Efficient synthesis of β-substituted α-chloro enones by rhodium(ii)-catalyzed reactions of cyclic diazodicarbonyl compounds with acid chlorides

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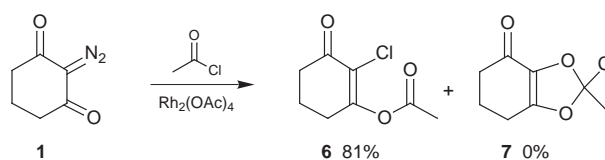
An efficient synthesis of α-chloro α,β-enones is achieved by rhodium(ii)-catalyzed reaction of cyclic diazodicarbonyl compounds with a variety of acid chlorides in good yield.

α-Halo enones have been widely used as valuable and versatile intermediates in the synthesis of α-carbon substituted enones[1] and biologically active natural products.[2] There are many convenient methods available for the preparation of α-bromo and α-iodo enones.[3] However, these procedures are not suitable for the preparation of α-chloro enones. α-Chloro enones are typically prepared by an addition–elimination reaction of enones with PhSCl,[4] ring opening of dichlorocyclopropane with aq. AcOH,[5] and oxidative chlorination of enones with HCl/MCPBA/DMF.[6] Although several methods for the synthesis of these compounds have been developed, their synthetic exploitation has been limited by the difficulties in handing the required strong acidic conditions, and side reactions involving overoxidation. The necessity for overcoming these serious problems has prompted a search for new methods for the preparation of α-chloro enones.

We have been interested in rhodium-catalyzed reactions of diazodicarbonyl compounds with several substrates.[7] Recently, the rhodium-catalyzed reaction of diazocarbonyl compounds with furans, pyrroles, alkynes and nitriles has been widely studied by several groups.[8] However, the rhodium-catalyzed reaction of diazocarbonyl compounds with acid halides has not been investigated. We report here a new and efficient synthesis of β-substituted α-chloro enones utilizing rhodium(ii)-catalyzed reactions of cyclic diazodicarbonyl compounds with a variety of acid chlorides.

The strategy that we have developed begins with the reaction of cyclic diazodicarbonyl compounds **1–5** and acid chlorides (ten-fold excess), which serve as a solvent and a reactant, in the presence of 1 mol% of Rh₂(OAc)₄, as shown in Scheme 1.
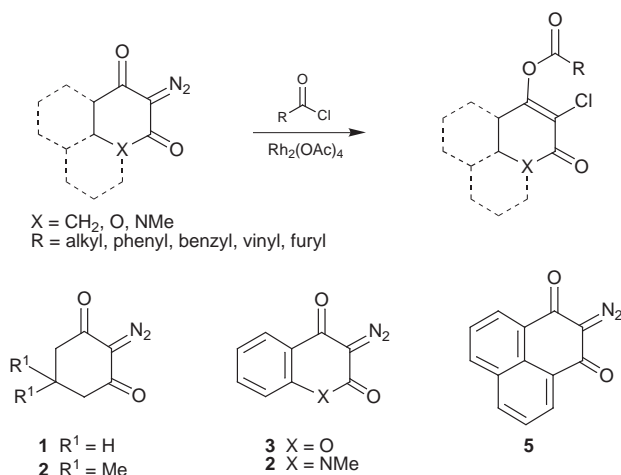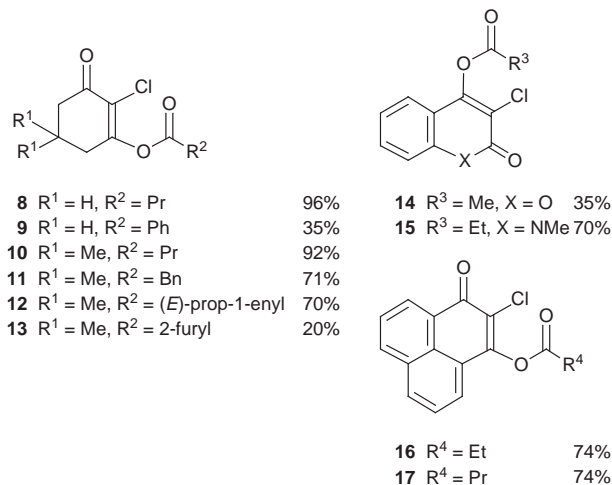
Treatment of 2-diazocyclohexane-1,3-dione **1** with AcCl at room temperature for 3 h gave the 3-acetoxy-2-chlorocyclohex-2-enone **6** in 81% yield, without a trace of expected 1,3-dioxole

