Pergamon

Tetrahedron Letters 44 (2003) 5601–5604

TETRAHEDRON LETTERS

Addition of aldehydes and their equivalents to electron-deficient alkenes using *N*-hydroxyphthalimide (NHPI) as a polarity-reversal catalyst

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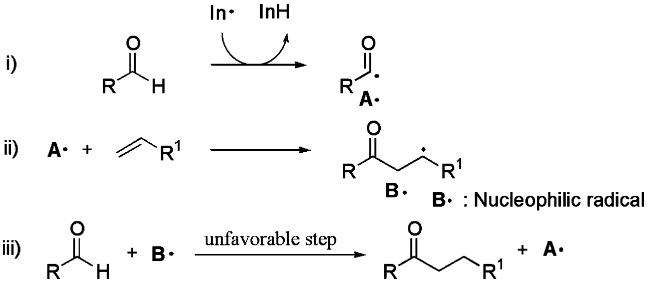
Received 13 May 2003; revised 29 May 2003; accepted 2 June 2003

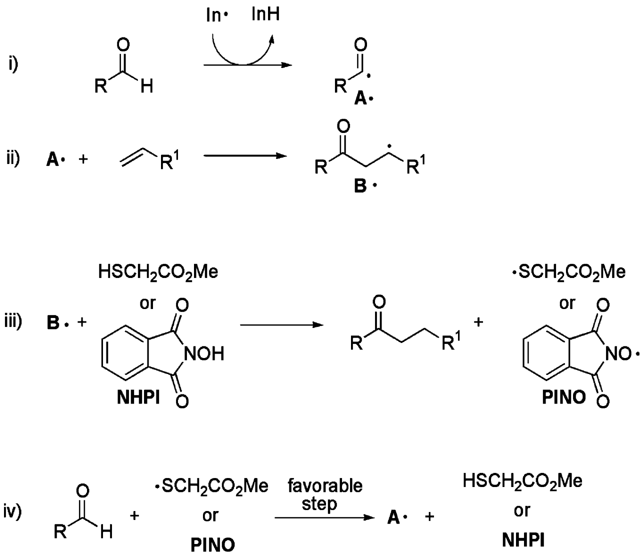
Abstract—Radical addition of aldehydes and masked aldehydes like 1,3-dioxolanes to electron-deficient alkenes was achieved by the use of catalytic amounts of BPO and *N*-hydroxyphthalimide (NHPI) as a polarity-reversal catalyst under mild conditions. Three-component radical coupling of 1,3-dioxolanes, maleates, and alkenes was performed in the presence of BPO and NHPI under similar conditions.

Hydroacylation involving the addition of acyl radicals derived from aldehydes to simple alkenes is usually difficult to carry out, since an unfavorable step of aldehydic hydrogen abstraction by the resulting adduct radical ($B^•$) is involved in the radical chain process (Scheme 1).[1]



Scheme 1. Hydroacylation of alkenes with aldehydes.

Recently, it is reported that the hydroacylation between electron-rich alkenes and aldehydes becomes feasible to carry out by the use of methyl thioglycorate ($HSCH_2CO_2Me$) which serve as a polarity-reversal catalyst (PRC) (Scheme 2).[2] Thus, the adduct radical $B^•$ can easily abstract the hydrogen atom from $HSCH_2CO_2Me$ which is preferred for nucleophilic radicals to give adduct and $^•SCH_2CO_2Me$ which abstracts the hydrogen atom from aldehyde. For instance, the addition of butanal to isopropenyl acetate in the presence of a radical initiator and methyl thioglycorate is easily achieved and gives 1-acetoxyhexan-3-one in high yield. In a previous paper, we showed that *N*-hydroxyphthalimide (NHPI) serves as an alternative polarity-reversal catalyst in the hydroacylation between aldehydes and simple alkenes (Scheme 2),[3] and the



Scheme 2. Hydroacylation of alkenes with aldehydes using PRC.

