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Oligosubstituted Pyrroles Directly from Substituted Methyl Isocyanides and Acetylenes

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Dedicated to Professor Alan R. Katritzky on the occasion of his 80th birthday

Abstract: The formal cycloaddition of α-metallated methyl isocyanides **1** onto the triple bond of electron-deficient acetylenes **2** represents a direct and convenient approach to oligosubstituted pyrroles **3**. The scope and limitations of this reaction (24 examples, 25–97% yield) are reported along with an optimization of the reaction conditions and a rationalization of the mechanism. In addition, a related newly developed Cu^{I}-mediated synthesis of 2,3-disubstituted pyrroles by the reaction of copper acetylides derived from unactivated terminal alkynes with substituted methyl isocyanides is described (11 examples, 5–88% yield).

Keywords: catalysis · copper · cycloaddition · isocyanides · pyrroles

Introduction

Oligofunctional pyrroles play a pivotal role among five-membered heterocycles, being basic constituents of numerous natural products,[1] potent pharmaceuticals,[2] molecular sensors and other devices.[3] Therefore, considerable attention has been paid to develop efficient general methods for the synthesis of pyrroles,[4,5] and in recent years, a large number of new pyrrole syntheses has indeed been reported.[6] Among them, the addition of isocyanides onto the triple bond of acetylenes is one of the most promising. Due to their formally divalent terminal carbon atom, isocyanides are unique organic nitrogen derivatives. Consequently, they have found wide use in organic synthesis,[7] especially in multicomponent reactions,[8] different types of insertions[9,10] and cycloadditions,[11] giving rise to a large variety of nitrogen-containing compounds. Cycloadditions are possible due to the ability of substituted methyl isocyanides to be metallated in the α-position, as first observed by Schöllkopf and Gerhart.[12] Recently, the synthesis of oligosubstituted pyrroles by the formal cycloaddition of isocyanides across the triple bond of electron-deficient alkynes has been reported independently by de Meijere et al.[13] and by Yamamoto et al.[14] It has been shown, that a base-mediated as well as a copper-catalyzed reaction of substituted methyl isocyanides with electron-deficient acetylenes afforded 2,3,4-trisubstituted pyrroles in good to excellent yields. Herein we present a more detailed study of this reaction and a novel copper(I)-mediated synthesis of 2,3-disubstituted pyrroles from isocyanides and unactivated terminal acetylenes.

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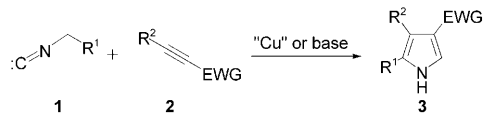
Results and Discussion

Synthesis of 2,3,4-trisubstituted pyrroles: Scope and limitations of both the base-mediated and the copper-catalyzed synthesis of pyrroles **3** were tested with a series of different acetylenes **2** and various acceptor-substituted methyl isocyanides **1** (Scheme 1, Table 1). Apparently, quite a number of different 2,3,4-trisubstituted pyrroles, bearing sulfonyl, dialkoxyphosphoryl, trifluoromethyl, cyano and secondary amino groups are easily accessible in one step from readily available acetylenes and commercial acceptor-substituted methyl isocyanides.

Some of the prepared pyrroles can be employed in the synthesis of biologically active compounds. For example, the pyrrole **3eg** is a possible precursor for a potent inhibitor of HMG-CoA reductase.[8] Apart from that, it also exhibits a notable anti-inflammatory activity.[15]

Interestingly, the steric and electronic effects of the substituents may significantly influence the reaction efficiency



1 2 3

Scheme 1. Preparation of 2,3,4-trisubstituted pyrroles by formal cycloaddition of acceptor-substituted methyl isocyanides to acetylenes. For details see Table 1.

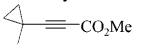
and the nature of the product. Thus, the phenyl substituent in acetylene **2g** was expected to cause reduced reactivity towards nucleophiles. Indeed, the reaction of **2g** with **1e** was quite sluggish at 80 °C, but readily furnished the pyrrole **3eg** at higher temperature (120 °C). Other acetylenes with aryl (**2h–j**) and heteroaryl substituents (**2k**, **l**) were also efficiently converted into the respective pyrroles **3ah–3al** using this method (entries 12–16). The reaction of the diacetylene **2m** with an excess of the isocyanide **1a** at prolonged reaction times yielded the monocycloadduct **3am** as the sole product and no trace of the twofold cycloadduct. This may arise from the considerable steric encumbrance of the pyrrole **3am**. On the other hand, reactive acetylenes bearing additional electron-withdrawing substituents, as for example, ethyl trifluoromethylpropiolate **2e**, tend to overreact and undergo a second addition with the intermediate **11** (see Scheme 3), eventually leading to oligomerization. This may cause a significant decrease of the yields.

Therefore, the initial procedure, utilizing potassium *tert*-butoxide (KO*t*Bu) (method A), was modified to avoid any excess of the acetylene in the reaction mixture. Thus, the reactive acetylene **2e** was added simultaneously with the base [potassium bis(trimethylsilyl)-amide (KHMDS) proved to be the base of choice in this case] from two separate syringes at −78 °C (method B) to give the desired pyrrole **3be** in 76% yield. Similarly, the highly reactive cyanomethyl isocyanide **1d** was employed under the conditions of Method B to give the 2-cyanopyrrole **3db** in 83% yield, whereas with potassium *tert*-butoxide (method A) the product was obtained with a lower purity and in a poor yield.

With electron-acceptor substituted terminal acetylenes, the yields of pyrroles **3** were dramatically lower. Thus, the CuSPh-catalyzed reactions of isocyanides **1** with methyl propiolate **2p** gave the corresponding pyrroles **3** in only 25–44% yields, and in the presence of KO*t*Bu the yields of pyrroles **3** were also low (Table 1, entries 21–24). It is known, that methyl propiolate **2p** easily dimerizes forming dimethyl hex-2-en-4-ynedioate both under base[16] and copper(I)[17] catalysis, complicating this reaction. Even with an excess of **2p**, the yields of pyrroles **3** were not any better.

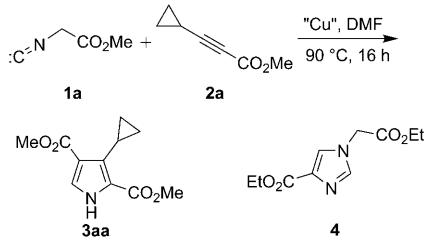
The copper(I)-catalyzed variant of the reaction is of great interest, because it may bring along certain advantages in cost efficiency and compatibility with base-sensitive substrates. Different solvents were tested in the copper-catalyzed cycloaddition of *p*-toluenesulfonylmethyl isocyanide (TosMIC, **1b**) to methyl cyclopropylacetylenecarboxylate (**2a**). Dimethylformamide (DMF) turned out to be the solvent of choice giving a better yield of pyrrole **3ba** than any other tested solvent (toluene, ethanol, ethyl acetate, acetonitrile, 1,2-dichloroethane, dioxane). Although higher conversions of TosMIC were achieved, when the reaction was carried out in toluene, ethanol, ethyl acetate or dioxane, the yields of **3ba** were lower than in DMF. In a screening of various copper catalysts, copper(I) thiophenolate and preactivated nanosize metallic copper powder in DMF at 90 °C turned out to be the most efficient, providing the pyrrole **3aa** in 93 and 92% yield, respectively (Table 2, entries 1 and

Table 1. Various 2,3,4-trisubstituted pyrroles **3** prepared by the formal cycloaddition of substituted methyl isocyanides **1** to acetylenes **2**.

