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PAPER

Direct acetoxylation and etherification of anilides using phenyliodine bis(trifluoroacetate)†

Huan Liu, Xuemin Wang and Yonghong Gu*

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Treatment of various anilides with 1.5 equiv. of phenyliodine bis(trifluoroacetate) (PIFA) and 1.0 equiv. of $BF_3{\cdot}OEt_2$ in AcOH at room temperature afforded the corresponding *para*-acetoxylated products with high regioselectivity. In addition, this reaction could be expanded to the etherification of anilides. In the presence of 2.0 equiv. of PIFA and 2.0 equiv. of $BF_3{\cdot}OEt_2$, the reaction of anilides with alcohols provided the corresponding *para*-etherified products in good yields.

Introduction

Selective and efficient oxygenation of aromatic compounds is one of the most challenging reactions in organic synthesis. Recently, oxidation by using hypervalent iodine compounds as metal-free reagents has received much attention for low toxicity compared with heavy metal oxidants, mild reaction conditions, easy handling and special reactivity in oxidation reactions.[1] In last two decades, this area has grown rapidly and many new applications for hypervalent iodine compounds in oxidative transformations of various kinds of functionalities have been developed.[2–4] Among them hypervalent iodine compound mediated oxygenation of aromatic compounds is one of the attractive processes. In 1994, Kita and co-workers found that the reaction of *para*-substituted phenol ethers with TMSOAc in the presence of phenyliodine(III) bis(trifluoroacetate) (PIFA) provided the *ortho*-acetoxylated products.[5] The mechanism of this reaction has been found to be *via* cation radical intermediate, followed by nucleophilic substitution to provide the product. After that, significant progress in the development of nucleophilic substitution of phenol derivatives using hypervalent iodine reagents has been achieved, in contrast there are few reports on oxidation of aniline derivatives.[6] Kigukawa and co-workers reported the *para*-hydroxylation of anilides with PIFA and trifluoroacetic acid (TFA). However, this reaction is limited to only electron-rich anilides, requiring electron-donating substituents on either a phenyl ring or an acyl group of anilides.[6a] Thus, we became interested in investigating other oxygen nucleophiles to synthesize substituted anilides, an important structural motif in small molecule drug discovery.[7] Herein, we report our studies on the acetoxylation and etherification of anilides using hypervalent iodine reagents.

Department of Chemistry, University of Science and Technology of China, Hefei, Anhui, 230026, China. E-mail: ygu01@ustc.edu.cn; Fax: +86-551-3601592; Tel: +86-551-3602470

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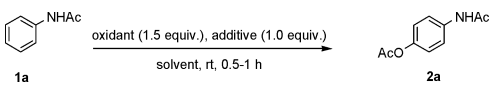
Results and discussion

Acetanilide was chosen as a model compound, AcOH was used as an oxygen nucleophile and solvent.[8] A survey of results for the acetoxylation of acetanilides under various conditions is summarized in Table 1. The initial attempt at the reaction of acetanilide (**1a**) with AcOH using 1.5 equiv phenyliodine(III) diacetate (PIDA) as an oxidant gave the *para*-acetoxylated product **2a** in only 5% isolated yield with very low conversion at room temperature after 1 h (entry 1). To our delight, when more reactive PIFA was employed, the reaction of **1a** with AcOH afforded **2a** in 62% yield using otherwise the same conditions; no *ortho*-substituted product was observed in this reaction (entry 2). This result indicates that the electron-withdrawing ligand trifluoroacetate in PIFA facilitates this transformation. Therefore

Table 1 Optimization of reaction conditions[a]

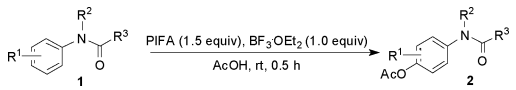


1a 2a

entry	oxidant	additive	solvent	yield[b]
1	PIDA	none	AcOH	5%
2	PIFA	none	AcOH	62%
3	PIDA	TFA	AcOH	40%[c]
4	PIDA	$BF_3{\cdot}OEt_2$	AcOH	43%
5	PIFA	$BF_3{\cdot}OEt_2$	AcOH	83%
6	PIFA	$BF_3{\cdot}OEt_2$	CH_2Cl_2	68%[d]
7	H_2O_2	none	AcOH	n.d.[e]
8	*t*-BuOOH	none	AcOH	n.d.
9	*m*-CPBA	none	AcOH	n.d.
10	Oxone	none	AcOH	n.d.
11	$K_2S_2O_8$	none	AcOH	n.d.

[a] Unless otherwise specified, all the reactions were carried out in the presence of 0.2 mmol of **1a**, 0.3 mmol of oxidant and 0.2 mmol of additive in 0.5 mL of solvent at room temperature for 0.5–1 h. [b] Isolated yield after column chromatography. [c] 0.6 mmol of TFA was employed. [d] 1.0 mmol of AcOH and 0.5 mL of CH_2Cl_2 were used. [e] No desired product was detected by TLC analysis.

