Letter

Four-Component Reactions for the Synthesis of Perfluoroalkyl Isoxazoles

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Four-Component Reactions for the Synthesis of Perfluoroalkyl Isoxazoles

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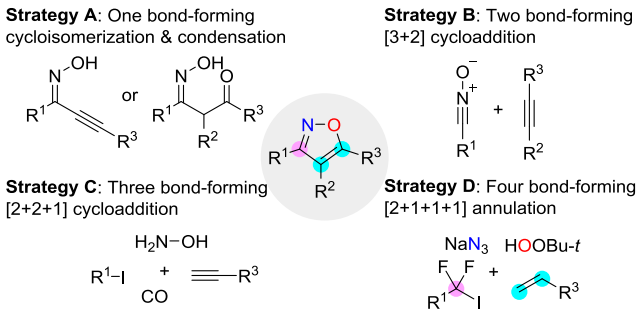
ABSTRACT: A four-component strategy for the synthesis of isoxazole skeleton is developed. The approach achieves the synthesis of perfluoroalkyl isoxazoles by using simple perfluoroalkyl reagents. In addition, the unprecedented 3-azido-5-arylisoxazole formation demonstrates Togni's reagent as a C-1 unit to be used in the isoxazole formation. The advantages of the method include readily available starting materials, structural diversity, and late-stage functionalization. Mechanistic studies support that the transformation includes a tandem process of perfluoroalkylation-peroxidation of alkene, Kornblum-DeLaMare rearrangement, elimination, substitution, N-O bond formation to give the isoxazoles.

KEYWORDS: multicomponent reaction, cobalt catalysis, isoxazoles, radical reaction, perfluoroalkylation, peroxidation, organic peroxide

Multicomponent reactions (MCRs) achieve multi-bond formation in a single procedure from readily available starting materials.[1] MCRs provide fast access to structurally complex and functionally diverse compounds and thus have attracted much attention from both academia and industry. Isoxazole is one of prevalent motifs in the field of synthetic and medical chemistry.[2] Over the last three years, 33 isoxazole compounds have been approved as drugs by FDA, which have entered the market.[2a] Isoxazole can be employed as a directing group and as a synthon that provides access to numerous *N*-heterocycles (such as isoxazolines, 2-aminopyrroles, 2-aminoquinolines, 7-acylindoles, imidazo[1,2-a]pyridines, etc.) and other functional groups (for example, as masked 1,3-dicarbonyl equivalents).[3] Great efforts have been made to achieve efficient synthesis of isoxazole derivatives.[4] The strategies for the construction of isoxazole ring are summarized in Scheme 1. Cycloisomerization and condensation present the straightforward access to isoxazoles, in which C-O bond is formed (Strategy A). [3+2] Cycloaddition is arguably the most reliable method to synthesize isoxazoles (Strategy B). The isoxazole ring was also constructed by the formation of C-C, C-O and C-N bonds through a four-component coupling of a terminal alkyne, hydroxylamine, carbon monoxide, and an aryl iodide (Strategy C).[5] Herein, we disclose a novel [2+1+1+1] annulation for the synthesis of isoxazoles (Strategy D). This discovery is the first example of the construction of four of the five bonds of the isoxazole ring from four components.[6]



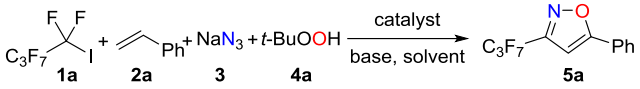
Scheme 1. Strategies for the Construction of Isoxazole Ring

Organofluorinated molecules have numerous applications, including in medicinal chemistry, agrochemistry, and material science because of the unique properties of fluorine. Nevertheless, it is not surprising that the synthesis of fluorinated isoxazoles depends on the developed methods using the synthesized fluorinated substrates (Scheme 1, Strategies A and B).[7] To the best our knowledge, simple perfluoroalkyl reagents have never been used as a starting material for the construction the fluorinated isoxazole ring.[8]

