N-Trifluoromethyl Hydrazines, Indoles and Their Derivatives
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Abstract: Reported herein is the first efficient strategy to synthesize a broad range of unsymmetrical N-CF3 hydrazines, which served as platform to unlock numerous currently inaccessible derivatives, such as tri- and tetra-substituted N-CF3 hydrazines, hydrazones, sulfonyl hydrazines, and valuable N-CF3 indoles. These compounds proved to be remarkably robust, being compatible with acids, bases, and a wide range of synthetic manipulations. The feasibility of RN(CF3)-NH2 to function as a directing group in C–H functionalization is also showcased.

Hydrazines (R,N-NR2) are ubiquitous motifs in materials,[3] pharmaceuticals,[2] agrochemicals,[2d] dyes[3] (Figure 1) as well as enabling functional groups in synthesis, being popular directing groups in catalysis[4] and valuable precursors to heterocycles (such as indoles).[5] or tetrazanes. Consequently, there is a significant interest in devising efficient synthetic strategies to novel hydrazine motifs. While mono-substituted hydrazines (i.e. R-NH-NH2) are readily accessible via arylation of NH2-NH2 (and protected NH2-NH-PG),[6] the syntheses of higher substituted, and especially unsymmetrically substituted hydrazines as well as their fluorinated derivatives have been challenging to date.[7] In this context, a straightforward method to generate trifluoromethylated and unsymmetrically substituted hydrazines would be particularly impactful, owing to the powerful effects of fluorination on the (metabolic) stabilities as well as physical properties of organic molecules.[4] However, the current methodological repertoire to access N-CF3 hydrazines is of limited scope,[9,10] (see Figure 1, middle), relying on harsh photolysis or unselective oxidations with XeF2 (to yield I) as well as pyrolysis to yield polytrifluoromethylated hydrazines (III), or low-yield trifluoromethylation of a single class of diazo compounds (to yield II), for which the feasibility of Boc deprotection and potential derivatizations has not been demonstrated however.[6a]

In this context, we envisioned that if we could develop a general method to access pharmaceutically and agrochemically relevant aromatic N-CF3 hydrazines, this might potentially allow us to unlock valuable and currently inaccessible N-CF3 derivatives, such as N-CF3 hydrazones, sulfonyl hydrazines, or indoles. While the former have never been made, N-CF3 indoles can currently only be synthesized with strongly basic or oxidizing conditions that limit generality and functional group tolerance, involving either deprotonation of the indole N-H and reaction with gaseous CF3I (of unknown efficiency; no yield reported),[11] or trifluoromethylation of the non-aromatic indoline precursor, followed by re-aromatization under highly oxidizing conditions.[12] Interestingly, the N-deprotonation of indoles, followed by reaction with an electrophilic CF3 source, such as Togni’s reagent, does not yield N-CF3 indoles.[13]

We herein describe an efficient strategy to N-CF3 hydrazines and showcase their robustness in follow-up transformations to yield N-CF3 indoles, tri- and tetra-substituted hydrazines, sulfonyl hydrazines, acyl hydrazines, as well as their functionalizations via modern catalytic strategies (cross coupling, C–H activation, thiolation, cyanation and borylation).

Our group previously developed a strategy to trifluoromethylation secondary amines,[14] however, we found that the application of the same protocol to N3-protected hydrazines was not a viable strategy to N-CF3 hydrazines, as the key thiocarbamoyl fluoride intermediate did not form. We therefore embarked on developing an alternative strategy: building

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Figure 1. Importance of the hydrazine motif (top), current limited approaches to N-CF3 hydrazines (middle) and this work (bottom).
After reacting the corresponding bromo compounds, we uncovered that envisioning Curtius-type rearrangement is unknown for N-CF₃ carbamoyl compounds; certainly the key N-CF₃ migration is not free of challenges, as fluoride elimination from the transient and partially negatively charged N-CF₃ could alternatively take place.

