ORGANIC LETTERS

2013
Vol. 15, No. 19
4996–4999

A Novel Tandem Sequence to Pyrrole Syntheses by 5-*endo*-*dig* Cyclization of 1,3-Enynes with Amines

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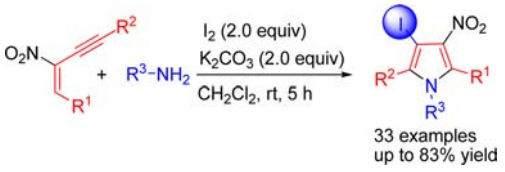
Received August 13, 2013

ABSTRACT



The synthesis of pentasubstituted pyrroles has been described using molecular iodine from 1,3-enynes and amines via a sequential tandem aza-Michael addition, iodocyclization, and oxidative aromatization. The protocol is simple and efficient to afford the target products at ambient conditions.

Substituted pyrroles are important structural motifs of many natural products[1] and pharmaceutically active substances.[2] They also find widespread applications in material science and supramolecular chemistry.[3] Thus, several classical and modern methods have been developed for the synthesis of pyrroles and their derivatives.[4−6] However, the strategies for the synthesis of pentasubstituted pyrroles from the readily available substrates are somewhat limited[7] because of lack of selectivity.[8] More recently, electrophilic iodocyclization of alkynes has been found to be a powerful tool for the synthesis of carbocycles and heterocycles.[9] The designing of enynes makes this process attractive for the construction of the target cyclic compounds (Scheme 1). In continuation of our studies on

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10.1021/ol402305b
Published on Web 09/13/2013

heterocycle synthesis,[10] we wish to report herein a synthetic approach to pentasubstituted pyrroles from 1,3-enynes[11] and amines using iodine via a tandem aza-Michael addition,[12] iodocyclization, and oxidative aromatization at ambient conditions. The protocol provides a potential route for the synthesis of pentasubstituted pyrroles in moderate to good yields.

The optimization of the reaction conditions was performed using different solvents and bases with (*E*)-2-nitro-1,4-diphenylbut-1-en-3-yne **1a** and *p*-toluidine **2a** as the model substrates in the presence of molecular iodine (Table 1). We were pleased to observe that the reaction proceeded efficiently to afford the target 3-iodo-4-nitro 2,5-diphenyl-1-*p*-tolyl-1*H*-pyrrole **3a** in 83% yield when the substrates were stirred with 2 equiv of iodine in the presence of K_2CO_3 in CH_2Cl_2 for 5 h at ambient conditions. CH_2Cl_2 was found to be the solvent of choice; other solvents such as CH_3CN, THF, and toluene gave the target product in moderate yields (entries 1−4). K_2CO_3 gave superior results compared to other bases such as $NaHCO_3$, NaOAc, K_3PO_4, Et_3N, DBU and DIPEA (entries 4−11). A complete disappearance of the substrate **1a** was observed with isolated yield of 83% when the amine **2a** quantity was increased to 1.5 equiv (entry 8). The decrease of the amount of iodine to 1.5 equiv led to the formation of **3a** in 62% yield (entry 12). The control experiment carried out without iodine did not afford the target product (entry 13).

With the optimal conditions in hand, the scope of the protocol was examined for the reactions of a series of substituted 1,3-enynes **1a**−**k** with aniline **2b** as a standard substrate (Table 2). The reactions occurred readily to afford the target products in moderate to high yields. For example, the substrate **1a** with R^1 and R^2 = Ph underwent reaction to give the pyrrole derivative **3b** in 82% yield. Similarly, the enynes **1b**, **1d**, **1g**, and **1i** having electron-donating methoxy group in the aryl ring (R^1 or R^2) proceeded in reaction to afford the desired products **3c**, **3e**, **3h**, and **3j** in 68−72% yields, whereas **1c** and **1h** with electron-withdrawing substituents in the aryl ring exhibited moderate reactivity, furnishing **3d** and **3i** in 58 and 56% yields, respectively. The mono- and disubstituted enynes **1e**, **1f** and **1j** with dimethyl phenyl and tolyl groups in the aryl ring underwent reaction to give the target products **3f**, **3g**, and **3k** in high yield, whereas the benzyloxymethyl substitued enyne **1k** underwent decomposition,

