Organic & Biomolecular Chemistry



View Article Online

COMMUNICATION

Check for updates

Cite this: Org. Biomol. Chem., 2024, **22**, 5734

Received 23rd May 2024, Accepted 26th June 2024 DOI: 10.1039/d4ob00859f

rsc.li/obc

Enal-azomethine ylides: application in the synthesis of functionalized pyrroles[†]‡

Pratap Kumar Mandal, 🔟 Sandeep Patel and Sreenivas Katukojvala 🔟 *

Rhodium-catalyzed [3 + 2] annulation of diazoenals and *N*-alkyl imines resulted in *N*-alkyl-pyrrole-3-carbaldehyde derivatives. The reaction involves thermal 6π -electrocyclization and aromatization of a new class of enal-azomethine ylides (EAYs). The EAYs derived from dihydroisoquinoline and 2*H*-azirine gave fused-pyrrole and pyridine derivatives, respectively. The synthetic importance of pyrrole products has been demonstrated by one-step synthesis of the biologically relevant pyrrolo[3,2-c]quinoline scaffold as well as pyrrolo[2,1-a]isoquinoline which is a core structure of lamellarin alkaloids.

The azomethine ylide (AY), originally introduced by Huisgen, is a fundamentally important 1,3-dipole that finds broad applications in the construction of N-heterocycles (Scheme 1a).¹⁻⁶ AYs have been used as three-atom 4π -synthons in electrocyclizations and [3 + n] cycloadditions leading to the construction of valuable 3-membered and 5–7-membered monocyclic, fused, and bridged nitrogen heterocycles.¹⁻⁶ Inspired by the synthetic potential of azomethine ylides, herein we report the design of a conceptually new class of enal-functionalized azomethine ylides (Scheme 1b). The synthetic utility of enal-azomethine ylides (EAYs) has been demonstrated in the Rh-catalyzed [3 + 2] annulation of diazoenals and *N*-alkyl aldimines resulting in one-step synthesis of tetrasubstituted *N*-alkyl-3-formylpyrroles.^{7,8} The *N*-alkyl pyrroles are core structures of many natural products and pharmaceuticals.⁹

Recently, we have introduced a new class of bench-stable enal-functionalized diazo compounds (diazoenals) which serve as precursors to the highly electrophilic Rh-enalcarbenoids.^{10a} Our studies showed that Rh-enalcarbenoids react with a variety of carbon and heteroatom nucleophiles resulting in valuable functionalized enals which are used in the subsequent cycliza-

†Dedicated to Professor Sukh Dev on the occasion of his 100th birthday.

tion reactions to access diverse carbo/heterocycles.^{10b-h} Continuing our studies, we have investigated the reactivity of Rh-enalcarbenoids with *N*-alkyl imines. Preliminary experiments showed that the reaction of diazoenal **1a** with imine **2a** in the presence of 3 mol% $Rh_2(OAc)_4$ in toluene solvent at 40 °C gives an unstable enal-azomethine ylide (EAY).¹¹ Gratifyingly, at an elevated temperature (110 °C), the reaction gave *N*-allyl-3-formylpyrrole **3a** in 57% yield (Table 1, entry 1) *via* an overall [3 + 2]-annulation involving 6π -electrocyclization of the EAY and the subsequent *in situ* oxidation. It is worth mentioning that this is the first report on enal-functionalized



Scheme 1 Construction of N-heterocycles by azomethine ylide cyclizations.

Department of Chemistry, Indian Institute of Science Education and Research, Bhopal, Madhya Pradesh, 462066 India. E-mail: sk@iiserb.ac.in

[‡] Electronic supplementary information (ESI) available. CCDC 2213403. For ESI and crystallographic data in CIF or other electronic format see DOI: https://doi. org/10.1039/d4ob00859f



 a **1a**/2**a** = 0.2:0.13 mmol. b Yield was calculated after excluding the recovered benzaldehyde.

azomethine ylides and their application in densely functionalized *N*-alkyl pyrrole synthesis.

