An Efficient Protocol for the Synthesis of O-Fluoroalkylisoureas through Copper-Catalysed, Three-Component Reaction of Cyanamides, Fluoroalcohols and Diaryliodonium Triflates

Jihui Li a,b
Weiguang Yu a,b
Yifeng Hou a,b
Wenxing Fu a,b
Shuying Xu a,b
Yucang Zhang a,b

a Key Laboratory of Ministry of Education for Advanced Materials in Tropical Island Resources in Hainan University, Haikou 570228, P. R. of China
b College of Materials and Chemical Engineering, Hainan University, Haikou 570228, P. R. of China
xushuying1980@hainu.edu.cn
yczhang@hainu.edu.cn

Abstract A copper-catalysed, three-component reaction involving cyanamides, fluoroalcohols and diaryliodonium triflates is disclosed for the synthesis of O-fluoroalkylisoureas. Various O-fluoroalkylisoureas were obtained in good yields by using simple and readily available substrates. Moreover, C–H activation of O-fluoroalkylisoureas mediated by PhI(OAc)2 was established to obtain 2-fluoroalkoxybenzimidazoles in high yields at room temperature.

Key words copper-catalysis, three-component reaction, O-fluoroalkylisourea, 2-alkoxybenzimidazole, C–H activation

Isoureas, an important class of versatile organic reagent, have been widely used as guanylating and alkylating agents.1 Additionally, they are key precursors for constructing various bioactive molecules, such as the hypertension drug Candesartan,2 glucocerebrosidase inhibitor fused oxazolidin-2-imines and nanomolar enzyme activity enhancer spiro oxazolidin-2-imines.3 Despite their widespread applications, only a limited number of synthetic routes to isoureas have been reported, mainly relying on nucleophilic addition of alcohols to carbodiimides (Scheme 1, a). Initially, thermal acid- or base-promoted reactions were developed by Stieglitz4 and Dains,5 respectively, providing more efficient routes for the preparation of both N-arylisoureas and N-alkylisoureas. Recently, uranium and thorium amide catalysts have also been applied to the reaction, which is reported by Eisen to be a highly efficient synthetic protocol.8 These approaches are all similar, and more diverse methodologies involving simple and easily available starting materials are clearly required for the synthesis of isoureas.

Inspired by our work on transition-metal-catalysed multicomponent reactions for the synthesis of N-molecules,9 we have recently developed a copper-catalysed, three-component reaction of cyanamides, amines and diaryliodoniums for the synthesis of guanidines. Here, an extension of this methodology to fluoroalcohols was explored for the rapid synthesis of O-fluoroalkylisoureas that can be useful synthons for potentially bioactive cyclic fluoro-isoureas10 (Scheme 1, b).

We started our study by investigating the reaction of p-tolylcyanamide (1a), di(p-tolyl)iodonium triflate (2a) and 2,2,2-trifluoroethanol (3a) in the presence of K2CO3 using CuCl (5 mol%) as catalyst with bipy (2,2′-bipyridyl) in toluene at 80 °C under N2 for 2 h (Table 1, entry 1). Gratifyingly, the reaction afforded the desired isourea 4a in 62% yield, and the reaction under air produced 4a in 47% yield (entry 2). The reaction conditions including bases, solvents, ligands, and copper catalysts were then screened in detail (Table 1). Other bases such as NaHCO3, Cs2CO3, K3PO4,
t-BuOK and Et$_3$N all afforded inferior yields (entries 3–7), and the reaction without base did not produce any product (entry 8).

