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Tandem hydroformylation/aldol condensation reactions: Synthesis of unsaturated ketones from olefins

László Kollár, Péter Pongrácz*

Department of Inorganic Chemistry, University of Pécs and János Szentágothai Research Centre, MTA-PTE Research Group for Selective Chemical Syntheses, H-7624, Pécs, P.O. Box 266, Hungary

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ABSTRACT

Platinum-catalysed tandem hydroformylation/aldol condensation reaction of vinyl aromatics and ketones toward the corresponding α,β-unsaturated ketones were performed under syngas atmosphere in the presence of acid co-catalysts. The *in situ* generated catalysts modified with various ligands proved to be efficient under applied conditions. The presence of acids promotes side reactions like hydrogenation of the alkene substrate and that of the aldehyde to the corresponding alkane and alcohol, respectively. Interestingly, the hydrogenation of the condensed products is not preferred, only trace amounts of saturated products can be detected by GC-MS. In general, moderate yields can be achieved with several ketones using styrene and α-methylstyrene as substrate in hydroformylation reaction. Linear aldehydes proved to be more active in aldol condensation step, furthermore, aromatic and cyclic ketones are also feasible coupling partners to generate the corresponding unsaturated ketones. Contrary to the preceding literature, ketones possessing α-methylene group(s) showed exclusive preference for methylene functionalization in the aldol condensation reaction.

1. Introduction

Hydroformylation represents an efficient and selective method for the transformation of alkenes to valuable aldehydes [1–3]. The reaction discovered accidently by Otto Roelen in 1938, represents one of the large scale catalytic reactions. It has an especially high importance among homogenous catalytic reactions in industry today. Regioselective hydroformylation of propene to n-butyraldehyde (basic compound of 2-ethylhexanol used as alcohol component in the production of diisooctyl phthalate plasticizer), or the enantioselective hydroformylation of vinylaromatics to 2-arylpropanals (intermediate of non-steroidal anti-inflammatory drugs (NSAIDs)) are only two important examples for the process [4]. Beside the well-studied cobalt- and rhodium-containing catalysts, platinum-phosphine-tin(II)halide type systems were also developed focusing on the enantioselective reactions [5–9], and reaction mechanism. Seminal work by Casey et al. on the kinetics of enantioselective hydroformylation [10] and asymmetric hydroformylations of a set of 4-substituted styrenes by our group [11,12] were carried out to rationalise the reversal of enantioselectivity as a function of temperature.

In most cases the aldehydes are not the final products and the reactivity of these substantial materials allow us to perform numerous additional reactions even under hydroformylation conditions. Aldehydes can be considered as ideal substrates for further transformations, like oxidations, reductions or condensation reactions. In the presence of N- or O-nucleophiles versatile domino reactions are known like hydroaminomethylation, cyclohydrocarbonylation, acetalization or aldol condensation [13,14]. The first hydroformylation/aldol condensation reactions were reported by Breit and Eilbracht with rhodium catalysts using proline organocatalyst [15,16]. Breit described hydroformylation/Knoevenagel condensation reaction in the presence of piperidine base and acetic acid [17], and further tandem decarboxylative Knoevenagel reactions, which allowed an efficient one-pot synthesis of α,β-unsaturated acids and esters [18]. Recently, Beller and co-workers developed an efficient hydroformylation/aldol condensation/hydrogenation protocol using piperidine and benzoic acid cocatalysts [19,20]. In this study, a set of substrates and ketones proved to be suitable for the production of normal chain saturated ketones, *i.e.*, the consecutive hydrogenation of the unsaturated ketones formed via condensation was observed. Examples of intramolecular hydroformylation/aldol reactions of unsaturated ketones were also

* Corresponding author.
E-mail address: pongracz@gamma.ttk.pte.hu (P. Pongrácz).

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reported, which afforded the corresponding cyclic aldol adducts in good yields [21].

Herein, we present the application of platinum(II)-phosphine complexes and *para*-toluenesulfonic acid as efficient catalyst systems for domino hydroformylation/aldol condensation reactions. Styrene and α-methylstyrene as model substrates are transformed to *unsaturated ketones* under moderate conditions in the presence of various ketones used as solvents or reactants.

2. Experimental

2.1. General

The $PtCl_2(PhCN)_2$ [22] precursor was synthesized as described earlier. Toluene was distilled and purified by standard methods [23] and stored under argon. Styrene, tin(II) chloride (anhydrous) and ketones were used as obtained from Sigma-Aldrich without any further purification. All reactions were carried out under argon atmosphere using standard Schlenk technique.

The GC and chiral GC measurements were run on a Chrom-Card Trace GC-Focus GC gas-chromatograph. The enantiomeric excesses were determined on a capillary Cyclodex-column. The ^1H and ^{13}C NMR spectra were recorded on a Bruker Avance III 500 spectrometer. Chemical shifts are reported in ppm relative to TMS (downfield) for ^1H and ^{13}C NMR spectroscopy.

