

## REVIEW

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# Primary nitro compounds: progress in the synthesis of isoxazoles by condensation with aldehydes or activated ketones

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Among the known strategies directed towards the synthesis of isoxazole derivatives, the reactions of aldehydes with primary nitro compounds deserve a comprehensive treatment, including the historical development as well as the more recent applications. The reactions of aldehydes with primary nitro compounds in a 1 : 2 molar ratio have been shown to lead to isoxazoline-*N*-oxides or isoxazole derivatives, via  $\beta$ -dinitro derivatives. Several modifications of the process allowed the formation of products bearing substituents at various positions of the heterocyclic ring with control of regioselectivity. Ketones are reported to react with primary nitro compounds, only if activated ( $\beta$ -diketones,  $\alpha$ -nitroketones, or strained ketones), to give isoxazole derivatives. Symmetric 2,4-dinitroglutarates formed from aromatic aldehydes and nitroacetate undergo ring closure to form isoxazole derivatives or, according to reaction conditions, 5-hydroxy-6-oxo-4-aryl-6*H*-1,2-oxazine-3-carboxylates ("oxazinones"), by loss of alcohol instead of water. Isoxazole-4-carbaldehydes are obtained by the reaction of 3-oxetanone with primary nitro compounds.

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## 1. Introduction

The isoxazole ring represents one of the privileged structures in organic and medicinal chemistry, and there have been an increasing number of studies on isoxazole-containing com-



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Francesco De Sarlo, FRSC, was Professor of Organic Chemistry at Università di Firenze and retired in 2010. He published papers on the synthesis and tautomerism of isoxazole derivatives; nitrile oxide- and base-catalysed polymerisation and cycloadditions; nitrile oxide or nitron cycloadditions to methyl-encyclopropane and rearrangement of the adducts; and the synthesis of isoxazole derivatives by cycloaddition of primary nitro compounds.



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Fabrizio Machetti graduated in Chemistry from the Università di Firenze (Italy) and received his PhD in Chemical Sciences from the same university in 1996. After two years of post-doctoral research and holding several intermediate positions, he was appointed as a Researcher at the Consiglio Nazionale delle Ricerche (Italy) where he is currently a Senior Researcher. Since 2008, he has been teaching Food Chemistry and Fragrances at the Università di Firenze as a contract professor. His main research activities include organic synthesis, development of new synthetic methodologies, mechanistic studies, catalysis, organocatalysis, and materials chemistry. His current research interests are focused on the chemism of nitro compounds and the chemistry of isoxazoles. He recently wrote a book chapter "Isoxazoles" in *Comprehensive Heterocyclic Chemistry*.

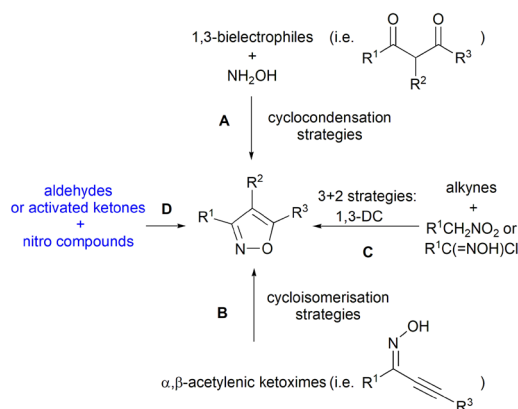


pounds.<sup>1</sup> Various starting materials are used for their preparation, either as a single substrate (B) or in combination (A, C, and D) (Scheme 1). One of the most popular approaches for their synthesis involves the cyclocondensation of hydroxylamine with 1,3-bielectrophiles, mainly  $\beta$ -diketones (Scheme 1, A). In a similar manner, three-carbon 1,3-difunctionalised units with  $sp$  or  $sp^2$  carbons such as propargyl ketones,  $\alpha,\beta$ -unsaturated ketones, enaminones,  $\beta$ -chloro/alkylthioenones,  $\alpha,\beta$ -unsaturated nitriles, or  $\alpha$ -oxoketenedithioacetals (Scheme 1, A) have been widely employed in this context.<sup>2</sup> The cycloisomerisation of  $\alpha,\beta$ -acetylenic ketoximes is related to these methods and in recent years has emerged as a powerful tool for the synthesis of isoxazoles (Scheme 1, B).<sup>3</sup>

A quite different approach for the synthesis of these heterocycles involves the use of alkynes and nitro compounds or hydroximoyl chlorides (Scheme 1, C). These substrates give the isoxazole ring through 1,3-DC (1,3-dipolar cycloaddition), often generating the dipole *in situ*. The synthetic methodologies for the generation of the dipole have evolved over the years by using different ways according to the Mukaiyama reaction,<sup>4</sup> Huisgen protocols,<sup>5</sup> and Machetti-De Sarlo reaction.<sup>6</sup>

Most of these reactions have been extensively discussed in many reviews and book chapters<sup>7</sup> and their recent development has been described.<sup>8</sup>

Aldehydes have been known for a long time to react with primary nitro compounds in excess to produce isoxazole derivatives, and the process has been the object of investigations that allowed the identification of several intermediates and an accepted mechanism (Scheme 1, D). Moreover, several activated ketones are known to react with primary nitro compounds; usually, a cycloaddition step is assumed to rationalise the formation of isoxazole derivatives (section 4). Although some of these reactions have been mentioned among the known isoxazole preparations, a review of the reactions of nitro compounds with carbonyl derivatives (aldehydes or ketones) is lacking (Scheme 1, D). Moreover, recent developments of this procedure introduced modifications that allowed the selective preparation of polysubstituted isoxazole derivatives.



Scheme 1 Synthesis of isoxazoles.

This review is aimed at comprehensively summarising the development of synthetic preparations of functionalised isoxazoles which utilise aldehydes or ketones with nitro compounds as starting substrates. We expect that this review will be useful for medicinal and synthetic organic chemists and will also stimulate further interesting reaction design and developments in this area.

## 2. Aldehydes with nitro compounds

Primary nitro compounds contain the C–N–O sequence which has been embedded into an isoxazole ring since a long time ago; thus 3,4,5-trimethylisoxazole was obtained from nitroethane on treatment with alkalis. Although no mechanism was offered for this complex reaction, the “doctrine of tautomerism” was invoked as possibly contributing to a future rationalisation.<sup>9</sup> 1-Nitropropane behaves similarly, but not nitromethane, which undergoes deeper transformations.

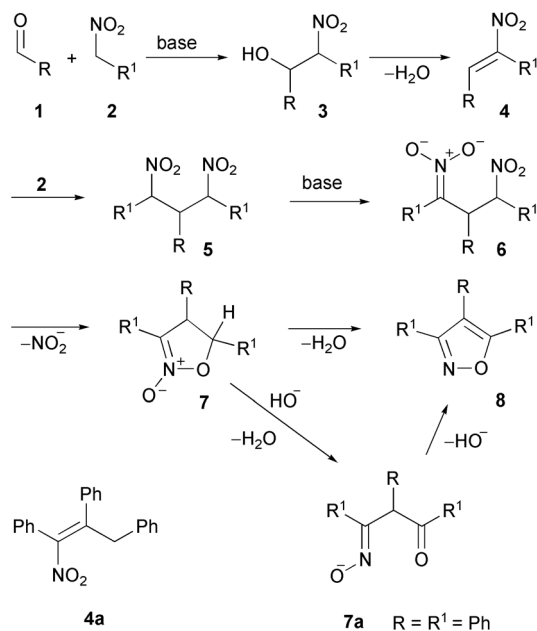
Aldehydes condense with primary nitro compounds under basic conditions, the ease of the reaction depending on the substituent geminal to the nitro group. In excess of nitro compounds, the resulting unsaturated nitro derivative can react with a second molecule, thus leading to  $\beta$ -dinitro compounds which are considered as key intermediates to isoxazole derivatives.

