Iron(III) promoted oxidative annulation of benzylic C-H bonds in (α-amino)arylacetic acids for synthesis of 4-aryl pyrrolo[1,2-*a*]quinoxalines

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Abstract:

Using amino acids for synthesis of heterocycles is a synthetically promising field. However, developing the practical methods for transformations of amino acids into heterocycles is still challenging. Given that alpha amino acids are abundant or easily prepared, herein we report a method for annulation of benzylic C-H bonds in derivatives of 2-phenylglycine with 1-(2-nitroaryl) pyrroles. The reactions proceeded well in the presence of iron(III) acetylacetonate catalyst and potassium carbonate base. Scope of pyrrolo[1,2-*a*]quinoxalines was studied. Regardless of electronic properties of substituents, the pyrrolo[1,2-*a*]quinoxaline derivatives were successfully isolated, as yields varied from 42% to 52%. Pyrrolo[1,2-*a*]quinoxalines substituted with heterocycles at C4 positions as pyridine and thiophene were competent substrates. Reaction mechanism was proposed to start with a decarboxylative/deaminative sequence of 2-phenylglycine to afford benzaldehyde. The iron catalyst was presumed to facilitate the reduction of 1-(2-nitroaryl)pyrroles to furnish the corresponding aniline. Imine condensation followed by cyclisation and oxidation would yield the pyrrolo[1,2-*a*]quinoxaline. Our method would offer a convenient tactic to transform abundant alpha amino acids into synthetically useful heterocycles.

Keywords: **amino acid, annulation, iron, redox, 1-(2-nitroaryl)pyrroles.**

Classification numbers: **2.1, 2.2**

1. Introduction

Pyrrolo[1,2-*a*]quinoxaline is a valuable scaffold ubiquitously utilised in biological studies and in synthesis of functional materials [1-3]. Thus, numerous methods have been developed, specifically those for the synthesis of 4-aryl pyrrolo[1,2-*a*] quinoxalines. For example, the synthesis of fused *N*,*N*-heterocycles from 1-(2-aminoaryl)pyrroles have been extensively reported. Recently, using more upstream starting materials such as 1-(2-nitroaryl)pyrroles has witnessed substantial emergence. Annulation of those nitroarenes with a benzyl synthon including benzyl amines [4], arylacetic acids [5], aromatic aldehydes [6], alcohols [7], and 1,2-diols [8] to yield substituted pyrrolo[1,2-*a*] quinoxalines is also known. Some methods feature the benefit of using metal-free tactics [4, 7]. Meanwhile, transition metal complexes have been utilised to convert arylacetic acids and 1,2-diols to the corresponding pyrrolo[1,2-*a*]quinoxalines [5, 8]. Notably, coupling of 1-(2-nitroaryl)pyrroles with amino acids such as derivatives of phenylglycine has also been reported.

The oxidation of benzylic C-H bonds in phenylglycine derivatives for the synthesis of *N*-heterocycles has been precedented. One stand-alone method was presented by M. Kumar, et al. (2015) [9], where the annulation of 2-nitrobenzonitriles and phenylglycines successfully yielded quinazolinones. In this report, the authors proposed the redox conversion of phenylglycine and 2-nitrobenzonitrile to benzaldehyde and 2-aminobenzonitrile, respectively, in the presence of an iron(III) catalyst and potassium carbonate base. We envisaged that those redox transformations could be leveraged to couple 1-(2-nitroaryl)pyrroles with phenylglycines. Herein, we report a method affording 4-aryl pyrrolo[1,2-*a*]quinoxalines from 1-(2-nitroaryl)pyrroles and phenylglycines as the benzyl equivalence. The reactions utilised an $Fe(acac)_3$ (acac = acetylacetonate) catalyst and K_2CO_3 base, while showing good tolerance of functional groups.

2. Experiments

Organic chemicals and metal salts were commercially obtained from Acros, Aldrich, Energy chemicals, and Bidepharm, and were used as received unless otherwise noted. The synthesis of 1-(2-nitroaryl)pyrroles followed known procedures reported in previous studies [10, 11]. A typical reaction was run in an 8-ml vial equipped with a magnetic stir bar. During the study of reaction conditions, yields were Gas chromatography (GC) yields obtained from a Shimadzu GC2010-Plus equipped with a flame ionisation detector (FID) and an SPB-5 column, with diphenyl ether as the internal standard. Nuclear magnetic resonance spectra (^{1}H-NMR and ^{13}C-NMR) were recorded on Bruker AV 500 or 600 spectrometers.

