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Palladium(II)-mediated oxidative cyclization of *N*-carbamoyl aminoalkynes: a new route to γ-lactams

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Abstract

Transformation of *N*-carbamoyl or acetyl-4-trimethylsilyl-3-alkyn-1-amines to diversely substituted 2-pyrrolidinones, via a Wacker-type reaction, is described.

Keywords: alkynes; carbamates; cyclization; γ-lactams; palladium catalysts.

γ-Lactams are widespread compounds. The γ-lactam ring system is sparingly found in Nature,[1a,b] yet it is present in a large number of molecules possessing great medicinal values such as psychotropic agents,[2a,b] muscarinic acid agonists,[3] antihypertensive agents,[4] peptide mimics[5] etc. γ-Lactams are also used as derivatizing agents[6] and are versatile synthetic intermediates,[7–9] particularly of pyrrolidine and pyrrolizidine alkaloids[8a–c] and γ-aminobutyric acid (GABA) analogues.[9a–c] Consequently, much effort has been devoted in the development of new methods for γ-lactam preparation.[10,11]

We have recently reported a new synthetic approach to γ-butyrolactones involving the oxidative cyclization of 4-trimethylsilyl-3-alkyn-1-ols catalyzed by Pd(II) in the presence of $CuCl_2$ and O_2 as oxidants.[12a,b] In order to extend the cyclization process to homopropargylic amines, we initially explored the reaction with a substrate bearing a *p*-toluenesulfonyl-protected nitrogen nucleophile. Disappointingly, no reaction occurred whatever the reaction conditions tested.[12b]

We here report the study of Pd(II)-catalyzed heterocyclization of diversely *N*-substituted aminoalkynes[13] leading, in most cases, to *N*-protected γ-lactams in fair yields (Scheme 1).

As seen in Table 1, unlike free or *N*-benzylamine derivatives (entries 4 and 5), *N*-carbamoyl or acetyl aminoalkynes exhibited the appropriate balance of nucleophilicity versus basicity required for successful cyclization. McDonald and Chatterjee have observed the same type of requirement for the success of molybdenum-promoted cycloisomerization of aminoalkynes.[14]

Cyclization of 1,1′-(cycloalkyl)aminoalkynes **1g–i** led in good yields (71–78%) to 5,5-spiro-2-pyrrolidinones **2g–i**. Spiro-γ-lactams are key intermediates in the synthesis of natural products[15a–c] and

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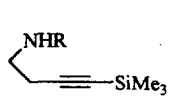
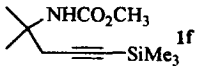
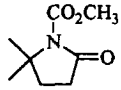
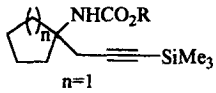
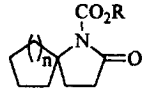
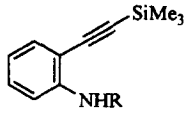
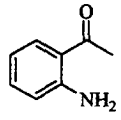
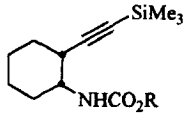
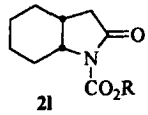
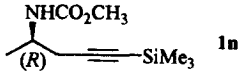
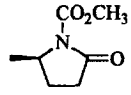
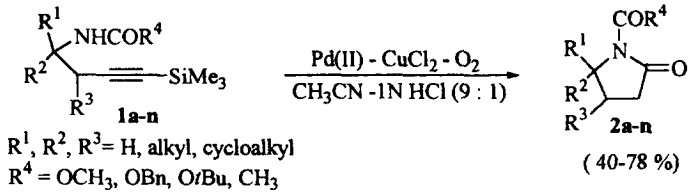
Table 1
Synthesis of substituted 2-pyrrolidinones from 4-trimethylsilyl-3-alkyn-1-amines

Entry	Aminoalkyne [a]	Reaction time (h)	Product	% Isolated yield
				
1	R=CO_2CH_3 **1a**	24	**2a**	50
2	R=CO_2*t*Bu **1b**	16	**2b**	50
3	R=$COCH_3$ **1c**	24	**2c**	40
4	R=Bn **1d**			0 [b]
5	R=H **1e**	72		0 [b]
6	 **1f**	48	 **2f**	66
	 n=1			
7	R=CH_3 **1g**	48	**2g**	78
8	R=Bn **1h** n=2	48	**2h**	71
9	R=CH_3 **1i**	48	**2i**	73
				
10	R=H **1j**	24	**3**	15
11	R=CO_2CH_3 **1k**	24		0 [b]
				
12	R=CH_3 **1l**	48	**2l**	48
13	R=Bn **1m**	48	**2m**	61
14	 **1n**	48	 **2n**	40

[a] The experimental protocol is identical with that described for the preparation of γ-lactones from homopropargylic alcohols; all reactions have been carried out under air in the presence of 5 mole % of Pd (II) catalyst and 25 mole % of $CuCl_2$ in CH_3CN-1N HCl except for **1b** the solvent used was CH_3CN-H_2O (9/1). [b] Mixture of unidentified products.



R^1, R^2, R^3= H, alkyl, cycloalkyl
R^4 = OCH_3, OBn, O*t*Bu, CH_3

Scheme 1.

our method of synthesis for this class of compounds compares favorably with those reported in the literature.[15,16]

Not unexpectedly, 2-alkynylanilines **1j,k** did not undergo cyclization[17] but, in the case of 2-(trimethylsilylethynyl)aniline **1j**, the methyl ketone **3** was obtained, albeit in low yield, via the Wacker reaction.[18]

Finally, we examined the cyclization of the enantiopure (*R*)-(*N*-carbomethoxy)-5-trimethylsilyl-4-pentyn-2-amine **1n**, readily available from (*S*)-propylene oxide.[19] It cyclized smoothly with retention of the optical purity to afford **2n** in 40% yield (not optimized). *N*-Carbomethoxy-γ-lactam **2n** was quantitatively transformed, in the presence of magnesium methoxide,[20] to (*R*)-5-methyl-2-pyrrolidinone,[21] a valuable building block in the synthesis of bioactive compounds.[22]

In summary, we have devised a mild method for the synthesis of γ-lactams substituted in 4 and 5 positions from readily available homopropargylic amine derivatives. Work is in progress to improve the efficiency of the process and to exploit this methodology in the field of natural products.

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