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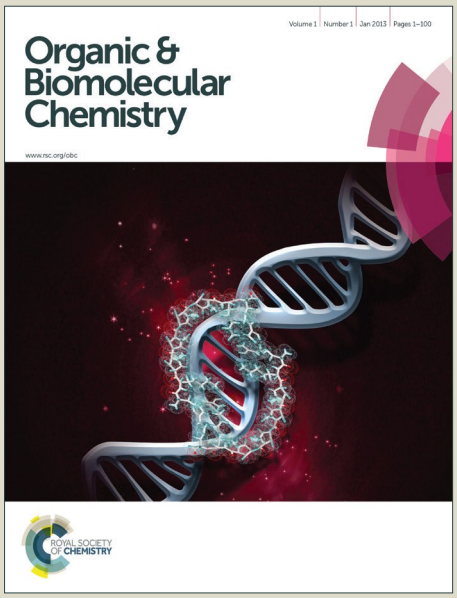

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Copper−catalyzed C(sp^3)−H functionalization of ketones with vinyl azides: Synthesis of substituted−1H−pyrroles

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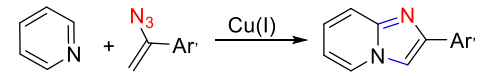
Copper−catalyzed C(sp^3)−H functionalization of ketones with vinyl azides for the synthesis of substituted pyrroles has been developed. The method is straightforward and efficient to access series of 2, 3, 5 – trisubstituted – 1H – pyrroles in modest to excellent yields with broad functional group tolerance under mild conditions.

Pyrroles are considered to be the privileged heterocycles due to their presence in biological systems and their therapeutic activities.[1a] Pharmaceuticals such as the antitumor agent, [1b] a potent blocker for potassium-competitive acid,[1c] the leading cholesterol-lowering drug lipitor[1d] and the numerous natural products[1e,f] are constituted with the pyrrole core structure. Additionally, pyrroles serve as useful building blocks in the synthesis of bioactive molecules[1g] and the functionalized materials.[1h-j]

Due to the importance of pyrrole moiety, organic chemists have been fascinated to develop the various synthetic strategies to obtain variety of pyrrole derivatives. Paal and Knorr independently synthesized pyrroles from condensation of 1, 4−dicarbonyl compounds with primary amines or ammonia.[2a,b] Later, a three component reaction of β-ketoesters with ammonia (or primary amines) and α-halo ketones to obtain pyrroles was reported by Hantzsch.[2c] Inspired by the aforementioned methods, over the last decade a significant progress has been observed for the synthesis of pyrrole derivatives.[3-6] Among the reported methods the synthesis of pyrroles from vinylazides is considered to be a convenient strategy. Recently, Chiba and co-workers synthesized various pyrrole derivatives starting from vinylazides and 1, 3 di carbonyl compounds or β-keto acids under metal or metal free conditions.[4b-d] However, to access 2,3,5-trisubstituted-1H-pyrroles starting from vinylazides and ketones remain unaddressed. Although, the methods for the synthesis of 2,3,5-triphenyl-1H-pyrroles does exist in the literature, but the use of noble transition metals or harsh reaction conditions or multi-step process to complete the reaction may confines the advantage of the reported methods.[5]



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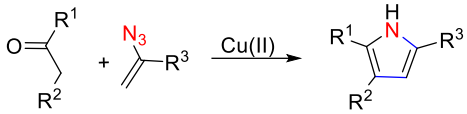

