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Vilsmeier–Haack reagent-promoted formyloxylation of α-chloro-*N*-arylacetamides by formamide

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Abstract

In this study, a Vilsmeier–Haack reagent-promoted formyloxylation of α-chloro-*N*-arylacetamides by formamide was developed. The reaction successfully provided the desired α-formyloxy-*N*-arylacetamides **4** and **7a**–**n** in moderate to excellent yields (70–96%) by use of 3.0 equivalents of PBr_3 at 80–90 °C and was applicable to substrates bearing electron-donating or withdrawing groups at the aryl moiety. For α-chloro-*N*-(naphthalenyl)acetamide (**8a**), α-chloro-*N*-(quinolin-8-yl)acetamide (**8b**), and α-chloro-*N*-(thiazol-2-yl)acetamide (**8c**) possessing the α-chloro group, the reaction also provided the desired formyloxylated products **9a**–**c** in 70–87% yields. A plausible mechanism was proposed through the activation of α-chloroacetamide by Vilsmeier–Haack reagent to account for the new transformation.

Introduction

In organic synthesis, formyloxylation reaction can be used to synthesize compounds with a protected hydroxyl group[1] from the corresponding alkyl halides. Use of a formate anion as the nucleophile is the conventional way to generate the desired formyloxylated product and is applicable to various substrates.[2] An alternative method is the use of amides like formamide and DMF as the formyloxy precursors through *O*-alkylation. Reaction of simple non-activated alkyl halides with formamide is reported to provide the corresponding formate ester at 140 °C.[3] If the substrates are activated, formyloxylation reaction can take place at lower temperature. For example, Dakanali et. al reported the formyloxylation of 2-bromoethylamines by DMF at 80 °C through the participation of neighboring group,[4] Abad et. al reported the use of silver salt as the catalyst to furnish the reaction at r.t. to 75 °C,[5] and Thirumamagal et. al reported the CuCN-mediated *O*-alkylation of DMF at room temperature.[6]

α-Formyloxy carbonyl compounds are important intermediates[7] for the construction of various heterocyclic compounds such as imidazopyrimidine-2,7-diones[8] and oxazoles.[9] α-Haloketones are also reported formyloxylated by formamides in the presence of copper catalyst[10] or Silphos agent [$PCl_{3-n}(SiO_2)_n$].[11] However, the scopes of the reactions are limited, no other α-halocarbonyl compound including amides and esters is reported. In our development of Vilsmeier–Haack reagent for the synthesis of heterocyclic compounds and performing functional group transformations,[12] we serendipitously found that the reagent was possible to active the α-halo group in the amide functionality toward nucleophilic substitution. In this study, we reported the formyloxylation of α-halo-*N*-arylacetamides by formamide promoted by Vilsmeier–Haack reagent. The reaction successfully provided the corresponding α-formyloxylated amide in moderate

to excellent yields. The reaction displayed the optimal results on α-chloroacetamides and was applicable to substrates with various substituents on the aryl group.

Result and discussion

To seek the optimal reaction conditions for the formyloxylation of α-halo-*N*-arylacetamides promoted by Vilsmeier–Haack reagent, compounds **1**–**3**[13] bearing α-chloro, bromo, and iodo groups served as the model substrates to react with formamide in the presence PBr_3 at 80–90 °C (Table 1). For compound **1** bearing the α-chloro group, the reaction did not take place without PBr_3, even in prolonged reaction time (64 h, see entry 1 in Table 1). When 0.20 equivalents of PBr_3 were used, the desired α-formyloxylated compound **4** was isolated in 10% yield (entry 2). Reaction of **1** with formamide in the presence of 0.50 equivalents of PBr_3 for 4.0 h gave the desired **4** in 53% yield (entry 3). Employing 1.0, 2.0 and 3.0 equivalents of PBr_3 to the reaction increased the yields of **4** to 84, 88, and 96%, respectively (entries 4–6). In these cases, a trace amount of hydrolyzed product **5** was observed. Prolongation of the reaction time to 8.0 h (data not shown) and the use of excess PBr_3 (10 equiv, entry 7) reduced the yield of **4**. As a result, reaction of α-halo-*N*-arylacetamides with formamide in the presence 3.0 equivalents of PBr_3 at 80–90 °C was chosen as the optimal reaction conditions for the following study.

Table 1

When *N*-phenylacetamide **2** possessing an α-bromo group served as the starting material, the reaction gave the desired **4** in lower yield (73%, entry 8 in Table 1) compared to that of **1** bearing an α-chloro group (96%, entry 6). Unlike the use of **1** that the major substance in the reaction other **4** was the un-reacted **1 (**entries 1–4), the major by-product was aniline resulted from the cleavage of C–N bond when **2** was used. Use of compound **3** possessing an α-iodo group as the starting material worsened the reaction, only provided the desired **4** in 9.0% yield and aniline had

become the major product. To realize the different results from the use of *N*-arylacetamides bearing different α-halo atoms, we reacted **2** and **3** with formamide without PBr_3 (entry 10 and 11). The reactions only provided aniline as the major product and no desired **4** could be isolated. Use of 0.50 equivalents of PBr_3 to **2** and **3** slightly improved the reaction, giving trace amounts of the desired **4** (entries 12 and 13). The results hinted the feasibility for the cleavage of C–N decreased in the order I > Br >> Cl in the reaction, and the cleavage was inhibited by PBr_3. Consequently, α-halo-*N*-arylacetamides bearing α-chloro group is the suitable substrate for the Vilsmeier–Haack reagent-promoted α-formyloxylation reaction.

