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Synthesis of (2-Aminophenyl)(naphthalen-2-yl)methanones *via* Intramolecular Rearrangement of (*E*)-3-Styrylquinolin-4(1*H*)-ones under Irradiation with 365 nm UV Light

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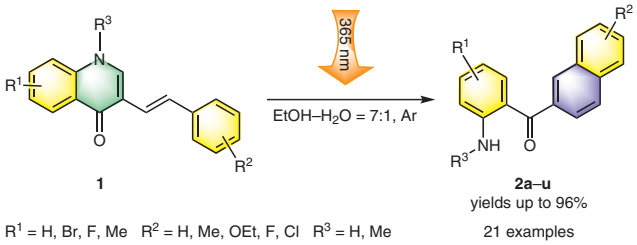

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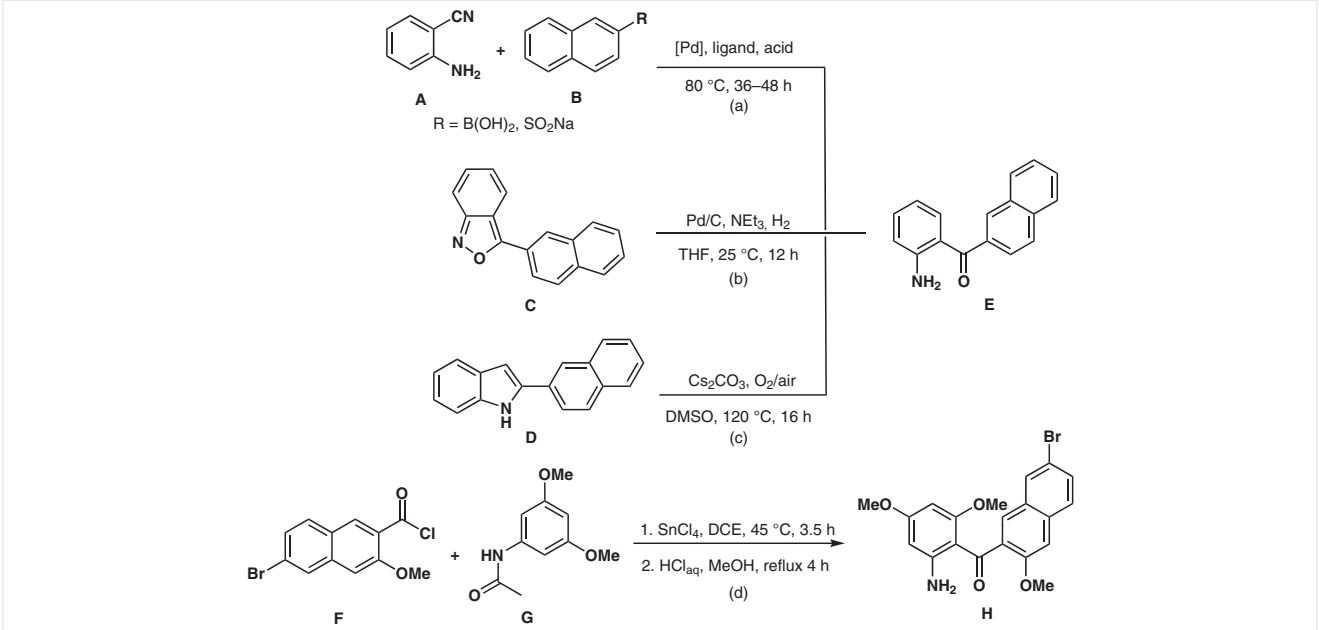
Abstract A highly efficient and environmentally friendly synthesis of (2-aminophenyl)(naphthalen-2-yl)methanones was developed. The (2-aminophenyl)(naphthalen-2-yl)methanone derivatives were obtained in high yields (up to 96%) by the irradiation of (*E*)-3-styrylquinolin-4(1*H*)-ones in EtOH–H_2O (7:1) with UV light (365 nm) at room temperature under Ar atmosphere. The demonstrated photoinduced intramolecular rearrangement has advantages over other transition-metal-catalyzed reactions, e.g. no requirement of additives, green solvent, broad substrate scope, and high atom efficiency.

