Three-component reactions of aromatic amines, 1,3-dicarbonyl compounds, and α-bromoacetaldehyde acetal to access *N*-(hetero)aryl-4,5-unsubstituted pyrroles

Wenbo Huang[1], Kaimei Wang[1], Ping Liu[2], Minghao Li[3], Shaoyong Ke[*1] and Yanlong Gu[*2,3]

Letter

Address:
[1]National Biopesticide Engineering Research Centre, Hubei Biopesticide Engineering Research Centre, Hubei Academy of Agricultural Sciences, 8 Nanhu Avenue, Hongshan District, Wuhan 430064, China, [2]School of Chemistry and Chemical Engineering, The Key Laboratory for Green Processing of Chemical Engineering of Xinjiang Bingtuan, Shihezi University, Shihezi City 832004, China and [3]Key laboratory of Material Chemistry for Energy Conversion and Storage, Ministry of Education, Hubei Key Laboratory of Material Chemistry and Service Failure, School of Chemistry and Chemical Engineering, Huazhong University of Science and Technology, 1037 Luoyu road, Hongshan District, Wuhan 430074, China

Email:
Shaoyong Ke[*] - shaoyong.ke@nberc.com; Yanlong Gu[*] - klgyl@hust.edu.cn

* Corresponding author

Abstract

N-(Hetero)aryl-4,5-unsubstituted pyrroles were synthesized from (hetero)arylamines, 1,3-dicarbonyl compounds, and α-bromo-acetaldehyde acetal by using aluminum(III) chloride as a Lewis acid catalyst through [1 + 2 + 2] annulation. This new versatile methodology provides a wide scope for the synthesis of different functional *N*-(hetero)aryl-4,5-unsubstituted pyrrole scaffolds, which can be further derived to access multisubstituted pyrrole-3-carboxamides. In the presence of 1.2 equiv of KI, a polysubstituted pyrazolo[3,4-*b*]pyridine derivative was also successfully synthesized.

Introduction

Among nitrogen-containing heterocycles, pyrroles have garnered significant attention in the literature because of their presence in various natural products [1-4] and pharmaceutically relevant drugs [5,6]. Accordingly, numerous synthetic methods to construct pyrrole skeletons were reported, including the classical Hantzsch [7,8] and the Paal–Knorr pyrrole syntheses

[9-11], which have been developed to harvest the pyrrole frameworks. In the past few years, the interest in developing new methods to synthesize this heterocyclic motif has rapidly grown; transition metal-catalyzed cyclization [12-14] and multicomponent reactions [15-18] are some of the commonly used approaches for the construction of pyrrole scaffolds. Additionally, the biocatalytic synthesis of substituted pyrroles was also developed [19]. Though sustained efforts have been achieved to develop efficient synthetic methods for the preparation of this structural motif [20-23], the development of cost-effective methods to access functionalized pyrrole skeletons has remained an ongoing challenge.

N-(Hetero)aryl-4,5-unsubstituted pyrroles are one of the most important types of pyrroles, which are frequently used as a core scaffold in pharmaceuticals (Figure 1) [24,25]. Therefore, many efforts have been paid to the synthesis of these privileged pyrroles. (Hetero)arylamines are readily available chemicals. The direct conversion of (hetero)arylamines into *N*-(hetero)aryl-4,5-unsubstituted pyrroles has a high intrinsic synthetic potential. At present, the transformations can generally be realized through the following three approaches (Scheme 1): (i) [1 + 1 + 3] annulation, in which (hetero)arylamines are reacted with a C_3 donor and a C_1 donor to construct pyrrole scaffolds. Kumar et al. [26] developed a proline-catalyzed Mannich reaction–cyclization sequence of succinaldehyde and an in situ-generated arylimine, in which the succinaldehyde contributes three carbon atoms to the pyrrole ring. α,β-Unsaturated aldehydes have also been used as the C_3 donor to construct pyrrole scaffolds [27,28]; (ii) [1 + 4] annulation, in which (hetero)arylamines are reacted with a C_4 donor to form the pyrrole ring; many functional molecules, such as bioderived furans [29], (*Z*)-enynols [30], 1-vinylpropargyl alcohols [31], doubly activated cyclopropanes [32], and enynals [33], can be used as C_4 counter reagents. The carbon-based 1,4-biselectrophiles, such as the 1,4-dicarbonyl compounds [34,35], γ-car-
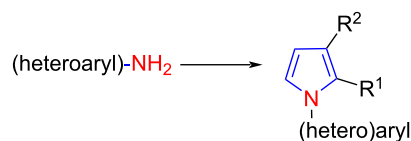
bonyl *tert*-butyl peroxides [36], and dihydrofurans [37] have also been reported to construct the pyrrole skeletons through this type of annulation; and (iii) [1 + 2 + 2] annulation, in which (hetero)arylamines are reacted with two different molecules, and each of them contributes two carbon atoms to construct a pyrrole ring [38-42]. Among these three approaches, the third is considered the most attractive route for *N*-(hetero)aryl-4,5-unsubstituted pyrrole synthesis. The reason is twofold: (i) the strategy uses easily available substrates and (ii) permits to synthesize pyrroles with a high potential of molecular diversity and complexity. However, to date, the productivity for creating molecular diversity and complexity has yet to be fully displayed. In addition, some of the reported approaches were established on the basis of using expensive and nonrecyclable homogeneous metal catalysts. To alleviate all these problems, herein, we used easily available α-bromoacetaldehyde acetal (**2a**) and a simple 1,3-dicarbonyl compound as a reagent couple to react with (hetero)arylamines. The established [1 + 2 + 2] annulation reaction provided a straightforward approach for accessing various *N*-(hetero)aryl-4,5-unsubstituted pyrroles, and some of the pyrrole products are not accessible with the methods reported hitherto.
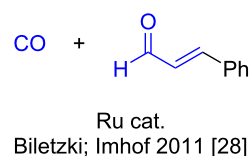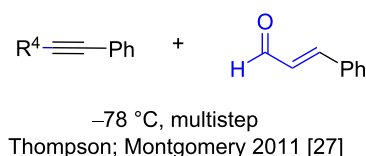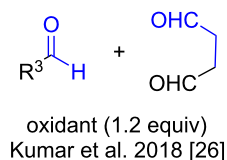
Results and Discussion

