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# Elucidation of Synthetic Mechanism Involved in the Conversion of Zwitterionic Clonixin to Carboxamide Side-Product

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***Abstract***

*N-(3-Chloro-2-methylphenyl)-2-oxo-1,2-dihydropyridine-3-carboxamide is obtained as a by-product during the synthesis and crystallization of Clonixin (2-(3-chloro-2-methylanilino)nicotinic acid) and its polymorphs, respectively. This conversion was unexpected and it changed the usual investigation path way enabling the formation of neutral and zwitterionic polymorphs in our study on Clonixin in contrary to studies of 2-(p-tolylamino) nicotinic acid investigation. The same conversion is checked in the other synthesized analogs such as 2-(phenylamino)nicotinic acid (PNA), 2-(methyl(phenyl)amino)nicotinic acid (MPNA), 2-(p-tolylamino)nicotinic acid (TNA) and 2-(methyl(p-tolyl)amino)nicotinic acid (MTNA) but they were all not going to any other side product formation like Clonixin. These ampholites were synthesized by the aromatic nucleophilic substitution reactions of respective aryl amines and 2-chloronicotinic acid in the presence of p-tolylsulfonic acid and pyridine in this report. However, the side product was separated from the crystallization of Clonixin in acetic acid during polymorph hunt. All other analogs were failed in giving this side product as those crystal structures of compounds were analyzed thoroughly by single crystal X-ray determination method. On comparison of this molecule with other ampholites, a new mechanism was proposed for the conversion of Clonixin to this by product in this study and the other molecules are under investigation for no conversion even though they are similar in structures.*

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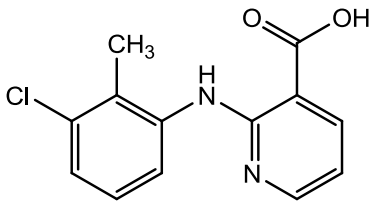
## INTRODUCTION

Arylamino nicotinic acids are the organic compounds which has many medicinal applications especially they all exhibit anti-inflammatory drug properties.[1,2] Based on their importance in medical field, many arylamino nicotinic acids were synthesized by different research groups in different occasions.[3,4] Recently these molecules have some immense interest in solid state chemistry corresponding to the polymorph investigations. They have been proven in many studies that they were more prone to be polymorphic. Tetramorphs and trimorphs were reported for these molecules by Li and coworkers.[4] Some of the neutral and zwitterionic crystal structures were also reported by Kumar and Nangia.[5] Molecular complexes for these molecules was also investigated by Kumar.[6] All these molecules fell in the category of ampholites in which they show acidic and basic behavior and exist as zwitterion in certain pH ranges. Li and coworkers[7] reported already the crystal structure of this *N*-(3-chloro-2-methylphenyl)-2-oxo-1,2-dihydropyridine – 3 - carboxamide compound while in synthesis of Clonixin (Scheme 1). The same product was also

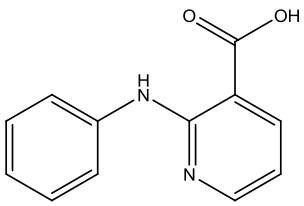
 

resulted from chemical reaction of Clonixin in our laboratory. This side product was also isolated during the crystallization of Clonixin in acetic acid. However, this was not obtained from other crystallizations with any other organic solvents. This crystallization technique helped us to find the suitable mechanism for this conversion. The other ampholites/analogs (Scheme 2) were not involved in the same conversion to any other side products. Therefore, the reaction mechanism is thoroughly investigated for Clonixin conversion to side product and hence it is found that it is not applicable to other analogs because of the absence of zwitterionic form/polymorph. In fact, the other molecules are not stable in zwitterionic structures to bring this conversion during the synthesis and crystallization conditions. TNA is the one which has neutral and zwitterionic structures but the proton transfer was incomplete in room temperature conditions so that it failed to give this side product even though it has zwitterionic form.[3]

