Research Article

Facile Access to Aldol Products from Aromatic and Heteroaromatic Aldehydes Using Ruthenium Catalyst

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A new method for the synthesis of aldol products is described. The reaction of aromatic and heteroaromatic aldehydes with 1-(thiophen-2-yl)ethanone in the presence of ruthenium chloride hydrate combined with ligand provided the related aldol adducts, in a short time at room temperature in good yields (77–84%).

1. Introduction

Lewis acid catalyzed reactions belong to one of the most powerful methods in modern synthetic chemistry. Among the many Lewis acids developed so far, ruthenium has received growing attention because of the unique combinations of their strong Lewis acidity mixed with mildness and usually high selectivity [1–3]. On the other hand, there has been great demand to develop one-pot procedures for successive reactions for the formation of several C–C bonds. The aldol reaction is generally regarded as one of the most powerful and efficient C–C bond forming reactions [4–6]. Aldol reactions can be catalyzed by bases. The reactions catalyzed by bases are not easily controlled, and the dehydration of the product is often unavoidable [7]. Organic molecules have also been used as the catalysts. However the byproduct from dehydration was still existed. Therefore, many efforts have been devoted to the development of catalytic aldol reactions [8–12].

In this research, cross-aldol reactions were carried out in a one-pot reaction by mixing the reaction components at room temperature. In the presence of catalytic quantities of $\text{RuCl}_3 \cdot n\text{H}_2\text{O}$ with triphenylphosphine, the reaction of 1-(thiophen-2-yl)ethanone with aldehydes resulted aldol adducts in good yields without the formation of any side product. Although a large number of catalytic and organocatalytic reactions exist, this work adds new

knowledge to the field because to the best of our knowledge Ru^{III} combined with ligand had never been used as a catalyst in catalytic cross aldol reactions of 1-(thiophen-2-yl)ethanone with aromatic and heteroaromatic aldehydes.

2. Results and Discussion

As part of our continuing studies toward ruthenium catalyzed aldol reactions [13], it was found that Ru^{III} in the presence of triphenylphosphine would be a more suitable catalyst for the mild formation of aldol adducts. In this method, the aldol products produced a shorter reaction times and simple experimental procedures. On the other hand, amount of PPh_3 ligand used in this work was lower than when Ru^{II} [14] was used. Here we report our new findings on the application of this catalytic system for the synthesis of aldol products at room temperature.

At the outset of this research, in order to optimize the reaction condition, the reaction of 1-(thiophen-2-yl)ethanone **1** (3 mmol) and 4-(Methylthio)benzaldehyde **2a** (1 mmol) as model substrates, in the presence of ruthenium chloride hydrate in dioxane (1 mL) at room temperature was carried out and the effect of PPh_3 to Ru mole ratio on the aldolization was studied (Table 1). Among the catalytic systems examined, commercial ruthenium trichloride hydrate was an efficient catalyst (Table 1, entry 1), but the yield

TABLE 1: Effect of the molar ratio of PPh_3 to $\text{RuCl}_3 \cdot n\text{H}_2\text{O}$ on the synthesis of aldol products.

Reaction conditions

Entry ^a	Catalyst (0.019 mmol)	Temp. (°C)	Time (h)	Yield (%) ^b
1	$\text{RuCl}_3 \cdot n\text{H}_2\text{O}$	RT	3	55
2	$\text{RuCl}_3 \cdot n\text{H}_2\text{O} + \text{PPh}_3$	RT	4	67
3	$\text{RuCl}_3 \cdot n\text{H}_2\text{O} + 2\text{PPh}_3$	RT	3	70
4	$\text{RuCl}_3 \cdot n\text{H}_2\text{O} + 3\text{PPh}_3$	RT	3	82
5	$\text{RuCl}_3 \cdot n\text{H}_2\text{O} + 4\text{PPh}_3$	RT	3	72
6	$\text{RuCl}_3 \cdot n\text{H}_2\text{O} + 5\text{PPh}_3$	RT	3	77
7	$\text{RuCl}_3 \cdot n\text{H}_2\text{O} + 6\text{PPh}_3$	RT	4	79
8	$\text{RuCl}_3 \cdot n\text{H}_2\text{O} + 3\text{PPh}_3$	Reflux	5.5	62
9	$\text{RuCl}_3 \cdot n\text{H}_2\text{O} + 6\text{PPh}_3$	80	5.5	76
10	$\text{RuCl}_3 \cdot n\text{H}_2\text{O} + 6\text{PPh}_3$	Reflux	6	65

^aAll products were characterized by ^1H NMR, ^{13}C NMR, and IR data. ^bYields after purification by chromatography.

