



## A metal-free three components procedure for the synthesis of perfluoroalkyl substituted amidines



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### ABSTRACT

An interesting multicomponent reaction for the synthesis of perfluoroalkyl substituted amidines has been developed. By using perfluoroalkyl iodides, *tert*-butyl isocyanides and amines as the substrates, the reactions proceed via somophilic isocyanide insertion. In this catalytic system, no transition-metal catalyst, additional ligands and additives were required. The reaction proceed smoothly and a variety of desired amidines were obtained in moderate to excellent yields.

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Over the past few decades, organo-fluorine compounds have drawn much attention for their lipophilicity, bioactivity, and metabolic stability.<sup>1</sup> They play an important role and have a wide range of applications across many disciplines.<sup>2</sup> Thus, a great efforts have been put for the construction of fluorine-containing compounds during these years.<sup>3</sup> On the other hand, among fluorine-containing compounds, perfluorinated compounds, are highly useful structural molecules, which could be utilized in medicinal chemistry, agrochemistry and material science.<sup>4</sup> In recent years, transition-metal catalyzed perfluoroalkylation reactions have regarded as one of the most attractive approaches and have drawn increasing attention.<sup>5</sup> Therefore, more efficient, economical, and environmental friendly perfluoroalkylation methods remain highly in demand.

Isocyanides are highly versatile building blocks for C–C,<sup>6</sup> C–N,<sup>7</sup> and C–O<sup>8</sup> bonds formation, and have widely applied in organic, medicinal, and combinatorial chemistry since the Passerini, Ugi, and related multicomponent reactions were reported.<sup>9</sup> Their unique properties make them well established radical acceptors in cascade reactions for the preparation of nitrogen-containing compounds via insertion reaction. Normally, palladium-catalyzed isocyanide insertion and somophilic isocyanide insertion are typical two approaches for recent developed isocyanide insertion

reactions. However, for environmental and practical reasons, insertion with isocyanide as somophile is more preferable and has more promising prospects.<sup>10</sup> Herein, we wish to report a multicomponent reaction of perfluoroalkyl iodides, *tert*-butyl isocyanides, and amines *via* somophilic isocyanide insertion under transition-metal free conditions.

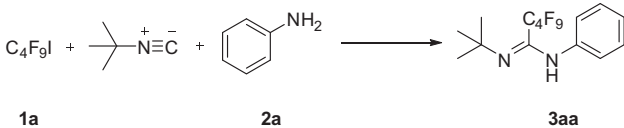
Perfluorobutyl iodide, *tert*-butyl isocyanide and aniline were used as initial substrates in 1,4-dioxane at 90 °C with Et<sub>3</sub>N as base, 20% yield of the target product was observed (Table 1, entry 1). Then the temperature was changed to 100 °C, 75% yield of the desired product was obtained (Table 1, entry 2). To our delight, the yield of the final product can be improved to 95% by setting the reaction temperature at 110 °C (Table 1, entry 3). Further raise the temperature to 120 °C, the yield decreased (Table 1, entry 4). Various other bases were examined as well, such as K<sub>2</sub>CO<sub>3</sub>, Cs<sub>2</sub>CO<sub>3</sub>, TMEDA, DiPEA, and DBU, the yield has no improvement (Table 1, entries 5–9). These results might due to the difference in basicity and solubility between bases. Moreover, solvent screening showed that 1,4-dioxane was the optimal media for this reaction (Table 1, entries 10–12).

With the best reaction conditions in hand,<sup>11</sup> substrate scope on amines was examined (Table 2). Aryl amines with electron-rich groups, including methyl, ethyl, *tert*-butyl, methoxy, and isopropyl groups, the corresponding products were isolated in moderate to excellent yields (3ab–3ai). Those substrate with di-substitution, such as 2,5-dimethyl, 3,5-dimethyl groups provided the target

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**Table 1**  
Screening of reaction conditions.<sup>a</sup>



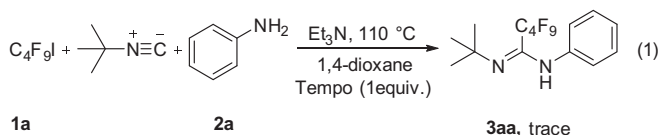
Entry	Base	Solvent	Temp. (°C)	Yield (%) <sup>b</sup>
1	Et <sub>3</sub> N	1,4-dioxane	90	20
2	Et <sub>3</sub> N	1,4-dioxane	100	74
3	Et <sub>3</sub> N	1,4-dioxane	110	95
4	Et <sub>3</sub> N	1,4-dioxane	120	81
5	K <sub>2</sub> CO <sub>3</sub>	1,4-dioxane	110	9
6	Cs <sub>2</sub> CO <sub>3</sub>	1,4-dioxane	110	90
7	TMEDA	1,4-dioxane	110	50
8	DiPEA	1,4-dioxane	110	62
9	DBU	1,4-dioxane	110	32
10	Et <sub>3</sub> N	Toluene	110	36
11	Et <sub>3</sub> N	DMF	110	4
12	Et <sub>3</sub> N	DMSO	110	3

<sup>a</sup> Reaction conditions: perfluorobutyl iodide (1.0 mmol), *tert*-butyl isocyanide (0.5 mmol), aniline (0.5 mmol), base (1.0 mmol), solvent (2.5 mL), 24 h.

