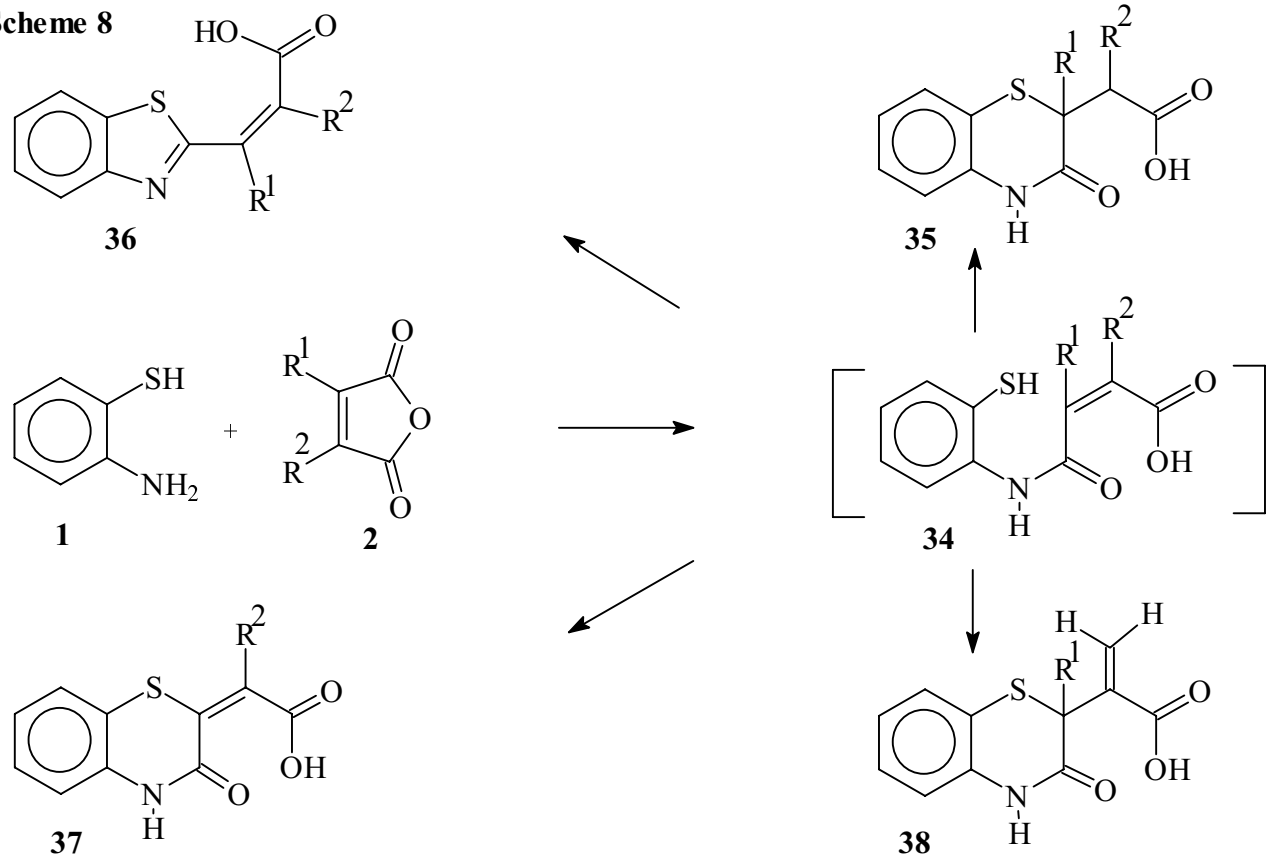
Entry	In Compound 31				Condition	Product	Yield %	Ref.
	X	R^1	R^2	R^3				
1	H	H	H	Me	iii	**32**	50	24
2	H	H	H	H	iv	**32**	82	25
3	H	Me	H	H	iv	**32**	84	25
4	OMe	H	H	H	iv	**32**	51	27
5	H	Cl	H	H	iv	**33**	89	28
6	H	Cl	Cl	H	iv	**33**	44	28

in presence of refluxing methanol and TEA in good yields. The same reaction with methylmaleic anhydride (MMA) has furnished the unexpected 2-methyl benzoxazinylacetates (Entry 3) and not the propionates, with initial nucleophilic attack of amino group of *o*-AP at the more hindered carbonyl of MMA. Similar orientation effects have also been observed[26] by Warren *et al*. This type of cyclization has been further used[27] (Entry 4) for the synthesis of complex bioactive pyrrolobenzoxazinone derivatives with antihistaminic properties. Teitei has also reported[28] that maleanilic acids obtained from the reactions of *o*-AP with chloromaleic anhydride and dichloromaleic anhydride under similar set of reaction conditions yield 1,4-benzoxazinone derivatives (**33**) (Entries 5 & 6). It appears that additional proof for the geometry of carbon-carbon double bond are desirable. Recently, Okafor *et al*. have claimed[29] that the reaction of *o*-AP with MA at 28 °C in toluene directly furnishes benzoxazinylacetic acid in 97% yield. The only proof given for structural assignments by them are UV, IR and elemental analysis data. In view of the above summary on this reaction, it appears that further characterization of this compound with ^{1}H NMR, ^{13}C NMR and MS Spectral data is necessary.

