Tetrahedron 73 (2017) 5841–5846

Contents lists available at ScienceDirect

Tetrahedron

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

Hypervalent iodine(III) catalyzed radical hydroacylation of chiral alkylidenemalonates with aliphatic aldehydes under photolysis

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ARTICLE INFO

Article history:
Received 7 July 2017
Received in revised form
28 July 2017
Accepted 10 August 2017
Available online 12 August 2017

Keywords:
Photolysis
Hydroacylation
Hypervalent iodine reagents
Chiral auxiliary
Radical reaction

ABSTRACT

Hypervalent iodine(III) catalyzed diastereoselective radical hydroacylation of alkylidenemalonates bearing (−)-8-phenylmenthol as a chiral auxiliary with aliphatic aldehydes is realized under photolysis. This work represent the first example of diastereoselective addition of acyl radicals to olefins to afford chiral ketones in a highly stereoselective fashion. The reaction is initiated by the photolysis of hypervalent iodine(III) catalyst under mild and metal-free conditions. The synthetic potential of this methodology was demonstrated by the short formal synthesis of (−)-methyleneolactocin.

1. Introduction

Research in the last few decades has witnessed an incredible development of new methods for the C–C bond formation *via* radical chemistry.[1] Atom economical reaction between aldehyde and olefin namely hydroacylation represent one of the synthetically useful transformation for the construction of ketones. Metal catalyzed hydroacylation[2] and *N*-heterocyclic carbenes (NHCs)[3] catalyzed Stetter reaction are most widely used approach for the addition of aldehydes to olefins (Scheme 1). In addition, the development of asymmetric metal catalyzed hydroacylation[4] and chiral *N*-heterocyclic carbenes (NHCs) catalyzed asymmetric Stetter reactions[5] to synthesize chiral ketones has also received greater attention in recent years. Alternatively, radical hydroacylation[6] through generation of acyl radical from aldehydes also has the potential to become an attractive atom economical method for the synthesis of ketones (Scheme 1). However, this approach has been less investigated due to the instability of acyl radical derived from branched aldehydes under reaction condition. During the course of our ongoing projects on the effective use of hypervalent iodine(III) reagents under photolysis,[6g,7] we investigated the hydroacylation reaction of cyclohexanecarboxaldehyde **2a** with ethyl crotonate **3a** or diethyl ethylidenemalonate **3b** under the influence of various hypervalent iodine(III) reagents[8] as catalyst (Table 1). The *in situ* generation of acyl radicals from branched aldehydes and its subsequent trapping with electrophiles have not been previously developed to a synthetically useful level. To our delight, catalytic use of DIB **1a** under the irradiation of UV light (365 nm) gave the hydroacylation product **4a** or **4b** in 11% or 81% yield respectively with high selectivity for ketone formation (**4a/5a** = 5.8/1 and **4b/5b** = 22.5/1; entry 1). Only trace amounts of reaction products were detected in the absence of **1a** or black light under given conditions (entry 2 and 3). These results strongly indicate that the reaction undergoes a radical pathway, thereby generating desired acyl radicals[9] in the reaction mixture. We also investigated other iodine(III) catalysts **1b-e** (entries 4–7), and found that **1d** gave a satisfactory result (entry 6). Among the screened iodine(III) catalysts **1d** shows higher solubility in CH$_3$CN solvent. Evaluation of different solvents revealed CH$_3$CN as best solvent for this reaction. The concentration of the reaction mixture is also crucial for obtaining the high yield as well as selectivity, and indeed use of a more concentrated CH$_3$CN (1.0 M or 1.6 M) solution including catalyst **1d** significantly

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http://dx.doi.org/10.1016/j.tet.2017.08.018
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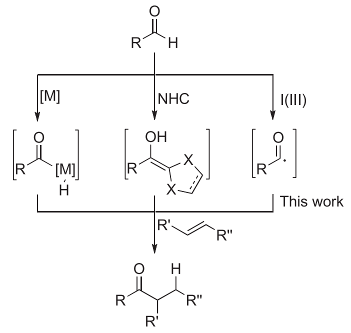
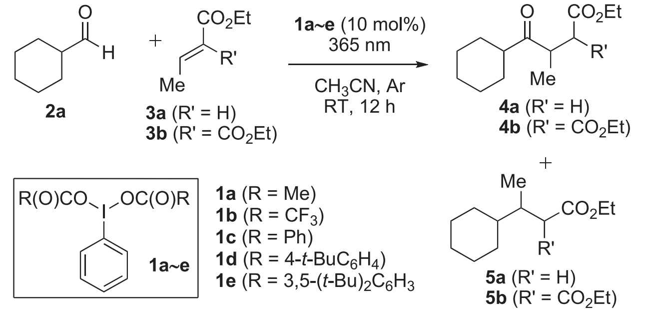


Scheme 1. Hydroacylation of olefins with aldehydes.

Table 1
Hydroacylation of cyclohexanecarboxaldehyde with ethyl crotonate or diethyl ethylidenemalonate by hypervalent iodine(III) catalysts.[a]



Entry	Catalyst	Yield (%)[b]	**4a/5a**[c]	Yield (%)[b]	**4b/5b**[c]
1	**1a**	11	5.8/1	81	22.5/1
2	none	trace	n.d	trace	n.d
3[d]	**1a**	trace	n.d	trace	n.d
4	**1b**	trace	ND	31	12.6/1
5	**1c**	32	3.0/1	67	23.2/1
6	**1d**	24	4.8/1	83	25/1
7	**1e**	trace	ND	40	14/1
8[e]	**1d**	95	5.2/1	99 (95)[h]	25/1
9[f]	**1d**	99 (97)[h]	6.4/1	88	17.4/1
10[g]	**1d**	95[f]	6.6/1	99[e]	25/1

[a] Unless otherwise specified, reaction of **2a** (0.75 mmol) and **3a** (0.5 mmol) was conducted in the presence of **1** (10 mol%) in CH_3CN (0.5 M) with irradiation of UV light ($\lambda = 365$ nm).

