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Palladium-Catalyzed Synthesis of Highly Substituted Endocyclic Enol Lactones via a Three-Component Coupling Reaction in an Ionic Liquid

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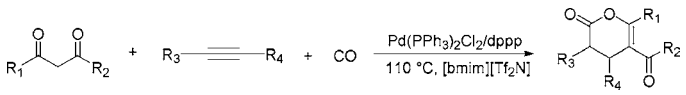
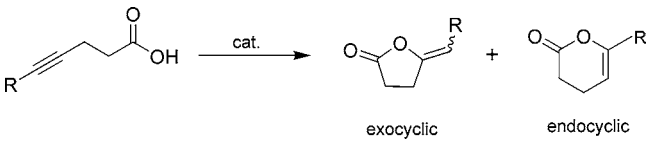
ABSTRACT



A new, efficient ionic liquid based synthetic procedure was developed for the preparation of highly substituted endocyclic enol lactones via the carbonylation coupling reactions of alkynes and 1,3-diketones in ionic liquid. The reactions proceeded in excellent regioselectivity and in reasonably good yields. The catalyst system can be recycled five times with only modest loss of its catalytic activity.

From the standpoint of atom efficiency,[1] the development of highly efficient catalytic addition reactions is an important synthetic goal because these reactions can occur without producing byproducts. Organic reactions in ionic liquids have recently attracted much attention, not only because of the unique reactivity observed but also because an ionic liquid is usually a safe and recyclable substitute for conventional organic solvents.[2] Thus, development of atom-economical reactions in ionic liquids is a desirable goal in synthetic chemistry. Endocyclic enol lactones are versatile synthetic intermediates for organic synthesis[3] and important structural elements of biologically active natural products.[4] In conventional methods, enol lactones were prepared by the cyclization of alkynoic acids under acidic conditions[5] or by employing transition-metal complexes as catalysts[6] (Scheme 1). However, the utility of the acid-catalyzed process suffers from limited scope, drastic conditions, and poor selectivity. Transition-metal complexes catalyze the cyclization of α,ω-alkynoic acids to give both exocyclic and endocyclic enol

Scheme 1. Cyclization of α,ω-Alkynoic Acids To Give Exocyclic and Endocyclic Enol Lactones



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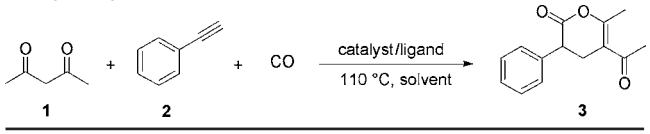
lactones, with the latter formed to a limited extent.[7] Thus, there is interest in developing new methods to prepare endocyclic enol lactones. The Michael addition of 1,3-dicarbonyl compounds to α,β-unsaturated compounds is considered as an alternative.[8] Recently, we described the regiospecific palladium-catalyzed aminocarbonylation of alkynes in the ionic liquid, [bmim][Tf_2N], affording α-methylene amides in good yields.[9] We herein report a convenient and practical one-pot synthesis of highly substituted endocyclic enol lactones from the reaction of an alkyne, a 1,3-dicarbonyl compound, and carbon monoxide in [bmim][Tf_2N].

The initial study was carried out using phenylacetylene and 2,4-pentanedione as the substrates to optimize the reaction conditions, and the results are summarized in Table 1.

Table 1. Optimization of the Reaction Conditions for the Palladium-Catalyzed Three-Component Coupling Reaction of Phenylacetylene with 2,4-Pentanedione and Carbon Monoxide[a]