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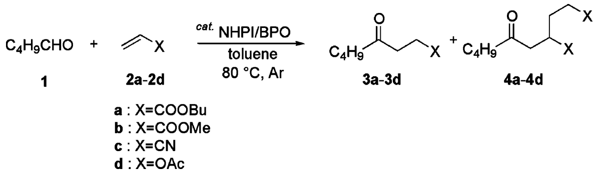
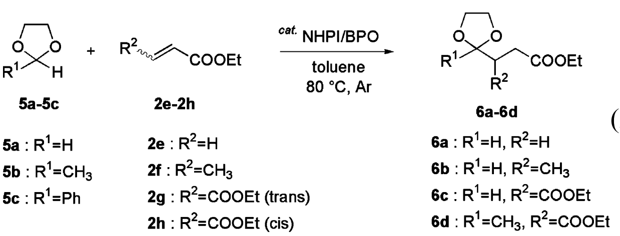
doi:10.1016/S0040-4039(03)01375-3

hydroacylation of 1-octene with pentanal was performed by the action of NHPI in good yield (88%). On the other hand, hydroacylation of aldehydes to electron-deficient alkenes like maleates smoothly takes place to give 1:1 adducts in fair yields.[4] However, the reaction is limited to several alkenes, since electron-deficient alkenes like acrylates and acrylonitrile are easily polymerized in the presence of a radical initiator. We have now found that aldehydes and masked aldehydes like 1,3-dioxolanes add smoothly to electron-deficient alkenes by the use of small amounts of BPO in the presence of NHPI as PRC under mild conditions. This paper shows the hydroacylation of electron-deficient olefins with aldehydes and masked aldehydes which has been difficult to carry out efficiently so far, although photosensitized addition of 2-substituted-1,3-dioxolanes to α,β-unsaturated carbonyl compounds is reported by Albini et al.[5] We also tried the three-component coupling of 1,3-dioxolanes, maleates, and alkenes using the NHPI catalyst.

The hydroacylation of pentanal (**1**) with butyl acrylate (**2a**) was chosen as a model reaction and carried out under various conditions (Eq. (1), Table 1).



(1)



(2)

The reaction of **1** (6 mmol) with **2a** (2 mmol) in the presence of NHPI (0.2 mmol) and BPO (0.2 mmol) in toluene (1 mL) at 80°C for 11 h produced small amounts of the corresponding hydroacylated product, **3a** (7%) and a 1:2 adduct, **4a** (2%) (Run 1). Under these conditions, it was found that most of **2a** was polymerized and aldehyde **1a** was recovered unreacted. In order to avoid rapid polymerization of **2a**, the reaction was carried out by adding slowly **2a** using a syringe pump to the reaction solution of **1**. As expected, the polymerization of **2a** was suppressed to considerable extent to give hydroacylated products, **3a** (48%) and **4a** (7%) (Run 2). When the amount of aldehyde **1** used was increased to 10 mmol, the yields of **3a** and **4a** became 61 and 13%, respectively (Run 3). The best results were obtained when 15 mmol of **1** was employed, and most of **2a** was converted to acylated products **3a** (88%) and **4a** (5%) (Run 4). Even by the use of a half-amount of BPO (0.1 mmol), almost the same results were obtained (Run 5).

Table 1. Hydroacylation of **2a** with **1** under various conditions

Run	**1** (mmol)	Method[a]	Conversion/%		Yield/%	
			2a	1	3a	4a
1	6	A	>99	15	7	2
2	6	B	>99	41	48	7
3	10	B	>99	38	61	13
4	15	B	>99	20	88	5
5[b]	15	B	95	26	83	7

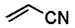
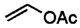
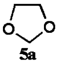
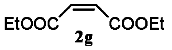
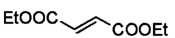
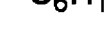
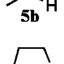
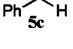
[a] Method A: **1** was reacted with **2a** (2 mmol) in the presence of NHPI (0.2 mmol) and BPO (0.2 mmol) at 80°C for 11 h under Ar atmosphere. Method B: **2a** (2 mmol) was added over a period of 9 h using syringe pump under stirring at 80°C, and the mixture was stirred for additional 2 h.

