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# General non-catalytic approach to spiroacenaphthylene heterocycles: multicomponent assembling of acenaphthenequinone, cyclic CH-acids and malononitrile

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ABSTRACT

The new type of non-catalytic cascade reaction was found: the direct multicomponent reaction of acenaphthenequinone, cyclic CH-acids, and malononitrile to form spiroacenaphthylene heterocycles. The direct heating in water acenaphthenequinone, cyclic CH-acids, and malononitrile at 80 °C results in the formation of spiroacenaphthylene heterocycles in 90–95% yields. Thus, a new simple and efficient green 'one-pot' method to synthesize substituted spiroacenaphthylene frameworks was found directly from simple starting compounds. The application of this convenient green multicomponent method is also beneficial from the viewpoint of diversity-oriented large-scale processes.



## 1. Introduction

The discovery of new synthetic methodologies that facilitate the preparation of organic compounds is a focal point of research activity in the field of modern organic, bioorganic, and medicinal chemistry.[1] One approach to address this challenge involves the development of multicomponent reactions (MCRs), in which three or more reactants are combined together in a single reaction flask to generate a product incorporating most of the atoms contained in the starting materials.[2]

In recent years the concept of 'privileged medicinal structures or scaffolds'[3] has emerged as one of the guiding principles of drug discovery process. These privileged scaffolds commonly consist of rigid hetero ring systems, among them spiro-chromene, -pyran, -pyrimidine, and -pyrazole cycles with well-defined orientations for target recognition.[4]

The chromene moiety often appears as an important structural component in both biologically active and natural compounds.[5] Moreover, in recent years functionalized chromenes and spirochromenes have played an ever increasing role in the synthetic approaches to promising compounds in the field of medicinal chemistry.[6]

Recently we suggested an electrocatalytic process as a facile and convenient way to create diversely substituted medicinally privileged 2-amino-4*H*-chromene scaffold directly from salicylaldehydes and two different CH-acids.[7] But an electrocatalytic procedure in the case of multicomponent reaction of acenaphthenequinone, cyclic CH-acids, and malononitrile was not successful.

Ammonium chloride (20 mol %) was found as catalyst for the multicomponent reaction of acenaphthenequinone, 1,3-cyclohexanedione or dimedone, and malononitrile for the formation of spiroacenaphthylenechromenes in 75–90% yields (4 examples).[8] Triethylamine (200 mol %) recently has been used to catalyze general multicomponent reaction of acenaphthenequinone, containing carbonyl group CH-acids and malononitrile with the formation of spiroacenaphthylenes in 40–85%.[9] This general method needs a long reaction time (1) heating in boiling ethanol for 4–8 h and (2) then crystallization at 4 °C overnight; moreover a large excess of catalyst ($Et_3N$, 200 mol %) was used and only moderate yields of spiroacenaphthylenes were achieved.

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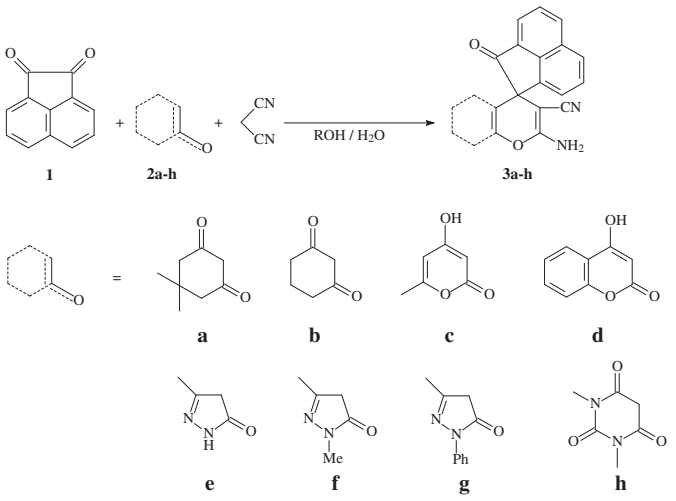
Thus, the two known procedures for the synthesis of spiroacenaphthylenes are catalytic[8,9] (and use large amount of catalyst: 20–200%). Both of them have their merits, but the essence of facile and convenient non-catalytic MCR methodology for the synthesis of spiroacenaphthylenes should yet to be developed. Thus, we were prompted to design a convenient and facile non-catalytic methodology for the efficient synthesis of functionalized spiroacenaphthylenes in water as a 'green' solvent.

## 2. Results and discussion

In the present study we report our results on the non-catalytic transformation of acenaphthenequinone **1**, cyclic CH-acids **2a**–**h**, and malononitrile into spiroacenaphthylene derivatives **3a**–**h** (Scheme 1, Tables 1 and 2).




