ORGANIC LETTERS

2001
Vol. 3, No. 16
2501−2504

Preparation of 2,5-Disubstituted Oxazoles from *N*-Propargylamides

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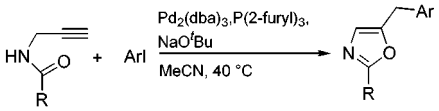
Received May 17, 2001

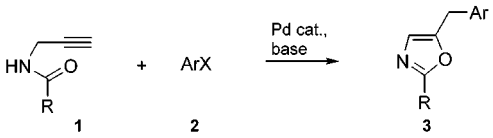
ABSTRACT



2,5-Disubstituted oxazoles have been prepared through the reaction of *N*-propargylamides with aryl iodides in the presence of $Pd_2(dba)_3$, tri(2-furyl)phosphine, and NaO^{t}Bu. The reaction appears to proceed through a palladium-catalyzed coupling step followed by the in situ cyclization of the resultant coupling product.

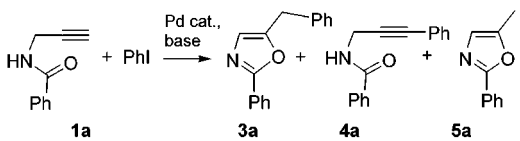
The occurrence of the oxazole nucleus in a wide variety of natural and unnatural biologically active compounds,[1] as well as the utilization of oxazoles as useful reagents in organic synthesis,[2] has provided a continuing stimulus for the development of more general and versatile synthetic methodologies to this class of compounds.[3] As part of our program devoted to the study of the heteropalladation−reductive elimination domino reaction of internal and terminal alkynes,[4] we decided to explore the possible utilization of this methodology for the preparation of functionalized oxazoles. Specifically, we thought that *N*-propargylamides **1** could represent suitable building blocks for the preparation of 2,5-disubstituted oxazoles **3** (Scheme 1), whose basic substitution pattern is present, for example, in a novel pseudomonic acid analogue exhibiting inhibition activity of the isoleucyl t-RNA synthetase from *Staphylococcus aureus* NCTC 6571.[5]

Scheme 1



The reaction of **1a** with iodobenzene (our model system) under conditions expected to give the desired oxazole product [$Pd_2(dba)_3$, PPh_3, K_2CO_3, 24 h, 40 °C], however, produced **3a** in low yield (10% in DMF and 8% in THF) along with the coupling derivative **4a** (19% in DMF and 10% in THF) (Scheme 2). The employment of a stronger base such as

Scheme 2



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10.1021/ol016133m CCC: $20.00
Published on Web 07/14/2001

NaO^{t}Bu, suggested by the idea that it could generate an anionic nucleophile and consequently favor the intramolecular nucleophilic attack across the activated carbon−carbon triple bond,[4,6] turned out to favor the coupling reaction. In the presence of NaO^{t}Bu, compound **4a** was isolated in 41% yield and the oxazole **3a** in only 21% yield (Table 1, entry 1), with the latter most probably generated through the base-catalyzed cyclization of **4a** formed initially and not via the oxypalladation−reductive elimination domino mechanism [i.e., (1) nucleophilic attack of the oxygen nucleophile across the carbon−carbon triple bond activated by coordination to the σ-phenylpalladium complex formed in situ, (2) reductive elimination of the resultant σ-vinyl-σ-phenylpalladium intermediate, (3) isomerization of the benzylidene derivative to the oxazole product]. Support for this view is provided by the observation that monitoring the reaction showed that **3a** was not present before **4a** was formed but that the amount of **3a** increased with time after **4a** became a component of the reaction mixture. In addition, subjection of **4a** to 2 equiv of NaO^{t}Bu in DMF at 40 °C for 4 h produced **3a** in 52% yield.

