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Selective access to dihydrophenanthridines and phenanthridinones via cyclisation of aryl amines onto N-tethered arynes†

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5,6-Dihydrophenanthridines are prepared from aryl amines via intramolecular addition to N-tethered arynes under mild conditions. A new o-silylaryl triflate precursor was developed to increase reactivity and enable electron-rich and electron-poor aryl amines to undergo cyclisation. A complete switch in product selectivity occurs when the reaction is conducted in air, affording the corresponding phenanthridin-6(5H)one as the sole product under otherwise identical reaction conditions.

Phenanthridines and phenanthridinones are privileged heterocyclic scaffolds found in a range of natural products and therapeutically active compounds. 1 They possess broad biological properties, including anticancer, 2a antitumour, 2b antiviral, 2c antimicrobial, 2d antifungal^{2e} and antimalarial^{2f} activity. In addition, a high charge mobility renders these frameworks versatile building blocks for functional materials.3 As a result, significant synthetic effort has been devoted to the synthesis of phenanthridines and their derivatives.4 This includes the Bischler-Napieralski reaction,5a photochemical,^{5b} radical^{5c} and microwave-assisted^{5d} cyclisations, transition metal free C-H arylation, 5e aza-Wittig, 5f anionic ringclosure, ^{5g} hypervalent iodine ^{5h} and metal catalysed approaches. ⁵ⁱ

Arynes have also been utilised in the synthesis of phenanthridine derivatives and related alkaloid natural products.^{6,7} These versatile reactive intermediates afford valuable benzenoid and heterocyclic frameworks⁸ and have experienced a recent resurgence in interest due to the advent of aryne precursors that act under mild conditions, namely the o-trimethylsilylaryl triflates (oSATs)9 and the hexadehydro-Diels-Alder reaction of polyalkynes. 10 Cyclisation onto a pendant aryne has proven a valuable method to furnish phenanthridine derivatives, most notably in the synthesis of natural products. 6a-e,g,h However, these approaches all generate arynes using organometallic reagents or strong bases at low temperatures

 $NH_3(I)$ ii) MnO₂ OMe (b) Anionic cylisation onto arynes via in situ aryllithium nucelophile [Barluenga & Sanz]:^{69,h} THF. -110 to 20 °C ii) E+, -78 to 20 °C E = H. p-TolC(H)OH4, X = CH₂ 42-65% (c) General aryl amine-aryne annulation under mild conditions [this work] N-tether atm. No or Air O = CH₂ CO 10 or 11 SiMe₃ 10 11

single product

SEA

rearomatisatior

which restricts the functional group tolerance. Methods that operate via electrophilic aromatic substitution (SEAr) have also

been limited to electron-rich aryl nucleophiles such as 1

(Scheme 1a), 6a-e which although common in the natural products,

precludes preparation of more diverse substrate analogues. Alter-

natively, Barluenga and Sanz utilised anionic cyclisation onto pendant arynes (accessed from 3) to yield phenanthridine deriva-

tives 4 and 5 by exploiting stronger in situ-formed aryllithium nucleophiles (Scheme 1b). 6g,h However, this strategy also required

organolithium reagents (in excess) to form both the aryne and the

(a) Isoquinoline alkaloid natural products via arvl amine-arvne annulation [e.g. Kessar]:60

Scheme 1 Cyclisation onto tethered arynes for the synthesis of phenanthridines and derivatives.

aryne

formation

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= Me, Bn

Atmosphere controls selectivity:

phénanthridinones (aerobic)

electron rich & poor aryl amines ✓ mild reaction conditions

odihydrophenanthridines (anaerobic)

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nucleophile, plus pre-functionalisation (o-bromination) of the

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pronucleophilic arene.

