Tetrahedron Letters 52 (2011) 6331–6335

Contents lists available at SciVerse ScienceDirect

Tetrahedron Letters

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

An efficient synthesis of 2-aminopyrroles from enaminone–amidine adduct and phenacyl/benzyl/heteroalkyl-halides

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ARTICLE INFO

Article history:
Received 25 June 2011
Revised 23 August 2011
Accepted 25 August 2011
Available online 1 September 2011

Keywords:
2-Aminopyrroles
Enaminone
Cyanamide
5-*Exo* trig
N-alkylation

ABSTRACT

Herein, we report an efficient and facile synthesis of substituted 2-aminopyrroles from the reaction of enaminone–amidine adduct and various phenacyl, benzyl, or heteroalkyl halides in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in good to excellent yields. The reaction proceeds through an intramolecular 5-*exo* trig cyclization resulting into diversely substituted 2-aminopyrroles.

Many natural and biologically active compounds like hemes, bile pigments, chlorophyll etc. have pyrrole as the basic scaffold which is also present in pharmaceuticals[1] and compounds of material sciences.[2] 2-Aminopyrroles are part of many different bioactive compounds with reported bioactivities like, IL-6 production inhibition, IkB kinase-β inhibition, intergrin antagonists, signals transduction modulators, antitumor, and antibacterial agents[3] are a few of them. Despite the large number of methods for the synthesis of pyrroles reported so far, it is still challenging to prepare 2-aminopyrroles with various substituents directly from readily available building blocks. Several methods were reported for the synthesis of 2-aminopyrroles by Domling,[4] Zhu,[5] Nair[6] and Shaabani[7] using multi-component reactions of acidic nitriles or isocyanides as starting materials. 2-Aminopyrroles are not readily available precursors; in general, such species are difficult to make and are notoriously prone to decomposition if the adjacent carbon attached to the carbon of the amino group is not bearing the electron withdrawing groups. To the best of our knowledge, there are no simple and convenient methods for the synthesis of substituted 2-aminopyrroles using the readily available and simple starting materials like enaminone–amidine adduct and phenacyl/benzyl/hetero-alkyl halides.

Enaminones (enamines) are versatile and readily available intermediates and their chemistry has received considerable attention in recent years.[8] As far as the chemical reactivity of enamines is concerned, they can react with both electrophiles as well as nucleophiles.[9,10] It is known that the electron rich double bond of enamino-ketones has stronger tendency to react as a nucleophile toward the electron deficient species. The existing methods for the synthesis of pyrroles from enamines and carbonyl compounds are facilitated by oxidizing agents for cyclization and results in pyrroles without amine function.[11]

The focus of our group is to develop new synthetic methods for the small heterocyclic compounds particularly bearing the amino group within the heterocycles. We have developed the synthesis of 2-aminothiophene,[12] 2-aminothiazole[13] and 2-aminoimidazole[14] using different adducts of isothiocyanates with enamines or amidines. We have been working on the reaction of enamines/enaminones with different isothiocyanates to produce the enaminone–isothiocyanate adducts which are useful intermediates for the synthesis of substituted 2-aminothiophenes.[15] Herein, our interest was to check the reactions of enaminones with various electrophiles, in particular their reactions with cyanamide to get the enaminone–amidine adduct.

We reasoned that, we can use the nucleophilic nature of the enaminone by reacting them with electrophilic cyanamide (carbodimide) in the presence of a mild acid to produce the enaminone–amidine adduct. Further reaction of this adduct with active methylene halides could give the desired pyrroles. Herein, we report a novel synthesis of 2-aminopyrroles (**3** and **5**) by the reaction of enaminone–amidine adduct **1** with various phenacyl bromides **2**, benzyl and heteroalkyl halides **4** in the presence of DBU in good to excellent yield (Scheme 1).

