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Synthesis of Diverse Indene Derivatives from 1-Diazonaphthalen-2(1*H*)-ones via Thermal Cascade Reactions

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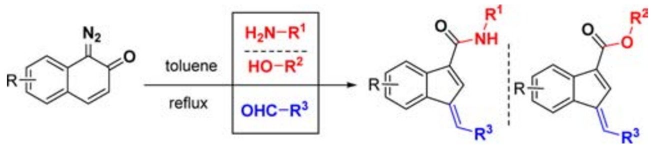
ABSTRACT



A sequential Wolff rearrangement of 1-diazonaphthalen-2(1*H*)-ones followed by trapping of the ketene intermediate with primary and aromatic amines or alcohols and phenols in the presence of various aldehydes generates 1*H*-indene-3-carboxamides or 1*H*-indene-3-carboxylates. This constitutes an unprecedented three-component coupling reaction that allows for the synthesis of functionalized indene derivatives under catalyst-free thermal conditions.

The indene framework is an important structural motif contained in many natural products and pharmaceuticals (Figure 1).[1] These indene-based molecules have shown a wide range of biological activities such as antineoplastic,[2] antimicrobial,[3] anti-inflammatory,[4] aromatase inhibitory,[5] and cytotoxic activities;[6] thus some of them are currently under evaluation for their potential as drug leads.[7] In addition, indene derivatives are widely used as building blocks for the synthesis of functional materials[8] and metallocene complexes for olefin polymerization.[9]

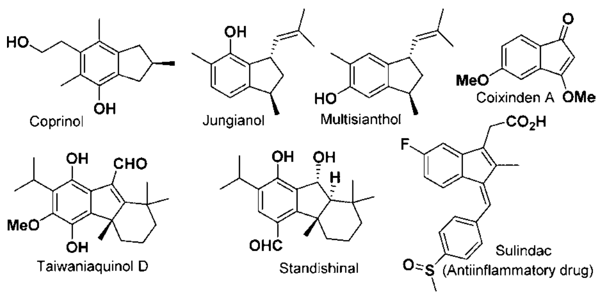


Figure 1. Selected examples of natural products and pharmaceuticals bearing the indene skeleton.

Because of their importance and usefulness, various synthetic approaches have been developed to construct indene derivatives based on intra-[10−14] and intermolecular cyclization reactions.[15−21] Representative intramolecular

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approaches include the ring expansion of suitably substituted cyclopropenes,[10] Lewis acid-catalyzed Friedel–Crafts cyclization,[11] the Brønsted acid-catalyzed cyclization of alkyl aryl-1,3-dienes,[12] the transition metal-catalyzed cyclization of alkynes,[13] and the gold-catalyzed cycloisomerization of benzene-1,2-dialkynes.[14]

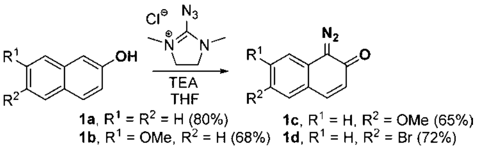
A variety of effective intermolecular approaches were also reported for indene synthesis, which include [3+2] annulation of aromatic aldimines and acetylenes,[15] copper-catalyzed arylative cyclization of arylalkynes and aromatic sulfonyl chlorides,[16] palladium-catalyzed carboiodination of aryl iodide and internal alkynes,[17] $FeCl_3$-catalyzed cyclization of *N*-benzylic sulfonamides and disubstituted alkynes,[18] Lewis acid-catalyzed cascade reaction between aziridines and propargyl alcohols,[19] the $FeCl_3$-catalyzed cyclization of arylallenes to *N*-alkyl sulfonamides,[20] and palladium-catalyzed carboannulation of diethyl 2-(2-(1-alkynyl)phenyl)malonate and organic halides.[21]