R: 4-MeSC₆H₄, 3-methylthiophen-2-yl, 5-methylthiophen-2-yl, thiophen-2-yl, furan-2-yl, 4-MeOC₆H₄, 4-MeC₆H₄, 2-MeOC₆H₄, C₆H₅

SCHEME 1: Ruthenium-catalyzed cross-aldol reaction using $\text{RuCl}_3 \cdot n\text{H}_2\text{O}/3\text{PPh}_3$ (**3a-i**).

of **3a** could be greatly increased by adding PPh_3 . Addition of an equal amount of PPh_3 ligand with the $\text{RuCl}_3 \cdot n\text{H}_2\text{O}$ enhanced the catalytic activity to give **3a** in yield of 67% (Table 1, entry 2). Moreover, when the amount of PPh_3 was increased to 0.057 mmol (Table 1, entry 4), the formation of the **3a** became the predominant product and no byproduct was detected. On the other hand, more addition of PPh_3 ligand did not improve the reaction. Thus, PPh_3 to Ru ratio was kept at 3 in the following experiments.

Therefore, when aldehydes (1 mmol), $\text{RuCl}_3 \cdot n\text{H}_2\text{O}$ (0.019 mmol), PPh_3 (0.057 mmol), and 1-(thiophen-2-yl)ethanone (3 mmol) were added at room temperature in dioxane (1 mL) (Scheme 1), the aldol products **3a-i** were generated within (3-4 hours) (Table 2).

Considering the results described above, the most plausible mechanism is illustrated in Scheme 2. The mechanism involves activation of the substrates within the coordination sphere of the metal.

3. Conclusions

Prompted by our findings and intrigued by diverse reactivities of ruthenium compounds [15–18], we have found that the coupling of aldehydes with 1-(thiophen-2-yl)ethanone is achieved in a short time under the influence of $\text{RuCl}_3 \cdot n\text{H}_2\text{O}$ combined with PPh_3 to give aldol products in good yields. We were pleased to find that catalytic amounts of ruthenium at room temperature cleanly produced aldol products. More importantly, there was no side product produced and the estimated molar waste was small.

4. Experimental

4.1. General Methods. All solvents, organic, and inorganic compounds were purchased from Merck and used without further purification. All reactions were followed by TLC with detection by UV light.

TABLE 2: Ruthenium-catalyzed cross-aldol reaction in the presence of $\text{RuCl}_3 \cdot n\text{H}_2\text{O}/3\text{PPh}_3$ (**3a–i**).

Entry ^a	Aldehyde	Product	Time (h)	Yield (%) ^b
1	4-(Methylthio)benzaldehyde	3a	3	82
2	3-Methylthiophen-2-carbaldehyde	3b	3.5	78
3	5-Methylthiophen-2-carbaldehyde	3c	4	80
4	Thiophen-2-carbaldehyde	3d	3.5	84
5	Furan-2-carbaldehyde	3e	3.5	77
6	4-Methoxybenzaldehyde	3f	3	80
7	4-Methylbenzaldehyde	3g	3.5	81
8	2-Methoxybenzaldehyde	3h	3.5	77
9	Benzaldehyde	3i	3	83

^aAll products were characterized by ^1H NMR, ^{13}C NMR, and IR data. ^bYields after purification by chromatography.

SCHEME 2: Proposed mechanism for ruthenium-catalyzed aldol reactions.

IR spectra were recorded on Shimadzu FTIR-8400S spectrometer. ^1H NMR spectra were obtained on a Bruker DRX-500 Avance spectrometer, and ^{13}C NMR were obtained on a Bruker DRX-125 Avance spectrometer. Samples were analyzed in CDCl_3 , and the chemical shift values are reported in ppm relative to (tetramethylsilane) TMS as the internal reference. Elemental analyses were made by a Carlo-Erba EA1110 CHNO-S analyzer and agreed with the calculated values. The isolation of pure products was carried out via preparative thin layer chromatography (silica gel 60 GF₂₅₄, Merck).

Excess of solvent was evaporated under reduced pressure at a bath temperature of 50 and 60 °C.

4.2. Typical Experimental Procedure for Synthesis of Aldol Products (3a–i). A mixture of aldehyde (1 mmol), 1-(thiophen-2-yl)ethanone (3 mmol), $\text{RuCl}_3 \cdot n\text{H}_2\text{O}$ (4 mg, 0.019 mmol), and PPh_3 (15 mg, 0.057 mmol) in dioxane (1 mL) was stirred at room temperature and monitored

by TLC. After the indicated reaction time (Table 2), the reaction mixture was purified by thin layer chromatography (EtOAc/petroleum ether 1:4 v/v), providing the aldol adduct. In this method, no other products were observed.