Entry	Isocyanide **1**		Acetylene **2**			Product	Method[a–c]
		R^1		R^2	EWG		Yield [%][d]
1	**a**	CO_2Me	**a**	cPr	CO_2Me	**3aa**	A, 91
2	**b**	SO_2Tol	**a**	cPr	CO_2Me	**3ba**	A, 93 C, 64
3	**c**	Ph	**b**	cPr	CO_2tBu	**3cb**	C,[e] 87
4	**b**	SO_2Tol	**b**	cPr	CO_2tBu	**3bb**	A, 93 C, 91
5	**b**	SO_2Tol	**c**	Me	CO_2Me	**3bc**	A, 76 C, 83
6	**a**	CO_2Me	**b**	cPr	CO_2tBu	**3ab**	A, 97 C, 94
7	**d**	CN	**b**	cPr	CO_2tBu	**3db**	B,[f] 83
8	**a**	CO_2Me	**d**	CH_2OMe	$PO(OEt)_2$	**3ad**	A, 53 C, 47
9	**b**	SO_2Tol	**e**	CF_3	CO_2Et	**3be**	B, 76
10	**b**	SO_2Tol	**f**		CO_2Me	**3bf**	A,[f] 45
11	**e**	CO_2tBu	**g**	Ph	CO_2Et	**3eg**	C,[g] 78
12	**a**	CO_2Me	**h**	4-EtO-C_6H_4	CO_2Me	**3ah**	C,[g] 75
13	**a**	CO_2Me	**i**	4-F-C_6H_4	CO_2Me	**3ai**	C,[g] 78
14	**a**	CO_2Me	**j**	4-CF_3-C_6H_4	CO_2Me	**3aj**	C,[g] 70
15	**a**	CO_2Me	**k**	2-pyridyl	CO_2Me	**3ak**	C,[g] 68
16	**a**	CO_2Me	**l**	2-thienyl	CO_2Me	**3al**	C,[g] 94
17	**a**	CO_2Me	**m**		CO_2Me	**3am**	C, 91 [h]
18	**a**	CO_2Me	**n**	CH(OMe)Me	CO_2Me	**3an**	C, 54
19	**a**	CO_2Me	**o**	CO_2Me	CO_2Me	**3ao**	B, 81
20	**f**	CO_2Et	**a**	cPr	CO_2Me	**3fa**	A, 89
21	**f**	CO_2Et	**p**	H	CO_2Me	**3fp**	A, 35 C,[i] 37
22	**b**	SO_2Tol	**p**	H	CO_2Me	**3bp**	A, 38 C,[i] 30
23	**c**	Ph	**p**	H	CO_2Me	**3cp**	A, 7 C,[i] 25
24	**g**	4-$O_2NC_6H_4$	**p**	H	CO_2Me	**3gp**	C,[i] 44

[a] Method A: Addition of KO*t*Bu (1.2 equiv), 1 h, then 1 h at 20 °C, THF. [b] Method B: Simultaneous addition of KHMDS (1.2 equiv) and the respective acetylene **2** to a solution of the respective isocyanide **1** in THF at −78 °C within 1 h, then 3 h at −78 °C. [c] Method C: Cu catalyst, DMF, 85 °C, 12 h. [d] Yield of isolated product. [e] CsO*t*Bu was used instead of KO*t*Bu. [f] Method C was not employed in view of the instability of the acetylene and/or the substituted isocyanide. [g] The reaction was carried out at 120 °C. [h] Only the monocycloaddition product was obtained. [i] The reaction was carried out at 60 °C.

Table 2. Optimization of the copper catalyst for the synthesis of **3aa**.[a]



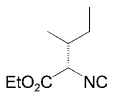
Entry	Cu catalyst	Yield **3aa** [%][b]
1	CuSPh	93
2	Cu^0-NP[c]	92
3	CuSePh	45
4	CuSHex	52
5	$CuPPh_2$	39
6	Cu_2O	78
7	Cu_2S	37
8	CuCl	6
9	CuBr	10
10	CuI	3
11	CuCN	24
12	$Cu(acac)_2$	24
13	$Cu(OAc)_2 \cdot H_2O$	19
14	$CpCuP(OMe)_3$	89[d]

[a] Reagents and conditions: **1a** (1.1 mmol), **2a** (1.0 mmol), copper salt (5 mol%), DMF (2 mL). [b] Determined by ^{1}H NMR with hexamethylbenzene as an internal standard. [c] The abbreviation Cu^0-NP stands for preactivated nanosize copper powder. [d] The reaction was carried out at 20°C with 10 mol% of catalyst and, according to TLC, was completed within 2 h.

2). With copper(I) oxide as a catalyst, **3aa** was obtained in a slightly lower yield of 78%, whereas other copper compounds gave inferior results. Surprisingly, some copper(II) compounds (copper(II) acetylacetonate, copper(II) acetate, entries 12, 13, respectively) catalyzed the formation of **3aa** as well, and gave even better results than CuI and other copper(I) halides. Copper(II) compounds are supposed to be (fully or partly) reduced by isocyanides to the corresponding Cu^I salts, which actually catalyze the reaction.

It is conceivable, that this reaction could be used for many other applications, for example, in biological systems, if it fulfilled the demands of Sharpless' so-called "click" chemistry",[18] that is, provided good yields and could be carried out at low temperatures. With the intention to achieve this kind of pyrrole formation at temperatures lower than 70°C, it was attempted to prepare a copper(I) compound, that would decompose to metallic copper at low temperatures. It is known, that cyclopentadienylcopper compounds[19] show interesting catalytic properties and serve as sources for copper of high purity,[20] as they decompose at relatively low temperatures. Thus, Saegusa, Ito et al.[21] reported that the cyclopentadienylcopper(I) *tert*-butylisocyanide complex catalyzes Michael-type additions of compounds containing active hydrogen, to acrylates and acrylonitrile. Indeed, η^5-(cyclopentadienyl)trimethylphosphite–copper(I) at 20°C efficiently catalyzes the reaction of **1a** with **2a** providing the pyrrole **3aa** in 89% yield within 2 h (Table 2, entry 14). However, all attempts to use this copper catalyst in the reaction of **1f** with both terminal and internal acetylenes without acceptor substituents, failed. Under the catalysis of $CpCuP(OMe)_3$ (5 mol%), the isocyanide **1f** dimerized to the imidazole **4**[22] in 85% yield at 20°C within 16 h.

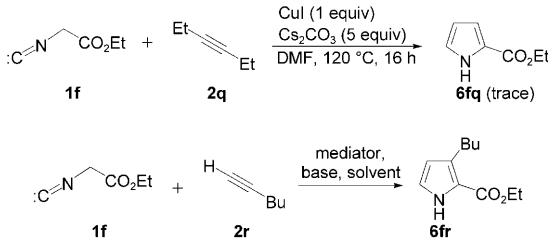
All catalysts (except nanosize-copper powder), which demonstrated moderate and good activity in the pyrrole formation (CuSPh, CuSePh, $CuPPh_2$, Cu_2O, Cu_2S), have one common feature, namely a σ-donating character of the counterion. Saegusa et al.[23] reported that copper(I) *tert*-butoxide with similar electronic properties, reveals a strong affinity toward π-accepting ligands like isocyanides, and this has not been observed for common cuprous salts. This feature of copper(I) compounds with σ-donating ligands may be ascribed to the enhancement of back-donation from the copper to π-accepting ligands, such as isocyanides. Enhanced affinity of copper(I) compounds with σ-donating counterions to isocyanides appears to be crucial for the pyrrole formation. Cu^I isocyanide complexes are known to abstract hydrogen from so-called active hydrogen compounds and to produce organocopper(I) isocyanide complexes,[24] which can undergo cycloadditions to form various heterocycles. In view of this, it is an open question, how copper(0) can be an active catalyst for the pyrrole formation. Metallic copper powder is known to dissolve in cyclohexyl isocyanide under an atmosphere of nitrogen to form a zero-valent copper–isocyanide complex, which can undergo an oxidative addition of a carbon–halogen bond.[25] Apart from the catalytic activity of metallic copper in the pyrrole synthesis demonstrated by us, Yamamoto et al.[11b] later reported, that metallic copper efficiently catalyzes the formation of imidazoles from two different isocyanides. These results indicate, that copper(0) isocyanide, like copper(I) isocyanide complexes, are able to deprotonate compounds with active hydrogen. To prove this hypothesis, the enantiomerically pure isocyanide **5**[26] was synthesized from L-isoleucine. Indeed, **5** underwent complete racemization upon heating at 85°C for three hours in DMF in the presence of pre-activated copper nanoparticles.



5

Synthesis of 2,3-disubstituted pyrroles: Although acetylenes without electron-withdrawing substituents have not been used earlier as cycloaddition partners for isocyanides in pyrrole syntheses[13,14] under usual conditions, an attempted reaction of 3-hexyne (**2q**) with ethyl isocyanoacetate (**1f**) at elevated temperature (120°C) in the presence of 1 equiv of copper(I) iodide as a mediator and 5 equiv of cesium carbonate as a base, gave a trace of the pyrrole **6fq** after 16 h (Scheme 2).

