A Practical and Highly Efficient Hydroacylation Reaction of Azodicarboxylates with Aldehydes in Water

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Abstract: The very efficient hydroacylation reaction of azodicarboxylates, with various aldehydes, was carried successfully out at room temperature in water without the use of a catalyst to obtain a variety of hydrazine imide products in high yields. A wide range of aldehydes, including aliphatic and aromatic compounds, was considered, and the reaction is believed to proceed via a radical mechanism, in which water plays an integral role in stabilizing the radical intermediate.

Key words: azo compounds, green chemistry, hydroacylation, aldehydes

The toxic and volatile nature of many organic solvents that are widely used in organic synthesis pose a serious hazard to the environment. Efforts aimed at replacing such organic solvents with environmentally friendly ones as reaction media have been actively pursued in recent years.² Carrying out reactions in aqueous media has received considerable attention because water is a safe, economical, nontoxic, and environmentally benign solvent, compared to typical organic solvents.³ Moreover, when a reaction is carried out in water, the water-insoluble products can be isolated easily by simple separation. As a result, research into organic reactions, which can be carried out effectively in water, has become an active area of research.

One of the most important reactions in organic synthesis is the formation of new carbon-nitrogen bonds from simple and easily available starting materials.⁴ There are various reactions, including those that use various polar substrates, radicals, and transition-metal catalysts that have been reported to construct such bonds.⁴ Of these reactions, the reaction that involves the use of azodicarboxylates as electrophiles is a very efficient reaction for the formation of C-N bonds. One of the reasons for the success of this reaction is that azodicarboxylates contain a strong electron-withdrawing group and a vacant orbital, which also serves as good nucleophilic acceptors; these features contribute to making this a favorable reaction.^{4a,b} There are many types of reactions involving azodicarboxylates that have been studied extensively for the formation of C-N bond, these include the zwitterion-mediated reactions (Scheme 1, path a),⁵ electrophilic α -amination of carbonyl compounds (Scheme 1, path b),⁶ the C-H activa-

SYNLETT 2010, No. 16, pp 2453–2456 Advanced online publication: 19.08.2010 DOI: 10.1055/s-0030-1258056; Art ID: S12510ST © Georg Thieme Verlag Stuttgart · New York tion at the α -position of amine and ethers (Scheme 1, path c),⁷ and the ene-type reaction with olefins (Scheme 1, path d).⁸ The direct hydroacylation reaction, which involves aldehydes has not been studied extensively (Scheme 1, path e),⁹ and is the focus of this report.

Scheme 1 Reactions involving azodicarboxylates

Hydroacylation reaction with direct functionalization of the aldehydic C-H to form a variety of hydrazine imides is a highly efficient synthetic methodology to form a carbon-nitrogen bond. The compounds that result are versatile building blocks for the synthesis of macrocyclic enamide.^{10b} Under photolytic or thermal conditions, the yields have been low and only a narrow scope of substrates can be utilized. The transition-metal catalyst, rhodium acetate, has proven to be an effective catalyst for the hydroacylation reaction involving aliphatic saturated or unsaturated aldehydes with azodicarboxylates under mild conditions to provide the hydrazine imides.¹⁰ A major drawback with this method, however, is that the reaction results in relatively low yields when aromatic aldehydes are used as the substrates. In addition, very costly precious metals are used. Therefore, the development of simple and efficient reaction conditions, while increasing the scope of the substrates without the use of expensive metal catalyst, have become a challenging and very important task.



Recently, we have demonstrated that the hydroacylation reaction can be carried out successfully in the presence of the ionic liquid, 1-*n*-butyl-3-methylimidazolium bis(tri-fluoromethane sulfonyl)imide without a catalyst.¹¹ Carrying out the above reaction in water would be of tremendous benefit, from a green chemistry perspective, and in this communication, we wish to report the hydroacylation reaction of azodicarboxylates with aldehydes without the use of a catalyst. The reaction in this study is conducted under mild reaction conditions in the presence of water.

