Unified Access to Pyrimidines and Quinazolines Enabled by N–N Cleaving Carbon Atom Insertion

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ABSTRACT: Given the ubiquity of heterocycles in biologically active molecules, transformations with the capacity to modify such molecular skeletons with modularity remain highly desirable. Ring expansions that enable interconversion of privileged heterocyclic motifs are especially interesting in this regard. As such, the known mechanisms for ring expansion and contraction determine the classes of heterocycle amenable to skeletal editing. Herein, we report a reaction that selectively cleaves the N–N bond of pyrazole and indazole cores to afford pyrimidines and quinazolines, respectively. This chlorodiazirine-mediated reaction provides a unified route to a related pair of heterocycles that are otherwise typically prepared by divergent approaches. Mechanistic experiments and DFT calculations support a pathway involving pyrazolium ylide fragmentation followed by cyclization of the ring-opened diazahexatriene intermediate to yield the new diazine core. Beyond enabling access to valuable heteroarenes from easily prepared starting materials, we demonstrate the synthetic utility of skeletal editing in the synthesis of a Rosuvastatin analog as well as in an aryl vector-adjusting direct scaffold hop.

Heterocycles are highly valuable scaffolds for medicinal chemistry, as evidenced by their presence in a majority of biologically active compounds.1,2 More specifically, pyrimidines and quinazolines are frequently featured substructures in drug discovery campaigns and remain popular, appearing, for example, in the recently approved kinase inhibitor Belumosudil and the classic HMG-CoA reductase inhibitor Rosuvastatin (Figure 1A).3−10

Despite the popularity of these targets, they remain challenging to prepare in a modular fashion, with syntheses often limited by substitutional constraints and the use of strong oxidants.11−13 To this point, the apparent structural similarity between pyrimidines and quinazolines is deceptive, as it does not translate to similarity in synthesis. These two heterocycles require surprisingly divergent retrosynthetic strategies, with pyrimidines typically prepared from dicarbonyl condensations whereas quinazolines are more commonly prepared from 2-aminophenyl carbonyl compounds.14−16 To date, there remain few strategies enabling access to both pyrimidines and quinazolines from analogous precursors,16−18 an unfortunate fact given that the enabling retrosynthetic simplicity of such unified methods is a common feature of workhorse transformations in medicinal chemistry.19,20 Herein, we report a strategy to access pyrimidines and quinazolines from pyrazoles and indazoles (also frequent scaffolds in medicinal chemistry), respectively, offering an intuitive, common carbon-insertion retrosynthetic disconnection to both motifs.

Our group’s recent work employing chlorodiazirines to promote ring expansion of indoles and pyrroles (Figure 1B) inspired us to continue investigating their reaction with other aromatic heterocycles.21,22 These reagents can be easily prepared from commercially available amidine salts in one step and serve as convenient halocarbene precursors.23−25 The

Figure 1. Introduction. (A) Selected examples of azoles and azines in drugs. (B) Chlorodiazirines for ring expansion of pyrroles and indoles. (C) Ring expansion of pyrazoles and indazoles to pyrimidines and quinazolines

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energetic properties of these compounds have been experimentally determined.\textsuperscript{26}

We hypothesized that pyrazoles would demonstrate analogous reactivity to that of pyroles in the presence of chlorocarbene intermediates, originally envisioning that a [2 + 1] cycloaddition could occur in a similar fashion and provide access to the corresponding pyridazine adducts.\textsuperscript{27–29} To our surprise, the anticipated reaction was not observed, instead affording pyrimidine products through an overall insertion into the N–N bond (Figure 1C). We discuss the mechanism of this serendipitous finding at greater length below; there is, however, a surprising dearth of literature surrounding functionalization of the relatively weak pyrazole N–N bond, especially toward the productive formation of other valuable products.

Under similar conditions to those optimized for indoles and pyroles (60 °C in acetonitrile, excess Na$_2$CO$_3$), model substrate 2a afforded the corresponding pyrimidine 3a in 67% yield alongside formation of the dimeric bis(pyrazolyl)methane side product 6 in 28% yield (Figure 2). Despite this promising start,

Figure 2. Solvent Effect. Reactions were carried out on 0.1–0.3 mmol scale. Yield by \textsuperscript{1}H-NMR using mesitylene as an internal standard.

these same conditions afforded dramatically lower yields for most pyrazoles and indazoles. For example, the unsubstituted pyrazole 2b afforded the corresponding pyrimidine in a mere 37% yield and quinazoline 5a was obtained in only 28% from the corresponding indazole 4a.