Key words (2-aminophenyl)(naphthalen-2-yl)methanones, (*E*)-3-styrylquinolin-4(1*H*)-ones, photo rearrangement reaction, photochemical reaction, synthesis

2-Aminobenzophenone and its derivatives arouse wide attention due to their various applications in pharmaceutical chemistry and heterocyclic synthesis.[2–11] Structure-activity relationship showed that the amino group introduced at the *ortho*-position of the benzophenone ring could inhibit the polymerization of tubulin.[2] A series of 2-aminobenzophenone derivatives containing nitrogen mustard substituent were known to possess antitumor activity as well.[3] Moreover, the sodium 2-(2-amino-3-benzoylphenyl)acetate has revealed anti-inflammatory and analgesic activity.[4] Last but not least, the 2-aminobenzophenones were also used as precursors for further transformations to various nitrogen-containing heterocyclic compounds, including the derivatives of quinolines,[5,6] quinazolines,[7–9] dibenzo[*b*,*f*][1,5]diazocines[10] and a hole-blocking material 1,3,5-tris(4-phenylquinolin-2-yl)benzene.[11] Since the structure of (2-aminophenyl)(naphthalen-2-yl)methanones is similar to 2-aminobenzophenones, it could have potential application values, such as antitumor, anti-inflammatory, analgesic, precursors of nitrogen-containing heterocyclic compounds.

A careful review of the literature reports appraised that all the substrates employed in the synthesis of (2-aminophenyl)(naphthalen-2-yl)methanone (**E**) contain a naphthalene moiety.[12–16] For instance, the palladium-catalyzed cross-coupling of naphthalen-2-ylboronic acid or sodium naphthalene-2-sulfinate (**B**) with 2-aminobenzonitrile (**A**) in the presence of ligands at 80 °C for 36–48 hours gave **E** in 81% or 91% yield (Scheme 1a).[12,13] Alternatively, analogue **E** could be also obtained from the reduction of 3-(naphthalen-2-yl)benzo[*c*]isoxazole (**C**) with hydrogen gas in the presence of Pd/C (Scheme 1b).[14] Interestingly, instead of reduction, the synthesis of analogue **E** was also reported by the oxidative cleavage of 2-(naphthalen-2-yl)-1*H*-indole (**D**) at 120 °C for 16 hours in the presence of Cs_2CO_3/O_2 along with the generation of CO_2 (Scheme 1c).[15] The reported method successfully eliminates the requirement of transition metals. However, it has to be performed in the presence of oxygen at elevated temperature for a long time (120 °C/16 h), which is risky and might destroy certain sensitive functional groups. A stepwise Friedel–Crafts acylation of *N*-(3,5-dimethoxyphenyl)acetamide (**G**) with 6-bromo-3-methoxy-2-naphthoyl chloride (**F**) in the presence of $SnCl_4$ at 45 °C for 3.5 hours followed by the acidic hydrolysis in methanol for additional four hours gave the desired aromatic ketone analogues **H** in good yields (Scheme 1d).[16]

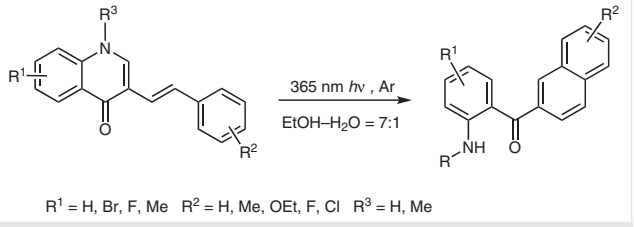
Photochemical reactions are a significant technology for green chemistry, which is highly atom efficient in some reactions.[17,18] The light itself, as a clean energy, does not produce any chemical by-product and the required energy could be easily adjusted with various wavelengths.[19] Since we have been focusing on the photoinduced intramolecular