### 2.1. Arylnitromethanes and primary nitroalkanes

In general, the reactions of aldehydes with primary nitro derivatives in the presence of bases lead to a variety of products such as 2-hydroxy nitro compounds 3,<sup>10</sup> condensed nitroalkenes 4,<sup>10</sup>  $\beta$ -dinitro compounds 5, isoxazoline-*N*-oxides 7,<sup>11</sup> and isoxazoles 8. The complete reaction sequence is reported in Scheme 2 but intermediates have been isolated, depending on substituents and reaction conditions. Condensation of benzaldehyde (1, R = Ph) with phenylnitromethane (2, R<sup>1</sup> = Ph) in the presence of bases (aliphatic amines) was found to lead to several products, besides benzylidenephenylnitromethane (4, R = R<sup>1</sup> = Ph). Among them, 3,4,5-triphenylisoxazole (8, R = R<sup>1</sup> = Ph) was later identified, as a result of nitrous acid and water elimination, on heating in a strongly basic medium (Scheme 2).<sup>12,13</sup>

This reaction sequence has been the object of many studies over the past century and several side products and possible intermediates containing nitro groups have been identified, depending on experimental conditions, such as 1,3-dinitro-1,2,3-triphenylpropane (5, R = R<sup>1</sup> = Ph), nitrobenzylstilbene (4a),<sup>12</sup> and 3,4,5-triphenylisoxazoline-2-oxide (7, R = R<sup>1</sup> = Ph)<sup>14,15</sup> (Scheme 2). According to a later study,<sup>16</sup> the route *via* nitrobenzylstilbene 4a has been disproved as 4a and its  $\beta,\gamma$ -isomer prepared by unambiguous routes were not shown to be converted into 3,4,5-triphenyl-2-isoxazoline-2-oxide under any conditions. Intramolecular removal of NO<sub>2</sub><sup>−</sup> was shown to occur in the nitronate anion (6, R = R<sup>1</sup> = Ph) by a “displacement mechanism”, thus leading to isoxazoline-2-oxide (7, R =





**Scheme 2** Sequence of aldehydes and various nitromethane derivatives (1 : 2 molar ratio).

$R^1 = \text{Ph}$ ). Base abstraction of 5-H converts 7 into 8 *via* ring-opening to the  $\beta$ -oximino ketone anion 7a.<sup>16,17</sup>

Replacement of phenyl with other aryl groups either in the starting materials 1 and/or 2 or in intermediate 4 leads to variously substituted isoxazole derivatives 8. Thus, treatment of anisaldehyde 1 ( $R = 4\text{-MeO-C}_6\text{H}_4$ ) with nitrostilbene 4 ( $R = R^1 = \text{Ph}$ ) is reported to afford mixtures of isoxazole derivatives with one to three anisyl residues, and this result is ascribed to the reversibility of condensations under the experimental conditions employed (base and heat).<sup>18</sup> Similarly, 3,5-di(*o*-tolyl)-4-phenylisoxazole was obtained from 4 ( $R = \text{C}_6\text{H}_5$  and  $R^1 = o\text{-tolyl}$ ) and 3,5-diphenyl-4-(*o*-tolyl)isoxazole from 4 ( $R = o\text{-tolyl}$  and  $R^1 = \text{C}_6\text{H}_5$ ).<sup>19</sup> Other isoxazoline *N*-oxide 7 and isoxazole 8 derivatives with various substituents at the C-4 and/or C-5 position (*p*-bromophenyl, anisyl, piperonyl, and *o*-chlorophenyl) are reported but scarcely documented.<sup>15</sup> However, product 4 ( $R = 2\text{-NO}_2\text{-C}_6\text{H}_4$  and  $R^1 = \text{Ph}$ ) from *o*-nitrobenzaldehyde 1 ( $R = 2\text{-NO}_2\text{-C}_6\text{H}_4$ ) and phenylnitromethane 2 ( $R^1 = \text{Ph}$ ) is reported to give with further phenylnitromethane the dinitro compound 1,2-dinitro-1,2-diphenyl-3-(2- $\text{NO}_2\text{-C}_6\text{H}_4$ ) propane (structural isomer of 5).<sup>20</sup> This leads eventually to 3,4-diphenyl-5-(2- $\text{NO}_2\text{-C}_6\text{H}_4$ )-isoxazole. This anomalous regioisomerism has been rationalised later.<sup>21</sup> Other examples of analogous regioisomerism have been reported, but scarcely documented.<sup>15,22</sup> Selectivity control has been achieved by replacing the second mole of 2 by pyridinium ylides<sup>23</sup> (see section 3.1).

Many reactions either from nitroalkanes, other aldehydes or intermediates, fitting in Scheme 2, have been reported. The results depend on substituents and experimental conditions. Several aromatic aldehydes, furfuraldehyde and pivalaldehyde (1,  $R = \text{Ar}$ , 2-furfuryl, *t*-Bu) undergo the reaction shown in Scheme 2 (NaOH heating) with nitroethane or 1-nitropropane

(2,  $R^1 = \text{Me}$ , Et) to form isoxazole derivatives 8, without evidenced intermediates. The isoxazoles 8 were obtained in good yields except for pivalaldehyde (6%). The reaction failed using aldehydes with  $\alpha$ -protons or  $\alpha,\beta$ -unsaturations.<sup>21</sup> Zeolite-catalysed condensation of aromatic aldehydes 1 with alkylnitromethanes 2 afforded 2-alkyl-2-nitrostyrene derivatives (4,  $R = \text{Ar}$  and  $R^1 = \text{alkyl}$ ), with substituted isoxazole 8 being observed as a minor product when  $R = 4\text{-ClC}_6\text{H}_4$  and  $R^1 = \text{Me}$  or Et.<sup>24</sup> The product obtained from nitroethane with 6-bromopiperonal (by heating in ethanol in the presence of *n*-butylamine and  $\text{Na}_2\text{CO}_3$ ) was investigated by  $^{13}\text{C}$  NMR spectroscopy and found to be 3,5-dimethyl-4(6-bromopiperonyl)isoxazole (8,  $R = 6\text{-bromopiperonyl}$ ,  $R^1 = \text{Me}$ , 3% yield); no intermediates were evidenced.<sup>25</sup>

$\beta$ -Dinitroalkanes 5, prepared by another route, undergo the same reactions of Scheme 2 to form 8 ( $R = \text{H}$ ,  $R^1 = \text{Me}$ , Et). Two regioisomeric isoxazoles are produced when the dinitro intermediate is not symmetric, as reported for 2,4-dinitroheptane.<sup>26</sup> Disodium 3,5-alkanedinitronates (salts of 6,  $R = \text{H}$  and  $R^1 = \text{alkyl}$ , Scheme 2) are stable in basic solution, yielding 3,5-dialkylisoxazoles (8,  $R = \text{H}$  and  $R^1 = \text{alkyl}$ ) only upon acidification.<sup>14</sup> No intermediates were intercepted in this case. 3,5-Dialkylisoxazole 8 ( $R = \text{H}$ ,  $R^1 = \text{Et}$ ) is formed from disodium heptane-3,5-bisnitronate (stabilised by H-bonding) upon acidification.

