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Copper-Catalyzed Double C−H Alkylation of Aldehyde-Derived *N,N*-Dialkylhydrazones with Polyhalomethanes: Flexible Access to 4-Functionalized Pyrazoles

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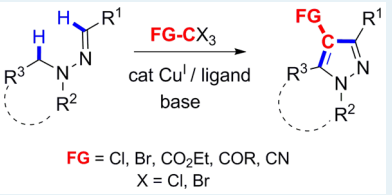
Supporting Information

ABSTRACT: Here, 4-functionalized pyrazoles have been made accessible in a single step from readily available aldehyde-derived *N,N*-dialkyl hydrazones and functionalized polyhalomethane derivatives. The process is believed to follow copper-catalyzed cascade C(sp^2)−H haloalkylation/C(sp^3)−H cyclization/aromatization reaction sequences.

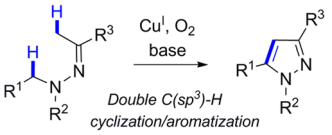


KEYWORDS: *copper, halomethanes, homogeneous catalysis, hydrazones, pyrazoles*

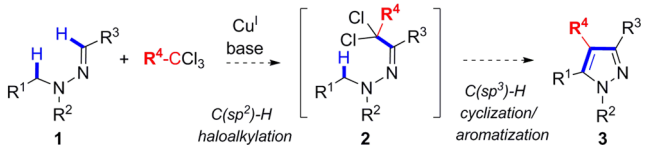
Pyrazoles are fascinating, highly essential heterocyclic compounds utilized extensively in various areas of the chemical industry, notably as pharmaceuticals and agrochemicals, as well as coloring agents.[1] Among other important applications, they can act as ligands in coordination compounds[2] and serve as units in supramolecular architectures.[3] In view of the functional diversity of pyrazoles, the development of new practical strategies to rapidly construct such aza-heterocycles with diverse substitution patterns is highly desirable. Among the conventional approaches developed over the past decades for the construction of the pyrazole skeleton,[4] the most commonly used include the cyclocondensation of hydrazine derivatives with 1,3-disubstituted three-carbon units, including 1,3-diketones and α,β-unsaturated ketones, and the [3 + 2] cycloadditions of nitrogen-based 1,3-dipoles with alkynes or alkenes. However, such procedures often suffer from regioselectivity issues, which greatly reduces their attractiveness. Hydrazones are important, easily available intermediates in synthetic organic chemistry involved in a plethora of applications[5] that also include the synthesis of functionalized pyrazoles.[6] In this area, the development of efficient and practical methods involving transition-metal-catalyzed intramolecular C−C or C−N bond formation through direct double functionalization of C−H bonds has been the recent target of synthetic chemists.[7] A notable illustration of this type of approach was given by Ge and coworkers,[7c] who reported, in 2013, an elegant copper-catalyzed dehydrogenative cyclization of acetophenone-derived *N,N*-dialkylhydrazones by a double C(sp^3)−H bond functionalization (Scheme 1a). An interesting feature of the process pertains to a direct functionalization at the sp^3-hybridized carbon atom α to the terminal hydrazone amino group.[8] However, despite its simplicity and high synthetic efficiency, the process was found to not be suitable to deliver C4-substituted pyrazoles.

Scheme 1. Transition-Metal-Catalyzed Double C−H Bond Functionalization of *N,N*-Dialkylhydrazones as a Strategy Toward Pyrazoles via C−C Bond Formation: (a) Dehydrogenative Cyclization of Acetophenone-Derived Hydrazones and (b) Tandem Haloalkylation/Cyclization of Aldehyde-Derived Hydrazones

a) Dehydrogenative cyclization of acetophenone-derived hydrazones (**Ge**, Ref. [7c])



b) Tandem haloalkylation/cyclization of aldehyde-derived hydrazones (**Our approach**)



