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Di-*tert*-butyl peroxide (DTBP) promoted dehydrogenative coupling: An expedient and metal-free synthesis of oxindoles via intramolecular C(sp^2)-H and C(sp^3)-H bond activation

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Abstract: An efficient di-*tert*-butyl peroxide (DTBP) promoted synthesis of oxindole has been developed. This methodology involves C(sp^3)-H and C(sp^2)-H bond activation under metal-free condition. This synthetic approach towards oxindole synthesis avoids base and hazardous iodine reagent unlike other methodologies developed so far. This metal- and base-free protocol is operationally simple and ecofriendly. It provides an expedient approach to access oxindoles in moderate to very good yields in DCE at 110 ^oC.

Key words: Di-*tert*-butyl peroxide (DTBP), radical reaction, C(sp^3)-H and C(sp^2)-H bond activation, metal-free intramolecular C-C coupling, oxindole synthesis.

Oxindoles are important heterocyclic scaffolds with unique biological activity found in a wide variety of bioactive compounds,[1] natural alkaloids[2,] and pharmaceutically active molecules.[3] As for example, oxindole derivatives have been demonstrated to have significant potential for use in a wide range of biological applications such as NMDA antagonist[4] and calcium channel blockers[5] as well as antiangiogenic,[6] anticancer agent[7] (sunitinib[8] **1**, Figure 1), the vasopressin V2 receptor antagonist (satavaptan[9] **2**, Figure 1). Oxindole derivatives show analgesic effect,[10] and antimalarial effect (**3**, Figure 1)[11] also.

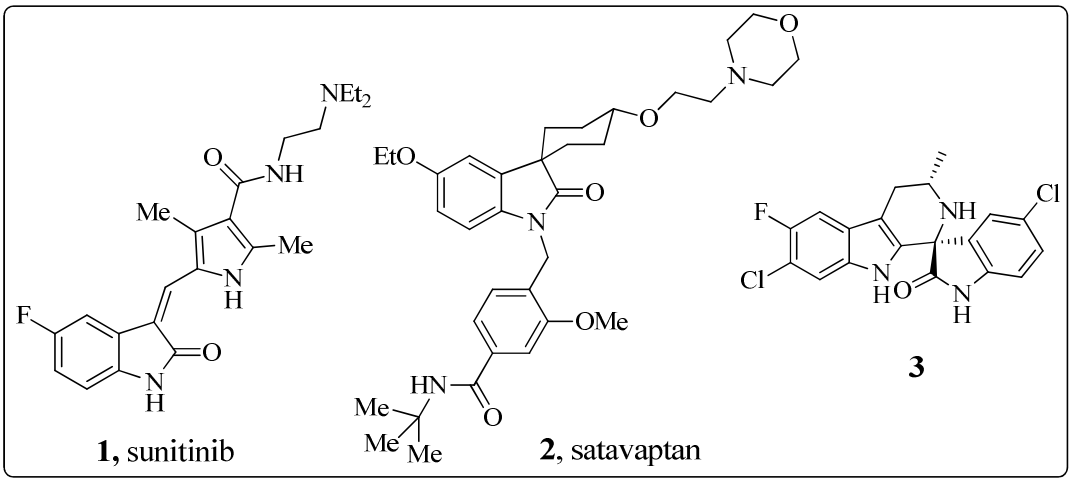
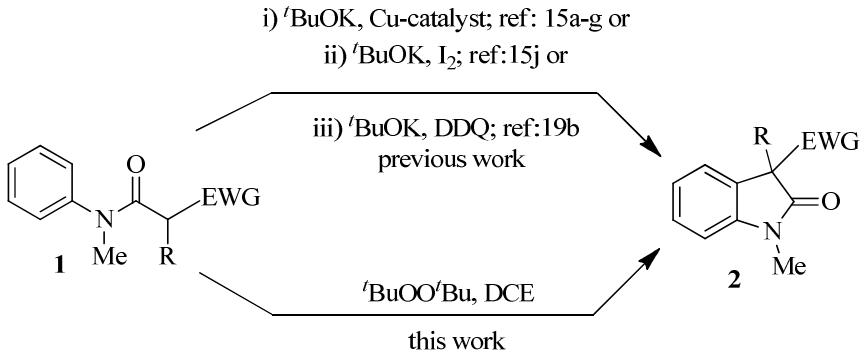


