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Facile reaction of thiols and amines with alkyl 4-hydroxy-2-alkynoates in water under neutral conditions and ultrasound irradiation

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A B S T R A C T

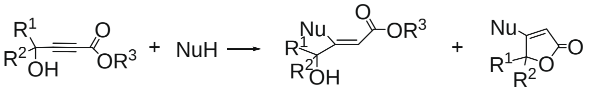
This Letter describes an alternative protocol for the Michael addition of thiols to 4-hydroxy-2-alkynoates. The reaction proceeds at room temperature in water under ultrasound irradiation. With amines instead of thiols a sequential conjugate addition/lactonization reaction leads to important 4-amino-furan-2-one derivatives.

Environmental concerns demand clean reaction processes by moving away from highly volatile and harmful organic solvents.[1] Water has attracted increasing attention over the last years in response to calls for sustainable chemistry.[2] In addition to its abundance and for economical and safety reasons, water has unique physical and chemical properties, and by utilizing these it would be possible to realize reactivity and selectivity that cannot be attained in organic solvents.[3] Then, the potential benefits of using aqueous medium for organic transformations including pericyclic reactions, free-radical reactions, aldol reactions, Michael additions, and organometallic reactions have been investigated.[4] Work-up and purification can be carried out by simple phase separation techniques. However, organic solvents are still used instead of water because most organic substrates are not soluble in water, and as a result, water cannot function as a reaction medium. Consequently, either organic co-solvents and/or substrate modifications are almost always employed in preparative reactions performed in water to improve the solubility of substrates.[5] A possible alternative could be represented by the development of organic microenvironments in the aqueous phase[6] through the use of surface-active reagents.[7] The same objective can be achieved by using MW heating.[8] Ultrasound is in many instances a complementary technique[9] to microwave for driving efficiently chemical reactions in water.[10]

As part of our ongoing research devoted to the development of green organic chemistry using water as the reaction medium,[11] we report an alternative procedure for the Michael-type addition of thiols or amines to 4-hydroxy-2-alkynoates[12] in water under neutral conditions and ultrasound irradiation (Scheme 1).

Sonochemistry shares with sustainable chemistry the search for milder and faster procedures in organic synthesis and can be readily adapted for scale-up.[13] Even if the Michael addition of amines and thiols to α,β-unsaturated ketones in water under neutral conditions was widely investigated,[14] to the best of our knowledge there is only a report of Michael addition of thiols or amines to dimethylacetylene dicarboxylate (DMAD) in water.[15] α,β-Unsaturated ynoates are expected to be poorer Michael acceptors relatively to DMAD and α,β-unsaturated ynones.[16]

We chose the addition of 2-naphthylthiol **2a** to 4-hydroxy-4-*p*-tolyl-but-2-ynoic acid ethyl ester[17] **1a** as the model system. The 4-hydroxy-2-alkynoates **1a** was added to a vessel flask containing 3 mL of water, immersed in a water bath (rt) and sonicated for 5 min. Afterwards the 2-naphthylthiol **2a** was added to the reaction mixture which was irradiated with ultrasound till completion



Nu = ArS, RS, ArNH, RNH, R_2N

Scheme 1. Michael-type addition of thiols and amines to 4-hydroxy-2-alkynoates **1**.

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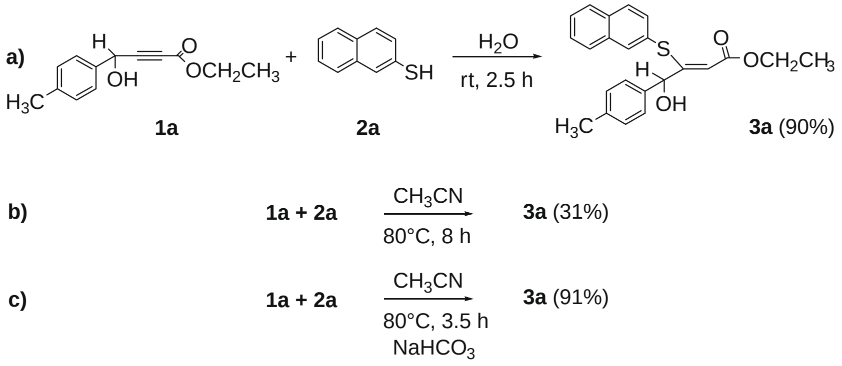