Table 1. Solvents, Ligands, and Concentration of the Base in the Reaction of **1a** with Iodobenzene[a]

	NaO^{t}Bu			rxn time	yield, %[b]		
entry	(equiv)	solvent	ligand	(h)	**3a**	**4a**	**5a**
1	1	THF	PPh_3	1	21	41	4
2	1	THF	ttmpp	18		6	58
3	1	THF	PCy_3	18	7		58
4	1	THF	tccp	1	9	49	6
5	1	THF	P(2-furyl)$_3$	0.5	10	53	
6	1	DMSO	P(2-furyl)$_3$	0.5	44	17	2
7	2	DMSO	P(2-furyl)$_3$	1.5	68		2
8	3	DMSO	P(2-furyl)$_3$	1			79
9	2	DMF	P(2-furyl)$_3$	5	44	1	25
10	2	DMA	P(2-furyl)$_3$	4	65		2
11	2	MeCN	P(2-furyl)$_3$	4	75	1	3

[a] Reactions were carried out on a 0.63 mmol scale at 40 °C in 3.5 mL of the selected solvent using the following molar ratios: **1a**:PhI:$Pd_2(dba)_3$:phosphine ligand:NaO^{t}Bu = 1:1.2:0.025:0.1:1−3. [b] Yields refer to single runs and are given for isolated products.

These results suggest that, at least in this case, the oxypalladation−reductive elimination domino mechanism is not operating. It also shows, however, that under these conditions the preparation of the oxazole derivatives **3** via a sequential coupling−cyclization process is feasible, a strategy that has been widely employed by us for the synthesis of indoles,[7] butenolides,[8] pyrazole,[9] quinolones,[10] and benzo[*b*]furans[11] from acetylenic compounds bearing a nucleophile close to the carbon−carbon triple bond.

To explore this possible synthetic route, the influence of base concentration, solvents, and ligands on the reaction outcome was briefly investigated. Table 1 summarizes some of our results and shows that, in the presence of 1 equiv of NaO^{t}Bu and using THF as the solvent, electron-rich phosphines such as tris(2,4,6-trimethoxyphenyl)phosphine (ttmpp) and tricyclohexylphosphine (PCy_3) favor the formation of **5** (Table 1, entries 2 and 3). Strongly coordinating ligands likely hamper the coordination of the alkyne to the palladium of the σ-phenylpalladium complex[12] formed in situ (most probably the first step along the path leading to the coupling product),[13] and the competitive base-catalyzed cyclization of **1a** to **5a**[3p,q] takes place preferentially. With phosphines bearing electron-withdrawing groups such as tris(*p*-chlorophenyl)phosphine (tccp)[14] (Table 1, entry 4) and P(2-furyl)$_3$ (Table 1, entry 5) the main reaction product is the coupling derivative **4a**. In the presence of P(2-furyl)$_3$ the highest reaction rate is observed and no evidence of the oxazole **5** was obtained.

Therefore, employing P(2-furyl)$_3$ as the ligand, other solvents (DMSO, DMF, DMA, MeCN) and base-to-alkyne ratios were explored. In DMSO and with 1 equiv of NaO^{t}Bu the oxazole **3a** was isolated as the main product (Table 1, entry 6) and its yield was increased up to 68% by using a 2:1 base-to-alkyne ratio (Table 1, entry 7). A further increase of this ratio, however, was found to favor the formation of **5a** (Table 1, entry 8).

The best results were obtained by employing 2 equiv of NaO^{t}Bu in the presence of P(2-furyl)$_3$ in MeCN (Table 1,

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entry 11), and these conditions were used when the methodology was extended to other *N*-propargylamides and aryl iodides (Table 2).[15]

Table 2. Preparation of 2,5-Disubstituted Oxazoles **3** from **1**[a]

