Transition-Metal-Free Intermolecular α -C-H Amination of Ethers at Room Temperature

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Abstract. We describe a new method for the intermolecular amination of the α -C-H bonds of ethers. A hypervalent iodine reagent was used as oxidant to enable the amination of cyclic and acyclic alkyl ethers with a wide range of amides, imides, and amines. The amination occurred at room temperature and without a transition metal catalyst. The method could be used to synthesize the anti-cancer prodrug Tegafur and its analogues.

Keywords: Amination; C-H functionalization; Hypervalent iodine; Radical; Nucleoside

Nitrogen is ubiquitous in pharmaceuticals, natural products and materials. The preparation of nitrogen-containing molecules is therefore a major task in synthetic chemistry. In recent years, direct C-H amination has emerged as an attractive method for the construction of new C-N bonds.^[1-6] Compared with conventional amination methods, C-H amination avoids the pre-installation of transformable functional groups so that it is potentially more efficient and environmentally friendly. Transition metal catalysis plays a dominant role in this area, however, transition-metal-free C-H amination methods are desirable alternatives because they do not require expensive or toxic metal in the synthesis.^[7] Although a number of transition-metal-free intermolecular C-H amination reactions have been reported,^[7-16] the scope of these transformations is still narrow. For example, the nitrogen sources were limited to N-haloamines, phthalimides, sulfonamides and some specific nitrogen heterocycles. Moreover, amination mostly worked on activated aryl, benzylic, and allylic C-H bonds. Amination of other C(sp³)-H bonds is rarely reported.

Guo and co-workers developed metal-free direct alkylation of purines with tetrahydrofuran (THF) and ethers, but the reactions required illumination and heating at 70 °C and only purines were alkylated.^[17] Ochiai and co-workers reported metal-free α -C-H amination of ethers, but only the triflylamino group could be transferred.^[18] Herein, we report a mild and

general method for the transition-metal-free direct C-H amination of ethers using a hypervalent iodine reagent^[19] as the sole oxidant at room temperature (Scheme 1). The protocol has a wide substrate scope, especially on the nitrogen-containing reaction partners. The resulting aminated ethers can serve as valuable synthetic intermediates to α,ω -amino alcohols^[20] and modified THF-containing natural products.^[21-22] The introduction of an alkyl ether moiety on a biologically active amine molecule may enhance the latter compound's lipophilicity. Thus, the current amination method can be a useful tool in medicinal chemistry. Indeed, a number of aminated THF derivatives are anti-viral and anti-tumor agents (Scheme 2).^[23-26] Fuchigami et al. reported several examples of amination of THF with alkyl amines using electrochemical oxidation; however, the conversions and yields were low.^[27] Feldman et al. reported a single example of amination of THF with cyclohexyltosylamide in a 45% yield using an alkynylodonium triflate as oxidant.^[28] Yu and co-workers reported tosylation of cyclic ethers using a Cu catalyst and PhI(OAc)₂ as oxidant.^[20] Compared with these precedents, our method is much more convenient, general, and synthetically useful.

Scheme 1. Intermolecular α -C-H amination of ethers

Scheme 2. Selected examples of aminated THF derivatives that exhibit biological activity

The direct α -C-H amination of THF (**1a**) with N-benzylmethanesulfonamide (**2a**) was used as the test reaction (Table 1). This formal oxidative coupling^[29] requires both an oxidant and a hydrogen acceptor. We found that amination product could be obtained by applying a one-pot, two-step reaction procedure. For example, deprotonation of N-benzylmethanesulfonamide by NaH followed by oxidation by (diacetoxyiodo)benzene (DIB), both in THF and at room temperature, gave **3a** in a 43% yield (entry 1, Table 1). Other oxidants such as O₂, K₂S₂O₈ and I₂ were ineffective (entries 2-5, Table 1). The yield could be improved to 85% and 87%, using Ph₂IOTf and Ph₂IPF₆ as the oxidant, respectively (entries 6-7, Table 1). NaH was the optimal base; replacement of NaH with Cs₂CO₃, KOtBu, or NaOH led to diminished yields (entries 8-10, Table 1). THF was the best solvent; reactions carried out in dichloromethane, dichloroethane, ethyl acetate and toluene using 10 equiv. of THF as the reagent were inefficient (entries 11-14, Table 1). However, an encouraging yield of 66% was obtained when the amination reaction was carried out in acetonitrile (MeCN) using 10 equiv. of THF at 40°C (entries 15-17, Table 1). Without the base, no product was formed (entry 18, Table 1).