Table 1 Optimization of Reaction Conditions

<table>
<thead>
<tr>
<th>Entry</th>
<th>Base</th>
<th>Solvent</th>
<th>L</th>
<th>Cat.</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>K$_2$CO$_3$</td>
<td>toluene</td>
<td>Bipy</td>
<td>CuCl</td>
<td>62</td>
</tr>
<tr>
<td>2</td>
<td>K$_2$CO$_3$</td>
<td>toluene</td>
<td>Bipy</td>
<td>CuCl</td>
<td>47</td>
</tr>
<tr>
<td>3</td>
<td>NaHCO$_3$</td>
<td>toluene</td>
<td>Bipy</td>
<td>CuCl</td>
<td>22</td>
</tr>
<tr>
<td>4</td>
<td>Cs$_2$CO$_3$</td>
<td>toluene</td>
<td>Bipy</td>
<td>CuCl</td>
<td>52</td>
</tr>
<tr>
<td>5</td>
<td>K$_2$PO$_4$</td>
<td>toluene</td>
<td>Bipy</td>
<td>CuCl</td>
<td>33</td>
</tr>
<tr>
<td>6</td>
<td>t-BuOK</td>
<td>toluene</td>
<td>Bipy</td>
<td>CuCl</td>
<td>46</td>
</tr>
<tr>
<td>7</td>
<td>Et$_3$N</td>
<td>toluene</td>
<td>Bipy</td>
<td>CuCl</td>
<td>28</td>
</tr>
<tr>
<td>8</td>
<td>–</td>
<td>toluene</td>
<td>Bipy</td>
<td>CuCl</td>
<td>0</td>
</tr>
<tr>
<td>9</td>
<td>K$_2$CO$_3$</td>
<td>dioxane</td>
<td>Bipy</td>
<td>CuCl</td>
<td>26</td>
</tr>
<tr>
<td>10</td>
<td>K$_2$CO$_3$</td>
<td>DMSO</td>
<td>Bipy</td>
<td>CuCl</td>
<td>20</td>
</tr>
<tr>
<td>11</td>
<td>K$_2$CO$_3$</td>
<td>H$_2$O</td>
<td>Bipy</td>
<td>CuCl</td>
<td>25</td>
</tr>
<tr>
<td>12</td>
<td>K$_2$CO$_3$</td>
<td>DMF</td>
<td>Bipy</td>
<td>CuCl</td>
<td>22</td>
</tr>
<tr>
<td>13</td>
<td>K$_2$CO$_3$</td>
<td>THF</td>
<td>Bipy</td>
<td>CuCl</td>
<td>31</td>
</tr>
<tr>
<td>14</td>
<td>K$_2$CO$_3$</td>
<td>toluene</td>
<td>1,10-Phen</td>
<td>CuCl</td>
<td>31</td>
</tr>
<tr>
<td>15</td>
<td>K$_2$CO$_3$</td>
<td>toluene</td>
<td>PPh$_3$</td>
<td>CuCl</td>
<td>61</td>
</tr>
<tr>
<td>16</td>
<td>K$_2$CO$_3$</td>
<td>toluene</td>
<td>–</td>
<td>CuCl</td>
<td>65</td>
</tr>
<tr>
<td>17</td>
<td>K$_2$CO$_3$</td>
<td>toluene</td>
<td>–</td>
<td>CuBr</td>
<td>54</td>
</tr>
<tr>
<td>18</td>
<td>K$_2$CO$_3$</td>
<td>toluene</td>
<td>–</td>
<td>Cuyl</td>
<td>53</td>
</tr>
<tr>
<td>19</td>
<td>K$_2$CO$_3$</td>
<td>toluene</td>
<td>–</td>
<td>CuCl</td>
<td>64</td>
</tr>
<tr>
<td>20</td>
<td>K$_2$CO$_3$</td>
<td>toluene</td>
<td>–</td>
<td>CuCl</td>
<td>51</td>
</tr>
<tr>
<td>21</td>
<td>K$_2$CO$_3$</td>
<td>toluene</td>
<td>–</td>
<td>CuCl</td>
<td>48</td>
</tr>
</tbody>
</table>

*Reaction conditions: p-tolylicyanamide 1a (0.3 mmol), di[p-tolyliodo]onium triflate 2a (0.3 mmol), 2,2,2-trifluoroethanol 3a (0.2 mmol), copper salt (0.01 mmol), solvent (1.0 mL), stirred under N$_2$, 80 °C, 2 h.
* Isolated yield.
* The reaction was performed under air.
* CuCl (0.02 mmol) was used.
* Ratio 1a/2a/3a=1.5:1.5:1.5.
* Ratio 1a/2a/3a=1:1:1.5.

Replacing toluene with other solvents such as dioxane, DMSO, H$_2$O, DMF or THF did not improve the reaction yield (Table 1, entries 9–13). The reactions with 1,10-phen or PPh$_3$ as ligands did not provide higher yields (entries 14 and 15), and the reaction without ligand afforded a slightly higher yield (entry 16). Other catalysts such as CuBr and Cul were inferior to CuCl (entries 17 and 18). Increasing the amount of CuCl (10 mol%) did not enhance the reaction yield (entry 19), and the absence of copper catalyst led to no desired isourea formation (entry 20). Finally, the substrate ratios (1a/2a/3a=1.5:1.5:1, 1.1:1.5:1.5, 1:1:1.5) were explored (entries 16, 21 and 22), and the 1a/2a/3a=1.5:1.5:1 ratio was found to be optimal.

