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Tetrabutylammonium decatungstate-catalyzed hydroalkylation/alkoxylation of 3-methyleneisoindolin-1-ones with alcohols/ethers through hydrogen atom transfer process

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A highly efficient tetrabutylammonium decatungstate (TBADT)-catalyzed synthesis of isoindolinones using activated alkenes and alcohols/ethers *via* hydrogen atom transfer process was developed. A variety of functionalized isoindolinones were obtained in good yields with high selectivity and broad functional group tolerance.

The isoindolinone (benzo-fused γ-lactam) scaffold is chemical constituent of various natural products and synthetic biologically active molecules due to their unique structural characteristics and physiological activities.[1] For example, JM-1232 is a sedative and hypnotic drug being researched as a potential anesthetic, Fenestin A analogue is marine derived natural cyclic peptides possessing a wide range of bioactivity, including anticancer (*S*)-PD 172938 is a noted dopamine D_4 ligand (Fig. 1).[2]

Due to the potential applications of the isoindolinone skeleton in various aspects, chemists have developed a variety of methods for synthesizing this skeleton using metal catalysis or metal free conditions.[3] 3-Hydroxyethyl isoindolinones is a highly functional building block that is commonly used for the preparation of biologically active compounds such as (*S*)-PD 172938.[4] Recently, it is found that the double bond of vinyl group in the skeleton of 3-methyleneisoindolin-1-ones could undergo a number of transformations to generate isoindolinone derivatives.[5] In 2024, Wang's group developed a facile synthesis of isoindolin-1-one and its deuterated analogues through the synergistic reaction of organic photoredox catalysis and hydrogen atom transfer (HAT) process (Scheme 1a).[6] In 2025, Abhishek Kumar and co-workers described an alkylation of 3-methylisoindolin-1-one with iodoalkanes in the presence of visible light catalyst through halogen atom transfer (XAT) process (Scheme 1a).[7]

Alcohols are one of the most important chemical raw materials, playing an important role in organic synthesis and chemical industry. The hydroxyl groups in alcohols makes them not only good solvents, but also serve as nucleophilic reagents.[8] In addition, the activation of α-C–H bond in alcohols has also attracted more attention, as various functionalized alcohols derivatives can be obtained through this method. While the development of free radical chemistry, the formation and their further transformations of α-carbon radicals in alcohols have been developed with transition metal catalysts or peroxides or visible light induced photoredox catalytic systems.[9] Ryu has found out that alcohols and electron deficient olefins can undergo addition reactions under the conditions of xenon lamp as a light source and TBADT as a catalyst.[10]

The photocatalytic transformations, including hydrogen atom transfer (HAT) strategy are attracting increasing interest from synthetic communities as a multifunctional strategy for post functionalization of complex molecules.[11] In order to achieve this type of HAT reaction, a batch of photocatalysts used for HAT reactions have been developed. Among them, tetrabutylammonium decatungstate (TBADT) was found to be an important one for HAT process, promoting numerous reactions involving C–H bond activation within a wide variety of hydrogen

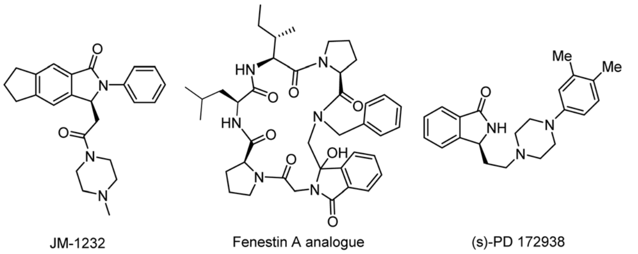

Fig. 1 Naturally occurring isoindolinones.

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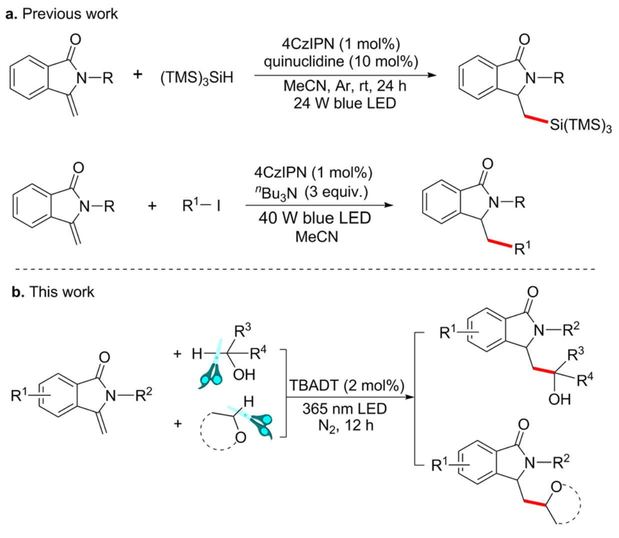
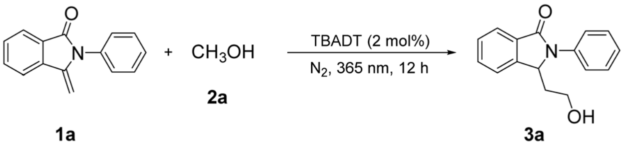