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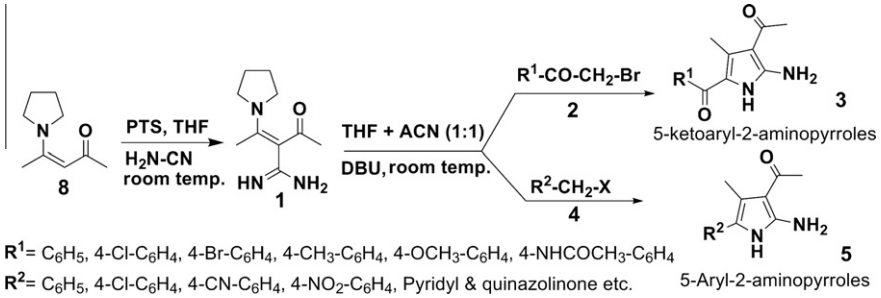
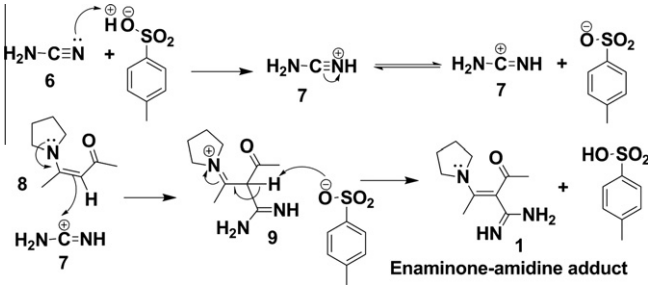
0040-4039/$ - see front matter © 2011 Published by Elsevier Ltd.
doi:10.1016/j.tetlet.2011.08.149



Scheme 1. Synthesis of 5-ketoaryl and 5-aryl-2-aminopyrroles.



Scheme 2. Plausible reaction mechanism for enaminone–amidine adduct formation.

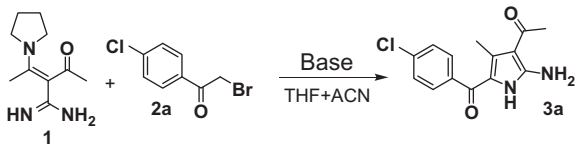
The first step of the reaction sequence starts with the reaction of enamino-ketone **8** with cyanamide **6** in the presence of mild acid (*p*-toluene sulfonic acid) in tetrahydrofuran (THF) at room temperature. After stirring for 3–4 h, a white solid was observed in the flask as enaminone–amidine adducts **1** (Ref. 16). The feasibility of this reaction may be attributed to the increased nucleophilic character of the double bond of enamino-ketone toward the electrophilic cyanamide facilitated by the lone pair of electrons of the pyrrolidine nitrogen atom. The protonation by PTS to the nitrogen atom of the cyano group increases electrophilic nature of the cyanamide carbon and hence allows the double bond to attack. This reaction may proceed similarly to that of the enamines with isothiocyanates for the preparation of adducts as mentioned in the literature.[13,14] The plausible reaction mechanism for the enaminone–amidine formation (Scheme 2), in which the cyanamide is protonated with the help of PTS to give species **7**, this carbocation bearing the electron deficient central carbon atom is further attacked by the double bond of nucleophilic enamino-ketone **8** to produce the species **9**. This intermediate further transforms to enaminone–amidine adduct **1**.

From the above reaction mechanism, one can rule out the possibility of the attack of the amino group of cyanamide on the carbonyl carbon of enaminone, because cyanamide is already in protonated form due to the presence of mild *p*-toluene sulfonic acid and hence behave predominantly as an electrophile.

Under the developed conditions for the synthesis of enaminone–amidine adduct **1**, we synthesized this adduct in multigram scale. The second step is the reaction of enaminone–amidine adducts with various phenacyl, benzyl, or heteroalkyl halides in the presence of DBU to give substituted 2-aminopyrroles. The reactions of the enaminone–amidine adduct **1** with different phenacyl bromides (**2a–h**) in the presence of DBU resulted in 5-ketoaryl-2-aminopyrroles (**3a**–**h**) in good to excellent yield. Further to check the efficiency of the base, we selected various bases to optimize the reaction conditions by selecting the reaction of **1** with 4-chlorophenacyl bromide **2a** for the survey. The representative results are summarized in Table 1. The results are clearly indicating that as compared to other bases, DBU should be selected for the cyclization reaction of pyrroles, because optimum yield and shorter reaction time was achieved when DBU was used as a base. Once the optimized protocol in hand, we turned to demonstrate the generality of this protocol using various benzyl halides (**4a–e**) and hetero alkyl halides (**4f–h**) in order to get 5-aryl and 5-heteroaryl-2-aminopyrroles (**5a**–**h**). The reaction with electron withdrawing groups present in the aromatic ring of phenacyl bromides resulted in excellent yield while the reaction of the electron releasing groups were observed with comparatively lower yields.

