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Tetrahedron Letters 47 (2006) 6297–6300
Tetrahedron Letters

New rhodium(II) catalyzed synthesis of 1,4-dicarbonyl compounds from α-diazo ketones using vinyl ethers as two-carbon synthons

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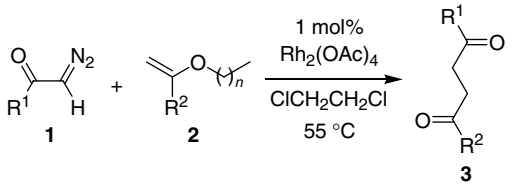
Received 7 April 2006; revised 9 June 2006; accepted 22 June 2006
Available online 18 July 2006

Abstract—Rhodium(II) acetate catalyzed reactions of various α-diazo ketones, and vinyl ethers afforded γ-ketoaldehydes or 1,4-diketones in a facile manner. In this process, oxycyclopropanes are formed as intermediates, and are subsequently ring opened in the presence of the rhodium(II) acetate catalyst to furnish the corresponding 1,4-dicarbonyl compounds. The scope of this protocol has been demonstrated with the synthesis of a serotonin antagonist.

Diazocarbonyl compounds are versatile chemical intermediates that undergo an array of chemical transformations such as cyclopropanation, insertion, ylide formation, and have found a wide range of applications in organic synthesis.[1] Transition metal catalyzed reactions of diazocarbonyl compounds with various electron rich as well as deficient olefins have been well documented[1,2] in the literature. Generally, reactions of metallo-carbenoids, generated from diazocarbonyl compounds, with olefins[1–3] were known to undergo cyclopropanation, C–H insertion, cycloaddition reactions, and often furnished a mixture of products. The reactions of rhodium–carbenoids with vinyl ethers have also been reported to furnish cyclopropanation,[4a–c] C–H insertion[4d] or cycloaddition[4e] products in a similar manner. As part of our research program on the chemistry[5] of diazocarbonyl compounds, we report herein a successful new synthesis of 1,4-dicarbonyl compounds by the reaction of α-diazo ketones, and vinyl ethers in the presence of rhodium(II) acetate as catalyst.

Initially, the reaction of α-diazo ketone **1** tethered to a cyclohexane ring, and an excess of ethyl vinyl ether **2** in the presence of a catalytic amount of $Rh_2(OAc)_4$ in dichloroethane at 55 °C furnished product **3a** (Scheme 1), Table 1) within 20 min and the evolution of nitrogen from the reaction mixture was observed. Product **3a** was characterized[6] as the corresponding γ-keto aldehyde, and obtained in 83% yield (Table 1, entry a). This result prompted us to investigate the reactivity of other α-diazo ketones tethered to alicyclic, aliphatic, aromatic ,or heteroaromatic substituents with vinyl ethers in the presence of the $Rh_2(OAc)_4$ catalyst. Thus, the reaction of



Scheme 1. Reaction of α-diazo ketones with vinyl ethers.

Table 1. Synthesis of 1,4-dicarbonyl compounds **3** from diazoketones **1**

Entry	*n*	R^1	R^2	Product	Time (min)	Yield[a] (%)
a	1	Cyclohexyl	H	**3a**	20	83
b	1	$MeO_2C–(CH_2)_3–$	H	**3b**	12	80
c	1	$CH_3–(CH_2)_8–$	H	**3c**	15	75
d	1	2-Thiophenyl	H	**3d**	10	75
e	0	Cyclohexyl	CH_3	**3e**	15	78[7a]
f	0	$CH_3–(CH_2)_8–$	CH_3	**3f**	15	77[7b]

[a] Yields (unoptimized) refer to isolated pure compounds **3**.

Keywords: Diazocarbonyl compounds; Diazo ketones; Rhodium(II) acetate; Vinyl ether.
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0040-4039/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2006.06.111

diazo ketones tethered to aliphatic or heteroaromatic units with vinyl ethers afforded the respective γ-keto aldehydes **3b–d** in good yields. The reaction of α-diazo ketone **1** tethered to a cyclohexane ring with 2-methoxypropene furnished 1,4-diketone **3e** in good yield. A similar reaction with the aliphatic diazo ketone afforded the respective 1,4-diketone **3f** (Table 1, entry f). These results infer the involvement of the vinyl group in the above reaction irrespective of the substituent on the vinyl ether.

