ORGANIC CHEMISTRY FRONTIERS

RESEARCH ARTICLE

View Article Online
View Journal

Cite this: DOI: 10.1039/d6qo00305b

The lateral lithiation of pyrazoles: direct, transition-metal-free access to pyrazolopyridinones and pyrazolopyranones

Kaijie Ji,[a] Jason An,[a] Kyle W. Rugg,[a] Shayla G. Wood,[b] Lakshi M. Thilakarathne,[b] Krishna P. Gnyawali,[b] Jesse D. Carrick[b] and Jonathan T. Reeves *[a]

Received 11th March 2026,
Accepted 13th April 2026

DOI: 10.1039/d6qo00305b

rsc.li/frontiers-organic

Lateral lithiation of amidopyrazoles enables an expedient, modular, transition metal-free synthesis of pharmaceutically relevant pyrazolopyridinones and pyrazolopyranones *via* reaction with nitriles or esters, respectively. The reactions are amenable to alkyl or (het)aryl groups at C-6 and N-1. Secondary amide and nitrile directing groups give access to N-5 alkyl and C-4 amino substitution, and functionalization of the C-3 and C-7 positions of the pyrazolopyridinones is also feasible. 2-Cyanopyridines and dinitriles furnish products with potential as ligands for transition metals.

Introduction

Pyrazoles and their heterocycle-fused analogues are privileged pharmacophores in medicinal chemistry.[1] Globally, more than 50 marketed drugs contain a pyrazole, a testament to the favourable properties it imparts.[2] Pyrazoles fused with pyridones form the cores of compounds for the treatment of cancer (**1**),[3a] respiratory disease (**2**)[3b] and neurodegenerative disease (**3**),[3c] while the ATR inhibitor (**4**)[3d] has the related aminopyridine fusion (Fig. 1). The anti-microbial **5** [ref. 3*e*] and hepatic cancer treatment **6** [ref. 3*f*] bear the related pyrazole-fused pyranone core. A recent drug development program in our labs required efficient access to both of these heterocycles. The five-step route shown in Fig. 2A or variations thereof comprised the known synthetic avenues to pyrazolopyridinones **9**.[4] In this route, the pyrazole ring was built in three steps from trichloropyridine **7**, and a Suzuki–Miyaura cross-coupling incorporated a 6-aryl group. The pyrazolopyranones **12** were prepared in four steps from malonate **10** (Fig. 2B).[5] Pyrazole formation followed by triflation gave **11**, which was cross-coupled with an alkyne and cyclized with acid to give **12**.[6] For efficiency and throughput, we sought shorter routes to **9** and **12**, ideally without the cost and challenges of metal removal often associated with palladium catalysts.[7] We also required an approach compatible with alkyl, aryl, or H groups on N-1 of the pyrazole. Lateral lithiation, a process in which an alkyl group on an aryl or hetaryl ring is deprotonated with assistance from an adjacent coordinating group, seemed potentially suited to these goals.[8] The lateral lithiation of *ortho*-methyl benzamides and reaction of the resultant anions with nitriles gives isoquinolones,[9] while esters afford isocoumarins.[10] In contrast, the lateral lithiation of amidopyrazoles is, to the best of our knowledge, unknown. The lithiation of a methylpyrazole with no directing group using *tert*-butyllithium and low-yield addition of the anion to ketones was reported in the patent literature, and underscores the difficulty of deprotonation when the coordinating and electron-withdrawing effects of an adjacent directing group are absent.[11] If an amido methyl pyrazole such as **13** were amenable to lateral lithiation, the resultant anion **14** could enable a short route to both pyrazolopyridinones **15** and pyrazolopyranones **16** *via* reactions with nitriles or esters, respectively (Fig. 2C). This route would

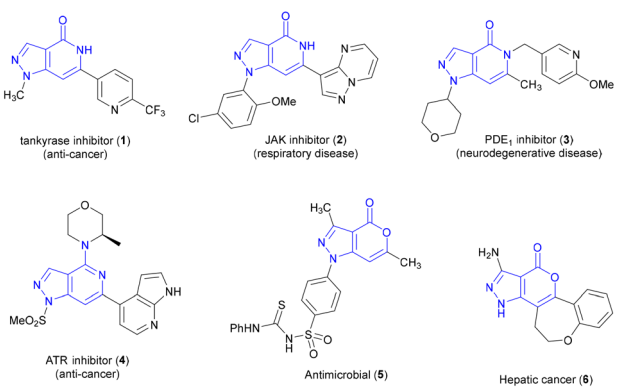


Fig. 1 Therapeutic compounds containing a pyrazolo[4,3-*c*]pyridin-4-one (**1–3**), pyrazolo[4,3-*c*]pyridin-4-ylamine (**4**) or a pyrano[4,3-*c*]pyrazol-4-one (**5–6**).

