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N-Propargylic β-Enaminones: Common Intermediates for the Synthesis of Polysubstituted Pyrroles and Pyridines

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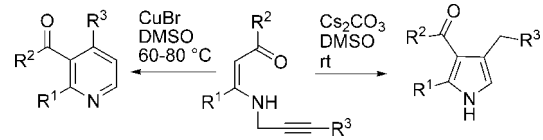
ABSTRACT



***N*-Propargylic β-enaminones have been used as common intermediates for the synthesis of polysubstituted pyrroles and pyridines. Best results have been obtained using DMSO as solvent. In the presence of Cs_2CO_3 *N*-propargylic β-enaminones are cyclized to pyrroles in good to high yields, whereas omitting bases and using CuBr leads to the selective formation of pyridines.**

Due to the presence of the ambident nucleophilic character of the enamine moiety and the ambident electrophilic character of the enone moiety, β-enaminones are useful synthetic intermediates[1] and their utilization in organic synthesis is a subject of great current interest. A variety of intra-[2] and intermolecular[3] reactions have been performed taking advantage of their electronic properties. Transition metal-promoted[4] and -catalyzed[5] processes have also been described. Because of our general interest in the alkyne-based synthesis of heterocycles,[6] we decided to tether a carbon−carbon triple bond to the enaminone framework and to

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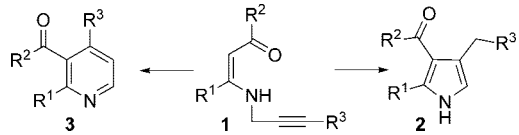
investigate the potential of the resultant alkyne-containing derivatives as precursors of heterocycles.

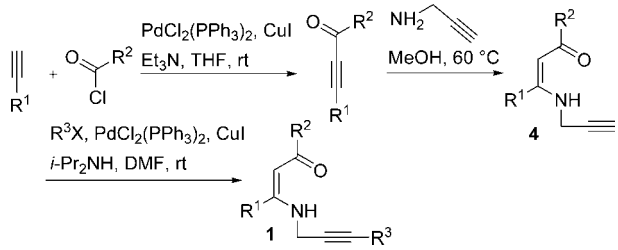
Herein we report that *N*-propargylic β-enaminones **1** are useful common intermediates for the synthesis of polysubstituted pyrroles **2** and pyridines **3** (Scheme 1).

Scheme 1



N-Propargylic β-enaminones **1** were readily prepared via Sonogashira cross-coupling of terminal alkynes with acyl chlorides,[7] followed by the conjugate addition of propargylamine with the resultant α,β-enones and further Sonogashira cross-coupling of the propargyl derivative **4** with aryl halides (Scheme 2). *N*-Propargylic β-enaminones **1** and **4** have

Scheme 2



always been isolated as single isomers. The *Z* stereochemistry of **1k** (R^1 = *n*-C_5H_{11}; R^2 = Ph; R^3 = *p*-Me-C_6H_4) and **4a** (R^1 = Ph; R^2 = Me; R^3 = H) has been assigned by NOESY experiments which showed also the presence of an intramolecular hydrogen bond (N−H···O). That of the other *N*-propargylic β-enaminones has been assigned on the basis of these data.

We started our study by examining the conversion of **1a** (R^1= Ph; R^2 = Me; R^3 = *p*-MeO-C_6H_4) into the corresponding NH free pyrrole derivative **2a**. After an initial screen of bases, solvents, and reaction temperatures, we found that the use of 2 equiv of Cs_2CO_3 in anhydrous DMSO at room temperature produced **2a** after 2 h in 75% yield.

Using these conditions, we next explored the scope and generality of the process. Our preparative results are summarized in Table 1. Pyrrole products containing a variety of neutral, electron-donating, and electron-withdrawing substituents were usually isolated in good to high yields. On

Table 1. Synthesis of NH Free Polysubstituted Pyrroles **2**[a]

entry	substrate **1** and **4** R^1	R^2		product **2** R^3	yield %[b]
1			**1a**	*p*-MeO-C_6H_4-	**2a** 75[c]
2			**1b**	*p*-EtO_2C-C_6H_4-	**2b** 65
3	Ph	Me	**1c**	*p*-MeCO-C_6H_4-	**2c** 69[c]
4			**1d**	*m*-Br-C_6H_4-	**2d** 86
5			**4a**	H	**2e** 69[c,d]
6			**1e**	*m*-Me-C_6H_4-	**2f** 59
7	Ph	Ph	**1f**	*m*-EtO_2C-C_6H_4-	**2g** 81
8			**1g**	*p*-NO_2-C_6H_4-	**2h** 42
9			**1h**	*p*-Cl-C_6H_4-	**2i** 69
10	C_5H_{11}	Ph	**1i**	*m*-CF_3-C_6H_4-	**2j** 95
11			**1j**	3,5-Me_2-C_6H_3-	**2k** 64
12			**1k**	*p*-Me-C_6H_4-	**2l** 60
13	Ph	*p*-MeO-C_6H_4	**1l**	*p*-MeCO-C_6H_4-	**2m** 96
14			**1m**	*m*-$HOCH_2$-C_6H_4-	**2n** 93
15	Ph	*p*-Cl-C_6H_4	**1n**	3,5-Me_2-C_6H_3	**2o** 74
16			**1o**	*m*-F-C_6H_4	**2p** 75

