

# Molecular iodine-catalyzed multicomponent reactions: an efficient catalyst for organic synthesis

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The multicomponent reactions (MCRs) consist of two or more synthetic steps which are carried out without isolation of any intermediate thus reducing time, saving money, energy and raw materials. The development of MCRs in the presence of molecular iodine is an efficient approach that meets with the requirements of sustainable chemistry. The aim of this review is to highlight the synergistic effect of the combined use of MCRs and molecular iodine for the development of new eco-compatible methodologies for organic chemistry.

## 1. Introduction

The length of a synthesis is dependent upon the average molecular complexity produced per operation, which depends in turn on the number of chemical bonds being created. Therefore, devising reactions that achieve multi-bond formation in one operation is becoming one of the major challenges in searching for step-economic syntheses. Multicomponent reactions (MCRs) processes, in which three or more reactants are combined in a single chemical step to produce products

that incorporate substantial portions of all the components, naturally comply with many of these stringent requirements for ideal organic syntheses.<sup>1</sup>

In fact, there have been various classification systems for MCRs. For example, three components can be divided into three different categories depending on the nature of the starting materials (Fig. 1). ABC designates a MCRs involving three different reagents; ABB (or ABB'),<sup>2</sup> a reaction that involves one molecule of reagent A and two molecules of reagent B; and finally, AAA, a reaction that involves three molecules of the same reagent.

In recent years, molecular iodine has been used for various organic transformations including Lewis acid catalyst.<sup>3–5</sup> Owing to numerous advantages associated with this eco-friendly element, molecular iodine has been explored as a powerful catalyst for MCRs. To the best of our knowledge,

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reviews on the MCRs use of molecular iodine have not been reported recently. This article will be divided in two sections. The first one concerns the use of molecular iodine as catalyst for ABC(D..) MCRs, the second one presents molecular iodine catalyzed ABB and ABB' MCRs.

## 2. Molecular iodine catalyzed ABC(D..) multicomponent reactions

### 2.1 Synthesis of highly substituted imidazoles from functionalized carbonyl compounds

Highly substituted imidazoles are very useful intermediates for the development of molecules of pharmaceutical or biological interest. The synthesis of highly substituted imidazoles *via* MCRs involving the cyclocondensation of a 1,2-diketone (or *α*-hydroxy ketones), an aldehyde and ammonia or ammonium acetate is a useful process. The catalytic activity of molecular iodine is remarkable and the use of low cost, commercially available iodine as catalyst for the synthesis of highly substituted imidazoles in excellent yields is also significant under the aspect of environmentally benign processes.

Kidwai *et al.*<sup>6,7</sup> reported the one-pot synthesis of 2,4,5-triarylimidazoles **1** using benzil (or benzoin), aldehydes and ammonium acetate using molecular iodine as catalyst under 75 °C (Scheme 1). The condensation of benzil, benzaldehyde and ammonium acetate in the presence of 5 mol% of catalyst give 99% yield of 2,4,5-triphenylimidazole after 15 min using ethanol as solvent. However, a longer reaction time (2 h) and more amount catalyst (10 mol%) would be necessary using benzoin as reagent, because the benzoin undergoes aerial oxidation to benzil under these conditions.

The authors<sup>7,8</sup> had also reported the one-pot synthesis of 1,2,4,5-tetraarylimidazoles **2** using benzil (or benzoin), aldehyde, amine and ammonium acetate under the same reaction conditions (Scheme 1). This method is effective for the preparation of 1,2,4,5-tetraarylimidazoles **2** from both electron efficient as well as electron deficient aromatic aldehydes. The aryl groups substituted with different groups and also the same groups located at different positions of the aromatic ring did not show any effect on the formation of 1,2,4,5-

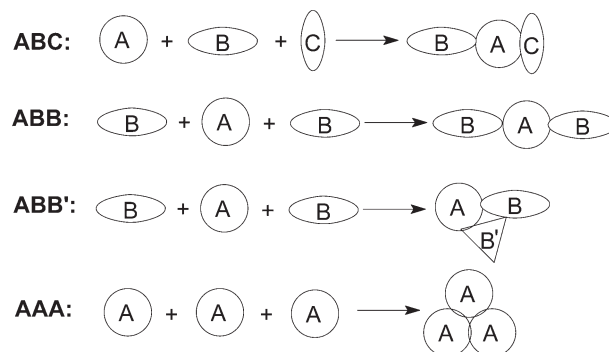


Fig. 1 The classification of MCRs.

tetraarylimidazoles **2**. Similarly, a longer reaction time (2 h) and more amount catalyst (10 mol%) would be necessary using benzoin as reactant. A series of some new tetrazolo[1,5-*a*]quinoline based tetrasubstituted imidazole derivatives had also been synthesized by a reaction of tetrazolo[1,5-*a*]quinoline-4-carbaldehyde, benzil, aromatic amine and ammonium acetate in the presence of iodine.<sup>9</sup> And one-pot synthesis of 1*H*-phenanthro[9,10]imidazol-2-yl from phenanthenquinone, aldehydes and ammonium acetate using molecular iodine as catalyst in ethanol was also described.<sup>10</sup>

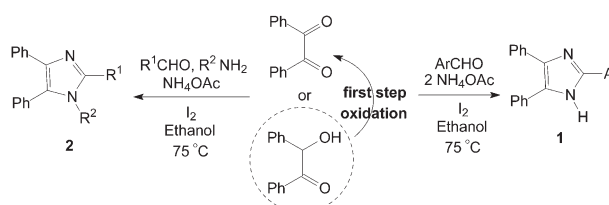
With the increasing public concern over environmental degradation, the use of environmentally benign solvents like water and solvent-free reactions represent very powerful green chemical technology procedures from both the economical and synthetic point of view. We<sup>11</sup> reported the synthesis of highly substituted imidazoles **1** and **2** by the reaction of 1,2-diketone, aldehydes and ammonium acetate or *via* one-pot four-component condensation of 1,2-diketone, aldehydes, amines and ammonium acetate in the presence of a catalytic amount of molecular iodine under solvent-free conditions. And Jayabharathi *et al.*<sup>12</sup> had also reported synthesis of 2,4,5-triarylimidazoles **1** under solvent-free conditions. The advantages of the “solvent-free” method are the elimination of the metals, organic solvents and toxic reagents, operational simplicity and high yields of products.

We<sup>13</sup> had also reported the synthesis of 1,2,4,5-tetraarylimidazoles **2** by three-component condensation of benzil, benzonitrile derivatives and primary amines in the presence of a catalytic amount of molecular iodine (10 mol%) under solvent-free conditions (Scheme 2). It was found that primary aliphatic amines reacted efficiently with benzil and benzonitrile derivatives promoted by molecular iodine within 1 h.

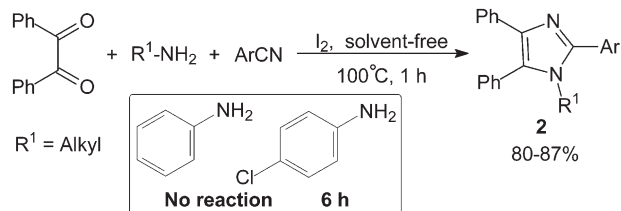


Ren-Chun Yang

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Scheme 1 Iodine catalyzed synthesis of highly substituted imidazoles.



**Scheme 2** Iodine catalyzed solvent-free synthesis of 1,2,4,5-tetraarylimidazoles.

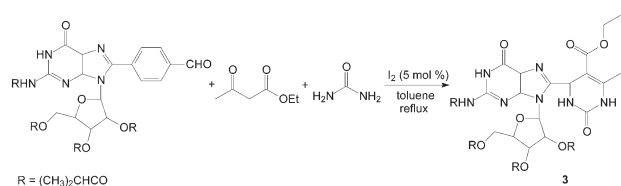
However, the reaction failed to proceed with aniline derivatives under the same reaction conditions, this may be due to the conjugated Schiff base formation by aniline and carbonyl being relatively stable and difficult to further react with the benzonitrile derivatives.

## 2.2 Biginelli reaction and Biginelli-like reaction

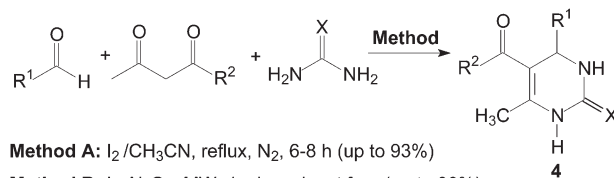
Dihydropyrimidinones and their sulfur analogues have attracted much attention in previous years due to the large range of biological activities such as calcium channel blockers, antiviral, antitumor, and anti-inflammatory drugs. *via* the Biginelli reaction, the synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones and thione have received renewed interest, and several improved procedures have recently been reported. Bhosale *et al.*<sup>14</sup> reported the synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones by iodine-catalyzed cyclocondensation of aldehyde, ethyl acetoacetate and urea. The reaction was carried out in toluene at reflux temperature for 3–5 h with high yields. This one-pot protocol has a simple work-up with excellent yields for substituted aromatic aldehydes. For example, the reaction proceeded very cleanly to afford **3** containing both guanosine and dihydropyrimidine moieties in 90% yield (Scheme 3). However, the cyclocondensation with aliphatic aldehydes such as *n*-butanal and *n*-hexanal were sluggish under the present reaction conditions and afforded the corresponding dihydropyrimidin-2(1*H*)-ones in 76% and 69% yields, respectively.

The three-components, aldehyde, 1,3-dicarbonyl compound and urea or thiourea were refluxed under N<sub>2</sub> in the presence of iodine as catalyst using CH<sub>3</sub>CN as a solvent (Scheme 4, **Method A**).<sup>15</sup> Most importantly aromatic aldehydes carrying either electron-donating or electron-withdrawing substituents reacted very well to give the desired products **4** in excellent yields. Even aliphatic aldehydes, which normally show poor yields in the Biginelli reaction afforded the products with high yields.<sup>16</sup> Thiourea also reacted in a similar manner like urea.

Meanwhile, some instruments were employed for the Biginelli reaction using molecular iodine as catalyst



**Scheme 3** Iodine catalyzed synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones.



**Method A:** I<sub>2</sub>/CH<sub>3</sub>CN, reflux, N<sub>2</sub>, 6–8 h (up to 93%)

**Method B:** I<sub>2</sub>-Al<sub>2</sub>O<sub>3</sub>, MW, 1 min, solvent free (up to 90%)

**Method C:** I<sub>2</sub>/CH<sub>3</sub>CN, ultrasound, 40–46 °C, 1.5–3 h (up to 95%)

R<sup>1</sup> = Alkyl, Aryl

R<sup>2</sup> = Alkyl-O, Alkyl

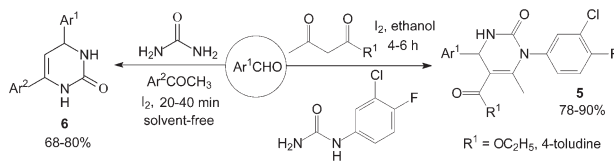
X = O, S

**Scheme 4** Iodine catalyzed synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones and thione.

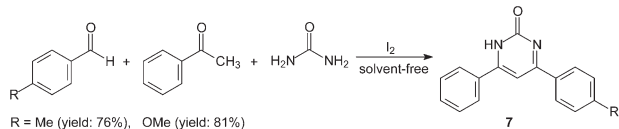
(Scheme 4, **Method B** and **C**). Saxena *et al.*<sup>17</sup> reported a quick and efficient one-pot method for the three component condensation of an aldehyde, urea/thiourea and a 1,3-dicarbonyl compound to synthesize 3,4-dihydropyrimidin-2(1*H*)-ones and thione **4** using iodine–alumina as the catalyst under microwave irradiation. The reactions were completed thoroughly and irradiated in a Prolabo fixed focus microwave reactor at a temperature of 90 °C for 1 min. Wang *et al.*<sup>18</sup> reported the Biginelli reaction catalyzed by iodine in CH<sub>3</sub>CN under ultrasound irradiation. When the frequency was 25 kHz, the condensation of 4-chlorobenzaldehyde, ethyl acetoacetate and urea gave the desired product in 95% yield within 2 h using iodine (40 mol%) as catalyst.

However, the scope of substrates for the Biginelli reaction is limited to aromatic aldehydes, acetoacetate (or acetylacetone) and urea or thiourea. Zalavadiya *et al.*<sup>19</sup> described the synthesis of some new 3,4-dihydropyrimidin-2(1*H*)-ones **5** from *N*-(3-chloro-4-fluorophenyl)urea (Scheme 5). Furthermore, the first Biginelli-like reaction, reported by Wang *et al.*<sup>20</sup> was conducted in CH<sub>3</sub>CN by condensation of aldehydes, ketones, and urea, using FeCl<sub>3</sub>·6H<sub>2</sub>O and TMSCl as catalysts, which remarkably broadened the Biginelli reaction. We<sup>21</sup> reported the synthesis of 5-unsubstituted-3,4-dihydropyrimidin-2(1*H*)-ones **6** *via* the Biginelli-like reaction in the presence of molecular iodine under solvent-free conditions (Scheme 5). The results showed that both various aromatic aldehydes and several aromatic ketones were converted to the corresponding products **6** in good yields and in a short time. However, the dehydrogenated products **7** were obtained when aromatic aldehydes with electron-donating groups, such as methoxy, methyl, were used (Scheme 6).<sup>21,22</sup>

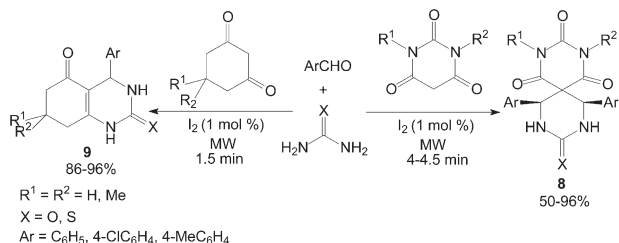
Cyclic 1,3-dicarbonyl compounds were also employed with urea and aromatic aldehydes to produce spiropyrimidines **8**



**Scheme 5** Iodine catalyzed synthesis of new 3,4-dihydropyrimidin-2(1*H*)-ones and 5-unsubstituted-3,4-dihydropyrimidin-2(1*H*)-ones.



Scheme 6 Iodine catalyzed Biginelli-like reaction.



Scheme 7 Iodine catalyzed Biginelli-like reaction.

and dihydropyrimidinones **9** under microwave irradiation in a solvent-free condition (Scheme 7).<sup>23</sup> Notably, The Biginelli-like reactions were carried out in presence of 1 mol% iodine under microwave irradiation within 4.5 min.