[b] BPO (0.1 mmol) was used.

On the basis of these results, the hydroacylation of several alkenes with aldehydes and masked aldehydes was examined under the influence of NHPI and BPO at 80°C (Eqs. (1) and (2), Table 2).

The reaction of methyl acrylate (**2b**) with **1** was performed under the same conditions as Run 4 in Table 1

Table 2. Hydroacylation of electron-deficient alkenes with aldehydes or oxolanes in the presence of NHPI and BPO[a]

Run	Alkene	Aldehyde	Method	Conv. / %[b]	Products (Yield / %)[c]
1	 **2b**	**1**	B	91	**3b** (80) **4b** (6)
2	 **2c**	**1**	B	>99	**3c** (72) **4c** (10)
3	 **2d**	**1**	B	93	**3d** (43) **4d** (0)
4	 **2e**	 **5a**	B	>99	Polymerized
5	 **2f**	**5a**	C	85	**6b** (70)
6	 **2g**	**5a**	C	95	**6c** (74)
7	 **2h**	**5a**	C	88	**6c** (41)
8	**2h**	**5a**	C	99	**6c** (46)
9		**5a**	C	No reaction	
10	**2g**	 **5b**	C	95	**6d** (80)
11	**2g**	 **5c**	C	No reaction	

[a] Alkenes (2 mmol) were reacted with aldehydes (15 mmol) or oxolanes (30 mmol) in toluene (1 mL) by the use of NHPI (0.2 mmol) and BPO (0.2 mmol) at 80 °C under Ar (1 atm). Method C : Alkene (2 mmol) was added all at once to oxolanes and was reacted for 1 h except for Run 8 (3 h).

[b] Conversion of alkenes. About 20% of aldehydes were consumed in every run.

[c] Based on alkenes used.

Table 3. Three-component coupling of oxolane, **2g** or **2f** and alkene or alkyne in the presence of NHPI and BPO[a]

Run	Oxolane (mmol)	**2g** or **2f**	Alkene or alkyne	Conv./%[b]	Product (Yield/%)[c]	
1	**5a** (15)	**2g**	1-Octene (**7**)	58	**8a** (40)	**6c** (6)
2[d]	**5a** (15)	**2g**	**7**	75	**8a** (4)	**6c** (6)
3	**5a** (30)	**2g**	**7**	81	**8a** (67)	**6c** (3)
4	**5a** (30)	**2g**	Norbornene (**9**)	90	**8d** (57)	**6c** (12)
5	**5a** (15)	**2g**	1-Octyne (**10**)	37	**8e** (39)	**6c** (5)
6[e]	**5a** (30)	**2f**	**7**	47	**8b** (30)	**6b** (5)
7	**5b** (15)	**2g**	**7**	90	**8c** (44)	**6d** (10)
8[e]	**5b** (30)	**2g**	**9**	99	**8f** (77)	**6d** (12)
9	**5b** (15)	**2g**	**10**	50	**8g** (52)	**6d** (20)

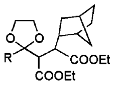
[a] A mixture of oxolane (15 mmol), **2g** or **2f** (2 mmol), and alkene or alkyne (10 mmol) in toluene (1 mL) was reacted in the presence of NHPI (0.2 mmol) and BPO (0.2 mmol) under Ar (1 atm) at 80°C for 15 h.

[b] Conversion of alkene or alkyne.

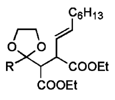
[c] Based on alkene or alkyne used.

[d] In the absence of NHPI.

[e] 0.4 mmol of NHPI was used.