Table 1. Optimization of reaction conditions^[a].

Entry	Base	Oxidant	Solvent	Yield (%) ^[b]
1	NaH	DIB	THF	43
2	NaH	I ₂	THF	-
3	NaH	I ₂ /DIB	THF	36
4	NaH	K ₂ S ₂ O ₈	THF	-
5	NaH	O ₂	THF	-
6	NaH	Ph ₂ IOTf	THF	85
7	NaH	Ph ₂ IPF ₆	THF	87
8	KOtBu	Ph ₂ IPF ₆	THF	38
9	Cs ₂ CO ₃	Ph ₂ IPF ₆	THF	25
10	NaOH	Ph ₂ IPF ₆	THF	18
11	NaH	Ph ₂ IPF ₆	CH ₂ Cl ₂	5 ^[c]
12	NaH	Ph ₂ IPF ₆	ClC ₂ H ₄ Cl	<1 ^[c]
13	NaH	Ph ₂ IPF ₆	EtOAc	12 ^[c]
14	NaH	Ph ₂ IPF ₆	Toluene	4 ^[c]
15	NaH	Ph ₂ IPF ₆	MeCN	66 ^[e]
16	NaH	Ph ₂ IPF ₆	MeCN	40 ^[c]
17	NaH	Ph ₂ IPF ₆	MeCN	37 ^[d]
18	-	Ph ₂ IOTf	THF	-

^[a] Reaction conditions: under N₂, deprotonation of **2a** (0.25 mmol) with base (0.25 mmol) in THF (1 ml) at rt for 1 h, then addition of oxidant (0.3 mmol) and reaction at rt for 10 h.

^[b] Calibrated GC yield using n-dodecane as an internal standard.

^[c] THF (2.5 mmol) in 1 ml of solvent, rt, 12 h.

^[d] THF (1.25 mmol) in 1 ml of MeCN, 40°C, 6 h.

^[e] THF (2.5 mmol) in 1 ml of MeCN, 40°C, 6 h.

The optimized reaction protocol (entry 7, Table 1) was then applied for the amination of THF (**1a**) with a wide range of sulfonamides (Table 2). To our delight, aryl, benzyl, allyl, and alkyl-substituted mesyl amines all could be alkylated (**3a-3h**, Table 2). Both primary and secondary alkyl mesyl amines were efficient reaction partners, giving high yields of amination products (**3b** and **3d**, Table 2). Alkyl group containing a terminal double bond was tolerated without isomerization (**3d**, Table 2). A tert-butyl-substituted mesyl amine was coupled in a modest yield of 39% (**3c**, Table 2), probably due to the steric encumbrance of the tertiary alkyl group. A similar scope was found for the coupling of tosyl amines (**3i-3n**, Table 2). Alkyl, benzyl, allyl-substituted tosyl amines could be used. Nosyl amines, however, could not be alkylated, and the starting sulfonamides could be recovered at the end of the reactions. The unreactivity of nosyl amines suggests that the acidity of the amine N-H bond is not the only determining factor in this type of direct amination reaction.

Table 2. Amination of THF with sulfonamides^[a].

1a	2	3	Yield (%)	Structure
73%	3a , 73%
76%	3b , 76%
39%	3c , 39%
78%	3d , 78%
77%	3e , 77%
75% ^[b]	3f-g , 75% ^[b]
59%	3h , 59%
67%	3i , 67%
43%	3j , 43%
63%	3k , 63%
			73%	3l , 73%
			73%	3m , 73%
			61%	3n , 61%

^[a] Reaction conditions: under N₂, deprotonation of a sulfonamide (0.5 mmol) with NaH (0.5 mmol) in 1 mL of THF at rt for 1 h, then addition of Ph₂IPF₆ (0.6 mmol) in 1 mL of THF and reaction at rt for 6 h, yields are of isolated products.

^[b] Yield of two diastereomers (**3f** and **3g**).