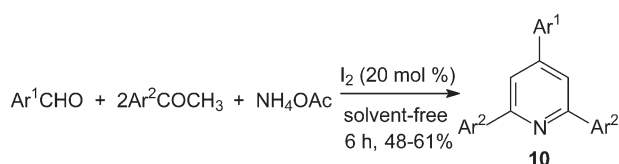
### 2.3 Synthesis of 2,4,6-triarylpyridines

One-pot, three-components synthesis of 2,4,6-triarylpyridines **10** were performed under solvent-free conditions using molecular iodine as the catalyst (Scheme 8).<sup>21</sup> The reaction medium had an influence on the reaction; the results showed that solvent-free conditions provided better yield than if solvents were used (Table 1). And the results showed that both electron-deficient and electron-rich aromatic aldehydes were converted to the corresponding 2,4,6-triarylpyridines **10** in moderate yields (48–61%).

### 2.4 Synthesis of Hantzsch 1,4-dihydropyridine compounds

In recent years, an increasing interest has been focused on the synthesis of Hantzsch 1,4-dihydropyridine compounds (1,4-DHPs) owing to their significant biological activity. Ko *et al.*<sup>24</sup> reported a novel synthesis of 1,4-DHPs **11** and **12** promoted by the catalytic amount of iodine under ambient conditions with excellent yields (Scheme 9). Both aliphatic and aromatic aldehydes react equally good to give the products with excellent yields. The aryl group substituted with different groups and same groups located at different positions of the aromatic ring has not shown much effect on the formation of the final product.

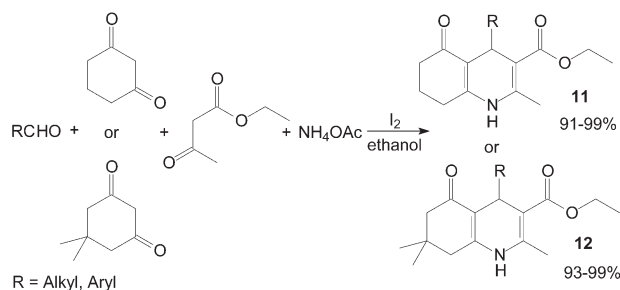
The first example of the synthesis of different kinds of methyl-1-hydroxyethyl-1,4-dihydro-2,6-dimethylpyridine-3,5-



Scheme 8 Iodine catalyzed synthesis of the 2,4,6-triarylpyridines.

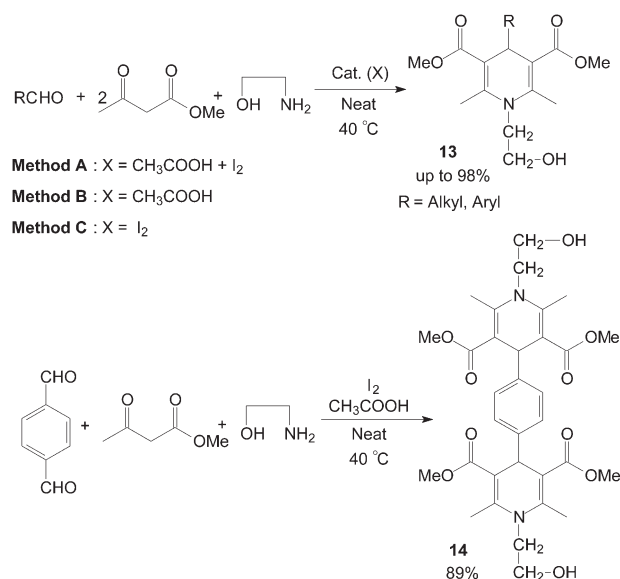
Table 1 Effect of the different solvent on the synthesis of 2,4,6-triphenylpyridines

| Entry | Solvent                         | T (°C) | Yield (%) |
|-------|---------------------------------|--------|-----------|
| 1     | —                               | 120    | 56        |
| 2     | EtOH                            | 78     | 22        |
| 3     | CH <sub>3</sub> CN              | 82     | 17        |
| 4     | DMF                             | 140    | 9         |
| 5     | CH <sub>2</sub> Cl <sub>2</sub> | 40     | 10        |
| 6     | Et <sub>3</sub> N               | 90     | Tace      |
| 7     | PhMe                            | 110    | 11        |



Scheme 9 Iodine catalyzed synthesis of the 1,4-DHPs.

dicarboxylates **13** and bis(methyl-1-hydroxyethyl-1,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxylates) **14** under mild and solvent-free conditions was reported by Zolfigol *et al.* (Scheme 10).<sup>25</sup> Although reactions occurred both in the presence and in the absence of molecular iodine but iodine catalyzed the described reaction efficiently and also improved the reactions yields (Table 2). Meanwhile, the reaction times and yields of reactions were not seriously changed but purification of crude products of the **method A** was more easier than **methods B** and **C**. Similarly, aniline also was



Scheme 10 Synthesis of the N-hydroxyethyl 1,4-dihydropyridine compounds.

**Table 2** Synthesis of Hantzsch *N*-hydroxyethyl 1,4-dihydropyridyl compounds

| <i>R</i>                           | Time (h) |          |          | Yield (%) |          |          |
|------------------------------------|----------|----------|----------|-----------|----------|----------|
|                                    | Method A | Method B | Method C | Method A  | Method B | Method C |
| 4-Cl-C <sub>6</sub> H <sub>4</sub> | 0.75     | 2        | 0.75     | 85        | 60       | 84       |
| 2-Furyl                            | 3        | 4.25     | 3        | 89        | 73       | 89       |

employed for synthesis of *N*-aryl-1,4-dihydropyridine **15** and **16** with good yields (Scheme 11).<sup>26,27</sup>

## 2.5 Strecker-type reaction

$\alpha$ -Aminonitriles are usually synthesized by the nucleophilic addition of a cyanide anion to imines. The Strecker-type reaction provides one of the most efficient methods for the synthesis of  $\alpha$ -aminonitriles **17** and **18** (Scheme 12). The treatment of benzaldehyde and benzyl amine with TMSCN in the presence of a catalytic amount of iodine afforded 2-(*N*-benzylamino)-1-phenylacetonitrile in 94% yield using acetonitrile as solvent at room temperature.<sup>28</sup> Wang *et al.*<sup>29</sup> reported a mild and convenient method for Strecker-type reactions of aldehydes, amines and tributyltin cyanide (Bu<sub>3</sub>SnCN) under the same reaction conditions. A longer reaction time (1–8 h) would be necessary using TMSCN as reagent.

## 2.6 Synthesis of homoallyl ethers and protected homoallylic amines

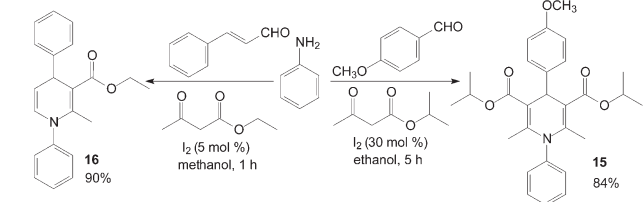
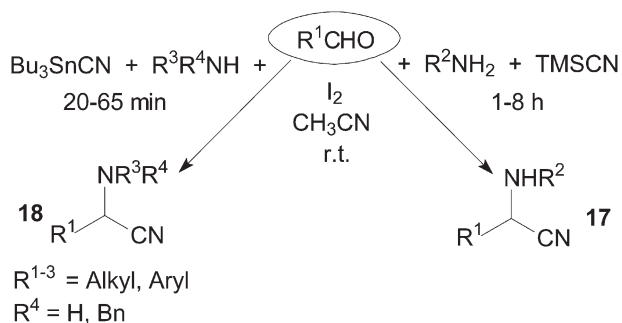
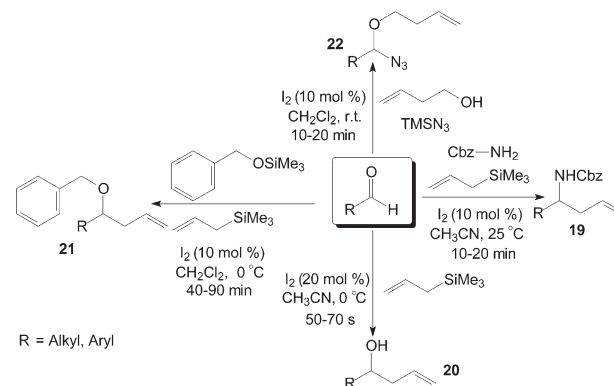
Aldehydes and aldimines react with allyltrimethylsilane in the presence of a catalytic amount of iodine to give the corresponding protected homoallyl amines **19** efficiently (Scheme 13).<sup>30</sup> In general, excellent yields of homoallyl amines **19** were obtained with 10 mol% of iodine at room temperature

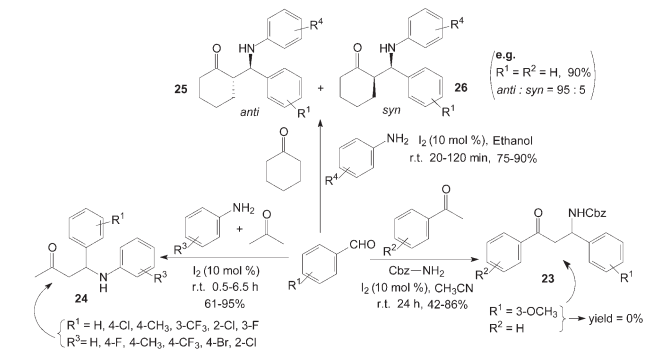
in acetonitrile. Both aromatic and aliphatic aldehydes undergo homoallylation with 66–82% yield irrespective of the nature of the substrate. Interesting, in this research, no traces of the corresponding homoallylic alcohol **20** resulting from direct addition of allyltrimethylsilane to the aldehyde were observed, even if the article by Yadav *et al.*<sup>31</sup> had shown that iodine could efficiently catalyse the allylation of aldehydes with allyltrimethylsilane in acetonitrile at 0 °C to afford the corresponding homoallyl alcohols **20** in high yields in about 1 min (Scheme 13).

Various homoallyl benzyl ethers **21** were synthesized in moderate to high yields by three-component condensation of aldehydes, benzyloxytrimethylsilane, and allyltrimethylsilane in presence of iodine (10 mol%) in dichloromethane at 0 °C (Scheme 13).<sup>32</sup> The reaction (based on benzaldehyde) was complete in 45 min with 86% yield of the corresponding homoallyl benzyl ether at 0 °C. However, the best result with a yield of 67% was obtained after 210 min of reaction at 27 °C. Yadav *et al.*<sup>33</sup> also reported a direct approach for the one-pot preparation of a range of  $\alpha$ -alkoxy azides **22** and homoallyl ethers **21** including benzyl, allyl, and propargyl ethers. In all cases, the reactions proceeded rapidly at room temperature under mild conditions (Scheme 13).

## 2.7 Mannich reaction

Iodine has been found to be very effective catalyst for a Mannich reaction<sup>34</sup> between an aromatic aldehyde, an aromatic ketone and benzyl carbamate, even though this is a less reactive amine, to produce Cbz-protected  $\beta$ -aryl  $\beta$ -amino carbonyl compounds **23** in high yields (Scheme 14).<sup>35</sup> According to a systematic study, moderate to high yields of  $\beta$ -amino carbonyl compounds **23** were obtained with 10 mol% of iodine at room temperature in acetonitrile for 24 h.

**Scheme 11** Synthesis of *N*-substituted 1,4-DHPs using aniline as reagent.**Scheme 12** Iodine catalyzed Strecker-type reaction.**Scheme 13** Synthesis of the homoallyl ethers and protected homoallylic amines.



Scheme 14 Iodine catalyzed Mannich reaction.

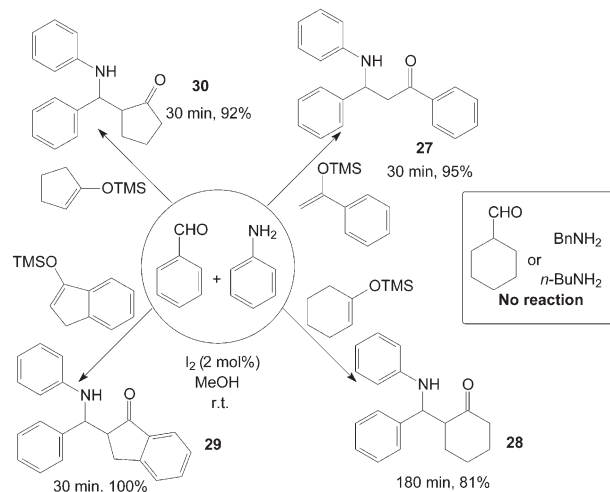
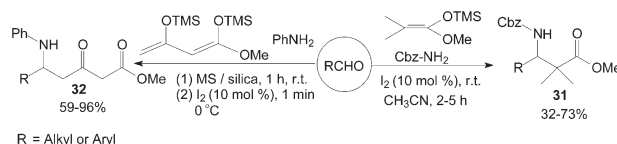
Substrates bearing various functional groups such as  $\text{CH}_3$ , OMe, Cl and Br all reacted successfully to produce the corresponding  $\beta$ -amino carbonyl compounds **23**. To our surprise, *ortho* and *para* substituted aldehydes gave good results, *meta*-substituted aldehydes such as 3-methoxybenzaldehyde failed to yield any product.

Owing to some special biological activity of fluorinated compounds, Xia *et al.*<sup>36</sup> described the direct three-component transformation into  $\beta$ -aminobutanones **24** containing fluorine atoms *via* iodine catalyzed coupling of aldehydes and amines in acetone (Scheme 14). There was remarkable electronic effect from the substituents on aniline moiety. For weak electron-withdrawing and electron-donating groups such as chloro- and methoxy, the three-component coupling could be executed smoothly in good yields within 1 h. And aliphatic amines were inert and unable to undergo such direct Mannich reactions. When butylamine was used with 4-fluorobenzaldehyde in acetone under 5 mol% iodine catalysis, none of expected product was obtained except the recycled substrates.

Recently, a variety of  $\beta$ -amino ketones **25** and **26** were readily prepared in high yields and with good to excellent *anti* selectivity under extremely mild conditions by means of three component coupling of aromatic aldehydes, aryl amines and ketones using 10 mol% of molecular iodine in ethanol (Scheme 14).<sup>37</sup>

$\beta$ -Amino ketones **27–30** were synthesized *via* a three-component reaction of benzaldehyde, aniline and silyl enol ether in the presence of catalytic amount of iodine at room temperature (Scheme 15).<sup>38</sup> All reactions were completed within three hours at room temperature, and corresponding products were obtained in good to excellent yields from aromatic aldehydes and aniline. However, no reaction was observed with aliphatic amines or aldehydes, the authors attribute this to the slow formation and unstable nature of the imine formed from either the aliphatic amine examined or the aliphatic aldehyde.