present work

Scheme 1

As part of our ongoing project towards the development of novel methods for synthesis of aza-heterocycles,[7] herein we report a convenient method for the synthesis of substituted pyrroles with copper acetate as a sole catalyst under the mild reaction conditions through the C(sp^3)−H functionalization of ketones with vinyl azides. Initially, we subjected deoxybenzoin **1a** and (1-azidovinyl) benzene **2a** with 10 mol% of copper acetate as a catalyst in 1mL of DMF at room temperature, after 24 h no desired product **3a** formation was observed (Table 1, entry 1). In order to check the necessity of an oxidant, same reaction was performed under oxygen atmosphere, but it also failed to yield the desired product (Table 1, entry 2). Surprisingly when the reaction performed under argon atmosphere, 60 % of the desired product **3a** was isolated (Table 1, entry 3). Screening of various solvents showed no improvement in the yield of the product **3a** (Table 1, entries 4 -14). Reaction at 40 ºC provided 78 % yield of **3a** (Table 1, entry 15). Further increase in temperature to 50 ºC does decrease the product yield (Table 1, entry 16). Other Cu(II) salts were found to be inefficient for this transformation (Table 1, entries 17 - 20) and no product formation in the absence of the catalyst (Table 1, entry 21), this indicates the crucial role of copper(II) acetate for the present transformation. Therefore the optimized reaction conditions for the present protocol are as follows: 10 mol % copper acetate as the catalyst, DMF as solvent under argon atmosphere at 40 ºC (Table 1, entry 15).

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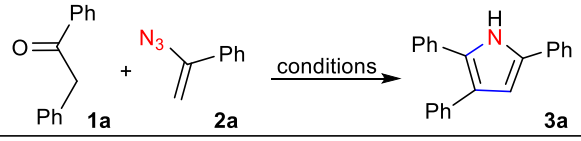
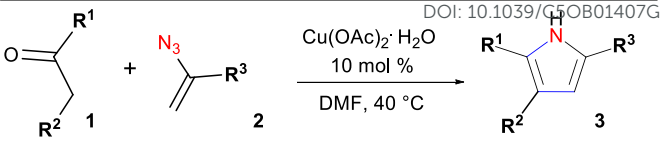
Table 1 Optimisation of reaction conditions[a]



S.No.	Catalyst	Solvent	yield of **3a**
1[b,c]	$Cu(OAc)_2{\cdot}H_2O$	DMF	0
2[b,c]	$Cu(OAc)_2{\cdot}H_2O$	DMF	0
3[c]	$Cu(OAc)_2{\cdot}H_2O$	DMF	60
4[c]	$Cu(OAc)_2{\cdot}H_2O$	Methanol	20
5[c]	$Cu(OAc)_2{\cdot}H_2O$	Ethanol	25
6[c]	$Cu(OAc)_2{\cdot}H_2O$	Toluene	5
7[c]	$Cu(OAc)_2{\cdot}H_2O$	DCE	6
8[c]	$Cu(OAc)_2{\cdot}H_2O$	Acetonitrile	Trace
9[c]	$Cu(OAc)_2{\cdot}H_2O$	THF	30
10[c]	$Cu(OAc)_2{\cdot}H_2O$	Dioxane	35
11[c]	$Cu(OAc)_2{\cdot}H_2O$	DMSO	50
12[c]	$Cu(OAc)_2{\cdot}H_2O$	NMP	50
13[c]	$Cu(OAc)_2{\cdot}H_2O$	NMA	52
14[c]	$Cu(OAc)_2{\cdot}H_2O$	H_2O	0
15	**$Cu(OAc)_2{\cdot}H_2O$**	**DMF**	**78**
16[d]	$Cu(OAc)_2{\cdot}H_2O$	DMF	55
17	$CuSO_2{\cdot}5H_2O$	DMF	5
18	$CuBr_2$	DMF	0
19	$CuCl_2$	DMF	0
20	CuF_2	DMF	4
21	---	DMF	0

[a]Reaction conditions otherwise stated: 0.45 mmol of **1a**, 0.3 mmol of **2a**, 0.03 mmol of catalyst and 1mL solvent, under argon atmosphere at 40 ºC for 24 h. [b]For entries 1 and 2 the reactions performed under open air and oxygen atmosphere respectively. [c]Reaction at room temperature. [d]Reaction at 50 ºC.

