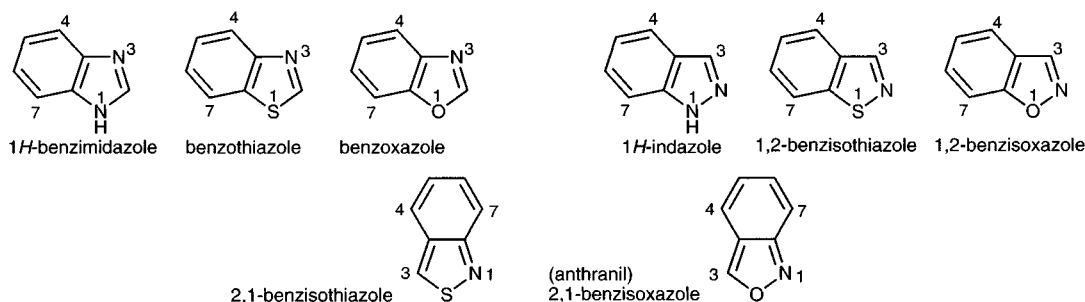
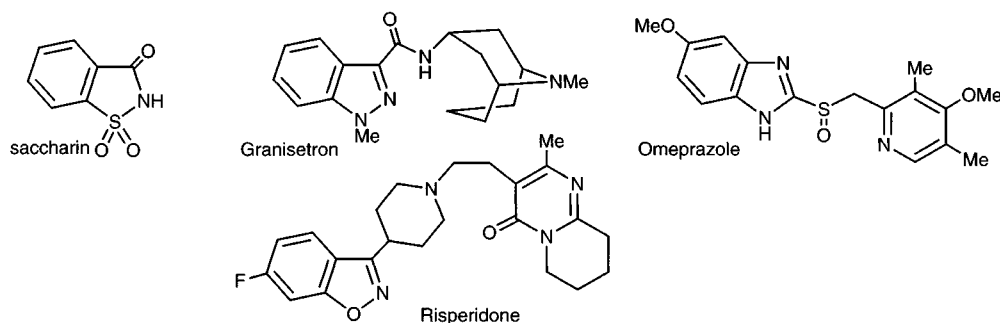


# 23 Benzanellated azoles: reactions and synthesis



There is only one way in which a benzene ring can be fused to each of the three 1,3-azoles, generating 1*H*-benzimidazole,<sup>1</sup> benzothiazole, and benzoxazole. Indazole<sup>2</sup> is the only possibility for the analogous fusion to a pyrazole; it exists as a 1-*H* tautomer – the 2-*H*-tautomer cannot be detected, though 2-substituted 2*H*-indazoles are known. Two distinct isomers each are possible for the other two 1,2-azoles: 1,2-benzisothiazole and 2,1-benzisothiazole,<sup>3</sup> and 1,2-benzisoxazole and 2,1-benzisoxazole,<sup>4</sup> respectively.

1,2-Benzisothiazolin-3(2*H*)-one 1,1-dioxide is saccharin the well known sweetening agent. Omeprazole, a gastric proton-pump inhibitor, is an anti-ulcerative, Risperidone is used in the treatment of schizophrenia, and Granisetron, a serotonin receptor antagonist, alleviates the nausea associated with chemotherapy.



## 23.1 Reactions with electrophilic reagents

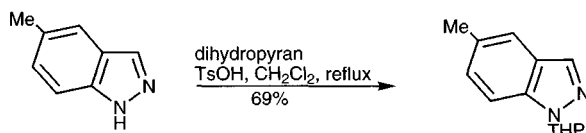
### 23.1.1 Addition at nitrogen

#### 23.1.1.1 Protonation

Benzimidazole is nearly two  $pK_a$  units weaker as a base and but somewhat stronger as an acid than imidazole. These trends are echoed in the other benzo-azoles: the bicyclic systems are weaker bases than the corresponding monocyclic heterocycles and indazole is a slightly weaker acid than pyrazole.

### 23.1.1.2 Alkylation at nitrogen

The neutral heterocycles form salts by reaction at nitrogen with alkyl halides. Normally, indazoles react at the imine nitrogen, N-2, but alkylation of 6-methylindazole with dihydropyran and acid produces the *N*-1-tetrahydropyranyl derivative;<sup>5</sup> as in *N*-1-acylation of indazoles, this 1-substituted product may be a thermodynamic product resulting from reversible alkylation.