The scope of the amine partner was then expanded to include acetamides and trifluoroacetamides. Gratifyingly, the reaction protocol was efficient for the direct amination of THF using these amides (Table 3). Increasing the amount of Ph_2IPF_6 to 1.5 equiv. was beneficial. Alkyl, allyl, benzyl and aryl-substituted amides could be coupled in good yields (**5a-5h**, Table 3). The functional group tolerance was demonstrated with aryl acetamides. Ester, nitrile, CF_3 , aryl-I, aryl-Br, and ether groups were all compatible (**5i-5n**, Table 3). N-(6-methylpyridin-2-yl)acetamide was also successfully alkylated (**5o**, Table 3). Phenol group was not tolerated due to competitive O-arylation. Significantly, the bulky tert-butyl trifluoroacetamide was coupled in a good yield of 58% (**5f**, Table 3). The reaction with N-benzyl-trifluoroacetamide (**4h**) was repeated in a 5 mmol scale leading to an 80% isolated yield of the desired N-benzyl-N-(tetrahydrofuran-2-yl) trifluoroacetamide (**5h**). It is noted that aryl substituted amides were coupled in very high yields, i.e., in the range of 90%. Finally, the commercially available potassium phthalimide could be coupled in a 75% yield in a modified procedure (without the base) (**5p**, Table 3).

Table 3. Amination of THF with acetamides and trifluoroacetamides ^[a].

^[a] Reaction conditions: under N_2 , deprotonation of an amide (0.5 mmol) with NaH (0.5 mmol) in 1 mL of THF at rt for 3 h, addition of Ph_2IPF_6 (0.75 mmol) in 1 mL of THF and reaction at rt for 6 h, the yields are of isolated products.

^[b] Ph_2IPF_6 (0.6 mmol) was added to potassium phthalimide (0.5 mmol) in 2 mL of THF and reaction at 40 °C for 12 h.

The α -C-H amination method could be applied on free secondary amines without a sulfonyl or acyl groups (Table 4). Imidazole, benzimidazole, indole, and carbazole could be alkylated in good to excellent yields. Aromatic amines worked better in these reactions.

Alkyl ethers other than THF were then tested for the direct amination reactions (Table 5). 1,4-Dioxane could be aminated in good yields (**8a-8b**, Table 5). Tetrahydropyran was also aminated (**8c-8d**, Table 5). 2-Methyl THF presented an interesting test for chemoselectivity. An amination occurred with 4:1 selectivity favoring the sterically less encumbered C-H bond at the 4 position (**8e**, Table 5). No diastereoselectivity was observed.

Table 4. Amination of THF with secondary amines ^[a].

^[a] Reaction conditions: under N_2 , deprotonation of an aromatic N-heterocycle (0.5 mmol) with NaH (0.5 mmol) in 1 mL of THF at rt for 1 h, then addition of Ph_2IPF_6 (0.75 mmol) in 1 mL of THF and reaction at rt for 6 h, the yields are of isolated products.

Table 5. Amination of α -C-H bonds of various alkyl ethers ^[a].

^[a] Reaction conditions: under N_2 , deprotonation of sulfonamide or amide (0.5 mmol) with NaH (0.5 mmol) in 2 mL of the corresponding ether at rt for 3 h, then addition of Ph_2IPF_6 (0.75 mmol) and reaction at rt for 6 h, the yields are of isolated products.

^[b] Ph_2IPF_6 (0.6 mmol) was added to potassium phthalimide (0.5 mmol) in 2 mL of dioxane, 10 h, 60 °C.

^[c] Combined yield of diastereomers.

^[d] Yield of major regioisomer.

The direct amination also worked on acyclic ethers such as dimethoxyethane (DME). The internal C-H bonds were preferentially aminated (**8f-8h**, Table 5). Unfortunately diethyl ether and methyl tert-butyl ether could not be aminated in reasonable yields using this protocol, probably due to the low solubility of the other reagents in these solvents.

The new α -C-H amination protocol was applied for the synthesis of biologically active molecules including the anticancer prodrug Tegafur using nucleobases as the nitrogen sources. The reaction of para-methoxybenzoyl-protected thymine with THF was first tested (Table 6). The corresponding nucleoside analogue was obtained in 85% yield. The PMB group on the thymine was difficult to remove.