Initially, the hydroacylation reaction with propionaldehyde and diisopropyl azodicarboxylate in various solvents was examined at room temperature in the absence of a catalyst.¹² As shown from the results summarized in Table 1, the reaction proceeded smoothly and gave the best yield in water after only 10 hours (Table 1, entry 1). The reaction yield in MeOH, which is a polar protic solvent and similar to water, is extremely low (Table 1, entry 2). Poor yields were also obtained when acetonitrile or ethyl acetate was used as a solvent (Table 1, entries 3 and 4). When THF and CH₂Cl₂ were used as solvents, the desired hydroacylation product **3a** was obtained in low yields, 35% and 20%, respectively (Table 1, entries 5 and 6).

 Table 1
 Optimization Reaction of Propionaldehyde 1a with Diisopropyl Azodicarboxylate 2a^a

H +	N=N 2C	solvent O	H N N CO ₂ <i>i</i> -Pr
1a	2a		3a
Entry	Solvent	Yield (%)) ^b
1	H ₂ O	97	
2	МеОН	<5	
3	MeCN	<5	
4	EtOAc	<5	
5	THF	35	
6	CH_2Cl_2	20	

^a Reaction were performed with a 2:1 ratio of 1a and 2a on a 0.5 mmol scale in 0.5 mL of H₂O.

^b Isolated yields of pure product.

The large-scale hydroacylation reaction was carried out, in which 10 mmol of diisopropyl azodicarboxylate **2a** was allowed to react with propionaldehyde **1a** under standard reaction conditions. After the reaction was completed, the reaction mixture was separated into two phases. The aqueous phase was removed by simple separation, and the organic phase was purified by flash chromatography on silica gel to give the hydroacylation product **3a** in 95%. Notably, the procedure is green and practical, and no organic solvent is required for the workup step.

 Table 2
 Hydroacylation Reaction of Aldehydes with Azobicarboxylates^a

R ¹	$H \stackrel{+}{=} N \stackrel{CO_2R^2}{\underset{R^2O_2C'}{N=N}} \stackrel{H_2}{\underbrace{H_2}}$	20, r.t.	► R ¹	0 H N N CO ₂ R ² 3	CO ₂ R ²
Entry	R ¹	R ²	Time (h)	Product ¹⁵	Yield (%) ^b
1	<i>n</i> -Bu	<i>i</i> -Pr	10	3b	97
2	<i>n</i> -C ₈ H ₁₇	<i>i</i> -Pr	20	3c	92
3	Me ₂ CHCH ₂	<i>i</i> -Pr	6	3d	97
4	Me ₂ CH	<i>i</i> -Pr	36	3e	92
5	cyclohexyl	<i>i</i> -Pr	8	3f	98
6	cyclopentyl	<i>i</i> -Pr	8	3g	98
7	PhCH ₂ CH ₂	<i>i</i> -Pr	25	3h	96
8	(cis) n -C ₅ H ₁₁ CH=CH(CH ₂) ₂	<i>i</i> -Pr	96	3i	70
9	CH ₂ =CHCH ₂ Me ₂ C	<i>i</i> -Pr	168	3j	42
10	Ph	<i>i</i> -Pr	76	3k	80
11	4-ClC ₆ H ₄	<i>i</i> -Pr	168	31	60
12	4-MeOC ₆ H ₄	<i>i</i> -Pr	360	3m	59
13	cyclohexyl	2b Et	3	3n	90
14	cyclohexyl	2c Bn	5	30	87

^a Reaction were performed with a 2:1 ratio of 1 and 2 on a 0.5 mmol scale in 0.5 mL of H_2O .

^b Isolated yields of pure product.

Next, we investigated a wide range of this hydroacylation reaction involving various aldehydes and azodicarboxylates. As revealed in Table 2, these reactions proceeded smoothly to give the hydroacylation products 3b-c. These results show that not only the linear saturated aldehydes **1b–c**, but also branched aldehydes **1e–h** can be employed successfully as nucleophiles to afford the desired products **3b-h** in excellent yields (Table 2, entries 1–7). The hydroacylation reactions with other aliphatic aldehydes 1i-j with unsaturation either at the terminal or internal position also provided the desired products **3i** and **3j**, respectively, but in low to moderate yields (Table 2, entries 8 and 9). The reason for the relatively low yields in these two cases is probably due to the ene-type reaction to generate the bisazodicarboxylates,¹³ which was also observed by Lee's research group using rhodium acetate as catalyst.^{10a} The aromatic benzaldehyde is also a good substrate for this reaction and afforded the hydroacylation product 3k in 76 hours with 80% yield (Table 2, entry 10). This result is superior to that obtained by Lee and Otte, in which rhodium acetate catalyst is used (120 h, yield 46%).^{10a} However, the reaction rates for the reactions involving aromatic aldehydes with the electron-withdrawing group Cl (11). and the electron-donating group OMe (1m) were very low and

