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Ligand and solvent-free iron catalyzed oxidative alkynylation of azoles with terminal alkynes

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ABSTRACT

A highly efficient and versatile iron catalyzed oxidative alkynylation of azoles with terminal alkynes under ligand and solvent-free conditions is described.

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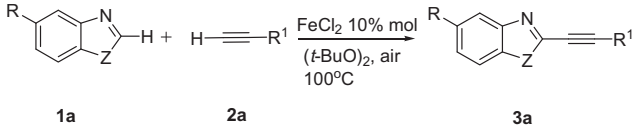
An efficient strategy for the direct functionalization of C–H bonds using transition-metal catalyst has been reported.[1] Mostly ruthenium,[2] rhodium,[3] and palladium-based[4] catalysts have been applied to effect either C–C or C–Het (Het = heteroatom) bond formation by the activation of a C–H bond. A few procedures have been described that employ iron as a catalyst[5] which is particularly attractive due to its low cost and low toxicity. In addition, the application of C–H functionalization of heterocycle has been scarce until now.

On the other hand, the alkynyl substituted azoles have attracted more attention in both industrial and academic fields for decades. The alkynyl substituted azoles act as DNA cleavage agents[6] and azole containing π-conjugated molecules are found in many natural products, pharmaceutical, and functional materials.[7] Owing to their important applications various synthetic methodologies for alkynylation of azoles have been reported. Literature methods involved direct alkynylation of azoles with alkynyl bromides in the presence of catalysts Ni[8] and Pd[9] and their efficiency was observed to be dependent on the ease of C(sp^2)–H bond activation. Recently literature survey revealed that terminal alkynes can be coupled with azoles under oxidative catalytic conditions using Au,[10] Cu,[11] Ni,[12] and Pd[13] catalytic systems. However, these catalysts are derived from heavy or rare metals and their toxicity and prohibitive prices constitute severe drawbacks for their applications. In contrast, iron being the most abundant metal on earth, and does not require coordination with expensive or/and toxic ligands, it was chosen as the catalyst.[14]

We herein describe a new procedure[15] for the oxidative alkynylation of azoles with terminal alkynes using ferrous chloride as the catalyst and (t-BuO)$_2$ as the oxidant under solvent and ligand-free condition (Scheme 1).

5-Methylbenzoxazole **1a** and phenylacetylene **2a** were chosen as model substrates in order to optimize the oxidative alkynylation conditions. The results of the study are summarized in Table 1.

In the initial study of reaction conditions we observed that the desired product **3a** was obtained *albeit* in a moderate yield when $FeCl_2$ catalyst was used in the presence of di-*tert*-butyl peroxide (t-BuO)$_2$ in solvent DMSO at 100 °C for 16 h (Table 1, entry 1). No improvement in the yield was observed with change in the solvent (Table 1, entry 2). We also examined other oxidants such as TBHP (*tert*-butyl hydroperoxide 5 M solution in *n*-hexane) which resulted in a low yield of the product. No reaction was observed when ceric ammonium nitrate (CAN) and iodobenzene diacetate (IBD) were employed (Table 1, entries 4 and 5). Other iron species such as Fe(acac)$_2$, $FeCl_3$, Fe(acac)$_3$ gave **3a** in 20%, 70%, and 63% yield, respectively, (Table 1, entries 9–11). The best result was observed with a combination of 10% mole of $FeCl_2$, 3 mol equiv of (t-BuO)$_2$ under solvent-free condition at 100 °C, (Table 1, entry 6) and atmospheric pressure. By lowering the catalyst loading and molar



Scheme 1. Oxidative alkynylation of azoles with terminal alkynes.

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Table 1
Optimization of reaction conditions

Entry	Catalyst (% mol)	Oxidant (mol equiv)	Solvent	Temp (°C)	Yield[a] (%)
1	$FeCl_2$ (10)	$(t\text{-BuO})_2$ (2)	DMSO	80	51
2	$FeCl_2$ (10)	$(t\text{-BuO})_2$ (2)	EDC	80	37
3	$FeCl_2$ (10)	TBHP (2)	DMSO	80	40
4	$FeCl_2$ (10)	CAN (2)	DMSO	80	0
5	$FeCl_2$ (10)	IBD (2)	DMSO	80	0
6	$FeCl_2$ (10)	$(t\text{-BuO})_2$ (3)	—[b]	100	85
7	$FeCl_2$ (5)	$(t\text{-BuO})_2$ (3)	—	100	43
8	$FeCl_2$ (10)	$(t\text{-BuO})_2$ (2)	—	100	68
9	$Fe(acac)_2$ (10)	$(t\text{-BuO})_2$ (3)	—	100	20
10	$FeCl_3$ (10)	$(t\text{-BuO})_2$ (3)	—	100	70
11	$Fe(acac)_3$	$(t\text{-BuO})_2$ (3)	—	100	63

[a] Yield is based on **1a**.
[b] "—", indicate reaction carried out without solvent.

