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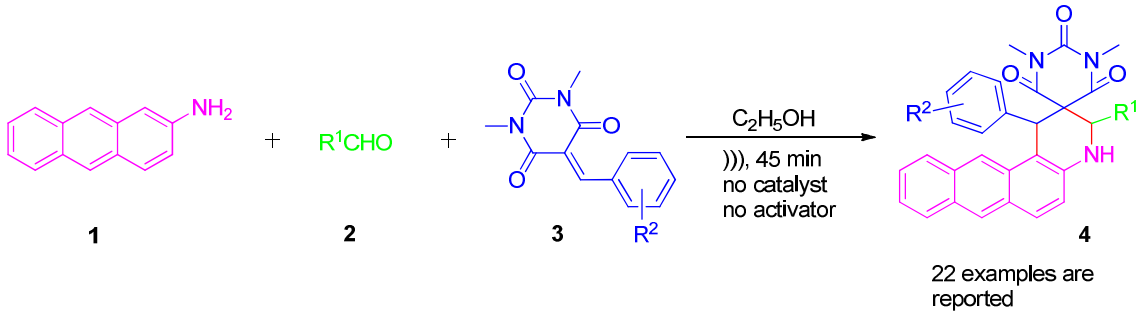
Spironaphthoquinolines can be obtained with good yields in an ultrasound-mediated pseudo one-pot condition from easily available starting materials. The association of the process with 'atom-economy' and 'procedural simplicity' makes it an attractive protocol to synthesize desired compounds.



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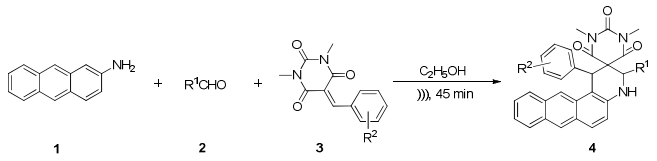
An atom-economical synthesis of spironaphthoquinolines from a mixture of 2-aminoanthracene, aldehyde, and Knoevenagel condensed product was developed. The association of the method with 'use of ultrasounds' and 'procedural simplicity' makes it an attractive protocol for formation of novel and important heterocycles.

Introduction

Organic synthesis requires the use of energy, chemical ingredients, catalysts, ligands and covers operations from separation to distribution after the end of the reaction. Chemists or industrial workers face many questions related to health and safety during these processes. Additionally, use of chemicals and their disposition as waste also raise the level of environmental problems. In this scenario, practice of 'Safety in academic/industrial chemistry laboratories' and/or 'Sustainable chemistry' has attracted attention and become an alluring topic for discussion in both scientific as well as governmental sectors of society.[1] The policy of UAOS (ultrasound-assisted organic synthesis) has proven to be a particularly significant discipline for meeting the goals for environmental problems by minimizing waste production and energy consumption.[2] The ultrasonic physical and chemical effects arise from the phenomenon of 'bubble formation and collapse,' referred to as 'cavitation' which produces extreme favorable conditions locally and consequently induce the formation of chemical species not easily achieved in conventional conditions.[3] Thus, UAOS has attracted extensive interest with beautiful characteristics such as selectivity, reaction time, catalyst and solvent recyclability, and operational simplicity.[4] These advantages make the acoustic radiation treatment an interesting alternative technique to synthesize essential organic compounds.[5]

The nucleus of naphthoquinoline is one of the appealing heterocyclic compounds and draws considerable attention from chemists together with biologists for their medicinal importance. For example, in a recent report Carrigan's group synthesized naphthoquinoline dicarboxylic acids which were enriched with vesicular glutamate transporter inhibition property.[6a] Compounds containing naphthoquinoline moiety were found to inhibit apoptosis signal-regulating kinase 1 (ASK1).[6b] Dzieduszycka[6c] and Bu's[6d,e] laboratories also carried out successful experiments and concluded with a positive note on antitumor activities of naphthoquinolines. It can also be mentioned that Dynemicin A, an enediyne antibiotic, indicates about the antitumor nature of naphthoquinoline templates.[6f] These discoveries have inspired us to develop efficient synthetic routes for generation of naphthoquinoline containing heterocyclic scaffolds.

