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A New Route to the Synthesis of (*E*)- and (*Z*)-2-Alkene-4-ynoates and Nitriles from *vic*-Diiodo-(*E*)-alkenes Catalyzed by Pd(0) Nanoparticles in Water

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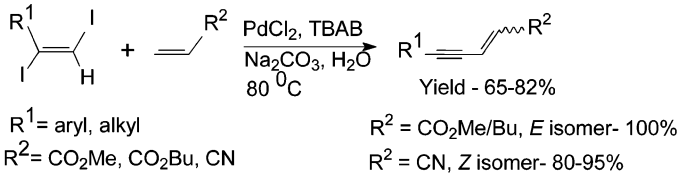
ABSTRACT



An efficient procedure for the stereoselective synthesis of (*E*)- and (*Z*)-2-alkene-4-ynoates and -nitriles by a simple reaction of *vic*-diiodo-(*E*)-alkenes with acrylic esters and nitriles catalyzed by in situ prepared Pd(0) nanoparticles in water has been developed. Addition of acrylic esters leads to (*E*)-isomers exclusively, whereas (*Z*)-isomers are obtained in high stereoselectivity from reactions of acrylonitrile. The aqueous slurry of Pd nanoparticles is recycled. A probable mechanism has been suggested.

The 1,3-enyne unit is of considerable interest in organic synthesis as these moieties are present in many naturally occurring and biologically active compounds[1] such as terbinafine,[2] a potent drug for superficial fungal infections, and calichemicin γ_1,[3] an effective antitumor antibiotic. The enynoates are also very useful synthetic intermediates.[4]

Only a limited number of procedures for the synthesis of conjugated enynes have been developed. One of the most prevalent protocols was Pd−Cu-catalyzed coupling between an alkyne or an organometallic alkyne and a vinyl halide.[5,6] Palladium-catalyzed oxidative alkynylation of alkenes has also been demonstrated to produce enynes.[7b,c] Another alternative approach involved copper-catalyzed coupling of alkynes or alkyne derivatives with vinyl iodides.[8] However, these methods suffer from some limitations such as preparation of an organometallic alkyne and stereodefined vinyl halide through lengthy procedures, poor functional group tolerance, and undesired side products resulting in low yields.[5a,7] We now report a new route involving a simple reaction of *vic*-diiodoalkenes with an activated alkene catalyzed by Pd(0) nanoparticles in water (Scheme 1). The use of metal nanoparticles in reactions generating carbon−carbon bonds has attracted considerable attention in recent times because of their high reactivity, selectivity, and improved yields of products.[9]

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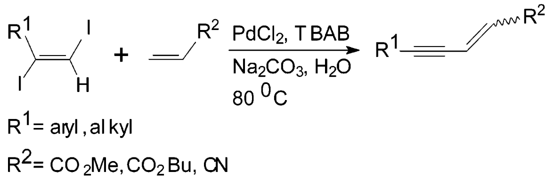
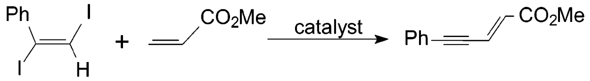
Scheme 1



To identify a suitable catalyst and standardize the reaction condition the reaction of *vic*-(*E*)-diiodostyrene with methyl acrylate was studied with a variety of Pd catalysts at varied experimental conditions. These include $Pd(OAc)_2$/n-Bu_4NBr/Na_2CO_3, $PdCl_2$/TBAB/Na_2CO_3/H_2O, $PdCl_2$/sodium dodecyl sulfate (SDS)/Na_2CO_3/H_2O, $PdCl_2$/TBAI/Na_2CO_3, and $Pd(dba)_3$/P(o-tol)$_3$/Et_3N/CH_3CN. The results were summarized in Table 1. As evident from the results, the $PdCl_2$/TBAB/Na_2CO_3/H_2O system was found to produce the best results in terms of reaction time and yield and thus this reagent system is selected to be used for all the reactions.