Table 2 Direct acetoxylation of anilides with PIFA[a]



1 2

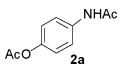
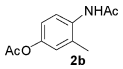
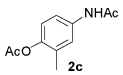
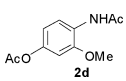
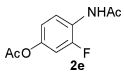
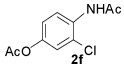
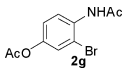
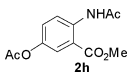
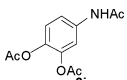
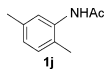
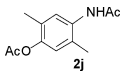
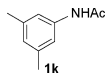
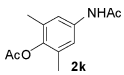
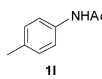
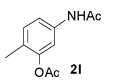
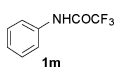
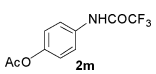
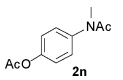
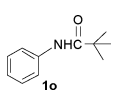
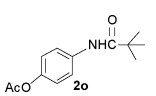
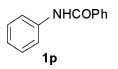
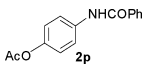
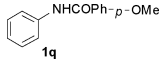
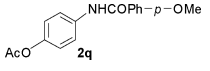
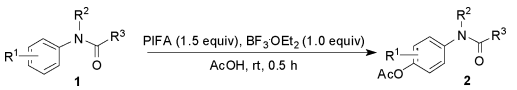
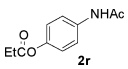
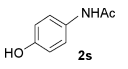
entry	substrate	product	yield%[b]
1			83
2			90
3			73
4			74[c]
5			90[d]
6			92[d]
7			61
8			60[d]
9			57
10			78
11			74
12			88
13			75[e]
14			80[f]
15			55
16			33
17			32

Table 2 *(Contd.)*



1 2

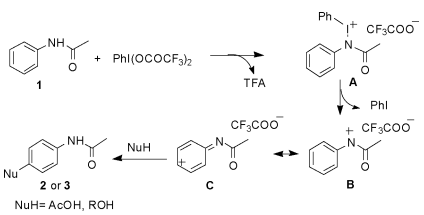
entry	substrate	product	yield%[b]
18			64[g]
19			89[h]

[a] Unless otherwise specified, all the reactions were carried out in the presence of 0.2 mmol of **1**, 0.3 mmol of PIFA and 0.2 mmol of $BF_3{\cdot}OEt_2$ in 0.5 mL of AcOH at room temperature for 0.5 h. [b] Isolated yield after column chromatography. [c] The reaction was carried out for 10 min. [d] 0.4 mmol of $BF_3{\cdot}OEt_2$ was used. [e] The reaction was carried out for 1 h. [f] 0.4 mmol of $BF_3{\cdot}OEt_2$ was employed and the reaction was carried out at 50 °C. [g] CH_3CH_2COOH was used instead of AcOH. [h] HCOOH was used instead of AcOH.

we also tested the use of a combination of 1.5 equiv. PIDA and 3.0 equiv. TFA. Indeed the reaction improved to provide **2a** in 40% yield (entry 3). As we expected, using $BF_3{\cdot}OEt_2$ as an additive accelerated the reaction and improved the yield of **2a** dramatically (entries 4 and 5).[9] It was found that using CH_2Cl_2 as a cosolvent resulted in slow reaction and a lower yield of **2a** (entry 6). Extensive examination of oxidants showed that only hypervalent iodine(III) oxidants were effective in this reaction. Some peroxides that are often used in cross-dehydrogenative coupling (CDC),[10] such as H_2O_2, *t*-BuOOH and *m*-CPBA, failed to yield any desired product using the same reaction conditions (entries 7–9). Other oxidants that were used in $Pd(OAc)_2$-catalyzed *ortho*-acetoxylation of anilides,[8] such as Oxone and $K_2S_2O_8$, didn't provide **2a** either (entries 10 and 11).

In order to generalize the scope of the reaction, a series of structurally diverse anilides were subjected to the optimized reaction conditions and the results are summarized in Table 2. In the presence of 1.5 equiv. of PIFA and 1.0 equiv. of $BF_3{\cdot}OEt_2$, the acetoxylation of various anilides with AcOH proceeded well to give only the *para*-substituted products at room temperature for 0.5 h in good to excellent yields. The acetoxylation of acetanilide with a methyl group at the *ortho*-position afforded **2b** in 90% yield (entry 2). When a methyl group was introduced to the *meta*-position of acetanilide, the reaction gave **2c** in 73% yield, probably due to the some steric effect (entry 3). Comparably, 2,5-dimethylacetanilide and 3,5-dimethylacetanilide were acetoxylated to give **2j** and **2k** in 78% and 74% yields respectively (entries 10 and 11). This reaction was tolerant to a diversity of functional groups, such as methoxy, fluoride, chloride, bromide, ester, acetoxy groups (entries 4–9). Notably, the acetoxylation of the substrate containing a moderately electron-withdrawing group, such as 2-chloroacetanilide (**1f**), provided **2f** in excellent yield in this transformation, in contrast, hydroxylation of **1f** gave only 37% *para*-hydroxylated product under Kigukawa's conditions (entry 6).[6a] It was found that electron-donating substituents facilitate this reaction. When a substrate containing an electron-donating group at the *ortho*-position (for example, 2-methoxyacetanilide) was employed, the reaction accelerated and gave **2d** in 74% yield