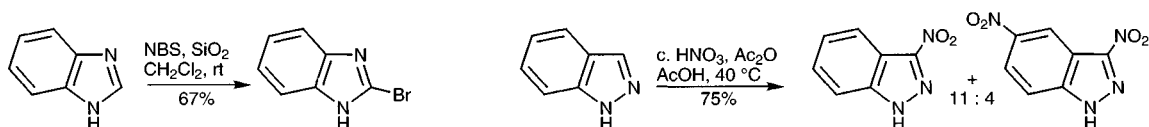


### 23.1.1.3 Acylation at nitrogen

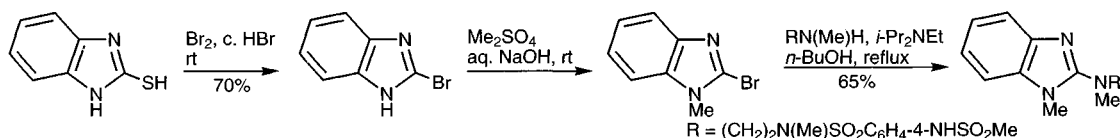
Acid anhydrides, with or without pyridine, bring about *N*-acylation of benzimidazoles, *N*-1-acylation of indazoles, and *N,N*-diacylation of benzimidazol-2-one.<sup>6</sup>

### 23.1.2 Substitution at carbon

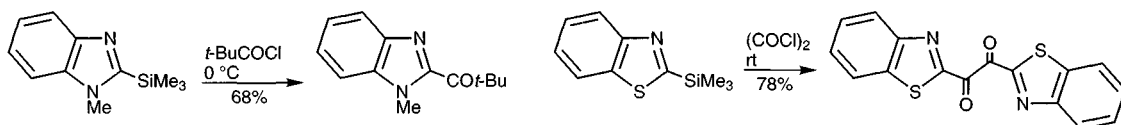
The only *C*-substitutions in the heterocyclic rings of any member of this group are the 2-bromination of benzimidazole with *N*-bromosuccinimide,<sup>7</sup> the 2-substitution of benzothiazole with bromine at 450 °C<sup>8</sup> and the 3-nitration of indazole.<sup>9</sup> The general rule is that electrophilic nitrations and halogenations can be achieved only in the benzene ring at the 5-, or 6- or 7-positions.



2-Bromobenzothiazole can be obtained from the reaction of benzothiazole-2-thiol with bromine<sup>10</sup> but in general, hetero-ring halides are prepared from the corresponding oxygen-substituted heterocycle by treatment with thionyl chloride or phosphoryl chloride.<sup>6</sup>



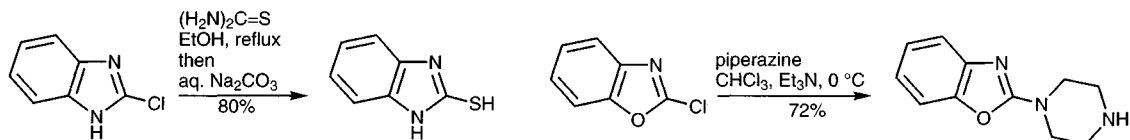
The reluctance to undergo electrophilic *C*-substitution in the five-membered ring can be overcome using silylated derivatives, as shown by the examples.<sup>11</sup>



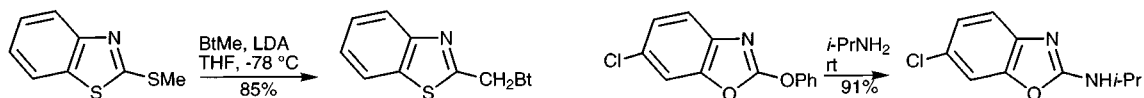
## 23.2 Reactions with nucleophilic reagents

The only position in these heterocycles where nucleophilic displacement of a leaving group is activated is that on the heterocyclic ring – one example was given above;

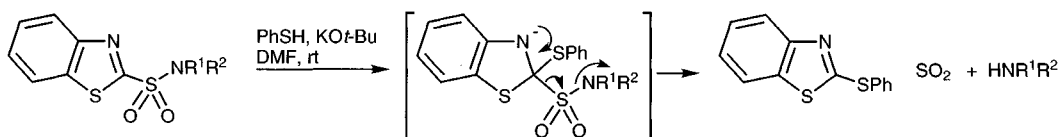
conversion to thiol using thiourea as the nucleophile, shown below, can be cited as another.<sup>12</sup> Palladium catalysis can improve the efficiency of such processes<sup>13</sup> though the 2-chlorobenzoxazole displacement shown proceeded under mild conditions.<sup>14</sup>



Both oxygen and sulfur substituents can be easily displaced from benzoxazoles<sup>15</sup> or benzothiazoles<sup>16</sup> by organolithiums or amines, respectively.



