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Three-component synthesis of hexahydropyridopyrimidine–spirocyclohexanetriones induced by microwave

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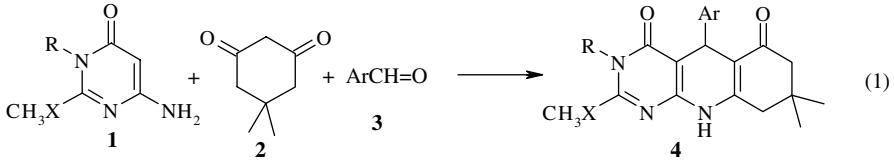
Abstract—Pyridopyrimidine–spirocyclohexanetriones (**5**, **6**) and pyrimido[4,5-*b*]quinolinones (**8**) were obtained in a three-component microwave-assisted reaction of 6-aminopyrimidin-4-ones (**1**) with dimedone (**2**) and formaldehyde solution or paraformaldehyde, respectively. A mechanism is proposed based on the presence of a basic catalyst (triethylamine in this case) and the fact that single condensation intermediates are isolated prior to the cyclization leading to the final products.

1. Introduction

Multicomponent reactions (MCRs) by virtue of their convergence, productivity, ease of execution and generally high yields of products have attracted considerable attention from the point of view of combinatorial chemistry. Over the last few years, there has been a tremendous development in three-component reactions and great efforts to afford new and effective MCRs.[1] Parallely, the potential application of microwave technology in organic synthesis,[2] and particularly under free-solvent conditions, is increasing rapidly because of its reaction simplicity, lesser environmental impact and reduced reaction time, providing rapid access to large libraries of diverse molecules.

The preparation of bioactive nitrogen containing heterocycles such as pyrido[2,3-*d*]pyrimidine derivatives, deaza-analogs of pteridines and their oxoderivatives is one of our ongoing projects due to their interesting bio-activities.[3] We have already reported some procedures for preparing fused dihydropyrido[2,3-*d*]pyrimidines,[4] including microwave-induced MCRs. Additionally, we have described a simple and efficient approach to prepare interesting biological[5] pyrimido[4,5-*b*]quinolines[4c] (**4**) in a three-component reaction from 6-aminopyrimidines (**1**), dimedone (**2**) and aromatic aldehydes (**3**) (Scheme 1).

Similarly, we report here an extension of the latter reaction using formaldehyde and microwave irradiation,



Scheme 1.

Keywords: 6-Aminopyrimidine; Formaldehyde; Dimedone; Pyrido[2,3-*d*]pyrimidine; Pyrimido[4,5-*b*]quinoline; Basic catalyst; Microwave irradiation.
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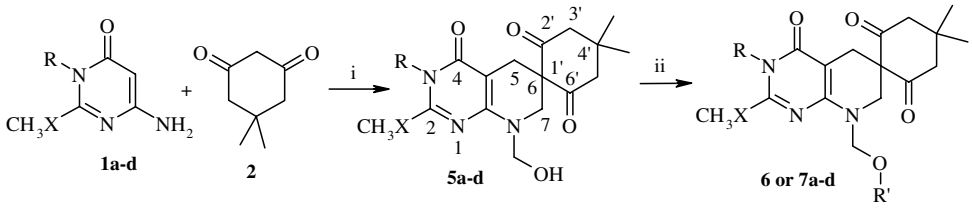


Comp.	5a	5b	5c	5d	6a	6b	6c	6d	7a	7b	7c	7d
R	H	H	CH_3	CH_3	H	H	CH_3	CH_3	H	H	CH_3	CH_3
X	S	O	S	O	S	O	S	O	S	O	S	O
Yield (%)	70	80	75	57	55	65	60	55	75	70	75	75

Scheme 2. Reagents and conditions: (i) excess of formaldehyde (37%) and microwave irradiation during 1–3 min; (ii) reflux in absolute ethanol or methanol.