Terminal acetylenes turned out to be more reactive under these conditions. Thus, ethyl 3-butylpyrrolecarboxylate (**6fr**) was obtained in 29% yield from 1-hexyne and ethyl isocyanoacetate (**1f**) (Table 3, entry 1). The best yield of **6fr** in this reaction was achieved at 120°C, being almost the same as at 140°C, while at 100°C it was significantly lower (en-



Scheme 2. Formation of pyrroles **6** from unactivated acetylenes and substituted methyl isocyanides. For details see Tables 3 and 4.

tries 3, 2, respectively). Different bases were tested, yet lithium and potassium carbonate were less effective than cesium carbonate, giving rise to 15 and 19% yield of **6fr** respectively, under the same conditions (entries 4, 5). Tertiary amines (Et_3N, $EtNiPr_2$, DBU, DABCO) were less effective than alkali carbonates, giving less than 10% yield of **6fr** under the same conditions. Although DMF was used as a solvent in most cases, *N*,*N*-dimethylacetamide worked as well (entry 6), in toluene **6fr** was obtained in a lower yield of only 23% (entry 9). With catalytic quantities of CuI, only traces of **6fr** were isolated, while 1.3 equiv of CuI did not provide an improvement compared to an equimolar quantity. Among the mediators used, $CuOTf{\cdot}0.5\,C_6H_6$ was completely ineffective as well as Cu_2O, while $CuI{\cdot}P(OMe)_3$ gave **6fr** in 10% yield. AgOAc was slightly worse (27% yield of **6fr**, entry 8) than CuI, and in view of the significantly lower prices of copper salts, no further silver mediators were tested. Surprisingly, copper(II) trifluoromethanesulfonate also achieved the formation of **6fr** in 21% yield (entry 7).

Table 3. Optimization of conditions for the synthesis of **6fr** (see Scheme 2).[a]

Entry	Mediator (equiv)	Base (equiv)	Solvent	*T* [°C]	Yield[b] [%]
1	CuI (1)	Cs_2CO_3 (5)	DMF	120	29
2	CuI (1)	Cs_2CO_3 (5)	DMF	100	10
3	CuI (1)	Cs_2CO_3 (5)	DMF	140	28
4	CuI (1)	Li_2CO_3 (5)	DMF	120	15
5	CuI (1)	K_2CO_3 (5)	DMF	120	19
6	CuI (1)	Cs_2CO_3 (5)	DMA	120	30
7	$Cu(OTf)_2$ (1)	Cs_2CO_3 (5)	DMF	120	21
8	AgOAc(1)	Cs_2CO_3 (5)	DMF	120	27
9	CuI (1)	Cs_2CO_3 (5)	toluene	120	23

[a] All reactions were carried out with 1 mmol of the isocyanide **1f** and 5 mmol of the acetylene **2r** in 10 mL of solvent in a sealed vessel with stirring and heating for 12 h. [b] Yields of isolated product.

The yield of **6fr** could be further improved by gradually adding the isocyanide **1f** to a mixture of the copper mediator, cesium carbonate and the acetylene **2r** in DMF kept at 120°C (Table 4). This procedure with a stoichiometric quantity of CuI provided the pyrrole **6fr** in 36% yield (entry 1). $CuBr{\cdot}SMe_2$, CuBr and CuCl were equally effective, and all three of them were better than CuI (entries 2, 4, 5). But with a substoichiometric quantity (0.1 equiv) of $CuBr{\cdot}SMe_2$, only a trace of **6fr** was formed. The ratio of reagents had a

Table 4. Further optimization of conditions for the synthesis of **6fr**.[a,b]

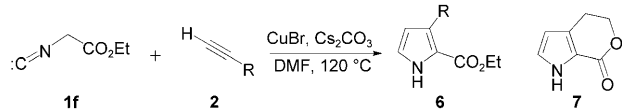
Entry	**1f** (equiv)	**2r** (equiv)	Mediator (equiv)	Base (equiv)	Yield[c] **6fr** [%]
1	1	1	CuI (1)	Cs_2CO_3 (5)	36[a]
2	5	1	$CuBr{\cdot}SMe_2$ (1)	Cs_2CO_3 (5)	64[a]
3	1	1	$CuBr{\cdot}SMe_2$ (0.1)	Cs_2CO_3 (5)	trace[a]
4	1	2	CuBr (1)	Cs_2CO_3 (3)	64[b]
5	1	2	CuCl (1)	Cs_2CO_3 (3)	64[b]
6	3	1	$CuBr{\cdot}SMe_2$ (1)	Cs_2CO_3 (1)	70[a]
7	2	1	$CuBr{\cdot}SMe_2$ (1)	Cs_2CO_3 (1)	70[a]
8	1.5	1	$CuBr{\cdot}SMe_2$ (1)	Cs_2CO_3 (1)	48[a]
9	1	1	$CuBr{\cdot}SMe_2$ (1)	Cs_2CO_3 (5)	43[a]
10	2	1	$CuBr{\cdot}SMe_2$ (1)	Cs_2CO_3 (1)	63[a]
11	2	1	$CuBr{\cdot}SMe_2$ (1)	Cs_2CO_3 (0.5)	trace[a]

[a] Method A: A solution of the isocyanide **1f** (1–5 mmol) in 5 mL of DMF was added dropwise at 120°C within 2 h to a mixture of Cs_2CO_3, the copper acetylenide generated in situ from the acetylene **2r** and the copper(I) salt in 5 mL of DMF, and the mixture was stirred at 120°C for 12 h. [b] Method B: A solution of the isocyanide **1f** (1 mmol) and the acetylene **2r** (1 mmol) in 5 mL of DMF was added dropwise within 2 h at 120°C to a mixture of Cs_2CO_3, the copper acetylenide generated in situ from the acetylene **2r** (1 mmol) and the copper(I) salt in 5 mL of DMF, and the mixture was stirred at 120°C for 12 h. [c] Yields of isolated product.

big influence on the yield as well. The yields of **6fr** were best, when two and more equivalents of isocyanide were used, whereas with the ratio of 1.5:1 and 1:1 of **1f** to **2r**, the yields of **6fr** were 48 and 43%, respectively (entries 8, 9). Interestingly, with an excess of the acetylene **2r** (2 equiv), **6fr** was obtained in 63% yield based on the isocyanide, indicating that the use of either an excess of the acetylene **2** or an excess of the isocyanide **1** are equally effective.

With the optimal conditions for the Cu^I-mediated cycloaddition in hand, the reactions of ethyl isocyanoacetate (**1f**) with various terminal alkynes without acceptor substituents were carried out (see Table 5). 1-Hexyne (**2r**) afforded the pyrrole **6fr** in 70 and 64% yield, respectively (entry 1), according to methods A and B (for details see footnotes under Table 5). 3-Methoxy-1-propyne (**2s**) with its donating methoxymethyl substituent, gave a lower yield of the pyrrole **6fs** (48%, entry 2). Bulky substituents R attached to the triple bond in **2** also led to decreased yields of the corresponding pyrroles **6**. Thus, **2y** with a *sec*-butyl group gave the pyrrole **6fy** in 58% yield (entry 8) compared to 70% of **6fr** (R = *n*-butyl). Phenylacetylene (**2u**), 2-pyridylacetylene (**2x**) and *tert*-butylacetylene (**2w**) afforded the corresponding pyrroles **6fu**, **6fx**, **6fw**/*iso*-**6fw** in 40, 16 and 5% yields, respectively (entries 4, 7, 6). In the latter case, a 5:1 mixture of the 2,3- **6fw** and the regioisomeric 2,4-disubstituted pyrrole *iso*-**6fw** was formed. The yields of pyrroles from cyclopropylacetylene (**2v**, entry 5) and from 3-methoxy-1-butyne (**2t**, entry 3) were the highest, although both of these acetylenes contain α-branched substituents. The cycloaddition of **1f** to 3-butyn-1-ol (**2z**) was accompanied by intramolecular transesterification of the ethoxycarbonyl group in the initial product, leading to the lactone-annelated pyrrole **7** in 44% (method A) and 37% yield (method B, entry 9).