Scheme 1. Iodine-Mediated Syntheses of Carbo- and Heterocycles

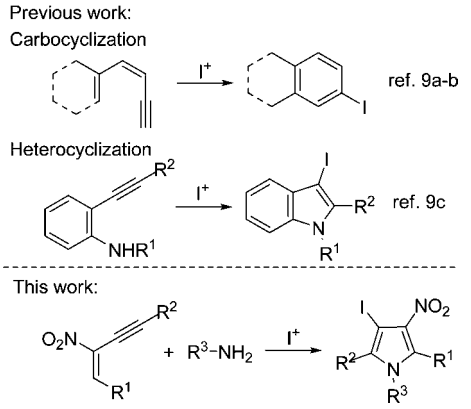
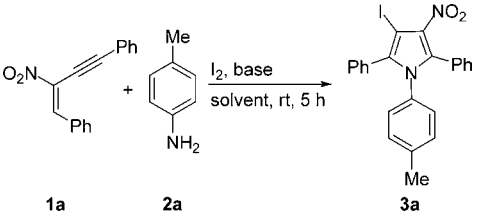


Table 1. Optimization of the Reaction Conditions[a]



entry	solvent	base	yield **3a** (%)[b]
1	CH_3CN	$NaHCO_3$	17
2	toluene	$NaHCO_3$	40
3	THF	$NaHCO_3$	50
4	CH_2Cl_2	$NaHCO_3$	52
5	CH_2Cl_2	NaOAc	31
6	CH_2Cl_2	K_2CO_3	58
7	CH_2Cl_2	K_3PO_4	37
8	**CH_2Cl_2**	**K_2CO_3**	**83**[c]
9	CH_2Cl_2	Et_3N	66[c]
10	CH_2Cl_2	DBU	73[c]
11	CH_2Cl_2	DIPEA	47[c]
12	CH_2Cl_2	K_2CO_3	62[d]
13	CH_2Cl_2	K_2CO_3	n.d.[e]

[a] Reaction conditions: 0.5 mmol of **1a**, 0.5 mmol of **2a**, I_2 (2.0 equiv), base (2.0 equiv) in solvent (3.0 mL) were stirred at room temperature under air for 5 h. [b] Isolated yield. [c] 1.5 equiv of **2a**. [d] 1.5 equiv of **2a** and 1.5 equiv of I_2 are used. [e] Without I_2. n.d. = not detected. DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene. DIPEA = *N*,*N*-diisopropylethylamine.

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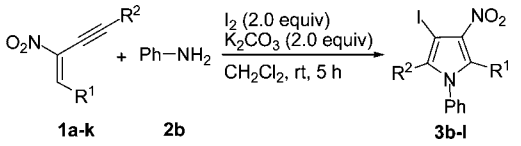
Table 2. Iodine-Mediated Electrophilic Cyclization of Various 1,3-Enynes with Aniline[a]



1a-k 2b 3b-l

entry	1	R^1	R^2	3	yield (%)[b]
1	**1a**	Ph	Ph	**3b**	82
2	**1b**	Ph	2-$MeOC_6H_4$	**3c**	71
3	**1c**	Ph	4-ClC_6H_4	**3d**	58
4	**1d**	Ph	4-$MeOC_6H_4$	**3e**	68
5	**1e**	Ph	3,4-$Me_2C_6H_3$	**3f**	74
6	**1f**	Ph	3,5-$Me_2C_6H_3$	**3g**	76
7	**1g**	2-$MeOC_6H_4$	Ph	**3h**	71
8	**1h**	4-FC_6H_4	Ph	**3i**	56
9	**1i**	4-$MeOC_6H_4$	Ph	**3j**	72
10	**1j**	4-MeC_6H_4	Ph	**3k**	80
11	**1k**	CH_2OBn	Ph	**3l**	n.d.

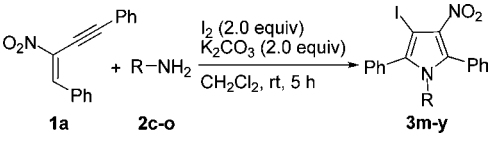
[a] Reaction conditions: 0.5 mmol of **1a**–**k**, 0.75 mmol of aniline **2b**, I_2 (2.0 equiv), base (2.0 equiv) in CH_2Cl_2 (3.0 mL) were stirred at room temperature for 5 h under air. [b] Isolated yield. n.d. = not detected

and the formation of the target product **3i** was not observed. The crystallization of the 3-iodo-4-nitro pyrrole **3g** in a 1:1 mixture of CH_3CN and MeOH gave a crystal whose structure was confirmed by X-ray analysis (see Supporting Information).