Initially, a mixture of aniline (**1a**), α-bromoacetaldehyde acetal (**2a**), and ethyl acetoacetate (**3a**) was treated under the conditions; the obtained results are listed in Table 1. The mixture was heated in 1,4-dioxane at 80 °C. No reaction occurred in the absence of the catalyst (Table 1, entry 1); however, in the presence of the strong Lewis acid Bi(OTf)$_3$, the expected product **4a** was obtained in 36% yield after 6 h of reaction (Table 1, entry 2). To our surprise, the *N*-aryl-4,5-unsubstituted pyrrole derivative **4a** was isolated in 80% yield when 10 mol % of AlCl$_3$ was used as the catalyst (Table 1, entry 3). FeCl$_3$ and NiCl$_2$ were also proven to catalyze this reaction, but the yield of **4a** was inferior to those obtained with AlCl$_3$ (Table 1, entries 4 and 5).
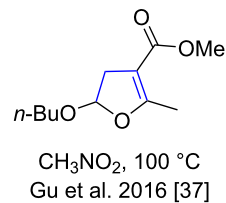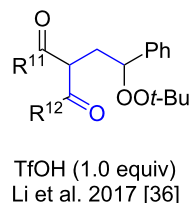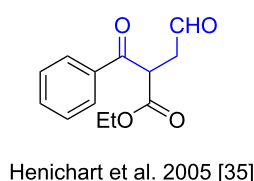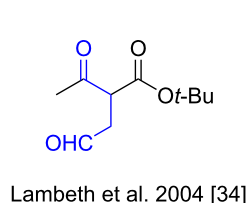

Figure 1: Representative biologically active *N*-(hetero)aryl-4,5-unsubstituted pyrrole scaffolds.
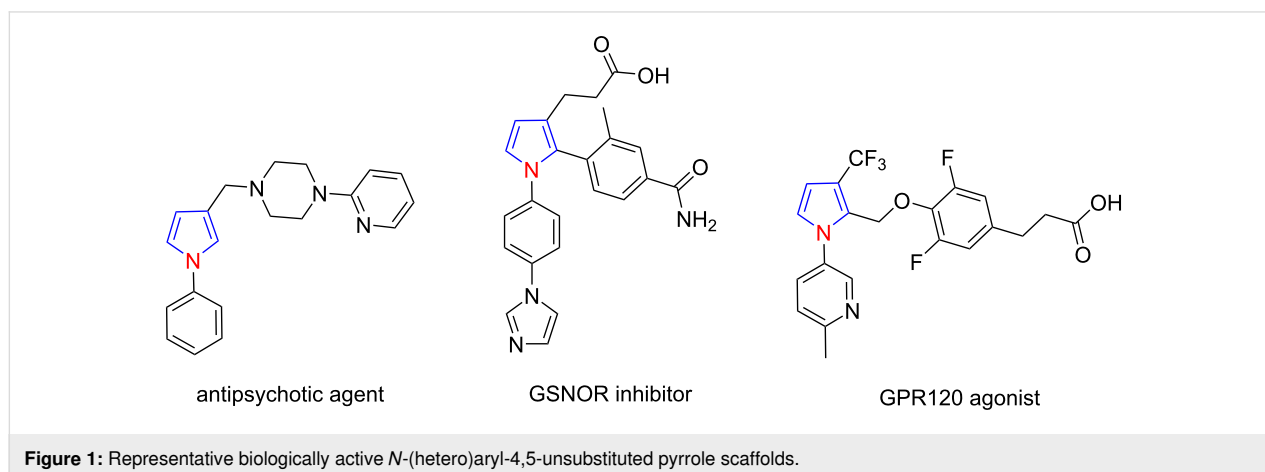
approaches to *N*-(heteroaryl)-4,5-unsubstituted pyrroles from (heteroaryl)amines:

(heteroaryl)-NH₂ ⟶

(hetero)aryl

[1 + 1 + 3] annulation:

oxidant (1.2 equiv)
Kumar et al. 2018 [26]

−78 °C, multistep
Thompson; Montgomery 2011 [27]

Ru cat.
Biletzki; Imhof 2011 [28]

[1 + 4] annulation:

150 °C
Cao et al. 2017 [29]

Ag–Au cat.
Liu et al. 2009 [30]

Ru cat., 100 °C
Haak et al. 2013 [31]

Fe cat. (0.5 equiv), 100 °C
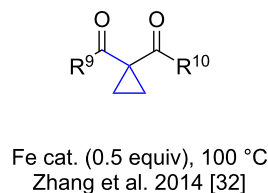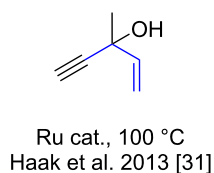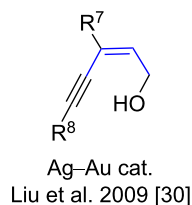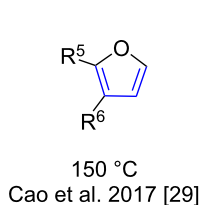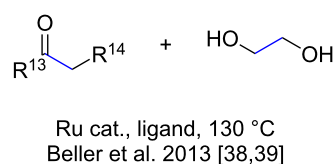Zhang et al. 2014 [32]