Table 2. Substrate scope for 2, 3, 5−triphenyl−1H−pyrroles



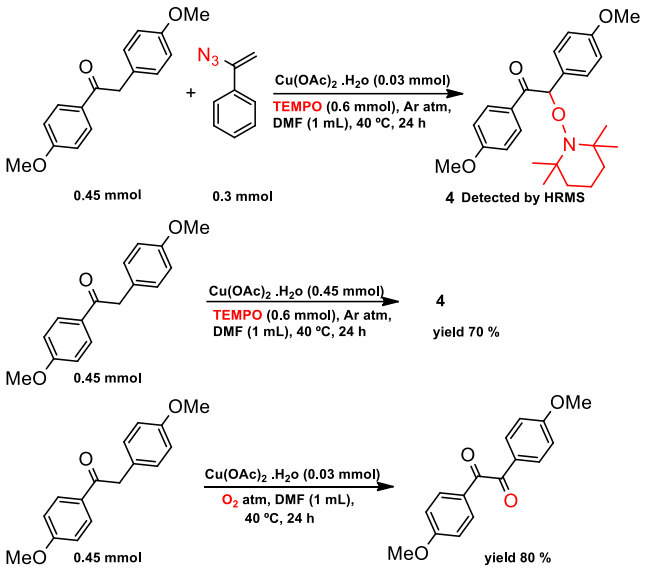
S. No.	R^1	R^2	R^3	3 (Yield %)
1	Ph	Ph	Ph	**3a** (78 %)
2	Ph	Ph	4-me-C_6H_4	**3b** (66 %)
3	Ph	Ph	4-*t*Bu- C_6H_4	**3c** (70 %)
4	Ph	Ph	4-F-C_6H_4	**3d** (57 %)
5	Ph	Ph	4-Cl-C_6H_4	**3e** (60 %)
6	Ph	Ph	4-Br-C_6H_4	**3f** (62 %)
7	Ph	Ph	4-MeO-C_6H_4	**3g** (51 %)
8	Ph	Ph	3-Me-C_6H_4	**3h** (57 %)
9	Ph	Ph	3-Cl-C_6H_4	**3i** (56 %)
10	Ph	Ph	3-NO_2-C_6H_4	**3j** (65 %)
11	Ph	Ph	2-MeO-C_6H_4	**3k** (50 %)
12	4-MeO-C_6H_4	4-MeO-C_6H_4	Ph	**3l** (69 %)
13	4-MeO-C_6H_4	4-MeO-C_6H_4	4-*t*Bu- C_6H_4	**3m** (65 %)
14	4-MeO-C_6H_4	4-MeO-C_6H_4	4-Cl-C_6H_4	**3n** (64 %)
15	4-MeO-C_6H_4	4-MeO-C_6H_4	3-Me-C_6H_4	**3o** (65 %)
16	4-MeO-C_6H_4	4-MeO-C_6H_4	3-Cl-C_6H_4	**3p** (68 %)
17	4-MeO-C_6H_4	4-MeO-C_6H_4	3-NO_2-C_6H_4	**3q** (66 %)
18	4-MeO-C_6H_4	4-MeO-C_6H_4	2-MeO-C_6H_4	**3r** (67 %)
19	4-Cl-C_6H_4	Ph	Ph	**3s** (65 %)
20	4-Cl-C_6H_4	Ph	4-Br-C_6H_4	**3t** (72 %)
21	4-Cl-C_6H_4	Ph	3-NO_2-C_6H_4	**3u** (80 %)
22	4-Cl-C_6H_4	Ph	2-MeO-C_6H_4	**3v** (72 %)
23	4-Br-C_6H_4	Ph	3-NO_2-C_6H_4	**3w** (80 %)
24	4-Br-C_6H_4	Ph	2-MeO-C_6H_4	**3x** (70 %)
25[b]	Me	Ph	Ph	**3y** (83 %)
26[b]	Me	Ph	2-MeO-C_6H_4	**3z** (81 %)
27[b]	Me	Ph	3-NO_2-C_6H_4	**3aa** (93 %)
28[b]	Me	Ph	4-Cl-C_6H_4	**3ab** (80 %)

[a]Reaction conditions: 0.45 mmol of **1**, 0.3 mmol of **2**, 0.03 mmol of $Cu(OAC)_2.H_2O$ and 1mL DMF as the solvent under argon atmosphere at 40 ºC for 24 h.[b] 0.9 mmol of ketone (3 equivalents w.r.t vinyl azide).

