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Letter

Trifluoromethylated Pyrazoles via Sequential (3 + 2)-Cycloaddition of Fluorinated Nitrile Imines with Chalcones and Solvent-Dependent Deacylative Oxidation Reactions

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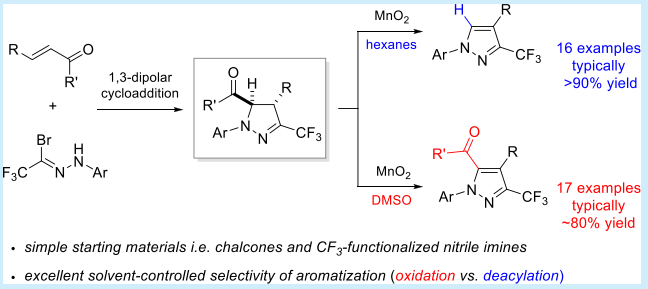
ABSTRACT: A general approach for preparation of two types of polyfunctionalized 3-trifluoromethylpyrazoles is reported. The protocol comprises (3 + 2)-cycloaddition of the *in situ* generated trifluoroacetonitrile imines with enones leading to *trans*-configured 5-acyl-pyrazolines in a fully regio- and diastereoselective manner. Initially formed cycloadducts were aromatized by treatment with manganese dioxide. Depending on the solvent used, the oxidation step either led to fully substituted pyrazoles (DMSO) or proceeded via a deacylative pathway to afford 1,3,4-trisubstituted derivatives (hexane) with excellent selectivity.



In the past two decades, great attention has been focused toward the chemistry of pyrazoles functionalized by introduction into the heterocyclic ring of either fluorine atom(-s) or fluoroalkylated groups.[1] In a series of recent publications they were reported as organic materials of remarkable practical importance, and specifically 3-trifluoromethylated pyrazole has been indicated as a privileged structural scaffold for a variety of agrochemicals, pharmaceuticals, and advanced materials.[1,2] For these reasons, development of new methods aimed at efficient and selective synthesis of multifunctionalized, fluorinated pyrazoles is a challenging problem in current organic synthesis.

In general, common access to 3-trifluoromethylpyrazoles relies on condensation of corresponding 1,3-dicarbonyl compounds (or their equivalents) with a functionalized hydrazines.[1−3] In addition, Lewis acid mediated cyclizations and related transformations of hydrazones are also applied.[4] Furthermore, some postcyclization, functional group interconversions leading to trifluoromethylated pyrazoles, and catalytic fluoroalkylations have been developed more recently.[5] Another powerful approach is based on 1,3-dipolar cycloadditions employing trifluoromethylated 1,3-dipoles and appropriate dipolarophiles. In the past decade, remarkable progress has been achieved in the chemistry of 2,2,2-trifluorodiazoethane; however, some drawbacks such as difficult handling, low selectivity, and the scope limited to pyrazoles lacking a substituent at N(1) have been pointed out.[6] In contrast, applications of alternative 1,3-dipolar intermediates, i.e. trifluoroacetonitrile imines **1**, offer access to *N*-functionalized heterocycles, and typically, their reactions proceed with excellent regio- and chemoselectivity.[7] Nevertheless, application of easily accessible nitrile imines **1** for preparation of the title 3-trifluoromethylated pyrazoles remain underexplored.

Some time ago, Oh (but also our group) demonstrated that by using electron-rich C=C dipolarophiles such as enamines or vinyl ethers,[8] the problem of low regioselectivity, reported by Tanaka in his pioneering work on 1,3-dipolar cycloadditions of **1** with nonactivated alkenes, could easily be overcome.[9] As shown in Scheme 1, the presence of $-NR_2$ or $-OR$ as a leaving group in an ethylenic dipolarophile assures complete regioselectivity in the (3 + 2)-cycloaddition step and the initially formed products undergo either spontaneous or Brönsted acid induced elimination of an amine or alcohol molecule, respectively, to give the final aromatized heterocycle. More recently, Ma and co-workers developed an interesting one-pot decarboxylative (3 + 2)-cycloaddition route leading to fully substituted CF_3-pyrazoles, starting with nitrile imines and isoxazolidinediones as dipolarophiles.[10] In that case, thermal extrusion of CO_2 from the corresponding intermediate was pointed out as a driving force leading to the final, aromatized product. Remarkably, neither of the methods developed thus far explores the orthogonal properties of the initially formed (3 + 2)-cycloadducts. Thus, in the search for new synthetic protocols toward polyfunctionalized 3-trifluoromethylpyrazoles, we envisioned possible access to three- and tetra-substituted analogues by using 5-acylpyrazolines as common