**Scheme 1.**

**Table 1**
Non-catalytic transformation of acenaphthenequinone **1**, dimedone **2a** and malononitrile into spiro[acenaphthylene-1,4′-chromene] **3a**[a]

| Entry | Solvent | Temperature, °C | Time, min | Yield of **3a**[b] (%) |
|---|---|---|---|---|
| 1 | MeOH | 20 | 15 | 15 |
| 2 | MeOH | 55 | 15 | 83 |
| 3 | EtOH | 78 | 15 | 92 |
| 4 | PrOH | 80 | 15 | 93 |
| 5 | $H_2O$[c] | 80 | 15 | 95 |
| 6 | $H_2O$[c] | 80 | 10 | 89 |
| 7 | $H_2O$[c] | 80 | 5 | 83 |

[a] Compound **1** (5 mmol), **2a** (5 mmol), malononitrile (5 mmol), solvent 10 mL.
[b] Yield of isolated **3a**.
[c] Solvent 3 mL.

The electrocatalytic reaction of acenaphthenequinone, dimedone, and malononitrile in methanol in the presence of sodium bromide as electrolyte at room temperature resulted in the formation of spiroacenaphthylene **3a** in 37% yield in 15 min when 0.1 F/mol of electricity was passed through the cell. The analogous process in methanol without electrolysis and in the absence of any catalyst resulted in spiroacenaphthylene **3a** formation in 15% yield (Table 1, entry 1). In methanol at 55 °C spiroacenaphthylene **3a** was obtained in 83% yield (Table 1, entry 2). The highest yields of **3a** under non-catalytic conditions were achieved with using EtOH, *n*-PrOH, and $H_2O$ as solvents at 78–80 °C (92–95%). A decreased reaction time (10 min) led to a lower yield (85%) of spiroacenaphthylene **3a** (Table 1, entry 6). Under the optimal non-catalytic conditions [i.e., water as solvent, 80 °C and 15 min reaction time] the non-catalytic transformation of acenaphthenequinone **1**, with cyclic CH-acids **2a**–**g** and malononitrile were transformed into corresponding substituted spiroacenaphthylenes **3a**–**g** in 90–95% yields (Table 2). Only in the case of *N*,*N*′-dimethylbarbituric acid **2h** the solvent (water) was changed to *n*-propanol to achieve a better yield of spiroacenaphthylene **3h** (93%, entry 8, Table 2); in water only 78% yield of **3h** was obtained.

Among spiroacenaphthylenes **3a**–**h**, four compounds **3a,b,d,e** were reported earlier.[8,9] But in our case the melting points of **3a**,**b** are at least on 20–35 °C higher than reported earlier.

Two special experiments were carried out to check the mechanism of the new non-catalytic multicomponent reaction. The reaction of acenaphthenequinone **1** with malononitrile in water at 80 °C resulted in the formation of the Knoevenagel condensation product, namely (2-oxoacenaphthylen-1(2*H*)-ylidene)malononitrile **4** in 98% yield in 15 min.

From acenaphthenequinone **1** and dimedone **2a** under the same conditions only the aldol addition product, namely 2-(1-hydroxy-2-oxo-1,2-dihydroacenaphthylen-1-yl)-5,5-dimethylcyclohexane-1,3-dione **5** was obtained in 81% yield.

Taking into consideration all this data, the following mechanism is proposed for the direct non-catalytic chain cascade transformation of acenaphthenequinone **1**, cyclic CH-acids **2**, and malononitrile into spiroacenaphthylenes **3** (Scheme 2, example for cyclic acid **2a** is shown). The initiation step of this non-catalytic chain process begins with the dissociation of a molecule of malononitrile, which is increased by the heating and leads to the formation of malononitrile anion (Scheme 2).

The subsequent reaction between the malononitrile anion and acenaphthenequinone **1** takes place with the formation of the Knoevenagel adduct **4** (Scheme 3).

The Michael addition of cyclic CH-acid **2a** to the Knoevenagel adduct **4** followed by intramolecular cyclization leads to the corresponding spiroacenaphthylene **3a** (Scheme 3).

## 3. Conclusion

In conclusion, the new simple non-catalytic muticomponent process in water as a solvent can produce an effective transformation of acenaphthenequinone **1**, cyclic CH-acids **2a**–**h**, and malononitrile into heterocyclic spiroacenaphthylene frameworks **3a**–**h** in high 90–95% yields. This novel non-catalytic chain cascade process offers a facile and convenient way to create substituted medicinally relevant spiroacenaphthylene heterocycles—the approved basis for the generation of molecule ligands with different biomedical properties including pronounced anticancer activities. Compare to known MCR protocols, this non-catalytic cascade procedure represents the most efficient and 'green' approach to the reliable design of heterocyclic spiroacenaphthylene frameworks. The developed non-catalytic multicomponent procedure utilizes simple equipment, and requires reasonable starting materials. It is easily carried out, the reaction products were isolated by an easy work-up procedure, and do not need any further purification steps. Finally, this new efficient multicomponent method to synthesize medicinally relevant spiroacenaphthylene heterocycles represents the combination of the synthetic virtues of conventional MCR strategy with ecological benefits and convenience of non-catalytic chain 'green' processes in water. Therefore, this novel type of MCR brings us a step closer to the notion of 'ideal synthesis'.[10]

## 4. Experimental section

### 4.1. General remarks

All melting points were measured with a Gallenkamp melting point apparatus and are uncorrected. $^1$H and $^{13}$C NMR spectra were recorded with a Bruker Avance II-300 spectrometer at ambient