We noted, however, that most indazoles were largely insoluble in acetonitrile even at elevated temperatures, prompting us to reexamine the reaction medium. Our prior studies had employed acetonitrile due to the absence of competitive side reactions with the chlorocarbene intermediate (e.g., O–H or C–H insertion).\textsuperscript{30} Ethereal solvents had initially been avoided for this reason, but the observation that indazoles are highly soluble in such solvents encouraged a more thorough survey. We discovered that methyl tert-butyl ether (MtBE) was a far more general solvent, affording higher yields for both pyrazole and indazole substrates and decreasing the extent of dimer formation. Unlike tetrahydrofuran, which forms substantial amounts of α-functionalized products in the presence of chlorozadine, MtBE affords only a trace of such side-products, likely a function of steric protection coupled with its marginally stronger α-CH bonds.\textsuperscript{30,31} Under these conditions, lower loadings of diazirine resulted in diminished yields (see Figure S1 for details).

With these conditions in hand, we began to explore the scope of this skeletal transformation, beginning with pyrazoles (Figure 3). A wide variety of ortho-, meta-, and para-substituted aryl chlorodiazirines were found to be suitable coupling partners (3a–3an). An interesting divergence from our previously reported chemistry was observed: whereas indoles and pyroles did not react with p-methoxylphenyl chlorodiazirine (leading instead to the corresponding benzaldehyde side product\textsuperscript{21}), pyrazoles underwent productive reactivity with this substrate. This enhanced reactivity can be attributed to the increased nucleophilicity of pyrazoles relative to pyroles (May N = 8.8 vs 4.6).\textsuperscript{7,20} No major constraints in substitution pattern on the pyrazole were observed (3a–3f), allowing one to decorate pyrimidines with any desired alky substitution pattern, in contrast to many existing pyrimidine syntheses.\textsuperscript{11} In addition, esters (3n), protected amines (3l), alcohols (3i), and bromides (3m) were all well-tolerated. Many of these functionalities were not compatible with our prior pyrole chemistry.

When the pyrazole is rendered sufficiently electron poor (e.g., 2p and 2q), the reaction often instead preferentially forms the bis(pyrazolyl)methane side-product even in MtBE solvent. This limitation can be overcome by employing a 2-(Trimethylsilyl)-ethoxymethyl (SEM) protecting group, which prevents dimer formation and rescues the pyrimidine product. This group is easily cleaved with a TBAT workup prior to isolation.

Unnatural nucleosides are recognized as a useful pharmacophore, with many high-profile antiviral and oncologic applications employing C-bound nucleoside analogs (e.g., Remdesivir, Galidesivir).\textsuperscript{41–43} Inspired by the potential of such unnatural nucleosides and the difficulty of their preparation, we synthesized a C-pyrazole nucleoside (as a mixture of anomers) and subjected it to our standard reaction conditions, offering pyrimidine 3o in high yield.\textsuperscript{44,45}

We next turned to the indazole substrate class (Figure 4). Similarly to pyrazoles, indazoles were tolerant of a wide variety of alkyl substitutions with no substituent requirement at the C3 position. Notably, a free alcohol (5q) and a thioether (5r) were all well tolerated. Lastly, indazoles featuring a variety of halogen substituents in various positions were competent reaction partners (5v–5z), again in contrast to the poor reactivity of haloindoles in our prior report.

For both substrate classes, two major limitations were observed (see Figure S2 for additional examples). First, substrates with low solubility in refluxing MtBE were typically poorly reactive—examples include tertiary amine and amide substituents which tended to produce poorly soluble diazoles. Second, inductive withdrawal can deactivate the nucleophilicity of the diazole and preclude productive reactivity, in a manner that is sensitive to substitution pattern. For example, whereas esters were generally tolerated (e.g., 3n or 3q), introduction of an ester substituent onto C3 of a pyrazole or C6 of an indazole impeded the reaction in a manner that was not rescued by SEM-protection.

In order to further demonstrate the potential for this method to prepare medicinally relevant compounds, we prepared a C2-aryl analog of the pyrimidine-containing HMG-CoA reductase inhibitor Rosuvastatin (Figure 5A). For this synthesis, the pyrazole precursor 2s-SEM could be rapidly prepared in high yield over three steps: (i) Claisen condensation of the requisite benzylo chloride and acetooacetate followed by direct hydrazine condensation to the pyrazole without further purification, (ii) SEM protection, and (iii) reduction of the ester moiety by DIBAL-H. Each step en-route to 2s-SEM afforded >90% yield, showcasing the simplicity with which highly substituted pyrazoles can be obtained (see Supporting Information (SI))
After carbon insertion, the statin was subsequently completed through formation of the phosphonium salt and olefination to install the side chain, affording the corresponding protected form of the Rosuvastatin analog 3t.

We were additionally motivated to showcase the potential of this transformation for direct scaffold hopping (Figure 5B). More specifically, we envisioned that N-aryl pyrazoles and 2-aryl pyrimidines would serve as interesting analogs of one another, with a direct interconversion enabled by our method. To this end, we conducted a series of experiments to explore the scope of the transformation.