Ag cat.
Ding et al. 2018 [33]

Lambeth et al. 2004 [34]

Henichart et al. 2005 [35]

TfOH (1.0 equiv)
Li et al. 2017 [36]

CH₃NO₂, 100 °C
Gu et al. 2016 [37]

[1 + 2 + 2] annulation:

Ru cat., ligand, 130 °C
Beller et al. 2013 [38,39]

Ru cat., 130 °C
Chandrasekhar et al. 2014 [40]

Cu–NHC cat., 140 °C
Dang; Seayad 2017 [41]

two steps, 1 example
Zhang et al. 2018 [42]

this work:

AlCl₃ cat., 80 °C

Scheme 1: Typical routes to *N*-(heteroaryl)-4,5-unsubstituted pyrroles.

p-Toluenesulfonic acid (PTSA), a strong Brønsted acid, also exhibited a promising catalytic ability, and the yield of **4a** reached 73% (Table 1, entry 6). When HOAc was used, only unreacted starting materials were recovered (Table, entry 7). The effect of the solvent on the model reaction was also examined. Anhydrous ethanol, acetonitrile, toluene, and DMSO did not bring any improvement with respect to the yield of **4a**

(Table 1, entries 8–11). The decrease of the catalyst loading from 10 to 5 mol % resulted in a slight decrease of the reaction yield (Table 1, entry 12). Further investigations revealed that the reaction was also affected by the temperature and time; a yield of only 51% was obtained at 50 °C (Table 1, entries 13 and 14). Therefore, the optimized reaction conditions were confirmed as the following: 10 mol % of AlCl₃ as a catalyst, 1,4-

Table 1: Optimization of the conditions for the reaction between **1a**, **2a**, and **3a**.[a]
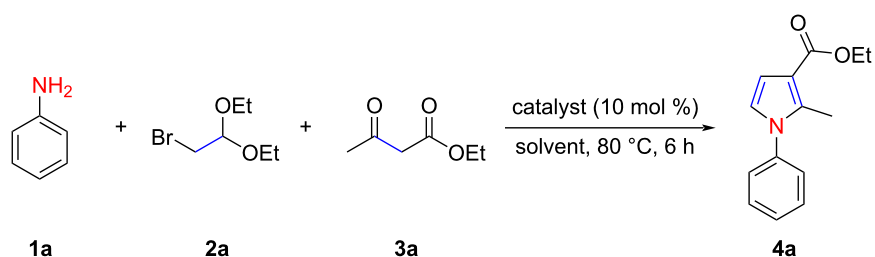
| entry	catalyst	solvent	yield (%)[b]
1	—	1,4-dioxane	0
2	Bi(OTf)$_3$	1,4-dioxane	36
3	AlCl$_3$	1,4-dioxane	80
4	FeCl$_3$	1,4-dioxane	44
5	NiCl$_2$	1,4-dioxane	21
6	PTSA	1,4-dioxane	73
7	HOAc	1,4-dioxane	trace
8	AlCl$_3$	EtOH	31
9	AlCl$_3$	MeCN	50
10	AlCl$_3$	PhMe	27
11	AlCl$_3$	DMSO	62
12[c]	AlCl$_3$	1,4-dioxane	55
13[d]	AlCl$_3$	1,4-dioxane	51
14[e]	AlCl$_3$	1,4-dioxane	40
15[f]	AlCl$_3$	1,4-dioxane	72

[a]**1a**: 0.5 mmol, **2a**: 0.6 mmol, **3a**: 0.6 mmol, catalyst: 0.05 mmol, solvent: 1 mL, 80 °C, 6 h. [b]Isolated yield, calculated with respect to **1a**.
[c]AlCl$_3$: 0.025 mmol. [d]50 °C. [e]2 h. [f]10 mmol-scale reaction.

dioxane as a solvent, 6 h, and 80 °C. It is worth noting that the reaction can be effectively scaled up with similar efficiency. In a gram-scale synthesis of **4a**, the corresponding pyrrole product was obtained in 72% yield (Table 1, entry 15).

The scope of this synthetic protocol for pyrroles was then investigated under the optimized reaction conditions. The substrate scope of the 1,3-dicarbonyl component was first examined (Scheme 2). Acetylacetone reacted smoothly with **1a** and **2a** to form **4b** in 52% yield. 1,3-Dicarbonyl compounds bearing an ester group readily participated in this reaction, affording the desired pyrroles **4c–e** in moderate to good yield. Notably, methyl 2-methyl-1-phenyl-1*H*-pyrrole-3-carboxylate (**4c**) is a key intermediate in the synthesis of a TRPM8 antagonist [43]. The substrate scope of the aromatic amine component was then examined, and the remarkable efficiency of our pyrrole synthesis was reflected by the tolerance of a broad range of functional groups attached to the aromatic amine. For example, anilines bearing methyl (in **4f**), phenyl (in **4g**), and halo functionalities (in **4h–m**) were readily compatible with the AlCl$_3$ and 1,4-dioxane system. In these cases, the pyrrole products were isolat-

ed in moderate to good yield. The presence of an electron-donating group in the phenyl ring facilitated the progress of the reaction to some extent, resulting in **4n**. Anilines with electron-withdrawing groups, such as an acetyl or carboxy group, can also be used in the reaction, but the yields obtained for **4o** and **4p** were slightly inferior. Gratifyingly, a 3,5-dichloro-4-(1,1,2,2-tetrafluoroethoxy)aniline also participated smoothly in this reaction, and the expected product **4q** can be obtained in 75% yield. This fluorinated substituent on the aniline ring has been identified as the key precursor to access the insect-growth regulators [44]. It is noteworthy that the sulfonamide group persisted during this transformation, and the desired pyrrole product **4r** could be obtained in 69% yield. A high yield was also obtained when the phenyl group was replaced with a naphthyl group in **4s**. Subsequently, aliphatic primary amines and ammonia, such as benzylamine and *N*-butylamine, were also examined as nitrogen donors; however, no desired product was detected.