To address the challenge of new approaches for the synthesis of perfluoroalkyl isoxazole, we commenced the study by the reaction of perfluorobutyl iodide (**1a**), styrene (**2a**), sodium azide (**3**), and *tert*-butyl hydroperoxide (70% in water, **4a**) (Table 1). 3-Perfluoropropyl-5-phenyl isoxazole (**5a**) was obtained in 8% yield by the use of $Co(acac)_2$ as catalyst and DABCO as base in MeCN (entry 1). This finding prompted us to further optimize the reaction conditions of this four-component reaction. Critical improvement was made by evaluating the reaction solvent (entries 1-5). Despite lower yields of **5a** were obtained in hexane and THF (entries 2 and 3), the mixture of hexane and THF (1:1 and 4:1) improved the yields of **5a** to 56% and 77% respectively

(entries 4 and 5). These results might indicate that a cosolvent is required for better efficiency and reactivity of the desired transformation. A 51% yield of **5a** was obtained in the absence of catalyst (entry 6), suggesting that the cobalt catalyst improves the reaction efficiency. Notably, the desired product **5a** was not observed in the absence of base (entry 7) and other tested bases (entries 8-12). These results indicated that base plays a key role in the present transformation. No improvement in yield was recorded when $Co(acac)_2$ was replace by $Co(acac)_3$, $CoCl_2$, $Cu(acac)_2$ as $Fe(acac)_2$ (entries 13-16). When *tert*-butyl hydroperoxide (5.5 M in decane, **4a**) replaced *tert*-butyl hydroperoxide (70% in water), an 81% yield of **5a** was achieved (entry 17). It should be noted that cumene hydroperoxide **4b** was also applicable as oxygen source in this reaction (entry 18).

Table 1. Evaluation of Reaction Conditions[a]