Aldehyde-derived *N,N*-disubstituted hydrazones are particularly attractive as umpolung carbonyl reagents, because of the presence of the electron-releasing amino component that activates the azomethine (CH═N) carbon atom position toward electrophilic substitution,[9] thereby enabling introduction of a functional group through direct C(sp^2)−H bond functionalization. The past few years have witnessed intense renewed activity in this research area, with contributions from our own group[10] and others.[11] Efficient catalytic radical

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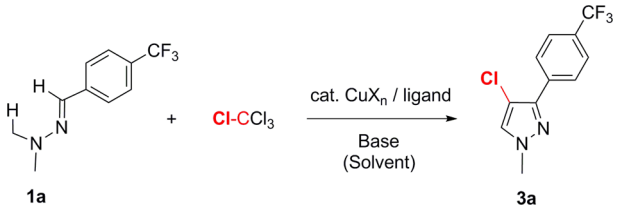
reactions using transition metals (Cu, Pd, Au, Ir) have been developed that allow the installation of a wide range of new functional groups (e.g., CF_3,[10a,b,11a] CF_2CO_2Et, CF_2CONR_2[10c,d,11a,c] $PO(OEt)_2$[11d]), and thereby create new opportunities for practical applications of these valuable synthetic intermediates. For instance, we have demonstrated[10d] the Cu-catalyzed C(sp^2)−H alkylation of *N,N*-dialkylhydrazones (**1**) with difluoromethyl bromides ($BrCF_2R$) that yields difluoroalkylated hydrazones as useful precursors toward *α,α*-difluorocarbonyl compounds.[10c] The transformation was suggested to be initiated by a radical/SET pathway involving the formation of an electrophilic haloalkyl radical that can add to the C=N bond of the hydrazone.[12] As part of our ongoing efforts to devise new applications of this methodology, it was envisioned that other nonfluorinated polyhalomethanes (i.e., CCl_4, R−CCl_3) may participate in the process[13] and open up direct access to hitherto unknown polyhalomethylated *N,N*-dialkylhydrazones (**2**) as expectedly reactive synthetic intermediates having high potential for further elaboration.[14] As we began exploring this possibility using CCl_4 as a CCl_3-transfer reagent, we made an interesting discovery: the reaction resulted in direct formation of a pyrazole derivative having incorporated a Cl atom at the C-4 position (**3**, R^4 = Cl) (Scheme 1b). Such unexpected reaction, whereby two new C−C bonds are formed in sequence, appeared very promising as a novel, practical, and convergent access to polysubstituted pyrazoles from simple, readily available starting materials, while allowing flexible attachment of chemical handles at the C-4 position that can further help to create diversity. Herein, we disclose our preliminary investigations regarding the scope and limitations of the method, and we provide some mechanistic insight into plausible reaction pathways.

Initial studies focused on the trichloroalkylation of *p*-trifluoromethylbenzaldehyde *N,N*-dimethylhydrazone **1a** using CCl_4 as a solvent and reagent in the presence of a base (i.e., Et_3N, DIPEA, KOAc, or K_2CO_3), and a copper catalyst combined with a nitrogen-based bidentate ligand (i.e., Tmeda, Bipy, or Phen) (see Table 1). Preliminary experiments established the following conditions as being optimal in affording the corresponding 4-chloropyrazole **3a** in satisfying yield (70%, ^{19}F NMR spectroscopy): 10 mol % CuCl (or CuI)/Phen, Et_3N (4 equiv), 80 °C, 2 h (see Table 1, entries 4 and 5). Importantly, the reaction would not proceed in the absence of catalyst under otherwise identical conditions (Table 1, entry 7). Also important was the fact that CCl_4 does not need to be used as a solvent. Indeed, the same reaction could be performed, for instance, in 1,4-dioxane in the presence of only 5 equiv of CCl_4, which gave pyrazole **3a** in identical yield (Table 1, entry 15). Other solvents (i.e., DCE, MeCN, or THF) proved less effective (Table 1, entries 12−14).