3-Hydroxy-3-(4-(methylthio)phenyl)-1-(thiophen-2-yl)propan-1-one (3a): yellow oil, IR (neat): 3400, 2920, 1700, 1645, 1465 cm^{-1} . ^1H NMR (500 MHz, CDCl_3): δ 2.53 (m, 3H), 3.30 (dd, $J = 16.0, 6.9$ Hz, 1H), 3.43 (dd, $J = 16.0, 6.9$ Hz, 1H), 3.57 (d, $J = 3.0$ Hz, OH), 5.33 (m, 1H), 7.41–7.14 (m, 4H), 7.79–7.65 (m, 3H) ppm. ^{13}C NMR (125 MHz, CDCl_3): δ 16.4, 45.7, 70.3, 127.3, 127.5, 128.4, 128.6, 132.6, 133.1, 134.2, 144.6 and 214.2 ppm. (Found: C, 60.42; H, 5.07; S, 23.03. Calc. for $\text{C}_{14}\text{H}_{14}\text{O}_2\text{S}_2$: C, 60.43; H, 5.03; S, 23.02%.)

3-Hydroxy-3-(3-methylthiophen-2-yl)-1-(thiophen-2-yl)propan-1-one (3b): yellow oil, IR (neat): 3578, 3118, 2965, 1674, 1564, 1465 cm^{-1} . ^1H NMR (500 MHz, CDCl_3): δ 2.40 (s, 3H), 3.45 (m, 2H), 4.01 (d, $J = 3.4$ Hz, OH), 5.30 (m, 1H), 6.70 (d, $J = 3.3$ Hz, 1H), 6.87 (d, $J = 3.3$ Hz, 1H), 7.21 (m, 1H), 7.72 (d, $J = 4.8$ Hz, 1H) and 7.81 (d, $J = 3.7$ Hz, 1H) ppm. ^{13}C NMR (125 MHz, CDCl_3): δ 15.9, 52.4, 67.5, 125.3, 125.9, 128.6, 134.7, 135.5, 138.6, 141.7, 142.0 and 192.1 ppm. (Found: C, 57.16; H, 4.80; S, 25.40. Calc. for $\text{C}_{12}\text{H}_{12}\text{O}_2\text{S}_2$: C, 57.14; H, 4.76; S, 25.39%.)

3-Hydroxy-3-(5-methylthiophen-2-yl)-1-(thiophen-2-yl)propan-1-one (3c): yellow oil, IR (neat): 3589, 3088, 2960, 1675, 1575, 1466 cm^{-1} . ^1H NMR (500 MHz, CDCl_3): δ 2.51 (s, 3H), 3.48 (m, 2H), 3.59 (d, $J = 3.5$ Hz, OH), 5.50 (m, 1H), 6.66 (d, $J = 3.3$ Hz, 1H), 6.86 (d, $J = 3.3$ Hz, 1H), 7.20 (m, 1H), 7.74 (d, $J = 4.9$ Hz, 1H) and 7.79 (d, $J = 3.7$ Hz, 1H) ppm. ^{13}C NMR (125 MHz, CDCl_3): δ 15.7, 50.2, 68.9, 125.6, 126.4, 128.4, 133.3, 134.5, 138.5, 141.5, 141.8 and 192.0 ppm. (Found: C, 57.18; H, 4.80; S, 25.41. Calc. for $\text{C}_{12}\text{H}_{12}\text{O}_2\text{S}_2$: C, 57.14; H, 4.76; S, 25.39%.)

3-Hydroxy-1,3-di(thiophen-2-yl)propan-1-one (3d): yellow oil, IR (neat): 3400, 3095, 2925, 1651, 1601, 1515, 1413 cm^{-1} . ^1H NMR (500 MHz, CDCl_3): δ 3.41 (dd, $J = 16.0, 6.0$ Hz, 1H), 3.53 (dd, $J = 16.0, 6.0$ Hz, 1H), 3.54 (d, $J = 3.5$ Hz, OH), 4.45 (m, 1H), 6.95–6.91 (m, 2H), 7.17 (m, 2H), 7.67 (m, 1H) and 7.81 (m, 1H) ppm. ^{13}C NMR (125 MHz, CDCl_3): δ 50.2, 69.0, 125.4, 126.1, 126.6, 128.6, 133.3, 134.5, 141.9, 142.9 and 192.2 ppm. (Found: C, 55.50; H, 4.24; S, 26.92. Calc. for $\text{C}_{11}\text{H}_{10}\text{O}_2\text{S}_2$: C, 55.46; H, 4.20; S, 26.89%.)