Scheme 2. Addition of 2-naphthylthiol **2a** to 4-hydroxy-4-*p*-tolyl-but-2-ynoic acid ethyl ester **1a**.

of the reaction. Interestingly only the formation of the only *Z* isomer **3a** in 90% yield was observed (Scheme 2a). By contrast, it was reported[14] that in the addition of **2a** to DMAD in water, the *E* isomer was the major product and the *E*/*Z* ratio was 0.67. Analogously, sulfur nucleophile addition reactions to β-(2-aminophenyl)-α,β-ynones proceeded with high *E* stereoselectivity and the stereochemical outcome resulted in the subsequent cyclization reaction.[18] In our case the formation of the *E* isomer can be ruled out because the formation of the corresponding 4-substituted-5*H*-furan-2-one derivative **4** has not been observed.

To investigate the advantageous role of water as a solvent for this method, comparative reaction was carried out in CH_3CN. We failed to obtain **3a** in satisfactory yield under neutral conditions by reacting **1a** with **2a** in CH_3CN at 80 °C (Scheme 2b). Accordingly to the results observed on the synthesis of β-keto-1,3-dithianes from conjugated ynones,[16] the Michael addition of **2a** to **1a** in CH_3CN at 80 °C proceeded in similar yield than in water at rt only under basic conditions (Scheme 2c).

The plausible role of water in promoting the reaction can be rationalized by the hydrogen bond formation between water and the carbonyl of the 4-hydroxy-2-alkynoate which increases the electrophilic character of the β-carbon of the α,β-unsaturated ynoate. Simultaneously, activation of the thiol can take place in dependence on its hydrogen bond formation capability. The hydrogen in water works as a Brønsted acid. Also, the oxygen in water may coordinate with the hydrogen of thiol, and as a result, functions as a Brønsted base. This dual activation mode[19] by water may be important in promoting Michael addition reactions more efficiently and under milder neutral conditions than in CH_3CN.

The scope of the reaction was investigated using a range of thiols **2a–d** and 4-hydroxy-2-alkynoates **1a–c** (Table 1, entries 1–9).[20] The nucleophilic addition to 4-hydroxy-2-alkynoates of aryl thiols proceeded stereoselectively to give exclusively the (*Z*)-4-hydroxy-3-arylsulfanyl-2-alkenoates **3a–f** in 63–90% yields. A worsening of the stereoselectivity of the addition reaction was observed with alkyl thiols **2e–f** (Table 1, entries 7–9): the 4-alkylsulfanyl-5*H*-furan-2-ones **4a–b** were isolated as minor products.

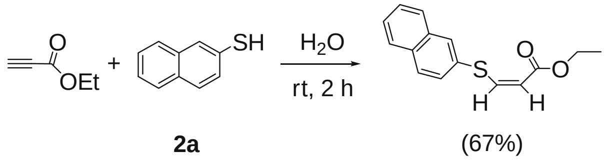
Interestingly, the procedure can be extended to other alkynoates. The *Z* isomer was still the major product in the reaction of **2a** with the ethyl propiolate. The *E* isomer was isolated in 5% yield together with the product of a double conjugate addition of **2a** to ethyl propiolate (5% yield) (Scheme 3). The stereochemistry of the *Z* and *E* isomers was assigned on the basis of the coupling constants (10.0 Hz vs 15.0 Hz).