Fig 1. Some biologically and pharmaceutically important oxindole derivatives

Efficient methodologies to switch C-H bonds directly to other functionalities remains a key challenge to modern synthetic organic chemists.[12] Therefore, new and efficient methods that could be carried out under milder and eco-friendly conditions always demand special importance to the field of synthetic organic chemistry. In this context, creation of carbon-carbon (C-C) bonds via oxidative coupling of carbon-hydrogen (C-H) bonds has gained acute attention in the development of different new synthetic methods.[13]

Since last decade, palladium-catalyzed C-C coupling reaction[14] was shown to be useful for the synthesis of oxindole derivatives. Recently, copper-catalysed[15a-g] oxindole synthesis via intramolecular oxidative coupling (intramolecular dehydrogenative coupling, IDC)[15] of Csp^2-H and Csp^3-H bond have been developed by different groups. Besides IDC, oxindole synthesis via cyclizations of *N*-arylacrylamides have received special attention in recent years.[14j, 16, 17] Nowadays transition-metal-free organic transformation is the topic of growing interest.[18] Very recently transition metal and iodine (molecular and hypervalent)-free synthesis of oxindole have

gained more importance due to their low toxicity and more eco-friendly nature.[19] These ground-breaking efforts led to the synthesis of a broad range of 2-oxindoles. Our interest has focused on the development of transition metal-free methodologies for carbon-carbon bond formation.[20] In this perspective, we planned a transition-metal-free protocol for the intramolecular dehydrogenative $C(sp^2)$-$C(sp^3)$ coupling of *β*-*N*-arylamido nitrile and esters to generate substituted oxindoles. Pioneering work[15a-d] in this field by Taylor and Künding showed that Cu-catalysed IDC reaction follows a radical pathway (SET), hence we envisioned a metal-free radical source to initiate the reaction. Thus we performed the reaction in presence of di-*tert*-butyl peroxide (DTBP) in 1,2-dichloroethane (DCE) at 110 ^oC in a sealed tube, without any base and iodine or metal based oxidant to establish the hypothesis (scheme 1).

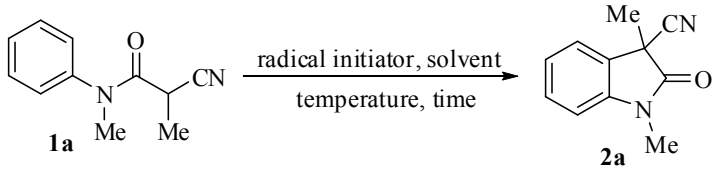


Scheme 1. Base-, metal- and iodine-free synthesis of oxindoles.

We started our initial studies with *β*-*N*-arylamido nitrile (**1a**) as the model substrate (Table 1). To our delight, a 43 % yield of product **2a** was obtained using di-*tert*-butyl peroxide (DTBP) (2 mmol) in toluene (Table 1, entry 1) for 10 h at 110 ^oC under nitrogen atmosphere. Lower yields of **2a** were isolated when DTBP was replaced by other peroxides such as *tert*-butyl peroxybenzoate (TBPB) and benzoyl peroxide (BPO) (28 % and 32 %, respectively) (Table 1, entry 2 and 3). Trace amounts of **2a** were found in the presence of H_2O_2 (35 % aqueous solution) and *tert*-butyl hydroperoxide (TBHP, 5.0-6.0 M in decane) (Table 1, entry 4 and 5). Solvent effect on the model reaction was also examined (Table 1, entries 6-11). Relatively lower yields were observed when the reactions were performed in actonitrile, ethyl acetate and under solvent-free condition (14 %, 24 % and 36 % respectively) (Table 1, entries 6-8). No sign of **2a** was found in THF and dioxane, total recovery of starting material (**1a**) was observed (Table 1, entry 9

and 10). Trace amount of **2a** was found in DMF and most of the starting material remained unchanged (Table 1, entry 11).