Susceptibility to nucleophilic displacement is central to a method for removing benzothiazol-2-ylsulfonamide protecting groups – reaction with a thiol at the heterocyclic ring 2-position releases the amine (either primary or secondary) as indicated.<sup>17</sup>



## 23.3 Reactions with bases

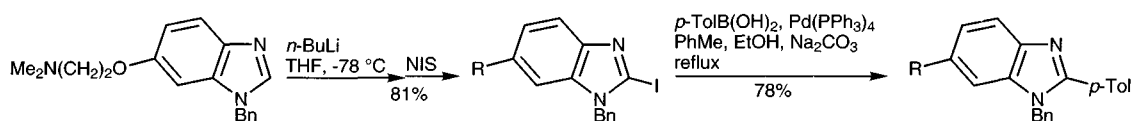
### 23.3.1 Deprotonation of *N*-hydrogen

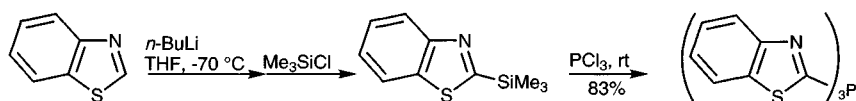
The benzimidazolyl and indazolyl anions react straightforwardly on nitrogen with electrophilic alkylating agents, though mixtures of *N*-1- and *N*-2-substituted products can result in the latter case. For example, amination with hydroxylamine *O*-sulfonic acid gives a 2:1 ratio of 1-amino-1*H*-indazole and 2-amino-2*H*-indazole<sup>18</sup> or to take another example, the ratio of *N*-1 to *N*-2-ethylated products from methyl indazol-3-ylcarboxylate can vary from 1:1 to 18:1 depending on the base and the solvent.<sup>19</sup>

## 23.4 Reactions of *C*-metallated derivatives

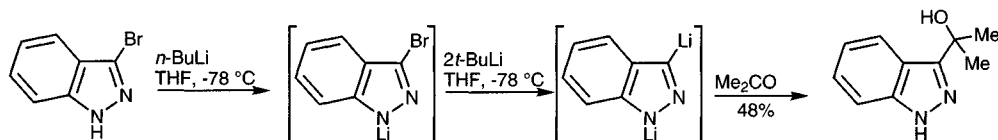
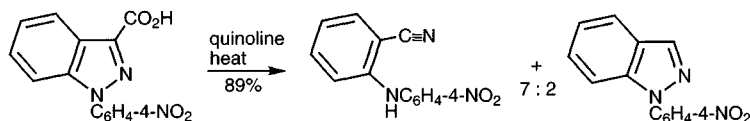
### 23.4.1 Lithium derivatives

The benzo-1,3-azoles (blocked or protected on nitrogen in the case of benzimidazoles) lithiate at the hetero ring 2-position. This allows reaction with the usual range of electrophiles; the examples<sup>20,21,22</sup> below show the introduction of iodine (followed by a palladium(0)-catalysed coupling with a boronic acid) and silicon (then the formation of a tris(benzothiazol-2-yl)phosphine).



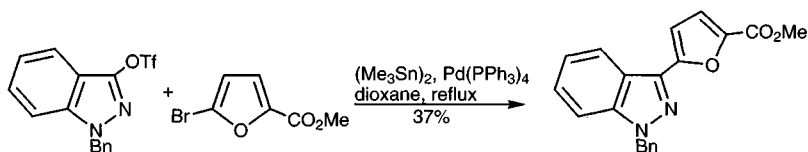
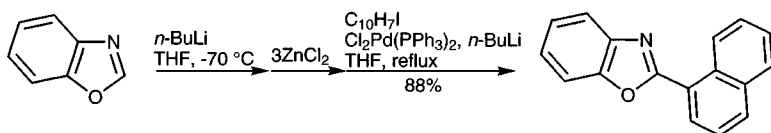


1,2-Benzisothiazole and 1,2-benzisoxazole have not been lithiated in the heterocyclic ring, no doubt because attempts to do so would lead to fragmentation of the heterocyclic ring in a way analogous to that observed when indazole-3-acids are heated in quinoline.<sup>23</sup> However, 3-bromoindazole can be converted into an *N,C*-dithio species – this takes advantage of the fact that following deprotonation of the *N*-hydrogen, *N*-1 is no longer a leaving group.<sup>24</sup>



### 23.4.2 Palladium-catalysed reactions

The comparatively small number of examples so far available suggest that coupling chemistry can be just as important in the benzoazoles as in other areas of heterocyclic chemistry: the two examples below show the use of a zinc benzoxazole<sup>25</sup> and an indazolyl triflate.<sup>26</sup>



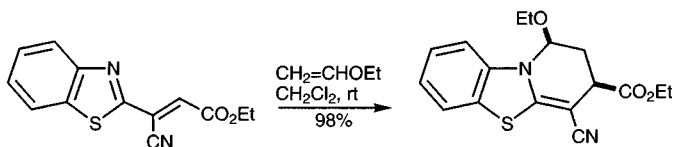
### 23.5 Reactions with reducing agents

The selective hetero ring reduction of the benzo-1,3-azoles or the benzo-1,2-azoles has not been reported.