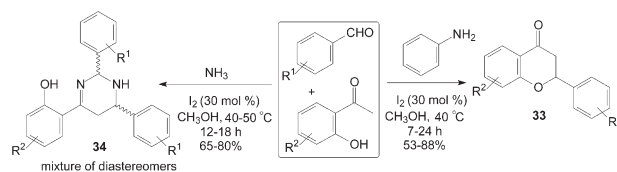
Kataki *et al.*<sup>39</sup> described the Mannich-type reaction of aldehydes, benzyl carbamate and silyl ketene acetal in a three component condensation to afford the corresponding Cbz protected  $\beta$ -amino esters **31** in moderate to high yields (Scheme 16). And Villano *et al.*<sup>40</sup> reported the one-pot, two steps synthesis of multifunctionalized  $\beta$ -ketoesters **32** using Chan's diene as substrate.

Scheme 15 Iodine catalyzed synthesis of the  $\beta$ -amino ketone.

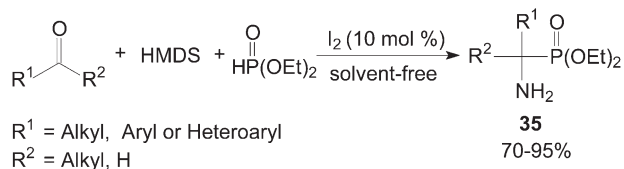
Scheme 16 Iodine catalyzed Mannich-type reaction.

A variety of functionalized flavanone **33** and tetrahydropyrimidine derivatives **34** were achieved under remarkably mild conditions by Mannich type reaction (Scheme 17).<sup>41</sup> The reaction for synthesis of flavanone **33** did not work when no amine was used. After systematic screening, the reaction trend suggests that the formation of imine as well as the elimination of amine is the key steps involved in the formation of flavanone derivatives. During the screening of the reaction conditions with various amines for synthesis of flavanone **33**, the authors obtained an interesting five component condensed products **34**, which comprised two aldehyde units, two ammonia molecules, and one 2-hydroxyacetophenone moiety. In the paper, plausible reaction mechanisms for the formation of flavanone **33** and tetrahydropyrimidine derivatives **34** were proposed as well.

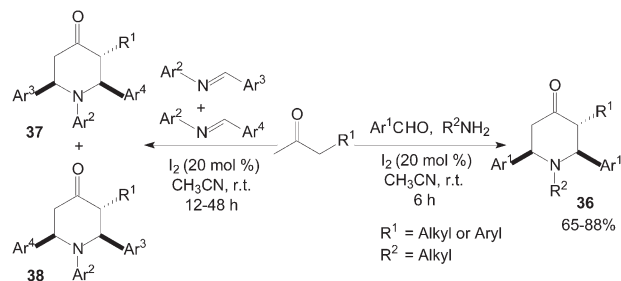
One-pot synthesis of primary 1-aminophosphonates **35** from coupling reaction of aldehydes/ketones, HMDS (1,1,1,3,3,3-hexamethyldisilazane) and diethyl phosphite under solvent-free conditions was developed by Sobhani *et al.* (Scheme 18).<sup>42</sup>



Scheme 17 Synthesis of flavanone and tetrahydropyrimidine by Mannich type reaction.



**Scheme 18** Synthesis of the primary 1-aminophosphonate compounds.



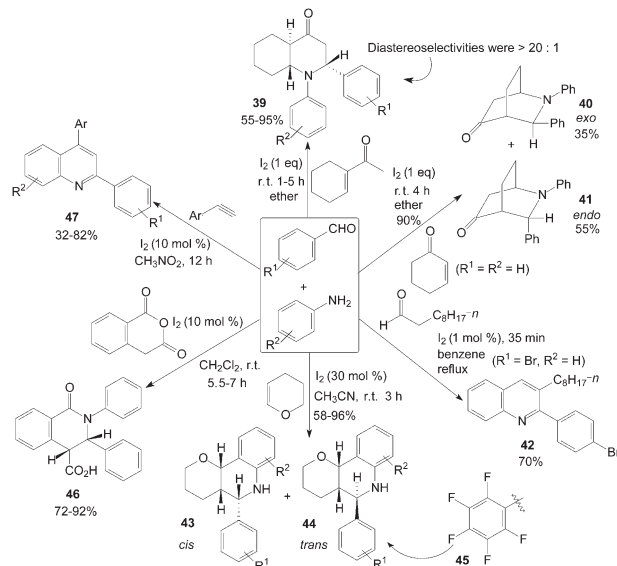
**Scheme 19** Iodine catalyzed double Mannich reaction.

Recently, Jia *et al.*<sup>43,44</sup> had reported that iodine could effectively catalyze the double Mannich reaction. A series of 4-piperidones **36–38** were prepared by treatment of aromatic aldehydes, amines with ketones (Scheme 19). In the “double” Mannich reaction, four new bonds could be formed *via* only one transformation with high bond forming efficiency.

## 2.8 Synthesis of quinoline and quinolinone derivatives from aldehydes and amines

Many quinoline and quinolinone derivatives from aldehydes and amines were prepared under mild conditions using molecular iodine as catalyst (Scheme 20). The diastereoselective synthesis of *trans-endo*-decahydroquinolin-4-one **39** *via* a three-component reaction of aldehydes, anilines and 1-acetylcyclohexene in the presence of iodine at room temperature was described by Lin *et al.*<sup>45</sup> The experiment results showed that most of the aldehydes reacted readily to produce the products **39** in excellent yields and high diastereoselectivity (>20 : 1). Cyclohexenone was also employed with benzaldehyde and aniline under the same conditions. 3-*Exo*-phenyl-2-phenyl-2-azabicyclo[2.2.2]octan-5-one **40** and 3-*endo*-phenyl-2-phenyl-2-azabicyclo[2.2.2]octan-5-one isomers **41** were obtained in high yields (Scheme 20). Furthermore, a two-step, one-pot synthesis of 2-arylquinolines **42** from an aniline, 4-bromobenzaldehyde and decanal was examined.<sup>46</sup>

The first example of the preparation for pyrano[3,2-*c*]quinolines **43** and **44** *via* an iodine-catalyzed three-component reaction of aldehydes, anilines, and 2,3-dihydropyran in a one-pot operation was described by Xia *et al.*<sup>47</sup> and Rai *et al.*<sup>48</sup> (Scheme 20). The most products were obtained as *cis/trans* isomers without any other isomer detected except for using 3-chloroaniline or 3-trifluoromethylaniline as reagent, and the *trans* isomer **44** was always the major product. Similarly, Jin *et al.*<sup>49</sup> had also reported synthesis of 2-perfluorophenyl tetrahydroquinolines **45** from pentafluorophenylaldehyde, anilines, and dihydropyran in CF<sub>3</sub>CH<sub>2</sub>OH by stirring for 14 h



**Scheme 20** Synthesis of quinoline and quinolinone derivatives from aromatic aldehydes and aniline derivatives.

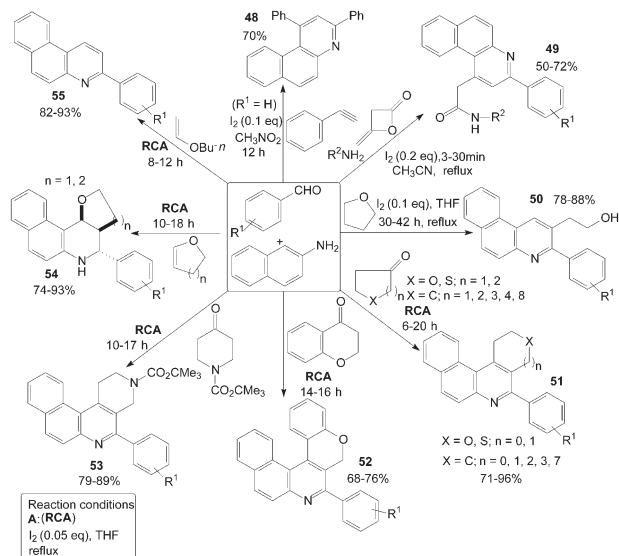
at room temperature using molecular iodine as catalyst (15 mol%). Similarly, the dihydrofuran was also employed for synthesis of furo[3,2-*c*]quinolines using molecular iodine as catalyst.<sup>50</sup>

Yadav *et al.*<sup>51</sup> reported the direct synthesis of highly substituted *cis*-oxoisoquinolinecarboxylic acids **46** from homophthalic anhydride, aromatic aldehydes and anilines in the presence of 10 mol% molecular iodine under neutral conditions (Scheme 20). It is very interesting that the only products were obtained as a *cis*-diastereomer.

Recently, a one-pot synthesis of quinolines **47** *via* iodine-catalyzed and air-mediated tandem condensation/imino-Diels-Alder/isomerization/oxidation of simple readily available amines, aldehydes, and alkynes was investigated (Scheme 20).<sup>52</sup> Based on the experimental results, the authors proposed a possible mechanism for the formation of quinolines **47**. In the possible mechanism, *via* imino-Diels-Alder reaction, intermediate is oxidized finally by O<sub>2</sub> in air to give the quinolines **47**.

Furthermore, naphthalene-2-amine was employed for the synthesis of a variety of functionalized quinolines (Scheme 21). According to the route of synthesis of **47**, benzo[*f*]quinoline **48** was produced in 70% yield by three-component reaction of naphthalenamine, phenylacetylene and benzaldehyde in a one-pot operation.<sup>52</sup>

The domino synthesis of benzo[*f*]quinolinyl **49** from diketene, amines, aromatic aldehydes and naphthalene-2-amine was developed by Zeng *et al.* (Scheme 21).<sup>53</sup> Meanwhile, the transformation proceeded successfully and benzo[*h*]quinolinyl acetamides were obtained when 4-chlorobenzylaldehyde or 4-methoxybenzaldehyde were employed with naphthalene-1-amine under the same conditions. However, because of the steric hindrance of *ortho*-substitution, the reaction was failed when 2-chlorobenzaldehyde was employed.

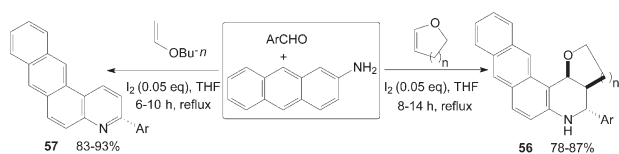


**Scheme 21** Synthesis of quinolines from aromatic aldehydes and naphthalen-2-amine.

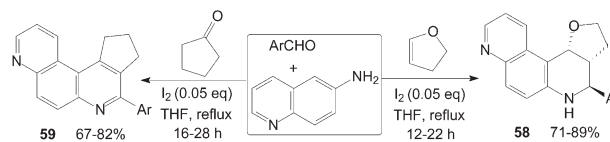
Initially, the unexpected products **50** were confirmed as “byproducts” in the reaction of 4-bromobenzaldehyde with naphthalen-2-amine in THF at room temperature to gain Schiff base.<sup>54</sup> In a systematic study, an efficient synthesis of 2-(3-arylbenzo[*f*]quinolin-2-yl)ethanol derivatives **50** by an unusual THF-involved reaction of aromatic aldehyde and naphthalen-2-amine promoted by iodine was demonstrated with good yields (Scheme 21). But the authors failed to get the expected products when naphthalen-1-amine or *p*-toluidine was used. Owing to the activity of naphthalen-1-amine or *p*-toluidine is less than that of naphthalene-2-amine.

A convenient, effective, and eco-friendly process had been developed by Wang *et al.*<sup>55–58</sup> leading to a library of quinolines derivatives, such as pyranoquinoline, thiopyranoquinoline, thienoquinoline, benzo(naphtho)quinoline and benzo[*f*]quinoline derivatives (**51–57**) (Scheme 21 and 22). The processes, which had similarly reaction conditions, provided a powerful tool toward the one-pot synthesis of diverse and complex compounds as well as small and drug-like heterocycles. Owing to their convergence and productivity, the novel synthetic method could attract considerable attention from the point of view of “combinatorial chemistry”.

The quinolin-6-amine was also employed for synthesis of phenanthrolines **58** and **59** using molecular iodine as catalyst (Scheme 23).<sup>59,60</sup>



**Scheme 22** Synthesis of quinolines from aromatic aldehydes and anthracen-2-amine.



**Scheme 23** Synthesis of phenanthrolines from aromatic aldehydes and quinolin-6-amine.

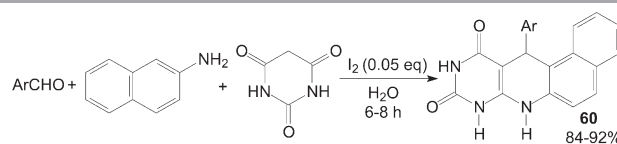
Wang *et al.* also reported the synthesis of benzo[*f*]pyrimido[4,5-*b*]quinoline derivatives **60** via one-pot three-component condensation of benzaldehydes, naphthalen-2-amine, and barbituric acid at room temperature in aqueous media (Scheme 24).<sup>61</sup>

In an initial assumption, 3*H*-pyrazolo[4,3-*f*]quinoline-8-carboxylate derivatives **61** might be obtained in high yields by reaction of aromatic aldehyde, 1*H*-indazol-5-amine, and methyl 3-oxobutanoate as reactants (Scheme 25).<sup>62</sup> However, the reaction gave 3-[(aryl)(1-methyl-1*H*-indol-3-yl)methyl]-1-methyl-1*H*-indole derivatives **64** in high yields.

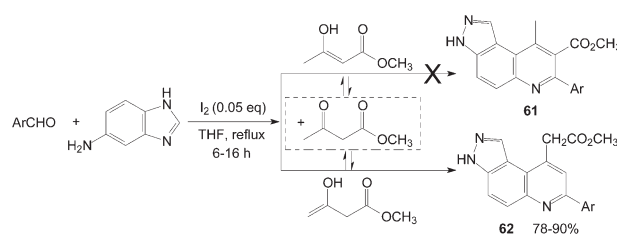
Wang *et al.*<sup>63</sup> reported an iodine-catalyzed Povarov reaction of synthesis of *exo*-indolo[3,2-*c*]quinoline **63** using indole as dienophile carried out in toluene at room temperature (Scheme 26). *N*-methylindole was also chosen as a dienophile to react with aldehyde and naphthalen-2-amine under the same conditions. It is interesting that the above reaction gave 3-[(aryl)(1-methyl-1*H*-indol-3-yl)methyl]-1-methyl-1*H*-indole derivatives **64** in high yields.