Given our interests in the chemistry of arynes, 11 we sought to develop a cyclisation approach to phenanthridine derivatives that exploited the benzylic oSAT precursor 7a previously used in our group (Scheme 1c). 11b Inspired by the strategy of both Kessar and Stermitz in their syntheses of alkaloid natural products, 6c,d it was proposed that aryl amines bearing an N-tethered aryne precursor (8) would undergo SEAr, upon generation of the aryne 9, to afford 5,6-dihydrophenanthridine derivatives 10. Given the propensity for such frameworks to undergo oxidation there would also be potential to access the corresponding phenanthridinones 11. Importantly, by using the oSAT precursor it removes the harsher reaction conditions of previous reports and should facilitate a wider range of aryl amine nucleophiles 6, especially those containing useful functional handles. Furthermore, tethering the arvne at nitrogen enables more facile synthesis of the starting materials, compared to linking via C-C bonds, ^{6a,b} thereby expediting the preparation of structural analogues.

To test this cyclisation hypothesis, benzylic *o*SAT precursor **7a** was tethered to *N*-methyl aniline to afford precursor **12**, which was then subjected to our standard aryne-forming conditions previously used with this tether (Scheme 2a). Unfortunately, this afforded a mixture of compounds and no clear evidence of cyclisation to dihydrophenanthridine **13** nor phenanthridinone **14**. Intriguingly, a significant by-product was observed in the HNMR spectrum of the crude reaction mixture that suggested intermolecular attack at the aryne was taking precedence over the desired intramolecular process (although we were unable to isolate a clean sample for characterisation). With a goal to promote the cyclisation and suppress undesired intermolecular reactivity, a modified

Scheme 2 Investigating cyclisation of aryl amine onto N-tethered aryne, (a) unsuccessful preliminary attempt to form 5,6-dihydrophenanthridine ${\bf 13}$ or phenanthridinone ${\bf 14}$. Reaction conditions: aryl amine (1.0 equiv.), KF (2.0 equiv.), 18-crown-6 (2.0 equiv.), DME: MeCN (3:1 by volume, 0.01 M), 90 °C, 24 h, N_2 atmosphere. (b) Synthesis of a new p-methoxy benzylic aryne precursor ${\bf 17}$. Reaction conditions: (i) ethylene glycol (5.0 equiv.), pyridinium p-toluenesulfonate (0.12 equiv.), PhMe, 110 °C, (ii) hexamethyldisilazane (0.8 equiv.), THF, 66 °C, 2 h, (iii) n-BuLi, THF, -78 °C, 30 min, (iv) trifluoromethanesulfonic anhydride (1.3 equiv.), pyridine (3.0 equiv.), CH₂Cl₂, 0 °C, 3 h, then HCl (4 M aq.), 16 h. Yields of isolated products throughout.

aryne precursor 17 was developed (Scheme 2b). It was rationalised that a p-methoxy substituent in 17 should increase reactivity by inductively polarising the aryne towards nucleophilic addition ortho to the tether – as supported by Garg and Houk's aryne distortion $model^{13}$ – in addition to providing increased stabilisation of the resulting aryl anion. ^{8a} To this end, the novel p-methoxybenzyl aryne precursor 17 was prepared in four steps from commercially available 2-bromo-isovanillin 15 with no purification of the intermediates required.

With the second generation aryne tether 17 in hand, the corresponding N-methyl aniline precursor 18a was then subjected to the conditions used for attempted cyclisation of 12. Gratifyingly, the new aryne tether promoted significant intramolecular reaction, affording dihydrophenanthridine 19a in 50% yield and the corresponding phenanthridinone 20a in 23% yield, with a marked decrease in deleterious N-arylation (8% by-product) (entry 1, Table 1). Having addressed the issue of overall reactivity, attention turned to optimising the reaction conditions to avoid mixtures of cyclisation products (see Table 1 for selected optimisation experiments). Evaluation of some common o-SAT activators (entries 2-5) identified CsF in acetonitrile and KF/18-crown-6 in THF as promoting cyclisation to the dihydrophenanthridine 19a in good yields, albeit with phenanthridinone and by-product still present. Encouragingly, replacing THF with DME led to an excellent yield of the desired dihydrophenanthridine 19a, with only trace amounts of the phenanthridinone 20a and no evidence of the competing intermolecular by-product (entries 5 & 6). Further investigations found that lowering the reaction temperature and concentration both decreased the overall yield (entries 7 and 8). Finally, increasing concentration led to more of the competing