Encouraged by the results, we studied the above reaction with α-diazo ketones tethered to various substituted aromatic ring systems. Thus, treating a dichloroethane solution of 2-diazo-1-(2-methylphenyl)ethanone with ethyl vinyl ether in the presence of $Rh_2(OAc)_4$ at 65 °C afforded the aryl substituted γ-keto aldehyde **5a** in 78% yield (Table 2, entry a).

Similarly, the methyl or methoxy substituted aromatic diazo compounds afforded the corresponding γ-keto aldehydes **5b**,[6]**c**. Reaction of the diazo ketone, derived from a naphthyl ring system, and ethyl vinyl ether afforded the corresponding γ-keto aldehyde **5d** in good yield. The presence of an electron withdrawing substituent on the aromatic ring provided a mixture of products including aldehyde **5e**, and the dihydrofuran product **6**.[4e,8] The diazo ketones derived from methyl or methoxy substituted aromatic ring systems as well as naphthyl systems when treated with 2-methoxypropene in the presence of a catalytic amount of rhodium(II) acetate yielded the corresponding 1,4-diketones **5f–i** in good yields.

It is worth mentioning that this protocol has versatile importance as 1,4-diketones are very useful synthetic intermediates for thienyl, pyrrolyl or furyl heterocycle synthesis, as well as terpenoid synthesis.[9] γ-Keto aldehydes are also important intermediates for the synthesis of arylpiperazine derivatives,[10] which are well known serotonin antagonists. The potential of this methodology prompted us to demonstrate a representative synthesis of known serotonin antagonist **10** starting from an α-diazo ketone. Thus, we synthesized the appropriate α-diazo ketone **7** having an aryl substituent on the carbon possessing the diazo functionality. Reaction of diazo ketone **7**, and ethyl vinyl ether in the presence of rhodium(II) acetate afforded the corresponding keto aldehyde **8**[6] in good yield (Scheme 3). Finally, reductive amination of **8** with 1-(2-methoxyphenyl)piperazine **9** in the presence of sodium triacetoxyborohydride was performed as described in the literature[10a] to furnish **10**,[6] which is a serotonin antagonist.[10b]

The reaction was further studied under different solvent conditions. Thus, a representative reaction of α-diazo ketone **4b** with ethyl vinyl ether was performed in dichloroethane, dichloromethane or tetrachloroethane to furnish the product **5b**. We found that there was a strong solvent dependence and the best yield was obtained using dichloroethane.

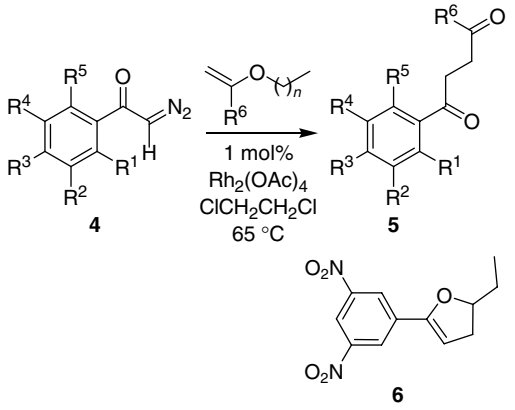
The reaction was also tested at different temperatures using dichloroethane from room temperature to 75 °C. A further increase in the temperature resulted in the decomposition of the diazo ketone **4b**. It is noteworthy that the reactions of diazo ketones with vinyl ether in diethyl ether[4a] at room temperature afforded the corresponding oxycyclopropanes whereas our experiment involves a high temperature and a different solvent. Thus, we have performed a representative reaction of α-diazo ketones **1d** and **4b** with ethyl vinyl ether in diethyl ether as described in the literature[4a] to furnish the respective oxycyclopropanes **11a**,**b**. On further treatment of **11** with $Rh_2(OAc)_4$ in dichloroethane at 65 °C, the corresponding 1,4-dicarbonyl compounds **3d** and **5b** were obtained, which confirms the ring-opening reactions of oxycyclopropanes **11** under the experimental conditions used in Schemes 1–3. As a control experiment, the cyclopropyl compound **11a** was heated at 65 °C without rhodium(II) acetate and the starting material remained unaffected. This experiment clearly infers the involvement of rhodium(II) acetate in the ring cleavage of oxycyclopropanes and that cyclopropane **11a** does not rearrange thermally (Scheme 4).