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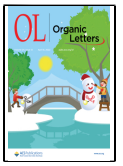
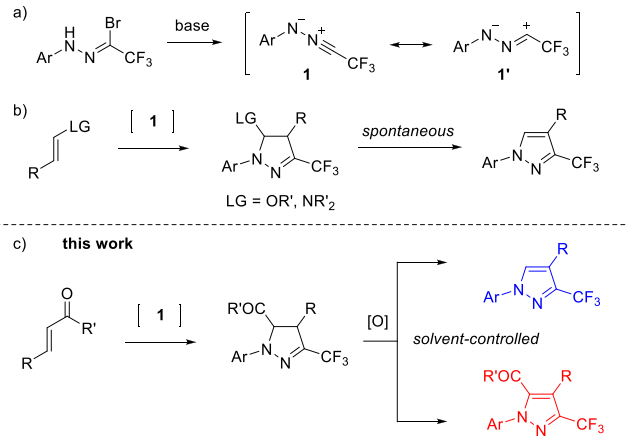


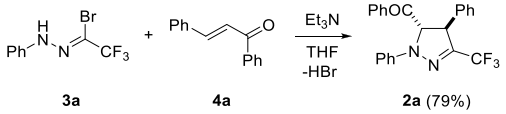
Scheme 1. General Schemes of (a) Generation of Nitrile Imines 1, (b) Their Reactions with Electron-Rich Alkenes, (c) and the Solvent-Controlled Synthesis of Polysubstituted 3-Trifluoromethylpyrazoles Reported Herein



precursors. The requisite starting materials can be obtained by employing azomethine imines as reported by Xie,[11] but they should also be accessible via anticipated regioselective (3 + 2)-cycloaddition of acyclic enones with *in situ* generated fluorinated nitrile imines **1** (Scheme 1). Here we report on the efficient synthesis of two distinct classes of polysubstituted 3-trifluoromethylpyrazoles via a two-step protocol comprising (*i*) diastereoselective (3 + 2)-cycloaddition of **1** with chalcones followed by (*ii*) solvent-controlled, competitive oxidation vs deacylative aromatization of the intermediate pyrazolines by using MnO_2 as a convenient oxidant.

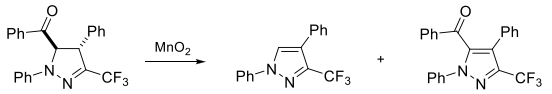
The model 5-benzoylpyrazoline **2a** was prepared by the reaction of chalcone **4a** with an excess of hydrazonoyl bromide **3a** in the presence of Et_3N as a base, at room temperature (Scheme 2).[7b] Gratifyingly, the expected *trans*-configured

Scheme 2. Synthesis of 3-Trifluoromethylpyrazoline 2a



pyrazoline **2a** was formed as the only product under the applied conditions. In the search for an efficient oxidizing reagent, we directed attention to MnO_2 as a common oxidant which has broadly been applied, e.g. in diverse dehydrohalogenation processes.[12,13] More importantly, despite its well-known mildness under neutral conditions, successful oxidation of some carbonyl compounds into respective carboxylic acids is also known.[14] The first experiment was aimed at oxidation of model pyrazoline **2a** with excess MnO_2 (ca. 85%, <10 μm), which was carried out in DCM solution, and the formation of a single product **5a** in ca. 37% yield was observed after 2 d at room temperature (Table 1, entry 1). Interestingly, in the ^{13}C NMR (151 MHz, $CDCl_3$) spectrum of 1,4-diphenyl-3-trifluoromethylpyrazole (**5a**), along with the expected quartets found at δ = 122.7 ($^1J_{C-F}$ = 269.9 Hz) and δ = 140.5 ($^2J_{C-F}$ = 36.6 Hz) attributed to the CF_3 group and the C(3) atom, respectively, the presence of another quartet at δ = 128.8 (J_{C-F} ≈ 1.2 Hz) resulting from through-space coupling between F atoms and the *ortho*-C atoms of the neighboring Ph ring additionally confirmed the expected substitution pattern in **5a**.