Table 1. Optimization of Reaction Conditions[a]

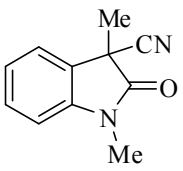


Entry	oxidant	Solvent	t (h)	Yield (%)[b]
1	DTBP	toluene	10	43
2	TBPB	toluene	10	28
3	BPO	toluene	10	32
4	H_2O_2	toluene	10	trace
5	TBHP	toluene	10	trace
6	DTBP	CH_3CN	10	14
7	DTBP	EtOAc	10	24
8	DTBP	-	10	36
9	DTBP	THF	10	NR
10	DTBP	Dioxane	10	NR
11	DTBP	DMF	10	trace
12	DTBP	DCE	10	64
13	DTBP	DCE	15	73
14	DTBP	DCE	20	71
15	**DTBP**	**DCE**	**15**	**83[c]**
16	DTBP	DCE	15	78[d]
17	DTBP	DCE	15	80[e]
18	DTBP	DCE	15	78[f]
19	DTBP	DCE	15	58[g]
20	DTBP	DCE	15	76[h]

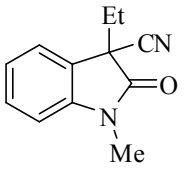
[a] Reaction conditions: 1a (1.0 mmol), radical initiator (2.0 mmol) (DTBP = di-*tert*-butyl peroxide, TBHP = *tert*-butyl hydroperoxide, TBPB = *tert*-butyl peroxybenzoate, BPO = benzoyl peroxide,), solvent (4.0 mL), under nitrogen atmosphere, sealed tube. [b] Isolated yield. NR = No reaction. [c] DTBP (3.0 mmol). [d] DTBP (4.0 mmol). [e] Under air. [f] Reaction performed at 120 °C. [g] Reaction performed at 100 °C. [h] Reaction performed in 6 mL DCE. Bold row implies optimized reaction conditions.

A steep rise in yield (64 %) of **2a** with full consumption of starting material was observed when the reaction was performed in 1, 2-dichloroethane (DCE) (Table 1, entry 12). The reaction afforded 73 % yield of desired product **2a** on prolonged heating for 15 h, but gave 71 % yield when heated for 20 h under the same reaction conditions (Table 1, entry 13 and 14). On increasing DTBP loading to 3 mmol the yield of **2a** increased to 83 % (Table 1, entry 15), while somewhat lower yield (78 %) was obtained with 4 mmol of DTBP (Table 1, entry 16). Finally, change of reaction atmosphere from nitrogen to air (Table 1, entry 17) and different reaction temperature showed that nitrogen and 110 °C were the optimal reaction atmosphere and temperature (Table 1, entry 18 and 19). With increasing the volume of solvent from 4 mL to 6 mL yield of this coupling reaction decreased slightly (Table 1, entry 20).

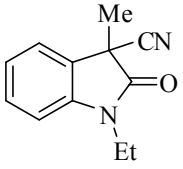
Table 2: Substrates scope for intramolecular dehydrogenative coupling (IDC).