The reactions of enaminone–amidine adduct **1** with aromatic alkyl halides in the presence of DBU resulted in 2-aminopyrroles with aryl substitution at 5th position of the pyrrole scaffold with reasonably good yields (Table 2, **5a**–**e**) suggesting the reactivity of enamine–amidine adduct toward the benzyl halide.[19] This has provided us a platform for testing the reactivity of the adduct **1** with heterocyclic alkyl halides **4** to get the 2-aminopyrrole with heterocyclic substitution at 5th position of pyrroles (Table 2, entry **5f**–**h**).[20]

Table 1
Optimization of reaction parameters for 2-aminopyrrole synthesis



Sr. No.	Base	Base (equiv)	Temp (°C)	Time (h)	Yield[a] (%)
1	DBU	1.0	25	2	89
2	Pyridine	1.0	25	12	51
3	Potassium tertiary butoxide	1.0	25	9	49
4	Triethylamine	1.0	25	10	42
5	Potassium carbonate	1.0	25	16	38

[a] Yields refer to chromatography pure product.

Table 2
Substituted 5-ketoaryl and 5-aryl/heteroaryl-2-aminopyrroles

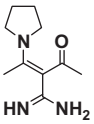
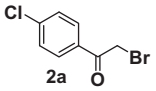
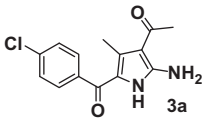
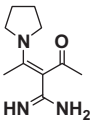
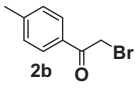
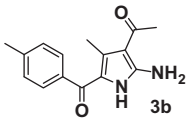
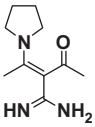
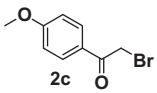
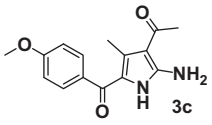
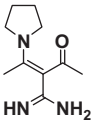
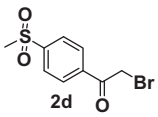
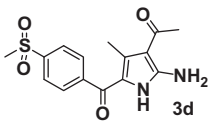
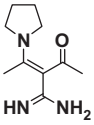
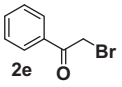
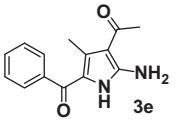
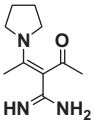
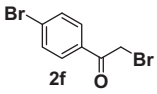
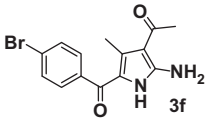
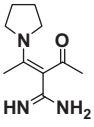
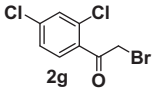
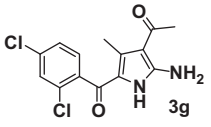
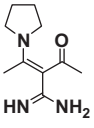
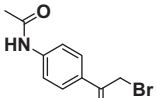
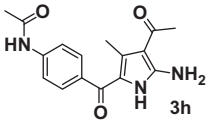
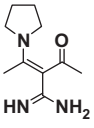
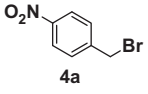
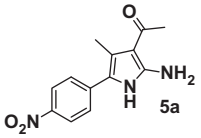
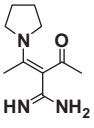
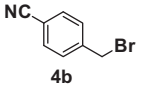
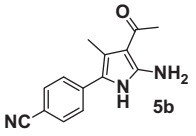
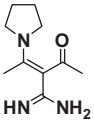
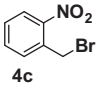
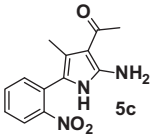
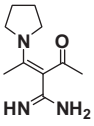
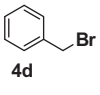
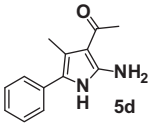
Sr. No.	Enamino-ketone **1**	Structure of compounds **2** and **4**	Products **3** and **5**	Yield[a] (%)
1		 2a	 3a	89
2		 2b	 3b	71
3		 2c	 3c	69
4		 2d	 3d	70
5		 2e	 3e	68
6		 2f	 3f	88
7		 2g	 3g	86
8		 2h	 3h	83
9		 4a	 5a	79
10		 4b	 5b	76
11		 4c	 5c	78
12		 4d	 5d	62