Table 1. Oxidation of 3-Trifluoromethylpyrazoline 2a with MnO_2[a]



			ratio [%][b] (isolated yield)		
entry	solvent	temp	**2a**	**5a**	**6a**
1	DCM	rt	63	37	–
2	hexane	rt	46	54	–
3	toluene	rt	79	21	–
4	hexane	60 °C	–	96 (94)	4
5	hexane[c]	60 °C	–	98 (97)	2
6	THF	rt	89	11	–
7	MeCN	rt	90	10	–
8	DMSO	rt	100	–	–
9	MeCN	75 °C	–	53	47
10	DMF	100 °C	–	33	67
11	DMF	130 °C	–	35	65
12	DMSO	100 °C	–	7	93 (79)
13	DMSO[c]	100 °C	–	10	90 (81)
14	DMSO[d]	100 °C	–	8	92
15	DMSO[e]	100 °C	100	–	–

[a]Reaction conditions: a solution of **2a** (0.20 mmol) in corresponding solvent (3 mL) and solid MnO_2 (20 equiv) were stirred magnetically in a 10 mL flask for 2 d. [b]Estimated based on ^1H NMR spectra of crude mixtures. [c]1 mmol (**2a**) scale. [d]Reaction performed in the presence of atmospheric moisture (open flask). [e]Heating in absence of MnO_2.

Examination of the solvent effects revealed that decreased polarity of the organic medium favors deacylative oxidation leading to pyrazole **5a** (54% in hexane, entry 2), whereas only traces or no formation of this product was observed in THF, MeCN, and DMSO solutions.[15] Increasing the temperature of the hexane solution resulted in complete conversion of starting pyrazoline **2a** into **5a** (96%) which was accompanied only by trace amounts of 5-benzoyl-functionalized pyrazole **6a** formed as a side product. On the other hand, oxidation of **2a** at elevated temperature in polar media such as MeCN, DMF, and DMSO proceeded partially with preservation of the benzoyl group and led to mixtures of **5a** and **6a** (entries 9−12). In the latter experiment performed in DMSO, preferential formation of the tetrasubstituted product was observed. Gratifyingly, both oxidation reactions could successfully be scaled up (1.0 mmol) without any remarkable loss of selectivity (entries 5 and 13). Furthermore, the optimized deacylative protocol was found to be operationally very simple; both the benzoic acid formed as the only byproduct and the remaining solid MnO_2 could be filtered off to give, after removal of the solvent, spectroscopically pure product **5a**. Subsequent filtration of this material through a short silica gel pad provided analytically pure sample. The observed switch of chemoselectivity also deserves a brief comment. Possibly, the reaction carried out in the nonpolar hexane solution is initiated by oxidation at the benzyl-like position C(4) of the *trans*-configured pyrazoline **2** and proceeds preferentially via deacylative fashion due to close proximity of the benzoyl group and the "activated surface" of MnO_2. Apparently, replacement of the nonpolar solvent by polar DMSO reduces the oxidative potential of MnO_2,[12] and hence, observed *trans* elimination of two H-atoms takes place.

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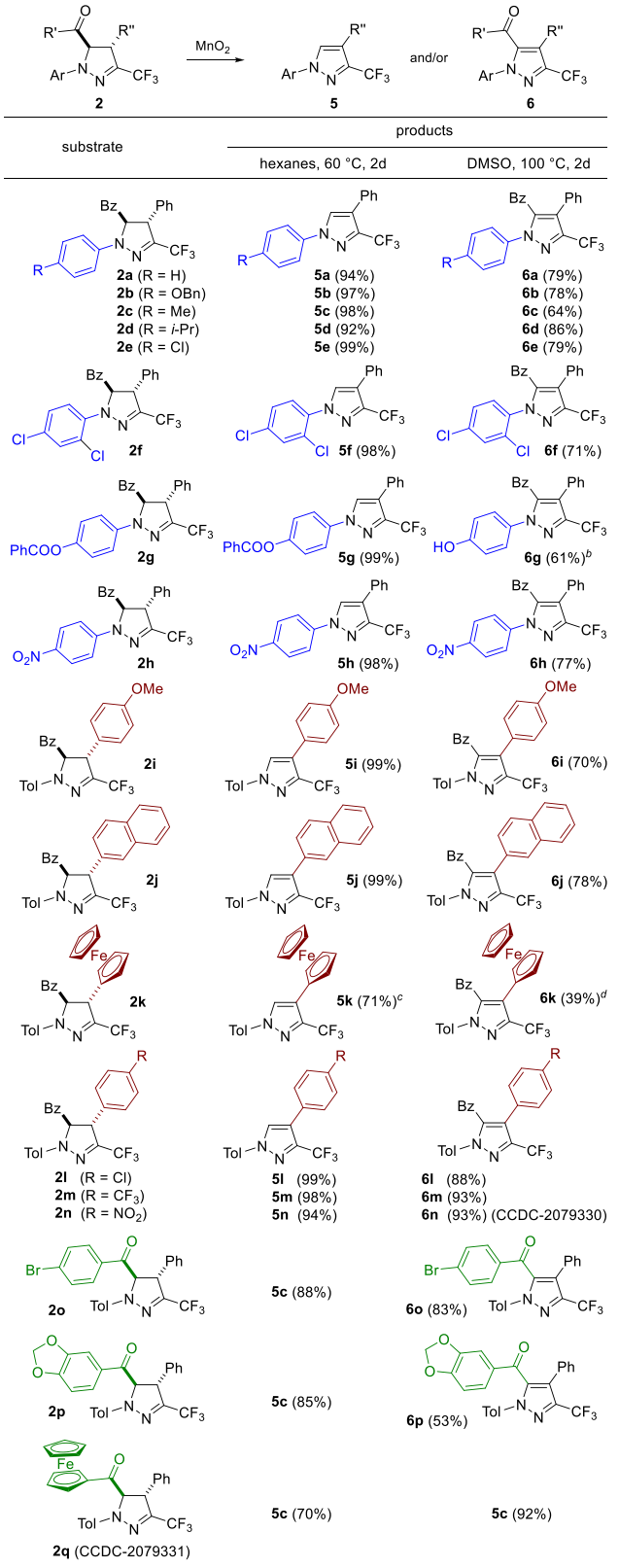
With the optimized conditions in hand, we investigated the scope and limitations of the developed solvent-controlled oxidation procedure. Hence, a series of 5-benzoylpyrazolines **2b**−**2q** were prepared in analogy to the model reaction depicted in Scheme 2 in acceptable yields of 44−96%, and next, the obtained products **2** were subjected to reaction with MnO_2 (Scheme 3; for detailed procedure, see Supporting Information). First, a series of pyrazolines **2b**−**2h**, derived from chalcone **4a** and differently substituted nitrile imines **1**, were examined in oxidation reactions.