Table 5. Synthesis of 2,3-disubstituted pyrroles **6** from the isocyanide **1f** and terminal acetylenes **2**.[a,b]



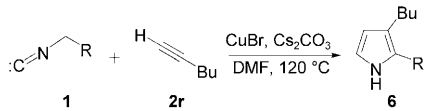
1f **2** **6** **7**

Entry	Acetylene	R	Product	Yield [%][c]
1	**2r**	*n*Bu	**6fr**	70[a], 64[b]
2	**2s**	CH_2OMe	**6fs**	48[a], 45[b]
3	**2t**	$CH(CH_3)OMe$	**6ft**	74[a]
4	**2u**	Ph	**6fu**	40[a]
5	**2v**	cPr	**6fv**	88[a]
6	**2w**	*t*Bu	**6fw**/*iso*-**6fw**	5[b]
7	**2x**	2-Py	**6fx**	16[a]
8	**2y**	*sec*-Bu	**6fy**	58[a]
9	**2z**	CH_2CH_2OH	**7**	44[a], 37[b]

[a] Method A: A solution of the isocyanide **1f** (1–5 mmol) in 5 mL of DMF was added dropwise at 120 °C within 2 h to a mixture of Cs_2CO_3, the copper acetylenide generated in situ from the acetylene **2** and the copper(I) salt in 5 mL of DMF, and the mixture was stirred at 120 °C for 1 h. [b] Method B: A solution of the isocyanide **1f** (1 mmol) and the acetylene **2** (1 mmol) in 5 mL of DMF was added dropwise within 2 h at 120 °C to a mixture of Cs_2CO_3, the copper acetylenide generated in situ from the acetylene **2** (1 mmol) and the copper(I) salt in 5 mL of DMF, and the mixture was stirred at 120 °C for 1 h. [c] Yields of isolated product.

Various other acceptor-substituted isocyanides **1** were compared with **1f** in their CuBr-mediated formal cycloadditions to 1-hexyne (**2r**) (Table 6). With its bulky *tert*-butyl ester moiety, **1e**, gave a lower yield of **6er** (47%, entry 2) than the ethyl ester **1f** gave **6fr** (70%, entry 1). *p*-Nitrophenylmethyl isocyanide (**1g**) afforded the corresponding pyrrole **6gr** in 20% yield only (entry 3). The methyl isocyanide with a diethylaminocarbonyl (**1h**), a dimethoxyphosphonyl (**1j**) and a *p*-toluenesulfonyl group (**1c**) did not give any of the respective pyrroles at all, although the consumption of the isocyanide was complete in all these cases (entries 4–6). All 2,3-disubstituted pyrroles **6** obtained in this way were colorless solids or oils except for pyrrole **6gr**, which was isolated as red crystals. Indeed, a red color is typical for many

Table 6. Synthesis of 2,3-disubstituted pyrroles **6** from various isocyanides **1** and 1-hexyne (**2r**).[a]



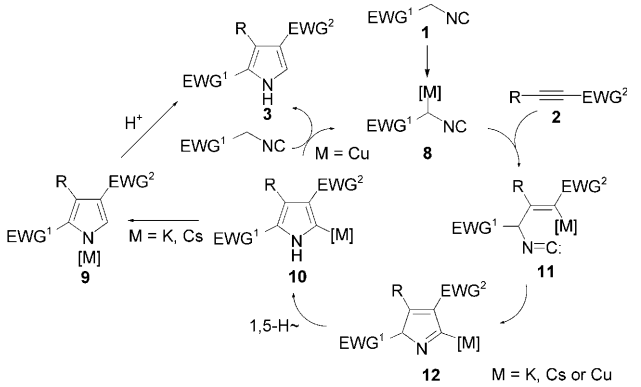
1 **2r** **6**

Entry	Isocyanide	R	Product	Yield[b] [%]
1	**1f**	CO_2Et	**6fr**	70
2	**1e**	CO_2tBu	**6er**	47
3	**1g**	$4\text{-}O_2NC_6H_4$	**6gr**	20
4	**1h**	$CONEt_2$	**6hr**	0
5	**1j**	$PO(OMe)_2$	**6jr**	0
6	**1b**	SO_2Tol	**6br**	0

[a] A solution of the isocyanide **1** (2 mmol) in 5 mL of DMF was added dropwise at 120 °C within 2 h to a mixture of Cs_2CO_3, the copper acetylenide generated in situ from the acetylene **2r** and CuBr in 5 mL of DMF, and the mixture was stirred at 120 °C for 1 h. [b] Yield of isolated product.

other known 2-(4-nitrophenyl)-substituted pyrroles: 3,4-dimethyl-2-(4-nitrophenyl)-5-phenyl-1*H*-pyrrole and 2-(4-nitrophenyl)-3,4,5-triphenyl-1*H*-pyrrole,[27a] 2,5-bis-(4-nitrophenyl)-1*H*-pyrrole,[27b] 5-methyl-2-(4-nitrophenyl)-1*H*-pyrrole,[27c] 5-phenyl-2-(4-nitrophenyl)-1*H*-pyrrole.[27d]

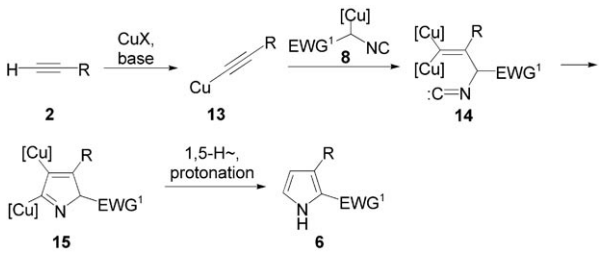
All experimental data of some preliminary kinetic investigations (see Supporting Information) are in agreement with an overall second order of the reaction, that is, first order with the respect to both, the acetylene and the isocyanide. Thus, a plausible mechanism of both the base-mediated and the copper(I)-catalyzed[14] pyrrole formation from substituted methyl isocyanides **1** and electron-acceptor substituted alkynes **2** can be proposed (see Scheme 3). The initiating



Scheme 3. Proposed mechanism for the formal cycloaddition of an α-metallated isocyanide **1** across the C,C-triple bond in an electron-deficient acetylene **2**.

step is the formation of an α-metallated isocyanide **8**. Not only Cu^I compounds, but also metallic copper powder and Cu^{II} salts (to some extent) must lead to the formation of such a species. Subsequent Michael-type addition onto the triple bond of an activated acetylene **2** furnishes an unstable vinyl-organometallic compound **11**, which readily undergoes cyclization to the 2*H*-pyrroleninemetallic species **12**. The latter then experiences a 1,5-hydrogen shift to yield **10**, and protonation of the latter by the isocyanide **1** gives the pyrrole **3**, completing the catalytic cycle for M = Cu. The intermediate **12** could also first be protonated, and then undergo a 1,5-hydrogen shift. There is no experimental evidence favoring either one of the two possibilities. In the base-mediated pyrrole formation, counterions like K^+ and Cs^+, which are harder than Cu^+, presumably lead to the *N*-metallated pyrrole **9**, which does not deprotonate to any significant extent a new molecule of isocyanide **1**, and this therefore requires a stoichiometric quantity of base for the pyrrole formation in good yields.

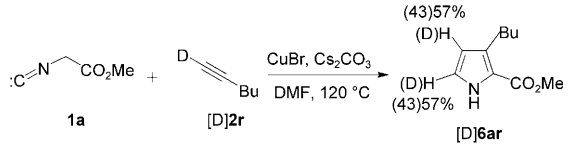
The pyrrole formation in the copper(I)-mediated reaction between substituted methyl isocyanides **1** and unactivated terminal acetylenes **2** can be rationalized as follows (Scheme 4). Carbocupration[28] of the copper acetylenide **13** by the deprotonated isocyanide **8** followed by cyclization of



Scheme 4. Mechanistic rationalization of the copper(I)-mediated reaction of isocyanides **1** with a terminal acetylene **2** to yield a 2,3-disubstituted pyrrole **6**.

the thus formed intermediate **14** would yield the 2*H*-pyrrolenline-4,5-dicopper derivative **15**, which by 1,5-hydrogen shift and twofold protonation would give the pyrrole **6**.