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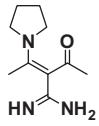
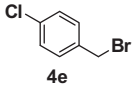
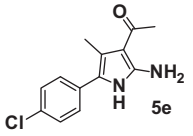
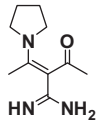
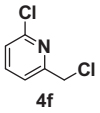
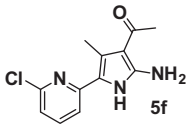
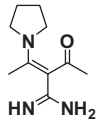
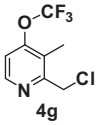
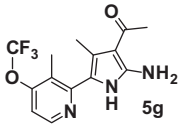
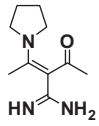
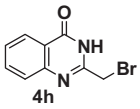
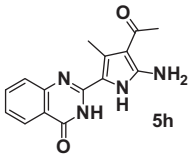
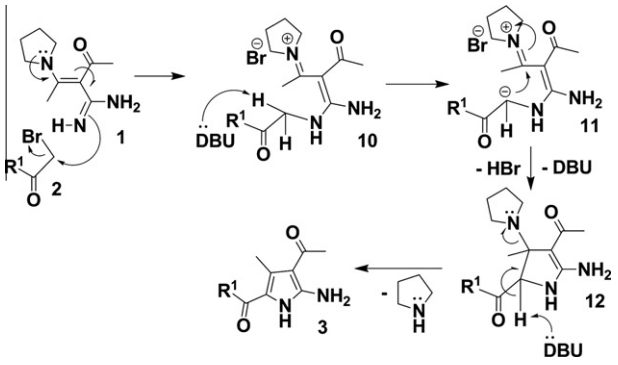
Table 2 (*continued*)

Sr. No.	Enamino-ketone **1**	Structure of compounds **2** and **4**	Products **3** and **5**	Yield[a] (%)
13		 4e	 5e	68
14		 4f	 5f	65
15		 4g	 5g	67
16		 4h	 5h	61

[a] Yields refer to isolated products by column chromatography.



Scheme 3. Mechanistic rationale for 2-aminopyrrole synthesis.

Thus, in a representative experiment, enaminone–amidine adduct **1** and 4-chlorophenacyl bromide **2a** were reacted in a mixture of solvent THF/ACN (1:1) at room temperature in the presence of DBU for 2–3 h. The progress of the reaction was monitored by TLC. The structure of the compound was assigned with the help of ^{1}H NMR, ^{13}C NMR and Mass spectrometry.[18]

A plausible reaction mechanism is shown in the Scheme 3. The reaction of enaminone–amidine adduct **1** with phenacyl bromide **2** in which the nucleophilic double bond of adduct attacks the acidic methylene group due to the N-alkylation to give the intermediate **10**. In the next step, an acidic proton of the methylene group is abstracted by the base to produce carbanion **11**. The most important step of this new method is the cyclization, which occurs between the newly generated carbanion at the α-position of the carbonyl group and an imine carbon to which the electron pulling quaternary nitrogen is attached. This carbanion then attacks the electrophilic imine carbon of enaminone to produce an intramolecular 5-*exo* trig cyclization to **12** followed by elimination of the pyrrolidine resulting into the formation of 5-ketoaryl-2-aminopyrroles (**3a**–**h**). A similar selective cyclization to produce imidazoles by the reaction of guanidines with phenacyl bromides have already been reported in the literature.[14] The same mechanism is followed in the case of benzyl halide/hetero alkyl halide instead of phenacyl halide resulting in 5-aryl/heteroaryl-2-aminopyrroles (**5a**–**h**).[17]

In conclusion, we have developed a novel synthesis of 5-substituted-2-aminopyrrole using enaminone–amidine adduct with phenacyl bromides, benzyl halides, and hetero alkyl halides through an intramolecular 5-*exo* trig cyclization in good to excellent yields. The advantage of this method is its mild conditions and the product can be isolated with good purity. This approach could be useful for the generation of compound libraries of pyrroles scaffold with diverse substitutions for biological screenings. The mild reaction condition of the present process makes it an interesting approach. Furthermore the presence of an amino group in the pyrroles makes them biologically important synthetic intermediates for the synthesis of further nitrogen containing other heterocyclic compounds.