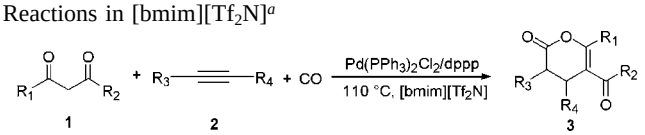
1 2 3

entry	catalyst/ligand	solvent	1:2	yield[b] (%)
1	$Pd(OAc)_2$/dppp	[bmim][Tf_2N]	1:2	43
2	$Pd(OAc)_2$/dppp	[bmim]PF_6	1:2	30
3	$Pd(OAc)_2$/dppp	[bmim][Tf_2N]	2:1	60
4	$Pd(OAc)_2$/dppp	Toluene	2:1	trace
5	$Pd(OAc)_2$/dppp	DCE	2:1	4
6	$Pd(PhCN)_2Cl_2$/dppp	[bmim][Tf_2N]	2:1	33
7	$Pd(PPh_3)_2Cl_2$/dppp	[bmim][Tf_2N]	2:1	63
8	$Pd(PPh_3)_2Cl_2$/dppp	[bmim][Tf_2N]	1:1	36
9	$Pd(PPh_3)_2Cl_2$/dppp	[bmim][Tf_2N]	2:1	9[c]
10	$Pd(PPh_3)_2Cl_2$/dppp	[bmim][Tf_2N]	2:1	43[d]
11	$Pd(PPh_3)_2Cl_2$/dppp	[bmim][Tf_2N]	2:1	0[e]
12	$Pd(PPh_3)_2Cl_2$/dppp	[bmim][Tf_2N]	2:1	46[f]
13	$Pd(PPh_3)_2Cl_2$	[bmim][Tf_2N]	2:1	trace
14	$Pd(PPh_3)_2Cl_2$/dppb	[bmim][Tf_2N]	2:1	49
15	$Pd(PPh_3)_2Cl_2/PPh_3$	[bmim][Tf_2N]	2:1	35
16	$Pd(PPh_3)_2Cl_2$/(+/-)-BINAP	[bmim][Tf_2N]	2:1	39
17	$Pd(PPh_3)_2Cl_2$/dppp	DMF	2:1	trace
18	$Pd(PPh_3)_2Cl_2$/dppp	CH_3CN	2:1	26
19	$Pd(PPh_3)_4$/dppp	[bmim][Tf_2N]	2:1	31

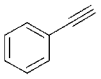
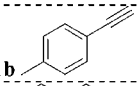
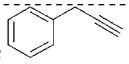
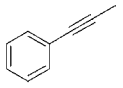
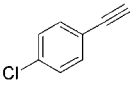
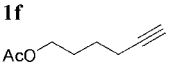
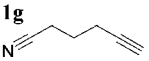
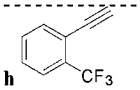
[a] Reaction conditions: **1** (1 or 2 mmol), **2** (2 or 1 mmol), palladium catalyst (0.03 mmol), ligand (0.06 mmol), CO (200 *psi*), solvent (2 g), 110 °C, 24 h. [b] Isolated yields. [c] 0.06 mmol of *p*-TsOH. [d] 0.06 mmol of Et_3N. [e] 1 mmol of K_2CO_3. [f] CO (400 *psi*).

The reaction is sensitive to solvents. The best result was achieved in the ionic liquid [bmim][Tf_2N]. It should be noted that only trace amount of the desired carbonylation product was detected when toluene, DMF, or DCE was used as the reaction medium (Table 1, entries 4, 5, and 17). Presence of an acid or base led to poor yields (entries 9−11). Increase of CO pressure resulted in a slight decrease of the yield (entry 12). Various palladium reagents and ligands were tested for the coupling reaction (Table 1). It was found that only trace amount of the product was detected without a ligand (entry 13). On the basis of the results, $Pd(PPh_3)_2Cl_2$/dppp was chosen as the catalyst precursor in [bmim][Tf_2N] at 200 *psi* of carbon monoxide.

Table 2. Palladium-Catalyzed Three-Component Coupling Reactions in [bmim][Tf_2N][a]



1 2 3

entry	alkyne	1,3-diketone	product	yield (%)[b]
1		**2a** R_1=R_2=Me	**3a**	63
2		**2b** R_1=Me, R_2=Ph	**3b**	60[c]
3	 **1a**	**2c** R_1=R_2=Ph	**3c**	61
4		**2d** R_1=Ph, R_2=OEt	**3d**	50
5		**2e** R_1=R_2=OEt		0
6		**2a**	**3e**	63
7		**2b**	**3f**	75
8	 **1b**	**2c**	**3g**	72[c]
9	 **1c**		**3h**	63
10	 **1d**			0[d]
11	 **1e** Cl	**2c**	**3i**	32
12	**1f**  AcO		**3j**	53[c]
13	**1g**  N		**3k**	51[c]
14	 **1h** CF_3	**2a**	**3l**	74
15	**1h**	**2c**	**3m**	44

[a] Alkyne **1** (2 mmol), 1,3-dicarbonyl compound **2** (1 mmol), $Pd(PPh_3)_2Cl_2$ (0.03 mmol), dppp (0.06 mmol), CO (200 *psi*), [bmim][Tf_2N] (2 g), 110 °C, 24 h. [b] Yields after isolation by silica gel column chromatography. [c] (±)-BINAP instead of dppp. [d] The starting material was recovered.