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Characterization of the annulation products was as follows:

4-Phenyl pyrrolo[1,2-*a*]quinoxaline (**3aa**): ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 8.10 (dd, J=7.8, 1.5 Hz, 1H), 8.02-7.99 (m, 3H), 7.88 (dd, J=7.9, 1.4 Hz, 1H), 7.57-7.50 (m, 4H), 7.45 (dd, J=7.8, 1.4 Hz, 1H), 7.00 (dd, J=4.2, 1.3 Hz, 1H), 6.89 (dd, J=4.1, 2.7 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$, ppm) δ 154.4, 138.4, 136.5, 130.2, 129.8, 128.8, 127.5, 127.3, 125.5, 125.3, 114.8, 114.1, 113.9, and 108.9.

4-(3-(Trifluoromethyl)phenyl)pyrrolo[1,2-*a*]quinoxaline (**3ab**): ^{1}H NMR (600 MHz, $CDCl_3$, ppm) δ 8.30 (s, 1H), 8.21 (d, J=7.7 Hz, 1H), 8.05 (dd, J=8.0, 1.4 Hz, 1H), 8.03 (dd, J=2.7, 1.2 Hz, 1H), 7.90 (dd, J=8.2, 1.2 Hz, 1H), 7.79 (d, J=7.8 Hz, 1H), 7.68 (t, J=7.8 Hz, 1H), 7.58-7.53 (m, 1H), 7.51-7.46 (m, 1H), 6.96 (dd, J=4.0, 1.2 Hz, 1H), 6.93 (dd, J=4.0, 2.7 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$, ppm) δ 152.9, 139.3, 136.2, 132.0, 131.2 (q, J=32.3 Hz), 130.5, 129.3, 128.1, 127.3, 126.6 (q, J=3.4 Hz), 125.7 (q, J=3.8 Hz), 125.6, 125.2, 124.2 (q, J=270.7 Hz), 115.1, 114.4, 113.9, and 108.5.

7-Methyl-4-(naphthalen-1-yl)pyrrolo[1,2-*a*]quinoxaline (**3bc**): ^{1}H NMR (600 MHz, $CDCl_3$, ppm) δ 8.02-7.98 (m, 3H), 7.94 (d, J=8.2 Hz, 1H), 7.89 (d, J=0.7 Hz, 1H), 7.84 (d, J=8.4 Hz, 1H), 7.80 (dd, J=7.0, 1.1 Hz, 1H), 7.61 (dd, J=8.2, 7.1 Hz, 1H), 7.51 (dd, J=8.0, 6.8, 1.0 Hz, 1H), 7.43-7.38 (m, 2H), 6.80 (dd, J=4.0, 2.7 Hz, 1H), 6.55 (dd, J=4.0, 1.3 Hz, 1H), 2.53 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$, ppm) δ 154.8, 136.2, 135.6, 135.3, 134.1, 131.7, 130.2, 129.6, 129.0, 128.4, 127.1, 127.0, 126.5, 126.2, 125.9, 125.3, 125.2, 114.5, 113.8, 113.6, 108.8, and 21.3.

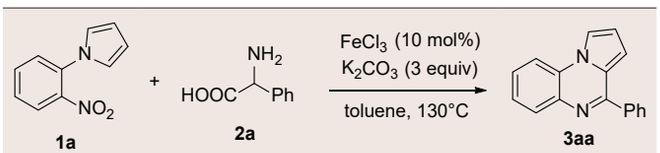
7-Methyl-4-(thiophen-2-yl)pyrrolo[1,2-*a*]quinoxaline (**3bd**): ^{1}H NMR (600 MHz, $CDCl_3$, ppm) δ 7.95 (dd, J=3.7, 1.1 Hz, 1H), 7.93 (dd, J=2.7, 1.3 Hz, 1H), 7.80 (d, J=0.7 Hz, 1H), 7.72 (d, J=8.3 Hz, 1H), 7.53 (dd, J=5.1, 1.1 Hz, 1H), 7.29 (ddd, J=8.3, 1.9, 0.5 Hz, 1H), 7.25 (dd, J=4.1, 1.3 Hz, 1H), 7.22 (dd, J=5.1, 3.7 Hz, 1H), 6.90 (dd, J=4.1, 2.7 Hz, 1H), 2.49 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$, ppm) δ 147.4, 142.7, 135.9, 135.2, 129.8, 128.7, 128.2, 127.8, 125.0, 124.1, 114.6, 113.9, 113.4, 107.7, 21.2.

