Tetrahedron Letters 51 (2010) 297–300

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

A novel access to bisformylated pyrroles via decarboxylation of *N*-aryl-γ-lactam-carboxylic acids under Vilsmeier reaction conditions

Gopa Barman, Jayanta K. Ray *

Department of Chemistry, Indian Institute of Technology, Kharagpur 721302, India

ARTICLE INFO

Article history:
Received 12 August 2009
Revised 28 October 2009
Accepted 2 November 2009
Available online 5 November 2009

Keywords:
Vilsmeier reagent
Diformylated pyrrole
γ-Lactam 2/3-carboxylic acids
Aromaticity
Decarboxylation

ABSTRACT

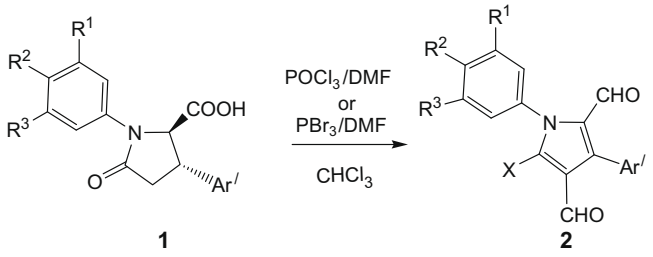
A simple methodology for the conversion of substituted *N*-aryl-γ-lactam 2/3-carboxylic acids to substituted *N*-aryl-diformylated pyrroles has been developed. Several γ-lactam 2/3-carboxylic acids were subjected to Vilsmeier reagent and substituted diformylated pyrroles are isolated in one-step process.

Highly substituted pyrroles are important structural features of many natural products and pharmaceutically active substances.[1] Moreover they are widely used in material science.[2] Pyrroles can be found in a large range of bioactive molecules, including the blockbuster drug atrovastatin calcium, as well as important antiflamatants, antitumor agents, and immunosuppressants.[3] This utility has driven the search for efficient methods to construct pyrroles. Several methods, such as the Knorr,[4] Paal-Knorr,[5] and Hantzsch synthesis[6] including multicomponent and metal-catalyzed routes[7] have been reported for the synthesis of pyrroles. But these above-said methodologies require the correctly substituted precursor(s) prior to cyclization, which can complicate both the synthesis and structural modification of substituted pyrroles.

We have recently reported that *N*-aryl-3-formylpyrroles can be synthesized from *N*-aryl-γ-lactam carboxylic acid derivatives by the successive treatment of $NaBH_4$–I_2 in THF and DDQ in benzene in two-step process.[8] Herein, we report a conceptually new synthetic approach to tetra- and penta-substituted pyrroles utilizing Vilsmeier reagent on γ-lactam carboxylic acid derivatives. In 1993 Balasundaram et al. have reported that *N*-glycine on treatment with Vilsmeier reagent at 90 °C led to the formation of diformylated product namely 2,4-dichloro-3,5-diformylpyrrole in good yield (82%)[9] but the procedure has some limitation. When they subjected *N*-acetyl amino acids like valine, leucine, and glutamic acids to Vilsmeier reagent at 80–90 °C, all these compounds gave mono formylated products namely 2-formylmethylene-4-substituted oxazolidin-5-ones in 30–38% yields. Recently, we reported that 4-chloro indanone under went bisformylation with Vilsmeier reagent.[10] Becher et al. showed that vicinal chloro-pyrrole-carboxaldehydes could be prepared by chloroformylation of arylpyrrol-5-ones.[11]

The starting materials for our work, 1,3-diaryl-5-oxopyrrolidin-2-carboxylic acids **1**, were synthesized following the general method[12,8] developed in our laboratory. We selected *N*-aryl-5-oxo-3-aryl/heteroaryl-pyrrolidine-2-carboxylic acids and treated this compound with Vilsmeier reagent ($POCl_3$/DMF or PBr_3/DMF) in $CHCl_3$ to get the *N*-aryl-5-chloro/bromo-3-aryl/heteroaryl-pyrrole-2,4-dicarbaldehyde derivatives **2** in good yield (Scheme 1, Table 1).