A series of benzo[*h*]pyrazolo[3,4-*b*]quinolines **65** were also prepared from 3-methyl-1-phenyl-1*H*-pyrazol-5-amine, 2-hydroxynaphthalene-1,4-dione and aromatic aldehydes in the presence of molecular iodine in refluxing H<sub>2</sub>O (Scheme 27).<sup>64</sup>

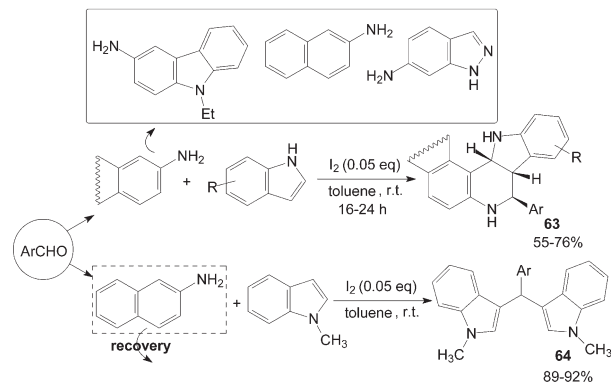
A two component aza-Diels–Alder cyclization of *N*-vinyl-2-pyrrolidinone with *N*-arylimine gave tetrahydroquinoline derivatives **66** and **67** in good yields and high stereo-selectivity under solvent-free conditions was described by Shen *et al.* (Scheme 28).<sup>65</sup> Interestingly, the three components aza-Diels–



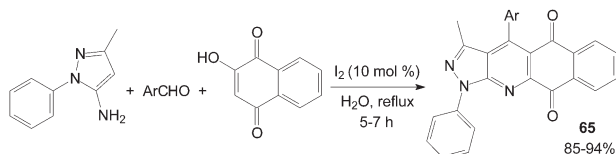
**Scheme 24** Synthesis of benzo[*f*]pyrimido[4,5-*b*]quinoline derivatives in aqueous media.



**Scheme 25** Synthesis of quinolines from aromatic aldehydes and anthracen-2-amine.



**Scheme 26** Iodine catalyzed Povarov reaction.



**Scheme 27** Synthesis of benzo[h]pyrazolo[3,4-b]quinolines from aromatic aldehydes.

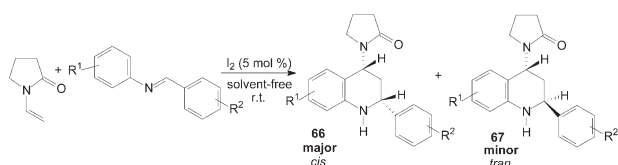
Alder reaction of *N*-vinyl-2-pyrrolidinone, anilines and indole-3-carbaldehydes under the same condition afford only *cis*-product **68** in good yields (Scheme 29).<sup>65</sup>

## 2.9 Synthesis of quinolines, piperidines and $\beta$ -amino carbonyl compounds from aldehydes, $\beta$ -ketoesters and amines

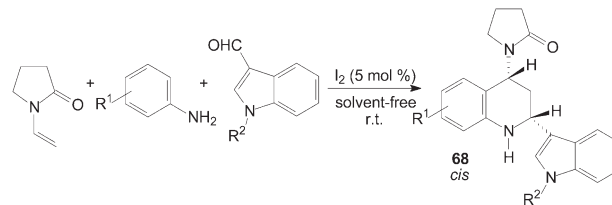
A mild, efficient and highly selective method for the synthesis of benzo[f]quinoline derivatives **69** *via* three-component reactions of aromatic aldehydes, naphthalen-2-amine and  $\beta$ -keto esters using iodine as catalyst in refluxing tetrahydrofuran (THF) was described (Scheme 30).<sup>66</sup> Interestingly, in methanol, functionalized piperidines **70** and **72** were obtained *via* five-component reactions of 1,3-dicarbonyl compounds, amines and aromatic aldehydes at room temperature (Scheme 30).<sup>67</sup> However, in case of diethylmalonate, the corresponding  $\beta$ -amino carbonyl compounds **71** was yielded under above reaction conditions (Scheme 30).<sup>67</sup> This can be attributed to the lack of enolizable alkyl group in the  $\beta$ -position.

## 2.10 Synthesis of $\beta$ -acetamido ketones, amidophenols and 4-amido tetrahydropyrans from carbonyl compounds and nitrile

A one-pot coupling of aromatic aldehydes, enolizable ketones or ketoesters, and acetonitrile in the presence of acetyl



**Scheme 28** Iodine catalyzed two component aza-Diels-Alder reaction.



**Scheme 29** Iodine catalyzed three components aza-Diels-Alder reaction.

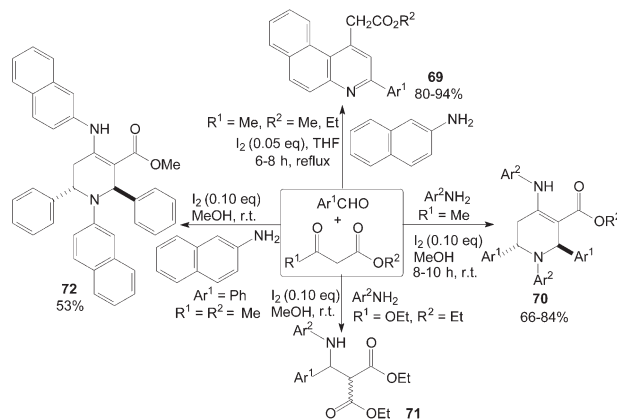
chloride to form  $\beta$ -acetamido ketones **73** at room temperature was described by Das *et al.* (Scheme 31).<sup>68</sup> In the reaction, When propiophenones (instead of acetophenones<sup>68,69</sup>) were used in the reaction both *anti* and *syn* products were formed.

Amidophenols derivatives **74** from acetonitrile, substituted phenol and aromatic aldehyde in the presence of catalytic amount of iodine and acetyl chloride were prepared under mild conditions (Scheme 31).<sup>70</sup> The reaction was amenable to a wide variation in phenol and aldehydes. The reaction proceeded well irrespective of the presence of electron withdrawing or electron donating group on aromatic aldehydes and phenols.

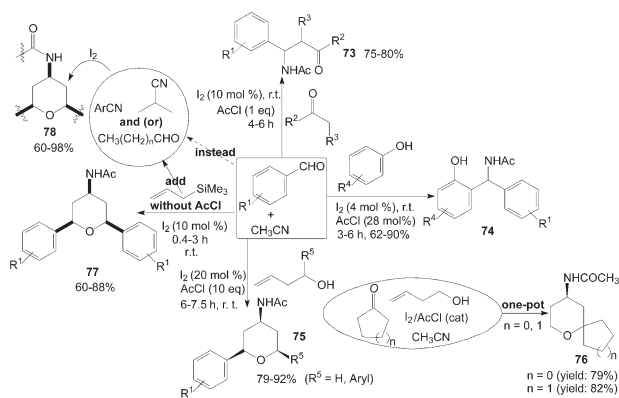
Three-component coupling of carbonyl compounds, homoallylic alcohols and acetonitrile was achieved using iodine and acetyl chloride at ambient temperature *via* the Prins-Ritter reaction sequence to furnish 4-amido tetrahydropyrans **75** and **76** in high yields with all *cis* selectivity (Scheme 31).<sup>71</sup> The formation of the products **75** and **76** could be explained by hemi-acetal formation followed by Prins-cyclization and subsequent Ritter amidation.

In the above reactions for the synthesis of compounds **73**–**76**, the acetyl group of the products was derived from acetonitrile. The presence of acetyl chloride was vital. In the absence of acetyl chloride, the reaction did not proceed. The role of acetyl chloride for the formation of product is not clear.

Sakurai-Prins-Ritter reaction,<sup>72</sup> which involved an aromatic aldehyde, allyltrimethylsilane and acetonitrile (without acetyl chloride), afforded the products of symmetrical 4-amido tetrahydropyrans **77** in satisfactory yields within a short time



**Scheme 30** Synthesis of quinolines, piperidines and  $\beta$ -amino carbonyl compounds from aldehydes,  $\beta$ -ketoesters and amines.



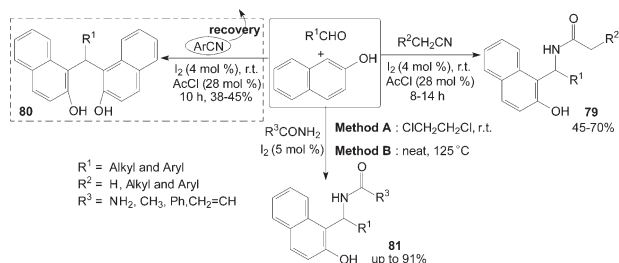
**Scheme 31** Synthesis of β-acetamido ketones, amidophenols and 4-amido tetrahydropyrans from carbonyl compounds and nitrile.

(Scheme 31). The reactions were also successful with aliphatic aldehydes and other nitriles (such as benzonitrile, 4-methyl benzonitrile, and isobutyronitrile) to produce the corresponding 4-amido tetrahydropyrans **78** in good yields.

## 2.11 Synthesis of amidoalkyl naphthols and bisnaphthols from carbonyl compounds and 2-naphthol

Similarly, based on the route of synthesis of **74** (Scheme 31), amidoalkyl naphthols **79** were obtained in 45–70% yields by three-component reaction of nitrile, aldehydes and 2-naphthol in the presence of catalytic amount of iodine and acetyl chloride (Scheme 32).<sup>70</sup> However, only α-hydrogenated nitriles involved in the reaction and yielded the corresponding amidoalkyl naphthols **79**, the reactions with aromatic nitriles did not yield the desired product, while bisnaphthols **80** were formed exclusively. The results showed that aromatic nitrile moiety was not involved in the reaction pathway.

Amidoalkyl naphthols **81** were readily prepared using urea or amides in high yields with two methods (Scheme 32).<sup>73</sup> The yields of the products were somewhat higher in **Method A** but the conversion times were much lower in **Method B** (Table 3). Aromatic aldehydes underwent facile conversions but aliphatic aldehydes afforded the products in low yields (Table 3). On the other hand, the reactions with thiourea were considered,<sup>74</sup> but no corresponding products were produced. Also, amines such as ethylamine and aniline were utilized and no amidoalkyl naphthol was obtained.



**Scheme 32** Synthesis of amidoalkyl naphthols and bisnaphthols from carbonyl compounds and 2-naphthol.

**Table 3** Synthesis of amidoalkyl naphthol compounds

| Entry | R <sup>1</sup>                | R <sup>3</sup>  | Time (h) |          | Yield (%) |          |
|-------|-------------------------------|-----------------|----------|----------|-----------|----------|
|       |                               |                 | Method A | Method B | Method A  | Method B |
| 1     | Ph                            | NH <sub>2</sub> | 12       | 4.5      | 91        | 87       |
| 2     | C <sub>2</sub> H <sub>5</sub> | NH <sub>2</sub> | 26       | 9        | 35        | 20       |

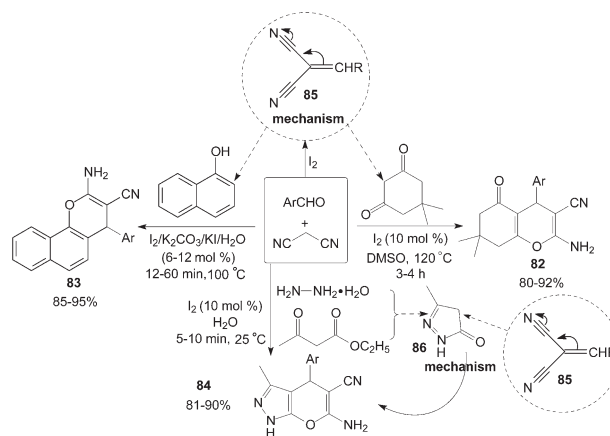
## 2.12 Synthesis of tetrahydrobenzo[b]pyrans, 2-amino-2-chromenes and pyranopyrazoles from aromatic aldehydes with malononitrile

A convenient and efficient method for synthesis of tetrahydrobenzo[b]pyran **82** via one-pot three-component condensation of aromatic aldehydes with malononitrile and 1,3-cyclic dimedones had been developed by using iodine/DMSO system (Scheme 33).<sup>75</sup> The I<sub>2</sub>/K<sub>2</sub>CO<sub>3</sub>/KI/H<sub>2</sub>O system was introduced as an environmentally friendly catalyst system in three component coupling reactions of substituted 2-amino-2-chromenes **83** synthesis.<sup>76</sup> The reaction for the synthesis **83** proceeds quickly (12–20 min) under very mild reaction conditions (aqueous medium). Various pyranopyrazoles **84** were also synthesized by an iodine catalyzed four component reaction at room temperature in water.<sup>77</sup>

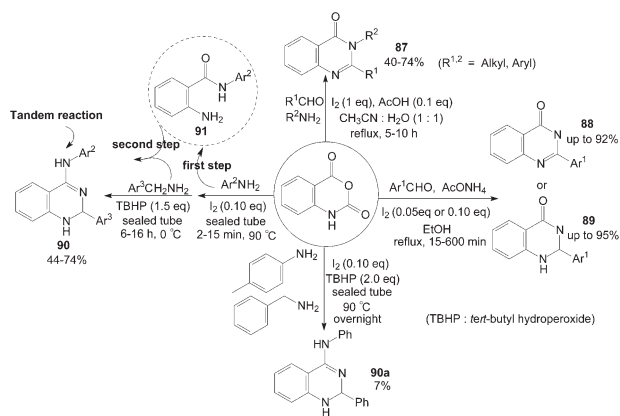
In the above reactions for the synthesis of compounds **82–83**, the reactions occur via initial formation of arylidenemalononitrile **85** in quantitative yield by the Knoevenagel condensation<sup>78,79</sup> of malononitrile to the aldehyde by loss of water molecules (Scheme 33). On the other hand, iodine catalyzed formation of pyrazolone **86** is expected to occur by the reaction between hydrazine hydrate and ethyl acetoacetate.<sup>77</sup>

## 2.13 Synthesis of quinazolinones and quinazolin-4-amines from isatoic anhydride or ortho esters

Isatoic anhydride reacted with ammonium acetate or primary amines and aldehydes in the presence of iodine and acetic acid to produce the corresponding quinazolinones **87** in moderate to good yields (Scheme 34).<sup>80</sup> After systematic



**Scheme 33** Synthesis of tetrahydrobenzo[b]pyrans, 2-amino-2-chromenes and pyranopyrazoles from aromatic aldehydes with malononitrile.