Scheme 1 Alternative routes to (2-aminophenyl)(naphthalen-2-yl)methanones

dehydrogenation/dehydration for the synthesis of polyheterocyclic compounds,[20–26] we would like to follow our interest and demonstrate the intramolecular rearrangement of (*E*)-3-arylvinyl-4*H*-chromen-4-ones under UV light (365 nm/Ar) at room temperature for the synthesis of (2-aminophenyl)(naphthalen-2-yl)methanones analogues (Scheme 2), which avoids a) high temperature, b) usage of transition metals and c) directly constructed the naphthalene ring during rearrangement rather than inherited from substrates.

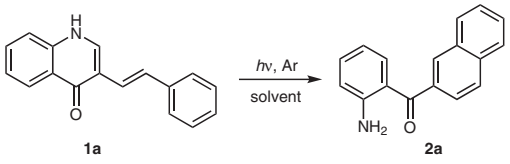
Recently, the synthesis of benzoaryl-5-yl(2-hydroxyphenyl)methanones via the photoinduced rearrangement of (*E*)-3-arylvinyl-4*H*-chromen-4-ones in high yields was reported.[27]



Scheme 2 Synthesis of (2-aminophenyl)(naphthalen-2-yl)methanones via the photoinduced rearrangement of (*E*)-3-styrylquinolin-4(1*H*)-ones

The (*E*)-3-styrylquinolin-4(1*H*)-one analogues **1** were synthesized according to literature reports.[28–30] The photoinduced rearrangement of (*E*)-3-styrylquinolin-4(1*H*)-one (**1a**) under various conditions was screened and the corresponding results are presented in Table 1. Initially, the irradiation of **1a** in EtOH with a 405-nm lamp (10 W) at

Table 1 Optimization of the Reaction Conditions[a]