[a]*Chemical Development, Boehringer Ingelheim Pharmaceuticals, Inc., Ridgefield, Connecticut 06877, USA. E-mail: jonathan.reeves@boehringer-ingelheim.com*
[b]*Department of Chemistry, Tennessee Technological University, Cookeville, Tennessee 38505, USA*

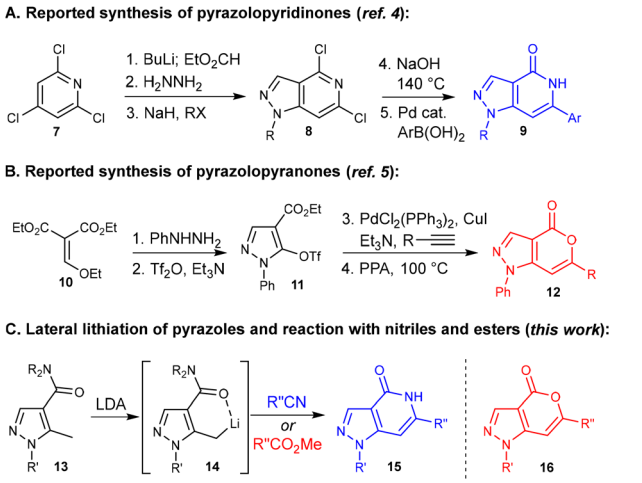


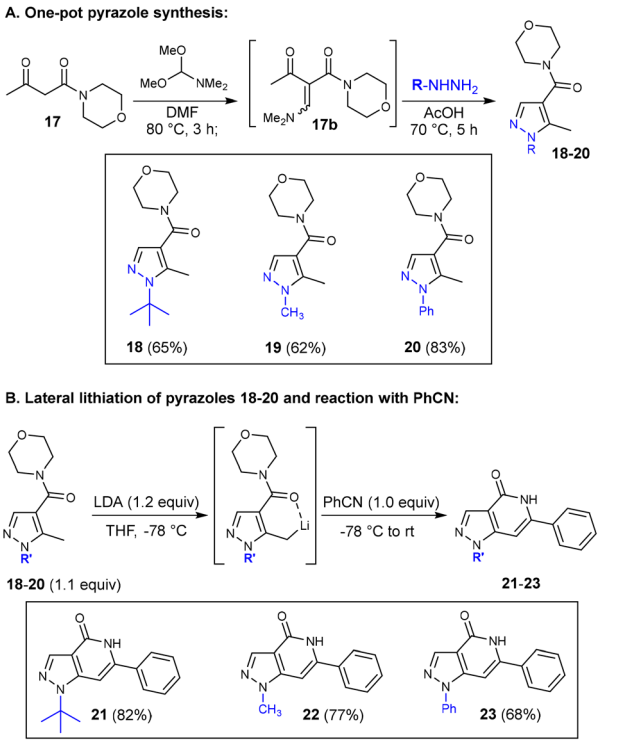
Fig. 2 Known syntheses of (A) pyrazolopyridinones and (B) pyrazolopyranones, and (C) our direct route to both *via* the lateral lithiation of amidopyrazoles.

allow ready variation of the pyrazole N-1 group and the pyridinone/pyranone C-6 group, avoid the use of Pd catalysts, and require only two steps from commercially available starting materials.

To succeed, lithiation must occur selectively at the C-5 methyl group and not the C-3 position, and the lithiated species must react with the intended electrophile and not undergo self-condensation. The development, substrate scope, and application of these reactions to provide access to ligands for transition metals are reported herein.