We have recently found that 1-aminonaphthalene is useful for foundation of desired products with good yields.[7a] We believe that fusion of aromatic ring/rings and/or modification in the position of amino group may lead to products which will provide informative set of structure-activity relationships (SARs) for their growth-inhibitory properties in tumor cells. Moreover, our expected products, *i.e.* naphtho[2,3-*f*]quinolines are promising candidates for organic electroluminescent media with their luminescent properties in blue region.[7b] In addition, our interest on UAOS is decorated by the production of 7-methyl substituted pyrido[4,3-*d*]pyrimidines.[7c] Amalgamation of these facts ignited us to consider 2-aminoanthracene as aromatic amine to construct products in sonochemical condition. As a consequence of our practice to synthesize novel and complex heterocyclic compounds[7a,c-e] we herein would like to describe a facile synthesis of spironaphthoquinoline derivatives (Scheme 1). To the best of our knowledge this is the first report on preparation of spironaphthoquinoline derivatives applying sonochemistry with 2-aminoanthracene as one of the starting materials.



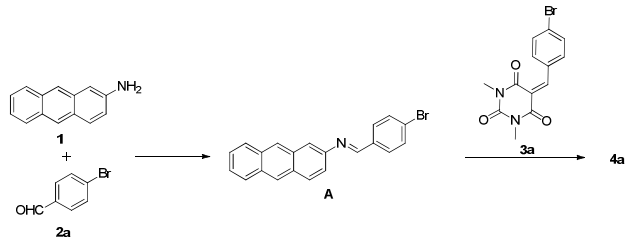
Scheme 1 Sonochemical synthesis of spironaphthoquinolines.

Results and discussion

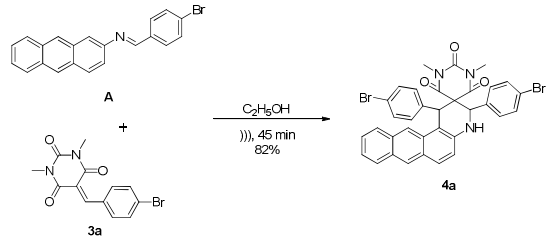
In our reaction strategy, the utilization of ethanolic solution of a 1:1:1 mixture of 2-aminoanthracene **1**, 4-bromobenzaldehyde **2a**, and 5-(4-bromobenzylidene)-1,3-dimethylpyrimidine-2,4,6-trione **3a** under sonochemical conditions afforded 1,3-bis(4-bromophenyl)-1′,3′-dimethyl-3,4-dihydrospiro[naphtho[2,3-*f*]quinoline-2,5′-pyrimidine]-2′,4′,6′-trione **4a** after work-up in very excellent yield (87%). The work-up procedure of the reaction is very simple. The reaction mixture was allowed to settle at room temperature after the ultrasound irradiation of 45 min. The pure

product was obtained by simple Buchner filtration of the heavy precipitate which was formed by the addition of cold distilled water into the reaction mixture treated with ultrasounds. The product was further purified by washing with cold ethanol. The structure of the compound was then established from different spectroscopic analyses. The ^{1}H NMR spectra of the compound **4a** showed the presence of one NH proton at δ 4.64 ppm and two tertiary CH protons at δ 4.92 and 5.69 ppm as singlets. The characteristic signal for two N-methyl groups appeared at δ 2.81 and 3.14, 'respectively'. The IR spectra showed the presence of the NH group at 3393 cm^{-1}. The *cis* orientation of two C-H protons of the compound **4a** was found by recording its bidimensional NOE NMR spectra.

Although the detailed mechanistic study of this reaction remains to be fully performed, the formation of compound **4a** can be explained by Scheme 2. We assume that an imine **A** is formed between 2-aminoanthracene **1** and 4-bromobenzaldehyde **2a** which then undergoes a cycloaddition reaction with 5-(4-bromobenzylidene)-1,3-dimethylpyrimidine-2,4,6-trione **3a** to form the final product **4a**. To verify our proposed mechanism, a two component reaction was carried out between a pre-formed imine, *N*-(4-bromobenzylidene)anthracen-2-amine **A** and 5-(4-bromobenzylidene)-1,3-dimethylpyrimidine-2,4,6-trione **3a** under the same reaction conditions (Scheme 3). As expected, the derivative **4a** was obtained in comparable yield (82%). We further confirmed our mechanistic postulate by monitoring the model reaction at different time intervals (by thin layer chromatography) and observed that an intense spot appeared with R_f value 0.71 (ethyl acetate:hexane 3:7) within 8 minutes which is accompanied by enhancement of the temperature of the reaction mixture (100 ^{o}C; the temperature remained constant till the conclusion of the reaction). After 10 minutes we stopped the reaction, allowed to settle down at room temperature, and isolated the compound responsible for the spot whose NMR spectra corresponded to **A**. These consequences showed that the experimental results were highly consistent with the proposed mechanism.