Inspired by the preliminary studies, we further optimized the [3 + 2] annulation. Although, other Rh(II)-catalysts such as Rh₂(oct)₄, Rh₂(esp)₂, Rh₂(TFA)₄, and Rh₂(*S*-DOSP)₄ are also effective, Rh₂(oct)₄, gave the highest yield of 72% (entries 2–5). Rapid decomposition of diazoenal was observed with the highly electrophilic Rh₂(TFA)₄ leading to a low yield of pyrrole (entry 5). At elevated temperatures, the imine was slowly dissociated to the aldehyde and amine, leading to a reduced yield of pyrrole (entry 7). On the other hand, the yield was diminished upon reducing the temperature due to sluggish reactivity (entries 6 and 8). The reaction was compatible with aromatic solvents whereas non-aromatic solvents are not suitable (entries 9 and 10).

With the optimized conditions (Table 1, entry 2), the scope of the [3 + 2] annulation was studied by varying the imines and diazoenals (Table 2). The reaction was compatible with diverse N-alkyl imines resulting in the corresponding N-substituted pyrroles 4-9 in 49-68% yields. The sterically hindered N-^tBu and N-cyclohexyl imines were also tolerated in the reaction (6, 7). Notably, N-Boc-protected 1,2-ethylenediamine derived aldimine successfully delivered pyrrole 9, an analogue of the drug aloracetam in 49% yield, despite the competing NH-insertion reaction of the side chain. N-Benzyl imine gave pyrrole 10 in 65% yield. Gratifyingly, N-propargyl imine furnished the desired pyrrole 11 in 68% yield despite potential cyclopropenation. Interestingly, N-aryl aldimines gave poor yields of annulation products 12-14 (11-36%) presumably due to the sluggish reactivity and competing NH-insertion of the dissociated arylamines at elevated temperatures. Subsequently, aldimines derived from electronically and sterically distinct aryl aldehydes were investigated. The reaction tolerated alkyl, trifluoroalkyl, and halo substituents on the aryl-ring and delivered the C-aryl pyrroles 15-25 in 53-69% yields. Aldimines





^{*a*} Reaction was performed using the optimized conditions in Table 1. ^{*b*} Isolated yield. ^{*c*} Yield was calculated after excluding the recovered aldehyde. ^{*d*} Reaction time.

with electron-rich and electron-deficient aryl groups also smoothly participated in the reaction and gave good yields of pyrroles **26–28**. The reaction was not hampered by sterically hindered aryl groups (**23–24**, **26** and **28**). Aldimines derived from naphthaldehyde and pyrenecarboxaldehyde gave π -extended pyrrole products **29** and **30**, respectively, in decent yields. With respect to the diazoenals, both keto and ester diazoenals reacted smoothly to give the desired pyrrole products in good yields (*e.g.* **4–7**, **10**, **17–22**).

Next, the synthetic utility of enal-azomethine ylides derived from the cyclic imines was investigated (Scheme 2a and b). A Rh-catalyzed reaction of 3,4-dihydroisoquinoline **2u** and diazoenal **1g** under standard conditions gave pyrroloisoquinoline **31** in 35% yield *via* EAY **32** (Scheme 2a). However, 3-phenyl-2*H*-



azirine **2v** under the same reaction conditions produced 4-formyl pyridine **33** in 40% yield *via* an overall [3 + 3] annulation. The reaction is proposed to involve strain-induced ring opening of azirine derived EAY **34**, 6π -electrocyclization of the resulting azatriene **35** and the subsequent aromatization of dihydropyridine **36** (Scheme 2b).¹²

The tetrasubstituted *N*-allyl-3-formyl-pyrroles obtained from [3 + 2] annulation are valuable substrates for structural diversification (Scheme 3a and b). The ethyl 1-allyl-4-formyl-5-(2-nitrophenyl)-1*H*-pyrrole-2-carboxylate **28** was converted to pyrrolo[3,2-c]quinoline **37** in 70% yield *via* reductive cyclization (Scheme 3a).¹³ The pyrrolo[3,2-c]quinoline derivatives are known to possess diverse biological properties, including anticancer and anti-Alzheimer activities.¹⁴ Next, an intramolecular Heck reaction of ethyl 1-allyl-5-(2-bromophenyl)-4-formyl-1*H*-pyrrole-2-carboxylate **23** gave pyrrolo[2,1-a]isoquinoline **38** in good yield (55%). Compound **38** has the core structure of the lamellarin D alkaloid (Scheme 3b).¹⁵ The *N*-propargyl pyrrole **11** smoothly participated in the click reaction with benzyl



Scheme 3 Synthetic applications.