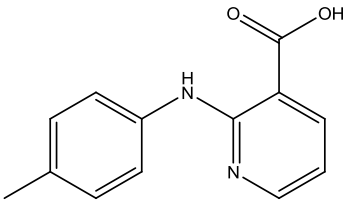



2-(3-chloro-2-methyl phenylamino)nicotinic acid

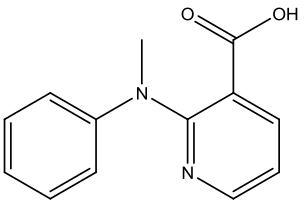
***Scheme 1.*** *Molecular Structure of Clonixin.*



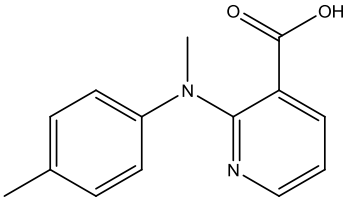

2-(phenylamino)nicotinic acid




2-(*p*-tolylamino)nicotinic acid




2-(methyl(phenyl)amino)nicotinic acid




2-(methyl(*p*-tolyl)amino)nicotinic acid

***Scheme 2.*** *Molecular Structures of Other Arylaminonicotinic Acids (PNA, TNA, MPNA and MTNA) Selected for Mechanical Investigation of Side Product Conversion. They All Failed to Give This Conversion in Crystallization.*

## RESULTS AND DISCUSSION

All these molecules were synthesized (detailed in experimental section) and crystallized in various crystallization techniques such as slow evaporation, melting, sublimation, slow cooling, flash cooling and crystallization in presence of acidic and basic coformers to enable the right mechanism for the carboxamide conversion. Our idea was changed here to find the crystal structure of unexpected side product with different kind of different organic solvents and with the addition of other coformers to establish the reaction mechanism involved in the conversion. The solvents are acetone, methanol, ethanol, ethyl acetate, acetonitrile, chloroform, acetic acid, pyridine, formic acid and THF used for the crystallizations. PNA, MPNA, TNA, MTNA and Clonixin are the molecules which are considered for the elucidation of reaction mechanism in the conversion of Clonixin to *N*-(3-Chloro-2-methylphenyl)-

2-oxo-1,2-dihydropyridine-3-carboxamide.[8] Except Clonixin, no other molecules in this study followed this conversion in the synthesis and crystallization methods as well. Solution crystallization of TNA and PNA with 2-aminopyridine from $CH_3CN$ has resulted corresponding molecular salts. 3-nitro benzoic acid (3-NBA) gave molecular salt with MPNA which has proton transfer from 3-NBA. No side product formation was observed in PNA, TNA and MPNA molecules in spite of its structure similarity with Clonixin. MTNA was failed in complex formation as well as side product conversion in this study.[6] Crystallographic parameter for the crystal structure of this side product is listed in Table 1.