Scheme 2 Mechanistic postulate for the formation of **4a**.



Scheme 3 Two-component synthesis of **4a**.

Our initial effort on this reaction in order to achieve suitable reaction condition was made with the treatment of ultrasounds to a 1:1:1 mixture of 2-aminoanthracene **1**, 4-bromobenzaldehyde **2a**, and 5-(4-bromobenzylidene)-1,3-dimethylpyrimidine-2,4,6-trione **3a** under a variety of solvent systems for 30 minutes. The starting compound 5-(4-bromobenzylidene)-1,3-dimethylpyrimidine-2,4,6-trione **3a** can be easily obtained following Knoevenagel condensation between 1,3-dimethylpyrimidine-2,4,6-trione and 4-bromobenzaldehyde.[8] It was found that when water was used as the reaction medium without any external template the yield of product was very low. The scheme was found to be friendly in all solvents such as DCM, DCE, THF, ethanol, methanol, dioxane, toluene, DMF, and DMSO under ultrasound conditions and provided good yields. However, reflection of toxic effects from most of the organic solvents encouraged us to consider ethanol as the solvent for all further reactions. An increase in the time duration of ultrasound irradiation (45 min) improved the yield of the product but a further increase in time (60 min) did not indicate about any enhancement in the yield of the product (Table 1). Therefore, ultrasound irradiation for 45 minutes in ethanolic medium was found to be the optimized reaction conditions to give the better yield of the desired product.

Table 1 Optimization studies for synthesis of **4a**[a]

Entry	Solvent	Time	Yield[b] (%)
1	Water	30 min	Trace
2	DCM	30 min	45
3	DCE	30 min	48
4	THF	30 min	45
5	EtOH	30 min	83
6	MeOH	30 min	84
7	Dioxane	30 min	67
8	Toluene	30 min	72
9	DMF	30 min	70
10	DMSO	30 min	65
11	EtOH	45 min	87
12	EtOH	60 min	87

[a] Reaction conditions: a mixture of 2-aminoanthracene (**1**, 1 mmol), 4-bromobenzaldehyde (**2a**, 1 mmol), and Knoevenagel condensed product (**3a**, 1 mmol) was dissolved in different solvents (10 ml) and ultrasonicated for appropriate time. [b] Isolated yield.

The feasibility of the reaction scheme was then verified for library production of spironaphthoquinoline derivatives employing different aromatic, heteroaromatic, and conjugated aromatic aldehydes and the results are summarized in Table 2. During our generalization studies we were satisfied to find that the reaction was effective with aldehydes bearing electron-withdrawing and -donating substituents on the aromatic ring. It can be stated here that in most of the cases aldehydes with electron withdrawing groups on the aromatic ring gave better yield of products in comparison to aromatic aldehydes with electron donating groups. It is also noteworthy that aromatic aldehydes containing *para*-substituted functionality gave better yields than *meta*-substituted one (Table 2, entries 4, 7) and these, in turn, gave better yields than their *ortho*-substituted counterpart

(Table 2, entries 7, 8). Applications of heteroaromatic and conjugated aromatic aldehydes gratified our methodology indicating their excellent impacts over the yields of desired products (Table 2, entries 10-12). These findings stimulated our group to further generalize the reaction by varying aldehydes and Knoevenagel condensed molecules and, the results obtained are summarized in Table 2, entries 13-22. The yield of the reaction was found to be satisfactory in all the cases. We were excited to notice that Knoevenagel condensed molecule with electron-withdrawing and -donating substituents on the aromatic ring underwent the reaction smoothly. On the other hand, we were unfortunate to obtain our desired products using aliphatic aldehydes even after prolonged reaction time. All the products obtained were characterized by spectroscopic analyses.

