Microwave Application and Anhydrous Cu(OAc)$_2$ Mediated O-Arylation of Aliphatic Amino Alcohols

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Abstract
Anhydrous Cu(OAc)$_2$ mediated efficient protocol has been developed in the area of C-O coupling from potassium aryltrifluoroborates and aliphatic amino alcohols such as β-hydroxy, γ-hydroxy, and δ-hydroxy amines. The scope of this transformation focuses on direct O-arylation and O-styrylation. The reaction vial loaded with reactants under argon atmosphere is microwaved at 140°C for 30 min to furnish the corresponding cross-coupling product, amino ethers, in good yields.

Keywords
Hydroxylamine; Amino Ether; O-Arylation; O-Styrylation; Microwave

1. Introduction
Amino ethers are important intermediates in organic synthesis and compounds of pharmaceutical interest such as tamoxifen (I), antihistamines (II), potent marine natural products such as quindolone (III), and also agricultural interest such as water-based organic coating amino ether surfactants [1]–[7] (Scheme 1).

Potassium organotrifluoroborates have already been proven as effective organoboron reagents in cross-coupling chemistry [8]–[10]. Recently, this reagent is used in copper-promoted carbon-oxygen cross-coupling reaction. Batey’s group has reported a protocol for the alkyl-aryl and alkyl-vinyl ethers via Cu (II)-catalyzed cross-coupling of organotrifluoroborates and aliphatic alcohols [11]–[17]. Chan [18]–[20] and Lam’s groups reported heteroatom arylation reaction for alkyl-aryl ether synthesis although this observation was limited to phenols only. Further development of copper-mediated C–O bond formation has explained by oxygen nucleophiles such as carboxylic acids, aliphatic alcohols, aryl oximes, silanols, N-hydroxyphthalimides, water with boron reagents [21]–[23].

But using aliphatic hydroxyl amine for similar cross-coupling reaction and making amino ether are rarely known. Very recently, Molander’s group [24]–[27] reported an effective protocol toward the O-arylation of β-hydroxy-α-amino acid substrates. Molander’s report of

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O-arylation of protected serines and threonines by introducing amino alcohols, such as β-hydroxy-α-amino acid derivatives with arylboronic acids and aryltrifluoroborates for the formation of C-O alkyl aryl ethers, is a new development of Chan-Lam cross-coupling process [24].

In this work, we also wanted to see whether anhydrous Cu(OAc)\(_2\) would be able to provide similar transformation in minutes under microwave irradiation and in the absence of air. Interest in exploring various organic transformations by using potassium organotrifluoroborates led to investigate the cross-coupling reaction of β-hydroxy, γ-hydroxy, and δ-hydroxy amines with potassium aryltrifluoroborates in the presence of anhydrous Cu(OAc)\(_2\) under microwave irradiation (Scheme 2). The C-O cross-coupling initiated with the optimization of the reaction partners and conditions for the formation of O-arylated amino ether moiety. We first investigated the catalytic activities of anhydrous Cu(OAc)\(_2\) (10 mole%, 20 mol%, and 50 mol%). No significant improvement was observed. Longer reaction time for more than 30 minutes and conventional heating system has no effect on increasing the yield. Other catalyst system such as palladium-catalyst was also employed and showed no product. Then we promote the model reaction of β-hydroxyamine such as 2-dimethylaminoethanol, 2a (1 equivalent), potassium tolyltrifluoroborate, 1a (2.5 equivalent), \(K_2CO_3\) (2.0 equivalent), and anhydrous Cu(OAc)\(_2\) (1 equivalent) in 2.0 mL 1,4-dioxane microwaved at 140°C for 30 minutes (Entry 1, Table 1). After chromatography 76% isolated amino ether product, 3a was obtained. The product was characterized by GC/MS (Saturn 2200 Benchtop GC/MS) and NMR (Varian 300 MHz). GCMS: Calculated for \(C_{11}H_{17}NO\) M\(^+\) 180. Found: 180. \(^1H\) NMR (Acetone-\(d_6\), 300 MHz) \(\delta\) 7.11 (d, \(J = 8.4\) Hz, 2H, aromatic), 6.90 (d, \(J = 8.7\) Hz, 2H, aromatic), 4.46 (t, \(J = 4.8\) Hz, 2H, CH\(_2\)), 3.85 (t, \(J = 4.8\) Hz, 2H, CH\(_2\)), 3.23 (s, 6H, 2 × CH\(_3\)), 2.25 (s, 3H, CH\(_3\)); \(^{13}C\) NMR (Ace-tone-\(d_6\), 75.5 MHz) \(\delta\) 129.9, 114.5, 61.9, 56.8, 43.4, 19.5.

