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Visible-light-mediated radical aryltrichloromethylation of *N*-arylacrylamides for the synthesis of trichloromethyl-containing oxindoles

DOI 10.1515/hc-2015-0097
Received May 17, 2015; accepted July 18, 2015; previously published online November 5, 2015

Abstract: A practical and unified strategy has been described for the construction of trichloromethylated oxindoles *via* a visible light-promoted aryltrichloromethylation reaction of *N*-arylacrylamides with tetrachloromethane. These reactions are carried out at room temperature in good to excellent chemical yields with good functional group tolerance.

Keywords: alkenes; aryltrichloromethylation; oxindole; photoredox; radical reactions.

Introduction

Trichloromethyl functionality is widely found in organic chemistry and natural products [1–3]. The introduction of trichloromethyl group into organic framework strongly attracts synthetic pursuit of chemists because of its diverse synthetic applications and important biological properties of the substituted compounds [4, 5]. Nevertheless, up to date, methods for the synthesis of trichloromethylated oxindoles are quite rare [6–8]. Recently, Loh and co-workers reported the Fe-catalyzed coupling of *N*-arylacrylamides with dichloro- and tetrachloromethane using diaryliodonium salt as oxidant [7]. However, the drawbacks are the use of an oxidant diaryliodonium salt (2.0 equiv.) as well as the requirement of high temperature. A more concise synthesis is highly desirable.

Recently, visible-light photoredox catalysis has attracted substantial attention because of its environmental compatibility and versatility in promoting a large number of synthetically important reactions [9–12]. The visible-light-induced radical reaction of organohalides is an environmentally friendly alternative to traditional radical transformation by avoiding the use of hazardous radical initiators, and substantial achievements have been made [13–18]. Polyhalogenated alkanes, such as tetrachloromethane and bromotrichloromethane have been used as common radical precursors in various transformations leading to trichloromethyl functionalized compounds. For example, Stephenson and co-workers reported a radical addition reaction between tetrachloromethane and unfunctionalized alkenes [18]. Inspired by these results and in connection with our interest in radical cyclizations [19–22], we envisioned the synthesis of trichloromethylated oxindoles by photocatalyzed radical reaction of tetrachloromethane with *N*-arylacrylamides. This transformation allows the direct formation of a C-CCl_3 bond and the construction of a oxindole ring in one reaction.

Results and discussion

At the outset of this investigation, *N*-arylacrylamide **1a** and tetrachloromethane were chosen as the model substrates to optimize the reaction conditions. The complex [*fac*-Ir(III)$(ppy)_3$] (ppy = 2-phenylpyridine) was chosen as the photocatalyst because of its superior reduction capacity in the excited state. Irradiation of the solution of **1a** and CCl_4 in DMF with a 5 W blue LED bulb in the presence of [*fac*-Ir(III)$(ppy)_3$] and Na_2HPO_4 for 48 h at room temperature afforded the desired product **2a** in 75% yield. Using CCl_3Br as $\cdot CCl_3$ radical precursor, oxindole **2a** was isolated in 63% yield with some unidentifiable products. Other photocatalysts, such as, $[Ir(ppy)_2(dtbbpy)]PF_6$, $Ru(bpy)_3Cl_2$, eosin Y were also tested, but none of them gave better results than [fac-Ir$(ppy)_3$]. A brief screen of the bases revealed that K_2CO_3 was the best choice for the reaction. Other inorganic bases, such as Na_2CO_3, NaOAc, and $NaHCO_3$ also gave good yields of the isolated products. Indeed, the replacement of inorganic bases by an organic