In all the tested examples, the expected products **5** and **6** were formed in high yields and with excellent selectivity, regardless of the electronic (OBn, NO_2) and steric (2,4-di-Cl) features of the substituent present in the aryl ring located at N(1). Only in the case of 4-benzoyloxy derivative **2g** oxidation in hot DMSO proceeded with complete deprotection of the ester unit to afford phenol **6g** as the only product. Next, a second set of pyrazolines (**2i**−**2q**) obtained by condensation of differently substituted chalcones **4** with *p*-tolyl functionalized nitrile imine was examined. Again, excellent selectivity and high yields were noticed for this series except from the ferrocenyl-functionalized analogues **2k** and **2q**. In the first case, the presence of the redox-active Fc group located at C(4) interfered with complete selectivity of the oxidation to provide *ca.* 7:3 and *ca.* 6:4 mixtures of **5k** and **6k** in hexane and DMSO, respectively. On the other hand, introduction of ferrocenoyl unit at C(5) in pyrazoline **2q** favored debenzoylative aromatization to provide pyrazole **5c** as a major product in both experiments. The structures of two representative compounds in this series, **2q** and **6n**, were unambiguously confirmed by X-ray analysis.[16]

In order to demonstrate the essential role of the electron-withdrawing C═O group located at the C(5) in the formation of 1,4-disubstituted 3-trifluoromethylpyrazoles **5**, the stilbene-derived *trans*-pyrazoline **7** was synthesized and applied for the reaction with MnO_2 in hexane (Scheme 4). In that case, the expected 1,4,5-triphenyl-3-trifluoromethylpyrazole (**8**, 90%) was obtained as the sole product after 2 d of heating at 60 °C. Next, (*E*)-4-phenyl-3-buten-2-one and methyl *trans*-cinnamate were also reacted with nitrile imine **1a** to yield the expected pyrazolines **9a** and **9b**, respectively. Subsequent treatment with MnO_2 in hot hexane provided the known pyrazole **5a** lacking a substituent at C(5), hence indicating also methoxycarbonyl- and acetyl-functionalized pyrazolines as suitable substrates for the described deacylative aromatization reaction. Furthermore, two more bis-trifluoromethylated pyrazoles **5r** and **6r** were efficiently prepared via solvent-controlled oxidation starting with pyrazoline **2r** obtained via (3 + 2)-cycloaddition of nitrile imine **1c** with the known CF_3-functionalized enone, namely, with (*E*)-4,4,4-trifluoro-1-phenyl-2-buten-1-one (Scheme 4).[17] This result demonstrates again that electron-deficient nitrile imines **1** derived from trifluoroacetonitrile are very prone 1,3-dipoles which are able to react even with strongly electron-deficient dipolarophiles such as fluorinated thioamides,[7d] and fluorinated enones. It is also worth noting that the presented protocol nicely supplements previously reported methods for the synthesis of rarely reported bis-trifluoromethylated pyrazoles, which are of interest in the context of not only pharmaceutical applications but also coordination chemistry.[1b,6d,18]