Scheme 1 Visible light-induced addition of 3-methyleneisoindolin-1-ones.

donors such as ethers, aldehydes and even alkanes of a radical type under near-ultraviolet-light irradiations.[12] It is worth noting that TBADT can be easily prepared in one step from inexpensive precursors. Based on our previous research on organic photochemistry using TBADT as photocatalyst,[13] herein, we wish to report a cross-coupling between activated alkenes and alcohols/ethers in the presence of TBADT *via* a HAT process, providing the corresponding isoindolinones in good yields (Scheme 1b).

Table 1 Optimization of reaction conditions[a]

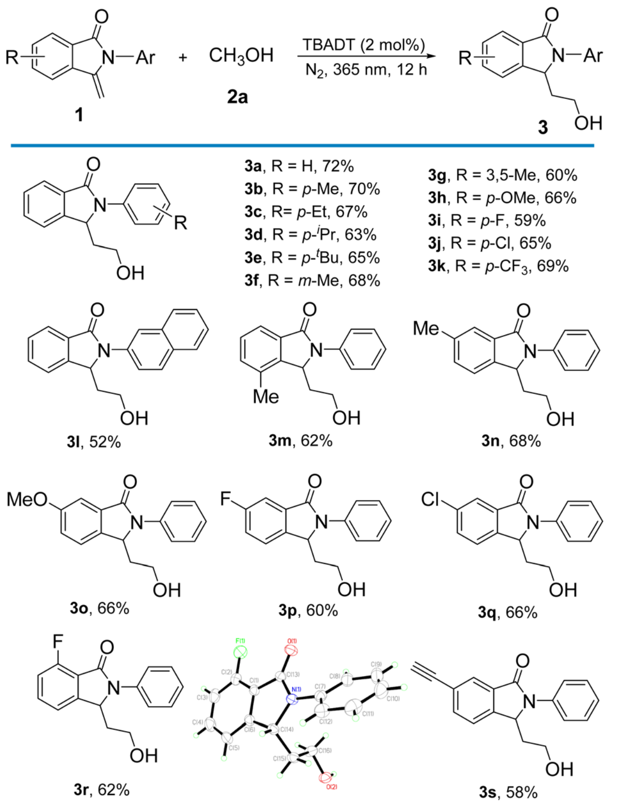


1a **2a** **3a**

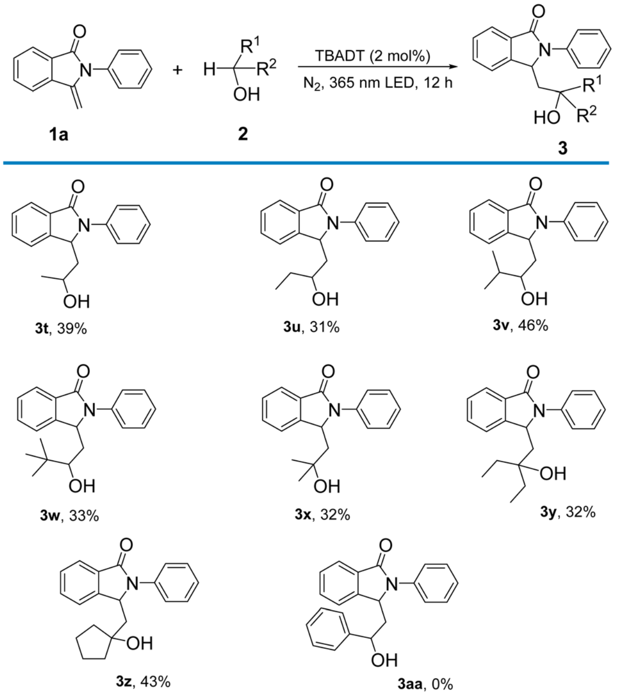
Entry	Variation	Yield (%)
1	None	72
2	NaDT instead of TBADT	56
3	Eosin Y	0
4	Mes-Acr-ClO$_4$	0
5	Ir[dF(CF$_3$)ppy$_2$(dtbpy)]PF$_6$	0
6	Benzophenone	45
7	390 nm instead of 365 nm	55
8	420 nm instead of 365 nm	47
9	1 mol% TBADT	45
10	5 mol% TBADT	62
11	Without TBADT	0
12	In the dark	0
13	Under air atmosphere	0

