NJC

PAPER

View Article Online
View Journal | View Issue

Cite this: *New J. Chem.*, 2025, **49**, 18970

Synthesis of a pyrroloquinoline-containing polycyclic scaffold *via* decarboxylative [3+2] cycloaddition and aza-Wittig reactions

Lee Price, Zonyuan Li and Wei Zhang *

Received 2nd August 2025,
Accepted 30th September 2025

DOI: 10.1039/d5nj03128a

rsc.li/njc

A two-step reaction process involving decarboxylative [3+2] cycloaddition followed by the intramolecular aza-Wittig reaction is developed for making novel 5,5,6,6-fused polycyclic scaffold-containing pyrroloquinolines. The use of polymer-supported Ph_3P in the aza-Wittig reaction simplified the removal of $Ph_3P(O)$ and reduced the loss of product during purification.

Introduction

Pyrroloquinoline is a tricyclic system that can be found in alkaloids[1,2] and synthetic drug molecules such as Blebbistatin.[3a] Pyrroloquinoline-derived molecules containing a maleimide moiety have been used in the development of antibody–drug conjugates (ADCs)[3b] (Fig. 1).

Literature methods for making pyrroloquinolines and associated polycyclic systems include the Partyka group's six-step synthesis[4] of pyrrololquinoline (Scheme 1a) and the Smalley group's method of using pre-assembled substrates for the aza-Witting reaction for the synthesis of 7*H*-benzo[4,5]isothiazolo[3,2-*b*]quinazolin-7-one-5,5-dioxide[5] and other substituted dihydroisoquinolines (Scheme 1b). We have employed decarboxylative [3+2] cycloaddition adducts for the *N*-acylation and aza-Wittig reactions to make tetrahydropyrrolo[1,2-*c*]quinazolines (Scheme 1c).[6] Reported in this paper is our effort to expand the scope of the intramolecular aza-Wittig reaction for making the dipyrrolodihydroisoquinoline ring system (Scheme 1Td).

Results and discussion

The synthesis of [3+2] adducts **4** was conducted by modifying reported procedures.[6–14] Thus, a three-component reaction of 2-azidobenzaldehyde **1a**, 2-amino-2-methylpropanoic acid **2a**, and *N*-methyl maleimide **3a** was optimized by exploring different solvents, reaction temperatures, heating methods and times (Table 1). It was found that the reaction of **1a**, **2a**, and **3a** in the ratio of 1 : 1.2 : 1.1 in MeCN and under microwave heating at 150 °C for 60 min gave product **4a** in 68% isolated yield.

This kind of [3+2] cycloaddition is highly diastereoselective, giving products **4** as single diastereomers if R^2 has two of the same groups.[15–18] The stereochemistry of **4a** was confirmed by ^1H–^1H NOESY, ^1H–^1H COSY, ^1H–^{13}C HMBC, and X-ray single crystal structure analysis. The X-ray single crystal structure for **4f** was also obtained. In total, 14 analogs of [3+2] adducts were prepared by using five azidobenzaldehydes **1**, six amino acids **2**, and seven maleimides (including maleic anhydride) **3**. The yields of [3+2] cycloaddition products **4a–4r** were in the range of 50–71% (Scheme 2).

The aza-Wittig reaction was first attempted by performing a one-pot synthesis of [3+2] cycloaddition to make **4a** followed by direct addition of Ph_3P or *n*-Bu_3P to the reaction mixture for the aza-Wittig reaction to make **5a**. However, the yields of the products were 29% and 13%, respectively. Water generated from the [3+2] cycloaddition reaction could hydrolyze Ph_3P