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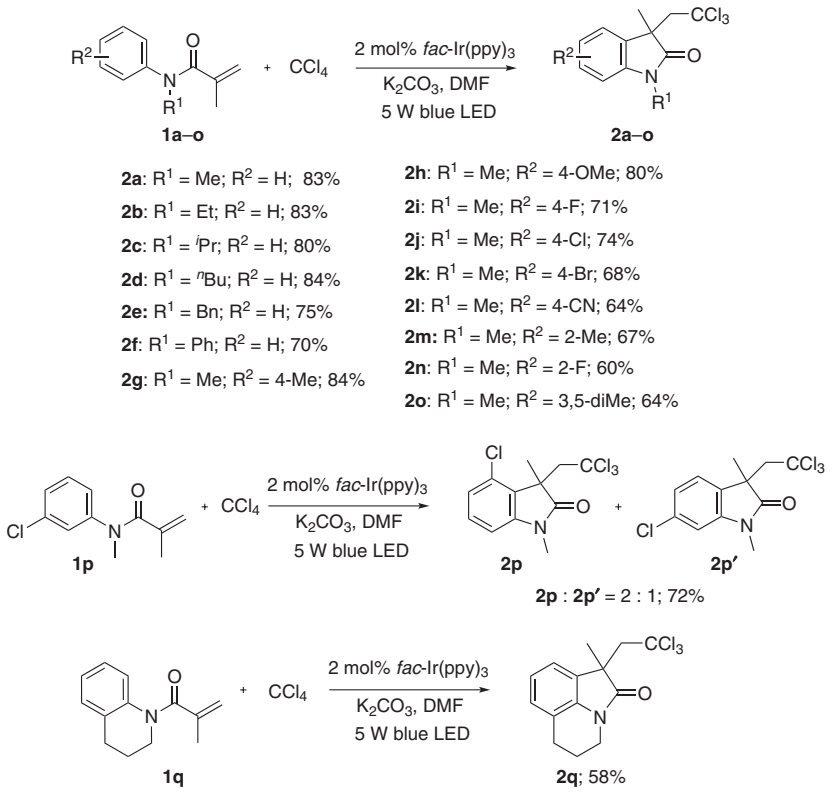

Scheme 1 Synthesis of trichloromethylated oxindoles.

base (triethylamine) had a marked effect on the reaction, affording product **2a** in only 52% yield. The reaction proceeds well in DMF and other solvents such as DMSO, CH_3CN. In the control experiments, the reaction was found to be completely restrained without the catalyst or light irradiation.

With the optimized reaction conditions in hand, we further explored the scope of trichloromethylation with a variety of *N*-arylacrylamides (Scheme 1). It was found that various *N*-protected substrates, such as ethyl, isopropyl, butyl, benzyl or phenyl could be used as effective substituent group for this transformation (**2a–f)**. Subsequently, the effect of substituents at the *N*-aryl moiety was examined. Both electron-donating and electron-withdrawing groups located in the *para*- or *ortho* position of the aromatic rings were found to be tolerated in this reaction, furnishing the corresponding oxindoles **2g–o** in moderate to good yields. *N*-arylacrylamides **2g–h** possessing electron-donating substituents gave the desired products in higher yields than the substrates **2i–l** with electron-withdrawing groups. Moreover, the procedure appears to be sensitive to steric effects. Generally, substitutents in the *para*-position on the benzene are well tolerated. By contrast, the presence of *ortho*-substituents on the benzene reduce the yields of **2m–n**. 3,5-Disubstituted *N*-arylacrylamide **1o** was also transformed into the desired product **2o** in 64% yield. Cyclization of *meta*-chloro-substituted substrates **1p** resulted in a mixture of two regioisomers in a 2:1 ratio. Additionally, good results were also obtained with tetrahydroquinoline derivative **1q** as a substrate.

Conclusions

We report a facile assembly of 3,3-disubstituted oxindoles by visible-light-promoted aryltrichloromethylation of *N*-arylacrylamides with tetrachloromethane. The reaction tolerates a wide range of functional groups.

Experimental

All reactions were performed in a 20 mL tube equipped with a rubber septum at room temperature. Photo-irradiation was carried out with a 5 W blue LED. Solvents were purified or dried in a standard manner. ^{1}H NMR spectra (400 MHz or 500 MHz), ^{13}C NMR spectra (100 MHz or 125 MHz), and ^{19}F NMR spectra were measured in $CDCl_3$.·HR-MS analyses were recorded on Q-TOF Global mass spectrometer.