**Scheme 34** Synthesis of quinazolinones and quinazolin-4-amines from isatoic anhydride.

screening, a mixture of water and acetonitrile (1 : 1) was utilized as the solvent, and no quinazolinones **87** were formed in the absence of acetic acid when using amine as reactant. However, using ammonium acetate instead of amine in the reaction (without acetic acid) produced 2-substituted quinazolinones **88** successfully in higher yields and shorter times compared to disubstituted analogues.

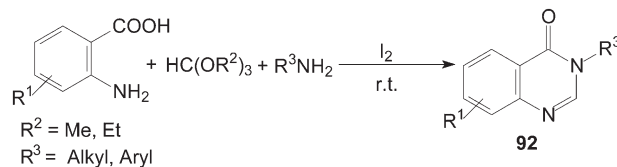
Zeng *et al.*<sup>81</sup> reported the same experiment results. The authors described an efficient one-pot three-component procedure for the selective synthesis of mono substituted quinazolin-4(3*H*)-ones **88** and 2,3-dihydroquinazolin-4(1*H*)-ones **89** using ammonium acetate instead of amine without acetic acid (Scheme 34). Initially, the unexpected product **88** was obtained using 20 mol% of molecular iodine as catalyst. Interestingly, the pure products **89** could be obtained with high yields when 5 mol% of molecular iodine as catalyst. The above result indicated that the catalytic iodine played the roles of both catalyst and oxidant. Similarly, under solvent-free conditions, one-pot synthesis of 2,3-dihydroquinazolin-4(1*H*)-ones **89** from coupling reaction of isatoic anhydride, aromatic aldehyde and ammonium acetate was developed by Rostamizadeh *et al.*<sup>82</sup>

Initially, Zeng *et al.*<sup>83</sup> tried to combine three reactants isatoic anhydride, *p*-toluidine and benzylamine for synthesis of 2-phenyl-*N*-(*p*-tolyl)-1,2-dihydroquinazolin-4-amine **90a** (Scheme 34). However, the one-pot three-component reaction gave a poor yield (only 7%) of product **90a**. After a series of attempts, the authors found an efficient two step route for the synthesis of products **90** (but one pot, avoiding the isolation of intermediate **91**) with moderate yields.

Furthermore, 3,4-dihydroquinazolin-4-ones **92** were also synthesized in high yields by three-component condensation of anthranilic acids, *ortho* esters and amines under solvent-free conditions (Scheme 35).<sup>84,85</sup>

## 2.14 Synthesis of tetrahydropyrimidines, pyrrolidines, tetrasubstituted pyrroles and dihydro-2-oxypyrroles from dialkylacetylene dicarboxylate

A short and simple synthesis of tetrahydropyrimidine **93** and pyrrolidine **94** derivatives were accomplished in good to



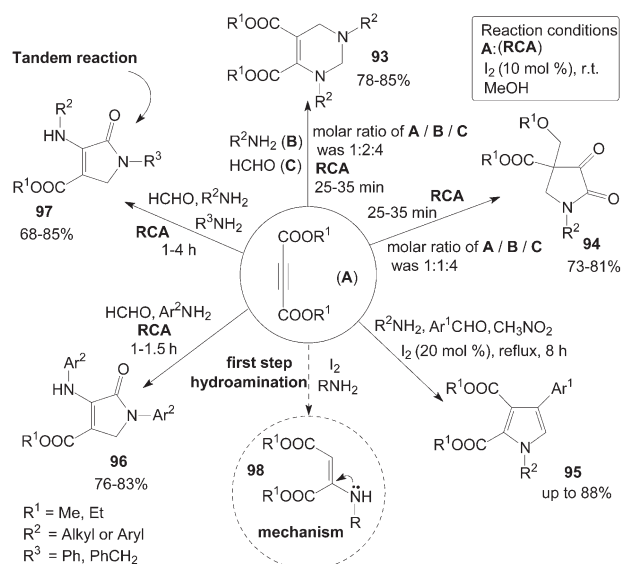
**Scheme 35** Synthesis of quinazolinones from *ortho* esters.

excellent yields at room temperature by the reaction of dialkylacetylene dicarboxylate (DAAD) **A**, amines **B**, and formaldehyde **C** in the presence of molecular iodine at room temperature (Scheme 36).<sup>86,87</sup> Interestingly, when the molar ratios of **A**, **B** and **C** were 1 : 2 : 4 and 1 : 1 : 4, tetrahydropyrimidine **93** and pyrrolidines **94** respectively, were formed.

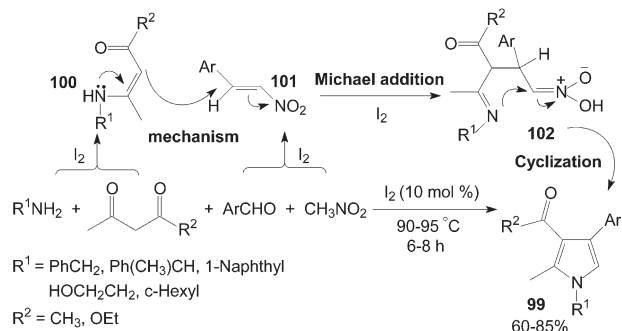
A series of 1,2,3,4-tetrasubstituted pyrroles **95** were subsequently prepared from aromatic aldehydes, amines, DAAD and nitromethane in the presence of molecular iodine as a catalyst (Scheme 36).<sup>88</sup> However, only a trace amount of product was detected when aliphatic aldehyde or nitroethane was employed.

On the other hand, polysubstituted pyrroles **99** would also be prepared using 1,3-dicarbonyl compound instead of DAAD in the reaction (Scheme 37).<sup>89</sup> The role of iodine in the present reaction was possibly the Michael addition reaction of intermediate  $\beta$ -enamino carbonyl compounds **100** with intermediate nitroalkenes **101** which was accelerated from intermediate **102** in presence of iodine.

A one-pot four-component coupling of DAAD, amines, and formaldehyde in the presence of molecular iodine to form multi-functionalized dihydro-2-oxypyrrole derivatives **96** and **97** at room temperature was described by Khan *et al.* (Scheme 36).<sup>90</sup> Initially, the reaction of DAAD, aniline derivatives, and formaldehyde for synthesis of products **96** were carried out in the presence of iodine in methanol with



**Scheme 36** Synthesis of various compounds from DAAD.



**Scheme 37** Synthesis of polysubstituted pyrroles from 1,3-dicarbonyl compounds.

high yields. Next, the authors explored the methods using two different amines for the synthesis of different substituted dihydro-2-oxypyrroles **97** in high yields *via* the tandem reaction.

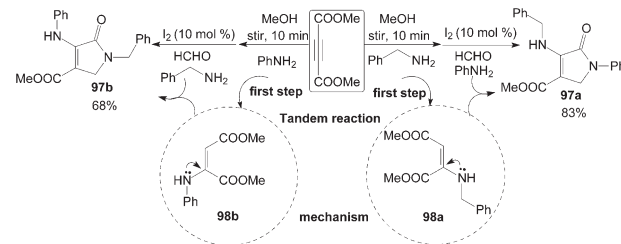
In the above reactions for the synthesis of compounds **93–97**, the hydroamination of DAAD with amines could rapidly form the active intermediate **98** (Scheme 36), which would then undergo nucleophilic addition reaction (or Michael reaction, or Mannich type reaction) to afford the desired products.

According to the above plausible mechanism, the desirable different substituted dihydro-2-oxypyrrole derivatives **97** could be obtained by changing the sequence of addition of amine with DAAD due to the formation of selective hydroamination products **98** (Scheme 38). For example, the mixture of dimethylacetylene dicarboxylate (DMAD) and benzylamine was stirred for 10 min to afford intermediate **98a**, and then aniline, formaldehyde, and iodine were added sequentially into the above reaction mixture. The product **97a** was isolated in 83% yield. Comparatively, the intermediate **98b** would be obtained firstly when DMAD and aniline was stirred for 10 min, and the product **97b** was isolated in 68% yield under the same conditions.

## 2.15 Synthesis of pyrimidine derivatives from 5-aminotetrazole

5-Aminotetrazole (5-AT) reacted with aromatic aldehydes and aromatic ketones in the presence of 10 mol% iodine in refluxing *i*-PrOH to produce the corresponding 5,7-diaryl-4,7-dihydrotetrazolo[1,5-*a*]pyrimidines **103** in moderate yields (Scheme 39).<sup>91</sup> Most of the substrates selected, including *para*-substituted benzaldehydes and *meta*-substituted acetophenone, participated in the reaction smoothly, and the desired products **103** were obtained in moderate yields. However, the *ortho*-substituted benzaldehydes failed to provide the expected products.

Under the above reaction conditions, using ethyl acetoacetate or dimedone instead of aromatic ketones in the reaction produced the desired products **104** and **105** successfully in moderate to high yields (Scheme 39).<sup>91</sup> Notably, the product **106** was obtained in 43% yield *via* treating 5-AT and cyclohexanone (2 equiv.) under the previous modified conditions (Scheme 39).<sup>91</sup>



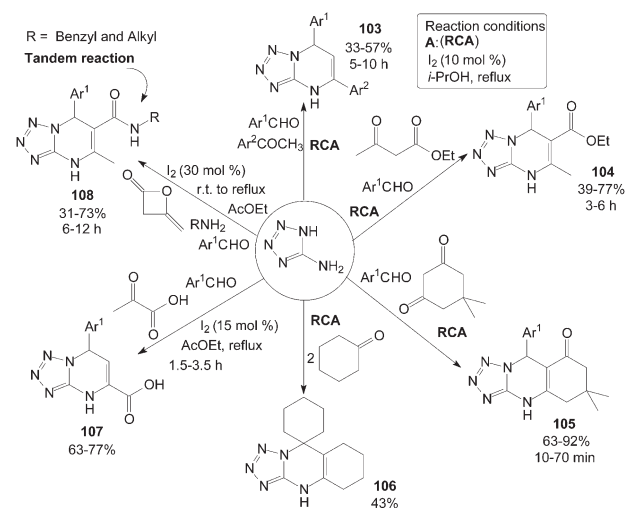
**Scheme 38** Synthesis of different substituted dihydro-2-oxypyrroles from DMAD.

Zeng *et al.*<sup>91,92</sup> also reported the direct synthesis of 5-aryl-5,8-dihydrotetrazolo[1,5-*a*]pyrimidine-7-carboxylic acids **107** from pyruvic acid, 5-AT and aromatic aldehydes in the presence of 15 mol% iodine in refluxing AcOEt (Scheme 39).<sup>91</sup> Both electron-deficient and electron-rich aromatic aldehydes were smoothly converted to the corresponding products **107** in moderate to good yields. However, sterically hindered aromatic aldehydes bearing groups such as 2-NO<sub>2</sub> and 2-Cl proceeded at a relatively slow rate and gave lesser yields than *para*-substituted aromatic aldehydes.

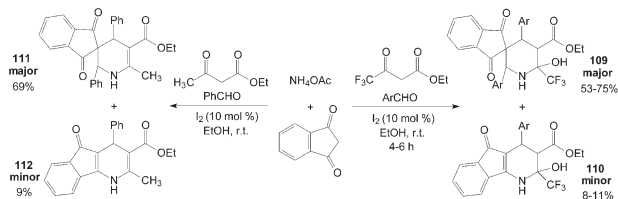
Four-component tandem procedure to prepare a series of dihydrotetrazolopyrimidinyl carbamides **108** starting from diketene, amines, 5-AT, and aromatic aldehydes was developed by Zeng *et al.* (Scheme 39).<sup>93</sup> In the procedure of tandem reaction, a solution of amine and diketene was stirred in AcOEt at room temperature for 2 h. Then, the aldehyde, 5-AT and iodine were added, and the temperature was increased to 78 °C. However, the expected product was not detected in the final mixture in the case of anilines or aliphatic aldehydes.

## 2.16 Synthesis of spiro[indene-2,3'-piperidine] derivatives

Dai *et al.*<sup>94</sup> described a facile, multi-component reaction involving condensation of ethyl trifluoroacetoacetate, 1,3-indanedione, ammonium acetate, and aromatic aldehydes in the presence of iodine at room temperature to afford a series



**Scheme 39** Synthesis of pyrimidine derivatives from 5-aminotetrazole.



**Scheme 40** Synthesis of spiro[indene-2,3'-piperidine] derivatives.

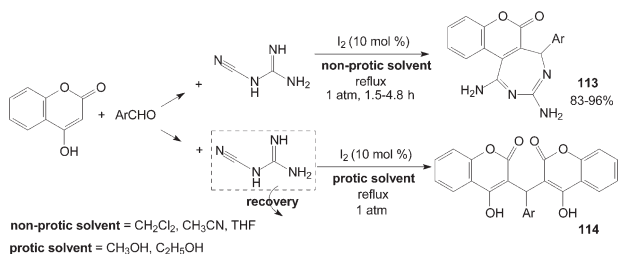
of novel trifluoromethyl-containing spiro[indene-2,3'-piperidine] scaffolds **109** in moderate yields, along with the minor products **110**, respectively (Scheme 40). Interestingly, the corresponding dehydrated products **111** as a major product in 69% yield, along with a minor dehydrated products **112** in 9% yield were produced when using non-fluorinated substrate ethyl acetoacetate instead of ethyl trifluoroacetate in the reaction under the same reaction conditions.

### 2.17 Synthesis of 7-arylbenzopyrano[1,3]diazepines and 3,3'-phenylmethylenebis-(4-hydroxycoumarin) from 4-hydroxycoumarin

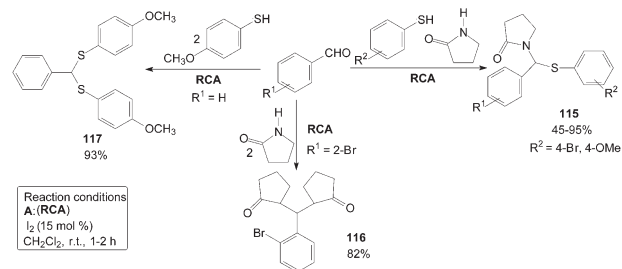
A novel and efficient method for 7-arylbenzopyrano[1,3]diazepines scaffold **113** using molecular iodine as a catalyst in non-protic solvents was reported by Kidwai *et al.* (Scheme 41).<sup>95</sup> The reactions in non-protic solvents like dichloromethane, acetonitrile and tetrahydrofuran leads to the formation of the products **113** with excellent yields. However, the surprising results were obtained when the same reaction was tried with protic polar solvents. In protic polar solvents like methanol, ethanol the condensation of 4-hydroxycoumarin with aromatic aldehydes facilitates bis adduct 3,3'-arylmethanebis-(4-hydroxycoumarin) **114**. Thus, it is concluded that formation of the products **113** are favoured only in the non-protic solvents.

