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CuCN-Mediated O-Alkylation of N,N,-Dimethylformamide with Alkyl Halides

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Abstract: This article reports the CuCN-mediated O-alkylation of formamide with 2-bromomethylindole. In addition, the formyloxylation products have been successfully exploited in the synthesis of novel indol-2-ylmethyl ether derivatives.

Keywords: O-Alkylation of amides, CuCN, formyloxylation, transition-metal cyanide

INTRODUCTION

The formate esters can be synthesized by O-formylation of alcohols using various formylating agents[1] including Vilsmeier–Haack reagent.[2] A more compelling alternative method for the synthesis of formate ester derivatives is via an O-alkylation of amides with alkyl halides.[3] Reports that exploit dimethylformamide (DMF) as a formate anion equivalent in the synthesis of formate ester have also been revealed.[4] CuCN is a widely renowned transition-metal cyanide in organometallic chemistry that has valuable synthetic capabilities[5] and a cascade of catalytic activities.[6] Herein we propose a method that could effectively make use of CuCN in the O-alkylation of amides with alkyl halides.

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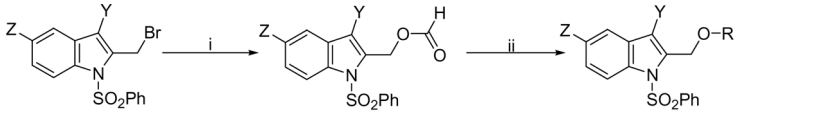
RESULTS AND DISCUSSION

Scheme 1 presents the strategies for the synthesis of the compounds of interest. Transition-metal cyanide CuCN was used in the direct O-alkylation of DMF with bromo compounds **1** and **2**, leading to the formation of formate esters **3** and **4**, respectively. Bromo compounds **1** and **2** were prepared sequentially via an allylic bromination of the corresponding methyl derivatives[7,8] using N-bromosuccinimide (NBS) in the presence of a catalytic amount of benzoyl peroxide in dry CCl_4 under reflux. Reaction of 1 equiv of bromo compound **1** with 3.5 equiv of CuCN in dry DMF followed by the conventional workup afforded formate ester **3** as a white spongy solid in 65% yield after purification. The ^{1}H NMR spectrum of formate ester **3** displayed O–CO–H and CH_2 protons as two singlets at δ 8.04 and δ 5.8, respectively, besides the aromatic protons. CuCN was also efficiently used with the other bromo compound **2** under the same reaction conditions to afford formate esters **4** in 51% yield after chromatographic purification (SiO_2) using hexanes/ethylacetate 6/4 as the eluting solvent. The utility of CuCN in the formyloxylation reaction has also been established by a plausible mechanism, which agrees with previous extensive reports,[9] although no intermediates were isolated. The fundamental role of cuprous ions has also been clearly demonstrated by the fact that the reaction was unsuccessful in the absence of cuprous cyanide as well as the fact that the bromo compounds **1** and **2** are stable in DMF.

Because there is no extensive report on the synthesis of ether derivatives **5–9**, it was therefore our interest to exploit the formate esters **3** and **4** in the synthesis of the former, which could be used as potential intermediates. The treatment of formate ester **3** in dry chloroform with thionyl



1. Z = H, Y = SPh
2. Z = H, Y = Cl
3. Z = H, Y = SPh
4. Z = H, Y = Cl
5. Z = H, Y = SPh, R = CH_3
6. Z = H, Y = SPh, R = CH_2CH_3
7. Z = H, Y = SPh, R = iso-Bu
8. Z = H, Y = SPh, R = p-Cresyl
9. Z = H, Y = Cl, R = iso-Bu

Scheme 1. CuCN-mediated synthesis of indol-2-ylmethylformate ester **3** and **4** and indol-2-ylmethyl ether derivatives **5–9**. Reagents and conditions: (i) (a) CuCN, DMF, 25–30°C, 6–10 h; (b) H_2O, yield 51–65%; (ii) $SOCl_2$, ROH, $CHCl_3$. 0–30°C, 7 h, 60–78%.

chloride followed by the addition of methanol, ethanol, isobutyl alcohol, and p-cresol at 0–30°C afforded ether derivatives **5–8** respectively in 70–78% yield after chromatographic purification (SiO_2) using hexanes/ethylacetate (8/2) as the eluting solvent. The ^1H NMR spectrum of the ether derivative **5** displayed OCH_3 and CH_2 protons as two singlets at δ 3.3 and δ 4.6 respectively, in addition to the aromatic protons. Reaction of isobutyl alcohol with other formate ester **4** under the same reaction conditions afforded ether derivative **9** in 60% yield (Scheme 1).