A conjugate addition/cyclization domino reaction leading to the 4-substituted-5*H*-furan-2-one derivatives **4** was prevalent when nitrogen nucleophiles were used instead of thiols as reagents under the same reaction conditions (Scheme 4; Table 1, entries 10–16). β-Amino-α,β-unsaturated esters **5** are typical push–pull ethylenes, which can undergo *Z* to *E* isomerization.[21]

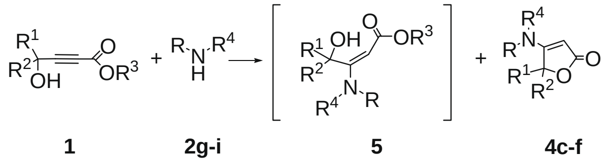
4-Aminofuranones are very interesting heterocyclic derivatives, since they are useful precursors for the preparation of tetronic acids,[22] whose biological activity is well known.[23] Moreover, several molecules incorporating the 4-amino-5*H*-furan-2-one core have shown interesting pharmacological activity.[24] It has been previously reported that the formation of enamine **5** was an energetically favored process in CH_2Cl_2, but the lactonization required acidic conditions and thermal activation (HCl, 2PrOH, reflux).[25]

Very likely, the sequential lactonization reaction observed under our milder reaction conditions is a consequence of the role played by water as a Brønsted acid catalyst both in Michael addition and in the transesterification step. The application of ultrasound irradiation significantly increased the reaction rate and yield compared to the traditional stirring (Table 1, entries 10 and 11). In order to show the general applicability of the method, the sequential amination/lactonization reaction of 4-hydroxy-2-alkynoates in water under ultrasound irradiation was studied by using structurally diverse amines. While when primary amines were used as nucleophiles only the corresponding 4-amino-2(5*H*)-furanones were isolated as products, with the secondary aliphatic piperidine **2j** the lack of selectivity was observed due the competitive formation of the amide derivatives **6** (Scheme 5).[26]

In summary, this Letter describes an efficient protocol for the highly regioselective Michael addition of thiols to 4-hydroxy-2-alkynoates in water under ultrasound irradiation. It is noteworthy that the present reactions proceeded without the addition of any acid or base. Significant rate acceleration is observed in water com-



Scheme 3. Addition of 2-naphthylthiol **2a** to ethyl propiolate.



Scheme 4. Conjugate addition/cyclization reaction of 4-hydroxy-2-alkynoates **1** with amines **2g–i**.

Table 1

Reaction of thiols[a] and amines[a] **2** with 4-hydroxy-2-alkynoates **1**

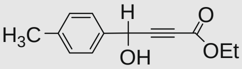
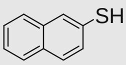
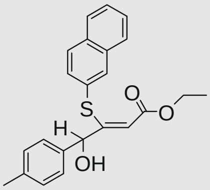
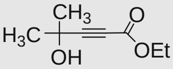
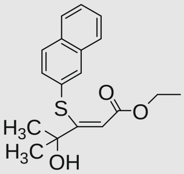
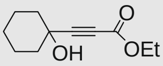
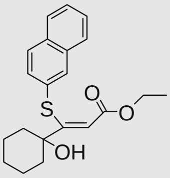
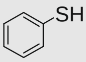
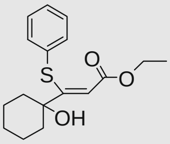
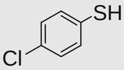
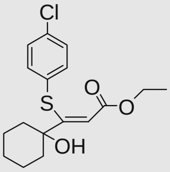
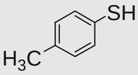
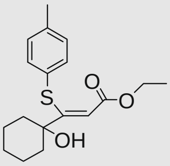
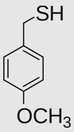
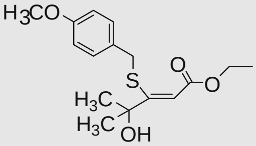
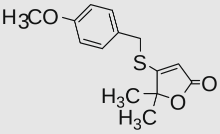
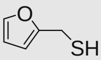
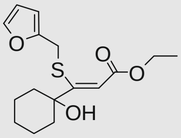
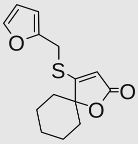
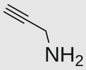
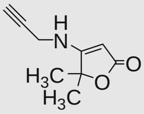
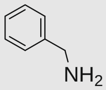
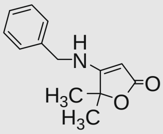
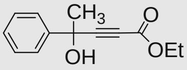
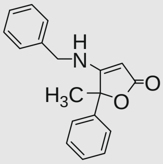
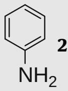
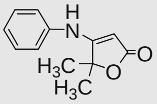
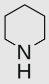
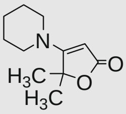
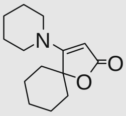
Entry	4-Hydroxy-2-alkynoates **1**	NuH **2**	Time (h)	Product **3** (yield%)[b]	Product **4** (yield%)[b]
1	 **1a**	 **2a**	2.5	 **3a** (90)	
2	 **1b**	**2a**	1.5	 **3b** (63)	
3	 **1c**	**2a**	2.5	 **3c** (67)	
4	**1c**	 **2b**	2	 **3d** (63)	
5	**1c**	 **2c**	1.5	 **3e** (70)	
6	**1c**	 **2d**	1.5	 **3f** (67)	
7	**1b**	 **2e**	2.5	 **3g** (59)	 **4a** (13)
8[c]	**1b**	**2e**	1	**3g** (59)	**4a** (21)
9	**1c**	 **2f**	24	 **3h** (52)	 **4b** (10)
10	**1b**	 **2g**	3		 **4c** (90)
11[d]	**1b**	**2g**	3		**4c** (69)