### 2.18 Synthesis of pyrrolidin-2-one derivatives and (phenylmethylen)bis((4-methoxyphenyl)sulfane)

A simple and efficient three components domino reaction of  $\gamma$ -butyrolactam, aromatic aldehydes and substituted thiophenols catalyzed by iodine resulted in the formation of 1-((phenylthio)(phenyl)methyl)pyrrolidin-2-one derivatives **115** (Scheme 42).<sup>96</sup> The reaction was allowed to proceed without adding thiophenol giving 1,1'-((2-bromophenyl)methylene)-bis(pyrrolidin-2-one) product **116** (Scheme 42).<sup>97</sup> Similarly, The reaction was also allowed to proceed without adding  $\gamma$ -



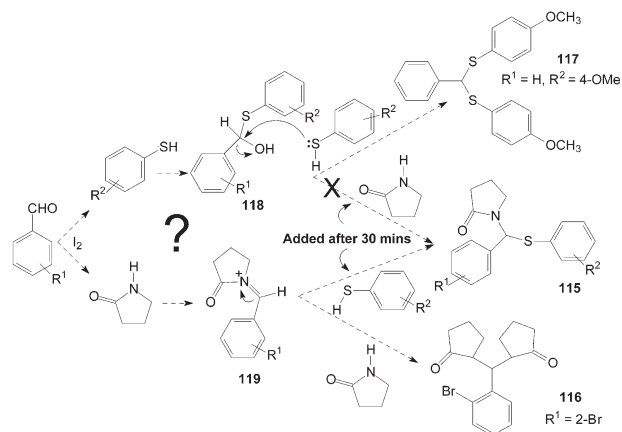
**Scheme 41** Synthesis of 7-arylbenzopyrano[1,3]diazepines and 3,3'-phenylmethylenebis-(4-hydroxycoumarin) from 4-hydroxycoumarin.



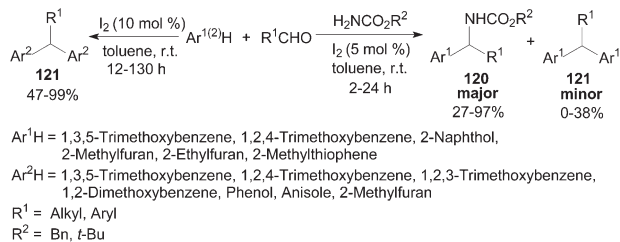
**Scheme 42** Synthesis of pyrrolidin-2-one derivatives and (phenylmethylen)bis((4-methoxyphenyl)sulfane).

butyrolactam it gives (phenylmethylen)bis((4-methoxyphenyl)sulfane) product **117** (Scheme 42).<sup>98</sup>

The authors think two mechanisms are possible for the synthesis of product **115** (Scheme 43). One possible mechanism is the formation of thiohemiacetal intermediate **118** in the first step and the second step is the attack of amide on intermediate **118** to yield the desired product **115**. Another possible mechanism is the generation of an *N*-acyliminium ion intermediate **119** in the first step followed by the attack of nucleophile (thiophenol) on the intermediate **119** leading to the formation of the desired product **115**. The reaction between  $\gamma$ -butyrolactam and benzaldehyde was stirred for 30 min firstly, and then thiophenol was added to the reaction mixture to get the product **115**. However, added  $\gamma$ -butyrolactam to the reaction mixture (thiopheno and benzaldehyde) after 30 min but did not get the product **115**. So, in the one-pot three-components reaction, the possible mechanism is iodine attacks the carbonyl oxygen of aldehyde and gives rise to the reaction, thereby carbonyl carbon gets bonded with nitrogen of  $\gamma$ -butyrolactam to form intermediate **119**. Nucleophilic attack of thiophenol on the intermediate **119** yields the desired product **115**.



**Scheme 43** A possible mechanism for the formation of pyrrolidin-2-one derivatives.



**Scheme 44** Iodine catalyzed (aza-)Friedel-Crafts reaction.

## 2.19 (aza-)Friedel-Crafts reaction

Jaratjaroonphong *et al.*<sup>99</sup> reported a highly efficient one-pot, three-component aza-Friedel-Crafts reaction of electron-rich arenes or heteroarenes, aldehydes, and benzyl or *tert*-butyl carbamates in toluene under “open-flask” and mild conditions (Scheme 44). After systematic screening, it was observed that when non-polar and weakly polar solvents such as toluene, CH<sub>2</sub>Cl<sub>2</sub>, or THF were used, the reaction gave the corresponding *N*-protected diarylmethylamines **120** as the major product and only a trace amount of double-addition products diarylalkane derivatives **121**. Notably, the products **121** were obtained in moderate to high yields without benzyl or *tert*-butyl carbamates (Scheme 44).<sup>100</sup>

## 2.20 Synthesis of 1,3-oxazinan-2-ones, xanthenes and anthracene-9,11-diones

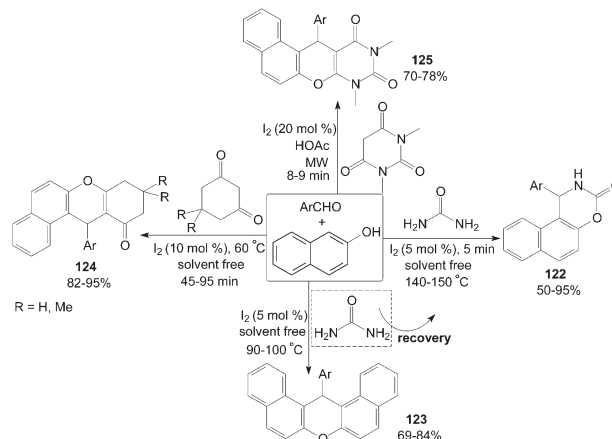
Molecular iodine catalyzed highly efficient one-pot three component coupling of  $\beta$ -naphthol, aromatic aldehydes and urea to produce 1-aryl-1,2-dihydro-naphtho[1,2-*e*][1,3]oxazin-3-one derivatives **122** under solvent free conditions was described by Sharma<sup>101</sup> and Nizam<sup>102</sup> *et al.* (Scheme 45). Interestingly, the product formation **122** is possible only at very high temperature (140–150 °C) and at lower temperature (90–100 °C) formation of 14-aryl-14-*H*-dibenzo[*a,j*]xanthenes **123** was observed. Previously, the articles<sup>103,104</sup> had shown that iodine could efficiently catalyse the reaction of 2-naphthol with aryl or alkyl aldehydes under neat conditions in acetonitrile at 90–100 °C to afford the corresponding products **123** in high yields (up to 95%) within 5 h.

Cyclic 1,3-dicarbonyl compounds were also employed with  $\beta$ -naphthol and aromatic aldehydes to produce tetrahydrobenzo[*a*]xanthene-11-one derivatives **124** and diazabenz[*a*]anthracene-9,11-dione derivatives **125** (Scheme 45).<sup>105–107</sup>

A variety of new tetrahydrobenzo[*c*]xanthene-1,11-dione **126** derivatives were also prepared by condensation of 4-hydroxycoumarin, aromatic aldehydes, and 5,5-dimethylcyclohexane-1,3-dione under microwave irradiation in good yields (Scheme 46).<sup>108</sup>

## 2.21 One-pot tandem reactions

A tandem reaction is a reaction in which several bonds are formed in sequence without isolating intermediates, changing reaction conditions, or adding reagents. So, the tandem reactions are commonly referred to under the nebulous phrase “multistep one-pot reactions.” Some instances of the tandem



**Scheme 45** Synthesis of 1,3-oxazinan-2-ones, xanthenes and anthracene-9,11-diones.

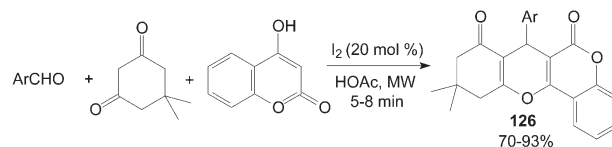
reaction have been presented in the above Schemes (Schemes 16, 34, 36, 38 and 39).

A variety of aldehydes reacted with iodine in ammonia water at room temperature to give the intermediate nitrile **127**, which were trapped by addition of hydrogen peroxide, dicyandiamide, or sodium azide to produce their corresponding amides **128**, 1,3,5-triazines **129**, and tetrazoles **130** in moderate to high yields (Scheme 47).<sup>109,110</sup>

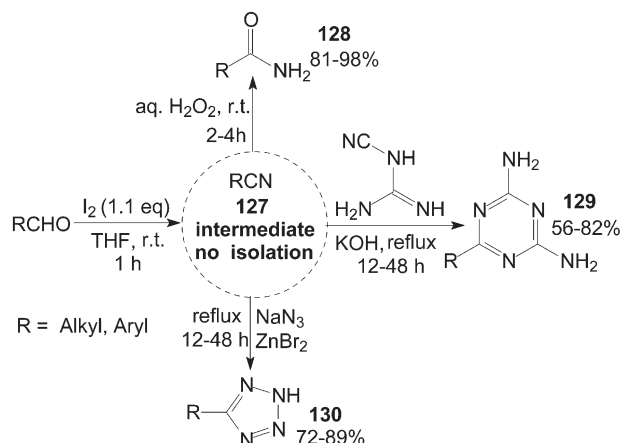
A highly efficient synthesis of hydantoins **132** had been developed from 1,3-dicarbonyl compounds, ureas, and methyl ketones or terminal aryl alkenes (Scheme 48).<sup>111</sup> This protocol involves a sustainable integration of two coupled domino processes: iodine-promoted synthesis of unsymmetrical intermediates 1,4-enediones **131** (domino process I)<sup>112,113</sup> and the sequential transformation into hydantoins **132** (domino process II). In the reaction, the presence of iodine is important for accelerating equilibrium toward the hydantoins **132**; otherwise, a mixture of products (without hydantoins **132**) would be obtained in the absence of iodine.

Kumar *et al.*<sup>114</sup> described an interesting iodine promoted sp<sup>3</sup> C–H bond activation of an alkyl azaarene to form alkyl azaarene pyridinium (AAP) zwitterions **135** in a new multi-component tandem reaction. 1-(Quinolin-2-ylmethyl)pyridinium iodide **133** is formed firstly by the reaction of methyl azaarenes and pyridine, which attacks an arylidene dione **134** (obtained from aldehydes and meldrum acid *via* Knoevenagel condensation in the presence of triethylamine) to form AAP zwitterions (Scheme 49).

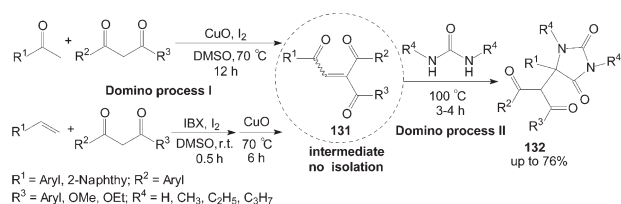
The intermediate products of hydrazones **136** were obtained firstly by the reaction mixture of 2-aminobenzohydrazide and



**Scheme 46** Iodine catalyzed synthesis of xanthenes.



Scheme 47 Iodine catalyzed tandem reaction.



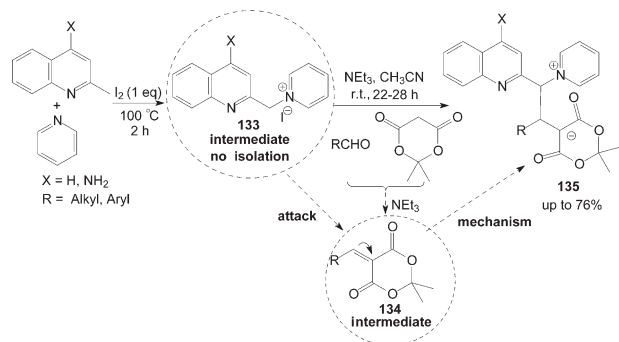
Scheme 48 Iodine catalyzed synthesis of hydantoin via tandem reaction.

acetophenone (or 3-nitrobenzaldehyde) stirring at room temperature (or 0 °C) for 2–3 h in ionic liquids (IL), then the aromatic aldehyde and iodine were added to the mixture for 2–8 h at 50 °C. The above tandem reaction provided structural diversification of 3-arylideneaminoquinazolin-4(1*H*)-one derivatives **137** in high yields (Scheme 50).<sup>115</sup>

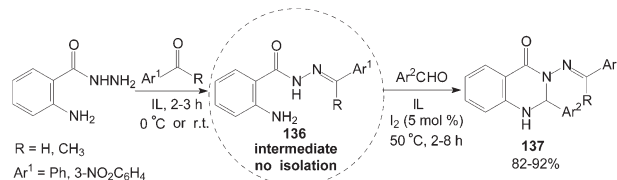
### 3. Molecular iodine catalyzed ABB and ABB' multicomponent reactions

#### 3.1 Synthesis of 1,5-benzodiazepine from *o*-phenylenediamine and ketones

2,3-Dihydro-1*H*-1,5-benzodiazepines **138** have been synthesized from *o*-phenylenediamine and ketones under solvent-free



Scheme 49 Synthesis of alkyl azaarene pyridinium zwitterions via tandem reaction.

Scheme 50 Synthesis of 3-arylideneaminoquinazolin-4(1*H*)-ones in ionic liquids.

conditions (Scheme 51).<sup>116</sup> All of the ketones, including cyclic ketones and acyclic ketones reacted smoothly with *o*-phenylenediamine to furnish products **138** in the presence of a catalytic amount of iodine within 10 min. In the reactions, the amino group of *o*-phenylenediamine attacks the carbonyl group of the ketone, which is activated by iodine, giving the intermediate diimine **139**. A 1,3-shift of the hydrogen attached to the methyl group then occurs to form an isomeric enamine **140**, which cyclizes to afford products **138**.