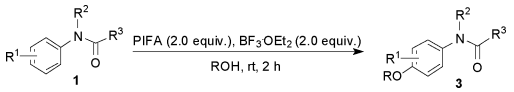
after 10 min at room temperature (entry 4). However, when a substrate containing an electron-withdrawing group at the *ortho*-position (for example, 2-methoxycarbonylacetanilide) was used, excess $BF_3{\cdot}OEt_2$ (2.0 equiv.) was needed to accomplish the reaction and a lower yield of **2h** was obtained (entry 8). Most importantly, when the substrate contained the two active groups (for example, acetamino and methoxy groups in 2-methoxyacetanilide), the reaction gave only the product **2d**, acetoxylated *para* to the acetamino group (entry 4).[11] A similar result was also observed with 3-acetoxyacetanilide (**1i**). The acetoxylation of **1i** gave mainly product **2i**, acetoxylated *para* to the acetamino group, in 57% yield (entry 9). These results indicate that an acetamino group has a stronger directing effect compared with other oxygen-containing groups in this transformation. It suggests that the reaction probably occurs through a nitrenium ion mechanism, which favors *para*-substitution by nucleophiles (Scheme 1). It should also be mentioned that when the *para*-position was blocked (for example, 4-methylacetanilide), the reaction gave the *meta*-acetoxylated product **2l** in 88% yield (entry 12). This is consistent with the observation by Nair *et al.* in the reaction of *para*-substituted acetanilide with PIDA and AcOH.[6b] Most likely the reaction occurs at the *para*-position first, and subsequently migrates to the *meta*-position. Next, we examined the substitute effect on the acetamino group. Gratifyingly, this reaction also applied to other acetanilides. Notably, the acetoxylation of the electron deficient trifluoroacetanilide (**1m**) proceeded well to give **2m** in 75% yield (entry 13). In addition, the acetoxylation of *N*-methylacetanilide (**1n**) afforded **2n** in 80% yield in the presence of excess $BF_3{\cdot}OEt_2$ (2.0 equiv.) at 50 °C (entry 14). Several types of anilides were also examined. It was found that when R^3 of anilide is substituted with the bulkyl *t*-butyl group, the reaction gave the *para*-acetoxylated product **2o** in 55% yield (entry 15). However, when R^3 of anilide is substituted with aryl groups (*e.g.* R^3 = phenyl, **1p**, R^3 = *p*-methoxyphenyl, **1q**), the reaction afforded the corresponding products **2p** and **2q** in moderate yields (entries 16 and 17). Finally, other acyloxylations were also explored. The propionoxylation of **1a** with CH_3CH_2COOH afforded the desired product **2r** in good yield (entry 18). And the reaction of **1a** with HCOOH gave the hydrolyzed product **2s** in excellent yield (entry 19).

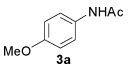
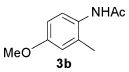
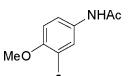
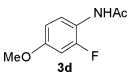
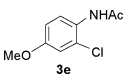
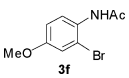
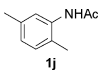
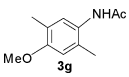
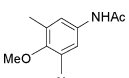
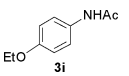
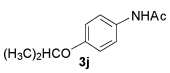
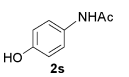
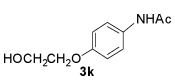


Scheme 1 Proposed mechanism of acetoxylation and etherification of anilides.

Next, we expanded this reaction to PIFA-induced etherification of acetanilides. We reasoned that changing the solvent from AcOH to alcohols might result in the formation of ether products. Gratifyingly, in the presence of 2.0 equiv. PIFA and 2.0 equiv. $BF_3{\cdot}OEt_2$, the reaction of acetanilide (**1a**) with MeOH afforded methyl ether **3a** in 82% yield (Table 3, entry 1). It should be noted that this ether-forming reaction required excess PIFA (2.0 equiv.) and $BF_3{\cdot}OEt_2$ (2.0 equiv.) to fully consume the reactant, compared with the acetoxylation reaction described above. This reaction was tolerant to various functional groups, such as methyl, fluoride, chloride and bromide substituents (entries 2–6).[12] In addition, reaction of disubstituted acetanilides **1j** and **1k** proceeded well to give the *para*-methoxylated products **3g** and **3h** in 80% and 75% yield respectively (entries 7 and 8). Finally, the etherification of acetanilide (**1a**) with other alcohols also went smoothly. The

Table 3 Direct etherification of anilides with PIFA[a]



entry	substrate	product	yield%[b]
1			82
2			85
3			73
4			61
5			63
6			64
7			80[c]
8			75[d]
9			57[e]
10			52[f]
11			56[g]
12			33[h]

[a] Unless otherwise specified, all the reactions were carried out in the presence of 0.2 mmol of **1a**, 0.4 mmol of PIFA and 0.4 mmol of $BF_3{\cdot}OEt_2$ in 0.5 mL of MeOH at room temperature for 2 h. [b] Isolated yield after column chromatography. [c] 0.3 mmol of PIFA and 0.2 mmol of $BF_3{\cdot}OEt_2$ were used and the reaction was carried out for 1 h. [d] 0.3 mmol of PIFA and 0.2 mmol of $BF_3{\cdot}OEt_2$ were used and the reaction was carried out at 0 °C for 1 h. [e] EtOH was used instead of MeOH. [f] $(CH_3)_2CHOH$ was used instead of MeOH. [g] *t*-BuOH was used instead of MeOH. [h] ethylene glycol was used instead of MeOH.

reaction of **1a** with EtOH or $(CH_3)_2CHOH$ provided ether products **3i** and **3j** in moderate yields (entries 9 and 10). Notably, the reaction of **1a** with *t*-BuOH gave phenol product **2s** in 56% yield, as the *t*-butyl group was removed using these conditions (entry 11). In addition, treatment of acetanilide (**1a**) with PIFA and $BF_3{\cdot}OEt_2$ in ethylene glycol at room temperature for 2 h provided the mono-etherified product **3k** in 33% yield (entry 12).