Table 1. Standarization of Catalyst



entry	catalytic system	time, condition	yield (%)
1	$Pd(OAc)_2$, TBAB, Na_2CO_3	24 h (rt)	
2	$Pd(OAc)_2$, TBAB, Na_2CO_3	microwave, 1 min (run time), 1 min (hold time), 100 °C, 100 W	20
3	$Pd(OAc)_2$, TBAB, Na_2CO_3 in water	6 h (80 °C)	65
4	$PdCl_2$, TBAB, Na_2CO_3 in water	6 h (80 °C)	82
5	$PdCl_2$, SDS, Na_2CO_3 in water	6 h (80 °C)	
6	$PdCl_2$, TBAI, Na_2CO_3 in water	12 h (80 °C)	10
7	$Pd_2(dba)_3$, P(o-tol)$_3$, Et_3N in CH_3CN	24 h (reflux)	25

The experimental procedure is very convenient.[10] A simple reaction of *vic*-diiodoalkene and conjugated alkene in the presence of the $PdCl_2$/TBAB/Na_2CO_3/H_2O system provided the product. The palladium(0) nanoparticles were produced in situ from this reagent system.[11] The formation of Pd nanoparticles was also detected by us from analysis of the reaction mixture by transmission electron microscopy (TEM) and Energy Dispersive X-ray spectroscopy (EDS). The TEM image and EDS showed the palladium nanoparticles with a size of 2−6 nm (Figures 1 and 2). The slurry of palladium nanoparticles in water was recycled for two runs without any loss of efficiency. After two runs the reactivity decreases.

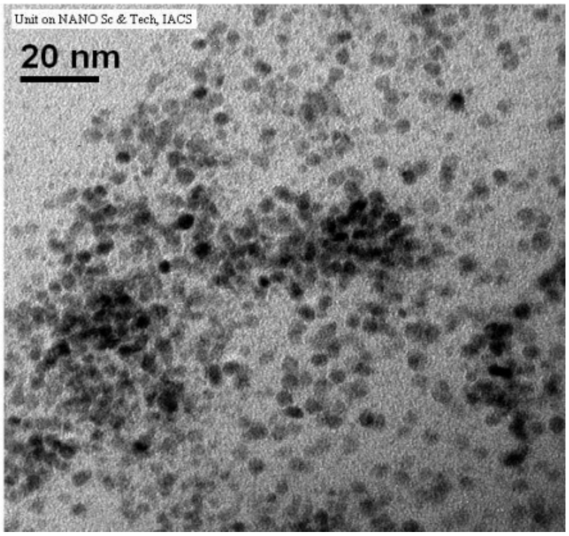


Figure 1. TEM image of Pd nanoparticle formed in the reaction mixture.

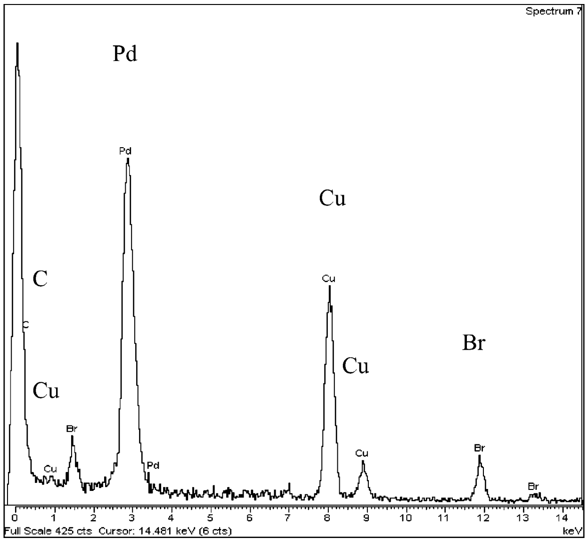


Figure 2. Energy dispersive X-ray spectra with use of a Cu-grid.

Several structurally diverse *vic*-diiodoalkenes underwent reactions with conjugated alkenes such as acrylic ester and