[a] Unless otherwise stated, reactions were carried out under argon on a 0.2 mmol scale using 2 equiv of Cs_2CO_3 in 3 mL of anhydrous DMSO at room temperature for 10−120 min. [b] Yields are given for isolated products. [c] Carried out on a 0.3 mmol scale using the same amount of solvent. [d] At 60 °C.

the basis of previous studies on base-catalyzed cyclizations of alkynes containing proximate nucleophiles,[8] it is likely that this carbocyclization proceeds through the following basic steps: (a) a 5-*exo-dig* cyclization involving an intramolecular nucleophilic attack of the C_α terminus of the anion generated in situ from **1** on the closer acetylenic carbon (one of the orbitals of the acetylenic system allows for a nearly planar mode of approach of the nucleophile; Figure 1a),[9]

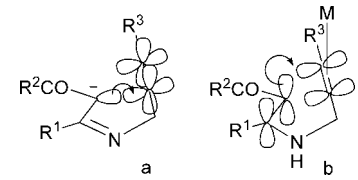


Figure 1. Suggested ring-closure pathways for the cyclization of **1**: (a) base-catalyzed 5-*exo-dig* cyclization; (b) transition metal-catalyzed 6-*endo-dig* cyclization (M = transition metal).

(b) a protonation step to afford a five-membered ring methylidene intermediate, and (c) an isomerization to the pyrrole product **2**.[10] We then decided to investigate the role of transition-metal catalysis in the cyclization step. In particular, the working hypothesis was that under neutral conditions and with a transition metal coordinating the C−C

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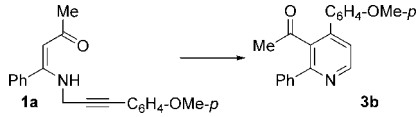
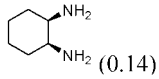
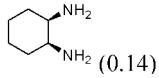
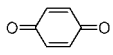
triple bond, stereoelectronic requirements might influence the cyclization process so as to favor the 6-*endo-dig* cyclization as shown in Figure 1b. Indeed, coordination of the C−C triple bond to the transition metal would decrease its bond order and introduce strain on the transition state leading to the 5-*exo-dig* cyclization product.[9]

The cyclization of **1a** was investigated as the model system and copper was selected as the transition metal catalyst. Representative optimization experiments are summarized in Table 2.

Table 2. Copper, Ligands, Solvents, and Temperature in the Cyclization of **1a** to **3b**[a]



entry	[Cu]	ligand or additive (equiv)	solvent	time (h)	**3b** yield %[b]
1	CuI	–	DMSO	20	31
2	CuCl	–	DMSO	2	44
3	$CuCl_2$	–	DMSO	24	27
4	CuBr	–	DMSO	4.5	47
5	CuBr	–	dioxane	24	35[c]
6	CuBr	–	DMF	1	–
7	CuBr[e]	–	DMSO	1	51
8	CuBr[e]	PPh_3 (0.3)	DMSO	26	53
9	CuBr[d,e]	(±)-BINOL (0.2)	DMSO	2	49
10	CuBr[e]	 (0.14)	DMSO	8	–[f]
11	CuBr[c,e]	 (0.14)	DMSO	24	40
12	CuBr[e,g]	–	DMSO	8	–[h]
13	CuBr[e]	 (1)	DMSO	5	43
14	CuBr[e,i]	–	DMSO	0.5	69
15	CuBr[i]	–	DMSO	1.5	54
16	CuBr[e,i]	1,10-Phen (0.4)	DMSO	6	65
17	–	–	DMSO	2.5	–[l]

[a] Unless otherwise stated, reactions were carried out under argon on a 0.25 mmol scale using 0.1 equiv of copper salt in 3 mL of solvent at 60 °C. [b] Yields are given for isolated products. [c] At 80 °C. [d] 0.2 equiv of CuBr. [e] Recrystallized CuBr. [f] **1a** was recovered in 77% yield. [g] Under an oxygen atmosphere (balloon). [h] **1a** was recovered in 36% yield. [i] 0.4 equiv of CuBr. [l] **1a** was recovered in 70% yield.