Table 1 (*continued*)

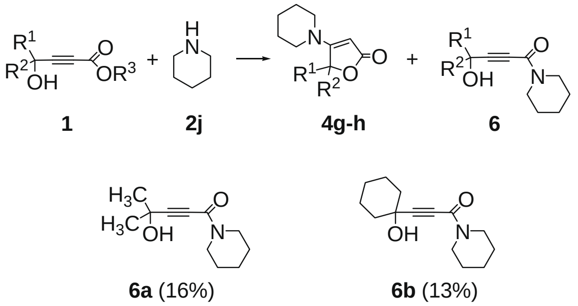
Entry	4-Hydroxy-2-alkynoates **1**	NuH **2**	Time (h)	Product **3** (yield%)[b]	Product **4** (yield%)[b]
12	**1b**	 **2h**	2		 **4d** (91)
13		**2h**	19		 **4e** (66)
14	**1b**	 **2i**	5		 **4f** (60)
15	**1b**	 **2j**	3		 **4g** (43)
16	**1c**	**2j**	2		 **4h** (50)

[a] Reactions were carried out in water at rt under ultrasound irradiation using the following molar ratios: **[1]**:**[2]** = [1]:[1.1].

[b] Yield refers to single run and is for pure isolated products.

[c] Reaction was carried out in water at rt under ultrasound irradiation using the following conditions: **[1]**:**[2e]**:[$NaHCO_3$] = [1]:[1.1]:[1.1].

[d] Reaction was carried out in water at rt without ultrasound irradiation.



Scheme 5. Reaction of 4-hydroxy-2-alkynoates **1** with piperidine **2j**.

pared to organic solvents. With amines instead of thiols a sequential conjugate addition/lactonization reaction leads to important 4-amino-furan-2-one derivatives. Ultrasound irradiation shows significant advantages compared to the traditional stirring.

Acknowledgment

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20. *General procedure*: Alkyl 4-hydroxy-2-alkynoate **1** (0.5 mmol) was added to a vessel flask containing 3 mL of water, immersed in water bath (rt) and sonicated for 5 min in a Falc Ultrasonic Model instrument. Afterwards the thiol or amine **2** (0.55 mmol) was added to the reaction mixture. Upon completion of the reaction (monitoring by TLC or GC-MS), the mixture was extracted with water (50 mL) and ethyl acetate (3 × 50 mL). The combined organic layers were dried (Na_2SO_4) and evaporated. The residue was purified by chromatography (hexane/ethyl acetate mixture) to give **3** or **4**.
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