Despite their own merits, many existing methods suffer from shortcomings including low tolerance of functionality, long reaction times, the necessity of expensive transition metal catalysts, and harsh reaction conditions. Therefore, more environmentally benign and efficient arsenals are still needed improving on these shortcomings, which prompt us to develop new approaches relying on the characteristic reactivity of diazo compounds. The decomposition of diazocarbonyl compounds is one of the significant reaction in organic synthesis.[22] Among these, Wolff rearrangement is a useful method for the formation of reactive ketene intermediates.[23] This method has a lot of applications in DNA cleavage, *β*-peptides, drug delivery, and photoaffinity labeling.[24]

In this context, we became interested in the decomposition of cyclic diazodicarbonyl compounds as a powerful means of synthesizing heterocycles and novel compounds;[25] for example, we prepared cyclic *β*-enaminoamides via the thermal Wolff rearrangement of cyclic 2-diazo-1,3-dicarbonyls.[26] As the result of our continued interest in this area, herein we describe catalyst-free thermal cascade reactions where the Wolff rearrangement of 1-diazonaphthalen-2(1*H*)-one induces the formation of structurally diverse indene derivatives. Although a photochemical Wolff rearrangement of 1-diazonaphthalen-2(1*H*)-one to give a ketene intermediate has been reported,[27] this is the first example of a one-pot synthesis of complex 1*H*-indene-3-carboxamide and 1*H*-indene-3-carboxylate derivatives under relatively mild conditions without catalysts.

Diazo compounds **1a**–**1d** were prepared from 2-naphthols and 2-azido-1,3-dimethylimidazolinium chloride following the Kitamura protocol (Scheme 1).[28]

Scheme 1. Preparation of Diazo Compounds **1a**–**1d**



Our investigation commenced with the optimization of reaction conditions for the thermal decomposition of **1a** in the presence of *n*-butylamine and benzaldehyde in various solvents and temperatures (Table 1). Treatment of **1a** (1.0 mmol) with *n*-butylamine (1.1 mmol) and benzaldehyde (1.1 mmol) in fluorobenzene at 85 °C for 18 h provided **2a** in 30% yield (entry 1), whereas that in chlorobenzene at 110 °C for 8 h afforded **2a** in 63% yield (entry 2). Reaction in toluene at 70 °C for 18 h remained starting material **1a** (entry 3), but at 110 °C, **2a** was obtained in 80% yield after 6 h (entry 4). Reaction in *m*-xylene under reflux for 4 h did not provide **2a** but only intractable material (entry 5). Although in 1,4-dioxane, **2a** was produced in 52% yield (entry 6), in more polar solvents such as acetonitrile and DMF, **2a** was not obtained at all (entries 7 and 8). The identity of **2a** was confirmed by spectroscopic analysis; the ^1H NMR of **2a** shows two vinylic protons at $\delta = 7.54$ and 7.22 ppm as the two signals for the indene and benzylidene moiety, respectively. The *E*-stereochemistry of **2a** was deduced from the X-ray crystallographic analysis of structurally related compound **2k** (see Supporting Information).

Next, rhodium(II)-catalyzed and microwave-assisted reactions were attempted. Reaction of **1a** with *n*-butylamine and benzaldehyde in the presence of 2 mol % of $Rh_2(OAc)_4$ in toluene at room temperature for 48 h provided **2a** (5%) and 2-naphthol (23%), and unreacted starting material was recorved (35%). MW irradiation of **1a** with *n*-butylamine and benzaldehyde in DMF at 400 W and 50 °C for 10 min afforded **2a** in 64% yield.