Acknowledgments

We gratefully acknowledge the financial support for this work from B.V. Patel PERD centre. We thank Professor H. Padh and C.J. Shishoo, Directors of B.V. Patel PERD centre, for their constant encouragement and support. H.B.J. thanks PERD Centre for the doctoral fellowship and Hemant Gadpe (Cadila Pharmaceuticals) for NMR analysis.

References and notes

1. (a) Vicek, A. V., Jr. *Chemtracts: Org. Chem.* **1996**, *9*, 322; (b) Ogoshi, H.; Kuroda, Y.; Mizutani, T.; Hayashi, T. *Pure Appl. Chem.* **1996**, *68*, 14112; (c) Gribble, G. W. In *Comprehensive heterocyclic chemistry II*; Katritzky, A. R., Rees, C. W., Scriven, E. F. V., Eds.; Elsevier: Oxford, UK, 1996; p 207. Vol. 2.
2. (a) 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; (b) Novak, P.; Muller, K.; Santhanam, K. S. V.; Haas, O. *Chem. Rev.* **1997**, *97*, 207.
3. (a) Su, S.; Porco, J. A., Jr. *J. Am. Chem. Soc.* **2007**, *129*, 7744; (b) Shindo, M.; Yoshimura, Y.; Hayashi, M.; Soejima, H.; Yoshikawa, T.; Matsumoto, K.; Shishido, K. *Org. Lett.* **2007**, *9*, 1963; (c) Wang, K.; Domling, A. *Chem. Biol. Drug Des.* **2010**, *76*, 277. and references cited in this Letter.
4. Wang, K.; Domling, A. *Chem. Biol. Drug Des.* **2010**, *76*, 277.
5. Fontaine, P.; Masson, G.; Zhu, J. *Org. Lett.* **2009**, *11*, 1555.
6. Nair, V.; Vinod, A. U.; Rajesh, C. *J. Org. Chem.* **2001**, *66*, 4427.
7. Shaabani, A.; Teimouri, M. B.; Arab-Ameri, S. *Tetrahedron Lett.* **2004**, *45*, 8409.