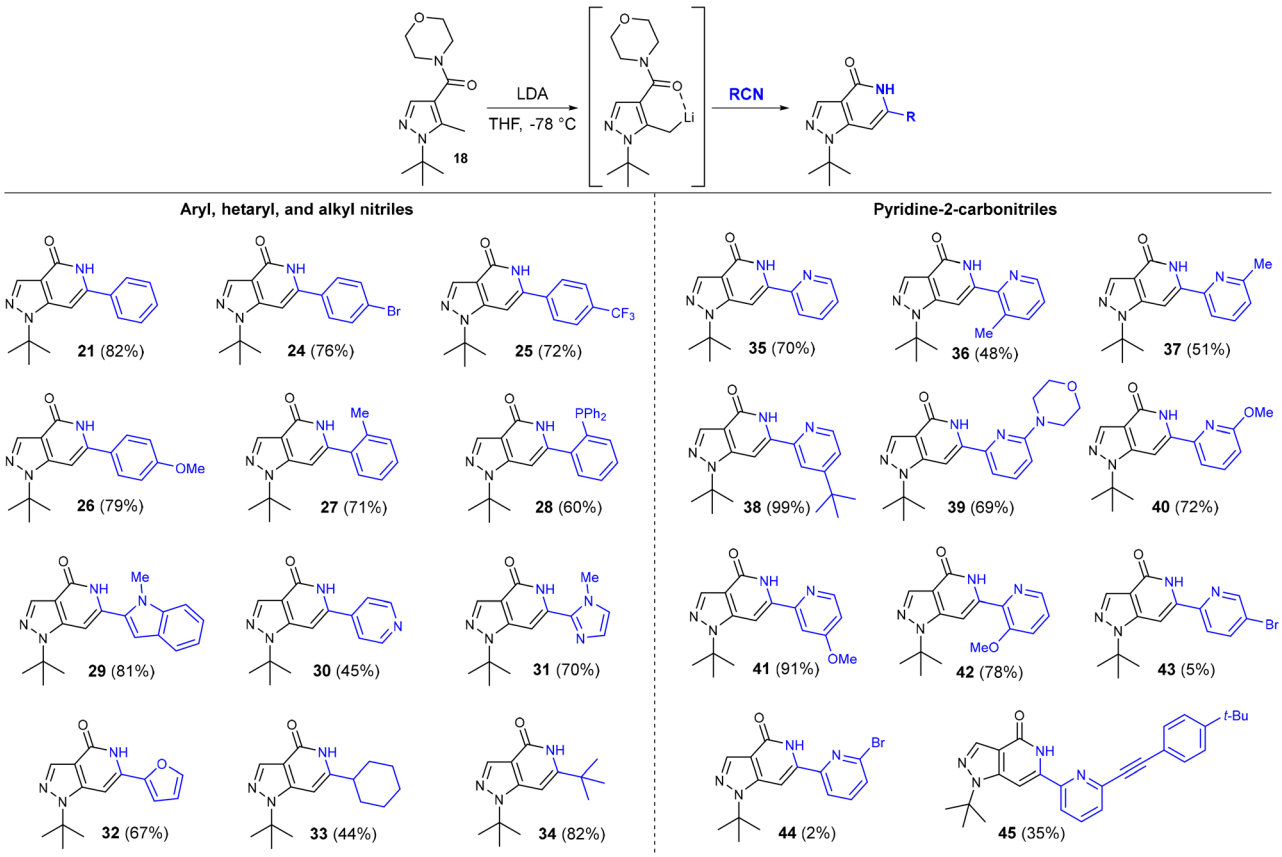
Results and discussion

The requisite pyrazoles were prepared in a one-pot process from commercially available acetoacetamide **17** (Scheme 1A). Heating **17** with *N*,*N*-dimethylformamide dimethyl acetal at 80 °C furnished enamide **17b**, and subsequent addition of AcOH and a substituted hydrazine led to the target pyrazoles. Product isolation was accomplished by direct crystallization upon addition of water to the reaction mixture and recrystallization for purification. This one-step preparation allows ready variation of the pyrazole N-1 group *via* the choice of the appropriate hydrazine, many of which are commercially available. The feasibility of the lateral lithiation was then explored using pyrazoles **18–20** (Scheme 1B). A slurry of the pyrazole (1.1 equiv.) in THF at −78 °C was treated with LDA (1.2 equiv.), resulting in immediate formation of a bright yellow solution of the anion. After 10 min of stirring, benzonitrile (1.0 equiv.) was added dropwise, and the reaction mixture was allowed to warm to ambient temperature. Quenching with aqueous NH_4Cl and removal of the organic solvent under vacuum led to crystallization of the desired products (**21–23**). Performing the reaction at 0 °C instead of −78 °C resulted in a substantial increase in impurities. While *n*-BuLi and *sec*-BuLi were also effective bases for the transformation, LDA was preferred due



Scheme 1 Concise pyrazole synthesis (A) and lateral lithiation/reaction with benzonitrile leading to pyrazolopyridinones (B). Typical reaction conditions: pyrazole (1.1 equiv.), LDA (1.2 equiv.), THF, −78 °C, 10 min; PhCN (1.0 equiv.), −78 °C to rt, 70 min. Isolated yields after purification.

to its greater functional group tolerance. LHMDS was not strong enough to perform the lithiation. The selectivity of the lithiation can be explained by the greater acidity of C-5 of 1-substituted pyrazoles compared to C-3.[12] The deprotonation proceeds *via* initial coordination of the Lewis-basic carbonyl oxygen of the amide with the lithium ion of LDA, followed by proton abstraction from the lateral methyl group, aided by the proximity and directing effect of the amide, as well as its inductive electron-withdrawing effect.[8a] Both alkyl and aryl groups were tolerated on the pyrazole nitrogen. Due to its convenient ability to be removed under mildly acidic conditions (*vide infra*), *tert*-butyl substituted pyrazole **18** was chosen to explore the nitrile scope (Scheme 2). The reaction worked well for a variety of substituted phenyl groups and was notably tolerant of a bromo-substituent (**24**). An *ortho*-diphenylphosphino moiety in the reacting nitrile led to **28**, a compound with potential as a metal ligand.[13] Heterocyclic nitriles provided compounds **29–32** in good yields. Aliphatic nitriles were amenable to the reaction, though in attenuated yield for pyridone **33** derived from cyclohexanecarbonitrile, perhaps due to the enolizability of the nitrile leading to unproductive deprotonation, as well as addition. The reaction of pyridine 2-carbonitriles was of particular interest due to the potential of the products to serve as bidentate ligands, either directly or following derivatization, and therefore, this class of nitriles was explored more deeply.[14] The parent compound gave 2-pyridyl pyridone