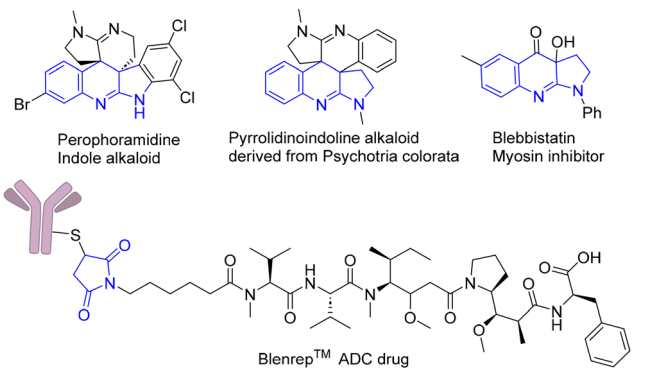
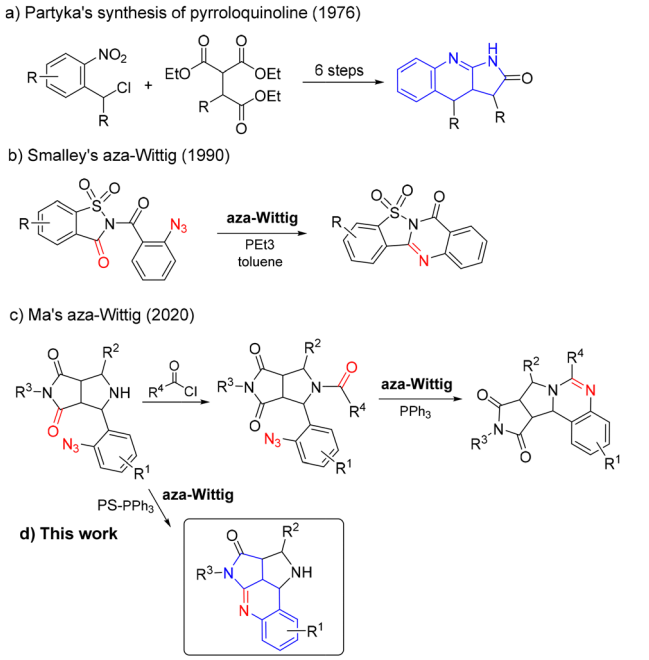


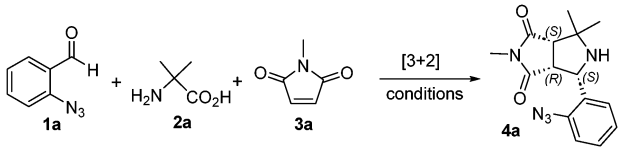
Fig. 1 Bioactive compounds containing pyrroloquinoline and a maleimide moiety.

Department of Chemistry and Centre for Green Chemistry, University of Massachusetts Boston, 100 Morrissey Boulevard, Boston, MA 02125, USA. E-mail: lee.price0214@gmail.com, wei2.zhang@umb.edu



Scheme 1 Reported (a–c) and this work (d) for aza-Wittig reactions to make pyroloquinolines.

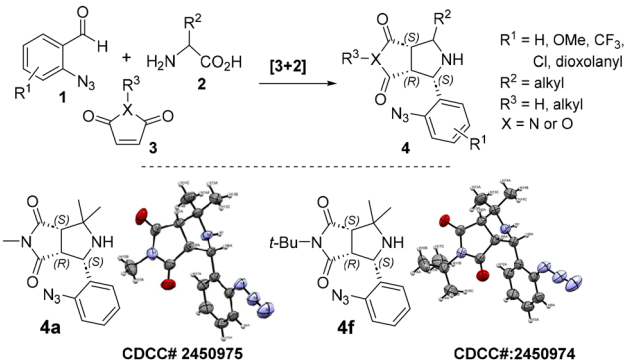
Table 1 Optimization of [3+2] cycloaddition[a]



Entry[d]	Solvent	T (°C)	Heating	t (min)	Yield[b] (%)
1	DMF	150	μw	15	19
2	THF	150	μw	60	21
3	DMAc	150	μw	60	36
4	MeCN + AcOH	110	Conventional[c]	360	63
5	MeCN + AcOH	150	μw	30	40
6	**MeCN**	**150**	**μw**	**60**	**68**

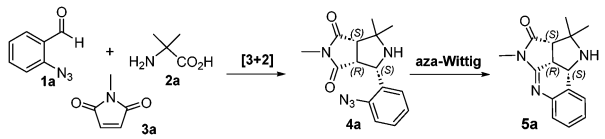
[a] 0.3 mmol scale; **1a**:**2a**:**3a** (1:1.2:1.1). [b] Isolated yield. [c] 110 °C oil bath. [d] Reaction conditions for entries 1–3, 5 and 6: 0.30 mmol azidobenzaldehyde, 0.36 mmol 2-amino-2-methylpropanoic acid, and 0.33 mmol *N*-methyl maleimide. Entry 4: 0.5 mmol azidobenzaldehyde, 0.60 mmol 2-amino-2-methylpropanoic acid, and 0.55 mmol *N*-methyl maleimide.

and *n*-Bu_3P and interrupted the reaction (Table 2). To address this issue, **4a** was isolated and used for the aza-Wittig reaction. The reaction proceeded well, but the removal of phosphine oxide by $ZnCl_2$ working up before flash column chromatography purification caused product decomposition and reduced the yield to <45%.[18] Using polymer-supported Ph_3P (PS-Ph_3P) for the aza-Wittig reaction allowed the removal of PS-Ph_3P(O) by filtration and avoided the step of $ZnCl_2$ workup. The aza-Wittig reaction was then optimized by evaluating the amount of PS-Ph_3P used, solvent, and other reaction conditions. It was found that the reaction of **5a** with 2.4 equiv. of PS-Ph_3P in



Scheme 2 Synthesis of [3+2] adducts.