γ-hydroxy amine such as 3-diethylamino-1-propanol, 2b and δ-hydroxyamine such as 4-(dimethylamino)-1-butanol, 2c were used with tolyltrifluoroborate under the same reaction conditions afforded the corresponding amino ethers 3b and 3c in good yields (Entries 2 and 3, Table 1). In several other instances, amino alcohols 2a, 2b, 2c are microwaved with various aryltrifluoroborates such as phenyltrifluoroborate, 1b, 4-fluorophenyltrifluoroborate, 1c, 4-trifluoromethylphenyltrifluoroborate, 1d, 4-trifluoromethoxyphenyltrifluoroborate, 1e, and 4-chlorophenyltrifluoroborate, 1f, in the presence of anhydrous Cu(OAc)\(_2\). In all cases, amino ether products were furnished (Products 3d-3k, Table 1).

To explore the generality and scope of the O-arylation of β-hydroxy and γ-hydroxy amines, we examined the reaction with styryltrifluoroborates under the same reaction conditions. It worked well as shown in Table 2. In all cases, reaction looked very clean with \(trans\) selectivity. When subjected to silica gel chromatography, product didn’t collect effectively and showed less than expected yield.

Cu(OAc)\(_2\) mediated cross-coupling reaction of O-arylation typically requires air in the system for REDOX process. But, O-arylation of amino alcohols in the presence of anhydrous Cu(OAc)\(_2\) reported herein is completed under argon atmosphere, not in air.
Excess K$_2$CO$_3$ may favor the transmetallation followed by reductive coupling and form the amino ether product.

In addition to Molander’s effective protocol toward copper(II)-mediated O-arylation of protected serines and threonines via Chan-Lam cross-coupling, this work of anhydrous copper acetate mediated reaction O-arylation and O-styrylation of amino alcohols for new series of aminoethers synthesis is interesting development.

2. Procedure

The product N, N-dimethyl-2-(p-tolyloxy) ethan-1-amine, 3a from the cross-coupling of potassium tolyltrifluoroborate, 1a and 2-dimethylaminoethanol, 2a is shown as a representative procedure. The reaction was performed on a 0.5 mmol scale. After purging with argon, a microwave reaction tube with a stirrer bar was loaded with 246.0 mg (1.25 mmol) of potassium tolyltrifluoroborate, 138.0 mg (1.0 mmol) of K$_2$CO$_3$, 90.8 mg (0.5 mmol) of anhydrous Cu(OAc)$_2$, and 50 μL (0.5 mmol) of 2-dimethylaminoethanol. The reaction tube was capped and flushed with argon followed by adding 2.0 mL of 1,4-dioxane. The resulting reaction mixture was then inserted in the microwave vessel (CEM Explorer 24, Discover SP, and 300 W) and irradiated at 140°C for 30 min. The crude reaction product was extracted from inorganic material using ethyl acetate followed by washing with brine and dried over anhydrous sodium sulphate. For purification the crude product was subjected to preparative TLC using hexane/ethyl acetate (2/1) as eluent and collected the 68.4 mg (76%) amino ether 3a. The product was characterized by GC/MS (Saturn 2200 Benchtop GC/MS) and NMR (Varian 300 MHz).