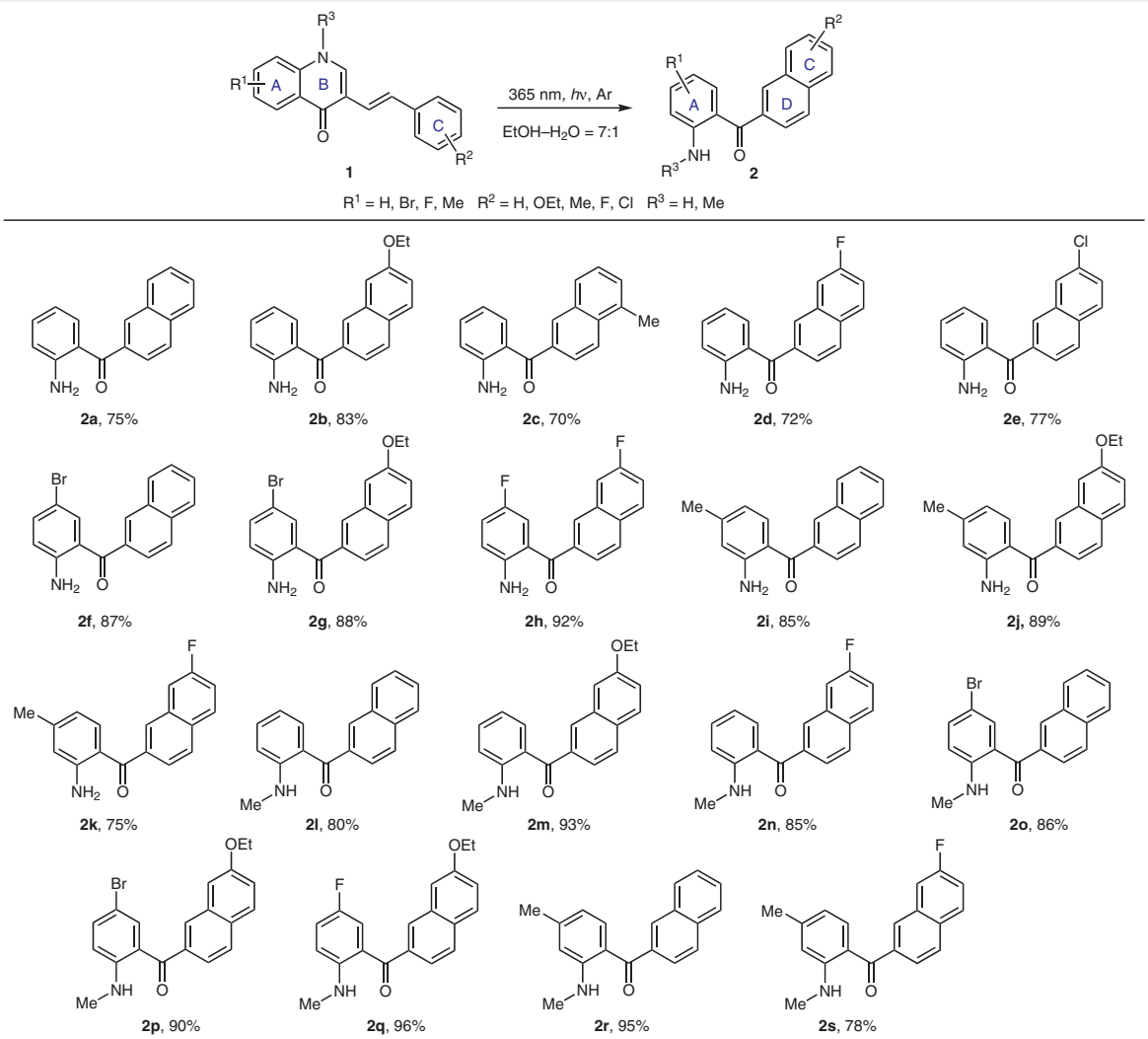
Entry	Solvent (v/v)	λ (nm)	Time (h)	Conversion (%)[b]	Yield (%)[b]
1	EtOH	405	5.0	88	15
2	EtOH	376	5.0	73	38
3	EtOH	365	5.0	87	65 (52)
4	MeOH	365	5.0	96	61 (46)
5	CH_2Cl_2	365	5.0	56	5
6	MeCN	365	5.0	85	17
7	acetone	365	5.0	92	27
8	EtOH–H_2O (9:1)	365	5.0	87	66 (57)
9	EtOH–H_2O (7:1)	365	5.0	88	70 (59)
10	EtOH–H_2O (5:1)	365	5.0	85	66 (58)
11[c]	EtOH–H_2O (7:1)	365	5.0	79	52
12	EtOH–H_2O (7:1)	365	7.0	91	75 (66)
13	**EtOH–H_2O (7:1)**	**365**	**9.0**	**91**	**84 (75)**
14	EtOH–H_2O (7:1)	365	11.0	92	85 (75)

[a] Reaction conditions: Compound **1a** (0.2 mmol, 5 mM) in various solvents (4 × 10 mL) was irradiated at a certain wavelength (10 W) at r.t. under argon atmosphere.
[b] Conversion percentage and yield were determined by ^{1}H NMR with 1,3,5-trimethoxybenzene as internal standard. Isolated yield is displayed in the parentheses.
[c] The concentration of **1a** was 1×10^{-2} mol/L.

room temperature under argon atmosphere for five hours showed a 15% ^{1}H NMR yield of **2a** and 88% conversion of **1a** (Table 1, entry 1). It is interesting that the shorter the wavelength was (with same wattage), the better the yield of **2a** was, obtained yet with similar conversion yields (Table 1, entries 2 and 3), which might be attributed to the higher energy of the light source. Replacement of EtOH with MeOH led to the formation of **2a** in a slightly lower yield (61%, Table 1, entry 4). While, employment of aprotic solvent, e.g. CH_2Cl_2, MeCN, acetone, yielded **2a** in only up to 27% yield (Table 1, entries 5–7). It is important to note that protic solvent[27] and acid[31] could significantly improve the rearrangement efficiency, which is consistent with the references.[27,31]

