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Dedicated to Professor Jayanta Kumar Ray (Department of Chemistry, Indian Institute of Technology)

A facile synthesis of diformylated pyrroles by dehydroxylation of *N*-aryl-5-hydroxy-γ-lactam derivatives under Vilsmeier reaction conditions

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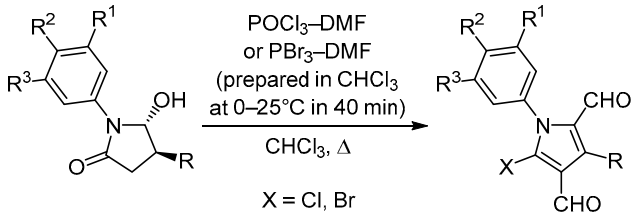


A simple and efficient methodology for the conversion of substituted *trans*-1,4-diaryl-5-hydroxypyrrolidin-2-ones to diformylated *N*-arylpyrroles by treatment with Vilsmeier–Haack reagent has been developed.

Keywords: *trans*-1,4-diaryl-5-hydroxypyrrolidin-2-ones, aromaticity, dehydroxylation, Vilsmeier–Haack reagent.

Pyrroles and their derivatives are one of the most important classes of heterocyclic compounds.[1] They exhibit diverse biological and pharmacological properties.[2] Highly functionalized pyrroles are subunits of considerable importance in heme, chlorophyll, bile pigments, vitamin B12, and marine-derived pyrrole alkaloids.[3] Since Knorr reported the first synthesis of pyrroles,[4] a lot of papers have been published on the synthesis of substituted pyrroles.[5] Although these methods provide efficient ways to construct pyrrole cycle, it is still necessary to develop novel and alternative methodologies so that the substitution patterns of these important heterocyclic compounds can be expanded.

γ-Lactams are *N*-containing five-membered heterocycles and very attractive cyclic systems because they are present in wide range of natural and nonnatural biologically active molecules and drug candidates.[1b] Modification of lactam cycle has been playing a vital role in determining the biological activities of these derivatives. Therefore, attempts to develop new methodologies for the synthesis of differently substituted *N*-heterocycles from γ-lactam derivatives are of considerable interest from the standpoint of the medicinal and organic chemistry. As I have reported recently, tetra- and pentasubstituted pyrroles can be synthesized by applying the Vilsmeier–Haack reagent to *N*-aryl-γ-lactam carboxylic acid derivatives.[6] The Vilsmeier–Haack reagent is an efficient, economical, and mild reagent for the formylation of reactive aromatic and heteroaromatic substrates.[7] It is now used as a powerful synthetic tool for the construction of many heterocyclic compounds.[8]

As a part of my continued interest in conversion of γ-lactam derivatives to other *N*-heterocycles[9] I initiated an investigation to find applications of the Vilsmeier–Haack reagent to different transformations of *N*-aryl-γ-lactams, and herein I wish to report on the feasibility of the formation of *N*-arylformylpyrroles together with the experimental and spectral details of my earlier results.[6]

I have selected *trans*-1,4-diaryl-5-hydroxypyrrolidin-2-ones **1a**–**h** as starting compounds and treated them with Vilsmeier–Haack reagent ($POCl_3$–DMF or PBr_3–DMF) in $CHCl_3$, thus obtaining *N*-aryl-5-chloro(bromo)-3-aryl-(hetaryl)pyrrole-2,4-dicarbaldehyde derivatives **2a**–**h** in good yields (Scheme 1, Table 1).

It was very difficult to perform the Vilsmeier–Haack reaction on the γ-lactam carbonyl group, as the carbonyl group of *N*-aryl-γ-lactam derivatives behaves like amide carbonyl functionality. However, presence of an acid functionality in *N*-aryl-γ-lactam ring at any position favors the lactam carbonyl group to react with Vilsmeier–Haack reagent.[6] Here it is reported that the presence of a hydroxyl group in lactam ring at position 2 favors the reaction of the lactam carbonyl group with Vilsmeier–Haack reagent. It was reasonable to hope that Vilsmeier–Haack reagent may bring about dehydroxylation along with oxidative aromatization of *N*-substituted pyrrolidin-2-one to produce the corresponding *N*-aryl-3,5-diformylpyrrole in one-step process.