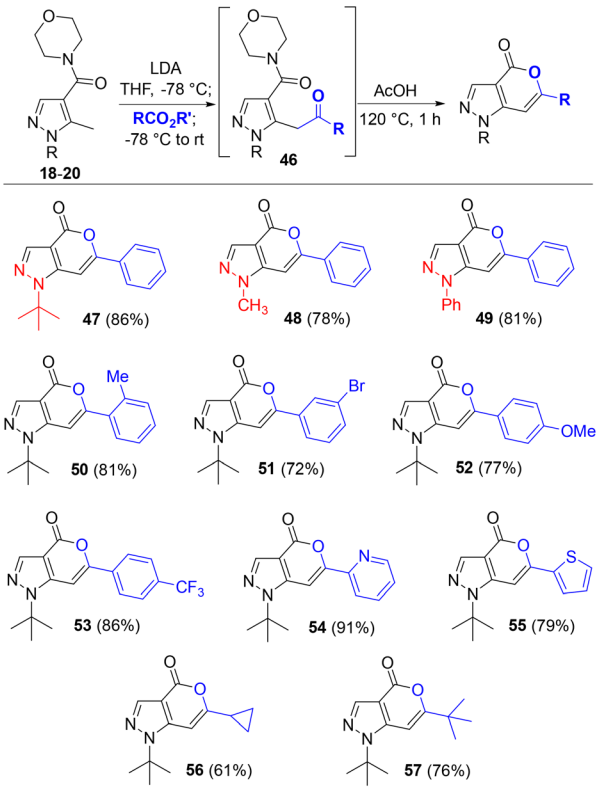


Scheme 2 Scope of the reaction with nitriles. Typical reaction conditions: pyrazole (1.1 equiv.), LDA (1.2 equiv.), THF, −78 °C, 10 min; RCN (1.0 equiv.), −78 °C to rt, 70 min. Isolated yields after purification.

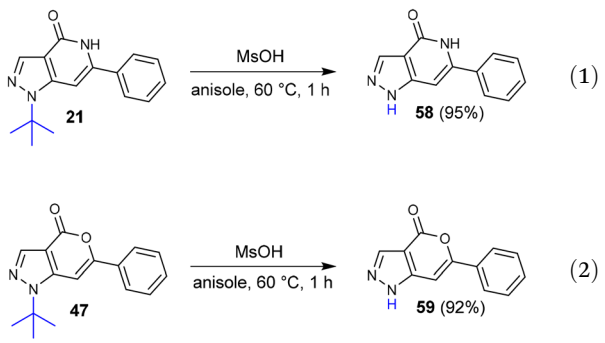
35 in 70% yield. Alkyl substitution at the 3-, 4-, or 6-positions of the pyridyl nitrile was tolerated, with excellent yields of compounds **36–38** being afforded. Nitriles with electron-donating groups, including morpholino (**39**) and methoxy (**40–42**) groups, were also competent substrates. A general trend of electron-rich nitriles working best in the reaction was noted. In contrast, more electron-poor 5- or 6-bromo substituted nitriles gave very low yields of products **43** and **44**. In these cases, the initial addition of the lithiated pyrazole to the nitrile proceeds, but the cyclization of the resultant adduct does not, underscoring the need for sufficient electron density to promote cyclization. Efforts to force cyclization (heat or microwave) were unsuccessful. Finally, the alkynyl-substituted pyridine adduct **45** was produced in a modest yield of 35%.

The reaction of laterally lithiated pyrazoles with esters was next examined (Scheme 3). Treatment of pyrazoles **18–20** with LDA at −78 °C and subsequent addition of an ester gave ketone intermediates **46**, which were cyclized *in situ* with the addition of AcOH (equal volume relative to THF) and heating at 120 °C for 1 h with concurrent distillation of THF.[10a] This smoothly cyclized the ketoamide intermediates into pyranones. Two equivalents of LDA were necessary to obtain complete conversion of ester electrophiles. We suspect this is attributable to competitive deprotonation of ketone intermediate **46** with laterally lithiated pyrazole. As with the pyrazolopyridinones, the pyrazolopyranones could often be isolated in pure form by crystallization of the crude product after workup. The reaction was tolerant of variation of the N-1 group, as shown by products **47–49**. Likewise, a diverse assortment of esters reacted smoothly. *ortho*-, *meta*- and *para*-substituted benzoates afforded good yields of products **47–50**. Heterocyclic esters performed equally well in furnishing products **54–55**. Notably, unlike in the case of nitriles, electron-poor substrates were well tolerated due to the different mode of cyclization. Aliphatic esters gave cyclopropyl and *tert*-butyl substituted pyranones **56–57** in good yields.