In summary, a novel protocol for the synthesis of two types of 3-trifluoromethylated pyrazoles, by using 5-acylpyrazolines as common precursors for highly selective, solvent-dependent

Scheme 3. Oxidation of Pyrazolines 2 with MnO_2; Scope of Substrates[a]



[a]If not stated otherwise, the yields refer to isolated yields. [b]Obtained from pyrazoline **2g**. [c]The formation of **6k** (*ca.* 27% based on ^{1}H NMR of crude mixture) was observed. [d]The formation of **5k** (59%) was observed; yield estimated based on ^{1}H NMR spectrum of crude mixture.

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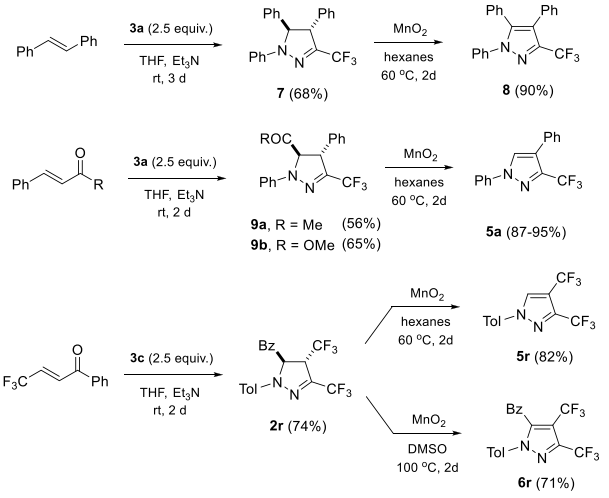
Scheme 4. Control Experiments Aimed at Aromatization of Pyrazole Ring



oxidative aromatization with MnO_2, was elaborated and examined in a series of experiments. Starting pyrazolines are readily available via fully regio- and diastereoselective (3 + 2)-cycloaddition reactions starting with corresponding chalcones and hydrazonoyl bromides applied as precursors of the *in situ* generated fluorinated nitrile imines, derived from trifluoroacetonitrile. The reported method is scalable and characterized by a wide tolerance of functional groups. For all these reasons it can be recommended for preparation of polysubstituted 3-trifluoromethylpyrazoles which can be of potential interest, e.g. for medicinal chemistry, crop protection industry, and materials chemistry. The presented work demonstrates once more the utility of 1,3-dipolar cycloaddition reactions (the Huisgen reaction[19]) in method development for synthesis of trifluoromethylated heterocycles.[20]

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.2c00521.

FAIR data, including the primary NMR FID files, for compounds **2a**−**2r**, **5a**−**5r**, **6a**−**6r**, **7**, **8**, **9a**, and **9b** (ZIP)

Experimental procedures, characterization data and NMR spectra of all compounds (PDF)

Accession Codes

CCDC 2079230−2079231 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Author Contributions

‡A.K. and G.U.-J. contributed equally

Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) (a) Fustero, S.; Simón-Fuentes, A.; Delgado, O.; Román, R. Fluorinated Pyrazoles and Indazoles. In *Fluorine in Heterocyclic Chemistry*, Vol. *1*; Nenajdenko, V., Eds.; Springer: Cham, 2014. (b) Mykhailiuk, P. K. Fluorinated pyrazoles: From synthesis to applications. *Chem. Rev.* **2021**, *121*, 1670.

(2) (a) Kirsch, P. *Modern Fluoroorganic Chemistry, Synthesis, Reactivity, Applications*, 2nd ed.; Wiley-VCH: Weinheim, 2013. (b) Giornal, F.; Pazenok, S.; Rodefeld, L.; Lui, N.; Vors, J.-P.; Leroux, F. R. Synthesis of diversely fluorinated pyrazoles as novel active agrochemical ingredients. *J. Fluorine Chem.* **2013**, *152*, 2. (c) Kaur, K.; Kumar, V.; Gupta, G. K. Trifluoromethylpyrazoles as anti-inflamatory and antibacterial agents: A review. *J. Fluorine Chem.* **2015**, *178*, 306.