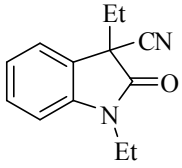
2a (83%) entry 1



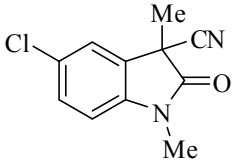
2b (79%) entry 2



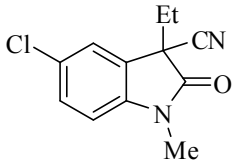
2c (81%) entry 3



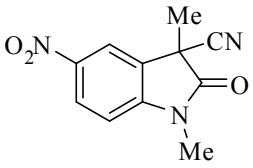
2d (77%) entry 4



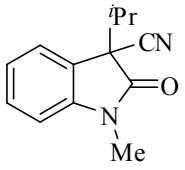
2e (68%) entry 5



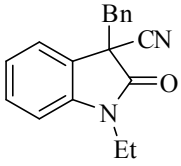
2f (71%) entry 6



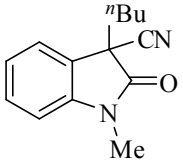
2g (59%) entry 7



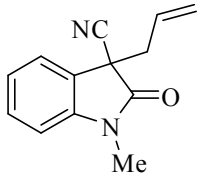
2h (77%) entry 8



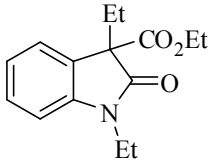
2i (76%) entry 9



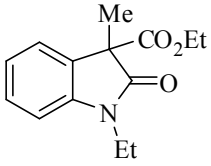
2j (80%) entry 10



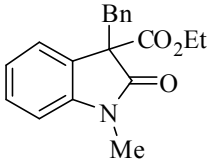
2k (63%) entry 11



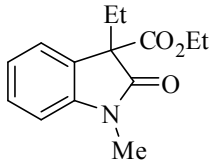
2l (76%) entry 12



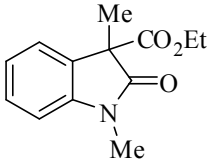
2m (81%) entry 13



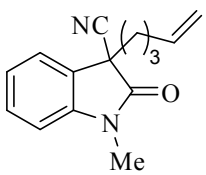
2n (73%) entry 14



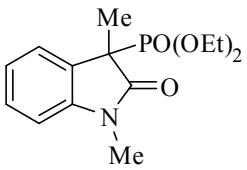
2o (83%) entry 15



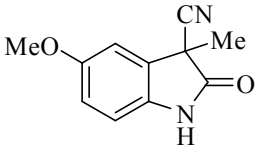
2p (86%) entry 16



2q (63 %) entry 17



2r (67 %) entry 18

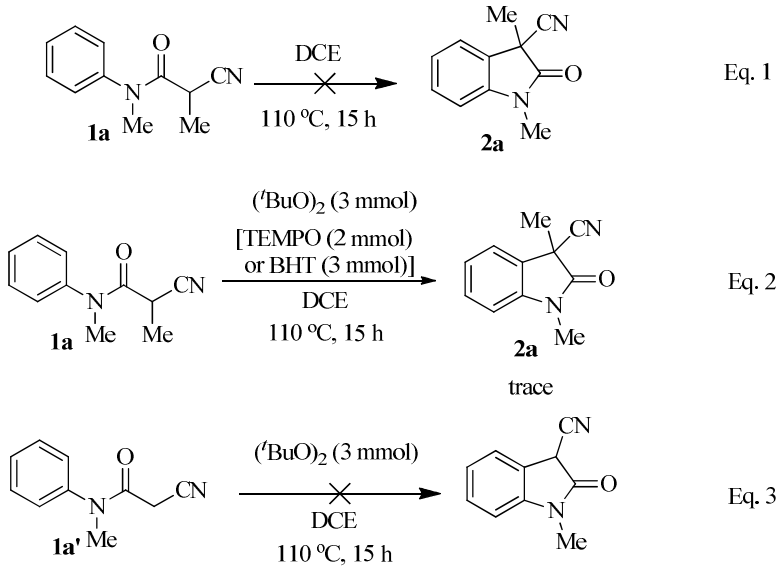


2s (0 %) entry 19
(decomposition of starting material)

With the optimized reaction conditions in our hand, we explored the scope and validity of this methodology with different *β*-*N*-arylamido nitrile and esters (Table 2). A range of oxindoles (**2a-r**, Table 2) were synthesized in moderate to very good yields (59-86 %).