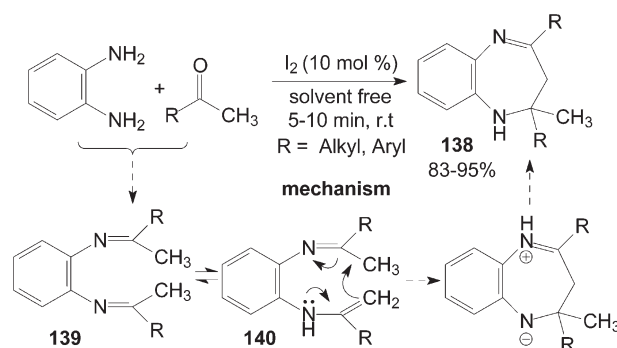
#### 3.2 Synthesis of 4,9-dihydro-2*H*-benzo[*f*]isoindoles

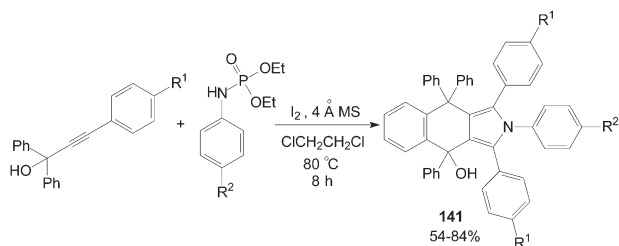
In the presence of iodine, 4,9-dihydro-2*H*-benzo[*f*]isoindole derivatives **141** could be efficiently constructed from propargyl alcohols and phosphoramides in the presence of iodine in a single step via ABB' MCRs (Scheme 52).<sup>117</sup>

#### 3.3 Synthesis of 1,2,3-triaroylindolizines

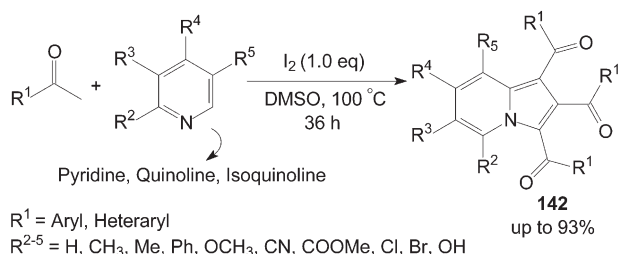
A very convenient and efficient method for the synthesis of 1,2,3-triaroylindolizines **142** directly from methyl ketones and pyridines was developed by Yang *et al.* (Scheme 53).<sup>118</sup> All methyl ketones, regardless of their electronic or steric properties, proceeded efficiently to afford their corresponding products **142** in moderate to excellent yields.

The regioselectivity of 3-substituted pyridines was addressed and the ratio of the corresponding indolizine isomers is highly dependent on the substituent nature (Scheme 54).<sup>118</sup> Although the electron-withdrawing group (CO<sub>2</sub>CH<sub>3</sub>) led to product **142a** in preference over **142** (Table 4, entry 1), the regioselectivity was reversed for 3-methylpyridine, 3-chloropyridine, and 3-bromopyridine, which yielded indolizines **142** as the major isomers (Table 4, entries 2–4). Interestingly, the active hydroxyl group was not only compatible under the same reaction

Scheme 51 Synthesis of 1,5-benzodiazepine from *o*-phenylenediamine and ketones.



**Scheme 52** Iodine catalyzed synthesis of 4,9-dihydro-2H-benzo[f]isoindoles.

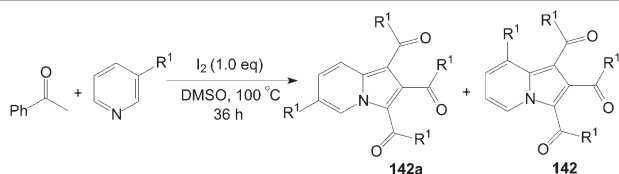


**Scheme 53** Synthesis of 1,2,3-triaroylindolizines.

conditions but also exclusively led to the regioisomer **142** (Table 4, entry 5).

### 3.4 Synthesis of xanthene, spiro dihydrofuran, cyclopropane and xanthenedione derivatives from 1,3-dicarbonyl compounds

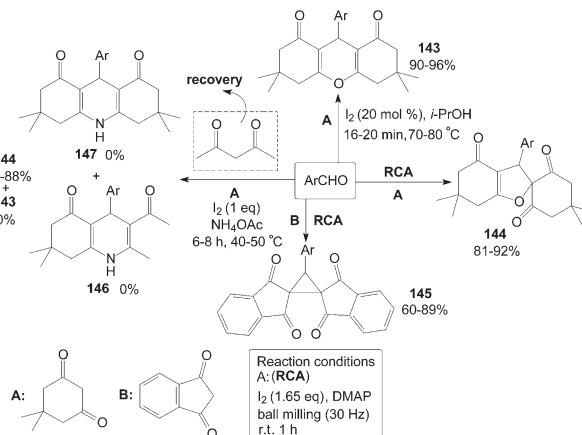
Molecular iodine facilitated the reaction of 5,5-dimethyl-1,3-cyclohexanedione with aromatic aldehydes in *iso*-propanol affording a variety of 1,8-dioxo-octahydroxanthenes **143** in high yields (Scheme 55).<sup>119</sup> However, spiro dihydrofurans **144** were obtained under the different reaction condition (Scheme 55).<sup>120</sup> Surprisingly, a new type of compound, cyclopropane derivative **145** were obtained rather than the expected products **144** *via* the reaction of aromatic aldehydes with 1,3-indandione in the presence of molecular iodine and



**Scheme 54** Synthesis of 1,2,3-triaroylindolizines.

**Table 4** Scope of 3-substituted pyridines

| Entry | R <sup>1</sup>                  | 142a : 142 | Yield (%) |
|-------|---------------------------------|------------|-----------|
| 1     | CO <sub>2</sub> CH <sub>3</sub> | 1.2 : 1    | 77        |
| 2     | CH <sub>3</sub>                 | 1 : 3.3    | 72        |
| 3     | Cl                              | 1 : 4.8    | 58        |
| 4     | Br                              | 1 : 3.9    | 54        |
| 5     | OH                              | 0 : 1.0    | 43        |



**Scheme 55** Synthesis of xanthene, spiro dihydrofuran and cyclopropane derivatives.

dimethylaminopyridine (DMAP) under mechanical milling conditions (Scheme 55).<sup>120</sup>

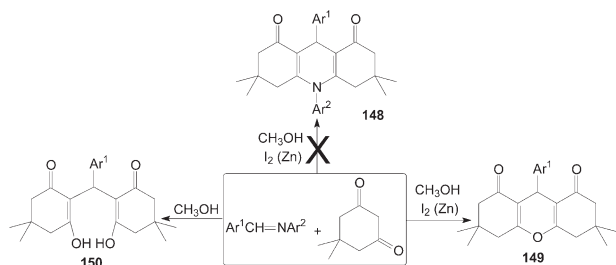
Initially, Sahu *et al.*<sup>121</sup> tried to combine four reactants dimedone, 4-anisaldehyde, acetylacetone and ammonium acetate in ethanol for synthesis of Hantzsch 1,4-dihydropyridine compound **146**. Interestingly, no desired product **146** could be isolated, and the products **143** and **147** were also not obtained under the same reaction conditions. The product **144** was the sole product isolated from the reaction mixture and acetylacetone was not incorporated in the reaction (Scheme 55). However, instead of the product **144**, the product **143** was isolated in good yield when the authors condensed dimedone and 4-chlorobenzaldehyde in refluxing methanol in the presence of iodine alone (without ammonium acetate). So, ammonium acetate is a key “promoter” for synthesis of the products **144** in the above reaction.

Similarly, Rong *et al.*<sup>122</sup> want to synthesize 1,4-dihydropyridine derivatives **148** by the reaction of imines with dimedone with the catalyst iodine and zinc powder in methanol (Scheme 56). However, they could not get the anticipated products **148**; surprisingly, xanthenediones derivatives **149** were obtained with excellent yields. And when the reaction was carried out without a catalytic amount of molecular iodine, ring-opening derivatives of xanthenediones **150** were obtained in high yields.

### 3.5 Synthesis of quinazolin-4-(1H)-one and quinoline derivatives

Similarly, based on the route of synthesis of **137** (Scheme 50), a combinatorial synthesis of quinazolin-4-(1H)-one derivatives **151** were accomplished by a reaction of 2-aminobenzohydrazides with two equivalents of aldehydes or ketones in ionic liquids (IL) catalyzed by iodine with good to excellent yields (Scheme 57).<sup>115</sup>

One-pot reactions of naphthalen-2-amine and alkyl aldehydes in the presence of iodine in refluxing THF to produce the corresponding 2,3-dialkylbenzo[f]quinolines **152** in moderate to good yields (Scheme 58).<sup>123</sup>



**Scheme 56** Synthesis of xanthenediones from dimedone.

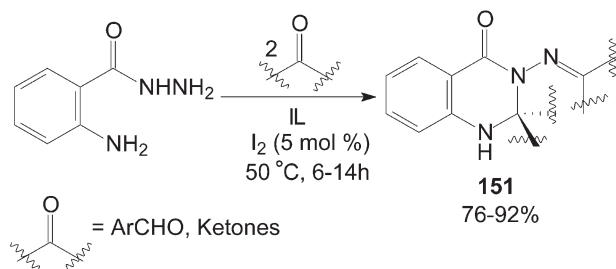
Anilines were also treated with aldehydes in the presence of iodine to give the corresponding 3,4-dialkyl-substituted quinolines **153** and quinazolines **154** in good yields (Scheme 59).<sup>46,52</sup>

The mechanism of the formation of substituted quinolines from anilines and ketones has been studied by the use of  $^{13}\text{C}$ -labeled ketones in the experiments. The reaction of 4-isopropylaniline with 5 equiv of acetone containing 20 mol% of  $^{13}\text{C}(2)$  acetone (100% labeled) at  $150^\circ\text{C}$  for 3 h in a sealed tube gave the quinoline **155** in 47% yield. The result showed clearly that the incorporation of two acetone molecules to form the quinoline **155** (Scheme 59).<sup>124</sup>

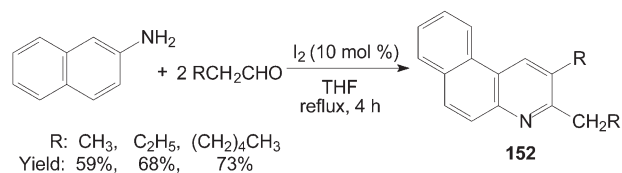
1,2,3,4-Tetrahydroquinoline derivatives **156** and **157** were obtained when cyclic enol ethers were reacted with anilines (Scheme 59).<sup>125</sup> After systematic screening, electron-rich anilines were more reactive than electron-deficient anilines. The strong electron-withdrawing group substituted 4-nitroaniline only gave a trace of product. In all cases, the products were obtained as a mixture of *endo/exo*-isomers.

### 3.6 Cross-aldol condensation

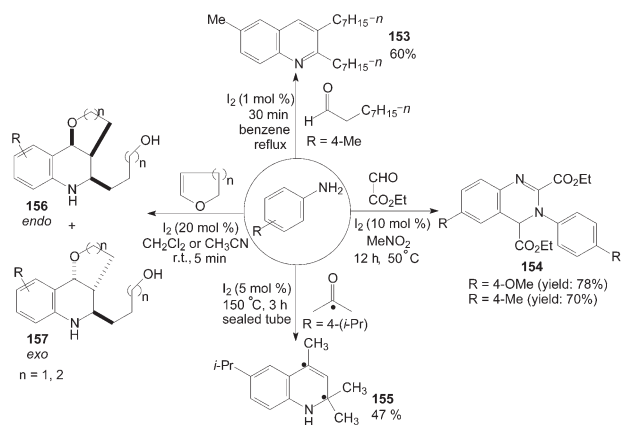
Cross-aldol condensation of aromatic aldehydes with cyclic ketones is an important synthetic reaction for the preparation of  $\alpha,\alpha'$ -bis(substituted-benzylidene) cycloalkanones **158**, 3,5-bis-(arylmethylidene)-tetrahydropyran-4-ones **159** and  $\alpha,\alpha'$ -bis(substituted benzylidene)-1-carbethoxy-4-piperidones **160**. The above reactions were accomplished at room temperature using iodine as catalyst with good to excellent yields (Scheme 60).<sup>126–128</sup> Notably, in all cases of the synthesis of products **159**, the reactions proceed rapidly and go to completion within 30–60 min at room temperature.



**Scheme 57** Synthesis of quinazolin-4(1H)-one derivatives from carbonyl compounds.



**Scheme 58** Synthesis of 2,3-dialkylbenzo[*f*]quinolines from naphthalen-2-amine and alkyl aldehydes.

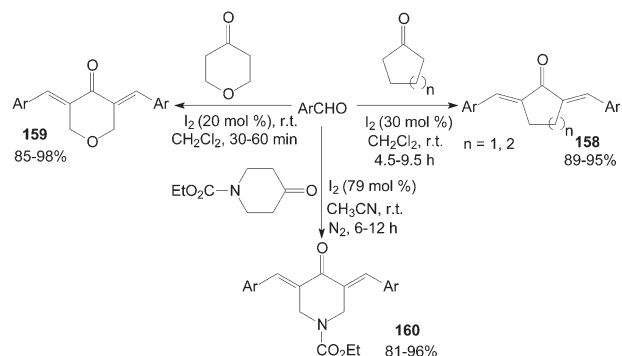


**Scheme 59** Synthesis of quinolines and quinazolines from anilines.

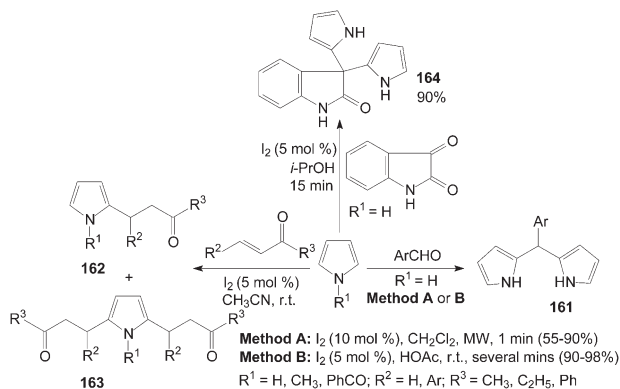
### 3.7 Synthesis of dipyrromethanes, 2,5-dialkylated pyrroles, porphyrins and cyclononatripyrrole from pyrroles

Dipyrromethanes **161** were readily prepared by the reaction of pyrrole and aromatic aldehydes in moderate to high yields with two methods (Scheme 61).<sup>129,130</sup> In the above two methods, all the reactions were accomplished within several minutes. However, the yields of the products were somewhat higher in **Method B**.

2-Alkyl pyrroles **162** and 2,5-dialkyl pyrroles **163** were obtained when the conjugate addition of pyrroles with methyl vinyl ketone using an equimolar ratio of reagents (Scheme 61).<sup>131</sup> Only products **163** were obtained by increasing the molar ratio of alkenes to pyrroles (3 : 1) in high yields within a short reaction time at room temperature. However, *N*-benzoyl pyrrole ( $\text{R}^1 = \text{PhCO}$ ) afforded only monoalkylated



**Scheme 60** Iodine catalyzed cross-aldol condensation.



**Scheme 61** Synthesis of dipyrromethanes and 2,5-dialkylated pyrroles from pyrroles.

products **162** in somewhat low yields. This can be attributed to the lower electron density on the ring carbon due to the electron withdrawing benzoyl group on the ring nitrogen.

