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Tetrahedron Letters 46 (2005) 2563-2566

Tetrahedron Letters

## Phosphine-catalyzed regioselective heteroaromatization between activated alkynes and isocyanides leading to pyrroles

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Received 15 January 2005; revised 7 February 2005; accepted 16 February 2005

Abstract—The organophosphine catalyzed reaction of activated alkynes with isocyanides produces the corresponding heteroaromatization products, pyrroles, regioselectively in good yields. The reaction proceeds most probably through the 1,4-addition of the nucleophilic phosphine catalyst to the alkynes, followed by a [3+2] cycloaddition between the resulting alkenyl phosphine intermediates and a carbanion derived from the isocyanides.

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One of the rapidly growing research areas in the field of synthetic organic chemistry is catalytic transformations using simple organic molecules called organocatalysts.<sup>1</sup> Various types of organic molecules have already been found to act as organocatalysts and phosphines are useful for this purpose. It is known that the isomerization, cyclization, and addition reactions of electron-deficient alkynes and allenes are catalyzed by organophosphines.<sup>2</sup> However, to the best of our knowledge, a phosphine-catalyzed intermolecular heteroaromatization reaction is not known.<sup>3</sup> We report herein that the reaction of the alkynes **1**, activated with an electron withdrawing group (EWG<sup>1</sup>), with isocyanides **2** bearing an EWG<sup>2</sup> is catalyzed by organophosphines to give the pyrroles **3**, regioselectively, in good yields Eq. 1.<sup>4</sup>



During research on the palladium–copper bimetallic catalyzed three-component coupling reaction between alkynes (or isocyanides), allyl carbonates, and TMS azide,<sup>5</sup> we discovered that copper-phosphine complexes catalyzed the reaction between ethyl 2-butynoate (1a)and ethyl isocyanoacetate (2a) to form the pyrrole 3ain variable yields. The effect of phosphine additives on the yields is summarized in Table 1. Arylphosphines

Table 1. Effect of phosphine additives on the yields of  $3a^{a}$ 

Entry	Phosphine	NMR yield <sup>b</sup> (%)	
1 <sup>c</sup>	PPh <sub>3</sub>	50	
2	$(p-MeO-C_6H_4)_3P$	38	
3	$(p-CF_3-C_6H_4)_3P$	0	
4	(o-Tolyl) <sub>3</sub> P	0	
5	PBu <sub>3</sub>	34	
6	(Cyclohexyl) <sub>3</sub> P	13	
7 <sup>d</sup>	dppe <sup>e</sup>	50	
8 <sup>d</sup>	dppp <sup>f</sup>	63	
9 <sup>d</sup>	dppb <sup>g</sup>	50	
10 <sup>d</sup>	dppf <sup>h</sup>	25	
11 <sup>d</sup>	BINAP <sup>i</sup>	0	

<sup>a</sup> Unless otherwise noted, the reaction of **1a** (R = Me, EWG<sup>1</sup> = CO<sub>2</sub>Et, 0.6 mmol) and **2a** (EWG<sup>2</sup> = CO<sub>2</sub>Et, 0.5 mmol) was conducted in 1,4-dioxane (1 mL) in the presence of CuCl (50 µmol, 10 mol%) and phosphine (150 µmol, 30 mol%) at 100 °C for 6 h.

<sup>b</sup> NMR yield using p-xylene as an internal standard.

 $^{\rm c}$  CuCl(PPh\_3)\_3 (50  $\mu mol,$  10 mol %) was used as a catalyst instead of CuCl and PPh\_3.

 $^{\rm d}$  15 mol % of bidentate phosphine was used.

<sup>e</sup> dppe = 1,2-bis(diphenylphosphino)ethane.

<sup>g</sup> dppb = 1,4-bis(diphenylphosphino)butane.

<sup>h</sup> dppf = 1,1'-bis(diphenylphosphino)ferrocene.

<sup>i</sup> BINAP = 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl.

*Keywords*: Organocatalyst; Phosphine catalyzed reaction; Heteroaromatization; Activated alkyne; Isocyanide; Pyrrole; [3+2] Cycloaddition.