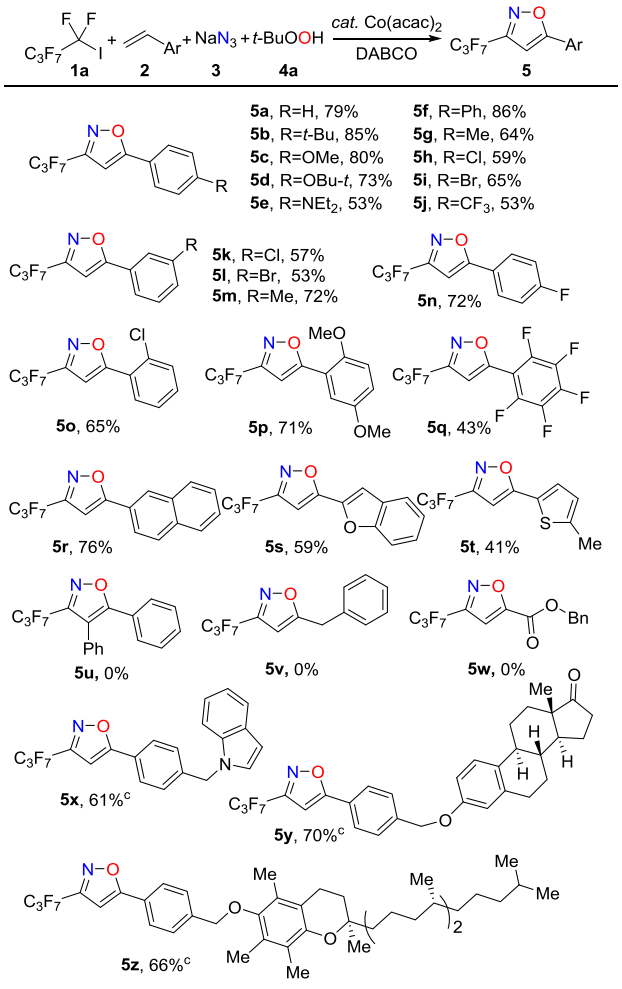


entry	catalyst	base	solvent	**5a** (%)[b]
1	$Co(acac)_2$	DABCO	MeCN	8
2	$Co(acac)_2$	DABCO	hexane	25
3	$Co(acac)_2$	DABCO	THF	23
4	$Co(acac)_2$	DABCO	hexane/THF[c]	56
5	$Co(acac)_2$	DABCO	hexane/THF[d]	77
6	-	DABCO	hexane/THF[d]	51
7	$Co(acac)_2$	-	hexane/THF[d]	N.D.[e]
8	$Co(acac)_2$	NEt_3	hexane/THF[d]	N.D.[e]
9	$Co(acac)_2$	DBU	hexane/THF[d]	N.D.[e]
10	$Co(acac)_2$	NaOH	hexane/THF[d]	N.D.[e]
11	$Co(acac)_2$	Py	hexane/THF[d]	trace
12	$Co(acac)_2$	K_2CO_3	hexane/THF[d]	trace
13	$Co(acac)_3$	DABCO	hexane/THF[d]	52
14	$CoCl_2$	DABCO	hexane/THF[d]	52
15	$Cu(acac)_2$	DABCO	hexane/THF[d]	54
16	$Fe(acac)_2$	DABCO	hexane/THF[d]	63
17[f]	$Co(acac)_2$	DABCO	hexane/THF[d]	81
18[g]	$Co(acac)_2$	DABCO	hexane/THF[d]	67

[a]Reaction conditions: **1a** (1.0 mmol), **2a** (0.5 mmol), **3a** (1.5 mmol), **4a** (70% in water, 3.0 mmol), catalyst (10 mol %), base (1.5 mmol), solvent (2.0 mL), 80 ℃, 12 h, under N_2, unless otherwise noted. [b]Reported yields were based on **2a** and determined by ^1H NMR using an internal standard. [c]1:1. [d]4:1. [e]Not detected. [f]**4a** (5.5 M in decane). [g]Cumene hydroperoxide **4b** instead of **4a**.

With the optimized conditions in hand, we investigated the scopes of the four-component method for the synthesis of the fluorinated isoxazoles (Tables 2 and 3). First, we investigated the reaction scope for alkene **2** by the use of **1a** as a model substrate (Table 2). Styrene derivatives with either electron-donating or electron-withdrawing groups on the phenyl ring reacted well with **1a**, **3** and **4a**, providing isoxazoles (**5a-5p**) in good yields. Styrene derivatives **2n** could be converted to the corresponding perfluorinated isoxazole **5n**[9] in 72% yield, which shows antibacterial activities against escherichia coli and staphylococcus albus.[10] 1,2,3,4,5-Pentafluoro-6-vinylbenzene was also applicable to give the corresponding product (**5q**), albeit in 43% yield. It is noteworthy that this method presents a significant route for the synthesis of perfluorinated isoxazoles. Other aromatic substrates including naphthyl and heteroaromatic ring gave the desired products (**5r-5t**) in medium to good yield. However, internal alkenes， aliphatic alkenes and acrylate derivatives are not viable substrates under the standard reaction conditions(**5u-5w**). At this point, we assumed that the present transformation is affected by the steric and electronic effects of alkenes. As examples of the application to the late-stage modification of more complex molecules, we were delighted to find that styrenes bearing the biologically active scaffolds afforded the desired products in 61-70% yield (**5x-5z**).

Table 2. Scope of Alkenes 2[a,b]