2.2. Tandem hydroformylation/aldol condensation experiments

In a typical experiment, $PtCl_2(PhCN)_2$ (4.7 mg, 0.01 mmol), diphosphine (0.01 mmol), and tin(II) chloride (3.8 mg, 0.02 mmol), *para*-toluenesulfonic acid (17.2 mg, 0.1 mmol) and 0.115 mL (1.0 mmol) of styrene was transferred under argon into a 100 mL stainless steel autoclave. Either 10 mL of ketone (Method A) or a mixture of 8 mL of toluene and 2 mL of the appropriate ketone (Method B) was added as solvent. The reaction vessel was pressurized to 80 bar total pressure ($CO/H_2 = 1/1$) and placed in an oil bath of appropriate temperature and the mixture was stirred with a magnetic stirrer. Sample was taken from the mixture and the pressure was monitored throughout the reaction. After cooling and venting of the autoclave, the pale yellow solution was removed and immediately analysed by GC.

2.3. Characterization of the products

2.3.1. 5-Phenyl-3-hexene-2-one (**2^i**)

δ_H (500 MHz, $CDCl_3$): 7.34–7.20 (5H, m, *Ph*), 6.92 (1H, dd, 7.0 Hz, 16.5 Hz, CHC*H*CH), 6.06 (1H, d, 16.5 Hz, COC*H*), 3.63–3.59 (1H, m, PhC*H*), 2.23 (3H, s, $COCH_3$), 1.43 (3H, d, 7 Hz, $CHCH_3$); δ_C (125.7 MHz, $CDCl_3$): 199.2, 151.9, 143.5, 129.9, 129.0, 127.6, 127.1, 42.5, 27.2, 20.4. MS *m/z* (rel int. %): 176 (3), 116 (20), 91 (100), 65 (13).

2.3.2. 6-Phenyl-3-hexene-2-one (**2^n**)

δ_H (500 MHz, $CDCl_3$): 7.34–7.20 (5H, m, *Ph*), 6.84 (1H, dt, 6.7 Hz, 16.0 Hz, CH_2CH), 6.12 (1H, d, 16.0 Hz, C*H*CO), 2.82 (2H, t, 7.5 Hz, $PhCH_2$), 2.58 (2H, td, 7,5 Hz, CH_2CH), 2.25 (3H, s, CH_3); δ_C (125.7 MHz, $CDCl_3$): 198.4, 146.9, 140.7, 131.7, 128.5, 128.3, 126.2, 34.5, 34.1, 26.9. MS *m/z* (rel int. %): 176 (34), 118 (65), 91 (100), 65 (24).

2.3.3. 3-Methyl-6-phenyl-3-hexene-2-one (**4a^i**)

δ_H (500 MHz, $CDCl_3$): 7.34–7.22 (5H, m, *Ph*), 6.14 (1H, d, 7.0 Hz, C*H*C), 3.92–3.86 (1H, m, PhC*H*), 2.19 (3H, s, $COCH_3$), 1.89 (3H, s, CCH_3), 1.46 (3H, d, 6.9 Hz, $CHCH_3$); δ_C (125.7 MHz, $CDCl_3$) 199.8, 147.2, 141.0, 133.1, 128.8, 128.6, 126.9, 39.0, 28.2, 21.1, 11.3; MS *m/z* (rel int. %): 188 (1), 159 (29), 116 (18), 91 (100), 65 (12).

2.3.4. 3-Methyl-5-phenyl-3-hexene-2-one (**4a^n**)

δ_H (500 MHz, $CDCl_3$): 7.34–7.22 (5H, m, *Ph*), 6.67 (1H, t, 7.0 Hz, C*H*), 2.82 (2H, t, 7.5 Hz, $PhCH_2$), 2.60 (2H, td, 7.4 Hz, 7.5 Hz, CH_2CH), 2.30 (3H, s, $COCH_3$), 1.76 (3H, s, CCH_3); δ_C (125.7 MHz, $CDCl_3$): 199.7, 142.1, 141.0, 138.2, 128.6, 128.5, 126.2, 34.8, 30.8, 25.4, 11.1. MS *m/z* (rel int. %): 188 (4), 173 (4), 145 (5), 116 (20), 91 (100), 65 (12).

2.3.5. 2-Methyl-7-phenyl-5-octene-4-one (**4b^i**)

MS *m/z* (rel int. %): 216 (8), 159 (100), 131 (92), 118 (46), 91 (71), 77 (28), 57 (24). (NMR characterization of the analytically pure sample was failed due to low yield. Using *i*Bu-Me-ketone both condensed products and branched aldehyde were obtained in low yield. Therefore, only the condensation product **4b^n**) obtained from the normal aldehyde was isolated in analytically pure form.)