**Compound 3a**

GCMS: Calculated for C$_{11}$H$_{17}$NO M$^+$ 180. Found: 180. $^1$H NMR (Acetone-d$_6$, 300 MHz) $\delta$ 7.11 (d, J = 8.4 Hz, 2H, aromatic), 6.90 (d, J = 8.7 Hz, 2H, aromatic), 4.46 (t, J = 4.8 Hz, 2H, CH$_2$), 3.85 (t, J = 4.8 Hz, 2H, CH$_2$), 3.23 (s, 6H, 2 × CH$_3$), 2.25 (s, 3H, CH$_3$); $^{13}$C NMR (Acetone-d$_6$, 75.5 MHz) $\delta$ 129.9, 114.5, 61.9, 56.8, 43.4, 19.5.

**Compound 3b**

GCMS: Calculated for C$_{14}$H$_{23}$NO M$^+$ 222. Found: 222. $^1$H NMR (Acetone-d$_6$, 300 MHz) $\delta$ 7.05 (d, J = 8.7 Hz, 2H, aromatic), 6.82 (d, J = 8.4 Hz, 2H, aromatic), 4.13 (t, J = 5.7 Hz, 2H, CH$_2$), 3.52 (m, 4H, 2 × CH$_2$), 3.4 (t, J = 7.5 Hz, 2H, CH$_2$), 2.24 (m, 2H, CH$_2$), 1.4 (t, J = 7.2 Hz, 6H, 2 × CH$_3$); $^{13}$C NMR (Acetone-d$_6$, 75.5 MHz) $\delta$ 130.7, 115.2, 65.8, 50.7, 48.7, 24.9, 20.5, 9.4.

**Compound 3c**

GCMS: Calculated for C$_{13}$H$_{21}$NO M$^+$ 208. Found: 208. $^1$H NMR (Acetone-d$_6$, 300 MHz) $\delta$ 7.08 (d, J = 8.7 Hz, 2H, aromatic), 6.80 (d, J = 8.4 Hz, 2H, aromatic), 3.97 (t, J = 5.7 Hz, 2H, CH$_3$), 2.60 (m, 2H, CH$_2$), 2.42 (s, 6H, 2 × CH$_3$), 2.23 (s, 2H, CH$_2$), 1.78 (m, 4H, 2 × CH$_2$); $^{13}$C NMR (Acetone-d$_6$, 75.5 MHz) $\delta$ 130.6, 115.1, 68.2, 45.1, 27.6, 24.2, 20.5.
**Compound 3d**

GCMS: Calculated for C_{10}H_{15}NO M^+ 166. Found: 166. \(^1H\) NMR (Acetone-d\(_6\), 300 MHz) \(\delta\) 7.27 (m, 2H, aromatic), 6.92 (m, 3H, aromatic), 4.07 (t, J = 6.0 Hz, 2H, CH\(_2\)), 2.67 (t, J = 6.0 Hz, 2H, CH\(_2\)), 2.26 (s, 6H, 2 \times CH\(_3\)); \(^{13}C\) NMR (Acetone-d\(_6\), 75.5 MHz) \(\delta\) 159.9, 130.3, 121.3, 115.3, 67.0, 59.0, 46.2.

**Compound 3e**

GCMS: Calculated for C\(_{13}\)H\(_{21}\)NO M^+ 208. Found: 208. \(^1H\) NMR (Acetone-d\(_6\), 300 MHz) \(\delta\) 7.26 (m, 2H, aromatic), 6.91 (m, 3H, aromatic), 4.05 (t, J = 6.3 Hz, 2H, CH\(_2\)), 2.67 (t, J = 6.6 Hz, 2H, CH\(_2\)), 2.57 (q, J = 7.2 Hz, 4H, 2 \times CH\(_2\)), 1.92 (m, 2H, CH\(_2\)), 0.93 (t, J = 7.2 Hz, 6H, 2 \times CH\(_3\)); \(^{13}C\) NMR (Acetone-d\(_6\), 75.5 MHz) \(\delta\) 160.1, 130.3, 121.2, 115.3, 66.5, 50.0, 47.8, 27.7, 12.1.