Then, we attempted to synthesize pharmaceutically active N-heterocyclic pyrrole derivatives with the aid of this three-

Scheme 2: Substrate scope of the pyrrole synthesis.
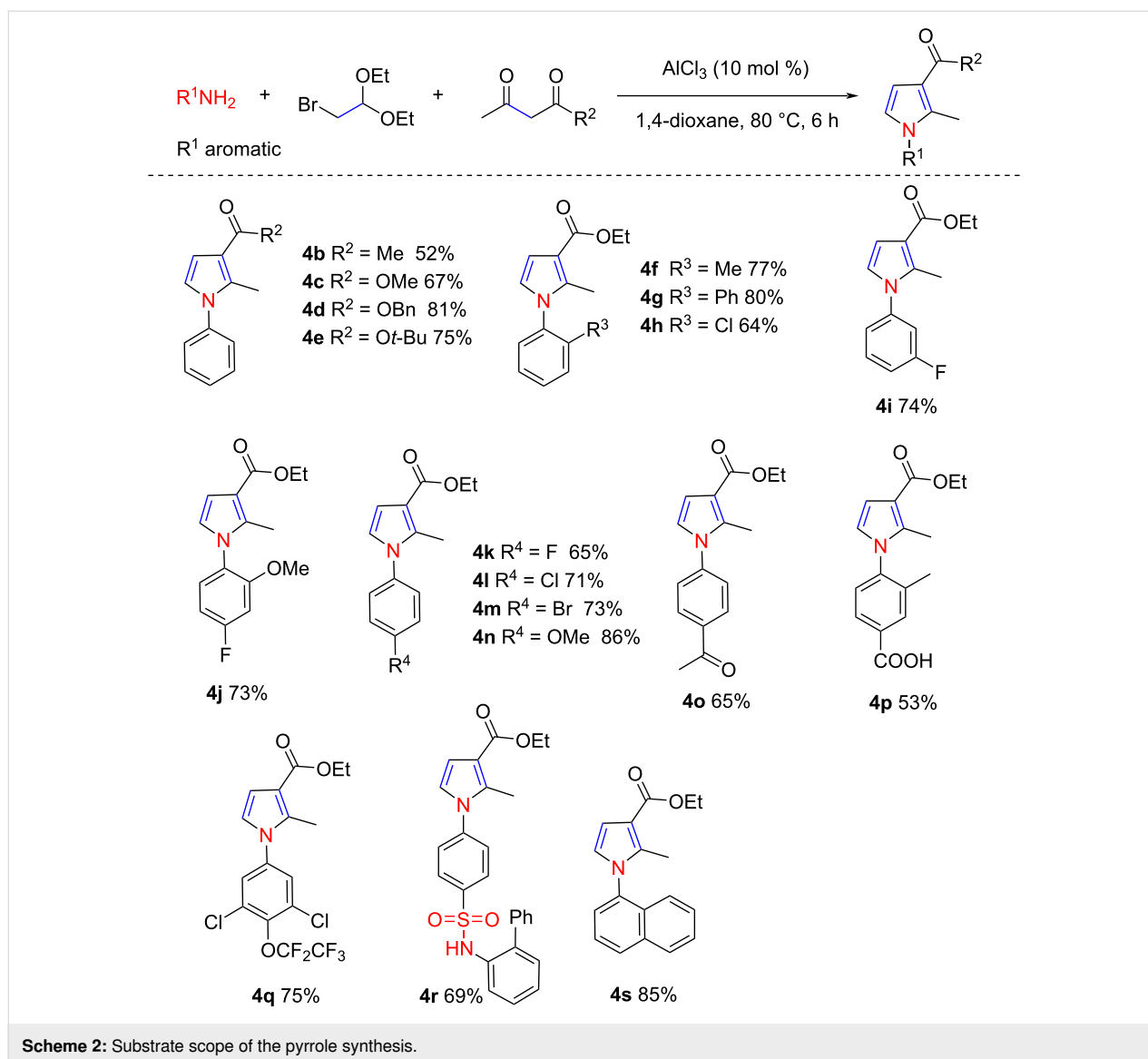
component reaction. To our great delight, the N-heterocyclic pyrrole skeletons **4t**–**v** were successfully synthesized in 51–85% yield by using our protocol (Scheme 3). It should be mentioned that the obtained *N*-pyridylpyrroles **4t** and **4u** are a class of very important intermediates for synthesizing the soluble guanylyl cyclase (sGC) activator. A reported method for accessing these similar scaffolds suffers from a low product yield and harsh reaction conditions (32%, 130 °C) [45,46].

One of the obtained *N*-aryl-4,5-unsubstituted pyrroles, **4l**, could undergo hydrolysis to form the (pyrrol-3-yl)carboxylic acid **4w**. The latter can react readily with aniline (**1a**) or amantadine in the presence of HATU or EDCI to form the multisubstituted pyrrole-3-carboxamide derivatives **4x** and **4y** (Scheme 4). These skeletons have been proven to be promising inhibitors for the production of cytokines [47].