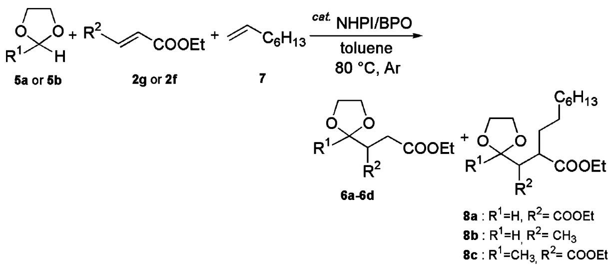
8d : R=H
8f : R=CH$_3$



8e : R=H
8g : R=CH$_3$

to afford **3b** (80%) and **4b** (6%) (Run 1). In a similar manner as **2b**, **1** added to acrylonitrile (**2c**) to give 4-oxooctanonitrile (**3c**) (72%) and a 1:2 adduct, **4c** (10%) (Run 2). The reaction of **1** with vinyl acetate (**2d**) afforded 3-oxoheptyl acetate (**3d**) in 43% yield (Run 3), but no 1:2 adduct was isolated in this reaction. 1,3-Dioxolane (**5a**), a synthetic equivalent of formaldehyde, was employed in place of aldehyde **1**. It is important that **5a** is capable of being used as an equivalent of formaldehyde, which is difficult to use in the laboratory because of easy evaporation. The reaction of ethyl acrylate (**2e**) with **5a** was attempted, but **2e** was polymerized to give no adducts (Run 4). This is believed to be due to the fact that the hydrogen abstraction from **5a** is more difficult than that from the aldehyde hydrogen atom. We found that **5a** adds very fast to ethyl crotonate (**2f**) to form the corresponding adduct (**6b**) in 70% yield (Run 5). Similarly, the reaction of **5a** with diethyl maleate (**2g**) afforded adduct **6c** in 74% yield; however, the reaction with diethyl fumarate (**2h**) took place with some difficulty to give the same product **6c** in moderate yield (41%) (Runs 6 and 7). Although the reaction was prolonged for 3 h, the yield of **6c** was not improved (Run 8). However, **5a** did not add to simple terminal alkenes like 1-octene (**7**), although aldehydes added to **7** under these conditions as reported previously (Run 9).[3] This is believed to be due to the fact that the oxolane radical, which is nucleophilic in nature, derived from **5a** is difficult to add to **7** which preferentially reacts with an electrophilic radical. 2-Methyl-1,3-dioxolane (**5b**) was reacted with **2g**, giving adduct **6d** in 80% yield (Run 10). However, 2-phenyl-1,3-dioxolane (**5c**) did not add to **2g** under these conditions.

We next tried the three-component coupling reaction of oxolanes, **2g** or **2f**, and simple terminal alkenes, since the adduct radical of oxolanes to **2g** is expected to possess an electrophilic character (Eq. (3)).



(3)

Thus, the coupling reaction of **2g** or **2f**, **5a** or **5b** and 1-octene (**7**) or norbornene (**9**) or 1-octyne (**10**) in the presence of NHPI and BPO under similar conditions as the hydroacylation was examined (Table 3).

A mixture of **2g** (10 mmol), **5a** (15 mmol) and **7** (2 mmol) in the presence of NHPI (0.2 mmol) and BPO (0.2 mmol) in toluene (1 mL) was stirred at 80°C for 15 h under Ar (1 atm), giving the desired three-component coupling product **8a** in 40% yield along with adduct **6c** (6%) (Run 1).