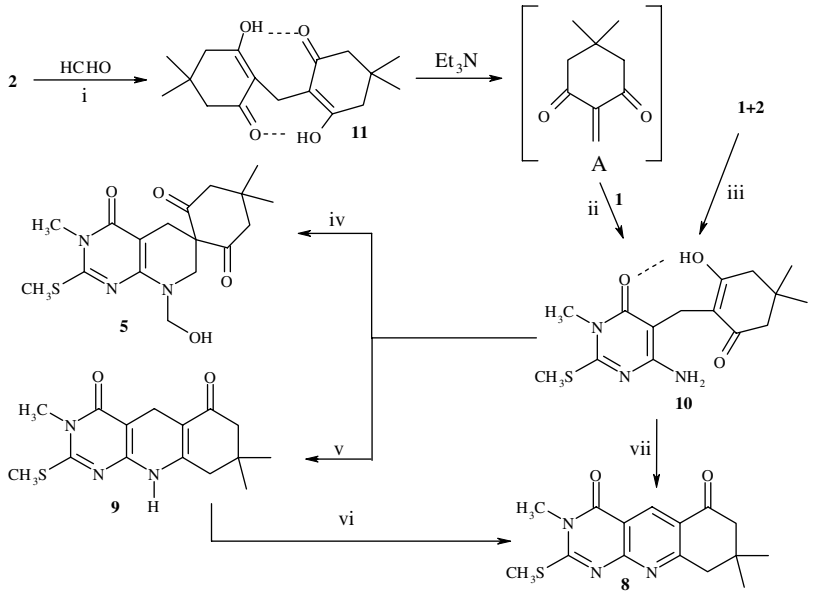
that renders, depending on the reaction media, either analogues of the reported pyrimido[4,5-*b*]quinolines (**4**) or the unexpected pyridopyrimidin-spirocyclohexanotriones.

2. Results and discussion

A facile three-component one-pot cyclocondensation takes place between 6-aminopyrimidines (**1**), dimedone (**2**) and formaldehyde affording pyridopyrimidin–spirocyclohexanetriones (**5a–d**) (Scheme 2). So, equimolar amounts of starting compounds **1** and **2** with a large excess of formaldehyde (37% in water) and triethylamine as catalyst were irradiated in a domestic microwave oven to give compounds **5** that were isolated in good yields (57–80%) (see Table 1 in Scheme 2); the reactions were repeated in different domestic microwave ovens to prove reproducibility, and no significant deviation was found.[6] Treatment of compounds **5a–d** with hot absolute ethanol or methanol lead to formation of compounds **6a–d** and **7a–d**, respectively (Scheme 2).[7]

Analogous reactions with paraformaldehyde in equimolar amount to dimedone, instead of a large excess in aqueous solution, yielded pyrimido[4,5-*b*]quinolinone (**8**),[8] when the mixtures were irradiated during 3–4 min (Scheme 3). Irradiation of the mixture during 2 min or heating in refluxing ethanol for 1 h afforded the dihydropyrimido[4,5-*b*]quinoline (**9**),[9] which with further heating gives the oxidized **8** (Scheme 3).

To prove the mechanism shown in Scheme 3, intermediates **10**[10] and **11** were isolated and left to evolve in the reaction conditions yielding the expected products. Therefore, the isolation of such intermediates permitted us to assume that the mechanism leading to the formation of **5** or **8** proceeds via an initial formation of the 2:1 dimedone/formaldehyde adduct **11**, that goes to the Knoevenagel adduct intermediate **A**, which suffers



Scheme 3. Reagents and conditions: (i) stirred in EtOH at rt for 2 h; (ii) reflux in ethanol during 4 h or MW during 2 min; (iii) formaldehyde (37%) and Et_3N at reflux in EtOH during 4.5 h or MW during 2 min; (iv) MW during 2 min and formaldehyde (37%) excess; (v) MW during 2 min or reflux in AcOH during 30 min; (vi) MW (2 min) or reflux in ethanol during 1 h; (vii) MW during 3–4 min.