To support this hypothesis, hexynylcopper[29] (**13**, R = *n*Bu) was prepared separately and treated with methyl isocyanoacetate (**1a**) in DMF at 120 °C, both in the presence of base and without it, to furnish the pyrrole **6ar** in 28 and 30 % yield, respectively. In addition, a reaction of **1a** with a twofold excess of 1-deutero-1-hexyne ([D]**2r**) employing method B was carried out (Scheme 5).



Scheme 5. Formation of the partly deuterated pyrrole [D]**6ar**.

This reaction, after work-up with H_2O, furnished a mixture of pyrroles [D]**6ar** with approximately equal deuterium incorporation (43 %) at positions 4 and 5, as evidenced by an ^{1}H NMR spectrum. This fact proves the intermediate formation of a 2*H*-pyrrolenline-4,5-dicopper species **15**, which is deuterated or protonated by [D]**2r** or **1a**, respectively to give pyrrole [D]**6ar** or [H]**6ar**, respectively.

Conclusion

The direct formation of pyrroles from substituted methyl isocyanides **1** and acceptor-substituted acetylenes **2** under copper(I) catalysis represents a convenient route to 2,3,4-trisubstituted pyrroles and 3,4-disubstituted pyrroles **3** with sufficient functionality for further elaboration. The newly found route to 2,3-disubstituted pyrroles **6** from substituted methyl isocyanides **1** and non-activated terminal acetylenes mediated by copper(I) compounds further enhances the versatility of these pyrrole syntheses. The prepared derivatives can also be easily transformed into pyrroles of higher or lower order of substitution according to established protocols.[30,31]

Experimental Section

General methods: NMR (^{1}H, ^{13}C, ^{19}F and ^{31}P) spectra were recorded at 300 (^{1}H), 75.5 [^{13}C, APT (Attached Proton Test)], 282.4 (^{19}F), and 121.7 (^{31}P) MHz on Varian Unity-300 and AMX 300 instruments with $CDCl_3$ solutions if not otherwise specified. TLC: Macherey-Nagel, TLC plates Alugram Sil G/UV254. Detection under UV light at 254 nm or development with MOPS (10 % molybdophosphoric acid, solution in ethanol). Chromatography: Separations were carried out on Merck Silica 60 (0.063–0.200 mm, 70–230 mesh ASTM). IR: measured as KBr pellets or as films between KBr plates. MS: EI-MS: Finnigan MAT 95, 70 eV, DCI-MS: Finnigan MAT 95, 200 eV, reactant gas NH_3; ESI-MS: Finnigan LCQ. High resolution mass spectrometry (HRMS): APEX IV 7T FTICR, Bruker Daltonic. M.p.: Büchi 540 capillary melting point apparatus, values are uncorrected. Elemental analyses: Mikroanalytisches Laboratorium des Instituts für Organische und Biomolekulare Chemie der Universität Göttingen.

Starting materials: Methyl cyclopropylpropiolate (**2a**),[32] *tert*-butyl cyclopropylpropiolate (**2b**),[33] 4-nitrophenylmethyl isocyanide (**1g**),[34] cyanomethyl isocyanide (**1d**),[35] diethyl (3-methoxyprop-1-ynyl)phosphonate (**2d**),[36] ethyl trifluoromethylpropiolate (**2e**),[37] methyl morpholin-4-ylpropiolate (**2f**),[38] methyl 3-(4-fluorophenyl)propiolate (**2i**),[39] methyl 3-(4-trifluoromethylphenyl)propiolate (**2j**),[40] methyl 3-(thiophen-2-yl)propiolate (**2l**),[41] methyl 3-(pyridin-2-yl)propiolate (**2k**),[42] methyl (1-methoxycarbonylethynylcyclopropyl)propiolate (**2m**),[43] cyclopropylacetylene (**2v**),[44] $CpCuP(OMe)_3$,[19] 1-deuterohex-1-yne ([D]**2r**)[45] were prepared according to literature procedures. Commercial nanosize-copper powder (Aldrich) was preactivated by heating in vacuo (0.05 mbar) at 150 °C overnight, and it was then stored under Ar. All other chemicals were used as commercially available.

Cesium *tert*-butoxide (CsO*t*Bu): *tert*-Butyl alcohol (6 mL) was added in three portions within 1 h to cesium metal (1.0 g, 7.52 mmol) under anhydrous toluene (30 mL) at 20 °C with gentle stirring under an atmosphere of Ar, and the mixture was stirred until the cesium metal had completely dissolved (≈1 h). The resulting solution was concentrated under reduced pressure and dried in vacuo (0.05 mbar) at 70 °C for 7 h to give cesium *tert*-butoxide (1.44 g, 93 %) as a colorless solid.

General procedure for the formal cycloaddition of substituted methyl isocyanides to acetylenes mediated by potassium *tert*-butoxide (GP 1, method A): To a solution of the respective acetylene **2** (5.0 mmol) and the respective substituted methyl isocyanide **1** (5.5 mmol) in THF (60 mL) was added dropwise at 20 °C within 1 h a solution of KO*t*Bu (616 mg, 5.5 mmol) in THF (35 mL). The mixture was stirred at 20 °C for 1 h, the reaction was then quenched with glacial AcOH (1 mL), and the solution concentrated under reduced pressure. The residue was triturated with CH_2Cl_2 (3×30 mL) at 20 °C to extract the crude product, which was purified by column chromatography.

General procedure for the formal cycloaddition of substituted methyl isocyanides to acetylenes mediated by KHMDS (GP 2, method B): To a solution of the respective substituted methyl isocyanide **1** (5.5 mmol) in THF (60 mL) were added dropwise and simultaneously from two separate syringes by means of a syringe pump at −78 °C within 1 h a solution of KHMDS (5.5 mmol) in THF (10 mL) and a solution of the respective acetylene **2** (5.0 mmol) in THF (10 mL). The mixture was stirred at −78 °C for 3 h, then the reaction was quenched with glacial AcOH (1 mL), and the solution concentrated under reduced pressure. The residue was triturated with CH_2Cl_2 (3×30 mL) at 20 °C to extract the crude product, which was purified by column chromatography.

General procedure for the copper-catalyzed formal cycloaddition of substituted methyl isocyanides to acetylenes (GP 3, method C): The copper catalyst [preferably preactivated nanosize copper powder (3 mg, 0.05 mmol, 5 mol %), or copper thiophenolate (9 mg, 0.05 mmol, 5 mol %)] was added to a solution of the respective substituted methyl isocyanide **1** (1.1 mmol) and the respective acetylene **2** (1.0 mmol) in DMF (2 mL), and the mixture was vigorously stirred at 70 °C (preactivated nanosize-copper powder) or 85 °C (CuSPh) for 16 h. The solvent

was removed in vacuo (0.05 mbar), and the residue was purified by column chromatography to give the corresponding pyrrole.

Dimethyl 3-cyclopropyl-1*H*-pyrrole-2,4-dicarboxylate (3aa): Following GP 1 (method A), the pyrrole **3aa** (1.01 g, 91%) was obtained from methyl cyclopropylpropiolate (**2a**) (620 mg, 5.0 mmol) and methyl isocyanoacetate (**1a**) (545 mg, 5.5 mmol), after column chromatography (cyclohexane/ethyl acetate 4:1) as a colorless solid. M.p. 123°C; ^{1}H NMR (300 MHz, $CDCl_3$, 25°C, TMS): δ = 9.78 (brs, 1H, NH), 7.43 (d, J = 3.6 Hz, 1H, NCH), 3.82 (s, 3H, CH_3), 3.76 (s, 3H, CH_3), 2.27–2.17 (m, 1H, cPr-H), 0.96–0.83 ppm (m, 4H, CH_2); ^{13}C NMR (75.5 MHz, $CDCl_3$, 25°C): δ = 164.5 (C), 161.4 (C), 135.4 (C), 127.5 (CH), 121.3 (C), 116.9 (C), 51.5 (CH_3), 51.0 (CH_3), 8.2 (CH_2), 7.3 ppm (CH); IR (KBr): $\tilde{\nu}$ = 3325, 3146, 3010, 2951, 1719, 1696, 1541, 1437, 1276, 1199, 1059, 785 cm^{-1}; MS (EI): m/z (%): 223.1 $[M]^+$; HRMS (ESI): m/z: calcd for $C_{11}H_{14}NO_4^+$ $[M+H]^+$: 224.0923; found: 224.0917.

