Tetrahedron Letters 50 (2009) 3338–3340

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

The effects of amine and acid catalysts on efficient chelation-assisted hydroacylation of alkene with aliphatic aldehyde

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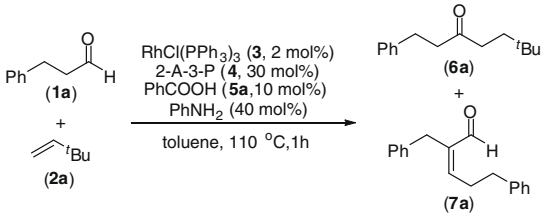
ARTICLE INFO

Article history:
Received 23 January 2009
Revised 7 February 2009
Accepted 12 February 2009
Available online 15 February 2009

ABSTRACT

Efficient intermolecular hydroacylation of 1-alkene with aliphatic aldehyde was achieved using a catalyst mixture of cyclohexylamine, *p*-trifluoromethylbenzoic acid, Wilkinson's complex and 2-amino-3-picoline. The formation of unwanted aldol side-product was avoided through the conjugate addition of cyclohexylamine to the aldol intermediate that was initially generated, followed by the retro-Mannich-type fragmentation of the resulting β-aminoaldimine.

Intermolecular hydroacylation is a useful synthetic method for obtaining ketone from aldehyde and olefin by C–H bond activation.[1] We developed an effective general intermolecular hydroacylation of 1-alkene using a catalyst mixture of Rh(I) complex and 2-amino-3-picoline.[2] The reactivity of this hydroacylation was improved when a mixture of benzoic acid and aniline was added as a cocatalyst.[3] However, substrates tested are generally aromatic aldehyde, not aliphatic aldehyde, due to the facile formation of α,β-unsaturated aldehyde from aliphatic aldehyde by aldol condensation under these conditions.



(1)

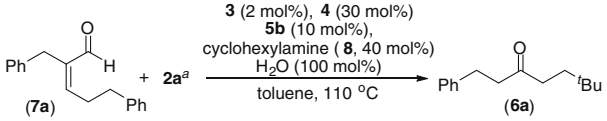
6a / **7a** = 61% / 39%

When the reaction of hydrocinnamaldehyde (**1a**) and 3,3-dimethyl-1-butene (**2a**) was carried out in toluene in the presence of $RhCl(PPh_3)_3$ (**3**), 2-amino-3-picoline (**4**), benzoic acid (**5a**) and aniline at 110 °C, a mixture of 61% hydroacylated product (**6a**) and 39% aldol condensation side-product (**7a**) was obtained, and none of the initial aldehyde **1a** remained (Eq. 1). In the past, primary alcohol and allylamine derivatives have been used as substrates to avoid the formation of aldol condensation product.[4] During the reaction, a small amount of aldehyde or aldimine is temporarily generated, and is utilized in the next chelation-assisted hydroacylation. It has also been determined that α,β-unsaturated ketone can be cleaved to generate ketone and aldehyde, or their imine derivatives, using cyclohexylamine and benzoic acid.[5] Based on these results, we were intrigued by the possibility that this protocol might be used to regenerate the initial aldehyde **1a** from the homoaldol side-product **7a** for hydroacylation.

In this Letter, we will discuss the efficient chelation-assisted hydroacylation of 1-alkene with aliphatic aldehyde through the regeneration protocol of aliphatic aldehyde or its imine derivative from the aldol condensation side-product using amine and acid.

In order to determine the feasibility of the regeneration of aldehyde **1a** as a transient intermediate from the homoaldol compound using cyclohexylamine and acid, α,β-unsaturated aldehyde **7a** was prepared[6] and allowed to react with 3,3-dimethyl-1-butene (**2a**) under the given reaction conditions to generate the hydroacylated product **6a** (Table 1). When 10 mol % benzoic acid (**5a**) and 40 mol % cyclohexylamine (**8**) were used, 20% of **7a** was trans-

Table 1
Hydroacylation of **2a** with **7a**



Entry	$CyNH_2$ (**8**)	Acid (**5**)	Time (h)	GC% of **6a**
1	40 mol %	**5a**	1	20
2	40 mol %	**5b**	1	36
3	40 mol %	**5b**	3	78
4	**40 mol %**	**5b**	**6**	**98**
5	none	**5b**	1	17
6	none	**5b**	3	18
7	none	**5b**	6	26

[a] 3.0 equiv based on the **7a** were used.