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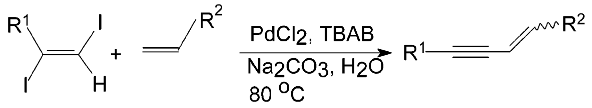
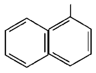
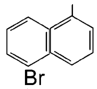
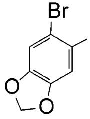
[10] **Representative Experimental Procedure for Enyne Synthesis (entry 4, Table 2).** To a stirred mixture of tetrabutylammonium bromide (323 mg, 1 mmol) and $PdCl_2$ (3.5 mg, 0.02 mmol) in water (3 mL) were added 1-(1,2-diiodovinyl)-4-methylbenzene (370 mg, 1 mmol), methyl acrylate (344 mg, 4 mmol; excess amount was used to avoid any loss during reflux), and Na_2CO_3 (424 mg, 4 mmol). The mixture was then heated at 80 °C (oil bath) for 6 h (TLC). After being cooled the reaction mixture was extracted with Et_2O (3×10 mL). The ether extract was washed with water and brine and dried (Na_2SO_4). The solvent was evaporated under reduced pressure to leave a crude product that was purified by column chromatography over silica gel (ether−hexane 5:95) to afford the pure product, 5-*p*-tolylpent-2-en-4-ynoic acid methyl ester (156 mg, 78%) as a yellow solid: mp 72−73 °C; IR (KBr) 2852, 2193, 1718, 1622 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.33 (s, 3H), 3.78 (s, 3H), 6.28 (d, $J = 15.7$ Hz, 1H), 6.98 (d, $J = 15.7$ Hz, 1H), 7.15 (d, $J = 8.1$ Hz, 2H), 7.37 (d, $J = 8.1$ Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 Hz) δ 21.7, 51.9, 86.0, 99.0, 119.2, 125.7, 129.1, 129.3 (2C), 132.0 (2C), 139.8, 166.6. Anal. Calcd for $C_{13}H_{12}O_2$: C, 77.98; H, 6.04. Found: C, 77.88; H, 5.99. The combined aqueous layer and extract was concentrated under reduced pressure and was used for the next reaction.

[11] Zhang, Z.; Zha, Z.; Gan, C.; Pan, C.; Zhou, Y.; Wang, Z.; Zhou, M.-M. *J. Org. Chem.* **2006**, *71*, 4339.

nitriles catalyzed by in situ prepared Pd(0) nanoparticles in water to produce the corresponding 1,3-enyne esters and nitriles in good yields. The results are summarized in Table 2. The substituents on the aromatic ring of the diiodoalkenes did not have any appreciable effect on the reaction. Both aryl- and alkyl-substituted alkenes participated in this reaction. However, reaction of dibromoalkenes in place of diiodoalkenes produced relatively low yields (30−40%). This method is compatible with a variety of substituents such as OMe, Cl, Br, and methylenedioxy. Significantly, coupling with acrylic esters always provided (*E*)-isomers exclusively, whereas acrylonitriles pushed the reaction to give (Z)-alkenes in high selectivity. This type of high selectivity with CO_2R compared to the relatively small CN group is well addressed in Heck coupling.[12]