We then turned to study the reactivity of various formamides as the formyloxy source. Employing the optimal reaction conditions to **1** with *N*-substituted formamides including *N*-methylformamide, *N*-*tert*-butylformamide, *N*,*N*-dimethylformamide, *N*,*N*-diisopropylformamide, pyrrolidine-1-carbaldehyde, and piperidine-1-carbaldehyde provided the desired α-formyloxylated compound **4** in 18–64% yields (Table 2). The yields for the use of these substituted formamides were lower than that for the use of unsubstituted formamide. As a result, formamide is the best formyloxy source for the α-formyloxylation reaction of α-chloro-*N*-arylacetamides promoted by Vilsmeier–Haack reagent.

Table 2

To explore the scope of the new formyloxylation reaction, α-chloro-*N*-arylacetamides **6a**–**n** bearing various substituents, including fluoro, bromo, trifluoromethyl, methyl, hydroxyl, methoxy, and cyano groups at the *ortho*, *meta*, or *para* position of the phenyl group were reacted with formamide in the presence of 3.0 equivalents of PBr_3 at 80–90 °C for 4.0 h (Table 3). The reaction successfully provided the desired α-formyloxylated products **7a**–**n** in 70–91% yields. In these reactions, compounds **6c**, **6f**, **6i**, and **6l** with a *para* substituent demonstrated better

yields than their *ortho* and *meta* analogs. For compounds **6n** bearing two electron-donating methoxy groups, the reaction also gave the desired **7n** in 76% yield. No formyl group was introduced to the π-excessive aryl moiety in this reaction. The results indicated that the new Vilsmeier–Haack reagent-promoted formyloxylation reaction is tolerable in substrates with these substituents at the phenyl group. All the α-formyloxy-*N*-arylacetamides **7a**–**n** were fully characterized by spectroscopic methods. For example, compound **7m** presented a singlet peak at δ 4.79 ppm for methylene group and 8.20 ppm for HC=O in ^{1}H NMR. In ^{13}C NMR spectrum, compound **7m** possessed characteristic absorptions at δ 164.57 ppm for H^{13}C=O, at δ 158.67 ppm for NH^{13}C=O, and at δ 62.26 ppm for –^{13}CH$_2$C=O. Its IR absorptions showed peaks at 1701 cm^{-1} for the stretching of –NHC=O group, 1732 cm^{-1} for the stretching of HC=O group, 2226 cm^{-1} for the stretching of–C≡N group, and at 3294 cm^{-1} for the stretching of the –NH group. Compound **7m** was further characterized by X-ray crystallography as shown in Figure 1.

Table 3

Figure 1

This new α-formyloxylation reaction was also applicable to α-chloro-*N*-(naphthalenyl)acetamide (**8a**), α-chloro-*N*-(quinolin-8-yl)acetamide (**8b**), and α-chloro-*N*-(thiazol-2-yl)acetamide (**8c**) as shown in Scheme 1**.** The reaction provided the corresponding α-formyloxylated products **9a**, **9b**, and **9c** in 86%, 87%, and 71% yields, respectively. Compounds **9a–c** were also fully characterized by spectroscopic methods. However, the α-formyloxylation reaction was limited to *N*-aryl substrates. Reaction of 2-chloro-*N*-hexylacetamide (**10**) with formamide in the presence of PBr_3 did not provide the corresponding α-formyloxylated product **11** and the starting material was recovered.

Scheme 1

Scheme 2

We proposed a plausible reaction mechanism in Scheme 3 for the formyloxylation of α-halo-*N*-arylacetamides using compound **1** as the example. As the solvent, formamide would preferentially react with PBr_3 to form the bromoiminium **12** (Vilsmeier–Haack reagent) upon heating. Reactive species **12** would acylate **1** to generate *O*-acylated intermediate **13** (X = $OCHN^+H_2$, Y = N) or bromoiminium intermediate **14** (X = Br, Y = N^+H). Species **13** and **14** might exist for the conjugation of their C=N double bond with the phenyl group would enhance the stability. For *N*-alkyl amide **10** in Scheme 2, the C=N would not form or form in little extent than its analog **1** for being not energetically favored. As a result, the C=N bond in *N*-aryl substrate might be important to progress the reaction.

It is known that the carbonyl group accelerates the S_N2 reaction at it α-carbon[14] through the interaction of its π LUMO with the transition state.[15] As a result, the displacement of the α-halo group in simple α-halocarbonyl compounds proceeds readily despite formamides are weak nucleophiles. In our case, however, the amide group was more electron-rich than carbonyl group and thus has high-lying π LUMO that provided less stabilization energy. The reaction did not take place even in prolonged reaction time (see entry 1 in Table 1). Intermediates **13** and **14** are more electron-withdrawing than the amide functionality in **1**, thus had lower-lying π LUMO that could stabilize the transition state of the S_N2 reaction.[16] The formyloxylation reaction took place smoothly to provide intermediates **15** and **16**. Subsequent hydrolysis of **15** and **16** provided the desired α-formyloxylated product **4** and by-product **5** to furnish the reaction.