2.3.6. 2-Methyl-8-phenyl-5-octene-4-one (**4b^n**)

δ_H (500 MHz, $CDCl_3$): 7.34–7.20 (5H, m, *Ph*), 6.86 (1H, td, 6.8 Hz, 15.6 Hz, C*H*CO), 6.13 (1H, d, 15.6 Hz CH_2CH), 2.82 (2H, t, 7.5 Hz, $PhCH_2$), 2.59–2.54 (2H, m, CH_2CH), 2.41 (2H, d, 7.0 Hz, $COCH_2$), 2.19–2.13 (1H, m, $CH(CH_3)_2$), 0.95 (6H, d, 6.6 Hz CH_3); δ_C (125.7 MHz, $CDCl_3$): 200.4, 145.9, 140.8, 131.2, 128.5, 128.4, 126.2, 49.2, 34.5, 34.1, 25.2, 22.7. MS *m/z* (rel int. %): 216 (1), 158 (29), 130 (13), 91 (100), 65 (13).

2.3.7. 4-Methyl-6-phenyl-4-heptene-3-one (**4c^i**)

δ_H (500 MHz, $CDCl_3$): 7.38–7.19 (5H, m, *Ph*), 6.72 (1H, d, 9.5 Hz, C*H*C), 3.90 (1H, dq, 6.9 Hz, 9.5 Hz, CH_3CH), 2.72 (2H, q, 7.4 Hz, CH_2CH_3), 1.90 (3H, s, CCH_3), 1.46 (3H, d, 7.0 Hz, $CHCH_3$), 1.11 (3H, t, 7.3 Hz, CH_2CH_3); δ_C (125.7 MHz, $CDCl_3$): 202.0, 144.5, 143.0, 135.5, 128.8, 127.0, 126.6, 38.9, 30.5, 21.1, 11.6, 8.8. MS *m/z* (rel int. %): 202 (29), 173 (67), 145 (100), 128 (34), 105 (81), 77 (39), 57 (22).

2.3.8. 4-Methyl-7-phenyl-4-heptene-3-one (**4c^n**)

δ_H (500 MHz, $CDCl_3$): 7.34–7.22 (5H, m, *Ph*), 6.67 (1H, t, 7.1 Hz, C*H*), 2.81 (2H, t, 7.5 Hz, $PhCH_2$), 2.70–2.66 (2H, m, CH_2CH), 2.59 (2H, q, 7.3 Hz, CH_2CH_3), 1.77 (3H, s, CCH_3), 1.11 (3H, t, 7.3 Hz, CH_2CH_3); δ_C (125.7 MHz, $CDCl_3$); 202.5, 141.0, 140.6, 137.5, 128.6, 128.4, 126.2, 34.8, 30.8, 30.4, 11.4, 8.8. MS *m/z* (rel int. %): 202 (1), 173 (29), 145 (10), 116 (13), 91 (100), 65 (13).

2.3.9. 1,4-Diphenyl-2-pentene-1-one (**4d^i**)

δ_H (500 MHz, $CDCl_3$): 7.91–7.24 (10H, m, *Ph*), 7.21 (1H, dd, 6.8 Hz, 15.5 Hz, C*H*CO), 6.86–6.80 (1H, m, C*H*CHCO), 3.77–3.72 (1H, m, PhC*H*), 1.51 (3H, d, 7.1 Hz, CH_3); δ_C (125.7 MHz, $CDCl_3$): 191.1, 153.1, 143.4, 137.9, 132.6, 128.7, 128.5, 128.4, 127.4, 126.7, 124.4, 42.5, 20.5. MS *m/z* (rel int. %): 238 (11), 133 (32), 120 (83), 105 (100), 91 (39), 77 (75), 51 (19).

2.3.10. 1,5-Diphenyl-2-pentene-1-one (**4d^n**)

δ_H (500 MHz, $CDCl_3$): 7.89–7.20 (10H, m, *Ph*), 7.09–7.04 (1H, m, CH_2CH), 6.87 (1H, d, 15.0 Hz, C*H*CO), 2.86–2.81 (2H, t, 7.0 Hz, $PhCH_2$), 2.66–2.62 (2H, m, CH_2CH_2); δ_C (125.7 MHz, $CDCl_3$): 190.8, 148.8, 140.7, 137.8, 132.6, 128.5, 128.5, 129.5, 128.3, 126.5, 126.1 34.5, 34.4. MS *m/z* (rel int. %): 236 (5), 145 (4), 116 (25), 105 (26), 91 (100), 77 (22), 65 (12), 51 (10).

2.3.11. 1,4-Diphenyl-2-methyl-2-pentene-1-one (**4e^i**)

δ_H (500 MHz, $CDCl_3$) 7.66–7.21 (10H, m, *Ph*), 6.42 (1H, d, 9.6 Hz, C*H*C), 3.96 (1H, qd, 7.2 Hz, 9.5 Hz, PhC*H*), 2.08 (3H, s, CCH_3), 1.44 (3H, d, 7.0 Hz, $CHCH_3$); δ_C (125.7 MHz, $CDCl_3$): 199.0, 147.4, 140.3, 137.5, 131.5, 129.8, 129.4, 128.7, 128.4, 128.0, 127.9, 39.2, 22.7, 14.1. MS *m/z* (rel int. %): 250 (49), 235 (37), 145 (51), 128 (31), 105 (100), 77 (96), 51 (25).