Scheme 4 Plausible mechanism of [3 + 2]-annulation.

azide to give triazole-tethered pyrrole **39** in 65% yield (Scheme 3c).

A plausible mechanism for the [3 + 2] annulation reaction is proposed in Scheme 4. The transient Rh-enalcarbenoid **39** generated from diazoenal **1** reacts with *N*-alkyl aldimine **2** to give metal-bound EAY **40**. The release of the Rh-catalyst leads to metal-free EAY **41**. The formation of *N*-benzyl imine derived EAY **41a** was detected using the HRMS data. The subsequent 6π -electrocyclization and spontaneous dehydrogenative aromatization^{7*i*,16} of dihydropyrrole (±)-**42** furnish the *N*-alkylpyrrole-3-carbaldehyde **43**.¹⁷

Conclusions

In conclusion, we have reported a new class of enal-functionalized azomethine ylides (EAYs). The synthetic utility of EAYs has been demonstrated by the Rh-catalyzed [3 + 2] annulation of *N*-alkyl imines and diazoenals resulting in the tetrasubstituted *N*-alkyl pyrrole-3-carbaldehyde derivatives. The EAYs derived from cyclic imines dihydroisoquinoline and 2*H*-azirine gave valuable fused pyrrole and pyridine derivatives. The synthetic utility of *N*-alkyl pyrrole products was demonstrated by the short synthesis of pyrrolo[3,2-c]quinoline and pyrrolo[2,1-a]isoquinoline scaffolds which are core structures of many biologically important compounds and natural products.

Data availability

The data supporting this article have been included as part of the ESI.‡

Crystallographic data for compound **19** have been deposited at the CCDC under accession number 2213403.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

This work was supported by the Science & Engineering Research Board (SERB Grants CRG/2018/001684 & CRG/2022/ 004022) and IISER Bhopal. PKM is the recipient of a research fellowship from the IISER Bhopal. We thank Jyoti Yadav (IISER Bhopal) for helping with the X-ray crystal structure determination. We are grateful to the NMR, X-ray and mass spectrometry facilities of the CIF-IISER Bhopal for the characterization data.