Scheme 3

Conclusions

We have successfully developed a Vilsmeier–Haack reagent-promoted

formyloxylation reaction for α-chloro-*N*-arylacetamides with formamide. The reaction gave the corresponding α-formyloxylated products in good to excellent yields (70–96%). Substituents including fluoro, bromo, trifluormethyl, methyl, hydroxyl, methoxy, and cyano groups are tolerable in the reaction. A plausible reaction mechanism involving the formation of reactive iminium intermediates was proposed to account the enhanced reactivity.

Experimental Section

All chemicals were reagent grade and used as purchased. All reactions were carried out under argon or nitrogen atmosphere and monitored by TLC. Flash column chromatography was carried out on silica gel (230–400 mesh). Analytical thin-layer chromatography (TLC) was performed on precoated plates (silica gel 60 F-254) purchased from Merck Inc. Mixtures of ethyl acetate and hexanes were used as eluants. Infrared (IR) spectra were measured on a Bomem Michelson Series FT-IR spectrometer. The wavenumbers reported are referenced to the polystyrene absorption at 1601 cm^{-1}. Absorption intensities are recorded by the following abbreviations: s, strong; m, medium; w, weak. Proton NMR spectra were obtained on a Bruker (200 MHz or 500 MHz) spectrometer by use of $CDCl_3$ as solvent. Multiplicities are recorded by the following abbreviations: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; *J*, coupling constant (Hz). Carbon-13 NMR spectra were obtained on a Bruker (50 MHz or 125 MHz) spectrometer by used of $CDCl_3$ as solvent. Carbon-13 chemical shifts are referenced to the center of the $CDCl_3$ triplet (δ 77.0 ppm). High-resolution mass spectra were obtained from a JEOL JMS-HX110 mass spectrometer.

General procedure for the formyloxylation of α-chloro-*N*-arylacetamides 1, 6a–n, 8a, 8b, and 8c with formamide in the presence of PBr_3. α-Chloro-*N*-arylacetamides **1**, **6a**–**n**, **8a**, **8b**, and **8c** (~1.0 mmol, 1.0 equiv) were dissolved in formamide (2.0 mL)

and added with PBr_3 (3.0 equiv). The reaction mixture was heated at 80–90 °C for 4.0 h. The solution was added with saturate aqueous $NaHCO_3$ (15 mL) and extracted with CH_2Cl_2 (15 mL × 2). The combined organic layers were washed with saturated aqueous $NaHCO_3$ (15 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel to give the corresponding α-formyloxylated products **4**, **7a**–**n**, **9a**, and **9c** in 70–96% yields.

2-Oxo-2-(phenylamino)ethyl formate (4). Yield: 96%; yellow liquid; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 4.72 (s, 2 H, CH_2), 7.11–7.15 (m, 1 H, ArH), 7.25–7.33 (dd, *J* = 8.2, 7.8 Hz, 2 H, ArH), 7.51 (d, *J* = 8.2 Hz, 2 H, ArH), 8.02 (br, 1 H, NH), 8.14 (s, 1 H, O=C–H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 62.36, 120.19, 125.15, 129.16, 137.04, 158.80 (NC=O), 164.11 (HC=O); IR (KBr) 3298 (br, NH), 3061, 1730 (s, C=O), 1680 (s, C=O), 1163, 759 cm^{-1}; EIMS *m*/*z* 179 (M^+, 43), 120 (17), 93 (100), 92 (17), 77 (24), 65 (20), 51 (6); HRMS Calcd for $C_9H_9NO_3$: 179.0582; Found: 179.0583.

2-[(2-Fluorophenyl)amino]-2-oxoethyl formate (7a). Yield: 74%; white solids; mp 43–45 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 4.79 (s, 2 H, CH_2), 7.06–7.14 (m, 4 H, ArH), 8.20 (s, 1 H, O=C–H), 8.29 (br, 1 H, NH); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 62.31, 114.81, 115.18, 121.91, 124.75, 125.20, 125.33, 150.88, 154.97, 158.87 (NC=O), 164.29 (HC=O); IR (KBr) 3275 (br, NH), 1732 (s, C=O), 1685 (s, C=O), 1458, 1161 (C–O), 756 cm^{-1}; EIMS *m*/*z* 197 (M^+, 26), 111 (100), 83 (15), 110 (10), 57 (5); HRMS Calcd for $C_9H_8FNO_3$: 197.0488; Found: 197.0490.

2-[(3-Fluorophenyl)amino]-2-oxoethyl formate (7b). Yield: 84%; white solids; mp 46–48 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 4.75 (s, 2 H, CH_2), 6.82–6.86 (m, 1 H, ArH), 7.13–7.28 (m, 2 H, ArH), 7.44 (dd, *J* = 10.7, 3.5 Hz, 1 H, ArH), 8.02 (br, 1 H, NH), 8.17 (s, 1 H, O=C–H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 62.17, 107.44, 107.96, 111.64, 112.06, 115.40, 130.13, 130.31, 137.89, 138.10, 158.94 (NC=O), 160.41, 164.46

(HC=O), 165.29; IR (KBr) 3290 (br, NH), 1732 (s, C=O), 1681 (s, C=O), 1543, 1157 (C–O), 775 cm^{-1}; EIMS *m*/*z* 197 (M^+, 40), 138 (12), 111 (100), 110 (16), 95 (16), 84 (11), 83 (19), 57 (8); HRMS Calcd for $C_9H_8FNO_3$: 197.0488; Found: 197.0485.