It was very difficult to perform the Vilsmeier reaction on the lactam carbonyl group, as it behaves like amide. However in above cases we saw that the presence of an acid functionality in *N*-aryl-γ-lactams at C-2 favors the lactam carbonyl group to react with



1 **2**

Scheme 1.

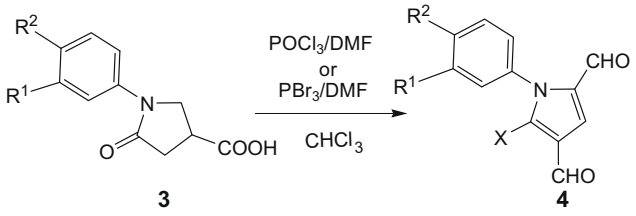
* Corresponding author. Tel.: +91 3222 283326; fax: +91 3222 282252.
E-mail address: jkray@chem.iitkgp.ernet.in (J.K. Ray).

0040-4039/$ - see front matter © 2009 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2009.11.005

Table 1
Synthesis of *N*-aryl-bisformylated pyrrole **2** from γ-lactam-2-carboxylic acids **1**[a]

Substrate *N*-Aryl-γ-lactam-2-carboxylic acid		Ar′	X	Products *N*-Aryl-bisformylated pyrrole	Yield (%)
1a	$R^1 = R^3 = H$, $R^2 = Cl$	Phenyl	Cl	**2a**	92
1b	$R^1 = R^3 = H$, $R^2 = Cl$	Phenyl	Br	**2b**	80
1c	$R^1 = R^3 = H$, $R^2 = Br$	Phenyl	Cl	**2c**	83
1d	$R^1 = H$, $R^3 = R^2 = F$	Phenyl	Cl	**2d**	80
1e	$R^1 = R^3 = R^2 = H$	Phenyl	Cl	**2e**	90
1f	$R^1 = Cl$, $R^2 = F$, $R^3 = H$	2-Thienyl	Cl	**2f**	76
1g	$R^1 = Cl$, $R^2 = F$, $R^3 = H$	2-Thienyl	Br	**2g**	76
1h	$R_1 = H$, $R_3 = R_2 = Cl$	Phenyl	Cl	**2h**	78

[a] Reagents and conditions: All the reactions were carried out with 6 equiv of DMF and 6 equiv of $POCl_3$ or PBr_3 in anhydrous $CHCl_3$ (10 mL) at 0 °C, then after stirring for 40 min 1 equiv of compounds was added by dissolving in $CHCl_3$ and the resulting mixture was refluxed at 80–90 °C for 3–8 h.



Scheme 2.

Vilsmeier reagent. To further examine the generality of the reaction we chose the γ-lactams with varied position of the acid group. These lactam carboxylic acid derivatives were then subjected to Vilsmeier reaction condition and observed that the results were in conformity with the previous observations.

Thus *N*-aryl-5-oxo-pyrrolidine-3-carboxylic acids (**3**) were refluxed with Vilsmeier reagent in $CHCl_3$ and we isolated the *N*-aryl-5-chloro/bromo-pyrrole-2,4-dicarbaldehyde (**4**) in good yields (Scheme 2, Table 2).[13]

But, the *N*-aryl-2-oxo-pyrrolidine-3-carboxylic acids[8] (**5**) with Vilsmeier reagent produce the *N*-aryl-5-chloro/bromo-pyrrole-2,4-dicarbaldehyde (**4**) in very poor yield (10–15%) after a long period of heating (Scheme 3, Table 3).

In all the above cases we saw that the lactam carbonyl group participate in Vilsmeier reaction and the compounds were converted to the bisformylated pyrrole derivatives that is, decarboxylative bisformylation occurred along with aromatization at the same reaction conditions. The above-mentioned observation and literature survey[9,14] have led us to propose a plausible mechanism of the above said reactions (Scheme 4).

The lone pair of nitrogen atom helps for the decarboxylation and the intermediate **6** is formed, which is then bisformylated and converted to aromatic bisformylated pyrrole derivatives.