Scheme 3: Synthesis of N-heterocyclic pyrroles.
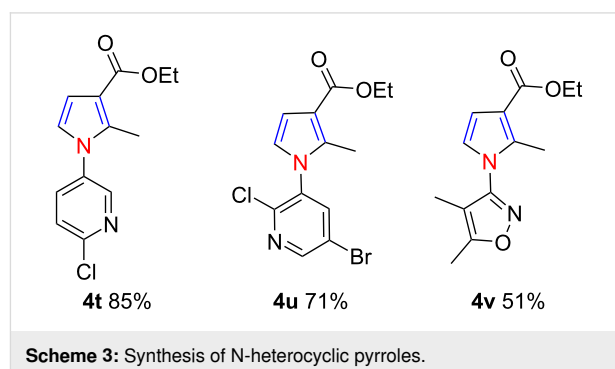
A plausible mechanism for the model reaction was proposed and is depicted in Scheme 5. Initially, a reaction of **1a** and **3a** occurred, providing an imine intermediate **I**, which tautomerized to the corresponding enamine form. Meanwhile, the activa-
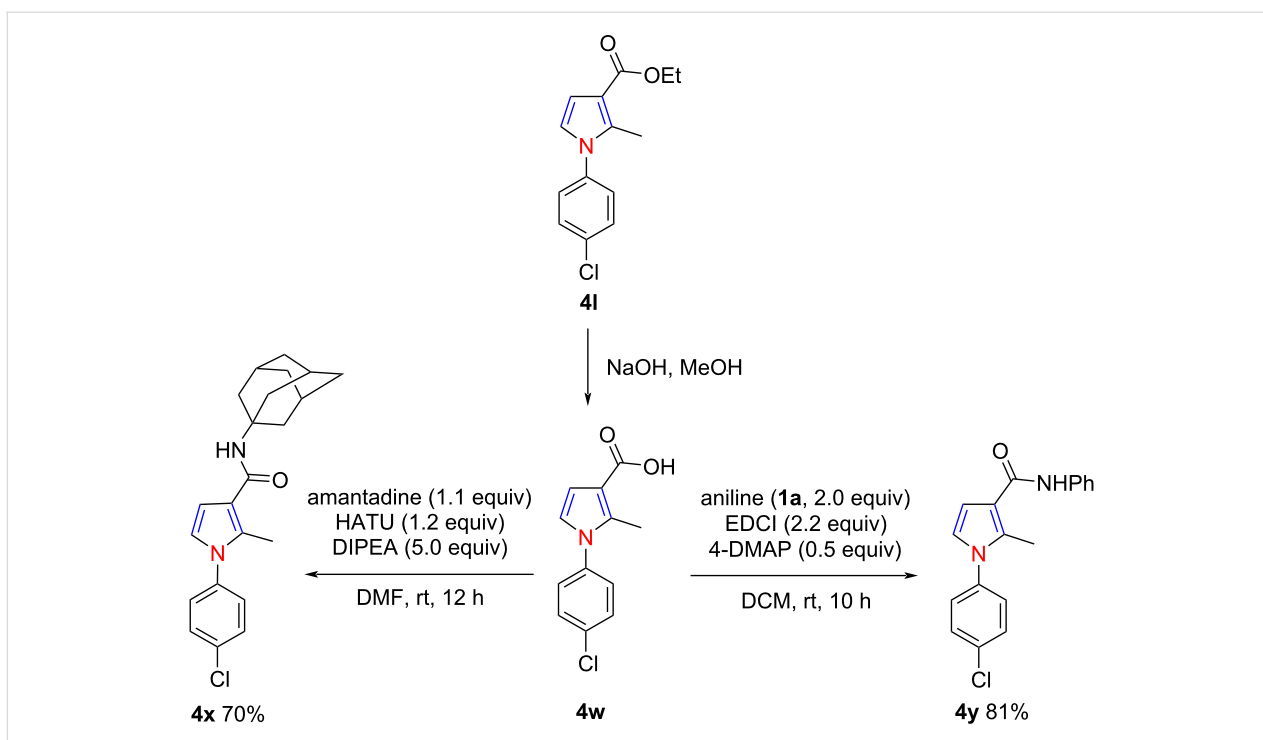
Scheme 4: Direct synthesis of pyrrole-3-carboxamide derivatives.
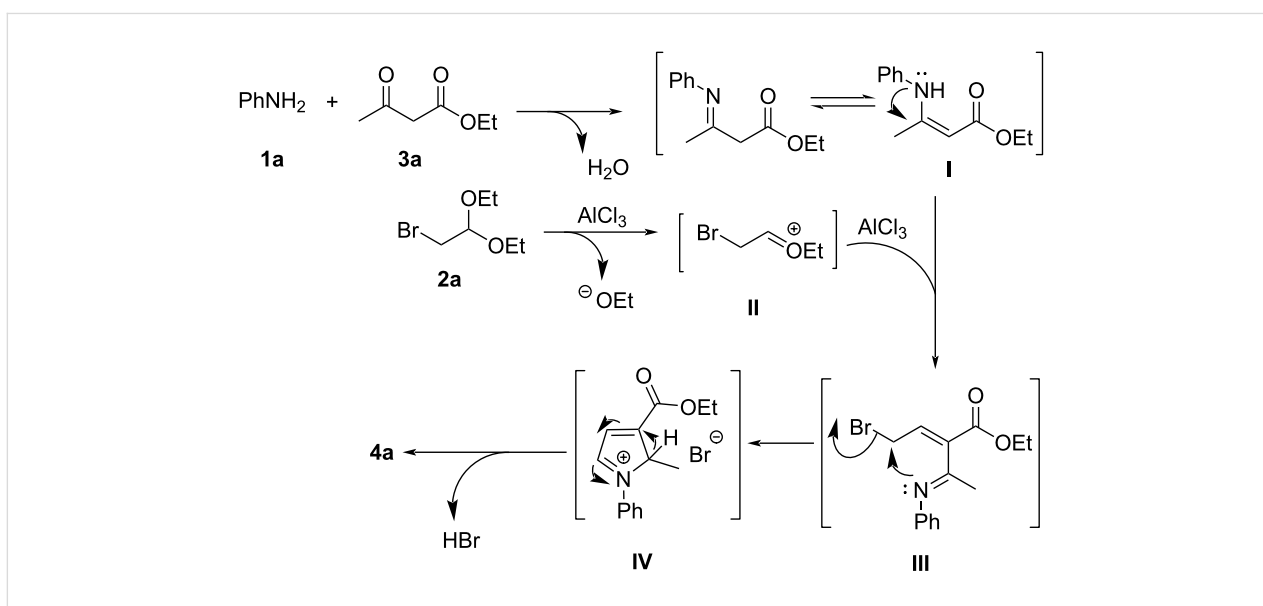
Scheme 5: Plausible mechanism of the three-component reaction.