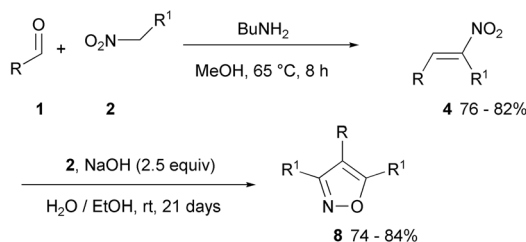
Nitroethane and phenylnitromethane (2,  $R^1 = \text{Me}$  and Ph) are reported to react with several aromatic ( $R = 4\text{-XC}_6\text{H}_4$ ,  $X = 4\text{-OMe}$ , 4-Cl, and 4- $\text{NMe}_2$ ) and heteroaromatic aldehydes ( $R = 3\text{-furyl}$  and 3-indolyl) 1 under treatment with basic alumina and microwave irradiation for a few minutes at 140 °C, affording 3,5-dimethyl-4-aryl isoxazoles 8 ( $R^1 = \text{Me}$ ,  $R = \text{Ar}$  and heteroaryl) or 3,5-diphenyl-4-aryl isoxazoles 8 ( $R^1 = \text{Ph}$ ,  $R = \text{Ar}$  and heteroaryl) in excellent yields.<sup>27</sup>

Heterocyclic aldehydes (1,  $R = \text{heteroaryl}$ ) react with nitroethane (2,  $R^1 = \text{Me}$ ) in the presence of *n*-butylamine to form the intermediate nitroalkene 4 ( $R = \text{heteroaryl}$  and  $R^1 = \text{Me}$ ) which then affords isoxazoles 8 ( $R = \text{heteroaryl}$  and  $R^1 = \text{Me}$ ) with more nitroethane in alkaline hydroalcoholic solution (during 21 days at r.t.) (Scheme 3). The long reaction time and ambient temperature avoided the formation of by-products and the resinification of the reaction mixture. Nitrobutane reacts similarly (2,  $R = n\text{-Pr}$ ).<sup>28</sup>

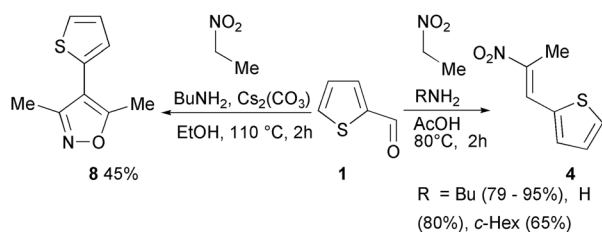
The reaction between nitroethane and thiophene-2-carbaldehyde can be selected as an illustrative case (Scheme 4). The reaction yields isoxazole 8 (45%,  $R^1 = \text{Me}$  and  $R = 2\text{-thienyl}$ ) by heating with an inorganic base ( $\text{Cs}_2\text{CO}_3$ ),<sup>29</sup> while it yields the Henry product 4 (65–95%,  $R^1 = \text{Me}$  and  $R = 2\text{-thienyl}$ ) by heating with ammonium acetates (acetic acid and *n*-butylamine or other amines like cyclohexylamine or  $\text{NH}_3$ ).<sup>30</sup>

The oxidation of nitroalkanes in an alkaline environment leads to the formation of aldehydes, which can react with excess nitroalkanes to give isoxazoles.<sup>31</sup> Thus, the oxidation of a nitroethane anion with ammonium persulfate in the presence of a double excess of  $\text{NaNO}_2$  produces acetaldehyde (1,  $R = \text{Me}$ ), which then gives 3,4,5-trimethylisoxazole (8,  $R = R^1 = \text{Me}$ ) along with 1,1-dinitroethane 9 (Scheme 5).<sup>32</sup>

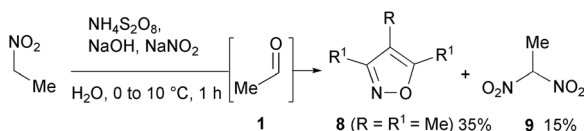




**Scheme 3** Isoxazole derivatives from nitroethane or nitrobutane ( $R^1 = \text{Me}$  and  $n\text{-Pr}$ ) and heterocyclic aldehydes ( $R = \text{Het}$ ).



**Scheme 4** Reactions of thiophene-2-carbaldehyde under different reaction conditions.



**Scheme 5** Isoxazole derivatives from nitroethane via oxidation to intermediate acetaldehyde.

## 2.2. Nitroacetic esters

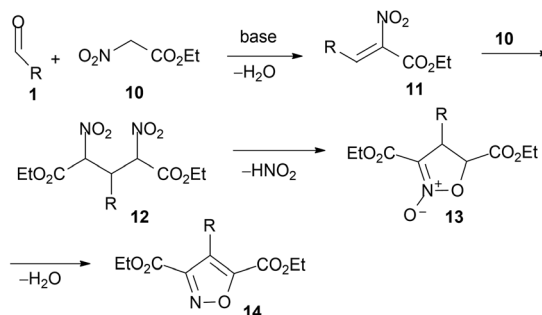
Aliphatic aldehydes react with ethyl nitroacetate **10** in the presence of amines.<sup>33</sup> For aromatic derivatives, Schiff bases are preferred as starting materials.<sup>34–36</sup>

Either dinitroglutarates **12**, isoxazole *N*-oxide derivatives **13**, isoxazole 3,5-dicarboxylic esters **14**, or their derivatives are possibly obtained (depending on experimental conditions). All these fit in the accepted reaction path, analogous to the sequence reported above (Scheme 2), as illustrated in Scheme 6.

Substituted nitro acrylic esters **11**<sup>37</sup> have been reported<sup>38,39</sup> while a general preparative procedure has been described starting from aldehydes and ethyl nitroacetate catalysed by  $\text{TiCl}_4$  and amine.<sup>40,41</sup>

Nitrocinnamates (**11**,  $R = \text{aryl}$ ) undergo Michael addition to **12** with excess nitroacetate, but can be intercepted by cycloaddition with good dipolarophiles (*e.g.* organic azides), as reported.<sup>42</sup>

The same intermediates (**12**,  $R = \text{alkyl}$ ,  $\text{aryl}$  or  $\text{heteroaryl}$ ) are reported to be obtained from Schiff bases with ethyl nitroacetate and converted into isoxazole derivatives **14**, in excess *n*-butylamine. No intermediate *N*-oxides were observed and the products were obtained as butylamides, in some cases, hydro-

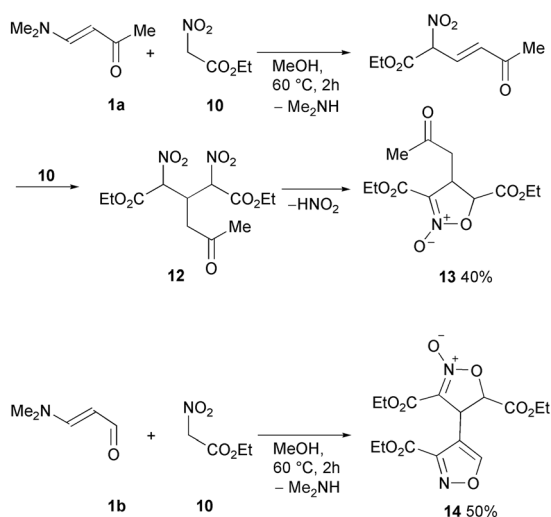


**Scheme 6** Isoxazole derivatives from aldehydes with ethyl nitroacetate via 2,4-dinitroglutarates.

lysed to 3,5-dicarboxylic acids.<sup>43,44</sup> Similar reactions with nitroacetates are reported for enaminoketone **1a** (enamine of aldehyde **1**,  $R = \text{CH}_2\text{COCH}_3$ ) leading to *N*-oxide **13** in 40% yield via intermediate **12**<sup>45</sup> (Scheme 7). As for enamino aldehyde **1b** (enamine of aldehyde **1**,  $R = \text{CH}_2\text{CHO}$ ), isoxazole **14** is directly afforded in 50% yield (Scheme 7).