From the literature survey one can see that γ-lactam derivatives undergo the Vilsmeier–Haack reaction to form diformylated pyrrole derivatives through the formation of 1,4-diaryl-1,5-dihydropyrrol-2-ones as intermediates.[6] One can

Scheme 1

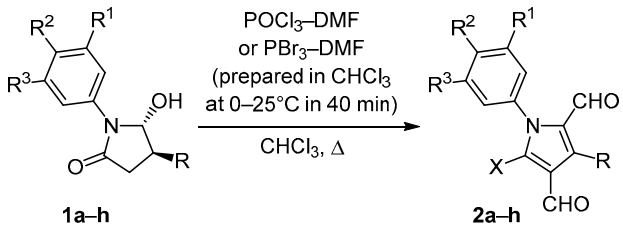


Table 1. Yields of diformylated *N*-arylpyrroles **2a**–**h**

Compound	R	R^1	R^2	R^3	X	Reaction time, h	Yield, %
2a	Ph	H	Cl	H	Cl	3.0	78
2b	Ph	H	Cl	H	Br	4.5	82
2c	Ph	H	H	H	Cl	5.0	77
2d	2-Thienyl	Cl	F	H	Cl	5.5	79
2e	2-Thienyl	Cl	F	H	Br	6.0	80
2f	Ph	H	Cl	Cl	Cl	4.5	78
2g	Ph	H	Br	H	Cl	5.0	81
2h	Ph	H	F	F	Cl	8.0	76

also suppose that 1,4-diaryl-1,5-dihydropyrrol-2-one **B** (**B'**) would be formed as an intermediate and the reaction would proceed along the mechanistic pathway proposed in Scheme 2, resulting in the formation of the diformylated pyrrole **2**.

The Vilsmeier–Haack reaction is widely used for formylations and can be applied to introduce an aldehyde group into activated aromatic compounds, but here it has been shown that conversions of saturated heterocycles to corresponding aromatic heterocycles can be achieved with this method.

All the compounds were characterized by spectroscopic (^{1}H and ^{13}C NMR) and analytical data

In conclusion, I have demonstrated that *trans*-1,4-diaryl-5-hydroxypyrrolidin-2-ones can be converted to diformylated *N*-arylpyrroles with good yields in one-step process by reaction with Vilsmeier–Haack reagent. The reagent system used is safe, simple, and inexpensive, so the operational simplicity and economic viability of this method will likely broaden the perspective of further study in this field.

Experimental

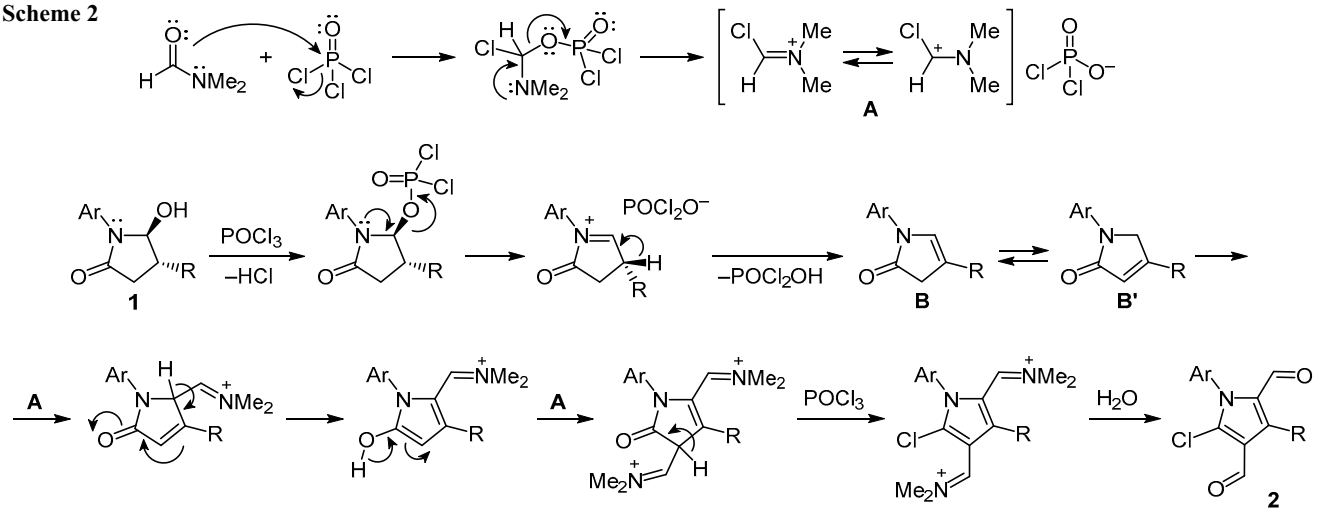
^{1}H NMR spectrum of compound **2c** and ^{13}C NMR spectra of compounds **2a**,**c**,**e** were recorded on a Bruker AC 400 spectrometer (400 and 100 MHz, respectively). ^{1}H and ^{13}C NMR spectra of remaining compounds were recorded on a Bruker AC 200 spectrometer (200 and 50 MHz, respectively). Solvent – $CDCl_3$, internal standard – signal of the solvent (7.26 ppm for ^{1}H nuclei, 77.0 ppm for ^{13}C nuclei). ^{13}C NMR spectra were recorded with complete proton decoupling. Elemental analyses were performed on CHN Analyzers. Chromatographic purification was performed on a column with 60–120 mesh silica gel (SRL), eluent petroleum ether (bp 60–80°C) – EtOAc, 40:1. For reaction monitoring, precoated silica gel 60 F254 TLC sheets (Merck) were used.