7-Methyl-4-(pyridin-2-yl)pyrrolo[1,2-*a*]quinoxaline (**3be**): ^{1}H NMR (600 MHz, $CDCl_3$, ppm) δ 8.80 (ddd, J=4.8, 1.8, 0.9 Hz, 1H), 8.41 (dt, J=7.9, 1.0 Hz, 1H), 7.96 (dd, J=2.7, 1.3 Hz, 1H), 7.88 (td, J=7.8, 1.8 Hz, 1H), 7.86 (d, J=0.7 Hz, 1H), 7.77 (d, J=8.3 Hz, 1H), 7.73 (dd, J=4.0, 1.3 Hz, 1H), 7.40 (ddd, J=7.5, 4.8, 1.2 Hz, 1H), 7.34 (ddd, J=8.4, 1.9, 0.4 Hz, 1H), 6.93 (dd, J=4.0, 2.7 Hz, 1H), 2.51 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$, ppm) δ 156.7, 151.3, 149.0, 136.7, 135.8, 135.0, 130.3, 129.3, 125.7, 124.8, 124.3, 123.5, 114.3, 114.2, 113.5, 110.4, 21.2.

3. Results and discussion

Our study started with the annulation of 1-(2-nitrophenyl)-1*H*-pyrrole (**1a**) and 2-phenylglycine (**2a**) to yield 4-phenyl pyrrolo[1,2-*a*]quinoxaline (**3aa**). Results of the brief optimisation are presented in Table 1. The first condition was nearly identical to that reported by M. Kumar, et al. (2015) [9]. The annulation product was obtained in 45% (GC) yield (entry 1). Anions of iron salts were pivotal to successful annulation (entries 2 and 3). The results showed that $Fe(acac)_3$ gave the most reasonable yield of **3aa**. Potassium carbonate was superior to salts of other alkali metals (entries 4 and 5). The use of polar aprotic solvents such as dimethylformamide (DMF) and dimethyl sulfoxide (DMSO) was not suitable for the annulation (entries 6 and 7). Those results agreed with those previously using potassium carbonate for decarboxylation and deamination of phenylglycine [9, 12]. Lastly, omitting the presence of iron salt gave trace amounts of **3aa** (entry 8), confirming the crucial role of the iron(III) salt. It should be noted that unreacting 1-(2-nitrophenyl)-1*H*-pyrrole 1a, together with the reduced product 1-(2-aminophenyl)pyrrole could be recovered after the reactions.

Table 1. Study of reaction conditions.



1a 2a 3aa

Entry	Changes from standard conditions[a]	Yield of 3aa (%)
1	None	45
2	$Fe(acac)_3$ instead of $FeCl_3$	57, 52[b]
3	$Fe(NO_3)_3.9H_2O$ instead of $FeCl_3$	15
4	Entry 2, Na_2CO_3 instead of K_2CO_3	50
5	Entry 2, Cs_2CO_3 instead of K_2CO_3	55
6	Entry 2, DMF instead of toluene	32
7	Entry 2, DMSO instead of toluene	28
8	No iron salt	trace

[a]: standard conditions: 1a (0.1 mmol), 2a (0.2 mmol), $FeCl_3$ (0.01 mmol), K_2CO_3 (0.3 mmol), toluene (0.5 ml), 130°C, under air, 24 hours; yields are GC yields; [b]: isolated yield.

With the reaction conditions in hand, we next investigated the scope of (α-amino)arylacetic acids. The results are shown in Fig. 1. Notably, the use of electron-poor phenylglycines still afforded pyrrolo[1,2-*a*]quinoxaline in a moderate yield (**3ab**). This result somewhat indicated that the decarboxylation and deamination was slowed down by electron-poor phenylglycines [9]. Sterically hindered phenylglycine was compatible with reaction conditions (**3bc**). (α-amino)heteroarylacetic acids were competent substrates (**3bd**, **3be**).