Several further reports deal with the conversion of **12** into **14**<sup>46,47</sup> and reactions of nitroacetates with aldehydes according to Scheme 6. Thus, from indole aldehyde (**1**,  $R = 3\text{-indolyl}$ ), the corresponding *N*-oxide **13** (as dibenzyl ester instead of ethyl ester, 51%) and isoxazole **14** (as dibenzyl ester instead of ethyl ester, 61%) were obtained,<sup>48</sup> while from aldose derivatives<sup>49</sup> the corresponding *N*-oxides **13** were obtained. From benzaldehyde and aliphatic aldehydes, 2,4-dinitroglutarates **12** ( $R = \text{alkyl}$ ,  $\text{C}_6\text{H}_5$ ), *N*-oxides **13** ( $R = \text{alkyl}$ ,  $\text{C}_6\text{H}_5$ ) and isoxazoles **14** ( $R = \text{alkyl}$ ,  $\text{C}_6\text{H}_5$ ) were obtained.<sup>17,50</sup> However, during reactions from **12** to **13** or to **14**, esters may be converted into acids,<sup>48,50</sup> or amides, when amines are used as bases.<sup>17,23,50</sup>

Aromatic aldehydes are reported to condense with ethyl nitroacetate (**10**) in water with catalytic DABCO (1,4-diazabicyclo[2.2.2]octane) on ultrasonication (40 °C, 24 h) to give 3,5-dicar-



**Scheme 7** Reactions of ethyl nitroacetate with an enamine.

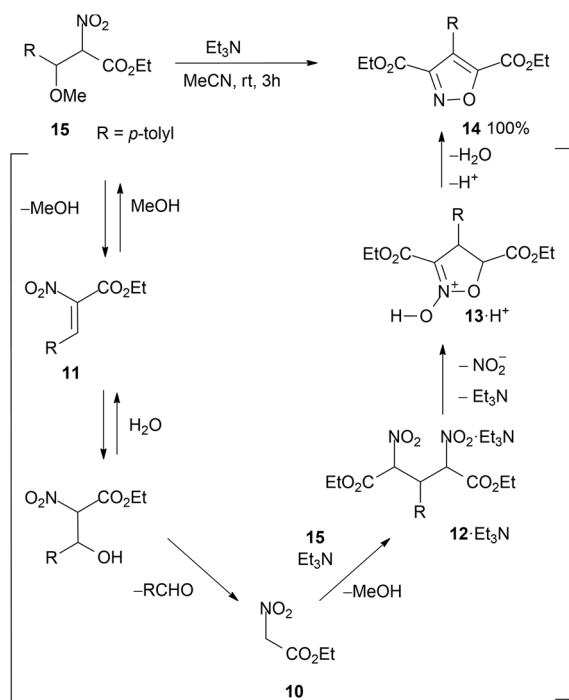




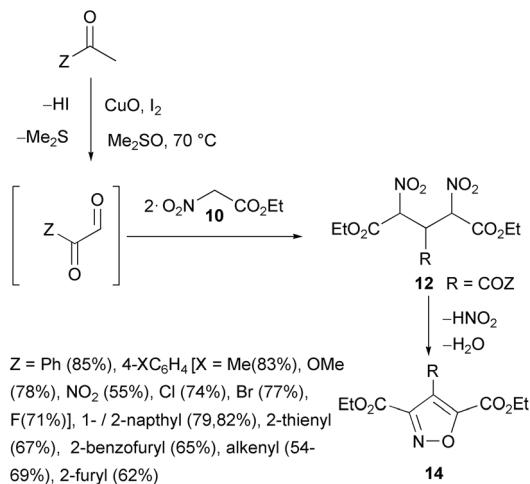
bethoxy-4-arylisoxazoline *N*-oxides **13** ( $R = Ar$ ) (20 examples, 72–92% yields). At a higher temperature of 80 °C, 3,5-dicarbethoxy-4-arylisoxazoles **14** ( $R = Ar$ ) are obtained (4 examples, 86–90% yields) as a result of dehydration of the corresponding *N*-oxides **13**. The same reaction (40 °C, 24 h) on aliphatic aldehydes gives 3,5-dicarbethoxy-4-alkylisoxazoline *N*-oxides **13** ( $R = alkyl$ ), besides the deoxidised products (3,5-dicarbethoxy-4-alkylisoxazolines) for the less hindered alkyl substituents such as ethyl, propyl, and butyl (64–76% yields). The formation of isoxazolines (in some cases even predominantly over their *N*-oxides) remains unexplained.<sup>51</sup>

Procedures are reported starting from intermediate  $\alpha$ -nitrocinnamates **11** ( $R = Ar$ , from **15** with loss of methanol) with nitroacetate **10**,<sup>23</sup> thus providing access to a variety of derivatives, including enantioselective preparation of *N*-oxides **13**.<sup>52</sup> Incidentally, conversion of ethyl *p*-methyl- $\alpha$ -nitrocinnamate **11** ( $R = p$ -tolyl) into 4-*p*-tolyl-3,5-dicarbethoxyisoxazole **14** ( $R = p$ -tolyl) has been observed in the course of a study on reactions of  $\alpha$ -nitrocinnamates with nucleophiles.<sup>53</sup> Isoxazole **14** was obtained on a small scale with an almost quantitative yield (Scheme 8).

Phenylglyoxal intermediate, obtained by *in situ* oxidation of acetophenone ( $Z = Ph$ , Scheme 9), is reported to react with nitroacetate **10** to give 4-benzoyl-3,5-dicarbethoxyisoxazole (**14**,  $R = COPh$ ) in 85% yield. The process is successfully applied to several substituted acetophenones and heterocyclic analogues to give **14** ( $R = COZ$ , 16 examples, 54–85% yields).<sup>54</sup> The same reaction starting from styrene or analogues gave products **14** ( $R = COZ$ , seven examples, 62–78% yields).



**Scheme 8** Intermediate  $\alpha$ -nitrocinnamate ( $R = p$ -tolyl) reacts with ethyl nitroacetate *in situ*, affording 3,5-dicarbethoxy-4-*p*-tolylisoxazole.



**Scheme 9** *In situ* preparation of glyoxals and a reaction with ethyl nitroacetate, affording 3,5-dicarbethoxy-4-acylisoxazoles.

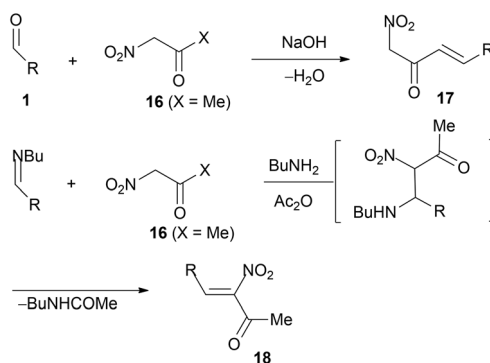
### 2.3. Nitro ketones

Nitroacetone (**16**) reacts with aryl(heteroaryl)aldehydes at the position away from the nitro group,<sup>55,56</sup> thus giving nitroenone **17** (Scheme 10). Nitroenones **18** have been prepared from the Schiff bases of aromatic aldehydes with *n*-butylamine; the addition product with nitroacetone (**16**), in acetic anhydride, affords **18** (Scheme 10,  $R = aryl$ , 5 examples, including 2-furyl).<sup>56</sup>

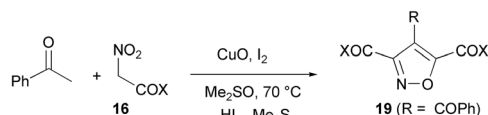
Other nitroenones **18** are reported under different experimental conditions:  $Al_2O_3$  in  $CH_2Cl_2$  at room temperature,<sup>57</sup> thionyl chloride in ethanol at rt or heating,<sup>58,59</sup> and  $\beta$ -alanine and acetic acid in benzene under reflux,<sup>60–65</sup> phosphoryl chloride in ethanol at room temperature,<sup>66</sup> acetic anhydride at 120–130 °C,<sup>67</sup> (2*S*)-2-{[diphenyl]([trimethylsilyl]oxy)methyl}pyrrolidine and 4-nitro-benzoic acid in dichloromethane;<sup>68</sup> and 4-methyl-morpholine and titanium tetrachloride at 0 °C.<sup>69</sup>

They can be isolated as they do not undergo Michael addition with nitro ketones under the reported conditions.