Table 2 One-pot *vs.* stepwise synthesis of aza-Wittig products **5**[a]



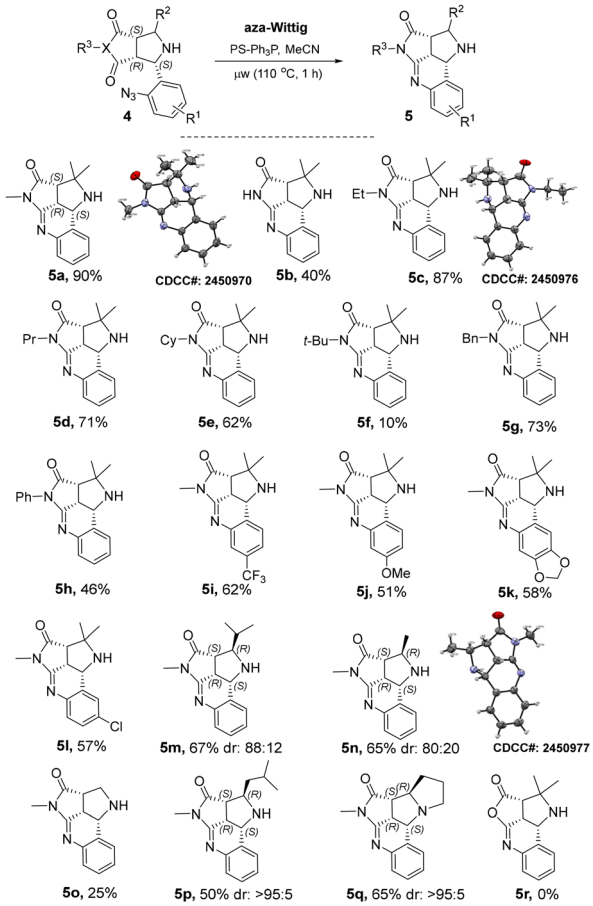
Entry	R_3P (equiv.)	Condition	Solvent[b]	Yield[c] (%)
1	Ph_3P, 2.4	One-pot	DMF	29
2	*n*-Bu_3P, 2.4	One-pot	DMF	13
3	PS-Ph_3P, 2.4	One-pot	MeCN	50
3	Ph_3P, 2.4	Stepwise	MeCN	45
4	*n*-Bu_3P, 2.4	Stepwise	MeCN	41
5	PS-Ph_3P, 1.2	Stepwise	DMF	21
5	PS-Ph_3P, 2.4	Stepwise	DMF	38
6	PS-Ph_3P, 2.4	Stepwise	DMAc	Trace
7	PS-Ph_3P, 2.4	Stepwise	THF	32
8	PS-Ph_3P, 2.4	Stepwise	Toluene	42
9	**PS-Ph_3P, 2.4**	**Stepwise**	**MeCN**	**90**

[a] 0.102 mmol scale of **4a**. PS-Ph_3P: 0.24 mmol: ~3 mmol g^{-1} loading, ~76% (w/w), 84.5 mg, Conditions: μw 110 °C, 1 h. [b] For the aza-Wittig reaction. [c] Isolated yield.

MeCN under microwave heating at 110 °C for 1 h afforded product **5a** in 90% yield (Table 2, entry 9).

Under the optimized aza-Wittig conditions, reactions of **4a–4r** were conducted to explore the substrate scope and make analogs of product **5**. The results presented in Table 3 indicate that the products were generated in up to 90% yield. The R^1 group on azidobenzaldehydes has no significant impact on the product yields. For the R^2 group on the amino acids, most products with R^2 as dimethyl were generated in good yields. R^2 is a single group leading to the formation of products **5m**, **5n**, **5p**, and **5q** as diastereomers. The yield of product **5o**, which has no substituent group at R^2, was only 25%. The R^3 on maleimides seems to have more influence on the product yields. If R^3 is a Me, Et, Pr, Cy, or Bn group, the products were formed in >50% yields. When R^3 was Ph, the yield of product **5h** was slightly lower (46%). With more hindered *t*-Bu as R^3, product **5f** was obtained in only 10% yield. Another interesting discovery was that the reaction of **4r**, which was derived from maleic anhydride, gave product **5r**, which was not stable enough to be isolated. A major by-product observed is the amine formation

Table 3 aza-Wittig reaction for making dipyrrolo-dihydroisoquinolines[a]



[a] PS-Ph_3P (2.4 equiv.) ~3.0 mmol g^{-1} loading, 0.1–0.38 mmol scale of **4**.

of the Staudinger reaction from hydrolysis of the imine, which would be the amine derivative of **4**, which arose from a trace amount of water from the solvents used.