2-[(4-Fluorophenyl)amino]-2-oxoethyl formate (7c). Yield: 88%; white solids; mp 49–51 °C; ^1H NMR ($CDCl_3$, 200 MHz) δ 4.76 (s, 2 H, CH_2), 6.98–7.06 (m, 2 H, ArH), 7.24–7.81 (m, 2 H, ArH), 7.81 (br, 1 H, NH), 8.19 (s, 1 H, O=C–H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 62.31, 115.80, 115.98, 122.06, 122.12, 132.51, 158.75, 158.89 (NC=O), 160.58, 164.16 (HC=O); IR (KBr) 3336 (br, NH), 2924, 1735 (s, C=O), 1681 (s, C=O), 1512, 1157 (C–O) cm^{-1}; EIMS *m*/*z* 197 (M^+, 40), 138 (12), 111 (100), 110 (16), 95 (16), 84 (11), 83 (19), 57 (8); HRMS Calcd for $C_9H_8FNO_3$: 197.0488; Found: 197.0492.

2-[(2-Bromophenyl)amino]-2-oxoethyl formate (7d). Yield: 71%; white solids; mp 49–52 °C; ^1H NMR ($CDCl_3$, 200 MHz) δ 4.80 (s, 2 H, CH_2), 6.99 (dd, *J* = 7.8, 7.2 Hz, 1 H, ArH), 7.30 (dd, *J* = 7.8, 7.2 Hz, 1 H, ArH), 7.53 (dd, *J* = 7.7, 6.0 Hz, 1 H, ArH), 8.22 (s, 1 H, O=C–H), 8.32 (dd, *J* = 7.7, 6.0 Hz, 1 H, ArH), 8.43 (br, 1 H, NH); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 62.30, 113.60, 121.84, 125.89, 128.49, 132.32, 134.49, 158.76 (NC=O), 164.25 (HC=O); IR (KBr) 3375 (br, NH), 1735 (s, C=O), 1531 (s, C=O), 1438, 1157 (C–O), 582 cm^{-1}; EIMS *m*/*z* 259 (M^+ + 2, 13), 257 (M^+, 13), 173 (57), 171 (59); HRMS Calcd for $C_9H_8BrNO_3$: 256.9688; Found: 256.9686.

2-[(3-Bromophenyl)amino]-2-oxoethyl formate (7e). Yield: 78%; yellow liquid; ^1H NMR ($CDCl_3$, 200 MHz) δ 4.75 (s, 2 H, CH_2), 7.13–7.29 (m, 1 H, ArH), 7.41 (dd, *J* = 9.8, 7.5 Hz, 2 H, ArH), 7.77 (s, 1 H, ArH), 8.17 (s, 1 H, O=C–H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 62.21, 118.59, 122.67, 123.06, 128.12, 130.41, 137.72, 158.81 (NC=O), 164.33 (HC=O); IR (KBr) 3305 (br, NH), 1732 (s, C=O), 1682 (s, C=O), 1423, 1161 (C–O), 590 cm^{-1}; EIMS *m*/*z* 259 (M^+ + 2, 8), 257 (M^+, 8), 231 (57), 229 (58), 200 (20), 198 (20), 173 (92), 171 (100); HRMS Calcd for $C_9H_8BrNO_3$: 256.9688; Found:

256.9686.

2-[(4-Bromophenyl)amino]-2-oxoethyl formate (7f). Yield: 89%; white solids; mp 47–50 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 4.73 (s, 2 H, CH_2), 7.37–7.44 (m, 4 H, ArH), 8.03 (br, 1 H, NH) 8.15 (s, 1 H, O=C–H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 62.14, 117.76, 121.71 (2 × CH), 132.04 (2 × CH), 135.57, 158.95 (NC=O), 164.38 (HC=O); IR (KBr) 3433 (br, NH), 1732 (s, C=O), 1689 (s, C=O), 1261, 1161 (C–O), 574 cm^{-1}; EIMS *m*/*z* 259 (M^+ + 2, 16), 257 (M^+, 16), 191 (100), 178 (25) , 173 (33), 171 (33), 152 (11), 91 (17); HRMS Calcd for $C_9H_8BrNO_3$: 256.9688; Found: 256.9683.

2-Oxo-2-{[2-(trifluoromethyl)phenyl]amino}ethyl formate (7g). Yield: 70%; white solids; mp 47–49 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 4.80 (s, 2 H, CH_2), 7.23–7.26 (m, 1 H, ArH), 7.57–7.63 (m, 2 H, ArH), 8.19 (s, 1 H, O=C–H), 8.20–8.24 (m, 1 H, ArH), 8.25 (br, 1 H, NH); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 62.19, 119.98, 120.20, 120.58, 120.87, 121.20, 124.08, 125.14, 126.27, 126.63, 133.08, 133.93, 158.62 (NC=O), 164.57 (HC=O); IR (KBr) 3433 (br, NH), 1712 (s, C=O), 1670 (s, C=O), 1319, 1114 (C–O), 767 cm^{-1}; EIMS *m*/*z* 247 (M^+, 32), 168 (41), 161 (100), 141 (32), 114 (11); HRMS Calcd for $C_{10}H_8F_3NO_3$:247.0456; Found: 247.0452.