(3) Recent work: (a) Pianoski, K. E.; Poletto, J.; Vieira da Silva, M. J.; Ascencio Camargo, J. N.; Jacomini, A. P.; Gonçalves, D. S.; Back, D. F.; Moura, S.; Rosa, F. A. 1,2-Addition to trifluoromethylated *β*-enamino diketones: Regioselective synthesis of trifluoromethyl-containing azomethine pyrazoles and isoxazoles. *Org. Biomol. Chem.* **2020**, *18*, 2524. (b) Muzalevskiy, V. M.; Sizova, Z. A.; Panyushkin, V. V.; Chertkov, V. A.; Khrustalev, V. N.; Nenajdenko, V. G. *α*,*β*-Disubstituted CF_3-enones as a trifluoromethyl building block: Regioselective preparation of totally substituted 3-CF_3-pyrazoles. *J. Org. Chem.* **2021**, *86*, 2385. (c) Wan, C.; Pang, J.-Y.; Jiang, W.; Zhang, X.-W.; Hu, X.-G. Copper-catalyzed reductive ring cleavage of isoxazoles: Synthesis of fluoroalkylated enaminones and application for the preparation of celecoxib, deracoxib, and mavacoxib. *J. Org. Chem.* **2021**, *86*, 4557.

(4) Selected examples: (a) Wen, J.-J.; Tang, H.-T.; Xiong, K.; Ding, Z.-C.; Zhan, Z.-P. Synthesis of polysubstituted pyrazoles by a Platinum-catalyzed sigmatropic rearrangement/cyclization cascade. *Org. Lett.* **2014**, *16*, 5940. (b) Ji, G.; Wang, X.; Zhang, S.; Xu, Y.; Ye, Y.; Li, M.; Zhang, Y.; Wang, J. Synthesis of 3-trifluoromethylpyrazoles via trifluoromethylation/cyclization of *α*,*β*-alkynic hydrazines using a hypervalent iodine reagent. *Chem. Commun.* **2014**, *50*, 4361. (c) Yang, Y.; Hu, Z.-L.; Li, R.-H.; Chen, Y.-H.; Zhan, Z.-P. Pyrazole synthesis

via a cascade Sonogashira coupling/cyclization of *N*-propargyl sulfonylhydrazones. *Org. Biomol. Chem.* **2018**, *16*, 197. (d) Muzalevskiy, V. M.; Nenajdenko, V. G. Electrophilic halogenation of hydrazones of CF_3-ynones. Regioselective synthesis of 4-halo-substituted 3-CF_3-pyrazoles. *Org. Biomol. Chem.* **2018**, *16*, 7935. (e) Zhu, C.; Zeng, H.; Liu, C.; Cai, Y.; Fang, X.; Jiang, H. Regioselective synthesis of 3-trifluoromethylpyrazole by coupling of aldehydes, sulfonyl hydrazides, and 2-bromo-3,3,3-trifluoropropene. *Org. Lett.* **2020**, *22*, 809. (f) Wang, H.; Ning, Y.; Sun, Y.; Sivaguru, P.; Bi, X. Cycloaddition of trifluoroacetaldehyde *N*-triftosylhydrazone (TFHZ-Tfs) with alkynes for synthesizing 3-trifluoromethylpyrazoles. *Org. Lett.* **2020**, *22*, 2012.

(5) For exemplary functional group interconversions, see: (a) Zhang, Y.; Chen, Z.; Nie, J.; Zhang, F.-G.; Ma, J.-A. Development of cyanopyrazoles as building blocks to fungicide fluxapyroxad and analogues. *J. Org. Chem.* **2019**, *84*, 7148. (b) Trofymchuk, S.; Bugera, M. Y.; Klipkov, A. A.; Razhyk, B.; Semenov, S.; Tarasenko, K.; Starova, V. S.; Zaporozhets, O. A.; Tananaiko, O. Y.; Alekseenko, A. N.; Pustovit, Y.; Kiriakov, O.; Gerus, I. I.; Tolmachev, A. A.; Mykhailiuk, P. K. Deoxofluorination of (hetero)aromatic acids. *J. Org. Chem.* **2020**, *85*, 3110. For trifluoromethylations, see: (c) Le, C.; Chen, T. Q.; Liang, T.; Zhang, P.; MacMillan, D. W. C. A radical approach to the copper oxidative addition problem: Trifluoromethylation of bromoarenes. *Science* **2018**, *360*, 1010. (d) Karmel, C.; Rubel, C. Z.; Kharitonova, E. V.; Hartwig, J. F. Iridium-catalyzed silylation of five-membered heteroarenes: High sterically derived selectivity from a pyridyl-imidazoline ligand. *Angew. Chem., Int. Ed.* **2020**, *59*, 6074. (e) Johansen, M. B.; Lindhardt, A. T. Copper-catalyzed and additive free decarboxylative trifluoromethylation of aromatic and heteroaromatic iodides. *Org. Biomol. Chem.* **2020**, *18*, 1417.