A possible mechanism of PIFA-induced acetoxylation and etherification of anilides is proposed according to the literature examples[6a] and our experimental results (Scheme 1). The mechanism of this reaction undergoes electrophilic substitution pathway. A nucleophilic attack of PIFA on anilide **1** forms the iodonium intermediate **A**. Cleavage of the N–I bond furnishes iodobenzene and a nitrenium ion **B**, which is stabilized by the charge delocalization on the phenyl ring. The extensively charge delocalized intermediate **C** is highly preferred and trapped with AcOH or alcohols to give the *para*-substituted products **2** or **3**.

Conclusions

In summary, we have developed a direct method for the acetoxylation and etherification of anilides. Using PIFA as an oxidant, the reactions of anilides with AcOH or alcohols provided the corresponding *para*-oxygenated anilides with high regioselectivity in good to excellent yields under mild conditions. The acetamino group in anilides is an efficient directing group in these reactions.

Experimental

General

^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker AC-300 FT (300 MHz and 75 MHz respectively) using TMS as an internal reference. The chemical shifts (δ) and coupling constants (J) were expressed in ppm and Hz respectively. IR spectra were recorded on a Perkin-Elmer 2000 FT-IR. HRMS analysis was performed on a Micromass CGT-MS. The chemicals purchased from commercial sources were used without further purification. The melting points were uncorrected. TLC analysis was performed on silica gel plates, the products were purified by column chromatography over silica gel (mesh 200–300).

General procedure for the direct *para*-acyloxylation of anilides 1a (1b–1q)

To a stirred solution of anilide **1a** (**1b–1q**, 0.2 mmol) and $BF_3{\cdot}OEt_2$ (0.025 mL, 0.2 mmol) in acid (0.50 mL) at room temperature was added PIFA (0.129 g, 0.3 mmol). The resulting mixture was stirred at room temperature for 0.5 h. The solvent was removed under reduced pressure and the residue was purified by flash column chromatography using petroleum ether/EtOAc as the eluent to afford the pure product **2a** (**2b–2s**).

4-Acetoxyacetanilide (2a). Yield (83%), white solid, mp 149–151 °C, ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.98 (br s, 1H, NH), 7.46 (d, J = 8.7 Hz, 2H), 6.98 (d, J = 8.7 Hz, 2H), 2.28 (s, 3H), 2.10 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.0, 168.9, 146.8, 135.9, 121.9 (2C), 121.1 (2C), 24.3, 21.2; IR (KBr) υ 3296, 3078, 1753, 1666, 1615, 1560, 1507, 1366, 1323, 1240, 849 cm^{-1}; HRMS (EI) Calculated for $C_{10}H_{11}NO_3$ (M^+) 193.0739, found 193.0730.

4-Acetoxy-2-methylacetanilide (2b). Yield (90%), white solid, mp 128–129 °C, ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.54 (d, J = 8.4 Hz, 1H), 7.46 (br s, 1H, NH), 6.85–6.83 (m, 2H), 2.26 (s, 3H), 2.11 (s, 3H), 2.10 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.9, 168.8, 147.7, 133.5, 131.8, 125.0, 123.4, 119.6, 24.1, 21.2, 17.9; IR (KBr) υ 3351, 1738, 1619, 1543, 1372, 1232, 919, 816 cm^{-1}; HRMS (EI) Calculated for $C_{11}H_{13}NO_3$ (M^+) 207.0895, found 207.0899.

4-Acetoxy-3-methylacetanilide (2c). Yield (73%), white solid, mp 145–146 °C, ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.65 (br s, 1H, NH), 7.38 (s, 1H), 7.25 (d, J = 8.4 Hz, 1H), 6.91 (d, J = 8.4 Hz, 1H), 2.31 (s, 3H), 2.13 (s, 3H), 2.11 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.8, 168.9, 145.5, 136.0, 130.6, 122.7, 122.1, 118.7, 24.3, 20.9, 16.3; IR (KBr) υ 3318, 1758, 1668, 1622, 1562, 1500, 1372, 1227, 1196, 904, 833 cm^{-1}; HRMS (EI) Calculated for $C_{11}H_{13}NO_3$ (M^+) 207.0895, found 207.0897.

4-Acetoxy-2-methoxyacetanilide (2d). Yield (74%), white solid, mp 174–176 °C, ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.33 (d, J = 8.7 Hz, 1H), 7.68 (br s, 1H, NH), 6.68–6.63 (m, 2H), 3.84 (s, 3H), 2.27 (s, 3H), 2.18 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.7, 168.2, 148.3, 146.6, 125.6, 120.2, 113.6, 104.5, 56.0, 24.9, 21.2; IR (KBr) υ 3333, 2928, 1749, 1664, 1609, 1531, 1243, 898, 810 cm^{-1}; HRMS (EI) Calculated for $C_{11}H_{13}NO_4$ (M^+) 223.0845, found 223.0849.