tion of **2a** with AlCl₃ allowed the formation of a carbocation intermediate **II**, which was then trapped by the enamine intermediate **I** to generate another intermediate **III**. Subsequently, **III** underwent an intramolecular electrophilic substitution to form the intermediate **IV**. Finally, **IV** underwent an elimination of HBr and a spontaneous aromatization to afford the pyrrole product **4a** [48,49].

Apart from the pyrrole synthesis, we also observed an unexpected reaction in which the pyrazolo[3,4-*b*]pyridine scaffold was constructed under analogous conditions. As shown in Scheme 6, In the presence of a catalytic amount of AlCl₃ and 1.2 equiv of KI, 3-methyl-1-phenyl-1*H*-pyrazol-5-amine (**1b**) reacted smoothly with **2a** and **3a**, affording the polysubstituted pyrazolo[3,4-*b*]pyridine **5a** in 53% yield. The formation of an

Scheme 6: Synthesis of polysubstituted pyrazolo[3,4-b]pyridine derivatives.
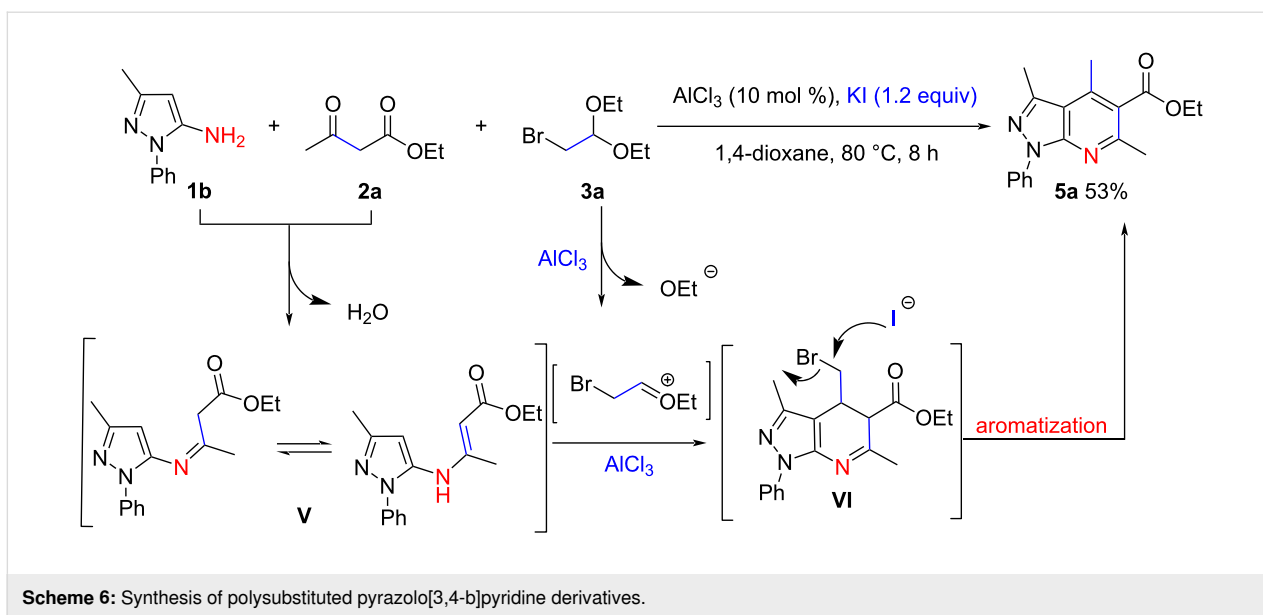
imine intermediate **V** may be involved in the reaction mechanism, and the enamine form of **V** contained two nucleophilic sites to react with a molecule of **3a**, which generated the intermediate **VI**. Finally, **VI** underwent an aromatization to produce **5a**. KI may play a key role in the last step, and we suspected that it can promote the removal of bromide. Although **5a** can theoretically be synthesized through a three-component reaction of **1b**, **2a**, and an appropriate aldehyde, for example, acetaldehyde [50,51] owing to the insufficient reactivity of aliphatic aldehydes, the reaction in Scheme 6 should be a wise choice for the synthesis of products similar in type to **5a**. This point deserves further investigation.