Interestingly, addition of water could slightly boost the yield of **2a** (66–70%, Table 1, entries 8–10). However, a lower yield of **2a** was observed with increased concentration of **1a** (1×10^{-2} mol/L, 52%, Table 1, entry 11). Finally, the effect of the irradiation time on the yield of **2a** was explored (Table 1, entries 10 and 12–14). With longer irradiation time, a better yield of **2a** was obtained. Since there was barely any difference in the yields of **2a** for 9 hours and 11 hours of irradiation time, irradiation for 9 hours was chosen as the optimal reaction time. Thus, irradiation of **1a** (5 mM) in EtOH–H_2O (7:1) with the UV light (365 nm, 10 W) at room temperature for 9 hours under the argon atmosphere was determined to be the optimal condition, which yielded **2a** in 84% yield.

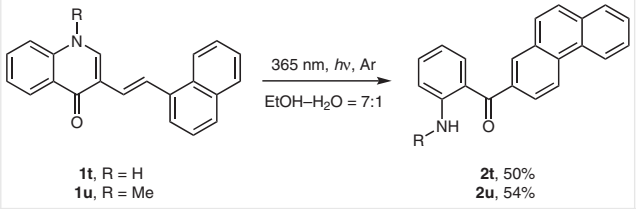
With the optimized reaction conditions in hand, the scope and generality for the rearrangement of **1** was subsequently examined (Scheme 3).[32] It has been found that the presence of electron-donating group on the C-ring



Scheme 3 Reaction scope of (*E*)-3-styrylquinolin-4(1*H*)-ones. Reaction conditions: Irradiation of **1** (0.2 mmol, 5 mM) in EtOH–H_2O (4 × 10 mL, 7:1) with a UV lamp (365 nm, 10 W) at room temperature under the argon atmosphere. The irradiation time of **1a–1k** was 9 hours and **1l–1s** was 4.5 hours. Isolated yields.

could give the corresponding rearrangement products **2** in higher yields compared to those bearing electron-withdrawing groups (**2b** vs. **2d**, **2e** and **2j** vs. **2k**). Regardless of the electron-withdrawing/-donating locations, all the rearrangement products **2** were obtained in good to high yields (70–96%). It is important to note that the presence of methyl group (R^3 = Me) at the nitrogen atom could dramatically shorten the irradiation time by half and give the corresponding rearrangement products **2l**–**2s** in higher yields.

To further explore the functional group tolerance, irradiation of (*E*)-3-[2-(naphthalen-1-yl)vinyl]quinolin-4(1*H*)-one (**1t**) and (*E*)-1-methyl-3-[2-(naphthalen-1-yl)vinyl]quinolin-4(1*H*)-one (**1u**) under the optimal condition gave **2t** and **2u** in 50% and 54%, respectively (Scheme 4).[32]



Scheme 4 Photoinduced rearrangement of **1t** and **1u** under the optimal condition

The UV absorption spectra of **1a** in ethanol [EtOH–H_2O (7:1)] is shown in Figure 1. The typical π → π* maximum absorption peaks at 349 nm (ε = 21010 L·mol^{-1}·cm^{-1}) can be attributed to the existence of the expanding aromatic rings and the wavelength was basically close to the excitation at 365 nm of the reaction.