3-(Furan-2-yl)-3-hydroxy-1-(thiophen-2-yl)propan-1-one (**3e**): yellow oil, IR (neat): 3400, 3382, 2925, 1656, 1517, 1465 cm^{-1} . ^1H NMR (500 MHz, CDCl_3): δ 3.40 (dd, J = 16.0, 6.0 Hz, 1H), 3.47 (dd, J = 16.0, 6.0 Hz, 1H), 3.70 (d, J = 3.5 Hz, OH), 4.21 (m, 1H), 6.12 (m, 1H), 6.27 (m, 1H), 7.32–7.15 (m, 2H), 7.67 (m, 1H) and 7.82 (m, 1H) ppm. ^{13}C NMR (125 MHz, CDCl_3): δ 47.5, 63.2, 105.8, 110.0, 128.5, 133.3, 134.2, 141.5, 141.8, 152.8 and 192.2 ppm. (Found: C, 59.43; H, 4.54; S, 14.43. Calc. for $\text{C}_{11}\text{H}_{10}\text{O}_3\text{S}$: C, 59.45; H, 4.50; S, 14.41%.)

3-Hydroxy-3-(4-methoxyphenyl)-1-(thiophen-2-yl)propan-1-one (**3f**): yellow oil, IR (neat): 3450, 2925, 1700, 1635, 1455 cm^{-1} . ^1H NMR (500 MHz, CDCl_3): δ 3.55 (m, 3H), 3.33 (dd, J = 16.0, 6.8 Hz, 1H), 3.40 (dd, J = 16.0, 6.8 Hz, 1H), 3.56 (d, J = 3.1 Hz, OH), 5.38 (m, 1H), 7.45–7.15 (m, 4H), 7.83–7.67 (m, 3H) ppm. ^{13}C NMR (125 MHz, CDCl_3): δ 42.7, 50.3, 70.3, 117.3, 117.5, 128.6, 128.7, 132.6, 133.1, 134.2, 154.6 and 214.1 ppm. (Found: C, 64.14; H, 5.31; S, 12.25. Calc. for $\text{C}_{14}\text{H}_{14}\text{O}_3\text{S}$: C, 64.12; H, 5.34; S, 12.21%.)

3-Hydroxy-1-(thiophen-2-yl)-3-*p*-tolylpropan-1-one (**3g**): yellow oil, IR (neat): 3450, 2925, 1700, 1635, 1455 cm^{-1} . ^1H NMR (500 MHz, CDCl_3): δ 3.50 (m, 3H), 3.30 (dd, J = 16.0, 6.8 Hz, 1H), 3.49 (dd, J = 16.0, 6.8 Hz, 1H), 2.50 (s, OH), 5.29 (m, 1H), 7.41–7.25 (m, 4H), 7.80–7.66 (m, 3H) ppm. ^{13}C NMR (125 MHz, CDCl_3): δ 42.7, 50.3, 70.3, 117.3, 117.5, 128.6, 128.7, 132.6, 133.1, 134.2, 154.6 and 214.1 ppm. (Found: C, 68.28; H, 5.73; S, 13.02. Calc. for $\text{C}_{14}\text{H}_{14}\text{O}_2\text{S}$: C, 68.29; H, 5.69; S, 13.00%.)

3-Hydroxy-3-(2-methoxyphenyl)-1-(thiophen-2-yl)propan-1-one (**3h**): yellow oil, IR (neat): 3452, 2935, 1700, 1615, 1445 cm^{-1} . ^1H NMR (500 MHz, CDCl_3): δ 3.55 (m, 3H), 3.31 (dd, J = 16.0, 6.8 Hz, 1H), 3.44 (dd, J = 16.0, 6.8 Hz, 1H), 3.54 (d, J = 3.2 Hz, OH), 5.35 (m, 1H), 7.46–7.12 (m, 4H), 7.81–7.69 (m, 3H) ppm. ^{13}C NMR (125 MHz, CDCl_3): δ 42.9, 55.3, 72.3, 117.1, 117.4, 128.6, 128.7, 132.6, 133.3, 134.2, 154.5 and 214.2 ppm. (Found: C, 64.11; H, 5.32; S, 12.23. Calc. for $\text{C}_{14}\text{H}_{14}\text{O}_3\text{S}$: C, 64.12; H, 5.34; S, 12.21%.)

3-Hydroxy-3-phenyl-1-(thiophen-2-yl)propan-1-one (**3i**): yellow oil, IR (neat): 3460, 2950, 1700, 1625, 1475 cm^{-1} . ^1H NMR (500 MHz, CDCl_3): δ 3.35 (dd, J = 16.0, 6.8 Hz, 1H), 3.45 (dd, J = 16.0, 6.8 Hz, 1H), 2.50 (s, OH), 4.80 (m, 1H), 7.25–7.19 (m, 5H), 7.59–7.20 (m, 3H) ppm. ^{13}C NMR (125 MHz, CDCl_3): δ 42.9, 72.3, 117.1, 117.4, 128.6, 128.7, 132.6, 133.3, 134.2, 154.5 and 214.2 ppm. (Found: C, 67.28; H, 5.18; S, 13.80. Calc. for $\text{C}_{13}\text{H}_{12}\text{O}_2\text{S}$: C, 67.24; H, 5.17; S, 13.79%.)

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