We initially set out to prepare the biphenyl carbamoyl fluoride from the corresponding R-NCS compound. To our delight, when we subsequently subjected sodium azide to in THF for 16 hours at room temperature, we successfully formed the corresponding carbamoyl azide, which we isolated by filtration over celite in quantitative (98%) yield (see Figure 2). We unambiguously confirmed the structural integrity of the N-CF₃ carbamoyl azide by x-ray crystallographic analysis (see Figure 2). With the key precursor in hand, we subsequently tested its propensity to undergo the Curtius-type rearrangement on hydrazines, which we found to be rather general, tolerating electron-rich as well as electron-deficient amines. The electron-withdrawing nitro- (13), sulfone- (15) and even OCF₃ (11) groups were equally compatible as the donating methoxy (12) and alkyl substituents (9). In this context, meta- and para-substitution were generally well tolerated, whereas the presence of ortho-substituents considerably slows the reaction, giving for example, 8 in only moderate yield (38%) after microwave irradiation for 36 h (along with unreacted carbamoyl azide). Non-aromatic carbamoyl fluorides, that is, alkyl derivatives, did not result in the corresponding hydrazines.

With a view towards potential follow-up diversifications, we next studied a derivative bearing an aromatic bromide (4). After reacting the corresponding bromo N-CF₃ carbamoyl fluoride with NaN₃ for 16 h at room temperature, we filtered and subsequently diluted the reaction mixture with THF and water, before subjecting to microwave irradiation. With this minimally disruptive reaction sequence free of any elaborate work-up or column chromatography, we were able to obtain 6 in 65% yield. However, the N-CF₃ carbamoyl azides proved to be robust and can also be isolated and purified by column chromatography. Alternative halides other than C-Br, that is, iodide (12), chloride and polyhalogenated compounds (8, 14) were similarly well tolerated (see Figure 2). Aside from being of value on their own to induce additional function via halogen bonding, which has become increasingly important in medicinal and material science, these halogen sites could serve as ideal handles for further diversification via established cross-coupling methodology. In our tests for compatibility of alternative functionalities, we found the protocol to be rather general, tolerating electron-rich as well as electron-deficient amines. The electron-withdrawing nitro-(13), sulfone-(15) and even OCF₃ (11) groups were equally compatible as the donating methoxy (12) and alkyl substituents (9). In this context, meta- and para-substitution were generally well tolerated, whereas the presence of ortho-substituents considerably slows the reaction, giving for example, 8 in only moderate yield (38%) after microwave irradiation for 36 h (along with unreacted carbamoyl azide). Non-aromatic carbamoyl fluorides, that is, alkyl derivatives, did not result in the corresponding hydrazines.

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We envisioned that instead of exploring modified conditions to better tolerate ortho-substituents in the Curtius-type rearrangement, a more powerful strategy might potentially be to build on the established ability of hydrazines to function as the directing group in C-H functionalizations. If the novel N-CF₃ hydrazines were similarly able to direct transition metals and simultaneously tolerate modern C-H activation catalysis conditions (which is currently unknown), then this would be a powerful diversification strategy to access a number of different derivatives from a common hydrazine precursor.

Pleasingly, the application of Rh-catalyzed C-H activation on hydrazines 6 and 9 allowed us to functionalize the ortho position upon reaction with an alkyne to give the corresponding olefins 20 and 21 (see Figure 3), showcasing that the CF₃ substituent does not impede the hydrazine’s ability to function as a directing group. A strong feature of
Encouraged by these stability observations, we next set out to tackle the challenge of accessing N-CF₃ indoles, and explored whether the N-CF₃ hydrazines could also sustain highly acidic conditions and participate in a Fischer indole synthesis. The application of the standard Fischer indole conditions, that is, using H₂SO₄ as a catalyst, methanol as a solvent, and heating at 80°C [24] indeed afforded the N-CF₃ indoles 22 and 27 in high yields (86–89%) and phenylindolylide 28, the X-ray crystallographic analysis of which unambiguously confirmed the structure (see Figure 3).

The N-CF₃ bond length of 28 in the solid state was determined to be 1.377 Å, which is slightly shorter than similar N-CH₃ indoles (1.457 Å). We reproduced this trend also computationally, that is, using DFT optimizations on a variety of compounds, we found fluorination to consistently shorten the N–C bond [25]. Another noteworthy characteristic was the pyramidalization of the nitrogen, which caused the N-CF₃ bond to be 13° out-of-plane with respect to the indole ring. This is analogous to the stereo-electronic situation of other fluorinated motifs, for example, PhOCF₃ or N-CF₃ amides [8a,e, 15, 26], resulting in conformers usually inaccessible for the non-fluorinated analogs.