X = CH₂, O, NMe
R = alkyl, phenyl, benzyl, vinyl, furyl

1 R¹ = H
2 R¹ = Me

3 X = O
2 X = NMe

5

Scheme 1

6 81%   **7** 0%

Scheme 2

7 (Scheme 2).[9] Support for the structural assignment comes from spectroscopic analysis. The enone **6** is identified by the IR carbonyl absorptions of the enone at 1693 cm⁻¹ and the vinyl ester at 1777 cm⁻¹, and the ¹H NMR peak of the methyl group of the vinyl acetate as a singlet at δ 2.26. Further support for the structural assignment of **6** is obtained from its ¹³C NMR spectrum, which clearly shows the expected eight carbons, including the two carbonyl carbons of the enone at δ 191.31 and the vinyl ester at δ 166.15.

Reaction of diazodicarbonyl compounds **1** and **2** with a range

8 R¹ = H, R² = Pr   96%
9 R¹ = H, R² = Ph   35%
10 R¹ = Me, R² = Pr   92%
11 R¹ = Me, R² = Bn   71%
12 R¹ = Me, R² = (*E*)-prop-1-enyl   70%
13 R¹ = Me, R² = 2-furyl   20%

14 R³ = Me, X = O   35%
15 R³ = Et, X = NMe   70%

16 R⁴ = Et   74%
17 R⁴ = Pr   74%

of acid chlorides gave compounds **8–13**. In all cases, only a single product was seen. In particular, reaction of diazodicarbonyl compound **2** with crotonyl chloride gave the enone **12** in 70% yield. In this reaction, no addition product to the C=C bond could be detected. Reaction of diazodicarbonyl compounds **2** and **3** with acid chlorides such as PhCOCl, 2-furoyl chloride and AcCl gave the expected enone **9** (35%), **13** (20%) and **14** (35%) in low yields. This is likely to be due to the instability of products. Importantly, our result is in clear contrast to that of Alonso who reported that the copper(ii)-catalyzed reaction of acyclic methyl 2-diazo-3-oxobutyrate with carbonyl compounds such as aldehydes or ketones afforded 1,3-dioxole adducts in moderate yields.[9]

In order to extend the utility of this methodology, reactions of more complex diazodicarbonyl compounds **3–5** with acid chlorides were examined. In these cases, only a single product was also detected. In particular, there is no direct precedent for Rh^II-catalyzed reactions of diazodicarbonyl compounds **3–5**

Scheme 3
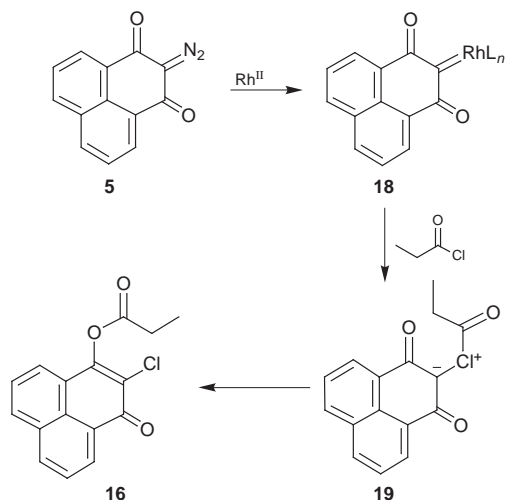
with other substrates such as alkenes, alkynes, furans, and carbonyl compounds, so it is noteworthy that reaction of **3–5** with acid chlorides give the α-chloro enone **14–17** in 35–74% yields.