However, phenylglyoxal generated *in situ* from acetophenone (Scheme 11) reacts with two moles of  $\alpha$ -nitro ketones **16** affording 4-benzoyl-3,5-diacylisoxazoles (**19**,  $R = PhCO$ , seven examples) in



**Scheme 10** Formation of 4-nitroenones from aldehydes and preparation of 2-nitroenones from Schiff bases.



X = *i*-Pr (44%), Ph (85%), *p*-Tolyl (83%), 4-ClC<sub>6</sub>H<sub>4</sub> (79%), 4-BrC<sub>6</sub>H<sub>4</sub> (75%), 4-NO<sub>2</sub>C<sub>6</sub>H<sub>4</sub> (81%), 4-OMeC<sub>6</sub>H<sub>4</sub> (79%)

**Scheme 11** Trioxoisoxazole derivatives from intermediate phenylglyoxal and  $\alpha$ -nitro ketones.

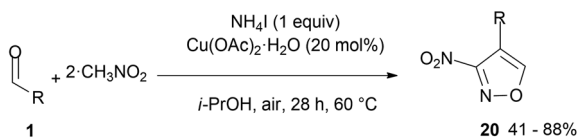
good yields for benzoylnitromethanes (X = Ar) and moderate yields in the case of aliphatic nitro ketone (X = *i*-Pr).<sup>54</sup>

#### 2.4. Nitromethane

The use of nitromethane, in combination with aldehydes, in the synthesis of isoxazoles has only recently been reported.<sup>70</sup> Nitromethane is a highly polar liquid with a weakly nucleophilic nature and is commonly used as a solvent.<sup>71</sup> It is the simplest nitro compound and also the least acidic.<sup>72</sup> Despite this, it can be deprotonated and used in the Henry reaction. These reactions are the first step towards the formation of the isoxazole ring but contrary to what one might expect, the condensation product of aldehydes with nitromethane does not turn out to be isoxazole **8** (R<sup>1</sup> = H, Scheme 2).

In fact, reactions of nitromethane (ten-fold excess) with aromatic aldehydes (21 examples, the reaction failed with 4-carboxybenzaldehyde) and heteroaromatic aldehydes (4 examples), under Cu(OAc)<sub>2</sub> catalysis in the presence of ammonium iodide, are reported to give 3-nitro-4-arylisoxazoles **20** (Scheme 12).

The process has been investigated in detail using 4-chlorobenzaldehyde (R = 4-Cl-C<sub>6</sub>H<sub>4</sub>, R<sup>1</sup> = H, Scheme 2). The proposed reaction mechanism follows part of the sequence reported above for primary nitro compounds, with the formation of 1-nitrostyrenes (**4**, R = Ar, R<sup>1</sup> = H, Scheme 2), which with a second molecule of nitromethane and NH<sub>4</sub>I (1 equiv) afford **5** (R = Ar, R<sup>1</sup> = H, Scheme 2) that follows a different evolution under Cu(OAc)<sub>2</sub> catalysis.<sup>70,73</sup> The anion of **5**, rather than losing NO<sub>2</sub><sup>−</sup>, undergoes intramolecular cyclisation and rearrangement to isoxazole derivatives, thus explaining the change of the sequence C–N–O of CH<sub>3</sub>NO<sub>2</sub> into the C–O–N unit of the isoxazole ring. In fact, deuterated nitromethane leads to the formation of isoxazole **20** deuterated in C-5. Compared to the general reaction in Scheme 2, the mechanism should involve oxidation at some stage while the details remain unclear.



**Scheme 12** 3-Nitroisoxazole derivatives from aromatic aldehydes and excess nitromethane under Cu(OAc)<sub>2</sub> (0.2 equiv.) and NH<sub>4</sub>I (1 equiv.) mediation.

### 3. Regioisomerism

#### 3.1. Selectivity *via* pyridinium salts

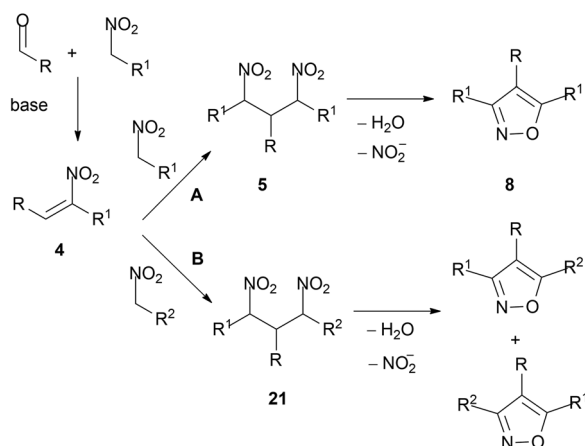
The reactions illustrated in Schemes 1 and 5 carried out in excess of nitro compounds give respectively symmetrical  $\beta$ -dinitro intermediates **5** and **12**; therefore the substituents at positions C-3 and C-5 of the products are identical (Scheme 13, A).

From the reactions of intermediate nitroalkene derivatives **4** with nitromethane derivatives, unsymmetrical  $\beta$ -dinitro intermediates **21** are obtained when R<sup>2</sup>  $\neq$  R<sup>1</sup>. These undergo in principle two alternative ring closure paths, leading to regioisomeric products with the substituents at positions 3 and 5 exchanged (Scheme 13, B). Several examples are known. Thus, the reactions of  $\alpha$ -nitrocinnamates **11** (R = C<sub>6</sub>H<sub>5</sub>, *p*-BrC<sub>6</sub>H<sub>4</sub>, 2-thienyl) with  $\alpha$ -nitroacetophenone **16** in excess of Et<sub>3</sub>N give mixtures in which the 5-benzoyl regioisomers **23** are predominant (69–78%) *vs.* the 3-benzoyl regioisomers (**24**, <6%). This result is rationalised *via* the preferred evolution of intermediate **22** because the carbon atom adjacent to the keto group is more electrophilic than the one adjacent to the ester (Scheme 14).<sup>23</sup> Analogous regioisomeric mixtures have been reported later.<sup>52</sup>

Improved selectivity has been achieved by replacing the second activated primary nitro compound by pyridinium ylides<sup>74</sup> obtained from  $\alpha$ -bromoesters or  $\alpha$ -bromoketones. Thus, a better leaving group selectively drives the ring closure: the reaction between  $\alpha$ -nitrocinnamate and analogues (**11**, R = C<sub>6</sub>H<sub>5</sub>, *p*-Br-C<sub>6</sub>H<sub>5</sub>, 2-thienyl) with pyridinium ylides (**25**, R<sup>3</sup> = COMe, CPh, COOEt, and Z = Br, Cl) leads to a single isoxazole derivative **23** (as illustrated in Scheme 15).<sup>23</sup>

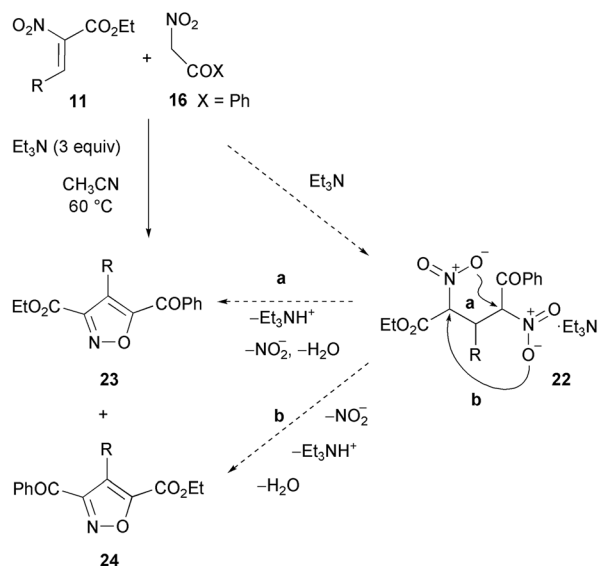
Moreover, excellent results are reported by a three-component procedure, using aromatic aldehydes, ethyl nitroacetate (**10**) and pyridinium salts **25** (12 examples, 50–92% yields).