***tert*-Butyl 2-(4-toluenesulfonyl)-3-cyclopropyl-1*H*-pyrrole-4-carboxylate (3bb)**: The pyrrole **3bb** (1.65 g, 91%) was obtained from *tert*-butyl cyclopropylpropiolate (**2b**) (830 mg, 5.0 mmol) and *p*-toluenesulfonylmethyl isocyanide (**1b**) (997 mg, 5.5 mmol) with CuSPh as a catalyst following GP3 (method C), after column chromatography (cyclohexane/ethyl acetate 4:1) as a colorless solid. M.p. 165°C. Alternatively, it was prepared following GP 1 (method A) with KO*t*Bu as a base (1.69 g, 93%). ^{1}H NMR (300 MHz, $CDCl_3$, 25°C, TMS): δ = 9.93 (brs, 1H, NH), 7.75 (d, J = 8.4 Hz, 2H, Ts-CH), 7.38 (d, J = 3.5 Hz, 1H, NCH), 7.26 (d, J = 8.4 Hz, 2H, Ts-CH), 2.38 (s, 3H, Ts-CH_3), 1.78 (dddd, J = 6.0, 6.0, 8.6, 8.6 Hz, 1H, CH), 1.48 (s, 9H, *t*Bu), 0.85–0.74 ppm (m, 4H, cPr-CH_2); ^{13}C NMR (75.5 MHz, $CDCl_3$, 25°C): δ = 163.0 (C), 144.1 (C), 138.9 (C), 132.0 (C), 129.7 (CH), 127.0 (2 CH), 126.9 (C), 120.0 (C), 80.4 (C), 28.2 (CH_3), 21.6 (CH_3), 7.9 (CH_2), 6.9 ppm (CH); IR (KBr): $\tilde{\nu}$ = 3314, 3092, 3006, 2973, 2934, 1932, 1713, 1594, 1532, 1503, 1448, 1392, 1372, 1353, 1305, 1238, 1198, 1137, 1101, 1080, 1036, 1018, 967, 891, 813, 738, 677, 607, 532 cm^{-1}; MS (EI): m/z (%): 361.1 (10) $[M]^+$, 305.1 (100), 288.1 (18), 261.0 (39), 196.1 (30); HRMS (ESI): m/z: calcd for $C_{19}H_{24}NO_4S^+$ $[M+H]^+$: 362.1421; found: 362.4626.

***tert*-Butyl 2-cyano-3-cyclopropyl-1*H*-pyrrole-4-carboxylate (3db)**: The pyrrole **3db** (687 mg, 83%) was obtained from *tert*-butyl cyclopropylpropiolate (**2b**) (416 mg, 2.5 mmol) and cyanomethyl isocyanide (**1d**) (198 mg, 3 mmol) following GP 2 (method B), after column chromatography (cyclohexane/ethyl acetate 4:1) as a colorless solid. M.p. 112°C; ^{1}H NMR (300 MHz, $CDCl_3$, 25°C, TMS): δ = 9.48 (brs, 1H, NH), 7.39 (d, J = 3.3 Hz, 1H, NHCH), 2.34–2.18 (m, 1H, CH), 1.05–0.89 (m, 4H, CH_2), 1.56 ppm (s, 9H, *t*Bu); ^{13}C NMR (75.5 MHz, $CDCl_3$, 25°C): δ = 163.3 (C), 139.1 (C), 128.5 (CH), 118.7 (C), 114.1 (C), 99.4 (C), 80.8 (C), 29.7 (CH), 28.3 (CH_3), 7.7 ppm (CH_2); IR (film): $\tilde{\nu}$ = 3232, 3012, 2977, 2931, 2220, 1683, 1668, 1560, 1379, 1264, 1155, 747 cm^{-1}; MS (EI): m/z (%): 232.2 (15) $[M]^+$, 176.2 (100), 158.1 (75), 130.1 (30), 104.1 (12), 57.1 (36); elemental analysis calcd (%) for $C_{13}H_{16}N_2O_2$: C 67.22, H 6.94, N 12.06; found: C 66.96, H 6.71, N 12.11.

Ethyl 2-(*tert*-butoxycarbonyl)-3-phenyl-1*H*-pyrrole-4-carboxylate (3eg): The pyrrole **3eg** (246 mg, 78%) was obtained from ethyl phenylpropiolate **2g** (174 mg, 1.0 mmol) and *tert*-butyl isocyanoacetate **1e** (155 mg, 1.1 mmol) following GP 3 (method C) with Cu^0-NP (3 mg, 0.05 mmol, 5 mol%) at 120°C, after column chromatography (cyclohexane/ethyl acetate 4:1) as a colorless solid. M.p. 125°C; ^{1}H NMR (300 MHz, $CDCl_3$, 25°C, TMS): δ = 10.18 (brs, 1H, NH), 7.53 (d, J = 3.4 Hz, 1H, NCH), 7.38–7.20 (m, 5H, Ph), 4.08 (q, J = 7.1 Hz, 2H, CH_2), 1.25 (s, 9H, *t*Bu), 1.07 ppm (t, J = 7.1 Hz, 3H, CH_3); ^{13}C NMR (75.5 MHz, $CDCl_3$, 25°C): δ = 164.0 (C), 161.1 (C), 134.6 (C), 131.7 (C), 130.0 (CH), 126.9 (CH), 126.7 (CH), 126.5 (CH), 122.4 (C), 117.0 (C), 81.5 (C), 27.9 (CH_3), 13.9 ppm (CH_3); IR (KBr): $\tilde{\nu}$ = 3289, 3126, 3057, 2977, 2933, 1687, 1552, 1517, 1400, 1367, 1285, 1175, 1115, 1021, 840, 761, 695 cm^{-1}; MS (EI): m/z (%): 315.3 (43) $[M]^+$, 259.2 (100), 241.1 (17), 214.2 (24), 196.2 (61); elemental analysis calcd (%) for $C_{18}H_{21}NO_4$: 68.55, H 6.71, N 4.44; found: 68.31, 6.50, 4.38.

Dimethyl 3-(thiophen-2-yl)-1*H*-pyrrole-2,4-dicarboxylate (3al): The pyrrole **3al** (250 mg, 94%) was obtained from methyl (thiophen-2-yl)propiolate (**2l**) (166 mg, 1.0 mmol) and methyl isocyanoacetate (**1a**) (149 mg, 1.5 mmol) following GP 3 (method C) with Cu^0-NP (3 mg, 0.05 mmol, 5 mol%) at 120°C, after column chromatography (hexane/ethyl acetate 2:1, R_f = 0.20) as a yellow solid. M.p. 146°C; ^{1}H NMR (300 MHz, $CDCl_3$, 25°C, TMS): δ = 9.50 (brs, 1H, NH), 7.56 (d, J = 3.3 Hz, 1H, NCH), 7.38 (t, J = 3.3 Hz, 1H, thienyl-5H), 7.05 (d, J = 3.0 Hz, 2H, thienyl-3,4H), 3.73 (s, 3H, CH_3), 3.70 ppm (s, 3H, CH_3); ^{13}C NMR (75.5 MHz, $CDCl_3$, 25°C): δ = 163.7 (C), 160.9 (C), 132.9 (C), 128.5 (CH), 126.9 (CH), 126.2 (CH), 126.0 (CH), 124.1 (C), 121.9 (C), 117.8 (C), 51.8 (CH_3), 51.2 ppm (CH_3); IR (KBr): $\tilde{\nu}$ = 2954, 1731, 1703, 1524, 1439, 1386, 1264, 1197, 1015, 921, 784, 689 cm^{-1}; MS (EI): m/z (%): 265.2 (90) $[M]^+$, 233.1 (78), 202.1 (62), 43.1 (100); elemental analysis calcd (%) for $C_{12}H_{11}NO_4S$: C 54.33, H 4.18, N 5.28; found: C 54.05, H 4.10, N 5.38.