Although the exact mechanism of the reaction is still not clear, it is best described as shown in Scheme 3. The diazodicarbonyl compound **5** first gives a carbenoid **18** (or a carbene) by displacement of nitrogen by $Rh_2(OAc)_4$. Nucleophilic addition of acid chloride to the electrophilic carbenoid **18** yields an ylide **19**, which subsequently undergoes intramolecular nucleophilic addition of oxygen to the carbonyl group and the cleavage of the acyl–Cl bond to give product **16**.

In conclusion, rhodium-catalyzed reaction of cyclic diazodicarbonyl compounds with a variety of acid chlorides offers a simple and facile method for the synthesis of α-chloro α,β-unsaturated ketones. Further application of this reaction will be investigated, and is now in progress in our laboratory.

Notes and references

† *Selected data* for **6**: δ_H(300 MHz, CDCl$_3$) 2.67 (2H, t, *J* 6.2), 2.59 (2H, dd, *J* 6.1, 5.1), 2.26 (3H, s), 2.06 (2H, m); δ_C(75 MHz, CDCl$_3$) 191.31, 166.15, 164.31, 121.97, 37.21, 29.84, 20.58, 20.13; ν_{max}(neat)/cm^{-1} 2959, 1777, 1693, 1630, 1427, 1371, 1352, 1281, 1169, 1065, 1007, 968, 912, 873, 845. For **12**: mp 59–60 °C; δ_H(300 MHz, CDCl$_3$) 7.18 (1H, m), 5.95 (1H, d, *J* 15.5), 2.58 (2H, s), 2.46 (2H, s), 1.95 (3H, d, *J* 7.0), 1.11 (6H, s); ν_{max}(neat)/cm^{-1} 3370, 2962, 2878, 1742, 1694, 1653, 1624, 1460, 1443, 1414, 1372, 1343, 1314, 1296, 1283, 1196, 1150, 1098, 1026, 1009, 970, 945, 833, 750. For **14**: mp 167–168 °C; δ_H(300 MHz, CDCl$_3$) 7.59 (1H, dd, *J* 8.2, 7.5), 7.49 (1H, d, *J* 7.8), 7.39 (1H, d, *J* 8.2), 7.34 (1H, dd, *J* 7.8, 7.5), 2.49 (3H, s); ν_{max}(neat)/cm^{-1} 3109, 3071, 3045, 1784, 1730, 1620, 1566, 1493, 1453, 1356, 1281, 1200, 1173, 1138, 1090, 1038, 1015, 1001, 903, 777 734. For **15**: mp 134–135 °C; δ_H(300 MHz, CDCl$_3$) 7.61 (1H, dd, *J* 8.2, 7.2), 7.58 (1H, d, *J* 7.3), 7.41 (1H, d, *J* 8.2), 7.28 (1H, dd, *J* 7.3, 7.2), 3.79 (3H, s), 2.79 (2H, q, *J* 7.5), 1.36 (3H, t, *J* 7.5); ν_{max}(neat)/cm^{-1} 2988, 2946, 2922, 1772, 1653, 1624, 1601, 1501, 1306, 1182, 1113, 1074, 1001, 972, 882, 866. For **16**: mp 146–147 °C; δ_H(300 MHz, CDCl$_3$) 8.69 (1H, d, *J* 7.5), 8.21 (1H, d, *J* 8.0), 8.30 (1H, d, *J* 8.3), 7.84 (1H, d, *J* 7.4), 7.76 (1H, dd, *J* 8.0, 7.6), 7.61 (1H, dd, *J* 8.3, 7.4); ν_{max}(neat)/cm^{-1} 2963, 2932, 2874, 1765, 1647, 1577, 1404, 1377, 1323, 1300, 1211, 1182, 1148, 1122, 1063, 965,842, 820, 777.

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