General procedure for the synthesis of trichloromethylated oxindoles 2a–q

To a mixture of *N*-arylacrylamide **1** (0.30 mmol), CCl_4 (0.9 mmol), and K_2CO_3 (0.6 mmol) in 2.0 mL of DMF was added *fac*-Ir(ppy)$_3$ (0.006 mmol, 2.0 mol%) under N_2 atmosphere. The solution was stirred at room temperature and irradiated with 5 W blue LED for 48 h. Then the reaction mixture was treated with EtOAc and brine. The aqueous layer was extracted with EtOAc. The combined organic layers were dried over $MgSO_4$, filtered and concentrated. The residue was purified by flash column chromatography on silica gel eluting with petroleum ether/ethyl acetate, 10:1, to give the oxindole **2a–q**.

3-(2,2,2-Trichloroethyl)-1,3-dimethylindolin-2-one (2a) [7] Yield 83%; yellow solid; mp 103–104°C; ^{1}H NMR: δ 7.26–7.35 (m, 2H), 7.06 (t, *J* = 7.4 Hz, 1H), 6.88 (d, *J* = 7.6 Hz, 1H), 3.69 (d, *J* = 15.2 Hz, 1H), 3.34 (d, *J* = 15.2 Hz, 1H), 3.23 (s, 3H), 1.40 (s, 3H).

3-(2,2,2-Trichloroethyl)-1-ethyl-3-methylindolin-2-one (2b) [7] Yield 83%; yellow solid; mp 95–97°C; ^{1}H NMR: δ 7.36 (d, *J* = 7.6 Hz, 1H), 7.26–731 (m, 1H), 7.05 (t, *J* = 7.6 Hz, 1H), 6.89 (d, *J* = 8.0 Hz, 1H), 3.82–3.94 (m, 1H), 3.64–3.75 (m, 2H), 3.34 (d, *J* = 15.2 Hz, 1H), 1.38 (s, 3H), 1.25 (t, *J* = 7.2 Hz, 3H).

3-(2,2,2-Trichloroethyl)-1-isopropyl-3-methylindolin-2-one (2c) [7] Yield 80%; yellow solid; mp 88–90°C; ^{1}H NMR: δ 7.36 (d, *J* = 7.2 Hz, 1H), 7.25–7.30 (m, 2H), 6.98–7.04 (m, 2H), 4.59–4.69 (m, 1H), 3.69 (d, *J* = 15.2 Hz, 1H), 3.33 (d, *J* = 15.2 Hz, 1H), 1.48 (dd, *J* = 7.2, 4.4 Hz, 6H), 1.37 (s, 3H).

1-Butyl-3-(2,2,2-trichloroethyl)-3-methylindolin-2-one (2d) Yield 84%; white solid; mp 94–95°C; ^{1}H NMR: δ 7.35 (d, *J* = 8.0 Hz, 1H), 7.27–7.30 (m, 1H), 7.03–7.06 (m, 1H), 6.90 (d, *J* = 8.0 Hz, 1H), 3.63–3.79 (m, 3H), 3.35 (d, *J* = 15.6 Hz, 1H), 1.60–1.69 (m, 2H), 1.36–1.43 (m, 5H), 0.95 (t, *J* = 8.0 Hz, 3H); ^{13}C NMR: δ 178.4, 142.8, 129.7, 128.4, 125.8, 121.7, 108.6, 96.3, 59.7, 48.0, 40.1, 29.2, 27.4, 20.3, 13.8. HR-MS. Calcd for $[M+H]^+$, $C_{15}H_{19}Cl_3NO$: *m/z* 334.0533. Found: *m/z* 334.0530.

1-Benzyl-3-(2,2,2-trichloroethyl)-3-methylindolin-2-one (2e) [7] Yield 75%; white solid; mp 80–82°C; ^{1}H NMR: δ = 7.19–7.37 (m, 7 H), 7.03 (t, *J* = 7.6 Hz, 1 H), 6.82 (d, *J* = 7.6 Hz, 1 H), 4.98 (d, *J* = 15.2 Hz, 1 H), 4.88 (d, *J* = 15.2 Hz, 1 H), 3.75 (d, *J* = 15.2 Hz, 1H), 3.38 (d, *J* = 15.2 Hz, 1H), 1.45 (s, 3 H).