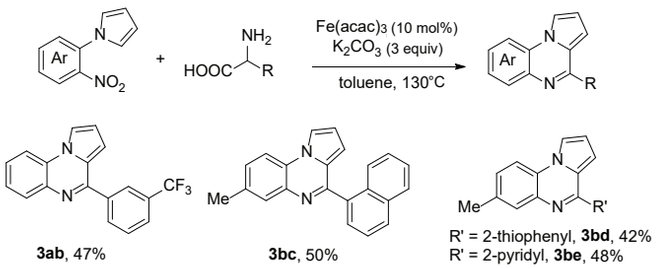


Fig. 1. Scope of (α-amino)arylacetic acids. Reaction conditions: 1-(2-nitroaryl)-1H-pyrroles (0.1 mmol), (α-amino)arylacetic acid (0.2 mmol), $Fe(acac)_3$ (0.01 mmol), K_2CO_3 (0.3 mmol), toluene (0.5 ml), 130°C, 24 hours. Yields are isolated yields.

At this moment, we hypothesised a plausible mechanism as that shown in Fig. 2 [9]. 2-Phenylglycine (2a) would undergo a decarboxylative/deaminative sequence to afford benzaldehyde 4 [13, 14]. Consequently, phenylglycine could be considered as the benzaldehyde equivalence in a Pictet-Spengler-type annulation. Ammonia obtained from the extrusion of 2a was likely involved in the reduction of the nitro group in 1-(2-nitrophenyl)-1H-pyrrole (1a), yielding the corresponding aniline 5. Traditional imine condensation of 4 and 5 would yield the adduct (6) followed by cyclization and hydrogen transfer to afford 7. Oxidation of 7 by 1a in the presence of $FeCl_3$ catalyst would furnish the desired product (**3aa**). Identical to the report of M. Kumar, et al. (2015) [9], we believe that iron salts were crucial for the overall condensation, although assignment of oxidation states at elementary steps (2a→4 or 1a→5) was not clear momentarily.

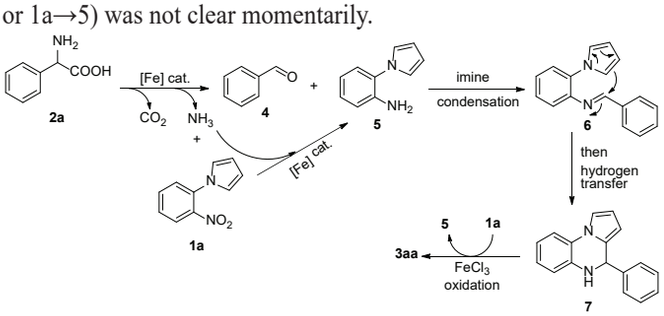


Fig. 2. Plausible mechanism.

4. Conclusions

To conclude, we developed a method for oxidative annulation of C-H bonds in (α-amino)arylacetic acids with 1-(2-nitroaryl)-1H-pyrroles. The reactions proceeded in the presence of an iron(III) acetylacetonate catalyst and a potassium carbonate base. Reaction conditions were tolerant of electron-poor and hetero (α-amino) arylacetic acids. The proposed mechanism involved two key steps: degradation of phenylglycine to afford ammonia followed by the reduction of 1-(2-nitrophenyl)-1*H*-pyrrole.

CRediT author statement

Tuan Hoang Ho: Methodology, Data analysis; Tung Thanh Nguyen: Conceptualisation, Data analysis, Writing, Editing; Tran Hoang Bao Ngo: Methodology; Nam Thanh Son Phan: Conceptualisation, Formal analysis, Writing, Reviewing.

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COMPETING INTERESTS

The authors declare that there is no conflict of interest regarding the publication of this article.

REFERENCES

[1] A.A. Kalinin, V. A. Mamedov (2011), "Pyrrolo[1,2-*a*]quinoxalines based on pyrroles (Review)", *Chem. Heterocycl. Compd.*, **12**, pp.1763-1787, DOI: 10.1007/s10593-011-0688-1 (in Russian).

[2] A.A. Kalinin, L.N. Islamova, G.M. Fazleeva (2019), "New achievements in the synthesis of pyrrolo[1,2-*a*]quinoxalines", *Chem. Heterocycl. Compd.*, **55(7)**, pp.584-597, DOI: 10.1007/s10593-019-02501-w.

