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A Pd-CATALYZED DOUBLE COUPLING REACTION TO 4,5-DISUBSTITUTED IMIDAZOLE ALKYNES

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Abstract: A palladium-catalyzed double coupling reaction of 4,5-diiodoimidazoles **2**, which were prepared by diiodination of imidazole, and terminal alkynes provided the corresponding imidazole diynes **3**.

Since the first introduction of the convenient Pd-catalyzed reaction of aryl halides and terminal alkynes in 1975,¹ numerous arylalkyne derivatives have been developed in pursuit of their new properties.² Especially, in developing new medicinal agents, heterocyclic alkynes prepared thus have been utilized as valuable intermediates.^{2b,3} And disubstitued alkynes have been furnished simultaneously or stepwise from the corresponding dihalides using same or different terminal ethynyl compounds.⁴

In line with our interest in the related derivatives we have tried to develop a practical method for the synthesis of 4,5-disubstituted imidazole alkynes. The imidazole moiety has its ubiquitous appearance in the structure of biologically

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active molecules and is known to play a critical role in the activity of these compounds.⁵ In addition to the core imidazole functionality, the 4,5-disubstituted disubstituted imidazole alkynes contain an enediyne moiety which may undergo Bergman reaction.⁶ As far as we have searched, however, disubstitution reactions of the imidazole to the corresponding alkynes have been rarely attempted. Therefore, herein we describe a practical way to the imidazole diynes.



In order to prepare the compounds, firstly, the precursor compounds of the palladium coupling reaction, 4,5-diiodoimidazoles 2, have been readily prepared by diiodination of 2-substituted imidazoles 1 using N-iodosuccinimide in DMF as described.⁷ The yields were 90% in the formation of 2b and quantitative in the formations of 2a, 2c, and 2d after crystallization from the reaction mixture or prompt silicagel column chromatography. Secondly, the cross coupling reaction of diiodides 2 and alkynes was carried out by a typical procedure employing a catalytic amount of dichlorobis(triphenylphosphine)palladium and copper(I) iodide with an organic base such as Et₃N or Hunig's base in THF or DMF solvent.⁸ The results appear in Table 1. Trimethylsilylacetylene was coupled with the diiodides

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Table 1. Diiodination and palladium-catalized coupling reactions

yield (%) ^b	32%	68%	17%	71%	34%	68%	44%	68
			_			ОТНР	ОТНР	OTHP
	R ₃ =TMS	I ₃ R ₃ =TMS	I ₃ R ₃ =CH ₂ OF	3₀=TMS	R ₃ =CH ₂ OH		R ₃ =	R ₃ =
diynes 3°	_з R ₂ =Н	H ₃ R ₂ =CH	H₃ R₂=CH	$R_2 = H F$	h R ₂ =H	R2=CH	R ₂ =CH ₃	R ₂ =CH ₃
	a' R,=CH	b,ª R,=CH	b2 [®] R ₁ =CI	a,ª R₁=Ph	c₂ ^d R1=PI	d₁ ^f R₁=Ph	l₂ ^f R₁=Ph	3 ^f R₁=Ph
	3,	3	3	30	ň	ñ	3d	39
yield (%) ^b	Quant.	%06		Quant.		Quant.		
2ª	$R_2=H$	$R_2 = CH_3$		R₂=H		R ₂ =CH ₃		
diiode	R ₁ =CH ₃	R ₁ =CH ₃		R,=Ph		R ₁ =Ph		
	2a	2b		20		2d		
entry	-	7	Э	4	5	Q	2	ω

4,5-DISUBSTITUTED IMIDAZOLE ALKYNES

 a Ref. (8) b Isolated yield c Ref. (9) d Pd(0) / NEt₃ / THF, π c Pd(0) / *i*Pr₂NEt / THF, π f Pd(0) / *i*Pr₂NEt / DMF, 60 $^{\circ}$ C

2a, 2b, and 2c to afford diynes 3a, $3b_1$, and $3c_1$ in 32%, 68%, and 71% yield, respectively. On the other hand, only 17% of $3b_2$ and 34% of $3c_2$ could be prepared in the couplings of 2b and 2c with propargyl alcohol. THP ethers of ethynylbenzyl alcohols were also coupled with 2d to yield the corresponding diynes $3d_1$, $3d_2$, and $3d_3$ in 68%, 44%, and 89% yields, respectively. By-products detected only in small yields have been found to be monosubstituted alkynes.