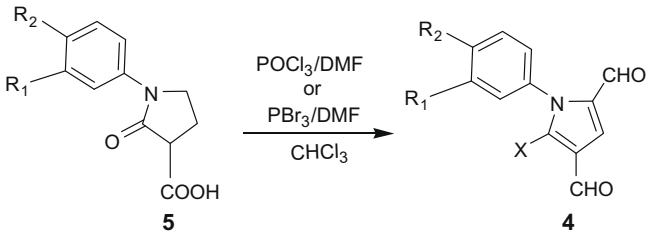
But for the lactam carboxylic acid derivatives **3** and **5** where the acid groups are not at the carbon atom vicinal to nitrogen atom, the decarboxylation occurs but not via the involvement of lone pair of nitrogen atom. In case of acid **3** the α-hydrogen atom of lactam carbonyl group takes part for decarboxylation and intermediate **7** is formed and by the same mechanistic pathway we got the bisformylated products (Scheme 5).

However in case of acid **5** due to less acidity of β-hydrogen atoms the intermediate **7** is formed in very small amount in the reaction mixture and we obtain the bisformylated pyrrole in very

Table 2
Synthesis of *N*-aryl-bisformylated pyrrole (**4**) from γ-lactam-3-carboxylic acids (**3**)[a]

Substrate *N*-Aryl-γ-lactam-3-carboxylic acid		X	Products *N*-Aryl-bisformylated pyrrole	Yield (%)
3a	$R^1 = H$, $R^2 = Cl$	Cl	**4a**	87
3b	$R^1 = H$, $R^2 = OCH_3$	Cl	**4b**	83
3c	$R^1 = H$, $R^2 = Br$	Cl	**4c**	70
3d	$R^1 = R^2 = Cl$	Cl	**4d**	79
3e	$R^1 = H$, $R^2 = Br$	Br	**4e**	70

[a] Reagents and conditions: All the reactions were carried out with 6 equiv of DMF and 6 equiv of $POCl_3$ or PBr_3 in anhydrous $CHCl_3$ (10 mL) at 0 °C, then after stirring for 40 min 1 equiv of compounds was added by dissolving in $CHCl_3$ and the resulting mixture was refluxed at 80–90 °C for 3–8 h.



Scheme 3.

poor yield (Scheme 6). In this case the starting materials mostly remain unchanged under the reaction conditions.

Are the intermediates of the types **6** and **7** actually formed in the reaction mixture and then it undergoes the Vilsmeier reaction to form the bisformylated pyrrole derivatives? To prove this, we performed the Vilsmeier reaction on a lactam derivatives (**8**) and surprisingly here also we isolated the same bisformylated pyrrole derivatives (**2**) (Table 4, Scheme 7). This is a strong proof in favor of the proposed mechanism as depicted in Schemes 4–6.

The lactam derivative 1,4-diphenyl-1,5-dihydropyrrole-2-one (**8**) has been prepared from trans-5-hydroxy-1,4-diarylpyrrolidin-2-ones (**9**)[15] by treatment with $InCl_3$ or $ZnCl_2$ in refluxing CH_3CN (Scheme 8).[16]