Table 1 Selected optimization studies for the preparation of dihydrophenanthridines^a

				Yield ^b (%)		
Entry	Activator	Solvent	T (°C)	19a	20a	By-product
1	KF 18-crown-6	DME: MeCN (3:1)	90	50	23	8
2	CsF	MeCN	90	69	2	7
3	CsF	PhMe: MeCN	90	64	10	11
4	$TBAF^c$	THF	90	36	_	_
5	KF 18-crown-6	THF	90	69	10	5
6	KF 18-crown-6	DME	90	84(82)	2	_
7	KF 18-crown-6	DME	70	69	2	5
8	KF 18-crown-6	DME^d	90	69	_	9
9	KF 18-crown-6	DME^e	90	46		35

^a Reaction conditions: aryl amine (1.0 equiv.), activator (2.0 equiv.), additive (2.0 equiv.), solvent [0.01 M], 16 h, $\rm N_2$ atmosphere. ^b ¹H NMR yield νs . dibromomethane internal standard, isolated yield in parentheses, all reactions proceeded to full conversion after 16 h. ^c 1.0 M in THF. ^d 0.002 M. ^e 0.05 M.

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intermolecular N-arylation and subsequent erosion of the dihydrophenanthridine yield (entry 9).

Having optimised the reaction conditions, attention turned to investigating substrate scope. Pleasingly, a range of substituted aniline derivatives were found to undergo cyclisation in generally good to excellent yields (Scheme 3). 4-Substituted anilines were evaluated first, with the electron-rich 4-methoxy derivative affording the corresponding dihydrophenanthridine 19b in 98% yield. The halogenated series showed an interesting trend, with the 4-iodo and 4-fluoro precursors undergoing efficient cyclisation to 19c (67%) and 19f (70%), respectively, however, the 4-bromo and 4-chloro derivatives furnished 19d and 19e in more moderate yields (52% and 48%). With the electron deficient 4-fluoro analogue proving highly amenable to the cyclisation, it was encouraging to observe that the 4-nitroaniline precursor also underwent the transformation to generate the corresponding electron-poor dihydrophenanthridine 19g in 34% yield. These are particularly noteworthy as

Scheme 3 Synthesis of 5,6-dihydrophenanthridine derivatives 15 Reaction conditions: aryl amine (1.0 equiv.), KF (2.0 equiv.), 18-crown-6 (2.0 equiv.), DME (0.01 M), 90 $^{\circ}$ C, 16 h, N₂ atmosphere. Yields of isolated products throughout. ^{a 1}H NMR yield vs. dibromomethane internal standard, note: 19l partially oxidised upon purification to give isolated 1:1.2 mixture of 19l and corresponding phenanthridinone 20l

most reports of intramolecular SEAr with arynes rely on markedly electron rich aromatic systems. A comparison of the propensity for cyclisation of the 3-methyl (18h) and 2-methylaniline (18i) precursors revealed a key role played by sterics. 3-Methylaniline 18h afforded the corresponding dihydrophenanthridine 19h in an excellent 83% yield, whereas only a trace of the 2-methyl analogue was observed. This suggested that 19i experiences significant 1,5-strain in the transition state required for cyclisation; instead favouring a mixture of the N-arylation by-product and an intramolecular dearomative aryne Diels-Alder cycloaddition.14 Interestingly, the more conformationally rigid indoline (18k) and tetrahydroquinoline (18l) precursors underwent efficient SEAr to furnish the corresponding tetracyclic products, 19k and 19l, respectively. It was noted that the THO-derived framework afforded 19l in 76% yield by ¹H NMR spectroscopic analysis; however, during attempted purification it proved susceptible to oxidation, leading to an isolated mixture (1:1.2) of 19l and the corresponding phenanthridinone.