8. El-assar, A. Z. A.; El-khair, A. A. *Tetrahedron* **2003**, *59*, 8463.
9. (a) Braibante, M. E. F.; Braibante, H. S.; Missio, L.; Andricopula, A. *Synthesis* **1994**, 898; (b) Mukhanova, Y. L.; Alekscyeva, L. M.; Kuleshova, Y. F.; Sheinker; Yu, N.; Granik, V. G.; Khim, V. G. *Khim. Farm. Zh.* **1993**, *27*, 60.
10. (a) Missio, L. J.; Braibante, H. S.; Braibante, M. E. F. *J. Heterocycl. Chem.* **1996**, *37*, 1219; (b) Bejan, E.; Haddou, H. A.; Daran, J. C.; Balanoine, G. G. A. *Synthesis* **1996**, 1012.
11. Tsai, A. I.; Chuang, C. P. *Tetrahedron* **2006**, *62*, 2235.
12. Pillai, A. D.; Rathod, P. D.; Franklin, P. X.; Padh, H.; Vasu, K. K.; Sudarsanam, V. *Bioorg. Med. Chem.* **2005**, *13*, 6685.
13. (a) Franklin, P. X.; Pillai, A. D.; Rathod, P. D.; Yerande, S.; Nivsarkar, M.; Padh, H.; Vasu, K. K.; Sudarsanam, V. *Eur. J. Med. Chem.* **2008**, *43*, 129.
14. (a) Kaila, J. C.; Baraiya, A. B.; Pandya, A. N.; Jalani, H. B.; Vasu, K. K.; Sudarsanam, V. *Tetrahedron Lett.* **2009**, *50*, 3955; (b) Kaila, J. C.; Baraiya, A. B.; Vasu, K. K.; Sudarsanam, V. *Tetrahedron Lett.* **2008**, *49*, 7220.
15. Jalani, H. B.; Kaila, J. C.; Baraiya, A. B.; Pandya, A. N.; Vasu, K. K.; Sudarsanam, V. *Tetrahedron Lett.* **2010**, *51*, 5686.
16. *General procedure for the synthesis of enaminone–amidine adduct* (**1**)*:* To a stirred solution of cyanamide (6.0 mmol) in THF (50 mL), para toluene sulphonic acid (0.3 mmol) was added and allowed to stir for half an hour at room temperature. To this, a solution of enamino-ketone (6.0 mmol) in THF (10 mL) was added within half an hour. The reaction was allowed to stir for 3–4 h and the progress of reaction was monitored by TLC (ethyl acetate/hexane 2:8). The completion of reaction was indicated by the formation of white solid. This solid was then filtered and washed with hexane (2 × 10 mL). This solid was air dried and used for the next step. Chemical formula: $C_{10}H_{17}N_3O$; off white solid; Yield: 59%; mp: 184–186 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 2.15 (s, 3H, CH_3), 2.16 (s, 3H, CH_3), 3.32 (t, 2H, CH_2), 3.47 (t, 2H, CH_2), 5.42 (s, 2H, NH_2), 11.65 (s, 1H, *NH*); ^{13}C NMR (300 MHz, DMSO-d_6): δ = 19.9, 28.7, 29.3, 47.7, 96.2, 157.1, 159.7, 196.8; mol. wt: 195.26; Found (LCMS): 196.1.
17. *General procedure for the synthesis of 2-aminopyrroles* (**3** and **5**)*:* To a stirred suspension of enaminone–amidine adduct (4.0 mmol) in a solvent mixture of ACN + THF (1:1) (30 mL), DBU (6.0 mmol) was added slowly at room temperature. Clear solution was observed. Then a solution of phenacyl bromide or benzyl halide or hetero alkyl halide (4.0 mmol) in 10 mL of THF was added within half an hour. Progress of the reaction was monitored by TLC using ethyl acetate/hexane (2:8). The reaction was then allowed to maintain for 2–3 h. After completion of reaction, silica gel was added to the reaction mixture and concentrated on rotavapor. The material was purified by column chromatography using ethyl acetate/methanol (85:15) as eluting phase.
18. *Analytical data of 1-(2-amino-5-(4-chlorobenzoyl)-4-methyl-1H-pyrrol-3-yl) ethanone (**3a**).*Chemical formula: $C_{14}H_{13}ClN_2O_2$; light gray solid; yield: 89%; mp: 142–144 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ = 8.09–8.06 (d, *J* = 8.7 Hz, 2H), 7.68–7.65 (d, *J* = 8.7 Hz, 2H), 6.35 (s, 1H, *NH*), 5.44 (s, 2H, NH_2), 2.24 (s, 3H), 2.229 (s, 3H); ^{13}C NMR (300 MHz, DMSO-d_6): δ = 192.3, 174.6, 159.6, 158.1, 156.1, 139.0, 133.1, 130.0, 129.0, 105.3, 24.6, 19.6; mol. wt: 276.72; Found (LCMS): 277.8 and 278.8.
19. *Analytical data of 1-(2-amino-4-methyl-5-(4-nitrophenyl)-1H-pyrrol-3-yl)ethanone (**5a**).* Chemical formula: $C_{13}H_{13}N_3O_3$; buff solid; yield: 79%; mp: 205–208 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ = 8.22–8.19 (d, *J* = 8.7 Hz, 2H), 7.42–7.39 (d, *J* = 8.7 Hz, 2H), 6.36 (s, 1H, *NH*), 5.32 (s, 2H, NH_2), 2.25 (s, 3H), 2.25 (s, 3H); ^{13}C NMR (300 MHz, DMSO-d_6): δ = 174.6, 157.7, 156.4, 146.7, 144.2, 133.6, 127.6, 123.8, 105.7, 24.6, 19.5; mol. wt: 259.26; Found (LCMS): 260.4.
20. *Analytical data of 1-(2-amino-5-(6-chloropyridin-2-yl)-4-methyl-1H-pyrrol-3-yl) ethanone* (**5f**). Chemical formula: $C_{12}H_{12}ClN_3O$; pinkish gray solid; yield: 65%; mp: 97–100 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ = 8.33–8.32 (d, *J* = 2.4 Hz, 1H), 7.68–7.65 (m, 1H), 7.49–7.46 (d, *J* = 8.4 Hz, 1H), 6.34 (s, 1H, *NH*), 5.19 (s, 2H, NH_2), 2.32 (s, 3H), 2.22 (s, 3H); ^{13}C NMR (300 MHz, DMSO-d_6): δ = 174.4, 159.6, 157.9, 156.3, 149.2, 148.6, 138.3, 131.8, 124.3, 105.8, 24.6, 19.6; mol. wt: 249.70; Found (LCMS): 250.7.