The more labile Boc group was used as the protecting group for the nucleobases. N3-Boc-5-fluorouracil was synthesized in two steps and was then reacted with different alkyl ethers (Table 6). Reaction with THF provided **10b** in a yield of 81%. **10b** was then converted quantitatively to N1-(tetrahydrofuran-2-yl)-5-fluorouracil, the Tegafur, by heating at 75°C in isopropanol. Alkylation with tetrahydropyran, dioxane, and DME also worked, albeit with lower yields. Therefore, this amination method might be useful for the rapid derivatization of biologically active compounds.

Table 6. Amination of alkyl ethers with protected 5-methyluracil and 5-fluorouracil^[a].

^[a] Reaction conditions: under N₂, deprotonation of protected uracil derivative (0.5 mmol) with NaH (0.5 mmol) in 2 mL of the corresponding ether at rt for 3 h, then addition of Ph₂IPF₆ (0.85 mmol) and reaction at rt for 6 h, the yields are of isolated products.

The mechanism of the direct C-H amination reported here remains speculative. A radical process is consistent with some experimental observations. The amination is completely quenched in the presence of 10 mol% of TEMPO, a radical inhibitor. Lithiated alkyl amides failed to undergo amination,

likely because alkyl aminyl radicals are too difficult to generate under the reaction conditions. Deuterium kinetic isotope effect (KIE) was measured in the reaction of acetanilide (**4d**) with THF and THF-d₈ at room temperature. A primary deuterium KIE of 4.6 was observed. This significant value of KIE suggests the rate determining step involves the breaking of α -C-H bond. Given previously proposed mechanism for the α -C-H amination of ethers^[20, 27-28] and the specific reaction conditions described here, we considered several possible reaction pathways in Figure 1. The salt metathesis reaction between Ph₂IPF₆ and sodium amide gives an ionic complex of diphenyl iodonium and amide (A). Oxidation of the amide by the diphenyl iodonium oxidant via single electron transfer (SET) then yields an aminyl radical (B) and a diphenyl iodide radical (C) (eq 1, Figure 1). Radical C decomposes to give PhI and Ph radical (eq 2, Figure 1). It is known that aminyl radicals are poor hydrogen atom abstractors^[30] so abstraction of hydrogen atom from THF by B is unlikely. Instead, the phenyl radical should react with THF to give the THF radical D (eq 3, Figure 1). Although combination of the two radicals, B and D, can lead to the formation of the amination product, due to the low concentration of both radical species, this pathway plays no major role here. Instead, two alternative pathways may be operating. In route I, D reacts with amidyl anion to form the corresponding anion-radical (E)^[31] which is easily oxidized by diphenyl iodonium cation to the amination product generating the diphenyl iodide radical (C) again and propagating the radical chain process (eq 4 and 5, Figure 1). In route II, the THF radical D is oxidized by diphenyl iodonium cation to give an oxonium ion (F) and radical C which also propagates the radical chain process (eq 6, Figure 1). Reaction of F with amide then gives the amination product (eq 7, Figure 1).

Figure 1. Proposed reaction pathways for the direct amination of alkyl ethers.

In summary, we have developed a mild and efficient method for the intermolecular α -C-H amination of cyclic and acyclic alkyl ethers. The method allows direct amination with a wide range of sulfonamides, amides, imide, and secondary amines with alkyl, aryl, allyl, and benzyl substituents. The utility of this method was demonstrated in the synthesis of Tegafur and its analogues. This transition-metal-free method provides a rapid access to a large number of nitrogen-containing organic molecules that may serve as useful synthetic intermediates or biologically active molecules.

Experimental Section

General procedure for the α -C-H bond amination of alkyl ethers

To a suspension of sodium hydride (60% dispersion in mineral oil, 20 mg, 0.5 mmol) in 2 mL of dry alkyl ether an amide or sulfonamide (0.5 mmol) was added at room temperature under nitrogen. After stirring for 3 hours at room temperature Ph_2IPF_6 (319 mg, 0.75 mmol) was added and the reaction mixture was stirred for 6 hours. The solvent was removed under reduced pressure and resulting solid was subjected to the column chromatography (silica gel) to afford the product.

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