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A General One-Pot Protocol for Hindered *N*-Alkyl Azaheterocycles from Tertiary Carboxylic Acids

Rohan R. Merchant,*,§ Simon B. Lang,*,§ Tingting Yu, Shuilian Zhao, Zhiqi Qi, Takao Suzuki, and Jianming Bao

Cite This: https://dx.doi.org/10.1021/acs.orglett.0c01254 Read Online

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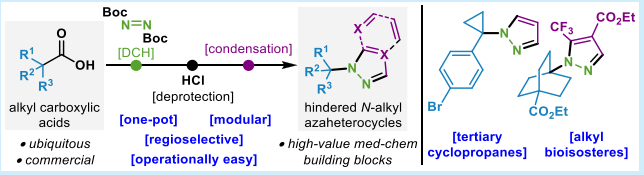
ABSTRACT: In this letter, we report a general one-pot strategy that utilizes three elementary steps (decarboxylative hydrazination, Boc deprotection, and heterocycle condensation) to regioselectively prepare hindered C(sp^3) substituted pyrazoles and triazoles. The operational simplicity of this sequence and ubiquity of tertiary carboxylic acids allow rapid access to hindered *N*-alkyl azaheterocycles that will be useful to practitioners of medicinal chemistry and agro-chemistry.



The regioselective synthesis of heterocycles is a core component of medicinal chemistry. Pyrazoles are one of the most common five-membered heterocycles (Figure 1A),[1] often employed for their ability to either π-stack or facilitate hydrophobic and hydrogen-bond interactions with proteins.[2] As such, myriad methods for the synthesis of "flat" *N*-aryl pyrazoles have been reported, with most employing the condensation of hydrazine or dipolar cycloadditions.[3] However, recently it has also been articulated that increasing the sp^3 character of molecules is positively correlated to their success in the clinic, as sp^3-rich scaffolds tend to have improved physiochemical properties and improved target specificity compared to their "flat" counterparts.[4,5] For example, in an effort to develop an inhibitor of Diacylglycerol Acyltransferase 2 (DGAT2) (**2**), a 1,1-disubstituted *N*-cyclopropyl pyrazole was employed to improve off-target pharmacology and minimize *N*-glucuronidation without raising lipophilicity, and retaining potency (Figure 1B).[6] Thus, the development of new methods to access these sp^3-rich scaffolds is an important goal in medicinal chemistry. We became interested in the synthesis of tertiary *N*-substituted pyrazoles to access metabolically stable 1,1-disubstituted cyclopropane to occupy a hydrophobic pocket (Figure 2A). Efforts to prepare an intermediate (**3**) using routine approaches such as reductive amination (to access hydrazine) or S_N1/S_N2 with activated electrophiles were not fruitful.[7] These initial results led us to evaluate a combination of one- and two-electron disconnections to enable an alternative retrosynthetic template.[8]

We were attracted to the condensations of hydrazines such as **6** to access pyrazoles, as they are one of oldest reported transformations and represent a cornerstone of synthetic organic chemistry due to their regioselectivity, modularity, and facile "dump and stir" protocols.[9]

Recently, Tunge, König, and Jin have reported the radical decarboxylative coupling of alkyl carboxylic acids (**9**) with azo dicarboxylates **8** under photoredox conditions to give

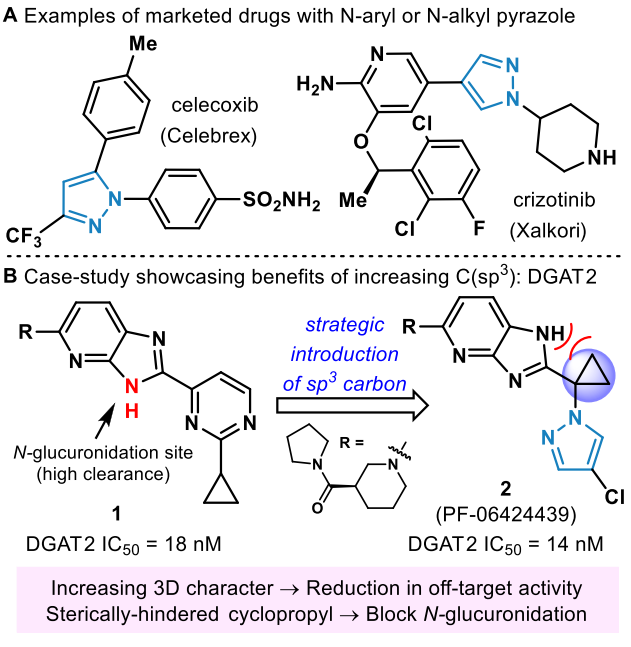


Figure 1. Importance of pyrazoles and increasing fraction sp^3 in medicinal chemistry.