Next, the reaction of the enyne **1a** was studied with different substituted amines **2c**–**o** (Table 3). As anticipated, the reactions occurred displaying a broad substrate compatibility and substituent tolerance. For example, aryl amines **2c**,**d** and **2g**,**h** with electron-withdrawing groups such as bromo, chloro, nitro, and trifluoromethyl substituents proceeded in reaction to give the corresponding pyrrole derivatives **3m**,**n** and **3q**,**r** in 60–71% yields. In addition, aryl amines **2e**,**f** bearing electron-donating groups such as ethyl and methoxy substituents on the aromatic rings underwent reaction to afford the target products **3o**,**p** in good yield. However, the bulky *ortho*-substituted aryl amine **2i** with dimethyl substituent was less reactive, providing **3s** in 10% yield. A similar result was observed with 2-fluorenyl amine **2k** furnishing **3u** in 18% yield, whereas 1-naphthylamine **2j** showed no reaction, and the starting material was recovered intact. However, aliphatic amines **2l**–**o** such as allyl, benzyl, isopropyl, and butyl amines were compatible, providing the target products **3v**–**y** in moderate yields.

To reveal the electronic effect, the reaction of a series of substituted enynes **1h**–**j** with substituted amines **2a**, **2f**, **2g**, and **2p** was further examined (Table 4). The reaction was general, and the substrates bearing electron-donating (methyl and methoxy) or electron-withdrawing (fluoro and nitro) or the combination electron-donating (methoxy) and electron-withdrawing (fluoro and nitro) groups in the aryl rings readily proceeded in reactions to give the target products **3z**–**ad** in moderate to good yields.

Table 3. Iodine-Mediated Electrophilic Cyclization of (*E*)-(2-Nitrobut-1-en-3-yne-1,4-diyl)dibenzene with Different Amines[a]

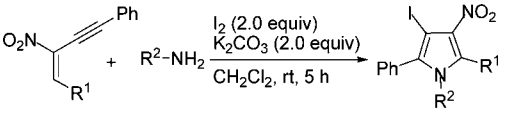


1a 2c-o 3m-y

entry	2	R	t (h)	3	yield (%)[b]
1	**2c**	2-BrC_6H_4	5	**3m**	60
2	**2d**	4-ClC_6H_4	5	**3n**	65
3	**2e**	4-EtC_6H_4	5	**3o**	75
4	**2f**	4-$MeOC_6H_4$	8	**3p**	57
5	**2g**	4-$NO_2C_6H_4$	5	**3q**	65
6	**2h**	4-$CF_3C_6H_4$	5	**3r**	71
7	**2i**	2,5-$Me_2C_6H_3$	24	**3s**	10
8	**2j**	1-naphthyl	24	**3t**	n.d.
9	**2k**	2-fluorenyl	24	**3u**	18
10	**2l**	allyl	5	**3v**	47
11	**2m**	Bn	5	**3w**	33
12	**2n**	*i*Pr	5	**3x**	35
13	**2o**	*n*Bu	5	**3y**	30

[a] Reaction conditions: 0.5 mmol of **1a**, 0.75 mmol of **2c**–**o**, I_2 (2.0 equiv), base (2.0 equiv) in CH_2Cl_2 (3.0 mL) were stirred at room temperature under air. [b] Isolated yield. n.d. = not detected

Table 4. Iodine-Mediated Electrophilic Cyclization of Various 1,3-Enynes with Different Amines[a]

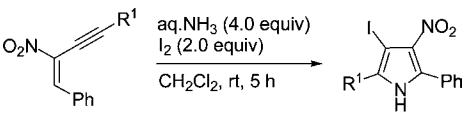


1h-j 2a, 2f-g, 2p 3z-ad

entry	1	R^1	2	R^2	3	yield (%)[b]
1	**1h**	4-FC_6H_4	**2f**	4-$MeOC_6H_4$	**3z**	30[c]
2	**1j**	4-MeC_6H_4	**2a**	4-MeC_6H_4	**3aa**	58[d]
3	**1h**	4-FC_6H_4	**2g**	4-$NO_2C_6H_4$	**3ab**	48[d]
4	**1i**	4-$MeOC_6H_4$	**2g**	4-$NO_2C_6H_4$	**3ac**	70
5	**1i**	4-$MeOC_6H_4$	**2p**	3,4-$Me_2C_6H_3$	**3ad**	56