4-Acetoxy-2-fluoroacetanilide (2e). Yield (90%), white solid, mp 117–119 °C, ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.28 (dd, J = 9.0, 8.4 Hz, 1H), 7.36 (br s, 1H, NH), 6.94–6.86 (m, 2H), 2.28 (s, 3H), 2.21 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.3, 168.5, 152.2 (d, J = 242.3 Hz), 146.5, 124.3, 122.3, 117.6, 109.4 (d, J = 22.6 Hz), 24.6, 21.1; IR (KBr) υ 3374, 1759, 1687, 1619, 1533, 1431, 1366, 1325, 1222, 1141, 973, 820 cm^{-1}; HRMS (EI) Calculated for $C_{10}H_{10}NO_3F$ (M^+) 211.0645, found 211.0649.

4-Acetoxy-2-chloroacetanilide (2f). Yield (92%), white solid, mp 127–128 °C, ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.36 (d, J = 8.7 Hz, 1H), 7.56 (br s, 1H, NH), 7.17 (d, J = 2.7 Hz, 1H), 7.01 (dd, J = 8.7, 2.7 Hz, 1H), 2.28 (s, 3H), 2.23 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.2, 168.5, 146.5, 132.5, 123.1, 122.5, 122.4, 120.9, 24.6, 21.0; IR (KBr) υ 3281, 1759, 1655, 1528, 1370, 1210, 1185, 929, 887, 615 cm^{-1}; HRMS (EI) Calculated for $C_{10}H_{10}NO_3{}^{35}Cl$ (M^+) 227.0349, found 227.0356.

4-Acetoxy-2-bromoacetanilide (2g). Yield (61%), white solid, mp 124–125 °C, ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.34 (d, J = 9.0 Hz, 1H), 7.54 (br s, 1H, NH), 7.33 (d, J = 2.4 Hz, 1H), 7.06 (dd, J = 9.0, 2.4 Hz, 1H), 2.28 (s, 3H), 2.23 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.2, 168.4, 146.7, 133.6, 125.5, 122.7, 121.5, 113.3, 24.7, 21.0; IR (KBr) υ 3269, 2925, 1758, 1663, 1528, 1368, 1210, 1184, 923, 878, 610 cm^{-1}; HRMS (EI) Calculated for $C_{10}H_{10}NO_3{}^{81}Br$ (M^+) 272.9824, found 272.9833.

5-Acetoxy-2-acetylaminobenzoic acid methyl ester (2h). Yield (60%), white solid, mp 103–105 °C, ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.98 (br s, 1H, NH), 8.74 (d, J = 9.0 Hz, 1H), 7.77 (d, J = 2.7 Hz, 1H), 7.27 (dd, J = 9.0, 2.7 Hz, 1H), 3.92 (s, 3H), 2.30 (s, 3H), 2.24 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.4, 169.0, 168.1, 145.1, 139.6, 128.0, 123.6, 121.6, 115.7, 52.6, 25.5, 21.1; IR (KBr) υ 3289, 2951, 1766, 1690, 1615, 1526, 1371, 1209, 934, 788 cm^{-1}; HRMS (EI) Calculated for $C_{12}H_{13}NO_5$ (M^+) 251.0794, found 251.0801.

3,4-Diacetoxyacetanilide (2i). Yield (57%), white solid, mp 143–144 °C, ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.57 (br s, 1H, NH), 7.44 (s, 1H), 7.15 (d, J = 8.7 Hz, 1H), 7.06 (d, J = 8.7 Hz, 1H), 2.28 (s, 3H), 2.27 (s, 3H), 2.12 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.6 (2C), 168.5, 142.2, 138.3, 136.5, 123.5, 117.7, 115.2, 24.4, 20.7 (2C); IR (KBr) υ 3364, 2925, 1767, 1672, 1612, 1546, 1505, 1372, 1211, 898, 834 cm^{-1}.

4-Acetoxy-2,5-dimethylacetanilide (2j). Yield (78%), white solid, mp 174–175 °C,^{1}H NMR (300 MHz, $CDCl_3$) δ 7.60 (s, 1H), 6.94 (br s, 1H, NH), 6.82 (s, 1H), 2.30 (s, 3H), 2.27 (s, 6H), 2.13 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.7, 168.9, 146.4, 133.4, 129.3, 128.0, 126.7, 123.5, 23.9, 20.8, 17.4, 15.9; IR (KBr) υ 3278, 2926, 1752, 1658, 1536, 1369, 1236, 1191, 917, 712 cm^{-1}; HRMS (EI) Calculated for $C_{12}H_{15}NO_3$ (M^+) 221.1052, found 221.1054.