Though it was perceived that CuCN could be principally used in the synthesis of nitrile derivatives, for the first time our study[10] has demonstrated the utility of CuCN in the formate ester synthesis at room temperature, which in turn has opened up an effective means for the formyloxylation reactions because it is simpler than other methods. In addition, we also report a synthesis of novel indol-2-ylmethyl ether derivatives.

EXPERIMENTAL

DMF was distilled from calcium hydride and stored over molecular sieves (pore size 3 Å). Chloroform was distilled from P_2O_5 and stored over molecular sieves (pore size 4 Å). CuCN was purchased from Aldrich Chemicals. ^1H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$, and tetramethylsilane (TMS) was used as an internal standard. Merck silica gel (ACME, l00–200 mesh) was used for column chromatography. All the other reagents were purchased commercially and used as such unless stated otherwise.

Synthesis of Formate Ester Derivatives: General Procedure

Cuprous cyanide (3.5 mmol) was added to a solution of 2-bromomethylindole **1** and **2** (1 mmol) in dry DMF (10 mL) and stirred at 25–30°C for 6–10 h. The solution color was changed to green, and the course of the reaction was followed by thin-layer chromatography (TLC). The reaction mixture was poured into crushed ice. The solid obtained was filtered and washed meticulously with ethylacetate (30–40 mL). The filtrate was extracted further with ethylacetate (3×20 mL) and brine (10 mL). Both the organic layers were combined and then dried over anhydrous Na_2SO_4. Solvent removal followed by the chromatographic (SiO_2) purification and recrystallization (absolute ethanol) of the residues afforded formate esters **3** and **4** in 40–65% yield.

Spectroscopic Data of Formate Ester Derivatives

Formic acid 1-benzenesulfonyl-3-phenylsulfanyl-1H-indol-2-ylmethyl ester (**3**)

Yield 65%; mp 140–142°C; IR (KBr) cm^{-1} 1722 (C=O), 1328, 1163; ^1H NMR ($CDCl_3$) δ 5.8 (s, 2H, CH_2), 7.0–8.3 (m, 14H, aromatic), 8.04 (s, 1H, O–CO–H); ^{13}C NMR ($CDCl_3$) δ 55.8, 103.1, 115.4, 120.0, 121.2, 122.1, 125.3, 126.5, 127.4, 128.2, 129.3, 129.1, 132.6, 134.1, 135.0, 138.5, 140.5, 165.0 m/z: 423 (M^+). Anal. calcd. for $C_{22}H_{17}NO_4S_2$: C, 62.39, H, 4.05; N, 3.31. Found: C, 62.09; H, 4.13; N, 3.11.

Formic acid 1-benzenesulfonyl-3-chloro-1H-indol-2-ylmethyl ester (**4**)

Yield 51%; mp 130–133°C; IR (KBr) cm^{-1} 1726 (C=O), 1331, 1160; ^1H NMR ($CDCl_3$) δ 5.5 (s, 2H, CH_2), 7.2–7.9 (m, 9H, aromatic), 8.1 (s, 1H, O–CO–H); ^{13}C NMR ($CDCl_3$) δ 56.3, 114.1, 120.2, 121.5, 125.8, 126.4, 127.7, 128.0, 129.5, 130.8, 134.4, 138.5, 139.9, 165.0 m/z: 349 (M^+), 351 ($M+2$). Anal. calcd. for $C_{16}H_{12}ClNO_4S$: C, 54.94; H, 3.46; N, 4.00. Found: C, 54.88; H, 3.73; N, 4.12.

Synthesis of Ether Derivatives: General Procedure

Thionyl chloride (0.5 mL) was added to a solution of indol-2-ylmethylformate esters **3** and **4** (1 mmol) in dry chloroform (10 mL) and stirred at 0°C for 1 h. Further alcohol (5 mL) was added and stirred at 30°C for 6 h. The course of the reaction was followed by TLC. The excess alcohol was removed, and the reaction mixture was poured into crushed ice and extracted with chloroform (3×30 mL). The chloroform layer was dried over anhydrous Na_2SO_4 and filtered. Solvent removal followed by the chromatographic (SiO_2) purification of the residue using hexanes/ethylacetate (8/2) as the eluting solvent afforded indol-2-ylmethyl ether derivatives **5–9**.

