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Synthesis of 4-azo-butenolides

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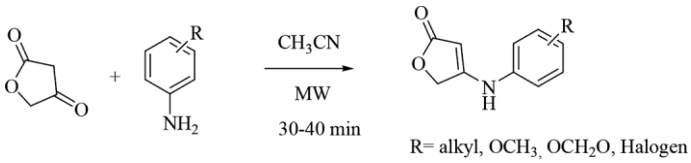
ABSTRACT

An efficient, catalyst free, microwave assisted approach has been developed for the synthesis of 4-azo-butyenolides derivatives by condensing tetronic acid with various anilines. This approach exhibited good functional group compatibility and produced the desired products in good to excellent yields in just 30–40 minutes. This approach can be seen as a better alternative to protocols with long reaction times used for the synthesis of these compounds, which are synthons for the obtaining of quinolines.

Graphical Abstract



KEYWORDS: microwave irradiation, quinolines synthons, short reaction time, substrate scope

Introduction

Heterocyclic natural or synthetic compounds are an important class of molecules for development of new drugs.[1–3] Several of these compounds containing the quinoline nucleus display innumerous biological properties and are used as drugs against malaria, cardiovascular diseases, allergies, and vasodilators.[4–15] The search for new drugs more potent and with less side effects requires chemical strategies of synthesis that facilitate the obtaining of intermediates for the construction of heterocycles in a quick way and in smaller reactional times, speeding up the process of the synthesis until the biological evaluation.[16]

4-Azo-butenolides are synthons for the synthesis of quinolines, dihydroquinolines, lactones and a large amount of derivatives of great pharmacological interest.[17–20] Despite the importance of these compounds, the syntheses described in the literature use reactional conditions that involve long reaction times and expensive purification processes.[20] These conditions make it difficult to obtain these intermediates for the construction of more complex molecules in quantity and structural variety for biological evaluation. In this work, a new method for synthesis of 4-azo-butenolide derivatives from reaction between tetronic acid (**1**) and anilines promoted by microwave is described.

Result and Discussion

Firstly, the reaction between equimolar quantity of tetronic acid (**1**) and 4-bromoaniline (**2a**) was used as a model to evaluation of better solvent and temperature for the synthesis (Scheme 1). Dioxane, water, ethanol, acetonitrile and trifluoroacetic acid (**Table 1**) were evaluated as solvent at room temperature and under microwave heating. Results are summarized in **Table 1**. The product **3a** was purified its structure was confirmed by ^{1}H NMR and ^{13}C NMR.

Table 1 shows that in the reaction with dioxane was obtained good yield at room temperature (entries 1, **Table 1**), but with a reaction time of 144 h. Under microwave heating at 200W the reaction time decreases, however, the yield also decreases with the formation of by-products as seen by thin layer chromatography (entry 2, **Table 1**). Microwave heating of dioxane occurs due the polarity of the starting materials. Water, ethanol and trifluoracetic acid at room temperature furnished the product **3a** in yield varying between 60 at 70% with reaction time of 72h. Under microwave irradiation these solvents provided the product **3a** in shorter reaction times in yields similar to those obtained at room temperature but with by-products formation. Acetonitrile in room temperature furnished the product **3a** in better yield in the time of 48h and 98% of yield after 30 minutes under microwave heating. In protic solvents used part of the aniline is ionized while in acetonitrile no there ionization and nucleophilic character of nitrogen is maintained. In dioxane also no there ionization, however the starting materials are insoluble, therefore the time reactional is longer.[21]

Based on these results, it was established a time of 30–40 min using acetonitrile as solvent under microwave heating for the others reactions performed.

After optimization of the reaction conditions, other anilines (**2b–j**) were examined for the synthesis of 4-azo-butenolides derivatives (**3b-j**) (**Table 2**).

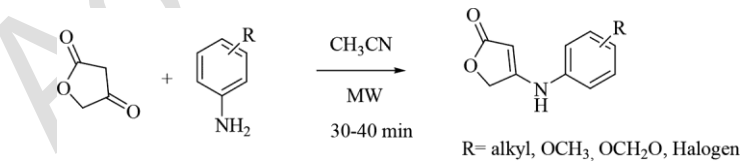
The results in **Table 2** show that by use of CH_3CN/MW in a time reaction of 30–40 min, it was possible to obtain 4-azo-butenolides derivatives (**3b-j**) with high yields (84–91%). Large yield differences was observed for aniline **2d** which furnished the product **3d** in yield of 74 %. The inductively electron withdrawing methoxy group in the position 3 of the aniline **2d** removes electron density from nitrogen, making it less nucleophilic.[22]

The nucleophilic attack of the nitrogen in the carbonyl of the tetronic acid (**1**) furnish the intermediate I. The MW heating causes increased of the molecular kinetic energy turning faster the reaction[23–26] and the acetonitrile (Lewis base) promote the remoting of proton α-carbonyl and subsequent loss of H_2O with formation of the product **3**.