[3] H.X. Le, T.T. Nguyen (2022), "Recent examples in the synthesis and functionalization of C-H bonds in pyrrolo/indolo [1,2-*a*]quinoxalines", *Chemistry Select*, **7(14)**, DOI: 10.1002/slct.202200166.

[4] Q. Sun, L. Liu, Y. Yang, et al. (2019), "Unexpected activated carbon-catalyzed pyrrolo[1,2-*a*]quinoxalines synthesis in water", *Chin. Chem. Lett*, **30(7)**, pp.1379-1382, DOI: 10.1016/j.cclet.2019.04.007.

[5] T.A. To, C.T. Nguyen, M.H.P Tran, et al.(2019), "A new pathway to pyrrolo[1,2-*a*]quinoxalines via solvent-free one-pot strategy utilizing FeMoSe nanosheets as efficient recyclable synergistic catalyst", *Journal of Catalysis*, **377**, pp.163-173, DOI: 10.1016/j.jcat.2019.07.008.

[6] S.A. Trujillo, D. Peña-Solórzano, O.R. Bejarano, et al. (2020), "Tin(II) chloride dihydrate/choline chloride deep eutectic solvent: Redox properties in the fast synthesis of *N*-arylacetamides and indolo(pyrrolo)[1,2-*a*]quinoxalines", *RSC Adv.*, **10**, pp.40552-40561, DOI: 10.1039/D0RA06871.

[7] T.H. Ho, N.T.A. Phan, T.T.C. Ho, et al. (2021), "Elemental sulfur mediated synthesis of pyrrolo[1,2-*a*]quinoxalines from 1-(2-nitroaryl)pyrroles", *Synthesis*, **53(21)**, pp.4117-4123, DOI: 10.1055/a-1534-0466.

[8] R. Hernández-Ruiz, R. Rubio-Presa, S. Suárez-Pantiga, et al. (2021), "Mo-catalyzed one-pot synthesis of *N*-polyheterocycles from nitroarenes and glycols with recycling of the waste reduction byproduct. Substituent-tuned photophysical properties", *Chem. Eur. J.*, **27(54)**, pp.13613-13623, DOI: 10.1002/chem.202102000.

[9] M. Kumar, S. Sharma, V. Bhatt, et al. (2015), "Iron(III) chloride-catalyzed decarboxylative-deaminative functionalization of phenylglycine: A tandem synthesis of quinazolinones and benzimidazoles", *Adv. Synth. Catal.*, **357(13)**, pp.2862-2868, DOI: 10.1002/adsc.201500335.

[10] C. Xie, L. Feng, W. Li, et al. (2016), "Efficient synthesis of pyrrolo[1,2-*a*] quinoxalines catalyzed by a Brønsted acid through cleavage of C–C bonds", *Org. Biomol. Chem.*, **36(14)**, pp.8529-8535, DOI: 10.1039/c6ob01401a.

[11] B. Budke, W. Tueckmantel, K. Miles, et al. (2019), "Optimization of drug candidates that inhibit the d-loop activity of RAD51", *Chem. Med. Chem.*, **14(10)**, pp.1031-1040, DOI: 10.1002/cmdc.201900075.

[12] L. Tang, Z. Yang, T. Sun, et al. (2018), "Unexpected decarboxylation-triggered *o*-hydroxyl-controlled redox condensation of phenylglycines with 2-nitrophenols in aqueous media", *Adv. Synth. Catal.*, **360(16)**, pp.3055-3062, DOI: 10.1002/adsc.201800586.

[13] H. Liu, F. Zhou, W. Luo, et al. (2017), "Application of α-amino acids for the transition-metal-free synthesis of pyrrolo[1,2-*a*]quinoxalines", *Org. Biomol. Chem.*, **34(15)**, pp.7157-7164.

[14] H. Liu, T. Duan, Z. Zhang, et al. (2015), "One-pot synthesis of pyrrolo[1,2-*a*] quinoxaline derivatives via a copper-catalyzed aerobic oxidative domino reaction", *Org. Lett.*, **17(12)**, pp.2932-2935, DOI: 10.1021/acs.orglett.5b01167.