3-(2,2,2-Trichloroethyl)-3-methyl-1-phenylindolin-2-one (2f) Yield 70%; white solid; mp 99–101°C; ^{1}H NMR: δ 7.55 (t, *J* = 8.0 Hz, 2H), 7.42–7.46 (m, 4H), 7.26 (t, *J* = 8.0 Hz, 1H), 7.13 (t, *J* = 8.0 Hz, 1H), 6.89 (d, *J* = 8.0 Hz, 1H), 3.82 (d, *J* = 15.2 Hz, 1H), 3.46 (d, *J* = 15.2 Hz, 1H), 1.56 (s, 3H); ^{13}C NMR: δ 177.9, 143.2, 134.5, 129.7, 129.3, 128.4, 128.1, 126.3, 126.0, 122.5, 109.8, 96.3, 60.1, 48.2, 27.4. HR-MS. Calcd for $[M+H]^+$, $C_{17}H_{15}Cl_3NO$: *m/z* 354.0214. Found: *m/z* 354.0210.

3-(2,2,2-Trichloroethyl)-1,3,5-trimethylindolin-2-one (2g) [7] Yield 84%; white solid; mp 108–109°C; ^{1}H NMR: δ 7.16 (s, 1H), 7.09 (d, *J* = 8.0 Hz, 1H), 6.76 (d, *J* = 8.0 Hz, 1H), 3.67 (d, *J* = 15.2 Hz, 1H), 3.30 (d, *J* = 15.2 Hz, 1H), 3.20 (s, 3H), 2.33 (s, 3H), 1.37 (s, 3H).

3-(2,2,2-Trichloroethyl)-5-methoxy-1,3-dimethylindolin-2-one (2h) [7] Yield 80%; white solid; mp 103–105°C; ^{1}H NMR: δ 6.96 (s, 1H), 6.85 (d, *J* = 8.4 Hz, 1H), 6.78 (d, *J* = 8.0 Hz, 1H), 3.79 (s, 3H), 3.68 (d, *J* = 15.2 Hz, 1H), 3.32 (d, *J* = 15.2 Hz, 1H), 3.21 (s, 3H), 1.38 (s, 3H).

3-(2,2,2-Trichloroethyl)-5-fluoro-1,3-dimethylindolin-2-one (2i) [7] Yield 71%; white solid; mp 117–119°C; ^{1}H NMR: δ 7.09–7.12 (m, 1H), 6.99–7.04 (m, 1H), 6.78–6.81 (m, 1 H), 3.69 (d, *J* = 15.2 Hz, 1H), 3.31 (d, *J* = 15.6 Hz, 1H), 3.22 (s, 3H), 1.39 (s, 3H).

5-Chloro-3-(2,2,2-trichloroethyl)-1,3-dimethylindolin-2-one (2j) [7] Yield 74%; white solid; mp 108–110°C; ^{1}H NMR: δ 7.45 (m, 2 H), 6.78 (d, *J* = 8.4 Hz, 1H), 3.69 (d, *J* = 15.6 Hz, 1H), 3.31 (d, *J* = 15.6 Hz, 1H), 3.22 (s, 3H),1.39 (s, 3H).

5-Bromo-3-(2,2,2-trichloroethyl)-1,3-dimethylindolin-2-one (2k) [7] Yield 68%; white solid; mp 123–124°C; ^{1}H NMR: δ 7.33 (d, *J* = 1.6 Hz, 1 H), 7.28 (dd, *J* = 8.4, 1.6 Hz, 1 H), 6.80 (d, *J* = 8.4 Hz, 1 H), 3.68 (d, *J* = 15.2 Hz, 1H), 3.30 (d, *J* = 15.2 Hz, 1H), 3.21 (s, 3H), 1.39 (s, 3H).

3-(2,2,2-Trichloroethyl)-1,3-dimethyl-2-oxoindoline-5-carbonitrile (2l) [7] Yield 64%; white solid; mp 112–114°C; ^{1}H NMR: δ 7.66–7.70 (m, 2H), 6.95 (d, *J* = 8.4 Hz, 1H), 3.70 (d, *J* = 15.2 Hz, 1H), 3.37 (d, *J* = 15.2 Hz, 1H), 3.26 (s, 3H), 1.43 (s, 3H).