The use of pyridinium salts in this context has been extended to  $\alpha$ -nitrostilbenes (with *N*-oxide intermediates):<sup>75–77</sup> different substitutions at positions 3 and 5 are selectively ensured.

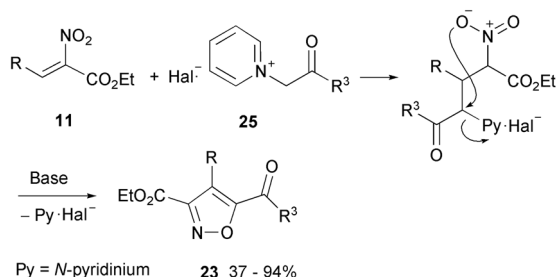


**Scheme 13** Regioisomerism.





Scheme 14 Formation of regioisomers.

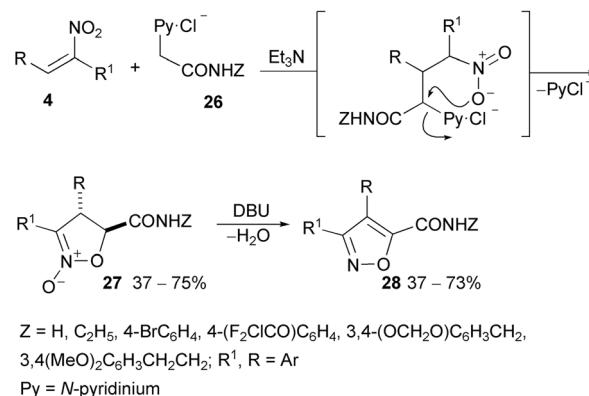


Scheme 15 Selectivity via pyridinium ylides.

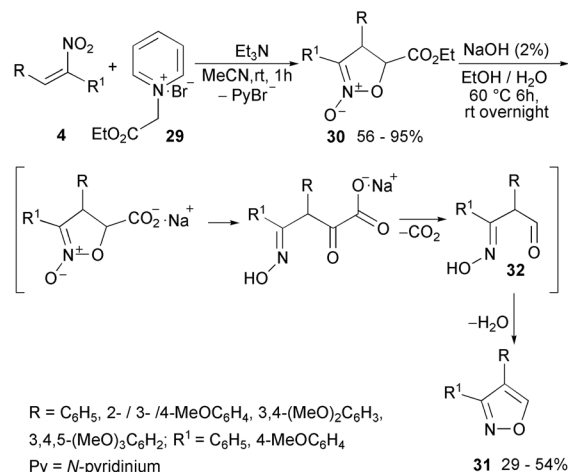
Thus, from aromatic or heteroaromatic aldehydes (10 examples) with phenylnitromethane or 4-methoxyphenylnitromethane intermediates, substituted nitrostilbenes **4** are obtained. These, with ethoxycarbonyl methylpyridinium bromide, selectively afford 3,4-diarylisoxazoline *N*-oxide-5-carboxylates.<sup>77</sup> Similarly,  $\alpha$ -nitrostilbenes with pyridinium acetamides (**26**) afford 3,4-diarylisoxazole-5-carboxamides (**28**, 9 examples) *via* intermediate *N*-oxides (**27**) (Scheme 16).<sup>76</sup>

Note that dehydration to isoxazoles requires in this case a very strong base (DBU) whereas *N*-oxides from nitrocinnamates are easily converted into isoxazoles, owing to the presence of two EW groups.<sup>75</sup>

A subsequent implementation of the procedure, using the ethoxycarbonyl methylpyridinium salt **29**, yielded a series of methoxy-substituted diarylisoxazoline *N*-oxides **30**, which were converted into the corresponding 5-unsubstituted diarylisoxazoles **31** *via* a one-pot hydrolysis/(*N*-O) cleavage/decarboxylation/cyclisation sequence (Scheme 17). A detailed mechanism of decarboxylation in a basic environment was not elucidated. However, a <sup>1</sup>H NMR reaction mixture control at a half-time reaction revealed the presence of oxyimino aldehydes **32**.<sup>77,78</sup> Isoxazoles **31** were tested for antimitotic antitubulin activity in



Scheme 16 Selective preparation of isoxazole-5-carboxamides.



Scheme 17 Selective preparation of 5-unsubstituted isoxazoles.

a sea urchin embryo model. A structure–activity relationship study revealed that isoxazoles **31** with an unsubstituted benzene ring at the C-3 of the isoxazole ring provide the appropriate configuration for the molecule to exhibit an antiproliferative effect by a microtubule destabilising mode of action.<sup>78</sup>

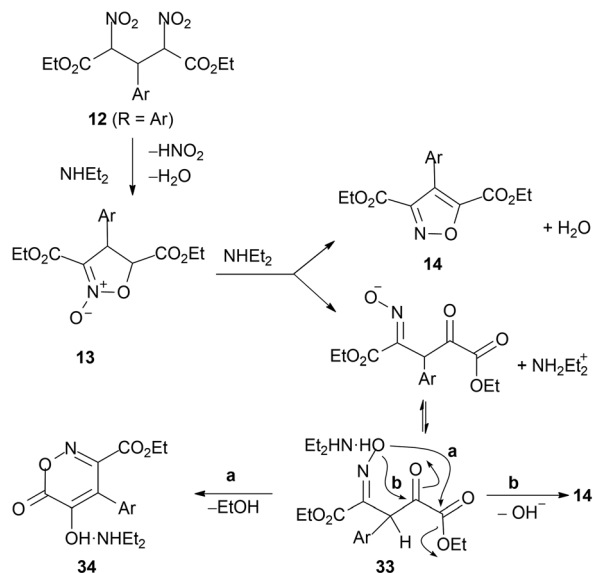
### 3.2. Selectivity *via* oxazinones

Another strategy to achieve selectivity in isoxazole synthesis from aldehydes and nitroacetates has been developed by means of intermediates 5-hydroxy-6-oxo-4-aryl-6*H*-1,2-oxazine-3-carboxylates (oxazinones) (**34**, Scheme 18).