<sup>b</sup> GC yield, with dodecane as the internal standard.

products in very high yields (**3aj**, **3ak**). In the case of aromatic amines with halo groups, the final products were formed in moderate to high yields (**3al–3ao**). Electron-deficient group like trifluoromethyl substitution afford the desired product in 50% yield (**3ap**). In addition, *N*-ethyl aniline was investigated as well, the target product was obtained in 32% yield (**3aq**). Moreover, alkyl amine like octyl amine can also be applied and give the desired product in 42% yield (**3ar**). We next turn our attention to perfluoroalkyl iodides. The desired products were isolated in very high yields with perfluoro-hexyl, and octyl iodides (**3ba**, **3ca**). Additionally, phenyl isocyanide was tested with perfluorobutyl iodide and aniline as well, but no desired product was observed.

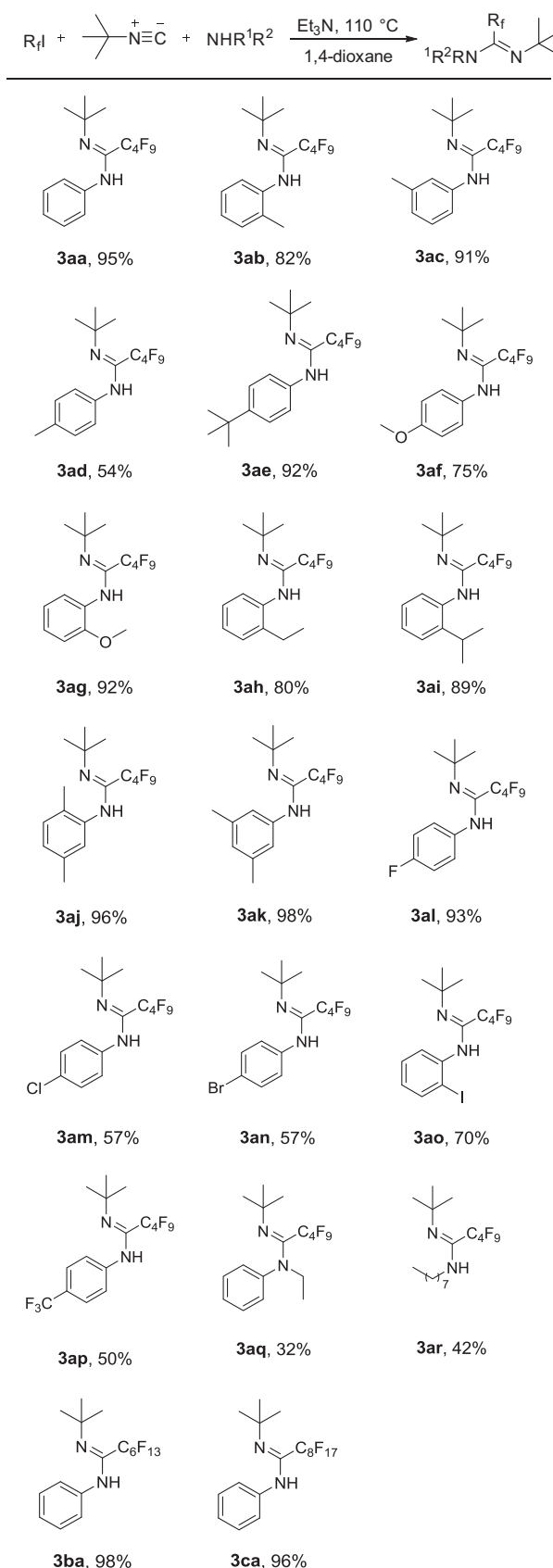
In order to support the radical nature of this reaction, 1 equiv. of 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO) as a radical scavenger was added to the reaction mixture under standard condition, the formation of desired product was completely suppressed (Eq. 1).



Based on these results, a possible reaction mechanism was proposed in Scheme 1. Perfluoroalkyl radical **A** was generated from perfluoroalkyl iodides **1** under thermal condition. Then Perfluoroalkyl radical **A** added to *tert*-butyl isocyanide carbon to form the imido radical intermediate **B**, which reacted with perfluoroalkyl iodides **1** to afford intermediate **C** and regenerated Perfluoroalkyl radical. Furthermore, intermediate **C** reacted with amine **2** to give the final product **3** under the assistant of Et<sub>3</sub>N. However, another possibility that intermediate **B** was oxidized by perfluoroalkyl iodides to give nitrilium ion and regenerate perfluoroalkyl radical cannot be excluded. Then the nitrilium ion reacted with amine to give the amidine products.

In conclusion, a transition-metal-free somophilic isocyanide insertion of *tert*-butyl isocyanides with amines, and perfluoroalkylated iodide as perfluoroalkyl radical precursors was explored. Under environmental benign reaction conditions, moderate to

**Table 2**  
Metal-free amidines synthesis.<sup>a</sup>



<sup>a</sup> Reaction conditions: perfluorobutyl iodide (1.0 mmol), *tert*-butyl isocyanide (0.5 mmol), amines (0.5 mmol), Et<sub>3</sub>N (1.0 mmol), 1,4-dioxane (2.5 mL), 24–36 h. Isolated yield.

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