References

- 1 (a) R. Huisgen, Proc. Chem. Soc., 1961, 357-369;
 (b) R. Huisgen, Angew. Chem., Int. Ed. Engl., 1963, 2, 565-598; (c) M. Breugst and H.-U. Reissig, Angew. Chem., Int. Ed., 2020, 59, 12293-12307.
- 2 (a) 1,3-Dipolar Cycloaddition Chemistry, ed. A. Padwa, Wiley, New York, 1984, vol. 1 and 2; (b) Synthetic Applications of 1,3-Dipolar Cycloaddition Chemistry Toward Heterocycles and Natural Products, ed. A. Padwa and W. H. Pearson, Wiley, New York, 2002; (c) P. A. Wade, Compr. Org. Synth., 1991, 4, 1111–1168; (d) C. Najera and J. M. Sansano, Curr. Org. Synth., 2003, 7, 1105–1150.
- 3 Selected reviews of [3 + 2] cycloadditions: (a) K. V. Gothelf and K. A. Jørgensen, Chem. Rev., 1998, 98, 863–909; (b) I. Coldham and R. Hufton, Chem. Rev., 2005, 105, 2765–2809; (c) S. Husinec and V. Savic, Tetrahedron: Asymmetry, 2005, 16, 2047–2061; (d) G. Pandey, P. Banerjee and S. R. Gadre, Chem. Rev., 2006, 106, 4484–4517; (e) L. M. Stanley and M. P. Sibi, Chem. Rev., 2008, 108, 2887–2902; (f) R. Narayan, M. Potowski, Z.-J. Jia, A. P. Antonchick and H. Waldmann, Acc. Chem. Res., 2014, 47, 1296–1310; (g) T. Hashimoto and K. Maruoka, Chem. Rev., 2015, 115, 5366–5412; (h) L. Wei, X. Chang and C.-J. Wang, Acc. Chem. Res., 2020, 53, 1084–1100.
- 4 [3 + 3] cycloadditions: (a) M.-C. Tong, X. Chen, H.-Y. Tao and C.-J. Wang, Angew. Chem., Int. Ed., 2013, 52, 12377–12380; (b) H. Guo, H. Liu, F.-L. Zhu, R. Na, H. Jiang, Y. Wu, L. Zhang, Z. Li, H. Yu, B. Wang, Y. Xiao, X.-P. Hu and M. Wang, Angew. Chem., Int. Ed., 2013, 52, 12641–12645; (c) S. Suárez-Pantiga, M. Colas, M. J. Johansson and A. Mendoza, Angew. Chem., Int. Ed., 2015, 54, 14094–14098; (d) W.-L. Yang, C.-Y. Li, W.-J. Qin, F.-F. Tang, X. Yu and W.-P. Deng, ACS Catal., 2016, 6, 5685–5690; (e) S.-M. Xu, L. Wei, C. Shen, L. Xiao, H.-Y. Tao and C.-J. Wang, Nat.

Commun., 2019, **10**, 5553; (*f*) X. Xu, P. Y. Zavalij and M. P. Doyle, *J. Am. Chem. Soc.*, 2013, **135**, 12439–12447.