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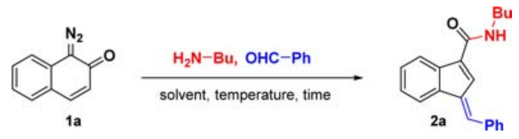
Table 1. Optimization of the Thermal Decomposition of **1a** in the Presence of *n*-Butylamine and Benzaldehyde



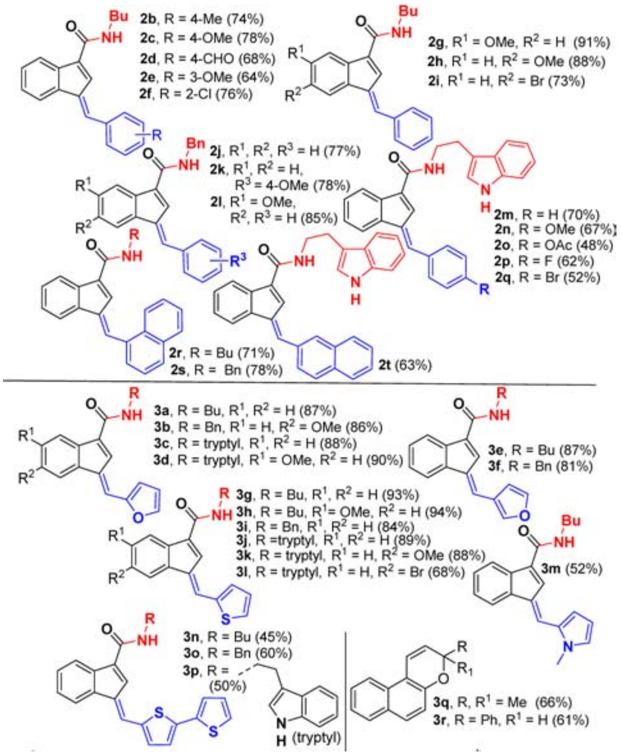
entry	solvent	temperature (°C)	time (h)	yield (%)
1	fluorobenzene	85	18	30
2	chlorobenzene	110	8	63
3	toluene	70	18	0
4	**toluene**	**110**	**6**	**80**
5	*m*-xylene	140	4	0
6	1,4-dioxane	100	15	52
7	acetonitrile	80	24	0
8	DMF	110	8	0

With the optimized conditions in hand, we further explored the generality of this thermal multicomponent reaction employing different primary amines and aldehydes (Scheme 2). Reactions of **1a** in refluxing toluene for 6 h in the presence of *n*-butylamine together with 4-methyl-, 4-methoxy-, 4-formyl-, 3-methoxy-, and 2-chlorobenzaldehyde afforded the expected products **2b**–**2f** in the range of 64–78% yield. Also, the cascade reactions of diazo compound **1b**–**1d** bearing electron-donating or -withdrawing groups on the aromatic ring were also successful. Reaction of **1b** and **1c** bearing electron-donating groups provided the desired products **2g** (91%) and **2h** (88%), and that of **1d** bearing an electron-withdrawing group afforded **2i** in 73% yield. The combinations of diazo compounds **1a** and **1b** with benzyl amine and benzaldehyde or 4-methoxybenzaldehyde afforded **2j** (77%), **2k** (78%), and **2l** (85%), respectively. With tryptamine together with benzaldehyde and its derivatives containing a substituent at the 4-position products **2m**–**2q** were obtained in a slightly lower range of yields (48–70%). The combinations of 1- and 2-napthaldehyde and butyl-, benzyl-, and tryptamine provided the corresponding products **2r**–**2t** in 71%, 78%, and 63% yield, respectively.

Next, we explored the multicomponent reaction of diazo compounds **1a**–**1d** with primary amines and various heteroaromatic aldehydes such as furfural, 3-furancarboxaldehyde, 2-thiophenecarboxaldehyde, *N*-methyl-2-pyrrolecarboxaldehyde, and 2,2′-bithiophene-5-carboxaldehyde under the optimized conditions. These reactions with heteroaromatic aldehydes generally afforded slightly increased yields of the expected products **3a**–**3p** in the range of 45–94%.