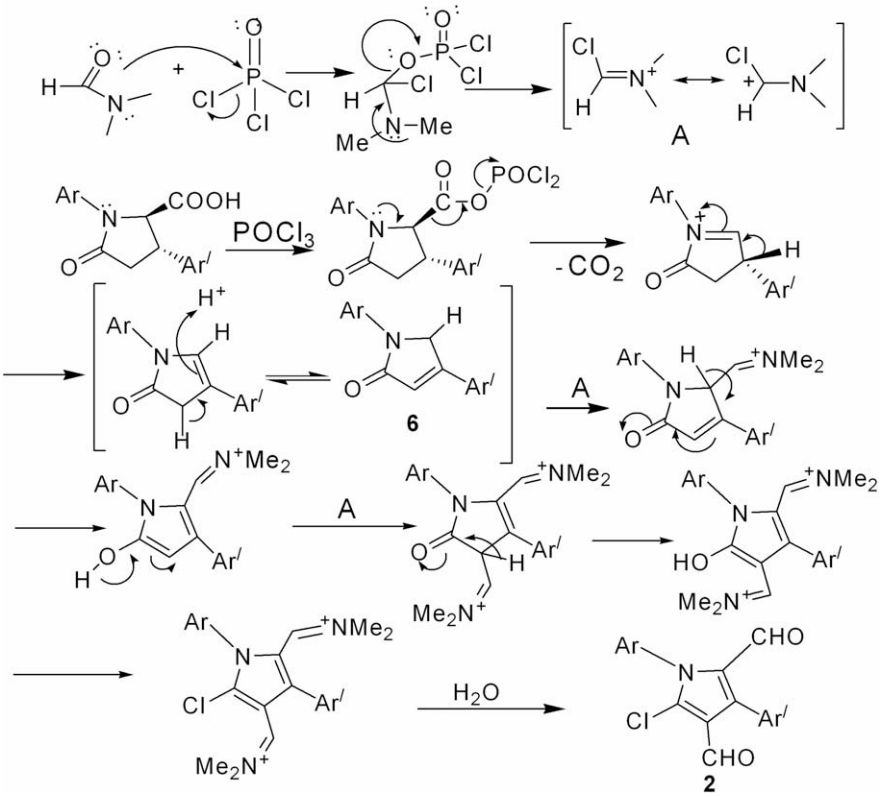
We also verify the effect of N-substituted phenyl ring on lactam derivatives to undergo the Vilsmeier reaction and in the absence of the N-substituted phenyl ring under the same conditions the reaction does not occur. Thus the lactam derivatives **10** remain unchanged under the reaction conditions (Scheme 9).

In conclusion, we have disclosed that *N*-aryl-bisformylated-pyrroles can be prepared from γ-lactam-carboxylic acids by the reaction with Vilsmeier reagent in one-step process with good yields. Thus this demonstrates that the Vilsmeier reagent can be used

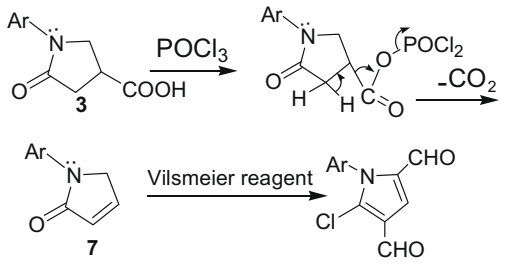
Table 3
Synthesis of *N*-aryl-bisformylated pyrrole **4** from γ-lactam-3-carboxylic acids **5**[a]

Substrate *N*-Aryl-γ-lactam-3-carboxylic acid		X	Products *N*-Aryl-bisformylated pyrrole	Yield (%)
5a	$R_1 = H$, $R_2 = Cl$	Cl	**4a**	10
5b	$R_1 = H$, $R_2 = OCH_3$	Cl	**4b**	15

[a] Reagents and conditions: All the reactions were carried out with 6 equiv of DMF and 6 equiv of $POCl_3$ or PBr_3 in anhydrous $CHCl_3$ at 0 °C, stirred for 40 min then 1 equiv of compounds was added by dissolving in $CHCl_3$ and the resulting mixture was refluxed at 80–90 °C for 3–8 h.



Scheme 4.

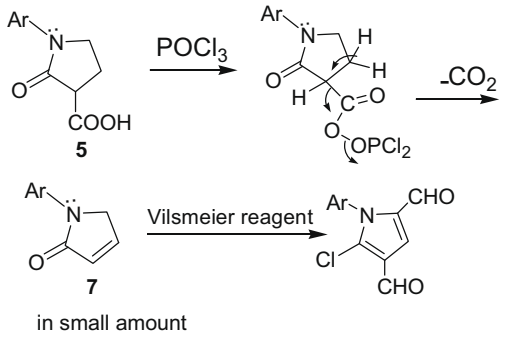


Scheme 5.