gave hydroacylation products **3l–m** in moderate yield (Table 2, entries 11 and 12). To broaden the scope of the reaction, a wide range of azodicarboxylates **2b,c**, were used in the reaction with cyclohexanecarboxaldehyde also gave the desired products **3n,o** in high yields (87–90%, Table 2, entries 13 and 14).

The mechanism for the hydroacylation reaction is still not clear, but we assume that when this reaction is carried out in water, it proceeds via a radical mechanism, which was described in previous studies.^{9,10a,14} The hydrogen of water plays an important role in stabilizing the radical transition state through hydrogen bonding and facilitating the addition of the acyl radical intermediate to azodicarboxylate to form the hydroacylation product.

In summary, we have developed an efficient hydroacylation reaction involving aldehydes and azodicarboxylates to give the hydrazine imide products in water. For these reactions, moderate to excellent yields are obtained under convenient conditions without the use of metal catalysts. The synthetic procedure presented is simple, practical, and environmentally benign. Further study on the reaction mechanism and the exploration of the scope of the reaction substrates are under way in our laboratory.

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- (15) Typical Procedure for the Hydroacylation Reaction in H_2O

To a stirred solution of aldehyde **1** (1.0 mmol) in H_2O (0.5 mL) was added azodicarboxylate **2** (0.5 mmol). The reaction was stirred at r.t. for the time as indicated in Tables 1 and 2. The reaction mixture was extracted with Et_2O for two times

 $(4 \times 5 \text{ mL})$. The Et₂O solution was combined, concentrated, and purified by flash chromatography on silica gel (hexane–EtOAc = 4:1) to afford the product **3**.

Data for the new hydroacylation products: Compound **3b**: ¹H NMR (400 MHz, CDCl₃): $\delta = 6.57$ (br, 1 H), 5.10–4.90 (m, 2 H), 2.94–2.84 (m, 2 H), 1.72–1.58 (m, 4 H), 1.40–1.15 (m, 20 H), 0.88 (t, *J* = 6.8 Hz, 3 H) ppm. ¹³C NMR (100 MHz, CDCl₃): $\delta = 173.9$, 155.1, 152.6, 72.1, 70.4, 37.0, 31.8, 29.3, 29.2, 29.1, 24.7, 24.6, 22.6, 21.9, 21.7, 14.1 ppm. Anal. Calcd for C₁₆H₃₂N₂O₅Na [M + Na]⁺: 367.2209; found: 367.2207. Compound **3n**: ¹H NMR (400 MHz, CDCl₃): $\delta = 6.68$ (br, 1 H), 4.30 (q, *J* = 7.2 Hz, 2 H), 4.21 (q, *J* = 7.2

Hz, 2 H), 3.44–3.34 (m, 1 H), 2.00–1.60 (m, 6 H), 1.52–1.17 (m, 10 H) ppm. 13 C NMR (100 MHz, CDCl₃): δ = 177.1, 155.6, 153.1, 63.7, 62.4, 62.2, 43.9, 29.3, 28.9, 28.8, 25.7, 25.6, 25.5, 25.3, 14.3, 14.1 ppm. Anal. Calcd for C₁₃H₂₂N₂O₅Na [M + Na]⁺: 309.1421; found: 309.1421. Compound **30**: ¹H NMR (400 MHz, CDCl₃): δ = 7.34 (br, 10 H), 6.76 (br, 1 H), 5.24 (s, 2 H), 5.17 (s, 2 H), 3.46–3.26 (m, 1 H), 2.00–1.14 (m, 10 H) ppm. 13 C NMR (100 MHz, CDCl₃): δ = 176.8, 155.4, 153.0, 135.3, 134.7, 128.6, 128.5, 128.4, 128.1, 69.1, 68.0, 43.9, 29.3, 28.8, 25.7, 25.5, 25.3 ppm. Anal. Calcd for C₂₃H₂₆N₂O₅Na [M + Na]⁺: 433.1734; found: 433.1738.