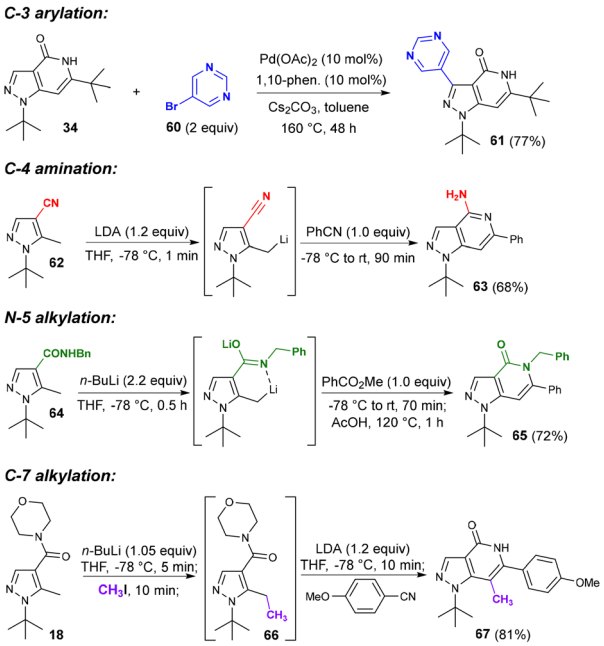
As previously noted, a key design principle was that the *tert*-butyl group could be deprotected from both pyrazolopyridinones and pyrazolopyranones under acidic conditions with MsOH. Deprotection of an N-1 *tert*-butyl group in a pyrazolopyrimidine thione using refluxing formic acid has been reported, but these conditions gave only trace amounts of product in the present case.[15] However, heating **21** in a mixture of MsOH and anisole at 60 °C for 1 h provided N–H pyrazole **58** cleanly in excellent yield (eqn (1)). Pyrazolopyranone **47** was deprotected with similar facility, and product **59** was isolated in 92% yield (eqn (2)).



Scheme 3 Scope of the reaction with esters. Typical reaction conditions: pyrazole (1.1 equiv.), LDA (2.0 equiv.), THF, −78 °C, 10 min; ester (1.0 equiv.), −78 °C to rt, 70 min; addition of AcOH, heating at 120 °C, 1 h. Isolated yields after purification.



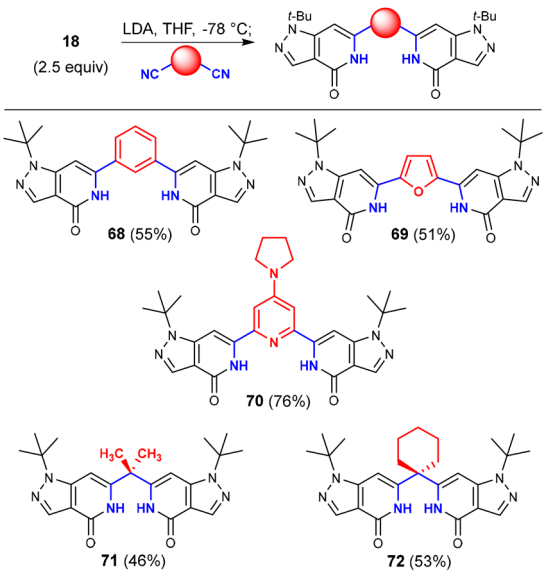
The pyrazolopyridinones could be functionalized at the four remaining positions (C-3, C-4, N-5 and C-7) as shown in Scheme 4. The conditions reported by Yu and co-workers for the C–H arylation of indazoles and pyrazoles were effective for the arylation of **34** with bromide **60**, furnishing the C-3 arylated **61** in 77% yield.[16] Lateral lithiation of nitrile **62**, which was accomplished by inverse addition to a solution of LDA and subsequent reaction with benzonitrile, gave the useful C-4 amino pyridinone **63** in 68% yield.[17] Alternatively, secondary amide **64**, which required the stronger base *n*-BuLi for dilithiation, reacted with methyl benzoate to give an amido ketone intermediate that cyclodehydrated upon treatment with AcOH to give the *N*-benzyl pyridone **65**.[18] Lateral lithiation of **18** with *n*-BuLi and addition of methyl iodide cleanly formed the alkylated pyrazole **66**.



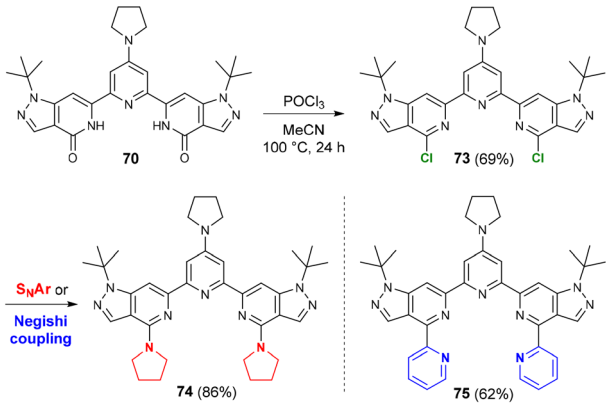
Scheme 4 Functionalization of the C-3, C-4, N-5 and C-7 positions of pyrazolopyridinones. See SI for detailed reaction conditions. Isolated yields after purification.