4-Acetoxy-3,5-dimethylacetanilide (2k). Yield (74%), white solid, mp 159–161 °C, ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.72 (br s, 1H, NH), 7.14 (s, 2H), 2.32 (s, 3H), 2.08 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.4, 168.8, 144.5, 135.6, 130.6 (2C), 120.3 (2C), 24.3, 20.5, 16.5 (2C); IR (KBr) υ 3305, 2923, 1753, 1666, 1624, 1575, 1485, 1371, 1228, 911, 857 cm^{-1}; HRMS (EI) Calculated for $C_{12}H_{15}NO_3$ (M^+) 221.1052, found 221.1054.

3-Acetoxy-4-methylacetanilide (2l). Yield (88%), white solid, mp 155–157 °C,^{1}H NMR (300 MHz, $CDCl_3$) δ 7.63 (br s, 1H, NH), 7.36 (s, 1H), 7.12–7.05 (m, 2H), 2.31 (s, 3H), 2.11 (s, 3H), 2.05 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.5, 168.5, 149.5, 137.1, 131.1, 125.7, 117.5, 113.9, 24.4, 20.9, 15.7; IR (KBr) υ 3302, 1752, 1665, 1606, 1543, 1408, 1316, 1217, 903, 807 cm^{-1}; HRMS (EI) Calculated for $C_{11}H_{13}NO_3$ (M^+) 207.0895, found 207.0899.

4-Acetoxytrifluoroacetanilide (2m). Yield (75%), white solid, mp 172–174 °C, ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.19 (br s, 1H, NH), 7.51 (d, J = 8.7 Hz, 2H), 7.06 (d, J = 8.7 Hz, 2H), 2.31 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.8, 155.0 (q, J = 37.3 Hz), 148.5, 133.0, 122.5 (2C), 121.8 (2C), 115.9 (q, J = 287.4 Hz), 21.1; IR (KBr) υ 3332, 2921, 1762, 1705, 1615, 1558, 1511, 1374, 1287, 1226, 1187, 1157, 1017, 915 cm^{-1}; HRMS (EI) Calculated for $C_{10}H_8NO_3F_3$ (M^+) 247.0456, found 247.0457.

4-Acetoxy-*N*-methylacetanilide (2n). Yield (80%), white solid, mp 96–98 °C, ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.21 (d, J = 8.7 Hz, 2H), 7.14 (d, J = 8.7 Hz, 2H), 3.26 (s, 3H), 2.32 (s, 3H), 1.88 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.7, 169.3, 149.9, 142.1, 128.2 (2C), 123.0 (2C), 37.3, 22.5, 21.2; IR (KBr) υ 1760, 1658, 1638, 1509, 1378, 1198, 913, 861 cm^{-1}; HRMS (EI) Calculated for $C_{11}H_{13}NO_3$ (M^+) 207.0895, found 207.0898.

Acetic acid 4-(2,2-dimethyl-propionylamino)phenyl ester (2o). Yield (55%), white solid, mp 160–161 °C, ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.53 (d, J = 9.0 Hz, 2H), 7.36 (br s, 1H, NH), 7.03 (d, J = 9.0 Hz, 2H), 2.28 (s, 3H), 1.30 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.8, 169.8, 146.8, 135.9, 121.9 (2C), 121.2 (2C), 39.6, 27.6 (3C), 21.1; IR (KBr) υ 3380, 2971, 1737, 1677, 1657, 1535, 1510, 1405, 1371, 835 cm^{-1}; HRMS (EI) Calculated for $C_{13}H_{17}NO_3$ (M^+) 235.1208, found 235.1208.

Acetic acid 4-benzoylaminophenyl ester (2p). Yield (33%), white solid, mp 172–173 °C, ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.94 (br s, 1H, NH), 7.86 (d, J = 7.2 Hz, 2H), 7.64 (d, J = 9.0 Hz, 2H), 7.55–7.45 (m, 3H), 7.08 (d, J = 9.0 Hz, 2H), 2.29 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.9, 166.0, 147.1, 135.8, 134.9, 132.0, 128.9 (2C), 127.2 (2C), 122.1 (2C), 121.4 (2C), 21.2; IR (KBr) υ 3333, 2971, 1764, 1655, 1581, 1530, 1510, 831 cm^{-1}; HRMS (EI) Calculated for $C_{15}H_{13}NO_3$ (M^+) 255.0895, found 255.0901.

Acetic acid 4-(4-methoxy-benzoylamino)-phenyl ester (2q). Yield (32%), white solid, mp 176–177 °C, ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.85 (br s, 1H, NH), 7.83 (d, J = 8.7 Hz, 2H), 7.63 (d, J = 9.0 Hz, 2H), 7.08 (d, J = 8.7 Hz, 2H), 6.97 (d, J = 8.7 Hz, 2H), 3.87 (s, 3H), 2.29 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.9, 165.5, 162.6, 146.9, 136.0, 129.1 (2C), 127.0, 122.0 (2C), 121.4 (2C), 114.0 (2C), 55.5, 21.2; IR (KBr) υ 3448, 3314, 2924, 1751, 1648, 1607, 1513, 1226, 1199, 847 cm^{-1}; HRMS (EI) Calculated for $C_{16}H_{15}NO_4$ (M^+) 285.1001, found 285.0999.