Having established the formation of dihydrophenanthridines from a range of electron rich and electron deficient aryl amines, we next investigated whether the product selectivity could be reversed to instead access phenanthridinones. During the initial optimisation studies, dihydrophenathridine 19a had been found to be susceptible to partial oxidation upon exposure to air, whilst 19l had part-oxidised during purification. This afforded mixtures of the dihydrophenanthridines and phenanthridinones; however a discrete second oxidative step was always required to effect complete conversion. With a view to accessing the phenanthridinone derivatives in a single step from the analogous aryl amine precursors 18, the reaction was performed in the presence of a range of oxidants, with most attempts affording mixtures of the two cyclisation products. However, it was extremely pleasing to observe that when 18a and 181 were exposed to the previously optimised cyclisation conditions, only in air rather than under an inert atmosphere, it resulted in a complete switch of selectivity to exclusively afford the corresponding phenanthridin-6(5H)-ones 20a and 20l in 62% and 79% yields respectively (Scheme 4).15

Finally, N-benzyl (18m) and N-allyl (18n) aniline precursors were also found to be amenable to cyclisation (Scheme 5). Given the increased potential for subsequent protecting group cleavage, the comparable yields obtained for the analogous

Scheme 4 Cyclisation in air exclusively affords phenanthridinones 20a and 201. Reaction conditions: aryl amine (1.0 equiv.), KF (2.0 equiv.), 18-crown-6 (2.0 equiv.), DME (0.01 M), 90 °C, 16 h, air. Yields of isolated products throughout

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Scheme 5 5,6-Dihydrophenanthridines bearing alternative N-protecting groups. Reaction conditions are as shown in Scheme 3. Yields of isolated

N-benzyl (19m, 85%), N-allyl (19n, 69%) and N-Me (19a, 82%) dihydrophenanthridines were particularly encouraging for the synthetic utility of the method.

In conclusion, the cyclisation of aryl amines onto N-tethered arynes has been developed under mild reaction conditions using a novel silylaryl triflate precursor. This enabled the new biaryl linkage to be generated by SEAr using both electron rich and poor aryl amines and furnished a range of phenanthridine derivatives with handles for subsequent functionalisation. Selective access to dihydrophenanthridines or the corresponding phenanthridinones is dependent upon a simple switch between anaerobic and aerobic reaction environments.

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Conflicts of interest

There are no conflicts to declare.

Notes and references

- 1 (a) F. Viladomat, J. Bastida, G. Tribo, C. Codina and M. Rubiralta, Phytochemistry, 1990, 29, 1307; (b) R. B. Macgregor, R. M. Clegg and T. M. Jovin, Biochemistry, 1987, 26, 4008; (c) Z. Jin, Nat. Prod. Rep., 2009, 26, 363.
- 2 (a) V. Holl, D. Coelho, D. Weltin, P. Dufour and P. Bischoff, Anticancer Res., 2000, 20, 3233; (b) T. C. Johnstone, S. M. Alexander, W. Lin and S. J. Lippard, J. Am. Chem. Soc., 2014, 136, 116; (c) G. T. Tan, M. J. Pezzuto and A. D. Kinghorn, J. Nat. Prod., 1991, 54, 143; (d) G. Y. Zuo, F. Y. Meng, X. Y. Hao, Y. L. Zhang, G. C. Wang and G. L. Xu, J. Pharm. Pharm. Sci., 2008, 11, 90; (e) X. J. Yang, F. Miao, Y. Yao, F. J. Cao, R. Yang, Y. N. Ma, B. Q. Qin and L. Zhou, *Molecules*, 2012, 17, 13026; (f) M. Rivaud, A. Mendoza, M. Sauvain, A. Valentin and V. Jullian, Bioorg. Med. Chem., 2012, 20, 4856.
- 3 (a) N. Stevens, N. O'Connor, H. Vishwasrao, D. Samaroo, E. R. Kandel, D. L. Atkins, C. M. Drain and N. J. Turro, J. Am. Chem. Soc., 2008, 130, 7182; (b) Y.-L. Chen, F.-H. Li and Z.-S. Bo, Macromolecules, 2010, 43, 1349; (c) P. Pang, X. Miao, L. Ying, G. Kong, C. Che and W. Deng, J. Phys. Chem. C, 2020, 124, 5665.
- 4 Selected reviews: (a) F. Rafiee, Appl. Organomet. Chem., 2017, 31, 12; (b) N. Kshirsager, R. Sonawane, S. Pathan, G. Kamble and G. P. Singh, Lett. Org. Chem., 2021, 19, 434; (c) R. R. Aleti, A. A. Festa, L. G. Voskressensky and E. V. Van der Eycken, Molecules, 2021, 26, 5560.