## Crystal structure Analysis

***Table 1.*** *Crystallographic Parameters of Carboxamide Side Product.*

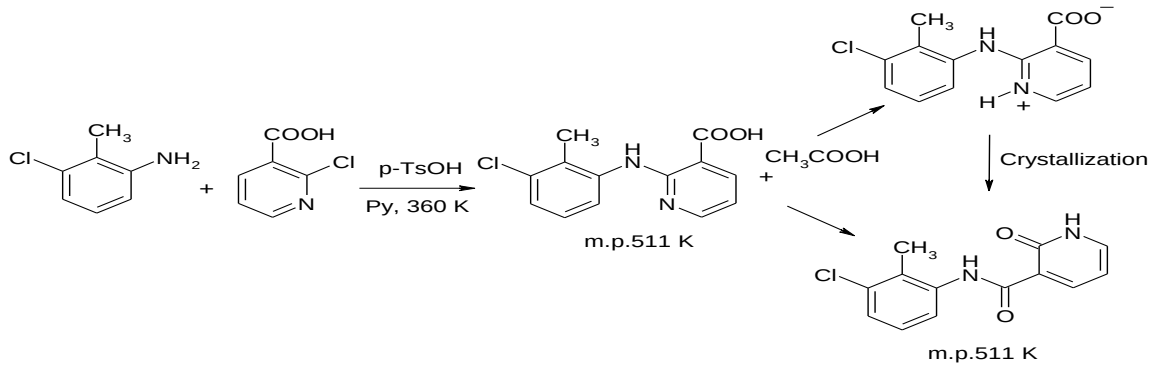
| **Compound** | ***N*-(3-Chloro-2-methylphenyl) -2-oxo-1,2-dihydropyridine-3-carboxamide** |
|---|---|
| Empirical formula | $C_{13}H_{11}ClN_2O_2$ |
| Formula weight | 262.69 |
| Crystal system | Triclinic |
| Space group | P-1 |
| T (K) | 298 K |
| *a*/Å | 7.2783(6) |
| *b*/Å | 7.6058(5) |
| *c*/Å | 10.4877(9) |
| *α*/° | 87.497(6) |
| *β*/° | 89.483(7) |
| *γ*/° | 89.253(6) |
| *V*/Å$^3$ | 579.95(8 |
| $D_{calcd}$ (g/cm$^3$) | 1.348 |
| μ (mm$^{-1}$) | 0.768 |
| Z/Z′ | 2/1 |
| Reflns collected | 2434 |
| Unique reflns | 2019 |
| Observed reflns | 1388 |
| $R_1$ [I > 2 σ(I)] | 0.0685 |
| $wR_2$ (all) | 0.0434 |
| Goodness-of-fit | 1.011 |
| Diffractometer | Xcalibur, Eos, Gemini |

## Crystal Structure of *N*-(3-Chloro-2-Methylphenyl)-2-Oxo-1, 2-Dihydropyridine-3-Carboxamide

Clonixin was synthesized by refluxing 2-chloronicotinic acid (2 mmol, 315.3 mg), 3-chloro-2-methylaniline (2 mmol, 297.3 mg), *p*-toluene sulfonic acid (0.5 mmol, 95.0 mg) and few drops of pyridine at 70–90°C in water and acetone solutions (1:4) overnight (Scheme 3).

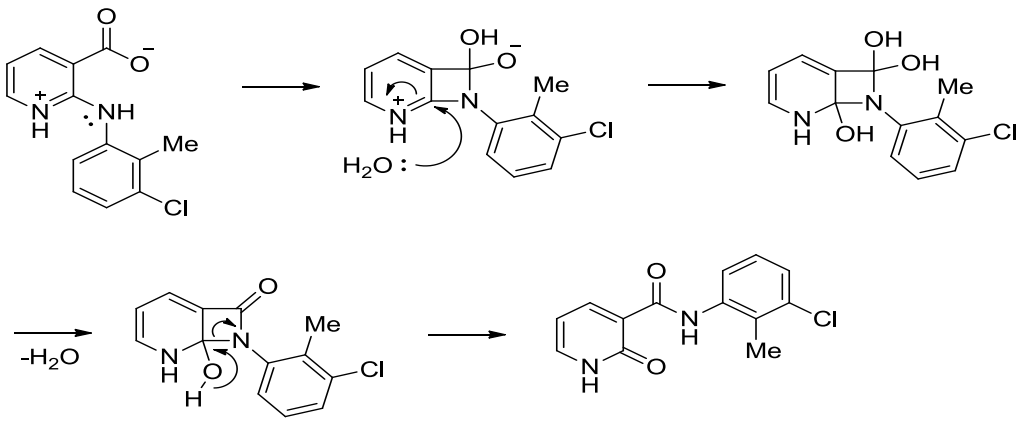
It is characterized by X-ray structure analysis.[9] When it was crystallized in acetic acid solvent the zwitterionic polymorph of Clonixin is the usual product however the product from this

crystallization is unexpected that is *N*-(3-Chloro-2-methylphenyl)-2-oxo-1,2-dihydropyridine-3-carboxamide (Scheme 3).