(6) (a) Li, F.; Nie, J.; Sun, L.; Zheng, Y.; Ma, J.-A. Silver-mediated cycloaddition of alkynes with CF_3CHN_2: Highly regioselective synthesis of 3-trifluoromethylpyrazoles. *Angew. Chem., Int. Ed.* **2013**, *52*, 6255. (b) Mykhailiuk, P. K. Three-component synthesis of fluorinated pyrazoles from fluoroalkylamines, $NaNO_2$ and electron-deficient alkynes. *Org. Biomol. Chem.* **2015**, *13*, 3438. (c) Britton, J.; Jamison, T. F. A unified continuous flow assembly-line synthesis of highly substituted pyrazoles and pyrazolines. *Angew. Chem., Int. Ed.* **2017**, *56*, 8823. (d) Li, F.; Wang, J.; Pei, W.; Li, H.; Zhang, H.; Song, M.; Guo, L.; Zhang, A.; Liu, L. Direct [3 + 2]-cycloaddition of electron-deficient alkynes with CF_3CHN_2: Regioselective one-pot Synthesis of 3-trifluoromethylpyrazoles. *Tetrahedron Lett.* **2017**, *58*, 4344. (e) Zhang, X.; Liu, Z.; Yang, X.; Dong, Y.; Virelli, M.; Zanoni, G.; Anderson, E. A.; Bi, X. Use of trifluoroacetaldehyde N-Tfsylhydrazone as a trifluorodiazoethane surrogate and its synthetic applications. *Nat. Commun.* **2019**, *10*, 284. (f) Lv, S.; Zhou, H.; Yu, X.; Xu, Y.; Zhu, H.; Wang, M.; Liu, H.; Dai, Z.; Sun, G.; Gong, X.; Sun, X.; Wang, L. Lewis base-catalyzed intermolecular triazene alkyne cycloaddition for late-stage functionalization and scaffold diversification. *Commun. Chem.* **2019**, *2*, 69. Selected reviews: (g) Mertens, L.; Koenigs, R. M. Fluorinated diazoalkanes − a versatile class of reagents for the synthesis of fluorinated compounds. *Org. Biomol. Chem.* **2016**, *14*, 10547. (h) Mykhailiuk, P. K. 2,2,2-Trifluorodiazethane (CF_3CHN_2): A long journey since 1943. *Chem. Rev.* **2020**, *120*, 12718.

(7) (a) Mlostoń, G.; Urbaniak, K.; Utecht, G.; Lentz, D.; Jasiński, M. Trifluoromethylated 2,3-dihydro-1,3,4-thiadiazoles via the regioselective [3 + 2]-cycloadditions of fluorinated nitrile imines with aryl, hetaryl, and ferrocenyl thioketones. *J. Fluorine Chem.* **2016**, *192*, 147. (b) Grzelak, P.; Utecht, G.; Jasiński, M.; Mlostoń, G. First (3 + 2)-cycloadditions of thiochalcones as C=S dipolarophiles: Efficient synthesis of 1,3,4-thiadiazoles via reactions with fluorinated nitrile imines. *Synthesis* **2017**, *49*, 2129. (c) Utecht-Jarzyńska, G.; Michalak, A.; Banaś, J.; Mlostoń, G.; Jasiński, M. Trapping of trifluoroacetonitrile imines with mercaptoacetaldehyde and mercaptocarboxylic acids: An access to fluorinated 1,3,4-thiadiazine derivatives via (3 + 3)-annulation. *J. Fluorine Chem.* **2019**, *222*−*223*, 8. (d) Utecht-Jarzyńska, G.; Mykhaylychenko, S. S.; Rusanov, E. B.; Shermolovich, Y. G.; Jasiński, M.; Mlostoń, G. Highly fluorinated 2,3-dihydro-1,3,4-thiadiazole derivatives via (3 + 2)-cycloadditions of tertiary thioamides with nitrile imines derived from trifluoroacetonitrile. *J. Fluorine Chem.* **2021**, *242*, 109702. For cycloadditions of closely related difluoromethylated nitrile imines see: (e) Han, T.; Wang, K.-H.; Yang, M.; Zhao, P.; Wang, F.; Wang, J.; Huang, D.; Hu, Y. Synthesis of difluoromethylated Pyrazoles by the [3 + 2] cycloaddition reaction of difluoroacetohydrazonoyl bromides. *J. Org. Chem.* **2022**, *87*, 498.