The ring opening of oxycyclopropanes is known[11] under acidic or basic conditions. The role of rhodium(II) acetate as a Lewis acid has also been demonstrated[12] in hetero-Diels–Alder reactions. The catalytic activity of Lewis acids can be elevated in polar solvents.[13] The reaction of α-diazo ketones tethered to tricarbonyliron coordinated dienes with vinyl ether in the presence of $Cu(acac)_2$ as catalyst was reported[14] to yield 1,4-dicarbonyl compounds. The ^1H NMR spectra of the crude

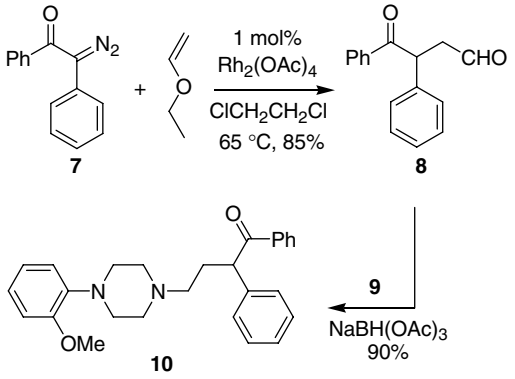
Table 2. Synthesis of 1,4-dicabonyl compounds **5** from diazoketones **4**

Entry	*n*	R^1	R^2	R^3	R^4	R^5	R^6	Time (min)	Yield[a] (%)
a	1	CH_3	H	H	H	H	H	15	78
b	1	H	CH_3	H	H	H	H	18	87
c	1	H	H	OMe	H	H	H	15	84
d	1	H	H	H	–CH=CH–CH=CH–		H	12	80
e	1	H	NO_2	H	NO_2	H	H	15	57
f	0	CH_3	H	H	H	H	CH_3	15	75
g	0	H	CH_3	H	H	H	CH_3	20	85
h	0	H	H	OMe	H	H	CH_3	18	80
i	0	H	H	H	–CH=CH–CH=CH–		CH_3	15	75[9d]

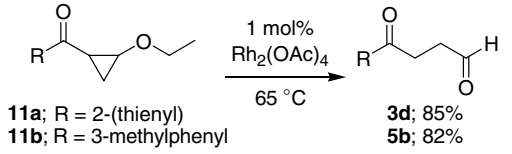
[a] Yields (unoptimized) refer to pure isolated compounds **5**.



Scheme 2. Reaction of α-diazo acetophenones with vinyl ethers.



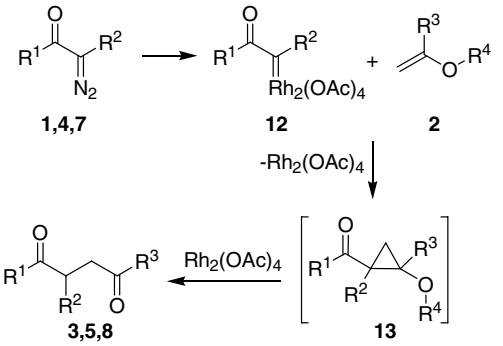
Scheme 3. Synthesis of serotonin antagonist **10** from α-diazo ketone.



Scheme 4. Ring opening of oxycyclopropanes by $Rh_2(OAc)_4$.

reaction mixtures of the reactions reported in Schemes 1–3 clearly indicated the formation of 1,4-dicarbonyl compounds before chromatographic purification. Based on these experiments, the following rationalization may be advanced to explain the product formation. The rhodium(II) carbenoid **12**, generated from an α-diazo ketone, adds to the vinyl ether affording an oxycyclopropane intermediate **13**, which in turn is ring opened in the presence of rhodium(II) acetate to furnish the corresponding 1,4-dicarbonyl compounds **3**,**5** or **8**. This confirms that rhodium(II) acetate acts as the catalyst for the cyclopropanation as well as ring opening reactions (Scheme 5).