Table 2. Cross-Coupling Reaction of Diiodo Compounds with Activated Alkenes

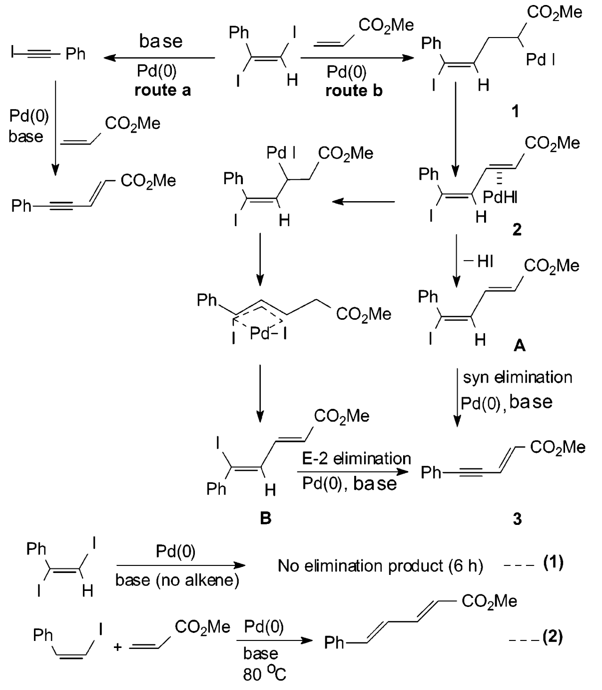


entry	R^1	R^2	time (h)	yield (%)[a]	*E*:*Z*	ref
1	C_6H_5	CO_2Me	6	82	100:00	7b
2	C_6H_5	CO_2Bu	7	78	100:00	7b
3	C_6H_5	CN	6.5	72	10:90	5a
4	*p*-Me-C_6H_4	CO_2Me	6	78	100:00	
5	*p*-Me-C_6H_4	CN	6	72	20:80	
6	*p*-Cl-C_6H_4	CO_2Me	6.5	72	100:00	
7	*p*-Cl-C_6H_4	CN	7	70	5:95	
8	*m*-Br-C_6H_4	CO_2Me	12	68[b]	100:00	
9	*m*-MeO-C_6H_4	CO_2Me	6.5	80	100:00	
10		CO_2Me	6.5	78	100:00	
11		CO_2Bu	7	74	100:00	
12	 Br O O	CO_2Me	9.5	65[b]	100:00	
13	*n*-C_4H_9	CO_2Me	26	78	100:00	
14	*n*-C_6H_{13}	CO_2Bu	24	72	100:00	7c

[a] Yields refer to those of purified products characterized by IR, ^1H, and ^{13}C NMR spectroscopic data [b] Reaction was carried out under sonication.

The mechanism of this reaction has also been investigated. Two alternative routes (a and b) as outlined in Scheme 2 have been considered. In route a the (*E*)-diiodoalkene is proposed to undergo elimination of HI to form iodoalkyne, which then couples with conjugated alkene in Heck fashion catalyzed by Pd(0) to form the enyne. Route b proposes the initial formation of an iodopalladium complex **1** via Heck coupling with conjugated alkene followed by β-elimination to form the hydridopalladium halide π complex **2**, which may give rise to two isomers **A** and **B** by hydridopalladium halide elimination.[13] Now, isomer **A** may lead to the product by syn elimination of HI, and on the other hand, **B** may produce the enyne through E-2 type elimination. On theoretical calculation it was found that **A** is energetically favorable by 0.3 kcal/mol compared to **B**.[14] Thus, the formation of product through intermediate **A** is predicted.

Scheme 2. Possible Mechanism of the Coupling Reaction



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[12] Beletskaya, I. P.; Cheprakov, A. V. *Chem. Rev.* **2000**, *100*, 3009.

[13] Shi, M.; Liu, L.-P.; Tang, J. *J. Org. Chem.* **2005**, *70*, 10420.

[14] The ground state structural calculations for the intermediate products such as *cis* and *trans* ester were computed by using Hartee−Fock (HF/STo-3G) levels with GAUSSIAN software: Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Montgomery, J. A., Jr.; Vreven, T.; Kudin, K. N.; Burant, J. C.; Millam, J. M.; Iyengar, S. S.; Tomasi, J.; Barone, V.; Mennucci, B.; Cossi, M.; Scalmani, G.; Rega, N.; Petersson, G. A.; Nakatsuji, H.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Klene, M.; Li, X.; Knox, J. E.; Hratchian, H. P.; Cross, J. B.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Ayala, P. Y.; Morokuma, K.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Zakrzewski, V. G.; Dapprich, S.; Daniels, A. D.; Strain, M. C.; Farkas, O.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Ortiz, J. V.; Cui, Q.; Baboul, A. G.; Clifford, S.; Cioslowski, J.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Gonzalez, C.; Pople, J. A. *Gaussian 03*, Revision B.03; Gaussian, Inc.: Pittsburgh, PA, 2003.

To check the feasibility of route a, a blank experiment with the starting diiodoalkene under identical experimental conditions without conjugated alkene was carried out, and significantly, no iodoalkyne as predicted in route a was obtained (eq 1). Thus, route a was eliminated. On the other hand, a reaction of *cis*-diiodostyrene with the same conjugated alkene under identical reaction conditions produced the corresponding 1,3-diene (eq 2). This certainly supports route b.

In conclusion, the present protocol using in situ prepared palladium(0) nanoparticles provides a very convenient and efficient method for a one-pot synthesis of conjugated enyne compounds from *vic*-diiodoalkenes. The significant improvements offered by this procedure are operational simplicity, excellent stereoselectivity, general applicability, high isolated yields of products, and reaction in aqueous medium avoiding hazardous organic solvents. To the best of our knowledge this strategy for the stereoselective synthesis of conjugated enynoates and nitriles from diiodoalkenes involving palladium nanoparticles is novel and not reported earlier.

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Supporting Information Available: Characterization (IR, ^{1}H, and ^{13}C NMR spectroscopic data and elemental analysis) for the new compounds reported in Table 2 (listed in entries 4−12 and 14) and ^{13}C NMR spectra of all compounds listed in Table 2. This material is available free of charge via the Internet at http://pubs.acs.org.

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