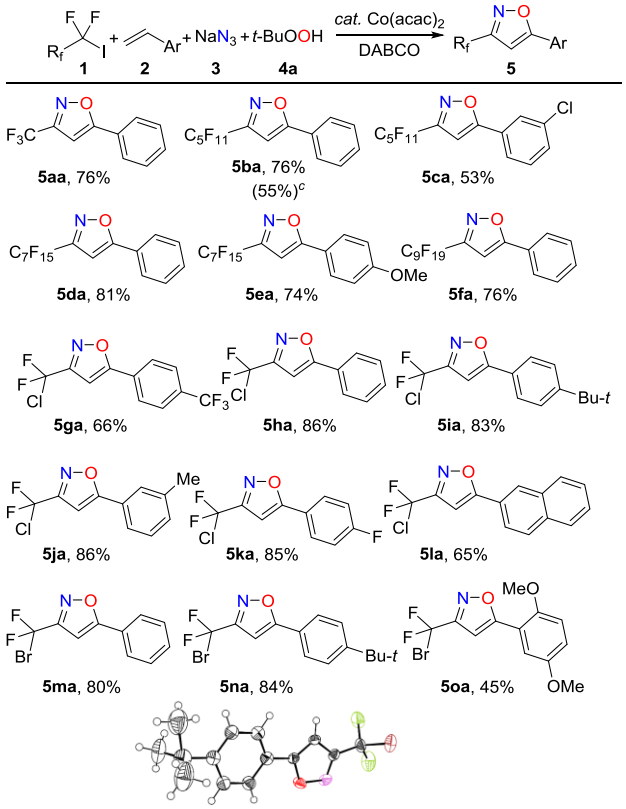


[a]Reaction conditions: **1a** (1.0 mmol), **2** (0.5 mmol), **3** (1.5 mmol), **4a** (5.5 M in decane, 3.0 mmol), $Co(acac)_2$ (10 mol %), DABCO (1.5 mmol), hexane/THF (4:1, 2.0 mL), 80 ℃, 12 h, under N_2. [b]Isolated yields. [c]hexane/THF (4:1, 4.0 mL).

Next, our attention turned to the reaction scope for fluoroalkyl reagents **1** (Table 3). To our delight, other perfluoroalkyl iodides (**1**) were also applicable under the standard reaction conditions to furnish the corresponding products (**5aa-5fa**) in good yields. It's worth mentioning that perfluorohexyl bromide **1c'** afforded the corresponding perfluoropentyl isoxazole product **5ba** in 55% yield, which is slightly lower than perfluorohexyl iodide **1c** did (76%). We were particularly interested in examining the chemoselectivity of perfluoroalkyl iodides pos-

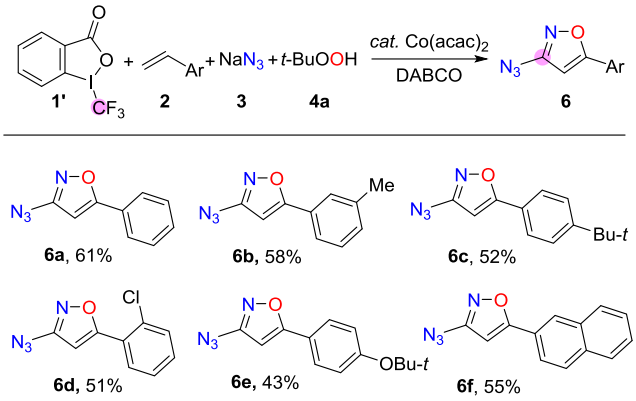
sessing chlorine and bromine atoms under these conditions. Remarkably, it was found that the perfluoroalkyl iodides possessing chlorine and bromine atoms underwent this four-component transformation in a selective manner to deliver chloro- and bromo-substituted isoxazoles (**5ga**-**5oa**) in good to excellent yields. Chloro-substituted difluoroalkyl isoxazoles are potential herbicide and bromo-substituted difluoroalkyl isoxazoles are potential difluoroalkyl reagents.[11] The structure of the product (**5na**) was confirmed by X-ray crystallographic analysis.[12]

Table 3. Scope of Perfluoroalkyl Reagents 1[a,b]