In summary, we have revealed a novel transformation of α-diazo ketones involving vinyl ethers as two carbon synthons in the presence of rhodium(II) acetate as the catalyst affording the corresponding γ-keto aldehyde or 1,4-diketones in a facile manner. The α-diazo ketones were initially transformed into oxycyclopropanes as



Scheme 5. Proposed mechanism.

intermediates, which were subsequently ring opened in the presence of rhodium(II) acetate to furnish the corresponding 1,4-dicarbonyl compounds. In this process, rhodium(II) acetate acts as the catalyst for two consecutive synthetic steps. This methodology demonstrates not only the efficiency but also the versatile application for the synthesis of serotonin antagonists and five-membered heterocycles such as pyrrole, furan, and thiophene derivatives from α-diazo ketones.

Acknowledgments

This research was supported by the Department of Science and Technology, New Delhi. P.S. thanks the CSIR, New Delhi, for the award of a research Fellowship.

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6. *General procedure for the synthesis of 1,4-dicarbonyl compounds. 4-Cyclohexyl-4-oxobutanal* (**3a**): A 50 mL two-necked round bottomed flask was charged with diazo ketone **1a** (80 mg, 0.5 mmol) and the flask purged with argon using vacuum. Under a positive argon flow, 50 mL of freshly distilled dichloroethane and an excess of ethyl vinyl ether (2 mL, 20.9 mmol) were added to the flask. The reaction flask was equipped with a condenser (circulating with water at 15 °C) to minimize evaporation of ethyl vinyl ether. The reaction flask was immersed in an oil bath maintained at 55 °C. Rhodium(II) acetate dimer (1 mol %) was added to the reaction mixture with stirring. After addition of the catalyst, rapid evolution of N_2 was observed. (The argon atmosphere was maintained throughout the course of the reaction.) The reaction was followed by TLC. The solvent was removed under reduced pressure. The crude reaction mixture was subjected to column chromatography using silica gel (ethyl acetate/hexanes 1:6, $R_f = 0.6$) to furnish 4-cyclohexyl-4-oxobutanal (**3a**) as a colorless liquid in 83% yield. FTIR (film): 2931, 2856, 1709, 1449, 1401, 1145, 997, 830 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 9.74 (1H, s, CHO), 2.70 (4H, s), 2.54 (1H, t, $J = 6.0$ Hz), 2.34–2.32 (1H, m), 1.79–1.74 (5H, m), 1.32–1.20 (4H, m); ^{13}C (50.3 MHz, $CDCl_3$): δ 200.8 (C=O), 177.1 (C=O), 50.5 (CH), 37.3 (CH_2), 34.7 (CH_2), 32.5 (CH_2), 28.4 (CH_2), 25.5 (CH_2); MS (EI) *m*/*z* 168 (M^+); 168 (M^+, 80), 143 (20), 129 (40), 111(55), 101 (30), 83 (100), 67 (27), 55 (56). Anal. calcd for $C_{10}H_{16}O_2$: C, 71.39; H, 9.59. Found: C, 71.53; H, 9.64. *4-(3-Methylphenyl)-4-oxobutanal* (**5b**): Diazo ketone **4b** (80 mg, 0.5 mmol) was allowed to react with ethyl vinyl ether (2 mL, 20.9 mmol) in 50 mL of dichloroethane at 65 °C in the presence of $Rh_2(OAc)_4$ as described in the above procedure to afford **5b** as a colorless liquid; FTIR (film): 2974, 2921, 2728, 1721, 