**Compound 3f**

GCMS: Calculated for C\(_{10}\)H\(_{14}\)NOF M^+ 184. Found: 184. \(^1H\) NMR (Acetone-d\(_6\), 300 MHz) \(\delta\) 7.0 (m, 4H, aromatic), 4.07 (m, 2H, CH\(_2\)), 2.73 (t, J = 5.86, 2H, CH\(_2\)), 2.31 (s, 6H, 2 \times CH\(_3\)); \(^{13}C\) NMR (Acetone-d\(_6\), 75.5 MHz) \(\delta\) 116.6, 116.3, 67.6, 60.6, 58.8, 46.0, 20.8, 14.5; \(^{19}F\) NMR (Acetone-d\(_6\), 300 MHz) \(\delta\) -125.8.

**Compound 3g**

GCMS: Calculated for C\(_{13}\)H\(_{20}\)NOF M^+ 225. Found: 225. \(^1H\) NMR (Acetone-d\(_6\), 300 MHz) \(\delta\) 6.98 (m, 4H, aromatic), 4.0 (t, J = 6.0 Hz, 2H, CH\(_2\)), 2.60 (d, J = 6.9 Hz, 2H, CH\(_2\)), 4H, CH\(_2\)), 2.53 (q, J = 7.2 Hz, 4H, 2 \times CH\(_2\)), 1.87 (m, 2H, CH\(_2\)), 0.99 (t, J = 6.9 Hz, 6H, 2 \times CH\(_3\)); \(^{13}C\) NMR (Acetone-d\(_6\), 75.5 MHz) \(\delta\) 116.6, 116.3, 67.3, 49.9, 47.7, 27.8, 12.3.

**Compound 3h**

GCMS: Calculated for C\(_{11}\)H\(_{14}\)NOF\(_3\) M^+ 234. Found: 234. \(^1H\) NMR (Acetone-d\(_6\), 300 MHz) \(\delta\) 7.62 (d, J = 8.4 Hz, 2H, aromatic), 7.12 (d, J = 8.7 Hz, 2H, aromatic), 4.17 (t, J = 5.7 Hz, 2H, CH\(_2\)), 2.70 (t, J = 6.0 Hz, 2H, CH\(_2\)), 2.27 (s, 6H, 2 \times CH\(_3\)); \(^{13}C\) NMR (Acetone-d\(_6\), 75.5 MHz) \(\delta\) 127.8, 127.7, 115.7, 67.5, 58.7, 46.1; \(^{19}F\) NMR (Acetone-d\(_6\), 300 MHz) \(\delta\) -61.8.

**Compound 3i**

GCMS: Calculated for C\(_{11}\)H\(_{14}\)NO\(_2\)F\(_3\) M^+ 250. Found: 250. \(^1H\) NMR (Acetone-d\(_6\), 300 MHz) \(\delta\) 7.23 (d, J = 9.2 Hz, 2H, aromatic), 7.03 (d, J = 9.3 Hz, 2H, aromatic), 4.12 (t, J = 6.0 Hz, 2H, CH\(_2\)), 2.73 (m, 2H, CH\(_2\)), 2.30 (s, 6H, 2 \times CH\(_3\)); \(^{13}C\) NMR (Acetone-d\(_6\), 75.5 MHz) \(\delta\) 158.8, 129.7, 123.4, 116.4, 115.4, 67.5, 58.8, 46.1; \(^{19}F\) NMR (Acetone-d\(_6\), 300 MHz) \(\delta\) 58.0.