With suitable reaction conditions in hand, we began to examine the scope of the reaction. We envisioned that many organic halides other than CCl_4 may prove to be suitable reacting partners and open access to pyrazoles featuring a diversity of functional groups at the C-4 position, having potential for further derivatization reactions. Therefore, we investigated the reaction of our model substrate **1a** with a series of polyhalogenated methanes (see Table 2). It is noteworthy that bromotrichloromethane (CCl_3Br) could not be used with similar success in the production of 4-chloropyrazole **3a** (Table 2, compare entries 1 and 2). A comparable reactivity was observed with tetrabromomethane (CBr_4), which furnished the corresponding 4-bromopyrazole **3b** in only moderate yield

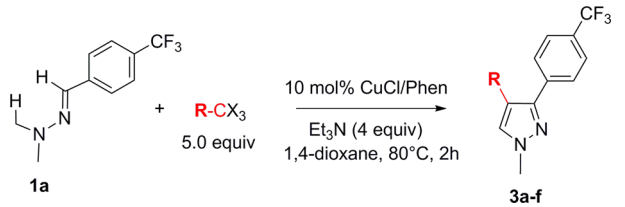
Table 1. Selected Optimization Experiments for the Cu-Catalyzed Trichloromethylation/Cyclization of Hydrazone 1a with CCl_4[a]



entry	cat	ligand	base	solvent	time (h)	yield[b] (%)
1	CuCl		Et_3N	CCl_4	24	57
2	CuCl	Tmeda	Et_3N	CCl_4	24	47
3	CuCl	Bipy	Et_3N	CCl_4	24	70
4	CuCl	Phen	Et_3N	CCl_4	2	69
5	CuI	Phen	Et_3N	CCl_4	2	70
6	$CuCl_2$	Phen	Et_3N	CCl_4	2	65
7			Et_3N	CCl_4	2	0
8	CuCl	Phen		CCl_4	2	0
9	CuCl	Phen	DIPEA	CCl_4	2	38
10	CuCl	Phen	KOAc	CCl_4	2	29
11	CuCl	Phen	K_2CO_3	CCl_4	2	0
12	CuCl	Phen	Et_3N	DCE[c]	2	31
13	CuCl	Phen	Et_3N	MeCN[c]	2	33
14	CuCl	Phen	Et_3N	THF[c]	2	60
15	CuCl	Phen	Et_3N	1,4-dioxane[c]	2	70
16	CuCl	Phen	Et_3N	1,4-dioxane[d]	2	58

[a]Reaction conditions: **1a** (0.3 mmol), base (4 equiv), 10 mol % copper salt, 10 mol % ligand (Tmeda = tetramethylethylenediamine, Bipy = 2,2′-bipyridine, Phen = 1,10-phenanthroline) in 2.0 mL of solvent at 80 °C. [b]Determined by ^{19}F NMR spectroscopy, using *α,α,α*-trifluorotoluene as an internal standard. [c]5 equiv of CCl_4. [d]2 equiv of CCl_4.

Table 2. Scope of Organic Polyhalides[a]



entry	R−CX_3	product	yield[b] (%)
1	CCl_4	R = Cl (**3a**)	70 (47)
2	CCl_3Br	R = Cl (**3a**)	48 (−)
3	CBr_4	R = Br (**3b**)	43 (21)
4	CCl_3CN	R = CN (**3c**)	84 (66)
5	CCl_3CO_2Et	R = CO_2Et (**3d**)	93 (72)
6	CCl_3COPh	R = COPh (**3e**)	45 (42[c])
7	CCl_3F	R = F (**3f**)	NR

[a]Reaction conditions: **1a** (0.5 mmol), R−CX_3 (5.0 equiv), Et_3N (4 equiv), 10 mol % CuCl/Phen in 3.0 mL of 1,4-dioxane at 80 °C for 2 h. [b]Determined by ^{19}F NMR spectroscopy using *α,α,α*-trifluorotoluene as an internal standard. Isolated yields are indicated in parentheses. [c]The isolated product contained about 7% of inseparable impurities.