entry	alkyne **1**	R	aryl iodide **2**	rxn time (h)	yield, %[b] **3**	**5**
1	**a**	Ph	*o*-Me-C_6H_4-I	8	83	
2	**b**	*p*-MeO-C_6H_4	*o*-Me-C_6H_4-I	20	62	
3	**a**	Ph	m-Me-C_6H_4-I	10	70	
4	**b**	*p*-MeO-C_6H_4	*m*-Me-C_6H_4-I	20	52	
5	**a**	Ph	*p*-Me-C_6H_4-I	8	72	4
6	**a**	Ph	3,5-Me_2-C_6H_3-I	10	71	4
7	**a**	Ph	*m*-MeO-C_6H_4-I	18	51	20
8	**b**	*p*-MeO-C_6H_4	*m*-MeO-C_6H_4-I	20	68	
9	**a**	Ph	*p*-MeO-C_6H_4-I	24	20	45
10	**a**	Ph	PhI	4	75	
11	**a**	Ph	*p*-Cl-C_6H_4-I	12	60	18
12	**b**	*p*-MeO-C_6H_4	*p*-Cl-C_6H_4-I	20	75	
13	**c**	*m*-CF_3-C_6H_4	*p*-Cl-C_6H_4-I	20	52	6
14	**d**	*p*-Me-C_6H_4	*p*-Cl-C_6H_4-I	20	11	49
15	**a**	Ph	*m*-CF_3-C_6H_4-I	10	35	35
16	**a**	Ph	*m*-F-C_6H_4-I	8	54	17
17	**a**	Ph	*p*-F-C_6H_4-I	8	58	13
18	**e**	CF_3	*p*-MeCO-C_6H_4-I	20	32	*c*
19	**a**	Ph	*p*-MeCO-C_6H_4-I	8	65	9
20	**c**	*m*-CF_3-C_6H_4	*p*-MeCO-C_6H_4-I	20	51	
21	**b**	*p*-MeO-C_6H_4	*p*-MeCO-C_6H_4-I	20	66	
22	**d**	*p*-Me-C_6H_4	*p*-MeCO-C_6H_4-I	20	62	6

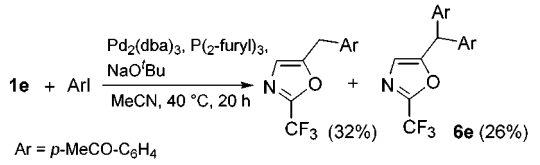
[a] Reactions were carried out on a 0.44−0.66 mmol scale at 40 °C in 3.5 mL of MeCN using the following molar ratios: **1**:ArI:$Pd_2(dba)_3$:P(2-furyl)$_3$:NaO^{t}Bu = 1:1.2:0.025:0.1:2. [b] Yields refer to single runs and are given for isolated products. All new products had satisfactory elemental analysis and spectra were consistent with the postulated structures. [c] Compound **6e** (Scheme 3) was isolated in 26% yield.

The reaction works well with a variety of aryl iodides and *N*-propargylamides. However, the nature of aryl iodides and *N*-propargylamides may influence the **3**:**5** ratio, and the optimized reaction conditions for preparing **3a** did not give the same good results for all of the aryl iodides and *N*-propargylamides that we have examined. For example, the reaction of **1a** with *m*-iodobenzotrifluoride produced the two oxazole products in equimolar amounts (Table 2, entry 15). In other cases (Table 2, entries 9 and 14) the oxazole **5a** was isolated as the main product. It seems likely that optimization for a particular case of importance may lead to further improvement.

(15) **Typical Procedure for the Palladium-Catalyzed Reaction of 1 with Aryl Iodides.** To a solution of $Pd_2(dba)_3$ (14.4 mg, 0.016 mmol) in 3.5 mL of anhydrous MeCN under argon was added P(2-furyl)$_3$ (14.6 mg, 0.063 mmol), and the solution was stirred at room temperature for 15 min. Then **1a** (100 mg, 0.63 mmol), *p*-iodotoluene (164 mg, 0.75 mmol), and NaO^{t}Bu (122 mg, 1.26 mmol) were added, and the mixture was stirred at 40 °C for 18 h. The reaction mixture was diluted with ethyl acetate and then placed in a separatory funnel, washed with 0.1 N HCl and saturated $NaHCO_3$, dried (Na_2SO_4), and concentrated under reduced pressure. The residue was purified on an axially compressed column (packed with 35 g of SiO_2 25−40 μm, Macherey Nagel, connected to a Gilson solvent delivery system and to a Gilson refractive index detector) eluting with a *n*-hexane/EtOAc 98/2 (v/v) mixture to give 4.0 mg (4% yield) of **5a** and 113 mg (72% yield) of 2-phenyl-5-[(*p*-methylphenyl)methyl]-oxazole as an oil: IR (neat) 825, 711, 695 cm^{-1}; ^{1}H NMR (200 MHz; $CHCl_3$) δ 8.02−7.94 (m, 2 H), 7.43−7.34 (m, 3 H), 7.19−7.07 (m, 4 H), 6.83 (s, 1 H), 3.98 (s, 2 H), 2.31 (s, 3 H); ^{13}C NMR (50.3 MHz; $CHCl_3$) δ 161.1, 151.6, 136.4, 133.5, 129.9, 129.3, 128.4, 128.3, 127.7, 126.0, 124.7, 31.7, 21.0; MS *m*/*e* (relative intensity) 249 (M^+, 100), 234 (20), 144 (80), 116 (100). Anal. Calcd for $C_{17}H_{15}NO$: C, 81.90; H, 6.06; N, 5.62. Found: C, 81.81; H, 6.05; N, 5.64.