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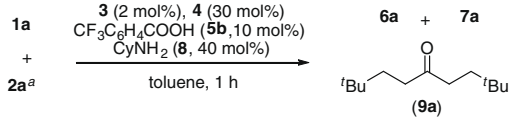
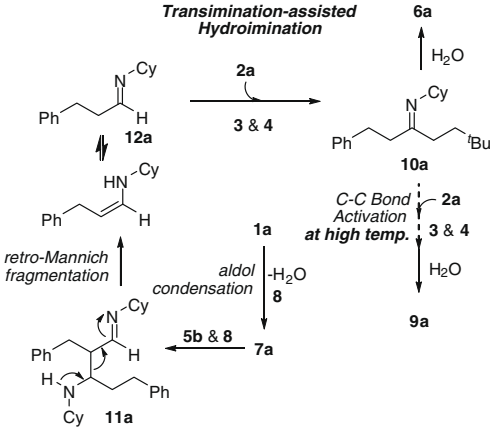
doi:10.1016/j.tetlet.2009.02.091

Table 2
Hydroacylation of **2a** with **1a** on the different temperatures



Entry	Temperature	Ratio of **6a**, **7a** and **9a** (%)		
		6a	**7a**	**9a**
1	**110 °C**	**77**	**23**	**0**
2	130 °C	84	13	3
3	150 °C	90	1	9
4	170 °C	89	0	12

[a]3.0 equiv of **2a** based on the aldehyde (**1a**) were used.



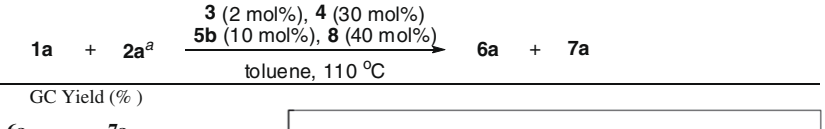
Scheme 1. Proposed mechanism of hydroacylation of **2a** with **1a** in the presence of **3**, **4**, **5b** and **8**.

formed into **6a** in 1 h (entry 1). By replacing benzoic acid (**5a**) with *p*-trifluoromethylbenzoic acid (**5b**), the conversion rate improved to 36% (entry 2), and the amount of product **6a** was increased during a prolonged reaction time. And **7a** was completely transformed to **6a** in 6 h (entries 3 and 4). However, without the addition of cylcohexylamine (**8**), the conversion efficiency and rate were very low (entries 5–7).

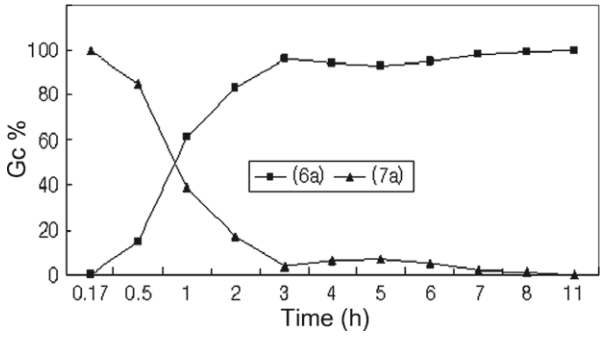
Based on the results noted above, the reaction of **1a** and **2a** was carried out in the presence of **3**, **4**, **5b** and **8** for 1 h at various temperatures: 110 °C, 130 °C, 150 °C and 170 °C (Table 2). At the reaction temperature of 110 °C, a mixture of 77% of **6a** and 23% of **7a** was obtained. In comparison, 3% of symmetric dialkyl ketone **9a** as well as a mixture of 84% of **6a** and 13% of **7a** was obtained at the reaction temperature of 130 °C (entries 1 and 2). As the reaction temperature increased, the proportional rate of **9a** and **6a** also increased, and that of **7a** decreased (entries 3 and 4). It is speculated that compound **9a** was produced by the chelation-assisted Rh(I)-catalyzed C–C bond activation of **6a**. This type of transformation of ketone bearing β-hydrogen into symmetric dialkyl ketone through the C–C bond activation has been studied previously under vigorous reaction conditions, such as high temperature (about 170 °C).[7] Therefore, the optimum temperature for hydroacylation with aliphatic aldehyde was selected as 110 °C, at which temperature C–C bond cleavage product **9a** was not produced.

To examine the effect of cyclohexylamine and acid on this hydroacylation with aliphatic aldehyde, the proportion of the product mixture from the reaction of **1a** with **2a** was monitored over a period of 11 h, as shown in Figure 1.[8] In 10 min, **1a** was completely transformed to **7a** by aldol condensation, as determined by gas chromatography (GC). After 30 min, a mixture of 15% of **6a** and 85% of **7a** was observed. The proportions of hydroacylated product **6a** increased, and those of **7a** decreased as the reaction time progressed. The reaction was complete after 11 h. This result indicates that aldol condensation product **7a** must be formed initially and then during a prolonged reaction time **7a** reacts with **2a** to produce **6a** by chelation-assisted hydroacylation.