2-Oxo-2-{[3-(trifluoromethyl)phenyl]amino}ethyl formate (7h). Yield: 78%; yellow liquid; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 4.79 (s, 2 H, CH_2), 7.38–7.52 (m, 2 H, ArH), 7.78–7.84 (m, 2 H, ArH), 7.98 (br, 1 H, NH); 8.20 (s, 1 H, O=C–H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 62.20, 116.79, 116.86, 121.63, 121.70, 123.18, 129.73, 130.73, 131.53, 131.82, 132.58, 132.83, 137.04, 158.78 (NC=O), 164.50 (HC=O); IR (KBr) 3425 (br, NH), 1728 (s, C=O), 1689 (s, C=O), 1161 (C–O), 1122, 698 cm^{-1}; EIMS *m*/*z* 247 (M^+, 32), 161 (100), 160 (13), 145 (15), 87 (22), 55 (37), 54 (15); HRMS Calcd for $C_{10}H_8F_3NO_3$: 247.0456; Found: 247.0455.

2-Oxo-2-{[4-(trifluoromethyl)phenyl]amino}ethyl formate (7i). Yield: 91%; white solids; mp 50–52 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 4.79 (s, 2 H, CH_2), 7.59 (d, *J* =

8.5 Hz, 2 H, ArH), 7.67 (d, *J* = 8.5 Hz, 2 H, ArH), 8.20 (s, 1 H, O=C–H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 62.32, 119.77 (2 × CH + CH), 121.43, 122.27, 122.63, 123.83, 123.07, 126.43, 126.46, 139.60, 158.67 (NC=O), 164.44 (HC=O); IR (KBr) 3441 (br, NH), 1743 (s, C=O), 1678 (s, C=O), 1539, 1165 (C–O), 740 cm^{-1}; EIMS *m*/*z* 247 (M^+, 34), 161 (100), 145 (21), 142 (12), 111 (7), 87 (13); HRMS Calcd for $C_{10}H_8F_3NO_3$: 247.0456; Found: 247.0461.

2-Oxo-2-(*p*-tolylamino)ethyl formate (7j). Yield: 89%; white solids; mp 39–41 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.30 (s, 3 H, CH_3), 4.75 (s, 2 H, CH_2), 7.13 (d, *J* = 8.3 Hz, 2 H, ArH), 7.40 (d, *J* = 8.3 Hz, 2 H, ArH), 7.77 (br, 1 H, NH), 8.18 (s, 1 H, O=C–H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 20.88, 62.30, 119.87, 120.30 (2 × CH), 129.62 (2 × CH), 134.92, 158.89 (NC=O), 164.14 (HC=O); IR (KBr) 3429 (br, NH), 1732 (s, C=O), 1678 (s, C=O), 1265, 1165 (C–O) cm^{-1}; EIMS *m*/*z* 193 (M^+, 26), 165 (18), 134 (12), 107 (100), 106 (76), 91 (23), 77 (39), 65 (18); HRMS Calcd for $C_{10}H_{11}NO_3$: 193.0739; Found: 193.0735.

2-[(4-Hydroxyphenyl)amino]-2-oxoethyl formate (7k). Yield: 87%; yellow liquid; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 4.77 (s, 2 H, CH_2), 7.09 (d, *J* = 8.8 Hz, 2 H, ArH), 7.55 (d, *J* = 8.8 Hz, 2 H, ArH), 7.84 (br, 1 H, NH), 8.19 (s, 1 H, O=C–H), 8.27 (s, 1 H, OH); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 62.29, 121.33 (2 × CH), 121.85 (2 × CH), 134.64, 158.77 (NC=O), 159.12, 164.22 (HC=O); IR (KBr) 3348.42 (br, NH + OH), 2920, 1728 (s, C=O), 1689 (s, C=O), 1192, 1165 (C–O) cm^{-1}; EIMS *m*/*z* 195 (M^+, 40), 109 (100), 108 (33), 81 (11); HRMS Calcd for $C_9H_9NO_4$: 195.0532; Found: 195.0531.

2-[(4-Methoxyphenyl)amino]-2-oxoethyl formate (7l). Yield: 91%; brown solids; mp 47–48 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 3.77 (s, 3 H, CH_3), 4.75 (s, 2 H, CH_2), 6.86 (d, *J* = 9.0 Hz, 2 H, ArH), 7.42 (d, *J* = 9.0 Hz, 2 H, ArH), 7.78 (br, 1 H, NH), 8.18 (s, 1 H, O=C–H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 55.47, 62.33, 114.28 (2 × CH), 122.11 (2 × CH), 129.50, 157.00, 158.85 (NC=O), 164.04 (HC=O); IR (KBr) 3309 (br,

NH), 1734 (s, C=O), 1668 (s, C=O), 1247, 1149 (C–O), 835 cm^{-1}; EIMS *m*/*z* 209 (M^+, 64), 123 (49), 122 (35), 113 (24), 108 (29), 91 (100), 77 (20); HRMS Calcd for $C_{10}H_{11}NO_4$:209.0688; Found: 209.0687.