- 5 [3 + 4] cycloadditions: (a) K. Liu, H.-L. Teng and C.-J. Wang, Org. Lett., 2014, 16, 4508–4511; (b) W.-L. Yang, T. Ni and W.-P. Deng, Org. Lett., 2021, 23, 588–594.
- 6 [3 + 6] cycloadditions: (a) M. Potowski, J. O. Bauer, C. Strohmann, A. P. Antonchick and H. Waldmann, Angew. Chem., Int. Ed., 2012, 51, 9512–9516; (b) H. Liu, Y. Wu, Y. Zhao, Z. Li, L. Zhang, W. Yang, H. Jiang, C. Jing, H. Yu, B. Wang, Y. Xiao and H. Guo, J. Am. Chem. Soc., 2014, 136, 2625–2629; (c) H.-L. Teng, L. Yao and C.-J. Wang, J. Am. Chem. Soc., 2014, 136, 4075–4080; (d) Q.-H. Li, L. Wei and C.-J. Wang, J. Am. Chem. Soc., 2014, 136, 8685–8692; (e) G. Bertuzzi, D. McLeod, L.-M. Mohr and K. A. Jørgensen, Chem. – Eur. J., 2020, 26, 15491–15496.
- 7 Pyrroles from azomethine ylides: (*a*) M. Ohno, M. Komatsu, H. Miyata and Y. Ohshiro, Tetrahedron Lett., 1991, 32, 5813-5816; (b) M. Reisser and G. Maas, J. Org. Chem., 2004, 69, 4913-4924; (c) M. P. Doyle, M. Yan, W. Hu and L. S. Gronenberg, J. Am. Chem. Soc., 2003, 125, 4692-4693; (d) K. Kawashima, M. Hiromoto, K. Hayashi, A. Kakehi, M. Shiro and M. Noguchi, Tetrahedron Lett., 2007, 48, 941-944; (e) C. V. Galliford and K. A. Scheidt, J. Org. Chem., 2007, 72, 1811-1813; (f) Z. Wang, Y. Shi, X. Luo, D.-M. Han and W.-P. Deng, New J. Chem., 2013, 37, 1742-1745; (g) I. Yavari, M. Naeimabadi and M. R. Halvagar, Tetrahedron Lett., 2016, 57, 3718-3721; (h) R. Robles-Machín, A. López-Pérez, M. González-Esguevillas, J. Adrio and J. C. Carretero, Chem. - Eur. J., 2010, 16, 9864-9873; (i) S. Wang, X. Zhu, Z. Chai and S. Wang, Org. Biomol. Chem., 2014, 12, 1351-1356; (j) V. A. Motornov, A. A. Tabolin, Y. V. Nelyubina and S. L. Ioffe, Org. Biomol. Chem., 2021, 19, 3413-3427; (k) S. Sayebani, H. Eshghi and M. Naeimabadi, Mol. Divers., 2022, 26, 2221-2230.
- 8 Selected references for *N*-alkyl pyrrole synthesis: (a) W. W. Tan and N. Yoshikai, Chem. Sci., 2015, 6, 6448-6455; (b) D.-S. Kim, Y.-S. Seo and C.-H. Jun, Org. Lett., 2015, 17, 3842–3845; (c) X.-Y. Zhang, Z.-W. Yang, Z. Chen, J. Wang, D.-L. Yang, Z. Shen, L.-L. Hu, J.-W. Xie, J. Zhang and H.-L. Cui, J. Org. Chem., 2016, 81, 1778-1785; (d) X. Zhang, X. Xu, G. Chen and W. Yi, Org. Lett., 2016, 18, 4864-4867; (e) J. Peng, Y. Gao, C. Zhu, B. Liu, Y. Gao, M. Hu, W. Wu and H. Jiang, J. Org. Chem., 2017, 82, 3581-3588; (f) O. M. P. Zúñigaa, Á. G. Sathicqa, J. J. M. Zambranob and G. P. Romanelli, Curr. Org. Synth., 2017, 14, 1–18; (g) K. Matsui, M. Shibuya and Y. Yamamoto, Commun. Chem., 2018, 1, 21; (h) D. Andreou, Kallitsakis, E. Loukopoulos, C. Gabriel, М. G. G. E. Kostakis and I. N. Lykakis, J. Org. Chem., 2018, 83, 2104-2113; (i) K. Luo, S. Mao, K. He, X. Yu, J. Pan, J. Lin, Z. Shao and Y. Jin, ACS Catal., 2020, 10, 3733-3740; (j) L. Zuo, Y. Yang and W. Guo, Org. Lett., 2021, 23, 2013-2018; (k) T. Shi, G. Yin, X. Wang, Y. Xiong, Y. Peng, S. Li, Y. Zeng and Z. Wang, Green Synth. Catal., 2023, 4, 20-34.
- 9 Selected references for *N*-alkyl pyrrole natural products and pharmaceuticals: (*a*) F. Fischer, M. Matthisson and

P. Herrling, Neurodegener. Dis., 2004, 1, 50-70; (b) S. I. Young, P. D. Thornton and A. Thompson, Nat. Prod. Rep., 2010, 27, 1801-1839; (c) V. Bhardwaj, D. Gumber, V. Abbot, S. Dhiman and P. Sharma, RSC Adv., 2015, 5, 15233-15266; (d) S. P. Adams, M. Tsang and J. M. Wright, Database Syst. 2015, Cochrane Rev., CD008226; (e) T. E. Mallinson, J. Paramed. Pract., 2017, 9, 522-526; (f) N. Singh, S. Singh, S. Kohli, A. Singh, H. Asiki, G. Rathee, R. Chandra and E. A. Anderson, Org. Chem. Front., 2021, 8, 5550-5573; (g) K. Seipp, L. Geske and T. Opatz, Mar. Drugs, 2021, 19, 514; (h) M. Elsayed, M. O. Aboelez, B. E. Elsadek, H. A. Sarhan, K. A. Khaled, A. Belal, A. Khames, Y. A. Hassan, A. A. Abdel-Rheem and E. B. Elkaeed, Pharmaceutics, 2022, 14, 880.