To determine the stereochemistry of the aza-Wittig products, representative product **5a** was subjected to 2D-NMR (HSQC, COSY, NOSEY, and HMBC) analysis (Fig. 2). The single

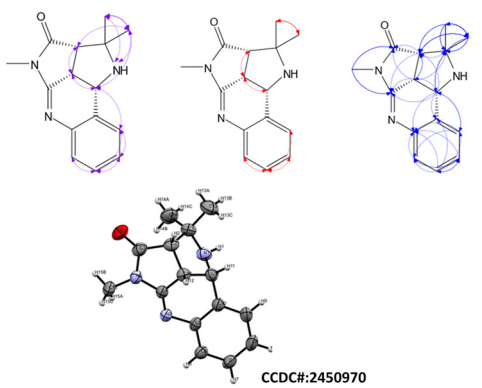
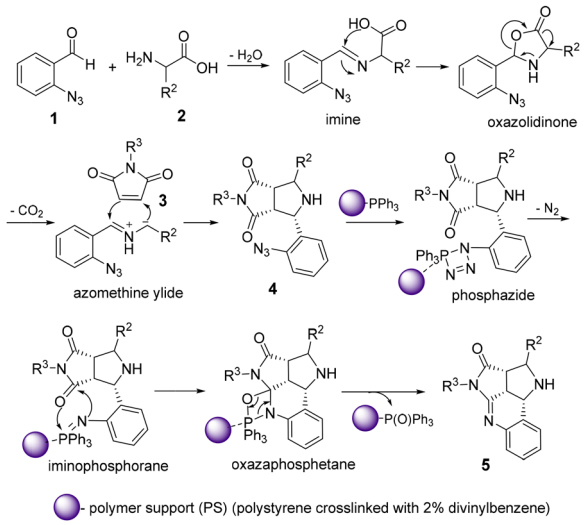


Fig. 2 $^1H-^1H$ NOESY (purple), $^1H-^1H$ COSY (red), and $^1H-^{13}C$ HMBC (blue) NMRs and X-ray structure of **5a**.



Scheme 3 Proposed mechanism for the [3+2] cycloaddition and aza-Wittig reactions.

crystal X-ray diffraction of **5a** was obtained for structure confirmation. Likewise, X-ray crystal structure determination for products **5c** and **5m** was also conducted.

The proposed reaction mechanism for the sequential decarboxylative [3+2] cycloaddition and aza-Wittig reactions is shown in Scheme 3. The condensation of azidobenzaldehyde **1** and α-amino acid **2** gives imine, which undergoes cyclization to form oxazolidinone. Decarboxylation of oxazolidinone gives the azomethine ylide, which undergoes 1,3-dipolar cycloaddition with maleimide **3** to form [3+2] adduct **4** stereoselectively.[15] Upon addition of Ph_3P, phosphazide is generated, which then converts to iminophosphorane after the elimination of N_2. The [2+2] cycloaddition reaction of iminophosphorane with the carbonyl group affords oxazaphosphetane, which is followed by the elimination of $Ph_3(O)P$ to give aza-Wittig product **5**.

Conclusions

In summary, we have developed a reaction sequence involving atom-economic and highly efficient three-component decarboxylative [3+2] cycloaddition for diastereoselective synthesis of precursors **4**. The following aza-Wittig reaction of **4** leads to the formation of a pyrroloquinoline-containing 5,5,6,6-fused polycyclic scaffold. The polymer PS-Ph_3P is used to simplify the removal of PS-$Ph_3P(O)$ and to avoid product decomposition during $ZnCl_2$ workup prior to flash column purification. This is a straightforward and sustainable method for making pyrroloquinoline-containing polycyclic compounds, which may have potential biological interest.

Conflicts of interest

There are no conflicts to declare.