The starting *trans*-1,4-diaryl-5-hydroxypyrrolidin-2-ones **1a**–**h** were synthesized by the known method.[10] DMF used in the experiments was dried, distilled, and stored over molecular sieves (4 Å). All reactions were carried out with access of air.

Synthesis of diformylated pyrroles 2a–h (General method). $POCl_3$ or PBr_3 (5 mmol) was added dropwise to a flask containing DMF (0.39 ml, 5 mmol) in anhydrous $CHCl_3$ (10 ml) at 0°C, and the resulting mixture was stirred for 40 min at 25°C. Then the reaction mixture was cooled again to 0°C, and a solution of *trans*-1,4-diaryl-5-hydroxypyrrolidin-2-one **1a**–**h** (1 mmol) in $CHCl_3$ (10 ml) was added dropwise. The resulting reaction mixture was refluxed for 3–8 h (monitored by TLC), then cooled to room temperature and poured into ice-cold water. Solid $NaHCO_3$ was carefully added to neutralize the acids, and the mixture was extracted several times with CH_2Cl_2. The combined organic extract was washed with cold water thoroughly, dried over Na_2SO_4, and evaporated. Purification of the residue was done by column chromatography. The obtained products **2a**–**h** are light-yellow viscous dense liquids.

5-Chloro-1-(4-chlorophenyl)-3-phenylpyrrole-2,4-dicarbaldehyde (2a). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 7.24–7.26 (2H, d, *J* = 8.0, H Ar); 7.48–7.52 (7H, m, H Ar); 9.38 (1H, s, CHO); 9.88 (1H, s, CHO). ^{13}C NMR spectrum, δ, ppm: 120.7; 122.0; 125.3; 128.1; 128.5 (2C); 128.6; 128.7 (2C); 129.2; 129.6 (2C); 130.9 (2C); 133.9; 135.9

Scheme 2



(C Ar); 178.7 (CHO); 184.7 (CHO). Found, %: C 62.66; H 3.59; N 4.26. $C_{18}H_{11}Cl_2NO_2$. Calculated, %: C 62.81; H 3.22; N 4.07.

5-Bromo-1-(4-chlorophenyl)-3-phenylpyrrole-2,4-dicarbaldehyde (2b). ^{1}H NMR spectrum, δ, ppm: 7.19–7.28 (2H, m, H Ar); 7.42–7.49 (6H, m, H Ar); 7.49–7.60 (1H, m, H Ar); 9.32 (1H, s, CHO); 9.90 (1H, s, CHO). ^{13}C NMR spectrum, δ, ppm: 121.1; 121.6; 128.5 (2C); 128.8; 129.1 (2C); 129.2 (2C); 129.6 (2C); 131.0 (2C); 135.3; 136.0; 140.1 (C Ar); 178.7 (CHO); 185.1 (CHO). Found, %: C 55.75; H 3.02; N 3.45. $C_{18}H_{11}BrClNO_2$. Calculated, %: C 55.63; H 2.85; N 3.60.

5-Chloro-1,3-diphenylpyrrole-2,4-dicarbaldehyde (2c). ^{1}H NMR spectrum, δ, ppm: 7.31–7.34 (2H, m, H Ar); 7.49 (5H, s, H Ar); 7.54–7.58 (3H, m, H Ar); 9.40 (1H, s, CHO); 9.90 (1H, s, CHO). ^{13}C NMR spectrum, δ, ppm: 118.6; 127.5 (2C); 128.4 (2C); 128.8; 129.1; 129.3 (2C); 129.8; 130.9 (2C); 132.3; 135.4; 139.2 (C Ar); 178.7 (CHO); 184.6 (CHO). Found, %: C 69.43; H 3.80; N 4.30. $C_{18}H_{12}ClNO_2$. Calculated, %: C 69.80; H 3.90; N 4.52.