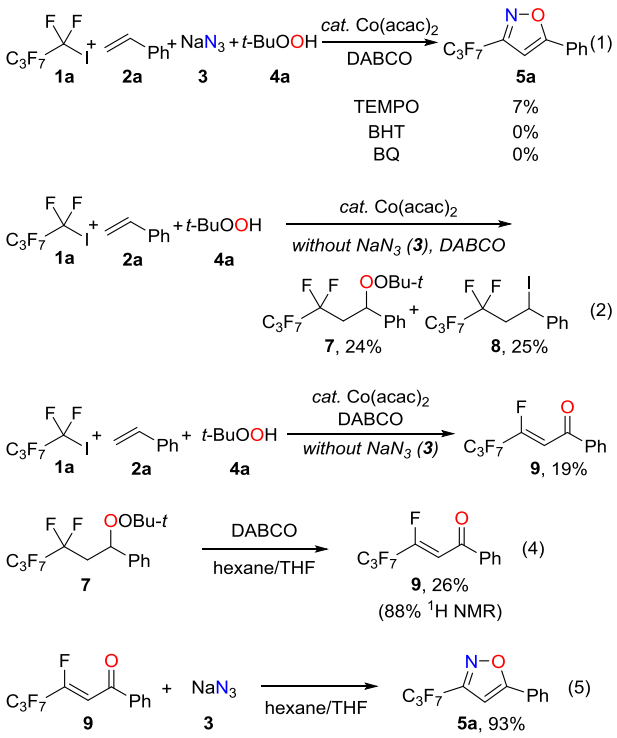
[a]Reaction conditions: **1** (1.0 mmol), **2** (0.5 mmol), **3** (1.5 mmol), **4a** (5.5 M in decane, 3.0 mmol), $Co(acac)_2$ (10 mol %), DABCO (1.5 mmol), hexane/THF (4:1, 2.0 mL), 80 ℃, 12 h, under N_2, unless otherwise noted. [b]Isolated yields. [c]Perfluorohexyl bromide **1c'** instead of perfluorohexyl iodide **1c**.

Furthermore, we envisioned that 3-fluoro-5-arylisoxazole might be generated if a CF_3 reagent was applied. To examine the feasibility of this hypothesis, Togni's reagent was tested as CF_3 source.[13] Surprisingly, 3-azido-5-arylisoxazoles (**6**) were generated and 3-fluoro-5-arylisoxazoles were not observed in these reactions (Scheme 2). These results indicated that two fluorine atoms in the intermediate are substituted by two azido groups before the formation of **6**.[14] Considering the importance of organic azides in the chemical biology, medicinal chemistry, supramolecular chemistry and materials science,[15] the present transformation might find its applications in these areas. This study presents an intriguing example of five-component reaction.



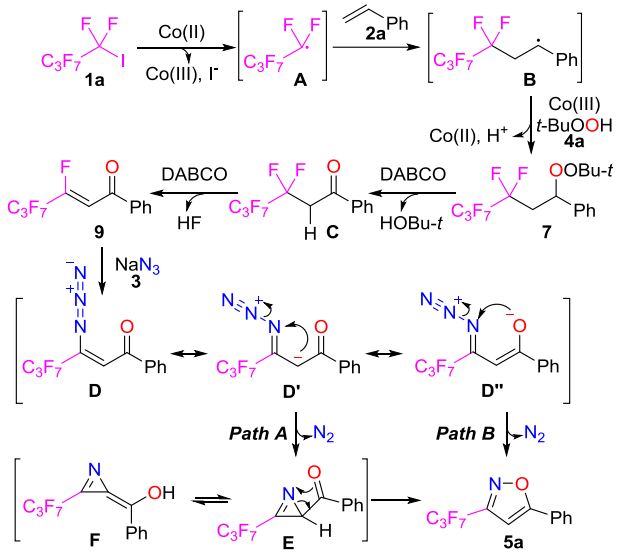
Scheme 2. Togni's Reagent as CF_3 Source

To obtain mechanistic insights, some control reactions were carried out (Scheme 3). The desired transformation was severely inhibited by radical scavengers, such as 2,2,6,6-tetramethylpiperidin-1-oxyl (TEMPO), 2,6-di-*tert*-butyl-4-methylphenol (BHT) and benzoquinone (BQ) (eq 1). The results indicated that the isoxazole formation most likely involves radical step(s). We found that in the absence of sodium azide (**3**) and DABCO (base), β-difluoro peroxide (**7**)[16] and iodide (**8**)[17] were afforded (eq 2). Notably, β-fluoro α,β-unsaturated ketone (**9**) was obtained in the presence of DABCO and without **3** (eq 3). These results indicated that: (1) the formation of **8** is suppressed in the presence of DABCO; (2) **7** might convert into **9**. To verify the hypothesis, β-difluoro peroxide (**7**) was subject to the basic condition (eq 4). A 88% ^1H NMR yield of **9** was obtained, albeit with a 26% isolated yield (probably due to the decomposition of **9** during the isolation). The results indicated that **9** comes from the deprotonation of **7** in the presence of base. Furthermore, the reaction of **9** with **3** led to the isoxazole **5a** in 93% yield (eq 5),[18,19] suggesting that the cyclization step to form O-N bond is facile.