Pleasingly, subjecting **1a** to several commercially available copper salts under neutral conditions afforded selectively the 6-*endo-dig* product **3b**, whose formation includes even an oxidation step. However, low to moderate yields were obtained (Table 2, entries 1−6).[11] Utilization of recrystallized CuBr[12] led to a faster reaction rate and a slightly higher yield (Table 2, entry 7 vs 4). Adding ligands such as PPh_3, (±)-1,1′-binaphthalene-2,2′-diol [(±)-BINOL], and 1,10-phenantroline did not affect a remarkable change to the reaction outcome compared with the same reactions carried out in the absence of ligands (Table 2, entries 8 and 9 vs 7; entry 16 vs 14). Using 1,2-cyclohexandiamine led to the recovery of **1a** in 77% yield at 60 °C (Table 2, entry 10) while increasing the reaction temperature to 80 °C formed **3b** in 40% yield along with other unidentified products (Table 2, entry 11). Even performing the reaction under a balloon of oxygen or adding 1,4-benzoquinone did not afford satisfactory results (Table 2, entries 12 and 13). Increasing the amount of recrystallized CuBr to 0.4 equiv led to isolation of **3b** in a satisfactory 69% in 0.5 h (Table 2, entry 14). With 0.4 equiv of nonrecrystallized CuBr, **3b** was isolated only in 54% yield (Table 2, entry 15). As expected, no reaction was observed omitting copper salts (Table 2, entry 17). On the basis of these studies, we decided to use 0.4 equiv of CuBr in DMSO at 60 °C omitting ligands and additives when the procedure was extended to include other *N*-propargylic *β*-enaminones. Our preparative results are summarized in Table 3.

Table 3. Synthesis of Polysubstituted Pyridines **3**[a]

entry	substrate **1** and **4** R^1	R^2		product **3** R^3	yield %[b]
1			**1a**	*p*-MeO-C_6H_4-	**3a** 69
2			**1d**	*m*-Br-C_6H_4-	**3b** 55
3	Ph	Me	**1c**	*p*-MeCO-C_6H_4-	**3c** 60
4			**1p**	Ph	**3d** 61
5			**4a**	H	**3e** 60
6	Ph	*p*-CN-C_6H_4-	**1q**	*p*-MeCO-C_6H_4-	**3f** 51[c]
7			**1h**	*p*-Cl-C_6H_4-	**3g** 66
8			**1k**	*p*-Me-C_6H_4-	**3h** 60
9	C_5H_{11}	Ph	**1r**	*m*-EtO_2C-C_6H_4-	**3i** 76
10			**1s**	*m*-MeO-C_6H_4-	**3j** 54

[a] Unless otherwise stated, reactions were carried out under argon on a 0.2−0.25 mmol scale using 0.4 equiv of recrystallized CuBr in 3 mL of anhydrous DMSO at 60 °C for 0.5−5 h. [b] Yields are given for isolated products. [c] At 80 °C.

By analogy with other Cu-catalyzed cyclizations of acetylenic compounds,[13] a likely mechanism for the formation of the pyridine ring from **1** involves (Scheme 3) the coordination of the alkyne moiety with copper to give **A**, followed by a

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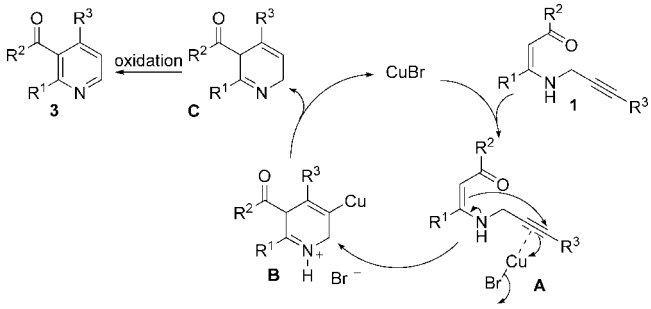
Scheme 3



6-*endo*-*dig* cyclization via the intramolecular nucleophilic attack of the carbon α to the carbonyl group to the activated C−C triple bond. Substitution of the C−H bond for the C−Cu bond of the resultant vinylic-copper intermediate **B** affords **C** with concomitant regeneration of CuBr. Subsequently, an oxidation step converts **C** into the pyridine derivative **3**. We have not investigated the details of this oxidation reaction and further studies would be required to clear this point up.

In conclusion, an efficient approach providing pyrroles and pyridines in good to high yields from readily available *N*-propargylic *β*-enaminones has been developed. The new method, which can be particularly useful for the preparation of libraries of three independently substituted pyrroles and pyridines, tolerates a variety of useful functional groups and requires only inexpensive reagents such as Cs_2CO_3 (pyrroles) and CuBr (pyridines).

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Supporting Information Available: A complete description of experimental details and product characterization. This material is available free of charge via the Internet at http://pubs.acs.org.

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(10) Since *N*-propargylic *β*-enaminones contain traces of Pd, palladium catalysis might be involved in the cyclization step. However, this hypothesis seems to be flawed by the observation that the same reaction rate was observed when **1l** was treated with Cs_2CO_3 in DMSO at rt with and without $PdCl_2$.

(11) A similar result was obtained with $PdCl_2$ as precatalyst. For example, **3b** was isolated in 29% yield upon treatment of **1l** with $PdCl_2$ in MeCN for 24 h at 80 °C. No evidence of pyrrole formation was attained.

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