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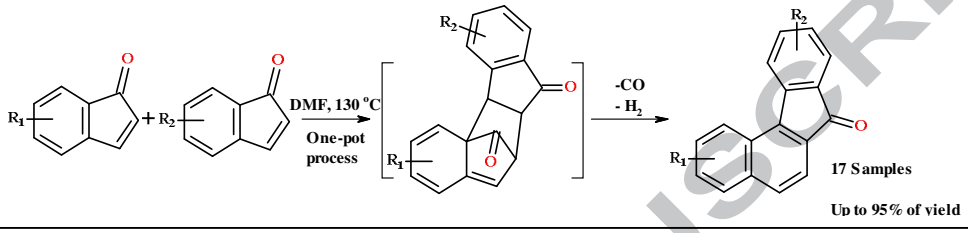

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Synthesis of benzo[c]fluorenone through a one-pot cascade reaction using inden-1-one derivatives

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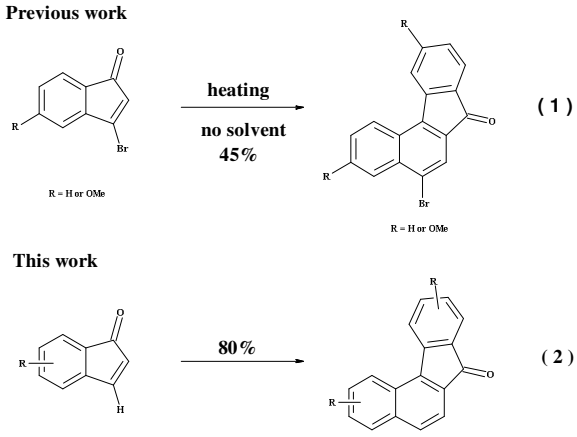
ABSTRACT

A novel one-pot thermal cycloaddition of two indenones followed by a decarbonylation and dehydrogenation cascade afforded benzo[c]fluorenones regioselectively. Various substituted indenone derivatives were converted into their corresponding benzo[c]fluorenones in good to excellent yields.

The Diels-Alder reaction is a cycloaddition reaction between a conjugated diene and a dienophile and is widely used to synthesise various six-membered ring systems. This ubiquitous [4+2] reaction often exhibits high regio- and stereo selectivity. Theoretically, an exocyclic double bond conjugated with an aromatic ring may act as diene moiety in a Diels-Alder reaction, but examples are rarely reported in the literature. This is because the electron delocalisation effect on the aromatic ring stabilises the molecule, hindering the molecule's ability to participate in the cycloaddition under mild conditions.[1] Indenones are useful intermediates for synthesising various molecules because they can participate in numerous types of reactions due to their unique combination of functionalities,. These reactions include Michael additions,[2] 1,3-dipolarcycloadditions,[3] [2+2] photodimerisations,[4] epoxidations[5] and aziridinations.[6] In addition, indenones are also extensively used as dienophiles in [4+2] cycloadditions.[7] However, to our knowledge, they have seldom been used as the diene moiety in Diels-Alder reactions. One exception was reported by Balci's group during the synthesis of the bromoindenones; side reactions (Scheme 1) occurred with 3-bromoindenone and 3-bromo-5-methoxyindenone.[8,9] Interestingly, there have been no reports of a Diels-Alder reaction involving indenone and a subsequent decarbonylation and dehydrogenation cascade, even though indenones have been used for many years in organic synthesis. This paper describes a Diels-Alder reaction using indenone derivatives with subsequent decarbonylation and dehydrogenation steps, generating a simple route to benzo[c]fluorenones.[10] Accessing these benzofluorenones will produce known flurostatin-based natural compounds[11] more efficiently and facilitate rapid exploration of related chemical structures with a fused ring motif, such as the



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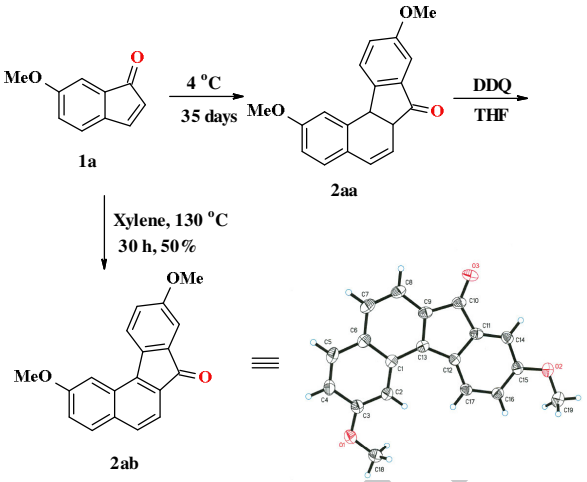
potentially therapeutic benfluron analogues.[12]

