# Accepted Manuscript

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Please cite this article as: Mamedov, V.A., Mamedova, V.L., Syakaev, V.V., Khikmatova, G.Z., Korshin, D.E., Kushatov, T.A., Latypov, S.K, A new and efficient method for the synthesis of 3-(2-nitrophenyl)pyruvic acid derivatives and indoles based on the Reissert reaction, *Tetrahedron Letters* (2018), doi: https://doi.org/10.1016/j.tetlet.2018.09.039

# A new and efficient method for the synthesis of 3-(2-nitrophenyl)pyruvic acid derivatives and indoles based on the Reissert reaction

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**A b s t r a c t**

The formation of 3-(2-nitrophenyl)pyruvic acid and its amide and ester derivatives – key compounds for the Reissert indole synthesis – was achieved under various reaction conditions *via* the acid catalyzed hydrolysis of 5-(2-nitrobenzyliden)-2,2-dimethyl-1,3-oxazolidin-4-one, which is readily available from 3-(2-nitrophenyl)oxirane-2-carboxamide. A new and highly efficient method for the synthesis of indole-2-carboxylic acid derivatives *via* the intramolecular reductive cyclization of *o*-nitrophenylpyruvic acid and its amide and ester derivatives was developed using $Na_2S_2O_4$ in dioxane/water at reflux.

## 1. Introduction

The indole moiety is one of the most widely distributed heterocyclic systems in Nature, and its derivatives continue to attract significant attention, especially in the pharmaceutical sector.[1] Owing to their structural diversity and remarkable biological functions, numerous efforts have been devoted to the development of methods for synthesizing indoles. Despite the considerable progress achieved for the synthesis of indole derivatives, the preparation of some specific substituted patterns remains difficult. Indole-2-carboxylic acid derivatives have been reported to display a wide range of biological functions such as inhibition of cPLA2,[2] cytosolic

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phosphorylase $A_2\alpha$,[3] HIV-1 integrase[4] and antagonism of the histamine H4 receptor.[5] The synthesis of these compounds is constantly improving and new methods are proposed, often using well-known named reactions such as the Reissert method,[6] Hemetsberg-Knittel indolization,[7] Cadogan-Sundberg synthesis,[8] Hech-Jeffery reaction,[9] Fisher cyclization[10] and Heck reaction.[11] Modern methods for the preparation of indole-2-carboxylic acid derivatives often do not differ in their starting material availability[12-14] or are associated with the use of metal catalysts.[15,16] No methods leading directly to amides of indole-2-carboxylic acid have been reported in the literature. For the preparation of indole-2-carboxylic acid esters, esterification with alcohols in the presence of sulfuric acid is often used.[17] The esterification of indole-2-carboxylic acid with diazomethane under mild conditions leads to methyl indole-2-carboxylate in good yields.[18] The known methods for the conversion of indole-2-carboxylic acid esters into amides are not easy to perform or require the use expensive catalysts.[19]

The Reissert method involves the condensation of *o*-nitrotoluenes with oxalates in the presence of a base, followed by reduction of the resulting *o*-nitrophenylpyruvates.[6] Despite the moderate yields of *o*-nitrophenylpyruvates in the first stage of the process, this method remains mostly in demand for the synthesis of indole-2-carboxylates. In this paper, we present a modification of the Reissert method and successfully use it to obtain indole-2-carboxylic acid, and its amide and ester derivatives, by-passing the hydrolysis, esterification and amidation steps.

## 2. Results and Discussion

As part of an ongoing research program regarding pyruvic acid derivatives, we were interested in developing a novel methodology based on the degradation of 5-benzyliden-2,2-dimethyl-1,3-oxazolidin-4-one). We recently published preliminary results, related to this work, where the reaction of *trans*-3-(2-nitrophenyl)oxirane-2,3-carboxamide (**1**)[20] with acetone in the presence of conc HBr was found to give *syn*-5-(α-bromo-2-nitrobenzyl)-2,2-dimethyl-1,3-oxazolidin-4-one (**2**) *via* acid catalyzed ring opening and ring closure processes.[21] It was also found that *syn*-5-(α-bromo-2-nitrobenzyl)-1,3-oxazolidin-4-one (**2**) was easily converted to *trans*-5-(2-nitrobenzylidene)-2,2-dimethyl-1,3-oxazolidin-4-one (**3**) when exposed to $K_2CO_3$ in MeOH at room temperature.[21] The substitution of conc HBr for HCl in this work led to the same result (Scheme 1).
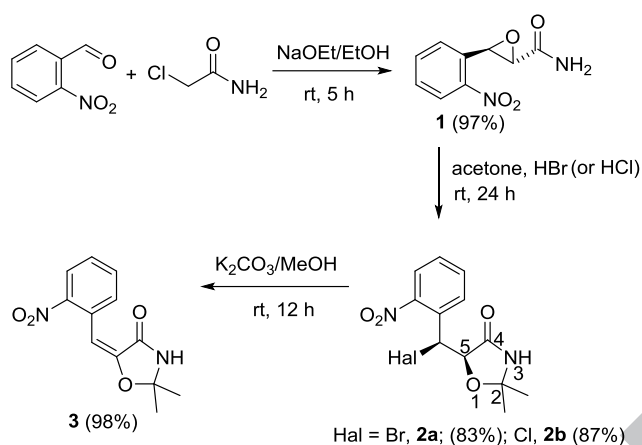
**Scheme 1.** Synthesis of 5-benzyliden-2,2-dimethyl-1,3-oxazolidin-4-one **3**.