With the optimised reaction conditions in hand, the scope of the reaction with respect to cyanamide was evaluated (Scheme 2). Phenylcyanamide gave 65% yield of 4b, and m- and o-tolyl cyanamides also formed the corresponding isoureas 4c and 4d, respectively, in good yields. Arylcyanamides with either electron-withdrawing or electron-donating groups likewise provided 4e and 4f in comparably good yields. Impressively, 1-naphthylcyanamide afforded the desired product 4g in high yield. Additionally, some aliphatic cyanamides were found to be suitable for the reaction. However, low yields were obtained for aliphatic cyanamides, as the cross-coupling products of the aliphatic cyanamides and di[p-tolyliodo]onium triflate were found to be major products. For instance, benzylcyanamide and cyclohexylcyanamide both produced the corresponding isoureas 4h and 4i with 24% and 20% yield, respectively, and t-butylcyanamide did not afford any of desired product 4j, which is probably due to the extreme steric hindrance of the t-butyl group.

A variety of the diaryliodonium triflates was then examined, as shown in Table 2. Symmetric diaryliodoniums with either electron-poor or electron-rich aryls produced the desired isoureas in good yields (entries 1–4). For example, di[p-chorophenyl]iodonium triflate and di[p-[t-buty]-phenyl]iodonium triflate gave 63% and 55% yield, respectively (entries 2 and 4). The reactions of sterically hindered di[2,5-dimethylphenyl]iodonium triflate and di[2,4,6-trimethylphenyl]iodonium triflate furnished the desired products in higher yields (entries 5 and 6), because the side reactions between cyanamides and sterically hindered diaryliodoniums were reduced. For the unsymmetrical diaryliodonium triflates, the reactions provide good yields comparable to those with symmetrical diaryliodoniums triflates. The phenyliodonium triflates with p-[t-buty]-phenyl and p-iodosophenyl both afforded a mixture of products with low chemoselectivities (entries 7 and 8). Interestingly, phenyl[p-N02-phenyl]iodonium only produced a single product 4q in low yield (entry 9). Phenyl[2,5-di-methylphenyl]iodonium triflate yielded two products 4n and 4n’ in 1.7:1 ratio (entry 10). These results suggest that the more electron-rich and bulkier aryl groups of the unsymmetrical diaryliodoniums were preferable transferred in this three-component reaction.

Finally, the scope of the reaction with respect to alcohol was explored (Scheme 3). We were pleased to find that the protocol was tolerant of many fluorine-substituted alcohols. Both mono- and di-fluoroethanols delivered the corresponding products 4r and 4s in 49% and 63% yield, respectively. 1,1,1,3,3,3-Hexafluoro-2-propanol furnished the desired product 4t in moderate yield (51%).
Moreover, ethanol was found to be suitable for the reaction, although a low yield of 4u was obtained (34%), indicating that fluorine plays an important role in activation of the alcohol (4r vs. 4s vs. 4u). The reaction of phenol was complex, with formation of unidentified products.

Considering 2-alkoxybenzimidazole is the core of the hypertension drug candesartan,2 the C–H activation of the isoureas was explored for the synthesis of 2-fluoroalkoxybenzimidazoles, which may have interesting bioactivities (Scheme 4).10
These results suggest that the reaction pathway involving nucleophilic addition of cyanamide 1 and fluoroalcohol 3 followed by C–N coupling with diaryliodonium trflate 2 is unlikely (Scheme 6, a).

The addition of the radical inhibitor 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO) did not reduce product formation (Scheme 5, b), ruling out a radical process. Thus, a plausible pathway is proposed (Scheme 6, b), involving oxidative addition of diaryliodonium trflate 2 with CuCl, followed by coordination with cyanamide 1 and isomerisation promoted by K₂CO₃ to form intermediate D. Then, D may undergo reductive elimination and nucleophilic addition with fluoroalcohol 3 to generate the desired product 4 via intermediate E or F. The N-arylation products of diarylcyanaamides have been proposed as intermediates for the copper-catalysed, three-component reaction of diarylcyanaamides, diaryliodoniums and H₂O. However, the N-arylation product E is barely detected in this reaction. Thus, it is reasonable to conclude that the desired product is produced via intermediate F.