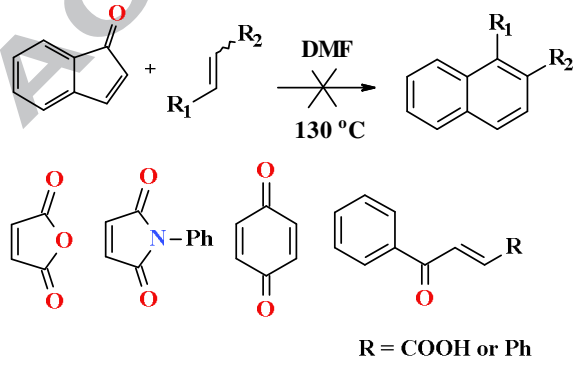
Scheme 1 Synthesis of benzo[c]fluorenone derivatives

The reaction was discovered when we attempted to use 6-methoxyindenone **1a** as a dienophile for a Diels-Alder reaction in an unrelated study. The compound had decomposed after one month of storage in a refrigerator (approximately 4°C). Fortunately, one of main products was isolated from the mixture, and its structure was assigned to be dihydrobenzo[c]fluorenone **2aa** based on the spectroscopic data (Scheme 2). Subsequent oxidation with DDQ yielded bright-red crystals and an X-ray crystal diffraction analysis confirmed the structure as dimethoxybenzo[c]fluorenone **2ab**. Further examination of this reaction indicated that the benzo[c]fluorenone could be easily produced after refluxing indenone **1a** in toluene.



Scheme 2. Reaction forming a benzo[c]fluorenone

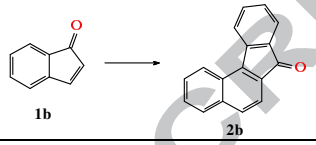
This unexpected result caught our interest immediately because indenone's role as a diene moiety in the Diels-Alder reaction was so unusual. In addition, the regioselectivity of the reaction was quite interesting because the benzo[c]fluorenone formed exclusively. Therefore, further investigations were carried out to understand the scope and the limitations of this reaction.



Scheme 3. Attempts at cross-coupling with various dienophiles

Readily available 1-indenone **1b** was chosen as the substrate to optimise the reaction conditions. Various reaction conditions were tested and some selected results are presented in Table 1.

Table 1. Optimization of reaction conditions for benzo[c]fluorenone formation



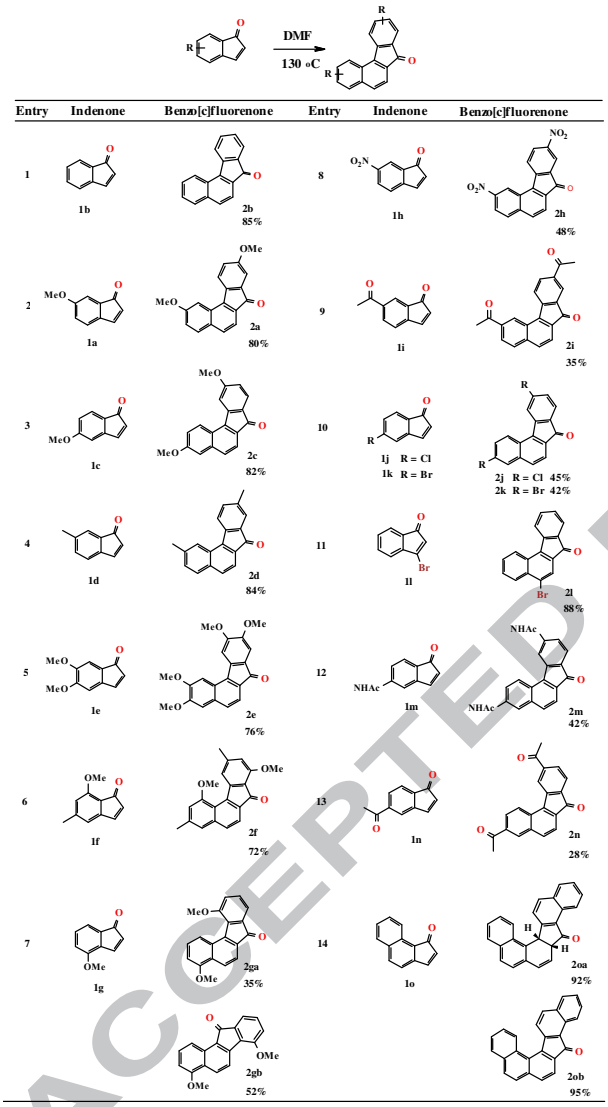
Entry	Solvent	Catalyst	Temp./ time	Yield (%)[d]
1[a]	Toluene		120 ℃ / 30 h	40
2[a]	Toluene	Et_2AlCl	120 ℃ /30 h	32
3	Toluene	$Sc(OTf)_3$	120 ℃ /20 h	68
4[a]	xylene		150 ℃ / 30 h	42
5[b]	CH_2Cl_2		Reflux 10 h	0
6[b]	CH_2Cl_2	ZnI_2	50 ℃/ 5 h	0
7[b]	$ClCH_2CH_2Cl$		80 ℃/ 10 h	0
8	$ClCH_2CH_2Cl$	$Sc(OTf)_3$	80 ℃/ 10 h	70
9	THF		80 ℃/ 10 h	28
10[c]	$HOCH_2CH_2OCH_3$		140 ℃/ 5 h	62
11[c]	EtOH		80 ℃/ 8 h	45
12	DMF		130 ℃/ 8 h	85
13	DMF	$Sc(OTf)_3$	80 ℃/ 5 h	82