[a] Reaction conditions: **1a** (0.20 mmol), **2a** (2.0 mL), TBADT (2 mol%) at room temperature for 12 h under the irradiation of LED (365 nm, 6 W) under N$_2$ atmosphere. Isolated yield of **3a** was given based on **1a**.

To examine hypothesis, our research initiated an exploratory synthesis involving a model reaction of 3-methylene-2-phenylisoindolin-1-one (**1a**) with CH$_3$OH (**2a**), delineated in Table 1. Gratifyingly, when the reaction was conducted in the presence of 2 mol% TBADT in CH$_3$OH at room temperature under irradiation of 365 nm light (6 W LEDs), the desired isoindolinone derivative **3a** was isolated in 72% yield (entry 1), and the structure of its analog **3r** was further confirmed by single-crystal X-ray analysis (CCDC: 2373595). Altering the counterion to sodium (Na) resulted in diminished product yield of 56% (entry 2). Virtually no desired product was observed when TBADT was replaced with Eosin Y or Mes-Acr-ClO$_4$ (entries 3 and 4). It was found that Ir[dF(CF$_3$)ppy$_2$(dtbpy)]PF$_6$ was not a suitable photocatalyst for the reaction and the desired product could not be obtained (entry 5). Other organic photocatalyst benzophenone led to decreased yield of **3a** (entry 6). The use of wavelength 390 nm and 420 nm LEDs significantly reduced the efficiency of the reaction (entries 7 and 8). Lowering the TBADT loading to 1 mol% or increasing the TBADT loading to 5 mol% led to decreased yield of **3a** (entries 9 and 10). Finally, control experiments verified that both HAT photocatalyst TBADT and near-ultraviolet light were essential to the success of the reaction (entries 11 and 12). However, the formation of the desired product **3a** was not observed when the reaction was conducted under air atmosphere (entry 13).



Scheme 2 Substrate scope of 3-methylisoindolin-1-ones (**1**) with methanol (**2a**). [a]Reaction conditions: **1** (0.20 mmol), **2a** (2.0 mL), TBADT (2 mol%) at room temperature for 12 h under the irradiation of LED (365 nm, 6 W) under N$_2$ atmosphere. Isolated yield of **3** was given based on **1**.

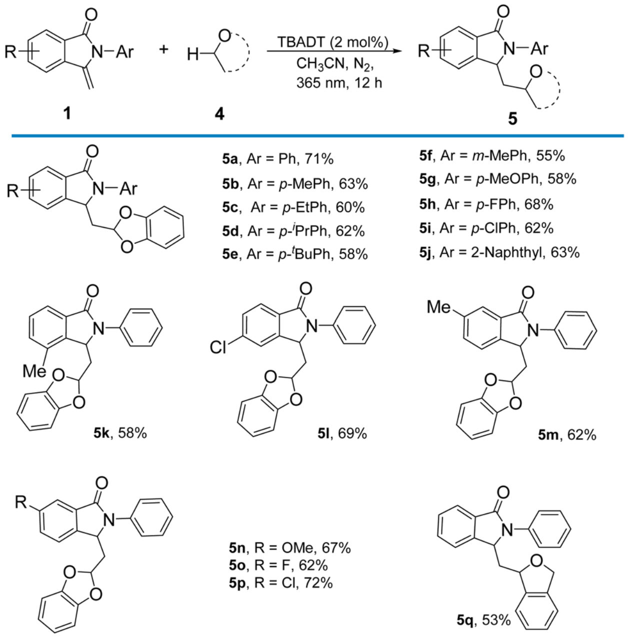


Scheme 3 Substrate scope of alcohols with **1a**. ^{a}Reaction conditions: **1a** (0.20 mmol), **2** (2.0 mL), TBADT (2 mol%) at room temperature for 12 h under the irradiation of LED (365 nm, 6 W) under N_2 atmosphere. Isolated yield of **3** was given based on **1a**.