- Synthetic applications of enalcarbene: (a) S. G. Dawande, V. Kanchupalli, J. Kalepu, H. Chennamsetti, B. S. Lad and S. Katukovala, Angew. Chem., Int. Ed., 2014, 53, 4076–4080; (b) S. G. Dawande, V. Kanchupalli, B. S. Lad, J. Rai and S. Katukojvala, Org. Lett., 2014, 16, 3700–3703; (c) J. Kalepu and S. Katukojvala, Angew. Chem., Int. Ed., 2016, 55, 7831– 7835; (d) V. Kanchupalli and S. Katukojvala, Angew. Chem., Int. Ed., 2018, 57, 5433–5437; (e) B. S. Lad and S. Katukojvala, ACS Catal., 2018, 8, 11807–11814; (f) V. Kanchupalli, L. A. Thorbole, J. Kalepu, D. Joseph, M. Arshad and S. Katukojvala, Org. Lett., 2022, 24, 3850– 3854; (g) P. K. Mandal and S. Katukojvala, Chem. – Eur. J., 2024, 30, e202303862; (h) P. K. Mandal, R. Chakrawarti and S. Katukojvala, Org. Lett., 2024, 26, 3463–3468.
- 11 For generation of azomethine ylides from diazo compounds, see: (a) A. Padwa and S. F. Hornbuckle, *Chem. Rev.*, 1991, 91, 263–309; (b) M. P. Doyle, M. A. McKervey and Y. Tao, *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds: From Cyclopropanes to Ylides*, Wiley-VCH, Weinheim, 1998, pp. 238–279.

- 12 N. S. Y. Loy, A. Singh, X. Xu and C.-M. Park, *Angew. Chem., Int. Ed.*, 2013, **52**, 2212–2216.
- S. Choudhary, J. Yadav, ??. Mamta, A. P. Pawar, S. Vanaparthi, N. A. Mir, E. Iype, R. Sharma, R. Kant and I. Kumar, *Org. Biomol. Chem.*, 2020, 18, 1155–1164.
- 14 (a) T. H. Brown, R. J. Ife, D. J. Keeling, S. M. Laing, C. A. Leach, M. E. Parsons, C. A. Price, D. R. Reavill and K. J. Wiggall, J. Med. Chem., 1990, 33, 527-533; (b) K. Grychowska, G. Satała, T. Koz, A. Partyka, Е. Colacino, S. Chaumont-Dubel, Bantreil, Х. A. Wesołowska, M. Pawłowski, J. Martinez, P. Marin, G. Subra, A. J. Bojarski, F. Lamaty, P. Popik and P. Zajdel, ACS Chem. Neurosci., 2016, 7, 972-983; (c) K. Grychowska, S. Chaumont-Dubel, R. Kurczab, P. Koczurkiewicz, C. Deville, M. Krawczyk, W. Pietruś, G. Satała, S. Buda, K. Piska, M. Drop, X. Bantreil, F. Lamaty, E. Pékala, A. J. Bojarski, P. Popik, P. Marin and P. Zajdel, ACS Chem. Neurosci., 2019, 10, 3183-3196; (d) K. Grychowska, U. Lopez-Sanchez, M. Vitalis, G. Canet, G. Satala, A. Olejarz-Maciej, J. Golebiowska, R. Kurczab, W. Pietrus, M. Kubacka, C. Moreau, M. Walczak, K. Blicharz-Futera, O. Bento, X. Bantreil, G. Subra, A. J. Bojarski, F. Lamaty, C. Becamel, C. Zussy, S. Chaumont-Dubel, P. Popik, H. Nury, P. Marin, L. Givalois and P. Zajdel, J. Med. Chem., 2023, 66, 14928-14947; (e) M. Haroum and C. Tratrat, Pyrrolo[3,2-c]quinoline compounds as CK2 inhibitors, U.S. Patent US11945818B1, 2024.
- 15 H. Fan, J. Peng, M. T. Hamann and J.-F. Hu, *Chem. Rev.*, 2008, **108**, 264–287.
- 16 J. Barluenga, G. Lonzi, L. Riesgo, L. A. López and M. Tomás, J. Am. Chem. Soc., 2010, 132, 13200–13202.
- 17 The formyl group was necessary for spontaneous dehydrogenative aromatization. See the ESI for control experiments.‡