[a]The conversion was low and the most of **1b** was recovered. [b] No reaction and **1b** was recovered. [c] The by-product was the Michael adduct between the alcohol and the indenone. [d] Isolated yield.

In a nonpolar solvent, such as toluene or xylene, the reaction proceeded very slowly, and the yields remained unsatisfactory (entry 1 and 4). However, when $Sc(OTf)_3$ was added as a catalyst, the yield of the reaction improved significantly (entry 3). In DCM or 1,2-dichloroethane, no reaction was observed, even the indenone was highly soluble in these two solvents. Interestingly, when a large amount of $Sc(OTf)_3$ (0.2 eq) was used in 1,2-dichloroethane, the substrate was completely converted (entry 8). THF could also be used as the solvent of this reaction, however, due to the poor solubility of the indenone in THF, the

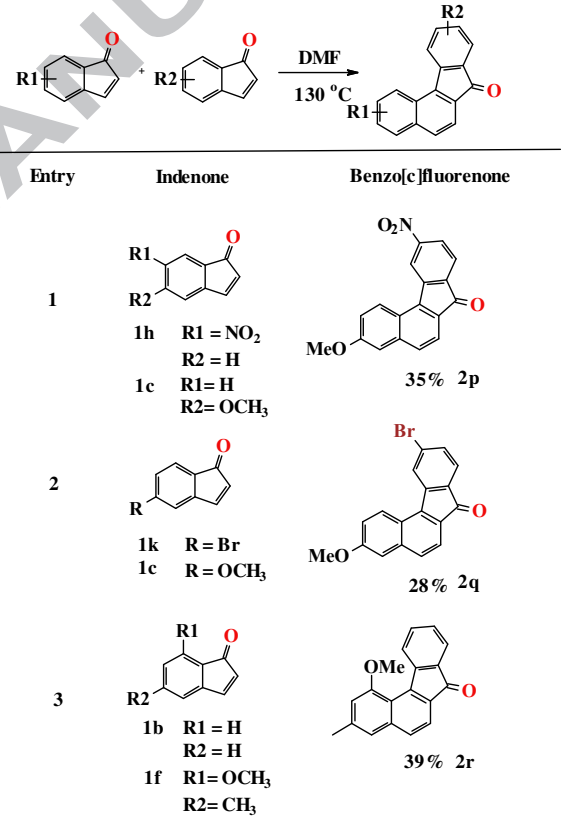
reaction's results were unsatisfactory. Protic solvents, such as EtOH and 2-methoxyethanol were unsuitable for this reaction because they reacted with the 1-indenone to form Michael adducts. Finally, DMF was identified as the most efficient solvent for this reaction (entry 12), it facilitating the complete conversion of the substrate and inducing the best yield. Although $Sc(OTf)_3$ could accelerate the reaction (entry 13), however, using DMF alone at 130 °C was chosen for this reaction because it already give satisfactory results.