### 23.6 Electrocyclic reactions

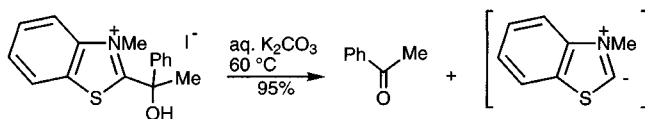
2,1-Benzisothiazole and 2,1-benzisoxazole seem not to display the tendency to act as aza-dienes which might have been expected on the basis of comparison with the typical reactivity of isoindoles, benzo[*c*]thiophenes and isobenzofurans (*cf.* section

19.2). In a different sense, electron-deficient 2-alkenylbenzothiazoles react with electron-rich alkenes as 1-aza-1,3-dienes.<sup>27</sup>

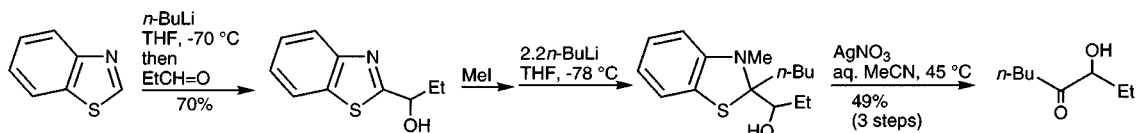


## 23.7 Quaternary salts

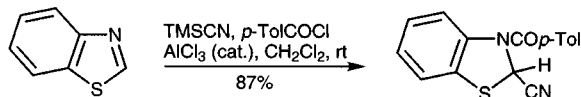
Benzo-1,3-azolium salts are susceptible to nucleophilic addition at C-2, for example, they are converted into the corresponding *ortho* substituted benzene, with loss of C-2, by aqueous base, a process which must involve addition of hydroxide at C-2 as an initiating step.<sup>28</sup> In a more constructive sense, cleavage of 2-(1-hydroxyalkyl)benzothiazolium salts, which can be assembled using 2-lithiobenzothiazole, to liberate the benzothiazolium ylide (*cf.* section 21.11) allows a synthesis of ketones, as illustrated.<sup>29</sup>



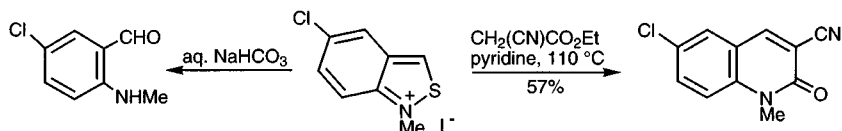
By an alternative sequence: 2-lithiation, reaction with an aldehyde, quaternisation, C-2-addition of an alkylolithium, and finally silver-promoted ring cleavage of the resulting dihydrobenzothiazole, the heterocycle can be made the means for the construction of  $\alpha$ -hydroxyketones.<sup>30</sup> Lithium enolates also add smoothly to benzothiazolium salts.<sup>31</sup>



Reissert-type adducts (*cf.* section 6.14) can be obtained from benzothiazole, benzoxazole and indazole, as illustrated below.<sup>32</sup>

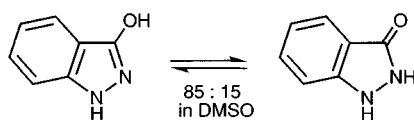


2,1-Benzisothiazolium salts are hydrolysed to *ortho*-aminobenzaldehydes; their use as synthons for such aldehydes is illustrated by the quinolone synthesis below.<sup>33</sup>

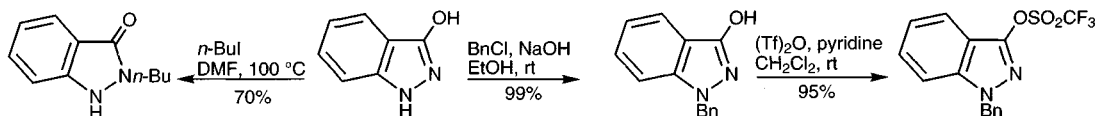


## 23.8 Oxy- and amino-1,3-azoles

The benzo-1,3-azol-2-ones exist in the carbonyl tautomeric forms. Indazol-3-one however, at least in dimethylsulfoxide solution, is largely in the hydroxy tautomeric form<sup>34</sup> in contrast to 1,2-benzisothiazol-3-one which is wholly in the carbonyl form, at least in the solid.<sup>35</sup>



It is possible to be quite selective in the introduction of alkyl groups onto one of the two nitrogens of 3-hydroxyindazole. Reaction with a halide in neutral solution, no doubt involving the imine tautomer, is selective for N-2.<sup>36</sup> In contrast, in basic solution, the anion reacts at N-1.<sup>26</sup>