[a] Reaction conditions: 0.5 mmol of **1**, 0.75 mmol of **2**, I_2 (2.0 equiv), base (2.0 equiv) in CH_2Cl_2 (3.0 mL) were stirred at room temperature for 5 h. [b] Isolated yield. [c] Reaction time for 24 h. [d] Reaction time for 8 h.

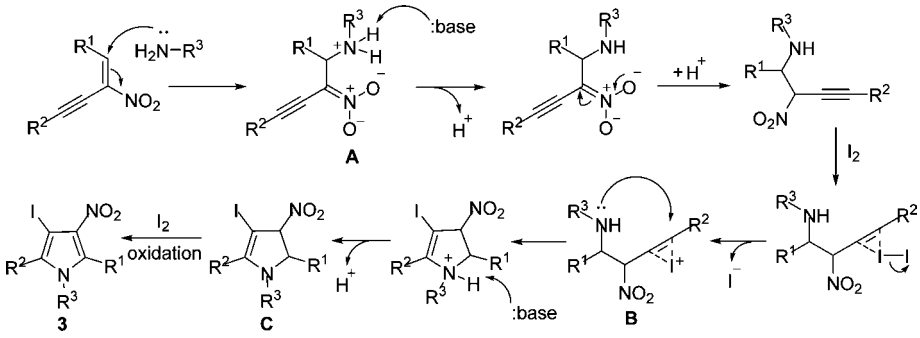
Scheme 2. Iodine-Mediated Synthesis of Tetrasubstituted Pyrrols Using 30% Aqueous Ammonia



1a, 1e-f 3ae-ag

R^1= Ph, **3ae**, 52% yield
R^1= 3,4-$Me_2C_6H_3$, **3af**, 59% yield
R^1= 3,5-$Me_2C_6H_3$, **3ag**, 55% yield

Scheme 3. Plausible Mechanism for the Formation of Pyrroles



Finally, the protocol was studied for the preparation of tetrasubstituted pyrrole using enynes **1a**, **1e**, and **1f** in the presence of aqueous ammonia as amine source (Scheme 2). As above, the reactions readily occurred to afford the target tetrasubstituted pyrrole **3ae**−**ag** in 52−59% yield. These observed results clearly suggest that the protocol is general and provides a potential route for the synthesis of a library of highly substituted pyrroles by varying the substituents in the substrate precursors.

A plausible mechanism for the formation of the pyrrole derivatives **3** is shown in Scheme 3. The intermolecular aza-Michael addition of the amine with the electron-deficient conjugated 1,3-enyne in the presence of iodine may lead to the formation of the intermediate **A**. The latter in the presence of base can give the iodonium intermediate[9n] **B**, which can undergo intramolecular cyclization to give the dihydropyrrole derivative **C**. The iodine mediated oxidative aromatization of **C** can lead to the formation of the target products **3**.

In summary, we have developed a new approach for the synthesis of tetra- and pentasubstituted pyrroles from 1,3-enynes and amines using molecular iodine via a sequential aza-Michael addition, iodocyclization, and oxidative aromatization under mild conditions. The results suggest that the electron-deficient conjugated 1,3-enynes are a potentially useful class of substrates for the synthesis of substituted pyrroles. The presence of iodo and nitro groups can permit further elaboration of the products to complex derivatives.

Acknowledgment. We thank Department of Science and Technology (SR/S1/OC-55/2011) and Council of Scientific and Industrial Research (02(0088)/12/EMR-II), New Delhi, for generous financial support. One of us (G.B.) thanks CSIR for Junior Research Fellowship. We also thank Central Instrumentation facility, IIT Guwahati, for NMR and X-ray analysis.

Supporting Information Available. Experimental procedure, characterization data, crystal stucture of **3g**, and NMR (^{1}H and ^{13}C) spectra of the products **3a**−**ag**. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.