With the C-Br being also present in indole 22, there is once again opportunity for diversification. Indeed, using dinuclear Pd²⁺ catalysis [23] it was possible to rapidly alkylate (24) and arylate (25) the indole core in less than 5 minutes at room temperature in excellent yields with the corresponding Grignard reagents as coupling partner (see Figure 3). The Pd⁰/Pd²⁺-catalyzed cyanation and Buchwald–Hartwig amination were also possible, giving 23 and 26, respectively, in high yields. As such, the indole N-CF₃ motif seems to not only tolerate highly acidic (Fischer indole synthesis [5e, 28]) but also strongly nucleophilic and basic conditions (e.g., Grignard), suggesting that they are highly robust entities, which should enable widespread applications.

With the free NH₂ group in the newly synthesized ArN(CF₃)-NH₂ hydrazines, there is further potential to access higher substituted and unsymmetrical derivatives, and we next set out to also explore this chemical space. We successfully obtained hydrazone 30 in quantitative yield after heating at 80°C for 3 h in acetic acid (see Figure 4). Hydrazones have uses in catalysis [29] and material science [11a,c] and are also useful synthetic intermediates, for example, in reductive aminations of amines to ultimately generate monoalkylated amines/hydrazines. Indeed, our mild reduction of 30 generated the N-alkylated hydrazone 31, leaving the aromatic C-I and N-CF₃ groups fully untouched (see Figure 4). Alternatively, we found that the NH₂ could also be selectively coupled with 3-chlorobromobenzene via Pd-catalysis in a Buchwald–Hartwig amination to give 32. Double arylation did not take place, which showcases that the RN(CF₃)NH₂ motif can be selectively alkylated and arylated to generate the N-CF₃ analogs of higher substituted hydrazines. Straightforward carboxylation with a chlorofor- matic gave carbamate 33, which demonstrates the possibility for protecting the NH₂, if desired. For this transformation, the stoichiometry had to be carefully controlled to avoid double addition of the chloroformate. Compound 33 was also further acylated to 34 in good yield using similar conditions to
generate a fully substituted N-CF₃ hydrazine with four different substituents. Since sulfonamides and their derivatives are also of significant interest in a medicinal and pharmaceutical context,⁹ we reacted 10 with sulfonyl chloride to prepare the sulfonyl hydrazide 29, which was fully characterized by X-ray crystallographic analysis (see Figure 4).

In summary, a straightforward method was developed to readily access a wide range of N-CF₃ hydrazines. These compounds proved to be very stable under a broad range of conditions, including strong acids, bases, and high temperatures. The hydrazine core was also showcased to readily serve as a platform for the construction of more complex and unsymmetrically substituted N-CF₃ derivatives, including N-CF₃ hydrazones, sulfonyl hydrazines, and N-CF₃ indoles. The feasibility for downstream diversification via modern metal catalysis was also shown. We anticipate numerous applications of this methodology in synthesis, materials sciences, as well as the pharmaceutical and agrochemical arenas to unleash the currently untapped potential of these novel N-trifluoromethylated compounds.

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Conflict of interest

The authors declare no conflict of interest.