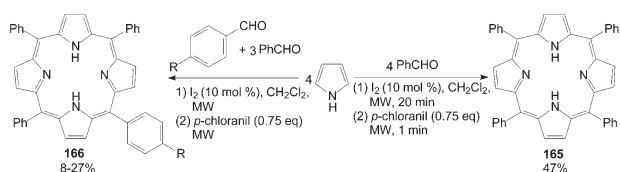
Furthermore, pyrrole also reacted efficiently with isatin in presence of iodine in *i*-PrOH to afford 3,3-dipyrrolyl-2-oxindole **164** (Scheme 61).<sup>132</sup>

The development of pyrrole chemistry has largely been associated with the synthesis of natural products. One of these natural products is porphyrins. The application is the well-known use of porphyrins as photosensitizers in photodynamic therapy.<sup>133</sup> However, the synthesis of unsymmetrical porphyrins presents a real challenge especially when practicable yields are needed. The well-known Little's mixed aldehyde method<sup>134</sup> leads to mono functionalized *meso*-substituted porphyrins in low yields (4-7%). Boëns *et al.*<sup>133</sup> reported an iodine-catalyzed, one-pot synthesis of functionalized porphyrins **165** and **166** (Scheme 62), a method that, contrary to the previous protocol, didn't require prior reactant or solvent distillation, and had higher yields (up to 47%) within a shorter reaction time.

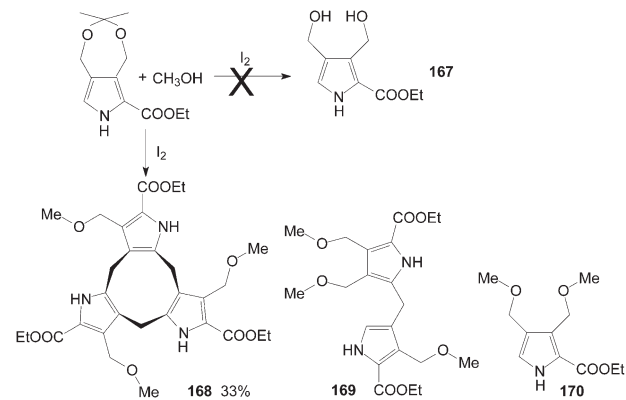
Initially, Stępień *et al.*<sup>135</sup> tried to synthesize dicarbinol **167** from ethyl 3,3-dimethyl-5,7-dihydro[1,3]dioxepino[5,6-*c*]pyrrole-6-carboxylate using iodine as catalyst. Interestingly, the unexpected major product formed was the cyclononatipyrrole **168**, accompanied by smaller amounts of the dipyrromethane derivative **169** and the monopyrrole **170** (Scheme 63).

### 3.8 Synthesis of di(indolyl)indolin-2-ones, bis(indolyl)methanes, indolo[2,3-*b*]carbazole and trisindolylalkanes from indoles

One-pot synthesis of di(indolyl)indolin-2-ones **171** was performed by the reaction of isatin with 1- or 2-substituted



**Scheme 62** Synthesis of porphyrins from pyrroles.



**Scheme 63** Synthesis of cyclononatipyrrole from pyrroles.

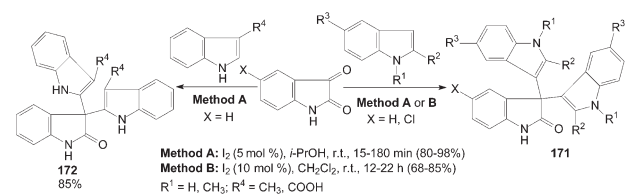
indoles in good to excellent yields with two methods (Scheme 64).<sup>132,136</sup> The yields of the products were somewhat higher in **Method A**. Meanwhile, the reaction times and amount of iodine were much lower in **Method A**. Interestingly, 3-substituted indoles underwent smooth coupling with isatin to give the corresponding bisindolyl oxindoles **172** in 85% yields (Scheme 64).<sup>132</sup>

In aqueous medium, molecular iodine had been used as an efficient catalyst for one-pot synthesis of 3,3'-arylmethylene-bis-(4-hydroxycoumarin) **173** and 2,2'-arylmethylenebis-(3-hydroxyl-5,5-dimethyl-2-cyclohexen-1-one) **174** in excellent yields (Scheme 65).<sup>137</sup>

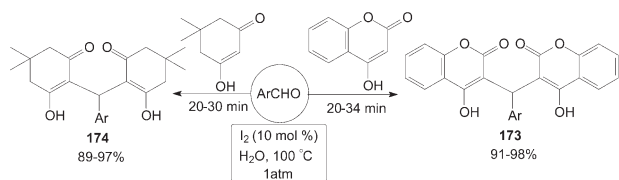
A highly efficient synthesis of bis(indolyl)methanes **175** has been developed from carbonyl compounds and indole in good to excellent yields with three methods (Scheme 66).<sup>138-140</sup> In the above three methods, most of products **175** were prepared within 10 min. Notably, the synthesis of products **175** by **Method B**<sup>139</sup> is in a very short time (<1 min). However, in **Method C**,<sup>140</sup> steric congestion around carbonyl carbon impedes the reaction rate substantially as reflected in the longer reaction time required (3-4.5 h) for sterically encumbered aromatic ketones.

The products **175** could be directly synthesized from benzyl alcohol and indole in up to 86% yield using molecular oxygen, visible light, and catalytic iodine (Scheme 66).<sup>141</sup> In the reaction, the catalytic iodine played the roles of both catalyst and oxidant. A new type of Schiff base *N*-tert-butanefulfinyl aldimine was also employed with indole to produce products **175** in good to excellent yields (Scheme 66).<sup>142</sup>

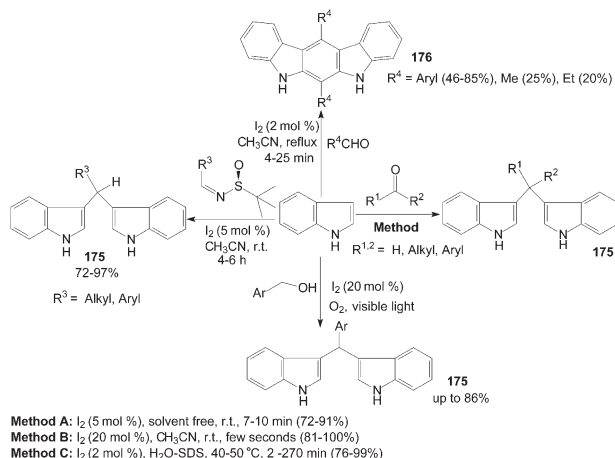
Interestingly, Deb *et al.*<sup>143</sup> reported the reaction using equimolar amounts of indole and an aldehyde under thermal



**Scheme 64** Synthesis of di(indolyl)indolin-2-ones from isatin and indoles.



**Scheme 65** Iodine catalysed aqueous mediated synthesis of Michael adduct.



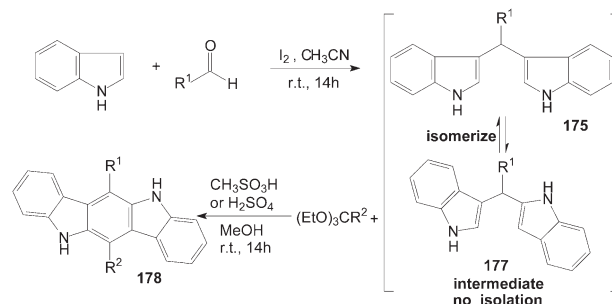
**Scheme 66** Synthesis of bis(indolyl)methanes and indolo[2,3-*b*]carbazole from indole.

conditions without giving time for isomerization of the products **175** formed during the reaction and allowing a second aldehyde molecule to become involved in the reaction to afford indolo[2,3-*b*]carbazoles **176** (Scheme 66). In a systematic study, it was observed that substituents in the aromatic ring of the aldehyde have a tremendous effect on the reaction process. Electron-withdrawing groups in the aromatic ring of the aldehyde retarded the reaction while electron-donating groups accelerated the reaction. And in the case of aliphatic aldehydes, the yields were low (20–25%).

Interestingly, the 3,3'-bis(indolyl)methanes **175** isomerized to 2,3'-bis(indolyl)methanes **177** when the condensations of indole and aldehyde were carried out for a longer time (14 h). Then acid-catalyzed intramolecular cyclizations were accomplished directly by treating the crude product **177** with different *ortho* esters in the presence of sulfuric acid or methanesulfonic acid as a catalyst to afford the corresponding indolo[3,2-*b*]carbazoles **178** (Scheme 67).<sup>144</sup>

Bis(indolyl)carbonyl compounds **179** were synthesized from 2-unsubstituted indoles such as indole, 5-bromoindole, and 5-methoxyindole, with 1,3-dicarbonyl compounds (Scheme 68).<sup>145</sup>

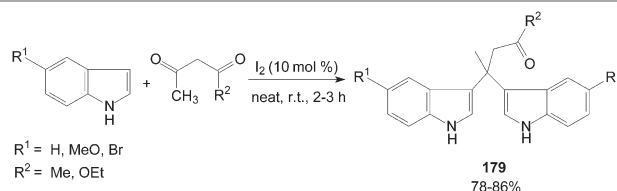
Furthermore, 4-[(indol-3-yl)-arylmethyl]-1-phenyl-3-methyl-5-pyrazolones **180** could be smoothly and effectively obtained in good yields by the three-component reactions of aldehydes, indole, and 1-phenyl-3-methyl-5-pyrazolones under solid-state conditions at room temperature (Scheme 69).<sup>146</sup> However, in the absence of iodine as a catalyst, the above three-component mixture could provide only the product 4-chlorophenyl-bis(1-phenyl-3-methyl-5-pyrazolon-4-yl)methane **181** at room tem-



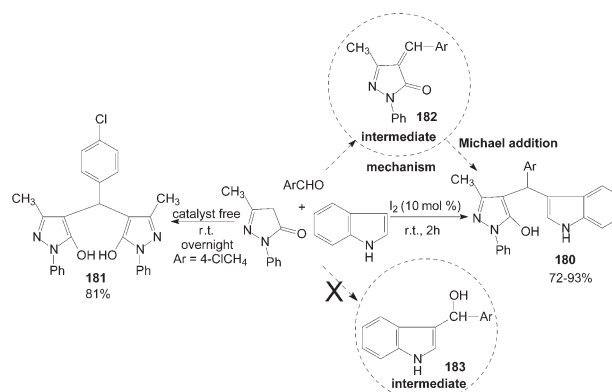
**Scheme 67** Synthesis of indolo[3,2-*b*]carbazoles from indole.

perature. And it was well known<sup>142</sup> that products **175** were obtained in low yields in the absence of Lewis acids. So, the authors gave the likely mechanism for the three-component reaction. Firstly, the intermediate **182** was offered in preference to the intermediate **183**, because the latter was too unstable to undergo the further transformation. Then, the subsequent Michael addition of indole with the intermediate **182** was successfully carried out to afford the target compounds **180** in excellent yields.

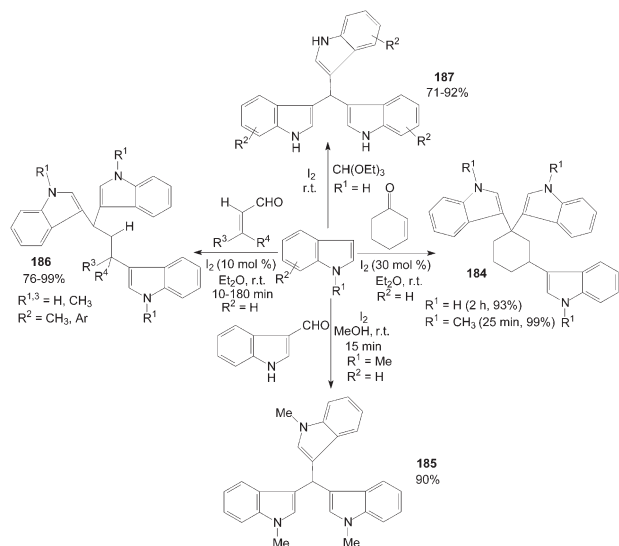
Trisindolylalkanes **184–187** had also been synthesized from indole or 1-methylindole with 2-cyclohexen-1-one, or  $\alpha,\beta$ -unsaturated aldehyde, or orthoformate at room temperature (Scheme 70).<sup>147–150</sup>



**Scheme 68** Synthesis of bis(indolyl)carbonyl compounds from indole.



**Scheme 69** Synthesis of 4-[(indol-3-yl)-arylmethyl]-1-phenyl-3-methyl-5-pyrazolones from indole.



**Scheme 70** Synthesis of trisindolylalkanes from indoles.

## 4. Conclusions

A large number of MCRs in the presence of molecular iodine have been presented, most of which show quite good conversion and selectivity for preparing products of industrial and pharmacological interest. Molecular iodine has broad transformation ability of functional groups and can be used widely in MCRs.

MCRs generally benefit from other aspects such as atom-economy, the use of readily available starting materials, resource effectiveness and bond-forming efficiency, which render these reactions useful environmentally friendly alternatives, in keeping with the greener direction in which organic chemistry is proceeding. Future research in the area of MCRs will include the discovery and design of novel MCRs, experimental improvements, and more and more applications in drug discovery, materials science, bioconjugates, and agrochemical compounds. It will not be surprising if more and more applications of molecular iodine in MCRs appear in near future.

The advantages of iodine are operational simplicity, low cost, and less toxicity. But the reuse of iodine is difficult because it has a good solubility in most organic solvents and easy sublimation at high temperature. Solid supported iodine with unreduced activity could considerably contribute to green chemistry. There have been a few reports of solid-supported iodine as a catalyst thus far. Such as the iodine supported on polyvinylpyrrolidone ( $I_2/PVP$ ),<sup>151</sup> aminopropyl silica gel ( $I_2/APSG$ ),<sup>152</sup> neutral alumina surface ( $I_2/Al_2O_3$ )<sup>17,153</sup> or natural phosphate ( $I_2/NP$ )<sup>154</sup> etc. However, the above supports were the preferred choice as supports to keep the reaction medium under mild and neutral conditions, and the reuse of iodine was also difficult. So simple, efficient supports for reusable iodine are still desirable.<sup>155,156</sup>

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