**Compound 3j**

GCMS: Calculated for C\(_{11}\)H\(_{14}\)NO\(_2\)F\(_3\) M^+ 250. Found: 250. \(^1H\) NMR (Acetone-d\(_6\), 300 MHz) \(\delta\) 7.02 (m, 4H, aromatic), 4.07 (m, 2H, CH\(_2\)), 2.61 (m, 2H, CH\(_2\)), 2.51 (m, 4H, 2 \times CH\(_2\)), 1.9 (m, 2H, CH\(_2\)), 0.99 (m, 6H, 2 \times CH\(_3\)); \(^{13}C\) NMR (Acetone-d\(_6\), 75.5 MHz) \(\delta\) 158.1, 122.4, 116.1, 115.3, 66.3, 48.9, 46.8, 26.9, 11.5.
Compound 3k
GCMS: Calculated for C\textsubscript{14}H\textsubscript{20}NOCl M\textsuperscript{+} 242. Found: 242. \textsuperscript{1}H NMR (Acetone-d\textsubscript{6}, 300 MHz) \(\delta 7.28\) (d, J = 7.2 Hz, 2H, aromatic), 6.94 (d, J = 6.9 Hz, 2H, aromatic), 4.07 (t, J = 6.6 Hz, 2H, CH\textsubscript{2}), 2.66 (m, 8H, 4 \times CH\textsubscript{2}), 1.07 (m, 6H, CH\textsubscript{3}); \textsuperscript{13}C NMR (Acetone-d\textsubscript{6}, 75.5 MHz) \(\delta 129.1, 115.9, 46.7\).

Compound 5a
GCMS: Calculated for C\textsubscript{13}H\textsubscript{23}NO M\textsuperscript{+} 234. Found: 234. \textsuperscript{1}H NMR (Acetone-d\textsubscript{6}, 300 MHz) \(\delta 7.22\) (m, 5 H, aromatic), 7.16 (d, J = 13.2 Hz, 1H), 5.86 (d, J = 12.9 Hz, 1H), 3.91 (t, J = 6.3 Hz, 2H, CH\textsubscript{2}), 2.49 (m, 6H, CH\textsubscript{2}), 1.79 (q, J = 7.2 Hz, 2H, CH\textsubscript{2}), 0.98 (t, J = 6.9 Hz, 6H, 2 \times CH\textsubscript{3}); \textsuperscript{13}C NMR (Acetone-d\textsubscript{6}, 75.5 MHz) \(\delta 148.4, 136.9, 132.7, 128.4, 124.8, 105.4, 67.9, 49.0, 46.7, 27.3, 11.6\).

Compound 5b
GCMS: Calculated for C\textsubscript{13}H\textsubscript{22}NOF M\textsuperscript{+} 252. Found: 252. \textsuperscript{1}H NMR (Acetone-d\textsubscript{6}, 300 MHz) \(\delta 7.62 − 7.01\) (m, 5H, aromatic), 6.8 (d, 1H, CH), 5.90 (d, J = 12.9 Hz, 1H), 3.94 (t, J = 6.6 Hz, 2H, CH\textsubscript{2}), 2.54 (m, 6H, 3 \times CH\textsubscript{2}), 2.5 (t, 2H, CH\textsubscript{2}), 1.82 (m, 2H, CH\textsubscript{2}), 1.0 (t, J = 6.9 Hz, 6H, 2 \times CH\textsubscript{3}); \textsuperscript{13}C NMR (Acetone-d\textsubscript{6}, 75.5 MHz) \(\delta 149.3, 132.2, 129.0, 127.2, 116.2, 105.3, 68.9, 49.9, 47.7, 28.2, 12.5\) \textsuperscript{19}F NMR (Acetone-d\textsubscript{6}, 300 MHz) \(\delta -115.8, -119.5\).

Compound 5c
GCMS: Calculated for C\textsubscript{16}H\textsubscript{25}NO M\textsuperscript{+} 247. Found: 247. \textsuperscript{1}H NMR (Acetone-d\textsubscript{6}, 300 MHz) \(\delta 7.08\) (m, 5H), 5.81 (d, J = 13.2 Hz, 1H, CH), 3.89 (t, J = 6.0 Hz, 2H, CH\textsubscript{2}), 2.48 (m, 6H, 3 \times CH\textsubscript{2}), 2.25 (s, 3H, CH\textsubscript{3}), 1.78 (m, 2H, CH\textsubscript{2}), 0.98 (t, J = 6.9 Hz, 6H, 2 \times CH\textsubscript{3}); \textsuperscript{13}C NMR (Acetone-d\textsubscript{6}, 75.5 MHz) \(\delta 148.7, 135.5, 130.2, 127.1, 125.7, 106.3, 68.8, 50.0, 47.7, 28.2, 21.0, 12.5\).