We also tried the reaction with aliphatic aldehydes, but we did not observe any desired indene products with these aldehydes and amines being incorporated. For example, reaction of **1c** with benzylamine and 3-methylbutanal in refluxing toluene for 6 h gave complex mixtures. However, reactions of **1a** with *n*-butylamine and 3-methyl-2-butenal or *trans*-cinnamaldehyde in refluxing toluene for 6 h provided unexpected cycloadducts **3q** and **3r** in 66% and 61% yield, respectively.

Scheme 2. Formation of Indene Derivatives **2b**–**2t** and **3a**–**3p** by Thermal Decomposition of **1a**–**1d** with Primary Amines and Aromatic/Heteroaromatic/Aliphatic Aldehydes[a,b]

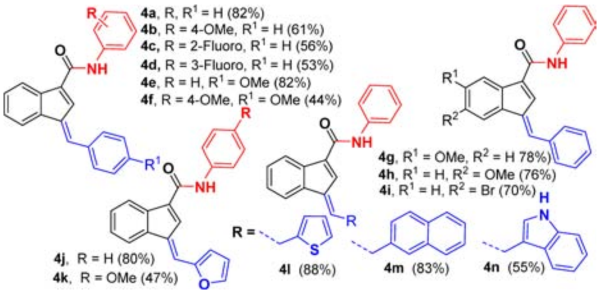


[a] Conditions: toluene, 110 °C, 6 h (**1**:amine:aldehyde = 1:1.1:1.1). [b] Reactions with aliphatic aldehydes failed in generating the desired products.

To further demonstrate the versatility of this multicomponent reaction, we examined reactions with aromatic amines and aromatic/heterocyclic aldehydes (Scheme 3). The thermal decoposition of **1a**–**1d** with aniline or substituted anilines and aromatic aldehydes in refluxing toluene for 6 h afforded the corresponding products **4a**–**4n** in 44–88% yield.

Having seen the general applicability of the multicomponent reaction by employing amines as the nucleophilic component, we were intrigued by the possibility of using oxygen-based nucleophiles, which will lead to the formation of 1*H*-indene-3-carboxylate derivatives. We were gratified to observe that the reactions of **1a**, **1b**, and **1d** with aliphatic alcohols or phenol derivatives together with aromatic/heteroaromatic aldehydes provided the expected products (Scheme 4). Reactions of **1a** with benzaldehyde in combination with 1-propanol, benzyl, and phenethyl alcohol provided desired products **5a**–**5c** in 56%, 55%, and 65% yield, respectively. Treatment of **1d** with 1-propanol and benzaldehyde provided **5d** in 56% yield, whereas that of **1b** with phenethyl alcohol and benzaldehyde afforded **5e** in 63% yield. With phenol and its derivatives, reactions were also successful. In general, the yields of the isolated 1*H*-indene-3-carboxylate derivatives **5f**–**5o** are somewhat lower (in the range of 39–57%) than those of the corresponding carboxamides (in the range of 45–94%).

Scheme 3. Formation of Indene Derivatives **4a**–**4n** by Thermal Decomposition of **1a**–**1d** with Aniline and Substituted Anilines and Aromatic/Heteroaromatic Aldehydes[a]

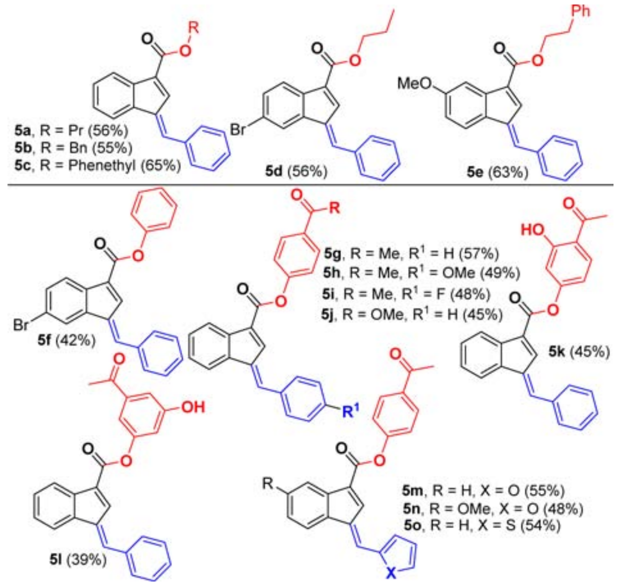


[a] Conditions: toluene, 110 °C, 6 h (**1**:amine:aldehyde = 1:1.1:1.1).