5-Chloro-1-(3-chloro-4-fluorophenyl)-3-(2-thienyl)-pyrrole-2,4-dicarbaldehyde (2d). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 7.13–7.20 (2H, m, H Ar); 7.33–7.37 (1H, m, H Ar); 7.52 (1H, dd, *J* = 1.2, *J* = 5.2, H Ar); 7.98 (2H, s, H Ar); 9.55 (1H, s, CHO); 9.96 (1H, s, CHO). ^{13}C NMR spectrum, δ, ppm: 117.5; 119.1; 127.6; 127.8 (2C); 128.3; 128.9 (2C); 129.4; 130.1; 131.2 (2C); 131.7; 135.6 (C Ar); 178.6 (CHO); 184.2 (CHO). Found, %: C 52.00; H 2.50; N 3.95. $C_{16}H_8Cl_2FNO_2S$. Calculated, %: C 52.19; H 2.19; N 3.80.

5-Bromo-1-(3-chloro-4-fluorophenyl)-3-(2-thienyl)-pyrrole-2,4-dicarbaldehyde (2e). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 7.15–7.21 (2H, m, H Ar); 7.24–7.26 (2H, m, H Ar); 7.34–7.37 (1H, m, H Ar); 7.54 (1H, dd, *J* = 1.2, *J* = 5.2, H Ar); 9.50 (1H, s, CHO); 9.95 (1H, s, CHO). ^{13}C NMR spectrum, δ, ppm: 117.1; 117.3; 128.0 (2C); 128.1; 128.8 (2C); 129.4 (2C); 129.8 (2C); 130.1; 130.3; 130.5 (C Ar); 178.4 (CHO); 184.7 (CHO). Found, %: C 46.20; H 2.12; N 3.03. $C_{16}H_8BrClFNO_2S$. Calculated, %: C 46.57; H 1.95; N 3.39.

5-Chloro-1-(3,4-dichlorophenyl)-3-phenylpyrrole-2,4-dicarbaldehyde (2f). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 7.19 (1H, dd, *J* = 2.4, *J* = 8.6, H Ar); 7.44–7.53 (6H, m, H Ar); 7.62 (1H, d, *J* = 8.4, H Ar); 9.39 (1H, s, CHO); 9.89 (1H, s, CHO). ^{13}C NMR spectrum, δ, ppm: 117.1; 117.3; 117.9; 118.1; 118.2; 118.9; 127.6 (2C); 127.7 (2C); 128.5 (2C); 129.3; 130.0; 130.8 (2C, C Ar); 178.7 (CHO); 184.3 (CHO). Found, %: C 56.73; H 2.81; N 4.09. $C_{18}H_{10}Cl_3NO_2$. Calculated, %: C 57.10; H 2.66; N 3.70.

1-(4-Bromophenyl)-5-chloro-3-phenylpyrrole-2,4-dicarbaldehyde (2g). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 7.20 (2H, dd, *J* = 6.6, *J* = 1.8, H Ar); 7.26–7.48 (5H, m, H Ar); 7.67 (2H, dd, *J* = 6.6, *J* = 1.8, H Ar); 9.39 (1H, s, CHO); 9.89 (1H, s, CHO). ^{13}C NMR spectrum, δ, ppm: 118.9; 124.1; 128.5 (2C); 128.7; 128.8; 129.2 (2C); 129.3; 130.9 (2C); 132.3; 132.6 (2C); 134.5; 139.6 (C Ar); 178.8 (CHO); 184.4 (CHO). Found, %: C 55.60; H 3.17; N 3.49. $C_{18}H_{11}BrClNO_2$. Calculated, %: C 55.63; H 2.85; N 3.60.

5-Chloro-1-(3,4-difluorophenyl)-3-phenylpyrrole-2,4-dicarbaldehyde (2h). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 7.07–7.15 (1H, m, H Ar); 7.19 (1H, s, H Ar); 7.24 (1H, d, *J* = 2.4, H Ar); 7.32–7.49 (5H, m, H Ar); 9.39 (1H, s, CHO); 9.89 (1H, s, CHO). ^{13}C NMR spectrum, δ, ppm: 117.4; 117.5; 117.8; 118.1; 118.9; 124.30; 124.34; 128.6 (2C); 128.8; 129.4 (2C); 130.9 (2C); 132.5; 139.7 (C Ar); 178.7 (CHO); 184.4 (CHO). Found, %: C 62.12; H 3.20; N 4.20. $C_{18}H_{10}ClF_2NO_2$. Calculated, %: C 62.53; H 2.92; N 4.05.

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