The generality of the present synthetic method was extended to different alkynes and 1,3-diketones. Treatment of phenylacetylene **1a** with different 1,3-dicarbonyl compounds afforded the corresponding endo enol lactones in excellent regioselectivity (Table 2, entries 2−4). However,

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diethyl malonate was unreactive (entry 5). Next, aliphatic and aromatic terminal alkynes and 1,3-diketones were employed for the coupling reaction (Table 2). Aliphatic alkynes were found to be less reactive than aromatic alkynes. In some instances, higher yields were obtained by using (±)-BINAP as the ligand instead of using dppp (entries 2 and 8, 12 and 13). Unfortunately, the use of internal alkynes, such as 3-phenyl-1-propyne, yielded none of the enol lactone under the same conditions (entry 10).

The recyclability of the catalyst system for the palladium-catalyzed three-component coupling reaction was investigated in [bmim][Tf_2N] (Table 3). After completion of the

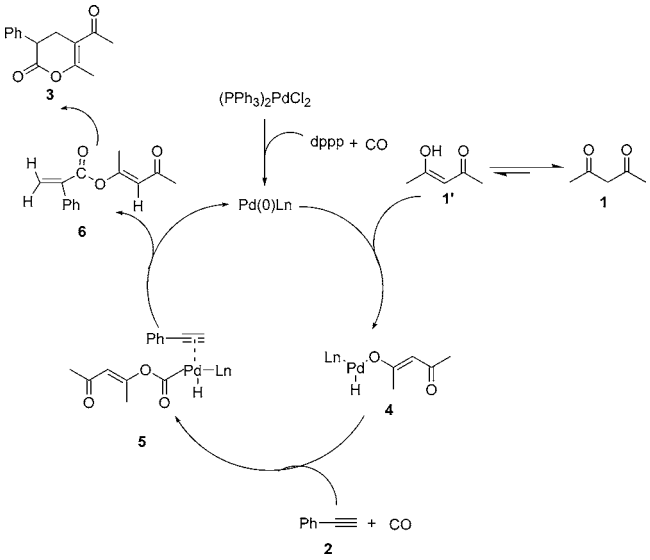
Table 3. Recycling of the Catalytic System for the Palladium-Catalyzed Three-Component Coupling Reaction

entry	alkyne	1,3-diketone	product	run/reaction time (h)	yield[b] (%)
1	**1a**	**2a**	**3a**	1/24	63
2				2/40	61
3				3/40	62
4				4/40	61
5				5/40	63
6	**1b**	**2c**	**3g**	1/24	72
7				2/26	64
8				3/36	80
9				4/40	74
10				5/40	77

first run, the product was isolated by simple extraction with diethyl ether. Fresh alkyne and 1,3-dicarbonyl compound were added to the remaining ionic liquid for the next run. Due to the good solubility of $Pd(PPh_3)_2Cl_2$ and dppp in the ionic liquid, reuse of the catalyst was performed with only modest loss of its catalytic activity after five runs.

A possible mechanism for the reaction is illustrated using the palladium-catalyzed carbonylation of phenylacetylene with 2,4-pentanedione (Scheme 2). The reaction may proceed by initial $Pd(PPh_3)_2Cl_2$ reduction to palladium(0),[10] followed by oxidative addition of the enol of 1,3-diketone **1′** to the palladium(0) complex to form **4**,[11] which undergoes coor-

Scheme 2. Proposed Reaction Mechanism



dination to the triple bond of the alkyne and then insertion of carbon monoxide to form **5**. Regioselective intramolecular acylpalladation of the latter and subsequent reductive elimination produces the linear precursor **6** and regenerates the palladium(0) species.[12] An intramolecular cyclization of the vinyl acetate on the activated double bond would then give the 6-membered enol lactone **3**.

In conclusion, we have developed a new, efficient synthetic procedure for preparing highly substituted endocyclic enol lactones via the carbonylation coupling of alkynes and 1,3-dicarbonyl compounds in [bmim][Tf_2N]. The reactions proceeded with excellent regioselectivity and in all cases compound **3** was formed as the only isolated product. Endocyclic enol lactones were obtained in moderate to good yields, and the catalyst system can be recycled five times with only modest loss of its catalytic activity.

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Supporting Information Available: Experimental procedures, spectroscopic data, and copies of ^1H and ^{13}C NMR spectra for the acrylamide products. This material is available free of charge via the Internet at http://pubs.acs.org.

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(12) A similar mechanism of acetylene insertion into Pd−COσ bonds was reported. See: Samsel, E. G.; Norton, J. R. *J. Am. Chem. Soc.* **1984**, *106*, 5505−5512.