Subsequent addition of LDA followed by 4-methoxybenzonitrile furnished the C-7 methylated pyridone **67** in good yield. The ability to functionalize the pyrazolopyridinone at all possible positions should increase the utility of the methodology, particularly for medicinal chemistry applications.

Scheme 5 shows the bidirectional reactions of dinitriles with **18**, which provide a convenient route to bis-pyridone pro-



Scheme 5 Reaction of laterally lithiated **18** with dinitriles. Typical reaction conditions: pyrazole (2.5 equiv.), LDA (3.0 equiv.), THF, −78 °C, 10 min; dinitrile (1.0 equiv.), −78 °C to rt, 70 min. Isolated yields after purification.



Scheme 6 Elaboration of bis-pyridone **70**. Reaction conditions. S_NAr: **70** (1.0 equiv.), pyrrolidine (20 equiv.), NMP, 80 °C, 24 h. Negishi: **70** (1.0 equiv.), 2-pyridylzinc chloride (10 equiv.), $Pd_2(dba)_3$ (2 mol%), X-Phos (8 mol%) THF/2-MeTHF, 75 °C, 48 h. Isolated yields after purification.

ducts. To the best of our knowledge, this is the first example of a dinitrile participating in a double lateral lithiation/addition reaction. The reaction of 1,3-dicyanobenzene gave bis-pyridone **68** in moderate yield (55%). 2,5-Dicyanofuran participated in the reaction, furnishing **69** in 51% yield. While 2,6-dicyanopyridine failed to give a bis-pyridone product, the more electron-rich 4-pyrrolidino analog was successful, providing bis-pyridonylpyridine **70** in 76% yield (5 g scale). Soft-*N*-donor **70** is especially interesting due to its potential application as a transition metal ligand (*vide infra*). Switching from (het)aryl dinitriles to alkyl dinitriles was feasible, as demonstrated by successful reactions of dimethylmalononitrile and 1,1-dicyanocyclohexane to give **71** and **72**. Although the yields were modest, the complexity produced in a single step from dinitriles could prove useful for the synthesis of pyridine or pyridone ligands,[14] or for applications in supramolecular chemistry.[19]

The bis-pyridone **70** was further elaborated by deoxychlorination with $POCl_3$ to give **73** (Scheme 6). Notably, no deprotection of the *tert*-butyl group occurred during the reaction with $POCl_3$. S_NAr reaction of **73** with pyrrolidine gave tripyridine **74**. Alternatively, Negishi cross-coupling with 2-pyridyl zinc chloride furnished pentapyridine **75**.[20] The chloropyridines derived from $POCl_3$ treatment of pyrazolopyridinones offer a convenient handle for derivatization into polydentate and electronically-tunable ligands.

Conclusions

In summary, a concise and modular method to access pyrazolopyridinones and pyrazolopyranones was developed by employing the first lateral lithiation of an amidopyrazole. This route is considerably shorter, free of transition metals, and of broader scope than previously reported routes to these structures. Conditions for one-pot preparation of the pyrazolyl amide starting materials were developed, making the entire route to the target structures just two steps. Most products prepared herein were conveniently isolated/purified *via* crystallization. The *tert*-butyl moiety was an efficient pyrazole protecting group that was removable in high yields using MsOH. Nitrile and secondary amide directing groups on the pyrazole were effective directing groups, and their reactions led to novel products. The pyrazolopyridinone could be directly C-3 arylated, or C-7 functionalized *via in situ* alkylation of the pyrazole. Applying the methodology to dinitriles provided a novel path to ligand-like bis-pyridones. S_NAr or Negishi cross-coupling reactions of the derived chloropyridines provided tri- and pentapyridine products, demonstrating the potential for making complex metal ligand scaffolds using this methodology.

Author contributions

J. T. Reeves conceptualized the work. J. T. Reeves and J. D. Carrick designed the experiments. K. Ji, J. An, K. W. Rugg, S. G. Wood, L. M. Thilakarathne, K. P. Gnyawali and J. T. Reeves performed the experiments. J. T. Reeves and J. D. Carrick co-wrote the manuscript.

Conflicts of interest

There are no conflicts to declare.

Data availability

The supporting data are provided as part of the supplementary information (SI). Supplementary information: experimental procedures, characterization data and copies of NMR spectra. See DOI: **https://doi.org/10.1039/d6qo00305b**.

Acknowledgements

We are grateful to Mr Scott Pennino for HRMS analysis and Dr Feng Yang for preliminary experiments.

References

1 (*a*) T. L. Gilchrist, *Heterocyclic Chemistry*, Longman Scientific & Technical, 1992; (*b*) M. A. Alam, Pyrazole: An Emerging Privileged Scaffold in Drug Discovery, *Future Med. Chem.*, 2023, **15**, 2011–2023; (*c*) A. Ansari, A. Ali, M. Asif and Shamsuzzaman, Review: biologically active pyrazole derivatives, *New J. Chem.*, 2017, **41**, 16–41.