Received: April 8, 2020

https://dx.doi.org/10.1021/acs.orglett.0c01254
Org. Lett. XXXX, XXX, XXX−XXX

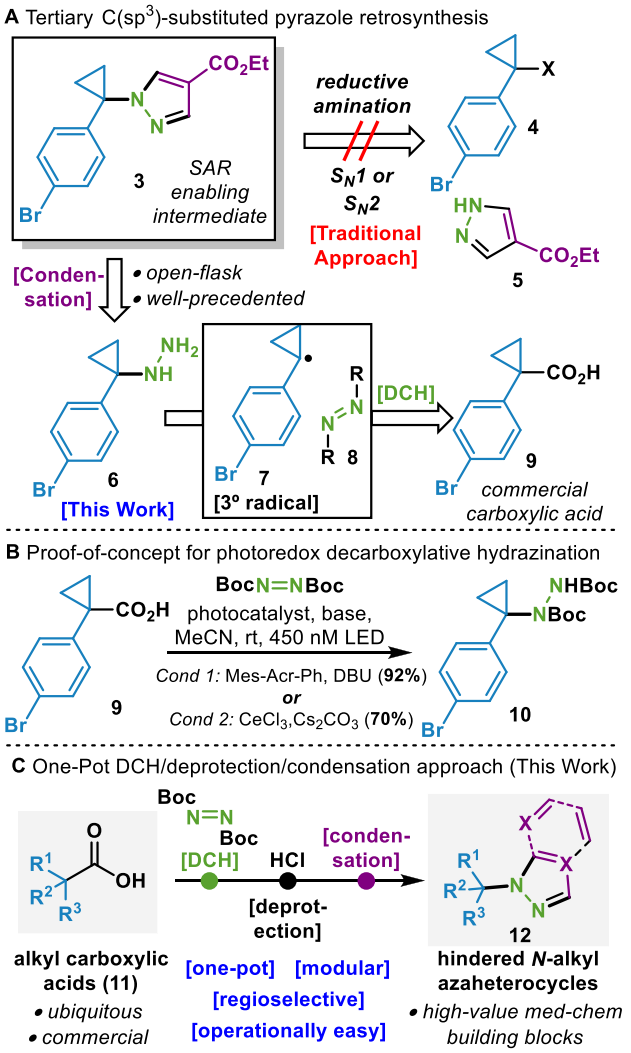


Figure 2. (A) Inspiration for a combination of one- and two-electron approach to hindered *N*-alkyl azaheterocycles. (B) See SI for experimental details.

hydrazination products.[10] Since tertiary carboxylic acids are one of the most widely available building blocks, we recognized that decarboxylative hydrazination (DCH) could provide a convenient entry to hindered hydrazines from commercial starting materials, thereby enabling a simple condensation approach to sterically encumbered *N*-alkyl pyrazoles. Notably, while traditional cross-coupling methods favor functionalization of the less hindered pyrazole nitrogens,[11] the regiocontrol this strategy provides facilitates access to the more hindered pyrazole isomers.

To obtain a proof of concept for the underlying strategy, cyclopropane hydrazine **10** was prepared via photoredox decarboxylative hydrazination (DCH) in excellent yield (Figure 2B). Considering the operational simplicity and robustness of the subsequent Boc-deprotection and condensation steps to access the desired heterocycles, we reasoned that our approach could be realized in a one-pot fashion from the corresponding carboxylic acid. This protocol (Figure 2C) minimizes workup and purification steps and provides direct access to tertiary azaheterocycles **12** whose synthesis thus far has been resource and step intensive.[12,13] Operationally, this was realized via two solvent exchanges, first after the DCH step, and second after the HCl promoted Boc-deprotection (open-flask). The crude hydrazine was then subjected to *in situ* condensation (open-flask) with the appropriate partner to afford the desired azahetereocycle after purification (see Supporting Information (SI) for details).