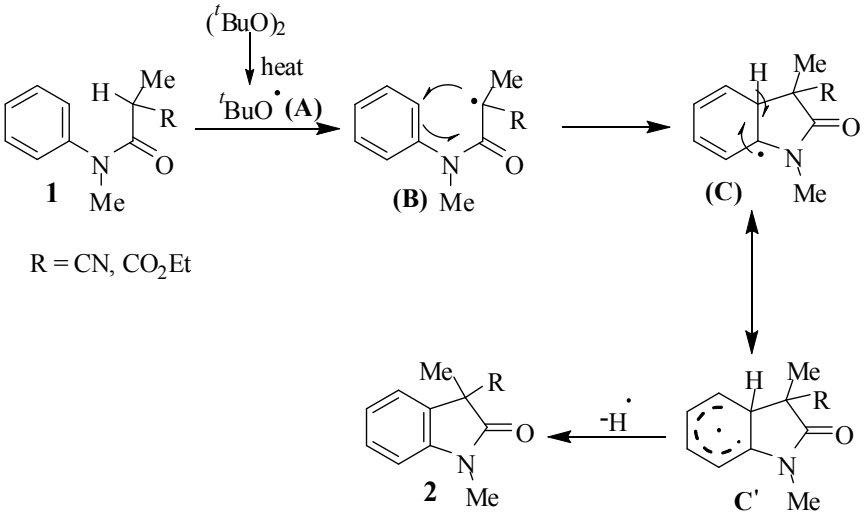
When the phenyl ring was substituted with a chloro group which has a mild electron withdrawing effect went smoothly in this reaction conditions and gave 68 % and 71 % yield of **2e** and **2f** respectively (Table 2, entry 5 and 6). A lower yield (59 %) of **2g** was isolated when the phenyl ring was substituted with strong electron withdrawing nitro-group (Table 2, entry-7). This reaction equally responded with a long chain alkenyl group (**2q**, 63 %) and phosponate ester (**2r,** 67 %). The reaction failed for the substrate with NH functionality (**2s**, substrate decomposed under this reaction conditions). However, the substrate **1a'** (Scheme 2, Eq. 3) remained unchanged under this reaction conditions.

Some control experiments were also performed to establish the mechanism, (Scheme 2). The reaction did not proceed at all in absence of radical initiator DTBP (Scheme 2, Eq. 1). When 2 mmol of 2,2,6,6-tetramethylpiperidine *N*-oxide (TEMPO) and butylated hydroxytoluene (BHT) were added under optimized reaction conditions separately and a trace amount of coupling product (**2a**) was isolated (Scheme 2, Eq. 2). These facts support that the reaction follows a radical pathway. The reaction did not occur with substrate **1a'** (Scheme 2, Eq. 3), this experiment suggest that the reaction goes through the generation of a more stable tertiary radical.



Scheme 2. Control experiments

Based on literature[21] and above experimental results, a plausible mechanism is postulated in Scheme **3**. Initially, on heating, homolytic cleavage of DTBP produces *tert*-butoxy radical **A**. This *tert*-butoxy radical (**A**) abstracts one H atom from *α*-position of nitrile or ester group of *β*-*N*-arylamido nitrile or esters (**1**) to give **B**, which then produces resonance stabilized aryl radical **C'** which eliminates one hydrogen radical and rearomatization leads to the final product **2**.



Scheme 3. Plausible mechanismistic pathway

In conclusion, we have developed a di-*tert*-butyl peroxide (DTBP) promoted transition-metal-free, atom economical and ecofriendly intramolecular dehydrogenative coupling (IDC) of Csp^2-H and Csp^3-H bond. This protocol provides a simple approach for the synthesis of a variety of oxindoles. This methodology avoided base and hazardous iodine reagent unlike other metal-free oxindole synthesis strategy. Further development of transition-metal-free strategy for the synthesis of bioactive heterocycles is being explored in our laboratory.

Acknowledgement:

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