(Table 2, entry 3). A series of functionalized trichloromethanes was then tested. Gratifyingly, trichloroacetonitrile (CCl_3CN) and ethyl trichloroacetate (CCl_3CO_2Et) participated efficiently in the process, giving the desired pyrazoles, having incorporated

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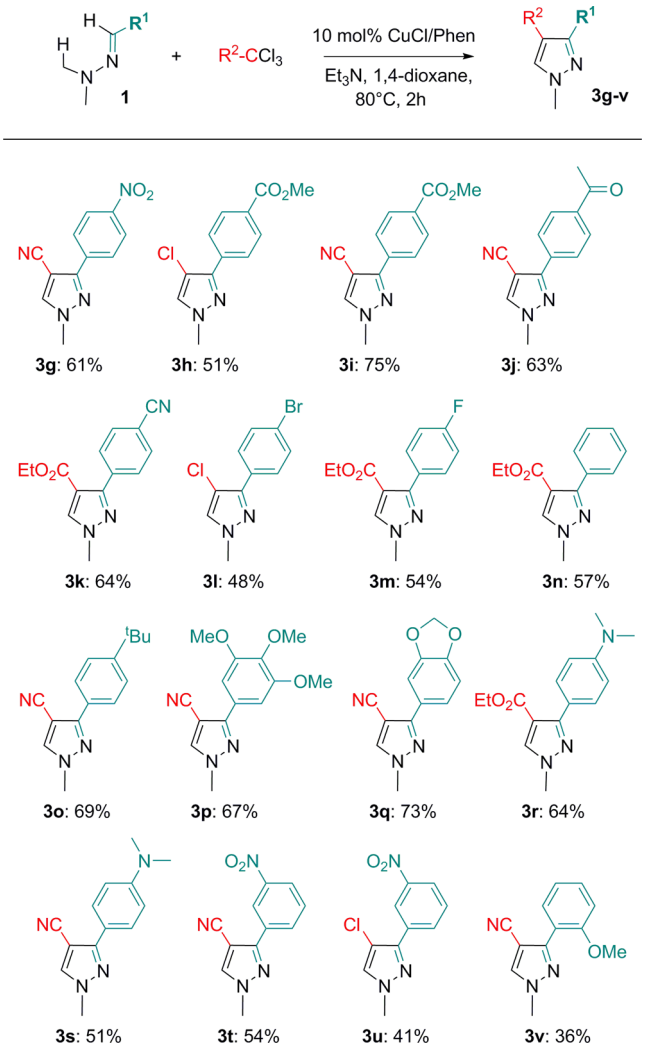
a cyano (**3c**) or ester group (**3d**) in good isolated yields (66% and 72%, respectively; see Table 2, entries 4 and 5). Trichloroacetophenone ($PhCOCCl_3$) also yielded the corresponding functionalized pyrazole (**3e**), albeit in moderate yield (Table 2, entry 6). Finally, we were attracted by the possibility of accessing a C4-fluorinated pyrazole (**3f**). Disappointingly, however, the reaction was not applicable to trichlorofluoromethane (CCl_3F) (Table 2, entry 7).

Next, we investigated the effect of substituents on the aryl moiety of various benzaldehyde *N*,*N*-dimethylhydrazones (Scheme 2). Relatively good yields were generally achieved

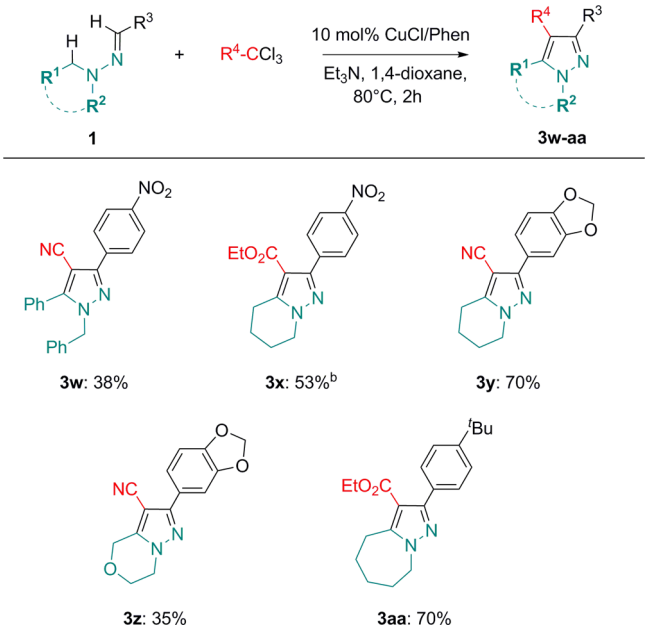
Scheme 2. Scope of Aldehyde Precursors[a]