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<sup>0040-4039/\$ -</sup> see front matter @ 2005 Elsevier Ltd. All rights reserved. doi:10.1016/j.tetlet.2005.02.104

<sup>&</sup>lt;sup>f</sup>dppp = 1,3-bis(diphenylphosphino)propane.

such as PPh<sub>3</sub> and electron rich tris(*p*-methoxyphenyl)phosphine produced the corresponding pyrrole 3a in moderate yields (entries 1 and 2), whereas electron deficient tris(*p*-trifluoromethylphenyl)phosphine and sterically congested tri(o-tolyl)phosphine did not catalyze the reaction at all (entries 3 and 4). Alkylphosphines were less effective than PPh<sub>3</sub> (entries 5 and 6). The reactivity of the bidentate phosphines, such as dppe, dppp, and dppb, were comparable to that of PPh<sub>3</sub> (entries 7-9). Among them,  $dppp^6$  gave the highest yield of the desired pyrrole 3a. The employment of dppf and BINAP did not improve the yield of 3a. Very interestingly, further studies disclosed that the present heteroaromatization could be catalyzed merely by a phosphine such as dppp, without the aid of CuCl. The reaction of various alkynes 1 with 2a was carried out under the optimal conditions; dppp (15 mol %) in 1,4-dioxane at 100 °C. The results are summarized in Table 2.

The reaction between 1a and 2a was completed in 2 h to give the corresponding pyrrole 3a in 60% yield (entry 1).<sup>7</sup> The alkyne **1b** bearing a hexyl group afforded the pyrrole **3b** in 73% yield (entry 2). Even the unprotected alkynyl alcohol 1c could be used directly as a starting material and produced the corresponding product 3c in 59% yield (entry 3). The reaction of the alkyne 1d having a cyclohexyl group proceeded smoothly to produce the pyrrole 3d in 66% yield after 24 h (entry 4). When this reaction was carried out in the presence of a catalytic amount of CuCl, the reaction time was reduced without affecting the yield of 3d (entry 5).<sup>8</sup> In the case of the alkyne **1e** bearing a bulky *t*-butyl group, no reaction took place even after 24 h and significant amounts of the starting materials were recovered (entry 6). The reactions of alkynes 1f-h conjugated with an aryl group gave the corresponding pyrroles **3f-h**, respectively (entries 7–9). The introduction of an electron donating group on the aromatic ring slightly retarded the consumption of the alkyne 1g, though the product 3g was obtained in a high yield (entry 8). On the contrary, the introduction of an electron withdrawing group shortened the reaction time but the yield of **3h** remained moderate (entry 9). The reaction of an electron deficient alkyne, diethyl acetylenedicarboxylate **1i**, gave a complex mixture of unidentified products, probably due to polymerization (entry 10). It is worthy to mention that the alkynyl ketone **1j** and alkynyl cyanide **1k** served as a starting material to afford the corresponding pyrroles **3j** and **3k** in 77% and 35% yields, respectively (entries 11 and 12).



We next examined the reactions between ethyl phenylpropiolate (1f) and the isocyanides 2b-d (Eq. 2). Installation of a bulky *t*-butyl group in the ester moiety, as shown in 2b, did not affect the reaction progress and the corresponding pyrrole 3l was produced in 70% yield. The isocyanides having amide 2c and phosphonate groups 2d afforded the corresponding pyrroles 3m and 3n, respectively, however the yields were rather low.

We applied this heteroaromatization reaction to the synthesis of the trail pheromone  $4^9$  of a leaf-cutting ant, which contains a pyrrole ring as a core structure (Scheme 1). The alkynoate 11 was prepared by DCC condensation between 2-butynoic acid and 2-(trimethylsilyl)ethanol. The phosphine-catalyzed heteroaromatization between 11 and methyl isocyanoacetate proceeded smoothly to afford the corresponding pyrrole 30 in 64% yield. Protection of the pyrrole nitrogen using Boc group, followed by treatment with TBAF gave the pyrrole carboxylic acid. Decarboxylation was carried out using Cu(OAc)<sub>2</sub> in <sup>i</sup>Pr<sub>2</sub>NEt/anisole<sup>10</sup> to produce the final target molecule 4.