3-(2,2,2-Trichloroethyl)-1,3,7-trimethylindolin-2-one (2m) [7] Yield 67%; white solid; mp 90–92°C; ^{1}H NMR: δ 6.97 (d, *J* = 7.6 Hz, 2H), 6.79 (t, *J* = 8.0 Hz, 1H), 3.79 (s, 3H), 3.69 (d, *J* = 15.2 Hz, 1H), 3.31 (d, *J* = 15.2 Hz, 1H), 3.21 (s, 3H), 1.39 (s, 3H).

3-(2,2,2-Trichloroethyl)-7-fluoro-1,3-dimethylindolin-2-one (2n) [7] Yield 60%; white solid; mp 103–105°C; ^{1}H NMR: δ 6.96–7.08 (m, 3H), 3.68 (d, *J* = 15.2 Hz, 1H), 3.44 (s, 3H), 3.32 (d, *J* = 15.2 Hz, 1H), 1.39 (s, 3H).

3-(2,2,2-Trichloroethyl)-1,3,4,6-tetramethylindolin-2-one (2o) [7] Yield 64%; white solid; mp 109–111°C; ^{1}H NMR: δ 6.63 (s, 1 H), 6.54 (s, 1 H), 3.61 (d, *J* = 15.2 Hz, 1H), 3.43 (d, *J* = 15.2 Hz, 1H), 3.19 (s, 3 H), 2.38 (s, 3 H), 2.35 (s, 3 H), 1.44 (s, 3 H).

4-Chloro-3-(2,2,2-trichloroethyl)-1,3-dimethylindolin-2-one (2p) and ethyl 6-chloro-3-(2,2,2-trichloroethyl)-1,3-dimethylindolin-2-one (2p′) (2:1) Yield 72%; white solid; mp 88–90°C; ^{1}H NMR: δ 7.24–7.29 (m, 1 H), 7.27 (s, 0.5 H), 7.04 (dd, *J* = 8.0, 2.0 Hz, 0.5 H), 6.98 (d, *J* = 8.0 Hz, 1 H), 6.89 (d, *J* = 2.0 Hz, 0.5 H), 6.80 (d, *J* = 8.0 Hz, 1 H), 3.75 (d, *J* = 15.2 Hz, 1H), 3.68 (d, *J* = 15.2 Hz, 0.5 H), 3.53 (d, *J* = 15.2 Hz, 1H), 3.33 (d, *J* = 15.2 Hz, 0.5 H), 3.23 (s, 3 H), 3.22 (s, 1.5 H), 1.54 (s, 3 H), 1.38 (s, 1.5 H); ^{13}C NMR: δ 178.5, 177.0, 144.9, 144.4, 134.3, 132.4, 129.9, 127.8, 126.6, 126.5, 123.6, 121.9, 109.2, 107.0, 96.03, 96.0, 59.7, 57.5, 48.8, 47.7, 26.8, 26.78, 26.72, 22.9. HR-MS. Calcd for $[M+H]^+$, $C_{12}H_{12}Cl_4NO$: *m/z* 325.9668. Found: *m/z* 325.9662.

1-(2,2,2-Trichloroethyl)-5,6-dihydro-1-methyl-1*H*-pyrrolo[3,2,1-ij]quinolin-2(4*H*)-one (2q) Yield 58%; white solid; mp 85–86°C; ^{1}H NMR: δ 7.9 (d, *J* = 7.6 Hz, 1H), 7.04 (d, *J* = 7.6 Hz, 1H), 6.95 (t, *J* = 7.6 Hz, 1 H), 3.69 (d, *J* = 15.2 Hz, 1H), 3.33 (d, *J* = 15.2 Hz, 1H), 3.67–3.78 (m, 2H), 2.78–2.84 (m, 2H), 1.97–2.03 (m, 2H), 1.40 (s, 3 H); ^{13}C NMR: δ 177.5, 139.0, 128.1, 127.2, 123.6, 121.5, 96.4, 59.8, 49.2, 39.2, 26.7, 24.7, 21.1. HR-MS. Calcd for $[M+H]^+$, $C_{14}H_{25}Cl_3NO$: *m/z* 318.0214. Found: *m/z* 318.0212.

Acknowledgments: We are grateful to the National Natural Science Foundation of China (project nos. 21202078 and U1204205) and the Program for Innovative Research Team (in Science and Technology) at the University of Henan Province (14IRTSTHN008).

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