D] Synthesis of benzothiazoles, benzothiazines and bis-benzothiazines with generation of sulfur-carbon bond

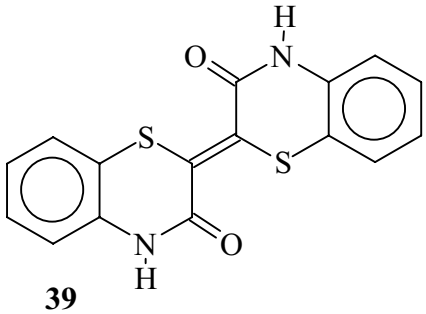
The reactions of symmetrical and unsymmetrical maleic anhydrides with *o*-aminothiophenol (*o*-ATP) have been systematically studied in our group and are summarized in Scheme 8. The reactions of alkyl and/or aryl substituted MA's with *o*-ATP furnish benzothiazines (**35**)[28-33] in excellent yields (Entries 1-6), the formation of which can be visualised to proceed by initial aminolysis of the anhydrides with amino function of *o*-ATP, followed by intramolecular Michael-type addition of thiol function to the α,β-unsaturated carbonyl system in the intermediate maleanilic acid (**34**) to furnish benzothiazines (**35**). A scrutiny of the orientation of the addition of the thiol in the reaction of *o*-ATP with unsymmetrically substituted MA's reveals the competitive role of steric/electrical effects in these cases. Thus, in the unsymmetrical anhydrides, initial aminolysis is regioselectively favored at a carbonyl, away from the bulkier substituent. The attenuation of carbonyl reactivity by hyperconjugative effect or mesomeric interaction does not seem to be strong enough to reverse the attack at apparently more hindered carbonyl. In the reaction of phenylmethylmaleic anhydride with *o*-ATP, formation of **35** (Entry 6) as the exclusive product again demonstrates the decreased electrical effect of the

Scheme 8

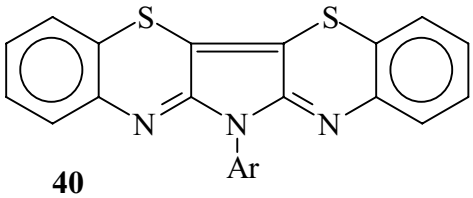


Entry	In Compound 2		Condition	Product	Yield %	Refs.
	R^1	R^2				
1	H	H	Et_2O, rt	**35**	98	15, 25, 28-32
2	H	Me	Et_2O, rt	**35**	85	30
3	Me	H	MeOH/H^+, reflux	**35**	70	25
4	Me	Me	AcOH, reflux	**35**	90	33
5	H	Ph	Et_2O, rt	**35**	90	30
6	Me	Ph	PhCl, reflux	**35**	87	33
7	OMe	H	Acetone, rt	**36**	89	33
8	OH	Ph	Pyridine, reflux	**36**	75	33
9	OMe	Ph	Pyridine, reflux	**36**	75	33
10	Cl	H	Acetone, rt	**37**	60	28
11	Me	CH_2Br	$CHCl_3$, -15 °C	**38**	90	19

phenyl ring. The possible non-planarity of phenyl group could justify such a view, also invoked earlier.[34] In contrast, hydroxy and methoxy substituted maleic anhydrides react with *o*-ATP to furnish benzothiazoles (**36**) (Entries 7-9), apparently by a different pathway,[33] indicating that hydroxy and alkoxy substituents on carbon-carbon double bond can prevent such Michael type additions. As happens with *o*-AP, the reaction of *o*-ATP with molar quantity of chloromaleic anhydride yields **37**[28] (Entry 10). Interestingly, the reactions of dichloromaleic anhydride and dichloromaleimide with two equivalents of *o*-ATP provide the *bis*-benzothiazines (**39**) and (**40**) respectively *via* addition-elimination pathway.[35] Alike *o*-PDA, the reaction of *o*-ATP with (bromomethyl)methylmaleic anhydride yields benzothiazine derivative (**38**)[19] (Entry 11).