Table 2
Iron catalyzed alkynylation of azoles

Entry	Z	R	R^1	Yield[a]	Time (h)	mp/bp (°C) (lit.)[b]
3a	O	Me	C_6H_5	85	16	102–104 (103–104)[13]
3b	O	Me	4-CF_3-C_6H_4	52	20	156–158 (157–158)[9]
3c	O	Me	4-Cl-C_6H_4	64	16	165–167 (166–167)[13]
3d	O	Me	4-F-C_6H_4	50	16	118–119 (117–118)[13]
3e	O	H	4-MeO-C_4H_4	90	16	120–123(122–123)[9]
3f	O	H	C_6H_5	88	16	101–102 (100)[8]
3g	O	H	1-Napthyl	63	20	116–118 (119)[8]
3h	O	Me	1-Napthyl	65	20	104–106 (104–105)[13]
3i	O	Me	n-C_6H_{13}	67	16	oil bp <250[13]
3j	O	H	n-C_6H_{13}	72	16	oil bp <250[8]
3k	O	Me	Thiophene	75	20	93–94 (93–94)[13]
3l	O	Me	Pyridyl	66	20	112–114 (113–115)[13]
3m	O	Me	Si(i-Pr_3)	84	16	oil bp <250[12]
3n	O	H	Si(i-Pr_3)	81	16	oil bp <250[12]
3o	S	H	Si(i-Pr_3)	88	16	oil bp <300[12]
3p	S	H	C_6H_5	86	16	72–75 (75)[8]

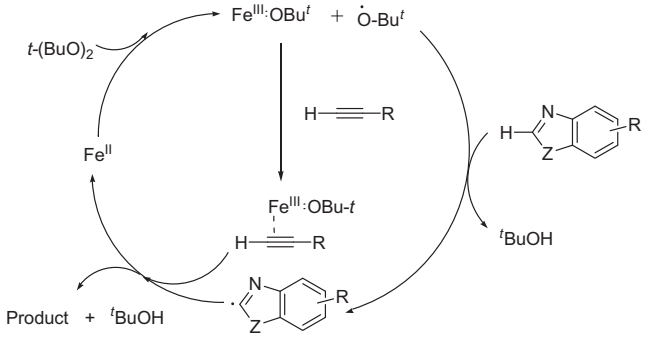
[a] Yield is based on compound **1**.
[b] (Lit) compound have been previously reported; physical and spectral data were comparable.

ratio of $(t\text{-BuO})_2$ the yield was found to be low (Table 1, entries 7 and 8). We explored the scope of this reaction with optimized reaction conditions and the results are summarized in Table 2.

It was found that phenylacetylene bearing a wide range of substituents undergoes an oxidative coupling reaction with **1** to afford the desired products in a good yield (Table 2, entries 3a–3h). The reaction of phenylacetylene bearing an electron donating group provides a higher yield (Table 2, entry 3e) while the electron withdrawing substituents resulted in lower yield of the products due to dimerization of the alkynes. The sterically hindered 1-naphthylacetylene also reacted under optimized conditions (Table 2, entries 3g and 3h).The silylethylnyl group could also be readily functionalized to benzoxazole and benzothiazole core (Table 2, entries 3n and 3o). The aliphatic terminal alkynes also participated in this coupling reaction. (Table 2, entries 3i and 3j). The alkynylation of **1** with heterocyclic acetylene with high efficiency provided good yield of the product (Table 2, entries 3k and 3l).

Although more comprehensive studies are required to describe the mechanistic details, a plausible pathway of the alkynylation of azole is shown in Scheme 2. It is postulated that an initial reaction of t-butyl peroxide with $FeCl_2$ generates Fe^{III}–O^{t}Bu and t-butyl radical. The deprotonation of an azole C(2)–H bond takes place by the action of t-butoxy radical leading to an azole radical that subsequently reacts with an in situ generated iron acetylide complex to give the 2-alkynylazole product and Fe(II) species.

In summary, we have described an effective iron catalyst system for the direct alkynylation of azoles with terminal alkynes



Scheme 2. A proposed mechanism for the alkynylation of azole.

using $(t\text{-BuO})_2$ as the oxidant, under solvent, base and ligand-free conditions. This methodology is beneficial from the economical point of view.

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15. **General procedure for the iron-catalyzed oxidative alkynylation of azoles** $FeCl_2$ (0.1 mmol), benzoxazole (1 mmol), terminal alkyne (1.2 mmol) and *tert*-butyl peroxide (3 mmol) were placed in a tube. The tube was purged with air

and then sealed with a cap under a positive pressure of air. The reaction mixture was stirred at 100 °C for the time mentioned in Table 2. After the completion of the reaction it was cooled to room temperature and diluted with dichloromethane (30 mL) and filtered through a pad of celite. The filtrate was concentrated under reduced pressure (rotavaporator). The residue was purified by flash chromatography on silica gel mesh size 60–120 (hexane/EtOAc, 97:3) as an eluent to give the desired product.