[b] Determined by ^1H NMR analysis using 1,1′,2,2′-tetrachloroethane as internal standard.

[c] Determined by ^1H NMR analysis of crude mixture.

[d] Reaction in the dark.

[e] Reaction in 1.0 M CH_3CN.

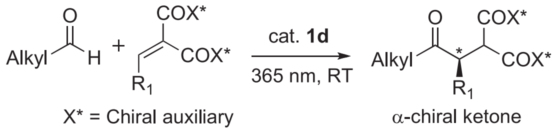
[f] Reaction in 1.6 M CH_3CN.

[g] Reaction performed for 18 h using 5 mol% of **1d**.

[h] Yield of isolated product.

enhanced both the selectivity (6.4/1 and >25/1) and the yield (>99%) for **4a** and **4b** respectively (entries 8 and 9). Lowering the catalyst loading of **1d** decelerates the reaction progress, however high yield was obtained with prolonged reaction time (entry 10).

To further demonstrate the synthetic potential of this approach, we have become interested in testing the possibility of adding acyl radical to chiral alkenes for the diastereoselective radical hydroacylation. Our approach also enables the use of various linear and branched aliphatic aldehydes, which have rarely been used with success in either metal catalyzed hydroacylation or NHC-catalyzed Stetter reaction.[10] Herein, we report the first diastereoselctive radical hydroacylation[11] of alkenes with aliphatic aldehydes for the stereoselective synthesis of chiral ketones (Scheme 2).



Scheme 2. Hypervalent iodine(III) catalyzed diastereo-selective radical hydroacylation of chiral olefins with aldehydes.

2. Results and discussion

At the outset, we first investigated the effect of chiral auxiliary for the diastereoselctive radical hydroacylation between cyclohexanecarboxaldehyde **2a** with various chiral alkenes **6a-h**. Chiral crotyl esters derived from alcohols such as (−)-menthol, (−)-8-phenylmenthol, (−)-borneol, (+)-fenchol afforded hydroacylated product **7a-h** in good yield with poor diastereoselectivity. Crotyl imides **6e** derived from (*S*)-4-benzyl-2-oxazolidinone also gave hydroacylated product in 1:1 diastereoselectivity. Interestingly, crotyl amide **6f** derived from (*R*)-(−)-1-phenylethylamine was found to remain unreactive under standard condition (Table 2).

Then we turned our attention to use chiral alkylidenemalonates as substrate. Since the crotyl ester derived from (−)-8-phenylmenthol **6b** shows higher reactivity and better selectivity among other chiral auxiliaries, the corresponding alkylidenemalonate[12] was synthesized and subjected to standard reaction condition. To our surprise, diastereoselectivity of the reaction increased significantly to 82:18 d.r. and afforded the corresponding ketone **7g** in high yield. It is worth mentioning here that with analogous (−)-menthol derived alkylidenemalonate **6h** diastereoselectivity of the hydroacylated product dropped drastically to 60:40 and afforded the corresponding ketone **7h** in moderate yield. Having identified the best chiral auxiliary for this reaction, we turned our attention to optimize other reaction parameter. A series of solvents was screened for the diastereoselective radical hydroacylation between cyclohexanecarboxaldehyde **2a** and (−)-8-phenylmenthol derived benzylidenemalonate **8b** (Table 3).

Non-polar solvents afforded hydroacylated product in high diastereoselectivity and yield than polar solvents such as CH_3CN (Table 3, entries 4–7 vs. entry 1). Interestingly, mixed solvent system CH_3CN/CH_2Cl_2 gave the corresponding product in higher diastereoselectivity (Table 3, entry 9). Slightly lowered yield and diastereoselectivity was observed, when the reaction performed under visible light ($\lambda = 400$ nm) irradiation (Table 3, entry 10).

To demonstrate the scope of the reaction, a series of aldehydes were hydroacylated with alkenes **8**, providing the corresponding ketones **9** in uniformly good yield and high diastereoselectivity (Table 4). When employing β-trifluoromethyl alkylidene-malonates **8a** as substrate, α-trifluoromethylated chiral ketone **9a** was obtained in moderate yield with 84:16 d.r. In the case on benzylidenemalonates, introduction of electron-withdrawing and electron-donating substituents on the aryl ring of **8b** did not affect the yield and diastereoselectivities (Table 4, **9c-e**). Introduction of heteroatom into the cyclohexane ring of aldehyde altered the reactivity and stereochemical outcome of the reaction (Table 2, **9b** vs **9f**). The reaction of ethene tricarboxylates **8g** with cyclohexanecarboxaldehyde **2a** proceeded efficiently to afford the corresponding ketones **9g** in good yield and diastereoselectivity (Table 2). In addition to α-branched and β branched aldehydes, various linear aldehydes **2l-o** were reacted efficiently with benzylidene malanote **8b** to give the corresponding ketones **9j-n**[13] with excellent yields and diastereoselectivities.

The further synthetic utility of the present diastereoselective radical hydroacylation was successfully demonstrated in the short formal synthesis of (−)-methyleneolactocin (Scheme 3),[14–16] which