2-[(4-Cyanophenyl)amino]-2-oxoethyl formate (7m). Yield: 87%; white solids; mp 50–52 °C; ^1H NMR ($CDCl_3$, 200MHz) δ 4.79 (s, 2 H, CH_2), 7.62 (d, *J* = 9.0 Hz, 2 H, ArH), 7.70 (d, *J* = 9.0 Hz, 2 H, ArH), 8.04 (br, 1 H, NH), 8.20 (s, 1 H, O=C–H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 62.26, 108.15, 118.52, 119.93 (2 × CH), 133.40 (2 × CH), 140.55, 158.67 (NC=O), 164.57 (HC=O); IR (KBr) 3294 (br, NH), 2225 (s, CN) 1732 (s, C=O), 1701 (s, C=O), 1315, 1161 (C–O) cm^{-1}; EIMS *m*/*z* 204 (M^+, 28), 119 (12), 118 (100), 117 (14), 91 (16), 90 (17); HRMS Calcd for $C_{10}H_8N_2O_3$: 204.0535; Found: 204.0537.

2-[(2,5-Dimethoxyphenyl)amino]-2-oxoethyl formate (7n). Yield: 76%; white liquid; ^1H NMR ($CDCl_3$, 400 MHz) δ 3.72 (s, 3 H, CH_3), 3.80 (s, 3 H, CH_3), 4.73 (s, 2 H, CH_2), 6.56 (dd, *J* = 11.6, 8.8 Hz, 1 H, ArH), 6.76 (d, *J* = 9.2 Hz, 1 H), 8.02 (d, *J* = 2.8 Hz, 1 H, ArH), 8.17 (s, 1 H, O=C–H), 8.43 (br, 1 H, NH); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 55.62 (OCH_3), 56.13 (OCH_3), 62.27, 106.26 (CH), 109.02 (CH), 110.68 (CH), 126.95 (C), 142.18 (C), 153.65 (C), 158.99 (NC=O), 163.90 (HC=O); IR (KBr) 3745 (br, NH), 3251, 1770 (s, C=O), 1666 (s, C=O), 1535, 1219 (C–O) cm^{-1}; EIMS *m*/*z* 239 (M^+, 70), 224 (16), 165 (11), 138 (100); HRMS Calcd for $C_{11}H_{13}NO_5$: 239.0794; Found: 239.0785.

2-(Naphthalen-1-ylamino)-2-oxoethyl formate (9a). Yield: 86%; white solids; mp 47–49 °C; ^1H NMR ($CDCl_3$, 200 MHz) δ 4.90 (s, 2 H, CH_2), 7.43–7.55 (m, 3 H, ArH), 7.71–7.90 (m, 4 H, ArH), 8.27 (s, 1 H, O=C–H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 62.75, 120.32, 121.19, 125.69, 126.23, 126.61, 126.68, 128.87, 128.89, 130.87, 134.14, 159.02 (NC=O), 164.89 (HC=O); IR (KBr) 3248 (br, NH), 1726 (s, C=O), 1666 (s, C=O), 1217, 1163 (C–O), 767 cm^{-1}; EIMS *m*/*z* 229 (M^+, 55), 179 (22), 143 (100), 115

(57), 93 (52), 77 (20); HRMS Calcd for $C_{13}H_{11}NO_3$: 229.0739; Found: 229.0734.

2-Oxo-2-(quinolin-8-ylamino)ethyl formate (9b). Yield: 87%; white solids; mp 46–48 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 4.90 (s, 2 H, CH_2), 7.47–7.56 (m, 3 H, ArH), 8.14 (d, *J* = 8.3 Hz, 1 H, ArH), 8.32 (s, 1 H, O=C–H), 8.68–8.82 (m, 2 H, ArH), 9.76 (br, 1 H, NH); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 62.61, 117.01, 121.78, 122.46, 127.29, 127.99, 136.41, 138.55, 148.56, 148.58, 159.30 (NC=O), 164.59 (HC=O); IR (KBr) 3331 (NH), 1734 (s, C=O), 1683 (s, C=O), 1153 (C–O), 788 cm^{-1}; EIMS *m*/*z* 230 (M^+, 10), 172 (17) , 171 (100), 144 (46), 135 (23), 91 (12); HRMS calcd for $C_{12}H_{10}N_2O_3$: 230.0691; Found: 230.0695.

2-Oxo-2-(Thiazolylamino)ethyl formate (9c). Yield: 71%; yellow liquid; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.90 (s, 2 H, CH_2), 7.03 (d, *J* = 3.6 Hz, 1 H), 7.47 (d, *J* = 3.6 Hz, 1 H), 8.17 (s, 1 H, O=C–H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 61.50, 114.39 (CH), 130.88 (C), 136.95 (CH), 159.07 (NC=O), 164.02 (HC=O); IR (KBr) 3745 (br, NH), 1728 (s, C=O), 1678 (s, C=O), 1276, 1161 (C–O) cm^{-1}; EIMS *m*/*z* 186 (M^+, 20), 127 (10), 100 (100), 91 (17), 73 (9), 58 (22), 55 (13); HRMS Calcd for $C_6H_6N_2O_3S$: 186.0099; Found: 186.0096.