In summary, we could prepare 4,5-diiodo imidazoles in good yield and the desired imidazole diynes, on the whole, in serviceable yields under standard palladium-catalyzed coupling conditions. Further studies on the transformation and the property of those molecules are under progress.

EXPERIMENTALS

Representative procedure: Dichlorobis(triphenylphosphine)palladium (100 mg, 0.144 mmol) and copper(I) iodide (28 mg, 0.144 mmol) were added to a mixture of diiodide **2b** (1.99 g, 2.87 mmol) and trimethylsilylacetylene (845 mg, 8.61 mmol) in THF (3 mL)/ triethylamine (2 mL) at rt. The reaction mixture was stirred overnight at rt and then diluted with ethylacetate, washed with water three times, and dried over MgSO₄. Removal of solvent followed by column chromatography (silica gel, hexane:ethylacetate = 10:1) afforded diyne **3b**₁ in 68% yield.

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- (8) 2a: mp: 208-210°C; ¹H NMR (300 MHz, CDCl₃) δ 2.78 (s, 3H). ¹³C NMR (75MHz, MeOH-d4) δ 150.57, 82.73, 13.14. 2b: mp: 200-202°C; ¹H NMR (300 MHz, MeOH-d4) δ 3.60 (s, 3H), 2.48 (s, 3H). ¹³C NMR (75 MHz, MeOH-d4) δ 149.34, 91.79, 82.35, 35.35, 13.52. 2c: mp: 199-201°C; ¹H NMR (300 MHz, DMSO-d6) δ 7.31-7.50 (m, 3H), 7.89 (m, 2H). ¹³C NMR (75 MHz, DMSO-d6) δ 124.7, 128.7, 128.7, 128.8, 128.9, 151.4.
- (9) 3a: ¹H NMR (300 MHz, CDCl₃) δ 8.84 (bs, 1H), 2.46 (s, 3H), 0.22 (s, 18H). 3b₁: ¹H NMR (300 MHz, CDCl₃) δ 3.49 (s, 3H), 2.35 (s, 3H), 0.26 (s, 9H), 0.21 (s, 9H). 3b₂: mp: 190-192 °C; ¹H NMR (300 MHz, MeOH-d4) δ 4.48 (s, 2H), 4.39 (s, 2H), 3.57 (s, 3H), 2.34 (s, 3H). 3c₁: ¹H NMR (300 MHz, CDCl₃) δ 9.63 (bs, 1H), 7.84 (m, 2H), 7.41 (m, 3H), 0.25 (s,18H). 3c₂: mp: 157-158 °C; ¹H NMR (300 MHz, MeOH-d4) δ 7.84 (m,

2H), 7.42 (m, 3H), 4.48 (s,4H). $3d_1$: ¹H NMR (300 MHz, CDCl₃) δ 7.70 (m, 2H), 7.58 (m, 4H), 7.47 (m, 3H), 7.41-7.22 (m, 4H), 5.03 (t, *J*=13.1 Hz, 2H), 4.84 (t, *J*=12.9 Hz, 2H), 4.72 (t, *J*=3.6 Hz, 1H), 4.69 (t, *J*=3.5 Hz, 1H), 3.86 (m, 2H), 3.83 (s, 3H), 3.48-3.38 (m, 2H), 1.68 (m, 4H), 1.49 (m, 6H). $3d_2$: 1H NMR (300 MHz, CDCl₃) δ 7.68 (m, 2H), 7.59 (m, 2H), 7.47 (m, 5H), 7.39 (m, 2H), 7.33 (m, 2H), 4.79 (2d, *J*=9.2 Hz, 2H), 4.73 (m, 2H), 4.51 (2d, *J*=9.2 Hz, 2H), 3.92 (m, 2H), 3.81 (s, 3H), 3.55(m, 2H), 1.52-1.88 (m, 12H). $3d_3$: ¹H NMR (300 MHz, CDCl₃) δ 7.68 (m,2H), 7.55 (m, 4H), 7.46 (m, 3H), 7.36 (m, 4H), 4.80 (2d, *J*=6.3Hz, 2H), 4.71 (m, 2H), 4.52 (2d, *J*=6.6 Hz, 2H), 3.90 (m,2H), 3.80 (s, 3H), 3.54 (m, 2H), 1.46-1.92 (m, 12H).

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