Trimethyl 1*H*-pyrrole-2,3,4-tricarboxylate (3ai):[46] The pyrrole **3ai** (489 mg, 81%) was obtained from dimethyl acetylenedicarboxylate (**2i**) (355 mg, 2.5 mmol) and methyl isocyanoacetate (**1a**) (327 mg, 3.3 mmol) following GP 2 (Method B), after column chromatography (cyclohexane/ethyl acetate 4:1) as a colorless solid. M.p. 87°C; ^{1}H NMR (300 MHz, $CDCl_3$, 25°C, TMS): δ = 10.12 (brs, 1H, NH), 7.45 (d, J = 3.3 Hz, 1H, NCH), 3.91 (s, 3H, CH_3), 3.81 (s, 3H, CH_3), 3.78 ppm (s, 3H, CH_3); ^{13}C NMR (75.5 MHz, $CDCl_3$, 25°C): δ = 165.9 (C), 163.1 (C), 160.1 (C), 126.5 (CH), 123.0 (C), 120.9 (C), 115.8 (C), 52.9 (CH_3), 52.4 (CH_3), 51.7 ppm (CH_3); IR (KBr): $\tilde{\nu}$ = 3298, 3300, 3124, 3016, 2960, 2920, 2854, 1707, 1567, 1520, 1469, 1444, 1393, 1370, 1290, 1197, 1172, 1070, 1016, 959, 935, 817, 785, 682, 618, 578, 531 cm^{-1}; MS (EI): m/z (%): 241.2 (100) $[M]^+$.

General procedure for the synthesis of 2,4-disubstituted pyrroles 3 (GP 4): Preactivated nanosize-copper powder (3.2 mg, 5 mol%) was added to a mixture of methyl propiolate (**2p**) (84 mg, 1.0 mmol) and the respective isocyanide **1** (1.0 mmol) in DMF (2 mL). The mixture was stirred at 60°C for 16 h, then the solvent was evaporated in vacuo, and the residue was purified by column chromatography.

Methyl 2-(ethoxycarbonyl)-1*H*-pyrrole-4-carboxylate (3fp):[47] The pyrrole **3fp** (73 mg, 37%) was obtained from methyl propiolate (**2p**; 84 mg, 1.0 mmol) and ethyl isocyanoacetate (**1f**; 113 mg, 1.0 mmol) following GP4, after column chromatography (hexane/ethyl acetate 4:1, R_f = 0.17) as a colorless solid. M.p. 98–99°C; ^{1}H NMR (300 MHz, $CDCl_3$, 25°C, TMS) δ = 9.98–9.76 (brs, 1H, NH), 7.55 (dd, J = 3.2, 1.5 Hz, 1H, CH), 7.31 (dd, J = 2.4, 1.6 Hz, 1H, NCH), 4.35 (q, J = 7.0 Hz, 2H, CH_2), 3.84 (s, 3H, CO_2CH_3), 1.37 ppm (t, J = 7.2 Hz, 3H, Et-CH_3); ^{13}C NMR (75.5 MHz, $CDCl_3$, 25°C): δ = 164.4 (C), 161.0 (C), 127.0 (C), 123.8 (CH), 117.8 (C), 115.8 (CH), 60.9 (CH_2), 51.3 (CH_3), 14.3 ppm (CH_3); IR (KBr):$\tilde{\nu}$ = 3293, 2981, 1690, 1562, 1499, 1441, 1403, 1280, 1216, 1122, 1085, 1022, 989, 964, 927, 853, 762, 604, 504 cm^{-1}; MS (EI) m/z (%): 197.0 (76) $[M]^+$, 166.1 (53), 152.1 (44), 120.1 (100); elemental analysis calcd (%) for $C_9H_{11}NO_4$: C 54.82, H 5.62, N 7.10; found: C 54.92, H 5.82, N 6.98.

Methyl 2-(4-toluenesulfonyl)-1*H*-pyrrole-4-carboxylate (3bp):[48] The pyrrole **3bp** (83 mg, 30%) was obtained from methyl propiolate (**2p**; 84 mg, 1.0 mmol) and tosylmethyl isocyanide (**1b**; 195 mg, 1.0 mmol) following GP 4, after column chromatography (hexane/ethyl acetate 2:1, R_f = 0.22) as a colorless solid. M.p. 157–158°C. Alternatively, it was prepared with KO*t*Bu as a mediator (105 mg, 38%). ^{1}H NMR (300 MHz, $CDCl_3$, 25°C, TMS): δ = 9.95 (brs, 1H, NH), 7.81 (d, J = 8.1 Hz, 2H, Ts-CH), 7.53 (dd, J = 3.1, 1.6 Hz, 1H, CH), 7.30 (d, J = 8.1 Hz, 2H, Ts-CH), 7.21 (dd, J = 3.1, 1.6 Hz, 1H, NCH), 3.80 (s, 3H, CO_2CH_3), 2.41 ppm (s, 3H, CH_3); ^{13}C NMR (75.5 MHz, $CDCl_3$, 25°C): δ = 163.8 (C), 144.6 (CH), 138.4 (C), 130.2 (C), 130.0 (2 CH), 127.3 (C), 127.1 (2 CH), 118.5 (C), 115.7 (CH), 51.6 (CH_3), 21.6 ppm (CH_3); IR (KBr): $\tilde{\nu}$ = 3250, 2950, 1691, 1595, 1546, 1473, 1433, 1392, 1319, 1228, 1183, 1145, 1116, 1076, 1017, 988, 930, 857, 813, 766, 744, 706, 676, 623, 604, 535, 492 cm^{-1}; MS (ESI): m/z (%): 302.0 $[M+Na]^+$, 278.3 $[M-H]^-$; HRMS (ESI): m/z: calcd for $C_{13}H_{14}NO_4S^+$ $[M+H]^+$: 280.06381; found: 280.06403.

GP A for the synthesis of 2,3-disubstituted pyrroles 6 (GP 5): An oven-dried Schlenk flask equipped with magnetic stirrer and rubber septum, was charged with CuBr (143.5 mg, 1.0 mmol), Cs_2CO_3 (326 mg, 1 mmol) and DMF (5 mL), evacuated and refilled with nitrogen. The respective acetylene **2** (1.0 mmol) was added from a syringe with stirring, and the mixture was heated at 120°C for 10 min, then a solution of the respective isocyanide **1** (2.0 mmol) in DMF (5 mL) was injected over a period of 2 h, after that the reaction mixture was stirred at 120°C for another 1 h.

After cooling and evaporation of the solvent in vacuo, the residue was purified by column chromatography on silica gel (eluting with 5:1 to 1:1 hexane/ethyl acetate) to provide the desired product.

GP B for the synthesis of 2,3-disubstituted pyrroles 6 (GP 6): An oven-dried Schlenk flask equipped with magnetic stirrer and rubber septum was charged with CuBr (143.5 mg, 1.0 mmol), Cs_2CO_3 (326 mg, 1 mmol) and DMF (5 mL), evacuated and refilled with nitrogen. The respective acetylene **2** (1.0 mmol) was added from a syringe with stirring, and the mixture was heated at 120 °C for 10 min, then solutions of the respective isocyanide **1** (1.0 mmol) and the respective acetylene **2** (1.0 mmol) in DMF (5 mL) were injected over a period of 2 h, after that the reaction mixture was stirred at 120 °C for another 1 h. After cooling and evaporation of the solvent in vacuo, the residue was purified by column chromatography on silica gel (eluting with 5:1 to 1:1 hexane/ethyl acetate) to provide the desired product.

Ethyl 3-butyl-1*H*-pyrrol-2-carboxylate (6 fr): The pyrrole **6 fr** (250 mg, 64 %) was obtained from 1-hexyne (**2 r**) (328 mg, 4 mmol), ethyl isocyanoacetate (**1 f**) (226 mg, 2 mmol) following GP 6, after column chromatography (hexane/ethyl acetate 4:1, $R_f = 0.45$) as a colorless oil. Alternatively it was obtained following GP 5 (273 mg, 70 %). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 9.10$–8.89 (br m, 1 H, NH), 6.81 (t, $J =$ 3 Hz, 1 H, CH), 6.10 (t, $J = 3$ Hz, 1 H, CH), 4.29 (q, $J = 7$ Hz, 2 H, Et-CH_2), 2.77 (t, $J = 8$ Hz, 2 H, CH_2), 1.60–1.20 (m, 7 H), 0.91 ppm (t, $J =$ 8 Hz, 3 H, Et-CH_3); ^{13}C NMR (75.5 MHz, $CDCl_3$, 25 °C): $\delta = 161.7$ (C), 133.3 (C), 121.5 (CH), 118.8 (C), 111.4 (CH), 59.9 (CH_2), 33.0 (CH_2), 26.6 (CH_2), 22.6 (CH_2), 14.4 (CH_3), 13.9 ppm (CH_3); IR (film): $\tilde{\nu} = 3322$, 2957, 2860, 1672, 1561, 1420, 1318, 1262, 1188, 1133, 1044, 783 cm^{-1}; MS (EI): m/z (%): 195 (72) $[M]^+$, 153 (40), 124 (100), 106 (56), 80 (40); elemental analysis calcd (%) for $C_{11}H_{17}NO_2$: C 67.66, H 8.78, N 7.17; found: C 67.71, H 8.51, N 7.02.