It may be added that, depending on the substitution pattern of the propargylamide, formation of compounds generated through the oxypalladation−reductive elimination domino mechanism (our initial task) can also be observed. For example, the reaction of *p*-iodoacetophenone with **1e** (Table 2, entry 18; compare with entries 19−22) produced the expected product (32% yield) along with a 26% yield of the oxazole **6e**, most probably derived from the oxypalladation−reductive elimination domino reaction[4] of the initially formed coupling intermediate (Scheme 3).

Scheme 3

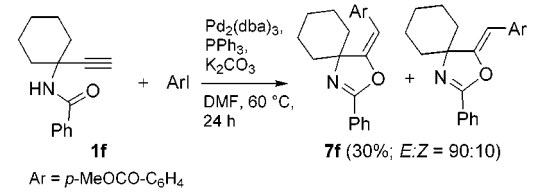


Accordingly, compound **6e** was isolated in 68% yield when the preformed coupling product was subjected to *p*-iodoacetophenone in the presence of $Pd(PPh_3)_4$ and K_2CO_3 (Scheme 4).

Scheme 4

As another example, the oxypalladation−reductive elimination domino mechanism appears to be operating, at least in part, even in the palladium-catalyzed reaction of the *N*-propargylamide **1f** with ethyl *p*-iodobenzoate (Scheme 5).

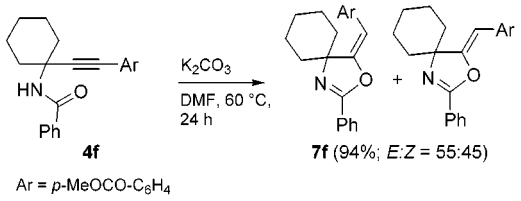
Scheme 5



The prevalence of the *E* isomer (*E*:*Z* = 90:10) of **7f** is consistent with this type of mechanism, involving a stereoselective *trans* addition of the oxygen nucleophile and the palladium complex across the carbon−carbon triple bond.[4]

The base-catalyzed cyclization of **4f** produced instead **7f** as an approximately 55:45 *E*:*Z* mixture (Scheme 6). This is in agreement with the intermediacy of a carbanion, derived from the base-catalyzed intramolecular nucleophilic attack

Scheme 6



of the oxygen to the carbon−carbon triple bond, that can isomerize and generate almost equimolar amounts of the two stereoisomers via protonation.

In conclusion, we have shown that the reaction of several *N*-propargylamides and aryl iodides in the presence of $Pd_2(dba)_3$ as the precursor of the catalyst species, $P(2\text{-furyl})_3$ as the ligand, NaO^{t}Bu as the base, and MeCN as the solvent provides a useful route to 2,5-disubstituted oxazoles through a sequential palladium-catalyzed coupling/base-catalyzed cyclization process. Under these conditions, various functional groups are well tolerated and compounds **3** are usually isolated in good overall yield. The formation of products generated through the oxypalladation−reductive elimination domino mechanism, which has been observed in some cases, may provide new synthetic opportunities. As to the latter point, however, further work is needed to understand the role of the substituents of the propargylamide system in controlling the reaction outcome.

Acknowledgment. Work carried out in the framework of the National Project "Stereoselezione in Sintesi Organica. Metodologie ed Applicazioni" supported by the Ministero dell'Università e della Ricerca Scientifica e Tecnologica, Rome. Financial support of this research by the University "La Sapienza", Rome, by the Consiglio Nazionale delle Ricerche (CNR), and by MURST, Rome, is also gratefully acknowledged.

Supporting Information Available: Characterization data for *N*-propargylamides **1** and 2,5-disubstituted oxazoles **3** (Table 2). This material is available free of charge via the Internet at http://pubs.acs.org.

OL016133M