Trifluoromethylated Pyrazoles via Sequential (3 + 2)-Cycloaddition of Fluorinated Nitrile Imines with Chalcones and Solvent-Dependent Deacylativive 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 trifluoroacetoniitride 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 fluororalkylated groups. 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. 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. In addition, Lewis acid mediated cyclizations and related transformations of hydrazones are also applied. Furthermore, some postcyclization, functional group interconversions leading to trifluoromethylated pyrazoles, and catalytic fluoroalkylation have been developed more recently. 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-trifluorodiaceoethane; 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. In contrast, applications of alternative 1,3-dipolar intermediates, i.e. trifluoroacetoniitride imines I, offer access to N-functionalized heterocycles, and typically, their reactions proceed with excellent regio- and chemoselectivity. Nevertheless, application of easily accessible nitrile imines I 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, 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. As shown in Scheme 1, the presence of −NR2 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 CF3-pyrazoles, starting with nitrile imines and isoxazolidinediones as dipolarophiles. In that case, thermal extrusion of CO2 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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precursors. The requisite starting materials can be obtained by employing azomethine imines as reported by Xie, 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-trifluoromethylpyrazolones 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 MnO2, 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 Et3N as a base, at room temperature (Scheme 2). Gratifyingly, the expected trans-configured pyrazoline 2a was formed as the only product under the applied conditions. In the search for an efficient oxidizing reagent, we directed attention to MnO2 as a common oxidant which has broadly been applied, e.g. in diverse dehydrohalogenation processes. More importantly, despite its well-known mildness under neutral conditions, successful oxidation of some carbonyl compounds into respective carboxylic acids is also known. The first experiment was aimed at oxidation of model pyrazoline 2a with excess MnO2 (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 13C NMR (151 MHz, CDCl3) spectrum of 1,4-diphenyl-3-trifluoromethylpyrazole (5a), along with the expected quartets found at δ = 122.7 (J_{C=CH} = 269.9 Hz) and δ = 140.5 (J_{C=CH} = 36.6 Hz) attributed to the CF3 group and the C(3) atom, respectively, the presence of another quartet at δ = 128.8 (J_{C=CH} ≈ 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 MnO2

| 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° | 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°   | 100 °C| − | 10 | 90 (81) |
| 14    | DMSO°   | 100 °C| − | 8 | 92 |
| 15    | DMSO°   | 100 °C| − | 100 | − |

° Reaction conditions: a solution of 2a (0.20 mmol) in corresponding solvent (3 mL) and solid MnO2 (20 equiv) were stirred magnetically in a 10 mL flask for 2 d. Estimated based on 1H NMR spectra of crude mixtures. °1 mmol (2a) scale. °Reaction performed in the presence of atmospheric moisture (open flask). °Heating in absence of MnO2.

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. 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 deacetylative protocol was found to be operationally very simple; both the benzoic acid formed as the only byproduct and the remaining solid MnO2 could be readily filtered off and washed, and the mother liquor could be evaporated directly.

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-Trifluoromethylpyrazolones Reported Herein

Scheme 2. Synthesis of 3-Trifluoromethylpyrazoline 2a
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 MnO₂ (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, NO₂) 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 ferrocenyl unit at C(S) 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(S) in the formation of 1,4-disubstituted 3-trifluoromethylpyrazoles 5, the stilbene-derived trans-pyrazoline 7 was synthesized and applied for the reaction with MnO₂ 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)-1-phenyl-3-trifluoromethylpyrazole 9, 90% was obtained by condensation of differently substituted chalcones 4 with p-tolyl functionalized nitrile imine 1a to yield the expected pyrazolones 9a and 9b, respectively. Subsequent treatment with MnO₂ in hot hexane provided the known pyrazole 5a lacking a substituent at C(S), 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 CF₃-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, 13 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−k

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

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**Scheme 3. Oxidation of Pyrazolines 2 with MnO₂; Scope of Substrates**

| Substrate | Hexanes, 60 °C, 2d | DMSO, 100 °C, 2d |
|-----------|-------------------|------------------|
| 2a (R = H) | 5a (94%) | 6a (79%) |
| 2b (R = OMe) | 5b (97%) | 6b (78%) |
| 2c (R = Mes) | 5c (99%) | 6c (84%) |
| 2d (R = 4-Pr) | 5d (92%) | 6d (86%) |
| 2e (R = Cl) | 5e (99%) | 6e (79%) |
| 2f | 5f (98%) | 6f (71%) |
| 2g | 5g (99%) | 6g (81%) |
| 2h | 5h (88%) | 6h (77%) |
| 2i | 5i (99%) | 6i (70%) |
| 2j | 5j (99%) | 6j (78%) |
| 2k | 5k (71%) | 6k (39%) |
| 2l (R = Cl) | 5l (99%) | 6l (88%) |
| 2m (R = CF₃) | 5m (98%) | 6m (93%) |
| 2n (R = NO₂) | 5n (94%) | 6n (93%) (CCDC-2079330) |
| 2o | 5o (88%) | 6o (83%) |
| 2p | 5p (85%) | 6p (53%) |
| 2q | 5q (70%) | 6q (92%) |

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**Note:**
- "If not stated otherwise, the yields refer to isolated yields.
- "Obtained from pyrazoline 2g. The formation of 6k (ca. 27% based on ¹H NMR of crude mixture) was observed.
- "The formation of 5k (59%) was observed; yield estimated based on ¹H NMR spectrum of crude mixture."
oxidative aromatization with MnO₂ 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 trifluoroacetoni trile. 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-
fluoromethyl heterocycles.20

ASSOCIATED CONTENT
Supporting Information
The Supporting Information is available free of charge at https://pubs.acs.org/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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