Based on the literature reports[33–37] and previous work,[27] a plausible mechanism for the formation of **2a** has been proposed and is depicted in Scheme 5. Upon the irradiation of **1a**-(*E*) with UV light (365 nm), the intermediate **1a**-(*Z*) is formed via photoisomerization, followed by a conrotatory 6π-electron-cyclization to give the intermediate **A**. A similar isomerization/cyclization has been well discussed and reviewed.[27,33] The proposed thermal suprafacial [1,9]-H shift leads to the formation of intermediate **B**, which might

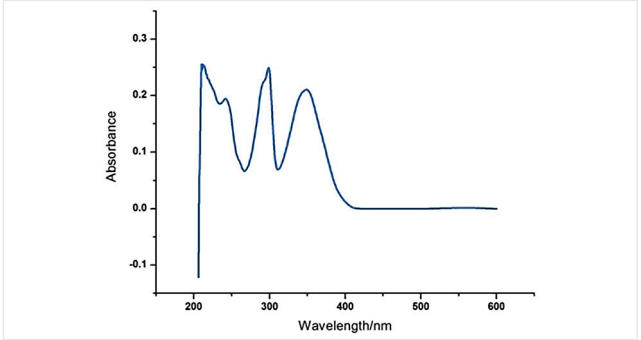


Figure 1 UV absorption spectra of **1a** in EtOH–H_2O (7:1)

be accelerated/facilitated by the presence of carbonyl group.[27,38] The final rearrangement product **2a** was isolated as the only product due to the restoration of aromaticity via proton migration as well as the opening of the heterocyclic quinolin-4(1*H*)-one ring at the C10–N bond. Additionally, the structure of **2a** could be further stabilized by the formation of an intramolecular hydrogen bond between the amino group and the carbonyl group, which pushes the formation of rearrangement product.

In summary, we have developed a highly efficient and environmentally friendly method for the synthesis of (2-aminophenyl)(naphthalen-2-yl)methanones by irradiation of (*E*)-3-styrylquinolin-4(1*H*)-ones in EtOH–H_2O (7:1) with 365-nm UV lamps at room temperature under Ar atmosphere. Compared with the previous work,[12–16] the advantages of the described photoinduced rearrangement are: a) transition-metal-catalyst-free, b) additives-free, c) uses ethanol as the solvent, d) tolerates various functional groups, e) involves the construction of naphthalene ring during the rearrangement, and f) exhibits high atom efficiency with high yield.

Funding Information

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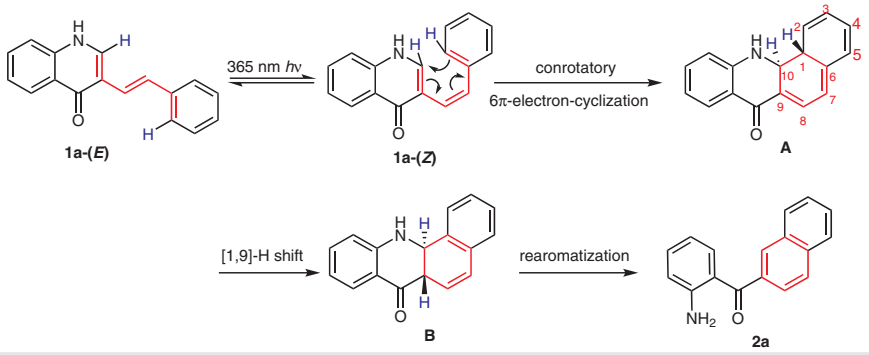

Scheme 5 Plausible reaction mechanism for the photoinduced rearrangement of **1a**

Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0037-1610176.

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(32) **General Procedure for the Synthesis of (2-Aminophenyl)(naphthalen-2-yl)methanones** (**2a–2u**): (*E*)-3-styrylquinolin-4(1*H*)-ones **1** (0.20 mmol, 5 mM) was dissolved or suspended in EtOH–H_2O (7:1, 40 mL) in four quartz tubes (4 × 10 mL). The solution/suspension was bubbled with argon (3 × 2 min) and sealed. The resulting mixture was irradiated with a UV lamp (365 nm, 10 W) at r.t. for 9.0 h (**1a–1k**, **1t**, **1u**) or 4.5 h (**1l–1s**). The reaction mixture in four quartz tubes was combined and volatiles were removed under reduced pressure. The oily residue was column chromatographed (petroleum ether/EtOAc = 20:1) to give (2-aminophenyl)(naphthalen-2-yl)methanones **2**.
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