Data availability

The data supporting this article have been included as part of the supplementary information (SI). Supplementary information: detailed experimental procedures, compound characterization, and NMR spectra. see DOI: **https://doi.org/10.1039/d5nj03128a**.

CCDC 2450970 (**4a**), 2450974 (**4f**), 2450975 (**5a**), 2450976 (**5c**) and 2450977 (**5n**) contain the supplementary crystallographic data for this paper.[19a–e]

Acknowledgements

This research was supported by the NSF-MRI award CHE-2117246. We thank Jason Evans and Mynaja Ferguson for performing the HRMS analysis of the compounds. We would also like to thank Takeru Saito for his insight in this project.

Notes and references

1 S. M. Verbitski, C. L. Mayne, R. A. Davis, G. P. Concepcion and C. M. Ireland, *J. Org. Chem.*, 2002, **67**, 7124–7126.
2 L. Verotta, T. Pilati, M. Tatò, E. Elisabetsky, T. A. Amador and D. S. Nunes, *J. Nat. Prod.*, 1998, **61**, 392–396.
3 (*a*) B. I. Roman, S. Verhasselt and C. V. Stevens, *J. Med. Chem.*, 2018, **61**, 9410–9428; (*b*) M. S. Kang, T. W. S. Kong, J. Y. X. Khoo and T.-P. Loh, *Chem. Sci.*, 2021, **12**, 13613–13647.
4 R. A. Partyka, H. M. Holava and W. N. Beverung, Bristol Myers Co, US3974165A, August 1976.
5 A.-B. N. Luheshi, S. M. Salem, R. K. Smalley, P. D. Kennewell and R. Westwood, *Tetrahedron Lett.*, 1990, **31**, 6561–6564.
6 X. Ma, X. Zhang, J. M. Awad, G. Xie, W. Qiu, R. E. Muriph and W. Zhang, *Tetrahedron Lett.*, 2020, **61**, 151392.
7 X. Zhang, K. Pham, S. Liu, M. Legris, A. Muthengi, J. P. Jasinski and W. Zhang, *Beilstein J. Org. Chem.*, 2016, **12**, 2204–2210.
8 X. Ma, S. Meng, X. Zhang, Q. Zhang, S. Yan, Y. Zhang and W. Zhang, *Beilstein J. Org. Chem.*, 2020, **16**, 1225–1233.
9 J. Muthengi, R. E. Erickson, R. E. Muriph and W. Zhang, *J. Org. Chem.*, 2019, **84**, 5927–5935.
10 X. Ma, X. Zhang, W. Qiu, W. Zhang, B. Wan, J. Evans and W. Zhang, *Molecules*, 2019, **24**, 601.
11 X. Zhang, M. Legris, A. Muthengi and W. Zhang, *Chem. Heterocycl. Comp.*, 2017, **53**, 468–473.
12 X. Zhang, M. Liu, W. Zhang, M. Legris and W. Zhang, *J. Fluorine Chem.*, 2017, **204**, 18–22.
13 X. Zhang, X. Ma, W. Qiu, J. Awad and W. Zhang, *Green Process. Synth.*, 2022, **11**, 1128–1135.
14 X. Ma, W. Qiu, L. Liu, X. Zhang, J. Awad, J. Evans and W. Zhang, *Green Synth. Catal.*, 2021, **2**, 74–77.
15 R. Grigg, J. Montgomery and A. Somasunderam, *Tetrahedron*, 1992, **48**, 10431–10442.
16 G. Pandey, P. Banerjee and S. R. Gadre, *Chem. Rev.*, 2006, **106**, 4484–4517.
17 I. Coldham and R. Hufton, *Chem. Rev.*, 2005, **105**, 2765–2810.
18 D. C. Batesky, M. J. Goldfogel and D. J. Weix, *J. Org. Chem.*, 2017, **82**, 9931–9936.
19 (*a*) CCDC 2450970: Experimental Crystal Structure Determination, 2025, DOI: **10.5517/ccdc.csd.cc2n8fky**; (*b*) CCDC 2450974: Experimental Crystal Structure Determination, 2025, DOI: **10.5517/ccdc.csd.cc2n8fp2**; (*c*) CCDC 2450975: Experimental Crystal Structure Determination, 2025, DOI: **10.5517/ccdc.csd.cc2n8fq3**; (*d*) CCDC 2450976: Experimental Crystal Structure Determination, 2025, DOI: **10.5517/ccdc.csd.cc2n8fr4**; (*e*) CCDC 2450977: Experimental Crystal Structure Determination, 2025, DOI: **10.5517/ccdc.csd.cc2n8fs5**.