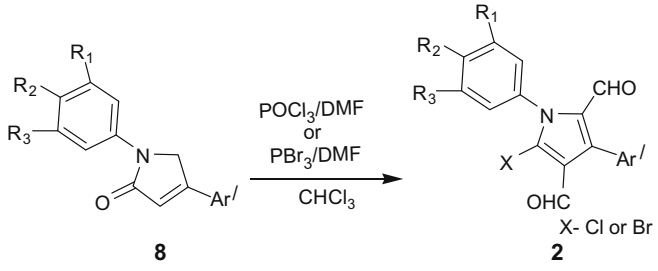
Table 4
Synthesis of *N*-aryl-bisformylated pyrrole **2** from 1,4-diphenyl-1,5-dihydro-pyrrole-2-one **8**[a]

Substrate 1,4-Diphenyl-1,5-dihydro-pyrrole-2-one		Ar′	Products *N*-Aryl-bisformylated pyrrole	Yield (%)
8a	$R_1 = R_3 = R_2 = H$	Phenyl	**2a**	87
8b	$R_1 = H$, $R_3 = Cl$, $R_2 = F$	Phenyl	**2b**	76
8c	$R_1 = R_3 = H$, $R_2 = Br$	Phenyl	**2c**	70
8d	$R_1 = H$, $R_3 = R_2 = F$	Phenyl	**2d**	80
8e	$R_1 = Cl$, $R_2 = F$, $R_3 = H$	2-Thienyl	**2f**	76

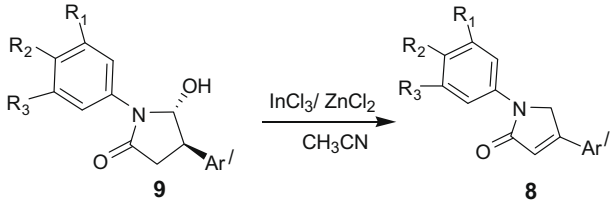
[a] Reagents and conditions: All the reactions were carried out with 6 equiv of DMF and 6 equiv of $POCl_3$ or PBr_3 in anhydrous $CHCl_3$ at 0 °C, stirred for 40 min then 1 equiv of compounds was added by dissolving in $CHCl_3$ and the resulting mixture was refluxed at 80–90 °C for 3–8 h.



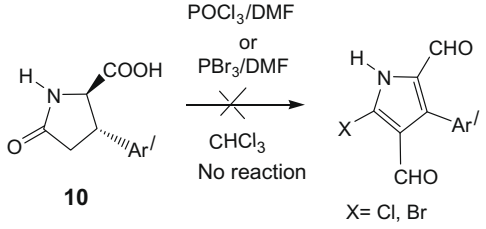
Scheme 6.



Scheme 7.



Scheme 8.



Scheme 9.

for decarboxylation as well as formylating reagent. These *N*-aryl-bisformylated-pyrroles can be used for the synthesis of pyrrole core bioactive products.

Acknowledgments

Financial support from DST and CSIR (New Delhi) is gratefully acknowledged.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.11.005.