Based on the above results, a proposed mechanism for this reaction can be depicted in Scheme 1. The initial step might be base-catalyzed aldol condensation of **1a** to produce **7a**.[9] In the presence of cyclohexylamine (**8**) and acid **5b**, the conjugate addition of **8** into **7a** followed by retro-Mannich type fragmentation of the resulting β-aminoaldimine (**11a**) produces the imine derivative **12a**. Transimination-assisted hydroimination of **2a** with **12a** in the presence of **3** and **4** leads to the formation of **10a**, which is then hydrolyzed to produce **6a**.[10] At high temperatures, chelation-assisted C–C bond activation of **10a** takes place to produce **9a** after hydrolysis.



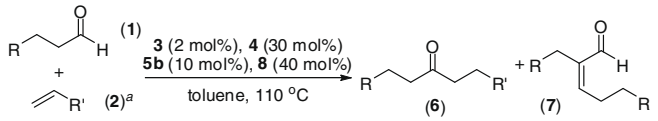
Entry	Time	GC Yield (%)	
		6a	**7a**
1	10 min	0	100
2	30 min	15	85
3	1 h	61	39
4	2 h	83	17
5	3 h	96	4
6	4 h	94	6
7	5 h	93	7
8	6 h	95	5
9	7 h	98	2
10	8 h	99	1
11	11 h	100	0



[a] 3.0 equivalents of **2a** based on **1a** were used.

Figure 1. GC yield (%) of **6a** and **7a** versus time plot in the reaction of **2a** with **1a** in the presence of **3**, **4**, **5b** and **8**.

Table 3
Hydroacylation of various aliphatic aldehyde with olefin under the different reaction conditions



Entry	Aldehyde (R, **1**)	Olefin (R', **2**)	$CyNH_2$ (**8**) (mol %)	Time (h)	GC yield (%) of **6** and **7**		Isolated yield (%) of **6**
1	Ph (**1a**)	$SiEt_3$ (**2b**)	0	1	52 (**6b**)	48 (**7a**)	38
2	Ph (**1a**)	$SiEt_3$ (**2b**)	0	12	62 (**6b**)	38 (**7a**)	43
3	Ph (**1a**)	$SiEt_3$ (**2b**)	40	1	50 (**6b**)	50 (**7a**)	41
4	**Ph (1a)**	**$SiEt_3$ (2b)**	**40**	**12**	**100 (6b)**	**0 (7a)**	**87**
5	Ph (**1a**)	Ph (**2c**)	0	1	11 (**6c**)	20 (**7a**)	6
6	Ph (**1a**)	Ph (**2c**)	0	12	33 (**6c**)	67 (**7a**)	27
7	Ph (**1a**)	Ph (**2c**)	40	1	44 (**6c**)	56 (**7a**)	36
8	**Ph (1a)**	**Ph (2c)**	**40**	**12**	**100 (6c)**	**0**	**82**
9	*n*-C_3H_7 (**1b**)	*t*-Bu (**2a**)	0	1	30 (**6d**)	70 (**7b**)	22
10	*n*-C_3H_7 (**1b**)	*t*-Bu (**2a**)	0	12	49 (**6d**)	51 (**7b**)	39
11	*n*-C_3H_7 (**1b**)	*t*-Bu (**2a**)	40	1	32 (**6d**)	68 (**7b**)	23
12	***n*-C_3H_7 (1b)**	***t*-Bu (2a)**	**40**	**12**	**100 (6d)**	**0**	**83**
13	*n*-C_6H_{13} (**1c**)	*t*-Bu (**2a**)	0	1	31 (**6e**)	40 (**7c**)	24
14	*n*-C_6H_{13} (**1c**)	*t*-Bu (**2a**)	0	12	51 (**6e**)	49 (**7c**)	43
15	*n*-C_6H_{13} (**1c**)	*t*-Bu (**2a**)	40	1	66 (**6e**)	34 (**7c**)	53
16	***n*-C_6H_{13} (1c)**	***t*-Bu (2a)**	**40**	**12**	**100 (6e)**	**0**	**86**

[a] 3.0 equiv of **2** based on aldehyde **1** were used.

Several combinations of varying aliphatic aldehydes and olefins were tested for intermolecular hydroacylation, and the results are summarized in Table 3. Under standard reaction conditions (**3**, **4** and **5b** at 110 °C) without cyclohexylamine (**8**), the reaction of **1a** and vinyltriethylsilane (**2b**) produced 52%/48% and 62%/38% mixtures of **6b**/**7a** in the reaction time of 1 h and 12 h, respectively (entries 1 and 2). It was observed that with the addition of **8** (40 mol %), a 50%/50% mixture was increased to a 100%/0% mixture of **6b**/**7a** by extending the reaction time from 1 h to 12 h (entries 3 and 4). This result indicates that the production of aldol condensation product **7** can be dramatically suppressed with the simple addition of cyclohexylamine (**8**) and acid **5b**. Similar results were observed in the reaction of other types of aliphatic aldehydes and olefins (entries 5–16).[11]

In conclusion, we demonstrated an efficient chelation-assisted hydroacylation of 1-alkene with aliphatic aldehyde using the cocatalyst system of cyclohexylamine and acid as well as Rh(I) and 2-amino-3-picoline. The homoaldol condensation side-product that is initially formed can be efficiently converted to a hydroacylated ketone product through the addition of cyclohexylamine to the aldol condensation intermediate and a retro-Mannich type fragmentation of the resulting β-aminoaldimine.