***Scheme 3.*** *Synthesis of Clonixin (m.p. 238ºC) and Crystallization of Zwitterionic Polymorph Leads to the Formation of N-(3-Chloro-2-Methylphenyl)-2-Oxo-1,2-Dihydropyridine-3-Carboxamide (m.p. 238ºC).*

This crystal was obtained by the crystallization of Clonixin in acetic acid. This same product was also isolated by different research groups in the synthesis of Clonixin. But the mechanism for this reaction was not disclosed by any other groups. However, this side product failed to give another tautomer which was also proposed by Li and coworkers.[7] The tautomer was absent in crystallizations. Only one tautomer was separated out in the lab experiment but identified with X-ray analysis. The reaction mechanism is proposed for the said reaction and it was elucidated in the scheme 4. This reaction is possible only through the formation of stable zwitterionic polymorph which plays vital role to enable this side product during the synthesis of Clonixin and crystallization of Clonixin in acidic solvent. The zwitterionic polymorph formation was not possible or stable in any of the other analogs (PNA, MPNA, TNA and MTNA) taken for this mechanism. In other words, zwitterionic polymorph was isolated for any other analogs except TNA. In TNA case also, the zwitterionic form is partially protonated at py N of nicotinic moiety. However, this TNA has no conversion. Therefore, the zwitterionic polymorph of Clonixin undergoes the series of changes in acidic catalyzed condition to bring this side product as it is in the mechanism proposed by us.




***Scheme 4.*** *Reaction Mechanism Proposed for the Conversion of Zwitterionic Polymorph to N-(3-Chloro-2-Methylphenyl)-2-Oxo-1,2-Dihydropyridine-3-Carboxamide Molecule. It Was Not Observed in Any of the Other Analogs in This Study.*

The crystal structure of this side product was solved in $P^{-1}$ space group and the structure is sustained by the amide-amide N1−H1···O (1.83 Å, 175º) dimer synthon (Figure 1) between the cyclic amide groups present in the carboxamide molecule. This crystal was crystallized only in the presence of acid. The strong intramolecular hydrogen bonding N1−H1···O (1.92 Å, 149º) was present in this molecule that is not allowing the molecule to crystallize it in another tautomer II which was assumed to be in equilibrium by Li and coworkers.

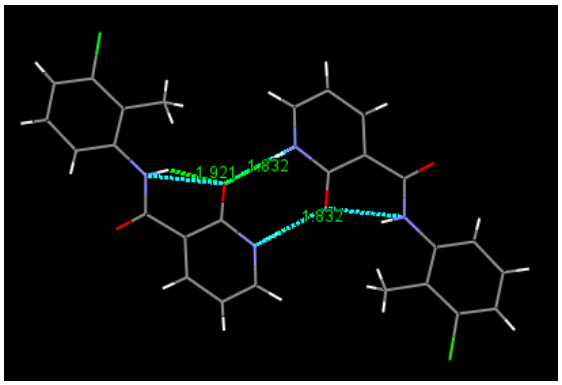



***Fig. 1.*** *Amide–Amide Dimer N−H···O Synthon in Carboxamide Molecule.*

## CONCLUSION

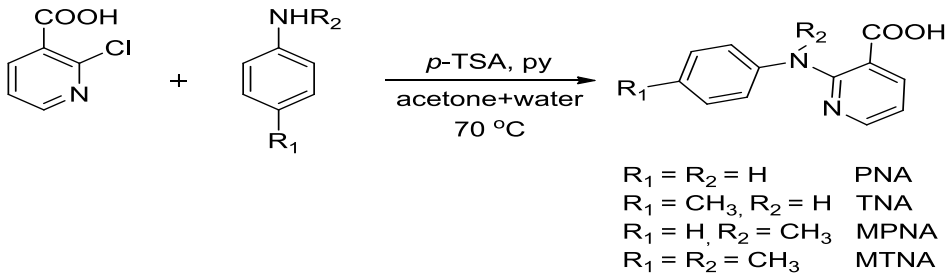
This *N*-(3-Chloro-2-methylphenyl)-2-oxo-1,2-dihydropyridine-3-carboxamide was not expected in the isolation of neutral and zwitterionic polymorphs of Clonixin; however, this product formed was investigated in order to support and control the protocols in those polymorph formation.