References and notes

1. (a) Sundberg, R. J.. In *Comprehensive Heterocyclic Chemistry II*; Katritzky, A. R., Rees, C. W., Scriven, E. F. V., Eds.; Elsevier: Oxford, UK, 1996; Vol. 2, p 119; (b) O'Hagan, D. *Nat. Prod. Rep.* **2000**, *17*, 435; (c) Jendralla, H.; Baader, E.; Bartmann, W.; Beck, G.; Bergmann, A.; Granzer, E.; Kerekjarto, B. v.; Kesseler, K.; Krause, R.; Schubert, W.; Wess, G. *J. Med. Chem.* **1990**, *33*, 61.
2. Lee, C.-F.; Yang, L.-M.; Hwu, T.-Y.; Feng, A.-S.; Tseng, J.-C.; Luh, T.-Y. *J. Am. Chem. Soc.* **2000**, *122*, 4992.
3. (a) Muchowski, J. M. *Adv. Med. Chem.* **1992**, *1*, 109; (b) Cozzi, P.; Mongelli, N. *Curr. Pharm. Des.* **1998**, *4*, 181; (c) Furstner, A.; Szillat, H.; Gabor, B.; Mynott, R. *J. Am. Chem. Soc.* **1998**, *120*, 8305.
4. Knorr, L. *Chem. Ber.* **1884**, *17*, 1635.
5. Paal, C. *Chem. Ber.* **1885**, *18*, 367.
6. Hantzsch, A. *Ber. Dtsch. Chem. Ges.* **1890**, *23*, 1474.
7. (a) Balme, G. *Angew. Chem., Int. Ed.* **2004**, *43*, 6238; (b) Nair, V.; Vinod, A. U.; Rajesh, C. *J. Org. Chem.* **2001**, *66*, 4427; (c) Bharadwaj, A. R.; Scheidt, K. A. *Org. Lett.* **2004**, *6*, 2465; (d) Tejedor, D.; Gonzalez-Cruz, D.; Garcia-Tellado, F.; Marrero-Tellado, J. J.; Rodriguez, M. L. *J. Am. Chem. Soc.* **2004**, *126*, 8390; (e) Braun, R. U.; Zietler, K.; Mu¨ller, T. J. J. *Org. Lett.* **2001**, *3*, 3297; (f) Nishibayashi, Y.; Yoshikawa, M.; Inada, Y.; Milton, M. D.; Hidai, M.; Uemura, S. *Angew. Chem., Int. Ed.* **2003**, *42*, 2681; (g) Shiraishi, H.; Nishitani, T.; Sakaguchi, S.; Ishii, Y. *J. Org. Chem.* **1998**, *63*, 6234; (h) Gorin, D. J.; Davis, N. R.; Toste, D. F. *J. Am. Chem. Soc.* **2005**, *127*, 11260; (i) Kel'in, A. V.; Sromek, A. W.; Gevorgyan, V. *J. Am. Chem. Soc.* **2001**, *123*, 2074; (j) Declerk, V.; Ribiere, P.; Martinez, J.; Lamaty, F. *J. Org. Chem.* **2004**, *69*, 8372; (k) Kamijo, S.; Kanazawa, C.; Yamamoto, Y. *J. Am. Chem. Soc.* **2005**, *127*, 9260; (l) Larionov, O. V.; de Meijere, A. *Angew. Chem., Int. Ed.* **2005**, *44*, 5664.
8. Haldar, P.; Barman, G.; Ray, J. K. *Tetrahedron* **2007**, *63*, 3049.
9. (a) Balasundaram, B.; Venugopal, M.; Perumaf, P. T. *Tetrahedron Lett.* **1993**, *34*, 4249; (b) Zaytsev, A. V.; Anderson, R. J.; Meth-Cohn, O.; Groundwater, P. W. *Tetrahedron* **2005**, *61*, 5831.
10. Mahato, K. T.; Pan, D.; Mal, K. S.; Ray, J. K. *J. Indian Chem. Soc.* **2003**, *80*, 969.
11. Becher, J.; Jmgensen, P. L.; Pluta, K.; Krake, N. J.; Fat-Hansen, B. *J. Org. Chem.* **1992**, *57*, 2127–2134.
12. (a) Ray, J. K.; Kar, G. K.; Roy, B. C.; Brahma, N. K. *Bioorg. Med. Chem.* **1994**, *2*, 1417; (b) Ray, J. K.; Kar, G. K.; Adhikari, S. D.; Ray, J. K.; Brahma, N. K. *Bioorg. Med. Chem.* **1998**, *6*, 2397–2403.
13. General procedure for the synthesis of bisformylated pyrroles (**2**) and (**4**).
General procedure for the synthesis of bisformylated pyrroles (**2b**) from γ-lactam-carboxylic acids (**1b**).