Acknowledgements

This work was supported by the Korea Research Foundation Grant funded by the Korean Government (KRF-2008-313-C00483) and WCU (World Class University) programme through the Korea Science and Engineering Foundation funded by the Ministry of Education, Science and Technology (R32-2008-000-102170) and CBMH. E.-A.J. acknowledges the fellowships of the BK21 programme of the Ministry of Education and Human Resources Development.

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6. *Synthesis of 2-benzyl-5-phenyl-pent-2-enal* (**7a**): Three millilitres of an aqueous NaOH solution (10%) were slowly added to hydrocinnamaldehyde (**1a**, 0.05 mol, 6.7 g) diluted in 50 ml of tetrahydrofuran (THF). Then the reaction mixture was stirred at room temperature for 12 h and neutralized with an aqueous solution of HCl (10%), and ether was added. The organic phase was dried on magnesium sulfate before filtration and purified via column chromatography (*n*-hexane ethyl acetate = 10:1) to give 3.9 g of **7a**.
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8. *General procedure* (Figure 1, entry 3): A screw-capped pressure vial (1 mL) equipped with a magnetic stirring bar was charged with 26.8 mg (0.2 mmol) of hydrocinnamaldehyde (**1a**), 50.4 mg (0.6 mmol) of 3,3-dimethyl-1-butene (**2a**), 3.7 mg (0.004 mmol) of $(PPh_3)_3RhCl$ (**3**), 6.5 mg (0.06 mmol) of 2-amino-3-picoline (**4**), 2.4 mg (0.02 mmol) of *p*-trifluoromethylbenzoic acid (**5b**), 7.9 mg (0.08 mmol) of cyclohexylamine (**8**) and 100 mg of toluene. The reaction mixture was sealed and stirred for 1 h in an oil bath that was preheated at 110 °C. After cooling to room temperature, the organic layer was analyzed on a GCD system to be a compound mixture of 6,6-dimethyl-1-phenylheptan-3-one (**6a**) and 2-benzyl-5-phenyl-2-pentenal (**7a**) in 61% and 39% ratio.
9. It can be also speculated that a small amount of aldehyde may be directly transformed to hydroacylation product without generating aldol condensation intermediate.
10. Jun, C.-H.; Hong, J.-B. *Org. Lett.* **1999**, *1*, 887–889.
11. Compound **6d**: ^1H NMR (400 MHz, $CDCl_3$): δ 2.42–2.33 (m, 4H), 1.59–1.55 (m, 2H), 1.48–1.44 (m, 2H), 1.35–1.24 (m, 4H), 0.90–0.87 (m, 12H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 212.2 (CO), 42.9, 38.5, 37.5, 31.5, 29.2, 23.7, 22.5, 14.0. MS: *m/z* (%): 184 (M^+, 10), 169 (23), 139 (42), 127 (43), 114 (10), 113 (82), 108 (13), 99 (100), 85 (24), 71 (81), 69 (32), 57 (58), 55 (26), 43 (88), 41 (40), 29 (19), 18 (17). IR ($CDCl_3$): 2957, 1715, 1366 cm^{-1}. HRMS (CI+) calcd for $C_{12}H_{25}O$ ([MH^+]) 185.1906, found 185.1905. Compound **6e**: ^1H NMR (250 MHz, $CDCl_3$): δ 2.43–2.32 (m, 4H), 1.58–1.26 (m, 14H), 0.88 (s, 12H). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 211.8 (CO), 42.8, 38.4, 37.4, 31.7, 29.9, 29.3, 29.2, 29.1, 23.9, 22.5, 14.0. MS: *m/z* (%): 226 (M^+, 6), 211 (32), 169 (93), 141 (87), 129 (17), 113 (87), 99 (17), 85 (24), 81 (12), 71 (89), 57 (100), 55 (29), 43 (61), 41 (40), 29 (19). IR ($CDCl_3$): 2925, 1715, 1465, 1363 cm^{-1}. HRMS (CI+) calcd for $C_{15}H_{30}O$ ([MNa^+]) 249.2297, found 249.2193. Anal. Calcd for $C_{15}H_{30}O$: C, 79.58; H, 13.36; Found: C, 79.56; H, 13.24.