39

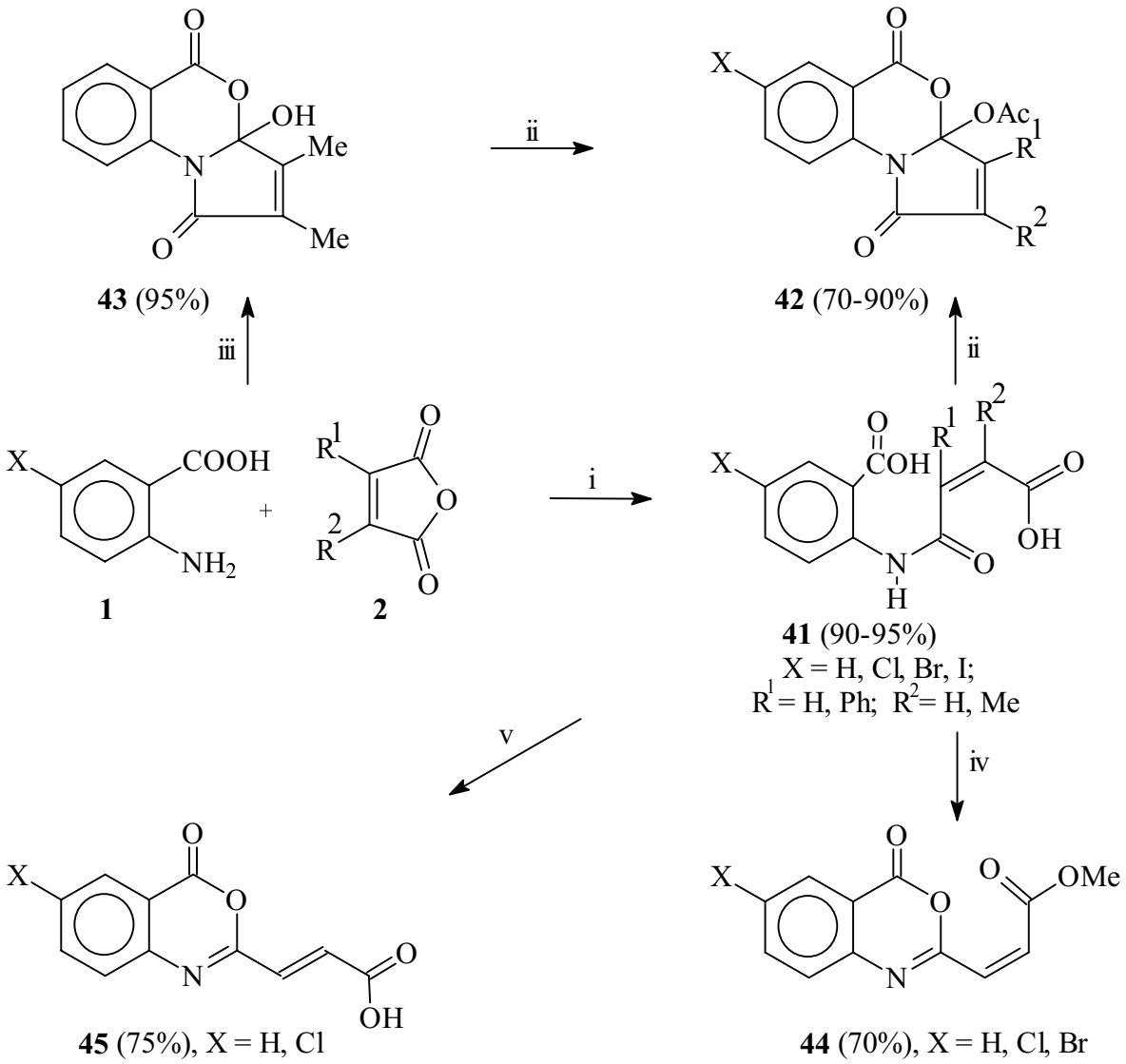


40

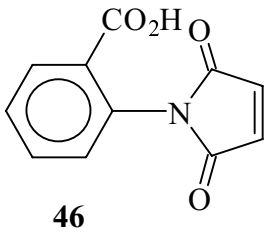
E] Synthesis of pyrrolobenzoxazinones and benzoxazinylacrylic acids with dehydrative cyclisations

The results obtained on dehydrative cyclisation reactions of *o*-carboxymaleanilic acids (**41**) have been summarised in Scheme 9. These acids offer multiple pathways for intramolecular (**41**) dehydration to imides, isoimides or benzoxazinones. The dicarboxylic acids (**41**) on treatment with acetic anhydride-sodium acetate furnish exclusively the corresponding pyrrolobenzoxazinones (**42**)[36,37] incorporating an angular oxygen function *via* double dehydrative double cyclisation reaction in one-pot. The reaction of dimethylmaleic anhydride with anthranilic acid in refluxing water directly yields the lactol (**43**). The formation of **42** from (**41**) can be visualised through *o*-carboxymaleimide (**46**) or the *Z*-isomer of benzoxazinone (**45**), although neither of them have been intercepted even under milder conditions. These reactions underwent monocyclisation by prior esterification of the side chain carboxyl group or by isomerisation of carbon-carbon double bond to obtain[38] benzoxazinylacrylic acid derivatives (**44**) and (**45**) respectively.

Scheme 9



i) Et_2O, rt, 30 min; ii) Ac_2O/AcONa, rt, 8 h; iii) H_2O, reflux, 3 h; iv) (a) MeOH/H^+, 8 h, (b) Ac_2O/AcONa, rt, 4 h; v) Aq. MeOH, thiourea, reflux, 3.5 h and condition iv (b)



46

III. CONCLUSIONS

The ring closure reactions of suitably *ortho*-substituted maleanilic acids have been elegantly employed to obtain 6-5, 6-6, 6-5-5 and 6-6-5 membered structurally interesting and biologically important heterocycles with one or two hetero atoms *via* intramolecular Michael additions, condensations and dehydrations with pivotal role of an *ortho*-substituent.[39] These

intramolecular cyclisation reactions will be further exploited to design new important heterocyclic systems.

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