Table 2. Phosphine-catalyzed pyrrole synthesis using various alkynes 1 and 2a<sup>a</sup>

R	$EWG^1$	1	Time (h)	3	Yield (%)
Me	CO <sub>2</sub> Et	1a	2	3a	60
CH <sub>3</sub> (CH <sub>2</sub> ) <sub>5</sub>	CO <sub>2</sub> Et	1b	12	3b	73
$HO(CH_2)_4$	CO <sub>2</sub> Et	1c	2	3c	59
$cyclo-C_6H_{11}$	CO <sub>2</sub> Et	1d	24	3d	66
$cyclo-C_6H_{11}$	CO <sub>2</sub> Et	1d	19	3d	64
t-Bu	CO <sub>2</sub> Et	1e	24	3e	c
Ph	CO <sub>2</sub> Et	1f	1.5	3f	79
<i>p</i> -MeO–C <sub>6</sub> H <sub>4</sub>	CO <sub>2</sub> Et	1g	3.5	3g	79
$p-CF_3-C_6H_4$	CO <sub>2</sub> Et	1h	0.75	3h	48
CO <sub>2</sub> Et	CO <sub>2</sub> Et	1i	0.5	3i	d
Ph	COMe	1j	1	3j	77
Ph	CN	1k	0.5	3k	35
	$\frac{R}{CH_3(CH_2)_5} \\ HO(CH_2)_4 \\ cyclo-C_6H_{11} \\ cyclo-C_6H_{11} \\ t-Bu \\ Ph \\ p-MeO-C_6H_4 \\ p-CF_3-C_6H_4 \\ CO_2Et \\ Ph \\ Ph \\ Ph \\ \end{array}$	R         EWG <sup>1</sup> Me $CO_2Et$ $CH_3(CH_2)_5$ $CO_2Et$ $HO(CH_2)_4$ $CO_2Et$ $cyclo-C_6H_{11}$ $CO_2Et$ $cyclo-C_6H_{11}$ $CO_2Et$ $PH$ $CO_2Et$ $P-MeO-C_6H_4$ $CO_2Et$ $p-CF_3-C_6H_4$ $CO_2Et$ Ph $CO_2Et$	$\begin{array}{c c c c c c c c c c c c c c c c c c c $	$\begin{array}{c c c c c c c c c c c c c c c c c c c $	REWG11Time (h)3Me $CO_2Et$ 1a23a $CH_3(CH_2)_5$ $CO_2Et$ 1b123b $HO(CH_2)_4$ $CO_2Et$ 1c23c $cyclo-C_6H_{11}$ $CO_2Et$ 1d243d $cyclo-C_6H_{11}$ $CO_2Et$ 1d193d $t^+Bu$ $CO_2Et$ 1e243ePh $CO_2Et$ 1f1.53f $p-MeO-C_6H_4$ $CO_2Et$ 1g3.53g $p-CF_3-C_6H_4$ $CO_2Et$ 1h0.753h $CO_2Et$ CO_2Et1i0.53iPh $COMe$ 1j13jPh $CN$ 1k0.53k

<sup>a</sup> Unless otherwise noted, the reaction between 1 (0.5 mmol) and 2a (EWG<sup>2</sup> = CO<sub>2</sub>Et, 0.6 mmol) was conducted in 1,4-dioxane (1 mL) in the presence of dppp (75 µmol, 15 mol%) at 100 °C for the time indicated.

<sup>b</sup> CuCl (25 μmol, 5 mol %) was added.

<sup>c</sup>A significant amount of the alkyne 1e and the isocyanide 2a were recovered.

<sup>d</sup> Complex mixture.