The efficacy of this reaction sequence was demonstrated using an array of readily available tertiary carboxylic acids to prepare a variety of azaheterocycles (Figure 3A and 3B). The carboxylic acid scope was investigated via subjection to the decarboxylative C−N formation, *in situ* Boc deprotection, and condensation to afford the unsubstituted pyrazole. It is worth noting that the starting carboxylic acids are commercially available for all but one example (**28**) and that the unsubstituted pyrazole is an ideal starting point for further functionalization via electrophilic aromatic substitution.[14] Under the reaction conditions bicyclo [1.1.1]- (**13**), [2.2.1]- (**14**−**15**), [2.2.2]- (**16**−**17**, **28**), and adamantyl carbocycles (**18**−**19**) proceeded smoothly. These carbocycles are important alkyl bioisosteres for the phenyl ring, and as such, new approaches for their modification are of great interest to medicinal chemists.[15] Cyclopropanes are privileged scaffolds that have a well-documented history as an alkyl isostere and as a means to address various issues encountered during drug discovery.[16] However, 1,1-disubstituted cyclopropyl hetereocycles are notoriously difficult to access, and it is therefore noteworthy that several tertiary *N*-cyclopropyl pyrazoles (**22**−**24**) could be prepared in a straightforward manner via this sequence. Similarly, 1,1-disubstituted cyclobutane carboxylic acids could also be converted to the desired sp^3-rich *N*-alkyl pyrazoles (**25**−**27**). Substrate **29** highlights the radical nature of the DCH, wherein the *trans*-stereochemistry of the cyclobutane is set by the neighboring di-Cl phenyl ring. Under the reaction conditions, various medicinal-chemistry-relevant heterocycles—such as pyridines (**23**, **26**), pyrimidine (**21**), and triazole (**28**), among others—were well tolerated. Additionally, a range of functional groups including aryl bromide (**20**−**22**, **27**), chloride (**23**, **25**−**26**, and **29**), protected amine (**17**), ester (**15**−**16**), alcohol (**19**), and ether (**14**) were also compatible under the reaction conditions. Notably, aryl halides are an important functional group handle, allowing for subsequent diversification using transition-metal catalysis in an orthogonal manner. Examples **23** and **26** also demonstrate that the conditions for this synthetic sequence are mild enough to tolerate activated 2-chloropyridines, which could then be further functionalized via S_NAr. Lastly, late-stage modification of carboxylic acid intermediate toward 11β-HSD1 inhibitors could also be performed (**28**).[17] Although either the organo-photocatalyst (Mes-Acr-Ph)[10a] or $CeCl_3{\cdot}7H_2O$[10b] could be used to access the Boc-protected alkyl hydrazines, we observed several substrate specific cases (see Figure 3) where one was advantageous over the other.

Figure 3B illustrates how the extensive hydrazine condensation literature could be leveraged to access a range of different substituted pyrazoles (**3**, **30**−**32**), aza-indazoles (**33**), and triazoles (**34**), from a common hydrazine precursor. The resultant esters (**3**, **30**-**31**), amine (**20**), and halides (**32**, **33**) are invaluable functionalities, allowing for divergent modification downstream. Unsymmetrical pyrazoles **30** and **31** are obtained with complete regioselectivity, underscoring a key advantage of utilizing well-studied condensation reactions to access pyrazoles. Even in situations where the canonical S_N2 or cross-coupling reaction to install the pyrazole were to work, poor regioselectivities are often observed and the less hindered