Table 2 Direct synthesis of spironaphthoquinolines **4a-x**[a]

Entry	R^1	R^2	Product	Yield[b] (%)
1	4-Br (**2a**)	4-Br (**3a**)	**4a**	87
2	4-CH_3 (**2b**)	4-OCH_3 (**3b**)	**4b**	86
3	4-Br (**2a**)	4-OCH_3 (**3b**)	**4c**	89
4	4-Cl (**2c**)	4-OCH_3 (**3b**)	**4d**	88
5	4-F (**2d**)	4-OCH_3 (**3b**)	**4e**	88
6	4-NO_2 (**2e**)	4-OCH_3 (**3b**)	**4f**	88
7	3-Cl (**2f**)	4-OCH_3 (**3b**)	**4g**	86
8	2-Cl (**2g**)	4-OCH_3 (**3b**)	**4h**	84
9	2-CH_3 (**2h**)	4-OCH_3 (**3b**)	**4i**	81
10	C_6H_5CH=CH (**2i**)	4-OCH_3 (**3b**)	**4j**	85
11	C_4H_3O (**2j**)	4-OCH_3 (**3b**)	**4k**	83
12	C_4H_3S (**2k**)	4-OCH_3 (**3b**)	**4l**	83
13	4-OCH_3 (**2l**)	4-OCH_3 (**3b**)	**4m**	88
14	4-Br (**2a**)	4-Cl (**3c**)	**4n**	88
15	4-Br (**2a**)	4-F (**3d**)	**4o**	87
16	4-Br (**2a**)	4-NO_2 (**3e**)	**4p**	87
17	4-Br (**2a**)	2-CH_3 (**3f**)	**4q**	85
18	2-CH_3 (**2h**)	4-Br (**3a**)	**4r**	83
19	2-CH_3 (**2h**)	4-F (**3d**)	**4s**	83
20	4-CH_3 (**2b**)	4-NO_2 (**3e**)	**4t**	82
21	4-CH_3 (**2b**)	4-Cl (**3c**)	**4u**	81
22	4-CH_3 (**2b**)	2-CH_3 (**3f**)	**4v**	80

[a] Reaction conditions: 2-aminoanthracene (**1**, 1 mmol), aldehyde (**2**, 1 mmol), and Knoevenagel condensed product (**3**, 1 mmol) was dissolved in ethanol (10 ml) and ultrasonicated for 45 min. [b] Isolated yield.

We extended our study to examine the scope of the reaction scheme in conventional heating process. Thus, a 1:1:1 mixture of 2-aminoanthracene **1**, 4-bromobenzaldehyde **2a**, and 5-(4-bromobenzylidene)-1,3-dimethylpyrimidine-2,4,6-trione **3a** when refluxed in ethanol for 5 hours, yielded 1,3-bis(4-bromophenyl)-1′,3′-dimethyl-3,4-dihydrospiro[naphtho[2,3-*f*]quinoline-2,5′-pyrimidine]-2′,4′,6′-trione **4a** in a yield of 75%. Further increase in reaction time resulted in decomposition of products thereby leading to lower yields. It can be added that no exciting results were noticed when the reaction mixture was refluxed for less than 5 hours where *N*-(4-bromobenzylidene)anthracen-2-amine **A** was obtained in higher amounts (72%) in comparison to product **4a** (60%). We also performed a set of reactions in different reaction times under classical conditions which is highlighted by Table 3. These observations made it clear that the reaction is assisted by ultrasound radiation with favorable reaction time.

Table 3 A set of comparative study of yield vs time under heating conditions[a]

Entry	R^1	R^2	Product	Time (h)	Yield[b] (%)
1	4-Br	4-Br	**4a**	5/4	75/60
2	4-Br	4-OCH_3	**4c**	6/4	72/61
3	C_4H_3O	4-OCH_3	**4k**	5/4	66/50
4	4-Br	4-Cl	**4n**	5/3	73/55
5	4-CH_3	4-NO_2	**4t**	5/4	70/57

[a] Reaction conditions: 2-aminoanthracene (**1**, 1 mmol), aldehyde (**2**, 1 mmol), and Knoevenagel condensed product (**3**, 1 mmol) was refluxed without catalyst in ethanol (10 ml). [b] Isolated yield.

Conclusions

In summary, we have demonstrated the first catalyst-free synthesis of spironaphthoquinolines through the application of ultrasound-assisted organic synthesis. Excellent yields of products can be obtained from this atom-economical procedure without the requirement of the traditional purifications, column chromatography, and recrystallization techniques. The filtrate, which contained the solvent ethanol, was successfully utilized for the second batch of the reaction. Overall, our developed methodology can be regarded as a valuable protocol for production of bioactive nitrogen containing compounds and will create interest among chemists towards sustainable chemistry.

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Notes and references

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