Scheme 1. Synthesis of the ant trail pheromone 4. Reagents and conditions: (a) 1,3-dicyclohexylcarbodiimide (DCC), pyridine,  $CH_2Cl_2$ , 0 °C, 1 h, 94%; (b) dppp (15 mol %), 1,4-dioxane, 100 °C, 7 h, 64%; (c) (Boc)<sub>2</sub>O, 4-dimethylaminopyridine (10 mol %),  $CH_3CN$ , rt, 13 h, 93%; (d) TBAF, THF, 60 °C, 8 h; (e)  $Cu(OAc)_2$  (2 equiv), anisole, <sup>*i*</sup>Pr<sub>2</sub>NEt, 130 °C, 12 h, 42% for two steps.



Scheme 2. A plausible mechanism for the phosphine-catalyzed heteroaromatization.

A plausible mechanism is depicted in Scheme 2. The present heteroaromatization is most probably initiated by the 1,4-addition of the nucleophilic phosphine catalyst to the activated alkynes 1 to form the zwitterionic intermediate A.<sup>11</sup> The abstraction of an acidic proton of the isocyanide 2 gives the cationic intermediate **B** and the carbanion 2'. The carbanion would attack the carbon bearing the EWG<sup>1</sup> of  $B^{12}$  and the newly formed anionic center would attack the isocyanide carbon of 2' to form the cyclic intermediate **C**; this is a [3+2] cycloaddition process. Intramolecular proton migration and elimination of the phosphine catalyst produces the intermediate **D**. Subsequent 1,5-hydrogen shift furnishes the pyrrole **3** as the final product.

We have developed a new phosphine-catalyzed condensation between the alkynes 1 and isocyanides 2, which produces the pyrroles 3 regioselectively. This new method was applied to the synthesis of ant trail pheromone 4. Further studies on the synthetic application of this new transformation and on the mechanistic details are underway in our laboratory.

## Acknowledgements

We thank the faculty members in the Research and Analytical Center for Giant Molecules at the Graduate School of Science, Tohoku University for the measurement of NMR spectra, mass spectra, and elemental analysis.

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- 7. Representative experimental procedure for the phosphinecatalyzed heteroaromatization leading to the pyrrole **3**: To a 1,4-dioxane solution (1 mL) of 1,3-bis(diphenylphosphino)propane (dppp) (30.9 mg, 75  $\mu$ mol) were added ethyl butynoate (**1a**) (58  $\mu$ L, 0.5 mmol) and ethyl isocyanoacetate (**2a**) (66  $\mu$ L, 0.6 mmol) under an Ar atmosphere. The solution was stirred at 100 °C for 2 h. After the consumption of **1a**, the reaction mixture was cooled to room temperature and filtered through a short Florisil pad and concentrated. The residue was purified by column chromatography (silica gel, *n*-hexane/AcOEt 50:1–3:1) to afford 2,3-di(ethoxycarbonyl)-4-methylpyrrole (**3a**) in 60% yield as a colorless oil (67.1 mg). <sup>1</sup>H NMR (600

MHz, CDCl<sub>3</sub>): δ 1.32 (3H, t, J = 7.2 Hz), 1.35 (3H, t, J = 7.2 Hz), 2.14 (3H, d, J = 0.6 Hz), 4.30 (2H, q, J = 7.2 Hz), 4.33 (2H, q, J = 7.2 Hz), 6.65 (1H, dd, J = 2.8, 0.8 Hz), 9.29 (1H, br s, *NH*); <sup>13</sup>C NMR (75.5 MHz, CDCl<sub>3</sub>): δ 10.87, 14.24 (× 2), 60.66, 60.79, 120.09, 120.55, 121.79, 122.11, 160.19, 165.56; IR (neat) 3308, 1705, 1699, 1279, 1259, 1194, 1126, 1078, 1036 cm<sup>-1</sup>; HRMS (EI) Calcd for C<sub>11</sub>H<sub>15</sub>NO<sub>4</sub> (M<sup>+</sup>) 225.099. Found: 225.099.

- 8. The CuCl catalyst probably coordinates both dppp and the isocyanide in this case. The coordination to the isocyanide makes it easy to generate the anionic intermediate 2' in Scheme 2 and stabilizes the derived species. Moreover, the ligation to the phosphine holds intermediates **B** and 2' close together and accelerates the formation of the cyclized intermediate **C**.
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