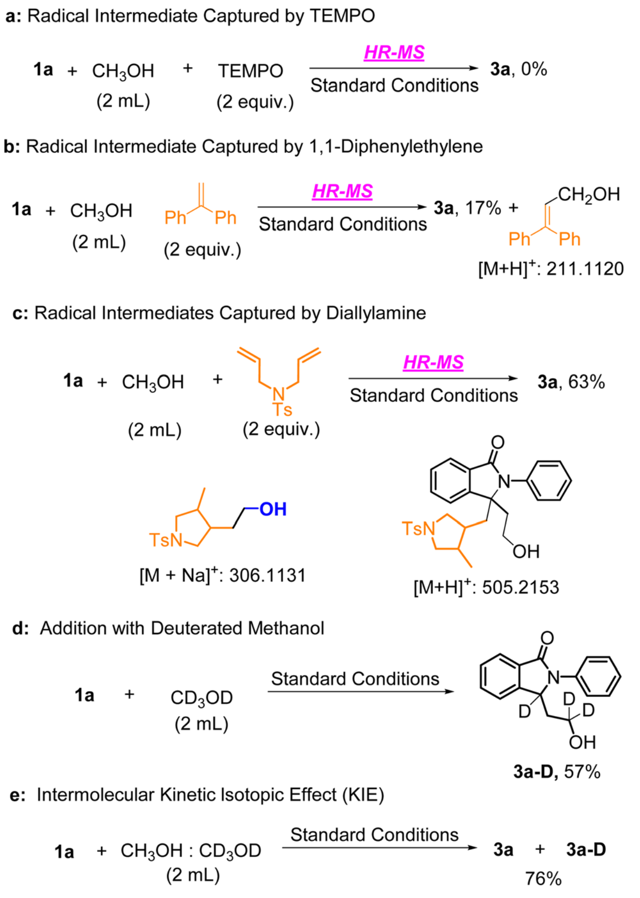
With the optimal reaction conditions in our hand, the general applicability of this protocol was further investigated, as shown in Scheme 2. For screening the results on substituents R of substrates **1**, in general, a broad spectrum of 3-methylene isoindolinones were suitable substrates, delivering the products in satisfactory yields. The substrates **1** bearing an electron donating substituent on the *N*-aryl substituted 3-methylene isoindolinones were reacted with CH_3OH (**2a**) under the optimized reaction conditions to give the corresponding products isoindolinones **3a–3h** with yields ranging from 60% to 72%. As for amide **1** substituted with an electron withdrawing group, the desired products **3i–3k** were obtained in 59–69% yields. In addition, the reaction conditions were also compatible with 3-methylene isoindolinones derived from 2-naphthyl amine, affording **3l** in 52% yield. We then explored the substituent effect of Ar in substrate **1**. When the substituted group on the aromatic ring (Ar) is methyl or methoxy could afforded the target products **3m–3o** with yields of 62 to 68%. The different type of halogen atom substituted 3-methylene isoindolinones provided the corresponding products **3p–3r** in 60–66% yields. When the substituted group on the aromatic ring (Ar) is ethynyl generated the desired product **3s** with yield of 58%. Afterwards, we turned our attention to the scope of alcohols for this photochemical transformation as presented in Scheme 3. It is delighted to find that a broad range of structurally diverse aliphatic alcohols participated in this transformation smoothly to yield the anticipated isoindolinones **3** exclusively. A range of structurally diverse primary alcohols including ethanol, *n*-propanol and 2-methyl-1-propanol were effectively to afford the corresponding radicals and further reacted with **1a** under the photochemical condition, forming the anticipated products **3t–3w** in 31–46% yields. Fortunately, secondary alcohols such as isopropanol, 3-pentanol and cyclopentanol were also suitable for this transformation, and the desired products **3x–3z** were isolated in 32–43% yields. Nevertheless, benzyl alcohol was unsuitable for this reaction, and no desired product (**3aa**) was detected.