The formation of **5k** was identified by ^{1}H NMR analysis, in which a proton peak of OH appeared downfield at δ 12.46 ppm due to the presence of intramolecular hydrogen bonding to a carbonyl group. These reduced yields compared to those of the other series are most likely the consequence of the lower nucleophilicity of aliphatic alcohols and phenol derivatives that undergo the initial addition to the ketene intermediate.

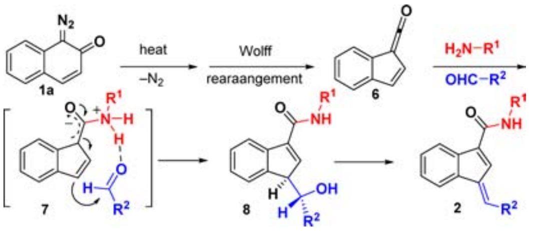
The formation of observed products **2** is assummed to be initiated by the thermal decomposition of 1-diazonaphthalen-2(1*H*)-one (**1a**) to the corresponding ketene intermediate, benzofulven-8-one (**6**), via the initial N_2 loss[27] followed by a Wolff rearrangenent (Scheme 5). The Wolff rearrangement induced by photolysis of 1-diazonaphthalen-2(1*H*)-one (**1a**) to generate ketene **6** and its subsequent reaction with water to form indene-3-carboxylic acid was previously reported by Wirz and Kasai.[27] Once formed, ketene **6** would undergo nucleophilic addition by either amines or alcohols in the presence of aldehydes. In the case of amine nucleophiles, zwitterionic ylide **7** would interact with an incoming aldehyde through hydrogen bonding to facilitate the carbonyl addition, leading to the formation of intermediate **8**. As evidence for intermediate **7**, a stable ketene–amine or ketene–pyridine ylide intermediate has been reported.[29] Finally, a thermodynamically driven stereospecific *anti*-elimination of water from **8** would lead to observed product **2**. The high selectivity for **2** might simply be a consequence of isomerization of the products formed through nonstereospecific processes driven by the steric interaction between the indene and phenyl moieties.

Scheme 4. Formation of Indene Derivatives **5a**–**5o** by Thermal Decomposition of **1a**, **1b**, and **1d** with Aliphatic Alcohols or Phenol Derivatives and Aromatic/Heteroaromatic Aldehydes[a]



[a] Conditions: toluene, 110 °C, 6 h (**1**:alcohol:aldehyde = 1:1.1:1.1).

Scheme 5. Proposed Mechanism for the Formation of **2**



In summary, we developed a novel one-pot cascade approach to the synthesis of 1*H*-indene-3-carboxamides and 1*H*-indene-3-carboxylate derivatives from the thermal decomposition of 1-diazonaphthalen-2(1*H*)-ones. Aliphatic or aromatic primary amines and aliphatic alcohols or phenol derivatives are used as the nucleophilic component together with various aromatic and heteroaromatic aldehydes. This catalyst-free multicomponent coupling reaction allows for the synthesis of various functionalized indene derivatives, which should find various applications in the synthesis of natural products and pharmaceuticals. Further expansion of the reaction scope using other nucleophilic components in the presence of amine and Lewis acid catalysts is in progress.

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Supporting Information Available. Experimental procedures and characterization data of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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The authors declare no competing financial interest.