Conclusion

In summary, an efficient and practical one-pot multicomponent reaction of (hetero)arylamines with α-bromoacetaldehyde acetal (**2a**) and 1,3-dicarbonyl compounds was developed by using AlCl₃ as a catalyst. The developed chemistry is also successful for the synthesis of functionalized pyrazolo[3,4-*b*]pyridine derivatives. This study offered a complementary method to construct pyrrole scaffolds through [1 + 2 + 2] annulation, and thus enriching the product diversity of the pyrrole derivatives.

Supporting Information

Supporting Information File 1

Experimental procedures and copies of NMR spectra.
[https://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-16-241-S1.pdf]

ORCID® iDs

Wenbo Huang - https://orcid.org/0000-0003-1507-6123

Preprint

A non-peer-reviewed version of this article has been previously published as a preprint: https://doi.org/10.3762/bxiv.2020.94.v1

References

1. O'Hagan, D. *Nat. Prod. Rep.* **2000**, *17*, 435–446. doi:10.1039/a707613d
2. Walsh, C. T.; Garneau-Tsodikova, S.; Howard-Jones, A. R. *Nat. Prod. Rep.* **2006**, *23*, 517–531. doi:10.1039/b605245m
3. Trost, B. M.; Dong, G. *Org. Lett.* **2007**, *9*, 2357–2359. doi:10.1021/ol070742y
4. Lindel, T.; Hochgürtel, M.; Assmann, M.; Köck, M. *J. Nat. Prod.* **2000**, *63*, 1566–1569. doi:10.1021/np000160o
5. Khajuria, R.; Dham, S.; Kapoor, K. K. *RSC Adv.* **2016**, *6*, 37039–37066. doi:10.1039/c6ra03411j
6. Osman, N. A.; Ligresti, A.; Klein, C. D.; Allarà, M.; Rabbito, A.; Di Marzo, V.; Abouzid, K. A.; Abadi, A. H. *Eur. J. Med. Chem.* **2016**, *122*, 619–634. doi:10.1016/j.ejmech.2016.07.012

7. Hantzsch, A. *Ber. Dtsch. Chem. Ges.* **1890,** *23,* 1474–1476. doi:10.1002/cber.189002301243

8. Leonardi, M.; Estévez, V.; Villacampa, M.; Menéndez, J. C. *Synthesis* **2019,** *51,* 816–828. doi:10.1055/s-0037-1610320

9. Knorr, L. *Ber. Dtsch. Chem. Ges.* **1884,** *17,* 1635–1642. doi:10.1002/cber.18840170220

10. Paal, C. *Ber. Dtsch. Chem. Ges.* **1885,** *18,* 367–371. doi:10.1002/cber.18850180175

11. Balakrishna, A.; Aguiar, A.; Sobral, P. J. M.; Wani, M. Y.; Almeida e Silva, J.; Sobral, A. J. F. N. *Catal. Rev.: Sci. Eng.* **2019,** *61,* 84–110. doi:10.1080/01614940.2018.1529932

12. Bunrit, A.; Sawadjoon, S.; Tšupova, S.; Sjöberg, P. J. R.; Samec, J. S. M. *J. Org. Chem.* **2016,** *81,* 1450–1460. doi:10.1021/acs.joc.5b02581

13. Billedeau, R. J.; Klein, K. R.; Kaplan, D.; Lou, Y. *Org. Lett.* **2013,** *15,* 1421–1423. doi:10.1021/ol400062w

14. Andreou, D.; Kallitsakis, M. G.; Loukopoulos, E.; Gabriel, C.; Kostakis, G. E.; Lykakis, I. N. *J. Org. Chem.* **2018,** *83,* 2104–2113. doi:10.1021/acs.joc.7b03051

15. Firoozi, N.; Torres, G. M.; Arndtsen, B. A. *J. Org. Chem.* **2016,** *81,* 11145–11152. doi:10.1021/acs.joc.6b02102

16. Zheng, Y.; Wang, Y.; Zhou, Z. *Chem. Commun.* **2015,** *51,* 16652–16655. doi:10.1039/c5cc05624a

17. Singh, K.; Kabadwal, L. M.; Bera, S.; Alanthadka, A.; Banerjee, D. *J. Org. Chem.* **2018,** *83,* 15406–15414. doi:10.1021/acs.joc.8b02666

18. Herath, A.; Cosford, N. D. P. *Org. Lett.* **2010,** *12,* 5182–5185. doi:10.1021/ol102216x

19. Xu, J.; Green, A. P.; Turner, N. J. *Angew. Chem., Int. Ed.* **2018,** *57,* 16760–16763. doi:10.1002/anie.201810555

20. Chelucci, G. *Coord. Chem. Rev.* **2017,** *331,* 37–53. doi:10.1016/j.ccr.2016.09.014

21. Estévez, V.; Villacampa, M.; Menéndez, J. C. *Chem. Soc. Rev.* **2014,** *43,* 4633–4657. doi:10.1039/c3cs60015g

22. Gulevich, A. V.; Dudnik, A. S.; Chernyak, N.; Gevorgyan, V. *Chem. Rev.* **2013,** *113,* 3084–3213. doi:10.1021/cr300333u

23. Estévez, V.; Villacampa, M.; Menéndez, J. C. *Chem. Soc. Rev.* **2010,** *39,* 4402–4421. doi:10.1039/b917644f

24. Ahmad, S.; Alam, O.; Naim, M. J.; Shaquiquzzaman, M.; Alam, M. M.; Iqbal, M. *Eur. J. Med. Chem.* **2018,** *157,* 527–561. doi:10.1016/j.ejmech.2018.08.002