As reported above (Scheme 8), aldehydes with ethyl nitroacetate in the presence of a secondary amine give products **12**, **13**, and **14**, and their derivatives (Dornow and his co-workers). A recent re-examination of the process<sup>79</sup> has shown that dinitroglutarate, under appropriate reaction conditions, undergoes a different ring-closure to oxazinones **34** (Scheme 18) and a general synthesis of these compounds is reported from nitroacetic esters and aromatic aldehydes (**1**, R = Ar) in acetonitrile and Et<sub>2</sub>NH (Baranov and his co-workers).<sup>79,80</sup>

The two CO groups differentiated in oxazinones prompted the way for selectively preparing isoxazole-5-carboxamide derivatives





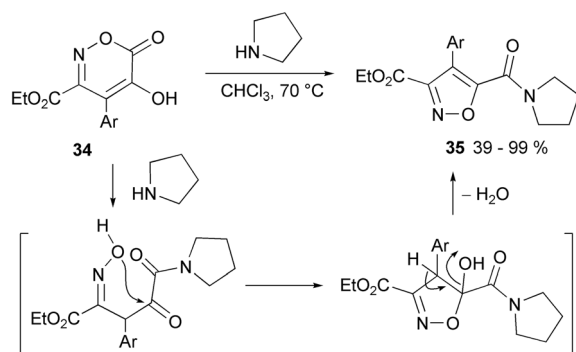
**Scheme 18** Isoxazoles and oxazinones from 2,4-dinitroglutarates.

by a reaction of oxazinones with amines (methylamine, pyrrolidine, cyclohexylamine, benzylamine, and morpholine). Thus, the regioselective preparation of 4-arylisoxazole-3,5-dicarboxylic acid derivatives **35** is described, including ester (Me, Et, and *i*-Pr) at C-3 with amide at C-5 (over 60 examples) and unsymmetrical diamides (2 examples) (Scheme 19).<sup>80</sup>

The Dornow reaction is updated<sup>34</sup> with further insight into its mechanism. It may be noted that one of the 3,4-diaryl-5-ethoxycarbonylisoxazoline *N*-oxides reported above, **30** ( $R^1 = \text{CO}_2\text{Et}$ ,  $R = [2,5-(\text{MeO})_2-3,4-\text{OCH}_2\text{OC}_6\text{H}_4]$ ),<sup>76</sup> has been reported to be converted into the corresponding oxazinone (33%) on treatment with a very strong base (DBU) in MeCN.<sup>76</sup>

## 4. Activated ketones with nitro compounds

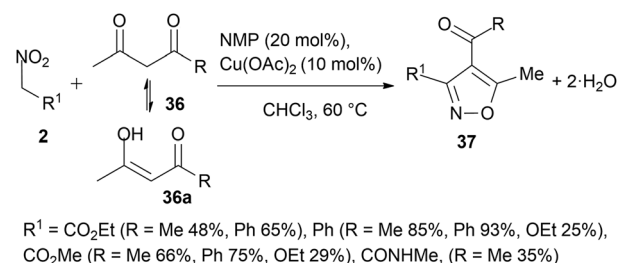
Unlike aldehydes, only activated ketones are reported to react with primary nitro compounds to afford isoxazole derivatives.



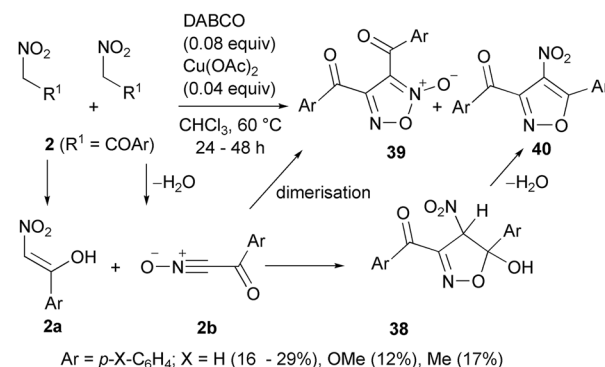
**Scheme 19** Example of 3-carbethoxy-5-carboxamide isoxazole derivatives from oxazinones and pyrrolidine.

### 4.1 Enolisable ketones

The treatment of activated nitro compounds **2** (2-nitroacetates, *N*-methyl-2-nitroacetamide and phenylnitromethane) with enolisable ketones **36** and **36a** (1,3-diketones and 1,3-ketoesters) in a 2:1 ratio with catalytic tertiary amines such as *N*-methylpyrrolidine (NMP) in the presence of a Cu(II) salt allowed the synthesis of highly functionalised isoxazoles **37** by a cycloaddition-condensation process (Scheme 20).<sup>81,82</sup> 5-Methyl trisubstituted isoxazoles were selectively obtained with high yields (85–93%) when only ketone groups were present in the substrates ( $R^1 = \text{Ph}$ ,  $R = \text{Me}$ ,  $\text{Ph}$ , Scheme 20). In this context, enolisable ketones could be considered synthetic equivalents of alkynes (Scheme 1, D). This procedure avoids the use of nitrile oxide intermediates (Scheme 1, C) requiring dehydrating agents that would interfere with the dipolarophile. An intriguing case is the reaction of benzoylnitromethanes under the above conditions (Scheme 21).<sup>81,83</sup> Here, the nitro compound as an enolised dipolarophile **2a** reacts with nitrile oxide **2b** derived from another mole of **2** to give selectively, after the loss of water from intermediates **38**, the corresponding 4-nitro-isoxazole cycloadducts **40**. A concomitant process was observed with the formation of furoxanes **39** derived from the dimerisation of nitrile oxides **2b**. Similarly, long-chain alkanoylnitromethanes **41** (3 examples) in the presence of potassium fluoride as a catalytic base gave 4-nitro-isoxazoles **42** in low yields, likely as a result of cycloaddition of the nitro compound (or possibly the corresponding nitrile oxide) to the enolic form of another mole of the nitro com-



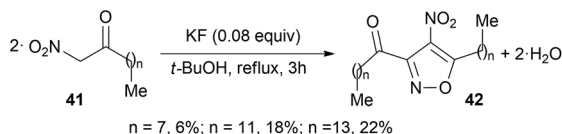
**Scheme 20** Catalysed condensation of nitro compounds with enolisable ketones.



**Scheme 21** Self-condensation of aryl nitromethanes.







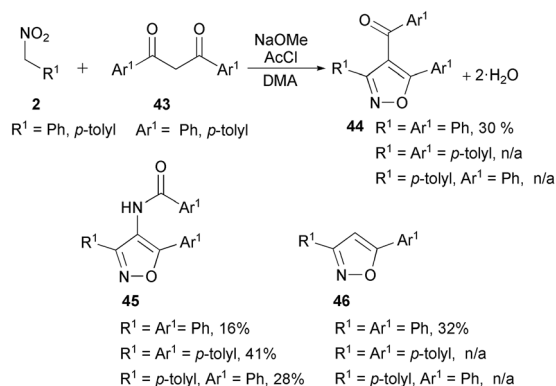
**Scheme 22** 4-Nitroisoxazoles by catalytic treatment of long-chain acylnitromethanes.

pound and dehydration (Scheme 22). A preferred solvent is anhydrous *tert*-butanol since the use of secondary alcohol or the presence of water further decreases the reaction yield with the formation of acids.<sup>84</sup> Diacyl furoxanes **39**, unlike the isomeric isoxazole **40**, were found to be peculiar prodrugs for the inhibition of GPX4 (glutathione peroxidase 4). The molecular mechanism of action of these small molecules, which are nothing more than masked nitrile oxides **2b**, consists of covalent binding that leads to the desired inhibition effect.<sup>83</sup>

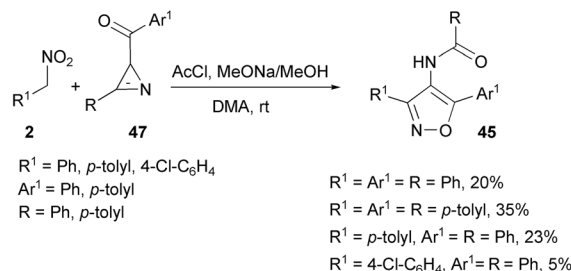
In a different way, the reaction of aryl nitromethanes **2** with dibenzoylmethanes **43** in the presence of stoichiometric acetyl chloride and sodium methoxide in dimethylacetamide (DMA) leads to the formation of a mixture of cycloadducts. Thus, direct cycloadduct 4-acyl isoxazoles **44** were obtained, albeit in low yields, along with 4-benzamidoisoxazoles **45** and 3,5-disubstituted isoxazoles **46** (Scheme 23).<sup>85</sup>

The above process is related to the reaction of keto-azirines **47** with aryl nitromethanes. Under the same reaction conditions as above, keto azirines **47** gave 4-benzamidoisoxazoles **45** along with isoxazole **46** (Scheme 24). The plausible mechanism for their formation (Scheme 23) is reported in Scheme 25.