With these optimized conditions, we examined the scope of this catalytic method for the synthesis of substituted pyrroles. As can be seen the results of Table 2; the electron-withdrawing groups as well as electron-donating groups in (1-azidovinyl) benzene moieties **2** were well tolerated and the reactions delivered the desired products in moderate to good yields **3a-3k**. It may be noted that, halide (F, Cl, and Br) substituted vinyl azide derivatives **3d-3f** were also well tolerated, and provided the corresponding products in good yields. The halide substituted products could be further applied in traditional cross-coupling reactions. Electronic effects associated with electron donating/withdrawing substituents at *meta*/*para* position on the arene ring of vinyl azide do not affect the efficiency of the process. Unfortunately, vinyl azides like [(2-azidoallyl)oxy]benzene, (E)-(1-azidoprop-1-en-1-yl)benzene and 4-azido-1,2-dihydronaphthalene are not amenable to this procedure. Then the substrate scope of the substituted deoxybenzoins was also evaluated. Deoxyanisoin reacts with various vinyl azide derivatives and afford the desired products in moderate to good yields **3l-3r**. Halo substituted deoxybenzoins such as benzyl 4-chlorophenyl ketone and benzyl 4-bromophenyl ketone reacts with vinyl azides and afford the desired products in good yields **3s-3x**. However, the substrates like acetophenone and propiophenone are unreactive under these conditions. The above examples indicates that, the phenyl group at the α-carbon of the ketone is crucial for the present transformation. Reaction of 1-phenylpropan-2-one with (1-azidovinyl) benzene under similar conditions offers only 30 % of desired product **3y**. But the yield of desired product **3y** was increased to 83 % with three equivalents of ketone (w.r.t. vinyl azide). Substituted vinyl azides also reacted smoothly with 1-phenylpropan-2-one to provide the products **3z**, **3aa** and **3ab** in excellent yields (80−93%).

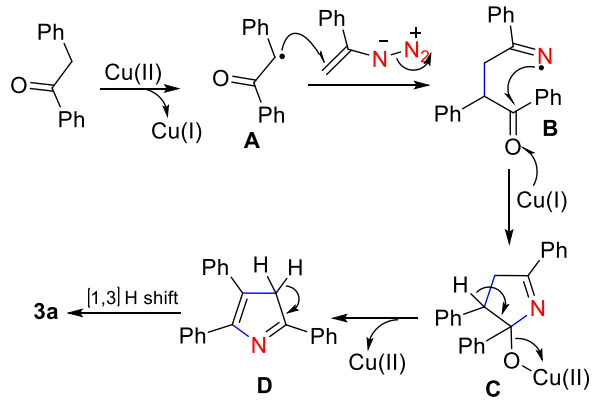
To understand the reaction mechanism, we performed the reaction with TEMPO as a radical scavenger and no formation of desired product **3l** was observed, however the formation of an adduct **4** was detected by the HRMS analysis (Scheme 2, eq.1). Further, 70% of **4** was isolated when the reaction was performed with deoxyanisoin

and TEMPO (Scheme 2, eq 2). The adduct 4 was well characterized by ^{1}H, ^{13}C NMR and HRMS analysis (SI pages S_{45} and S_{60}). Oxidation of deoxyanisoin to 1,2-bis(4-methoxyphenyl)ethane-1, 2-dione was also observed in the presence of oxygen atmosphere (Scheme 2, eq. 3). The above studies indicates that, the reaction may proceed through a radical mechanism.



Scheme 2

Based on the above results and literature reports,[8] a radical mechanism has been proposed (Scheme 3). Initially deoxybenzoin in the presence of Cu(II) gives a radical intermediate **A** and Cu(II) does convert to Cu(I).[8a] Intermediate **A** in the presence of **2a** generate iminyl radical intermediate **B**.[8b] In the presence of Cu(I), **B** immediately undergoes a radical addition and generates Cu(II) intermediate **C**. Finally elimination of Cu(II) followed by [1, 3] H-shift leads to the product **3a**.



Scheme 3. Proposed mechanism

Conclusions

In conclusion we have developed an efficient protocol for the synthesis of 2,3,5-trisubstituted-1H-pyrroles with copper as a sole catalyst under mild reaction conditions. Present strategy shows good functional group tolerance and wide range of substrate scope with modest to excellent yields of products.

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