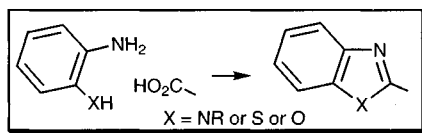
Aqueous base brings about hydrolytic cleavage of the heterocyclic ring of benzo-1,3-azol-2-ones giving the corresponding *ortho* substituted benzene.<sup>37</sup> Alkylation in basic medium generally leads to *N*- and *O*-substitution; thiones alkylate on the thione sulfur.<sup>38</sup>

## 23.9 Synthesis

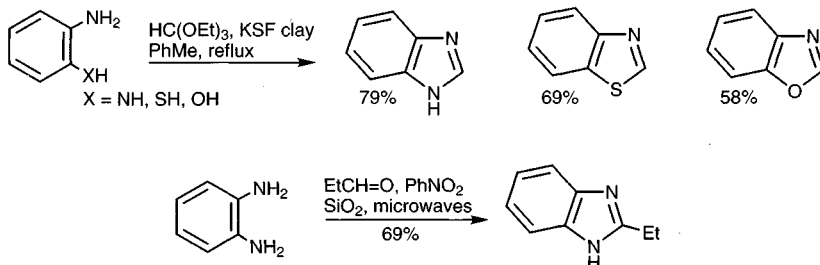
### 23.9.1 Ring synthesis of benzo-1,3-azoles

#### 23.9.1.1 From *ortho* heteroatom-substituted arenes

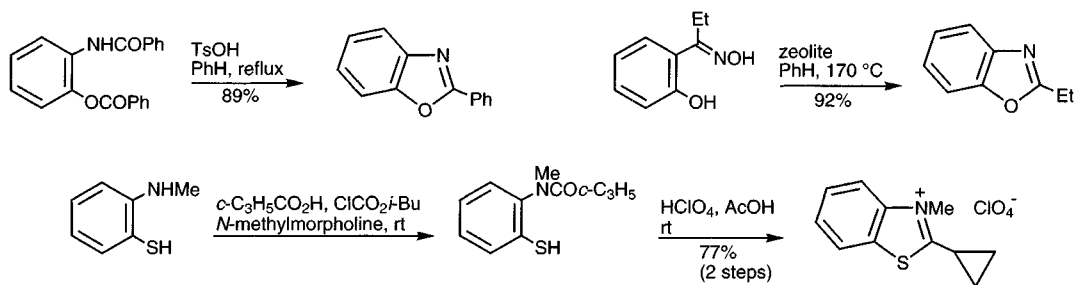
The most important strategy for the synthesis of benzothiazoles, benzimidazoles, and benzoxazoles is the insertion of C-2 into a precursor with *ortho* heteroatoms on a benzene ring. The component which is required for this purpose usually has the future C-2 at the oxidation level of an acid, but many variants on this have been described.



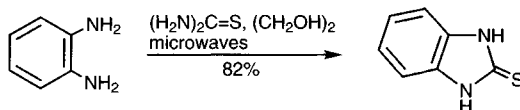
In the standard form of this route, a carboxylic acid is heated with the *ortho* disubstituted benzene. An iminoether will react at much lower temperature.<sup>39</sup> Ortho esters with a KSF clay is a highly recommended variant and can be used for the synthesis of all three unsubstituted benzo-1,3-azoles.<sup>40</sup> An important variant for the synthesis of benzimidazoles, allowing the use of aromatic or aliphatic aldehydes, rather than acids, incorporates nitrobenzene as an oxidant into the reaction mixture.<sup>41</sup>



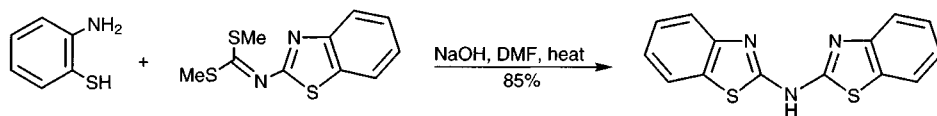
There are two efficient ways in which to use starting materials which have the carboxylic acid component already installed on *both* heteroatoms: conversion to bis(silyloxy) derivatives,<sup>42</sup> or simply heating with *p*-toluenesulfonic acid as shown.<sup>43</sup> A device which has been frequently used to produce a starting material with just one acyl group in place is to carry out a Beckmann rearrangement on an *ortho*-hydroxyaryl ketone, the Beckmann product cyclising *in situ* when the conditions are acidic; a modern version of this is illustrated below.<sup>44</sup> An excellent route to mono-acylated precursors utilises mixed anhydrides.<sup>37</sup> A very mild method for the dehydrative ring closure of *ortho*-hydroxyarylamino amides, employed in solid-supported benzoxazole syntheses, utilises typical Mitsunobu conditions – triphenylphosphine and diethyl azodicarboxylate.<sup>45</sup>