In summary, an efficient copper-catalysed, three-component reaction of cyanamide, fluoroalcohol and diaryliodonium trflate has been developed for the synthesis of O-fluoroalkoxyisoureas in good yields. The use of simple and readily available starting materials is a major practical advantage of this protocol. In addition, the PhI(OAc)₂-promoted C–H activation of O-fluoroalkoxyisoureas provides a convenient access to potentially valuable 2-fluoroalkoxybenzimidazoles. Further exploration of such three-component reactions to expand the diversity of this methodology is under way in our laboratory.

We were pleased to find that the C–H activation of isourea 4a can be mediated by PhI(OAc)₂ to form 2-(2,2,2-trifluoroethoxy)benzimidazole 5a in 91% yield at room temperature. The mild reaction conditions of this protocol mean that it could potentially have wide application.

Control experiments were also carried out for mechanistic studies. Nucleophilic addition of p-tolylcyanamide (1a) and 2,2,2-trifluoroethanol (3a) did not take place under the optimal conditions, with most of the p-tolylcyanamide being recovered (Scheme 5a).

In addition, the nucleophilic addition product 6 was not detected during the three-component reaction. Together, these results suggest that the reaction pathway involving...
Synthesis of O-Fluoroalkylisoureas through Copper-Catalysed, Three-Component Reaction of Cyanamides, Fluoroalcohols and Diaryliodonium Triflates; General Procedure

To a round-bottom sidearm flask, CuCl (0.01 mmol, 0.05 equiv), cyanamide (0.3 mmol, 1.5 equiv), and K2CO3 (0.45 mmol, 2.25 equiv) were sequentially added, and the mixture was heated to 80 °C, with stirring for 2 h. The mixture was cooled, the reaction was quenched with water and the mixture was extracted with EtOAc. The organic layers were combined, dried over MgSO4, filtered and concentrated under reduced pressure to give a residue that was purified by preparative TLC (SiO2) to obtain O-fluoroalkylisourea 4.

2.2.2-Trifluoroethyl N′-Phenyl-N-(m-toly)carbamimidate (4a)

Yield: 42 mg (65%); colourless waxy solid.

1H NMR (400 MHz, CDCl3): δ = 7.18 (d, J = 7.1 Hz, 2 H), 7.08 (d, J = 7.3 Hz, 2 H), 7.98 (d, J = 7.4 Hz, 2 H), 7.87 (d, J = 7.2 Hz, 2 H), 5.90 (br, NH), 4.76 (q, J = 8.6 Hz, 2 H), 2.39–2.27 (m, 6 H).

13C NMR (101 MHz, CDCl3): δ = 148.46, 143.98, 134.98, 133.49, 132.88, 130.41, 129.48, 122.16, 123.40 (q, J = 277.2 Hz), 121.12, 62.52 (q, J = 36.4 Hz), 20.76, 20.68.

IR: 3043.37, 2923.81, 1672.99, 1610.85, 1509.22, 1358.83, 1270.01, 1165.46, 1101.68, 820.81 cm⁻¹.


2.2.2-Trifluoroethyl N′-Phenyl-N-(o-toly)carbamimidate (4d)

Yield: 47 mg (76%); colourless oil.

1H NMR (400 MHz, CDCl3): δ = 6.93–7.42 (m, 9 H), 5.80–5.86 (m, NH), 4.82–4.90 (m, 2 H), 2.16–2.26 (m, 3 H).

13C NMR (101 MHz, CDCl3): δ = 147.76, 144.78, 137.48, 128.97, 123.83, 123.71, 123.36 (q, J = 277.4 Hz), 122.31, 121.98, 120.94, 119.20, 62.43 (q, J = 36.4 Hz), 17.67.

IR: 3450.15, 2925.72, 1674.72, 1595.07, 1498.11, 1361.69, 1270.72, 1166.90, 1103.05, 747.11 cm⁻¹.


2.2.2-Trifluoroethyl N-(2-Fluorophenyl)-N′-phenylcarbamimida- te (4e)

Yield: 39 mg (60%); pale-yellow oil.

1H NMR (400 MHz, CDCl3): δ = 6.97–7.46 (m, 8 H), 6.19 (br, 0.35 Hz), 5.82 (br, 0.59 Hz), 4.78 (q, J = 8.4 Hz, 2 H), 2.32 (s, 3 H).