- 5 (a) B. A. Lorsbach and M. Kurth, J. Chem. Rev., 1999, 99, 1549; (b) R. Alonso, P. J. Campos, B. Garcia and M. A. Rodriguez, Org. Lett., 2006, 8, 3521; (c) M. Tobisu, K. Koh, T. Furukawa and N. Chatani, Angew. Chem., Int. Ed., 2012, 51, 11363; (d) F. Portela-Cubillo, J. S. Scott and J. C. Walton, J. Org. Chem., 2008, 73, 5558; (e) C. Tang, Y. Yuan and N. Jiao, Org. Lett., 2015, 17, 2206; (f) S. P. Marsden, A. E. McGonagle and D. McKeever-Abbas, Org. Lett., 2008, 10, 2589; (g) M. Lysén, J. L. Kristensen, P. Vedsø and M. Begtrup, Org. Lett., 2002, 4, 257; (h) Q. Wang, X. Dong, T. Xiao and L. Zhou, Org. Lett., 2013, 15, 4846; (i) H. A. McManus, M. J. Fleming and M. Lautens, Angew. Chem., Int. Ed., 2007, 46, 433.
- 6 (a) T. Kametani and K. Ogasawara, J. Chem. Soc. C, 1967, 2208; (b) S. V. Kessar, N. Parkash and G. S. Joshi, J. Chem. Soc., Perkin Trans. 1, 1973, 1158; (c) S. V. Kessar, M. Singh and P. Balakrishnan, Indian J. Chem., 1974, 12, 323; (d) J. P. Gillespie, L. G. Amoros and F. R. Stermitz, J. Org. Chem., 1974, 39, 3239; (e) T. Nakanishi and M. Suzuki, Org. Lett., 1999, 1, 985; (f) J. Pawlas and M. Begtrup, Org. Lett., 2002, 4, 2687; (g) J. Barluenga, F. J. Fananas, R. Sanz and Y. Fernandez, Chem. - Eur. J., 2002, 8, 2034; (h) R. Sanz, Y. Fernandez, M. P. Castroviejo, A. Perez and F. J. Fananas, Eur. J. Org. Chem., 2007, 62; (i) R. S. Reddy, C. Lagishetti, S. Chen, I. N. Chaithanya Kiran and Y. He, Org. Lett., 2016, 18, 4586.
- 7 Selected examples: (a) C. Lu, A. V. Dubrovskiy and R. C. Larock, J. Org. Chem., 2012, 77, 8648; (b) Y. Yang, H. Huang, L. Wu and Y. Liang, Org. Biomol. Chem., 2014, 12, 5351; (c) X. Peng, W. Wang, C. Jiang, D. Sun, Z. Xu and C.-H. Tung, Org. Lett., 2014, 16, 5354; (d) S. Pimparkar and M. Jeganmohan, Chem. Commun., 2014, 50, 12116; (e) M. Feng, B. Tang, N. Wang, H.-X. Xu and X. Jiang, Angew. Chem., Int. Ed., 2015, 54, 14960; (f) C. Zhu and T. R. Hoye, J. Am. Chem. Soc., 2022, 144, 7750; (g) R. Fang, S. Liu, Q. Yan, Y. Wei, J. Wang, Y. Lan and J. Tan, Chem. Sci., 2023, 14, 4278.