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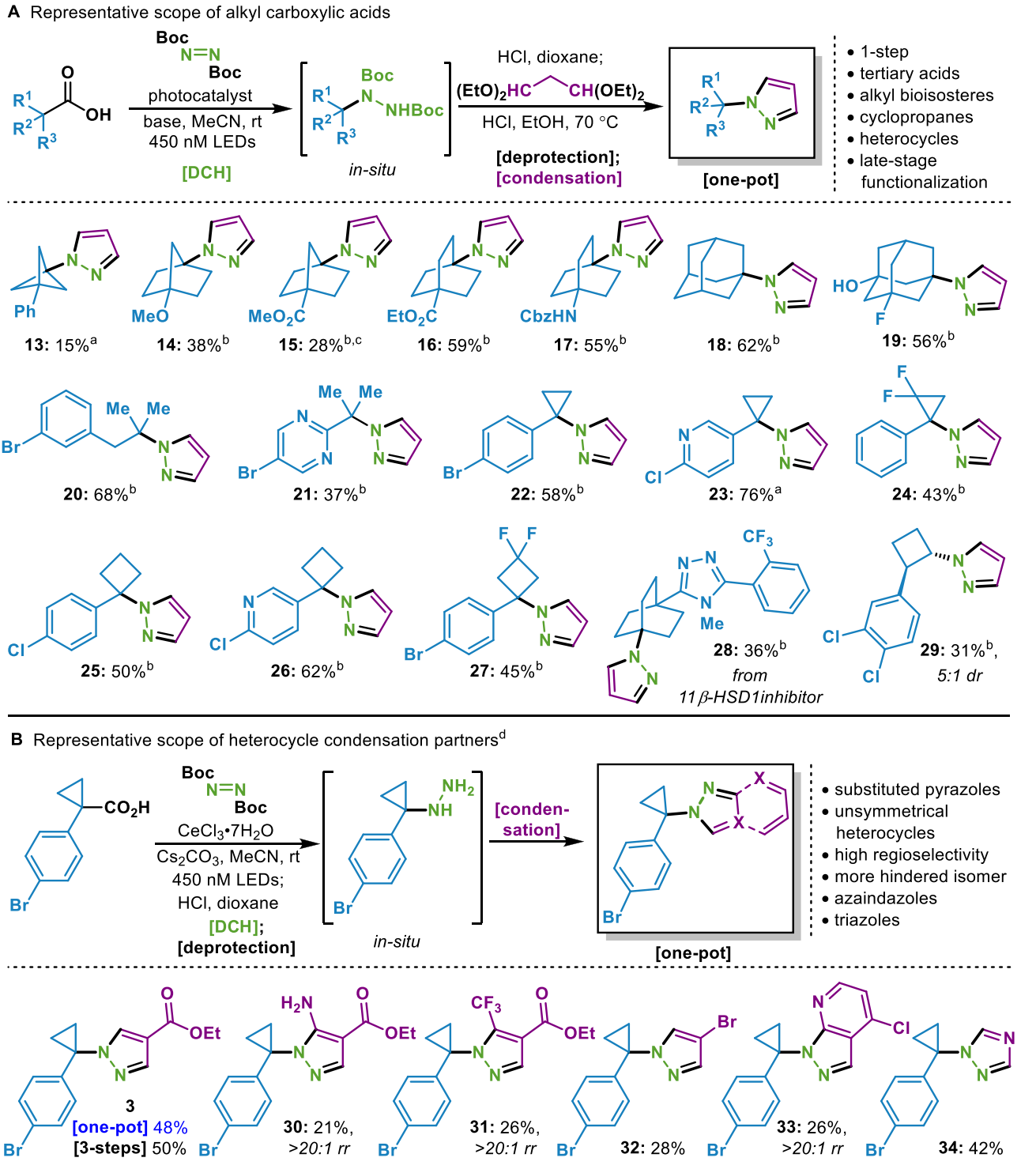

Figure 3. Initial scope for the one-pot synthesis of hindered *N*-alkyl azahetereocycles from carboxylic acids. Isolated yields reported. Standard reaction conditions for carboxylic acid scope: alkyl carboxylic acid (1.0 equiv), DBAD (1.5 equiv), photocatalyst, base, MeCN, rt, 4 × 450 nM blue LEDs; HCl (4 M in dioxane, 30.0 equiv), rt, 16 h; 1,1,3,3-tetraethoxypropane (1.5 equiv), HCl (37%, 3.0 equiv), EtOH (0.25 M), 70 °C, 3 h. [a] With $CeCl_3 \cdot 7H_2O$ (0.1 equiv), Cs_2CO_3 (0.25 equiv), MeCN (0.17 M), 24 h. [b] With Mes-Acr-Ph (photocatalyst, 0.02 equiv), DBU (0.25 equiv), MeCN (0.1 M), 4 h. [c] Condensation run in MeOH (0.25 M) at 60 °C instead of EtOH. [d] With DBAD (2.0 equiv), $CeCl_3 \cdot 7H_2O$ (0.1 equiv), Cs_2CO_3 (0.2 equiv), MeCN (0.1 M), rt, 40 h; see SI for experimental details for condensation step. DBAD = di-*tert*-butyl azodicarboxylate, DBU = 1,8-Diazabicyclo[5.4.0]undec-7-ene, Mes-Acr-Ph = 9-Mesityl-10-phenylacridinium tetrafluoroborate.