Table 2. Coupling reactions between two indenones



Subsequently, various indenone derivatives were used to further explore the scope and limitations of the reaction. The results are depicted in Table 2. Generally, electron-rich indenones furnished better results than electron-deficient substrates. The electron-rich indenones have increased electron density at the cyclopentadienone moiety, forming a 4-electron π system and becoming a more reactive diene in the Diels-Alder reaction. However, in the electron-deficient indenones, the cyclopentadienone moiety tended to occupy a 2-electron π system; this arrangement followed the [4n+2] rule and therefore remained quite stable. For example, indenone derivatives with electron-withdrawing groups, such as chloro, bromo and acetyl, were stable at room temperature and could even be stored as such for several months. However, under our standard reaction conditions, the benzo[c]fluorenones could only be obtained in moderate yields. The indenones with methoxyl, methyl and acetamido substituents (entry 1~7 and entry 12) were more reactive and could form the desired benzo[c]fluorenones smoothly. Interestingly, for 4-methoxyindenone (entry 7), the aromatic isosteroid was the major product of this reaction. This product may form because the steric hindrance of the group at the 4-position changed the [4+2] cycloaddition's regioselectivity. In fact, all other indenones without 4-substitution only form benzo[c]fluorenones. In addition, while synthesizing naphthalindenone (entry 14), we observed only dihydrobenzo[c]fluorenone 2oa; this compound could be converted into benzo[c]fluorenone via DDQ oxidation. However, the formation of dihydrobenzo[c]fluorenone clearly indicated that the dehydrogenation is the last mechanism step in the reaction cascade. For the reaction with 3-bromoindenone, 5-bromobenzo[c]fluorenone 2l was generated in a much better yield than what was previously reported (entry 11)[8].

Table 3. Coupling two different indenones

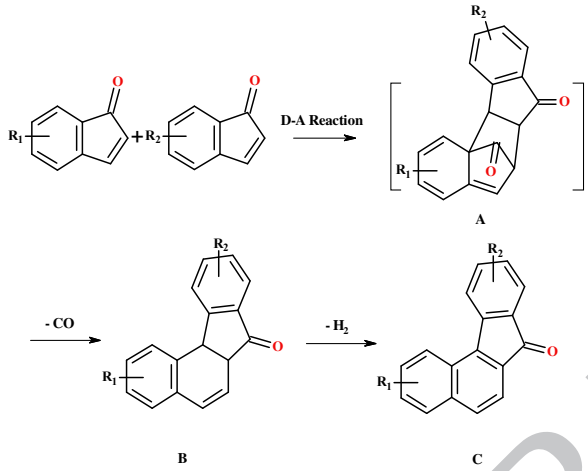


Subsequently, cross coupling reactions using two different indenones were examined, and the results are depicted in Table 3. Unfortunately, the yields for these reactions were unsatisfactory due to their limited chemoselectivity.

To continue exploring the use of indenone as a diene moiety in Diels-Alder reactions, indenone was tested with other

dienophiles (Scheme 3), such as p-benozquinone, maleric anhydride, N-phenylmaleimide and chalcone; unfortunately, no desired products were observed. The reasons of the failure of these cross couplings remain unclear.

Based on the above results, a reaction mechanism was proposed, as described in Scheme 4. First, a thermal Diels-Alder cycloaddition between two indenone molecules broke aromaticity to generate intermediate **A** regioselectively. Next, re-aromatisation drove the decarbonylation process, forming **B**.Subsequently, the final dehydrogenation was driven by the completion of the completed large π system, producing benzo[c]fluorenone. The isolation of the intermediate B in some reaction (entry 14, table 2) further confirmed the proposed mechanism.



Scheme 4. Proposed reaction mechanism

In summary, a one-pot cascade reaction that involves the cycloaddition of two indenones, followed by decarbonylation and dehydrogenation was discovered to form benzo[c]fluorenones regioselectively. This method is the most convenient way to synthesise benzo[c]fluorenone derivatives. Further research remains on-going to expand the scope of the reaction.

Acknowledgments

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Supplementary Material

The supplementary data (detailed experiment procedures, compound characterisation, and copies of spectra data) associated with this article can be found online.

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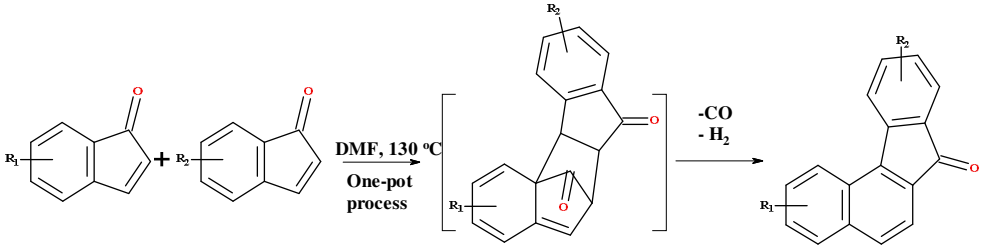

17 Samples

Up to 95% of yield