- 8 Selected reviews: (a) R. Sanz, Org. Prep. Proced. Int., 2008, 40, 215; (b) P. M. Tadross and B. M. Stoltz, Chem. Rev., 2012, 112, 3550; (c) A. V. Dubrovskiy, N. A. Markina and R. C. Larock, Org. Biomol. Chem., 2013, 11, 191; (d) R. W. Hoffmann and K. Suzuki, Angew. Chem., Int. Ed., 2013, 52, 2655; (e) D. Pérez, D. Peña and E. Guitían, Eur. J. Org. Chem., 2013, 5981; (f) J.-A. Garcia-Lopez and M. F. Greaney, Chem. Soc. Rev., 2016, 45, 6766; (g) O. J. Diamond and T. J. Marder, Org. Chem. Front., 2017, 4, 891; (h) F. I. M. Idiris and C. R. Jones, Org. Biomol. Chem., 2017, 15, 9044; (i) J. Shi, L. Li and Y. Li, Chem. Rev., 2021, 121, 3892.
- 9 Y. Himeshima, T. Sonoda and H. Kobayashi, Chem. Lett., 1983, 1211. 10 T. R. Hoye, B. Baire, D. Niu, P. H. Willoughby and B. P. Woods,
- Nature, 2012, 490, 208.
- 11 (a) P. Trinchera, W. Sun, J. E. Smith, D. Palomas, R. Crespo-Otero and C. R. Jones, Org. Lett., 2017, 19, 4644; (b) F. I. M. Idiris, C. E. Majesté, G. B. Craven and C. R. Jones, Chem. Sci., 2018, 9, 2873; (c) W. Sun, P. Trinchera, N. Kurdi, D. Palomas, R. Crespo-Otero, S. Afshinjavid, F. Javid and C. R. Jones, Synthesis, 2018, 4591; (d) Y. Yang, Y. Xu and C. R. Jones, Eur. J. Org. Chem., 2019, 5196; (e) E. A. Neal, A. Y. R. Werling and C. R. Jones, Chem. Commun., 2021, **57**, 1663; (f) Y. Xu, R. Xie, Q. Li, J. Feng, H. Luo, Q. Ye, Z. Guo, Y. Cao, M. Palma, G. Chai, M.-M. Titirici and C. R. Jones, Small, 2023, 2302795.
- 12 Unable to isolate pure sample of by-product. 1H NMR spectroscopic and mass spectrometric analyses of reaction mixture supported tentative assignment: postulated attack of aniline nitrogen onto second molecule of aryne affords quaternary ammonium species that could undergo cleavage of labile N-benzyl bond.
- 13 J. M. Medina, J. L. Mackey, N. K. Garg and K. N. Houk, J. Am. Chem. Soc., 2014, 136, 15798.
- 14 H. Takikawa, A. Nishii, H. Takiguchi, H. Yagashita, M. Tanaka, K. Hirano, M. Uchiyama, K. Ohmori and K. Suzuki, Angew. Chem., Int. Ed., 2020, 59, 12440.
- 15 H. Wang, Z. Wang, H. Huang, J. Tan and K. Xu, 18-Crown-6 ether was found to promote oxidation. No reduction in phenanthridinone yield when reaction conducted in the presence of TEMPO (1.3 equivalents) and no substrate-TEMPO adducts observed, Org. Lett., 2016, 18, 5680.