[a]Reaction conditions: **1** (0.5 mmol), R^2–CCl_3 (5.0 equiv), Et_3N (4 equiv), CuCl (10 mol %), and Phen (10 mol %) in 3.0 mL of 1,4-dioxane at 80 °C for 2 h. Isolated yields are given.

with para- and meta-substituted aryls regardless of the electron-donating or electron-withdrawing nature of substituents (**3g**–**3u**). Again, the nature of the substituent incorporated at the C-4 position influenced the yield, best results being achieved with a CN or CO_2Et group, compared to chlorine. As illustrated by **3v**, even sterically hindered *ortho*-substituted aryls were tolerated to some extent. Notably, the reaction displayed good tolerance toward a variety of functional groups, including cyano, carboxylic ester, acetyl, *N*,*N*-dimethylamino, and halide which may also serve as useful reaction handles for further elaborations. We then further explored the substrate scope, with regard to substitution pattern at the terminal hydrazone amino group that would enable installation of substituents at the C-5 position of the pyrazole ring (Scheme 3). Interestingly,

Scheme 3. Scope of Hydrazine Precursors[a]



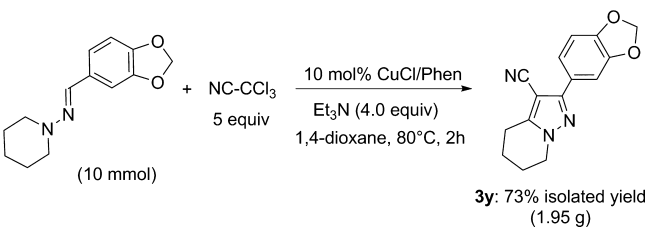
[a]Reaction conditions: **1** (0.5 mmol), R^4–CCl_3 (5.0 equiv), Et_3N (4 equiv), CuCl (10 mol %), and Phen (10 mol %) in 3.0 mL of 1,4-dioxane at 80 °C for 2 h. Isolated yields are given. [b]The product contained about 8% of inseparable impurities.

hydrazones bearing cyclic amino groups, i.e., 1-piperidinyl, 4-morpholinyl, and 1-homopiperidyl participated in the cyclization process, giving the desired pyrazolo-annelated products (**3x**–**y**, **3z**, and **3aa**, respectively) in moderate to good yields. An X-ray structure was obtained for **3x**, confirming its chemical structure.[15]

Importantly, the cost-effectiveness and mildness of the method created scale-up opportunities. For instance, a 10 mmol preparative-scale synthesis of 4-cyanopyrazole **3y** could be achieved without further optimization while still maintaining a high isolated yield of 73%, thus demonstrating the robustness of our protocol (see Scheme 4).

A preliminary investigation into the mechanism of the reaction was then conducted. The possibility of a radical/SET-initiated pathway similar to that previously postulated for difluoroalkylation reactions of hydrazones was first investigated.[10c,d,11c] Interestingly, addition of radical scavenger 2,2,6,6-tetramethyl-1-piperidinoxyl (TEMPO, 5 equiv) to the