2 G. Li, Y. Cheng, C. Han, C. Song, N. Huang and Y. Du, Pyrazole-containing pharmaceuticals: target, pharmacological activity, and their SAR studies, *RSC Med. Chem.*, 2022, **13**, 1300–1321.

3 (*a*) J. Feng, N. E. Haynes, J. C. Hermann, K. Kim, J.-J. Liu, N. R. Scott, L. Yi, M. Zak and G. Zhao, Preparation of pyrazolopyrimidones and pyrazolopyridones as tankyrase inhibitors, *PCT Int. Appl*, WO/2013/182546A1, 2013; (*b*) A. Accetta, F. Rancati, A. Rizzi, A. Cuzzolin, M. Mesic, R. Zadravec, D. Ziher and I. Elenkov, Heterocyclic Derivatives as Janus Kinase Inhibitors, *PCT Int. Appl*, WO/2022/194779A1, 2022; (*c*) K. Juhl, M. Jessing, M. Langgard, P. J. V. Vital, M. Marigo, J. Kehler and L. K. Rasmussen, 1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-ones and 1,5-dihydro-4H-pyrazolo[4,3-c]pyridin-4-ones as PDE1 Inhibitors, *US Pat*, US20170291901A1, 2013; (*d*) K. Long, Substituted condensed heterocyclic compound, preparation method and application thereof, *CN Pat*, CN202111571407, 2021; (*e*) F. H. Bamane, Synthesis and biological evaluation of some pyrano[4,3-c]pyrazole and pyrazolo[4,3-c]pyridine derivatives as antimicrobial agents, *Mansoura J. Pharm. Sci.*, 2010, **26**, 141–148; (*f*) H. K. Maurya, S. K. Gautam, R. Pratap, V. K. Tandon, A. Kumar, B. Kumar, S. Saxena, D. Tripathi, M. Rajwanshi, M. Das and V. J. Ram, Regioselective synthesis of polycyclic aza-oxa and aza-oxa-thia heteroarenes as Colo-205 and HepG2 carcinoma cells growth inhibitors, *Eur. J. Med. Chem.*, 2014, **81**, 367–377.

4 (*a*) S. Kumar, S. Gupta, L. F. Abadi, S. Gaikwad, D. Desai, K. K. Bhutani, S. Kulkarni and I. P. Singh, Synthesis and in vitro anti-HIV-1 evaluation of novel pyrazolo[4,3-c]pyridine-4-one derivatives, *Eur. J. Med. Chem.*, 2019, **183**, 111714; (*b*) J. W. Coe, C. M. Dehnhardt, P. Jones, Y. A. Sabnis, J. W. Strohbach, F. M. Wakenhut and G. A. Whitlock, Pyrazolopyridines and pyrazolopyrimidines, *PCT Int. Appl*, WO/2015/173683, 2015.

5 A. W. Taylor and R. T. Cook, A direct preparation of 2-aryl-4-ethoxycarbonyl-3-pyrazolin-5-ones from aryl hydrazines, *Tetrahedron*, 1987, **43**, 607–616.

6 (*a*) E. Arbaciauskiene, G. Vilkauskaite, A. Sackus and W. Holzer, Ethyl 3-and 5-Triflyloxy-1H-pyrazole-4-carboxylates in the Synthesis of Condensed Pyrazoles by Pd-Catalysed Cross-Coupling Reactions, *Eur. J. Org. Chem.*, 2011, 1880–1890; (*b*) D. R. Gorja, V. R. Batchu, A. Ettam and M. Pal, *Beilstein J. Org. Chem.*, 2009, **5**, DOI: **10.3762/bjoc.5.64**; (*c*) A. Cantos, P. de March, M. Moreno-Manas, A. Pla, F. Sanchez-Ferrando and A. Virgili, Synthesis of Pyrano[4,3-c]pyrazol-4(1H)-ones and -4(2H)-ones from Dehydroacetic Acid. Homo- and Heteronuclear Selective NOE Measurements for Unambiguous Structure Assignment, *Bull. Chem. Soc. Jpn.*, 1987, **60**, 4425–4431.

7 Residual Pd levels in active pharmaceutical ingredients must be controlled below 10 ppm; see International Council for Harmonisation (ICH), "ICH Guideline Q3D (R1) on elemental impurities," March 22, 2019.