(8) (a) Oh, L. M. Synthesis of celecoxib via 1,3-dipolar cycloaddition. *Tetrahedron Lett.* **2006**, *47*, 7943. (b) Utecht, G.; Fruziński, A.; Jasiński, M. Polysubstituted 3-trifluoromethylpyrazoles: Regioselective (3 + 2)-cycloaddition of trifluoroacetonitrile imines with enol ethers and functional group transformations. *Org. Biomol. Chem.* **2018**, *16*, 1252.

(9) Tanaka, K.; Maeno, S.; Mitsuhashi, K. Preparation of trifluoroacetonitrile phenylimine and its reactions with some dipolarophiles. *Chem. Lett.* **1982**, *11*, 543.

(10) Tian, Y.-C.; Li, J.-K.; Zhang, F.-G.; Ma, J.-A. Regioselective decarboxylative cycloaddition route to fully substituted 3-CF_3-pyrazoles from nitrilimines and isoxazolidinediones. *Adv. Synth. Catal.* **2021**, *363*, 2093.

(11) Xie, H.; Zhu, J.; Chen, Z.; Li, S.; Wu, Y. Reaction of a trifluoromethylated N-monosubstituted hydrazone with α,β-ethenyl ketones: A novel synthesis of substituted pyrazolindines and pyrazolines. *Synthesis* **2011**, *2011*, 2767.

(12) (a) Fatiadi, A. J. Active manganese dioxide oxidation in organic chemistry − part I. *Synthesis* **1976**, *1976*.65 (b) Cahiez, G.; Alami, M.; Taylor, R. J. K.; Reid, M.; Foot, J. S.; Fader, L.; Sikervar, V.; Pabba, J. Manganese dioxide. *Encyclopedia of reagents for organic chemistry (e-EROS)*; John Wiley & Sons: Hoboken, NJ, 2017.

(13) Selected oxidants such as DDQ, IBX, $NaIO_4$, and $K_3[Fe(CN)_6]$ were also briefly checked, but they were ruled out as either no oxidation or no deacylative processes could be observed.

(14) Menger, F. M.; Lee, C. Synthetically useful oxidants at solid sodium permanganate surfaces. *Tetrahedron Lett.* **1981**, *22*, 1655.

(15) Ortega-Martínez, A.; Molina, C.; Moreno-Cabrerizo, C.; Sansano, J. M.; Nájera, C. Deacylative reactions: Synthetic applications. *Eur. J. Org. Chem.* **2018**, *2018*, 2394.

(16) CCDC 2077330 (**6n**) and CCDC 2077331 (**2q**).

(17) (a) Davies, A. T.; Taylor, J. E.; Douglas, J.; Collett, C. J.; Morrill, L. C.; Fallan, C.; Slawin, A. M. Z.; Churchill, G.; Smith, A. D. Stereospecific asymmetric *N*-heterocyclic carbene (NHC)-catalyzed redox synthesis of trifluoromethyl dihydropyranones and mechanistic insights. *J. Org. Chem.* **2013**, *78*, 9243. (b) Rulev, A. Yu.; Romanov, A. R. Unsaturated polyfluoroalkyl ketones in the synthesis of nitrogen-bearing heterocycles. *RSC Adv.* **2016**, *6*, 1984.

(18) (a) Parasar, D.; Ponduru, T. T.; Noonikara-Poyil, A.; Jayaratna, N. B.; Dias, H. V. R. Acetylene and terminal alkyne complexes of copper (I) supported by fluorinated pyrazolates: Syntheses, structures, and transformations. *Dalton Trans.* **2019**, *48*, 15782. (b) Lin, Y.; Zhu, D. P.; Du, Y. R.; Zhang, R.; Zhang, S. J.; Xu, B. H. Tris(pyrazolyl)-borate cobalt-catalyzed hydrogenation of C = O, C = C, and C = N bonds: An assistant role of a Lewis base. *Org. Lett.* **2019**, *21*, 2693. (c) Li, C.; Zhang, X.; He, J.; Xu, S.; Cao, S. Et_3N-Catalyzed cycloaddition reactions of α-(trifluoromethyl)styrenes with 2,2,2-trifluorodiazoethane to access bis(trifluoromethyl)-substituted pyrazolines. *Chin. J. Chem.* **2021**, *39*, 301.

(19) Breugst, M.; Reissig, H.-U. The Huisgen reaction: Milestones of the 1,3-dipolar cycloaddition. *Angew. Chem., Int. Ed.* **2020**, *59*, 12293.

(20) Gakh, A. A.; Shermolovich, Y. Trifluoromethylated heterocycles. *Curr. Top. Med. Chem.* **2014**, *14*, 952.

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