Ethyl 3-(methoxymethyl)-1*H*-pyrrole-2-carboxylate (6 fs): The pyrrole **6 fs** (88 mg, 48 %) was obtained from ethyl isocyanoacetate (**1 f**; 226 mg, 2.0 mmol) and 3-methoxypropyne (**2 s**; 70 mg, 1.0 mmol) following GP 5 as a colorless solid. M.p. 74 °C; $R_f = 0.27$ (hexane/ethylacetate 4:1). Alternatively, it was prepared following GP 6 (83 mg, 45 %). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 9.39$ (br s, 1 H, NH), 6.88 (t, $J =$ 2.6 Hz, 1 H, CH), 6.34 (t, $J = 2.6$ Hz, 1 H, CH), 4.69 (s, 2 H, CH_2), 4.34 (q, $J = 7.2$ Hz, 2 H, Et-CH_2), 3.43 (s, 3 H, OCH_3), 1.37 ppm (t, $J = 7.2$ Hz, 3 H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 161.2$ (C), 128.4 (C), 121.9 (CH), 119.1 (C), 111.1 (CH), 67.2 (CH_2), 60.3 (CH_3), 58.1 (CH_2), 14.4 ppm (CH_3); MS (EI): *m*/*z* (%): 183.2 (40) $[M^+]$, 168.1 (52), 154.2 (45), 122.1 (100); IR (KBr): $\tilde{\nu} = 3288$, 1671, 1490, 1426, 1373, 1326, 1271, 1222, 1193, 1139, 1111, 963, 782, 751, 601 cm^{-1}; elemental analysis calcd (%) for $C_9H_{13}NO_3$: C 59.00, H 7.15, N 7.65; found: C 59.06, H 6.80, N 7.35.

Ethyl 3-cyclopropyl-1*H*-pyrrole-2-carboxylate (6 fv): The pyrrole **6 fv** (157 mg, 88 %) was obtained following GP 5 from ethyl isocyanoacetate (**1 f**; 226 mg, 2.0 mmol) and cyclopropylacetylene (**2 v**; 66 mg, 1.0 mmol) as a colorless solid. M.p. 51–52 °C; $R_f = 0.37$ (hexane/ethyl acetate 5:1); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 8.92$ (br s, 1 H, NH), 6.79 (t, $J = 2.9$ Hz, 1 H, CH), 5.78 (t, $J = 2.9$ Hz, 1 H, CH), 4.35 (q, $J = 7.2$ Hz, 2 H, CH_2), 2.57–2.48 (m, 1 H, cPr-CH), 1.37 (t, $J = 7.2$ Hz, 3 H, CH_3), 0.99–0.93 (m, 2 H, cPr-CH_2), 0.64–0.59 ppm (m, 2 H, cPr-CH_2); ^{13}C NMR (75.5 MHz, $CDCl_3$, 25 °C): $\delta = 161.7$ (C), 135.5 (C), 121.9 (CH), 119.7 (C), 106.2 (CH), 60.0 (CH_2), 14.5 (CH), 9.3 (CH_2), 7.9 ppm (CH_2); IR (KBr): $\tilde{\nu} = 3299$, 1673, 1422, 1391, 1322, 1279, 1218, 1185, 1141, 1036, 907, 781, 745, 602 cm^{-1}; MS (EI) *m*/*z* (%): 179.2 (100) $[M]^+$, 150.2 (45), 133.2 (39), 106.2 (62); elemental analysis calcd (%) for $C_{10}H_{13}NO_2$: C 67.02, H 7.31, N 7.82; found: C 67.66, H 6.80, N 7.36.

Ethyl 3-*tert*-butyl-1*H*-pyrrole-2-carboxylate (9 fq) and ethyl 4-*tert*-butyl-1*H*-pyrrole-2-carboxylate (*iso*-6 fw):[49] A 5:1 mixture of the regioisomeric pyrroles **6 fw** and *iso*-**6 fw** (10 mg, 5 %) was obtained following GP 6 from ethyl isocyanoacetate (**1 f**; 113 mg, 1.0 mmol) and *tert*-butylacetylene (**2 w**; 164 mg, 2.0 mmol) as a colorless oil, $R_f = 0.43$ (hexane/ethyl acetate 4:1). **6 fw**: ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 9.16$ (br s, 1 H, NH), 6.78 (t, $J = 2.6$ Hz, 1 H, CH), 6.21 (t, $J = 2.6$ Hz, 1 H, CH), 4.32 (q, $J = 7.2$ Hz, 2 H, CH_2), 1.40 (s, 9 H, *t*Bu), 1.25 ppm (s, 3 H, CH_3); ^{13}C NMR (75.5 MHz, $CDCl_3$, 25 °C): $\delta = 160.4$ (C), 142.6 (C), 120.0 (CH), 109.8 (CH), 109.2 (C), 60.0 (CH_2), 31.6 (CH_3), 30.2 (CH_3), 22.6 ppm (C); *iso*-**6 fw**: ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 8.95$ (br s, 1 H, NH), 6.83 (t, $J = 2.6$ Hz, 1 H, CH), 6.12 (t, $J = 2.6$ Hz, 1 H, CH), 4.31 (q, $J = 7.2$ Hz, 2 H, CH_2), 1.37 (t, $J = 7.2$ Hz, 9 H, *t*Bu), 0.93 ppm (t, $J =$ 7.2 Hz, 3 H, CH_3); ^{13}C NMR (75.5 MHz, $CDCl_3$, 25 °C): $\delta = 160.4$ (C), 142.6 (C), 121.4 (C), 117.9 (CH), 111.4 (CH), 59.9 (CH_2), 33.0 (CH_3), 29.7 (CH_3), 26.6 ppm (C); MS (EI) *m*/*z* (%): 195.2 (26) $[M]^+$, 180.2 (28), 134.2 (100).

4,5-Dihydro-1*H*-pyrano[3,4-*b*]pyrrol-7-one (7): The δ-lactone-annelated pyrrole **7** (51 mg, 37 %) was obtained from ethyl isocyanoacetate (**1 f**; 113 mg, 1.0 mmol) and but-3-yn-1-ol (**2 z**; 140 mg, 2.0 mmol) following GP 6, as a colorless solid. M.p. 123–124 °C. Alternatively, **7** was prepared following GP 5 (61 mg, 44 %). $R_f = 0.45$ (hexane/ethyl acetate 1:1); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 10.68$ (br s, 1 H, NH), 7.08 (t, $J = 2.8$ Hz, 1 H), 6.13 (t, $J = 2.8$ Hz, 1 H, CH), 4.56 (t, $J = 6.2$ Hz, 2 H, CH_2), 2.93 ppm (t, $J = 6.2$ Hz, 2 H, CH_2); ^{13}C NMR (75.5 MHz, $CDCl_3$, 25 °C): $\delta = 161.2$ (C), 130.8 (C), 126.4 (CH), 117.9 (C), 107.2 (CH), 69.5 (CH_2), 23.0 ppm (CH_2); IR (KBr): $\tilde{\nu} = 3274$, 1686, 1400, 1308, 1274, 1209, 1185, 1123, 1078, 1049, 1013, 773, 739, 599, 496, 460 cm^{-1}; MS (EI) *m*/*z* (%):137.1 (100) $[M]^+$, 107.1 (42), 79.1 (78); elemental analysis calcd (%) for $C_7H_7NO_2$: C 61.31, H 5.14, N 10.21; found: C 61.51, H 4.98, N 10.18.

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