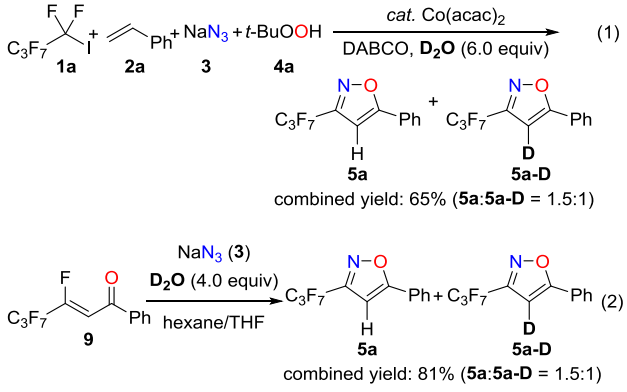
Scheme 3. Control Reactions

Based on the above results, a tentative reaction mechanism for the formation of the isoxazole (**5a**) is described in Scheme 4.[20] The SET reaction of perfluorobutyl iodide (**1a**) by Co(II) affords perfluorobutyl radical **A**, which adds to styrene (**2a**) to form the radical intermediate **B**. Radical coupling of **B** with *tert*-butylperoxy radical delivers β-difluoro peroxide (**7**). DABCO-catalyzed Kornblum-DeLaMare rearrangement of **7** leads to the carbonyl intermediate **C**,[21] which subsequently transforms into β-fluoro α,β-unsaturated ketone (**9**) by DABCO-promoted elimination of hydrofluoric acid. The substitution reaction of **9** with NaN_3 (**3**) affords the vinyl azide **D**. There are two possible pathways from **D** to the final isoxazole (**5a**): (1) The 3-exo-tet cyclization of **D'** (one of resonance structures of **D**) gives azirine (**E**),[22] which is converted into **5a** through azirine ring opening and cyclization (Path A); (2) Alternatively, the 5-exo-tet cyclization of **D''** (one of resonance structures of **D**) directly leads to **5a** by relieving N_2 (Path B).[23]



Scheme 4. Proposed Mechanism for the Formation of 5a

Furthermore, we performed the following experiments with the addition of deuterated water (D_2O) under the standard reaction conditions (Scheme 5). Both the normal product (**5a**) and the deuterated product (**5a-D**) were obtained in a ratio of 1.5:1. These results indicate that α-H of ketone **9** might partially occur H/D exchange through the keto-enol tautomerism eqilibriums (**E-F** and **D-D'-D''**) in Scheme 4.



Scheme 5. Experiments with the Addition of Deuterated Water

In conclusion, we have developed a new approach for the synthesis of perfluoroalkyl isoxazoles through four-component reactions. This protocol features the use of simple perfluoroalkyl reagents that enables the other three components to participate in the isoxazole formation. The method presents a practical, atom-economic, one-pot procedure that delivers functional isoxazoles without intermediate workup or solvent change. In addition, the unprecedented 3-azido-5-arylisoxazole formation demonstrates Togni's reagent as a C-1 unit to be used in the isoxazole formation. Mechanistic studies support that the transformation includes a tandem process of perfluoroalkylation-peroxidation of alkene, Kornblum-DeLaMare rearrangement, elimination, substitution, N-O bond formation to give the isoxazoles. We anticipate that the present results would likely offer new designs for the synthesis of isoxazoles and other heterocycles. Further investigation on the mechanism and the synthesis of isoxazoles are underway in our laboratory.

ASSOCIATED CONTENT

Supporting Information. The Supporting Information is available free of charge via the Internet at http://pubs.acs.org.

Experimental procedures, characterization data, crystallography data, and ^1H NMR and ^{13}C NMR for the compounds (PDF)

Crystallographic Information File for **5na** (CIF)

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Notes

The authors declare no competing financial interest.

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