1683, 1604, 1586, 1382, 1260, 1162, 1036, 1002, 787, 692 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 9.89 (1H, s, CHO), 7.76 (1H, d, $J = 10.6$ Hz, arom-*H*), 7.40–7.37 (3H, m, arom-*H*), 3.31 (2H, t, $J = 6.2$ Hz, CH_2), 2.91 (2H, t, $J = 6.2$ Hz, CH_2), 2.40 (3H, s, CH_3); ^{13}C (50.3 MHz, $CDCl_3$): δ 200.6 (*C*=O), 198.0 (*C*=O), 138.6 (*quat*-C), 134.2 (*C*H), 128.5 (*C*H), 127.6 (*quat*-C), 125.2 (*C*H), 37.6 (CH_2), 31.0 (CH_2), 21.3 (CH_3); MS (EI) *m*/*z* 176 (M^+). Anal. calcd for $C_{11}H_{12}O_2$: C, 74.98; H, 6.86. Found: C, 75.16; H, 6.90. *4-Oxo-3,4-diphenylbutanal* (**8**): Diazo ketone **7** (110 mg, 0.5 mmol) was allowed to react with ethyl vinyl ether (2 mL, 20.9 mmol) in 50 mL of dichloroethane at 65 °C in the presence of $Rh_2(OAc)_4$ as described in the above procedure to afford **8** as a colorless liquid; FTIR (film): 3057, 2986, 1720, 1682, 1571, 1449, 1265, 1177, 745, 702 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 9.77 (1H, s, CHO), 7.95 (2H, t, $J = 6.8$ Hz, arom-*H*), 7.48–7.18 (8H, m, arom-*H*), 5.12 (1H, dd, $J = 4.2$ Hz, $J = 9.6$ Hz), 3.58 (1H, dd, $J = 9.6$ Hz, $J = 18.6$ Hz), 2.80 (1H, dd, $J = 4.2$ Hz, $J = 18.4$ Hz); ^{13}C (50.3 MHz, $CDCl_3$): δ 199.8 (*C*HO), 198.0 (*C*=O), 138.1 (*quat*-C), 135.9 (*quat*-C), 132.6 (*C*H), 129.4 (*C*H), 128.8 (*C*H), 128.4 (*C*H), 127.9 (*C*H), 127.3 (*C*H), 48.1 (CH_2), 47.4 (*C*H); MS (EI) *m*/*z* 238 (M^+). *1-(2-Methoxyphenyl)-4-[3-(benzoyl)-3-(phenyl)propyl] piperazine* (**10**): To a flask charged with 4-oxo-3,4-diphenylbutanal **8** (200 mg, 2.1 mmol) in 5 mL of dry dichloromethane, 1-(2-methoxyphenyl)piperazine (450 mg, 2.5 mmol) in 5 mL of dry dichloromethane was added through a cannula and the resulting mixture stirred at room temperature under a positive flow of argon. Then, to the reaction mixture, sodium triacetoxyborohydride (900 mg, 4.2 mmol) was added. After stirring for 4 h, the reaction mixture was quenched with a saturated sodium bicarbonate solution and extracted with dichloromethane. The organic extracts were combined, dried (Na_2SO_4), and evaporated. The residue was chromatographed using silica gel to furnish **10** as a colorless liquid; FTIR (film): 2941, 2818, 1681, 1595, 1500, 1450, 1241, 1026, 749, 700 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 7.99 (2H, d, $J = 5.6$ Hz, arom-*H*), 7.44–7.17 (8H, m, arom-*H*), 6.98–6.80 (4H, m, arom-*H*), 4.74 (1H, t, $J = 6.6$ Hz, C*H*), 3.81 (3H, s, CH_3), 2.98 (4H, s, CH_2), 2.62–2.46 (5H, m, CH_2), 2.38 (2H, t, $J = 5.4$ Hz, CH_2), 2.02–1.92 (1H, m, CH_2); ^{13}C (50.3 MHz, $CDCl_3$): δ 199.4 (*quat*-C), 152.2 (*quat*-C), 141.4 (*quat*-C), 139.6 (*quat*-C), 137.1 (*quat*-C), 132.5 (*C*H), 128.7 (*C*H), 128.6 (*C*H), 128.3 (*C*H), 128.2 (*C*H), 127.7 (*C*H), 126.8 (*C*H), 122.6 (*C*H), 120.8 (*C*H), 118.0 (*C*H), 111.2 (*C*H), 56.2 (CH_2), 55.2 (CH_3), 53.2 (CH_2), 51.2 (*C*H), 50.4 (CH_2), 31.3 (CH_2); HRMS (ESI) calcd for $C_{27}H_{30}N_2O_2$ $(M+H)^+$ 415.2386, found 415.2395.

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