Acknowledgments

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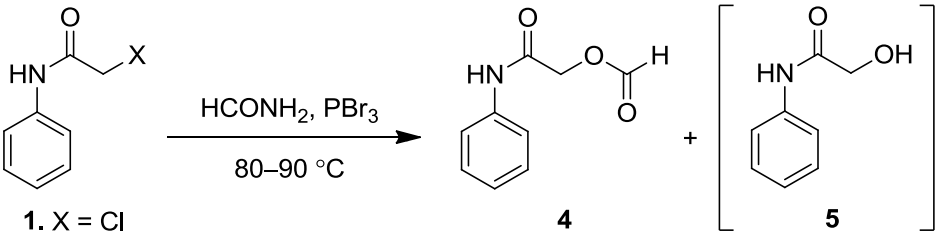
Table 1 Reaction of α-halo-*N*-arylacetamides **1**–**3** bearing α-chloro, bromo, and iodo groups with formamide in the presence of different amounts of PBr_3 at 80–90 °C

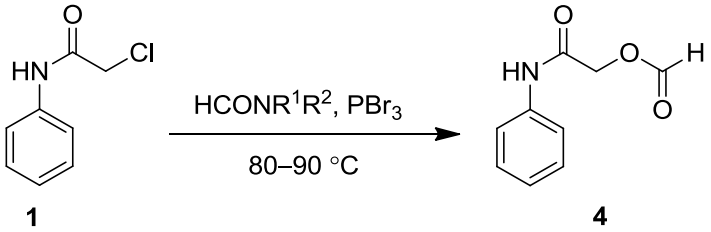


entry	*N*-arylacetamide	α-halo group	PBr_3 (equiv)	time (h)	yield of **4** (%)
1	**1**	Cl	–	64	–[a]
2	**1**	Cl	0.20	64	10
3	**1**	Cl	0.50	4.0	53
4	**1**	Cl	1.0	4.0	84
5	**1**	Cl	2.0	4.0	88
6	**1**	Cl	3.0	4.0	96
7	**1**	Cl	10	4.0	70
8	**2**	Br	3.0	4.0	73[b]
9	**3**	I	3.0	4.0	9.0[b]
10	**2**	Br	–	4.0	–[b]
11	**3**	I	–	4.0	–[b]
12	**2**	Br	0.50	4.0	trace[b]
13	**2**	I	0.50	4.0	trace[b]

[a] Recovery of starting material.

[b] Aniline was the major by-product or product.

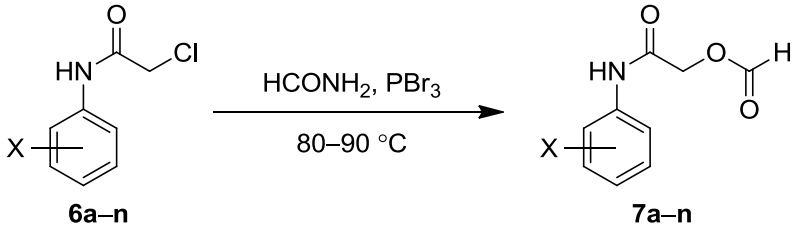
Table 2 Study of the reactivity of various formamides in the formyloxylation reaction of α-chloro-*N*-phenylacetamide (**1**) promoted by Vilsmeier–Haack reagent



1 **4**

entry	HCONR^{1}R^2		Yield of **4** (%)
	R^1	R^1	
1	H	Me	64
2	H	*t*-Bu	18
3	Me	Me	54
4	*i*-Pr	*i*-Pr	53
5	pyrrolidinyl		33
6	piperidinyl		52

Table 3 Reaction of α-chloro-*N*-arylacetamides possessing various substituents at the phenyl group with formamide in the presence of PBr_3.



6a–n **7a–n**

substrate	X	product	yield (%)
6a	*o*-F	**7a**	74
6b	*m*-F	**7b**	84
6c	*p*-F	**7c**	88
6d	*o*-Br	**7d**	71
6e	*m*-Br	**7e**	78
6f	*p*-Br	**7f**	89
6g	*o*-CF_3	**7g**	70
6h	*m*-CF_3	**7h**	78
6i	*p*-CF_3	**7i**	91
6j	*p*-Me	**7j**	89
6k	*p*-OH	**7k**	87
6l	*p*-OMe	**7l**	91
6m	*p*-CN	**7m**	87
6n	2,4-di-OMe	**7n**	76