13C NMR (101 MHz, CDCl3): δ = 149.23, 134.54, 134.18, 130.53, 129.55, 124.98, 124.45, 123.38 (q, J = 276.7 Hz), 122.95, 121.92, 116.68, 116.48, 115.30, 62.86 (q, J = 36.5 Hz), 20.80.

IR: 3411.56, 2925.80, 1674.91, 1610.99, 1513.44, 1415.46, 1363.78, 1272.02, 1167.65, 1103.94, 982.73, 753.19 cm⁻¹.


2.2.2-Trifluoroethyl N-(4-Methoxyphenyl)-N′-phenylcarbamimida- te (4f)

Yield: 41 mg (63%); pale-yellow waxy solid.

1H NMR (400 MHz, CDCl3): δ = 7.26–7.36 (m, 2 H), 6.83–6.70 (m, 7 H), 5.83–5.97 (m, NH), 4.46 (q, J = 7.6 Hz, 2 H), 3.79 (s, 3 H).

13C NMR (101 MHz, CDCl3): δ = 156.57, 155.99, 148.8, 146.79, 139.46, 137.60, 130.35, 129.79, 128.99, 123.61, 124.34, 123.37 (q, J = 278.0 Hz), 123.15, 122.42, 121.99, 120.72, 115.16, 114.11, 62.52 (q, J = 36.6 Hz), 55.42.
IR: 3404.79, 2925.49, 1672.80, 1492.03, 1360.44, 1270.70, 1167.44, 1096.49, 824.27 cm⁻¹.

2,2,2-Trifluoroethyl N′-(4-Bromophenyl)-N′-(p-tolylicarbimidate (4l)
Yield: 27 mg (35%); colourless waxy solid.
1H NMR (400 MHz, CDCl₃): δ = 7.39–7.45 (m, 2 H), 6.71–7.20 (m, 6 H), 5.80–5.92 (m, NH), 4.75 (q, J = 8.3 Hz, 1.79 H), 4.55 (q, J = 8.2 Hz, 0.11 H), 2.31 (s, 3 H).
13C NMR (101 MHz, CDCl₃): δ = 148.66, 132.79, 131.93, 130.41, 129.55, 124.23, 123.24 (q, J = 279.0 Hz), 122.32, 121.91, 121.41, 116.34, 62.66 (q, J = 36.4 Hz), 20.74.
IR: 3407.63, 2924.93, 1672.11, 1513.56, 1488.70, 1359.04, 1269.88, 1166.53, 821.60 cm⁻¹.

2,2,2-Trifluoroethyl N′-(4-(tert-Butyl)phenyl)-N′-(p-tolylicarbimidate (4n)
Yield: 40 mg (55%); colourless oil.
1H NMR (400 MHz, CDCl₃): δ = 7.30–7.37 (m, 2 H), 7.08–7.16 (m, 2 H), 6.87–6.98 (m, 4 H), 5.93 (br, NH), 4.77 (q, J = 8.0 Hz, 2 H), 2.31–2.34 (m, 3 H), 1.32 (s, 9 H).
13C NMR (101 MHz, CDCl₃): δ = 148.56, 130.40, 129.48, 126.67, 125.84, 122.15, 121.84, 121.26, 120.31, 62.51 (q, J = 35.9 Hz), 34.26, 31.38, 20.74.
IR: 3405.39, 2962.96, 1673.61, 1609.49, 1513.14, 1361.23, 1270.55, 1166.57, 1103.66, 824.92 cm⁻¹.
Synthesis of 2-Fluoroalkoxybenzimidazoles through PhI(OAc)₂-Promoted C–H Activation of 2,2-Difluoroethyl isourea; General Procedure

To a round-bottom flask, 2-fluoroalkylisourea (0.2 mmol, 1 equiv) and acetonitrile (3 mL) were added and the mixture was stirred at r.t. for 45 min, then concentrated under reduced pressure to give a residue, which was purified to obtain 2-fluoroalkoxybenzimidazole 5 after preparative TLC (SiO₂).
Funding Information
The authors acknowledge the Natural Science Foundation of Hainan Province (grant numbers 20162015, 20152027), the National Natural Science Foundation of China (S1263006) and Hainan Province International Science and Technology Specific (KJHZ2014-02) for financial support of this work.

Acknowledgment
The Analytical and Testing Center of Hainan University is acknowledged for excellent technical and analytical support.

Supporting Information
Supporting information for this article is available online at https://doi.org/10.1055/s-0036-1590828.

References