Herein, we have extended our studies to the syntheses of 3-(2-nitrophenyl)pyruvic acid derivatives **4** and indoles **5**. *trans*-5-(2-Nitrobenzyliden)-2,2-dimethyl-1,3-oxazolidin-4-one **3** was the starting compound in the syntheses of 3-(2-nitrophenyl)pyruvic acid (**4a**), its amide (**4b**) and ester derivatives (**4c-e**) (Scheme 2), which are key compounds in the Reissert indole synthesis. Compound **4b** was obtained by a short-term (3 min) heating of **3** in conc HCl. In this case the process was terminated with the addition of water. A longer (2 h) heating of **3** in hydrochloric acid resulted in **4a**. Esters **4c-e** were obtained by bubbling gaseous HCl through the corresponding alcohol solution of **3** until it was completely saturated. Then the solutions were kept for 16 h at room temperature, or in the case of **4e** heated at reflux in *i*-PrOH for 2 h.
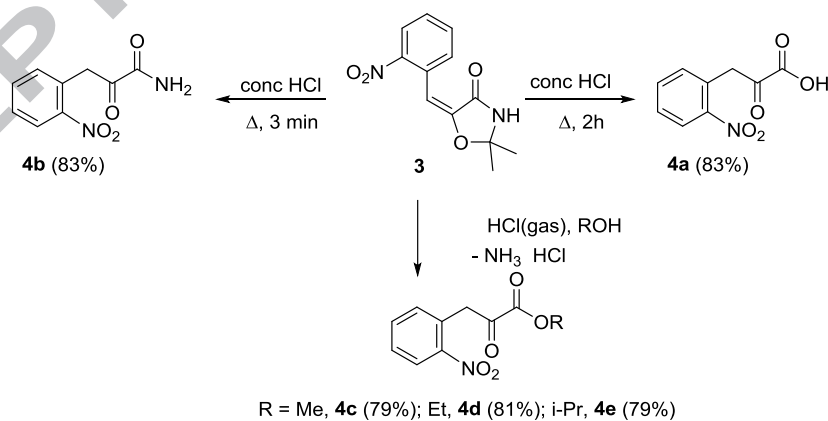


**Scheme 2.** Transformation of 5-benzyliden-2,2-dimethyl-1,3-oxazolidin-4-one **3** to 3-(2-nitrophenyl)pyruvic acid and its derivatives (all compounds gave elemental analysis for C, H, N, within 0.2% of the calculated value and the structures were confirmed by IR, and $^1$H NMR, $^{13}$C NMR spectroscopy, isolated yield is shown).

A notable feature of phenylpyruvic acid derivatives **4** is their tautomerism, allowing the compounds to exist in solution as a mixture of two isomers: the keto form and the enol form.

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Compounds **4** may exist in solution as 3-(2-nitrophenyl)pyruvic acid (**A**) and 2-hydroxy-3-(2-nitrophenyl)acrylic acid (**B**) derivatives (Scheme 3). In the $^1$H NMR spectrum of amide **4b** in DMSO-$d_6$, only tautomer **A** is detected. The $^1$H NMR spectra of compounds **4a**, **4c-e** in DMSO-$d_6$ exhibited the signals from both tautomeric forms: for **4a** the molar ratio is close to 1:1, for **4c** and **4d** the enol form predominates (**A:B** = 1:1.5 and 1:1.2, respectively) and for **4e** the ketone form predominates (**A:B** = 1.2:1). At the same time in the $^1$H NMR spectra of esters **4c** and **4d** in CDCl$_3$ the ketone form was mainly detected (**A:B** = 16:1 and 19:1, respectively).
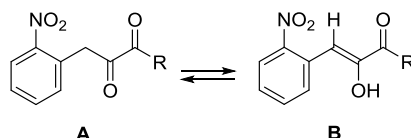


**Scheme 3.** Keto-enol tautomerism of **4**.

The geometry of **B** (Scheme 3) was determined by NMR long-range coupling constants ($^3J_{C(O)-H}$) in the $^{13}$C($^1$H) NMR spectra in DMSO-$d_6$ (see ESI). It is well known that the $^3J_{C-H}$ coupling constant across the double bond is 9.5-15.2 Hz for isomers with *trans* arrangement of the interacting nucleuses C and H and 2.9-6.2 Hz for isomers with *cis* arrangement of these atoms.[22] The values of $^3J_{C(O)-H}$ for tautomers **B** of **4c-d** were 3.6, 2.8, and 3.0 Hz, respectively, and indicate *cis* configuration, which corresponds to the literature data[23] regarding the geometry of similar compounds.