The use of microwaves allows reaction with amides in lieu of acids; when urea or thiourea are used, 2-ones (2-thiones) are obtained, carbon disulfide and potassium hydroxide also leads to 2-thiones, and with isocyanates (or isothiocyanates<sup>46</sup>), 2-acylamino derivatives result.<sup>47</sup> Reaction with cyanogen bromide gives 2-aminobenzimidazoles.<sup>1b</sup>

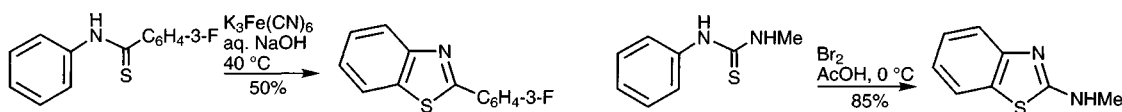


Bis(methylthio)imines (dithiocarbonimidates), readily available from the reaction of an arylamine with carbon disulfide and base and then methyl iodide, react to form heterocyclic rings with a 2-arylamino substituent.<sup>48</sup>

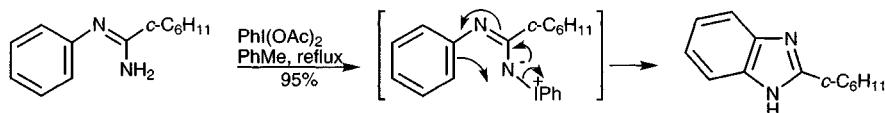


### 23.9.1.2 Other methods

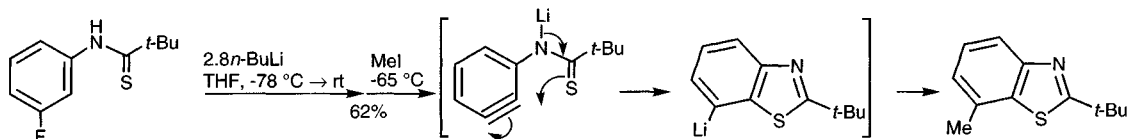
Chief amongst alternative methods, and of importance in that it does not require an *ortho* diheteroatom starting material, is the oxidative ring closure of arylamine thioamides giving benzothiazoles. Typically, potassium ferricyanide or bromine are utilised: examples are shown below.<sup>49</sup>



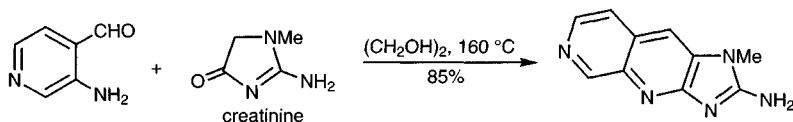
An oxidative ring closure giving benzimidazoles results when *N*-arylamidines are reacted with iodobenzene diacetate; a possible intermediate is shown in the scheme.<sup>50</sup>



Benzothiazoles can also be produced from thioanilides with a *meta* fluorine by a sequence of *ortho*-assisted lithiation, leading to elimination of fluoride and the formation of an aryne, and then intramolecular addition of the sulfur to generate the heterocycle, and finally trapping with an electrophile placing a substituent at C-7.<sup>51</sup>



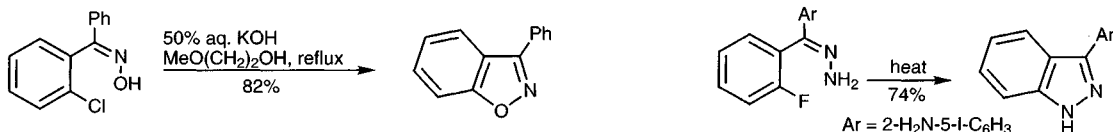
In what is essentially a Friedländer quinoline synthesis (*cf.* section 6.16.1.3), creatinine condenses with an *ortho*-aminoaldehydes giving polycyclic 2-aminobenzimidazoles, or heteroaryl analogues as illustrated.<sup>52</sup>



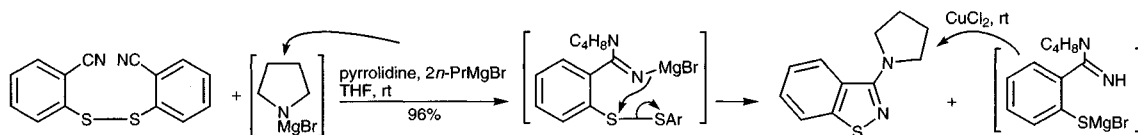
## 23.9.2 Ring synthesis of benzo-1,2-azoles

### 23.9.2.1 Ring synthesis of 1*H*-indazoles, 1,2-benzisothiazoles, and 1,2-benzisoxazoles

The earliest syntheses of 1,2-benzisoxazoles depended on the cyclisation of an *ortho*-haloarylketone oxime, typical conditions are shown below.<sup>53</sup> Only one geometrical isomer of the oxime will ring close. Applying this approach to amidoximes is easier, because the two imine geometrical isomers in such compounds are easily interconvertible.<sup>54</sup> Comparable reaction with hydrazones produces indazoles.<sup>55</sup>