There are in the literature methodologies describing the synthesis of 4-azo-butenolides derivatives, [27–31] however, most of them use anhydrous and toxic solvents such as benzene, low yields, long reaction times and chromatographic purification methods. Our methodology has the advantage not only of the higher yield, but also of the shortest reaction time and the higher purity of the products that do not require chromatographic purification.

Experimental

General procedure for synthesis of 4-azo-butenolides 3a



A mixture of tetronic acid (1.0 mmol) and anilines (1.2 mmol) in acetonitrile (2 mL) was taken in a reaction flask equipped with a small magnetic stirring bar, and the reflux condenser. The mixture was then irradiated in a microwave reactor for 40 min (reflux temperature of the solvent)

at a power of 200 W. Completion of the reaction was monitored by TLC (20 % ethyl acetate in hexane). The reaction mixture was then cooled to room temperature and the solvent was removed on rota-evaporator. The precipitated crude product was washed with mixture of hexane-ethyl acetate (8:2) and dried under vacuum to give **3a** (31.1 mg, 98%) as a yellow solid; mp 239–241 °C.

It was obtained as brown solid having m. p. 247–249 °C in 98% yield. ^{1}H NMR (400 MHz, DMSO-d6): δ (ppm) 9.83 (s, 1 H, NH), 7.53 (d, 2H arom, J = 8.8 Hz), 7.16 (d, 2H arom, J = 8.8 Hz), 5.36 (s, 1H), 4.87 (s, 2H). NMR ^{13}C (100 MHz, DMSO-d6): δ (ppm) 174.80, 162.32, 139.52, 132.18, 120.47, 114.58, 84.47, 68.04. HRMS (ESI $^{+}$): m/z [M + H] $^{+}$ calculated for $C_{10}H_9NBrO_2$: 253.9816; found: 253.9810.

Conclusion

Finally, we can conclude that the use acetonitrile and MW heating in the reaction between tetronic (**1**) and aniline derivatives (**2a–j**) produces new 4-azo-butenolides derivatives with excellent yields, in a very efficient manner. This reaction condition can be applied using anilines with electron-withdrawing as well as electron-donating substituents at different positions on the aromatic ring.

Supporting Information

Full experimental detail, ^{1}H and ^{13}C NMR spectra have been provided in supporting information. This material can be found via the “Supplementary Content” section of this article’s webpage.

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Table 1. Results obtained to the reaction between tetronic acid (**1**) and Br-aniline (**2a**) in different solvents

Entry	Solvente	Temperature[b]	Time (h)	Yield[a] %
1	DX	r.t.	144	86
2		MW	2	68
3	H_2O	r.t.	72	60
4		MW	0.5	65
5	EtOH	r.t.	72	68
6		MW	0.6	60
7	TFA	r.t.	72	70
8		MW	0.6	60
9	CH_3CN	r.t.	48	75
10		MW	0.5	98

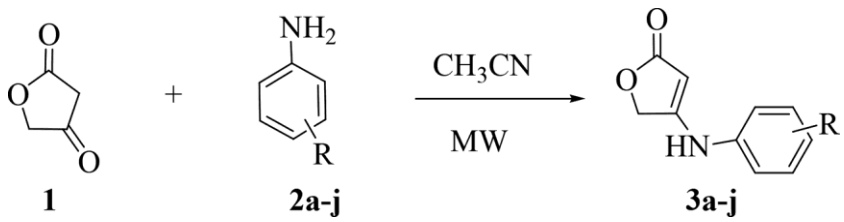
[a] Isolated product. [b] MW- reflux temperature of the solvent, 200 W, open vessel

Table 2. Results obtained by reaction between tetronic acid (**1**) and anilines derivatives (**2a–j**) promoted by MW

Entry	Aniline	Product	Yield[a] (%)
1	4-Br* **(2a)**	**3a**	98
2	3,4 (OC_2H_4O) **(2b)**	**3b**	97
3	4-(OCH_3) **(2c)**	**3c**	90
4	3-(OCH_3) **(2d)**	**3d**	74
5	4-Cl **(2e)**	**3e**	84
6	4-$CH(CH_3)_2$ **(2f)**	**3f**	84
7	3,4 (OCH_2O) **(2g)**	**3g**	96
8	3,4-$(OCH_3)_2$ **(2h)**	**3h**	93
9	3,4,5-$(OCH_3)_3$ **(2i)**	**3i**	89
10	4-CF_3 (**2j**)	**3j**	88

[a] Isolated yields. [b] MW- Microwave reflux, 200 W, open vessel

Scheme 1. Reaction between tetronic acid (1) and benzaldehyde derivatives (2a–j) promoted by microwave.



Scheme 2. Mechanistic proposal for reaction between tetronic acid and aniline.