This product was already isolated as a side product in the synthesis of Clonixin and it was also obtained as a byproduct of zwitterionic polymorphs in crystallization with acetic acid. The reaction mechanism involved in this conversion was established in this study and may provide a pathway to avoid this side product and neutral form formation in the isolation of zwitterionic polymorphs.

## EXPERIMENTAL SECTION

### Synthesis

Arylaminonicotinic acids (PNA, MPNA, TNA, and MTNA) were synthesized[4] by refluxing 2-chloronicotinic acid (2 mmol, 315.3 mg), respective arylamines (aniline, *p*-toludine, *N*-methylaniline and *N*-methyl-*p*-toluidine (2 mmol, 214.3 mg), *p*-toluene-sulfonic acid (0.5 mmol, 95.0 mg) and few drops of pyridine at 70–90°C in water and acetone solutions (1:4) overnight (Scheme 5).




***Scheme 5.*** *Synthesis of Arylaminonicotinic Acid Derivatives (PNA, TNA, MPNA, and MTNA).*

### X-Ray Crystallography

Structure solution and refinement were carried out using Bruker SHELXTL.[10] X-ray reflection for *N*-(3-Chloro-2-methylphenyl)-2-oxo-1,2-dihydropyridine-3-carboxamide (RT data) collected in Oxford Diffraction Ltd., (Version 1.171.33.55) using Mo Kα, radiation. Data reduction was performed using CrysAlisPro, Oxford Diffraction Ltd.,

Version 1.171.33.55. OLEX2-1.0[11] and SHELXTL 97 were used to solve and refine the data. All non-hydrogen atoms were refined anisotropically, and C−H hydrogens were fixed. N–H and O–H hydrogens were located from difference electron density maps and C–H hydrogens were fixed. Packing diagrams were prepared in Mercury-CCDC (CCDC No. 1473669).

**ACKNOWLEDGMENT**

This work is dedicated to the celebration of centenary birthday (19th May 1914) of Chemist, Molecular Biologist and Human Rights Activist Max F. Perutz (Nobel laureate, 1978).

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**SUPPORTING INFORMATION**

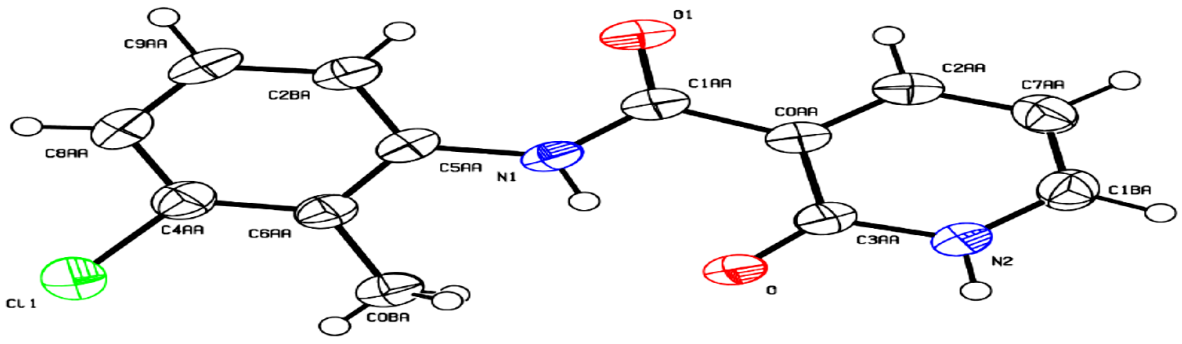


***Fig. S1.*** *ORTEP at 35% Probability of Thermal Ellipsoid for the Heavy Atoms. N-(3-Chloro-2-Methylphenyl)-2-Oxo-1,2-Dihydropyridine-3-Carboxamide at Room Temperature (298 K).*