We next explored the scope of a variety of 3-methylene isoindolinones with 1,3-benzodioxole (**4a**). A number of substituents including Ph, *para*-MePh, *para*-EtPh, *para*-^{i}PrPh, *para*-^{t}BuPh, *para*-MeOPh, *para*-FPh, *para*-ClPh, and *meta*-MePh on the substituted 3-methylene isoindolinones underwent the radical cyclization smoothly to produce the corresponding 3-hydroxyisoindolin-1-one products **5a–5i** in 55–71% yields. The reaction was compatible with 3-methylene isoindolinones derived from 2-naphthylamine, affording the desired **5j** in 63% yield. When the substituted group (R) on the aromatic ring is an electron donor (methyl or methoxy) or halogen atom (F or Cl) could afford the corresponding products **5k–5p** in 58–72% yields. The substrate scope of **1a** reacted well with isobenzofuran and desired product **5q** was obtained with yield of 53% (Scheme 4).

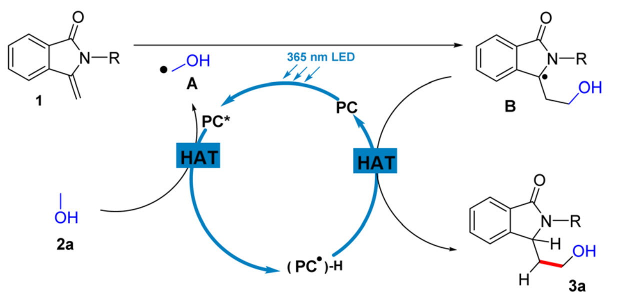
To gain mechanistic insights into this radical cascade, several control experiments were conducted as summarized in Scheme 5. The reaction was completely inhibited when TEMPO (2,2,6,6-tetramethyl-1-piperidinyloxyl) was added and an alkyl radical was successfully trapped through HR-MS analysis (Scheme 5a, SI for detail). Moreover, an adduct resulting from the sequestration of α-hydroxyl radical by 1,1-diphenylethylene was also detected by HR-MS analysis (Scheme 5b, SI for detail).



Scheme 4 Substrate scope of **1** with **4**. ^{a}Reaction conditions: **1** (0.20 mmol), **4** (0.40 mmol), CH_3CN (2.0 mL), TBADT (2 mol%) at room temperature for 12 h under the irradiation of LED (365 nm, 6 W) under N_2 atmosphere. Isolated yield of **5** was given based on **1**.



Scheme 5 Mechanistic studies.



Scheme 6 Proposed mechanism.

When *N*-Ts-diallylamine was used as a radical capture, both $^{\bullet}CH_2OH$ and alkyl radical were trapped and confirmed by HR-MS analysis (Scheme 5c, SI for detail). Interestingly, D_4-methanol could be reacted with **1a** to give a α-deuterated alcohol (**3a-D**) in 57% yield without H–D exchange at the α-position and with exclusive H–D exchange on the hydroxyl group (Scheme 5d). A further intermolecular competitive reaction of methanol and D_4-methanol with (**1a**) was performed and KIE value of $K_H/K_D = 2.3$ was observed (Scheme 5e). These results suggest that the C–H cleavage of methanol was probably not involved in the rate-determining step. The light on/off profile illustrated that the radical chain reaction might not be involved in the mechanism (SI for detail).

Based on the above results of mechanistic experiments and previous reports,[6,7,12] a plausible mechanism for this transformation was proposed as illustrated in Scheme 6. First, upon absorption of LED (365 nm) light, the excited state of TBADT (*W**) reacts with C–H bond of α-C-position in CH_3OH (**2a**) *via* a hydrogen atom transfer (HAT) process, yielding a carbon centered α-oxymethyl radical **A**. Then, the obtained **A** undergoes a free-radical addition to carbon–carbon double bond of **1**, affording an alkyl radical **B**. The **B** abstracts a hydrogen atom from the TBADT to deliver the final product **3a**.

In summary, we have developed a TBADT-catalyzed synthesis of isoindolinones using activated alkenes and alcohols/ethers *via* a hydrogen atom transfer process. A variety of functionalized isoindolinones were obtained in good yields. This protocol represents a highly efficient example of TBADT-induced C–H activation to obtain carbon-centered radical under mild reaction conditions, displaying well functional group compatibility. It is believed that the strategy would enrich the radical chemistry and may have potential application for the discovery of carbon-centered radical systems.

Conflicts of interest

There are no conflicts to declare.

Data availability

The data underlying this study are available in the published article and its SI.

CCDC 2373595 contains the supplementary crystallographic data for this paper.[14]

General procedure for the synthesis of **1**, detailed mechanistic studies, ^1H and ^{13}C NMR data for **3** and **5** and copies of the spectra. See DOI: **https://doi.org/10.1039/d5ra05071e**.

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