To a flask containing DMF (5 mmol) in anhydrous $CHCl_3$ (10 mL) at 0 °C $POCl_3$ or PBr_3 (5 mmol) was added drop by drop and the resulting mixture was stirred for 40 min at room temp (25 °C). The reaction mixture was then cooled down to 0 °C and a solution of γ-lactam-carboxylic acids (1 mmol, 0.316 g) in chloroform (10 mL) was added drop-wise. The resulting reaction mixture was refluxed at 80–90 °C for 3–8 h (monitored by TLC) and then cooled to room temperature. The reaction mixture was then poured into ice-cold water and solid sodium bicarbonate was carefully added to neutralize the acids and the mixture was extracted several times (3–4 times) with 10 mL dichloromethane. The organic part was then washed with cold water thoroughly, dried with anhydrous sodium sulfate, and evaporated. Purification of the residue was done by silica gel (60–120 mesh) column chromatography [petroleum ether (60–80 °C)–ethylacetate (20:1)].
Physical properties and spectral data of representative compounds.
Compound **2b**, 1-(4-chlorophenyl)-3-phenyl-5-bromopyrrole-2,4-dicarbaldehyde.
Light yellow viscous liquid, ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 7.19–7.28 (m, 2H), 7.48 (s, 6H), 7.49–7.60 (m, 1H), 9.32 (s, 1H), 9.90 (s, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ: 121.09, 121.61, 128.50 (2C), 128.75, 129.11 (2C), 129.23 (2C), 129.63 (2C),130.95 (2C), 135.34, 135.95, 140.12, 178.71, 185.06. Anal. Calcd for $C_{18}H_{11}BrClNO_2$: C, 55.63; H, 2.85; N, 3.60. Found: C, 55.75; H, 3.02; N, 3.45.
Compound **4b**, 1-(*p*-methoxy)-5-chloropyrrole-2,4-dicarbaldehyde.
Light yellow solid; mp 128–131 °C. ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 3.87 (s, 3H), 6.97–7.06 (m, 2H), 7.23–7.30 (m, 2H), 7.47 (s, 1H), 10.17 (s, 1H), 10.29 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 55.69, 114.83 (2C), 120.19, 124.37, 127.45 (2C), 127.96, 128.29, 128.60, 160.52, 185.33, 186.25. Anal. Calcd for $C_{13}H_{10}ClNO_2$: C, 59.22; H, 3.82; N, 5.31. Found: C, 58.79; H, 3.68; N, 5.31.
14. Marson, C. M. *Tetrahedron* **1992**, *48*, 3659–3726.
15. (a) Haldar, P.; Ray, J. K. *Tetrahedron Lett.* **2008**, *49*, 3659–3662; (b) Barman, G.; Roy, M.; Ray, J. K. *Tetrahedron Lett.* **2008**, *49*, 1405.
16. General procedure for the synthesis of 1,4-diphenyl-1,5-dihydro-pyrrole-2-one derivatives (**8e**).
To a flask containing 1-(3-chloro-4-fluoro-phenyl)-5-hydroxy-4-(2-thienyl)-pyrrolidine-2-one (1 mmol, 0.3 g) in acetonitrile, (10 mL) catalytic amount of $InCl_3$ or $ZnCl_2$ was added. The resulting mixture was refluxed for 6–8 h (monitored by TLC) and then cooled to room temperature. The solvent was evaporated under reduced pressure and the residue was extracted with 20 mL CH_2Cl_2. The combined organic layer was washed with brine. After drying the organic layer with anhydrous Na_2SO_4, the solvent was evaporated under reduced pressure. The product thus obtained was purified by silica gel (60–120 mesh) column chromatography [petroleum ether (60–80 °C)–ethylacetate (18:1)].
Compound **8e**, 1-(3-chloro-4-fluoro-phenyl)-4-(2-thienyl)-1,5-dihydro-pyrrole-2-one.
Yellow viscous liquid; ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 4.73 (d, J = 1.2 Hz, 2H), 6.32 (s, 1H), 7.03–7.15 (m, 2H), 7.19–7.35 (m, 1H), 7.49 (dd, J = 1, 5 Hz, 1H) 7.6–7.68 (m, 1H), 7.84 (dd, J = 2.6, 6.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ: 53.05, 116.97, 117.22, 118.11, 118.24, 119.30, 120.64, 126.41, 127.13, 128.34, 134.82, 135.75, 147.70, 170.09 Anal. Calcd for $C_{14}H_9ClFNOS$: C, 57.24; H, 3.09; N, 4.77. Found: C, 56.66; H, 3.30; N, 4.97.