Spectroscopic Data of Ether Derivatives

1-Benzenesulfonyl-2-methoxymethyl-3-phenylsulfanyl-1H-indole (**5**)

Viscous liquid; 75% yield; IR (KBr) cm^{-1} 1318, 1167, 1143; ^1H NMR ($CDCl_3$) δ 3.3 (s, 3H, CH_3), 4.6 (s, 2H, CH_2), 7.2–7.9 (m, 14H, aromatic);

^{13}C NMR ($CDCl_3$) δ 58.8, 66.1, 115.4, 118.0, 120.5, 125.2, 127.0, 127.1, 127.5, 128.7, 129.2, 129.3, 130.4, 130.9, 134.0, 134.4, 138.5, 141.0; *m/z*: 409 (M^+). Anal. calcd. for $C_{22}H_{19}NO_3S_2$: C, 64.52; H, 4.68; N, 3.42. Found: C, 64.43; H, 4.53; N, 3.37.

1-Benzenesulfonyl-2-ethoxymethyl-3-phenylsulfanyl-1H-indole (**6**)

Viscous liquid; 78% yield; IR (KBr) cm^{-1} 1320, 1170, 1150; ^{1}H NMR ($CDCl_3$) δ 1.09–1.12 (t, $J = 7.1$ Hz, 3H, OCH_2CH_3), 3.3–3.4 (q, $J = 7.6$ Hz, 2H, OCH_2), 4.7 (s, 2H, CH_2O), 7.2–7.8 (m, 14H, aromatic); ^{13}C NMR ($CDCl_3$) δ 14.8, 65.7, 66.9, 114.1, 118.7, 120.0, 125.2, 126.1, 127.0, 127.5, 128.4, 129.2, 129.3, 129.4, 130.4, 134.0, 134.3, 138.5, 140.7; *m/z* 423 (M^+). Anal. calcd. for $C_{23}H_{21}NO_3S_2$: C, 65.22; H, 5.00; N, 3.31. Found: C, 65.52; H, 4.73; N, 3.23.

1-Benzenesulfonyl-2-isobutoxymethyl-3-phenylsulfanyl-1H-indole (**7**)

Viscous liquid; 70% yield; IR (KBr) cm^{-1} 1329, 1161, 1148; ^{1}H NMR ($CDCl_3$) δ 0.95 [d, $J = 6.9$ Hz, 6H, $(CH_3)_2$], 1.8–1.9 (m, 1H, CH), 3.2 (d, $J = 7.0$ Hz, 2H, OCH_2), 4.6 (s, 2H, CH_2O), 7.2–7.9 (m, 14H, aromatic); ^{13}C NMR ($CDCl_3$) δ 20.0, 29.1, 65.8, 76.2, 114.3, 118.0, 120.5, 125.3, 126.9, 127.0, 128.9, 129.1, 129.2, 129.5, 130.4, 131.0, 134.0, 134.4, 138.5, 140.7; *m/z*: 451 (M^+). Anal. calcd. for $C_{25}H_{25}NO_3S_2$: C, 66.49; H, 5.58; N, 3.10. Found: C, 66.32; H, 5.23; N, 2.98.

1-Benzenesulfonyl-3-phenylsulfanyl-2-p-tolyloxymethyl-1H-indole (**8**)

Mp 130–132°C; 72% yield; IR (KBr) cm^{-1} 1321, 1180, 1153; ^{1}H NMR ($CDCl_3$) δ 2.2 (s, 3H, CH_3), 5.3 (s, 2H, CH_2), 6.8–7.8 (m, 18H, aromatic); ^{13}C NMR ($CDCl_3$) δ 21.0, 65.2, 107.6, 116.2, 118.0, 120.5, 125.2, 125.7, 126.1, 126.7, 127.1, 127.8, 128.0, 128.3, 129.0, 129.4, 130.1, 131.6, 134.1, 135.0, 138.5, 141.0, 156.0; *m/z* 485 (M^+). Anal. calcd. for $C_{28}H_{23}NO_3S_2$: C, 69.25; H, 4.77; N, 2.88. Found: C, 69.02; H, 4.67; N, 2.35.

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