It was also found that 2-nitrophenylpyruvic acid and its amide and ester derivatives can be reduced using a threefold excess of Na$_2$S$_2$O$_4$ at reflux in dioxane/water (1:1) for 3 h with formation of the corresponding indole derivatives **5a-e**, which were easily isolated in almost quantitative yields after aqueous workup (Table 1).

**Table 1.** Reissert indole synthesis by the reduction of 2-nitrophenylpyruvic acid derivatives with Na$_2$S$_2$O$_4$
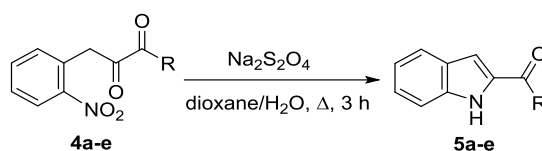


| Entry | Substrate | R | Product[a] | Yield[b] (%) |
|-------|-----------|-----|-----------|-------------|
| 1 | **4a** | OH | **5a** | 96 |
| 2 | **4b** | NH$_2$ | **5b** | 97 |
| 3 | **4c** | OMe | **5c** | 96 |

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| 4 | **4d** | OEt | **5d** | 98 |
| 5 | **4e** | *i*-OPr | **5e** | 97 |

[a] All compounds gave elemental analysis for C, H, N, within 0.2% of the calculated value and the structures were confirmed by IR, and $^1$H NMR, $^{13}$C NMR spectroscopy.
[b] Isolated yield.


It should be noted that methyl indol-2-carboxylate **5c** can be obtained *via* intramolecular reductive cyclization with $Na_2S_2O_4$ directly from methyl 3-(2-nitrophenyl) oxirane-2-carboxylate **6**, which in turn is synthesized by the Darzens condensation of 2-nitrobenzaldehyde and methyl monochloroacetate with *t*-BuOK in dry THF (Scheme 4). When a threefold excess of $Na_2S_2O_4$ was used and the reaction mixture was heated at reflux in water-dioxane for 3 h, the formation of methyl indol-2-carboxylate **5c** was observed only in 20% yield (in the $^1$H NMR spectra of the crude product were also found starting compound **6**). However, the yield of **5c** was increased to 80% when a fivefold excess of $Na_2S_2O_4$ was used and the reaction time was increased to 12 h.
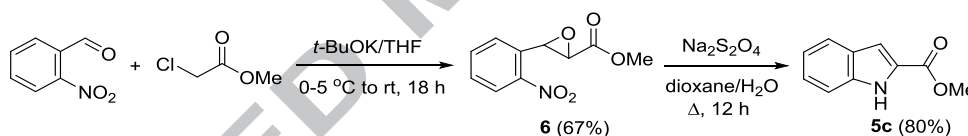


**Scheme 4.** Synthesis of methyl indol-2-carboxylate **5c** directly from methyl 3-(2-nitrophenyl)oxirane-2-carboxylate **6**.


## 3. Conclusion


In summary, we have reported an efficient approach to the synthesis of 3-(2-nitrophenyl)pyruvic acid, and its amide and ester derivatives, as well as a modified Reissert indole synthesis *via* reduction of the 2-nitrophenylpyruvic acid derivatives with $Na_2S_2O_4$. It has been shown that methyl indol-2-carboxylate **5c** can be obtained in high yield *via* intramolecular reductive cyclization with $Na_2S_2O_4$ directly from methyl 3-(2-nitrophenyl)oxirane-2-carboxylate. Given the value of pyruvic acid and indole derivatives in medicine, biology and materials science, this work may become valuable for further transformations involving these building blocks.


**Acknowledgements**

**Supplementary data**

Supplementary data ($^1$H NMR and $^{13}$C NMR spectra, detailed Experimental procedures) associated with this article can be found, in the online version, at …

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**Highlights:**

From: *A new and efficient method for the synthesis  of 3-(2-nitrophenyl)pyruvic acid derivatives and indoles based on the Reissert reaction*

•      3-(2-Nitrophenyl)oxirane-2-carboxylate is used as a new reagent
•      3-(2-Nitrophenyl)pyruvic acid derivatives are used in the synthesis of indoles
•      3-(2-Nitrophenyl)oxirane-2-carboxamide is used as a new reagent
•      Methyl indol-2-carboxylate is obtained from 3-(2-nitrophenyl)oxirane-2-carboxylate

## Graphical abstract

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