4-Propionyloxyacetanilide (2r). Yield (64%), white solid, mp 135–136 °C, ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.46 (d, J = 8.4 Hz, 3H), 7.01 (d, J = 8.4 Hz, 2H), 2.58 (q, J = 7.5 Hz, 2H), 2.14 (s, 3H), 1.26 (t, J = 7.5 Hz, 3H);^{13}C NMR (75 MHz, $CDCl_3$) δ 173.5, 168.8, 146.9, 135.8, 121.9 (2C), 121.1 (2C), 27.8, 24.4, 9.1; IR (KBr) υ 3261, 2943, 1755, 1666, 1612, 1558, 1509, 1363, 1203, 1153, 893, 836 cm^{-1}; HRMS (EI) Calculated for $C_{11}H_{13}NO_3$ (M^+) 207.0895, found 207.0892.

4-Hydroxyacetanilide (2s). Yield (89%), white solid, mp 164–165 °C,^{1}H NMR (300 MHz, d-DMSO) δ 9.60 (br s, 1H, OH), 9.09 (br s, 1H, NH), 7.30 (d, J = 8.4 Hz, 2H), 6.64 (d, J = 8.4 Hz, 2H), 1.94 (s, 3H); ^{13}C NMR (75 MHz, d-DMSO) δ 167.7, 153.3, 131.2, 121.1 (2C), 115.2 (2C), 23.9; IR (KBr) υ 3329, 3209, 2926, 1661, 1617, 1559, 1510, 1453, 1375, 1323, 1243, 835 cm^{-1}; HRMS (EI) Calculated for $C_8H_9NO_2$ (M^+) 151.0633, found 151.0635.

General procedure for the direct *para*-etherification of anilides 1a (1b–1k)

To a stirred solution of anilide **1a** (**1b–1k**, 0.2 mmol) and $BF_3{\cdot}OEt_2$ (0.050 mL, 0.4 mmol) in alcohol (0.50 mL) at room temperature was added PIFA (0.172 g, 0.4 mmol). The resulting mixture was stirred at room temperature for 2 h. The solvent was removed under reduced pressure and the residue was purified by flash column chromatography using petroleum/EtOAc as the eluent to afford the pure product **3a** (**3b–3k**).

4-Methoxyacetanilide (3a). Yield (82%), white solid, mp 126–128 °C, ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43 (br s, 1H, NH), 7.37 (d, J = 9.0 Hz, 2H), 6.83 (d, J = 9.0 Hz, 2H), 3.77 (s, 3H), 2.13 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.5, 156.7, 131.2, 122.1 (2C), 114.3 (2C), 55.6, 24.4; IR (KBr) υ 3244, 2960, 1651, 1606, 1563, 1514, 1369, 1246, 1031, 838 cm^{-1}; HRMS (EI) Calculated for $C_9H_{11}NO_2$ (M^+) 165.0790, found 165.0793.

4-Methoxy-2-methylacetanilide (3b). Yield (85%), white solid, mp 128–130 °C, ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37 (br s, 1H, NH), 7.31 (d, J = 8.4 Hz, 1H), 6.67 (d, J = 8.4 Hz, 2H), 3.75 (s, 3H), 2.17 (s, 3H), 2.11 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.2, 157.5, 133.5, 129.5, 126.5, 115.9, 111.5, 55.4, 23.6, 18.1; IR (KBr) υ 3285, 2933, 1649, 1617, 1534, 1498, 1370, 1256, 1050, 857, 808 cm^{-1}; HRMS (EI) Calculated for $C_{10}H_{13}NO_2$ (M^+) 179.0946, found 179.0942.

4-Methoxy-3-methylacetanilide (3c). Yield (73%), white solid, mp 103–104 °C, ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30–7.26 (m, 2H),

7.20 (s, 1H), 6.75 (d, J = 8.7 Hz, 1H), 3.80 (s, 3H), 2.19 (s, 3H), 2.13 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.4, 154.9, 130.6, 127.3, 123.6, 119.2, 110.3, 55.7, 24.4, 16.3; IR (KBr) υ 3248, 2952, 1650, 1572, 1505, 1398, 1231, 1035, 881, 765 cm^{-1}; HRMS (EI) Calculated for $C_{10}H_{13}NO_2$ (M^+) 179.0946, found 179.0947.

4-Methoxy-2-fluoroacetanilide (3d). Yield (61%), white solid, mp 105–107 °C, ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.01 (t, J = 9.0 Hz, 1H), 7.29 (br s, 1H, NH), 6.66–6.62 (m, 2H), 3.76 (s, 3H), 2.17 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.3, 156.9, 153.8 (d, J = 242.1 Hz), 123.7, 119.5, 109.5, 101.9 (d, J = 23.0 Hz), 55.8, 24.4; IR (KBr) υ 3247, 2972, 1656, 1602, 1544, 1509, 1372, 1214, 1103, 1034, 942, 839 cm^{-1}; HRMS (EI) Calculated for $C_9H_{10}NO_2F$ (M^+) 183.0696, found 183.0698.

4-Methoxy-2-chloroacetanilide (3e). Yield (63%), white solid, mp 114–115 °C, ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.13 (d, J = 9.0 Hz, 1H), 7.40 (br s, 1H, NH), 6.92 (d, J = 2.4 Hz, 1H), 6.81 (dd, J = 9.0, 2.4 Hz, 1H), 3.77 (s, 3H), 2.20 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.3, 156.5, 128.0, 124.3, 123.5, 114.6, 113.3, 55.8, 24.7; IR (KBr) υ 3289, 2925, 1658, 1534, 1400, 1280, 1049, 883, 813, 606 cm^{-1}; HRMS (EI) Calculated for $C_9H_{10}NO_2{}^{35}Cl$ (M^+) 199.0400, found 199.0392.