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[1] a) X. Su, I. Aprihantam, Chem. Soc. Rev. 2014, 43, 1963; b) G. Men, J.-M. Lohn, J. Am. Chem. Soc. 2017, 139, 2474; c) R. Lygaitis, V. Getautis, J. V. Grazulevicius, Chem. Soc. Rev. 2008, 37, 770; d) A. Mahmodoo, M. Ebrahimii, Prog. Org. Coat. 2018, 114, 223.
[2] a) R. Narang, B. Narasimhan, S. Sharma, Curr. Med. Chem. 2012, 19, 569; b) D. K. Kolmel, E. T. Kool, Chem. Rev. 2017, 117, 10358; c) C. S. Meira, J. M. dos Santos Filho, C. A. Sousa, P. S. Anjos, J. V. Cerqueira, H. A. Dias Neto, M. Al. Ali, M. Alam, J. Pharm. Bioall. Sci. 2014, 6, 69; e) E. Nieddu, B. Pollaro, M. T. Mazzei, M. Anzaldi, S. Schenone, N. Pedemonte, L. J. V. Galietta, M. Mazzei, Arch. Pharm. Chem. Life Sci. 2016, 349, 112; f) F. López-Muñoz, C. Álamo, G. Jackel, H.-J. Assion, J. Clin. Psychopharmacol. 2007, 27, 555.
[3] a) M. P. Elizalde-González, S. A. Lozano-Morales, Mater. Chem. Phys. 2019, 228, 15; b) A. Matoliukstyte, R. Lygaitis, J. V. Grazulevicius, V. Gaidelis, V. Jankauskas, E. Montrimas, Z. Tokarski, N. Jurbun, Mol. Cryst. Liq. Cryst. 2005, 427, 107[149].
[4] C. Sambigio, D. Schönauer, R. Bliek, T. Dao-Huy, G. Pototschnig, P. Schaaf, T. Wiesinger, M. F. Zia, J. Wencel-Delort, T. Besset, B. U. W. Maes, M. Schirch, Chem. Soc. Rev. 2018, 47, 6603; b) Y. Xue, Z. Fan, X. Jiang, K. Wu, M. Wang, C. Ding, Q. Yao, A. Zhang, Eur. J. Org. Chem. 2014, 7481.
[5] a) P. Xu, G. Wang, Z. Wu, S. Li, C. Zhu, Sci. Chem. 2017, 8, 1303; b) C. Song, C. Yang, F. Zhang, J. Wang, J. Zhu, Org. Lett. 2016, 18, 4510; c) S. Han, Y. Shin, S. Sharma, N. K. Mishra, J. Park, M. Kim, M. Kim, J. Jung, I. S. Kim, Org. Lett. 2014, 16, 2494; d) B. W. Boil, A. W. Schammel, N. K. Garg, Org. Lett. 2009, 11, 3458; e) D. L. Hughes, Org. Prep. Proced. Int. 1993, 25, 607.
[6] a) M. Wolter, A. Klapsar, S. L. Buchwald, Org. Lett. 2001, 3, 3803; b) P. Ruiz-Castillo, S. L. Buchwald, Chem. Rev. 2016, 116, 12564; e) A. DeAngelis, D.-H. Wang, S. L. Buchwald, Angew. Chem. Int. Ed. 2013, 52, 3434; Angew. Chem. 2013, 125, 3518.
[7] U. Ragnarsson, Chem. Soc. Rev. 2001, 30, 205.
[8] a) K. Müller, C. Faeh, F. Diederich, Science 2007, 317, 1881; b) S. Purser, P. R. Moore, S. Swallow, V. Gouvrénaire, Chem. Soc. Rev. 2008, 37, 320; c) C. Isanbor, D. O’Hagan, J. Fluorine Chem. 2006, 127, 303; d) O. A. Tomashenko, V. V. Grushin, Chem. Rev. 2011, 111, 4475; e) L. E. Zimmer, C. Spar, R. Gilmour, Angew. Chem. Int. Ed. 2011, 50, 11860; Angew. Chem. 2011, 123, 12062; f) P. A. Champagne, J. Desroches, J.-D. Hamel, M. Vandamme, J.-F. Paquin, Chem. Rev. 2015, 115, 9073; g) A. Tlili, F. Toulgoat, T. Billard, Angew. Chem. Int. Ed. 2016, 55, 11726; Angew. Chem. 2016, 128, 11900; h) N. A. Meanwell, J. Med. Chem. 2018, 61, 5822.
[9] a) T. Milcent, B. Crouse, Comptes Rendus Chimie 2018, 21, 771; b) T. Liang, C. N. Neumann, T. Ritter, Angew. Chem. Int. Ed. 2013, 52, 8214; Angew. Chem. 2013, 125, 8372.
[10] a) G. H. Sprenger, J. M. Shreeve, J. Am. Chem. Soc. 1974, 96, 1770; b) W. Lutz, W. Sundmeyer, Chem. Ber. 1979, 112, 2158; c) R. Fisher, R. N. Haszeldine, A. E. Tipping, J. Fluorine Chem. 1983, 22, 155; d) R. E. Banks, M. S. Falou, A. E. Tipping, J. Fluorine Chem. 1988, 38, 279; e) G. Newsholme, A. E. Tipping, J. Fluorine Chem. 1994, 68, 39; f) W. Sundmeyer, M. Witz, J. Fluorine Chem. 1986, 34, 251; g) M. Mamone, E. Morvan, T. Milcent, S. Ongerli, B. Crouse, J. Org. Chem. 2015, 80, 1964.
[11] a) S. W. C. Cheng, H. Joyce Li, US Patent US2019016971 A1, 2018; b) K. W. Bair, Patent WO 2014164767 A1, 2013; c) K. W. Bair, D. R. Lancia, H. Li, J. Loch, W. Lu, M. W. Martin, D. S.
The first synthetic access to N-trifluoromethyl hydrazines, indoles and their derivatives is described. These compounds proved to be remarkably robust, being compatible with acids, bases, and a wide range of synthetic manipulations.