Figure 3. Scope of pyrazole-to-pyrimidine ring expansion. Conditions: 2 (1 equiv), 1 (3 equiv), Na₂CO₃ (3 equiv), MIBE (0.1M), 60 °C, 12 h. Isolated yields unless otherwise noted, 0.1−0.3 mmol scale. *6 equiv of diazirine were added over 24 h. *Yield by ¹H-NMR using mesitylene as an internal standard. #TBAF (3 equiv) added during workup.

Figure 4. Scope of indazole-to-quinazoline ring expansion. Conditions: 4 (1 equiv), 1 (3 equiv), Na₂CO₃ (3 equiv), MIBE (0.1M), 60 °C, 12 h. Isolated yields, 0.3 mmol scale. *6 equiv of diazirine were added over 24 h.
end, initial removal of the para-methoxyphenyl (PMP) vector of an ester derivative of the NSAID Tepoxalin (2u-PMP) can be achieved using cerium ammonium nitrate in good yield.\(^{48}\) Though carbon insertion can be conducted directly on the N−H analog 2u, prior SEM protection of the dearylated pyrazole afforded a higher yield of isosteric pyrimidine 3u. As shown in the computed overlay, this skeletal edit enables subtle adjustment of the aryl vectors in the scaffold hop from pyrazole 2u-PMP to pyrimidine 3u while maintaining the displayed functionality.
Having demonstrated the synthetic potential of this method, we sought an understanding of its underlying mechanism. Our mechanistic proposal, as supported by Density Functional Theory calculations at the B3LYP-D3BJ/6-311+g(d,p)-PCM-(Et₂O)//B3LYP-D3BJ/6-31g(d)-PCM(Et₂O) level of theory, is shown in Figure 6A. Dinitrogen extrusion from the chlorodiazirine is proposed to generate free chlorocarbene, which is attacked by N-2 of the azole to form ylide INT1. The ylide fragments with cleavage of the N–N bond to form diazahexatriene intermediate INT2, reminiscent of the intermediates formed during ANRORC substitutions. This ring-opened intermediate is primed to undergo ring closure, in what we initially expected to proceed by a 6π-electrocyclization, followed by rearomatization through loss of chloride.

Unexpectedly, this last step proceeds directly from TS3 to the HCl salt of the pyrimidine 3a, bypassing the chloride-bound dihydropyrimidine intermediate INT3 altogether, as confirmed by an intrinsic reaction coordinate computation. In fact, INT3 could only be located as a stationary point when the C—Cl bond length was frozen during optimization; scanning elongation of its C—Cl distance leads to monotonic stabilization with no further transition state prior to aromatization (see SI for details). Indeed, the 1.83 Å C—Cl σ-bond in INT2 (cf. 1.80 Å for acetyl chloride, experimental) further extends to 1.90 Å in TS3 (cf. 1.89 Å for cumyl chloride, computed) and the imidoyl chloride carbon undergoes significant pyramidalization (P = 0.38), consistent with the transition state developing meaningful sp³ character.

This analysis is further supported by measurement of TS3 aromacity by its Nucleus Independent Chemical Shift, which revealed a positive NICS(1) value of 1.78, in contrast to the NICS(1) value of pyrimidine 3a (−7.12), suggesting that the transition state lacks aromatic character. Together, these measurements indicate that TS3 is best described as a concerted, asynchronous nucleophilic substitution with a dihydropyrimidine-like structure.

We suspect that the observed bis(pyrazol)methane side product is a result of competitive proton transfer of INT1 followed by subsequent substitution of the chloride with a second equivalent of starting material. This is supported by the observation that 6 predominates in cases where pyrazoles were more electron poor (i.e., acidic), and by the observation of a fragile N-chloroalkyl pyrazole species (7) as the sole product in the case of extremely electron-poor pyrazole 2v (Figure 6B). In conclusion, we have demonstrated the application of α-chlorodiazirine reagents as competent carbon atom insertion reagents to promote ring-expansion of pyrazoles and indazoles to their respective pyrimidine and quinazoline products through N—N bond cleavage. This method provides rapid access to valuable heteroaromatic cores from easily prepared starting materials in a synthetically intuitive fashion. Interrogation of the mechanism by Density Functional Theory supports an ylide fragmentation—cyclization sequence initiated by trapping of the chlorocarbene at the N-2 terminus of the azole and proceeding via an unusual, concerted ring-closing substitution. This method can be adopted in the synthesis of complex molecules, such as a statin analog and unnatural nucleoside. It is also useful for the purposes of scaffold hopping to enable quick interrogation of a vector adjusted scaffold, as shown with a derivative of Tepoxalin. This novel skeletal editing technique should prove valuable in a wide variety of contexts.

![ASSOCIATED CONTENT](https://pubs.acs.org/doi/10.1021/jacs.2c09616)

**Supporting Information**

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.2c09616.

Experimental procedures, supporting characterization data and spectra, computational methods, and optimized geometries. (PDF)

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