4-Methoxy-2-bromoacetanilide (3f). Yield (64%), white solid, mp 124–126 °C, ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.11 (d, J = 9.0 Hz, 1H), 7.36 (br s, 1H, NH), 7.09 (d, J = 2.7 Hz, 1H), 6.87 (dd, J = 9.0, 2.7 Hz, 1H), 3.78 (s, 3H), 2.21 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.2, 156.7, 129.2, 123.7, 117.6, 114.7, 114.0, 55.8, 24.6; IR (KBr) υ 3300, 2932, 1660, 1602, 1520, 1340, 1278, 1037, 877, 575 cm^{-1}; HRMS (EI) Calculated for $C_9H_{10}NO_2{}^{81}Br$ (M^+) 244.9874, found 244.9880.

4-Methoxy-2,5-dimethylacetanilide (3g). Yield (80%), white solid; mp 163–165 °C, ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.20 (br s, 1H, NH), 7.16 (s, 1H), 6.60 (s, 1H), 3.78 (s, 3H), 2.17 (s, 3H), 2.13 (s, 3H), 2.11 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.1, 155.8, 130.6, 130.4, 127.9, 124.6, 112.0, 55.5, 23.7, 18.0, 15.8; IR (KBr) υ 3296, 2927, 1653, 1592, 1534, 1467, 1400, 1210, 1030, 884, 719 cm^{-1}; HRMS (EI) Calculated for $C_{11}H_{15}NO_2$ (M^+) 193.1103, found 193.1099.

4-Methoxy-3,5-dimethylacetanilide (3h). Yield (75%), white solid, mp 136–138 °C, ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.07 (br s, 1H, NH), 7.10 (s, 2H), 3.64 (s, 3H), 2.20 (s, 6H), 2.11 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.2, 153.7, 133.4, 131.2 (2C), 121.0 (2C), 59.8, 24.1, 16.1 (2C); IR (KBr) υ 3322, 2929, 1659, 1613, 1561, 1480, 1408, 1369, 1222, 1010, 862, 750 cm^{-1}; HRMS (EI) Calculated for $C_{11}H_{15}NO_2$ (M^+) 193.1103, found 193.1100.

4-Ethoxyacetanilide (3i). Yield (57%), white solid, mp 134–136 °C, ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36 (d, J = 9.0 Hz, 2H), 7.28 (br s, 1H, NH), 6.83 (d, J = 9.0 Hz, 2H), 4.00 (q, J = 6.9 Hz, 2H), 2.13 (s, 3H), 1.39 (t, J = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.5, 155.9, 131.0, 122.1 (2C), 114.9 (2C), 63.8, 24.4, 14.9; IR (KBr) υ 3366, 2927, 1665, 1605, 1512, 1374, 1280, 1124, 829, 745 cm^{-1}; HRMS (EI) Calculated for $C_{10}H_{13}NO_2$ (M^+) 179.0946, found 179.0939.

4-Isopropoxyacetanilide (3j). Yield (52%), white solid, mp 130–132 °C, ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36 (d, J = 9.0 Hz, 2H), 7.16 (br s, 1H, NH), 6.83 (d, J = 9.0 Hz, 2H), 4.48 (septet, J = 6.0 Hz, 1H), 2.14 (s, 3H), 1.31 (d, J = 6.0 Hz, 6H); ^{13}C NMR (75MHz, $CDCl_3$) δ 168.6, 154.8, 131.1, 122.1 (2C), 116.5 (2C), 70.5, 24.3, 22.1 (2C); IR (KBr) υ 3267, 2925, 1656, 1613, 1560, 1510, 1376, 1242, 1114, 837, 771 cm^{-1}; HRMS (EI) Calculated for $C_{11}H_{15}NO_2$ (M^+) 193.1103, found 193.1103.

4-(2-Hydroxy-ethoxy)acetanilide (3k). Yield (33%), white solid, mp 118–119 °C, ^{1}H NMR (300 MHz, d-DMSO) δ 9.79 (br s, 1H, NH), 7.46 (d, J = 9.0 Hz, 2H), 6.85 (d, J = 9.0 Hz, 2H), 4.86 (t, J = 4.8 Hz, 1H, OH), 3.92 (t, J = 4.8 Hz, 2H), 3.69 (t, J = 4.8 Hz, 2H), 1.99 (s, 3H);^{13}C NMR (75 MHz, d-DMSO) δ 167.9, 154.5, 132.6, 120.7 (2C), 114.4 (2C), 69.7, 59.7, 23.3; IR (KBr) υ 3426, 3069, 3005, 2935, 1678, 1595, 1573, 1021, 861 cm^{-1}; HRMS (EI) Calculated for $C_{10}H_{13}NO_3$ (M^+) 195.0895, found 195.0899.

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12 When acetanilides containing an electron-donating group (for example, **1d**) or an electron-withdrawing group (for example, **1h**) were employed, the etherification reactions were much less effective and only trace amounts of desired product was obtained.