Acknowledgments
Linda Quinones gratefully acknowledges the receipt of a MARC fellowship from NIH’s MARC program for her undergraduate research study (National Institutes of Health 2T34GM007663-32).

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Scheme 1.
Amino ethers.
Scheme 2.
O-Arylation of alcohols and amino alcohols.

Batey’s work, Org Lett. 2003, 5, 1381.

\[
\text{R}_1^1\text{BF}_3\text{K} \xrightarrow{\text{I} \quad \text{Cu(OAc)}_2\cdot\text{H}_2\text{O} \ (10 \text{ mol} \ %)} \text{DMAP, CH}_2\text{Cl}_2, \ 4 \text{ Å MS, rt, 5 min} \rightarrow \text{R}_1^1\text{O}\rightarrow\text{R}_2^1

\]

Molander’s work, Org. Lett. 2014, 16, 4944.

\[
\text{HO} \quad \text{OR}_1 \quad \text{HN} \quad \text{Pg} \quad + \quad \text{Ar BF}_3\text{K} \xrightarrow{\text{Cu(OAc)}_2\cdot\text{H}_2\text{O} \ (10 \text{ mol} \ %) \quad \text{DMAP} \ (20 \text{ mol} \ %), \text{H}_2\text{O, CH}_2\text{Cl}_2 \quad \text{air, rt, 12 h}} \rightarrow \text{Ar} \quad \text{O} \quad \text{OR}_1 \\
\text{HN} \quad \text{Pg}
\]

This work

\[
\text{HO} \quad \text{N}^+\text{R} \quad \text{N}^+\text{R} \quad + \quad \text{Ar BF}_3\text{K} \xrightarrow{\text{Anhydrous Cu(OAc)}_2 \quad \text{K}_2\text{CO}_3, \ 1,4\text{-dioxane \ mW, 140 °C, 30 min}} \rightarrow \text{Ar} \quad \text{O} \quad \text{N}^+\text{R} \quad \text{N}^+\text{R}
\]
Table 1

C–O bond by cross-coupling of potassium aryltrifluoroborates and hydroxamines

| Amino alcohols | Aryltrifluoroborates | Amino ether | Yields (%) |
|----------------|---------------------|-------------|------------|
| 2a             | 1a                  | 3a          | 76         |
| 2b             | 1a                  | 3b          | 50         |
| 2c             | 1a                  | 3c          | 87         |
| 2a             | 1b                  | 3d          | 51         |
| 2b             | 1b                  | 3e          | 91         |
| 2a             | 1c                  | 3f          | 48         |
| 2b             | 1c                  | 3g          | 40         |
| 2a             | 1d                  | 3h          | 42         |
| 2a             | 1e                  | 3i          | 30         |
| 2b             | 1e                  | 3j          | 32         |
| 2b             | 1f                  | 3k          | 90         |

a Cu(OAc)$_2$ (1.0 eq), ArBF$_3$K 1 (2.5 eq), Hydroxylamine 2 (1.0 eq), K$_2$CO$_3$ (2.0 eq), 1,4-dioxane 2.0 mL, MW, 140°C, 30 min.
### Table 2

C–O bond by cross-coupling of potassium styryltrifluoroborates and hydroxylamines<sup>a</sup>.

| Amino alcohol | Stryltrifluoroborates | Amino ether (yields) |
|---------------|-----------------------|---------------------|
| 2b            | 4a                    | 5<sup>a</sup> (54%)  |
| 4b            | 5b (48%)              |                     |
| 4c            | 5c (51%)              |                     |

<sup>a</sup>Cu(OAc)<sub>2</sub> (1.0 eq), StyrylBF<sub>3</sub>K 4 (2.5 eq), Hydroxylamine 2 (1.0 eq), K<sub>2</sub>CO<sub>3</sub> (2.0 eq), 1,4-dioxane 2.0 mL MW, 140°C, 30 min.