8 (*a*) R. D. Clark and A. Jahangir, Lateral lithiation reactions promoted by heteroatomic substituents, *Org. React.*, 1995, **47**, 1–314; (*b*) J. N. Reed, Product subclass 13: Benzyllithium compounds and (lithiomethyl)hetarenes, *Sci. Synth.*, 2006, **8a**, 329–355; (*c*) A. E. H. Wheatley, The directed lithiation of benzenoid aromatic systems, *Eur. J. Inorg. Chem.*, 2003, **18**, 3291–3303; (*d*) R. L. Vaulx, W. H. Puterbaugh and C. R. Hauser, Metalation of *N*-Methyl-o-toluamide with Excess *n*-Butyllithium. Condensations with Ketones and Aldehydes. Cyclizations, *J. Org. Chem.*, 1964, **29**, 3514–3517; (*e*) R. E. Ludt, J. S. Griffiths, K. N. McGrath and C. R. Hauser, Comparison of the synthetic utility of *n*-butyllithium and lithium diisopropylamide in the metalations of *N*,*N*-dialkyltoluamides, *J. Org. Chem.*, 1973, **38**, 1668–1674.

9 (*a*) G. S. Poindexter, Convenient Preparation of 3-Substituted 1(2H)-Isoquinolinones, *J. Org. Chem.*, 1982, **47**, 3787–3788; (*b*) T. R. Kelly, S. H. Bell, N. Ohashi and R. J. Armstrong-Chong, Synthesis of (±)-fredericamycin A, *J. Am. Chem. Soc.*, 1988, **110**, 6471–6480; (*c*) T. N. Le, S. G. Gang and W.-J. Cho, A facile synthesis of benzo[c]phenanthridine alkaloids: oxynitidine and oxysanguinarine using lithiated toluamide-benzonitrile cycloaddition, *Tetrahedron Lett.*, 2004, **45**, 2763–2766.

10 (*a*) S. Ohta, Y. Kamata, T. Inagaki, Y. Masuda, S. Yamamoto, M. Yamashita and I. Kawasaki, Synthesis of 3-substituted isocoumarins and related natural products, *Chem. Pharm. Bull.*, 1993, **41**, 1188–1190; (*b*) N. Thasana and S. Ruchirawat, The synthesis of wrightiadione via directed remote metalation, *Synlett*, 2003, 1037–1039; (*c*) C. N. Lewis, P. L. Spargo and J. A. Staunton, A Convenient Synthesis of 3-Substituted 8-Methoxy- and 6,8-Dimethoxyisocoumarins, *Synthesis*, 1986, 944–946.

11 D. S. Hays, R. B. Prince, C. A. Haraldson and J. D. Bonk, Preparation of 1-substituted pyrazolo[3,4-c]pyridines, 6,7,8,9-tetrahydro/pyrazolo[3,4-c]quinolines, and pyrazo-lo[3,4-c]naphthyridines as modulators of cytokine biosynthesis for treatment of viral and neoplastic diseases, *PCT Int. Appl*, WO/2006/107851A1, 2006.

12 (*a*) K. D. Muldur, A. Zukaustaite, A. Sackus and E. Arbaciauskiene, Recent Synthetic Advances in C–H/N–H Functionalization of 1*H*-Pyrazoles: Diverse Strategies Across Variously Substituted Scaffolds, *Chem. Rec.*, 2025, e202500024; (*b*) E. Kang, H. T. Kim and J. M. Joo, *Org. Biomol. Chem.*, 2020, **18**, 6192–6210.

13 C. Zeng, N. Wang, T. Peng and S. Wang, Copper(I) Complexes Bearing 1,2-Phenyl-Bridged P^N, P^N^P, and N^P^N Chelate Ligands: Structures and Phosphorescence, *Inorg. Chem.*, 2017, **56**, 1616–1625.

14 A. Fedulin and A. J. von Wangelin, 2-Pyridonates: a versatile ligand platform in 3d transition metal coordination chemistry and catalysis, *Catal. Sci. Technol.*, 2024, **14**, 26–42.

15 P. Giori, T. Poli, C. B. Vicentini, M. Manfrini, M. Guarneri and V. Brandolini, Synthesis and Antifungal Activity of Pyrazolo[3,4-d]pyrimidin-4(5H)-thiones, *Farmaco Sci.*, 1985, **40**, 795–802.

16 M. Ye, A. J. F. Edmunds, J. A. Morris, D. Sale, Y. Zhang and J.-Q. Yu, A robust protocol for Pd(II)-catalyzed C-3 arylation of (1H) indazoles and pyrazoles: total synthesis of nigellidine hydrobromide, *Chem. Sci.*, 2013, **4**, 2374–2379.

17 M. A. H. de Zwart, H. van der Goot and H. Timmerman, Synthesis and copper-dependent antimycoplasmal activity

of 1-amino-3-(2-pyridyl)isoquinoline derivatives. 1. Amides, *J. Med. Chem.*, 1988, **31**, 716–722.
18 R. S. Mali, B. K. Kulkarni and K. Shankaran, A Convenient Synthesis of *N*-Methyl-1(2H)-isoquinolones, *Synthesis*, 1982, 329–330.
19 J. M. Lehn, Supramolecular Chemistry, *Science*, 1993, **260**, 1762–1763.
20 M. R. Luzung, J. S. Patel and J. A. Yin, A Mild Negishi Cross-Coupling of 2-Heterocyclic Organozinc Reagents and Aryl Chlorides, *J. Org. Chem.*, 2010, **75**, 8330–8332.