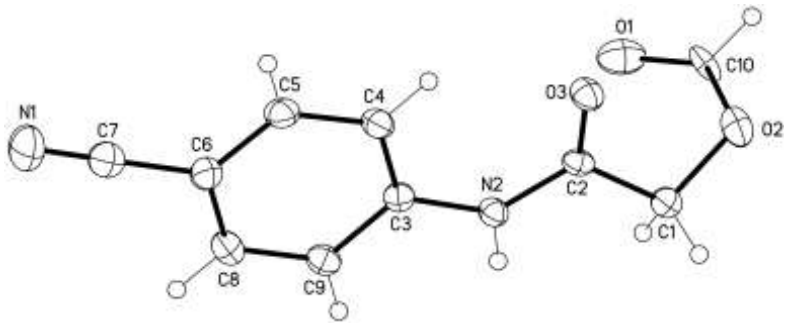
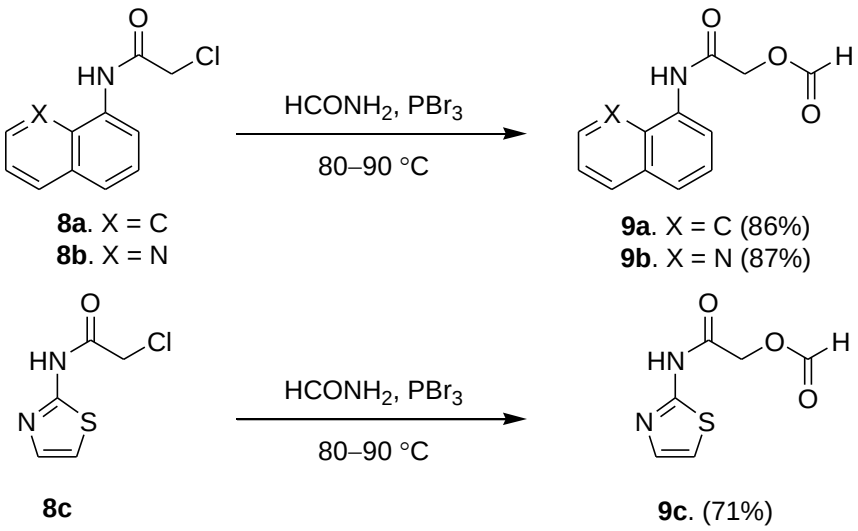
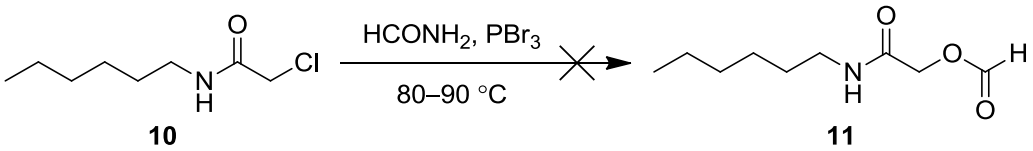


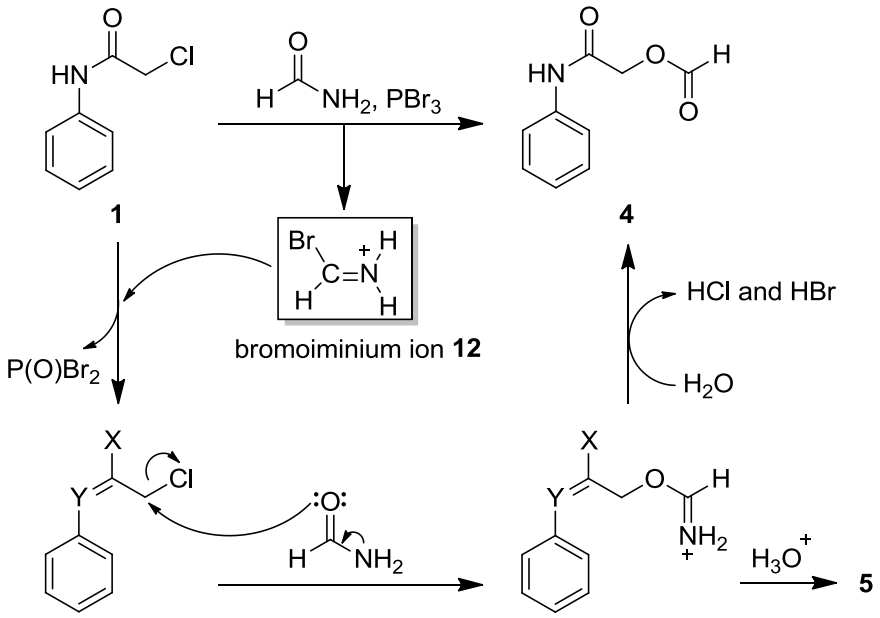
Figure 1 An ORTEP diagram of 2-formyloxy-*N*-(4-cyanophenyl)acetamide (**7m**)



Scheme 1 Formyloxylation of α-chloro-*N*-(naphthalenyl)acetamide (**8a**), α-chloro-*N*-(quinolin-8-yl)acetamide (**8b**), andα-chloro-*N*-(thiazol-2-yl)acetamide (**8c**)



Scheme 2 Formyloxylation of 2-chloro-*N*-hexylacetamide (**10**). The reaction did not provide the desired α-formyloxylation product **11** and recovery of **10** was observed.



13. X = $OCHN^+H_2$, Y = N
14. X = Br, Y = N^+H
15. X = $OCHN^+H_2$, Y = N
16. X = Br, Y = N^+H

Scheme 3 Proposed mechanism of the Vilsmeier–Haack reagent-promoted formyloxylation of α-chloro-*N*-phenylacetamide (**1**) by formamide

Graphical abstract

Vilsmeier–Haack reagent-promoted formyloxylation of α-chloro-*N*-arylacetamides by formamide

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α-formyloxylation of α-chloro-N-arylacetamides