The same reaction in the absence of NHPI gave **8a** in a very low yield (Run 2). When 30 mmol of **5a** was employed, the yield of **8a** was improved to 67% (Run 3). The use of norbornene (**9**) and 1-octyne (**10**) in place of **7** resulted in the corresponding adduct **8d** (57%) and **8e** (39%), respectively, consisting of an approximately 1:1 diastereoisomeric mixture (Runs 4 and 5). The reaction of ethyl crotonate **2f**, **5a** and **7** took place with some difficulty to give **8b** in moderate yield (30%) (Run 6). It is reported that the reaction of pentanal with an equimolar mixture of methyl crotonate or 1-hexene in the presence of perester under irradiation at 78°C afforded 1:1 adducts of pentanal to crotonate or 1-hexene rather than the three-component coupling product.[6] This is due to the difference in polarity between the acyl radical and the oxolane radical derived from **5a**. The reaction of **2g**, **5b** and **7** or **9** afforded **8c** or **8f** in 44% or 77% yields, respectively (Runs 7 and 8). Similarly, the reaction with **10** under these conditions gave **8g** (52%) (Run 9).

The three-component coupling reaction using pentanal **1** instead of oxolanes, however, brought about a complex mixture, since acyl radical generated from **1** can add to both ethyl maleate **2g** and 1-octene **7** assisted by the NHPI which serves as a PRC.

In conclusion, hydroacylation of aldehydes involving masked aldehydes to alkenes was successfully performed by the use of NHPI and BPO in fair yields. Furthermore, the three-component coupling reaction of oxolanes, electron-deficient alkenes like maleates, and electron-rich alkenes like 1-octene under similar conditions as those of the hydroacylation has been achieved.

Spectral data: **8d** (*exo*-**8d** was obtained as diastereoisomeric mixture, and the representative peaks were shown here): ^{1}H NMR ($CDCl_3$, 270 MHz): $\delta = 5.21$ (d, $J = 4.6$ Hz, 1H), 4.21–4.09 (m, 5H), 3.96–3.81 (m, 4H), 3.00–2.96 (m, 1H), 2.17–2.04 (m, 1H), 1.47–1.03 (m, 16H); ^{13}C NMR ($CDCl_3$, 68 MHz): $\delta = 172.6$, 170.8, 103.3, 64.8, 61.0, 60.6, 51.4, 48.6, 42.6, 39.6, 36.2, 35.5, 34.8, 30.4, 28.2, 14.1, 14.0; IR (NaCl) 2952, 1733, 1314, 1155, 1033 cm^{-1}. **8f** (*exo*-**8f** was obtained as diastereoisomeric mixture, and the representative peaks were shown here): ^{1}H NMR ($CDCl_3$, 270 MHz): $\delta = 4.18$–4.07 (m, 4H), 3.97–3.88 (m, 4H), 3.17–3.12 (m, 1H), 2.15 (br, 1H), 2.04 (br, 1H), 1.52 (s, 3H), 1.52–1.08 (m, 16H); ^{13}C NMR ($CDCl_3$, 68 MHz): $\delta = 172.8$, 170.9, 109.2, 64.8, 63.6, 60.5, 59.9, 49.8, 43.6, 39.8, 36.8, 36.3, 35.7, 34.4, 30.6, 28.2, 12.6, 14.0, 13.9; IR (NaCl) 2956, 1724, 1370, 1156, 1043 cm^{-1}. **8e** (*exo*-**8e** was obtained as diastereoisomeric mixture, and the representative peaks were shown here): ^{1}H NMR ($CDCl_3$, 270 MHz): $\delta =$ 5.55–5.08 (m, 5H), 4.21–4.04 (m, 4H), 3.87–3.78 (m, 4H), 3.32–3.00 (m, 1H), 1.91–1.89 (m, 2H), 1.26–1.16 (m, 16H), 0.79–0.62 (m, 3H); ^{13}C NMR ($CDCl_3$, 68 MHz): $\delta = 171.9$, 169.6, 135.9, 129.5, 103.3, 64.8, 64.7, 61.0, 60.6, 52.3, 48.4, 32.3, 31.6, 29.2, 28.9, 28.6, 22.5, 14.0; IR (NaCl) 2928, 1736, 1247, 1154, 1032 cm^{-1}.

Acknowledgements

This work was partially supported by a Grant-Aid for Scientific Research (KAKENHI) (S) (No. 13853008) from Japan Society for the Promotion of Science (JSPS).

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