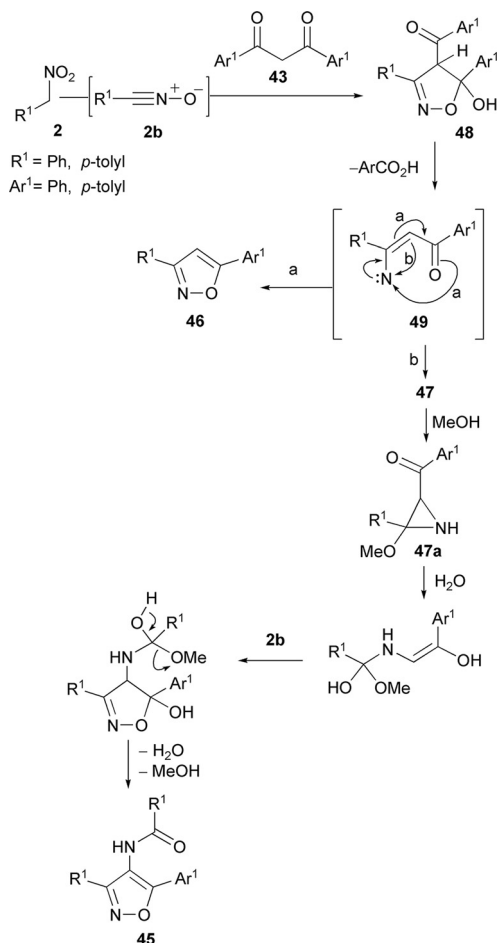
Nitrile oxide generated from **2** reacts with dibenzoylmethanes in 1,3-DC to give isoxazoline intermediates **48**. A fission of the N–O bond under basic conditions followed by elimination of benzoic acid affords nitrene intermediates **49** which isomerise in MeOH to aziridines **47a**. Isomerisation of nitrene **49** is not selective and the formation of isoxazole **46** is observed along with isoxazole **45**. The latter is obtained by water C–C bond breaking of aziridines **47a** to an olefin intermediate which undergoes 1,3-DC with dipole **2b** followed by H<sub>2</sub>O and MeOH elimination. Another approach for circumventing the use of a dehydrating agent in the presence of an enolisable



**Scheme 23** Isoxazoles from enolisable ketones.



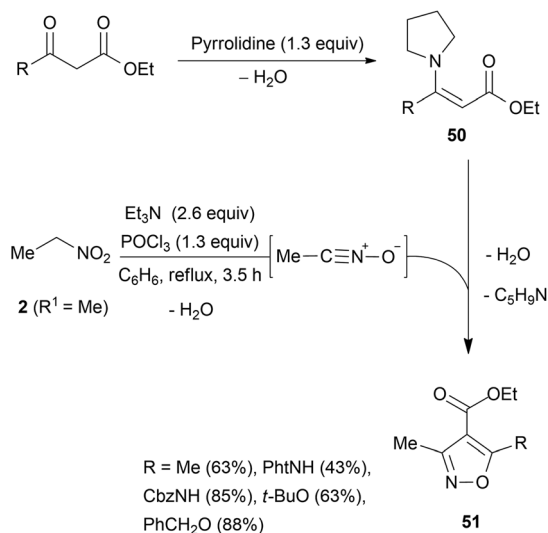
**Scheme 24** Isoxazoles from keto-azirines.



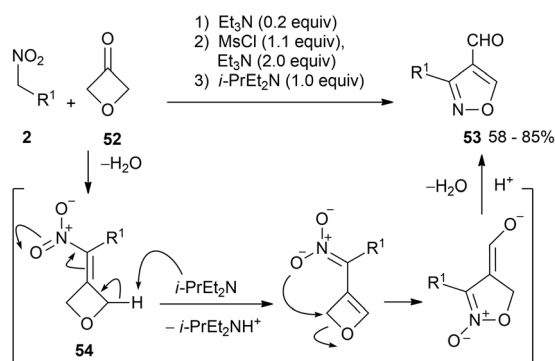
**Scheme 25** Plausible mechanism for the formation of isoxazoles **45** and **46**.

ketone was reported. The pyrrolidine enamine of ethyl acetoacetate (**50**, R = Me) was reacted (benzene reflux) with acetonitrile oxide, generated *in situ* from nitroethane, to give selectively the corresponding 4-carboxyisoxazoles **51** in modest yields. The procedure has been extended to protected  $\gamma$ -amino esters (*N*-phthaloyl and *N*-carbobenzyloxy) or protected  $\gamma$ -hydroxy- $\beta$ -keto esters (*O*-*tert*-butyl and *O*-benzyl) (Scheme 26).<sup>86</sup>

4-Carboethoxy isoxazole **51** (R = Me) was designed as a precursor for the synthesis of  $\alpha$ -cyclopiazonic acid<sup>87</sup> and as a precursor of isoxazole-chenodeoxycholic acid hybrids. The latter



**Scheme 26** 4-Carboxy isoxazoles from pyrrolidine enamines of ethyl aceto acetates.



**Scheme 27** Isoxazole-4-carboxaldehydes from primary nitro compounds and 3-oxetanone.

were synthesised and evaluated for their lipid-lowering effects.<sup>88</sup>

## 4.2 Strained ketones

Condensation of 3-oxetanone **52** with various primary nitro derivatives (either aliphatic or aromatic) is reported, through an intriguing cascade sequence in a one-pot procedure. A variety of 3-substituted isoxazole-4-carbaldehydes **53** are obtained in high overall yields (16 examples). They originate by rearrangement of nitromethyleneoxetane intermediates **54** after deprotonation with a suitable base (Scheme 27).<sup>89</sup>

## 5. Conclusions

There are various reported methods for preparing isoxazoles, but few are general and versatile. Many methods suffer from low functional group tolerance and poor selectivity and yields. From each case, it is therefore necessary to choose the most suitable method

for preparing the desired isoxazole derivatives. Studies on the title reactions carried out in the last century have highlighted the steps involved and their preparative potential.

One of the advantages of using the combination of nitro compounds with activated aldehydes or ketones is the possibility of preparing 3,4,5-trisubstituted isoxazoles (*i.e.* processes reported in Schemes 8 and 17) and 3,4-disubstituted isoxazoles selectively (*i.e.* processes reported in Schemes 12, 17, and 27). The latter are difficult to obtain with other current methods and consequently rarely used as building blocks in the drug discovery process.

In recent years, modified procedures starting from intermediates have added synthetic value allowing the preparation of variously substituted products. Thus, the method has been employed for the preparation of a variety of selectively substituted isoxazoline *N*-oxides and isoxazole derivatives, affording compounds and libraries useful in medicinal chemistry. The reaction between activated ketones and nitro compounds leads to isoxazoles only under certain conditions, the most effective of which involves using a copper catalyst to control the process.

Many improvements in these methods have been described in this review. Their observation suggests that the future development of new and more efficient methods must focus on the identification of intermediates. These allow the control of the reaction selectivity and efficiency when isolated or replaced by suitable synthetic equivalents (*i.e.* intermediates in Scheme 17). The use of new catalysts, hopefully, simple in structure and cheap, to activate the process and direct it selectively towards the products, is another area of development.

## Author contributions

All authors contributed equally to this work.

## Conflicts of interest

There are no conflicts to declare.

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