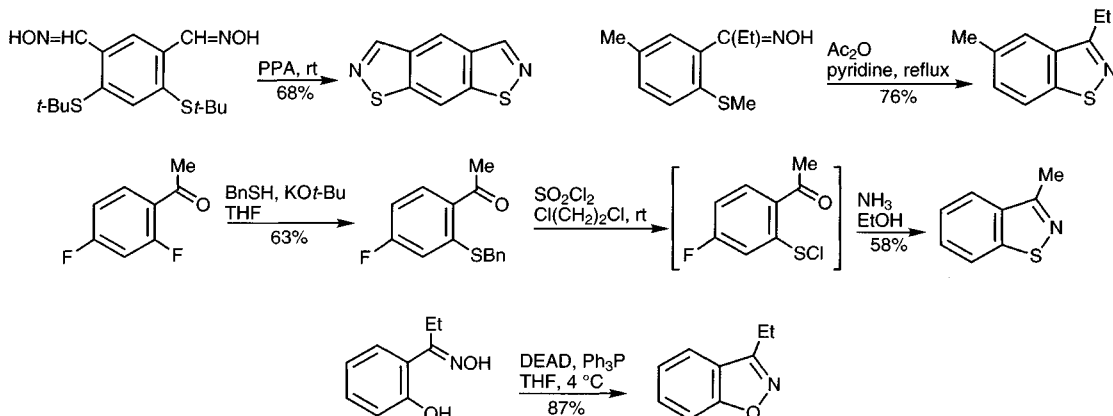


A number of routes involve formation of the bond between the two hetero atoms: typical is the conversion of di(2-cyanophenyl) disulfide into 3-chlorobenzisothiazole with chlorine<sup>56</sup> and into 3-aminobenzisothiazoles with magnesium amides, as shown, one 'half' of the starting material is converted directly into the heterocycle, the second 'half' requiring oxidation.<sup>57</sup>

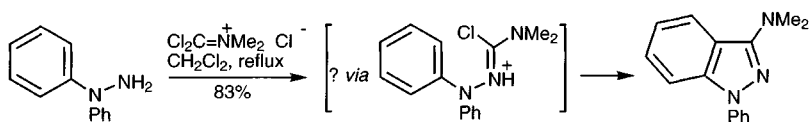


Generally speaking, one of the hetero atoms must carry a leaving group – the hydroxyl of oximes has served this purpose either via protonation<sup>58</sup> or acetylation.<sup>59</sup>

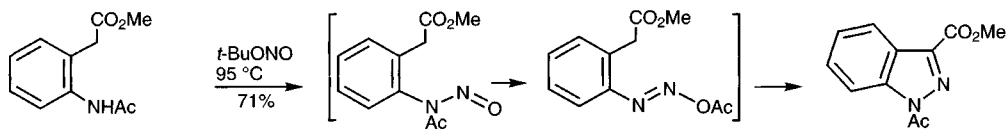
The generation of a chlorosulfide serves the purpose in the opposite sense.<sup>60</sup> Probably the best method for the cyclisation of salicylaldehyde oximes (or *ortho*-hydroxyarylketoximes) is the application of Mitsunobu-type conditions.<sup>61</sup>



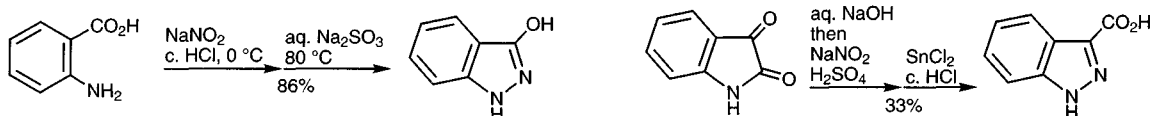
Electrophilic cyclisation onto the aromatic ring achieves the synthesis of 3-aminindazoles when arylhydrazines are reacted with *N*-(dichloromethylene)-*N,N*-dimethylammonium chloride, as shown.<sup>62</sup> The formation of 1-benzyl-3-hydroxyindazole by heating *N*-benzylphenylhydrazine with urea at 285 °C involves the electrophilic cyclisation of a first formed semicarbazide.<sup>2</sup>



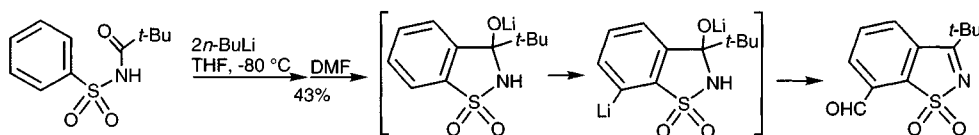
A classical,<sup>63</sup> but still used,<sup>5,64</sup> route to indazoles involves *N*-nitrosation of an acetanilide followed by cyclisation onto an *ortho* alkyl group – even unactivated methyl groups enter into reaction, though in the example shown below the *ortho* substituent carries an activating ester. The sequence probably involves a diazoacetate as intermediate, as shown.