25. Winters, M. P.; Sui, Z.; Wall, M.; Wang, Y.; Gunnet, J.; Leonard, J.; Hua, H.; Yan, W.; Suckow, A.; Bell, A.; Clapper, W.; Jenkinson, C.; Haug, P.; Koudriakova, T.; Huebert, N.; Murray, W. V. *Bioorg. Med. Chem. Lett.* **2018,** *28,* 841–846. doi:10.1016/j.bmcl.2018.02.013

26. Singh, A.; Mir, N. A.; Choudhary, S.; Singh, D.; Sharma, P.; Kant, R.; Kumar, I. *RSC Adv.* **2018,** *8,* 15448–15458. doi:10.1039/c8ra01637b

27. Thompson, B. B.; Montgomery, J. *Org. Lett.* **2011,** *13,* 3289–3291. doi:10.1021/ol201133n

28. Biletzki, T.; Imhof, W. *Synthesis* **2011,** 3979–3990. doi:10.1055/s-0031-1289584

29. Tao, L.; Wang, Z.-J.; Yan, T.-H.; Liu, Y.-M.; He, H.-Y.; Cao, Y. *ACS Catal.* **2017,** *7,* 959–964. doi:10.1021/acscatal.6b02953

30. Lu, Y.; Fu, X.; Chen, H.; Du, X.; Jia, X.; Liu, Y. *Adv. Synth. Catal.* **2009,** *351,* 129–134. doi:10.1002/adsc.200800490

31. Thies, N.; Gerlach, M.; Haak, E. *Eur. J. Org. Chem.* **2013,** 7354–7365. doi:10.1002/ejoc.201300803

32. Zhang, Z.; Zhang, W.; Li, J.; Liu, Q.; Liu, T.; Zhang, G. *J. Org. Chem.* **2014,** *79,* 11226–11233. doi:10.1021/jo5018487

33. Kong, H.-H.; Pan, H.-L.; Ding, M.-W. *J. Org. Chem.* **2018,** *83,* 12921–12930. doi:10.1021/acs.joc.8b01984

34. Tracey, M. R.; Hsung, R. P.; Lambeth, R. H. *Synthesis* **2004,** 918–922. doi:10.1055/s-2004-815976

35. Delayen, A.; Goossens, L.; Goossens, R.; Henichart, J.-P. *Heterocycles* **2005,** *65,* 1673–1678. doi:10.3987/com-05-10386

36. Lu, S.; Qi, L.; Li, Z. *Asian J. Org. Chem.* **2017,** *6,* 313–321. doi:10.1002/ajoc.201600608

37. Wang, M.; Liu, C.; Gu, Y. *Tetrahedron* **2016,** *72,* 6854–6865. doi:10.1016/j.tet.2016.09.014

38. Zhang, M.; Neumann, H.; Beller, M. *Angew. Chem., Int. Ed.* **2013,** *52,* 597–601. doi:10.1002/anie.201206082

39. Zhang, M.; Fang, X.; Neumann, H.; Beller, M. *J. Am. Chem. Soc.* **2013,** *135,* 11384–11388. doi:10.1021/ja406666r

40. Chandrasekhar, S.; Patro, V.; Chavan, L. N.; Chegondi, R.; Grée, R. *Tetrahedron Lett.* **2014,** *55,* 5932–5935. doi:10.1016/j.tetlet.2014.08.105

41. Dang, T. T.; Seayad, A. M. *Chem. – Asian J.* **2017,** *12,* 2383–2387. doi:10.1002/asia.201701045

42. Zeng, J.-C.; Xu, H.; Huang, R.-L.; Yu, F.; Zhang, Z. *Tetrahedron Lett.* **2018,** *59,* 1576–1580. doi:10.1016/j.tetlet.2018.03.025

43. Shishido, Y.; Ohmi, M.; Ando, K. Azaspiro derivatives as trpm8 antagonists. WO Patent WO2015136947A1, Sept 17, 2015.

44. Sun, R.; Liu, Y.; Zhang, Y.; Xiong, L.; Wang, Q. *J. Agric. Food Chem.* **2011,** *59,* 2471–2477. doi:10.1021/jf104578j

45. Hirth-Dietrich, C.; Sandner, P.; Stasch, J.-P.; Hahn, M.; Follmann, M. The use of sGC stimulators, sGC activators, alone and combinations with PDE5 inhibitors for the treatment of systemic sclerosis (SSc). Eur. Patent EP2594270A2, May 22, 2013.

46. Boyer, T.; Dodic, N.; Evans, B.; Kirk, B. E. 2,6-disubstituted pyridines and 2,4-disubstituted pyrimidines as soluble guanylate cyclase activators. WO Patent WO2009068652A1, June 4, 2009.

47. Ushio, H.; Hamada, M.; Watanabe, M.; Numata, A.; Fujie, N.; Takashima, T.; Furukawa, H.; Ando, J. Amide derivative and use thereof. WO Patent WO2012050159A1, April 19, 2012.

48. Huang, W.; Liu, C.; Gu, Y. *Adv. Synth. Catal.* **2017,** *359,* 1811–1818. doi:10.1002/adsc.201700074

49. Huang, W.; Chen, S.; Chen, Z.; Yue, M.; Li, M.; Gu, Y. *J. Org. Chem.* **2019,** *84,* 5655–5666. doi:10.1021/acs.joc.9b00596

50. Tu, S.; Wang, Q.; Zhang, Y.; Xu, J.; Zhang, J.; Zhu, X.; Shi, F. *J. Heterocycl. Chem.* **2007,** *44,* 811–814. doi:10.1002/jhet.5570440409

51. Gunasekaran, P.; Indumathi, S.; Perumal, S. *RSC Adv.* **2013,** *3,* 8318–8325. doi:10.1039/c3ra00136a