Scheme 4. Gram-Scale Experiment



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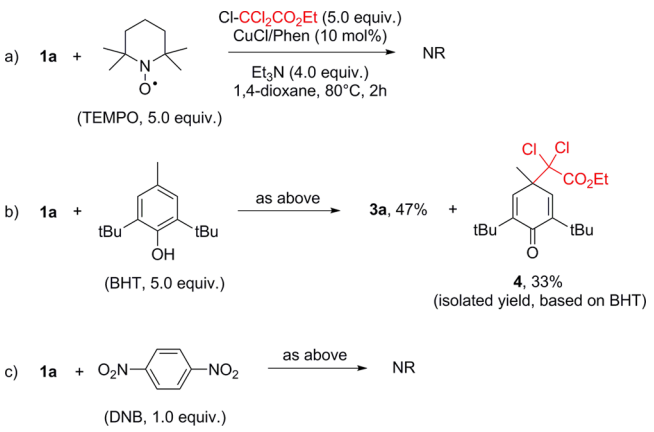
standard reaction of **1a** with CCl_3CO_2Et totally inhibited the formation of **3a** (Scheme 5a). In addition, when butylated

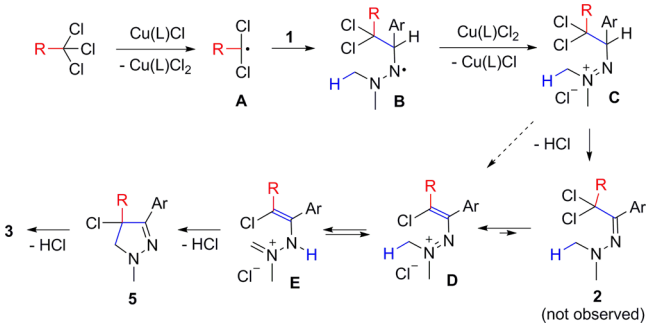
Scheme 5. Mechanism Experiments



hydroxytoluene (BHT, 5.0 equiv) was used as a radical scavenger in this reaction, **3a** was produced in a significantly diminished yield (47%). Interestingly, a BHT-CCl_2CO_2Et adduct was also isolated in the form of the cyclohexadienone **4** (33% yield based on BHT) (Scheme 5b). Moreover, the presence of 1 equiv of the electron transfer scavenger *p*-dinitrobenzene (DNB) had also a dramatic deleterious effect, leading to inhibition of the reaction (Scheme 5c).

In light of the above observations, and on the basis of previous reports, a cascade copper-catalyzed haloalkylation/cyclization/aromatization sequence may be proposed as a plausible reaction pathway (see Scheme 6). This mechanism

Scheme 6. Possible Mechanistic Pathway



would involve the formation of an electrophilic haloalkyl radical (**A**) from the polyhalomethane species via halide abstraction by the copper(I) complex with concomitant generation of copper(II).[13] The radical would then be trapped by the hydrazone[10,11] to generate a haloalkylated aminyl radical intermediate (**B**). Oxidation of this intermediate with copper(II) would recycle copper(I) and lead to the diazenium species **C**, which would then undergo proton elimination to provide the haloalkylated hydrazone **2**.[10d] The lone pair of the terminal nitrogen atom would induce elimination of a Cl^- anion to form a diazenium species (**D**). Alternatively, the latter may be accessible from **C** directly through the loss of HCl. Tautomerization of diazenium cation **D** into the corresponding iminium cation (**E**) by proton abstraction from the *N*-methyl group,[8b,c,16] and subsequent intramolecular cyclization of the enamine-type structure,[7c,8c,d] would then provide pyrazoline **5**. Aromatization to the pyrazole (**3**) would finally occur via the elimination of HCl.[17]

In summary, we have developed a cost-efficient, scalable protocol for the preparation of 4-functionalized pyrazoles based on readily available aldehyde-derived *N,N*-dialkylhydrazones, functionalized polyhalomethanes, and copper salt catalyst. The reaction exhibits a broad substrate scope and excellent functional-group tolerance, and it allows flexible attachment of chemical handles at the C-4 position that may be used for further chemistry. The process is believed to follow a cascade copper-catalyzed C−H haloalkylation/C−H cyclization/aromatization reaction sequence, whereby two new C−C bonds are formed. Further studies into the scope and limitations, as well as the mechanistic understanding of this reaction, are currently underway in our laboratories.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acscatal.6b02439.

Experimental procedures including characterization and NMR spectra for all new compounds (PDF)
X-ray data for compound **3x** (CIF)

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Notes

The authors declare no competing financial interest.

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