Diazotisation of anthranilic acid and immediate reduction of the diazo group is a very simple route to 3-hydroxyindazole<sup>2</sup> and hydrolysis, diazotisation and reduction starting from isatin produces indazole-3-carboxylic acid.<sup>65</sup>

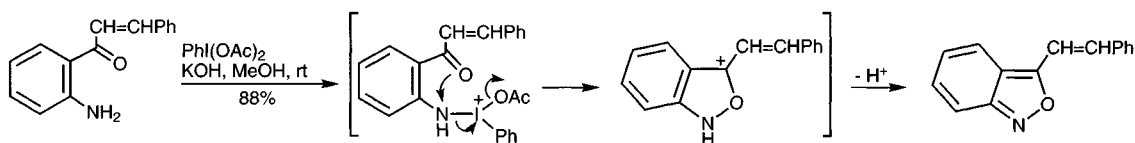
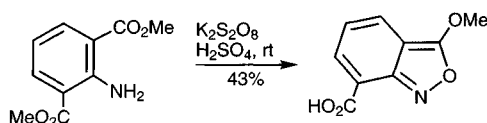


A neat use of lithiation methods allows the synthesis of 7-substituted benzisothiazole *S,S*-dioxides, thus when two mol equivalents of the lithiating agent are used, two successive lithiations *ortho* to the sulfonamide unit take place, the first leading to ring closure and the second allowing introduction of an added electrophile at C-7.<sup>66</sup>

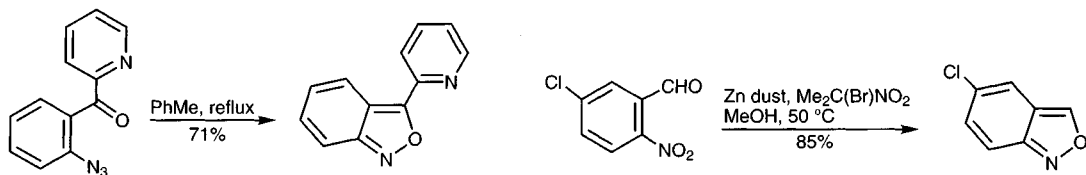


### 23.9.2.2 Ring synthesis of 2H-indazoles, 2,1-benzisothiazoles, and 2,1-benzisoxazoles

Appropriate oxidations of *ortho*-aminoaryl ketones<sup>67</sup> or esters<sup>68</sup> produce 2,1-benzisoxazoles; these ring closures may involve the intermediate formation of a nitrene, or a conventional sequence like that shown for the formation of the 3-styryl derivative below.

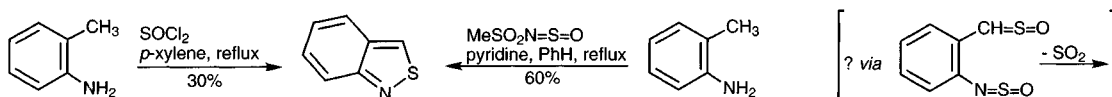


Involvement of a nitrene seems more likely in sequences where an *ortho*-azidoaryl ketone is decomposed thermally producing 3-substituted 2,1-benzisoxazoles,<sup>69</sup> though an intermediate in which the azide has cycloadded in a 1,3-dipolar sense to the carbonyl group has been suggested.<sup>70</sup>



In the opposite sense, reduction of *ortho*-nitroaraldehydes is a very efficient route to 3-unsubstituted 2,1-benzisoxazoles. Both the zinc and the 2-bromo-2-nitropropane are essential components of the reducing mixture, though the mechanistic details of the sequence are as yet not understood. Note the survival of the aromatic halogen in the example shown above.<sup>71</sup>

*ortho*-Aminotoluenes can be converted into 2,1-benzisothiazoles by reaction with thionyl chloride<sup>72</sup> or with *N*-sulfinylmethanesulfonamide.<sup>73</sup>



## References

- (a) 'The chemistry of benzimidazoles', Wright, J. B., *Chem. Rev.*, **1951**, 48, 397; 'Synthesis, reactions and spectroscopic properties of benzimidazoles', Preston, P. N., *ibid.*, **1974**, 74, 279; (b) '2-Aminobenzimidazoles in organic synthesis', Rastogi, R. and

- Sharma, S., *Synthesis*, **1983**, 861; (c) 'Imidazole and benzimidazole synthesis', Grimmett, M. R., Academic Press, London, **1997**.
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