isomer is typically favored.[11,18] Importantly, a similar yield was observed when the reaction was performed as three discrete steps, involving purification of the di-Boc protected hydrazine, compared to the one-pot procedure (**3**), highlighting the operational convenience. Although in some instances low to moderate yields were observed over the entire sequence (*ca.* 20%), this still represents a moderate 60−80% yield for each step. Additionally, we believe the operational ease and lack of

https://dx.doi.org/10.1021/acs.orglett.0c01254
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direct methods to access these motifs help to offset the limitations.

The retrosynthetic simplification enabled by this reaction sequence is further demonstrated by the improved synthesis of an example from the patent literature, a [2.2.2] bicycle substituted CF_3 pyrazole **36** (Figure 4). This key intermediate

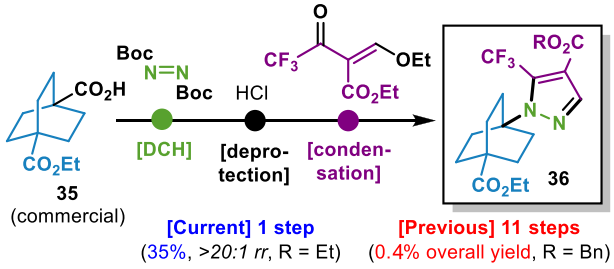

Figure 4. Simplified synthesis of *N*-alkyl pyrazole **36** toward RORγ inhibitors. See SI for experimental details.

toward RORγ inhibitors was previously accessed in 11 steps and 0.4% overall yield.[19] Instead, when applying the one-pot DCH/deprotection/condensation template, the commercial bicyclo[2.2.2]octane carboxylic acid **35** can be converted to the pyrazole **36** in just one step (35% isolated yield) with complete regioselectivity.

In summary, we have developed a general one-pot protocol to access sp^3-rich substituted pyrazoles and triazoles from the corresponding carboxylic acids. By leveraging the ubiquity of tertiary alkyl carboxylic acids, and the breadth of hydrazine condensation reactions, this operationally simple, modular, and regioselective approach simplifies the synthesis of previously difficult-to-prepare hindered *N*-alkyl azaheterocycles. This method has already proven to be invaluable in several internal medicinal chemistry programs and has been employed by our external partners as well. As such, we anticipate that this approach will have meaningful impacts within the drug discovery and synthetic chemistry communities.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c01254.

Detailed experimental procedures and analytical data (PDF)

■ AUTHOR INFORMATION

Corresponding Authors

Rohan R. Merchant − *Department of Discovery Chemistry, Merck & Co., Inc., South San Francisco, California 94080, United States;* orcid.org/0000-0002-5472-8780; Email: rohan.merchant@merck.com

Simon B. Lang − *Department of Discovery Chemistry, Merck & Co., Inc., South San Francisco, California 94080, United States;* orcid.org/0000-0001-5380-2996; Email: simon.lang@merck.com

Authors

Tingting Yu − *IDSU, WuXi AppTec Co., Ltd., Shanghai 200131, China*

Shuilian Zhao − *IDSU, WuXi AppTec Co., Ltd., Shanghai 200131, China*

Zhiqi Qi − *IDSU, WuXi AppTec Co., Ltd., Shanghai 200131, China*

Takao Suzuki − *IDSU, WuXi AppTec Co., Ltd., Shanghai 200131, China*

Jianming Bao − *Department of Discovery Chemistry, Merck & Co., Inc., South San Francisco, California 94080, United States*

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.orglett.0c01254

Author Contributions

§R.R.M. and S.B.L. contributed equally to this work.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We are grateful to Ethan Wappes, James Roane, W. Michael Seganish, Donna Hayes (all from Merck & Co., Inc., South San Francisco, CA, USA), and Brett Ambler (Merck & Co., Inc., West Point, PA, USA) for feedback on the manuscript. We would like to thank Melissa Lin (Merck & Co., Inc., South San Francisco, CA, USA) and Wilfred Pinto (Merck & Co., Inc., Rahway, NJ, USA) for assistance with NMR spectroscopy and HRMS, respectively.

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https://dx.doi.org/10.1021/acs.orglett.0c01254
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